MAPPING THE LANGUAGE-SPECIFIC CEREBROCEREBELLAR NETWORK OF THE HUMAN BRAIN THROUGH DIFFUSION TENSOR IMAGING

A Dissertation

Presented to

The Faculty of the Graduate School

At the University of Missouri

In Partial Fulfillment

Of the Requirements for the Degree

Doctor of Philosophy

By

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MAY 2015

The undersigned, appointed by the dean of the Graduate School,

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MAPPING THE LANGUAGE-SPECIFIC CEREBROCEREBELLAR NETWORK OF THE HUMAN BRAIN THROUGH DIFFUSION TENSOR IMAGING

Presented by Ian Douglas George

A candidate for the degree of

Doctor of Philosophy

And hereby certify that, in their opinion, it is worthy of acceptance.

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This work is dedicated to Lego. Thank you for making everything awesome.

ACKNOWLEDGEMENTS

I think it is fitting that the word dissertation comes from the Latin word dissertātiō, which means path. My research that lead to this dissertation was a journey, and all along my path to this document I was helped by many many people, both directly concerning my research, and also indirectly supporting me as a researcher and a person. First I have to thank my advisor Kris Aldridge. Kris took a chance on me and gave me the opportunity to become a Ph.D. student even though my academic achievements at that point were sorely lacking. During my years as her graduate student, Kris allowed me the freedom to explore research questions, even if they were outside of her lab and her own research focus, and find my own project, which ultimately lead to my dissertation and my future career. During the development process I often felt lost and as if I was drifting but looking back, I now recognize that Kris would nudge me back on track when I needed it and was there for me whenever I really needed it.

My dissertation committee - Carol Ward, Shawn Christ, and David Beversdorf all were also instrumental in the development and implementation of my dissertation research. I am grateful for their aid in the theoretical and logistics of my dissertation project. I have to thank the other faculty that have helped me with my graduate career at Missouri also, especially Casey Holliday, Kevin Middleton, and Mark Flinn for their assistance in thinking about my research and presenting it to others. Scott Maddux and Mary Shenk, thank you for your help in developing my grant applications, which

ultimately lead to my research getting funded. Special thank you to Cheryl Hill who helped me through the early years of graduate school, both academically and personally, and her advice in taking the next steps past my PhD.

My fellow Integrative Anatomy graduate students cannot be forgotten either – Rachel, Ashley, Henry, Elizabeth, Amanda, Sarah, Kaleb, Sharon, and Ian. Thank you for making it fun and interesting as we took classes together, did community outreach, went to conferences, and endured our graduate student experience. I look forward to working with you all in our future careers. Along these lines I also have to thank the Heidelberg for their half-priced appetizers and Shakespeare's for pizza and $4 triple wells for aiding in our graduate experience and giving us places to discuss our research and develop our ideas. I also thank past members of the Aldridge Lab – Kim, Jordan, Cortaiga, Sheldon, and Erin, all who listened to all my crazy ideas and suffered through Analyze, Amira, 3dMD, and EDMA with me.

None of my research would have been possible without the generous support of my granting agencies, the MU Life Sciences Fellowship, the Wenner-Gren Foundation, Pearson, and the Brain Imaging Center, all who helped with support of data collection, research tools, and supporting me as a graduate student.

I would not have been able to do any of my research without the support of my family, who cheered me on and poked holes in my hypotheses. Especially to my mom Sarah for her support and help teaching me how to write and submit the human subjects research paperwork that was part of my dissertation. Lastly and surely not least, Elizabeth for propping me up during the most trying times, as I had grants rejected, study subjects

go AWOL, committee members go missing, and as I wrote up my dissertation and prepare for the next stage of my career. You reminded me every day why my research was interesting and convinced me to keep going when I wanted to throw in the towel, thank you.

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ABSTRACT

Language was arguably a key influence in the evolution of the human brain and the evolution of this behavior in humans was likely associated with gross morphological changes and novel neural networks. My dissertation looked at one such network and verified anatomical connectivity between regions of the cerebellum, thalamus, and frontal lobe active during language using a combination of magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI). The results of the DTI analysis and fiber tracking support the hypothesis that there is discrete anatomical connectivity in a language-specific network.

The second aim of my dissertation to characterize and quantify this anatomical connectivity in the language-specific functional network between the cerebrum and cerebellum. We analyzed the language-specific cerebrocerebellar network (LSCN) in 59 right-handed neurotypical males through DTI images. My results show the white matter tracts in the LSCN have greater connectivity than that of the white matter in the whole brain, indicating that there is a discrete network between the cerebrum and cerebellum exclusively for language. This anatomical connectivity information about this neural network can now be used in conjunction with behavioral measures in future research on the evolution of the human brain, evolution of language, and pathologies that affect language production.

Chapter 1: Background

Introduction

Human language is a unique form of communication and forms the substrate upon which human thought is formed. The selection for structures in the brain to support this communication and cognitive system were essential steps in the evolution of the human brain. It is therefore impossible to fully understand how the human brain evolved without also understanding the network of specialized areas in the brain that support language. Endocast, which are an internal cast of the skull, are our only direct evidence of the what the potential brains of human ancestors may have looked like. There are few consistent trends observed in the evolution of the human brain beyond extensive expansion of the overall size (Holloway, 1982; Aiello, 1993; Dunbar, 1993; Rilling, 1999, 2008a; Semendeferi, 2000; Schoenemann, 2005; Sherwood, 2008) and a disproportionate increase in size of the cerebellum relative to the cerebrum (Rilling, 1998); this increased cerebellar volume has been associated with an apparent increase in cognitive complexity and may have coincided with the appearance of language in human ancestors (Weaver, 2005). Recently, there is increasing recognition of the role of the cerebellum in a neural network that modulates language production and comprehension in concert with the cerebrum (Schmahmann, 1991, 1996; MacLeod, 2003; Ben-Yehuda, 2007; Strick, 2009; Stoodley, 2010). However, details of the functional and anatomical connections of this cerebro-cerebellar network used in language modulation are poorly understood.

It is the goal of this dissertation to map the anatomical connectivity between the cerebrum and cerebellum and relate this morphology to both cognitive measures of language and the surface complexity of the brain. I will test the hypothesis that cortical regions in the cerebrum and cerebellum, along with the bundles of myelinated axons between them, compose a language-specific cerebrocerebellar network (LSCN) within the human brain. Further I will test to see if this subcortical structure can be predicted from the morphology of the surface of the brain alone. The cortical surface is the only part of the brain that may leave an osteological correlate on the inside of fossil hominid skulls so it is essential to test whether deeper brain tissues can be detected from surface data alone. This evidence is essential to gain new understanding of the brains of human ancestors from endocast data beyond cranial capacity and gross morphology alone.

Human Language

Language has been described as, "The driving force behind brain evolution, serving as the structure and substance of thought and cognition as well as a system of communication" (Bickerton, 1990). Spoken language is a hallmark ability of humans and is therefore central to the study of human brain evolution (Jerison, 1973; Lieberman, 1975, 1984; Dunbar, 1988, 1993; Deacon, 1990, 1997). There is a wide spectrum of communication abilities among extant animal species, both verbal and nonverbal, but no other communication system is able to transmit complex, advanced information as efficiently as human speech (Schepartz, 1993; Hauser, 2002; Lieberman, 1984, 2007). The human larynx is specialized for the production of the vocal aspect of human speech (Laitman, 1993; Lieberman, 1971, 2002), but the human brain has evolved specific

functional networks to support comprehension and production of complex language (Pinker, 1994; Aboitiz, 2002, 2006). For example, our closest living relatives, chimpanzees, are only able to match the language abilities of a two-and-a-half year old human child as assessed through nonverbal sign language (Savage-Rumbaugh, 1993), suggesting that the neural architecture for human language evolved since our last common ancestor (Jerison, 1973; Blumenberg, 1983; Sawaguchi, 1990; Dunbar, 1992; Pinker, 2010).

In the human grammatical language system, words are assigned to concepts and can be arranged almost infinitely to convey new meanings based on the component parts (Lieberman, 1984; Pinker, 1991, 1999; Jackendoff, 2003; Chomsky, 2006). This open ended, re-combinatorial property of human language makes it one of the most efficient ways to communicate where a finite number of sounds or letters, which are meaningless by themselves, can be recombined to form a theoretically infinite number of words and sentences (Miller, 1951; Pinker, 1999; Nowak, 2000; Trask, 2004). The breadth of meaning that the symbolic nature of human language is able to convey, and the ability to adapt and change with new experience and context-specific meanings makes spoken language one of the key adaptations during human cognitive evolution.

From a communication standpoint, it is useful to consider spoken human language as the process of transforming an individual's thoughts into audible sounds that are recognizable to the intended audience. Research on spoken language has indicated that there are two distinct computational stages involved in the production of a single word (Levelt, 1993; Bock, 1999; Martin, 2001). The first stage is selecting the correct word, or lexical item, that will express a concept. At this stage information about the word's

meaning and word class (e.g., noun or adjective or verb) is accessed to use in sentence construction. Many different languages are spoken by humans, each having shared rules among each language as to the meaning of words, or semantic portion of language (Bickerton, 1990; Crosson, 1999). The lexical portion of language production deals with the rules of each language such as how new words are created, how words go together to make meaning, and how to uses these groups of words (sentences) appropriately and in context for a given situation (Lieberman, 1975; Pinker, 1991; Shelton, 1999; Chomsky, 2006). In this study I will refer to the lexical and semantic processes as language production or cognitive portion of language production.

The second stage, the phonological stage, involves how to make the sounds to produce the word (Shtyrov, 2010), and actually speaking. This is also referred to as speech and is the actual expression of thoughts or ideas through vocal communication (Miller, 1951; Lieberman, 1975). Speech involves tightly controlled motor movements in the human vocal tract and involves articulation, which is the way speech sounds are produced and fluency, the proper rhythm of speaking without hesitation (Crosson, 2007; Ghosh, 2008). The phonological portion of language production is predominantly a motor control function but there are also motor planning portions of the phonological stage in the production of speech (Miller, 1951; Lieberman, 1975, 2002). Language and speech as concepts work together in human language with "language" is the idea to be communicated and "speech" is the process of *how* to communicate the idea.

The process of transforming sounds into meaning also is thought to have two stages. The first involves the analysis of phonological information, or sound structure, and the second involves access to information that puts the sounds into words and words

into sentences that have meaning, or lexical-semantic information (McClelland, 1986; Marslen-Wilson, 1987). It is worth noting that there might be shared processing between language perception and production, and additional processing about the individual features of speech and language (Shelton, 1999, Stevens, 2002). Both language production and comprehension require additional information processing related to sentence structure to aid in meaning of words, accessing both current context and past experience.

Within the context of the present study, I will use the first step of expressive language, the lexical and semantic processes, as the basis for investigating the neuroanatomical basis for language production.

Nervous System Organization

The study of neuroanatomy and the function of the brain has long been characterized by a debate between those who ascribe aspects of human cognition to discrete areas of specialized function versus those who view the functions of the brain to be distributed across the entire organ (John, 1978; Young, 1970; Finger, 2001). This debate extends to the study of neuroevolution and to whether there was a mosaic evolution of different brain regions or a concerted evolution of entire neural networks (Brown, 2001; De Winter, 2001). A more thorough understanding of the relationship between the structure of the brain and its function can be achieved through analyzing the brain from a network perspective.

Clinical studies of patients showing behavioral deficits associated with lesions in or damage to specific regions their brains were the basis of the first hypothesis about

functional localization. These clinical findings by researchers such as Paul Broca and Carl Wernicke were later confirmed through histological investigations of brain tissue. Basic central nervous system architecture has been studied in great detail previously through invasive techniques in animal models, including non-human primates (Felleman, 1991; Hilgetag, 1996; Preuss, 2000). Fundamental concepts about how the nervous system is organized were first shown through the work of Santiago Ramón y Cajal, Camillo Golgi, Franz Nissl, Theodore Schwann and others (reviewed in Shepherd, 1991; Finger, 2001). Using a silver nitrate-based staining method invented by Golgi in 1873 (Golgi's stain), Ramón y Cajal (Ramón y Cajal, 1909) showed that the nervous system was made up of contiguous arrangements of individual cells forming a network, a view which became known as the neuron doctrine (Shepherd, 1991; Finger, 2001; De Carlos, 2007). This view was in sharp contrast to other early ideas about how the brain was organized which theorized that the nervous system was made up of a net of continuous neuronal tissue. Ramón y Cajal and Golgi shared the Nobel Prize in 1906 for their work demonstrating that the brain is a network of cells and any study of its functions should take place within a network-based theoretical framework. Even though the neuron doctrine is over 100 years old, the tendency towards ascribing brain functions to discrete regions, *i.e.*, functional localization has persisted and has been reinforced by modern neuroscience techniques.

Prior to the neuron doctrine, neuroscience research relied on direct observation of the brain through gross anatomical measurements and through microscopic examination of explanted nervous tissue. Looking at the folding and patterns of the gyri and sulci, Ramón y Cajal, Golgi, and Joseph Dejerine performed detailed descriptions of the

microstructure of the nervous system through sectioning and staining brains of deceased patients (Dejerine, 1895, reviewed in Krestel, 2013). These novel histological techniques resulted in detailed descriptions of the cellular morphology of the nervous system, but it was not until later in the 20th century that the function of the nervous system, first electrical and later metabolic function, was investigated through newer and less invasive techniques that could be performed *in vivo*. Early electrophysiological measurements of single and patches of neurons on live subjects allowed direct observation of neural activity in the human brain with high resolution, but involved invasive surgery. Examining complex cognitive neural networks through traditional invasive connectivity techniques has been difficult as no suitable animal model exists that displays a cognitive behavior as complex as human language production (Rugg, 1999).

Cytoarchitecture Studies Of Brain Function

Clinical neurology research has long shown that lesions in localized parts of the brain result in predictable deficits in cognition, specifically in relation to language (Broca, 1861; Naeser, 1989), supporting ideas of functional localization. Histological studies of the cytoarchitecture of the brain by Korbinian Brodmann and Alfred Campbell also reinforced this idea by demonstrating regional differentiation of neural tissues and neuron types in the cerebral cortex (Brodmann, 1909, Campbell, 1905). It is important to note that research on the cytoarchitecture of the brain, even in modern studies, is a destructive process performed on deceased tissue; therefore, it is usually carried out on a minimal number of subjects and intraspecific variation is not, and cannot be, acknowledged. While Brodmann understood that cytoarchitectonic regions function

through connections among one another, he did not include fiber pathways in his histological investigations (Garey, 2006). Campbell, however, believed that the differential cytoarchitecture observed in his and Brodmann's research was the result of regionally specific connectivity patterns rather than the cause of them (ffytche, 2005).

Modern cytoarchitecture studies have confirmed the classical cerebral cortical regions identified by Brodmann and Campbell, and have revealed numerous additional anatomical subdivisions (Schleicher, 1999; Amunts, 2001) suggesting that early research underestimated regional differences in the cerebral cortex. Current research also has demonstrated significant inter-individual and inter-hemispheric variability (Amunts, 2000; Uylings, 2005), necessitating that maps of the brain's cytoarchitecture be probabilistic, rather than having fixed boundaries. To account for this inter-individual variability, other research has suggested that cytoarchitecture across individuals is related to differences in inter-regional connectivity (Barbas, 1997; 2002). The cytoarchitecture of a specific region is defined by both its inherent cellular identity and with which other regions it is anatomically connected. These two factors are thought to be a consequence of development and the topology of this connectivity can help in defining boundaries of different functional regions (Johansen-Berg, 2009). The myelinated axons of the neurons that construct the anatomical connections across functional networks in the brain are the basic components of white matter pathways. It is essential to investigate the morphology and connection patterns of these pathways when determining how the intrinsic cytoarchitecture of different brain regions and anatomical connectivity across the brain are related to neural function.

Non-Invasive Measures of Brain Activity

Current non-invasive techniques for observing and quantifying brain activity in clinical and research settings vary depending on what part of the brain is being screened or what is trying to be measured. The most common techniques include electroencephalography (EEG), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). EEG is a non-invasive technique that places sensors on the head to detect electrical activity in the brain, and was the first to allow direct measurement of brain function without opening the skull. EEG was first demonstrated by Richard Caton in 1875 on exposed cerebral hemispheres of rabbits and monkeys and improved upon by Hans Berger in 1924 with a surface device, the electroencephalogram, (Swartz, 1988; Haas, 2003). While EEG is non-invasive and has a high temporal resolution, it does not allow for detailed sourcing of electrical signals so localization of brain function is limited to very broad regions, such as a hemisphere or a lobe of the brain.

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are more specific in localizing function in the brain but both techniques are indirect measures of activity. PET involves injecting radioactive tracers into the bloodstream, most commonly a radioactive sugar or oxygen molecule with a short half-life. The body's metabolism will incorporate these tracers and concentrate them into specific areas (Sweet, 1955; Ter-Pogossian, 1975; Phelps, 1975; Bailey, 2005). During a PET scan, areas where the radioactive tracer is concentrated show up as "hot spots" on a PET image and these regions are inferred to have higher activity due to the increased metabolic signal. PET is not ideal for looking at connectivity, though due to temporal

limitations. Additionally, the necessity of using a radioactive tracer introduces unnecessary risks to patients and does not allow for repeated testing. Like PET, fMRI is also an indirect measurement of neural activity. fMRI measures neuronal activity based on the blood oxygen level-dependent (BOLD) signal, where regions of the brain with higher activity require more oxygen and affect the oxygenation in blood (Ogawa, 1990; Logothetis, 2004). PET and fMRI have proven to be robust means for localizing activity in the brain during behavior-specific experimental tasks, but each method measures different aspects of brain metabolism and function (Logothetis, 2001). Given that each method of observing the activity of the brain reveals different information about nervous system organization, each method also has shown that different types of connectivity exist in the brain's various networks (Horowitz, 2003; Lee, 2003; Friston, 1994; Jirsa, 2007; Schubert, 2007).

Diffusion Tensor Imaging

One non-invasive way to map white matter pathways is through a relatively new, specialized form of MRI called diffusion tensor imaging (DTI). DTI tracks the movement of water molecules, and in the brain, water diffuses along axons due to the tendency of water molecules to diffuse along cell membranes, the path of least resistance, rather than across them, where there is more resistance. DTI data are used to create anisotropy (directionality) maps of the brain that show the movement of water molecules on a voxel-by-voxel basis. From these anisotropy maps, DTI mapping, or tractography, can be performed to approximate the white matter pathways in the brain.

During DTI tractography, pathways are mapped from a "seed" location outward across the scan with no predetermined direction, showing all possible paths. The tractography results from several seed locations, each originating within language regions, can be overlaid upon one another. Because language requires the integration of several motor, sensory, and cognitive functional brain networks, regions of interest will project to areas in the brain that serve other functions in addition to language. The common tracts that are retained after overlaying all of the tractography results will show the connections between language seed locations that can be then be further analyzed. DTI is ideally suited to investigate connections among functionally active regions that are known to support the language specific functional networks in the human brain (Glasser, 2008; Rilling, 2008a, 2011; Ramayya, 2010; Li, 2011; Hecht, 2012). Through comparisons of the differential routes that neural signals travel to share information between functionally connected regions, subtle variation in neural networks among individuals may be uncovered that correlate with variation in performance (Rubinov, 2010; Zielinski, 2010).

Different ways to quantify white matter tracts in the brain have been used previously, including simple volume of white matter measured from histological thick sectioning and MRIs. DTI characterizes the anisotropic diffusion of water in biological tissues with the primary assumption that the probability of displacements from water diffusion is a three-dimensional (3D) multivariate Gaussian distribution, where the diffusion tensor is the covariance matrix of diffusion displacements (Basser, 1994). From this tensor I get eigenvalues (λ_1, λ_2, and λ_3) and eigenvectors (e_1, e_2, and e_3), each decreasing in magnitude). With DTI, commonly used measures of water diffusion,

including mean diffusivity (MD) and fractional anisotropy (FA), are used to infer connectivity (Pierpaoli, 1996). Specifically, MD is a mean of the three different directional vectors (eigenvalues) that a water molecule can diffuse within a voxel, which can be used to infer cell membrane integrity in brain tissues. FA is a measure of the degree of anisotropy, or the variance, of a diffusion process, which can be used to infer the microstructural arrangement of myelinated axons of nerve cells. Most research focuses on FA as it ranges from zero (meaning that diffusion is isotropic, equal in all directions), to one (meaning that diffusion is only proceeding in one direction). MD on the other hand can be informative also as it increases with edema and decreases with cell proliferation as seen in tumors (Alexander, 2007). The mean, range, and variation of each of these measures can be used to infer axon fiber density, axonal diameter, and degree of myelination of the white matter tracts. FA is high in white matter tracks where there is high myelination and dense axon bundles. FA is low in grey matter and CSF because water diffusion is more random in those areas. A lower FA can also indicate axonal degeneration and potentially demyelination. MD is roughly equal in white and gray matter and is sensitive to cell membrane integrity so it tends to be higher in tissue experiencing edema and necrosis. MD will also be higher in white matter where the axons are demyelinating or degenerating (Feldman, 2010; Alexander 2011).

Previous research using measures of white matter volume and DTI measures have demonstrated trends related to cognition and brain function in clinical conditions. For example, whole brain white matter volume has been shown to correlate with cognitive performance in individuals with multiple sclerosis (Edwards, 2001). Executive function is correlated with age-related declines in FA paired with increases in MD (O'Sullivan,

2001). Individuals with Alzheimer's disease have reduced integrity of the association white matter fiber tracts, as measured by anisotropy in major white matter tracts (Rose, 2000). In patients with multiple sclerosis, a significant correlation exists between white matter diffusion properties and verbal fluency and spatial recall (Rovaris, 2002). An investigation of the white matter associated with regions of the brain that are functionally active during language though structural MRI and DTI measures is necessary to characterize structural connectivity within this network, This connectivity information will tell us whether the variation I see in language behavior is a related to microstructural variation in the axon bundles linking active cortical regions.

Neural Connectivity

Connectivity in the brain can be conceptualized as three types, structural connectivity, functional connectivity, and effective connectivity (Friston, 2011). Structural, or anatomical, connectivity refers to the physical arrangement of neurons and other nervous system tissues, such as glial cells. Structural connectivity is considered to be stable over timeframes on the order of seconds or minutes, but can change with the passage of days or weeks (Honey, 2007). Functional connectivity, which can be measured through EEG, PET, and fMRI, looks at brain regions that share functional properties. It can be defined as the timed correlation between spatially remote neurophysiological events, expressed as deviation from statistical independence across these events in distributed neuronal groups and areas (Biswal, 1997). These correlations can be from resting-state activity, default network connectivity, or between stimulus or response in a behavioral task and are highly time-dependent. Effective connectivity

measures functionally active parts of the brain and looks at causal effects between regions (Büchel, 2000; Friston, 2011). Effective connectivity, like functional connectivity, is also highly time-dependent and looks at correlations between neurophysiological events and may also be from resting-state, default, or task driven network activity. Causation in effective connectivity is determined through significant modeling where several assumptions about the connectivity are set prior to analysis (Valdes-Sosa, 2011). None of these categories of connectivity can alone explain the how the brain works, and any analysis of a network in the brain must consider data from multiple sources.

Neuroanatomy of Language

The classical neurological model of language centers in the brain was based on early medical research in patients with language disorders (aphasias), which found damage to common areas in the brain (reviewed in Turken, 2011). This model included two distinct regions in the left hemisphere of the cerebrum (Figure 1.1). The first, Broca's area, is associated with speech production (Broca, 1861) and is located in the posterior region of the inferior frontal gyrus (IFG), later described as Brodmann's areas 44 and 45. The second region is Wernicke's area, associated with speech comprehension (Wernicke, 1874) and is located in the posterior portion of the superior temporal gyrus (STG), later described as Brodmann's area 22. Broca's and Wernicke's areas are anatomically connected by a large bundle of white matter (WM) called the arcuate fasciculus (Dejerine, 1895). However, lesions in other regions of the brain have also been associated with language impairment (Lieberman, 2002, 2007), specifically the subcortical basal

ganglia (Booth, 2007), the inferior parietal cortex (Turken, 2011), and the lateral lobules of the cerebellum (Booth, 2007; Schmahmann, 2008). These more recent findings suggest that language is mediated by a larger network within the brain beyond the classic focus of Broca's and Wernicke's areas (Wise, 2003), and beyond the cerebral cortex.

The classic view of the cerebellum has been limited to control of posture and coordination of voluntary movement (Schmahmann, 1991), but recent work has linked the cerebellum to distinctly non-motor functions (Leiner, 1986, 1989; Balsters, 2010). This non-motor functionality was confirmed by functional imaging studies in the 1990s (reviewed in Schmahmann, 1997). It is now recognized that there is a functional topography to the cerebellum (see Stoodley, 2014, Figure 1.2) that is based upon its anatomical connectivity to the sensorimotor and cognitive domains of the cerebrum (Schmahmann, 1991, 2004; Stoodley, 2010). Cerebellar damage is associated with cognitive deficits, including problems with short-term memory (Ackerman, 2007) and increasingly with language (Marien, 2001; Stoodley, 2009). Functional imaging studies have demonstrated that the cerebellum is involved with overt speech planning and production rather than its motor execution, indicating a modulatory role for the cerebellum in language (Snider, 1950; Leiner, 1986, 2004; Schmahmann, 1991, 1996; Turkeltaub, 2002; MacLeod, 2003; Bohland, 2006; Spencer, 2007; Ghosh, 2008). Anatomical studies in macaques have shown that the lateral lobules of the cerebellum are anatomically connected with the frontal lobe through several subcortical regions forming cortico-ponto-cerebellar projections with return through the thalamus (Ramnani, 2006). However, it is unknown whether this anatomical connectivity between the cerebrum and

cerebellum exists in humans and it is unclear whether this non-human primate pattern can be extrapolated to the human brain (Ramnani, 2006).

Evolution of the Human Brain

The primary focus of the study of human neuroevolution has been on the large brain size seen in humans. In general, brain size is positively correlated with body mass with the largest absolute brain size seen in animals such as elephants and whales (Gould, 1975; Nowak, 1999). Within primates, larger bodied animals such as great apes and humans have absolutely larger brains than those of smaller primates such as lemurs and tarsiers (Stephan, 1981; Nowak, 1999). How "brainy" an animal is can be calculated though the encephalization quotient (EQ) which measures the deviation of measured brain mass (M) from the allometrically expected brain mass (E) or $EQ = M_{brain}/E_{brain}$ (Jerison, 1973). The expected mass of the brain for a given body mass is defined by the equation $E_{brain} = 0.12M_{body}^{2/3}$ (Jerison, 1973). While this formula predicts brain mass from body mass for most vertebrates, some taxonomic groups have larger brains than body size would predict, necessitating alterations of this formula. The slope of the regression line of allometric scaling of brain mass vs. body mass is currently measured as 0.66 for most mammals (Macphail, 1982) and 0.76 for primates (Sherwood, 2008). An EQ value above 1 is generally interpreted as a given species having "excess" brain tissue, which is used for controlling abilities beyond somatic control of a large body. Some researchers interpret these extra functions, no matter how basic, as "cognition" (MacLeod, 2003). The encephalization quotient for humans varies from ~5.3 to ~8.1 depending on which adjusted formula a particular study uses (Jerison et al., 1973, Martin

1984). Despite this variance, human EQ is the largest compared to all other species. This means that humans have significantly larger brain mass than would be predicted for an animal of human size regardless of which formula is used (Falk, 1980; Holloway, 1982; Rilling 1999), as much as three times larger than expected (Martin, 1990; Deacon, 1997). Human cognition and intelligence has been attributed to this excessively large brain, which is the most relatively expanded and differentiated part of the body during human evolution (Holloway, 1982, Sherwood, 2008).

Aside from size, the various ways in which the human brain differs from nonhuman primates and what forces have driven these changes are perhaps the most interesting questions in the study of neuroevolution. Evidence of the divergence of the brain from other primates is observed not only in the relative size of the whole brain, but also the disproportionate increases in the size of the different brain regions. It is implicitly assumed that more tissue equals greater processing ability (Schoenemann, 1997) and that humans should have larger brain components dedicated to particular behaviors such as complex social systems and foresight to plan for future events. In contrast, the human olfactory bulb, which is approximately 30% smaller than scaling would predict for a primate brain of human body size (Stephan, 1981), is an example of a brain component, and function, that may have been deemphasized during human evolution.

In the human brain, when investigating the anatomical connectivity in a given functional network, the basic trends directing neural architecture must be considered (Laughlin, 2003). Billions of synapses and miles of axons have to be arranged into a network that occupies the space inside of the skull. The cranial capacity of the skull, and

accompanying brain volume within the skull, can only become so large before a human's neck will be unable to hold the head up, not to mention effectively move the head to face objects of interest in the environment. To develop and maintain an arrangement of tissue to fit into this 1,400 cm^3, significant constraints are imposed on both space and metabolism (Nelson, 1990; Striedter, 2005). Research has shown that the human brain has responded to these constraints through optimization of white matter wiring that has resulted in clustering of cortical regions based on connectivity (Hilgetag, 2000) and minimizing axon length (Sporns, 2000; Bullmore, 2009). Research on the metabolic costs associated with developing and delivering resources to an adult brain show that, in proportion to the total energy budget of the body, neural tissue gets a disproportionate allocation of nutrients relative to its size (Aiello, 1995, Laughlin, 2003). Thus the brain is an "expensive tissue" and selection might favor developmental steps that make it more energetically economical. To help reduce the amount of white matter volume necessary to maintain connectivity in the brain, Ruppin (1993) has shown that there are more short-range white matter connections than long-range ones. Paired with research on the spatial layout of the macaque brain showing that arrangement of the cortical areas minimizes volume of interconnecting axons (Klyachko, 2003, Kaiser, 2006), it suggests a tradeoff in brain architecture between having a highly connected cortex and having too much white matter tissue. From a structural standpoint, Van Essen (1997) first suggested that tension in axons during development might lead regions that share connectivity being physically closer to one another by maintaining short distances between neuron cell bodies not migrating away. This tension hypothesis also describes the mechanism leading to more compact white matter connectivity being paired with increased cortical folding. It is

possible then, that as brains become larger, they will naturally become more folded to maintain white matter connectivity, independent of processing ability.

A brain architecture scheme that minimizes both white matter length and volume would appear to be the most efficient form from a structural and metabolic standpoint, but long-range projections do exist in the brain. Research on brains of mammals and *C. elegans* suggests that axon length and volume in humans [?] could be reduced an additional 30% (Hilgetag, 2005, 2006), but the long-range interneurons between cortically distant regions are maintained for efficient information conduction.

The network topology of the human brain, *i.e.*, local cortical area clusters with high short-range interconnectivity and long-range connectivity between cortically distant regions, is exemplified in the cerebral language network. A long-range fiber tract that appears to have been elaborated upon during human evolution is the arcuate fasciculus, the white matter bundle that connects Broca's and Wernicke's areas. These two distant cortical regions are attributed to language production and comprehension, respectively (Broca, 1861; Wernicke, 1875), two functions that would need fast intercommunication. Comparing the anatomy of this tract in nonhuman primates, Rilling (2008) found that it was smaller and organized differently in macaques and chimpanzees as compared to humans. The expansion of the arcuate fasciculus strongly suggests that language is not simply a byproduct of humans having a large brain, but evidence of existing functional networks in the brain being elaborated upon to create novel patterns of connectivity that contribute to complex behaviors.

Summary

Human language, beyond being a unique form of communication, forms the substrate upon which human thought is formed. The selection for structures in the brain to support this communication and cognitive system were essential steps in the evolution of the human brain. It is therefore impossible to fully understand how the human brain evolved without also understanding the network of specialized areas in the brain that support language. Studies of endocasts have revealed few consistent trends during evolution beyond extensive expansion of the overall size of the human brain (Holloway, 1982; Aiello, 1993; Dunbar, 1993; Rilling, 1999, 2008a; Semendeferi, 2000; Schoenemann, 2005; Sherwood, 2008) and a disproportionate increase in size of the cerebellum relative to the cerebrum (Rilling, 1998) which has been associated with an apparent increase in cognitive complexity and may have coincided with the appearance of language in human ancestors (Weaver, 2005).

Recent neuroimaging and clinical studies have led to increasing recognition of the role of the cerebellum in a neural network that modulates language production and comprehension in concert with the cerebrum (Schmahmann, 1991, 1996; MacLeod, 2003; Ben-Yehuda, 2007; Strick, 2009; Stoodley, 2010). However, details of the functional and anatomical connections of this cerebro-cerebellar network used in language modulation remain unclear.

There is no clear consensus on the exact role of the cerebellum in modulating cognitive cerebral functions, including language (Stoodley, 2012). The uniform cytoarchitecture of the cerebellum and its robust connections to the cerebrum suggest that it processes information in a general way known as the universal cerebellar transform

(Schmahmann, 2000, 2010). The computational role of the cerebellum in motor and non-motor function has been hypothesized as predictor of future states, or forward model (Courchesne, 1997; Desmond, 1997), an internal clock that detects deviations in timing of actions (Ivry, 1997, 2002), a sequential event monitor (Ackermann, 2008; Leggio, 2011), and a control over attention (Courchesne, 1997; Salmi, 2009). What is missing from this literature is anatomy-focused research that looks at the actual physical connections, the white matter pathways between language regions of the cerebrum and the cerebellum to provide evidence of reciprocal connections.

It is the goal of this dissertation to map the anatomical connectivity between the cerebrum and cerebellum and relate this morphology to both cognitive measures of language and the surface complexity of the brain. Using cutting-edge *in vivo* imaging techniques, I will map the white matter pathways between regions of the cerebrum and cerebellum that are functionally active during language production. I hypothesize that these cortical regions in the cerebrum and cerebellum, along with the bundles of myelinated axons between them, compose a language-specific cerebrocerebellar network (LSCN) within the human brain. This dissertation has three objectives designed to determine how the cerebrum and cerebellum in modern humans are anatomically interconnected to support language production.

Objective 1) Determine the morphology of the language-specific cerebrocerebellar network (LSCN) in healthy adult humans by tracking the white matter connections between language regions in the brain. I will test the hypothesis that there is a discrete, language-specific anatomical network connecting the cerebrum and cerebellum.

Objective 2) Determine whether there is a correlation between language ability and the morphology of the LSCN in healthy adult humans. Accordingly, I will test the hypothesis that the structure of the LSCN is significantly correlated with quantitative measures of language ability.

Objective 3) Identify the relationship between morphology of the cerebral surface and corresponding underlying white matter in the LSCN. Specifically, I will test the hypothesis that the complexity of the cerebral surface is directly proportional to the degree of underlying white matter connectivity in the LSCN.

It is impossible to reconstruct how the human brain evolved without understanding how I developed language, which is arguably the key factor that has influenced the evolution of the human brain. This research will be the first to establish the pattern and variability of the LSCN in the human brain and yield significant new insights into how humans developed a brain capable of complex language. Mapping the connections among the cerebellum and classical language areas in the cerebrum and verifying that the cerebellum is a key component of the language network in the brain would represent a major paradigm shift in our understanding of human brain evolution. This research will also be the first to directly relate the anatomy of the language network in the brain to language ability, providing important conclusions regarding the structure-function relationships of this human cognitive neural network.

In addition, this research will provide critical data on what can be inferred about language from the study of fossil brain endocasts by testing the assumption that surface morphology reflects the architecture of underlying brain structure, specifically in the LSCN. This evidence is essential for making predictions about fossil hominin ancestors

from endocast data. If patterns of brain surface features co-vary with an individual's language ability, we will be able to test the hypothesis that these same suites of features are reliably reproduced on endocasts in future work. This will significantly inform neuroevolutionary studies beyond what isolated fossil and comparative analyses have shown previously and potentially reveal whether human ancestors were capable of language. Beyond the scope of this project, the connectivity analysis developed for this research can be applied to any other cognitive functional network in the brain that was adaptively important to humans, such as complex tool making or social cognition.

Important conclusions regarding the structure-function relationship in the human brain will also be uncovered from this study. Previous studies of fMRI data have demonstrated functional connectivity between spatially separate regions in the brain and anatomical connectivity has subsequently been assumed. The proposed research will use structural MRI and DTI to verify, characterize, and quantify this anatomical connectivity within the LSCN in the human brain. Knowledge of the entire morphology of this network will inform future research about additional brain regions that may be involved in language that were not previously detected through functional analysis alone.

Knowledge of the typical anatomy of a functional network will serve as a powerful normative framework for comparison in many diseases that affect language as well as other aspects of cognition. Large networks in the brain are responsible for many higher functions (Zielinski, 2010) so by analyzing the entirety of these functional networks, subtle pathologies that have been overlooked by a more mosaic analysis can be found. Finding the alterations in these morphologies is key in guiding further research to determine how pathologies in these large cognitive networks result in many observed

neurodevelopmental and neurodegenerative disorders, including autism, ADHD, Alzheimer's, and many others.

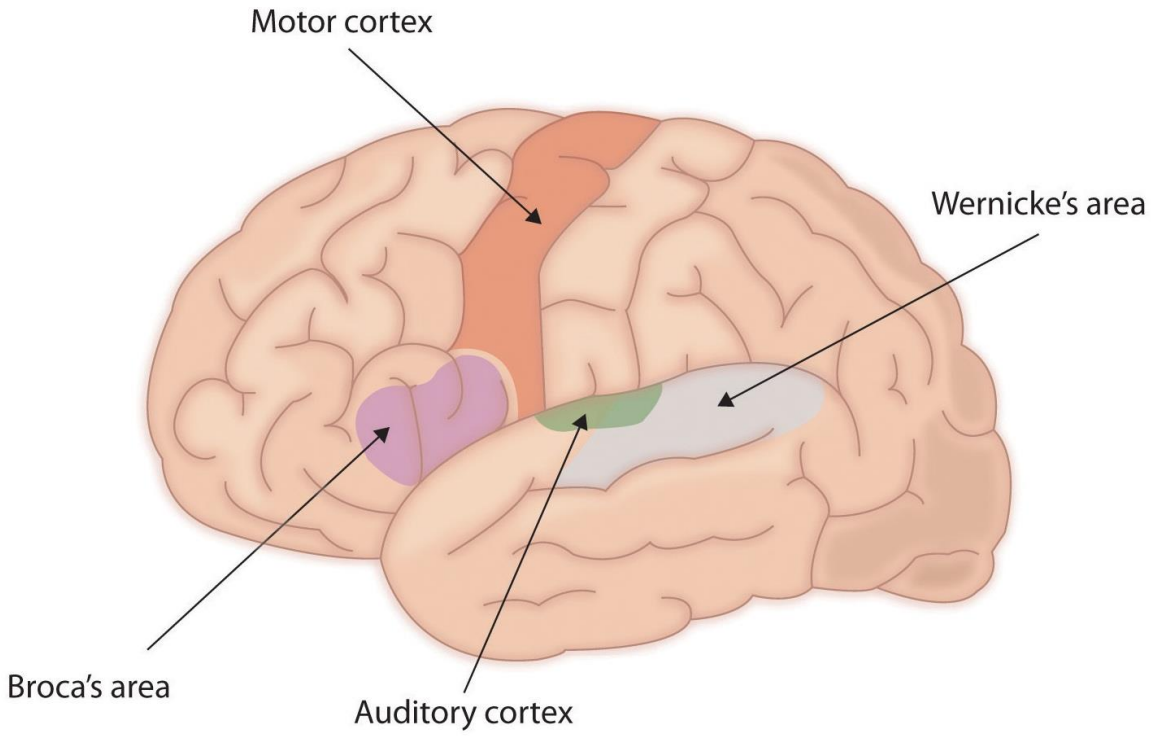

Figure 1.1 – Left lateral view of the cerebrum showing Broca's area in the inferior frontal lobe, the primary motor cortex in the precentral gyrus of the frontal lobe, the auditory cortex in the superior temporal gyrus of the temporal lobe, and Wernicke's area in the temporal lobe.

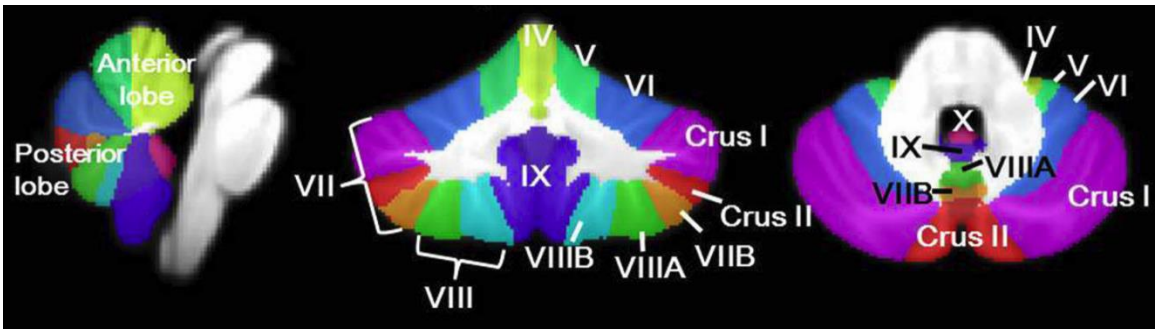

Figure 1.2 – Anatomical divisions of the cerebellum, modified from Stoodley (2014). Lobules listed in roman numerals.

Chapter 2: Mapping Language in the Human Brain

Introduction

Human language is one of the most complex behaviors exhibited by any species. Language allows an individual to efficiently communicate their thoughts, ideas, and intentions to those around them, as well as to produce novel responses that are appropriate to their current situation. This learned behavior becomes an essential part of a person's self-image and is inseparable from their cultural identification. The development of language was a key innovation during human evolution, forming the infrastructure for additional complex behaviors unique to humans, including higher-order executive functions like empathy, secondary theory of mind, and instruction based learning.

While many species employ unique forms of communication, what is unique to human language is that we do not require a distinct sound for each word, but we use phonology to recombine and reuse sounds to make a vast array of words (Berent, 2013). The unique ability of humans to produce and comprehend phonological language requires a network of specialized areas and connections in the brain that controls both the motor pathways to the anatomical structures that produce the complex vocalizations as well as the neural pathways involved in processing this advanced form of communication (Pinker, 1994; Aboitiz, 2002a, 2002b, 2006). It is hypothesized that the rudimentary neural architecture for human language existed in our last common ancestor and was elaborated on during the evolution of the human lineage (Jerison, 1973; Blumenberg,

1983; Sawaguchi, 1990; Dunbar, 1992, 1993; Pinker, 2010). In order to fully understand how the human brain has evolved to accommodate the production of human language and how evolving this unique communication system has reciprocally influenced this structure, we first must know which neural regions are part of the language network and what each region's role is in language.

The classical neurological model of language included two distinct regions in the left hemisphere of the cerebrum (Figure 2.1). The first, Broca's area in the inferior frontal gyrus (IFG), is associated with speech production (Broca, 1861) and the second is Wernicke's area in the superior temporal gyrus (STG), associated with speech comprehension (Wernicke, 1874). More recent studies have found that other regions of the brain are associated with language as well (Lieberman, 2002, 2007), specifically the subcortical basal ganglia (Booth, 2007), the inferior parietal cortex (Turken, 2011), and the lateral lobules of the cerebellum (Booth, 2007; Schmahmann, 2008). These more recent findings suggest that language is mediated by a larger network within the brain beyond the classic focus of Broca's and Wernicke's areas (Wise, 2003).

The inclusion of the cerebellum as potentially associated with language function contrasts with the classic view of its function, which was limited to control of posture and coordination of voluntary movement (Schmahmann, 1991). Recent work has linked the cerebellum to distinctly non-motor functions (Leiner, 1986, 1989; Balsters, 2010), including short-term memory (Ackerman, 2007) and increasingly with language (Marien, 2001; Stoodley, 2009). Functional magnetic resonance imaging (fMRI) studies have demonstrated that the lateral cerebellum is involved with overt speech planning and production rather than simply its motor execution, indicating a modulatory role for the

cerebellum in language (Snider, 1950; Leiner, 1991, 1993; Schmahmann, 1991, 1996; Turkeltaub, 2002; MacLeod, 2003; Bohland, 2006; Spencer, 2007; Ghosh, 2008). Recent research has shown that the lateral lobules of the cerebellum are anatomically connected with the cerebrum, including the primary cerebral language centers through several subcortical regions (Ramnani, 2006). The combination of these studies has led to a hypothetical functional topography of the cerebellum (Schmahmann, 1991, 2004; Stoodley, 2009, 2010, 2011, 2012).

In order to understand the language network comprehensively, the specific neural architecture involved must be defined, mapped, and quantitatively characterized. Regions that are simultaneously functionally active are assumed to be anatomically connected, or the common saying, "neurons that fire together, wire together" (Hebb, 1949). While this is the basic assumption of functional connectivity analyses, the underlying anatomical connectivity may be more complicated than simply, "region A fires with region B, therefore region A is directly connected with region B." Thus, it is necessary to test these hypotheses to confirm connections among disparate regions.

The purpose of this study is to test the hypothesis that regions of the cerebrum and cerebellum that are simultaneously active during language production share anatomical connectivity and thus constitute a language-specific cerebrocerebellar network (LSCN). I analyze *in vivo* structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) of a sample of healthy young adult males to define and analyze the white matter tracts that constitute the hypothesized anatomical connections of the LSCN.

Materials and Methods

Identifying regions of interest (ROIs)

To identify regions of interest (ROIs) in the brain that are active during normal language production, i.e., lexical and semantic processing, I performed an Activation Likelihood Estimation (ALE) meta-analysis (Turkeltaub, 2002; Wager, 2007). An ALE meta-analysis examines the results of many fMRI studies and pools these data, producing whole-brain images of the convergent findings, and has been shown repeatedly to be a reliable proxy for functional data (Turkeltaub, 2002; Laird, 2005, 2011; Eickhoff, 2009). Results are identified as clusters of specific coordinate locations in one of two standardized brain atlases, the Talairach atlas (Talairach, 1998), or the Montreal Neurological Institute atlas (MNI; Mazziotta, 1995). Previous meta-analyses of normal language production (Turkeltaub, 2002) have focused on the two primary language centers described in the classical model of language, rather than the larger network of regions, and have not included the cerebellum. One possible reason for this is the cerebellum is often not included in the field of view during the fMRI scan in many neuroimaging studies.

Inclusion criteria for the fMRI studies used in the ALE meta-analysis were: 1) the studies presented coordinate-based analyses of the data, 2) overt speech was used as part of the task, 3) English was the primary language of the study participants, and 4) the cerebellum was functionally active in the results of the study. Following these criteria, 34 studies were incorporated in the meta-analysis, which included 57 experiments and 661 individuals. Coordinate data from these selected studies were analyzed using software called GingerALE (version 2.3), developed at the Research Imaging Institute at the

University of Texas Health Science Center in San Antonio, Texas (RII-UTHSCSA) (http://brainmap.org/ale).

The ALE meta-analysis defined 13 ROIs active during language production (ALE cluster coordinates shown in Table 2.2) These ROIs are shown overlaid onto a standard anatomical template in the Talairach coordinate system (Figure 2.2) (Talairach, 1988). These ROIs were used as the basis for hypothetical nodes of the LSCN, to be tested with tractographic analysis.

MRI Data Acquisition and Study Subjects

Our study included 31 right-handed males (age range 18-26 years). The study is limited to right-handed males in order to avoid potential differences related to sex and handedness. Ten of the participants were originally recruited as a control group for an ongoing study at the University of Missouri (Beversdorf, 2015), with the remaining 21 recruited specifically for the present study. All included participants were healthy, monolingual English speakers and right-handed. All recruitment, data collection, and analysis was conducted under protocols approved by the University of Missouri Health Sciences Institutional Review Board (HSIRB) and is compliant with the Health Insurance Portability and Accountability Act (HIPAA).

All MRI data were collected at the Brain Imaging Center at the University of Missouri (www.bic.missouri.edu) using a 3T Siemens Magnetom Trio scanner. High-resolution T1-weighted anatomical images were acquired using a 3D MP-RAGE pulse sequence. DTI data were acquired for 64 directions and one nondiffusion-weighted (b0) image. All imaging parameters are presented in Table 2.1.

MRI Data Analysis

Raw structural and diffusion data were transferred to a secure server and stored as DICOM files for pre-processing. All images were visually inspected for artifacts or gross anomalies then converted from DICOM to NIFTI files using the "dcm2nii" module of the software MRIcron (Rorden, 2000). For each individual, Amira 5.5® was used to delineate the ROIs representing the hypothetical nodes in structural MRIs and then to perform fiber tracking between nodes using the DTI data via the following three steps (Figure 2.3). First, each ROI was manually segmented on the T1 structural MRI data using Amira's "Segmentation Editor." Sulcal, gyral, and subcortical boundaries dictated by standard anatomical definitions (Brodmann, 1909; Damasio, 2005) were used to define the boundaries of each ROI.

Next, the diffusion-weighted volumes were resampled to match the resolution of the T1 structural scan and registered to one another using the "Resample" and "Registration" tools in Amira. The "ComputeTensor" module in Amira was used to estimate a symmetric second order tensor from one b0 volume, a volume with no diffusion weighting, and 64 diffusion weighted b1000 volumes, a directionally weighted volume. Amira automatically extracts the gradient directions for each volume from the DICOM headers, and then creates a diffusion tensor volume, using "ComputeTensor," which describes the principal direction of diffusion within each voxel (Figure 2.3). In order to visualize these diffusion directions, ellipsoids are overlaid onto each voxel to view the diffusion direction in three dimensions.

The diffusion tensor volume, which was registered with T1 structural volume and accompanying ROIs, is now used for fiber tracking in a deterministic fashion following

(Conturo, 1999; Basser, 2000; Glasser, 2008; Mori, 2009). All clusters from the ALE meta-analysis were transformed into native space for each subject to avoid artifacts due to normalization. During fiber tracking (Figure 2.4), each ROI acts as a starting point or a waypoint for fiber tracts. Fibers proceed from each ROI in each direction along the principal diffusion vector until they reach the boundary with the neighboring voxel. Fractional anisotropy (FA) is used to determine fiber directionality. FA is a measure of how restricted diffusion is in each voxel with zero being random movement and 1 being highly restricted and directional. If the FA threshold between the neighboring voxels is less than 0.2 the fiber will proceed to the next voxel and continue tracking. The fiber will proceed along voxel to voxel until it reaches a boundary where the difference in FA threshold is too great, and fiber tracking will cease. The resulting fiber tracts between ROIs are an indirect measure of their interconnections. These measures are described both qualitatively and quantitatively to infer the connectivity and morphology of white matter tracts.

I performed our fiber tracking by first using the cluster from our ALE meta-analysis that was located in the right cerebellum. I placed a seed location in the white matter just deep to cerebellar Lobule VI and Crus I. Multiple fiber tracking trials were performed, and each of these trials terminated within the left thalamus. Thus, it can be inferred that the neurons from the right cerebellar ROI synapse in one of the sub regions in the left thalamus. Fibers from the left thalamus seed, another cluster from the ALE meta-analysis, tracked over most of the cerebrum, cerebellum, and brainstem.

Next, I used the “Selectlines” function on the fiber tract sets from both the right cerebellar seed and the left thalamus seed, and did an addition where only the fibers that

were sharing voxels between the two sets were maintained. This simplified and combined both fiber tract sets; the remaining fiber tract set is described below.

Results

Nodes in the LSCN

As expected, results included previously identified cerebral language centers, Broca's area (frontal lobe, left inferior frontal gyrus) and Wernicke's area (temporal lobe, left superior temporal gyrus). In addition to these regions, the right anterior and right posterior lobes of the cerebellum (lobule VI and Crus I), as well as several sub-cortical structures that are major sites of cerebellar outflow were identified (Figure 2.2). These results are similar to those found by Stoodley (2009) and Chen (2014) in their meta-analyses of the cerebellum and cognition, including language. These ROIs were used as hypothetical nodes of the LSCN, to be tested with tractographic analysis.

LSCN tractography

I began fiber tracking using the ALE meta-analysis cluster located in the right cerebellum. I placed a seed location in the white matter just deep to cerebellar Lobule VI and Crus I. The LSCN fiber tract sets identified for each individual were overlaid and registered to produce a group average LSCN (Figure 2.5). Following inter-subject registration, only common fiber tracts were retained (Figure 2.5), and are described as follows. The average LSCN tracks from the white matter in the right cerebellar hemisphere (Lobule VI and Crus I), through the right superior cerebellar peduncle where it decussates in the pons, ascends in the left cerebral peduncle, and terminates in the left thalamus. Three fiber tracking trials were performed per individual, and each of these

trials terminated throughout the left thalamus. Thus, it can be inferred that the neurons from the right cerebellar ROI synapse in one of the sub regions in the left thalamus.

The left thalamus was identified as another cluster in the ALE meta-analysis, indicating that a second seed be placed here. Fibers from the left thalamus seed tracked over most of the cerebrum, cerebellum, and brainstem. Fibers from the second seed within the left thalamus proceeded through the anterior limb of the internal capsule and terminated near Brodmann's area 44 in the inferior frontal gyrus of the frontal lobe, a ROI previously defined by the ALE meta-analysis as a hypothetical node in the LSCN.

I then combined the two fiber tract sets where only the fibers sharing voxels between the two sets were maintained. The only fiber tracts in this new set that passed into any of the other clusters identified in our ALE meta-analysis were fibers that proceeded anteriorly from the left thalamus seed and terminated near Brodmann's area 44 in the inferior frontal gyrus of the frontal lobe. This ROI was previously defined by the ALE meta-analysis as a hypothetical node in the LSCN, indicating it to be the termination of the anatomical connectivity between the right cerebellum seed, the left thalamus seed, and Brodmann's area 44.

Discussion

In this study, I test the hypothesis that there is a discrete language-specific cerebrocerebellar anatomical network in the human brain. Specifically, I analyzed *in vivo* DTI data collected from healthy young adult males to measure the brain's white matter tracts linking regions in the cerebrum and cerebellum that are functionally active during language production. The results of our ALE meta-analysis support previous research

identifying that the cerebellum is involved in non-motor brain function and specifically language (Schmahmann, 1991, 2010; Stoodley, 2009b, 2011). Our results show that the specific regions of the right posterior lobe of the cerebellum (Lobule VI and Crus I) that are functionally active during language production are connected to Brodmann's area 44, a sub-region of Broca's area, in the inferior frontal gyrus of the cerebrum, via the left thalamus. The fiber tracts described by the DTI tractography to infer this discrete pattern of white matter connectivity between the cerebrum and cerebellum were present in all study participants.

These results confirm that the network of regions involved in language span multiple gross anatomical structures of the brain, extending beyond the classic centers of Broca's and Wernicke's areas. These findings support findings of previous functional neuroimaging research that expand the classical neurological model of language (reviewed in Wise, 2003). This network includes regions of the right lateral cerebellum, left thalamus, and left frontal lobe that are functionally active during language production. This observed anatomical connectivity concurs with previous functional connectivity studies of language production (see ALE meta-analysis). Further, this anatomical connectivity supports the hypotheses that "neurons that fire together, wire together" first put forth by Hebb (1949).

The anterior portion of the LSCN projecting from the thalamus to Brodmann's area 44, a sub-region of Broca's area, is where we observe our fiber tracts terminating in the frontal lobe. Although no specific sub-region of the thalamus is hypothesized from the fiber tracking in the present study, we observe the fiber tracts in the ventral and lateral portions of the thalamus (Figure 2.6). Previous research indicates that the ventral lateral,

ventral anterior, intralaminar and mediodorsal regions receive output from the cerebellum (Barbas, 2012). These same nuclei are part of a frontal loop, including the thalamus, basal ganglia, and Broca's area, that are hypothesized to enhance language generation by selecting context dependent language to express a concept (Barbas, 2013; Crosson, 2013). The results of my fiber tracking in the anterior portion of the LSCN supports these hypotheses and may be a portion of this loop as this experiment aimed at mapping a language production network.

There are a number of important clinical implications of these results. First, a clear definition of the typical anatomy of the LSCN will serve as a powerful normative framework for evaluating many diseases that affect language, as well as other aspects of cognition, such as working memory and executive functioning. By analyzing both the functional connectivity in active cortical areas, and the anatomical white matter connections between them in the LSCN, subtle pathologies that may have been overlooked by previous analyses of isolated brain regions may also be identified. Indeed, a network analysis of the brain that can identify subtle patterns of dysmorphology or altered connectivity in a large cognitive network, such as the one that serves language in the human brain, may be the key to discovering the anatomical basis for several syndromes such as Autism Spectrum Disorder (ASD) or Specific language impairment (SLI).

Furthermore, observation of a morphological change in the LSCN following a clinical intervention may permit evaluation of the treatment's efficacy long before the desired functional or behavioral change is actually detected. Further analysis of this network in a larger and more diverse sample, including females and a broader age range,

is necessary though to determine the configuration and normal range of variation of this network.

Further analysis of the LSCN that considers direct quantitative measurements of language ability is an essential next step. Through comparisons of the differential anatomical connectivity between functionally connected regions, subtle differences in neural networks among individuals may be uncovered that correlate with differences in performance (Rubinov, 2010; Zielinski, 2010). The ultimate question comes down to the relationship between brain structure and brain function. In this case, are measurable behavioral differences in language production correlated with structural differences in the brain, and specifically in the LSCN? A robust evaluation of language using standardized psychological assessment tools paired with the DTI analysis described here is an ideal combination of data and methodologies to test hypotheses about structure-function relationships in the brain.

Our results have important implications for the evolution of the human brain. Language has been described as, "The driving force behind brain evolution, serving as the structure and substance of thought and cognition as well as a system of communication" (Bickerton, 1990; Schepartz, 2005). The evolution of spoken language is a hallmark ability of humans and is therefore central to the study of human brain evolution (Jerison, 1973; Lieberman, 1975, 1984; Dunbar, 1988, 1993; Deacon, 1990, 1997). Throughout human evolution, the brain has expanded in both relative and absolute size to outpace all other primates (Falk, 1980; Stephan, 1981; Holloway, 1982; Passingham, 1982; Rilling, 1999; Striedter, 2005) while also undergoing significant reorganization (Tobias, 1975; Holloway, 1976; Falk, 1987; MacLeod, 2003; Striedter,

2005; Weaver, 2005). Recent studies have shown that regions of the brain that share anatomical connectivity expanded in concert during human evolution (Barton, 2000, 2002; Whiting, 2003). Much like the cerebrum, not all regions of the cerebellum have expanded uniformly during evolution (Balsters, 2008). The more lateral, frontal-projecting lobes have expanded at a greater rate than more medial portions of the cerebellum (Rilling, 1999; Balsters, 2010). Importantly, these lateral parts of the cerebellum are the same areas that neuroimaging studies have shown to be functionally connected to regions in the cerebrum that are active during language production in humans (Schmahmann, 2004; Stoodley, 2009). Our findings support these hypotheses by showing that the functionally connected regions of the cerebrum and cerebellum also share anatomical connectivity in the language network, suggesting that they may have been subject to common selection pressures.

Although it will never be known at what point during human evolution specific structural networks expanded or were reorganized to arrive at their modern form, we can hypothesize timing of functional changes (i.e., behavior) related to these networks based on cultural materials associated with hominin fossils (Schick, 1999). Artifacts in the fossil record, such as stone tools and expressive art, are used as indicators of cognitive expansion in the brains of human ancestors, and it has been postulated that language would have facilitated more efficient manufacturing and refinement of these objects (Wynn, 2002). Through analysis of functional networks in the brains of modern humans, we can identify regions that are responsible for complex behaviors that are considered unique to humans, such as complex tool use (Frey, 2007; Philip, 2014) and language (Leiner, 1986; Morgan, 2009; Vannest, 2009). The present study may serve as a model

for future work to test further hypotheses regarding the development and evolution of these functional networks that support unique human behaviors.

Table 2.1. MRI Scan Parameters		
Sequence	T1 MRI MPRAGE	DTI EPI
Orientation	Sagittal	Axial
TR (ms)	> 1900	> 5000
TE (ms)	2-4	> 100
TI (ms)	1000	N/A
Matrix size	256 x 256	128 x 128
# of slices	176	36
Slice thickness (mm)	1.0	3.0
Voxel size (mm)	1 x 1 x 1	3 x 3 x 3
Directions	N/A	64
Time (minutes)	~5.00	~10.00

Scan parameters for the imaging data collected in this study. Abbreviations: MPRAGE – magnetization prepared-rapid gradient echo; DTI EPI- diffusion tensor imaging; echo-planar imaging; TR – repetition time; TE – echo delay time; TI- inversion time; Matrix size- resolution in pixels; Voxel- cubed pixel.

Table 2.2. Major ALE foci from the meta-analysis						
Lobe	**Region**	**X**	**Y**	**Z**	**ALE ($x 10^2$)**	**Size (mm^3)**
Frontal						
Left	Precentral gyrus (4, 44)	-47.68	-2.43	14.52	5.78	21360
	Superior frontal gyrus (32)	-1.05	7.04	46.58	6.44	7368
Right	Precentral gyrus (6)	47.46	-8.62	32.94	5.24	5704
	Middle frontal gyrus (46)	-47.15	22.33	19.17	2.63	632
Temporal						
Left	Superior temporal gyrus (22)	-37.23	-32.34	13.74	2.64	360
Right	Superior temporal gyrus (21, 22, 41)	54.12	-23.21	5.98	5.79	6632
Occipital						
Left	Lingual gyrus (17)	-12.44	-91.18	3	3.14	1336
	Middle occipital gyrus (19)	-25.26	-86.57	-2.34	2.28	368
Sub-lobar						
Left	Putamen	-23.91	-4.7	3.8	2.12	432
Right	Thalamus	-6.77	-19.36	5.5	4.24	6048
	Caudate	28.08	15.31	4.19	2.78	1416
Cerebellum						
Right	Posterior lobe uvula	-6.16	-58.42	-17.9	5.87	30712
	Posterior lobe declive	22.23	-79.73	-16.41	2.56	656

Major clusters of Talairach coordinate data results from the activation likelihood estimation ALE meta-analysis. XYZ – coordinates of the center of each major cluster. ALE ($x10^2$) - size of the activation. Size (mm^3) - volume of the cluster.

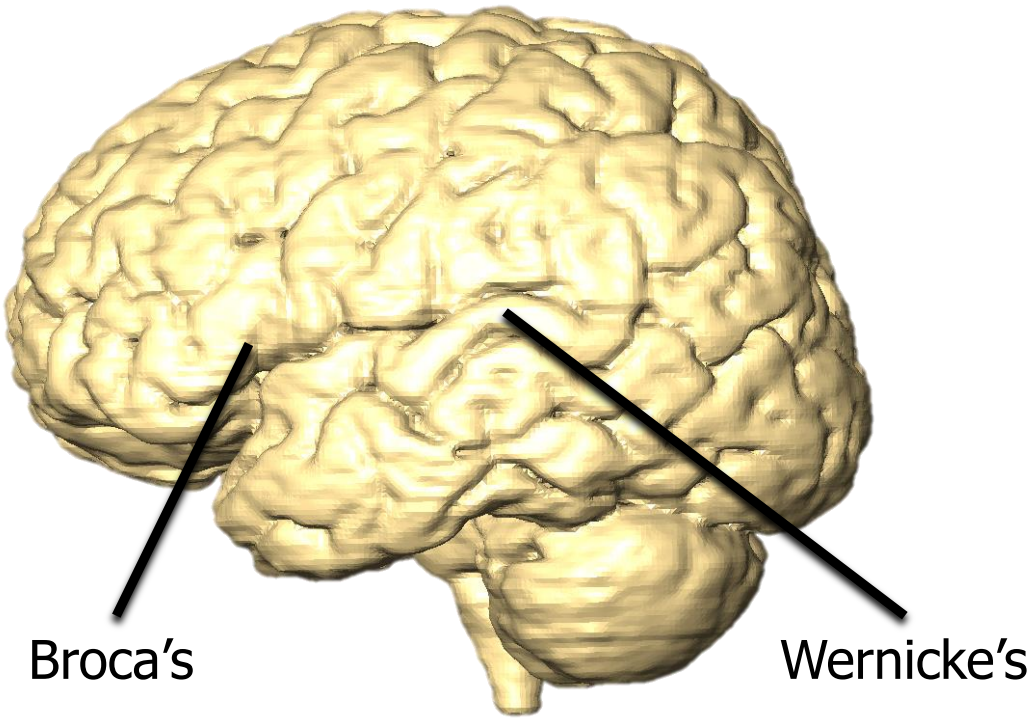

Figure 2.1 – Left lateral view of a human brain render pointing out locations of Broca's area and Wernicke's area.

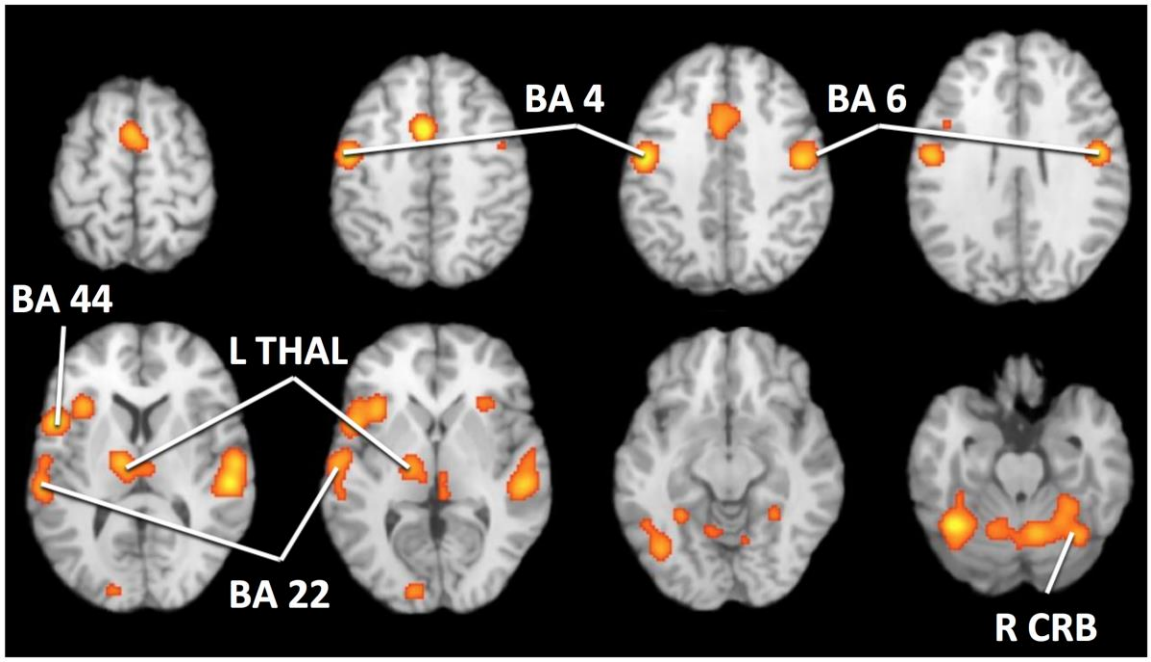

Figure 2.2 – Major ALE foci clusters visualized on a standard MRI series. Abbreviations: BA44, Brodmann's Area 44 (Broca's area); BA22, Brodmann's Area 22 (Wernicke's area); L THAL, left thalamus; BA4, Brodmann's Area 4 (primary motor cortex); BA 6, Brodmann's Area 6 (supplementary and premotor cortex); R CRB, right cerebellum.

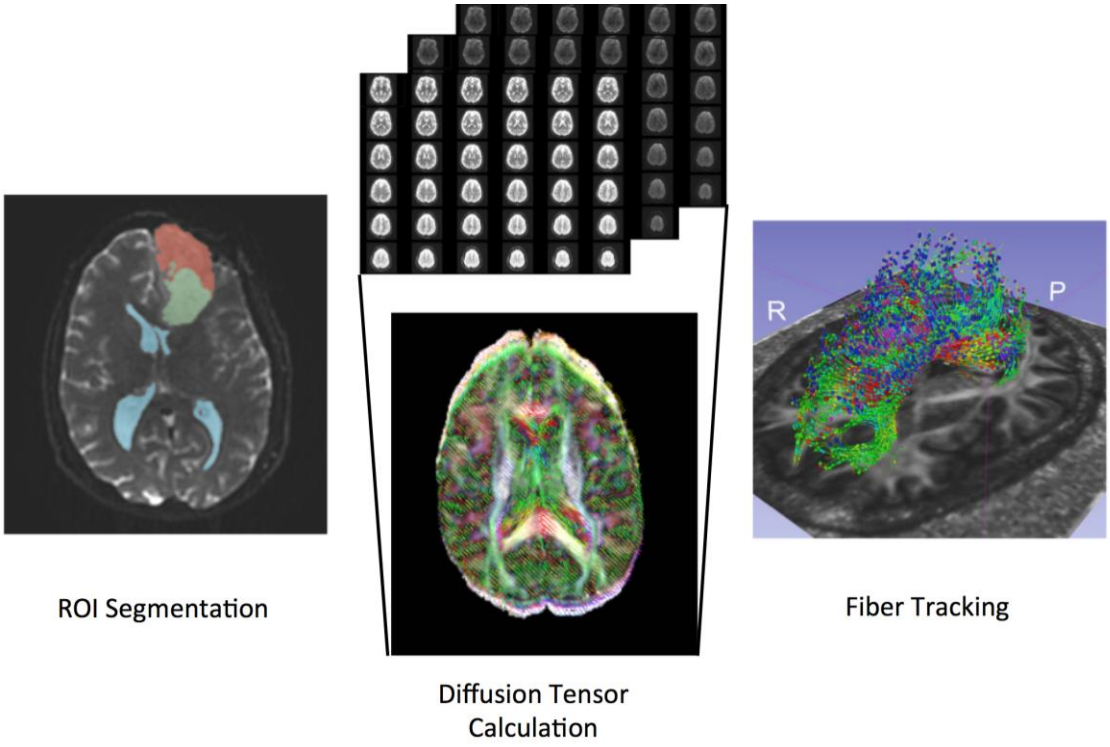

Figure 2.3 – Workflow of diffusion tensor imaging (DTI) tractography. Step 1, region of interest segmentation. Step 2, diffusion tensor calculation from DTI volumes. Step 3, fiber tracking on tensor map.

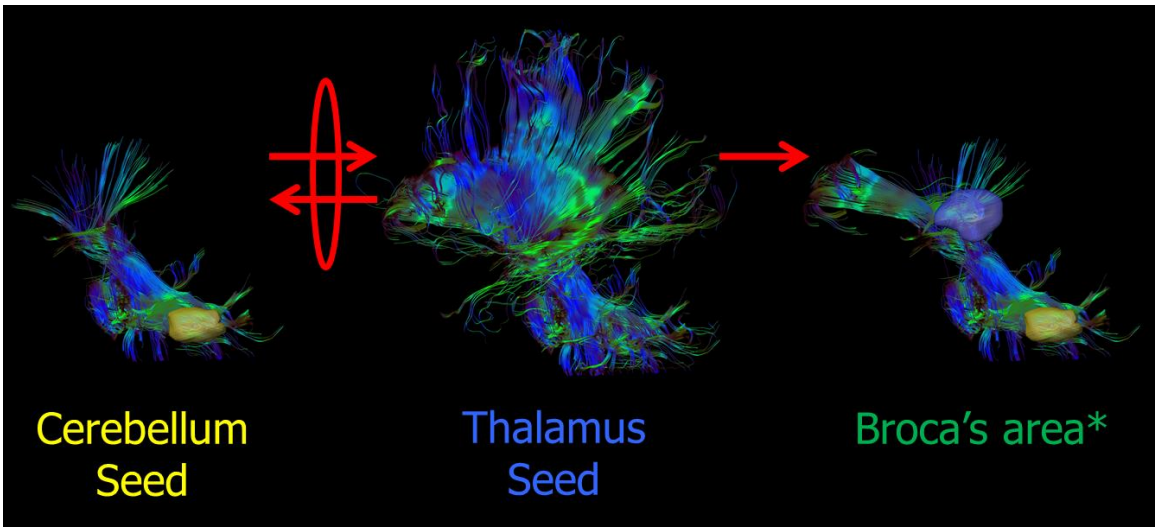

Figure 2.4 – Group average fiber tracking from the cerebellum seed (yellow) and the thalamus seed (blue). Final fiber tracts that project to Broca's area after restriction to only maintain cerebellum and thalamus seed location tracts.

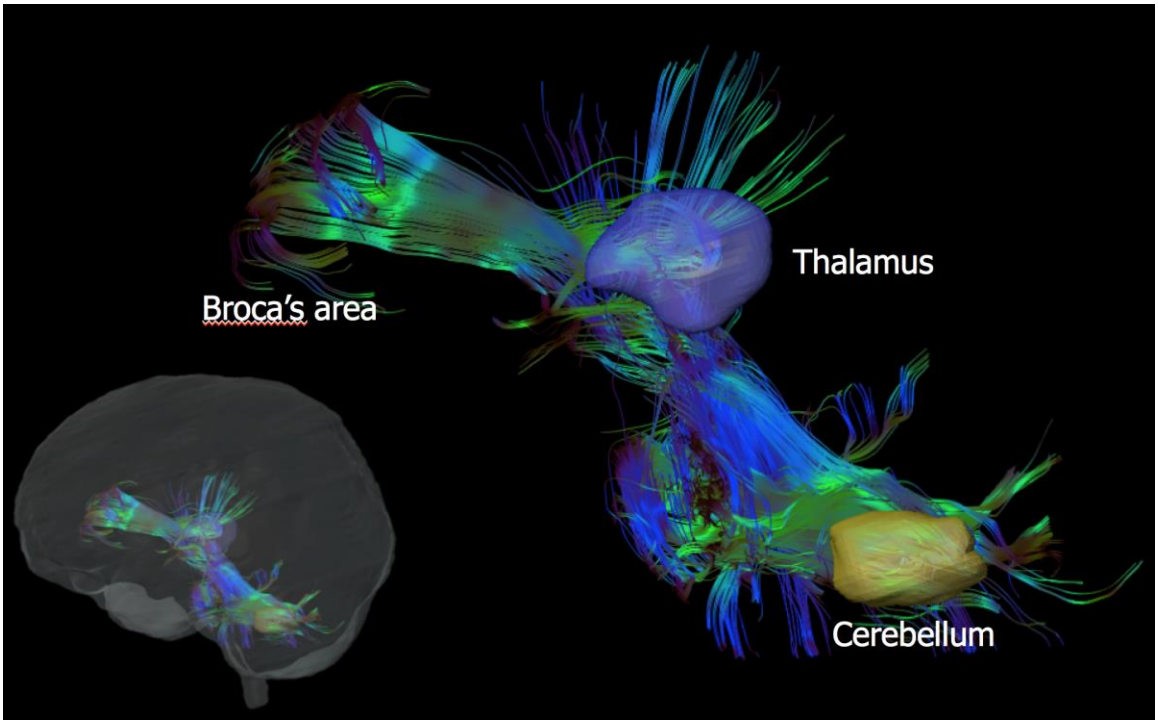

Figure 2.5 – The language-specific cerebrocerebellar network shown from DTI fiber tracking and with an endocast overlaid (inset). Fiber tracking between seed locations in right cerebellum (yellow) and left thalamus (blue). Directionally encoded coloring (DEC) where green indicates anterior-posterior fiber direction, blue superior-inferior, and red medial-lateral.

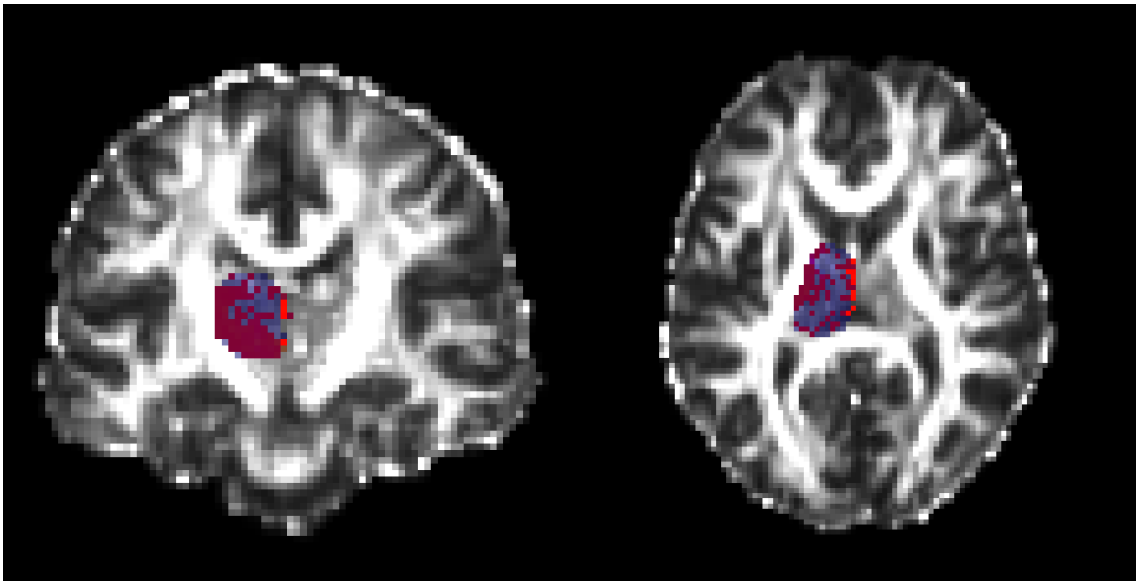

Figure 2.6 – Detail of fiber tracking through the thalamus on coronal slice (left) and axial slice (right). Fiber tracking is shown through the ventral and lateral portions of the thalamus.

Chapter 3: Language Ability and Connectivity in the LSCN

Introduction

The study of neuroanatomy and the function of the brain has long been a debate between those who ascribe aspects of human cognition to discrete areas of specialized function versus those who view the functions of the brain to be distributed across the entire organ (John, 1978; Young, 1990; Finger 2001). Neurons are interconnected by bundles of their myelinated axons, making up the white matter of the brain. The study of language in the human brain has shifted from focusing on specific, isolated cortical gray matter regions like Broca's and Wernicke's areas (Broca, 1861; Wernicke, 1874) to language networks linked by subcortical white matter pathways (Pulvermuller, 2002; Demonet, 2005; Markris, 2005). Clinical studies have shown that lesions affecting the arcuate fasciculus, the white matter pathway linking Broca's and Wernicke's areas (reviewed in Catani 2008), are associated with impairments of speech production in similar ways to a Broca's lesion (Marchina, 2011). Therefore the structural integrity of the arcuate fasciculus and other white matter tracts are as crucial for language function as the cortical areas they connect (Breier, 2008; Hosomi, 2009; Schlaug, 2009). Functional localization of language in the human brain could be greatly affected by the structural properties and microstructural arrangement within the white matter tracts (Benson, 1973; Ellmore, 2010). To determine the relationship between the structure and function of the parts of the brain that support language, the entire network of specialized areas (Pinker, 1994; Aboitiz, 2002, 2006) must be considered. A thorough understanding of the

relationship between the structure of the brain and its function can only be achieved through analyzing the brain from a network perspective.

Diffusion tensor imaging (DTI) is a relatively new technique and is ideally suited to investigate connections among functionally active regions that are known to support the language specific functional network in the human brain (Glasser, 2008; Rilling, 2008a, 2011; Li, 2010; Ramayya, 2010; Hecht, 2012). Through comparisons of the differential routes that neural signals travel to share information between functionally connected regions, subtle variation in neural networks among individuals may be uncovered that correlate with variation in performance (Rubinov, 2010; Zielinski, 2010).

In the current study I test the hypothesis that language ability can be predicted from measures of connectivity in the language-specific cerebrocerebellar network (LSCN) in a normal population (George et al., in prep). I obtained measures of LSCN connectivity from DTI and quantitative measures of language ability in a sample of healthy young adults. If there is a significant relationship between LSCN connectivity and measures of language behavior, then we can then form testable hypotheses about the influences of development and evolution on this network, and the potential impact on language as a result.

Materials and Methods

Subjects

I recruited and screened 66 right-handed males (age range 18-25 years). The study is limited to right-handed males in order to avoid potential differences related to sex and handedness. All included participants were monolingual English speakers and right-

handed. Exclusion criteria included: history of major medical or neurological conditions, being bilingual, being left handed or ambidextrous. Subjects were recruited from the Psychology 1000 subject pool at the University of Missouri. Subjects were first consented and given a language evaluation prior to having an MRI scan. All subjects' MRI images were screened for gross brain abnormalities a radiology technologists specializing in MRI before analysis. Of the original 66 subjects who were recruited, 10 subjects failed the screen due to having a permanent retainer, one for being left handed, and one for not being a monolingual English speaker. Five subjects had gross brain abnormalities that were ruled not clinically significant by a radiologist. , Data from 49 subjects were ultimately included in our study. All recruitment, data collection, and analysis were conducted under protocols approved by the University of Missouri Health Sciences Institutional Review Board (HSIRB) and in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

Language Evaluation

Language production and comprehension varies across neurotypical (i.e., "normal") humans. This natural variation in the population can be evaluated through the Clinical Evaluation of Language Fundamentals (CELF-5), a norm-referenced test for the evaluation of language and communication in individuals 5–21 years old (Semel, 2013). The CELF-5 was used to evaluate multiple facets of language function in our subjects. From the CELF-5 I computed the Core Language Score (CLS) and four additional language index scores (Table 3.2). The CLS is a measure of overall language ability. The Receptive Language Index (RLI) is a measure of listening and auditory comprehension. The Expressive Language Index (ELI) is a measure of language production. The

Language Content Index (LCI) is a measure of the ability to understand and use appropriate word meaning. The Language Memory Index (LMI) measures application of working memory to linguistic content and structure. Each CELF-5 index has a mean of 100 and a standard deviation of 15 in a standardized sample of 2380 students (Semel, 2013).

MRI Data Acquisition

All MRI data were collected at the Brain Imaging Center at the University of Missouri (www.bic.missouri.edu) using a 3T SIEMENS Magnetom Trio scanner. High-resolution T1-weighted structural images were acquired using a 3D MP-RAGE pulse sequence. DTI data were acquired for 64 directions and one nondiffusion-weighted (b0) image. All imaging parameters are presented in Table 3.1.

Raw structural and diffusion data were transferred to a secure server and stored as DICOM files for pre-processing. All images were visually inspected for artifacts or gross anomalies then converted from DICOM to NIFTI files using the "dcm2nii" module of the software MRIcron (Rorden, 2000).

Quantitative measurement of tracts

FDT (FMIRB's Diffusion Toolbox; Behrens, 2003a, 2003b; Johansen-Berg, 2004; Behrens, 2007; Sotiropoulos, 2011; Jbabdi, 2012), part of the FMRIB Software Library (FSL version 5.0.7 www.fmrib.ox.ac.uk/fsl; Smith, 2004; Woolrich, 2009; Jenkinson, 2012), was used to quantify connectivity between ROIs along each inferred white matter tract. Each diffusion-weighted volume was corrected for motion and eddy currents using FMRIB's Linear Image Registration Tool (FLIRT, Jenkinson, 2002). On volume without any diffusion weighting (b0 volume) had all non-brain voxels removed

using FSL's Brain Extraction Tool (BET, Smith, 2002) and a binary brain mask was created to mask each diffusion-weighted volume for image registration. Each diffusion-weighted volume was co-registered with the T1 structural volume using FLIRT with six degrees of freedom and a correlation-ratio-based cost function. The diffusion-weighted and structural volumes were then registered with the MNI152 average template using FLIRT with 12 degrees of freedom and a correlation-ratio-based cost function and the affine transformations were obtained.

Within FDT, DTIFIT was used to fit a diffusion tensor model to each voxel, creating whole-brain maps representing several measures of the white matter tracts, including mean diffusivity (MD) and fractional anisotropy (FA). Specifically, MD is a mean of the three different directional vectors that a water molecule can diffuse within a voxel, while FA is a measure of the degree of anisotropy, or the variance, of a diffusion process. Each of these measures ranges from zero (meaning that diffusion is isotropic, equal in all directions), to one (meaning that diffusion is only proceeding in one direction). The mean, range, and variability of each of these measures were used to infer axon fiber density, axonal diameter, and degree of myelination of the white matter tracts that connect the ROIs of the LSCN.

In FDT, BEDPOSTX (Behrens, 2004, 2007) was next run to fit the probabilistic diffusion model on to each of the diffusion-weighted volumes. The output of BEDPOSTX was used to perform probabilistic tractography with the PROBTRACKX (Behrens, 2004, 2007) tool in FDT. The left thalamus, Broca's area (Brodmann's areas 44 & 45), and right cerebellum regions of interest from the ALE meta-analysis were used as a seed mask and waypoint masks in the tractography analysis (Figure 6). The

following analysis parameters were used for iteration of the tracts: number of pathways = 5000, curvature threshold = 0.2, maximum steps = 2000, waypoints considered one pathway in both directions with the AND condition, only accepted if the pathway intersects both waypoints. The tracts for each subject from PROBTRACKX were then used as a mask on the standard space (MNI152) MD and FA maps and using the fslmeants utility to measure FA and MD in each of these tracts.

Data analysis

The Pearson product-moment correlation (r) was used to determine a relationship between the FA and MD in the LSCN and the Core Language Score (CLS) and four individual indices (Receptive Language Index, Expressive Language Index, Language Content Index, and Language Memory Index), and the significance of the relationship. The FA and MD for the anterior portion of the LSCN, between the thalamus and Broca's area (LSCN-A), and the posterior portion, between the thalamus and the right cerebellum (LSCN-P), were also collected and correlated with the language evaluation indices. Correction for multiple comparisons was done using the Bonferroni method (Rohlf, 2011). Definitions of strength of correlation of r follow Cohen (1988), with 0.1 as weak effect size, 0.3 as moderate effect size, and 0.5 as strong effect size.

Results

Language evaluation

Analysis of the language evaluation measures in the CELF-5 indicate that the mean values for the Core Language Score (CLS) and the four indices were above the CELF's standardized average in our sample, though within one standard deviation (Table

3.2, Figure 3.3). The mean CLS was 110.0 (+/- 8.2), the mean Receptive Language Index (RLI) was 108.2 (+/- 7.9), the mean Expressive Language Index (ELI) was 106.9 (+/- 7.2), the mean Language Content Index (LCI) was 104.5 (+/- 6.9), and the mean Language Memory Index (LMI) was 108.2 (+/- 8.2). Together, these results show that measures of language ability in our sample of normal young adult males have a marked range of variation.

Measures of LSCN connectivity

The probabilistic tracking performed in FDT resulted in tracts that followed the LSCN as it tracked from the right cerebellum, through the left thalamus, and into Broca's area (Figure 3.2). The mean value of fractional anisotropy (FA) of the LSCN as a whole was 0.3440. In LSCN-A mean FA was mean 0.3588, while mean FA in LSCN-P was 0.3294. The mean value of mean diffusivity (MD) of the LSCN as a whole was 0.0008290. In LSCN-A, mean MD was 0.0007916 as compared to a mean of 0.0008445 in LSCN-P. See Table 3.2 for full results.

Correlation of LSCN connectivity and language ability

Correlations of fractional anisotropy (FA) in the LSCN as a whole with index scores from the CELF-5 were statistically significant (Table 3.4). Strong correlations with FA in the entire LSCN were found with the CLS ($r = 0.52$; $p<0.001$) and with the LMI ($r = 0.49$; $p<0.001$). A moderate correlation with FA in the LSCN was found with the ELI ($r = 0.35$; $p<0.05$). A weak correlation with FA in the LSCN was found with the RLI, which was not statistically significant ($r = 0.28$; $p=0.052$). No significant correlation was found between LSCN FA and the LCI. No significant correlations of any of the

language measures with mean diffusivity (MD) of the whole LSCN were found (Table 3.4).

In LSCN-A, significant moderate correlations with FA were found with the CLS ($r = 0.42$; $p<0.01$) and with the LMI ($r = 0.49$; $p<0.01$). No significant correlations were found in the LSCN-A with the RLI, the ELI, or the LCI ($p > 0.05$). In the LSCN-A, a significant moderate negative correlation was found with MD and CLS ($r = -0.41$; $p<01$). No other language evaluation indices had significant correlations with MD in the LSCN-A.

In the LSCN-P, significant moderate correlations with FA were found with the CLS ($r = 0.38$; $p<0.01$) and with the LMI ($r = 0.32$; $p<0.05$). No significant correlations were found in the LSCN-P and the RLI, the ELI, or the LCI ($p > 0.05$). No significant correlations of MD in the LSCN-P were found with any of the language measures (Table 3.4).

Discussion

Our previous research has demonstrated shared anatomical connectivity of regions of the brain that are functionally active during language production, forming a network that I refer to as language-specific cerebrocerebellar network (LSCN), specifically in Brodmann's area 44 in the left frontal lobe, the left thalamus, and the right cerebellum (George et al., in prep). Thus, I hypothesized that measures of the LSCN would be correlated with quantitative measures of language production. The results of the present study show that the connectivity of the LSCN, as measured by fractional anisotropy (FA), has strong positive correlations with language ability as evaluated with

the CELF-5. These findings support the hypothesis that the LSCN plays a significant role in language production.

Our study sample is representative of a normal, healthy, young adult population, with the exception of our study being limited to right-handed males who are college students. The mean language evaluation scores were above the standardized average, but did not exceed one standard deviation. This upward skewing of scores is likely the result of recruiting from a college population. Also, despite the above average mean scores, individual scores ranged substantially around the mean, showing a broad range of language ability exists within a normal, healthy population in the absence of pathology or disorder.

The strong correlation of overall measure of language performance, as measured by the CLS, with LSCN connectivity (FA, specifically) supports the hypothesis that the cerebellum plays a significant role in language processing. Correlations CLS in the individual anterior and posterior portions of the LSCN are lower than the whole network suggesting that both are important for language behavior. The anatomical connectivity that I mapped in the anterior portion of LSCN (LSCN-A), specifically the thalamocortical portion to Broca's area, is also strongly correlated with overall language. This portion of the pathway has been studied previously in connection with language function and lesion studies of the basal ganglia (Crosson, 1999; Copland, 2000; Robles, 2005; Assaf, 2006). The basal ganglia and the thalamus are involved in lexical selection, syntactic processing, and higher-level language processing (Ullman, 2001, 2004; Friederici, 2009). White matter tracts between Broca's area and the thalamus that are involved in language processing are hypothesized to represent the cortico-thalamic-cortical connectivity

(Fisher, 1959; Schaltenbrand, 1965, 1975; Crosson et al., 2003) much like the structural organization the prefrontal cortex has with the basal ganglia (Alexander, 1986; Middleton, 2000a, 2000b). Recent research has shown that the basal ganglia are not involved in primary language functions, but these structures help with language processing (Mink, 1996; Nambu, 2000). It has been hypothesized that the basal ganglia along with the thalamus enhance language generation by helping to select the proper language to express a concept (Crosson, 2007, 2012). Following hypotheses that the cerebellum modulates and smoothens cognitive processes through a Universal Cerebellar Transform (UCT) (Schmahmann, 1991, 2004) the results of this research demonstrate connectivity of right cerebellum to Broca's area through the LSCN. It is this network that helps modulate language processing in the frontal lobe through connectivity with the cerebellum.

FA in the posterior portion the LSCN, spanning the right cerebellum to the left thalamus (LSCN-P), also showed a strong correlation with overall language. This evidence, along with the hypothesized role of the cerebellum in the modulation of cognition (Schmahmann, 1991, 2004; Ackermann 2007; Stoodley, 2010), suggests that the portion of language function that I are measuring through the connectivity in the LSCN is not primary control of language but the modulation of language processing.

Among the indices of distinct subdomains of language from the CELF-5, I find a strong significant correlation between LSCN FA and the LMI, and a moderate significant correlation with the ELI. The LMI is a measure of linguistic content and structure in language, and Broca's area and the basal ganglia are together hypothesized to be involved in the combination of relevant phonemes into meaningful structures, such as words

(Ullman, 2001; Booth, 2007). Appropriate articulation and structuring of language content is essential in language production. The significant positive correlation of FA in the whole LSCN with LMI and moderate correlation of FA in the anterior and posterior portions of the LSCN with LMI in the present study further supports the hypothesis that the cerebellum, connected through posterior leg of the LSCN is involved in the modulation of language processing, not solely the anterior portion of the LSCN from the thalamus to Broca's area, leading to proper language production. The stronger correlation with LMI in the whole network compared to the anterior and posterior legs indicates that the whole network, including the cerebellum is important in language memory modulation.

The ELI evaluates an individual's language production so a significant moderate correlation of FA in the LSCN with the ELI supports our hypothesis that the LSCN in involved this behavior. There are addition cerebral regions involved in expressive language (Cabeza, 2000, Hickok, 2004, Catani, 2007; Glasser 2008, Friederici, 2009) and other white matter tracts such as the superior longitudinal fasciculus and the arcuate fasciculus. Measuring the FA in these tracts will most likely also have significant correlations with behaviors associated with cortical regions they connect.

I found no significant correlations of any measures of the LSCN with the RLI and the LCI. The RLI is an evaluation of an individual's listening and auditory comprehension skills and the LCI is a measure of the ability to understand appropriate word meaning. These indices are measuring the receptive parts of language and the meanings of auditory information. The lack of significant correlations between the LSCN and these indices further supports the hypothesis that the LSCN is associated with

language production and modulation, rather than reception and comprehension. A future study looking at additional white matter tracts, such as ones that connect to Wernicke's area, is necessary to determine whether measures of connectivity in this region would have correlations with these indices of receptive language.

The only significant correlation of MD with the LSCN was a negative correlation with the LSCN-A, spanning the white matter tract between the thalamus and Broca's area. This is to be expected as MD measures the magnitude of diffusion in a tissue and is used to infer cell membrane integrity. In healthy white matter the myelinated axons are packed tightly and generally constrain diffusion in one principal direction. The white matter tract in the LSCN-A, from the thalamus to Broca's area, has a dominant single direction fiber orientation, so MD should be consistently lower at that location and the negative correlation shows that MD will be lowest where there are tightly packed cell membranes, like in myelinated white matter tracts, allowing very little diffusion. In the LSCN-P, there are many more crossing fibers and research has shown that MD is more much more variable in white matter with more complex fiber orientations (Vos, 2012).

In conclusion, the present study demonstrates the cognitive significance of connectivity measures of the language-specific cerebrocerebellar network in the human brain. This network that includes the right cerebellum, Brodmann's area 44, the left thalamus, and the white matter tracts linking them, shows significant correlations with measures of overall language ability and measures of language content and structure. From these results, I propose that the cerebellum is associated with modulation of language processing in the cortex through its connectivity via the thalamus. The results of our research are the first to show that measures of anatomical connectivity in the LSCN

are significantly correlated with language performance in a normal, healthy adult population. Future research is necessary to map other components of language networks in the brain beyond those described here. Other regions that are functionally active during language may have additional anatomical connections to the LSCN. Mapping this connectivity and determining whether there are structure/functions relationships in those other white matter tracts, and the nature of those relationships, may account for the aspects of language that did not show significant correlations in this study.

Table 3.1. MRI Scan parameters		
Sequence	T1 MRI MPRAGE	DTI EPI
Orientation	Sagittal	Axial
TR (ms)	> 1900	> 5000
TE (ms)	2-4	> 100
TI (ms)	1000	N/A
Matrix size	256 x 256	128 x 128
# of slices	176	36
Slice thickness (mm)	1.0	3.0
Voxel size (mm)	1 x 1 x 1	3 x 3 x 3
Directions	N/A	64
Time (minutes)	~5.00	~10.00

Scan parameters for the imaging data. Abbreviations: MPRAGE – magnetization prepared-rapid gradient echo; DTI EPI- diffusion tensor imaging; echo-planar imaging; TR – repetition time; TE – echo delay time; TI- inversion time; Matrix size- resolution in pixels; Voxel- cubed pixel.

Table 3.2. CELF-5 Scores			
CELF subtest	**Range**	**Mean**	**SD**
CLS	95-126	109.98	8.25
RLI	92-125	108.23	7.92
ELI	89-122	106.92	7.22
LCI	95-123	104.50	6.91
LMI	91-124	108.21	8.19

Individual subtests and CELF-5 Indices. Abbreviations: CLS – Core Language Score; RLI – Receptive Language Index; ELI – Expressive Language Index; LCI – Language Content Index; LMI – Language Memory Index.

Table 3.3. Quantitative measures of LSCN connectivity			
	Range	**Mean**	**Standard Deviation**
Age (years)	18-25	19	1.444
FA			
LSCN	0.2805-0.4375	0.3440	0.0249
LSCN-A	0.2646-0.4625	0.3588	0.0310
LSCN-P	0.2798-0.4188	0.3294	0.0273
MD			
LSCN	7.462×10^{-4} - 9.109×10^{-4}	8.290×10^{-4}	2.888×10^{-5}
LSCN-A	7.192×10^{-4} - 8.445×10^{-4}	7.916 x 10-4	3.225×10^{-5}
LSCN-P	7.494×10^{-4} - 9.329×10^{-4}	8.445 x 10-4	4.091×10^{-5}

Measures of age of our sample and DTI measures; fractional anisotropy (FA), and mean diffusivity (MD) in the LSCN, the LSCN-A, and the LSCN-P.

Table 3.4. Correlation of LSCN connectivity and language ability					
	CLS	**RLI**	**ELI**	**LCI**	**LMI**
FA					
LSCN	0.5148**	0.2820	0.3467*	0.0639	0.4881**
LSCN-A	0.4179**	0.1934	0.2579	0.0703	0.3708**
LSCN-P	0.3840**	0.2142	0.2390	-0.0359	0.3479*
MD					
LSCN	-0.1739	-0.0338	-0.0683	0.0976	-0.0950
LSCN-A	-0.4094**	-0.2106	-0.2370	-0.0487	-0.2755
LSCN-P	0.0320	0.1137	0.0128	0.1398	-0.0480

Pearson's product-moment correlation of LSCN measures with CELF-5 language indices. CLS – Core Language Score; RLI – Receptive Language Index; ELI – Expressive Language Index; LCI – Language Content Index; and LMI - Language Memory Index. **p<0.01, *p<0.05

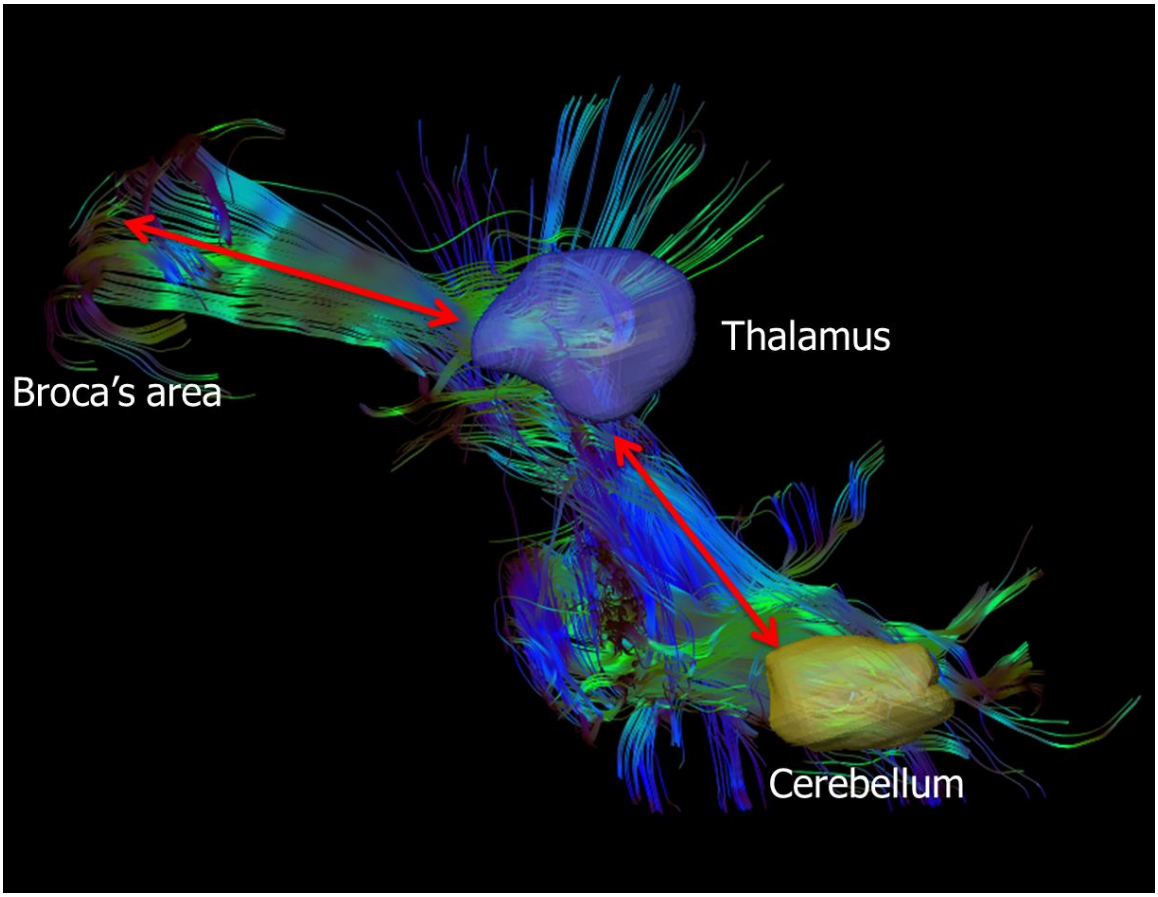

Figure 3.1 – The language-specific cerebrocerebellar network (LSCN). Red arrows denote each portion. The anterior portion between the thalamus and Broca's area and the posterior portion between the cerebellum and thalamus.

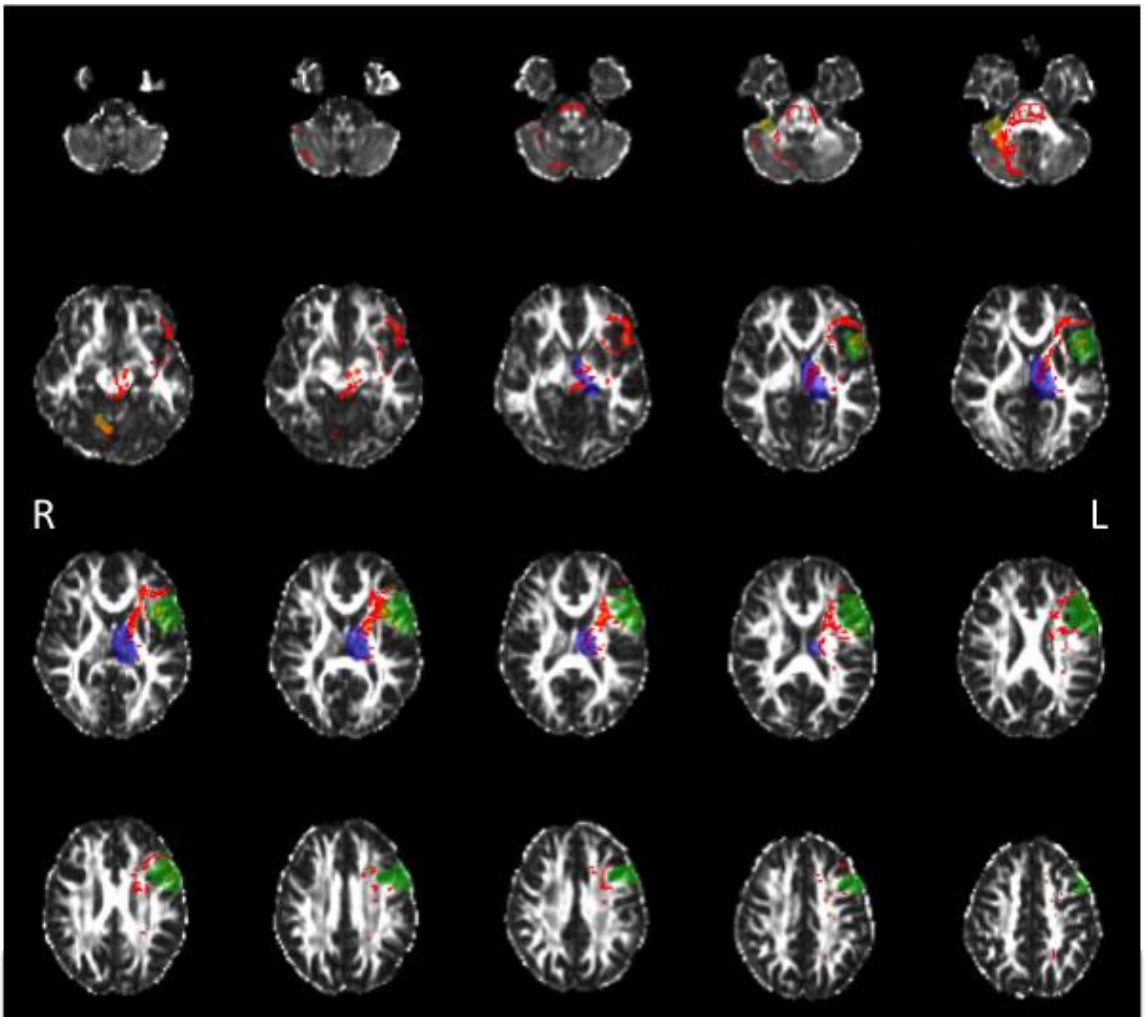

Figure 3.2 – Fiber tracking from PROBTRACKX on axial slices. Fiber tracts shown in red, cerebellum seed shown in yellow, left thalamus shown in blue, and Broca's area shown in green.

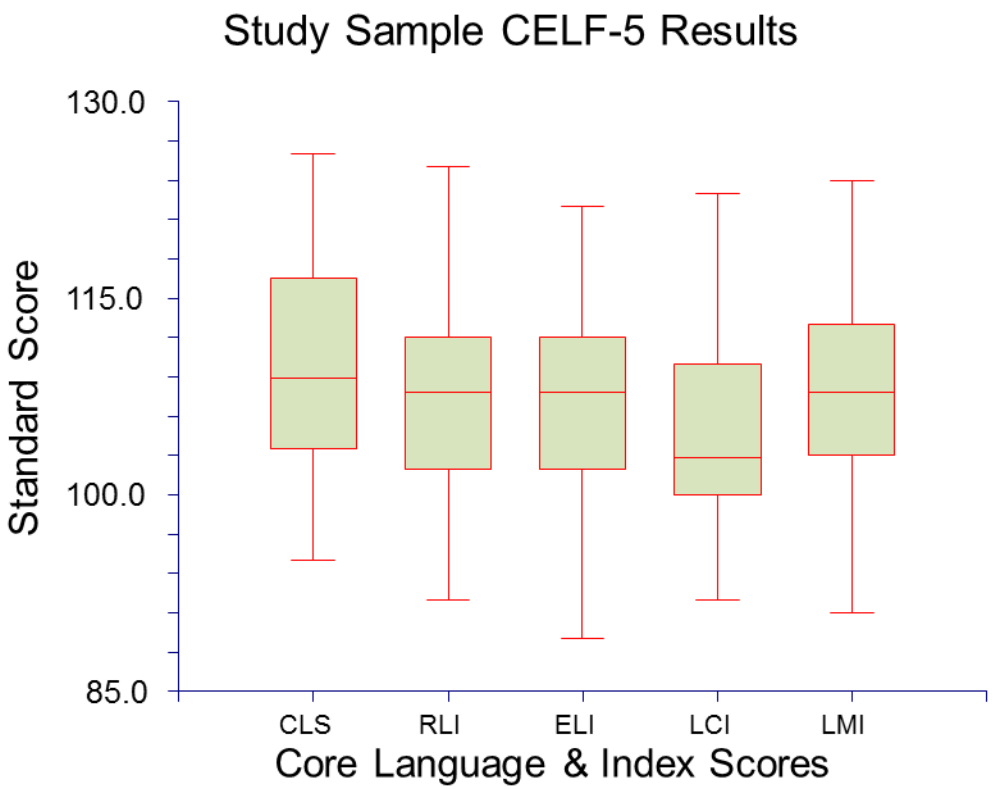

Figure 3.3 – CELF-5 results from the study sample. Abbreviations: CLS – Core Language Score; RLI – Receptive Language Index; ELI – Expressive Language Index; LCI – Language Content Index; and LMI - Language Memory Index.

Chapter 4: Cortical Surface and Connectivity in the LSCN

Introduction

Language is considered to be the foundation of human culture, making possible the development of other uniquely human traits, such as complex technologies, agriculture, and symbolism (Gibson, 1991; Aiello 1993). It is therefore crucial to reconstruct the development of language in order to understand how the human brain has evolved. There are numerous competing hypotheses for the selective pressures responsible for advanced cognitive capabilities in the human brain. Almost all of these theories focus on size as a varying factor, in relation to the whole brain or its constituent parts (Holloway, 1968, 1982; Falk, 1987; Deacon, 1990), largely because this is one of the few traits we can reliably measure in fossil specimens.

Endocasts, impressions of the internal skull surface (Figure 4.1), are our only direct evidence of the brains of human ancestors. From studies of hominin fossil endocasts, total volume and some gross surface features of the brain can be reliably measured (see Holloway 2004 for review). Across the hominin fossil record, the size of the brain has increased in both relative and absolute terms to outpace all other primates (Falk, 1980; Stephan, 1981; Holloway, 1982; Passingham, 1982; Rilling, 1999; Striedter, 2005), and has undergone significant reorganization since our last common ancestor with other great apes (Tobias, 1975; Holloway, 1976; Falk, 1987; MacLeod, 2003; Striedter, 2005; Weaver, 2005). There is a shared global pattern of directional asymmetries among hominid taxa, both extant and extinct (LeMay, 1978; Amunts, 2000; Hopkins, 2000;

Balzeau, 2011). Leftward lateralization is unique to the human brain, and arose in hominins as early as *Homo erectus* (Holloway, 2008). Additionally, Broca's cap, a projection of an endocast overlying the presumed Broca's area, has been used to associate a leftward lateralization of the brain with language abilities (Broadfield, 2001; Sherwood, 2003; Schoenemann, 2012). However, it is important to note that the brain's cytoarchitechtural boundaries, specifically in Broca's area (Amunts, 1999), often do not coincide with sulcal boundaries (Amunts, 2007) making functional localization problematic even in extant specimens. Thus, there remains considerable debate regarding the functional consequences of this leftward expansion of the brain, especially concerning language specialization (Gannon, 1998; Hopkins, 2000; Cantalupo, 2001; Rilling, 2008a).

Recent studies have shown that regions of the brain that are anatomically connected, show correlated expansion during mammalian brain evolution (Barton, 2000, 2002; Whiting, 2003). Although it will never be known at what point, and in what order, specific structural networks expanded or were reorganized during human evolution, we can hypothesize the timing of functional changes (i.e., behavior) related to these networks based on cultural material associated with hominin fossils (Schick, 1999). Artifacts in the fossil record, such as stone tools and expressive art, are used as indicators of cognitive expansion in the brains of human ancestors, and it is hypothesized that language would have facilitated more efficient manufacturing and refinement of these objects (Wynn, 2002). It is during this time when complex tools and expressive art are found that that Weaver (2005) identifies a significant expansion of the cerebellum relative to the cerebrum in endocasts of late Pleistocene *Homo*. This cerebellar expansion has been

hypothesized to support behavioral advances in later hominins, including language production (De Smet, 2007; Thach, 2007; Rilling, 2008b).

The two regions of the left cerebral cortex that are attributed to language production and comprehension, respectively, are Broca's and Wernicke's areas (Broca, 1861; Wernicke, 1874), with the arcuate fasciculus being the white matter tract connecting them. The arcuate fasciculus is smaller and organized differently in macaques and chimpanzees relative to humans (Rilling, 2008), suggesting that the human cerebral language network was not a novel structure, but was an elaboration of a rudimentary communication network present in the last common ancestor between humans, macaques, and chimpanzees. The arcuate fasciculus is an example of a long-range subcortical white matter tracts, which are known to increase neural processing efficiency (Fair, 2007; Rivkin, 2013), they may have been elaborated and expanded during evolution and are possible targets of selection.

The amplification in size and change in organization of the arcuate fasciculus and its extension into different cortical areas during evolution is indicates that human language is not a byproduct of having a large brain but rather elaboration of a functional network (Rilling, 2008a). However, neural tissue does not fossilize and only some detail of the brain's cortical surface may be reconstructed from an endocast. Further, subtle features of the surface of the brain, such as fine details of sulci and gyri (wrinkles), however, are obscured by dural structures (Symington, 1916; Holloway, 1964, 1967, 1968), and not all areas of the brain are equally reproduced (Connolly, 1950). This information is important because discrete regions of increased surface complexity, defined by increased gyrification (folding) of the surface of the brain, have been used as

indicators of increased underlying connectivity and complexity (Van Essen, 1997), despite the regional differences availability of detail.

It is the purpose of this study to determine whether cortical morphology of the cerebral surface may be used to infer the connectivity of the underlying white matter tracts required for language production. I will test the hypothesis that the complexity of the cerebral surface is directly proportional to the degree of underlying white matter connectivity in language production. My previous work has mapped the language-specific cerebrocerebellar network (LSCN) in modern humans *in vivo*, showing anatomical connectivity between the cerebellum and Broca's area (see chapter 2). I have also measured the connectivity in the white matter tracts of this network and demonstrated that it is strongly correlated with overall language and verbal working memory (see chapter 3). In this study, I will correlate the connectivity in the LSCN to the morphology of the cortex in Broca's area. This is an important first step in determining whether it is possible to reconstruct the evolution of language capabilities based on analyses of endocasts of fossil hominins.

Materials and Methods

Subjects

The study included data from a total of 59 subjects. The study is limited to right-handed males in order to avoid potential differences related to sex and handedness. All included participants were healthy, monolingual English speakers and right-handed. Exclusion criteria included: history of major medical or neurological conditions, being bilingual, being left handed or ambidextrous. Ten of the participants were originally

recruited as a control group for an ongoing study at University of Missouri (Beversdorf, 2015). I recruited and screened an additional 66 right-handed males (age range 18-25 years) from the Psychology 1000 subject pool at the University of Missouri. Subjects were first consented and given a language evaluation prior to having an MRI scan. Of these 66 subjects, 54 subjects met inclusion criteria, were enrolled in our study, and completed a language evaluation and MRI scan. All subjects' MRI images were screened for gross brain abnormalities by the licensed radiology technologist at the Brain Imaging Center before analysis. Five subjects had gross brain abnormalities that were ruled not clinically significant by the radiologist, but were excluded from analysis. Thus, data from these 49 subjects and the 10 subjects recruited previously were included in our study. All recruitment, data collection, and analysis were conducted under protocols approved by the University of Missouri Health Sciences Institutional Review Board (HSIRB) and in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

MRI Data Acquisition

All MRI data were collected at the Brain Imaging Center at the University of Missouri (www.bic.missouri.edu) using a 3T SIEMENS Magnetom Trio scanner. High-resolution T1-weighted anatomical images were acquired using a 3D MP-RAGE pulse sequence. DTI data were acquired for 64 directions and one nondiffusion-weighted (b0) image. All imaging parameters are presented in Table 4.1. Raw structural and diffusion data were transferred to a secure server and stored as DICOM files for pre-processing. All images were visually inspected for artifacts or gross anomalies then converted from

DICOM to NIFTI files using the "dcm2nii" module of the software MRIcron (Rorden, 2000).

Volume Segmentation and Cortical Parcellation

To measure brain surface morphology I used the Freesurfer Image analysis suite for cortical reconstruction and volumetric segmentation. Freesurfer (http://surfer.nmr.mgh.harvard.edu/) performs the following processes to produce cortical surface models of each brain: 1) removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne, 2004), 2) automated Talairach transformation, 3) segmentation of the subcortical white matter and deep gray matter structures, including hippocampus, amygdala, caudate, putamen, ventricles (Fischl, 2002, 2004a), 4) intensity normalization (Sled et al., 1998), 5) tessellation of the gray matter-white matter boundary, 6) automated topology correction (Fischl, 2001; Segonne, 2007), and 6) surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders (Dale, 1993, 1999;Fischl, 2000). Once the cortical models are complete, the brains are registered to a spherical atlas using individual cortical folding patterns to match cortical geometry (Fischl, 1999b), parcellation of the cerebral cortex into units based on gyral and sulcal structure (Desikan, 2006; Fischl, 2004b), and measures of a variety of surface-based data including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness (Fischl, 2000). Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han, 2006; Reuter, 2012). The

technical details of these procedures have been described extensively previously (Dale, 1993, 1999; Fischl, 1999a, 1999b, 2000, 2001, 2002, 2004a, 2004b; Segonne, 2004; Han, 2006; Jovicich, 2006).

From Freesurfer, I obtained volume measures for whole brain and whole cerebellum,. I collected surface area and volume data on specific cortical regions that I hypothesized to be correlated with connectivity in the subcortical white matter of the LSCN: left Brodmann's area 44 (BA 44), the posterior portion of Broca's area,. I also collected cortical regions that I hypothesized to not correlate with connectivity in the subcortical white matter of the LSCN: left BA 45 (the anterior portion of Broca's area), right Brodmann's areas 44 & 45 , and right BAs 44 & 45 (Table 4.2).

Quantitative Measurement of Tracts

Quantification of diffusion properties in the LSCN was performed following the method described in Chapter 2. Briefly the workflow was as follows. Each diffusion-weighted volume was corrected for motion and eddy currents using FLIRT (Jenkinson, 2002). All non-brain voxels were removed using BET (Smith, 2002) and a binary brain mask was created. Each diffusion-weighted volume was co-registered with the T1 structural volume using FLIRT. The diffusion-weighted and structural volumes were then registered with the MNI152 average template using FLIRT. Within FMIRB's Diffusion Toolbox (FDT), DTIFIT was used to fit a diffusion tensor model onto motion and distortion corrected data. Also in FDT, BEDPOSTX (Behrens, 2004, 2007) was next run to fit the probabilistic diffusion model on to each of the diffusion-weighted volumes. The output of BEDPOSTX was used to perform probabilistic tractography with the

PROBTRACKX (Behrens, 2004, 2007) tool in FDT. The tracts for each subject from PROBTRACKX were then used as a mask on the standard space (MNI152).

Mean diffusivity (MD) and fractional anisotropy (FA) were collected from this tracking. MD is a mean of the three different directional vectors that a water molecule can diffuse within a voxel, while FA is a measure of the degree of anisotropy, or the variance, of a diffusion process. MD and FA maps were masked using the fslmeants utility to measure FA and MD in each of these tracts.

Data analysis

The Pearson product-moment correlation (r) was used to determine the correlation its statistical significance between FA and MD in the LSCN with the volumes and surface areas in each cortical region. The FA and MD for the anterior portion of the LSCN, between the thalamus and Broca's area (LSCN-A), and the posterior portion, between the thalamus and the right cerebellum (LSCN-P), were also collected and correlated with volume and surface area measures. Correction for multiple comparisons was done using the Bonferroni method (Rohlf, 2011). Definitions of strength of correlation (r) follow Cohen (1988), where ≥ 0.1 is a weak effect size, ≥ 0.3 a moderate effect size and ≥ 0.5 a strong effect size.

Results

I measured volumes of the whole brain and the whole cerebellum. I also measured volume and surface area of the gray matter of left and right BAs 44 and of left and right BAs 45, See Table 4.2 for results.

LSCN connectivity and brain measures

MD of the LSCN, a measure of amount of diffusion in tissue used to infer white matter integrity, is not significantly correlated with any of the measurements of cerebral cortex or cerebellum ($p > 0.05$). FA in the LSCN, indicating directional movement, is strongly correlated with whole brain volume ($r = 0.4875$, $p<0.001$). With respect to specific cortical areas, FA in the LSCN is strongly correlated with left BA 44 surface area ($r = 0.4745$, $p<0.001$) and gray matter volume ($r = 0.4715$, $p<0.001$) (See Table 4.3). I also found a moderate correlation of FA with whole cerebellum volume ($r = 0.3343$, $p = 0.0202$), and right BA 44 volume ($r = 0.2977$, $p = 0.0390$). The surface area and volume of left BA 45, the anterior portion of Broca's area, were not significantly correlated with connectivity in the LSCN, nor were the surface area and volume of right BA45 or surface area of right BA 44.

LSCN-A connectivity and brain measures

MD of the LSCN-A, the tract between Broca's area and the thalamus, is not significantly correlated with any of the measurements of cerebral cortex or cerebellum ($p > 0.05$). FA in the LSCN-A is moderately correlated with whole brain volume ($r = 0.4488$, $p = 0.0013$), left BA 44 surface area ($r = 0.3918$, $p = 0.0059$), and left BA 44 volume ($r+ 0.3646$, $p = 0.0108$). No other surface area or volume measures of left BA 45 or right BA 44 or 45 were significantly correlated with LSCN-A FA.

LSCN-P connectivity and brain measures

MD of the LSCN-P, the tract between the right cerebellum and the thalamus, is not significantly correlated with any of the measurements of cerebral cortex or cerebellum ($p > 0.05$). FA in the LSCN-P is moderately correlated with whole brain volume ($r = 0.3758$, $p = 0.0085$), whole cerebellum volume ($r = 0.2965$, $p = 0.0407$), left

BA 44 surface area ($r = 0.3516$; $p = 0.0143$), and left BA 44 volume ($r = 0.3832$, $p = 0.0072$). No other surface area or volume measures of left BA 45 or right BA 44 or 45 were significantly correlated with LSCN-P FA.

Discussion

I have demonstrated previously that measures of the anatomical network that I refer to as the language-specific cerebrocerebellar network (LSCN) are significantly positively correlated with language ability and language processing (see Chapter 3). The results of the present study demonstrate the same measures of LSCN connectivity are strongly correlated with surface area and volume of left Brodmann's area 44, the posterior portion of Broca's area, which has long been associated with language production. Together, these studies suggest that it is possible to predictions about functional subcortical white matter networks from measures of the related surface morphology.

The results of the present study are in line with the findings of previous studies on the correlations of behavior with cerebral cortex and subcortical white matter. Learning tasks that require the integration of visual information have shown an increase in gray matter in the visual cortex (Draganski, 2004; Driemeyer, 2008). The process of learning a complex motor task, juggling, has been shown to result in alterations to the underlying white matter (Scholz, 2009; Taubert, 2010). Purely cognitive tasks have also been associated with changes in brain morphology (Takeuchi, 2010). Cognitive tests that evaluate the speed of information processing correlate with FA in association tracts (Bartzokis, 2008; Muetzel, 2008; Konrad, 2009) and higher FA in the frontal lobe is

correlated with executive function (Kochunov, 2009, 2010; Konrad, 2009). Cognitive changes associated with normal ageing are also hypothesized to be the result of loss of integrity, lower FA, in the white matter (Bartzokis, 2004, 2008; Charlton, 2009, Kennedy, 2009, Kochunov, 2009, 2010, Schiavone, 2009).

With respect to language networks in the brain, previous research has shown that fractional anisotropy in the arcuate fasciculus connecting Broca's and Wernicke's areas is correlated with normal language function (Breier, 2008; Schlaug, 2009) and predictive of outcomes in patients with white matter lesions in the arcuate fasciculus (Bernal, 2009; Marchina, 2011). I previously have shown that LSCN FA is strongly correlated with language behavior (see Chapter 3), and the present study suggests that the morphology of the cortex of the LSCN also is correlated with FA of the network's white matter. This supports research showing leftward asymmetry of the surface area of the two sub-regions of Broca's area, Brodmann's area 44 (pars opercularis, Pop) and Brodmann's area 45 (pars triangularis, PTr) (Foundas, 1994, 1995, 1996). Our correlation of surface area and volume of the left BA 44 with FA in the LSCN provides evidence for the first time that the cortex of the brain can be used to predict subcortical white mater tracts and connectivity. The relationship between LSCN FA and the morphology of BA44, or POp, is a strong, statistically significant correlation although the LSCN is not the only white matter tracts terminating in this region. The arcuate fasciculus is another long-range white matter tract terminating here that may also account for the shape of the surface of the brain. Further research investigating relationships among white matter tracts related to language that may have anatomical connectivity with Broca's area are necessary to determine the whole story.

In contrast, the surface area and volume of the anterior portion of Broca's area, left BA 45, did not correlate with connectivity in the LSCN. This is in part due to the white matter tracts of the LSCN not directly connecting with BA 45. Although both BA 44 and BA 45 are involved in several aspects of language and verbal fluency, BA 44 has been reported to be involved with the processing of language production while BA 45 is involved with semantic aspects of language production (Amunts, 2004). Broca's area as a whole is also involved with both verbal and non-verbal communication (Jundas, 2007), with BA 45 hypothesized to be associated with inner-speech (Friedman, 1998; Tremblay, 2006) while BA 44 is associated with more high-level language processing, such as abstract grammar (Sahin, 2006) and syntactic and semantic fluency (Heim, 2008). The different roles of BA 44 and BA 45 in language production, as measured through fMRI studies, do not follow the same pattern between surface morphology and language behavioral. Although the surface area and volume of left BA 44 correlate with connectivity (FA) in the white matter tracts that were mapped in the LSCN, these surface measures do not correlate directly with behavior. This finding has important implications for drawing conclusions from brain surface data alone. The findings of this research suggest that isolated regions of cortical morphology should not be considered to have behavioral significance without taking into account the entire functional network associated with the behavior of interest and other cortical regions that overlay those functional regions.

The present study has focused on the relationship of cerebral morphology with the white matter pathway of the LSCN. It is important to remember that the other end of this pathway resides in the cerebellum. Weaver (2005) identified a significant expansion of

the cerebellum relative to the cerebrum in endocasts of late Pleistocene *Homo*, opposite to the earlier trend where the cerebrum vastly expanded paired with a relatively moderate cerebellar size. The expansion of the cerebellum during the late Pleistocene has been hypothesized to support behavioral advances in later hominins such as language production (De Smet, 2007; Thach, 2007; Rilling, 2008b). However, Semendeferi et al. (2000) reported that among extant great apes, humans have the smallest relative cerebellum. This disparity in interpretation of the relative size of the human cerebellum in a comparative context can be attributed to the variation in the scaling factor used in the different studies (e.g., body size, whole brain volume). Much like the cerebrum, recent research indicates that not all regions of the cerebellum have expanded uniformly during evolution. The more lateral, frontal projecting lobes have expanded at a greater rate than more medial portions of the cerebellum (Rilling 1999, Balsters 2010). These lateral parts of the cerebellum are the same areas that neuroimaging studies have shown to be functionally connected to regions in the cerebrum that are active during language production in humans. Thus, as the precise role of the cerebellum in language production has not been fully determined, consequently, the significance of relative cerebellar expansion in modern humans as compared to our fossil hominin ancestors (Weaver, 2005) also remains undetermined.

The findings of the present study are an essential first step in determining whether endocasts can be used to make inferences about the evolution of the brain and language abilities in human ancestors. Endocasts only preserve cortical surface features, and assumptions have long been made about the behavior of early humans based on these data alone (Carlson, 2011; Balzeau, 2012; Gómez-Robles, 2013; Pearce, 2013;

Zollikofer, 2013), as the necessary technology and methods have not been available to test the assumptions directly. In this study I have shown that the morphology of the cortex can be used to predict connectivity in subcortical white matter structures in the LSCN. If we are able to reliably extract information about the surface area of different cortical regions from endocast data, we may now be able to make more specific and previously untestable predictions about the subcortical structures of fossil hominins. Determining when particular long-range white matter tracts arise during evolutionary history and with which structures, either cortical or subcortical, they may have interconnected is an essential next step in the study of human neuroevolution. These data would finally allow us to determine when specific anatomical networks appeared in the brain and what behaviors may be associated with them, such as expressive art, tool making, and language.

Table 4.1. MRI Scan parameters		
Sequence	T1 MRI MPRAGE	DTI EPI
Orientation	Sagittal	Axial
TR (ms)	> 1900	> 5000
TE (ms)	2-4	> 100
TI (ms)	1000	N/A
Matrix size	256 x 256	128 x 128
# of slices	176	36
Slice thickness (mm)	1.0	3.0
Voxel size (mm)	1 x 1 x 1	3 x 3 x 3
Directions	N/A	64
Time (minutes)	~5.00	~10.00

Scan parameters for the imaging data. Abbreviations: MPRAGE – magnetization prepared-rapid gradient echo; DTI EPI- diffusion tensor imaging, echo-planar imaging; TR – repetition time; TE – echo delay time; TI- inversion time; Matrix size- resolution in pixels; Voxel- cubed pixel.

Table 4.2. Quantitative LSCN measures		
	Mean	**S.D.**
FA		
LSCN	0.3440	0.0249
LSCN-A	0.3588	0.0310
LSCN-P	0.3294	0.0273
MD		
LSCN	8.290×10^{-4}	2.888×10^{-5}
LSCN-A	7.916 x 10-4	3.225×10^{-5}
LSCN-P	8.445 x 10-4	4.091×10^{-5}

Abbreviations: FA – fractional anisotropy; MD – mean diffusivity; LSCN – language specific cerebrocerebellar network (entire tract); LSCN-A – language specific cerebrocerebellar network, anterior portion of the tract; LSCN-P – language specific cerebrocerebellar network, posterior portion of the tract

Table 4.3. Brain surface measures and correlations with LSCN connectivity							
Measure	**Mean (SD)**	**LSCN FA**		**LSCN-A FA**		**LSCN-P FA**	
		r	**p**	**r**	**p**	**r**	**p**
WBV	1291.94 (±111.92)	0.4875	0.0005**	0.4488	0.0013**	0.3758	0.0085**
WCb	159.49 (±13.24)	0.3343	0.0202	0.2458	0.0922	0.2965	0.0407
LBA44SA	28.90 (±4.02)	0.4745	0.0007**	0.3918	0. 0059**	0.3516	0.0143*
LBA44V	8.54 (±1.20)	0.4715	0.0008**	0.3646	0.0108*	0.3832	0.0072*
RBA44SA	17.69 (±2.43)	0.2584	0.0760	0.2246	0.1248	0.2209	0.1312
RBA44V	5.67 (±0.80)	0.2977	0.0390*	0.2723	0.0612	0.2839	0.0515
LBA45SA	34.58 (±4.18)	-0.0849	0.5878	0.0109	0.9416	-0.0597	0.6866
LBA45V	10.92 (±1.39)	-0.0790	0.6067	0.0145	0.9220	-0.0526	0.7227
RBA45SA	23.94 (±3.78)	-0.0789	0.5936	-0.0591	0.6897	-0.0550	0.7102
RBA45V	7.36 (±1.27)	-0.0801	0.5882	-0.0471	0.7508	-0.0538	0.7166

Volumes of brain regions measured in this study reported in cm^3, surface areas in cm^2. Pearson correlations between cortical regions and connectivity in the LSCN as measured by fractional anisotropy.
Abbreviations: WBV – whole brain volume; WCb – whole cerebellum volume; LBA44SA – left Brodmann's area 44 surface area; LBA44V – left Brodmann's area 44 volume; RBA44SA – right Brodmann's area 44 surface area; RBA44V – right Brodmann's area 44 volume; LBA45SA – left Brodmann's area 45 surface area; LBA45V – left Brodmann's area 45 volume; RBA45SA – right Brodmann's area 45 surface area; RBA45V – right Brodmann's area 45 volume.
**p<0.01, *p<0.05

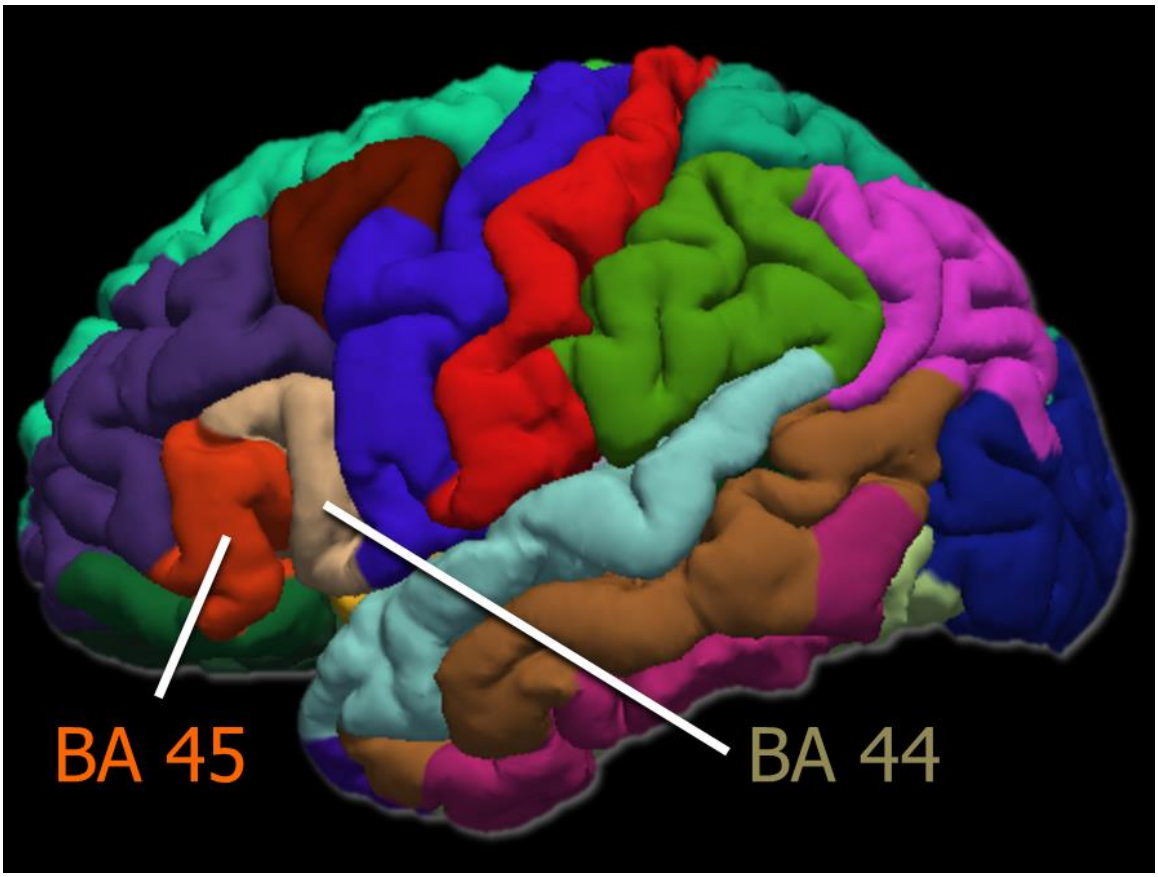

Figure 4.1 – Left lateral view of cortical segmentation. Sub-regions of Broca's area are shown, Brodmann's area 45 (BA45, pars triangularis) and Brodmann's area 44 (BA44, pars opercularis).

Chapter 5: Conclusions

Introduction

It is the goal of this project to map the anatomical connectivity between the regions of the cerebrum and cerebellum that are active during language production and relate this morphology to both cognitive measures of language and the surface geometry of the brain. The language-specific cerebrocerebellar network (LSCN), was mapped from the right cerebellum, through the left thalamus, and into the posterior portion of Broca's area, Brodmann's area 44 (BA 44). Next, I tested the hypothesis that cognitive tests that quantitatively assess language ability are correlated with connectivity measures of the LSCN. The final step tests the hypothesis that the morphology of the surface of the cortical area that represents the termination of the LSCN pathway predicts LCSN connectivity measures. Results demonstrate that 1) there is definitive anatomical connectivity between regions of the right cerebellum and Broca's area within the left inferior frontal lobe, via the left thalamus, that are known to be functionally active during language production. 2) Connectivity of the LSCN, as quantified by measures of fractional anisotropy (FA), is significantly correlated with overall language and verbal working memory, as evaluated by the Clinical Evaluation of Language Fundamentals – 5th Edition (CELF-5). 3) LSCN anatomical connectivity also was found to be significantly correlated with the morphology of the cortical surface of BA 44, a sub-region of Broca's area. Results of each hypothesis test, caveats, and potential confounding issues, and implications of these findings are summarized here.

Caveats and Potential Confounding Issues

Study Sample

All of the subjects in this study were recruited for the investigation of the normal human brain and were screened prior to inclusion in the study. Their eligibility for inclusion was based upon self-reporting the following information: male, no history of major medical or neurological conditions, no metal devices or implants in or on the head, right-handed, and a native monolingual English speaker. Without medical record screening, which was beyond the scope of this study, it cannot be known for certain whether all included subjects met this criterion for inclusion. During the screening process each subject was evaluated to meet the handedness and monolingual requirements with only two problematic subjects. I suspected one subject might have reported handedness incorrectly when he signed his name with his left hand, and admitted to being ambidextrous after questioning. Another subject was clearly not a native English speaker as he had difficulty following directions during the scheduling of the MRI scan, and then admitted that he was not a native English speaker. Neither of these subjects completed the study and their data were not included in any analysis.

All MRI images of all study subjects were screened for gross brain abnormalities prior to analysis by the licensed MRI technician and myself. Five subjects with any suspected abnormal brain anatomy were referred out to a radiologist affiliated with the Brain Imaging Center; no subject's anomalies were found to be clinically significant by the neuroradiologist. One subject whom the radiologist determined had clinically insignificant mild agenesis of the corpus callosum was excluded from analysis.

To eliminate variation due to sex and handedness, and due to time and financial constraints, this research was limited to right-handed males. This is not uncommon in this kind of study, to investigate a question with a subset of a population (right-handed, male, monolingual), then to expand the research in later studies to include other variables (left-handed, female, bilingual/multi-lingual). The study sample was recruited from a large population of undergraduate students, which most likely explains the skewing of the sample's mean language evaluation scores to above average, but still within one standard deviation. Despite these caveats, I consider the sample to be representative of a healthy population of young adult, right-handed males.

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is an imaging modality that does not measure connectivity in the brain directly, but measures the randomness of the diffusion of water molecules. Water diffuses through tissues in the body and is primarily affected by random thermal fluctuations and is modulated through interactions with cell membranes (Alexander, 2007). In fibrous tissues like the myelinated axon bundles that make up the white matter tracts in the brain, water will preferentially diffuse parallel to axons rather than perpendicular to them. This allows for the non-invasive inference of white matter anatomy though DTI. This is, however, an indirect measure of white matter anatomy; biological processes in body tissues such as edema (Lu, 2004) and abnormal cell proliferation (Beppu, 2005) affect quantitative measures calculated from DTI data. However, both edema and abnormal cell proliferation (neoplasia or brain tumor) show distinct signatures on DTI and MRIs. Edema will cause measures of MD to be

abnormally high, appearing as a hyperintensity on a MD map, and measures of FA to be abnormally low. Abnormal cell proliferation will also appear as a gross abnormality on a structural MRI or DTI map (Alexander, 2007). As stated above, all imaging data in this study were screened for gross abnormalities by the licensed MRI technician at the Brain Imaging Center and no clinically significant findings were found in any subjects, so the likelihood of any pathologies affecting my study is minimal.

It is vitally important to know typical neuroanatomy and understand what each trait measured might be indicating based on the specific location in the brain, and its underlying cytoarchitecture. Fractional anisotropy (FA) is highly influenced by white matter integrity and morphology. It is important to evaluate FA in relationship to *a priori* knowledge of the typical arrangement of axons in the white matter. In sulcal white matter and in white matter tract "crossroads," there is less preferential directionality of axons and more crossing fibers resulting in lower FA values on average. It is the responsibility of the researcher to use their knowledge of how white matter typically is arranged in each part of the brain to inform what inferences can be drawn from FA values and whether it is an appropriate proxy for connectivity across the brain.

Functional Correspondence

The regions of interest that were used to map the language-specific cerebrocerebellar network (LSCN) in this research, *i.e.*, functionally active clusters during language production tasks, were derived from a meta-analysis of previously published functional imaging studies. The subjects in the present study did not complete a language task while functional magnetic resonance images (fMRI) were collected. Thus,

it is possible that the regions that were mapped as nodes in the language-specific network are not actually used during language production in every individual. The clusters from the activation likelihood estimation (ALE) meta-analysis were derived from data from 34 studies, which included 57 experiments and 661 total individuals, and were statistically significant ($p<0.001$, $p<0.05$ after FDR correction). The mapped fiber tracts were also averaged across the study, with only tracts that were common among all individuals retained before any quantitative data was collected. Due to the conservative methodology used in this study, it is unlikely that a study including structural and functional data from the same subjects would result in substantially different findings, though it is a goal of future research into the LSCN to ensure that this is the case.

Summary of Study Results

Hypothesis 1: There is a discrete, language-specific anatomical network connecting the cerebrum and cerebellum.

The ALE meta-analysis defined 13 ROIs active during language production (ALE cluster coordinates shown in Chapter 2, Table 2.2) These ROIs are shown overlaid onto a standard anatomical template in the Talairach coordinate system (Chapter 2, Figure 2.2) (Talairach, 1988). As expected, results included previously identified cerebral language centers, Broca's area (frontal lobe, left inferior frontal gyrus) and Wernicke's area (temporal lobe, left superior temporal gyrus). In addition to these regions, the posterior lobes uvula and posterior lobe declive of the cerebellum (lobule VI and Crus I) were identified (Chapter 2, Figure 2.2). These ROIs were used as hypothetical nodes of the LSCN that I tested with tractographic analysis.

Results show that the specific regions of the right posterior lobe of the cerebellum (lobule VI and Crus I) are connected to BA 44, the pars opercularis (POp) sub-region of Broca's area in the inferior frontal gyrus of the cerebrum, via the left thalamus. No individual nucleus of the thalamus is hypothesized from the fiber tracking in our study due to the resolution of the MRI scans and the great deal of normal variation found in boundaries of the nuclei, Previous research indicates that the ventral lateral, ventral anterior, intralaminar and mediodorsal nuclei each receive output from the cerebellum (Barbas, 2013). Our fiber tracking from the white matter deep to lobule VI and Crus I of the right cerebellum was widespread throughout the left thalamus but it tended to be in more ventral and lateral portions (Chapter 2, Figure 2. 6). Previous research indicates that the ventral lateral, ventral anterior, intralaminar and mediodorsal regions receive output from the cerebellum (Barbas, 2012) and these nuclei are part of a frontal loop that are hypothesized to enhance language generation by selecting context dependent language to express a concept (Barbas, 2013; Crosson, 2013). The results of my fiber tracking in the anterior portion of the LSCN and the strong correlations with language production behavior and connectivity in the LSCN found my research support supports these hypotheses.

These results confirm that the network of regions involved in language span multiple gross anatomical structures of the brain, extending beyond the classic centers of Broca's and Wernicke's areas in the cerebrum. These findings support those of previous functional neuroimaging research that expand language in the brain beyond the cerebrum (reviewed in Wise, 2003). The anatomical connectivity that delineated here concurs with previous functional connectivity studies of language production (see ALE meta-analysis

above). Our results also agree with clinical research on cerebellar lesions that affect language (Ackermann, 2007; Stoodley, 2009, 2011).

Finally, these results fit well into the theoretical framework advocated by Ramón y Cajal and Golgi from the late 19th century that any analysis of brain function must consider the entire functional network. Further, this anatomical connectivity supports the hypotheses first put forth by Hebb (1949) that "neurons that fire together, wire together."

Hypothesis 2: The microstructure of the language-specific cerebrocerebellar network, as evaluated through diffusion tensor imaging, is significantly correlated with quantitative measures of language ability.

The results of these analyses demonstrate that the connectivity of the language-specific cerebrocerebellar network (LSCN), as measured by fractional anisotropy (FA), has strong positive correlations with language ability as evaluated with the CELF-5. The strong, statistically significant correlation of overall measures of language performance, as measured by the Core Language Score (CLS), with LSCN connectivity (FA, specifically) supports the hypothesis that the cerebellum plays a significant role in language processing. The anatomical connectivity mapped in the LSCN, specifically the thalamocortical portion to Broca's area, has previously been studied along with language function and lesion studies of the basal ganglia (Crosson, 1999; Copland, 2000; Robles, 2005; Assaf, 2006). The basal ganglia and the thalamus are involved in lexical selection, syntactic processing, and higher-level language processing (Ullman, 2001, 2004; Friederici, 2009) and our significant strong correlations with connectivity in the anterior portion of the LSCN, between the thalamus and Broca's area, and behavioral measures of

language production supports these previous studies. Recent research has shown that the basal ganglia are not involved in primary language functions, but these structures help with language processing (Mink, 1996; Nambu, 2000) and that the basal ganglia along with the thalamus enhance language generation by helping to select the proper word or a given situation (Crosson, 2007, 2012). The growing consensus through clinical findings and neuroimaging has shown that the cerebellum is involved with higher brain functions beyond motor control, and is associated with many cognitive tasks such as language (Schmahmann, 1991, 2004; Ackermann 2007; Stoodley, 2010). Clinical research into the role of the cerebellum in language has shown activation during semantic and phonological processing tasks in the lateral regions (Stoodley, 2009) and damage to the posterolateral cerebellum is linked to language deficits (Marien, 2001). These results of this research showing that connectivity in the posterior portion of the LSCN, between the cerebellum and thalamus, also have strong significant correlations with the CLS and LMI of the CELF-5 suggests that the portion of language function that I am measuring through the connectivity in the LSCN is modulation of language processing, and that both the anterior and posterior portions of the LSCN are important for this function.

Among the indices of distinct subdomains of language from the CELF-5, there is a strong significant correlation between LSCN FA and the language memory index (LMI), and a moderate significant correlation with the expressive language index (ELI). Appropriate articulation and structuring of language content is essential in language production and the correlations with LMI and the ELI support the hypothesis that the LSCN is involved in the modulation of language processing, leading to proper language production. Further, both the anterior and posterior portions of the LSCN are significantly

correlated with the CLS and LMI, demonstrating the importance of the tract as a whole in language function, rather than simply the cerebral contribution. The lack of significant correlations with the receptive language index (RLI) and language content index (LCI) also support our hypothesis that the LSCN is involved in modulation of language processing as these two indices would involve white matter tracts projecting from the temporal lobe and other frontal regions not mapped in this study. Together, these behavioral findings support that there is a quantifiable relationship between the structure of LSCN connectivity with language production and processing that includes the network as a whole and not individual elements of the network.

Hypothesis 3: The morphology of the cerebral surface is directly proportional to the degree of underlying white matter connectivity in the language specific cerebrocerebellar network.

Results of these analyses indicate that we can infer the presence of the LSCN from measurements of frontal cortical areas alone. Fractional anisotropy (FA) in the LSCN is strongly significantly correlated with whole brain measures, including whole brain volume and whole cerebellar volume. With respect to specific cortical areas, LSCN FA is strongly correlated with left BA 44 surface area and gray matter volume, and moderately correlated with the right Brodmann's area 44 volume. Additionally, when the LSCN is separated into anterior and posterior portions, both segments of the tract are significantly correlated with the same measures of left BA 44. Given that left Brodmann's area 44 is known to be associated with language production, and the results of the present study showing surface area and volume of this region to be significantly

correlated with LSCN white matter connectivity, it is now possible to make predictions about subcortical white matter from surface morphology alone.

Discussion

For the first time, this study demonstrates that functionally connected regions in the cerebrum and cerebellum which are active during language production, do in fact have robust white matter tracts interconnecting them. The language-specific cerebrocerebellar network (LSCN), which includes the right lateral cerebellum, left thalamus, and left Broca's area, has connectivity that correlates with overall language and verbal working memory. Analyzing functional activity in cortical regions in isolation is not sufficient to definitively answer questions about how the brain works. The correlation of white matter connectivity with behavior shows that the connections between functionally active regions are just as important as the regions themselves when ascribing function to different parts of the brain.

This study demonstrates that the cerebellum, a part of the brain that has been ignored with respect to study of cognition until very recently, must now be considered. The results of this study correlating cerebellar connectivity in the LSCN to language processing indicate that the role the cerebellum plays in cognitive networks is a smoothing, modulatory effect, much like its role in motor activity. It is likely that the cerebellum plays a similar role in many cognitive functions in the brain beyond language. Working within a theoretical framework that views the cerebellum as an important structure in both the normal functioning of the modern human brain, and as an important target of selection during neuroevolution, raises many interesting possibilities in

answering questions about how the brain functions and how it may have evolved. Perhaps it is not only our very large brain but also our intricately interconnected cerebellum, efficiently managing the raw processing power in our cerebrum, which has been the driving force behind human cognitive evolution.

This study complements Weaver's (2005) findings of significant expansion of the cerebellum relative to the cerebrum in endocasts of late Pleistocene *Homo,* opposite to an earlier trend where the cerebrum vastly expanded paired with a relatively moderate cerebellar size. The expansion of the cerebellum during the late Pleistocene has been hypothesized to support behavioral advances in later hominins such as language production (De Smet, 2007; Thach, 2007; Rilling, 2008b). Demonstrating that the cerebellum is anatomically connected to cerebral language regions strongly suggests the cerebellum to have been a target of selection, evolving in concert with the functional network. Previous work indicating that the more lateral, frontal projecting lobes have expanded at a greater rate than more medial portions of the cerebellum (Rilling 1999, Balsters 2010) supports this hypothesis. Through analyses similar to those described in this *in vivo* study of functional neural networks, we can identify regions that are associated with complex behaviors that are considered unique to humans, such as complex tool use (Frey, 2007; Philip, 2014) and language (Leiner, 1986; Morgan, 2009; Vannest, 2009). The present study may serve as a model for future work to test additional hypotheses regarding the development and evolution of these functional networks that support modern human behaviors that were important for complex social networks and global expansion of the species.

This study shows that we can infer the presence of a long-range white matter tract, with connectivity that is functionally significant, from cortical measurements alone. These findings are an essential first step in determining whether endocasts can be used to make inferences about the evolution of the brain and cognitive abilities in human ancestors. Endocasts only preserve cortical surface features, and assumptions have long been made about the behavior of early humans based solely on these data (Carlson, 2011; Balzeau, 2012; Gómez-Robles, 2013; Pearce, 2013; Zollikofer, 2013). If we are able to reliably extract information about the surface area, volumes, and connectivity of different cortical regions from endocast data, then we can then make more specific predictions about the subcortical structures of fossil hominins to which we were previously blinded.

Determining when long-range white matter tracts appear during history and which cortical regions they may have interconnected is an essential next step in the study of human neuroevolution. We can hypothesize timing of functional changes (*i.e.*, behavior) related to these networks based on cultural materials associated with hominin fossils (Schick, 1999). Artifacts in the fossil record, such as stone tools and expressive art, are used as indicators of cognitive expansion in the brains of human ancestors, and it has been postulated that language would have facilitated more efficient manufacturing and refinement of these objects (Wynn, 2002). Results such as those generated in this study may finally allow us to know when specific anatomical networks appeared in the brain and what behaviors are associated with them, such as expressive art, tool making, and language. Our findings that cortical regions can predict subcortical structure and connectivity in anatomical networks have important implications for the use of endocasts. The final information we need is to determine how well the interior surface of the skull

represents the surface of the brain, whether this representation is uniform across the entire cortex, and whether there is significant intraspecific or interspecific variation in this representation.

Clinically, this project supports the recent recognition through neurological and neuroimaging studies that the cerebellum is not just associated with motor functions, but is also involved with higher brain functions and cognitive tasks such as language (Schmahmann, 1991, 2004; Ackermann 2007; Stoodley, 2010). Knowledge of the typical anatomy of this functional network will serve as a powerful normative framework for comparison in many diseases that affect language, as well as other aspects of cognition. Clinical research into the role of the cerebellum in language has shown activation during semantic and phonological processing tasks in the lateral regions (Stoodley, 2009) and damage to the posterolateral cerebellum is linked to language deficits (Marien, 2001). This study has confirmed that the functional activation seen in these language tasks has anatomical connectivity to the language areas in the cerebrum. In any condition resulting in language impairment, the integrity of the tissue in the cerebellum and the white matter tracts interconnecting the cerebrum must be considered. Large networks that span several cortical areas in the brain are responsible for many higher functions (Zielinski, 2010); therefore, by analyzing the entirety of these networks through in-depth morphological and connectivity measures, subtle patterns that result in dysfunction can be identified. Finding the alterations in these morphologies is key in guiding further research to determine how pathologies in these large cognitive networks result in many observed neurodevelopmental and neurodegenerative disorders and may be key to understanding pathologies such as autism spectrum disorder, ADHD, Alzheimer's, and many others.

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