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Relationships Between Domain-Specific Cognition and Regional Brain Structure in a Typically Developing Cohort

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Cognitive Science

by

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2019

The Dissertation of Lauren Butler Curley is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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DEDICATION

I would like to dedicate the following work to my family, who have supported and encouraged me throughout my academic career.

EPIGRAPH

"For every complex problem, there is an answer that is clear, simple, and wrong."
Adapted from H.L. Mencken

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LIST OF ABBREVIATIONS

SSRT: Stop-signal reaction time
CTOPP BW: Comprehensive Test of Phonological Processing, Blending Words
BSE: Between-search errors
MRI: Magnetic resonance imaging
DTI: Diffusion tensor imaging
FA: Fractional anisotropy
MD: Mean diffusivity
PO: Pars opercularis
PLT: Posterolateral temporal
SLF: Superior longitudinal fasciculus
tSLF: temporal branch of the superior longitudinal fasciculus
pSLF: parietal branch of the superior longitudinal fasciculus
AF: Arcuate fasciculus
ILF: Inferior longitudinal fasciculus
SIFC: superior-inferior frontal cortex
IFSFC: inferior frontal superior frontal cortex
CCA: canonical correlation analysis
mfPCA: multivariate functional principal components analysis

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ABSTRACT OF THE DISSERTATION

Relationships Between Domain-Specific Cognition and Regional Brain Structure in a Typically Developing Cohort

by

Lauren Butler Curley

Doctor of Philosophy in Cognitive Science

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Professor Terry Jernigan, Chair
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Human development is a dynamic, protracted process influenced by genetics, the environment, experience, and many other factors. During development, an individual develops an entirely unique neural architecture along with a unique set of cognitive skills and abilities. Through recent large-scale pediatric neuroimaging initiatives, we now have a better understanding of the protracted structural changes occurring in the developing brain. We are also beginning to map out relationships between developing brain structure and domain-specific cognition, although we haven't fully characterized these relationships and

their variability throughout typical development. The goal of this work is to assess how individual differences in regional cortical and subcortical brain structure are related to behavioral and cognitive variability in different domains during childhood and adolescence, which is a period of rapid dynamic change. This work also aims to investigate overlapping as well as distinguishing characteristics of the relationships between developing neural systems and domain-specific cognition.

In this dissertation, I focus on three cognitive domains: phonological awareness, spatial working memory, and response inhibition. These three cognitive domains are thought to involve relatively distinct brain regions and networks, allowing us to investigate the specificity of associations between structure and function in the developing brain. In addition, these three domains have been well studied in pediatric, clinical, and adult populations in behavioral and functional neuroimaging studies, leading to relatively well-defined region-specific hypotheses. Utilizing three distinct cognitive domains also supports the investigation of domain-general aspects of cognitive development, such as latent factors or skills supporting multiple areas of cognitive development. In addition, studying multiple cognitive domains allows me to study the reflection of any shared features in the neural architecture. I will first address the region-specific associations between cortical and white matter regions thought to be principally related to each cognitive domain. Following that, I will carry out a more data-driven analysis aimed at exploring possible latent factors underlying the associations between these cognitive domains and structural regions. These results may provide insight into the neurobiological correlates of cognitive development and the nature of individual difference variability during development.

CHAPTER 1: COGNITIVE AND NEURAL DEVELOPMENT

1.1 Overview

Human development is an extremely complicated process spanning decades and is influenced by interactions between genes, experiences, and the environment. A major goal of the field of human development is to better understand the individual variability we observe across cognitive domains and skills during development, as well as what types of factors affect these differences. In addition, understanding when and how individual variability in cognition emerges will greatly inform our understanding of the extremely complicated and lengthy process of human development. The goal of this dissertation is to explore the relationship between domain-specific cognition and regional brain structure in a typically developing cohort, and to conduct a more data-driven analysis aiming to describe the overlap and dissociation between the implicated neural systems. In the process, this work aims to begin to answer some fundamental questions about human development such as:

(1) How much individual variability do we observe in regional cortical and white matter structure? How much individual variability do we observe in cognitive performance across domains?

(2) Is there a relationship between individual variability in regional brain structure and domain-specific cognition during development? If so, does this relationship change over the course of development?

(3) Are the cortical and white matter regions related to performance on one task distinct from (or related to) performance on another task? Can we identify any latent structure in the neural architecture that is predictive of domain-specific performance?

In recent years, large-scale pediatric studies have allowed us to better understand both the variability among and between children in both task-specific cognitive development as well as in regional and global brain structure. A large cross-sectional study of typically developing children illustrated that age-related performance on different cognitive tasks exhibited distinct, primarily nonlinear improvements from 3 to 20 years of age (Akshoomoff et al., 2014). In terms of brain structure, global cortical surface area was observed to increase from approximately ages 5 to 12, after which it began to contract, continuing through age 20. Mean cortical thickness decreased linearly from the ages of 5 to 20 years (Brown et al., 2012, Wierenga et al., 2014b). This difference in developmental trajectories of cortical surface area and thickness expands on previous work evaluating cortical volume, which is a product of surface area and thickness. In addition to the distinct developmental trajectories, these two structural features of the cortex are subject to distinct genetic influences (Panizzon et al., 2019, Chen et al., 2013). Although surface area can be fairly consistently measured using today's tools, cortical thickness is sometimes referred to as *apparent* thickness, as the thickness of the cortex as measured by MRI can be highly influenced by the properties of the specific scanner, the degree of observable grey-white contrast, and the development of the white matter underlying the cortex. Furthermore, studies investigating the

development of subcortical white matter have suggested that fractional anisotropy generally increases during development, whereas mean diffusivity decreases (Krogsrud et al., 2016; Lebel & Beaulieu, 2011). Fractional anisotropy (FA) is a measure of the degree of both intracellular and extracellular diffusion of water molecules along a primary axis, and FA tends to increase with degree of myelination, axonal diameter, and fiber density. Mean diffusivity (MD), in contrast, is the average degree of diffusion of water molecules along three primary axes, and MD tends to decrease with increasing myelin. Both measures can also be influenced by tissue properties such as cellular density, cell size, and other factors. Regional variability in both cortical and subcortical development has been observed (Brown et al., 2012a, 2012b; Jernigan et al., 2011, Wierenga et al., 2014a, 2014b), although very little work has investigated how these regional changes in brain structure relate to developing cognition. The observed regional variability could be modulated by many possible influences, including genetics, environment, and experience. Understanding individual differences in regional variability may help inform our understanding of these interactions.

This research seeks to better define the relationship between individual differences in cognitive performance across domains and individual differences in regional brain structure among children of the same age and across development. The general outline of the investigation is as follows:

(1) Is there a relationship between regional cortical and white matter structure and phonological awareness?

(2) Is there a relationship between regional cortical and white matter structure and spatial working memory?

(3) Is there a relationship between regional cortical and white matter structure and response inhibition?

(4) Can we identify any latent structure in the neural architecture that is related to performance in a specific cognitive domain?

Question (1) is discussed in chapter two, which focuses on examining the relationship between regional cortical and white matter regions of interest and phonological processing. Question (2) is discussed in chapter three in a similar manner, and Question (3) is discussed in chapter four. Question (4) is explored in the final chapter.

There are still many unanswered questions about human brain and cognitive development, and this body of work will address relatively limited but foundational questions about the relationships between the developing brain and cognition. The results of this work may begin to describe relationships between co-developing brain structure and cognition that could then inform future investigations into causal relationships in typically developing children and interventions in atypically developing children.

1.2 Cognitive Development

Over the course of development children gain proficiency in a wide range of cognitive skills at various rates. Rapid improvement is made in areas such as language,

working memory, attention, and inhibitory control (Akshoomoff et al., 2014). A conventional view is that some children have higher general intelligence than others and that these children perform better on all cognitive tasks. However it is also clear that children may perform well in specific cognitive areas, such as language, and less well in others, such as mathematics. The profile of an individual's variability in cognition and behavior in different domains can be defined as his or her "behavioral phenotype" (Jernigan et al., 2015). Behavioral phenotypes can take the form of differences in skills, expertise, preferences, knowledge, etc. but are generally considered stable traits. We know relatively little about how much individual variability there is in developing cognition during childhood and adolescence and whether the degree of variability changes with age.

Many methods have been used to investigate the relationship between domain-specific cognition and brain structure and function. Lesion studies, functional neuroimaging, structural and diffusion-based imaging, electroencephalography and magneto-encephalography as well as positron emission tomography and near-infrared spectroscopy have all been utilized in the quest to understand regional and whole-brain relationships to cognition. Research done using these various methods has converged on specific cortical and subcortical regions thought to underlie specific cognitive functions. The three cognitive domains of interest – phonological processing, spatial working memory, and response inhibition – have been well studied using these various methods, allowing us to hypothesize that specific structural regions of the brain will be disproportionately related to each distinct cognitive domain. However, previous research

has most often been carried out in adult populations or clinical patients, with relatively little work done on the changes occurring during typical human development. We also have evidence that individual differences in cognition are moderately heritable, with genes accounting for 50-70% of the variation in cognition (Tucker-Drob et al., 2013). However, the relative contribution of genetic variation on cognition seems to vary during development, with heritability increasing from about 20% in infancy to as much as 80% in adulthood (Plomin and Deary, 2015). In addition, genetic variation accounts for about 60% of the variance in academic achievement in school-age children, with unique environmental influences explaining the remainder (Haworth et al., 2008).

Understanding the variability inherent in typical human development would greatly increase our ability to identify children who may be at risk for learning deficits or clinical diagnoses and who may benefit from early educational interventions. In addition, it would help answer basic questions about the relationship between developing brain structure and cognition. This work aims to begin to address this gap regarding the relationships between regional brain structure and domain-specific cognition in typically developing children and adolescents.

1.3 Cortical and white matter development

The brain undergoes many temporally variable, protracted changes in both grey and white matter structure (Brown et al., 2012; Jernigan et al., 2011, Wierenga et al., 2014; Jernigan et al., 2015). Although global developmental trajectories are observed, there is substantial variability in these structures and their development (Jernigan et al.,

2011; Brown et al., 2012; Brain Development Cooperative Group, 2012). The differing developmental trajectories of cortical surface area, cortical thickness, and diffusion properties of subcortical tracts are more than likely inter-dependent. Although there is little evidence supporting explanations of direct mechanisms in humans, work in non-human primates and other mammals has suggested mechanisms by which these different trajectories co-develop. By measuring the development of both cortical and subcortical structures in the same population, we can gain a much better understanding of the unique influences each has on developing domain-specific cognitive skills.

Cortical surface area and cortical thickness show distinct developmental trajectories (Brown et al. 2012, Wierenga et al., 2014) and have distinct genetic influences (Chen et al. 2011; 2013; Panizzon et al., 2009). Total cortical surface increases through about age 12, after which it begins to contract. Conversely, a steady decrease in cortical thickness is observed throughout development (Brown et al., 2012). Evidence suggests that there is a general developmental trend for higher-order association areas of cortex to mature after somatosensory, visual, and phylogenetically older areas of cortex (Gogtay et al., 2004). Many previous studies into structural brain development examine changes in cortical volume (Giedd et al., 1996; Lenroot and Giedd, 2006; Lebel and Beaulieu, 2011) and less commonly, cortical thickness. Previous studies showing increases in apparent thickness in the school-aged years may be conflating surface area and thickness, especially in younger age ranges. With advancements in neuroimaging processing and segmentation, we now have more reliable methods to separate surface

area and thickness, and investigate how changes in each relate to cognition independently.

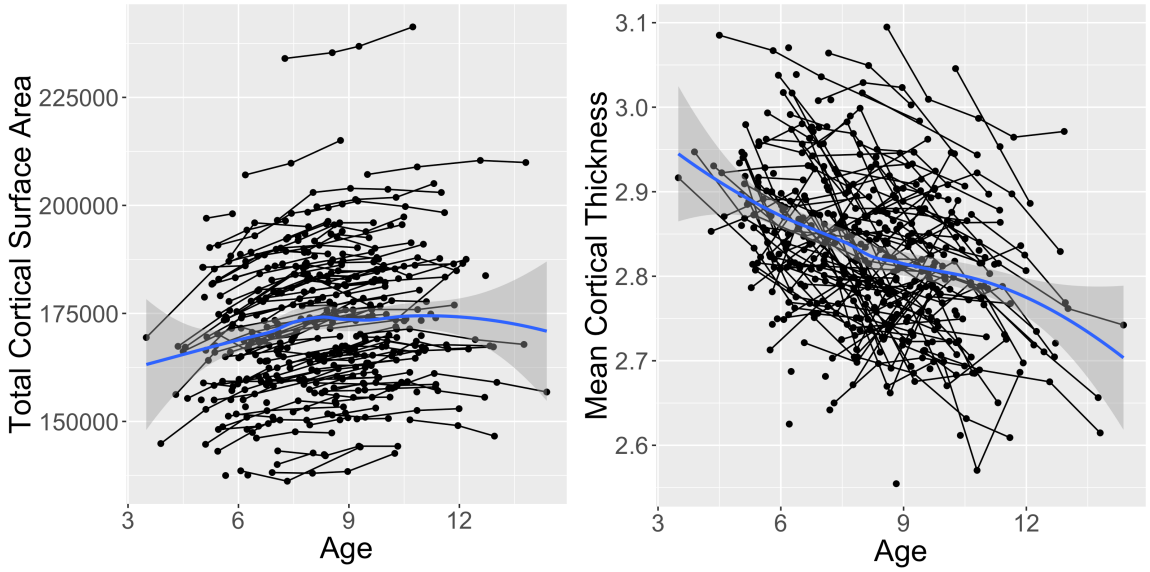

Figure 1.1. Total cortical surface area (left) and mean global cortical thickness (right) for a cohort of the PLING study (183 subjects, 464 observations). Blue loess fit line with shaded 95% confidence intervals around the mean.

Previous work has suggested that cortical structure is highly heritable (Schmitt et al., 2014; Chen et al., 2011; Chen et al., 2013; Baare et al., 2001). Using adult twin data, Chen et al. (2011) examined cortical areal patterning based on genetic correlations from twin data. Regionalization is largely organized hierarchically, first patterning along an anterior-posterior dimension and at higher levels, clustering by genetic association into largely frontal, temporal, somatosensory, and occipital regions, which is largely consistent with previous nonhuman animal models (O'Leary et al., 2007). Further work by Chen et al. (2013) examined genetic influences on cortical thickness, comparing and contrasting them with the genetic influences on cortical regionalization. Surface area clusters tend to fall within lobes, whereas thickness correlations tend to cluster more

based on mechanisms of maturation. In addition, the set of genetic factors influencing cortical surface area and thickness appear to be relatively distinct, with genetic correlation between surface area and thickness in homologous regions reaching only 0.01-0.15 (Chen et al., 2013). Some studies have suggested that sensory and motor areas of the brain seem to develop at earlier stages, followed by parietal and temporal regions, and finally by association areas such as prefrontal cortex (Gogtay et al. 2004; Sowell et al., 2003, 2004; Giedd et al., 2004), although some of these studies conflate surface area and thickness, making it hard to interpret developmental trends. Some developmental trends from structural imaging in humans are supported by human and other primate postmortem dissections (Huttenlocher, 1979), although results are inconsistent (Burgeois et al. 1994). If, in fact, it is the case that sensorimotor areas do develop before higher-order association areas in frontal cortex, this would parallel cognitive developmental trends (Casey et al., 2005).

Work by Schmitt et al. (2014) evaluated the degree of genetic influence on regional brain structure in childhood and adolescence. Longitudinal analyses evaluating changes in genetic contribution to regional cortical structure during development demonstrated that the heritability of cortical thickness increases in late childhood and adolescence. Complementary to genetic contributions, environmental contributions to regional cortical structure also seemed to vary during development. In particular, the dorsolateral prefrontal cortex and inferior parietal lobe showed a significant degree of change based on environmental influences. Overall, in childhood there is heterogeneity in genetic influences across the cortex with notably high between-subjects variance in

frontal and parietal areas (Schmitt et al., 2014).

Diffusion tensor imaging studies in children and adolescents have characterized the major trends of white matter development, which are supported by postmortem examination of tissue properties (Catani et al. 2002, 2008). In addition to the high heritability of cortical structure, white matter volume is also highly heritable, up to 88% (Báare et al., 2001). Fractional anisotropy, a measure of the strength of directionality of diffusion, is shown to increase throughout development. Conversely, mean diffusivity, which is a measure of average diffusivity, decreases throughout development (Brown et al., 2012). The fine-tuning of these connections during development is an important and delicate process, influenced by factors such as genetics and the environment. One study suggests that genetic influence accounts for about 75-90% of the individual variation in fractional anisotropy in large portions of white matter, and that there is some genetic mediation of the relationship between white matter and intelligence (Chiang et al., 2009). Some studies have suggested links between the environment, genetics, behavioral training, and white matter changes, although interpreting the findings from these studies is challenging (Johansen-Berg, 2010; Draganski et al., 2004; Keller et al., 2009; Hofstetter et al., 2013).

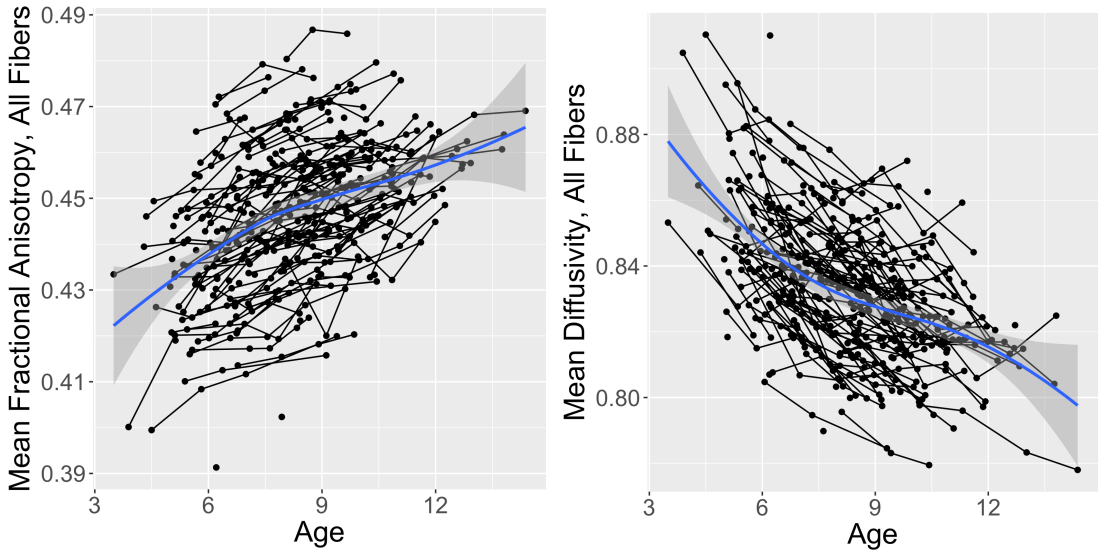

Figure 1.2. Average fractional anisotropy for all fibers (left) and average mean diffusivity for all fibers (right) for a cohort of the PLING study (183 subjects, 445 observations). Blue loess fit line with shaded 95% confidence intervals around the mean.

A recent longitudinal investigation into changes in white matter between the ages of 4 and 11 years evaluated age-based changes in tract-based white matter microstructure (Krogsrud et al., 2016). The results suggest a linear, global increase in fractional anisotropy and a decrease in both mean diffusivity and radial diffusivity across the subject group. In addition, there was regional, tract-based variation in both the linearity and the strength of the relationship of white matter microstructure and age. The largest increases in FA were in the superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), uncinate, and inferior fronto-occipital fasciculus (IFOF). In addition, there was an overall larger rate of change in frontal regions during this developmental period (Krogsrud et al., 2016). Similarly, another longitudinal study examining changes in white matter during childhood, adolescence, and early adulthood, which spanned a larger age range of 5-23 years, suggested nonlinear changes in global and regional white

matter microstructure across tracts (Lebel & Beaulieu, 2011). However, this study seemed to indicate relatively linear increases in the earlier age range, similar to the one studied by Krogsrud and colleagues (2016), and nonlinear effects in later stages of development, closer to 15 years old.

1.3.1 Anatomy: tissue dissections and fiber tracking

When using magnetic resonance imaging and diffusion tensor imaging to extract information about tissue morphology, it is important to keep in mind the strengths and limitations of these methods. Previous research has sought to identify the correspondence of in-vivo structural imaging with grey and white matter tissue properties using translational animal models or postmortem dissections. For example, in a study utilizing diffusion-weighted MRI of postmortem brains, there was about 80% correspondence between the tracts inferred from neuroimaging and histologically traced tracts (Seehaus et al., 2013). Accurately interpreting the imaging signal requires understanding how it reflects the underlying tissue properties and structure. We can ground our interpretation of the MRI and DTI signal in our knowledge of the underlying tissue properties and developmental processes inferred based on nonhuman primate and postmortem studies.

The few studies of synaptic density, commonly measured as the number of synaptic contacts per area of $100\mu m^2$ or volume of $100\mu m^3$ (Huttenlocher, 1979; Goldman-Rakic et al., 1997; Bourgeois et al., 1994) across the human lifespan have suggested that synaptic density in frontal cortex is highest around age 2, after which there is a decline in synaptic density from age 2 to 16 years. Concurrently, there is a slight

decrease in neuronal density during this period (Huttenlocher, 1979, 1984). However, findings among studies of postmortem tissue properties are not uniform. Alternate investigations suggested synaptic density is highest in childhood and does not begin to decline until puberty (Bourgeois et al., 1994; Goldman-Rakic et al., 1997). In general, it seems that dendritic growth and synaptogenesis develop in similar ways. In humans, synaptogenesis occurs first in primary sensory areas, such as auditory cortex, and later in prefrontal cortex (Huttenlocher & Dabholkar, 1997), which parallels developmental neuroimaging studies showing that development of primary sensory regions occurs first, and higher-order processing areas develop later. For example, Broca's speech area reaches adult levels of synaptic density early in development, around the age of 5 (Huttenlocher 1999). Areas such as middle frontal gyrus show decreases in synaptic density starting around age 7 and ending in early adolescence, whereas prefrontal cortex does not resemble adult levels of synaptic density until mid-adolescence. Evidence suggests that there is regional variability in synaptogenesis during human development, and synaptogenesis seems to develop concurrently with dendritic and axonal growth and with myelination of the underlying white matter (Huttenlocher & Dabholkar, 1997). Additionally, the authors interpret the findings to suggest that synapse elimination (as opposed to synaptogenesis), is heavily influenced by the environment, especially true for later-maturing regions such as prefrontal cortex (Huttenlocher & Dabholkar, 1997). However, other researchers have suggested that due to the high levels of synaptic density maintained during childhood, during which time children are gaining various cognitive skills, synaptogenesis may not be the most crucial process for behavioral maturation

(Luciana & Nelson, 2002). They also suggest that regional functional maturation is tied to increased synaptic efficiency through elimination of unnecessary connections, although we do not yet have the evidence to support this conclusion (Luciana & Nelson, 2002).

The early maturation of primary sensory areas and relatively late maturation of prefrontal regions is further supported by studies of synaptogenesis in rhesus monkeys (Bourgeois et al., 1994; Bourgeois & Rakic, 1993). In visual cortex, maximum synaptic density is observed around 3 months of age in rhesus monkeys, followed by a slight decrease in density through 2 years of age. Decreases in density accelerate during puberty, up to a total loss of about 40% (Bourgeois & Rakic, 1993). In prefrontal regions of the rhesus monkey, a similar maximum level of synaptic density is reached between 2 months and 3 years of age, remains constant through puberty, and is followed by a decrease in density through 20 years of age (Bourgeois et al., 1994). The parallel evidence from non-human primate studies of synaptic density and postmortem studies in humans support the global developmental trajectory of increasing synaptic density in early childhood, with region-dependent gradual decreases in density during later childhood and adolescence.

In addition to studies focusing on synaptic density, developmental changes in the molecular components of synapses can also inform our understanding of postnatal changes in cortical structure. Work by Webster et al. (2011) evaluated molecular components of synaptic growth in frontal cortex. Results supported previous findings that the growth and strengthening of synapses occurs throughout childhood, and

developmental processes may maintain a stable level of synapse-associated molecules throughout adolescence. Investigations into synaptic marker proteins in the prefrontal cortex also support the idea that synaptic density increases from birth to late childhood, decreases in early adolescence, and stabilizes in late adolescence when it resembles adult levels (Glantz et al., 2007). Levels of synaptic spine density are two to three times higher in childhood compared to adulthood, and generally begin to decrease during puberty (Petanjek et al., 2011). However, there is some evidence that overproduction and pruning of synaptic spines as well as remodeling of connections can occur after adolescence, through the third decade of life, before stabilizing (Petanjek et al., 2011). This process of overproduction and pruning may reflect a degree of "experience-expectant" neural circuitry, whereby overproduction ensures the availability of necessary connections during a critical period of development, after which the necessary connections are strengthened and the remaining, unutilized connections are pruned. A separate study suggested increases in molecular signaling tied to synaptic growth during childhood, which remain high during adolescence and attenuate in adulthood (Webster et al., 2011). Converging evidence from neuroimaging and studies of tissue density seems to suggest early brain development is an intrinsically guided process, consisting of overproduction of neurons and synapses, allowing for the plasticity crucial for responding and adapting to environmental influences. Thus, one interpretation of these findings may be that later development and pruning of neurons and synapses is more heavily influenced by environmental factors, when experience guides the removal of unnecessary connections (Huttenlocher & Dabholkar, 1997; Petanjek et al., 2011; Luciana & Nelson, 2002). This

overabundance of neurons and synapses in early development may be crucial for the plasticity and flexibility we see in developing children, and the subsequent pruning may be necessary for forming the specialized networks we see in adults.

Studies focusing on the white matter pathways connecting these cortical regions support the anatomical descriptions of these tracts in neuroimaging. One illustration of this is the temporoparietal junction, thought to be involved in many important functions such as language, visuospatial attention, and working memory, which is located near the junction of multiple white matter tracts including branches of the superior longitudinal fasciculus (SLF) and the arcuate fasciculus (AF). Using a combination of diffusion tensor imaging and surgical dissections, De Benedictis and colleagues (2014) traced the anatomical projections of the fiber tracts underlying this region. They demonstrated connections between one portion of the SLF (branch III) and the superior and middle temporal gyri as well as the supramarginal gyrus and angular gyrus. The anterior projection of the SLF was found to extend to the pars opercularis of the inferior frontal gyrus (IFG).

De Benedictis et al. (2014) determined the AF extended from posterior and middle temporal areas to the insula and to the posterior part of the inferior frontal gyrus (IFG) and middle frontal gyrus (MFG). The arcuate fasciculus (AF) is often conflated with the inferior branch of the SLF. Yagmurlu et al. (2015) segments the arcuate fasciculus into two segments, ventral and dorsal. In this definition, the ventral AF extends from middle-posterior superior temporal gyrus to the pars opercularis, pars triangularis,

and ventral premotor cortex and the dorsal AF passes from the inferior temporal gyri to the pars opercularis, ventral premotor cortex, and posterior middle frontal gyrus.

Further research by Yagmurlu et al. (2015) investigated the tracts thought to be involved in the dorsal language stream, including the ventral and dorsal segments of the arcuate fasciculus and three segments of the superior longitudinal fasciculus (SLF). Using postmortem fiber dissection and diffusion imaging, this study describes the distinct divisions and projections of the AF and SLF. Expanding on previous research, these authors determined that SLF I lies directly underneath the superior cingulate sulcus, connecting the superior parietal lobe to the medial superior frontal gyrus. Furthermore, the SLF II extends from the occipital lobe to the dorsolateral prefrontal cortex and the lateral frontopolar cortex. There also seems to be a vertical fiber pathway extending from the supplementary motor area towards the posterior section of the inferior frontal gyrus. Some studies have called this tract the fronto-aslant tract, passing through SLF II (Catani et al., 2012). The ventral extension of the SLF, here termed the SLF III, connects the supramarginal gyrus to the pars opercularis (Yagmurlu et al., 2015), similar to the description provided by De Benedictis et al. (2014). Additional work by Hecht et al. (2015) examined the projections of the three branches of the SLF in both chimpanzees and humans, demonstrating distinct morphology in human tract organization. In humans, SLF II (the middle branch) showed stronger connectivity with the dorsolateral prefrontal cortex. SLF III (the inferior/ventral branch) was right-lateralized and had a larger volume, and showed stronger projections to the right anterior inferior frontal gyrus. This suggests

that in humans, relative to chimpanzees and possibly other primates, there are enhanced structural networks relevant to action and spatial attention (Hecht et al., 2015).

A study focusing on the dorsal projections of the SLF as well as other fronto-parietal projections investigated the composition and projections of these tracts in humans using postmortem dissections (Maldonado et al., 2012). In contrast to the appearance of long horizontal association fibers in neuroimaging, the authors suggested that primarily short association pathways connect dorsal regions of the frontal and parietal lobes. These are primarily composed of short "U"-shaped fibers connecting adjacent regions of cortex. Long, horizontal projection fibers were only found in more inferior sections of the superior parietal lobe, likely the lower part of the SLF or arcuate fasciculus (Maldonado et al., 2012).

De Benedictis and colleagues also examined the inferior longitudinal fasciculus (ILF). The long fibers of the ILF projected horizontally along the inferior temporal lobe to anterior temporal cortex, with more posterior fibers reaching dorsolateral regions of the occipital lobe. All of the fiber tracking and orientations found via dissections were confirmed using diffusion tensor imaging reconstructions, confirming the anatomical basis of white matter pathways identified and segmented using diffusion tensor imaging (De Benedictis et al., 2014).

Investigations into the neural structure of cortical regions and white matter tracts in animal models and postmortem dissections provide crucial information for interpreting the neuroimaging signal often used in human studies and allow researchers to ground their interpretations in anatomical connections. Extrapolating these studies and results to

human neuroimaging is quite challenging, and as yet there is no clear correspondence between the two. This is in large part due to the inability to interpret the relatively large voxels measured in human imaging in terms of the cellular-level complexity of structure and tissue measured using animal models and/or dissections. For example, one major shortcoming of diffusion tensor imaging is its inability to adequately describe crossing white matter fibers. Similarly, one major shortcoming of magnetic resonance imaging is its inability to differentiate cell types throughout the cortex (in most in-vivo studies when scan time is constrained). Although both MRI and DTI are invaluable tools for investigating human brain structure, it is important to consider the source and possible composition of the signal during interpretation and to keep in mind the relative shortcomings of these methods.

1.4 Correspondence Between Developing Brain Structure and Function

For decades, functional imaging has been a cornerstone of the investigations into the connection between the brain and behavior. Many studies into the connections between the brain and cognition focus on functional relationships, as measured in functional magnetic resonance imaging (fMRI), electroencephalography (EEG), or magnetoencephalography (MEG) experiments. In order to gain an even deeper understanding of the connections between specific brain regions and cognition, we need to include investigations into the physical, structural properties of the brain as a complement to examining functional activation. Mapping relationships between cognitive performance and related regions of cortex and the connecting white matter tracts will

greatly inform decades of functional research based on inferring functional connections and brain activation. Furthermore, functional studies in both clinical and healthy populations focusing on links between specific cortical regions and specific cognitive functions allow us to develop strong hypotheses about the connections between region-specific structural morphology and performance. The cognitive domains of phonological processing, spatial working memory, and response inhibition have been independently studied in various populations and are hypothesized to involve somewhat anatomically distinct cortical regions and association tracts. Due to a substantial foundation of functional research in these cognitive domains relating them to cortical and subcortical regions, as well as the potential distinct networks involved in each and the relative breadth of cognitive function covered by these tasks, these cognitive domains serve as a strong foundation for mapping out the relationships between regional brain structure and domain-specific cognition during typical development.

Both functional and structural organizations of the human brain change dramatically over the course of development. There is evidence that from childhood to adulthood, there is a general shift between widespread, diffuse activation during domain-specific cognitive tasks to a more focal pattern of activation, suggesting the development of specialized networks (Durston et al., 2006; Dosenbach et al., 2010; Luna & Sweeney, 2004). Similar to predicting biological age from structural imaging biomarkers (Brown et al., 2012), data-driven analyses of functional MRI have also been able to predict individual brain maturity in a large cohort of typically developing children, adolescents, and adults ages 7 to 30 years (Dosenbach et al., 2010). Some authors have speculated that

developmental synaptic pruning or remodeling allows for more efficient local neural communication and increasing myelination allows for increased speed of transmission to more distant neural regions (Petanjek et al., 2011; Luciana & Nelson, 2002), although current evidence cannot support any strong conclusions. Together, these developmental trends may suggest the development of increasingly specialized, distributed networks for cognitive tasks. This changing neural structure might be reflected in functional activation, with a trend toward more focal activation with development (Durston et al., 2006; Fair et al., 2009; Dennis et al., 2013; Luna & Sweeney, 2004). In order to map out these developmental changes in regional brain activation, longitudinal studies have proven to be very important.

There is evidence supporting the idea that functional changes during development coincide with structural changes in the same regions. As previously mentioned, functional studies report a general developmental pattern of widespread activation becoming more focal during development, which coincides with developmental trends in brain structure from lower sensorimotor areas to higher-order association networks. An example of this is the development of prefrontal cortex and maturation of higher-order cognitive abilities such as suppressing irrelevant information and responses (Casey et al., 1997, 2002; Shaw et al., 2006, 2011). Studies of both cortical and white matter development in cross-sectional and longitudinal studies support the notion that ongoing maturation of prefrontal regions reflects a protracted process of maturation, involving the recruitment of a more focal and specialized network and fine-tuning of regional structure

and connections (Casey et al., 1997, 2002; Madsen et al., 2010; Shaw et al., 2007, 2011; Brown et al., 2012).

1.5 Cross-sectional and Longitudinal Analyses

One question regarding human brain and cognitive development is whether brain maturation precedes cognitive gains, or whether experience in a cognitive domain facilitates brain growth of that area or network. An opinion piece by Klingberg (2014) discusses some of the hypotheses surrounding the development of cognition during childhood. One major hypothesis about child development is that brain maturation precedes and drives cognitive development. The complementary hypothesis is that experience and environmental influences are what drive development. The third major hypothesis focuses on interactions between the environment and brain maturation. In fact, all of these hypotheses about human development may be true to some degree, and most likely the third hypothesis postulating some interaction is the closest to the truth. There is some evidence that skill-learning and development share similar underlying mechanisms, based on evidence of increased working memory capacity after training and during development associated with stronger functional connectivity (Klingberg, 2014). It may be that genetics predispose a certain rate or timing of myelination between cortical areas involved in a cognitive task, such as fronto-parietal connections for tasks of attention and working memory, independently of environmental influences or training. It is also possible there are interactions between genetic predispositions to myelination and brain maturation in specific networks during training of that cognitive task.

Learning new skills likely occurs in parallel with brain maturation during development, influenced both by the environment and experience as well as genetic influences on rate and timing of brain maturation. One approach to assessing the relative influence of brain maturation on cognitive performance at different stages of development is to utilize cross-sectional and longitudinal analyses to assess the variability in performance at different ages. By assessing the relative contribution of changes in regional brain structure in this way, we can gain a better understanding of how the relationship between regional brain structure and cognition changes during development. Therefore, these analyses include both cross-sectional and longitudinal analyses, which serve unique purposes for assessing variability in the relationship between cognition and brain structure during development. Cross-sectional analyses will make use of the "baseline" data for each participant, acquired during their first visit. This allows us to assess the variability in performance among children before factors such as practice effects can influence the behavioral measures. The baseline data is also, by definition, composed of children of a younger age relative to the whole longitudinal cohort. This will allow us to describe the degree of individual variability present in regional brain structure and domain-specific cognitive performance in this slightly younger cohort, and later to compare these results to similar analyses when including the entire longitudinal cohort. The baseline data is also, by definition, a smaller dataset relative to the entire longitudinal cohort. The cross-sectional analyses on the baseline data can therefore serve as a sort of pilot study to determine the presence of any correlations between specific, hypothesized cortical regions and/or white matter tracts and task

performance. In other words, we can determine whether or not there seems to be any regional specificity in the relationships between neural structure and task performance, as opposed to global relationships or no relationships, before moving on to more complex analyses involving longitudinal cohorts. At this stage, we can also assess any age by region interactions that may affect task performance and that may become more or less pronounced at later ages. For example, previous research has suggested that younger and older children may rely on recruitment of different neural regions when performing a given task (Scherf et al., 2006; Olesen et al., 2003; Holland et al., 2007). However, cross-sectional studies fall short of predicting developmental trends. In order to fully understand how individual differences in brain structure relate to different aspects of cognition during development, we must use longitudinal imaging paradigms. Following the cross-sectional analyses, each cognitive domain will be assessed using the complete longitudinal cohort, allowing us visualize the developmental trajectory of each factor and to utilize a much larger dataset.

The human brain undergoes dynamic structural changes during development that are protracted into adulthood. The use of longitudinal data in studying cognitive and brain development allows for the evaluation of developmental trajectories, rates of change, and dissociating global, stable patterns of development from domain-specific or region-specific trajectories. The use of longitudinal data also results in an increase in power and sensitivity to detect and measure relationship between developing cognition and brain structure. This research utilizes linear mixed-effects models to investigate how age,

gender, and changes in regional brain structure are related to changes in cognitive performance in a longitudinal, typically developing cohort.

1.6 Summary of Background and Significance

These analyses aim to evaluate the relationship between phonological processing, spatial working memory, and motor inhibitory performance and the regional brain structure of both cortical regions and white matter tracts hypothesized to underlie these functions, utilizing both cross-sectional and a longitudinal analyses on a typically developing cohort. Utilizing these three separate cognitive domains will allow us to answer questions about the distinctiveness of their behavioral and neural correlates, and examine whether or not these domains reflect some common mechanism or variance such as memory capacity or attention. From these analyses, we may be able to determine if and how cognitive development depends on the development of specific neural circuitry and if so, whether or not the relationship between the development of domain-specific neural circuitry and a specific cognitive domain is dissociable from other domain-specific neural circuitry and another cognitive domain. Understanding how developing brain structure relates to domain-specific cognitive performance would allow us to assess what type of variability is typical during normal development, how the relationship between brain structure and cognition changes over time, and what factors may contribute to a child's future performance in different areas.

1.7 General Methods

1.7.1 Participants: Pediatric Longitudinal Imaging, Neurocognition, and Genetics (PLING) study

All analyses will include a subset of data from the Pediatric Longitudinal Imaging, Neurocognition, and Genetics (PLING) study. This is a longitudinal study of typically developing children carried out at University of California, San Diego with data collection beginning in 2010 and concluding in 2016. Prior to participation, subjects under 7 years old provided verbal assent, subjects over 7 years old provided written assent, and parents or guardians provided written consent after an oral description of the study was provided. Subjects had to be able to understand directions presented in English and have normal or corrected-to-normal hearing and vision. Subjects were screened for neurological disorders, significantly preterm birth, daily illicit drug use by the mother during pregnancy for more than one trimester, a diagnosis of autism spectrum disorder, mental retardation, bipolar disorder or schizophrenia in the participating child, and any head trauma with loss of consciousness lasting more than 30 minutes.

For each of the cognitive domains and tasks examined in this dissertation, there will be a different subset of participants who have completed different tasks on a different number of visits. Therefore, although all participants in this body of work originate from the PLING study, the study-specific population for each analysis may differ. In addition, some participants in the PLING study were enrolled from a previous cross-sectional study (PING), in which many of the same measures were studied. The target enrollment age for PLING was 5-8 years old, although this requirement was flexible in order to

improve recruitment and retention of siblings from the same family who may not fall precisely within the target age range. The target age range of the previous cross-sectional study, PING, was 3-20 years old. So for some analyses, particularly the phonological processing analyses, there may be participants as young as 4-5 years old who have taken the cognitive tasks of interest – those subjects who began in the cross-sectional PING study at a younger age and then continued on into the PLING study. Therefore, the age range of PLING participants in the following analyses ranges from 4.25 to 13 years old at their first visit, with the average age of the first visit occurring between 6-7 years old.

1.7.2 Neuroimaging Data Acquisition

All neuroimaging data were collected at UC San Diego using the PING protocol (see Jernigan et al., 2016 for details). The protocol involves acquiring multiple modality, high-resolution MRI images. Participants underwent a one-hour imaging session including acquisition of TI, T2 and diffusion weighted images. All data were evaluated for quality at multiple stages during processing, including registration, motion-correction and removal of artifacts, using automated quality control systems as well as visual inspection from trained technicians. Automated protocols available in Freesurfer (Fischl, 2012) in addition to analyses developed at UC San Diego Multimodal Imaging Laboratory were used for processing and morphometric analysis. During manual inspection of the imaging data, expert raters left quality control (QC) ratings and notes for each acquisition. In addition to using numerical QC values to reject poor imaging data, the expert rater notes were also used to screen out suspect imaging data. Notes were

examined on a case-by-case basis and examples of notes that were used as grounds for excluding imaging data include “borderline”, “excessive motion”, or “motion artifacts impact surfaces”.

1.7.3 Behavioral Quality Control

During data collection, test administrators recorded notes regarding test conditions including technical issues, behavioral observations of the participant, and anything else they deemed relevant. These notes were used to create a “quality control” (QC) rating. Two independent, expert test administrators used the administrator notes to assign a QC rating of 0, 1, or 2. A QC rating of 0 indicated no test administration notes and/or no test administration issues. A QC rating of 2 reflected notes suggesting the test results were not valid, most frequently due to compliance issues such as not following instructions with repeated correction from the test administrator or indications that the child was not paying attention to the task or not attempting to complete the task. A QC rating of 1 indicated there were test administration notes that were of mild or moderate consequence: it was not immediately clear if the notes indicated a severe enough problem that the data point should be thrown out without review. QC 1 ratings were evaluated by the investigator on a case-by-case basis to determine if they should be left in or excluded based on the investigator’s hypothesis and how restrictive they want to make their screening criteria. For the analyses included here, all QC scores of 2 were removed.

The primary investigator (LC) manually inspected all QC ratings of 1 for the three behavioral tasks of interest here. These scores were grouped into further categories such

as “mild behavioral issues”, “technical issues”, and “non-compliance”. These QC ratings of 1 were resolved into either QC 0 and kept in the analyses, or QC 2 and removed from the analyses. Further explanations of included and excluded behavioral data can be found in the methods section for each aim.

1.7.4 Behavioral Data Transformations

For all primary analyses, all predictors were centered (demeaned) to standardize and ease interpretation of the effects, with the exception of the scanner variable(s), which were nuisance variables.

Preliminary inspection of the behavioral measures of interest suggested heteroskedasticity for the stop-signal task measuring response inhibition, so a log transform was used on the SSRT as a variance-stabilizing transformation. Tests for heteroskedasticity on baseline data of the other two tasks (blending words and between-search errors) suggested no heteroskedasticity, therefore no transform was used. For the stop-signal task (SSRT) and the between-search errors task (BSE), scores were inverted for all analyses so that higher scores indicated better performance (i.e. faster reaction times and lower error counts) to ease interpretation of relationships.

CHAPTER 2: STRUCTURAL NEURAL CORRELATES OF PHONOLOGICAL PROCESSING IN A TYPICALLY DEVELOPING COHORT

2.1 Introduction

The ability to recognize and maintain speech sounds in working memory is important for language learning, yet we know relatively little about the structural correlates of individual variability in phonological awareness during typical development. Phonology, semantics, grammar, pragmatics, the lexicon, and discourse are all aspects of language that have to be experienced, learned, and practiced during development. Children's performance on various language tasks, such as picture vocabulary and oral reading, increase nonlinearly from the ages of five to twenty years old (Akshoomoff et al., 2014). One of the more foundational aspects of language learning in typically developing children is phonological awareness and processing – the level at which speech sounds come together to form words. Without intact and typically developing phonological systems, children have difficulty reaching stages of word recognition and meaning, semantics, and grammar in spoken language. Phonological processing abilities are highly related to reading and writing skills. Evidence from intervention-based and longitudinal studies suggests that better phonological processing can lead to better reading skills (Bentin, 1982; Ehri, 1987; Griffith & Olson, 2004; Tangel & Blachman, 1992; Wagner, Torgesen, & Rashotte, 1994; Wagner et al., 1997).

Phonological working memory is necessary for the storage and manipulation of linguistic information for cognitive manipulation or interpretation. The development of this system involves both a phonological buffer to recognize and store phonological input

and an articulatory system for internal rehearsal and communication. Relevant information may also be retrieved from long-term memory to assist the recognition and interpretation of speech sounds, which can go on to activate a cascade of relevant memories and information as language skills develop. Although many studies have investigated the brain regions thought to underlie language comprehension and production, fewer studies focus on the structural regions related to the acquisition of phonological awareness in children.

Research into the cortical areas involved in language processing has suggested a dual-stream model of language processing and production (Hickcok & Poeppel, 2004, 2007; Dick & Tremblay, 2012). The model proposed by Hickock & Poeppel suggests a ventral stream for processing speech information involved in comprehension and a dorsal stream for mapping acoustic speech information to the articulatory regions in the frontal lobe. This model posits that the ventral stream functions bilaterally to map sound onto meaning, but the dorsal stream relies on left-dominant structures for rehearsal and articulation (Hickock & Poeppel, 2004). In addition, the proposed model specifies the inferior frontal gyrus (IFG), premotor cortex, and anterior insula are involved in articulation, and the mid-posterior superior temporal sulcus (STS) is involved in phonological processing. Similarly, Dick & Tremblay propose a dorsal processing stream involved in matching auditory speech to motor representations and a ventral processing stream involved in attributing meaning to auditory speech (2012). More nuanced investigations into the neural correlates of language have shown evidence of a more widespread network and activation that depends heavily on specific task demands. Other

areas involved in language tasks can include middle and inferior temporal areas, fusiform and angular gyri, and prefrontal areas (Powell et al., 2006; Binder et al., 1997). Reviews on the functional correlations of speech processing suggest that bilateral regions in the temporal lobe process the incoming sounds at earlier stages of speech processing, and lateralization occurs further downstream (Hickock & Poeppel, 2007; Binder et al., 2000). Specifically, temporal regions such as the bilateral mid to posterior superior temporal sulcus (STS) play a role in phonological processing of speech sounds (Hickok & Poeppel, 2007, Price, 2000). The left middle STS has also been shown to respond more strongly to familiar consonant-vowel sounds compared to similarly complex, non-language sounds (Liebenthal et al., 2005).

There is evidence that over the course of development, as language learning progresses from early foundational speech recognition to the development of complex lexicons and extraction of semantic meaning, different brain regions are recruited as the underlying network becomes more specialized (Holland et al., 2007). In general, language function is thought to elicit higher functional activation in the left hemisphere towards the end of development, but this observed lateralization in function depends heavily on age as well as the task used to measure language function and the brain region examined (Holland et al., 2007). A large cross-sectional study of children ages 5-18 used a variety of language and control tasks to demonstrate that functional activation becomes more lateralized as a child gains domain-relevant expertise (Holland et al. 2007). Shtyrov and colleague (2005) found reliable left hemisphere dominance in functional activation when phonetic sounds (as opposed to noise) were placed in a word context. This may

suggest that language laterality is constrained by processing sound units as frequently occurring and meaningful items that can be linked to a memory. This also highlights the unique neural response of developing children to language-specific auditory stimuli.

Diffusion tensor imaging (DTI) and tractography have been used to investigate ventral and dorsal pathways hypothesized to be involved in language processing (Parker et al 2005). An area of posterior temporal lobe known as Wernicke's area is thought to be involved in recognition and comprehension of speech, while the frontal region known as Broca's area is thought to be important for spoken and expressive language. These two cortical areas are connected by a major white matter tract known as the arcuate fasciculus (Catani et al., 2005). The arcuate fasciculus, which composes the dorsal language pathway, is also known as the temporal branch of the superior longitudinal fasciculus (tSLF). Anatomically, this tract extends from posterior temporal lobe through the parietal lobe into inferior frontal regions (Catani et al., 2008; Hagler et al., 2009). Research exploring the relationship between developmental dyslexia and white matter integrity suggest that white matter regions underlying mid-to-posterior temporal areas, such as the arcuate fasciculus and the inferior longitudinal fasciculus, may be involved in phonological awareness (Saygin et al., 2013).

Research combining functional imaging with diffusion tensor imaging suggest asymmetries in the white matter tracts connecting Broca's and Wernicke's areas, with slightly larger tract volumes and higher fractional anisotropy in the left hemisphere (Powell et al., 2006; Parker et al, 2005). In addition, there was a positive correlation between subjects with more lateralized functional magnetic imaging results and more

lateralized white matter morphology (Powell et al., 2006). The white matter tracts in the ventral language pathway were also shown to be stronger in the individual's dominant hemisphere, in line with previous work on the laterality of language processing (Parker et al, 2005). In a study evaluating the relationship between regional white matter and ability to learn novel speech sounds, participants who were better phonetic learners had more white matter in left parietal regions. A similar pattern was found for learning rapidly-changing stimuli as opposed to steady tones, suggesting those participants might be more efficient at processing temporal variation in auditory stimuli (Golestani et la., 2002). In general, there seems to be evidence for some lateralization of language processing, although at what stage of language learning and language processing this occurs in a typically developing cohort is not well understood. In addition, there is evidence for the protracted development of white matter tracts, including those associated with language, throughout childhood and adolescence (Asato et al., 2010). This highlights the importance of evaluating changes in brain regions underlying phonological processing over the course of development in a longitudinal, typically developing cohort to form a more complete picture of the processes by which the foundations of language are formed.

Currently, there is little work defining the developmental trajectories of the cortical and white matter pathways thought to underlie phonological awareness in typically developing children. Furthermore, the process by which lateralization occurs and at what rate is not well understood. The following aims would outline the relationship between phonological performance and regional cortical and white matter structure in a typically developing cohort of children and adolescents. Here, we focus on

a phonological processing task from the Comprehensive Tests of Phonological Processing (CTOPP) battery called the Blending Words task. This subtask targets the phonological loop and language-specific working memory system by utilizing common English words of increasing difficulty while avoiding image-dependent stimuli that may depend more heavily on visual systems rather than language-specific auditory systems. In summary, this aim seeks to examine the relationship between regional cortical and white matter and phonological performance in a group of typically developing children.

2.1.1 Task: Comprehensive Tests of Phonological Processing (CTOPP): Blending Words (BW) subtest

The Comprehensive Test of Phonological Processing (CTOPP) is a battery of tests that was developed for use in both clinical evaluation and research. The term "phonological processing" refers to the use of phonological information, specifically the sound structures of a person's spoken language, in processing and evaluating both written and oral language (Jorm & Share, 1983; Wagner & Torgesen, 1987). The CTOPP battery segments phonological processing into three types: phonological awareness, phonological memory, and rapid naming. Phonological awareness, which is defined by an individual's access to and awareness of the sound structure of his or her primary language (Mattingly, 1972), is our primary domain of interest. Tests of phonological awareness consist of subtests evaluating a child's ability to put together a string of auditorily presented phonemes to form an English word [blending words], repeating a given word after removing one of its phonemes [elision], listening to a repeating non-word [nonword

repetition] and sound matching. For our investigation, we focused on the blending words subtest, which evaluates a child's ability to take distinct English phonemes and combine them to form a coherent English word. We chose this particular subtask for its relevance to language learning and its previously demonstrated associations with specific areas of the brain in contrast to the other subtasks available (Saygin et al., 2013). In the blending words subtask, participants are auditorily presented with a series of phonemes and are asked to combine the phonemes and verbally repeat back the resulting word; e.g. /t/oy/ = "toy". Scores reflect the number of correct responses out of 20 possible items (see appendix for details). In a normative sample of typically developing children, scores ranged from an average of 5 points for 5-year-olds to an average of 16 points for subjects aged 15 years and up. In this normative sample, the correlation between blending word scores and age was r=0.57 (CTOPP instructional manual). In the current cohort, the correlation between blending word scores and age was r=0.60.

2.1.2 Behavioral Quality Control

For the CTOPP blending words task, the expert rater QC ratings of 0 were included in the cohort and the QC ratings of 2 were excluded. The QC ratings of 1 were reviewed by the primary investigator (LC) on a case-by-case basis to determine which observations should be included or excluded. Among the QC ratings of 1, comments were generally categorized into three areas:

A. Administrator errors:
    a. Example: "skipped/not in folder/not administered", "standardization"

B. Technical issues:

    a. Example: “program crashed in the middle, correct answers recorded on paper”, “had problems replaying”

C. Performance observations:

    a. Example: “had a hard time #4”, “was sick and hard to understand”

Among the QC 1 ratings, “A” type comments were left in the cohort since these few cases of administrator error usually referred to a missing page in the test packet that was remedied or in one case, to standardization errors based on inaccurate age, which doesn’t apply in this case since we are utilizing raw scores. Among the “B” type technical issues, one referred to problems replaying the stimuli, which is usually a rare occurrence during test administration and does not necessarily invalidate the participant’s response; there was likely just a longer delay between presentations. This datapoint was left in. The other technical issue indicated that the script used to play the audio recordings crashed, and it was inferred that the test administrator switched to another method (such as vocal), which may affect performance, so this data point was removed. The “C” type comments regarding performance observations included one observation of a specific test item; this datapoint was left in as it did not appear to invalidate the test results. The other performance observation described the participant as sick and hard to understand, which could affect both performance and scoring, and so this datapoint was removed. Among the 8 QC1 data points in the BW cohort:

A (administration.): 4 converted to QC0

B (technical): 1 converted to QC0; 1 converted to QC2

C (performance): 1 converted to QC0; 1 converted to QC2

In total, among the 8 QC1 data points for Blending Words, 6 were converted to QC0 and kept in the cohort, 2 were converted to QC2 and excluded.

2.1.3 Regions of Interest

The CTOPP blending words task requires subjects to listen to a string of auditorily presented phonemes and then to articulate the resulting word. Due to the specific demands of this task, the primary regions of interest are those hypothesized to be involved in the retention of phonemic information and articulation, as described by Hickock & Poeppel (2004, 2007), Scott and Johnsrude (2003), and Dick and Tremblay (2012). The primary cortical region of interest is the bilateral posterolateral temporal region for auditory processing of phonemic information. This region of interest was extracted from work done by Chen et al. (2012), which is the result of a fuzzy clustering algorithm based on genetic contribution. This parcellation scheme best matched the posterior region of the temporal cortex that was of interest, as opposed to other available parcellation schemes that segmented the temporal cortex into superior, middle, and inferior. The measurement units for the surface area of this region are arbitrary and not the typical squared millimeters (mm^2) due to the fuzzy clustering algorithm. However, thickness of the region is still measured in mm. White matter tracts of interest focus primarily on the arcuate fasciculus, which extends from the posterior temporal lobe into the superior and inferior frontal lobe, and the inferior longitudinal fasciculus, which extends anteriorly-posteriorly through the temporal lobe and connects posterior temporal

regions with areas thought to be involved in articulation in the frontal lobe. Both fractional anisotropy and mean diffusivity is examined.

2.1.4 Participants

All participants came from the pediatric longitudinal imaging, neurocognition and genetics (PLING) database at UC San Diego (Jernigan et al., 2016). Participants were only included in these analyses if they had complete data for their first visit (referred to as "baseline"), meaning they had both behavioral and imaging data that passed quality control metrics for their first visit in the study. In addition, only native English speakers were included in the analyses, although a subset of participants were bilingual. All participants are typically developing children between the ages of 5 and 13 years. A total of 77 children were included in the analyses (40 male, 37 female). The average age of the children at baseline was 6.80 years (s.d. = 1.23 years). Additional demographic information such as parental education, household income, handedness, and race/ethnicity are presented in Table 2.1 below.

Table 2.1 Demographic information for the CTOPP Blending Words cohort

Demographics		Total	Male	Female
Number of participants (M/F)		77	40	37
Parental Education*		6.4(0.9)	6.2(0.9)	6.6(0.8)
Household Income*		7.4(1.7)	7.2(1.5)	7.6(1.8)
Handedness (R/L/Amb)		62/14/1		
Monolingual/Bilingual		66/11		
Race/Ethnicity*				
Caucasian		55		
African American		3		
Hispanic/Latino		18		
Asian		3		
Pacific Islander		1		
Mixed Race		12		
Other/ Unknown		3		
Age	Baseline (N=77)	6.79(1.24)	7.02(1.26)	6.55(1.18)
(mean, s.d.)	Time point 2 (N=58)	7.90(1.22)	8.03(1.25)	7.74(1.19)
	Time point 3 (N=46)	8.84(1.21)	9.08(1.24)	8.54(1.12)
	Time point 4 (N=45)	10.03(1.19)	10.33(1.25)	9.68(1.04)
	Time point 5 (N=16)	10.98(1.33)	11.65(1.54)	10.58(1.07)
	Time point 6 (N=2)	12.38(0.64)	NA	12.38(0.64)
Blending words	Baseline (N=77)	11.30(4.22)	11.25(4.39)	11.35(4.10)
(mean, s.d.)	Time point 2 (N=58)	13.67(4.22)	13.94(3.56)	13.37(2.37)
	Time point 3 (N=46)	14.58(2.74)	14.04(3.14)	15.23(2.05)
	Time point 4 (N=45)	14.73(3.38)	14.79(3.54)	14.67(3.28)
	Time point 5 (N=16)	15.88(2.60)	15.50(3.94)	16.10(1.60)
	Time point 6 (N=2)	17.50(0.71)	NA	17.50(0.71)

* Parental Education scale: 1 (less than 7 years); 2 (7-9 years); 3 (10-11 years); 4 (High School Diploma); 5 (1-3 years of college); 6 (Bachelor's Degree); 7 (Professional Degree, e.g. Masters, Doctorate, MD, JD). 10 participants were missing Parental Education information and were excluded from the summary statistics in this table.

* Household Income scale (annual): 1 (less than $5,000); 2 ($5-9,999); 3 ($10-19,999); 4 ($20-29,999); 5 ($30-39,999); 6 ($40-49,999); 7 ($50-99,999); 8 ($100-199,999); 9 ($200-249,999); 10 *$250-299,999); 11 ($300,000 or more). 10 participants were missing Household Income information and were omitted from the summary statistics in this table.

* Handedness: 1 participant did not identify handedness, or reports of handedness varied by task/questionnaire.

* Participants were free to mark whichever race/ethnicity options they chose: if multiple races were checked, s/he was categorized as ''Mixed race''; if none was selected, s/he was categorized as ''Other/Unknown". Some participants marked only ''Hispanic/Latino'', while others marked ''Hispanic/Latino'' in addition to a race. Therefore, the total number reported in each category does not sum to the total number of participants.

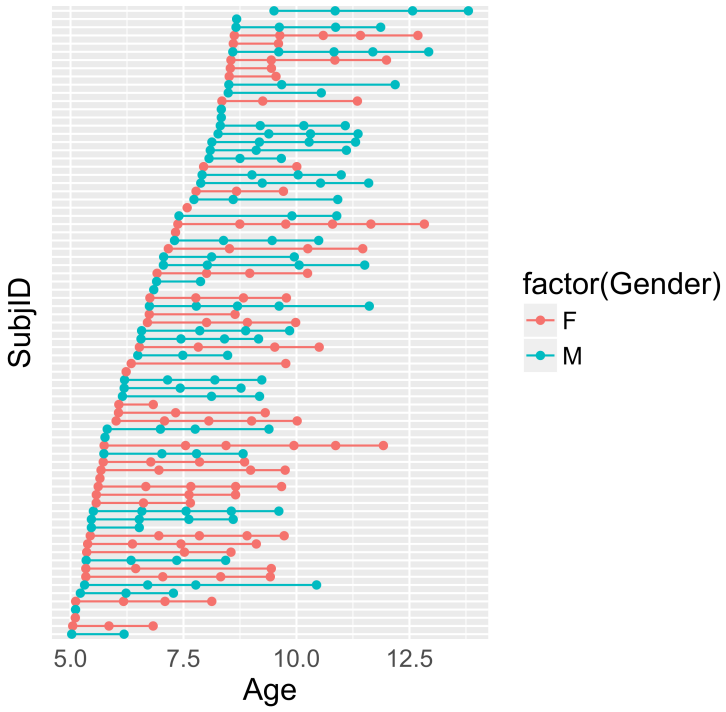

Figure 2.1. Summary of longitudinal CTOPP Blending Words cohort

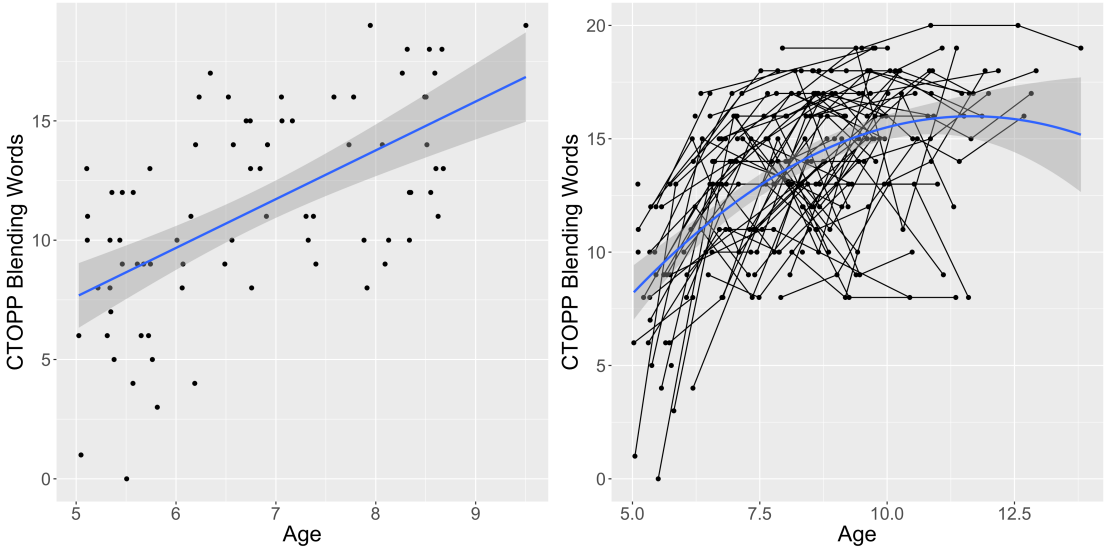

Figure 2.2. Predicting phonological performance scores as a function of age for the baseline cohort (left) with a linear fit line and the longitudinal cohort (right) with a quadratic fit line.

2.1.5 Behavioral results

Behavioral scores on the CTOPP BW ranged from 0 to 19 in the baseline cohort, with an average score of 11.3(s.d.=4.2). Scores ranged from 0 to 20 in the longitudinal cohort with an average score of 13.5 (s.d.=3.8). First, we examined the effects of age and gender on behavioral performance at the first visit (baseline). Age showed a strong and significant relationship, as expected (t=6.66, p<0.00) whereas gender did not show a significant relationship to performance (t= -1.40, p=n.s.).

Table 2.2. Effects of age and gender on CTOPP Blending Words performance in the baseline cohort

Predictors	*B* value	*t* value	*p* value
Age	2.13	6.66	0.000***
Gender	-1.10	-1.40	0.167

All predictors have been centered (demeaned)
Female is coded as negative

When examining the effect of age and gender on performance in the longitudinal cohort, we observe both linear and nonlinear effects of age, so both age terms were included in all primary analyses for the longitudinal cohort. Gender did not show a significant relationship to performance.

Table 2.3. Effects of age and gender on CTOPP Blending Words performance in the longitudinal cohort

Fixed Effects	*B* value	*t* value	*p* value
Age	1.11	10.35	0.000***
Age^2	-0.20	-4.70	0.000***
Gender	-0.81	-1.45	0.150

Random effect: Subject
All predictors have been centered (demeaned)
Female is coded as negative

Preliminary models exploring the effects of bilingual status, parental education, and household income on behavioral performance while controlling for age and gender suggested no relationship.

2*.1.6 Methods*

For both the cortical and white matter regions of interest, two series of analyses were conducted (as described in section 1.5, above): the first was done using only the baseline data as a way to investigate individual differences and the degree of individual variability at the start of the study. The second set of analyses were carried out using the longitudinal data, as a way to investigate the relationship between task performance and brain structure in a larger, typically developing cohort. The following results are presented first for the baseline-only data, and then for the longitudinal data.

2.2 Specific aim 1: To investigate the relationship between posterolateral temporal structure and phonological processing

2.2.1 Region of interest

The bilateral posterolateral temporal area was chosen from a set of genetically informed cortical surface area parcellations (Chen et al., 2012). To create this parcellation, a fuzzy clustering algorithm was used to analyze a genetic correlation matrix for vertex-wise estimates of relative cortical surface area expansion in a large twin study. For the cortical region of interest, a Bonferroni correction of p=0.025 was used to account for the two measures examined (surface area and thickness).

2.2.2 Baseline

Primary analyses on the baseline cohort used multiple linear regression models to evaluate the relationship of age, gender, and hypothesized bilateral region of interest on performance. When examining regional surface area, total surface area was included as a covariate. Scanner was included as a covariate of no interest. Among the 77 participants, 3 were collected on scanner 1 and 74 were collected on scanner 2. Scanner 2 had undergone a software update during the course of the study, so "scanner" in the following models has been coded to reflect unique combinations of scanner + software version. Among the 74 participants scanned on scanner 2, 38 participants were scanned using software A and 36 were scanned using software B.

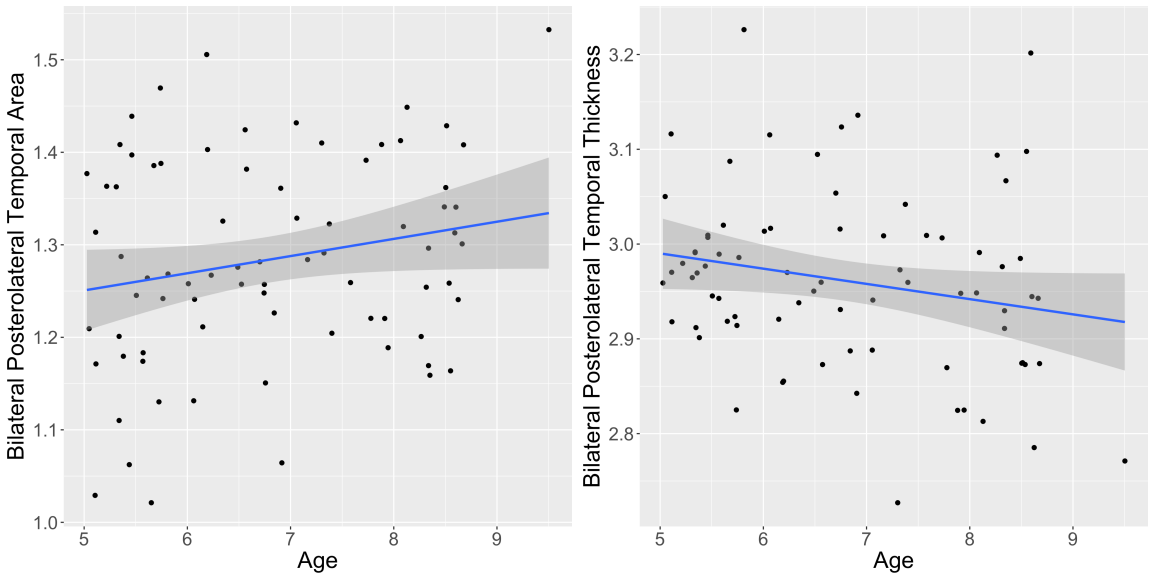

Figure 2.3 Bilateral posterolateral temporal area (left) and thickness (right) in the baseline cohort with a linear fit line (blue).

2.2.2.1 Results

In a model predicting blending words scores from bilateral posterolateral temporal cortical area while covarying for age, gender, total cortical area, and scanner, our primary region of interest was positively related to performance (t=2.40, p=0.02). Age was also a significant predictor, as expected (t=6.36, p<0.00). Total cortical area was also significant, but in the opposite direction (t=-2.01, p=0.05). This suggests that having a relatively or proportionally larger bilateral temporal surface area is related to better performance.

In a model predicting blending words scores from bilateral posterolateral temporal cortical thickness and covarying for age, gender, and scanner, the only significant predictor was age (t=6.38, p<0.01).

Table 2.4. Effect of bilateral posterolateral temporal (PLT) area and thickness on performance in the baseline cohort

Predictors	*B* value	*t* value	*p* value
Model 1 (Area)			
Age	2.03	6.36	0.000***
Gender	-1.40	-1.43	0.157
Bilateral PLT area	21.08	2.40	0.019*
Total area	-0.00	-2.01	0.048*
Scanner1	2.13	1.01	0.316
Scanner2	1.33	0.63	0.534
Model 2 (Thickness)			
Age	2.11	6.38	0.000***
Gender	-1.07	-1.27	0.210
Bilateral PLT thickness	-0.62	-0.14	0.889
Scanner1	0.83	0.39	0.695
Scanner2	0.18	0.09	0.931

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Follow-up models examined the right and left posterolateral temporal area in separate models, including the same covariates as above. In both models, age was a significant predictor of performance, as expected. The left posterolateral temporal area did not quite reach significance (t=1.89, p=0.06), whereas the right posterolateral temporal area did reach an unadjusted level of significance (t=2.18, p=0.03). No other predictors reached significance, although total area was trending in the right posterolateral temporal area model (t=-1.72, p=0.09). Given these results, there does not seem to be strong evidence for a unilateral hemispheric effect. Separate models exploring interactions between age, gender, and left and right PLT area found no evidence of any interactions. Finally, in post-hoc models exploring the relationship of global cortical effects on performance neither total cortical area nor mean cortical thickness approached significance. Therefore there does not seem to be a relationship between global cortical morphology and performance.

2.2.3 Longitudinal

We tested our primary hypothesis for the longitudinal cohort using linear mixed-effects regression models to predict CTOPP BW scores from cortical surface area and thickness of the bilateral posterolateral temporal (PLT) region. We co-varied for age, gender, and scanner by entering them as fixed effects in the model, while subject was entered as a random effect. Total cortical surface area was also included as a covariate in the surface area model. If the primary analysis investigating the contribution of the bilateral PLT was significant, follow up analyses examined the left and right PLT in

separate models. A Bonferroni correction of 0.05/2 = 0.025 was used for the two primary models of interest (bilateral surface area and bilateral thickness).

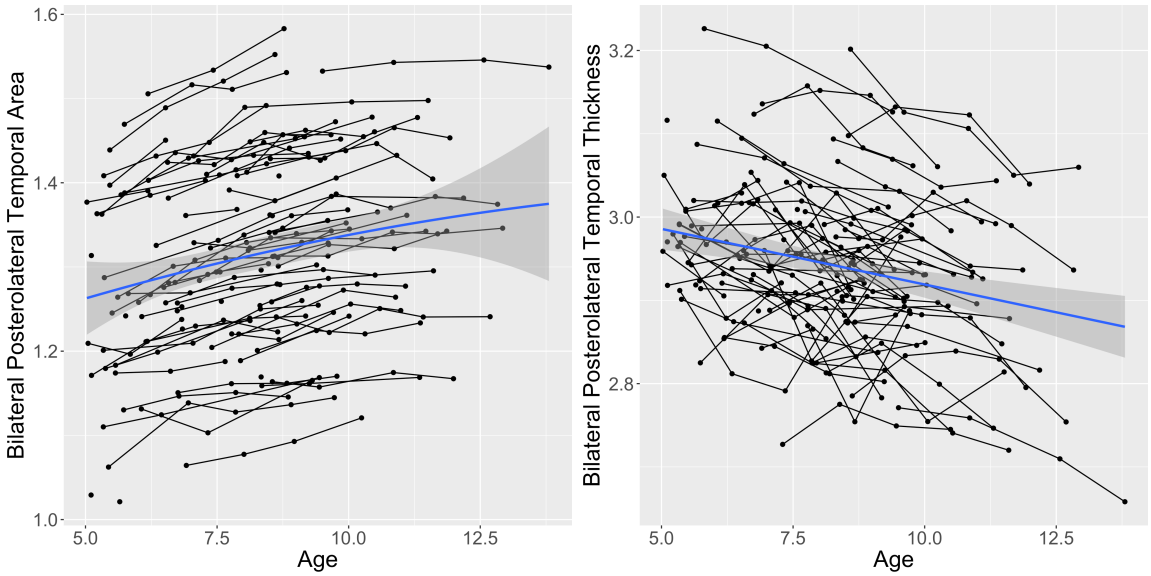

Figure 2.4. Bilateral posterolateral temporal surface area (left, quadratic fit line) and thickness (right, linear fit line) by age with shaded 95% confidence intervals.

2.2.3.1 Results

In the model investigating the relationship of bilateral PLT area to performance, both linear and quadratic age terms were significant predictors of performance. The relationship between bilateral PLT surface area and performance did not survive our correction for multiple comparisons, and there were no other significant effects, although total area was trending in the negative direction. In the model investigating bilateral PLT thickness, both linear and nonlinear age effects were still significant predictors of performance, but there was no relationship between bilateral PLT thickness and performance. These results are broadly consistent with the baseline analyses conducted in

the previous section. However, the relationship between the bilateral PLT area and performance failed to reach significance in the longitudinal cohort.

Table 2.5 Effects of bilateral posterolateral temporal (PLT) area and thickness in the longitudinal cohort.

Fixed Effects	*B* value	*t* value	*p* value
Model 1 (Area)			
Age	1.27	7.35	0.000***
Age^2	-0.18	-4.10	0.000***
Gender	-0.89	-1.36	0.178
Bilateral PLT area	11.97	2.06	0.041*
Total area	-0.00	-1.84	0.068
Scanner1	0.14	0.08	0.933
Scanner2	0.00	0.00	0.999
Scanner3	-0.96	-0.54	0.590
Model 2 (Thickness)			
Age	1.35	7.75	0.000***
Age^2	-0.18	-4.12	0.000***
Gender	-0.76	-1.35	0.183
Bilateral PLT thickness	2.10	0.74	0.460
Scanner1	-0.13	-0.08	0.937
Scanner2	-0.20	-0.12	0.904
Scanner3	-1.21	-0.68	0.499

Random effect: Subject

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Post-hoc models investigated any potential effects of total cortical area or mean cortical thickness on performance. In models including the same covariates as above, neither global cortical measure approached significance when predicting blending words performance.

2.3 Specific Aim 2: To investigate the relationship between the inferior longitudinal and arcuate fasciculi and phonological processing

2.3.1 Regions of interest

The white matter regions of interest for the CTOPP blending words task were the arcuate fasciculus (AF) and the inferior longitudinal fasciculus (ILF) (Saygin et al., 2013; Dick & Tremblay, 2012). These tracts of interest were extracted from AtlasTract (Hagler et al., 2009), which uses a probabilistic atlas derived from previous results of manual tractography of major fiber tracts in normal subjects to define tract ROIs. In this atlas, the arcuate fasciculus is notated as the temporal branch of the SLF, or the tSLF. A Bonferroni correction of 0.05/4 = 0.0125 was used to adjust for the two tracts of interest and the two parameters examined (FA and MD). If there is evidence of a relationship between the microstructure of the tract of interest and performance, follow-up analyses will include average FA or MD from all fibers to determine if the effect is region-specific.

2.3.2 Baseline

Primary analyses on the baseline cohort used multiple linear regression models to evaluate the relationship of age, gender, and hypothesized bilateral region of interest on performance. Scanner was included as a covariate of no interest, similar to above (Section 2.2.2).

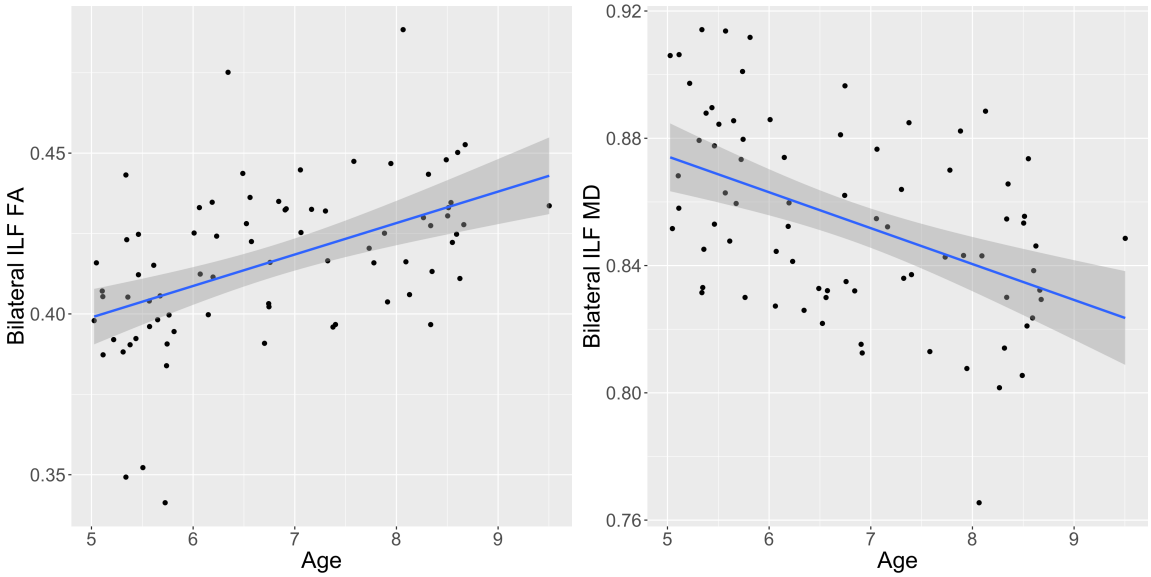

Figure 2.5 Bilateral ILF FA (left) and MD (right) with a linear fit line and shaded 95% confidence intervals.

2.3.2.1 Results

When covarying for age, gender, and scanner, bilateral ILF FA showed a significant relationship to blending words performance (t=2.91, p=0.005) where higher FA corresponded to better performance. However, bilateral ILF MD did not show a relationship to performance (Table 2.6). Age showed a strong, significant positive relationship to performance in both models, as expected.

In a follow-up model including total mean fractional anisotropy, the bilateral ILF FA remained significant (t=2.80, p=0.007) whereas total FA was not a significant predictor.

Table 2.6. Effects of bilateral ILF FA and MD on performance in the baseline cohort

Predictors	*B* value	*t* value	*p* value
Model 1 (FA)			
Age	1.62	4.61	0.000***
Gender	-1.01	-1.30	0.199
Bilateral ILF FA	53.27	2.91	0.005**
Scanner1	-1.12	-0.53	0.595
Scanner2	-01.45	-0.70	0.489
Model 2 (MD)			
Age	1.86	5.19	0.000***
Gender	-1.01	-1.24	0.218
Bilateral ILF MD	-23.24	-1.55	0.126
Scanner1	0.02	0.01	0.991
Scanner2	-0.61	-0.28	0.778

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Additional post-hoc models examined the left and right ILF FA in separate models and included total FA as a covariate. Results suggest that both the left and right ILF FA show a significant relationship to performance, although the effect may be slightly stronger in the right ILF FA (Table 2.7).

Table 2.7 Effects of right and left ILF FA on performance in the baseline cohort

Predictors	*B* value	*t* value	*p* value
Model 1 (Right)			
Age	1.83	5.15	0.000***
Gender	-1.19	-1.52	0.133
Right ILF FA	62.88	2.71	0.008**
Total FA	-33.39	-0.92	0.360
Scanner1	-1.94	-0.88	0.383
Scanner2	-2.27	-1.03	0.305
Model 2 (Left)			
Age	1.66	4.44	0.000***
Gender	-0.86	-1.08	0.286
Left ILF FA	50.11	2.33	0.023*
Total FA	-11.48	-0.35	0.730
Scanner1	-0.30	-0.15	0.884
Scanner2	-0.76	-0.37	0.715

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Post-hoc models examining interactions between age, gender, and ILF FA suggested no interactions. In a model examining interactions with the right ILF FA, the only significant terms were age and right ILF FA (t=2.46, p=0.02). In a model examining interactions with the left ILF FA, the only significant term was age. Therefore there does not seem to be any evidence of age interactions with ILF FA in the baseline cohort.

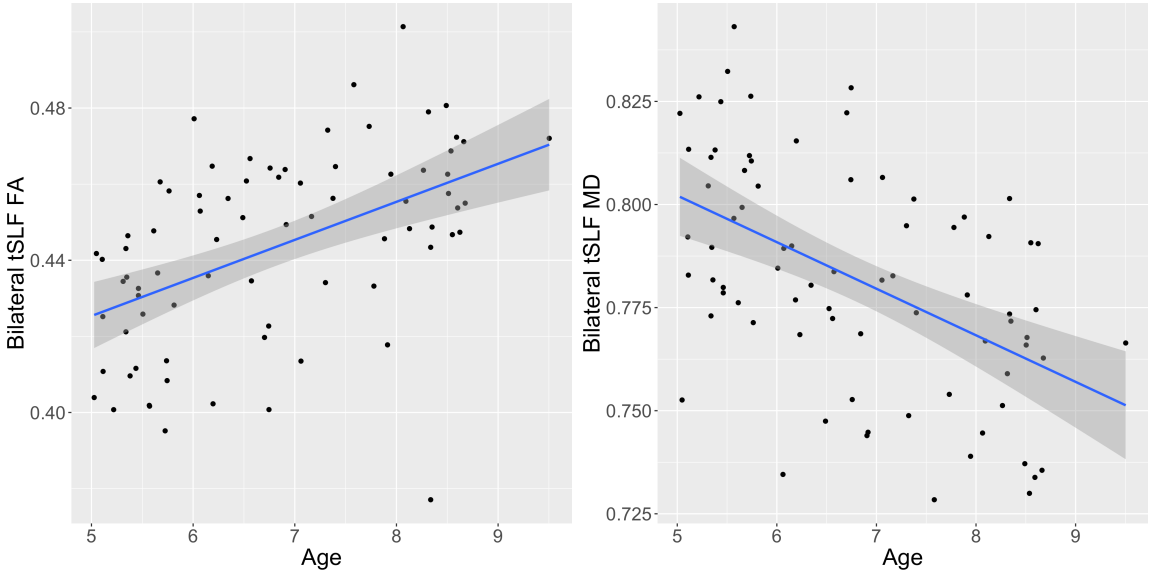

Figure 2.6. Bilateral tSLF FA (left) and MD (right) with a linear fit line and shaded 95% confidence intervals.

In primary models investigating the relationship between the bilateral tSLF and blending words performance in the baseline cohort, the only significant predictor in each model was age. Therefore there does not seem to be evidence for a relationship between tSLF FA or MD and blending words performance.

Table 2.8 Effects of tSLF FA and MD on performance in the baseline cohort

Predictors	*B* value	*t* value	*p* value
Model 1 (FA)			
Age	1.97	5.28	0.000***
Gender	-1.00	-1.22	0.227
Bilateral tSLF FA	14.67	0.80	0.428
Scanner1	0.63	0.30	0.766
Scanner2	0.07	0.03	0.974
Model 2 (MD)			
Age	1.91	5.00	0.000***
Gender	-0.91	-1.10	0.276
Bilateral tSLF MD	-4.59	-0.17	0.867
Scanner1	0.18	0.08	0.937
Scanner2	-0.56	-0.25	0.805

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Post-hoc models examining the effects of mean global FA and mean global MD in separate models suggested no effect on performance.

2.3.3 Longitudinal

We tested our primary hypothesis for the longitudinal cohort using linear mixed-effects regression models to predict CTOPP BW scores from the bilateral ILF and bilateral tSLF. We co-varied for age, gender, and scanner by entering them as fixed effects in the model, while subject was entered as a random effect. If the primary analysis investigating the contribution of the bilateral tract was significant, follow up analyses examined the left and right tract in separate models. A Bonferroni correction of 0.05/4 = 0.0125 was used for the four primary models of interest (ILF FA and MD, tSLF FA and MD).

2.3.3.1 Results

In the model examining the relationship between bilateral ILF FA and performance, both linear and quadratic age terms were significantly related to performance. The Bilateral ILF FA showed a trending relationship to performance but did not survive our correction for multiple comparisons. Similarly, the bilateral ILF MD showed a trending relationship to performance that did not survive our correction for multiple comparisons (Table 2.9).

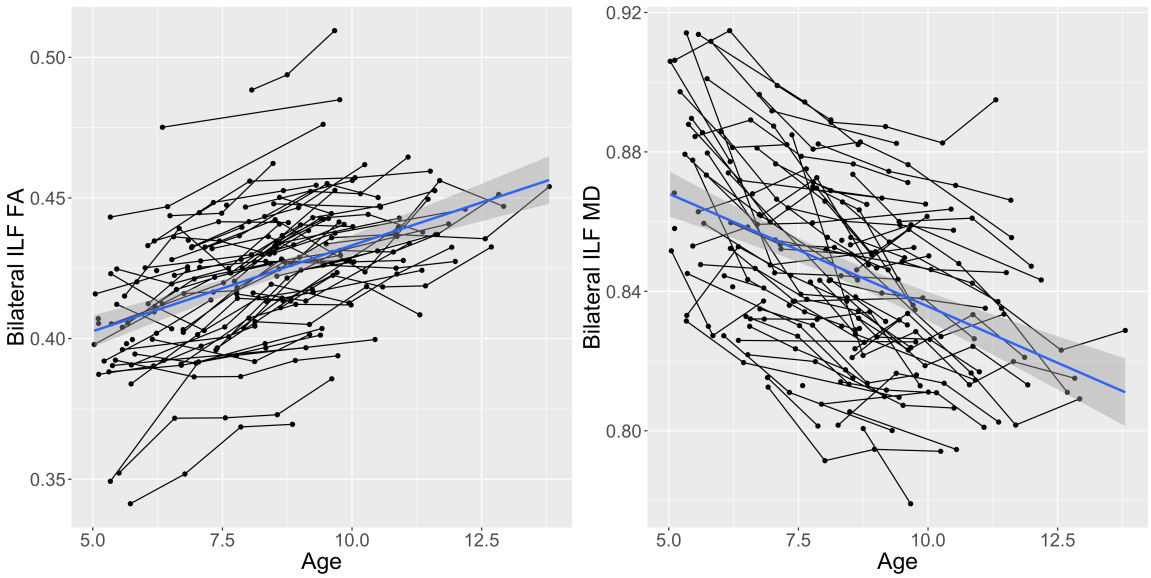

Figure 2.7 Bilateral ILF FA (left) and MD (right) with a linear fit line and shaded 95% confidence intervals.

Table 2.9 Effects of bilateral ILF FA and MD on performance in the longitudinal cohort

Fixed Effects	*B* value	*t* value	*p* value
Model 1 (FA)			
Age	1.11	6.02	0.000***
Age^2	-0.17	-3.98	0.000***
Gender	-0.88	-1.64	0.105
Bilateral ILF FA	29.76	2.46	0.015*
Scanner1	-0.79	-0.48	0.632
Scanner2	-0.72	-0.44	0.1663
Scanner3	-1.62	-0.91	0.364
Model 2 (MD)			
Age	1.17	6.48	0.000***
Age^2	-0.17	-3.90	0.000***
Gender	-0.80	-1.46	0.148
Bilateral ILF MD	-20.59	-1.99	0.048*
Scanner1	-0.93	-0.56	0.578
Scanner2	-0.91	-0.54	0.105
Scanner3	-1.89	-1.04	0.299
Random effect: Subject			

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Although the bilateral ILF FA did not reach our corrected level of significance, post-hoc models investigating the contribution of total FA as well as the left and right ILF FA were conducted to follow up on the baseline results from Section 2.2.3.1. In a follow up model including mean global FA as a covariate, bilateral ILF FA remained significant (t=2.40, p=0.02) whereas global FA was not significant. Post-hoc models investigated the right and left ILF FA in separate models and included total FA as a covariate. In this longitudinal cohort, there seems to be a similar effect size of both the right and left ILF FA and blending words performance (Table 2.10). In general, these results seem to be consistent with the baseline analyses performed above.

Table 2.10 Effects of right and left ILF FA on performance in the longitudinal cohort

Fixed Effects	*B* value	*t* value	*p* value
Model 1 (Right ILF)			
Age	1.21	6.62	0.000***
Age^2	-0.18	-4.03	0.000***
Gender	-0.97	-1.79	0.077
Right ILF FA	30.96	2.05	0.042*
Total FA	-15.43	-0.63	0.529
Scanner1	-1.02	-0.61	0.543
Scanner2	-1.02	-0.60	0.550
Scanner3	-2.01	-1.11	0.270
Model 2 (Left ILF)			
Age	1.11	5.80	0.000***
Age^2	-0.18	-4.03	0.000***
Gender	-0.79	-1.44	0.153
Left ILF FA	29.55	2.12	0.036*
Total FA	-9.32	-0.42	0.678
Scanner1	-0.40	-0.25	0.804
Scanner2	-0.39	-0.23	0.815
Scanner3	-1.22	-0.69	0.493
Random effect: Subject			

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Although bilateral ILF MD did not reach our corrected significance level, we examined a follow up model including mean global MD as a covariate to explore whether or not global MD contributed to this hypothesized regional trend. This weakened the effect of bilateral ILF MD (t=-1.69, p=0.09) and mean global MD was not related to performance.

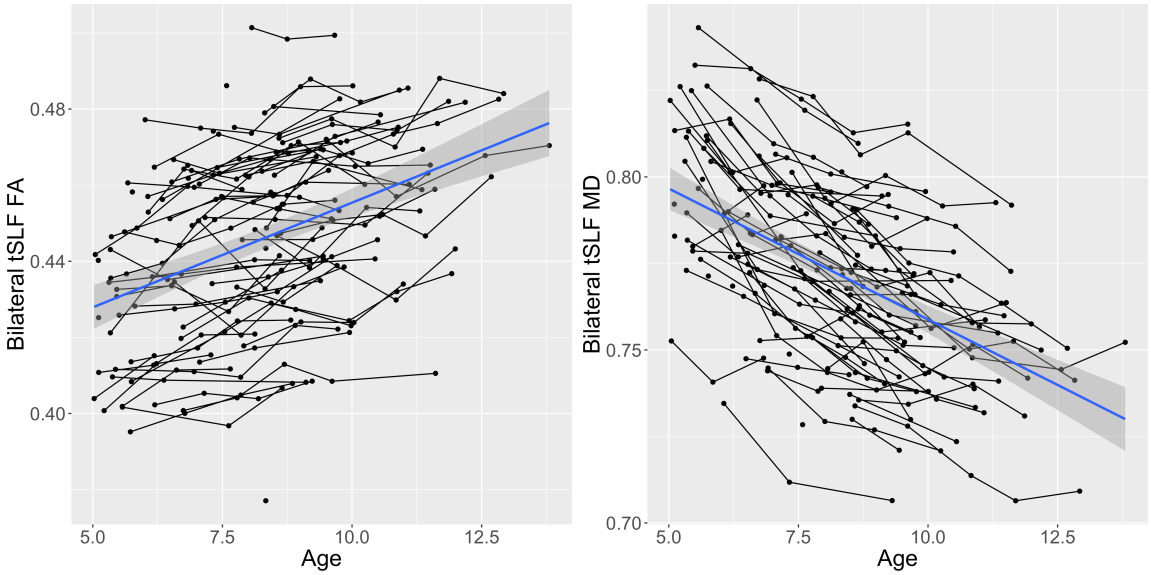

Figure 2.8 Bilateral tSLF FA (left) and MD (right) with a linear fit line and shaded 95% confidence intervals.

Table 2.11 Effects of bilateral tSLF FA and MD on performance in the longitudinal cohort

Fixed Effects	*B* value	*t* value	*p* value
Model 1 (FA)			
Age	1.22	6.58	0.000***
Age^2	-0.18	-4.14	0.000***
Gender	-0.85	-1.54	0.127
Bilateral tSLF FA	14.61	1.20	0.231
Scanner1	-0.22	-0.13	0.893
Scanner2	-0.15	-0.09	0.925
Scanner3	-1.07	-0.60	0.550
Model 2 (MD)			
Age	1.19	6.17	0.000***
Age^2	-0.18	-4.05	0.000***
Gender	-0.77	-1.38	0.172
Bilateral tSLF MD	-15.44	-1.33	0.186
Scanner1	-0.46	-0.78	0.782
Scanner2	-0.59	-0.35	0.727
Scanner3	-1.48	-0.82	0.411
Random effect: Subject			

All predictors have been centered (demeaned) except scanner
Female is coded as negative

As in the baseline analyses above, neither bilateral tSLF FA nor MD showed a relationship to performance (Table 2.11). Age was the only significant predictor of

performance. In separate post hoc models, neither total mean FA nor total mean MD showed a relationship to performance.

2.4 Discussion

The current analyses investigated the relationship between regional cortical and white matter structure and phonological performance in a typically developing cohort of children and adolescents. Based on previous literature, our cortical analyses focused on the posterolateral region of the temporal cortex. The results suggested a region-specific relationship between posterolateral temporal surface area and performance, although thickness of this region did not show a relationship to performance. We also examined measures of white matter microstructure in the inferior longitudinal fasciculus and temporal branch of the superior longitudinal fasciculus (arcuate). The fractional anisotropy of the ILF was related to performance, but mean diffusivity of the same tract as well as FA and MD of the temporal SLF did not exhibit a relationship to performance.

The results described above from both the cross sectional and longitudinal analyses suggest that a relatively larger surface area of the PLT is associated with better performance on a measure of phonological processing. However, we did not find evidence for a relationship between thickness of this same area and performance. This pattern of results is similar to previously published work from our group (Curley et al., 2017) which found a relationship between regional surface area of the pars opercularis and performance on a stop-signal task, but failed to find a relationship between thickness of the same area and performance. Likewise, work by Newman et al. (2015) found evidence for a relationship between surface area of the ventromedial prefrontal cortex and

anxiety, but did not detect a relationship between thickness of this region and anxiety (although there was evidence of a relationship with global mean thickness). It may be that in these typically developing cohorts, regional surface area is more strongly related to individual differences in behavioral performance than regional thickness. However, regional surface area is difficult to interpret in a typically developing cohort, as regional surface area continues to expand and contract across the age range examined here (Brown et al., 2012; Newman et al., 2015; Wierenga et al., 2014). The relationship between regional PLT surface area was present in the baseline cohort and was trending in the longitudinal cohort, although it did not reach our corrected level of significance. This suggests that this relationship is stronger in the baseline cohort. This cohort is younger, on average, than the full longitudinal dataset as it contains only the data from a participant's first visit. Therefore the stronger relationship in the baseline cohort may reflect the fact that surface area is still expanding relatively uniformly across this younger age range (approximately 5-9 years) relative to the longitudinal cohort (approximately 5-13 years), where more regions of the cortex have begun to contract. However, there was no evidence of interactions between age and bilateral PLT area. The inclusion of total surface area as a covariate is meant to emphasize the contribution of the region of interest *relative* to global area, although this can also complicate interpretation as the region of interest is included in the total area, and the total area is comprised of both expanding and contracting regions of cortex.

In addition, we found evidence that fractional anisotropy of the ILF was positively related to phonological processing, whereas mean diffusivity of the same area

showed no significant relationship to performance. We did not find evidence for a relationship between the microstructure of the temporal SLF (arcuate) and performance. Similarly to the pattern of results observed with the cortical findings, the relationship between ILF FA and performance seemed to be slightly stronger in the baseline cohort relative to the longitudinal cohort. Follow up analyses suggested there may be a slightly stronger relationship between right ILF FA and performance relative to left ILF FA, and there was no evidence for an age by ILF interaction. In the longitudinal cohort, the relationship between ILF FA and performance did not quite reach the corrected level of significance, and there was a trending relationship of ILF MD where lower MD corresponded to better performance, although this result also did not meet a corrected level of significance. This trending relationship was in the expected direction, as MD continues to decrease throughout development and therefore may indicate that a slightly more mature microstructure of the ILF corresponds to better performance.

Previous work by Saygin et al. (2013) had examined the ILF as well as the temporal and parietal branches of the SLF and their relationship to performance on multiple measures of reading ability from the same battery of tests examined here, the comprehensive test of phonological processing (CTOPP). However, this analysis focused on kindergarteners with dyslexia. Contrary to the results presented here, Saygin and colleagues found a relationship between both the volume and FA of the left arcuate and phonological performance, such that lower volume and lower FA correlated with worse phonological performance in children with dyslexia. It is not clear how these results may translate to a group of typically developing children, so it may not be surprising that a

different pattern of results was found here. Future work could continue to investigate the relative similarities and differences between the structural neural correlates of language learning in both typically developing children and adolescents and those with learning disorders or developmental delays.

Finally, it should be kept in mind that the task performance analyzed here is a relatively short number of items and child performance can be influenced by a variety of factors outside of the ones analyzed here. In addition, when examining performance in later ages, there may be a ceiling effect occurring by the time children are reaching ages 11-13 years. There is a clear nonlinear developmental trend, with much larger improvements in performance at the younger ages relative to the older ages. This may also affect any observed relationship between regional cortical and white matter structure. Similarly, the tools used to measure relative cortical morphology and white matter microstructure are indirect measures of actual brain structure and likely include sources of noise that are not accounted for here. Failing to find an association between regional posterolateral temporal thickness and microstructure of the temporal SLF (arcuate) does not necessarily mean that these relationships do not exist, only that we were unable to detect them in this participant pool using these tools. The participant population used for these analyses was a comparatively small subset of the participants in the PLING study, partly due to the switch from using version one of the CTOPP to an updated version two, which includes a different set and a greater number of test items. Future studies should continue to investigate how regional cortical and white matter structure in developing children relates to different aspects of developing language skills.

2.5 Conclusion

The primary aim of this study was to show preliminary evidence for a relationship between regional cortical and white matter structure and phonological processing in a group of typically developing children and adolescents. We found evidence that a relatively larger surface area of the posterolateral temporal cortex was related to better phonological performance and that higher fractional anisotropy of the ILF was also related to better performance. These relationships seemed to be stronger when considering only the baseline data and were weaker when analyzing the longitudinal cohort. Among the many possible influences on developing cognitive function, this study focused only on the contribution of the hypothesized structural regions of interest and primary covariates of age and gender. To our knowledge, this was the first study to investigate the relationship between regional cortical morphology as well as tract-specific white matter morphology and phonological performance in a longitudinal, typically developing cohort.

Chapters 2 and 3 benefitted from general contributions, feedback, and review from Akshoomoff, N., Brown, T.T., Thompson, W.K., Hagler, D.J., Dale, A.M., and Jernigan, T.L. The dissertation author was the primary investigator and author of this paper.

CHAPTER 3: STRUCTURAL NEURAL CORRELATES OF SPATIAL WORKING MEMORY IN A TYPICALLY DEVELOPING COHORT

3.1 Introduction

Spatial working memory is an important, multifaceted ability that develops during childhood and adolescence and underlies many important cognitive functions. Working memory is defined as the ability to maintain and manipulate information in pursuit of a goal, such as performance on a specific task (Baddeley, 1983), and spatial working memory is the maintenance of specific spatial information for these purposes. Most, if not all spatial working memory tasks rely on a form of sustained attention and executive control, which are required to perform the task successfully. Working memory tasks requiring the maintenance of multiple pieces of visuospatial information over the course of seconds or minutes are highly correlated with reasoning ability and overall intelligence (Conway et al., 2003; Klingberg et al., 2006). Furthermore, tasks requiring an ongoing maintenance of spatial locations are related to performance on complex reasoning tasks (Fry & Hale, 1996; Klingberg et al., 2005).

During development, there are marked improvements in spatial working memory ability between early childhood and adolescence. At younger ages, 4-year-olds perform worse than 5-7 year olds on almost every type of executive or working memory task. By the age of 8 years, children tend to perform better on tasks requiring complex problem solving skills, but do not yet perform as well as adults (Luciana & Nelson, 1998). In fact, many skills such as planning and working memory are not yet mature by 12 years of age (Luciana & Nelson, 2002). Luciana & Nelson suggest that working memory functions

develop dimensionally – sensory and perceptual skills develop before higher-order, complex working memory functions, and develop concurrently with distributed neural systems supporting this type of cognition (1998). Therefore, evidence suggests that working memory skills develop on a relatively long timescale and we could expect to see continuous improvements in performance from early childhood until late adolescence or beyond.

Although our work here focuses on structural correlates of spatial working memory, there has been extensive research on the functional neural correlates of spatial working memory. One example of these investigations into the functional correlates of spatial working memory found that maintenance of previously identified spatial locations activates regions such as the right superior frontal gyrus, right dorsolateral prefrontal cortex, right superior parietal cortex, and bilateral inferior parietal cortex in both children and adults (Thomas et al., 1999). In addition, Klingberg (2006) used functional neuroimaging to demonstrate that the intraparietal cortex is active in tasks requiring executive control of visual attention. Although much of the work investigating the relationship between spatial working memory and the brain focuses on functional relationships, some researchers have found that regional cortical morphology also demonstrates a relationship to spatial working memory performance in children and adolescents. Thinning of frontal lobe regions appears to be related to performance on tasks of visuospatial memory in children and adolescents ages 7 to 16 years (Sowell et al., 2001). In addition, independent of age, thinning in the parietal cortices was related to better performance on tasks of visuospatial functioning and spatial planning in children

ages 12 to 14 years (Squeglia et al., 2013). A large cross-sectional study of participants ages 6-25 years expanded on this previous work, demonstrating that relatively thinner parietal cortex was related to working memory performance (Darki & Klingberg, 2014).

In addition to the described relationships between regional brain morphology and spatial working memory performance, there is also evidence that these relationships change during the course of normal development. Specifically, research has described changes in the recruitment of different neural systems for visual attention and working memory as children age. Older children tend to have increased brain activity in the intraparietal cortex and the posterior superior frontal sulcus during working memory tasks, relative to younger children (Klingberg, 2006). Scherf and colleagues (2006) examined visuospatial working memory across a wide range of ages, from children age 8 years through adults age 47, and discovered that dissociable networks develop with age. In younger children, there was limited activation of DLPFC and parietal regions and more activation of regions such as the caudate and anterior insula. During adolescence, a more diffuse network (relative to younger children), including DLPFC, anterior cingulate, anterior insula and posterior parietal cortex were activated during a visuospatial working memory task. Finally, in adult subjects, the most targeted network was observed, including left DLPFC, VLPFC and the supramarginal gyrus (Scherf et al, 2006). This work emphasizes the changes in neural recruitment for the same task over the course of development and into adulthood. Olesen and colleagues (2003) sought to discover whether or not changes in regional and functional activation were mediated by increased fractional anisotropy of the underlying white matter by comparing the BOLD

signal with underlying fractional anisotropy (FA). In fact, there were positive correlations observed between FA in fronto-parietal regions and BOLD response in nearby superior frontal sulcus and inferior parietal areas, suggesting co-maturation of cortical and white matter regions involved in working memory (Olesen et al., 2003). This further emphasizes the necessity of measuring changes in behavioral and neural recruitment in longitudinal studies spanning childhood and adolescence, as recruitment of different regions changes nonlinearly with age as brain networks continue growing, shaping, and pruning connections.

One recent study combined region-of-interest identification using functional neuroimaging with a cross-sectional and longitudinal analysis of white matter correlates of visuospatial working memory in a cohort aged 6-25 years (Darki and Klingberg, 2014). In the cross-sectional analysis, working memory was positively correlated with functional activation in frontal cortex, functional activation and thickness of the parietal cortex, and fractional anisotropy and volume of fronto-parietal tracts connecting the cortical regions of interest. The longitudinal analyses suggested that working memory was related to functional activation and cortical thickness measured at the same time point, but neither cortical measure predicted future working memory performance. However, structural attributes of white matter were significantly correlated with working memory performance at a later time point (Darki & Klingberg, 2014). The authors suggest that these findings indicate a strong role of white matter integrity for future working memory capacity. Another study by Umarova et al (2010) investigated possible ventral pathways related to visuo-spatial working memory by utilizing both functional

MRI and diffusion-based imaging (DTI). During the fMRI portion of the study, the cortical regions activated by a visuospatial attention task were extracted and used as seed regions for the DTI investigation. The resulting probability maps suggested frontal and temporoparietal regions both play a role in spatial attention. Specifically, the dorsal connections linked temporoparietal regions to the frontal eye field and inferior frontal gyrus. Conversely, the ventral projections included the white matter linking the insular cortex and putamen parallel to the sylvian fissure (Umarova et al, 2010). This study in particular suggests a much wider, more diffuse and interconnected network for spatial working memory, although the approach used in this study was different than studies examining the direct structural correlates of performance in cortical regions and white matter tracts. In addition, some studies utilizing electrophysiology have led researchers to infer which regions of cortex and their related white matter connections play a role in visuospatial processing and attention. One electrophysiology study investigating cortical regions related to visuospatial perception found that stimulation of right inferior parietal cortex and/or posterior superior temporal sulcus affects performance. This finding was specific to these more posterior regions of the hypothesized network, as opposed to anterior temporal cortex, suggesting disruption of the information being sent along this posterior-anterior pathway. Based on these results, a parietal-frontal white matter pathway, possibly part of the superior occipitofrontal fasciculus, is thought to be important for processing of visuospatial information (Thiebaut de Schoten et al 2005). Taken together, the results of these studies suggest that through the use of functional

cortical analyses, we can begin to infer the relationships between regional white matter structure and connectivity and spatial working memory performance.

As discussed above, some studies have suggested that spatial working memory performance can be tied to regional white matter structure. However, this relationship had not been examined directly in a developing cohort until a relatively recent study by Vestergaard et al., (2011). This study examined the white matter correlates of spatial working memory in children, suggesting that diffusion parameters in the superior longitudinal fasciculus and including the white matter underlying the dorsolateral prefrontal cortex and superior parietal cortex are correlated with performance (Vestergaard et al., 2011). Specifically, higher FA in the white matter underlying the left dorsolateral prefrontal cortex, parietal cortex, and in the SLF correlated with better spatial working memory performance. This relationship seemed to be driven mainly by FA the left superior longitudinal fasciculus (Vestergaard et al., 2011). Research investigating these same regions as they relate to sustained attention also shows a relationship similar to spatial working memory, but with hemispheric differences. Work by Klarborg et al (2012) demonstrated that better sustained attention was associated with higher fractional anisotropy (FA) in the right superior longitudinal fasciculus and the white matter underlying the right dorsolateral prefrontal cortex and parietal cortex. This relationship between white matter microstructure and performance was driven primarily by the right SLF and superior parietal cortex. These results may indicate a relationship between maturing white matter and improved spatial working memory performance.

In general, previous work on regional brain structure underlying visuo-spatial working memory performance have found evidence for relationships between performance and different regions of the frontal cortex and parietal cortex as well as the superior longitudinal fasciculus, which connects frontal and parietal cortices (Madsen et al., 2011; Vestergaard et al., 2011; Klarborg et al., 2012). These findings suggest a distributed network of cortical and white matter tracts underlying spatial working memory: a network that changes during the course of development, becoming more specialized by the end of adolescence. There are innumerable variations of spatial working memory tasks in the literature, and experimental results likely rely heavily on the specific task demands. In the following analyses, we utilize the Spatial Working Memory (SWM) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB). This task involves the major components of most spatial working memory tasks, most importantly, the maintenance of specific visuo-spatial locations in working memory.

3.1.1 Task: Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory, Between-Search Errors

The spatial working memory task used for this investigation was the CANTAB spatial working memory task, which is a type of self-ordered search task (Cambridge Neuropsychological Test Automated Battery: Fray et al., 1996; Robbins et al., 1996; Sahakian & Owen, 1992). The CANTAB spatial working memory (SWM) task is administered using a touch-screen computer, on which participants are shown an array of

colored boxes. Participants must find the token located in one of the boxes, after which they click to move the token to the storage column to the right of the screen and begin a new search with the same array of boxes. The token is now in one of the previously empty boxes. After a token has been found in each box, a new trial begins with a new array of boxes. The number of boxes onscreen will gradually increase from 2 boxes to 3, 4, 6, and 8 boxes. For each set, the position of the boxes varies. The primary measure is the between-search errors score, which is the number of times a participant re-checks a box in which a token has already been found during a particular set (see Appendix for details).

In a previous normative cohort of children ages 4-12 years, between-search error scores for 3- to 8-item search trials ranged from 32 to 64. Significant age effects on performance based on difficulty (an increase in the number of boxes on each trial) were only evident for 4-, 6-, and 8-box searches (Luciana & Nelson, 2002) Four-year olds seemed to have the most difficulty because of the time demands and increasing difficulty of the task. Five- to eight-year-olds were able to reach ceiling performance on easier levels and only seemed to struggle on the most difficult levels of the task. Nine- to twelve-year olds also reached ceiling on the easier levels of the task but do not yet resemble adult levels on the most difficult levels (Luciana & Nelson, 2002).

3.1.2 Behavioral QC

For the CANTAB spatial working memory task (between search errors score), the expert rater QC ratings of 0 were included in the cohort and the QC ratings of 2 were

excluded. The QC ratings of 1 were reviewed by the investigator (LC) on a case-by-case basis to determine which observations should be included or excluded.

Among the QC ratings of 1, comments were generally categorized into two areas:

A. Fatigue: comments indicating fatigue, boredom, or mild behavioral observations.
    a. Examples: “fatigue”, “fingers tired”, “tired”, “fidgety”
B. Technical issues: comments indicating SWM had to be restarted after a crash or an issue with the touch screen
    a. Examples: “first trial crashed”, “crashed and didn’t save; reran”, “computer auto-update; restarted”, “screen froze, hard to restart SWM”, “screen not sensitive to tapping”

Among the QC 1 ratings, all “A” type comments were left in the cohort since they likely did not invalidate the test results. These comments were generally broad and non-specific. Since comments were left for the entire CANTAB battery and did not always identify specific subtests, it was also ambiguous as to whether or not these comments applied specifically to the SWM subtask as opposed to another subtask. Based on administration experience that participants often indicated they enjoyed this subtask, the investigator decided to leave these observations in the cohort. Among the “B” type technical issues, those that happened early (within the few trials) and were caught and resolved immediately were kept in the cohort. The “B” type technical issues that were more disruptive, such as crashes during the middle of the test, were excluded. It was often unclear from the comments if the subtask was restarted from where it left off or from the beginning, which may lead to practice effects or other psychometric effects on

performance, and in these cases the investigator took a conservative approach and removed these data points since there was lower confidence in the quality of the data. Among the 14 QC1 data points in the SWM cohort:

A (fatigue): 7 converted to QC0

B (technical): 5 converted to QC0; 2 converted to QC2

In total, among the 14 QC1 data points for SWM, 12 were converted to QC0 and kept in the cohort, 2 were converted to QC2 and excluded.

3.1.3 Regions of Interest

Based on the specific demands of this spatial working memory task, regions of interest include both cortical and subcortical regions thought to be involved primarily in maintenance of spatial locations in working memory and spatial attention. Specifically, both the superior frontal and the superior parietal regions of the Desikan atlas were examined, as these regions seemed most analogous to regions previously identified using functional methods and structural analyses (Klingberg et al., 2006, 2002; Scherf et al., 2006). The primary white matter region of interest is the parietal branch of the superior longitudinal fasciculus (pSLF; Klarborg et al., 2012, Vestergaard et al., 2011) as this tract extends from superior parietal to superior frontal regions. The SLF has previously been shown to be related to spatial working memory performance (Vestergaard et al., 2011).

3.1.4 Participants

All participants were typically developing children between the ages of 4 and 13 years. A total of 122 children were included in the analyses (60 male, 62 female). The average age of the children at baseline was 7.4 years (s.d. = 1.7 years). Female participants were 7.4 (s.d. = 1.8) years on average, and males were 7.4 (s.d. = 1.6) years on average. Further demographic information including handedness, parental education and household income, and race and ethnicity can be found in the table below. Summaries of age and performance at each visit are also included in the table below.

Table 3.1 Demographic information for the BSE cohort

Demographics		Total	Male	Female
Number of participants		122	60	62
Parental Education*(mean,sd)		5.6(1.6)	5.7(1.5)	5.6(1.7)
Household Income*(mean, sd)		6.2 (2.3)	6.3(2.3)	6.2(2.2)
Handedness (R/L/Amb/NA)		100/18/2/2		
Monolingual/Bilingual		73/49		
Race/Ethnicity*				
	Caucasian	66		
	African American	6		
	Hispanic/Latino	57		
	Asian	4		
	Pacific Islander	1		
	Burmese	1		
	Mixed Race	15		
	Other/Unknown	29		
Age (mean, s.d.)	Baseline (N=122)	7.38(1.68)	7.41(1.56)	7.35(1.81)
	Time point 2 (N=68)	8.24(1.66)	8.16(1.29)	8.31(1.97)
	Time point 3 (N=50)	9.27(1.54)	9.41(1.49)	9.14(1.60)
	Time point 4 (N=40)	10.29(1.42)	10.60(1.41)	9.87(1.36)
	Time point 5 (N=12)	11.12(1.39)	10.67(1.62)	11.35(1.33)
Between-Search Errors (mean, s.d.)	Baseline (N=122)	51.2(19.9)	51.5(18.8)	50.9(21.1)
	Time point 2 (N=68)	41.9(18.5)	41.6(16.8)	40.8(20.3)
	Time point 3 (N=50)	33.1(16.5)	28.6(14.9)	35.7(17.6)
	Time point 4 (N=40)	27.6(15.3)	27.4(15.0)	27.9(16.1)
	Time point 5 (N=12)	21.6(16.1)	22.0(24.0)	21.4(12.7)

* Parental Education scale: 1 (less than 7 years); 2 (7-9 years); 3 (10-11 years); 4 (High School Diploma); 5 (1-3 years of college); 6 (Bachelor's Degree); 7 (Professional Degree, e.g. Masters, Doctorate, MD, JD). There were 22 participants missing Parental Education information and so were omitted from the summary statistics in this table.

* Household Income scale (annual): 1 (less than $5,000); 2 ($5-9,999); 3 ($10-19,999); 4 ($20-29,999); 5 ($30-39,999); 6 ($40-49,999); 7 ($50-99,999); 8 ($100-199,999); 9 ($200-249,999); 10 *$250-299,999); 11 ($300,000 or more). There were 30 participants missing Household Income information and so were omitted from the summary statistics in this table.

* Handedness: 2 participants did not identify handedness, or reports of handedness varied by task/questionnaire.

* Participants were free to mark whichever race/ethnicity options they chose: if multiple races were checked, s/he was categorized as ''Mixed race''; if none was selected, s/he was categorized as ''Other/Unknown''. Some participants marked only ''Hispanic/Latino'', while others marked ''Hispanic/Latino'' in addition to a race. Therefore, the total number reported in each category does not sum to the total number of participants.

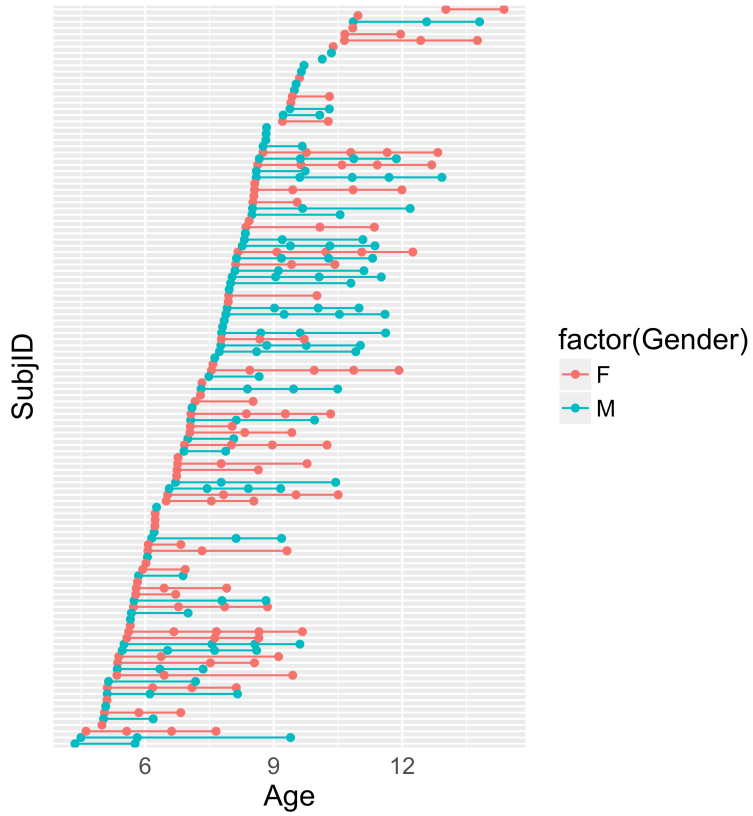

Figure 3.1: Summary of BSE cohort.

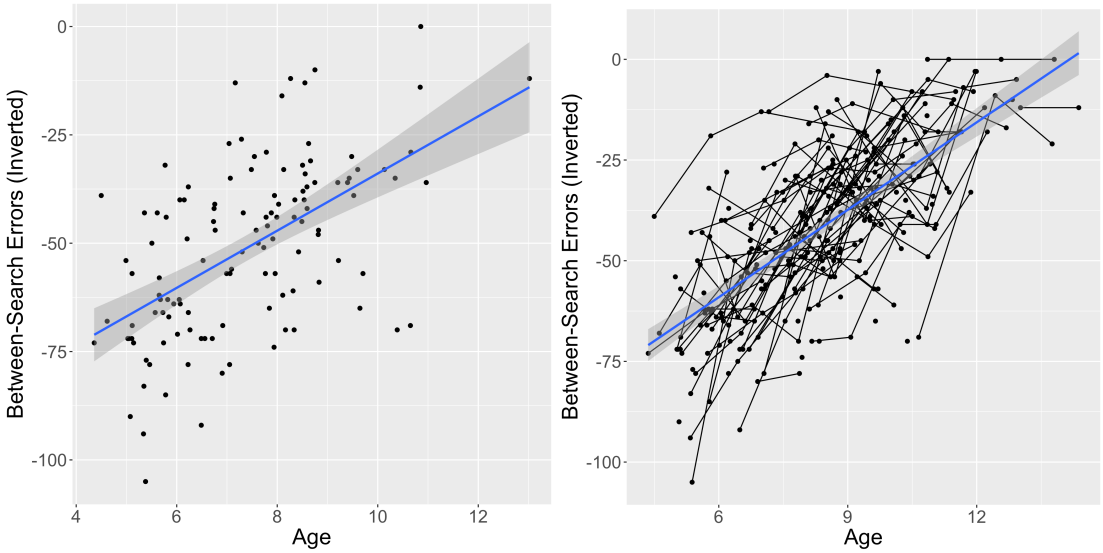

Figure 3.2: Inverted BSE scores as a function of age for the baseline cohort (left) and the longitudinal cohort (right) with a linear fit line and shaded 95% confidence intervals

3.1.5 Behavioral Results:

The average spatial working memory between-search error (BSE) score at baseline was 51.2 (s.d.=19.9) with a range of 0 to 105, with females scoring 50.9 (s.d.=21.1) on average and males scoring 51.5 (s.d.=18.8) on average. Note that these scores are error counts, so lower scores indicate better performance. For all following analyses, these error scores were inverted so they higher scores indicate better performance in order to make interpretation of results more straightforward. For the baseline model, a multiple linear regression was used to predict inverted BSE from age and gender. There was a strong effect of linear age ($t=7.36$, $p<0.01$) and no effect of gender. Preliminary models suggested no effect of nonlinear age, so only a linear age term was included in primary models of interest. Other preliminary models examined the effect of parental education and household income on performance. There was a significant effect of parental education on performance when controlling for age and gender, where higher parental education was related to better spatial working memory performance (Table 3.3). Follow up models found no evidence for any interaction effects between age, gender, and parental education. Parental education did not seem to play a mediating role in the primary region-of-interest analyses, so the results reported below do not include this covariate as it greatly reduces the available subject population (from 122 to 100, as 22 participants are missing data on parental education).

Table 3.2 Effects of age and gender on BSE performance in the baseline cohort

Predictors	*B* value	*t* value	*p* value
Age	6.060	7.36	0.000***
Gender	-0.96	-0.32	0.749

All predictors have been centered (demeaned)
Female is coded as negative

Table 3.3 Effect of parental education on BSE performance in the baseline cohort

Predictors	*B* value	*t* value	*p* value
Age	6.57	6.97	0.000***
Gender	-3.19	-1.06	0.294
Parental Education	3.11	3.26	0.002**

N=100 subjects (22 in full cohort are missing parental education data)
All predictors have been centered (demeaned)
Female is coded as negative

In a mixed-effects model predicting inverted BSE scores from age and gender in the full longitudinal cohort, only linear age was a significant predictor of performance. In follow up models examining the effect of parental education and household income on behavioral performance while covarying for age and gender, the relationship between parental education and performance found in the baseline analyses above persisted in this longitudinal cohort. When covarying for age and gender, parental education is positively related to performance ($t=4.62$, $p<0.001$).

Table 3.4 Effects of age and gender on BSE performance in the longitudinal cohort

Fixed Effects	*B* value	*t* value	*p* value
Age	6.98	15.33	0.000***
Gender	-1.21	-0.54	0.593
Random effect: Subject			

All predictors have been centered (demeaned)
Female is coded as negative

3.1.6 Methods

For both the cortical and white matter regions of interest, two series of analyses were conducted: the first was done using only the baseline data (from the first visit) as a way to investigate individual differences and the degree of individual variation at the start of the study. The second set of analyses were carried out using the longitudinal data, as a way to investigate the relationship between task performance and brain structure in a larger, typically developing cohort. The results are presented first for the baseline-only data and then for the longitudinal data.

3.2 Specific aim 3: To investigate the relationship between superior frontal and superior parietal cortical structure and spatial working memory performance

3.2.1 Regions of interest

The region of interests included the superior frontal and the superior parietal cortex, which were extracting from the Desikan parcellations using Freesurfer (Desikan et al., 2006). We examined both surface area and thickness of these two cortical regions in relation to between search errors performance.

3.2.2 Baseline

Primary analyses on the baseline cohort involved using multiple linear regression models to evaluate the relationship of age, gender, and hypothesized bilateral region of interest on performance. Scanner was included as a covariate of no interest. Total cortical

area was included as a covariate when examining regional cortical area. For each primary cortical analysis, a Bonferroni correction of p=0.05/4 =0.0125 was used to correct for the two primary tests of surface area and thickness on the two regions of interest.

All participants were scanned on the same scanner but there were two software updates during the course of the study, which are captured and coded by "scanner". Thirty-five subjects were scanned on software version A, 50 were scanned on software version B, and 37 were scanned on software version C. Scanner was included in all primary models as a covariate of no interest.

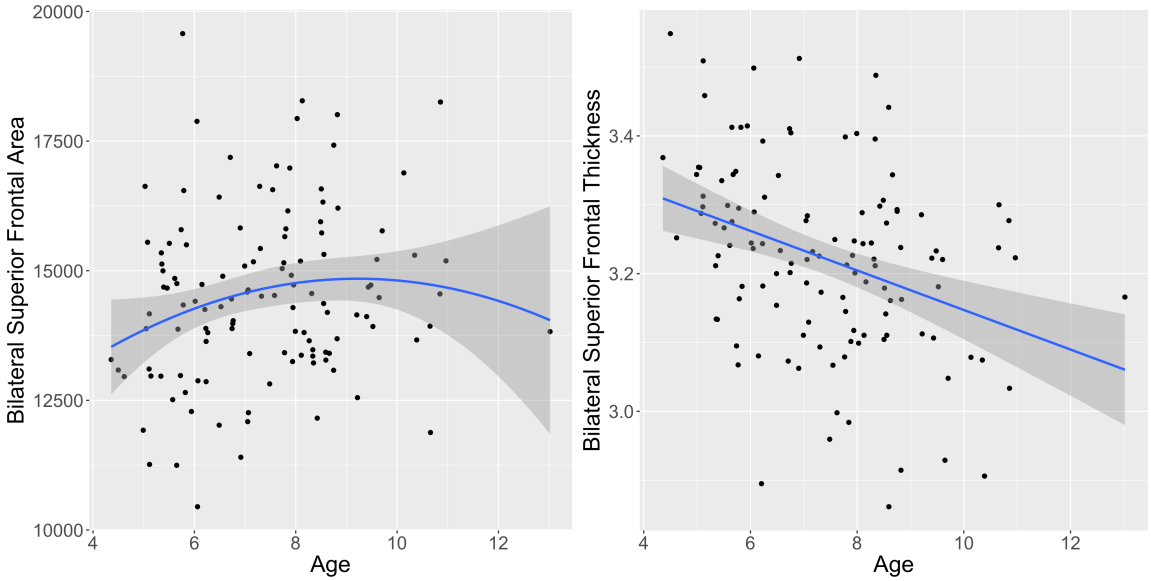

Figure 3.3 Bilateral superior frontal area (left) with a quadratic fit line and thickness (right) with a linear fit line and shaded 95% confidence intervals.

3.2.2.1 Results

Neither bilateral superior frontal surface area nor thickness showed a relationship to inverted BSE scores. In both cases, only age was a significant predictor of performance (Table 3.5).

Table 3.5 Effect of bilateral superior frontal area and thickness on performance in the baseline cohort

Predictors	*B* value	*t* value	*p* value
Model 1 (Area)			
Age	6.91	7.46	0.000***
Gender	-2.97	-0.85	0.399
Bilateral SF area	0.00	1.24	0.216
Total area	-0.00	-0.35	0.726
Scanner1	-7.33	-2.04	0.043
Scanner2	-10.09	-2.52	0.013
Model 2 (Thickness)			
Age	7.80	8.14	0.000***
Gender	1.13	0.37	0.714
Bilateral SF thickness	20.82	1.68	0.096
Scanner1	-8.24	-2.30	0.023
Scanner2	-9.99	-2.51	0.014

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Neither superior parietal area nor thickness showed a relationship to performance on the spatial working memory task. In both cases, only age was a significant predictor of performance (Table 3.6). Follow-up models included parental education as a covariate, but this additional covariate did not affect the primary relationship between either region of interest and performance.

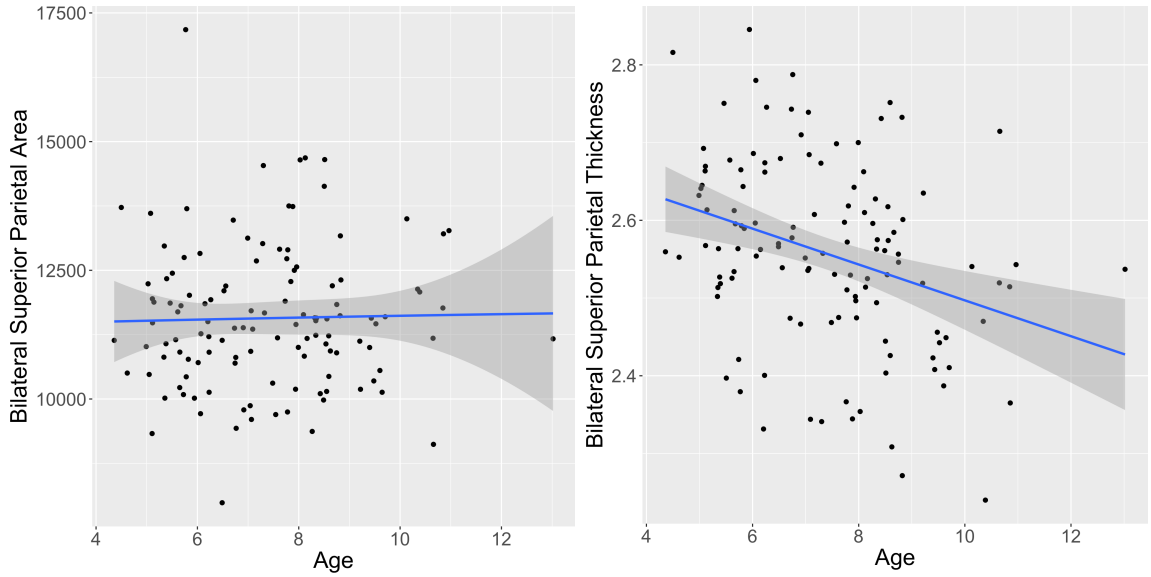

Figure 3.4. Bilateral superior parietal area (left) with a quadratic fit line and thickness (right) with a linear fit line and shaded 95% confidence intervals around the mean.

Table 3.6 Effect of bilateral superior parietal area and thickness on performance in the baseline cohort

Predictors	*B* value	*t* value	*p* value
Model 1 (Area)			
Age	7.08	7.58	0.000***
Gender	-3.51	-1.00	0.319
Bilateral SP area	0.00	0.30	0.762
Total area	0.00	0.76	0.452
Scanner1	-7.14	-1.96	0.053
Scanner2	-9.85	-2.44	0.016
Model 2 (Thickness)			
Age	7.78	8.03	0.000***
Gender	0.44	0.15	0.884
Bilateral SP thickness	20.04	1.50	0.138
Scanner1	-8.68	-2.39	0.018
Scanner2	-11.68	-2.92	0.004

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Exploratory models including parental education suggested the lack of relationship between our regions of interest and performance were not affected by the inclusion of parental education for either superior frontal or superior parietal regions.

Follow-up models examining the effect of total cortical surface area and global mean thickness on performance in separate models also suggested no relationship between either global measure and performance.

3.2.3 Longitudinal

Linear mixed-effects models were used to investigate the cortical regions of interest for the longitudinal cohort. For the cortical regions of interest, a Bonferroni correction of 0.05/4 = 0.0125 was used to account for the two primary cortical regions of interest and the two tissue measures examined.

3.2.3.1 Results

There was no relationship between surface area of the bilateral superior frontal region and performance on the SWM task while covarying for age, gender, and total cortical surface area using linear mixed-effects models. Only age was a significant predictor of performance. There was a weak but trending effect of bilateral superior frontal thickness. However, when total mean thickness is included as a covariate this relationship disappears ($t = 0.84$, $p=0.40$). Therefore there does not seem to be evidence for a relationship between either bilateral superior frontal area or thickness and performance (Table 3.7).

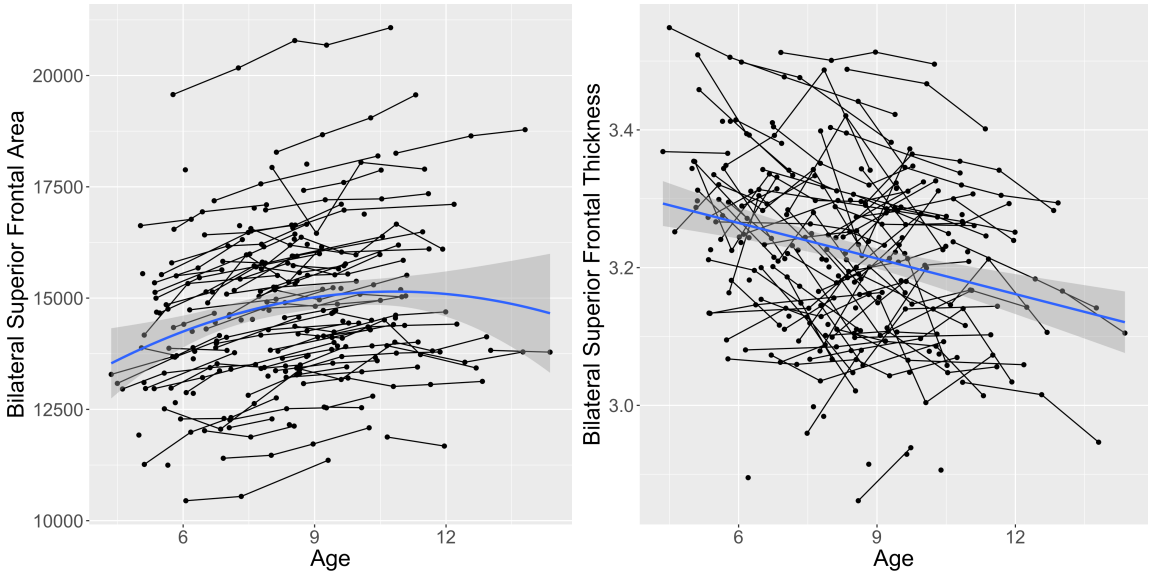

Figure 3.5 Bilateral superior frontal area (left) with a quadratic fit line and thickness (right) with a linear fit line and shaded 95% confidence intervals.

Table 3.7 Effect of bilateral superior frontal area and thickness on performance in the longitudinal cohort

Fixed Effects	*B* value	*t* value	*p* value
Model 1 (Area)			
Age	6.90	11.05	0.000***
Gender	-3.80	-1.46	0.146
Bilateral SF area	0.00	0.93	0.356
Total area	0.00	0.20	0.843
Scanner1	-3.02	-1.18	0.238
Scanner2	-8.10	-2.37	0.019
Scanner3	-2.73	-0.82	0.412
Model 2 (Thickness)			
Age	7.51	11.45	0.000***
Gender	0.19	0.08	0.935
Bilateral SF thickness	15.77	1.74	0.084
Scanner1	-3.26	-1.28	0.204
Scanner2	-8.21	-2.40	0.018
Scanner3	-3.47	-1.03	0.305
Random effect: Subject			

All predictors have been centered (demeaned) except scanner
Female is coded as negative

There was no relationship of either bilateral superior parietal thickness or surface area with SWM performance. Only age was a significant predictor of performance.

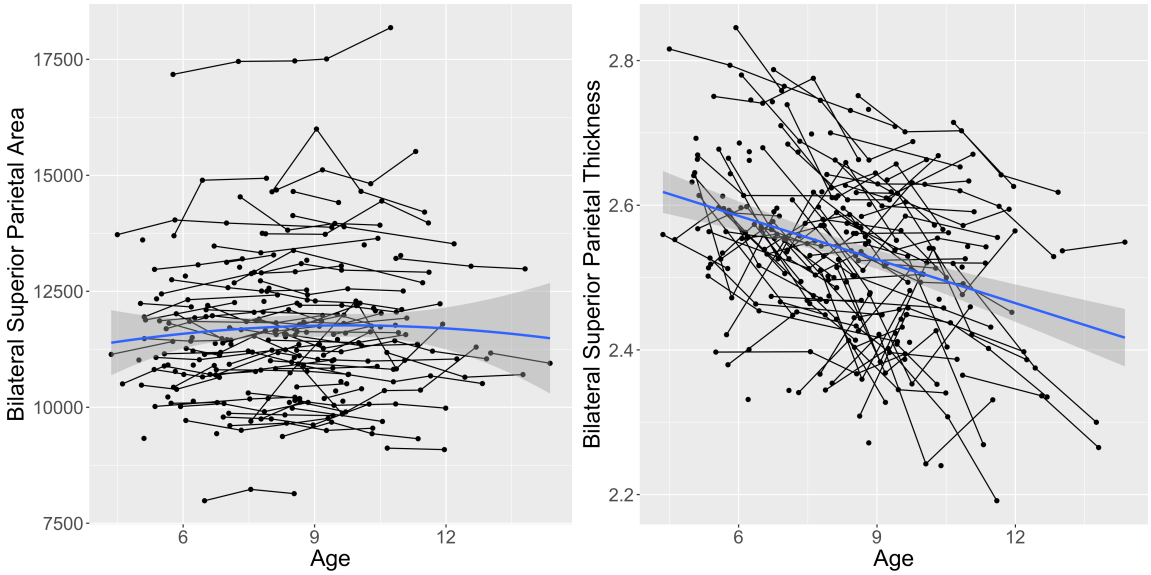

Figure 3.6 Bilateral superior parietal area (left) with a quadratic fit line and thickness (right) with a linear fit line and shaded 95% confidence intervals.

Table 3.8 Effect of bilateral superior parietal area and thickness on performance in the longitudinal cohort

Fixed Effects	*B* value	*t* value	*p* value
Model 1 (area)			
Age	7.00	11.19	0.000***
Gender	-3.94	-1.52	0.131
Bilateral SP area	0.00	0.45	0.651
Total area	0.00	0.91	0.365
Scanner1	-2.94	-1.15	0.251
Scanner2	-8.08	-2.36	0.019
Scanner3	-2.62	-0.79	0.432
Model 2 (thickness)			
Age	7.44	11.27	0.000***
Gender	-0.64	-0.29	0.773
Bilateral SP thickness	13.12	1.39	0.167
Scanner1	-3.22	-1.26	0.211
Scanner2	-9.23	-2.69	0.008
Scanner3	-2.91	-0.87	0.385
Random effect: Subject			

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Follow up models suggested no effect of total cortical surface area nor mean global thickness on performance when covarying for age and gender.

3.3 Specific aim 4: To investigate the relationship between the parietal superior longitudinal fasciculus and spatial working memory

3.3.1 Region of interest

The primary tract of interest for the spatial working memory task is the parietal branch of the superior longitudinal fasciculus (pSLF), which projects from superior parietal regions into frontal regions (Vestergaard et al., 2011; Madsen et al., 2011). The pSLF was extracted from AtlasTract (Hagler et al., 2009). A Bonferroni correction of 0.05/2 = 0.025 was used to account for models examining both fractional anisotropy and mean diffusivity.

3.3.2 Baseline

As above, primary analyses investigating the relationship between the parietal branch of the SLF and spatial working memory performance were first investigated using only the baseline cohort with multiple linear regression models. Age, gender, and scanner were included as covariates.

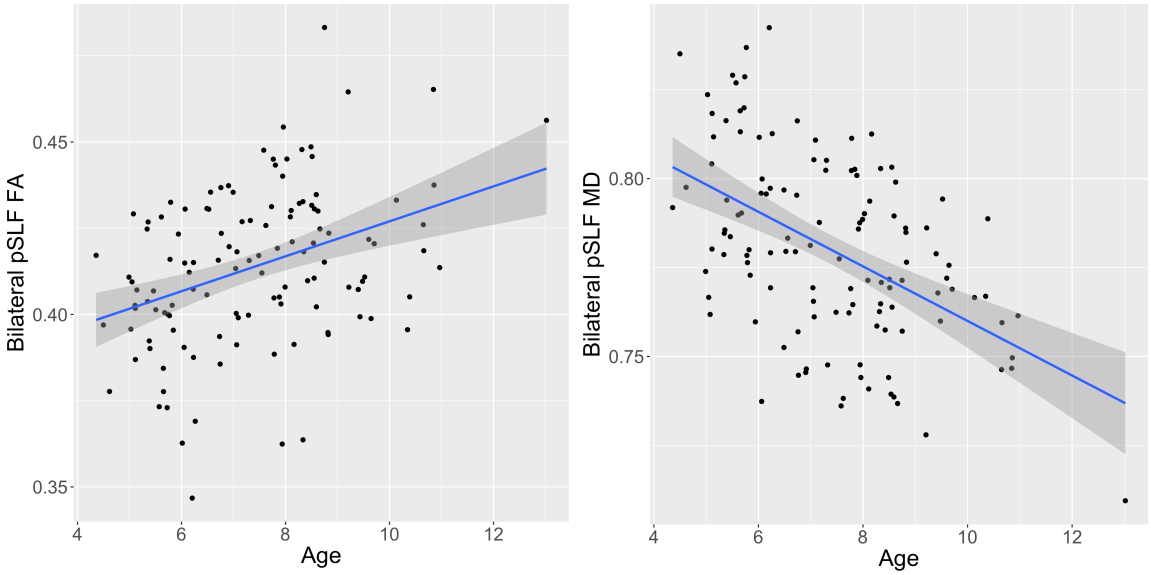

Figure 3.7 Bilateral pSLF FA (left) and MD (right) with a linear fit line and shaded 95% confidence intervals.

3.3.2.1 Results

Neither fractional anisotropy (FA) nor mean diffusivity (MD) of the bilateral superior longitudinal fasciculus was related to between search errors on the spatial working memory task in the baseline cohort when covarying for age effects and gender. Only age was a significant predictor of performance. Follow up models examining the effects of global FA and MD on performance suggested no relationship when covarying for age and gender.

Table 3.9 Effect of bilateral pSLF FA and MD on performance in the baseline cohort

Predictors	*B* value	*t* value	*p* value
Model 1 (FA)			
Age	6.52	6.20	0.000***
Gender	-0.56	-0.19	0.850
Bilateral pSLF FA	123.45	1.19	0.236
Scanner1	-7.59	-2.11	0.037
Scanner2	-8.97	-2.17	0.032
Model 2 (MD)			
Age	7.14	6.73	0.000***
Gender	-0.38	-0.13	0.899
Bilateral pSLF MD	-18.43	-0.27	0.786
Scanner1	-8.00	-2.17	0.032
Scanner2	-10.90	-2.72	0.007

All predictors have been centered (demeaned) except scanner
Female is coded as negative

3.3.3. Longitudinal

Our primary analyses investigated the relationship between the parietal branch of the SLF and spatial working memory performance in the longitudinal cohort using linear mixed effects models. Age, gender, and scanner were included as covariates. A Bonferroni correction of 0.05/2 = 0.025 was used to account for the two tissue measures evaluated for the bilateral pSLF, FA and MD.

3.3.3.1 Results

When covarying for age, gender, and global effects, there was no relationship between either bilateral pSLF FA or MD and SWM scores. In both models, only age was a significant predictor of performance. Follow-up analyses indicated there was no effect of global FA or MD on behavioral performance when covarying for age and gender.

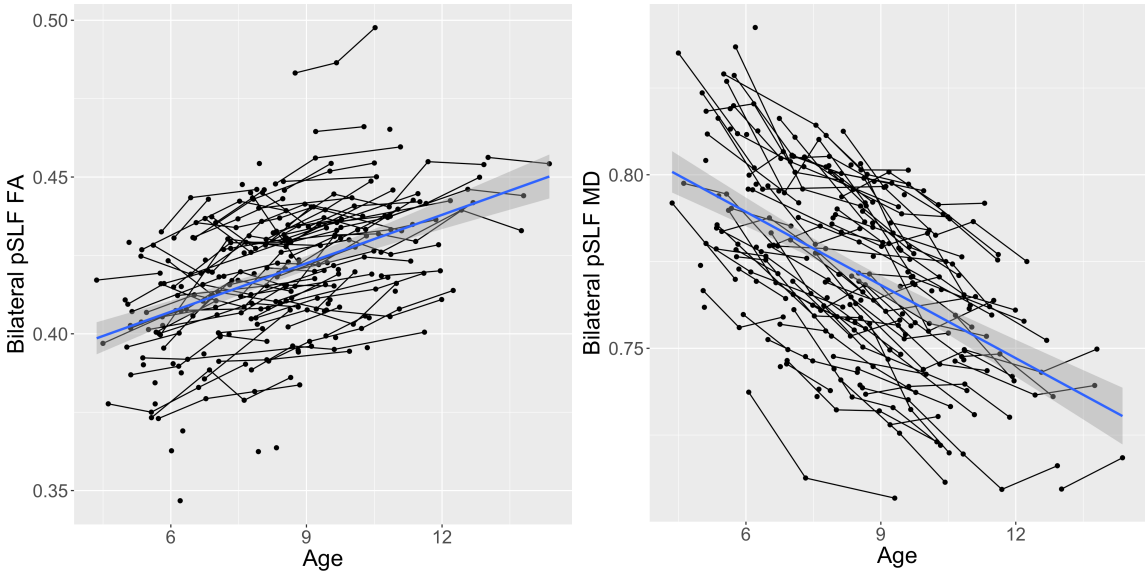

Figure 3.8 Bilateral pSLF FA (left) and MD (right) with a linear fit line and shaded 95% confidence intervals.

Table 3.10 Effect of bilateral pSLF FA and MD on performance in the longitudinal cohort

Fixed Effects	*B* value	*t* value	*p* value
Model 1 (FA)			
Age	6.70	9.70	0.000***
Gender	-1.12	-0.51	0.613
Bilateral pSLF FA	78.86	1.43	0.154
Scanner1	-2.86	-1.12	0.263
Scanner2	-7.79	-2.23	0.027
Scanner3	-2.08	-0.62	0.536
Model 2 (MD)			
Age	7.20	9.96	0.000***
Gender	-1.14	-0.51	0.613
Bilateral pSLF MD	9.63	0.19	0.846
Scanner1	-2.80	-1.08	0.282
Scanner2	-8.79	-2.56	0.011
Scanner3	-2.46	-0.74	0.463
Random effect: Subject			

All predictors have been centered (demeaned) except scanner
Female is coded as negative

3.4 Discussion:

The preceding analyses investigated possible relationships between regional cortical and white matter properties and a spatial working memory task, the between-search error score from the CANTAB battery. These analyses did not find any strong evidence for a relationship between either regional cortical or regional white matter structure and SWM performance in the regions of interest examined here.

We expected relatively larger surface area of the superior frontal and parietal regions to be related to better spatial working memory performance, as this may indicate either an advantageous pattern of regionalization of the cortex, or a slightly more mature neural phenotype for age. Previous work has suggested that regional cortical surface area may be related to task-specific performance (Newman et al. 2015; Curley et al., 2017). However, we did not find any evidence for either a regional or global relationship between cortical surface area and performance. Similarly, we also expected relatively thinner superior frontal and parietal regions to be related to better performance, as this may also indicate a more mature neural phenotype. Previous work has suggested that relatively thinner frontal and parietal regions may be related to spatial working memory performance (Sowell et al., 2001; Squeglia et al., 2013; Darki & Klingberg, 2014). However, we could not confirm a relationship between regional or total thickness and performance in this study. The specific cortical regions examined here may not have shown a relationship to performance for a variety of reasons. The cortical regions of interest were chosen based on previous functional research demonstrating a relationship between these regions and SWM performance in addition to the few studies examining

relationships between regional cortical structure and performance. The cortical regions selected for these analyses were chosen from an existing cortical atlas and were the nearest approximations to previously identified areas. Previous literature has suggested a role for dorsolateral prefrontal regions in tasks requiring executive attention and control, and working memory performance may be mediated by cortical activation and the underlying white matter tracts in this frontal network (Sauseng et al, 2005; Olesen et al, 2003). Therefore, it would be informative to also examine the hypothesized region of the DLPFC and its relationship to performance, although an analogous region was not available in the cortical parcellation atlas used here. Alternative approaches such as manually drawn regions of interest or use of a different regional cortical atlas would likely have shown different results. In addition, during this period of development cortical surface area is both expanding and contracting across different regions of the brain (Jernigan et a., 2015). There is a high degree of regional variability within and across children between the ages of 5 and 13 years old in terms of regional cortical surface area expansion, which makes investigations into regional and global surface area during this developmental period difficult to interpret.

We expected higher fractional anisotropy and lower mean diffusivity of the pSLF to be positively related to performance, as these measures of microstructure may reflect a more mature neural system. Similar research has also suggested that relatively higher FA of the SLF is related to spatial working memory performance and sustained attention (Vestergaard et al, 2011; Madsen et al., 2011). However, we did not find evidence of any relationship between white matter microstructure of the pSLF and performance. Although

we observe the expected age trends for both measures of FA and MD in this tract, the lack of relationship between these measures of white matter microstructure and performance could be due to many factors, including population or methodological differences between the current study and previous work. Vestergaard and colleagues found evidence that higher FA in the left fronto-parietal network was related to better performance on this same spatial working memory task in children ages 7 to 13 years (2011). This relationship persisted independently of age and global FA measures, and also seemed to be mediated by decreasing perpendicular diffusivity, which was not examined here. In addition, Vestergaard and colleagues utilized tract-based spatial statistics (TBSS), in which a set of tract voxels is created for the study-specific population by creating a mean FA image and thinning to reach a "skeleton", or the approximate core of the white matter tracts as represented in the group map. Individual FA volumes are registered and adjusted to achieve homology across skeleton voxels of different individuals. Researchers drew the SLF region of interest based on anatomical landmarks visible in the (group) mean FA map. This approach can produce different results than the probabilistic tract atlas used in the present study (Hagler et al., 2009). The atlas method may include more voxels near the edges of tracts that may or may not belong to the tract of interest and could include voxels with lower FA, crossing fibers, or other tissues. This type of tract delineation may make it harder to detect strong relationships between regional white matter morphology and performance.

Finally, it may be of note that we found an association between parental education and performance on this task independently of age and gender, which was not found for

the other two tasks examined in this body of work. Although this effect did not seem to play a role in any of the primary region-of-interest analyses, it could be a possible route of future study into the role of environment on individual variability in spatial working memory performance. Importantly, the participant population in the present study was specifically curated to include a more diverse group of children and adolescents that would be more representative of the local demographic population. It may be that the participant population examined here varied to a higher degree in race, ethnicity, socioeconomic status, and other demographic factors relative to previous studies on the same age ranges. This may also have affected the findings, as demographic factors such as SES can have a notable effect on brain structure development as well as performance measures (Noble et al., 2015).

3.5 Conclusion

These analyses sought to investigate relationships between structural variation in hypothesized cortical and white matter regions of interest and performance on a spatial working memory task in a typically developing cohort of children and adolescents. However, we did not observe a significant relationship between regional superior frontal or parietal cortical morphology, nor between white matter microstructure of the parietal branch of the superior longitudinal fasciculus and spatial working memory performance. We did find evidence for a relationship between parental education and spatial working memory performance that may be of interest in future studies.

Chapters 2 and 3 benefitted from general contributions, feedback, and review from Akshoomoff, N., Brown, T.T., Thompson, W.K., Hagler, D.J., Dale, A.M., and Jernigan, T.L. The dissertation author was the primary investigator and author of this paper.

CHAPTER 4: STRUCTURAL NEURAL CORRELATES OF RESPONSE INHIBITION IN A TYPICALLY DEVELOPING COHORT

Prologue:

Chapter 4 contains both published and unpublished material. For clarity, this chapter has been separated into three sections. The first section (4.1) contains unpublished baseline cortical analyses. The second section (4.2) is a reproduction of the published longitudinal cortical findings in its entirely (Curley et al., 2017). The customary background and introduction section for 4.1 can be found in section 4.2, as both sections cover the cortical region of interest. The third section (4.3) contains both the baseline and longitudinal white matter analyses for this domain of interest.

4.1 **Specific aim 5: To examine the relationship between the pars opercularis and response inhibition.**

4.1.1 Methods

Primary analyses used multiple linear regression models to evaluate the relationship of age, age^2, gender, and hypothesized bilateral region of interest on performance. The same transformation was applied to the SSRT as stated in section 4.2 (using the natural logarithm and inverting scores). For each bilateral cortical region of interest, a Bonferroni correction of $p=0.05/2 =0.025$ was used to correct for the two primary tests of pars opercularis surface area and thickness. Pending any significant bilateral regional effects, post hoc analyses investigated the right and left hemisphere region of interest in separate models.

4.1.2 Behavioral Results

A multiple regression model was used to predict transformed SSRT scores using age, age^2, and gender as predictors for the baseline cohort. Both the linear and quadratic age terms showed a strong relationship to performance ($p<0.05$). The effect of gender was also significant, with females performing better than males. Preliminary models investigating the effects of parental education and household income found no relationship to performance.

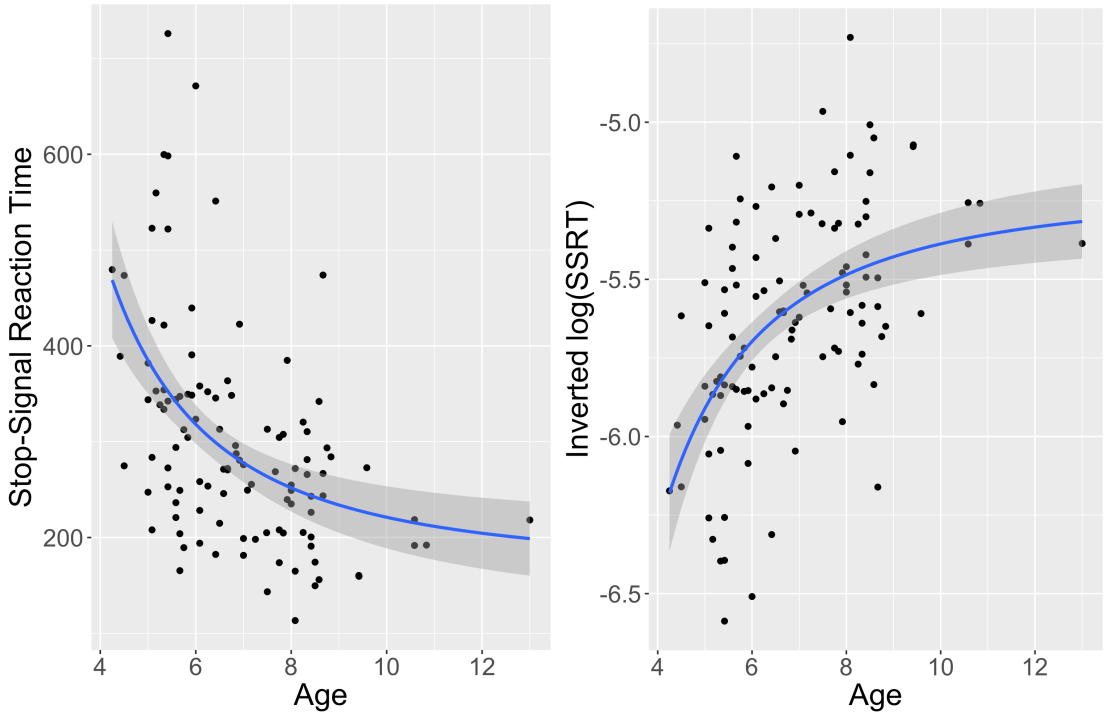

Figure 4.1 Raw stop-signal reaction time (left) and inverted log(SSRT) (right) with quadratic fit lines and shaded 95% confidence intervals.

Table 4.1Effects of age and gender on stop-signal performance

Predictors	*B* value	*t* value	*p* value
Age	0.10	5.65	0.000***
Age^2	-0.02	-2.33	0.021*
Gender	-0.13	-2.28	0.024*

All predictors have been centered (demeaned)
Female is coded as negative

4.1.3 Results

Surface area of the bilateral pars opercularis showed a positive relationship to performance when controlling for linear and quadratic age, gender, and total area. Conversely, total area showed a negative but non-significant relationship to performance, highlighting the relative contribution of the pars opercularis area in contrast. Bilateral pars opercularis thickness did not show a relationship to performance (Table 4.2).

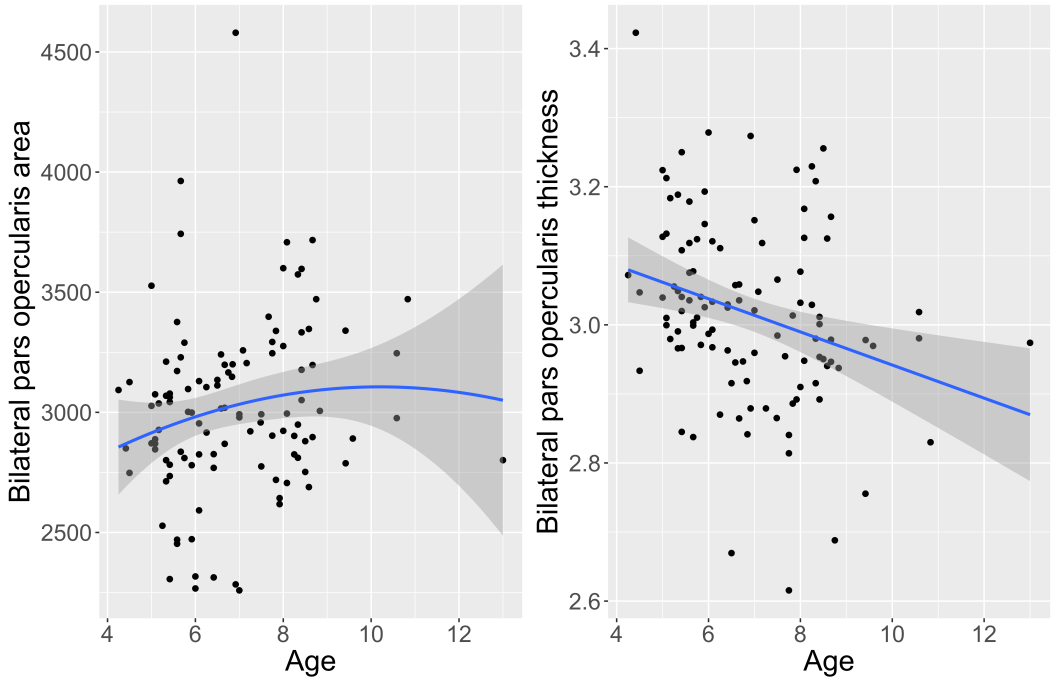

Figure 4.2 Pars opercularis area (left, quadratic fit line) and thickness (right, linear fit line) with shaded 95% confidence interval around the mean.

Table 4.2 Effect of bilateral pars opercularis area (model 1) and thickness (model 2) on response inhibition performance

Predictors	*B* value	*t* value	*p* value
Model 1 (Area)			
Age	0.10	5.27	0.000***
Age^2	-0.02	-2.33	0.022*
Gender	-0.15	-2.37	0.020*
Bilateral PO area	0.00	3.10	0.003**
Total area	-0.00	-1.35	0.181
Model 2 (Thickness)			
Age	0.10	5.11	0.000***
Age^2	-0.02	-2.22	0.029*
Gender	-0.15	-2.50	0.014*
Bilateral PO thickness	-0.27	-1.14	0.257

All predictors have been centered (demeaned)
Female is coded as negative

The right and left pars opercularis surface areas were examined in separate models to investigate the relative strength of association of each with performance. Both the left and right pars opercularis showed a relationship to performance at an uncorrected level of significance ($p<0.05$), although the right pars opercularis surface area seemed to exhibit a slightly stronger relationship (Table 4.3).

Table 4.3 Effect of right pars opercularis surface area (model 1) and left pars opercularis surface area (model 2) on response inhibition performance

Predictors	*B* value	*t* value	*p* value
Model 1 (Right PO area)			
Age	0.10	5.32	0.000***
Age^2	-0.07	-2.13	0.036*
Gender	-0.13	-1.95	0.054
Right PO area	0.00	2.47	0.015*
Total area	-0.00	-0.89	0.375
Model 2 (Left PO area)			
Age	0.10	5.47	0.000***
Age^2	-0.02	-2.46	0.016*
Gender	-0.16	-2.46	0.016*
Left PO area	0.00	2.05	0.043*
Total area	-0.00	-0.41	0.686

All predictors have been centered (demeaned)
Female is coded as negative

Additional follow up models investigated possible interactions between age, gender, and unilateral pars opercularis surface area on performance. In the right pars opercularis surface area model, only age and our region of interest were significant predictors of performance ($p<0.05$). In the left pars opercularis surface area model, age was a significant predictor of performance. In addition, there was a significant age by left pars opercularis area interaction as well as an age by gender interaction (both $p<0.05$). The main effect of left pars opercularis significant was no longer present. Similarly, the main effect of gender is no longer present in either model (Table 4.4).

Table 4.4 Effects of interactions with right PO surface area (model 1) and left PO surface area (model 2) on performance

Predictors	*B* value	*t* value	*p* value
Model 1 (Right PO area)			
Age	0.10	5.45	0.000***
Gender	-0.06	-0.86	0.393
Right PO area	0.00	2.56	0.012*
Age x Right PO area	-0.00	-0.06	0.951
Gender x Right PO area	0.00	1.29	0.201
Age x Gender	0.06	1.44	0.153
Age x Gender x Right PO area	0.00	0.47	0.642
Total area	-0.00	-1.01	0.315
Model 2 (Left PO area)			
Age	0.11	5.60	0.000***
Gender	-0.06	-0.71	0.480
Left PO area	0.00	0.42	0.676
Age x Left PO area	-0.00	-2.13	0.035*
Gender x Left PO area	-0.00	-0.29	0.773
Age x Gender	0.09	2.12	0.036*
Age x Gender x Left PO area	-0.00	-0.30	0.767
Total area	-0.00	-0.26	0.797

All predictors have been centered (demeaned)
Female is coded as negative

4.1.4 Discussion

This baseline analyses above were conducted to investigate the relationship between the bilateral pars opercularis and behavioral response inhibition. The goal of the analyses on the baseline cohort was primarily to assess individual differences at first exposure to the task without influence of experience or practice effects and to assess the hypothesized relationships in a set of typically developing children and young adolescents. The bilateral pars opercularis area showed a significant positive relationship to better SSRT performance, whereas the bilateral pars opercularis thickness did not show a relationship to performance.

The current analyses on the baseline cohort suggested a relationship between both the right and left PO area and performance at an uncorrected level of significance, although the relationship between the right PO and performance seemed marginally stronger. Follow-up interaction models suggested a main effect of right PO area but no interactions. However, the left PO area interaction model found an effect of both age x gender and age x left PO area, although these relationships were not particularly robust. We see some evidence for interactions with age and left pars opercularis area as well as age and gender in the baseline analyses. This may be influenced, in part, by the large degree of individual variation present in the younger ages relative to the older ages. However, further research is needed to fully explore the relationship between developing regional cortical surface area and age-dependent developmental changes in behavioral performance.

4.2 Curley, L.B., Newman, E., Thompson, W.K., Brown, T.T., Hagler, D.J., Akshoomoff, N., Reuter, C., Dale, A.M., Jernigan, T.L. (2017) "Cortical morphology of the pars opercularis and its relationship to motor inhibitory performance in a longitudinal, developing cohort.". *Brain Structure & Function*. DOI: 10.1007/s00429-017-1480-5

4.2.1 Abstract

Introduction: This study investigates the relationship between variability in cortical surface area and thickness of the pars opercularis of the inferior frontal gyrus and motor-inhibitory performance on a stop-signal task in a longitudinal, typically developing cohort of children and adolescents.

Methods: Linear mixed effects models were used to investigate the hypotheses that (1) cortical thinning and (2) a relatively larger cortical surface area of the bilateral pars opercularis of the inferior frontal gyrus would predict better performance on the stop-signal task in a cohort of 110 children and adolescents 4 to 13 years of age, with one to four observations (totaling 232 observations).

Results: Cortical thickness of the bilateral opercular region was not related to inhibitory performance. However, independent of age, gender, and total cortical surface area, relatively larger cortical surface area of the bilateral opercular region of the inferior frontal gyrus was associated with better motor inhibitory performance. Follow-up analyses showed a significant effect of surface area of the right pars opercularis, but no evidence for an effect of area of left pars opercularis, on motor inhibitory performance.

Conclusion: These findings are consistent with previous work in adults showing that cortical morphology of the pars opercularis is related to inhibitory functioning. It also expands upon this literature by showing that, in contrast to earlier work highlighting the importance of cortical thickness of this region in adults, relative cortical surface area of the pars opercularis may be related to developing motor-inhibitory functions during childhood and adolescence. Relationships between cortical phenotypes and individual differences in behavioral measures may vary across the lifespan.

4.2.2 Introduction

Research has long focused on the neural substrates of psychiatric disorders. However, in recent years there has been a greater shift toward identifying neurobiological correlates of basic behavioral phenotypes that can be measured dimensionally and cut

across disorders (Insel et al. 2010). One behavioral phenotype that has received attention is response inhibition (Casey et al, 1997; Liddle et al. 2001; Johnstone et al. 2007; Forstmann et al. 2008; Tamm et al. 2002; Newman et al. 2015a; Madsen et al. 2010). Motor response inhibition is typically defined as the ability to withhold a planned motor response to a stimulus or to stop an ongoing response (Aron et al. 2004). Impairment in this basic process has been most commonly associated with attention-deficit/hyperactivity disorder (ADHD) (Barkley 1997), though it has been associated with other psychiatric disorders as well, such as anxiety and mood disorders (Wright et al. 2014), and schizophrenia (Ethridge et al. 2014).

Response inhibition is most often measured using standardized, continuous-performance tasks such as the stop-signal paradigm (Logan and Cowan 1984) or a variant of the go/no-go task (GNG) (Conners et al. 2003; Rosvold et al. 1956). The ability to inhibit a preplanned motor response has been linked to a highly interconnected, predominantly right-lateralized circuit involving frontal, motor, and striatal regions (Chambers et al. 2009). According to one model, the inferior frontal gyrus (IFG) is thought to be the origin of a "stop" signal, inhibiting the motor response via direct stimulation of the subthalamic nucleus and resulting in inhibition of motor output of the thalamus (Chambers et al. 2009). This description of the neural system underlying response inhibition is supported by functional magnetic resonance imaging (fMRI) studies. Functional studies, both in adults and in clinical populations, implicate the IFG as a region involved in successful response inhibition (Aron et al. 2006; Eagle et al. 2008). Some previous investigations into the functional correlates of cognitive control and

response inhibition suggest gender differences in regional activation (Bell et al. 2006; Garavan et al. 2006; Liu et al. 2012; Weiss et al. 2003) and age by gender interactions during adolescence (Rubia et al. 2013; Rubia et al. 2010).

Despite the extensive work on brain functional correlates of response inhibition in healthy populations, research on the relationship between response inhibition and cortical morphology is limited, particularly in developing children and adolescents. Several studies have addressed this indirectly by examining neuroanatomical differences between children with ADHD and comparison groups. Previous studies comparing children and adolescents with and without ADHD symptoms found thinner cortex in ADHD and a relationship between increased rate of cortical thinning and the severity of ADHD symptoms (Shaw et al. 2011, 2013; Batty et al. 2010; Proal et al. 2011). Shaw and colleagues argued their findings supported a dimensional approach to ADHD, where the disorder is considered one extreme of a continuum of a behavioral phenotype. In other words, rather than simply investigating binary groups of participants with or without a diagnosis, a better approach to studying typical development and the development of clinical disorders would be examining the entire range of cognitive and behavioral performance.

Madsen and colleagues (2010) used diffusion-weighted imaging to examine associations between stop-signal reaction time (SSRT) performance, which is operationally defined as the ability to withhold or cancel an initiated motor response, and white matter microstructure in children. They found that after controlling for age, better response inhibition was associated with higher fractional anisotropy in the white matter

underlying the IFG. However, no studies have examined relationships of SSRT to both thickness and surface area of the IFG in this age group. In a study of young adults with or without a childhood diagnosis of ADHD, our group found a thinner opercular region was related to better performance on a Go/No Go task, independent of ADHD status (Newman et al. 2015). However, cortical surface area of the same region was unrelated to performance.

The relationships among surface area, thickness, and response inhibition observed in adults may not translate directly to brain-behavior relationships in children. Cortical surface area and cortical thickness show distinct developmental trajectories, which may be mediated by distinct developmental processes and distinct genetic influences (Panizzon et al. 2009; Brown et al. 2012; Jernigan et al. 2011; Chen et al. 2012). It is therefore also necessary to begin to investigate differences in these relationships as a function of age (Casey et al. 2014). Our group recently took this approach in order to determine neural architectural correlates of anxiety in typically developing children and adolescents (Newman et al. 2015b). We found that higher anxiety was associated with thinner cortex globally and decreased relative surface area of the ventromedial prefrontal cortex, but that the strength of these associations diminished with age. It is therefore reasonable to consider whether a similar age interaction may be present in any association between response inhibition and cortical morphology. In addition, our group found that relatively larger surface area of the anterior cingulate was positively related to better performance on a flanker task in children under 12 years of age, but this relationship was not present in older adolescents examined in the same study (Fjell et al.

2012). Thus, it is reasonable to hypothesize that in our younger developing cohort, there may be a relationship between regional surface area and motor-inhibitory performance.

The current project aims to build on and extend our previous findings in adults (Newman et al. 2015a) by examining the relationship between both cortical thickness and cortical surface area and motor-inhibitory performance in typically developing children and adolescents. Due to the distinct developmental trajectories of cortical surface area and thickness (Brown et al. 2012; Wierenga et al. 2014), we may observe a different pattern of results relative to adults. Our primary hypotheses were (1) that apparent thinning of the pars opercularis of the inferior frontal gyrus would correspond to better performance, independent of age and gender, and (2) that a relatively larger surface area of the same region would correspond to better response inhibition, independent of age and gender. Given the inconsistent laterality of previous findings, we did not have strong hypotheses about laterality, and so for both primary hypotheses we examined the bilateral pars opercularis. Contingent upon finding significant effects in the bilateral region of interest and in light of previous findings suggesting that these associations may differ as a function of age and/or gender, follow-up analyses examined age and gender interactions. Finally, we examined associations with the right and left pars opercularis separately.

4.2.3 Methods

4.2.3.1 Participants

Participants were part of the Pediatric Longitudinal Imaging, Neurocognition, and Genetics study at the University of California, San Diego. Prior to participation,

participants under seven years old provided verbal assent, participants over seven years old provided written assent, and parents or guardians provided written consent after an oral description of the study was provided. Participants were required to understand directions presented in English and have normal or corrected-to-normal hearing and vision. Potential participants with neurological disorders, significantly preterm birth, a diagnosis of autism spectrum disorder, mental retardation, and/or head trauma with loss of consciousness lasting more than 30 minutes, or daily drug or alcohol use by the mother during pregnancy, were excluded.

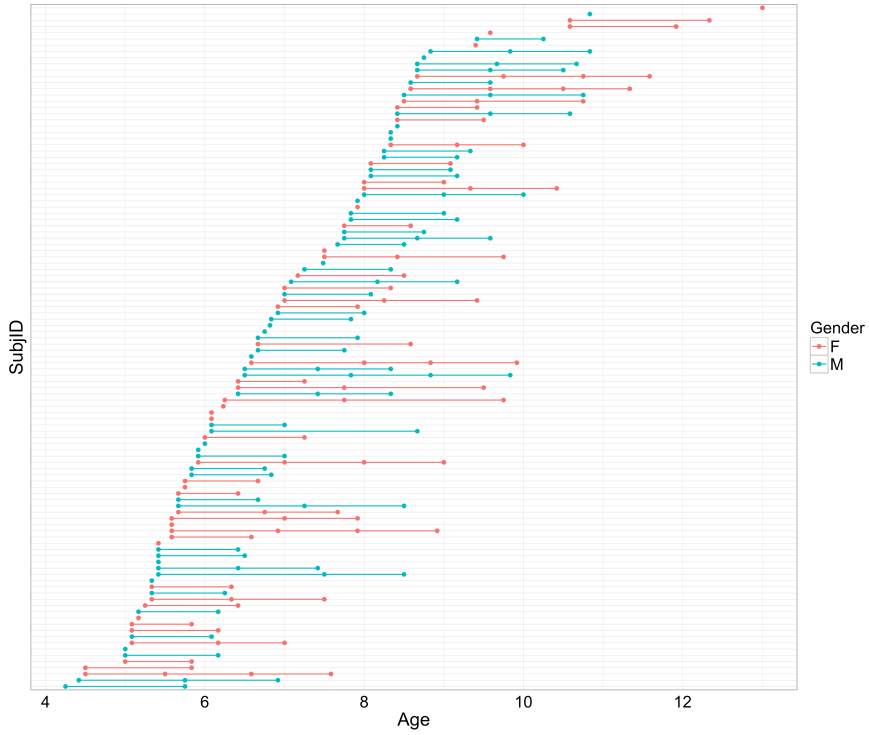

Figure 4.3 Summary of repeated-measures. Age is plotted on the x-axis, grouped by subject on the y-axis. Female participants are shown in red, male participants in light blue.

The sample consisted of 110 typically developing children (59 male) between the ages of 4 and 13 years. Of these 110 participants, 82 had complete measurements for two visits, 32 had three visits, and 8 had four visits taken at approximately one-year intervals, for a total of 232 visits. The average age of participants at the first visit was 6.9 years (s.d. = 1.57 years, n=110). At the second visit, the average age was 7.90 years (s.d.=1.45 years, n=82), at the third visit 9.07 years (s.d.=1.31 years, n=32), and the fourth visit 9.71 years (s.d.=1.30 years, n=8) (see Table 1 and Fig 1).

Table 4.5 Summary of demographic and repeated measures data. Number of participants, age, and stop-signal reaction time are outlined for the overall sample and also by male/female subgroups. Age and stop-signal reaction time means and standard deviations (s.d.) are given for each time point for the overall sample and by male/female subgroups. Handedness is reported for the overall sample (R= right-handed, L=left handed, Amb = ambidextrous, NA = not reported). Race and ethnicity is reported for the overall sample.

Demographics		Total	Male	Female
Number of participants		110	59	51
Age (mean, s.d. in yrs)	Baseline (N=110)	6.9(1.57)	6.92(1.41)	6.87(1.76)
	Time point 2 (N=82)	7.90(1.45)	7.95(1.29)	7.85(1.63)
	Time point 3 (N=32)	9.07(1.31)	9.26(1.27)	8.90(1.37)
	Time point 4 (N=8)	9.71(1.30)	9.83(0.00)	9.69(1.41)
Stop-signal reaction time (mean/s.d. in ms)	Baseline (N=110)	298.62(114.33)	316.06(129.68)	278.45(90.64)
	Time point 2 (N=82)	258.50(95.04)	267.00(99.84)	248.65(89.46)
	Time point 3 (N=32)	232.77(98.38)	241.52(121.76)	225.05(75.13)
	Time point 4 (N=8)	232.47(112.52)	238.80(0.00)	231.56(121.51)
*Handedness (R/ L/ Amb/ NA)		83/ 14/ 9/ 4		
**Race/ Ethnicity	Caucasian	54		
	African American	5		
	Hispanic/Latino	36		
	Asian	13		
	Pacific Islander	1		
	American Indian	1		
	Mixed race	22		
	Other	3		

*4 participants did not identify handedness

**Participants were free to mark whichever race/ethnicity options they chose: if multiple races were checked s/he was categorized as "Mixed race", if none was selected s/he was categorized as "Other". Some participants marked only "Hispanic/Latino", while others marked "Hispanic/Latino" in addition to a race. Therefore, the total number reported in each category does not sum to the total number of participants.

4.2.3.2 Stop-Signal Reaction Time (SSRT)

We administered the stop signal task from the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition Ltd., Cambridge, UK; Fray et al. 1996). While seated at a computer, participants rested the index finger of each hand

on left and right response buttons. A fixation circle was presented for 500ms, after which an arrow appeared in the center pointing either right or left. The participant was instructed to respond with the relevant response key (right or left) corresponding to the direction of the arrow, as quickly as possible. The stop signal task is made up of 'go' trials (75%) and 'stop' trials (25%) presented over five blocks of 64 trials each. On the 'stop' trials, a tone is presented at a variable delay after the 'go' signal, indicating that the participant should withhold the response. A participant's stop-signal delay (SSD) is the delay at which he/she can successfully withhold his/her response 50% of the time. The stop-signal reaction time (SSRT) is calculated for each participant by subtracting the SSD from the median reaction time on 'go' trials. This measure indicates the time each individual participant needs to refrain from executing a preplanned motor action upon presentation of a stop signal, with lower reaction times indicating better performance. For all behavioral and structural analyses, the logarithm of stop-signal reaction time was used as a variance stabilizing transformation. The log(SSRT) measure was then inverted so that higher scores correspond to better performance allowing for more intuitive interpretation of results (see Fig. 2a and 2b).

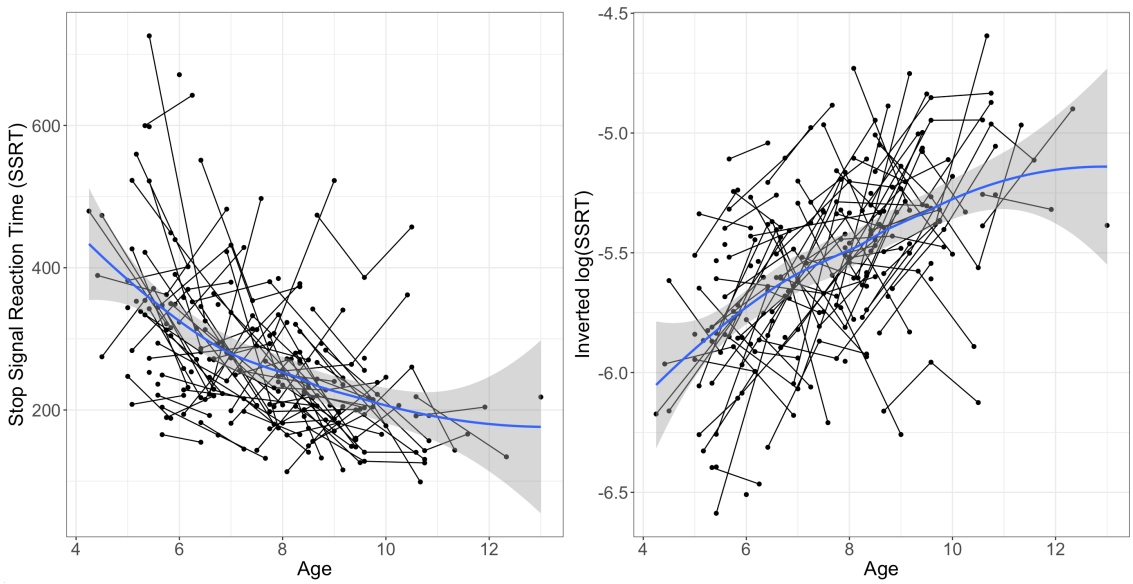

Figure 4.4 (a) Stop-signal reaction time (SSRT) as a function of age. Lower SSRT scores indicate better performance (i.e. faster reaction times). The blue line is a smooth loess fit to the raw data, with shaded 95% confidence intervals around the mean at each point. (b) Inverted log(SSRT) scores as a function of age, where higher scores indicate better performance. Inverted log(SSRT) scores were used as the dependent measure in all models.

4.2.3.3 Neuroimaging

All neuroimaging data were collected at UC San Diego using the PING protocol (see Jernigan et al. 2016b for details). This is a multiple modality, high-resolution magnetic resonance imaging (MRI) protocol during which participants underwent a one-hour imaging session including acquisition of TI, T2, and diffusion weighted images. All data were evaluated for quality at multiple stages during processing, including registration, motion correction, and removal of artifacts. Automated protocols available in Freesurfer (Fischl, 2004) in addition to analyses developed at UC San Diego Multimodal Imaging Laboratory were used for processing and morphometric analysis. The right and left pars opercularis were extracted using the Desikan atlas available in Freesurfer (Desikan et al. 2006). To create the bilateral pars opercularis thickness region

of interest, the right and left pars opercularis measures were averaged. To create the bilateral pars opercularis surface area region of interest, the right and left pars opercularis areas were added together (see Fig 3). Post-hoc cortical surface-based mapping analyses relied upon nonlinear, surface-based registration constrained by cortical folding patterns (Fischl et al. 1999), and used surface-constrained, iterative smoothing with 705 iterations, equivalent to ~33 mm full width at half maximum (Hagler et al. 2006).

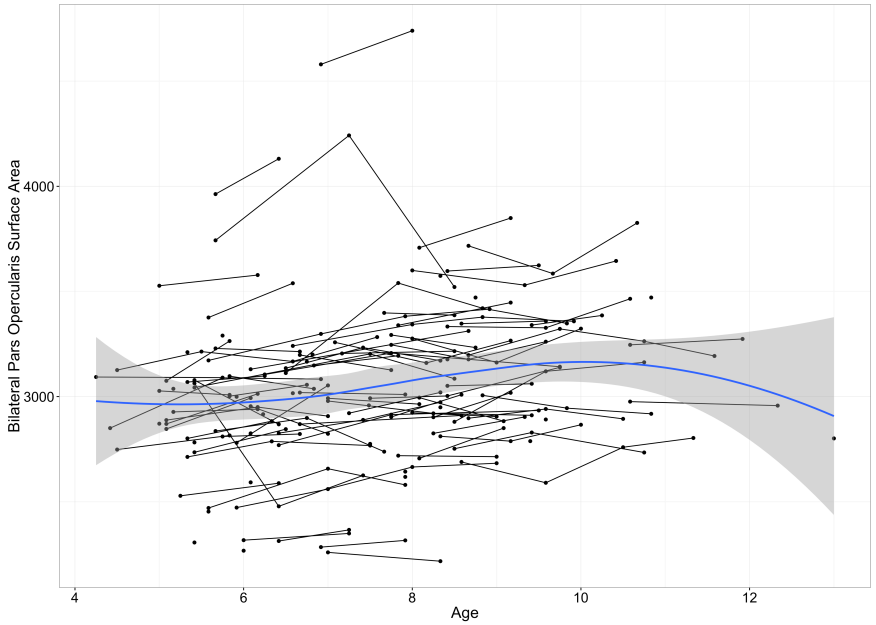

Figure 4.5 Bilateral pars opercularis surface area is shown on the y-axis and age is shown on the x-axis. The blue line is a smooth loess fit to the raw data, with shaded 95% confidence intervals for the mean at each point.

4.2.3.4 Analysis

We tested the primary hypotheses with two separate region of interest analyses using longitudinal mixed-effects regression models to predict inverted log(SSRT) scores from cortical thickness and surface area of the pars opercularis. Analyses were carried out using the nlme package in R with a covariance structure of AR(1). Bilateral pars

opercularis thickness and surface area were both centered (demeaned) prior to analysis and entered as fixed effects. Preliminary analyses investigating age and gender effects on stop-signal performance indicated an effect of gender, which was then included in all primary models investigating region-of-interest effects. Age and gender were centered (with female coded as negative and male as positive) and entered as fixed effects in the model, while subject ID was entered as a random effect. Total cortical surface area was centered and also included as a covariate in the surface area model in order to estimate the effect of *relative* surface area of the pars opercularis. Scanner was included as a covariate of no interest. For each of the two main hypotheses, a Bonferroni-corrected p-value of 0.025 was used as the threshold for significance.

If either of the primary models examining bilateral pars opercularis were significant, interactions between age, gender, and the bilateral pars opercularis were included in a later model to determine if significant interactions were present. Finally, the left and right pars opercularis were examined in separate models.

4.2.4 Results

The average stop-signal reaction time (SSRT) for all participants at baseline was 298.62 ms (s.d. = 114.33 ms, n=110). At the second visit, the average score was 258.50 ms (s.d.=95.04 ms, n=82), at the third visit the average score was 232.77 ms (s.d.=98.38 ms, n=32), and at the fourth visit the average was 232.47 ms (s.d.=112.52 ms, n=8) (see Table 1).

The hypothesis that cortical thickness in the bilateral pars opercularis would significantly predict inverted log(SSRT) scores was tested using a linear mixed-effects model covarying for age and gender (Table 2). Age and gender were both significant predictors of inverted log(SSRT) scores, with older participants ($t = 7.62$, $p < 0.001$) and females ($t = -2.09$, $p = 0.04$) performing better. However, there was no significant relationship between bilateral pars opercularis thickness and inverted log(SSRT) scores ($t = -1.33$, $p = 0.19$).

Table 4.6 Inverted log(SSRT) scores were predicted using a linear mixed-effects model. Predictors included bilateral pars opercularis thickness and covariates were age, gender, and scanner. Where noted, predictors were centered (demeaned).

Fixed effects	B value	t-value	p-value
ºAge	0.10	7.62	0.0000***
ºGender	-0.11	-2.09	0.0389*
ºBilateral pars opercularis thickness	-0.27	-1.33	0.1853
Scanner	0.12	1.37	0.1682
Random effect: Subject			

º predictor has been centered (demeaned)
* $p < 0.05$
*** $p < 0.001$

The hypothesis that relative surface area in the bilateral pars opercularis would significantly predict inverted log(SSRT) scores was tested with a similar linear mixed-effects model with total surface area as an additional covariate (Table 3). We found a significant, positive relationship between bilateral pars opercularis surface area and inverted log(SSRT) scores ($t = 2.53$, $p = 0.01$), where larger surface area was associated with better performance on the stop-signal reaction time task. Consistent with the

thickness model, older participants ($t = 7.76$, $p < 0.001$) performed better. Total cortical surface area was not related to inverted log(SSRT) scores.

Table 4.7 Inverted log(SSRT) scores were predicted using a linear mixed-effects model. Predictors included bilateral pars opercularis surface area and covariates were age, gender, total cortical surface area, and scanner. Where noted, predictors were centered (demeaned).

Fixed effects	B value	t-value	p-value
ºAge	0.10	7.76	0.0000***
ºGender	-0.11	-1.94	0.0553
ºBilateral pars opercularis surface area	0.00	2.53	0.0127*
ºTotal cortical surface area	-0.00	-0.84	0.4049
Scanner	0.10	1.15	0.2535
Random effect: Subject			

º predictor has been centered (demeaned)
* $p < 0.05$
*** $p < 0.001$

Because the model examining bilateral pars opercularis surface area was significant, an additional follow-up analysis examined interactions between age, gender, and bilateral pars opercularis surface area (Table 4). In a model including all interactions between age, gender, and bilateral pars opercularis surface area there were no significant interaction terms. We then performed follow-up analyses investigating left and right pars opercularis surface area separately (Table 5). Right pars opercularis surface area was positively related to better SSRT performance ($t = 2.60$, $p = 0.01$), but the effect of left pars opercularis surface area was not significant ($t = 1.21$, $p = 0.23$). Of note, we had two main a-priori hypotheses regarding both bilateral pars opercularis surface area and thickness, and thus we corrected for two statistical tests (see 'Analysis', above). The additional models exploring interactions between age, gender, and bilateral pars opercularis surface area and then left and right pars opercularis were not corrected for

multiple comparisons as they were post-hoc tests contingent upon prior significant effects.

Table 4.8 Inverted log(SSRT) scores were predicted using a linear mixed-effects model. Predictors included bilateral pars opercularis surface area and covariates were age, gender, total cortical surface area, and scanner. All interaction terms for age, gender, and bilateral pars opercularis surface area were included. Where noted, predictors were centered (demeaned).

Fixed effects	B value	t-value	p-value
ºAge	0.10	7.20	0.0000***
ºGender	-0.11	-1.97	0.0516
ºBilateral pars opercularis surface area	0.00	2.27	0.0250*
ºTotal cortical surface area	-0.00	-0.91	0.3664
ºAge x ºGender	0.04	1.53	0.1289
ºAge x ºbilateral pars operc	-0.00	-0.56	0.5780
ºGender x º bilateral pars operc	0.00	0.81	0.4191
ºAge x ºGender x º bilateral pars operc	0.00	1.49	0.1384
Scanner	0.10	1.14	0.2574
Random effect: Subject			

º predictor has been centered (demeaned)
* $p < 0.05$
*** $p < 0.001$

Table 4.9 Inverted log(SSRT) scores were predicted using linear mixed-effects models. (a) Surface area of the left pars opercularis with covariates age, gender, total cortical surface area, and scanner. (b) Surface area of the right pars opercularis with covariates age, gender, total cortical surface area, and scanner. Where noted, predictors were centered (demeaned).

a) Left pars opercularis model	B value	t-value	p-value
ºAge	0.11	7.92	0.0000***
ºGender	-0.12	-1.98	0.0505
ºLeft pars opercularis surface area	0.00	1.21	0.2295
ºTotal cortical surface area	0.00	0.10	0.9196
Scanner	0.11	1.18	0.2399
b) Right pars opercularis model	B value	t-value	p-value
ºAge	0.10	7.75	0.0000***
ºGender	-0.10	-1.62	0.1084
ºRight pars opercularis surface area	0.00	2.60	0.0106*
ºTotal cortical surface area	-0.00	-0.73	0.4659
Scanner	0.11	1.23	0.2214
Random effect: Subject			

º predictor has been centered (demeaned)
* $p < 0.05$
*** $p < 0.001$

To visualize the relationship between age and surface area, we created post-hoc, vertex-wise maps of (uncorrected) t-statistics for the surface area effects on inverted log(SSRT) scores, controlling for age, gender, total cortical surface area (which were all demeaned, as above) and scanner. For this visualization, we used the baseline observations only (N=110). The color scale codes t-statistic values, ranging from -5 to 5 with the boundary between warm and cool colors at zero. As reported above, there appears to be an association between relative surface area of the pars opercularis and SSRT performance. In addition, the visualization suggests that there may be modest positive and negative associations across both the left and right cortical surface in other regions (see Fig 4).

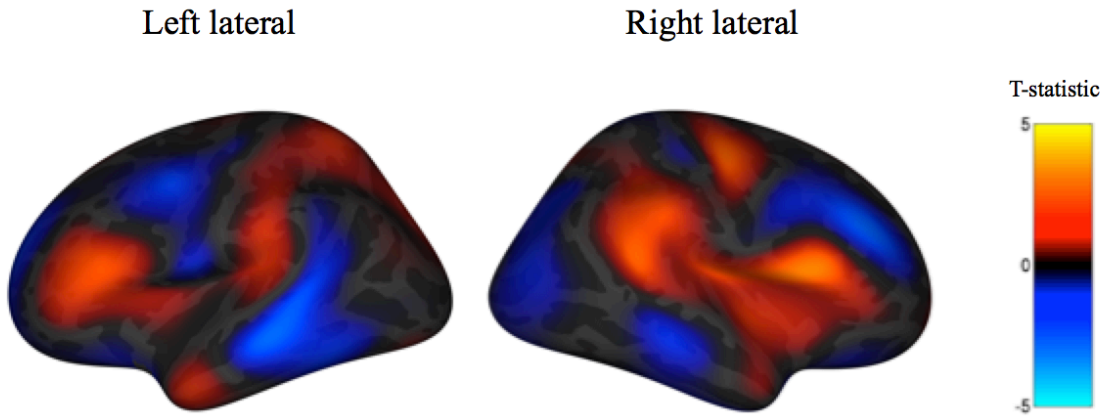

Figure 4.6 Post-hoc exploratory vertex-wise maps depicting effect of inverted log(SSRT) on cortical surface area. Covariates include, demeaned age and gender, and scanner. Heat maps reflect the t-statistic values on a scale from -5 to 5.

4.2.5 Discussion

This study investigated the relationship between variation in regional cortical morphology and performance variability on a response-inhibition task in a longitudinal, typically developing cohort. Based on previous work, we focused our analyses on the pars opercularis of the inferior frontal gyrus (Aron et al. 2006; Chambers et al. 2009; Eagle et al. 2008, Newman et al. 2015a). The primary finding from this study was that greater relative cortical surface area in the bilateral pars opercularis was associated with better response inhibition. Thickness in this region showed no significant relationship with inhibitory functioning.

These results stand in contrast to a recent study in an adult sample showing that cortical thickness in this region, but not surface area, was associated with response inhibition. Specifically, better inhibitory functioning was associated with thinner cortex in the IFG. A number of methodological differences could contribute to the differences

observed in these two studies. First, the previous study used percentage of commission errors on a go/no go task to measure response inhibition, whereas the current study used an estimate of time needed to successfully inhibit a response on a stop signal task. Second, the previous sample was comprised entirely of young adults, whereas the current sample was comprised of children ranging in age from 4 to 13. Third, the sample in the previous study was comprised of individuals diagnosed with ADHD as well as comparison participants, and therefore reflected wide variability in inhibitory functioning. The current sample was of typically developing children.

While there are differences in task demands between the go/no go and stop signal tasks, functional studies have linked both to the function of the IFG (Chikazoe et al. 2007; Chikazoe, 2010; Aron et al. 2015). It may be that age plays a larger role in the different relationships observed between the pars opercularis and performance observed in these two studies. In a recent cross-sectional study linking anxiety to regional cortical morphology in children and adolescents, our group found that regional surface area, but not regional thickness, predicted behavior (Newman et al. 2015b). Specifically, greater relative surface area expansion of the ventromedial prefrontal cortex was associated with lower self-reported anxiety.

Recent studies have shown that there is very little overlap between the genetic factors that influence surface area and thickness, although they are both highly heritable (Chen et al. 2011; Chen et al. 2012; Panizzon et al. 2009), and their developmental trajectories are markedly different (Brown et al. 2012). On average, surface area increases steadily until middle childhood and begins to taper off and then contract in adolescence

and early adulthood, and these changes occur at different rates in different regions of the cortex. In contrast, cortical thickness decreases consistently and continuously over the course of development (Brown et al. 2012; Walhovd et al. 2016). Therefore, future work should aim to assess the differential contributions of regional surface area and thickness to cognitive performance in developing cohorts.

The exploratory vertex-wise surface maps of the relationship between regional surface area and response inhibition show the predicted effect in the pars opercularis. These maps provide additional information to readers about the degree of variability across the cortical surface in the direction and magnitude of the relationship between relative surface area expansion and SSRT performance.

4.2.6 Conclusions & Limitations

In this study we examined a large number of typically developing children in a longitudinal cohort to determine whether we could confirm an association between regional morphology of the inferior frontal gyrus and performance on the stop-signal task. The results suggested a relationship between regional cortical surface area of the pars opercularis and performance on this motor inhibitory task. In contrast to our group's earlier work highlighting the relationship between the cortical thickness of this region and inhibitory control task performance in adults (Newman et al. 2015a), it appears that the relative cortical surface area of the pars opercularis may be especially important for the development of inhibitory control, although directly assessing this relationship requires further examination. This highlights the possibility that different cortical phenotypes may

show differential or unique relationships to behavioral functions at different points during development. However, among the many possible influences on developing brain structure and response inhibition, this study evaluated only age and gender as covariates. In addition to age and gender, there is evidence that genetics, experience, socioeconomic status, and many other factors could affect both measures of brain structure and cognitive performance (Chen et al. 2012; Noble et al. 2015). Future analyses should also evaluate other covariates thought to relate to both structural brain development and response inhibition in order to form a more complete picture of the factors influencing these relationships.

4.3 **Specific aim 6: To investigate the relationship between the striatal inferior frontal cortical white matter (SIFC) and inferior frontal – superior frontal cortical white matter (IFSFC) and response inhibition**

4.3.1 Introduction

Executive control and inhibitory functions improve drastically during childhood and adolescence (Madsen et al., 2010; Luna et al., 2001; Tillman et al., 2008). Response inhibition, typically defined as the ability to withhold a planned motor response to a stimulus or to stop on ongoing response, displays a protracted, nonlinear developmental trajectory during childhood and adolescence (Aron et al. 2004, 2007; Jernigan et al., 2001). The current study aims to investigate the relationship between subcortical white matter projections underlying cortical regions involved in response inhibition and performance. Although the subcortical and white matter regions hypothesized to be involved in successful response inhibition have not been as extensively studied as cortical regions, we can infer which white matter projections may be important to successful inhibition based on their relationships to the hypothesized cortical network for response inhibition. The ability to inhibit a preplanned motor response has been tied to frontal, motor, and striatal cortical regions using a mix of functional and structural MRI (Chambers et al., 2007; Eagle et al., 2008; Stevens et al., 2007; Aron et al., 2007). The specific cortical regions most often implicated in motor response inhibition are the inferior frontal gyrus, opercular regions, and presupplementary motor areas. In addition, there is some evidence for a relationship between response inhibition and the subthalamic nucleus (STN) in the basal ganglia (Aron et al., 2006, 2007; Madsen et al.; 2010; Chambers et al., 2007). The primary driver of the actual stopping mechanism in response

inhibition paradigms seems to stem from the inferior frontal gyrus (Aron et al. 2004, 2007; Verbruggen and Logan, 2008; Tillman et al., 2007; Shaw et al., 2007, 2011, Rubia et al., 2003).

A study previously conducted in a typically developing cohort of children and adolescents found evidence for a relationship between regional white matter structure and stop-signal performance. Madsen and colleagues (2010) investigated regional white matter using tract-based spatial statistics to measure microstructure of the white matter underlying the right IFG and preSMA, regions hypothesized a-priori to be involved based on previous fMRI findings. Their results suggest that better response inhibition performance is related to higher FA and lower perpendicular diffusivity in both of the regions examined. In addition, these effects were still present after controlling for age and whole-brain estimates of the parameters measured. Madsen and colleagues suggest the results may be due to variation in the participant's maturational stage, changes in the response inhibition network due to environmental factors, or they may be a product of stable, underlying individual differences (2010).

Response inhibition is a crucial component of typical human development, although the relationship between regional brain structure and response inhibition during typical human development is still poorly defined. Previous studies investigating the development of response inhibition in longitudinal cohorts of typically developing children as well as children with attention-deficit-hyperactivity disorder suggested a protracted pattern of development, highlighting the importance of examining these relationships in both cross-sectional as well as developing cohorts (Shaw et al., 2011;

2007). However, prior longitudinal studies have focused primarily on cortical associations with performance, and it is unknown whether these patterns will be present when examining white mater associations. The following analyses will investigate relationships between regional white matter microstructure and response inhibition in a typically developing cohort of children and adolescents using the stop-signal reaction time task.

Previous work in developing populations suggests that the white matter underlying the inferior frontal gyrus and the presupplementary motor areas may be related to performance on this task (Madsen et al., 2010). This aim seeks to extend previous findings by measuring changes in regional white matter microstructure and its relationship to response inhibition in a typically developing cohort of children and adolescents spanning a study period of 1-5 years. Based on the cortical regions implicated in successful response inhibition and the previous study on white matter correlates of response inhibition, the analyses carried out below focus primarily on white matter projections between inferior frontal regions and premotor areas as well as projections to basal ganglia.

4.3.2 Behavioral Quality Control

For the Cantab stop-signal task (stop signal reaction time), the expert QC ratings of 0 were included in the cohort and the QC ratings of 2 were excluded. The QC ratings of 1 were reviewed by the investigator (LC) on a case-by-case basis to determine which observations should be included or excluded.

Among the QC ratings of 1, comments were generally categorized into three areas:

A. Fatigue: comments indicating fatigue, boredom, or mild behavioral observations.
    a. Examples: “fatigue”, “fingers tired”, “tired”, “fidgety”, “concerned about performance graph”
B. Technical issues: comments indicating the stop-signal task (SST) had to be restarted after a crash or an issue with the button box.
    a. Examples: “first trial crashed”, “crashed and didn’t save; re-ran”, “computer auto-update; restarted SST”, “SST froze, had to restart”
C. Compliance: comments indicating the child wasn’t following instructions in some way, such as switching hands, using one hand only, or taking hands off the button box in between trials.
    a. Examples: “pushed too early, pushed both buttons”, “pushed before arrows appeared”, “tried to go really slow to wait for the beep”, “took fingers off keys in between”

Among the QC 1 ratings, “A” type comments were left in the cohort. These comments were pervasive throughout the course of the study and due to the length of the stop-signal task, it was reasonable that a portion of this cohort would exhibit some degree of fatigue or restlessness. The investigator concluded that these observations likely did not invalidate the results of the task. The data associated with “C” type comments regarding compliance issues were excluded from the sample, since it was likely that these issues would invalidate the test results, or it was unclear from the comments how

pervasive the issue was and so the investigator took a conservative approach and assumed the compliance issues lasted longer than a few discrete trials. Among the “B” type technical issues, those that happened early (within the few trials), and/or the issues like "button box not working” that seemed to be caught and resolved immediately or comments that only applied to one discrete trial (i.e. “arrow didn’t appear on one trial”) were kept in the cohort. The data indicated by “B” type technical issues that were more disruptive, such as crashes during the middle of the test, were excluded. It was often unclear from the comments if the subtask was restarted from where it left off or from the beginning, which may lead to practice effects or other psychometric effects on performance. The investigator took a conservative approach and removed these data points since there was lower confidence in the quality of the data.

Among the 31 QC1 data points in the SST cohort:

A (fatigue): 16 converted to QC0

B (technical): 6 converted to QC0; 3 converted to QC2

C (compliance): 6 converted to QC2

In total, among the 31 QC1 data points for SST, 22 were converted to QC0 and kept in the cohort, 9 were converted to QC2 and excluded.

4.3.3 Regions of Interest

The white matter regions of interest were selected based on their relationship to the cortical regions of interest hypothesized to be involved in motor-inhibitory response, particularly projections to inferior frontal cortex originating either in premotor cortex or

striatal/basal ganglia regions. Two regions of interest were selected from a probabilistic atlas-based method for automated segmentation of white matter tracts (AtlasTrack, Hagler et al., 2009). The original parcellations did not include these two regions of interest, which were added later as described in Hagler et al., 2018. The first region of interest was the striatal inferior frontal cortex (SIFC), which includes corticostriate projects to the inferior frontal cortex. The second white matter region of interest was the inferior frontal superior frontal cortex (IFSFC), which includes corticocortical projects from the inferior frontal cortex to the superior frontal cortex. Both FA and MD of each bilateral region were examined in a separate model.

4.3.4 Participants

All participants were typically developing children between the ages of 4 and 13 years old. A total of 120 children were included in the analyses (60 male). The average age of the children at baseline was 7.43 years (s.d. = 1.69 years). Further demographic descriptions of the cohort can be found below in table 4.10, including information about parental education, household income, handedness, bilingual status, and race/ethnicity.

Table 4.10 Demographic summary of the SSRT cohort

Demographics		Total	Male	Female
Number of participants		120	60	60
Parental Education*(mean,sd)		5.6(1.6)	5.6(1.6)	5.6(1.7)
Household Income*(mean, sd)		6.2 (2.2)	6.3(2.3)	6.2(2.2)
Handedness (R/L/Amb/NA)		100/16/2/2		
Monolingual/Bilingual		72/48		
Race/Ethnicity*				
Caucasian		64		
African American		6		
Hispanic/Latino		56		
Asia		4		
Pacific Islander		1		
Burmese		1		
Mixed Race		15		
Other/Unknown		29		
Age (mean, s.d.)	Baseline (N=120)	7.38(1.69)	7.41(1.58)	7.35(1.81)
	Time point 2 (N=66)	8.27(1.67)	8.22(1.31)	8.31(1.97)
	Time point 3 (N=47)	9.35(1.54)	9.55(1.45)	9.15(1.64)
	Time point 4 (N=41)	10.29(1.40)	10.60(1.41)	9.89(1.32)
	Time point 5 (N=11)	11.09(1.46)	10.67(1.62)	11.33(1.43)
Stop-Signal Reaction Time (mean, s.d.)	Baseline (N=120)	283.7(112.8)	298.1(121.5)	269.3(102.4)
	Time point 2 (N=66)	252.3(101.4)	268.9(114.5)	236.6(86.2)
	Time point 3 (N=47)	213.0(76.5)	214.1(79.0)	212.0(75.7)
	Time point 4 (N=41)	203.9(68.4)	193.1(55.7)	217.7(81.4)
	Time point 5 (N=11)	175.7(41.5)	192.4(51.1)	166.1(35.3)

* Parental Education scale: 1 (less than 7 years); 2 (7-9 years); 3 (10-11 years); 4 (High School Diploma); 5 (1-3 years of college); 6 (Bachelor's Degree); 7 (Professional Degree, e.g. Masters, Doctorate, MD, JD). There were 21 participants missing Parental Education information and so were omitted from the summary statistics.
* Household Income scale (annual): 1 (less than $5,000); 2 ($5-9,999); 3 ($10-19,999); 4 ($20-29,999); 5 ($30-39,999); 6 ($40-49,999); 7 ($50-99,999); 8 ($100-199,999); 9 ($200-249,999); 10 *$250-299,999); 11 ($300,000 or more). There were 29 participants missing Household Income information and so were omitted from the summary statistics
* Handedness: 2 participants did not identify handedness, or reports of handedness varied by task/questionnaire.
* Participants were free to mark whichever race/ethnicity options they chose: if multiple races were checked, s/he was categorized as ''Mixed race''; if none was selected, s/he was categorized as ''Other/Unknown''. Some participants marked only ''Hispanic/Latino'', while others marked ''Hispanic/Latino'' in addition to a race. Therefore, the total number reported in each category does not sum to the total number of participants.

The average stop-signal reaction (SSRT) time at baseline was 283.7 ms (sd=112.8), at time point two was 252.3 ms (s.d.=101.4 ms), at time point three was 213.0 ms (s.d.=76.5), at time point four was 203.9 ms (s.d.=68.4 ms) and at time point five was 175.7 ms (s.d.=41.5 ms). For all analyses, logarithm was used as a variance-normalizing transformation, and the results were then inverted so that higher scores corresponded to better performance (faster reaction times), which was the same procedure used for the analyses in sections 4.1 and 4.2.

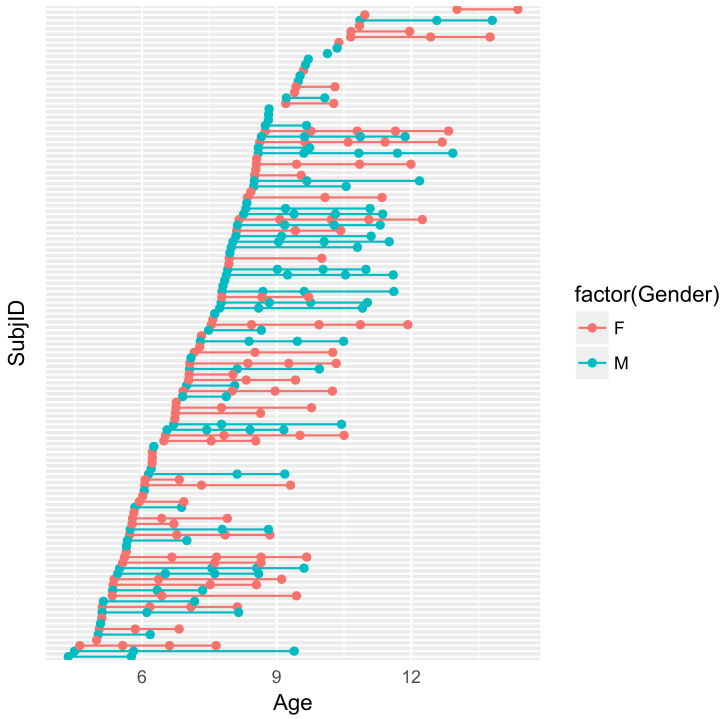

Figure 4.7 Summary of the response inhibition cohort for the white matter analyses

4.3.5 Baseline

4.3.5.1 Behavioral Results

A multiple regression model was used to predict transformed SSRT scores using age, age^2, and gender as predictors for the baseline cohort. Both the linear and quadratic age terms showed a strong relationship to performance ($p<0.05$). The effect of gender was trending but not statistically significant, with females performing better than males. Preliminary models investigating the effects of parental education and household income found no relationship to performance.

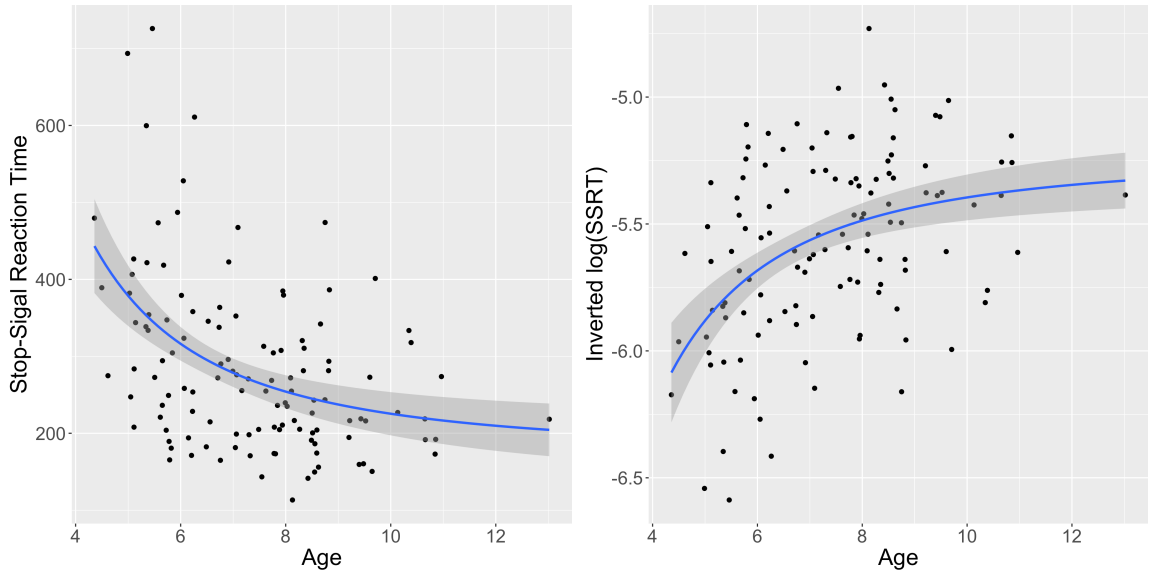

Figure 4.8 Stop-signal reaction time (left) and inverted log(SSRT) (right) with quadratic fit lines and shaded 95% confidence intervals.

Table 4.11 Effects of age and gender on inverted log(SSRT) in the baseline cohort

Predictors	*B* value	*t* value	*p* value
Age	0.06	2.66	0.010*
Age^2	-0.02	-2.53	0.013*
Gender	-0.11	-1.90	0.060

All predictors have been centered (demeaned)
Female is coded as negative

4.3.5.2 Analysis

Primary analyses were carried out using multiple linear regression predicting transformed SSRT from the bilateral region of interest. If there was a significant relationship between the bilateral region of interest and SSRT performance, the left and right regions were examined in follow-up models. Age, age^2, gender, and scanner were included as covariates in all models. All participants in this cohort were scanned on the same scanner, although this scanner underwent two software updates during the course of the study and these changes are captured by the "scanner" covariate. In this cohort, 35 participants were scanned with software version A, 48 were scanned with software version B, and 37 were scanned with software version C. This scanner variable was included in all models as a covariate of no interest. A Bonferroni correction was used for the two primary analyses, examining SIFC and IFSFC, and the two tissue properties measured, FA and MD ($p=0.05/4 = 0.0125$).

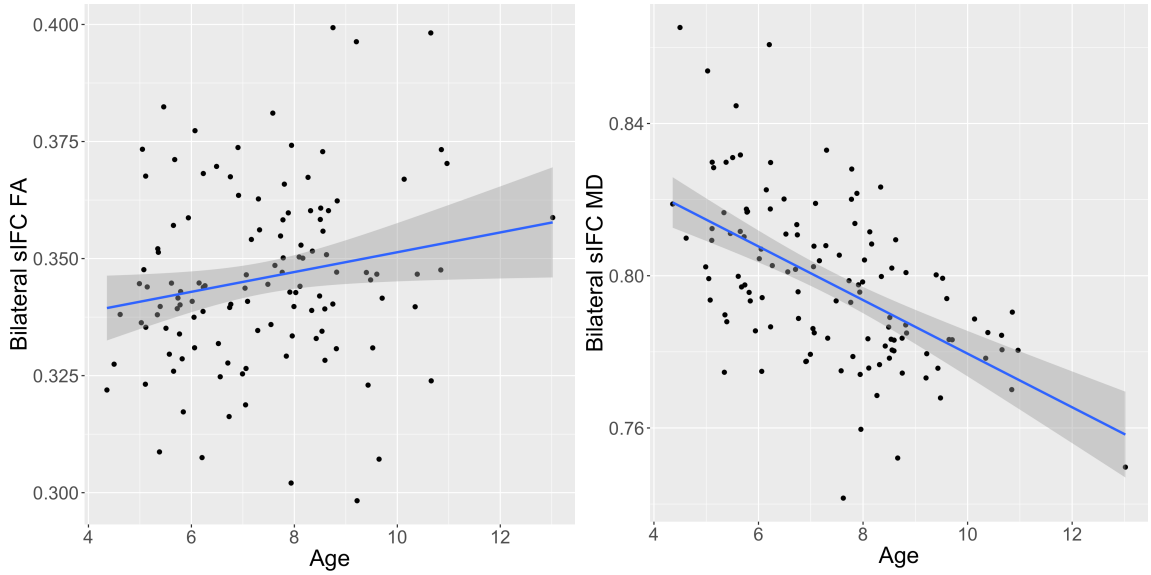

Figure 4.9 Bilateral SIFC FA (left) and MD (right) with a linear fit line and shaded 95% confidence intervals.

4.3.5.3 Results

There was a trending negative relationship of bilateral SIFC FA to performance when controlling for age and gender that did not reach significance. When total mean FA was included in the model, the relationship between bilateral SIFC FA and performance was no longer approaching significance (t=-0.94, p=0.35).

Table 4.12 Effect of bilateral SIFC FA on performance in the baseline cohort.

Predictors	*B* value	*t* value	*p* value
Age	0.07	3.22	0.002**
Age^2	-0.02	-2.66	0.009**
Gender	-0.12	-2.04	0.044
Bilateral SIFC FA	-3.08	-1.81	0.072
Scanner1	-0.03	-0.42	0.677
Scanner2	-0.14	-1.80	0.075

All predictors have been centered (demeaned) except scanner
Female is coded as negative

The bilateral SIFC MD demonstrated a relationship to performance, where higher MD was related to better performance (t=2.58, p=0.01). When total mean MD was included in the model, the relationship between bilateral SIFC MD and performance weakened (t=2.17, p=0.03) and no longer reached our corrected level of significance (Table 4.13).

Table 4.13 Effect of bilateral SIFC MD on performance in the baseline cohort

Predictors	*B* value	*t* value	*p* value
Model 1 (SIFC only)			
Age	0.09	3.79	0.000***
Age^2	-0.02	-2.82	0.006**
Gender	-0.12	-2.05	0.042*
Bilateral SIFC MD	4.23	2.58	0.011*
Scanner1	-0.04	-0.58	0.565
…….Scanner2	-0.11	-1.35	0.180
Model 2 (including total MD)			
Age	0.09	3.77	0.000***
Age^2	-0.02	-2.78	0.006**
Gender	-0.11	-1.78	0.078*
Bilateral SIFC MD	6.91	2.17	0.032*
Total MD	-2.84	-0.98	0.329
Scanner1	-0.04	-0.63	0.532
Scanner2	-0.10	-1.21	0.229

All predictors have been centered (demeaned) except scanner
Female is coded as negative

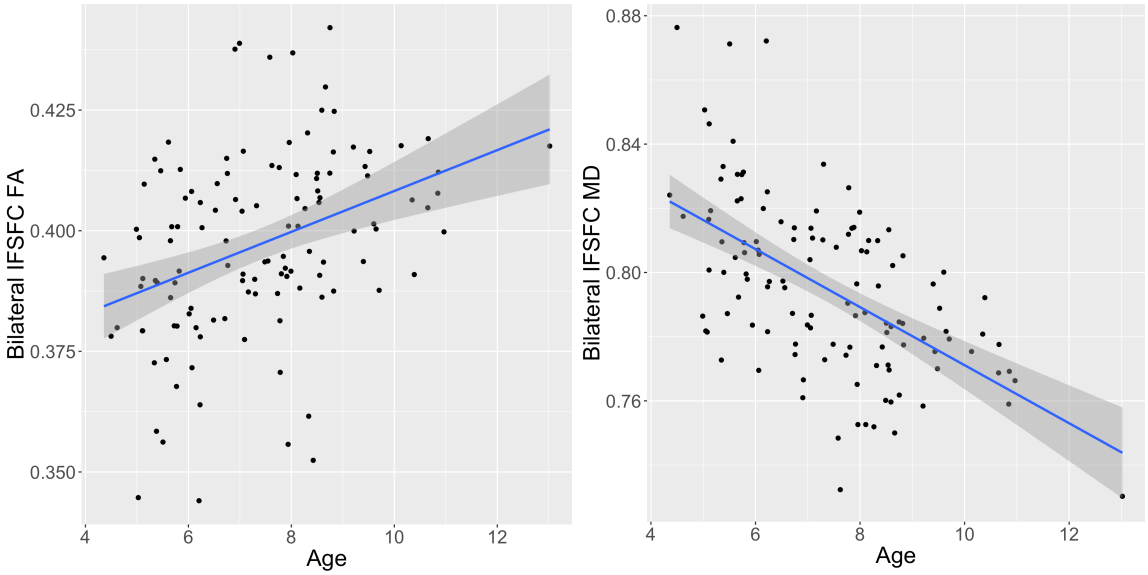

Figure 4.10 Bilateral IFSFC FA (left) and MD (right) with a linear fit line and shaded 95% confidence intervals.

When examining the bilateral IFSFC FA and MD, both demonstrated a relationship to performance independent of age, gender, and scanner. First, contrary to our hypothesis, lower bilateral IFSFC FA corresponded to better performance t=-3.17, $p<0.01$). Including total FA in the model reduced the effect of bilateral IFSFC FA on performance, although the relationship was still significant at an uncorrected level (t=-2.37, p=0.02). The left and right IFSFC FA were examined in separate post-hoc models. Total FA was included as a covariate as it seemed to have an effect on the relationship of the bilateral IFSFC FA to performance.

Table 4.14 Effect of bilateral IFSFC FA on performance in the longitudinal cohort

Predictors	*B* value	*t* value	*p* value
Model 1 (IFSFC alone)			
Age	0.09	3.87	0.000***
Age^2	-0.02	-2.90	0.005**
Gender	-0.09	-1.63	0.106
Bilateral IFSFC FA	-5.22	-3.17	0.002**
Scanner1	-0.07	-1.01	0.316
Scanner2	-0.17	-2.15	0.033
Model 2 (with total FA)			
Age	0.08	3.67	0.000***
Age^2	-0.02	-2.88	0.005**
Gender	-0.09	-1.62	0.109
Bilateral IFSFC FA	-5.46	-2.37	0.019*
Total FA	0.46	0.16	0.877
Scanner1	-0.07	-1.00	0.321
Scanner2	-0.17	-2.10	0.038

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Post-hoc analyses suggested a relationship between the right IFSFC FA and performance ($t=-2.65$, $p<0.01$) but no relationship between the left IFSFC FA and performance ($t=-1.55$, p=n.s.) when including total FA as well as age, gender, and scanner as covariates. In both cases, total FA did not approach significance, suggesting that the effect of the IFSFC FA was not due to global mean FA. The relationship between the right IFSFC FA and performance was in the opposite direction as predicted, with lower FA corresponding to better performance.

Table 4.15 Effect of right and left IFSFC FA on performance in the longitudinal cohort

Predictors	*B* value	*t* value	*p* value
Model 1 (Right)			
Age	0.08	3.64	0.000***
Age^2	-0.02	-3.05	0.003**
Gender	-0.09	-1.55	0.125
Right IFSFC FA	-5.32	-2.65	0.009**
Total FA	0.45	0.16	0.874
Scanner1	-0.07	-1.03	0.305
Scanner2	-0.18	-2.29	0.023
Model 2 (Left)			
Age	0.08	3.61	0.000***
Age^2	-0.02	-2.71	0.008**
Gender	-0.10	-1.73	0.087
Left IFSFC FA	-3.10	-1.55	0.124
Total FA	-1.67	0.59	0.557
Scanner1	-0.07	-0.92	0.358
Scanner2	-0.15	-1.90	0.059

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Conversely, when examining the bilateral IFSFC MD, higher MD corresponded to better performance ($t=2.88$, $p<0.01$). Including total MD in the model seemed to have a minimal impact on this relationship (see table 4.16). Follow-up analyses examined the right and left IFSFC MD in separate models. Total MD was included in these models for completeness.

Table 4.16 Effect of bilateral IFSFC MD on performance in the longitudinal cohort

Predictors	*B* value	*t* value	*p* value
Model 1 (IFSFC alone)			
Age	0.09	3.94	0.000***
Age^2	-0.02	-2.92	0.005**
Gender	-0.12	-2.12	0.037
Bilateral IFSFC MD	3.83	2.88	0.005*
Scanner1	-0.00	-0.06	0.950
Scanner2	-0.09	-1.12	0.267
Model 2 (with total MD)			
Age	0.09	3.93	0.000***
Age^2	-0.02	-2.93	0.004**
Gender	-0.11	-1.79	0.077
Bilateral IFSFC MD	6.91	2.72	0.008**
Total MD	-4.02	-1.42	0.158
Scanner1	0.02	0.26	0.800
Scanner2	-0.06	-0.73	0.465

All predictors have been centered (demeaned) except scanner
Female is coded as negative

In follow up models examining the relationship between the right and left IFSFC MD and performance in separate models, both the right and left IFSFC MD were positively related to performance. Total MD showed a non-significant negative relationship to performance in each model. Both the right IFSFC MD ($t=2.49$, $p<0.02$) and the left IFSFC MD ($t=2.65$, $p<0.01$) showed a similar relationship to performance.

Table 4.17 Effect of right and left IFSFC MD on performance in the longitudinal cohort

Predictors	*B* value	*t* value	*p* value
Model 1 (IFSFC alone)			
Age	0.09	3.90	0.000***
Age^2	-0.02	-2.85	0.005**
Gender	-0.11	-1.81	0.074
Right IFSFC MD	6.40	2.49	0.014*
Total MD	-3.39	-1.21	0.230
Scanner1	0.02	0.24	0.814
Scanner2	-0.06	-0.77	0.441
Model 2 (with total MD)			
Age	0.09	3.83	0.000***
Age^2	-0.02	-2.96	0.004**
Gender	-0.11	-1.83	0.070
Left IFSFC MD	6.02	2.65	0.009**
Total MD	-3.33	-1.25	0.215
Scanner1	0.01	0.12	0.908
Scanner2	-0.07	-0.84	0.401

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Finally, in follow-up models examining the relationship between the global measures of microstructure and performance while covarying for linear and quadratic age, gender, and scanner, total FA showed a small, negative relationship to SSRT performance (t=-2.05, p=0.04) with lower FA corresponding to better performance. Total MD did not show a significant relationship to performance (t=1.678, p=0.10) although the relationship was in the positive direction.

4.3.6 Longitudinal

4.3.6.1 Behavioral Results

In the longitudinal cohort, there was a significant effect of linear age on performance. There was a trending effect of gender, with females performing better. There was no evidence for a quadratic age effect on the transformed stop-signal scores, and so only a linear age term was used in primary analyses.

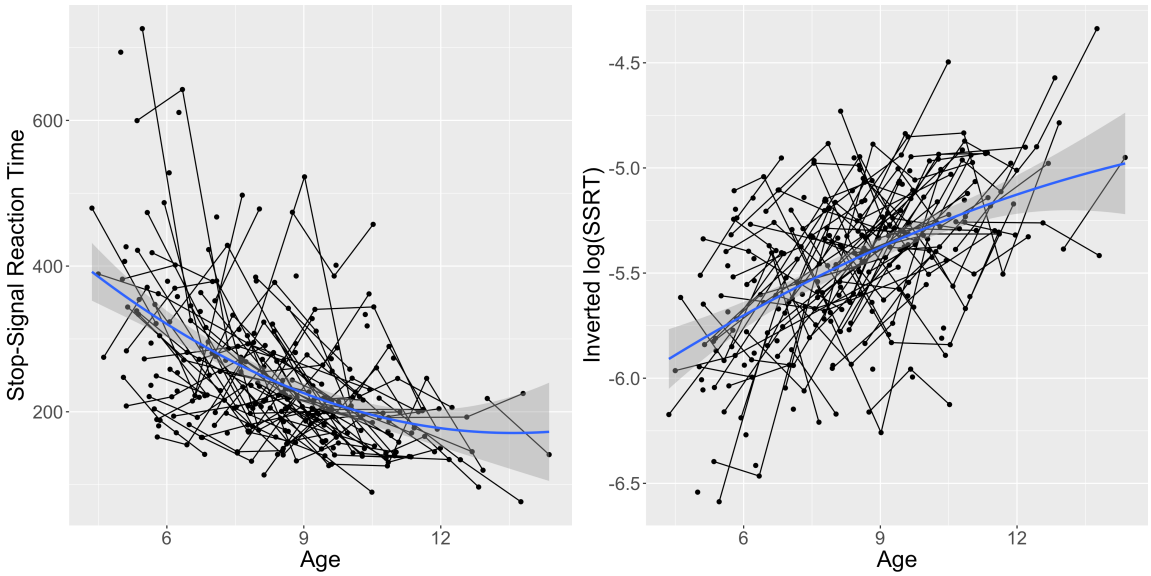

Figure 4.11 Stop-signal reaction time (left) and inverted log (SSRT) (right) with a quadratic fit line and shaded 95% confidence intervals.

Table 4.18 Effect of age and gender on inverted log(SSRT) performance in the longitudinal cohort

Fixed Effects	*B* value	*t* value	*p* value
Age	0.10	9.84	0.000***
Gender	-0.08	-1.72	0.088
Random effect: Subject			

All predictors have been centered (demeaned)
Female is coded as negative

4.3.6.2 Analyses

For all primary region-of-interest models, a Bonferroni correction of 0.05/4=0.0125 was used to correct for the two primary regions of interest, the SIFC and the IFSFC, and the two tissue measures examined for each, FA and MD. Pending any significant bilateral region of interest effects, post hoc analyses examined the right and left region of interest in separate models.

4.3.6.3 Results

Contrary to results in the baseline analyses, neither the bilateral SIFC FA nor MD showed any relationship to SSRT performance. In both models, only age was a significant predictor of performance.

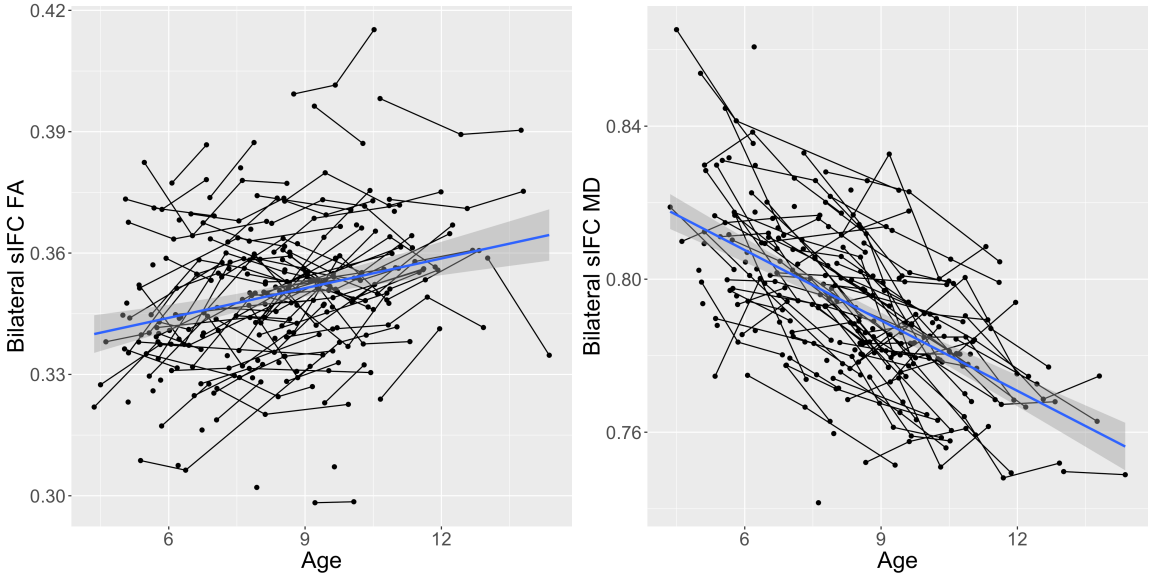

Figure 4.12 Bilateral SIFC FA (left) and MD (right) with a linear fit line and shaded confidence intervals.

Table 4.19 Effect of bilateral SIFC FA and MD on performance in the longitudinal cohort

Fixed Effects	*B* value	*t* value	*p* value
Model 1 (FA)			
Age	0.09	6.58	0.000***
Gender	-0.08	-1.76	0.081
Bilateral SIFC FA	-1.00	-0.75	0.454
Scanner1	-0.04	-0.79	0.434
Scanner2	-0.12	-1.64	0.103
Scanner3	0.03	0.38	0.708
Model 2 (MD)			
Age	0.10	6.41	0.000***
Gender	-0.08	-1.77	0.079
Bilateral SIFC MD	1.73	1.33	0.185
Scanner1	-0.05	-0.91	0.262
Scanner2	-0.11	-1.50	0.136
Scanner3	0.03	0.38	0.702
Random effect: Subject			

All predictors have been centered (demeaned) except scanner
Female is coded as negative

The bilateral IFSFC FA did not show any relationship to performance. However, the bilateral IFSFC MD showed a positive trending relationship to performance although this relationship did not reach our adjusted significance threshold. However, when total MD is included in the model, the relationship between bilateral IFSFC MD and SSRT performance became stronger (see Table 4.21). This relationship was not in the expected direction, as lower MD would be expected to correspond to better performance since it may indicate a more mature neural phenotype.

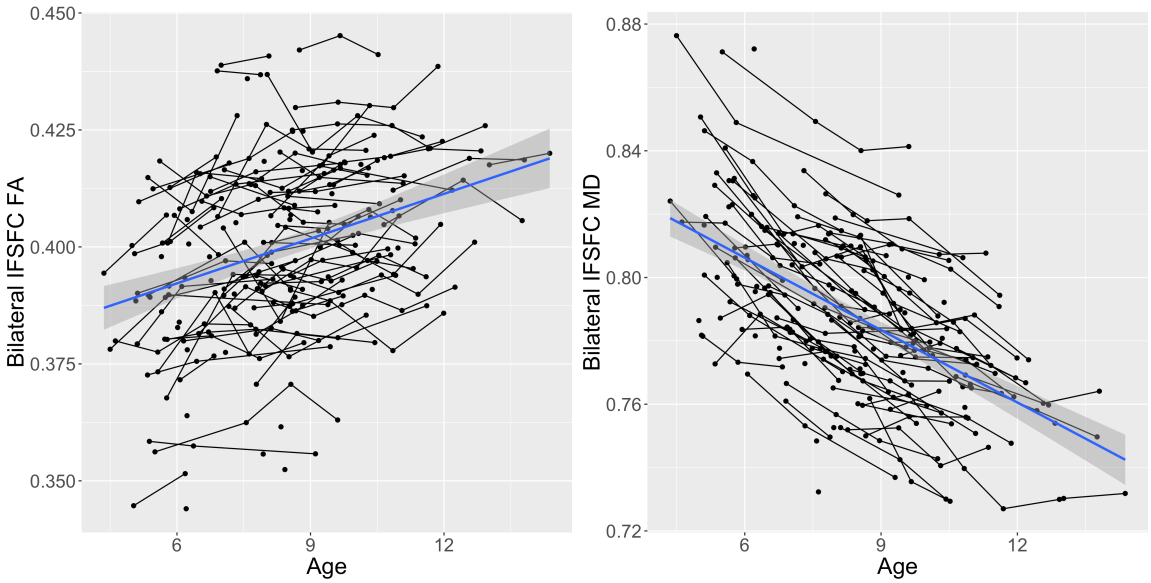

Figure 4.13 Bilateral IFSFC FA (left) and MD (right) with a blue linear fit line and shaded 95% confidence intervals.

Table 4.20 Effect of bilateral IFSFC FA on performance in the longitudinal cohort

Fixed Effects	*B* value	*t* value	*p* value
Age	0.09	6.51	0.000***
Gender	-0.08	-1.59	0.114
Bilateral IFSFC FA	-1.30	-0.98	0.330
Scanner1	-0.05	-0.94	0.348
Scanner2	-0.12	-1.68	0.096
Scanner3	0.01	0.17	0.867

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Table 4.21 Effect of bilateral IFSFC MD on performance in the longitudinal cohort

Fixed Effects	*B* value	*t* value	*p* value
Model 1 (ROI)			
Age	0.11	6.76	0.000***
Gender	-0.09	-1.87	0.064
Bilateral IFSFC MD	2.25	2.09	0.038*
Scanner1	-0.03	-0.61	0.546
Scanner2	-0.10	-1.33	0.185
Scanner3	0.03	0.47	0.642
Model 2 (ROI with total MD)			
Age	0.10	6.63	0.000***
Gender	-0.07	-1.43	0.155
Bilateral IFSFC MD	5.16	2.71	0.007**
Total MD	-3.92	-1.85	0.067
Scanner1	-0.02	-0.36	0.723
Scanner2	-0.08	-1.00	0.317
Scanner3	0.04	0.58	0.560
Random effect: Subject			

All predictors have been centered (demeaned) except scanner
Female is coded as negative

Follow-up models assessed the relationship of right and left IFSFC MD and performance in separate models. Results suggested that both the right and left IFSFC contributed to the bilateral effect shown above (t=2.60, p=0.01 for right; t=2.54, p=0.01 for left). Total MD was not significant in either model but was trending in the negative direction. Post-hoc models assessed any effects of total FA and total MD on performance. These models suggested no relationship to performance when controlling for age, gender, and scanner.

4.3.7 Discussion

This study sought to identify white matter phenotypes related to stop signal reaction time performance. By evaluating a group of 120 children and measuring regional white matter microstructure, we were able to demonstrate that higher domain-specific

performance was related to IFSFC microstructure, particularly for the longitudinal cohort. However, the relationships between microstructure of the IFSFC and performance were not in the predicted direction. Lower FA of this region corresponded to better performance, whereas higher MD of this region corresponded to better performance.

In the baseline cohort, there was evidence of a negative relationship between fractional anisotropy of the right IFSFC and performance. This relationship was not in the expected direction, as we hypothesized higher FA would be related to better performance. However, this relationship between IFSFC FA and performance was not present in the longitudinal cohort. There was evidence for a positive relationship between the IFSFC MD and performance in both the baseline and longitudinal analyses. Neither baseline nor longitudinal results suggested a strong hemispheric effect. However, this relationship was also not in the expected direction, as we expected lower MD to correspond to better performance as MD declines during development and may therefore reflect a more mature neural phenotype.

There was some evidence for a relationship between the SIFC and stop-signal performance in the baseline cohort, where higher MD corresponded to better performance, but including total MD in this model reduced the effect so that it no longer reached our adjusted significance threshold. Furthermore, this relationship was not present in the longitudinal cohort. There was no evidence for a relationship between SIFC FA and performance in either the baseline or longitudinal analyses.

The current analyses failed to replicate previously published results by Madsen et al., (2010) suggesting that higher FA and lower perpendicular diffusivity in the white

matter underlying the right IFG and right preSMA was associated with better performance. However, the regions examined in the currently analyses are not identical to those measured in the previous study. The previous study also made use of tract-based-spatial statistics, which is a more precise and population-specific way to delineate tracts of interest compared to the atlas-based method used here.

The directions of the effects were not in the expected direction. We would have expected higher FA to correspond to better performance since this may indicate a higher degree of myelination, larger axon diameter, increased fiber density, and linear organization of fibers. Fractional anisotropy may also increase due to a decrease in perpendicular diffusivity or an increase in parallel diffusivity. Increasing fractional anisotropy is generally associated with the developing neural systems underlying performance on the stop signal task. We would also have expected lower MD to correspond to better performance since it reflects the average diffusion within a voxel and is influenced by many similar tissue properties as FA, and typically decreases very steadily throughout development. However, many different complementary processes occurring in the developing brain influence our ability to infer the effects of white matter microstructure on diffusion parameters. There is no particular anatomical tissue property that can be measured by a single magnetic resonance measure, and therefore interpretation of these measures can become very complicated. Furthermore, the regions examined here were fairly small and may vary greatly among participants in terms of exact anatomical location, size, morphology, etc., reducing our ability to detect a strong, coherent effect in the expected direction.

The focus of the current set of analyses was the relationship between measures of white matter microstructure and response inhibition performance, although these results should be taken in context with previous aims investigating the relationships between regional cortical structure and performance. There may be an association between anatomical cortical features, such as a larger bilateral pars opercularis surface area, and nearby subcortical white matter microstructure measures. Particularly in this developing cohort, white matter fiber development continues to extend outward into the cortex as myelination of small subcortical fibers continues into young adulthood. When examining smaller subcortical projection fibers as we did for these analyses, measures of white matter microstructure such as FA and MD are likely highly interdependent with this ongoing myelination as well as expansions and contractions of regional surface area and global cortical thinning. These changes in cortical structure may be mediating some of the effects observed here for FA, and potentially more so for MD, on response inhibition performance.

This study was unique in that it utilized a moderately large cohort of typically developing children to assess the relationship between developing response inhibition and regional white matter microstructure. There is evidence that genetics, experience, socioeconomic status, and many other factors could affect both measures of brain structure and cognitive performance (Chen et al., 2012; Noble et al., 2012). The primary aim of this study was to show preliminary evidence for correspondence between regional white matter microstructure and domain-specific response inhibition performance, while covarying for the effects of age and gender. Following research should strive to integrate

additional confounding factors influencing these developmental processes to form a more complete picture of how genetics, environment, and experience work together to shape brain structure and cognition, in addition to evaluating a variety of cognitive and behavioral tasks.

4.3.8 Conclusions & Limitations

These analyses focused on investigating the effects of regional white matter microstructure on response inhibition performance in a typically developing, longitudinal cohort. We found no evidence for a relationship between bilateral SIFC FA nor MD and performance. However, although there was no strong evidence for an effect of IFSFC FA on performance, there was an effect of bilateral IFSFC MD, independently of whole-brain MD. This relationship was not in the expected direction, with higher regional MD corresponding to better performance on the SSRT. White matter microstructure can be difficult to measure and interpret in developing cohorts and further research is needed to better understand how measures of white matter microstructure develop in children and adolescents, especially smaller subcortical tracts, and how those changes correspond to increasing cognitive and behavioral performance as well as other ongoing changes in cortical and subcortical regional brain structure.

Chapter 4 includes material that has been published in Brain Structure and Function (2017). The coauthors include Curley, L.B., Newman, E., Thompson, W.K., Brown, T.T., Hagler, D.J., Akshoomoff, N., Reuter, C., Dale, A.M., and Jernigan, T.L. The dissertation author was the primary investigator and author of this paper. The

remainder of chapter 4 also benefitted from contributions of Akshoomoff, N., Brown, T.T., Thompson, W.K., Hagler, D.J., Dale, A.M., and Jernigan, T.L.

CHAPTER 5: LATENT FACTORS UNDERLYING THE NEURAL CORRELATES OF DISTINCT COGNITIVE DOMAINS

5.1 Introduction

The relationship between developing cognition and brain structure is complex and multifaceted. Much of the previous work investigating the relationships between developing cognition and brain structure, along with the preceding analyses in this body of work, focuses on a single task or domain and a small number of hypothesized regional relationships. This approach has the benefit of examining more isolated relationships in a simple and more easily interpretable model. However, this approach fails to take into account the complex and nonlinear relationships within and between different brain regions and those relationships with task performance. This chapter aims to expand on the approach used in previous chapters by utilizing canonical correlation analysis as a means to investigate possible latent structure underlying the relationships between performance on multiple behavioral tasks and multiple regions of interest in the same model.

Common methods for investigating relationships between cognition and brain structure

A common approach in developmental neuroscience is to examine the relationship between task performance and one or few regions of the brain. Decades of neuroimaging research have suggested that particular regions play a specialized role in specific cognitive tasks, and other regions play less of a role, or none at all. An implicit

assumption of this approach is that the brain regions *not* included in the analysis are less important or have less influence on the task or behavior of interest. When this assumption is applied across cognitive domains, we infer that particular regions may be related to performance in particular cognitive areas and not others, but that assumption is rarely directly tested. This approach often introduces limitations, a major one being the omission of analyses examining non-hypothesized brain regions. In these cases, there may be regional or global relationships with task performance outside the region(s) included in the analyses, and these regions may also show a relationship to task performance, either independently of the hypothesized region or as a mediating factor. Therefore, single-ROI approaches often fail to examine the role of that single ROI as part of a network or whole brain system, and often fail to examine multiple brain regions due to the problem of multiple comparisons.

Some studies attempt to address the shortcomings of single-region analyses with whole-brain voxel-wise analyses as either a post-hoc follow up to regional analyses or as a primary method in itself. Voxelwise approaches allow the investigator to test relationships between behavior and measures of brain structure or function at every location across the cortex. However, by using a whole-brain voxel-wise analysis, the investigator sacrifices the ability to include any a-priori knowledge about these brain-behavior relationships to guide the analyses. Because no a-prior knowledge about brain-behavior relationships is included in the model, the major shortcoming with a voxelwise approach is the loss of power to detect regional or whole brain relationships due to the correction for such a large number of comparisons (i.e. thousands of voxels). Although

this is not always the case, researchers often have an expectation of which brain regions or networks play a role in performance, and since voxelwise approaches do not make use of a-priori knowledge they therefore lose some power to detect these relationships due to the wide net they cast.

There are many other approaches that could be used to investigate relationships between behavior and brain structure or function, although single region or voxelwise analyses are most common. Both of these methods can be useful for specific hypotheses but each method also has some limitations. A major challenge for developmental neuroscience could then be summarized as the difficulty in identifying a principled way to test both region-specific hypotheses while also exploring non-hypothesized regional effects or global effects without losing significant power to detect those effects. In this aim we seek to make use of a principled, multiple-ROI approach that both makes use of our current understanding and knowledge regarding which regions of the brain are thought to be related to performance on specific tasks while also more directly assessing whether or not performance on a specific task is related to non-hypothesized regions.

Multifactorial nature of measures of cognitive performance and regional brain structure

Many behavioral and cognitive assessments in developmental neuroscience are designed to test a specific aspect of cognitive function or ability. However, as is the case with most skills and abilities, there are usually multiple skills that play a role in successfully executing a task. This could be described as cognitive performance having underlying, latent components that affect performance on the task of interest. This may

lead to the construction and interpretation of models that oversimplify the relationship between isolated task performance and a single brain region.

Previous research has suggested evidence for relationships between performances on different cognitive tasks. Work done by Vugs and colleagues (2013) investigated visuospatial working memory in specific language impairment (SLI). Their meta-analysis suggested that impaired visuospatial storage was related to worse specific language impairment, independently of age. Using language successfully requires a person to accurately attend to and encode auditory or written language-relevant stimuli, which activates and then retrieves the relevant semantic, grammatical, or lexical content from memory. Thus, there is a working memory component to language and phonological processing that may underlie possible correlations between performance in these two domains and extend past a language-specific working memory system.

Visuospatial working memory has also been shown to be related to response inhibition in children with attention-deficit hyper disorder (ADHD) (Westerberg et al., 2004). Performance on a visuospatial working memory (VSWM) task accurately predicted cognitive deficits in ADHD. These results suggest that visuospatial working memory is impaired in a disorder heavily characterized by deficits in response inhibition (Westerberg et al., 2004). In other words, working memory deficits may be an important component of ADHD symptoms – further supported by research suggesting improvement of ADHD symptoms with working memory training (Westerberg et al., 2004; Klingberg et al., 2002).

There is also some evidence that inhibitory mechanisms may play a role in language processing. Work by Borella and colleagues (2011) examined the roles of working memory and inhibition in text processing while manipulating whether text remained present or was absent when participants had to answer questions about the text content. They found that working memory explained a large amount of age-related differences in performance, and the contributions of inhibition and speed of processing to performance were mediated through working memory. It seems inhibitory functioning may not directly contribute to language competency, but may contribute indirectly through its role in attention and working memory (Im-Bolter et al., 2006). One study of children ages 7-11 years examined measures of inhibition and phonological processing by studying participants with ADHD, reading disability (RD), or comorbidity. The expected relationships between impaired inhibitory functioning and ADHD and impaired phonological processing and RD were present. In addition, there was a relationship between RD and impaired inhibitory control as measured by the stop-signal task, suggesting that inhibitory deficits are not a unique marker of ADHD and may also show a relationship to other developmental disorders. Furthermore, in typically developing children, better phonological short-term capacity was associated with faster reaction times but longer stop times on a stop-signal task (Schmid et al., 2011). Interrupting phonological processing does not impair regulation of response inhibition (Kray et al., 2009). Therefore response initiation and phonological processing may utilize similar cognitive resources or pathways, whereas response inhibition may be a distinct cognitive

process. This may suggest the existence of latent, underlying constructs or skills contributing to what are typically considered distinct cognitive domains or abilities.

Cognitive tasks used to evaluate a participant's performance have a specific set of task-relevant demands. Some components are likely common to many tasks (such as those requiring some maintenance of attention or working memory) but the tasks may also require the task-specific components of interest. This is also true of the cognitive domains and tasks used in previous analyses. When we examine the CTOPP Blending Words task, we infer that the participant must recognize (process) speech sounds, maintain them in working memory, manipulate that phonological information, and verbally respond with an answer. If we apply the same analysis to the stop-signal task, we infer that participants must maintain visual attention and recognize visual cues, map that onto the appropriate motor response, and also simultaneously attend to auditorily presented cues that would signal withholding a response. Therefore we can see some commonalities in each task, such as sustained attention and an aspect of auditory attention and processing, but also the task-specific demands of manipulation of phonological information and withholding a preplanned motor response, respectively.

In addition to the overlap discussed between cognitive domains and assessments, there is also evidence for specific brain regions' involvement in different cognitive domains. One relevant example is the inferior frontal cortex. This region has been implicated to some degree in language-based tasks as well as response inhibition tasks. The pars opercularis has been shown to be related to performance on response inhibition tasks, whereas Broca's region (including the pars opercularis and pars triangularis) plays

a role in spoken language. This example in particular highlights the complexity inherent in inferring relationships between specific brain regions and task performance in cases where multiple tasks and/or regions are examined in the same model. The distinctions between regional brain relationships with domain-specific task performance may not be as clear as many a-priori regional hypotheses imply. The analyses described below seek to further examine the possible overlap and dissociations between regional cortical and white matter and specific task performance using a data-driven approach.

Review of previously identified relationships between developing cognition and brain structure

The main goal of the analyses carried out in the preceding chapters was to establish whether or not there was any evidence for relationships among performance on domain-specific cognitive tasks and regional cortical or white matter morphology. Although it is understood that these relationships are necessarily much more complex, the lack of available tools and methods for approaching such complex questions necessitated a more straightforward approach. The benefits of a single-ROI approach include being able to accurately measure and interpret an isolated relationship before trying to contextualize it in a more nuanced view of the relevant network or brain as a whole. The aim of the following analyses is to move beyond single-task and single-region models to investigate simultaneous regional relationships and possible latent factors underlying hypothesized relationships between domain specific cognition and regional brain structure.

In chapter two, there was some evidence that relatively larger posterolateral temporal cortical surface area was associated with better phonological processing. Furthermore, there was some evidence that better phonological processing was related to higher fractional anisotropy in the inferior longitudinal fasciculus. Chapter three did not yield any significant relationships between regional cortical or white matter and spatial working memory performance. Chapter four found evidence that relatively larger pars opercularis surface area was associated with better response inhibition. Also, there seemed to be some evidence that higher mean diffusivity of the white matter underlying the inferior frontal/ superior-frontal cortex was associated with better performance. When considering these sparsely investigated regional associations with performance, it begs a larger question about how domain-specific cognitive performance is related to regional brain structure. In this final chapter, we aim to explore one possible method of investigating the possible latent structure underlying the relationship between performances in different cognitive domains and hypothesized cortical and white matter regions.

Rationale for current approach

We aim to explore the underlying pattern of association between the previously described neuroimaging biomarkers of cortical and white matter architecture and behavioral variability in the domains of interest. We've chosen to focus on the two behavioral tasks that have shown regional relationships to cortical and white matter structure in previous chapters: phonological processing and response inhibition. We will

include the cortical and white matter regions that have shown an association with each task: the bilateral pars opercularis and bilateral posterolateral temporal surface area as well as FA of the bilateral ILF and MD of the bilateral IFSFC. This selection results in two behavioral tasks, each with one hypothesized cortical and white matter association. Restricting the following analyses to include only those tasks and regions that have shown a task-region relationship in previous analyses will allow us to investigate and contextualize the specificity of these previously identified relationships. By including only a small number of tasks and regions, we increase our ability to interpret, understand, and contextualize the results. Consideration was given to including more regions, such as every cortical parcellation in a particular atlas, which may also be a useful and informative analysis. However, the primary aim for this final analysis was to take a more data-driven approach to better understanding and expanding upon the previously identified regional relationships and to do so, we decided to focus on the minimum number of variables in order to ease interpretation.

These single-ROI relationship analyses explored above restrict the focus to only the area thought to be related to that domain-specific performance without investigating the *specificity* of the relationship. If we were to examine regional specificity, we may look for a double dissociation, where a researcher could demonstrate that one or a set of brain regions were uniquely related to performance in domain "A" and were not related to performance in domain "B". A double dissociation in this case would support evidence that one region or network plays a significantly larger role in performance in one domain as compared to another.

One approach to identifying a double dissociation is canonical correlation analysis (CCA). This approach is not as commonly used in developmental neuroscience, although it has been utilized more often in other research areas such as education, psychology, and other social sciences. CCA determines the weighted combination of the first set of variables that best predicts the variability in the second set, and then will attempt to find an orthogonally weighted combination of the first set of variables that can explain the remaining variability in the second set, and so on. Since overlapping factors often contribute to variability on both the behavioral measures and the regional brain measures, CCA is well suited to our questions about the relationships between regional brain structure and performance.

5.2 Specific aim 7: Investigate possible latent factors influencing the relationships between regional cortical and white matter structure and domain-specific cognitive performance.

5.2.1 Method

Canonical correlation analysis was used to investigate the relationship between the two behavioral tasks of interest (inverted log SSRT scores and CTOPP blending word scores) and a set of regions-of-interest. Two cortical regions of interest are included: the bilateral pars opercularis surface area and the bilateral posterolateral temporal surface area. In addition, two white matter regions of interest are included: the bilateral IFSFC mean diffusivity and the bilateral ILF fractional anisotropy. In previous analyses, two of the included regions were related to stop-signal performance (bilateral pars opercularis area and bilateral IFSFC MD) and the other two regions were related to performance on phonology (bilateral posterolateral temporal area and bilateral ILF FA).

There are a few possible patterns of results that we may observe. First, we may observe a double dissociation represented by two significant canonical variates. These canonical variants may represent the relationship between first the SSRT, the bilateral pars opercularis area, and the IFSFC MD and secondly the CTOPP blending words task, bilateral PLT area, and ILF FA. This pattern of results would suggest that each cortical and white matter region patterns with the previously associated task and not the other, suggesting a distinct set of structural neural correlates. However, if we find two significant canonical variates, they may not pattern with previously associated regions in a clear way. These new canonical variates, which represent latent associations between our sets of variables, may better capture relatively independent sources of co-variation than our original variables of interest. Another pattern of results may include only one significant canonical variate. This may suggest that the regions of interest account for some variance in the behavioral tasks, but there is not a clear boundary between each set of regions and each task performance. Finally, we may see no significant canonical variates, suggesting that this model fails to explain a significant amount of covariance between this set of behavioral tasks and the regional measures included.

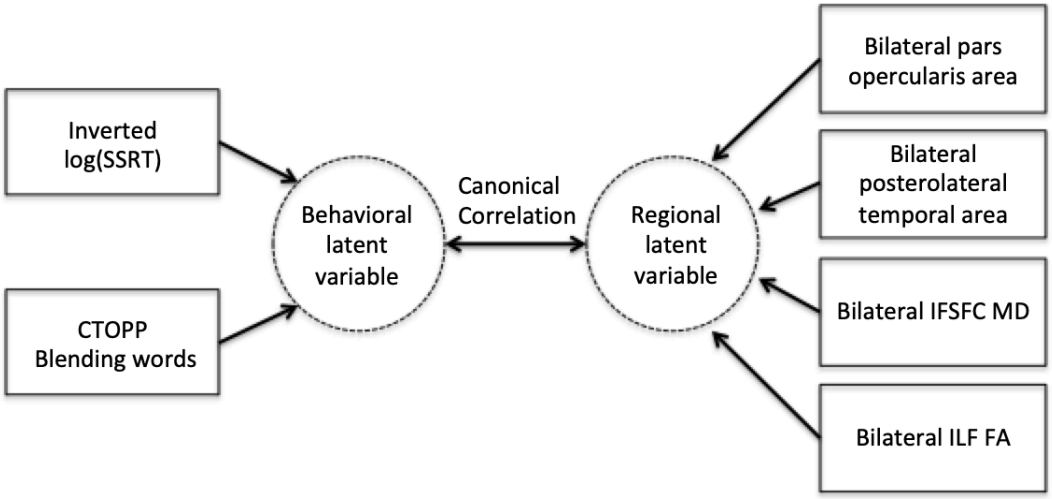

Figure 5.1 Graphical representation of the canonical correlation analysis

Because of the number of variables in these analyses, the results will include two canonical variates. We will use a Wilks test of significance to determine if one, both, or neither of the canonical variates is significant. If we observe a significant canonical variate, we can examine the weights associated with each task and region of interest to determine whether the pattern of results follows relationships identified in previous chapters (as listed in Table 5.1), or whether there seems to be evidence for a more complex relationship between these two sets of variables.

First, we conducted a canonical correlation on the baseline-only cohort to determine if there was evidence for a significant canonical variate representing a latent relationship between our behavioral and regional measures of interest. We also wanted to conduct an analysis that leverages the available longitudinal data, however a traditional canonical correlation is not designed to handle repeated measures. Following the baseline CCA, we conducted a CCA on the full longitudinal cohort by utilizing a data-reduction

technique described in section 5.3.2 which resulted in one measure summarizing each participant's behavioral and regional trajectory.

Table 5.1 Variables of interest for the canonical correlation analyses

Task	**Cortical region**	**White matter region**
Response Inhibition (inverted log SSRT)	Bilateral pars opercularis surface area	IFSFC MD
Phonological Processing (CTOPP BW)	Bilateral posterolateral temporal surface area	ILF FA

5.2.2 Participants

The cohort used for the analyses here included a subpopulation of the PLING study that had behavioral data for both tasks of interest as well as MRI and DTI data that passed quality control (described in previous chapters). Thus, this cohort consists of 101 typically developing children between the ages of 5 and 13 years (50 male, 51 female). There are a total of 294 observations spanning one to five years for each participant with a median of two visits.

5.2.3 Results

First we assessed the pearson correlations within our tasks of interest and our regions of interest after residualizing for age and age^2. The two cortical regions were also residualized for total cortical area. In the baseline cohort, our behavioral tasks exhibited a correlation of -0.21. In our longitudinal cohort, our behavioral tasks exhibited a correlation of -0.10. In both the baseline and longitudinal data, we observe a small negative correlation between performance on these two tasks. Although performance in

both domains generally increases during development, there may be evidence that these two tasks rely on distinct cognitive processes (Kray et al., 2009; Schmid et al., 2011).

In the baseline cohort, the bilateral pars opercularis area and bilateral PLT area had a correlation of -0.08 after residualizing for age, age^2, and total cortical area. This same relationship was -0.26 in the longitudinal cohort. The relationship between different cortical surface area regions during development can be complicated as the total cortical area as a whole is expanding until early adolescence, but different regions of the cortex are likely expanding and contracting at different rates. The fact that we observe a negative correlation between these two regions may suggest that they are expanding or contracting at different rates or at different stages of development, and this may be more pronounced in the longitudinal cohort.

The two white matter regions of interest, the ILF FA and the IFSFC MD, had a -0.48 correlation in the baseline cohort and a -0.14 correlation in the longitudinal cohort after residualizing for age and age^2. Because FA tends to increase with age and MD tends to decrease, we would expect to see a small to moderate negative correlation between these two regions. The ILF is a relatively larger tract extending posteriorly-anteriorly through the temporal lobe, whereas the IFSFC is a much smaller tract confined to the frontal lobe. Therefore, we may expect to see greater variability in measures of microstructure in the smaller IFSFC tract, which may also be affecting any observed correlations.

Recall in previous analyses, the association between IFSFC MD and response inhibition performance was in the positive direction, although this was not expected.

Generally, as mean diffusivity decreases with age and performance increases, we expected to see a negative relationship. However, the previously observed relationship is in the same direction as the positive relationship between ILF FA and CTOPP blending words performance. Therefore, when interpreting the pattern of the results we should keep in mind that all previous associations between our regions of interest and tasks were in the positive direction (for all cortical and white matter regions examined here).

5.2.3.1 Baseline

First, we conducted canonical correlation on the baseline cohort including the two tasks and four regions of interest (Table 5.2). A Wilks test of significance indicates a significant effect of both canonical variates ($p=0.003$) but the second canonical correlation did not reach significance on its own ($p=0.152$). When we examine the weights in the first (larger) canonical variate, we see a larger negative loading on stop-signal performance and a smaller positive loading on blending words performance. For the regions of interest, this corresponds to a large positive weighting on the bilateral ILF FA and a smaller positive weighting on the bilateral PLT area. There is a large negative weighting on the bilateral IFSFC MD and virtually no contribution of the bilateral pars opercularis area. This generally seems to suggest that stop-signal performance is patterning in the same direction as bilateral IFSFC MD (both in the negative direction) and the opposite direction as bilateral ILF FA. The overall pattern of results contains a mixture of positive and negative weights across both the behavioral and regional variables, which suggests some differences in contribution to the relationship between the

latent canonical constructs. The first canonical variate explains approximately 17% of the variance between our two sets of variables.

Our second canonical variate only explains about 5% of the variance. When we examine the second, non-significant canonical variate, we still see a negative weight associated with stop-signal performance and a much smaller negative weight on blending words performance. The strongest regional contribution in this canonical variate is a negative weight on the bilateral PLT area with smaller negative weights on the bilateral ILF FA and bilateral IFSFC MD. In this case, every variable has a negative weight, although this canonical variate is not significant.

Table 5.2 Baseline canonical correlation test of dimensions

Dimension	Canonical Corr.	F	df1	df2	p
1	0.410	3.01	8	190	0.003
2	0.231	1.80	3	96	0.152

Table 5.3 Baseline canonical correlation coefficients

	Canonical variate 1	Canonical variate 2
Inverted log(SSRT)	-2.672	-2.290
CTOPP blending words	0.150	-0.276
Bilateral pars opercularis area	-0.002	-0.004
Bilateral PLT area	10.810	-36.183
Bilateral ILF FA	23.224	-4.614
Bilateral IFSFC MD	-23.142	-9.271

5.3.2 Longitudinal

Following the canonical correlations on the baseline cohort, we utilized a dimensionality-reduction technique to conduct a CCA on the full longitudinal cohort. In order to incorporate trajectory information into a CCA, which typically does not handle longitudinal data, we utilized a technique described in Zhou et al., 2013. This technique is known as multivariate functional principal components analysis (mfPCA) and is used to summarize the trajectory of each variable into a single component. Both the raw data and the smoothed mfPCA fits for inverted log(SSRT) scores and CTOPP blending word scores are shown in Figure 5.3 (a), the two cortical regions of interest are shown in Figure 5.3 (b), and the two white matter regions are shown in Figure 5.3 (c). In each figure, the top row of depicts the raw data and the bottom row depicts the smoothed model fits.

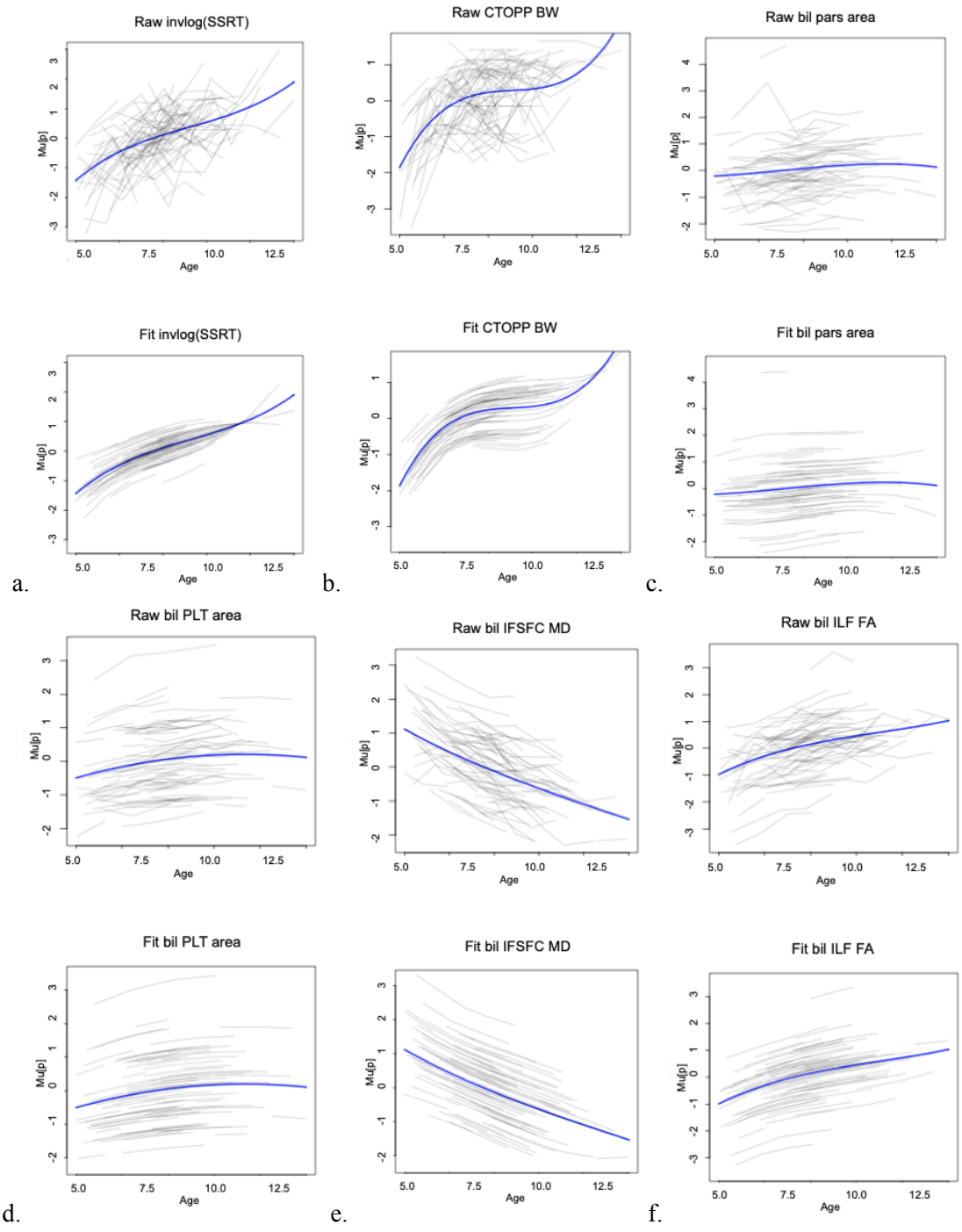

Figure 5.2 Raw data and smooth fits for the behavioral variables of interest (a, b), cortical regions (c, d), and white matter regions (e, f) using the multivariate functional PCA approach

The smooth model fit for each participant (black lines) seems to generally follow the mean trend line (blue line). Therefore, in this analysis, the single component resulting from the mfpca fit represents essentially this participant-level shift above or below the mean trend line. Therefore the measure we are including in the CCA models for the longitudinal cohort is primarily representing a level shift above or below the mean for either task performance or regional brain structure. For the behavioral tasks, this level shift corresponds to generally better (above the mean) or generally worse (below the mean) performance on average. For the regional measures, this shift represents either larger or smaller surface area or higher or lower FA or MD on average. Figure 5.4 depicts the functional principal component for each behavioral and regional variable, as determined by the mfPCA model fits.

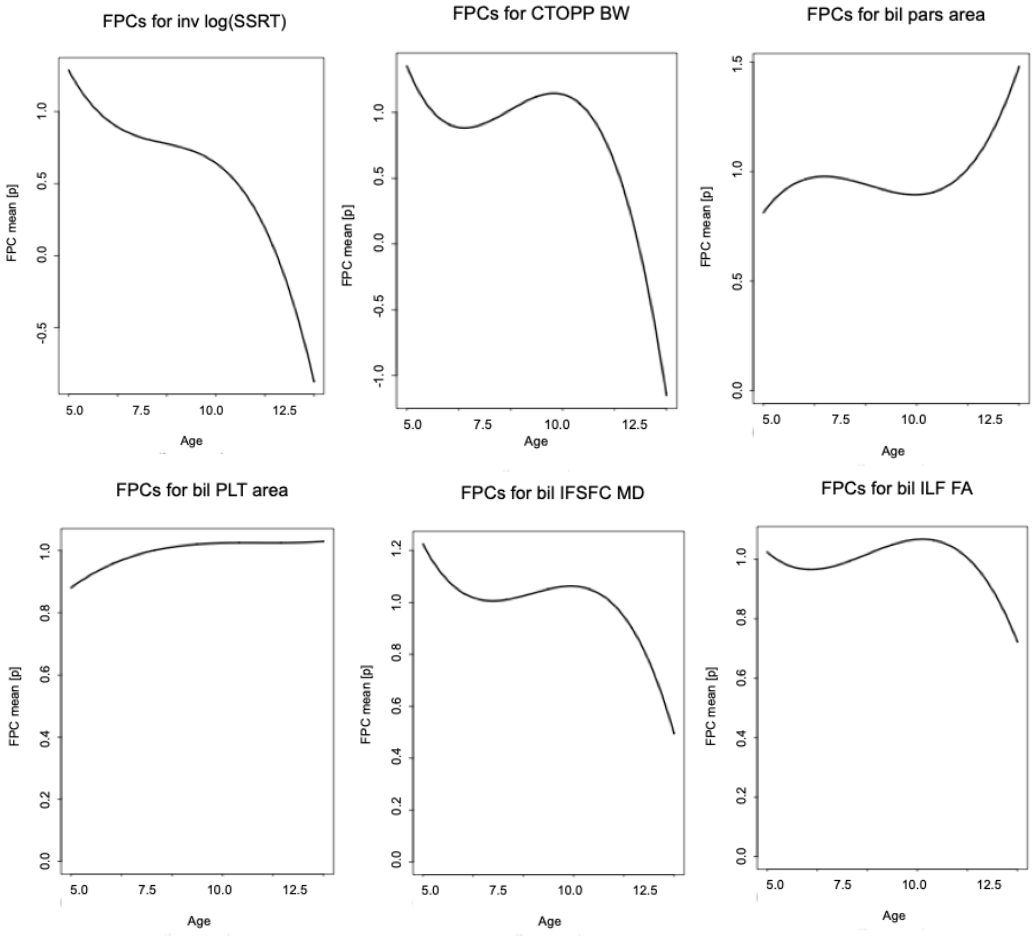

Figure 5.3 Functional principal components for the behavioral and regional variables of interest from mfPCA

The longitudinal canonical correlation model includes the mfPCA fits for each behavior and region of interest. A Wilks test of significance suggests a significant overall effect (p=0.002) but the second canonical variate is not significant on its own (p=0.277) as shown in Table 5.4. When we examine the weights in the first canonical correlation, we see a larger negative weight on response inhibition and a smaller positive weight on blending words performance. This corresponds to a positive weight on the ILF FA, a small negative weight on the bilateral pars opercularis, and a small positive weight on the

bilateral PLT area. This pattern of results is broadly similar to the baseline analyses, where stop signal performance is patterning in the opposite direction as bilateral ILF FA. Overall, stop signal is patterning in the negative direction along with the two regions previously associated with stop-signal performance, the bilateral pars area and bilateral IFSFC MD, and in the opposite as the two regions previously associated with blending words performance. However, these coefficients are fairly small in magnitude, especially compared to the relatively larger differences observed in the baseline model.

When we examine the second canonical variate, which is not significant, we again see a negative weight on both behavioral tasks, similar to the baseline model, although blending words now has a larger coefficient. This corresponds to a negative weight on the bilateral pars area and bilateral ILF FA and positive weights on the bilateral PLT area and bilateral IFSFC MD. However, this second canonical variate is not significant. The first canonical variate explains approximately 19% of the variance between these two sets of variables, and the second canonical variate explains roughly 4% of the variance.

Table 5.4 Longitudinal canonical correlation test of dimensions

Dimension	Canonical Corr.	F	df1	df2	p
1	0.433	3.12	8	190	0.002
2	0.196	1.28	3	96	0.286

Table 5.5 Longitudinal canonical correlation coefficients

	Canonical variate 1	Canonical variate 2
Inverted log(SSRT)	-1.876	-1.319
CTOPP blending words	1.301	-1.775
Bilateral pars opercularis area	-0.378	-1.119
Bilateral PLT area	0.279	0.410
Bilateral ILF FA	1.036	-0.417
Bilateral IFSFC MD	-0.101	0.099

To better visualize the relationship between the mfPCA fits and the resulting weights from the canonical correlation analysis, we transformed the results back into trajectory space (Figure 5.5). To do this, we multiplied the weights from the canonical correlation model by the summated mean curve for the two behavioral tasks (top left) and summated mean curve for all regions of interest (top right). We also wanted to create a visual representation of the canonical model and the FPC curves in the same manner. The CCA-weighted summation of the behavioral FPC curves is shown in the bottom left and the summated regional FPC curve is shown in the bottom right (Figure 5.5). Therefore the column on the left represents the summated behavioral curves and the column on the right represents the summated ROI curves. The top row depicts CCA-weighted mean curves and the bottom row depicts CCA-weighted FPC curves. For the behavioral curves, the SSRT is weighted more negatively and the CTOPP is weighted positively, as per the CCA model results, so the exaggerated nonlinear mean curve may reflect the nonlinear developmental trend of both tasks as well as their contrasting weights. Similarly with the summated regional curves, there is a contrast of positive and negative weights across the four regions, which makes direct interpretation of the curve more difficult. If we focus on broad trends in the FPC curves, we may be able to infer that the CCA-weighted combination of behavior indicates a larger effect at later ages (bottom left), whereas the CCA-weighted combination of regions suggests larger differences at younger ages and a trend toward zero at later ages indicating convergence (bottom right). However, data at the ends of the age distributions is much more sparse than the data in the center of the age

distribution, so interpreting any sharp trajectory deviations at the beginning or end of this range may prove difficult.

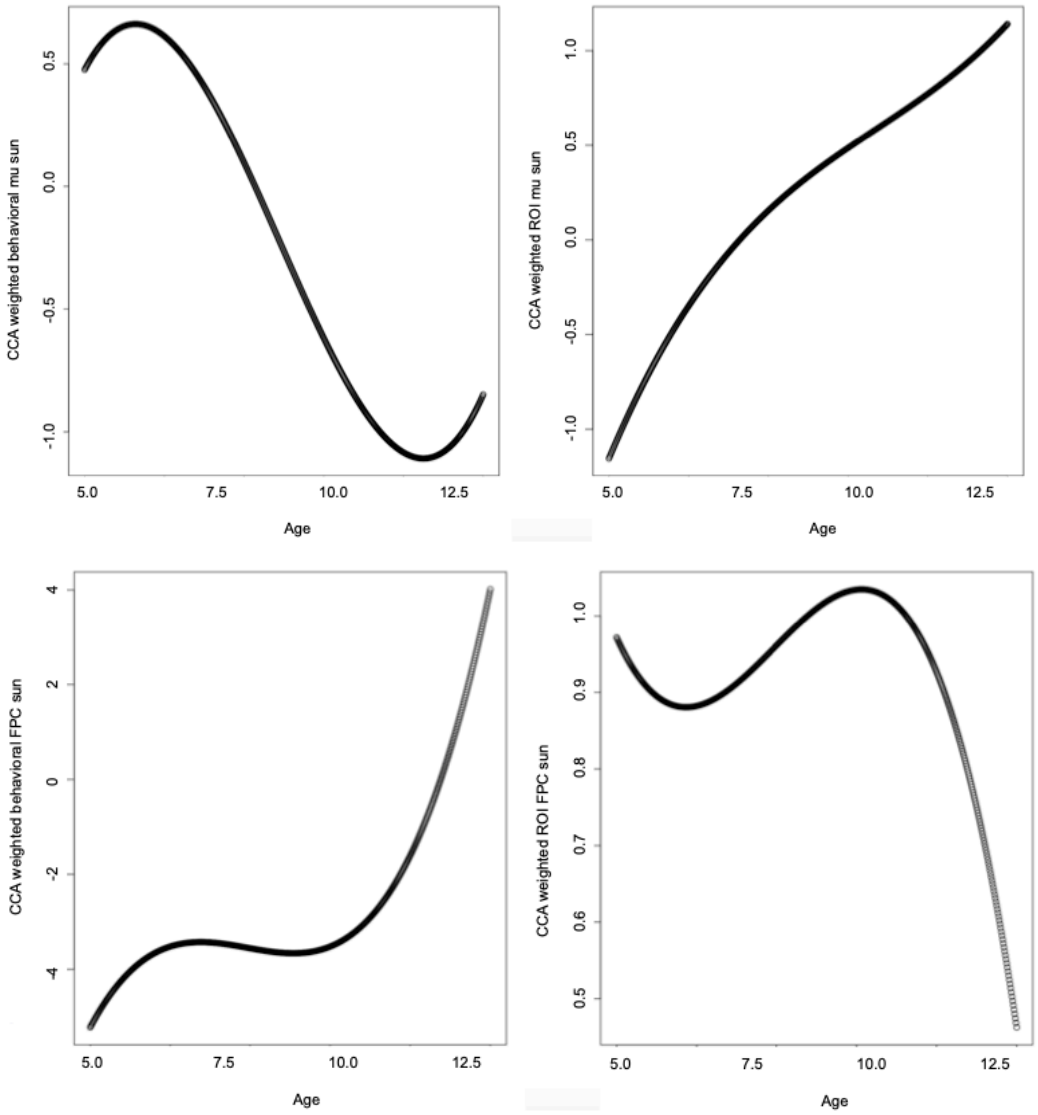

Figure 5.4 Outcome of CCA model on mfPCA outputs. The CCA-weighted sum of the variables of interest are represented in the top row (behavior on the left, ROIs on the right). The CCA-weighted sum of the FPCs of the variables of interest are represented in the bottom row (behavior on the left, ROIs on the right).

5.3 Discussion

The pattern of results identified in the canonical correlation analyses above reflects only one significant canonical correlation for both the baseline and longitudinal analyses. This suggests only one significant latent variable representing the relationship between our set of behavioral measures and our regions of interest. However, both models include a contrast of positive and negative weights on the two behavioral measures and the four regions of interest, suggesting a nuanced relationship between these sets of variables.

The first and only significant canonical variate in each model was roughly the same magnitude (baseline=0.41, longitudinal=0.43) and therefore explained roughly the same amount of variance in both the behavioral and longitudinal analysis. In addition, the overall pattern of resulting weights across the behavioral variables and regions was similar in both the baseline and longitudinal models. Stop-signal performance had a larger negative weight and CTOPP had a smaller, positive weight. The regions of interest suggested a contrast of positive and negative contributions to the latent representation. One interpretation of this pattern of results may be that it is a reflection of an underlying cortical regionalization phenotype that is related to a discrepancy between phonological and inhibitory functions in children at this age. We saw in our preliminary analyses that performance on these two tasks exhibits a small negative correlation after controlling for age effects. However, this analyses on its own is insufficient to fully explain or explore the possibility of cortical regionalization phenotypes, and future work could expand on the pattern of results observed here to investigate this possibility.

In addition, as previously mentioned, the pars opercularis is part of the inferior frontal gyrus, which has been previously implicated in both response inhibition and language functions. The pattern of results observed for the regions included in these canonical correlations may suggest in independent association of pars opercularis area on performance of both tasks examined here. Although we did not include an a-priori analysis of the role of the inferior frontal gyrus on phonological processing in this cohort, this pattern of results may be in line with previous functional and anatomical work suggesting a role for the IFG in language processing as well as response inhibition mechanisms. The overlap and dissociation of the role this area plays in different cognitive processes would also be an interesting area to explore in future studies.

When examining the results from the longitudinal analyses using the mfPCA model fits, we observe a pattern of results largely in line with previous analyses suggesting relationships between task performance and regional brain structure seem to be stronger at younger ages relative to older ages in our cohort of 5-13 years. In previous chapters, this manifests as stronger relationships in the baseline analyses vs. longitudinal analyses and in the present analyses, in the CCA-weighted trajectories shown in Figure 5.5. There are many possible explanations for the observation of larger differences or larger associations in children of younger ages, some of which may have meaningful developmental implications and some that may not. Younger children generally differ to a larger degree on behavioral performance as well as variation in regional brain structure compared to children and adolescents at later stages of development.

One remaining question in developmental neuroscience is the role that developmental delay may play in associations we see in behavioral performance and brain structure. When we observed differences in children of the same age, such as better or worse behavioral performance and differences in regional brain morphology, we do not know if those differences are stable individual differences that will persist over time or whether the child indicating worse performance or slower brain development will in fact " catch up" to average peer metrics over the course of development. When examining the smooth model fit results from the mfPCA analysis (Figure 5.3), we do see a large degree of uniformity in individual trajectories, such that children above the curve tend to stay above the curve and children below the curve tend to stay below the curve for both behavioral measures as well as measures of regional brain structure. However, not every individual's trajectory matches the mean curve exactly, which is more apparent in the behavioral results. When examining the CCA-weighted FPC curves in Figure 5.5, this pattern of results would be consistent with a developmental delay hypothesis, where there are greater differences in children at younger ages in regional brain structure which converge towards zero at later ages (bottom right) while behavioral performance is improving overall. However, interpreting these plots resulting from the CCA-weighted mfPCA trajectories is quite complex.

Trying to identify robust associations between developing cognition and brain structure in a typically developing cohort of children and adolescents using noninvasive neuroimaging measures of neural architecture and task-specific behavioral phenotypes is a challenging task. There is a significant amount of noise and variability both in the

collection, quality, and processing of structural brain imaging data and also in the administration and collection of task-specific behavioral phenotypes. This makes the detection of specific associations or dissociations much more difficult due to the lower signal to noise ratio. Structural and anatomical measures of regional brain structure may not show consistently strong relationships with complex or high-level behaviors, especially since our ability to measure them with noninvasive imaging techniques results in fairly coarse estimates. It is also not obvious that features such as larger surface area or higher fractional anisotropy should necessarily relate to better relative behavioral performance, as brain structure and functional activity are not synonymous. In previous analyses, we saw evidence that larger relative surface area corresponded to better performance. Although the exact mechanism is not yet known, this could be due to accelerated development of the associated neural system (opposite what we might call a developmental delay), either due to individual differences, experience, or other factors. A similar hypothesis could be applied to the association between higher regional FA and better behavioral performance, although the mechanism behind this association is also not well known. It is reasonable to expect that brain structure may show a weaker relationship to behavioral performance than measures of brain function or activation. However, the pattern of results identified in previous chapters and in the models described above may still provide interesting and potentially useful information about how the developing brain is influenced by or influences developing behaviors and cognition.

Overall, the results identified in the baseline and longitudinal CCA models above suggest one primary canonical variate representing the relationship between response inhibition and phonological processing and our four regions of interest. The pattern of resulting weights suggests a contrast between the behavioral and regional measures of interest, which suggests some complexity to the underlying latent structure. Future research could expand on this line of analyses to investigate larger sets of behavioral performances and regional brain structures to investigate possible latent structure between the associations observed in the developing brain.

5.4 Conclusions & Limitations

The relatively small sample size (N=101) reduced our power and our ability to detect significant associations between regional brain structure and behavioral performance. Additionally, we restricted our analysis to a small set of behavioral measures and brain structures that had demonstrated an association in previous analyses, which limited the scope of our investigation but also increased our ability to interpret the resulting pattern of associations. We found evidence for one significant canonical correlation between response inhibition and phonological processing a set of associated brain regions. Although we did not identify two significant canonical variables, the contrasting weights associated with the first canonical variate for the behavioral and regional structures of interest provided an interesting look into the latent association between these variables.

Chapter 5 includes significant contributions from Thompson, W.K., in particular the implementation and interpretation of mfPCA, as well as feedback from Brown, T.T., Akshoomoff, N., Hagler, D.J., Dale, A.M., and Jernigan, T.L. The dissertation author was the primary investigator and author of this paper.

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APPENDIX A: BEHAVIORAL TASKS

i. Comprehensive Test of Phonological Processing (CTOPP): Blending Words

The Blending words subtest of CTOPP is a set of 20 items designed to measure an individual's ability to combine sounds to form words. Subjects are presented pre-recorded items via audiocassette. Each item is presented as a series of separate phonemes (auditorily) and the subject is then asked to put the separate sounds together to make a whole word.

Test administration:

The subject must respond correctly to at least one practice item (below) before testing can proceed. The instructor provides feedback for practice items and the first three test items. Prompts can be used during the practice items.

Test items:

1. Number
2. Pencil
3. Answer
4. It
5. Toy
6. Saw
7. She
8. Nap
9. Miss
10. Bone
11. Moon
12. Stamp
13. Jump
14. Mistake
15. Circus
16. Almost
17. Grasshopper
18. Testify
19. Understand
20. Mathematics

Practice items:

a. Candy
b. Hammer
c. Sun
d. Take
e. No
f. Mad

Scoring:

The test is terminated when the subject misses three items in a row. The subject receives 1 point for a correct response and 0 for an incorrect response. The total score is the number of correct items (the "raw" score).

ii. Cambridge Neuropsychological Test Automated Battery (CANTAB): Spatial working Memory, Between-Search Errors

The spatial working memory test of CANTAB falls under the "tests of executive function, working memory, and planning". This test was designed to measure a subject's ability to retain spatial information and to manipulate remembered items in working memory (CANTAB manual).

Test administration:

Subjects are shown a screen beginning with 2 colored boxes. Subjects should search, by process of elimination, for the blue token hidden under one of the boxes. They then add that blue token to the column on the right and search the remaining boxes for the next blue token. A blue token will not be found under a box where one was previously found on any given trial. The trial ends when a blue token has been found once under each box. The number of boxes increases from 2 to 3, 4, 6 and 8 boxes. The color and position of the boxes are changed between trials to discourage stereotyped search strategies. The subject decides the order in which to search the boxes.

Example image from an 8-item trial: (left) trial presentation of the array of boxes; (right) presentation after participant selects the bottom-left box highlighted in blue.

Scoring:

Touching any box where a blue token has already been found on a given trial is counted as an error. Between-errors are defined as instances where a subject re-checks a box where a token has previously been found. This is calculated only for trials of 4 or more boxes. Lower scores indicate better performance.

iii. Cambridge Neuropsychological Test Automated Battery (CANTAB): Stop-Signal Task, Stop-Signal Reaction Time

The stop-signal test of CANTAB falls under the "tests of decision making and response control". This test is designed to measures response inhibition using staircase functions to generate an estimation of the stop-signal reaction time, or the "ability to inhibit a prepotent response" (CANTAB testing manual).

Test administration:

The subject is instructed to press the left hand button when they see a left-pointing arrow and the right hand button for a right-pointing arrow. If the subject hears an auditory signal (beep), they should withhold their response and not press any button. After each block, a feedback screen shows a graph of the subject's performance. The test administrator should encourage the subject to go faster.

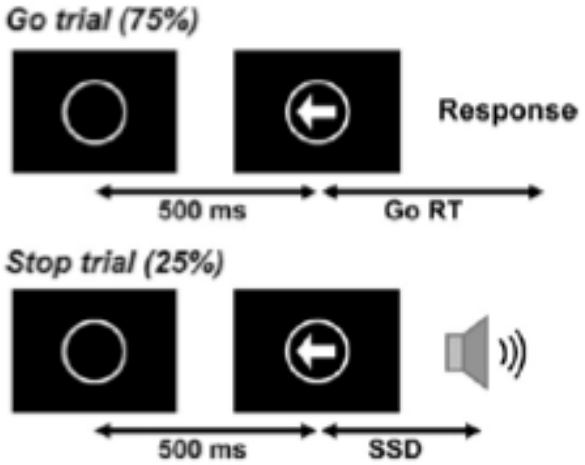

Image by Madsen et al. (2010): (top) example of a "go" trial with presentation of a fixation circle followed by the "go" signal, here an arrow indicating the left button should be pressed, (bottom) example of a "stop" trial, indicating that the "go" signal is followed by an auditory "stop" signal at some delay (stop-signal delay: SSD)

Scoring:

There are 5 blocks of trials, each with 64 trials. There are four sub-blocks of 16 trials in each block of 64 trials. In those 16 trials, there are 12 "go" trials with no auditory stop signal and 4 "stop" trials with an auditory stop signal. The "go" and "stop" trials are presented in a random order in each sub-block of 16 trials. The stop-signal delay (SSD) is the time between the presentation of the "go" signal and the auditory "stop" signal. For each of the 4 "stop" trials in a sub-block, the SSD is one of the following 4 staircases: 100ms for left arrow, 200ms for right arrow, 400ms for left, or 500ms for right. The timing of these SSD's changes throughout the test based on the subject's past performance. The staircase adapts so that the subject successfully withholds a response on 50% of stop trials. The shorter the SSD, the harder it is to withhold a response. Shorter stop-signal reaction times indicate better performance.

APPENDIX B: SUPPLEMENTARY MODEL FOR CHAPTER 4

Chapter 4 (section 4.2) contains published material from the longitudinal cortical analyses. The white matter analyses were conducted later with a cohort that has additional observations. This cohort (N=120 with 285 observations) includes an additional 10 participants and an additional 53 observations. This final cohort was used for the analyses in Chapter 5 and so the published cortical results are reproduced below with the additional data for comparison.

Fixed effects	B value	t-value	p-value
ºAge	0.09	6.68	0.0000***
ºGender	-0.10	-1.68	0.0948
ºBilateral pars opercularis surface area	0.00	0.04	0.9664
ºTotal cortical surface area	0.00	0.35	0.7245
Scanner	0.01	0.64	0.5236
Random effect: Subject			

º predictor has been centered (demeaned)
Female is coded as negative
* $p < 0.05$
*** $p < 0.001$

This model does not produce the same pattern of results found in the original cohort. There are a few potential reasons why the pattern of results observed with the additional data is not the same as the previous analysis. In the two years since publication and the conclusion of the study, additional quality control measures were employed over the final years of data collection such as manual quality control review of behavioral data and experimenter notes and re-processing of a portion of the neuroimaging data. In the final year of the study, we also discovered a significant effect of a software update on one of the two scanners used to collect MRI data which is controlled for in later analyses. In addition, there is the potential that a small number data points were removed from the cohort after publication due to errors matching the subject's behavioral data with the correct corresponding MRI data collection based on date (observations had to occur within a 3 month period of each other). However, these potential issues as a whole should have affected less than 5-10% of the original cohort and so it is surprising that the previously identified effect of the bilateral pars opercularis surface area is no longer detectable.