A review of the lifetime trajectories of cortical development and how they may differ in people who stutter

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Cortical trajectories across the lifespan

Abstract: This paper is directed towards an audience who is less familiar with cortical development across the lifespan. We summarized brain imaging research that has examined cortical growth in the typical population and highlighted this growth as it relates to the speech relevant regions of the brain. Following this, we used previously collected pilot data to illustrate how cortical growth in people who stutter may be abnormal.

A review of the lifetime trajectories of cortical development and how they may differ in people who stutter

The growth of the human cerebral cortex is a complex and dynamic process. Throughout the lifespan, tissues of the cortex undergo periods of progression and regression that vary in timing and significance across different regions of the brain (Colby, Hare, Bramen, & Sowell, 2013; Post & Weiss, 1997; Rubenstein & Rakic, 2013; Tzarouchi et al., 2009). But just how important is it for the cortex to present a defined developmental size or pattern? Processes like thought, memory, attention, personality, and language emerge from this mass of neural tissue. So what happens when the structure or developmental design of the cortex deviates from expectations?

Our objective is to summarize the current research mapping the general developmental trajectory of typical cortical growth with a focus on those regions involved in speech and language function. Once we establish a general pattern for typical cortical development, we will contrast it with pilot data that measures the cortical growth of people who stutter. Following this, we will conclude by comparatively discussing the cortical developmental trajectories of the typical and stuttering population, and how abnormal cortical trajectories may potentially impact speech production.

Types of Brain Tissue

Brain matter is composed of three types of tissues: grey matter, white matter, and cerebral spinal fluid. Functionally, grey matter is recognized as the neuronal cells that coordinate all of the brain's active processes. White matter, on the other hand, is composed mostly of glial cells which support neurons, and axons which conduct signals between neurons

within and across cortical regions, and from the cortex to sub-cortical structures.

While measurements of each tissue type can yield important information about development, this paper will primarily focus on grey matter maturation. Due to the limited scope of this paper, we will for the most part discuss white matter in comparative terms relative to the developmental structure and function of grey matter.

How the Cortex is Measured

The growth of the cortex can be observed in vivo via magnetic resonance imaging (MRI) which allows for identification and measurement of brain structures. A general picture of typical cortical growth throughout the lifespan is established by capturing cortical images of multiple participants at different ages, and then averaging the data. Measurement of the cortex can focus on different objective variables. For example, in previous research, some studies evaluated cortical thickness (Sowell, Thompson, Leonard, Welcome, Kan, & Toga, 2004a), while others collected data on volume (Beal, Gracco, Brettschneider, Kroll, & De Nil, 2013).

While not entirely interchangeable these dimensions can be collectively discussed to reflect the general size and/or quantity of the cortex. Cortical thickness represents a straight line equal to the distance from where white matter and grey matter meet to the border between grey matter and cerebral spinal fluid (Sowell et al., 2004a; Sowell, Peterson, Thompson, Welcome, Henkenuis, & Toga, 2003). Cortical thickness is measured in millimeters, and varies in size across regions of the cortex. Volumetric studies commonly rely on a method called Voxel Based Morphometry (Aganj, Sapiro, Parikshak, Madsen, & Thompson, 2009). This method obtains a snapshot of a cortical region using tiny cubic spaces (or voxels), and then calculates the amount of voxels present in the specified area. Figure 1 presents an illustration

of how cortical thickness is measured.

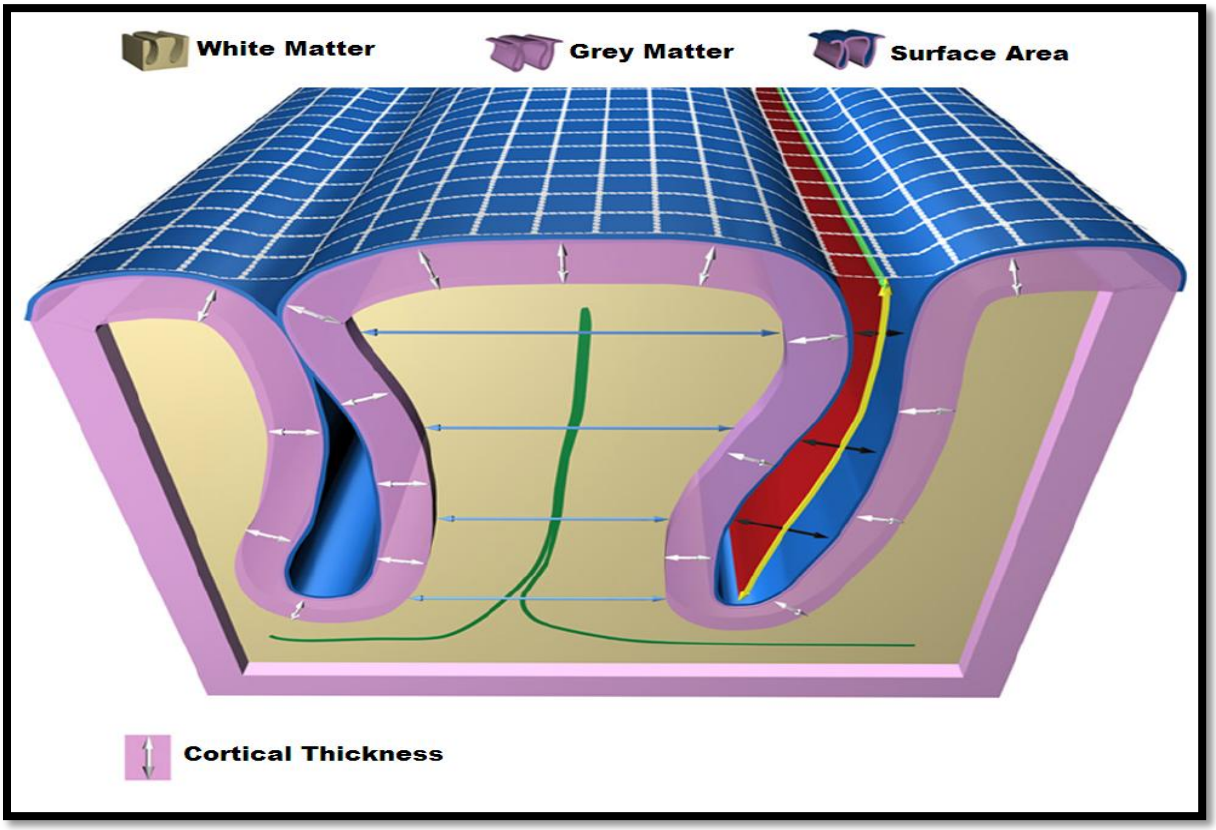

Figure 1. **Illustration of Cortical Thickness. In contrast to measurements of thickness, volume is determined by measuring the total amount of grey matter present in a specific region, not just the distance represented by the arrows. Image retrieved from http://lfcd.psych.ac.cn/ccs.html.**

TRAJECTORIES OF CORTICAL THICKNESS IN THE TYPICAL POPULATION

As people age from childhood to adulthood there is a general volume decrease in grey matter while white matter volume gradually increases (Giedd et al., 1999; Pfefferbaum, Mathalon, Sullivan, Rawles, Zipursky, & Lim, 1994; Reiss, Abrams, Singer, Ross, & Denckla, 1996). This change occurs so that the grey matter to white matter ratio decreases rapidly from early childhood (19-33 months) to later adulthood (50-60 years) (Courchesne et al., 2000). Some speculate that this developmental decrease in grey matter may be in response to the

increase of white matter (Rubenstein & Rakic, 2013), although it is uncertain if this is the case. On average, total white matter volume increases approximately 74% from infancy (19-33 months) to adolescence (12-15), and is followed by a slower growth rate that plateaus in the fourth decade of life (Courchesne et al., 2000). White matter increase is triggered by a process known as myelination, which normally begins close to the second trimester of fetal development, and continues until early adulthood. Myelination is an accumulation of fatty tissue surrounding neuronal axons, and is responsible for the most significant growth of the brain during the lifespan (Courchesne et al., 2000; Giedd et al., 1999).

Grey matter develops globally in a non-linear trajectory that presents a pre-adolescent increase followed by a post-adolescent decrease (Sowell et al., 2003; Sowell, Thompson, & Toga, 2004b). On average, the total volume of grey matter increases 13% from infancy (19-33 months) to later childhood (6-9 years), and is followed by a linear decrease of approximately 5% per decade (Courchesne et al., 2000). Whole brain volume decreases by 26% between the ages of 16-80 (Courchesne et al., 2000). In this sense, the whole-brain volume of a person at 80 years old is on average similar to that of a young child (2-3 years old) (Courchesne et al., 2000).

General Implications of Cortical Development

The significant progressive cortical growth that occurs between infancy and childhood is attributed to dendritic expansion. Dendrites are branches that surround the cell body of a neuron, and conduct electrical signals from the synapses of other neurons. As the brain matures new connections are made between neurons to facilitate development, for example, the acquisition of a motor skill (Draganski et al., 2004).

In contrast, maturational factors can also be attributed to a reduction of grey matter by

way of synaptic pruning (Sowell, Thompson, Tessner, & Toga, 2001). Unlike dendritic expansion, synaptic pruning is a regressive process which creates a more efficient neural structure through the reduction or elimination of potentially unnecessary neural connections and cells. This removal of weaker or neglected cells and connections is thought to improve the efficiency of the remaining neuronal signals. Furthermore, thinning of the cortex continues to some degree for the remainder of the lifespan. However, unlike the efficient regression of synaptic pruning, this age related type of neuronal loss tends to be degenerative (Colby et al., 2013; Sowell et al., 2004a; Sowell et al., 2004b). Figure 2 provides the general volumetric trajectories of both white matter and grey matter that takes place across the lifespan.

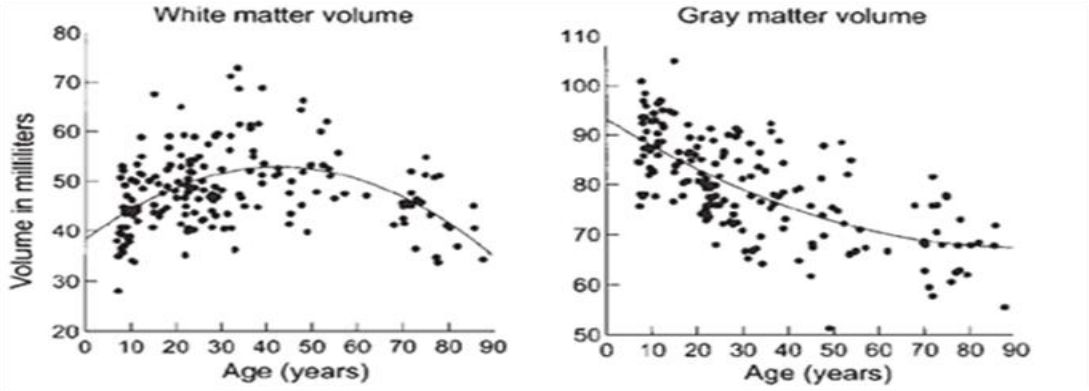

Figure 2. **Volume Changes for white matter and grey matter plotted across lifespan.** ***(Sowell et al., 2003)***

Hemispheres

In regards to broad physiological organization, the cortex is divided into a left and right hemisphere. The two hemispheres closely mirror one another on a structural level, and to the same extent on a functional level. For instance, the left hemisphere is primarily responsible for motor and sensory processes of the contralateral right side of the body, while the right hemisphere controls the left side. In more specific comparisons, however, there appears to be

asymmetries related to language and communication. For example, in most of the population, the left hemisphere is associated with the identification, processing and comprehension of linguistic elements such as phonetics, vocabulary, and syntax (Bookheimer, 2002; Friederici, 2006). In contrast, the right hemisphere pragmatically works to monitor topics of conversation, comprehend narratives, and integrate prosodic information to both implicitly and explicitly interpret a speaker's message (Bookheimer, 2002; Friederici, 2006).

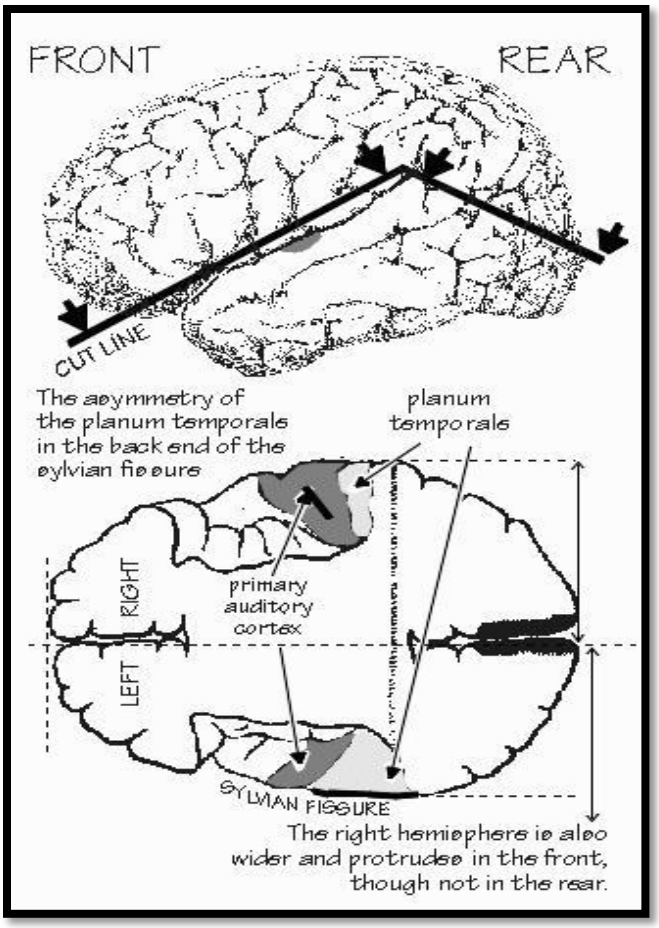

Figure 3. **Structural Development of the Hemispheres. Retrieved from williamcalvin.com/bk7/bk7ch3.htm**

In addition to the functional lateralization of language, there are subtle structural asymmetries. Post-mortem studies conducted on adults indicate that the sylvian fissure is typically longer in the left hemisphere (Galaburda, Sanides, & Geschwind, 1978; Ide, Rodriguez, Zaidel, & Aboitiz, 1996). Furthermore, these hemispheric asymmetries are already present in childhood. Post-mortem examinations of infants show that the planum temporale, which is located in the sylvian fissure, is longer in the left compared to the right hemisphere (Witelson & Pallie, 1973). The sylvian fissure of the left hemisphere and regions surrounding it are considered to be heavily involved with language and communication. While grey matter asymmetry between

hemispheres tends to remain static through the lifespan, this asymmetry of the sylvian fissure which is present in infancy typically becomes more pronounced as people age (Sowell et al., 2002a; Sowell, Thompson, Tessner, Rex, Kornsand, Jernigan, & Toga, 2002b). Figure 3 provides an illustration of this left and right structural asymmetry. These studies, which capture both ends of the lifespan, suggest that although asymmetrical patterns exist during infancy, further asymmetric development related to peri-sylvian regions may be associated with language acquisition and development (Sowell et al., 2002; Sowell et al., 2002b, Sowell, Trauner, Gamst, & Jernigan, 2002c). This interesting development of peri-sylvian regions will be examined in more detail in a later section.

Lobes

Both hemispheres are further categorized into four lobes labelled the frontal, parietal, temporal, and occipital. Each lobe generally executes certain cognitive, motor, and sensory processes. Of the four lobes only the frontal, parietal, and temporal are considered to have direct functions related to speech and language. Figure 4 provides a picture of the general functional responsibilities attributed to each lobe.

There are also sub-cortical structures like the cerebellum and basal ganglia which coordinate and sequence speech movements (Reiss, Abrams, Singer, Ross, & Denckla, 1996). However, automatized measurements of grey matter thickness are not yet available for sub-cortical structures. Therefore, because of this constraint and the limited comparative stuttering data, this discussion will focus only on typical development and function at the cortical level.

Developmentally, the frontal, temporal, and parietal lobes grow at different trajectories. Functionally, the brain matures from the back (posterior) to front (anterior). For example,

auditory skills found in the more posterior temporal lobe fully mature before motor skills located in the frontal lobe (Sowell, Thompson, Holmes, Batth, Jernigan, & Toga, 1999). Furthermore, primary sensory areas which are active in the parietal lobe mature prior to higher order areas such as emotional regulation and problem solving which are carried out by the

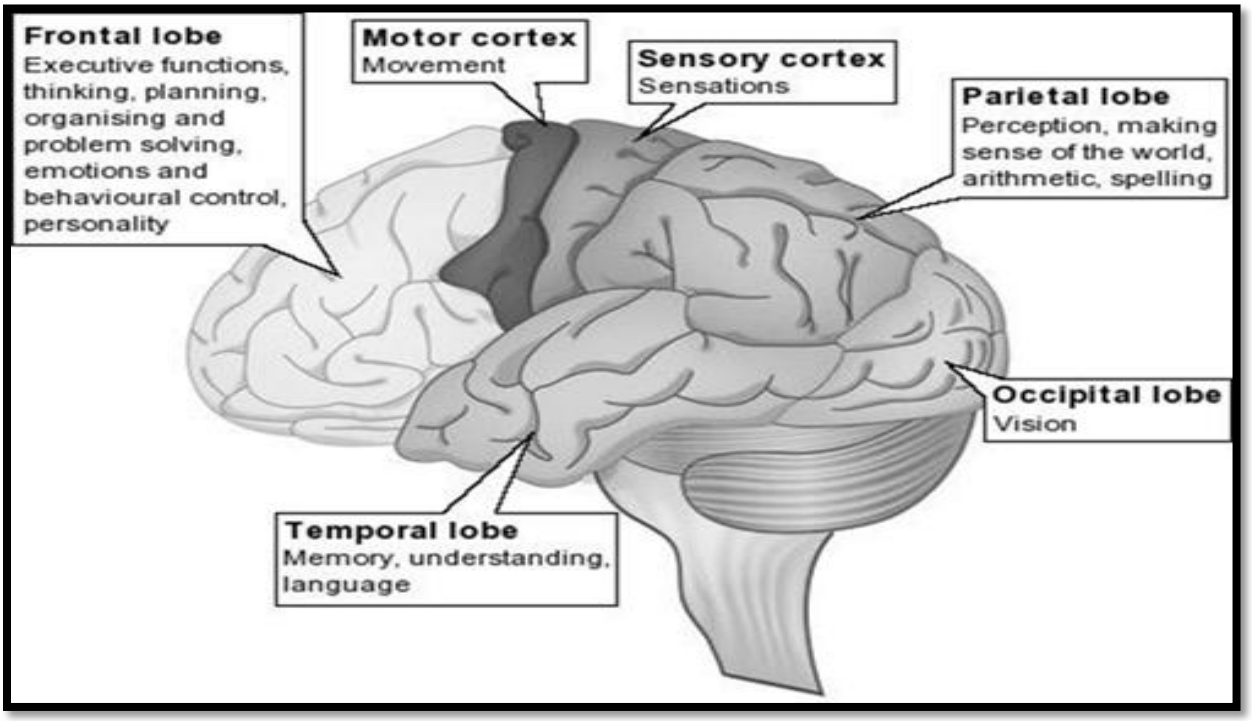

***Figure 4*. Lobar Functions. Image retrieved from www.headway.org.uk/executive-dysfunction-after-brain-injury.aspx.**

frontal cortex (Sowell et al., 1999). Structural post-mortem data supports this functional emergence, and has determined that synaptic pruning ends at around age 12 in the primary sensory regions of the parietal cortex, but continues until about the age of 16 in the prefrontal cortex (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997).

Developmental MRI research also supports the ordered maturation of posterior to anterior dorsal regions. Grey matter of both the frontal and parietal lobes increases during childhood and is followed by a decrease during adolescence (Giedd et al., 1999; Giedd et al.,

2006). In males, both the parietal and frontal regions typically achieve this peak growth of grey matter around the age of 12. After this peak growth, the frontal and parietal grey matter returns to a density relative to earlier childhood years (Sowell et al., 2003; Sowell, Delis, Stiles, & Jernigan, 2001a).

In contrast to frontal and parietal growth which tends to peak around age 12, temporal grey matter typically peak at around age 16.5 (Giedd et al., 1999). After this, development tends to plateau, and slowly decline. While the temporal lobe demonstrates less dramatic change between childhood and adolescence compared to the frontal and parietal lobes, it has the same non-linear pattern of trajectory (Sowell et al., 2002c; Giedd et al., 1996). Within the temporal lobe, the most significant developmental change occurs in the dorsal regions surrounding the sylvian fissure rather than the ventral regions (Giedd et al., 1999; Jernigan, Trauner, Hesselink, & Tallal, 1991). Figure 5 compares the volumetric trajectories of the frontal, parietal, and temporal lobes.

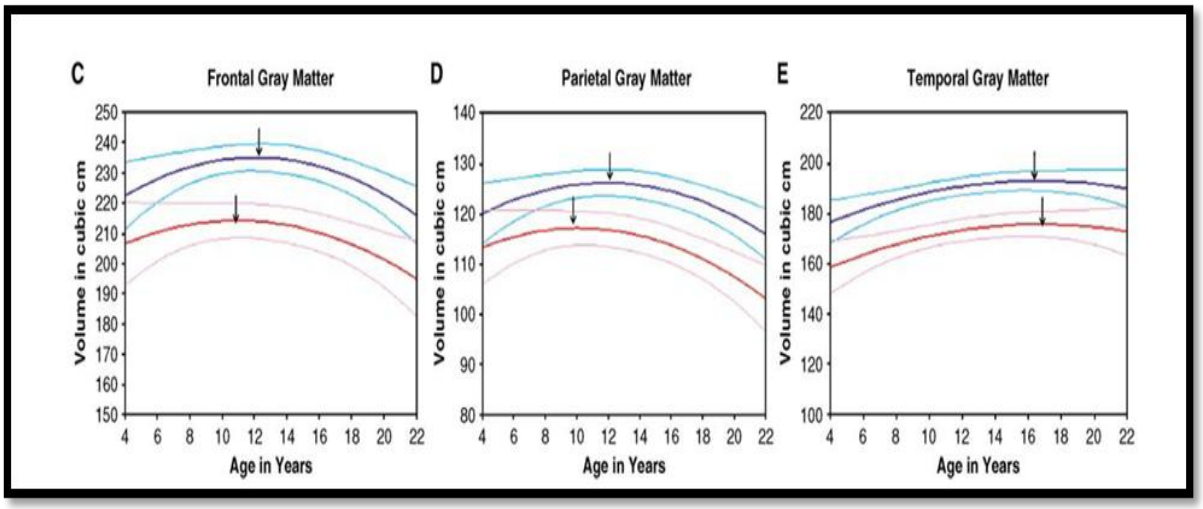

***Figure 5*. Volumetric trajectories of grey matter amongst the lobes. Males are represented by purple lines and Females are represented by red lines. Arrows indicate peak grey matter volume (Thompson et al., 2005).**

To summarize, the most prominent reduction of grey matter takes place between

childhood and adolescence in the dorsal regions of the frontal and parietal lobes, with the least dramatic change observed in the ventral region of the temporal lobe (Jernigan et al., 1991; Giedd et al., 1996; Sowell et al., 2002c). Functionally, the thinning of frontal grey matter during adolescence correlates with improved verbal learning between the ages 7-16 (Sowell et al, 2001a). Furthermore, reductions of grey matter density in the left dorsolateral frontal and lateral parietal regions during adolescence are correlated with improved vocabulary scores and better performance during verbal learning tasks (Lee et al., 2007). Improved motor skills are also associated with thinning in more dorsal regions of frontal cortex (Lu et al., 2007).

Speech Network

Continued structural examination of the frontal, parietal and temporal lobes highlight more precise regions of interest related to the speech network. This is important because many of these speech regions demonstrate different cortical growth trajectories compared to the rest of the cortex (Beal, Gracco, Laffaille, & De Nil, 2007; Beal et al., 2013). The speech and language regions located in the frontal lobe include the primary motor cortex (or M1, precentral gyrus), and the inferior frontal gyrus. Regions of interest identified in the temporal lobe include the superior temporal gyrus which contains the primary auditory cortex. Regions of interest found in the parietal lobe include the supramarginal gyrus, and, the primary sensory cortex (or S1) (Beal et al., 2007, Foundas, Bollich, Corey, Hurley, & Heilman, 2001). Figure 6 incorporates information and models from existing cortical development studies (Beal et al., 2007; Foundas et al., 2001) to highlight the cortical regions associated with the speech network.

We will discuss the speech network by independently examining the perisylvian and non-perisylvian regions. This is because perisylvian growth patterns differ from the non-

perisylvian speech regions and the rest of cortex (Sowell et al., 2003; Sowell et al., 2004a; Sowell et al., 2004b; Gogtay et al., 2004). The perisylvian network involves all of the specific regions of interest surrounding the sylvian fissure such as the inferior frontal gyrus and the superior temporal gyrus. Two non-perisylvian regions associated with the speech network are the primary motor and sensory cortices. Cortical growth here develops in a manner that resembles the rest of the cortex (Sowell et al., 2003; Sowell, Delis, Stiles, & Jernigan, 2001a).

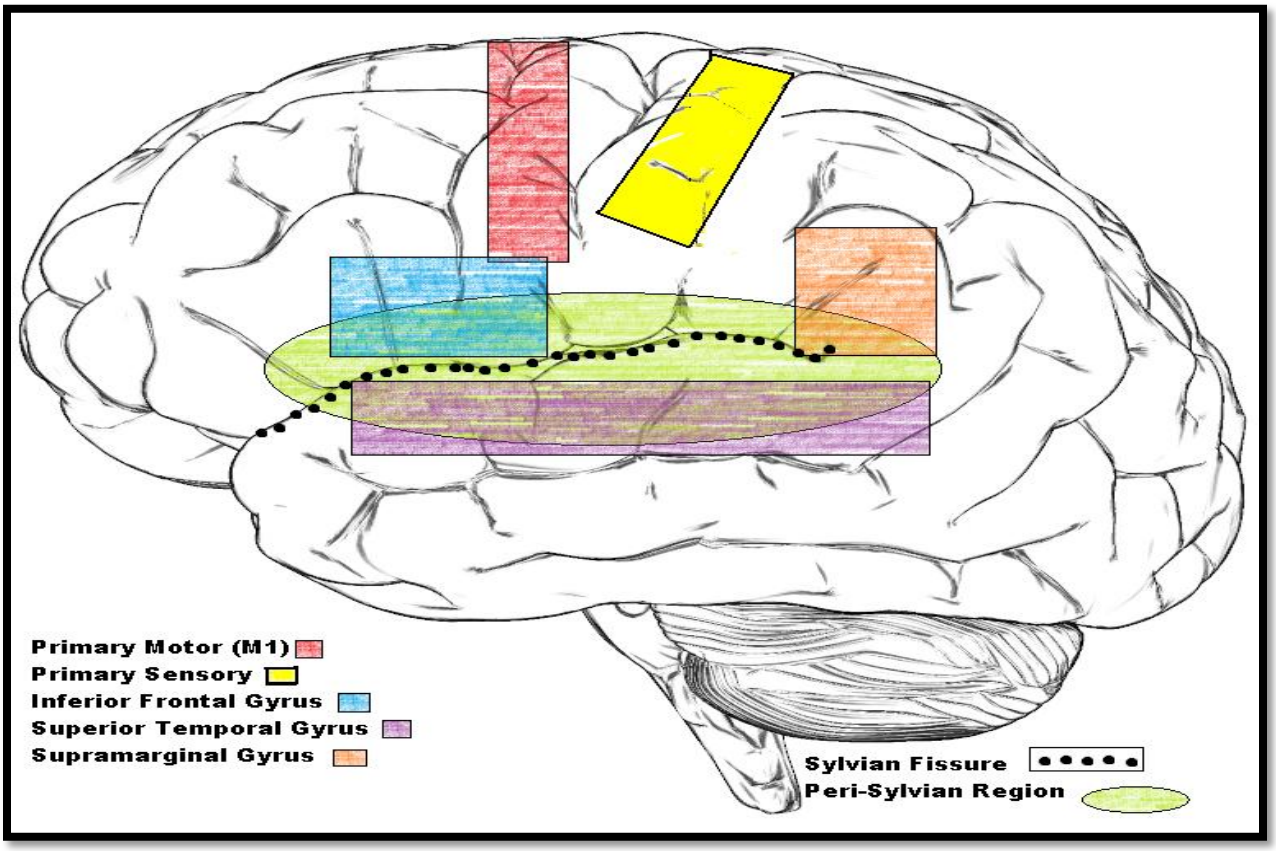

***Figure 6*. Cortical regions associated with the speech network.**

While most of the cortex, including these non-perisylvian regions, experiences a decrease in grey matter density between 7-60 years, the anterior and posterior regions surrounding the sylvian fissure continue to subtly increase through the first 3 decades of the lifespan (Sowell et al., 2003; Gogtay et al., 2004). These regions specifically include the inferior

frontal gyrus and the posterior region of the superior temporal gyrus (Sowell et al., 2004a; Sowell et al., 2004b). Commonly, these perisylvian regions are referenced as Broca's and Wernicke's area. While neural growth of perisylvian regions does occur bilaterally, this thickening is extended more anteriorly in the left hemisphere to encompass the inferior frontal gyrus (Sowell et al., 2004b). Furthermore, the localized grey matter increase in the left hemisphere corresponds with the previously mentioned increase in sylvian fissure asymmetry from childhood to adulthood. That is, there is a greater asymmetry between left and right sylvian fissure in adulthood compared to childhood (Galaburda et al.,1978; Ide et al., 1996).

Functional Implications of Abnormal Cortical Thickness

Although the relationship between behavioural patterns and the structure of the brain are not precisely defined, there are many studies that link the thickness of the cortex to specific cognitive skills and behaviours (Bonner & Grossman, 2012; Ehrlich et al., 2012; Richardson et. al, 2011; Shaw et al., 2006). These studies have established correlations between cortical thickness with measures of intelligence, and cognitive functioning. They have also highlighted the potential significance abnormal developmental trajectories may impact on aspects of cognition and behaviour (Bonner & Grossman, 2012; Ehrlich et al., 2012; Richardson et. al, 2011; Shaw et al., 2006). Figure 7 presents the results from a longitudinal study by Shaw et al. (2006) that examined the correlation between intelligence levels and cortical thickness. Shaw's results indicate that a pre-adolescent increase in cortical thickness followed by a post-adolescent decrease in cortical thickness correlates with higher levels of intelligence (2006). Comparing the thickness of the cortex as well as the trajectory of growth between these populations may shed light on how the development of the cortex in these regions contributes

to fluent speech production.

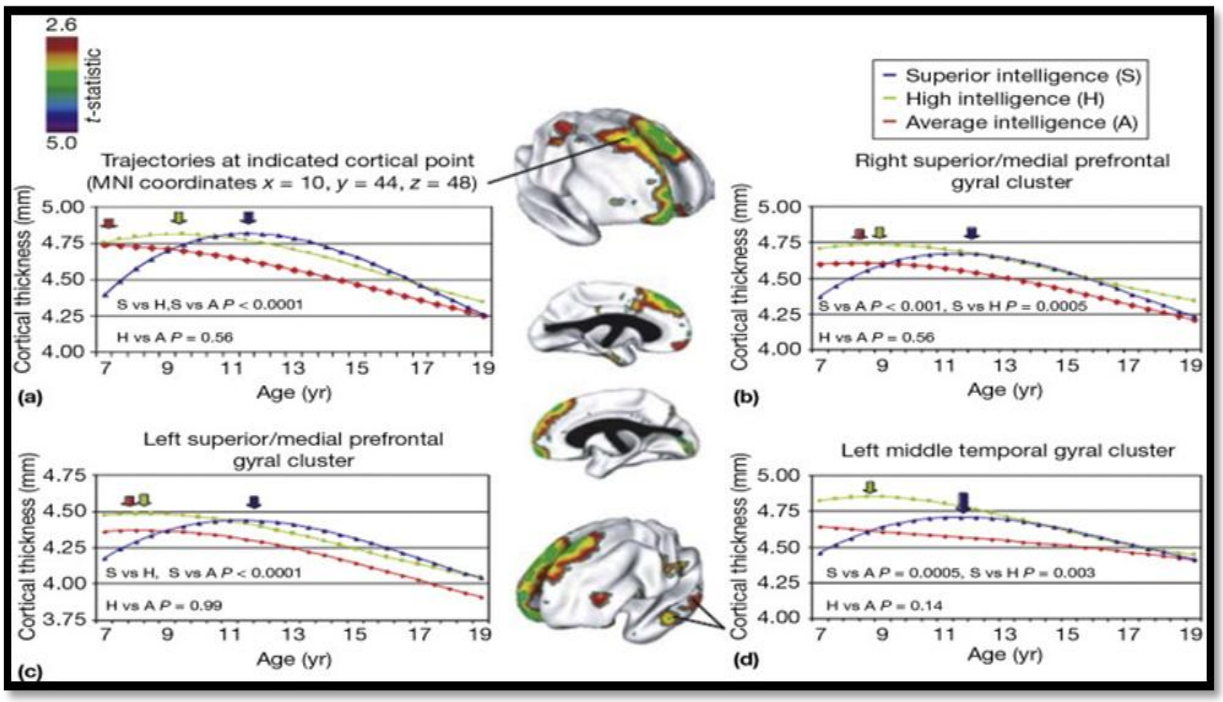

Figure 7. **Correlations between intelligence and cortical thickness (Shaw et al., 2006)**

TRAJECTORIES OF CORTICAL THICKNESS IN PEOPLE WHO STUTTER

Background on Stuttering

Stuttered speech is an abnormal disruption of fluency. Persistent developmental stuttering commonly emerges in 5% of pre-school children, and may or may not continue throughout the lifespan (Bloodstein, 1995). It typically first appears in childhood at around ages 2 to 5 as borderline stuttering, and progresses through stages of beginning, intermediate, and advanced stuttering as the child matures through adolescence and adulthood (Guitar, 2014).

The disorder is primarily characterized by core behaviours that include frequent and involuntary speech sound repetitions, prolongations, and silent blocks. There are also

secondary characteristics that may emerge in people who stutter, such as “escape” and “avoidance” behaviours (Guitar, 2014). These two characteristics reference strategies used by people who stutter to cope with or avoid stuttered speech, for example, eye blinks and word changes. In addition to these primary and secondary behaviours, people who stutter may also present a variety of more subtle cognitive emotional characteristics such as frustration, embarrassment, stress, and anxiety (Erikson & Block, 2013). The characteristics of stuttering can occur in a spectrum of severities that can range from mild to severe. These differences in severity can fluctuate both between and within people who stutter.

Abnormal Developmental Trajectory

When compared to aged matched peers, there appears to be neuroanatomical abnormalities related to regions of the speech network in both children and adults who stutter. In a pediatric study by Beal et al. (2013), children (boys ages 6-12) who stutter showed reduced grey matter volume in the bilateral inferior frontal gyrus and right middle temporal gyrus compared to their age matched peers (Beal et al., 2013; Chang, Erikson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008). It is interesting to note that measurements of increased grey matter volume were only identified in the right hemisphere (Beal et al., 2013). Compared to fluent children, children who stutter presented increased levels of grey matter volume in the right superior temporal gyrus, the right rolandic operculum, middle frontal gyrus, and inferior parietal lobe, with the most significant increase being found in the superior temporal gyrus (Beal et al., 2013). The right middle frontal gyrus, and inferior parietal lobule are areas both known to over-activate in adults who stutter in positron emission tomography and fMRI studies of speech production (Beal et al., 2013; Brown et al., 2012).

Prior to the pediatric study (2013), Beal et al. compared the cortical MRI data of adults who stutter with fluent aged matched peers (2007). This study determined that adults who stutter were found to have increased levels of cortical thickness in left inferior frontal gyrus and right middle temporal gyrus relative to fluent adults (Beal et al., 2007; Beal et al., 2013). These results are in contrast to the reduced grey matter found in the left inferior frontal gyrus and right middle temporal gyrus of children who stutter. This structural information from pediatric and adult MRI data suggests that people who stutter have an abnormal developmental trajectory of grey matter development in these two regions. That is, there is a likelihood that grey matter of the left inferior frontal gyrus develops at a later age and to a lesser extent in children who stutter. Furthermore, post-adolescent synaptic pruning of this region also appears delayed and less significant.

Additional results by Beal et al. (2007) also indicated that compared to fluent speakers, adults who stutter presented increased levels of grey matter volume in other speech related regions that include the bilateral superior temporal gyrus (specifically the primary auditory cortex), and the left middle temporal gyrus, with the largest increases observed on the primary auditory cortex of the right superior temporal gyrus (Beal et al., 2007).

Figure 8 plots the cortical trajectories of the specific speech regions in both people who stutter and their controlled matched peers. The pilot data presented in figure 8 are derived from a subgroup of participants from both the study by Beal et al. (2007) which examined cortical volume of adults who stutter and the study by Beal et al. (2013) which examined the cortical volume of children who stutter, as well as some novel participants.

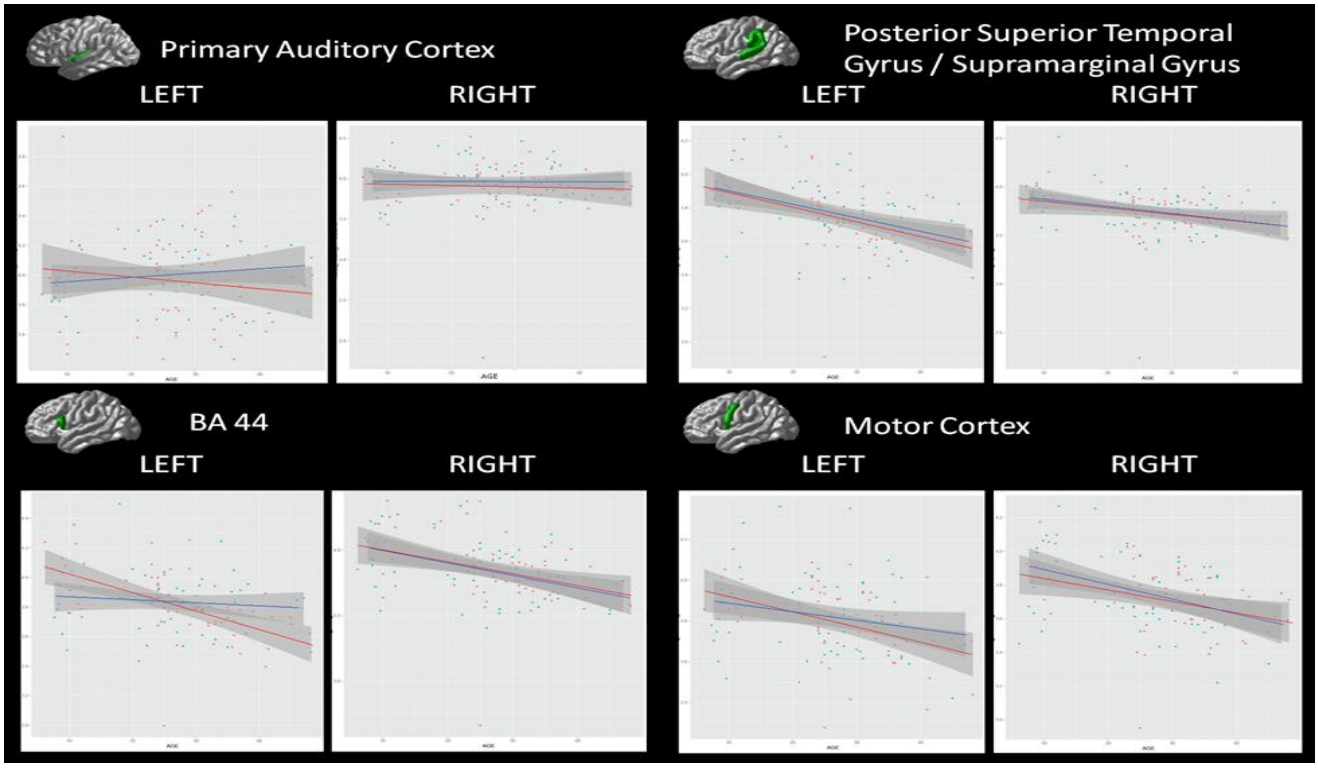

***Figure 8*. Cortical Developmental Trajectories of People who stutter compared to fluent speakers. Blue lines represent people who stutter and red lines represent fluent speakers. Notice the most significant difference in the inferior frontal gyrus, otherwise referred to as BA 44 (Beal, et al., 2007).**

Comparative Discussion

The results of these studies indicate that the cortical thickness of specific speech regions in people who stutter remained relatively stable throughout the lifespan, compared to fluent speakers who experienced more dramatic cortical thinning after childhood. The left inferior frontal gyrus, particularly the left pars opercularis, displayed an abnormal developmental trajectory of cortical thickness in people who stutter relative to their age matched fluent speakers (Beal et al., 2007; Beal et al., 2013). In terms of speech production, the left pars opercularis of the inferior frontal gyrus is activated during both language processing and production tasks (Chang & Zhou, 2013). The left pars opercularis is hypothesized to hold

representations for phonemes and syllables in the brain (Beal et al., 2007) which are crucial to the planning of articulation for speech sounds. The anatomical findings with regards to cortical thickness measures in people who stutter are in line with our current understanding of the functional role of the inferior frontal gyrus, and particularly the left pars opercularis. They highlight the idea that children who stutter may not have adequate neural resources for speech sound processing, and that this underdevelopment may lead to an inability to establish stable speech motor plans (Beal et al., 2013).

Furthermore, adults who stutter display larger volumes of grey matter in the left inferior frontal gyrus (Beal et al., 2007). This suggests that the cortical thinning of the inferior frontal gyrus in adults who stutter is lesser compared to fluent speaking adults. The abnormal trajectory observed here may represent a failure to engage synaptic pruning processes during childhood, and may result in an inefficient neuronal organization within the speech network and subsequent abnormalities in articulatory coding of phonemes.

In addition, there is functional data to suggest abnormal activity in the inferior frontal gyrus of adults who stutter. During speech, the left inferior frontal gyrus of adults who stutter was found to be overactive compared to fluent speakers (Watkins et al., 2008). This functional data along with the previously mentioned structural abnormalities contributes to the growing body of evidence that grey matter in the left inferior frontal gyrus, particularly the left pars opercularis, is important for the establishment and maintenance of fluent speech production. Figure 9 provides a hypothesized visualization of the speech network in action, and where the breakdown may potentially occur in the cortex of people who stutter.

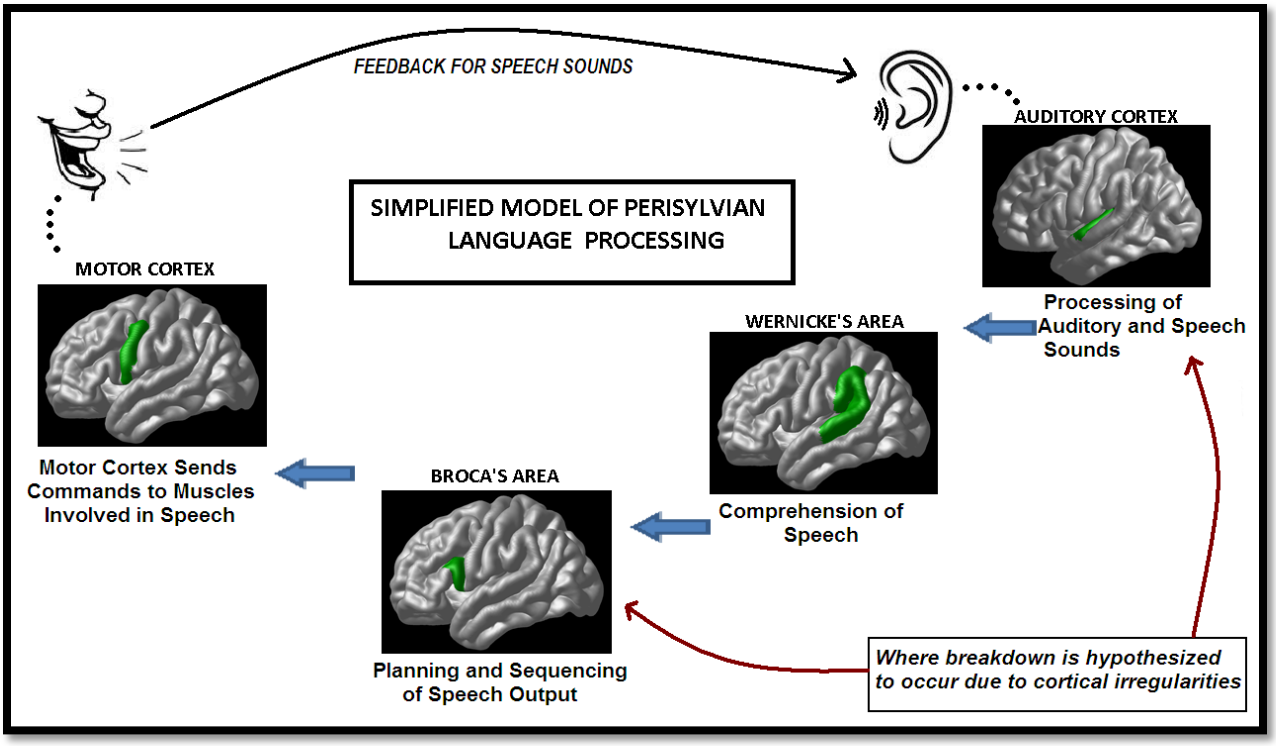

***Figure 9*. Hypothesized representation of where the breakdown in speech motor planning occurs. Images modified from pilot data presented in a poster by Beal et al. (2007).**

As mentioned earlier, adults who stutter present increased levels of grey matter volume in the superior temporal gyrus compared to fluent adults. This area which contains the primary auditory cortex is known to significantly participate in auditory processing for speech production (Beal, 2007). More specifically, this region is believed to actively monitor the speech output of a speaker's phonemes and articulatory patterns. Abnormally increased volumes of grey matter in this region may hypothetically reduce the efficiency of auditory processing for speech sounds in people who stutter (Foundas, Bollich, Feldman, Corey, Hurley, Lemen, & Heilman, 2004; Tourville, Reilly, & Guenther, 2008). Using a delayed auditory feedback listening device has even been marketed as a potential means to treat dysfluent speech production. However, despite initial enthusiasm, the benefits of this device are only short term, and the positive effects of delayed auditory feedback consistently fade (Foundas et al., 2004).

CONCLUSION

These recent studies that compared the grey matter volumes of non-fluent and fluent speakers in both childhood and adulthood have established evidence to indicate the presence of an abnormal developmental trajectory in the cortical speech regions of people who stutter. Based on the current literature, children who stutter display reduced levels of grey matter in important speech regions such as the inferior frontal gyrus, while in this same region, adults who stutter demonstrate increased levels of grey matter volume. Moreover, larger amounts of grey matter are also observed bilaterally in the superior temporal gyri of people who stutter. We can hypothesize how abnormal neuro-physiologies in these speech regions can impact motor planning and auditory feedback for speech, but research has not yet determined a comprehensive explanation to account for a conclusive aetiology of developmental stuttering.

No doubt, future studies will benefit from continually improved brain imaging technologies to provide a more precise examination of cortical development. Recent studies have also explored data that compares the connectivity of white matter pathways in fluent versus non-fluent speakers (Chang & Zhu, 2013; Watkins, Smith, Davis, & Howell, 2008). This information combined with the research on cortical thickness discussed in this paper, and exploration into sub-cortical regions related to speech planning will together provide a more holistic picture of abnormal versus typical brain development across the lifespan. Other variables to consider for future directions related to this body of research could include a more in depth examination of female, and non-English speaking people who stutter.

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