# AN INVESTIGATION OF CEREBELLAR MORPHOLOGY IN CHILDHOOD STUTTERING

By

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**ABSTRACT**

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While many studies have connected structural and functional cerebellar differences to developmental stuttering, there are limited studies of cerebellar gray matter morphology in young children who stutter. These examinations include small sample sizes of children and use morphometry methods that might not be best suited for examining the cerebellum (e.g., Chang et al., 2008). This dissertation examines how the structure of specific cerebellar lobules differs in a larger cohort of children who stutter and children who do not stutter as well as in persistent and recovered children who stutter. These data will provide evidence to better inform predictions of how the morphology of cerebellar areas are likely involved in aspects of speech motor control in developmental stuttering.

In this study, gray matter morphology of the cerebellum was examined in children who do and do not stutter using voxel-based morphometry and a specialized toolbox and atlas for the cerebellum (Diedrichsen, 2006). Here we examined cerebellar gray matter volume (GMV) based on structural MRI data from children who stutter and children who do not stutter, 116 preschool-age children (stuttering N= 57) between the ages of 3-5 years, and a school-age cohort of 72 children (stuttering N=37) six years of age and up. This dissertation is the first study to examine cerebellar GMV in a large group of children who stutter using a specialized toolbox and atlas for the cerebellum.

Results from this study showed that there were no overall significant group differences of lobular GMV between the stuttering and non-stuttering groups in any of the groups of children.

There were significant age-related associations, however, that differentiated children who do and do not stutter in specific age ranges. In particular, the following cerebellar lobules differed significantly in GMV between children who do and do not stutter with age: 1) cerebellar lobule VII, which may correspond with cerebellar functions that support speech planning, 2) lobule VIII, which has been linked to various functions including corrections during perturbation studies, and 3) lobule IV which has been reported to be involved in feedforward control speech motor control processes. Notably, GMV of cerebellar lobule VI was associated negatively with Stuttering Severity Instrument (SSI) score in preschool-age persistent children who stutter. Associations between SSI score and GMV in cerebellar lobule VI may mean that feedforward control mechanisms are associated with the frequency of stuttering in children who stutter.

In summary, significant findings of this investigation indicate that 1) children who do and do not stutter do not show an overall difference in cerebellar GMV, 2) GMV of the cerebellum is associated with SSI score, 3) age-related differences in GMV in the cerebellum differentiate children who do and do not stutter. The results from this study indicate that feedforward control is associated with disfluencies while age-related variations of cerebellar areas that may support both the feedback and feedforward control pathways are connected to aspects of stuttering, such as age.

This dissertation is dedicated to my grandparents, Faye M. Vincent and Fred T. Johnson, who have always supported my dreams and given me the means to pursue them.

This work is also dedicated to the memory of my late grandparents Charlotte A. Adams and Elvin O. Adams and great-grandparent Anna M. Hall, who I wish were here to celebrate this major accomplishment with me.

Lastly, I dedicate this dissertation to my father, Fred V. Johnson. I can't imagine a parent who could have supported me better through this journey or loved me more. You have made this dissertation possible.

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## 1.0 INTRODUCTION

Stuttering is a neurodevelopmental disorder that affects approximately 1% of the world's population and 5-8% of preschool-aged children (Bloodstein & Bernstein Ratner, 2008; Yairi & Ambrose, 2013). Eighty percent of preschool-aged children will naturally recover from stuttering, but the neural mechanisms that support persistence versus recovery from stuttering are still largely unknown (Yairi & Ambrose, 2013). Stuttering is a complex neurological disorder characterized by atypical speech motor control influenced by multiple cognitive processes that combine differently and dynamically across individuals who stutter (Smith & Weber, 2017). Despite reported findings implicating cognitive processes such as language and attention are affected in developmental stuttering, we do not understand how these processes interact to produce neurodevelopmental changes resulting in stuttering onset or natural recovery in childhood.

## 1.1 RELEVANCE OF CEREBELLAR REGIONAL ANATOMY TO THE NEURAL BASES OF STUTTERING

One way to study the possible influence of multiple etiological factors related to stuttering onset and different clinical outcomes is to examine in detail the brain's "hub" areas that support the integration of multiple functions. One such area is the basal ganglia, which plays a major role in coordinating movement, and has been of interest in the context of stuttering (Chang et al., 2019; Chang & Guenther, 2020; Craig-McQuaide et al., 2014). The basal ganglia comprise multiple sub-structures that support not only the initiation and sequencing of speech movements (Tourville & Guenther, 2011) but also various higher-order cognitive functions such as reward processing (e.g., Schultz et al., 2000), learning (e.g., Packard & Knowlton, 2002), and language (e.g., Booth et al., 2007), among others. Thus, the basal ganglia and the closed loop it forms with the cortex via the thalamus-- the basal ganglia thalamocortical loop (BGTC)-- have been explored in several studies in the context of stuttering (see also Alm, 2004 for a review). However, the basal ganglia are only one potential hub area in the brain that influence the integration of multiple brain areas that may be affected in developmental stuttering.

Figure 1: Posterior view of the cerebellar cortex

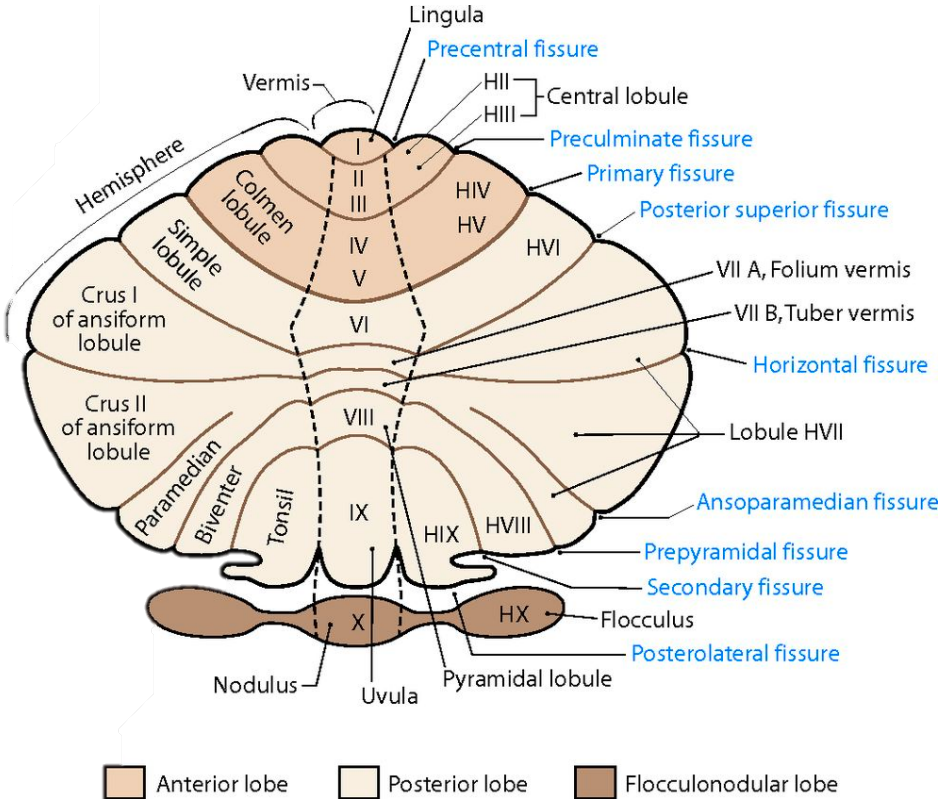


Figure Caption: Posterior view of the cerebellar cortex, unfolded at the level of the horizontal fissure and laid flat to display the lobules of the three cerebellar lobes. Lobules I-V are located in the most superior aspects of the cerebellum and comprise the anterior lobe. The lightest, medial section of the figure comprises the posterior lobe, lobules VI-IX. The inferior, brown section of the figure consists of the flocculonodular lobe, lobule X. Adapted from Klein et al., 2016.

The cerebellum is another crucial hub area that has ample connections with most parts of the brain, including the basal ganglia (Figure 1; Akkal et al., 2007; Bostan et al., 2013; Bostan et al., 2010; Brodal, 1978; Glickstein et al., 1985; Hoover & Strick, 1999; Hoshi et al., 2005; Kelly & Strick, 2000, 2003; Leichnetz et al., 1984; Middleton & Strick, 1994, 2001; Schmahmann & Pandya, 1991, 1993, 1997; Snider & Maiti, 1976; Strick et al., 2009; Tourville & Guenther, 2011; Vilensky & Van Hoesen, 1981; Zemanick et al., 1991) and the cerebral cortex (e.g., Strick et al., 2009). Although the cerebellum was traditionally linked primarily to motor functions, more recent studies have shown strong evidence supporting the cerebellum's substantial role in functions outside of motor control. For example, working memory, semantic judgment, spatial awareness tasks, procedural learning, decision making, and emotion all engage the cerebellum (for a review, see Stoodley & Schmahmann, 2010). Cerebellar function and structure differences have also been reported in the context of developmental stuttering (Beal et al., 2007; Brown et al., 2005; Budde et al., 2014; Chang et al., 2015; Chang et al., 2008, 2016; Chang & Zhu, 2013; Chow & Chang, 2017; Connally et al., 2014; De Nil et al., 2001; Garnett et al., 2018; Kell et al., 2018; Lu et al., 2009, 2012; Lu et al., 2010; Lu et al., 2010; Sitek et al., 2016; Song et al., 2007; Watkins et al., 2007, 2007; Yang et al., 2016). Mainly, the cerebellum's right-lateralized areas, which interconnect with left hemisphere cortical regions, are associated with orofacial movements and speech motor control and have been reported to be overactive in people who stutter (e.g., De Nil et al., 2003; Lu et al., 2009; Lu et al., 2010). Additionally, the cerebellar peduncles, which contain efferent and afferent fibers of the cerebellum that interconnect it with cerebral and brainstem areas, have also been shown to differ in adults who stutter and persistent children who stutter (Chow & Chang, 2017; Connally et al., 2014; Garnett et al., 2018; Johnson et al., 2022; Watkins et al., 2007). However, what is less known to date is how the morphology

of cerebellar lobules – each linked to different motor and cognitive functions -- differ in people who stutter and how the morphological differences are associated with stuttering during childhood.

The cerebellum comprises functionally-distinct lobules that support specific cognitive processes (e.g., Schmahmann, 1996; Stoodley & Schmahmann, 2009). While previous neurophysiological studies have studied the cerebellum, few have described how the function and structure of cerebellar lobules differ in developmental stuttering. Examining lobular function and anatomy will likely help elucidate how multiple motor and cognitive functions linked to each lobule develop differently in children who stutter. This information could explain how and to what extent each of these functions contribute to stuttering onset and persistence. Examining the cerebellum's developmental trajectories could thus provide an opportunity to further our understanding of the neural bases of stuttering persistence and recovery.

## 1.2 THE CEREBELLUM'S ROLE IN SUPPORTING SELF-INITIATED MOVEMENTS VIA INTERNAL MODELS AND EFFERENCE COPIES

Apart from the accruing evidence pointing to the cerebellum as a possible hub area that integrates motor and cognitive functions that are relevant to speech control, a detailed examination of cerebellar function is essential given its critical role in generating the "efference copy" signal, which has been posited to be affected in stuttering (Brown et al., 2005; Max et al., 2004). Well-learned, self-initiated movement is supported by a forward internal model (Kawato, 1999), which is provided with a copy of the movement-producing signal ("efference") called the efference copy (Brodal & Bjaalie, 1992; Miall & Wolpert, 1996; Rhodes & Bullock, 2002; Wolpert et al., 1998). The efference copy is an internal copy of a motor command that codes for its predicted movement and the sensory feedback (auditory, somatosensory) resulting from the movement. Namely, efference copies are duplicate predictions of planned movements that further refine motor plans and generate new motor commands when errors are detected (Brodal & Bjaalie, 1992; Miall & Wolpert, 1996; Rhodes & Bullock, 2002; Wolpert et al., 1998). An influential model of speech motor control, the Directions Into Velocities of Articulators (DIVA) model, provides a theoretical framework to discuss how efference copies are essential for speech motor control (Tourville & Guenther, 2011).

According to DIVA, the efference copy is sent from the premotor cortex to sensory and motor areas through cortico-cerebellar loops. Cortico-cerebellar loops include different cerebellar cortex areas, the pons, and the thalamus that mediate signals between cortical areas. In the DIVA model, there are four different cortico-cerebellar loops (see Figure 5a-d). While each of the four cortico-cerebellar loops in the DIVA model deal with efference information, each loop's role is different. For example, the neural connections between the left premotor cortex and

motor cortex update efference copies based on the current contextual information, such as the system's sensory state, which is important to the current state of the movement being executed (Figure 5a). In addition, the two cortico-cerebellar loops leading to the feedback control system use internal models from the left ventral premotor cortex to detect speech errors that fall outside of sensory targets learned throughout development (Figure 5c-d). Lastly, the loop leading from the right premotor cortex to the ventral motor cortex is heavily involved with refining corrective motor responses from efference copies that result from subtracting the predicted speech outcome from sensory feedback (Figure 5b; Tourville & Guenther, 2011).

## 1.3 THEORETICAL AND EMPIRICAL EVIDENCE POINTS TO DIFFERENCES IN EFFERENCE COPY USAGE IN ADULTS WHO STUTTER BUT MIXED RESULTS IN CHILDREN WHO STUTTER

Stuttering theories that involve efference copy mechanisms argue that efference copy information is misused in developmental stuttering. However, these theories fail to discuss how efference copy mechanisms may change over development differently in persistent and recovered people who stutter and which pathways that process the efference copy may be involved differently over a lifetime of stuttering. The cerebellum is a critical aspect of the cortico-cerebellar loops that utilize efference copy mechanisms (for a discussion, see Figure 2 and corresponding text). Understanding how the cerebellum is involved in stuttering neurophysiology will help us flesh out efference copy theories to more clearly describe mechanisms that they may be involved in that are important to developmental stuttering.

An inefficient efference copy mechanism affects a speaker's ability to compute online corrections to speech movements in response to a perceived mismatch in expected and actual auditory feedback. Auditory perturbation experiments measure online corrective speech adaptations in response to altered auditory feedback during speech. Adults who stutter have attenuated corrective speech responses relative to that observed in adults who do not stutter during auditory perturbation paradigms. However, compared to adults (Cai et al., 2012, 2014; Daliri et al., 2017; Daliri & Max, 2018; Kim et al., 2020; Loucks et al., 2012; Sares et al., 2018), results from the two auditory perturbation studies with children who stutter have been less consistent. One pediatric study found comparable corrective speech responses to auditory feedback perturbations in children who stutter compared to children who do not stutter (Daliri et al., 2017). However, in another study, children who stutter relative to their age-matched peers

who do not stutter exhibited less speech compensation to auditory perturbation, similar to many auditory perturbation studies of adults who stutter (Kim et al., 2020). Although the Daliri et al. and Kim et al. studies seem to contradict one another, there are important differences in the study designs that merit a discussion, which complement efference copy theories of stuttering and other stuttering findings.

Kim et al. (2020) suggest that the speech tasks used by their team and Daliri et al. (2017) may have measured different sensorimotor learning processes. They argue that the paradigm from Daliri et al. (2017) triggered an explicit learning process while their own speech task-induced higher levels of intrinsic learning processes. Allegedly, auditory feedback during speech in Daliri et al. (2017) was perturbed such that participants could consciously perceive that the auditory feedback they heard did not match that of expected auditory feedback of the vowel they produced. For example, the words *bed*, *head*, and *Ted* may have sounded like *bad*, *had*, and *Tad* to the participants. *Bad*, *had*, and *Tad* are different words altogether, which may have caught the conscious attention of those in the study.

The study by Kim et al. (2020), on the other hand, used a perturbation design that did not lead to perceived phonemic errors due to altered feedback during the study session. Because the formants were altered in a way that may have made the perturbation more implicit, the Kim et al. (2020) task could have measured a different sensorimotor learning process than their colleagues in Daliri et al. (2017). Using the Kim et al. (2020) auditory perturbation task, the authors observed significant differences between the children who do and do not stutter. A second task from Kim et al. (2020) also supports the argument that implicitly may be what differentiates sensorimotor adaptation between children and adults who stutter due to the inclusion of explicit aspects of the task.

The second task in Kim et al. (2020) involved both intrinsic (i.e., implicit) and extrinsic (i.e., explicit) learning. This task involved upper limb sensorimotor adaptation and showed that children who stutter did not differ from children who do not stutter. Alternatively, the two adult groups showed significant differences in the rate of learning during the same study. Several studies have suggested that upper limb sensorimotor tasks involve explicit and implicit forms of learning (Mazzoni, 2006; McDougle et al., 2015; Schween & Hegele, 2017; Taylor et al., 2014). Therefore, it could be that the inclusion of explicit learning allowed children who stutter to perform more like their peers who do not stutter during the upper limb task in Kim et al. (2020), and potentially, the auditory perturbation task in Daliri et al. (2017). An essential aspect of stuttering physiology might be how different aspects of sensorimotor learning abilities change over development. These two studies suggest that children and adults who stutter have different implicit systems of sensorimotor learning compared to populations who do not stutter; explicit sensorimotor learning processes may differ only in adults who stutter.

The cerebellum is a crucial area of motor control for implicit sensorimotor learning but may not initially interfere with explicit learning strategies (e.g., Taylor et al., 2010). However, damage to the cerebellum and its implicit strategies may, in turn, disrupt the generation of other explicit learning processes over time (Ito, 2008). Therefore, any change in cerebellar functioning over development could first lead to mostly atypical implicit functioning but extend to explicit aspects of sensorimotor learning as one continues to live with a disorder that involves the cerebellum. Namely, explicit sensorimotor learning may be less critical to stuttering onset but degrades with time in persistent people who stutter.

This idea supports the discussion of the available childhood auditory perturbation evidence reviewed above. Other discussions of stuttering etiology, outside of the already discussed studies,

also support this theory. For example, studies examining implicit learning in children who stutter have found that they perform worse on implicit verbal response inhibition but not explicit tasks (Anderson & Wagovich, 2017). Additionally, several studies have found that adults who stutter also perform differently on implicit learning tasks as compared to children who do not stutter (Smits-Bandstra & De Nil, 2013; Smits-Bandstra & Gracco, 2013) as well as on some explicit learning tasks (Smits-Bandstra et al., 2006). Studies of brain function, especially that involving the cerebellum, also offer some support.

## 1.4 SPEECH AUTOMATICITY IS SUPPORTED BY THE CEREBELLUM, WHICH MAY BE LINKED TO RECOVERY FROM STUTTERING

Craig-McQuaide et al. (2014) suggest that cerebellar activity may be important to speech automaticity in people who stutter, another way to describe the implicity of their speech. Craig-McQuaide et al. (2014) argue that results from studies such as De Nil et al. (2001), which measured the cerebellar activity of adults who stutter during different speech tasks, support this hypothesis. De Nil et al. (2001) found that adults who stutter always had higher cerebellar activity than children who do not stutter; however, cerebellar activity decreased a year after stuttering therapy to levels much lower than pre-therapy. Craig-McQuaide et al. (2014) argue that baseline measurements of adults who stutter in their study, which indicated increased cerebellar activity, could indicate that speech is less implicit in people who stutter. In addition, the decrease in cerebellar activity observed in the study during follow-up measurements after therapy may mean that the long-term effects of treatment include more automatic speech than before the intervention.

One important caveat to the argument in Craig-McQuaide et al. (2014) is that measurements immediately following therapy and a year after intervention are relatively comparable in adults who stutter and still higher than that of the group who does not stutter. Notably, in some conditions of De Nil et al. (2001), immediate post-therapy measurements of cerebellar activation are *higher* than pre-therapy measurements. However, a year later, all speech conditions have significantly lower cerebellar activation than both the pre-therapy and immediate post-therapy measurements.

Although it may seem like higher activation of the cerebellum after therapy is incongruous with the theory from Craig-McQuaide et al. (2014), I maintain the argument in this

thesis that therapy manipulates the level of implicit learning processes during speech. Particularly, the cerebellum may be active around the intervention period because it is involved in more calculations of implicitly generated corrective speech responses to detected errors. However, once motor systems begin to apply adjustments to speech that have already been learned through error-based implicit learning from this rise in cerebellar activity, the cerebellum is not as crucial to accurate speech production, and activity decreases (for a review, see Johnson et al., 2019). Namely, once corrective speech responses are well-learned, cerebellar activity would be reduced during the speech production, as seen in De Nil et al. (2001) (e.g., Doyon et al., 2003).

The adults who stutter in De Nil et al. (2001) are thought to have had less automatic speech, which leads to increased cerebellar activity during the pre-therapy and immediate post-therapy measurements. During these time points, cerebellar activity indicates that the cerebellum is still applying active, implicitly controlled adaptations to speech because appropriate adjustments needed during speech production are not yet well-learned in people who stutter. Higher cerebellar activations immediately after therapy compared to pre-therapy could also indicate greater learning-related activity due to the therapeutic intervention. This jump in learning-related computation could also lead to less reliance on cerebellar computations a year after the intervention, lowering the activity of the cerebellum. This hypothesis is also worth considering in the context of other results from De Nil et al. (2001), which found that cerebellar activity after therapy was associated with less stuttering-like disfluencies. An increased ability to actively correct speech errors, due to therapy-induced learning processes, could be the mechanism behind this result. Namely, people who stutter were more able to execute corrective responses to reduce disfluencies because of learning processes accomplished due to therapy.

The above argument fits nicely with efference copy theories that predict that people who stutter do not develop internal models of speech the same way as typical speakers, making their speech-motor programs less automatically controlled (e.g., Max et al., 2004). The studies discussed above all underline that stuttering and aspects of persistence versus recovery from stuttering are associated with different sensorimotor control patterns due to variable sensorimotor learning across development. The error-based sensorimotor learning for speech heavily involves the cerebellum (for a discussion, see Rhodes & Bullock, 2002). To date, very few studies have examined how cerebellar structure changes during development in childhood stuttering and, further, in persistent and recovered children who stutter. Because the cerebellum has extensive connections throughout subcortical and cortical pathways that exert influence on motor control, including motor adaptations to auditory feedback perturbations, it is plausible that subtle changes in specific cerebellar lobules that are hubs in these motor pathways have significant implications for developmental stuttering. Additionally, the cerebellum may play a different role in speech motor control over a lifetime of stuttering.

## 1.5 EXAMINING CEREBELLAR MORPHOLOGY WILL PROVIDE INSIGHTS INTO DEVELOPMENTAL CHANGES IN PEOPLE WHO STUTTER

One way to examine cerebellar lobular anatomy is to investigate gray matter volume. Gray matter changes measured via structural MRI scans of the brain have been associated with learning-induced plasticity, indicating that MRI can capture subtle gray matter differences related to short-term learning. Fluctuations in gray matter volume reflect structural changes that parallel learning across various domains, including motor learning (for a review, see Anderson, 2011). Gray matter volume is relevant to how cerebellum-mediated learning may change the functionality of neural systems that support speech in the onset and persistence of stuttering. Therefore, studying gray matter volume in children who stutter may help us better understand how changes in the cerebellum are associated with learning processes that may explain how speech motor control differs at onset in all children who stutter and across development in persistent people who stutter (Cai et al., 2012, 2014; Daliri & Max, 2018; Loucks et al., 2012; Sares et al., 2018).

While some studies have shown that gray matter volume changes in critical areas of the cerebellum in both persistent and recovered children who stutter, methods of exploring the cerebellum and its lobules have advanced significantly (e.g., Chang et al., 2008). Gray matter changes can be objectively assessed using voxel-based morphometry (VBM), which measures regional gray and white matter volume across the whole brain (Ashburner & Friston, 2000; Good et al., 2001). Voxel-based morphometry is also unique in that it is a method that uses algorithms to standardize each subject's brain to a template, which can then be analyzed using atlases to define and extract measures in regions of interest during analyses. Newer cerebellar normalization techniques using VBM, such as the spatially unbiased atlas template of the

cerebellum and brainstem (SUIT), provide a superior method that allows researchers to parcellate the cerebellum more accurately and effectively (Diedrichsen et al., 2011; Diedrichsen, 2006). SUIT is a method of accurately defining the small, tightly folded lobules of the cerebellum efficiently. Studies of children who stutter have not used these newer, more advanced methods to examine cerebellar anatomy. A detailed parcellation and analysis of the cerebellum's lobules will help provide a better description of the processes that may be affected during childhood stuttering. Furthermore, examining how cerebellar areas develop differently over time in persistent and recovered children who stutter could help the field better understand how neural regions that support efference copies may influence persistence versus recovery.

## 1.6 PURPOSE OF THIS DISSERTATION

The primary aim of this dissertation is to conduct a careful investigation of cerebellar morphology associated with stuttering neurophysiology. A secondary aim is to examine how altered morphology in specific cerebellar regions are associated with age in recovered versus persistent children who stutter. Many previous theories and empirical studies involving speech learning and adaptation in stuttering have implicated atypical usage of internal model/efference copy for speech production, which is mediated by the cerebellum. Additionally, MRI studies have consistently connected change in cerebellar function and anatomy to stuttering, as well to stuttering therapy. However, perturbation studies such as Kim et al. (2002) and Daliri et al. (2017) further highlight the need to understand how cerebellar morphology differs in children who stutter. Because of the open question of how aspects of sensorimotor learning may be associated with stuttering onset and persistence, a detailed investigation of cerebellar morphology using advanced methods allowing more reliable measurement of the different cerebellar lobules in young children who stutter is timely. This investigation expects to contribute to a better understanding of neural patterns linked to stuttering onset and persistence.

# 2.0 LITERATURE REVIEW

## 2.1 NEURAL PATHWAYS THAT WORK WITH THE CEREBELLUM TO SUPPORT SPEECH MOTOR CONTROL

### 2.1.1 Speech motor control concepts and the DIVA model

To discuss the cerebellum in the context of speech motor control, this dissertation will use the Directions Into Velocities of Articulators (DIVA) model (Tourville & Guenther, 2011) as a theoretical framework. The DIVA model is an influential speech motor control theory supported by numerous empirical and neurocomputational studies (Golfinopoulos et al., 2010; Guenther et al., 1998; Guenther, 1995; Guenther et al., 2006; Nieto-Castanon et al., 2005; Terband et al., 2014). Most relevant to the cerebellum, the DIVA model has two central systems, feedforward and feedback control, which are both supported by the cerebellum (Figure 5). For relevant terms in the discussion below, please see Table 1.

Table 1: Definition of major speech motor control terms and corresponding neural substrates that form networks which support aspects of the DIVA model linked to each process

| Term | Definition | Neural substrates |
|---|---|---|
| **Internal Model** | Learned representation of associations between motor commands and sensory outcomes. Can refer to forward and inverse models. | Those included in both the forward and inverse models |
| **Forward Model** | Transform motor commands into sensory goals. | Left ventral premotor cortex; Pons; Cerebellar lobule VI; Cerebellar lobule VII*; Medial geniculate nucleus of the thalamus; Ventral posterior medial nucleus of the thalamus; Posterior auditory cortex; Ventral somatosensory cortex |
| **Inverse Model** | Given the sensory consequences of a motor command, maps these sensations into commands that will cause a desired motor outcome. | Right ventral premotor cortex; Pons; Cerebellar lobule VIII*; Ventral lateral thalamus |
| **Efference Copy** | Copies of internal model signals, either forward or inverse models, are used to refine and update motor commands. | Cerebellar lobule VI; Cerebellar lobule VII*; Cerebellar Lobule VII*; Pons; Ventral lateral thalamus; Ventral posterior medial nucleus of the thalamus; Medial geniculate nucleus of the thalamus |

Table Caption: Cerebellar areas marked with * are hypothesized areas based on the discussion below.

2.1.2 The feedforward control system

The DIVA model's feedforward control system uses internal models that plan future movements needed to execute speech. Internal models are learned relationships between the sensory outcomes of speech and articulatory motor commands. Efference copies use internal model “copies” and update them based on the system's current state to further refine predictions that help plan movements. Predictions from internal models and efference copies in the feedforward control system revolve around predicting the body's resulting state after the action's

execution. Internal models are learned throughout development as well. In the feedforward control system, the cerebellum likely impacts two significant aspects of speech motor control: the articulation circuit/ the learning of internal models and the initiation circuit.

The articulation circuit is heavily involved in learning internal models and sending information from the speech sound map (posited to be in the IFG/ventral premotor area) to the ventral motor cortex for articulation. The articulation circuit starts at the speech sound map and sends direct and indirect signals to the articulation map in the ventral motor cortex. A cortico-cerebellar loop forms an indirect pathway from the speech sound map to the articulation map. In this loop, information from internal model predictions from the ventral premotor cortex, called an efference copy, first enters the pons in the brainstem and then travels to the cerebellum and is funneled through the ventral lateral thalamus, which sends information back to the ventral motor cortex.

The articulation circuit within the DIVA model is unique because it is the only area of the DIVA model that names a specific cerebellar lobule in its cortico-cerebellar loop, e.g., lobule VI. Lobule VI is activated during the production of unique sequences of syllables as opposed to repetitive sequences (Bohland & Guenther, 2006). Ataxic dysarthria is also associated with damage to areas of the cerebellum around lobule VI and results in inconsistent errors in articulation during speech (e.g., Ackermann et al., 1992). Lobule VI was confirmed as an area in the DIVA model using neural model simulations necessary for feedforward control and motor learning (Guenther et al., 2006). These studies suggest that lobule VI is involved in coordinating speech movements and would support the fine-tuning of articulatory control needed in the articulation circuit.

The articulation circuit's cortico-cerebellar loop is a gateway that children who do not stutter what kind of information eventually reaches the motor cortex. This system is very much involved with determining if the current context is appropriate for the intended movement (e.g., Rhodes & Bullock, 2002). Using this information, the cerebellum crafts a forward model, or a prediction of the changes in sensory states, as a response to the planned action (Wolpert et al., 1998). Error-based learning in the cerebellum develops forward models.

Figure 2: Cortico-cerebellar loop connectivity

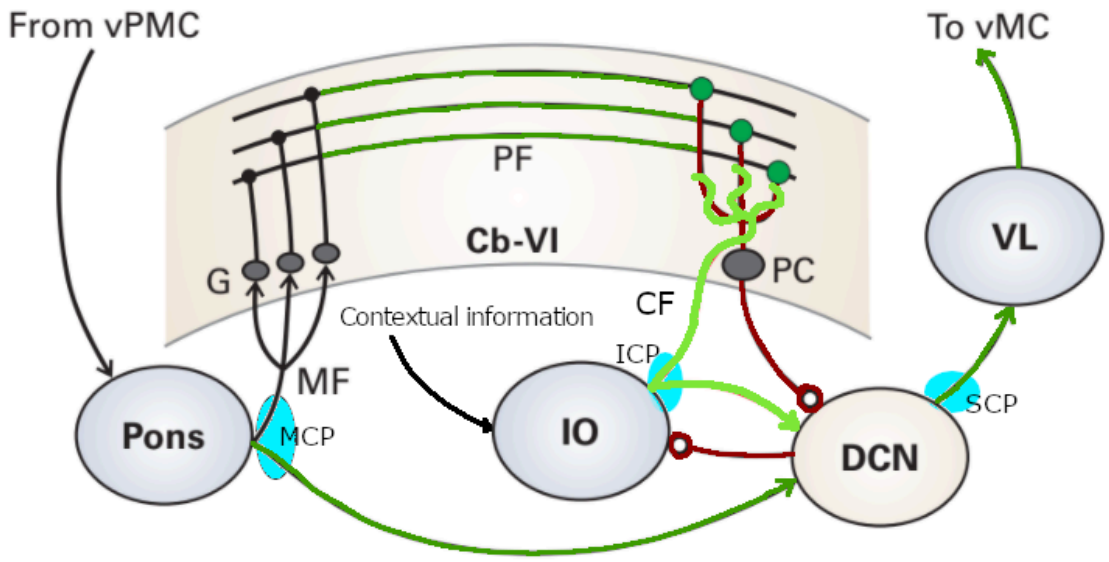


Figure Caption: Figure adapted from Guenther, 2016. Significant inhibitory (red), excitatory (green) connections, and the cerebellar peduncles (blue) were added for clarification in the discussion below. vPMC, ventral premotor cortex; Cb-VI, cerebellar lobule VI; MF, mossy fibers; G, granule cells; PF, parallel fibers; PC, Purkinje cells; CF, climbing fibers; IO, inferior olive; DCN, deep cerebellar nuclei; VL, ventral thalamus; vMC, ventral motor cortex; MCP, middle cerebellar peduncles; ICP, inferior cerebellar peduncles; SCP, superior cerebellar peduncles

Specialized circuits support error-based learning in the cerebellum. First, internal model information, called an efference copy, is sent to the pons from the ventral premotor cortex (For a schematic, see Figure 2; Brodal & Bjaalie, 1992; Miall & Wolpert, 1996). Information entering and leaving the cerebellum passes through one of the three bilateral white matter bundles: the inferior, middle, and superior cerebellar peduncles. As part of this circuit, sensory information enters the cerebellum from the inferior peduncle. The cerebellum receives most of its afferent input from the middle cerebellar peduncle, which receives information about motor commands from the brain's corticospinal and corticobulbar tracts. The Mossy fibers from the pons also enter the cerebellum through the middle cerebellar peduncle. Mossy fibers that arise from these peduncles synapse onto granule cells in the cerebellar cortex and deep cerebellar nuclei. Connectivity with deep cerebellar nuclei is necessary because these are where efferent fibers leave the cerebellum. However, to begin, let us consider the granule cells in the cerebellar cortex.

The axons of the granule cells split in the cerebellar cortex and run along its surface. Axons of the granule cells that travel along the cortical layer of the cerebellum are called parallel fibers. Parallel fibers are finely tuned to fire only during particular contexts, called sparse coding, so that very few granule cells are active at any given time (e.g., Albus, 1971; Rhodes & Bullock, 2002). Sparse coding is one of the features of the cortico-cerebellar loop that make it specialized for learning. Sparse coding has been shown to support learning and memory in many studies (for discussions, see Brunel et al., 2004; Schweighofer et al., 2001).

The specialized firing from the parallel fibers is crucial for correctly activating Purkinje cells that parallel fibers synapse on. Learning in the cerebellum is driven by the connectivity between these two structures through processes described in the Recurrent Slide and Latch Model (Rhodes & Bullock, 2002). Over time, each Purkinje cell becomes sensitive to specific

sensorimotor contexts, helping the cerebellum predict movement consequences. For example, a Purkinje cell with efferents influencing voicing would only be sensitive to voicing in sensorimotor contexts (e.g., Guenther, 2016, p. 212). Purkinje cells inhibit deep cerebellar nuclei that send efferents through the ventral thalamus and on to the ventral motor cortex, so they need to activate during sensorimotor contexts appropriate for the motor command currently being executed. Inhibition of Purkinje cells results in disinhibition of deep cerebellar nuclei, so controlling when and why these cells fire is crucial to cortico-cerebellar loop functioning.

If a Purkinje cell were to fire outside of the sensory context it is sensitive to, it becomes "punished" through error-based learning. Error-based learning is mediated through long-term depression between the Purkinje cells and parallel fibers by afferents from the inferior olive in the brainstem (Figure 3; Rhodes & Bullock, 2002). Long-term depression weakens the connectivity between the Purkinje cells' dendrites and the parallel fiber that caused it to fire in the wrong context, making it less likely for a Purkinje cell to fire during the wrong context again.

Figure 3: Demonstration of the Recurrent Slide and Latch Model

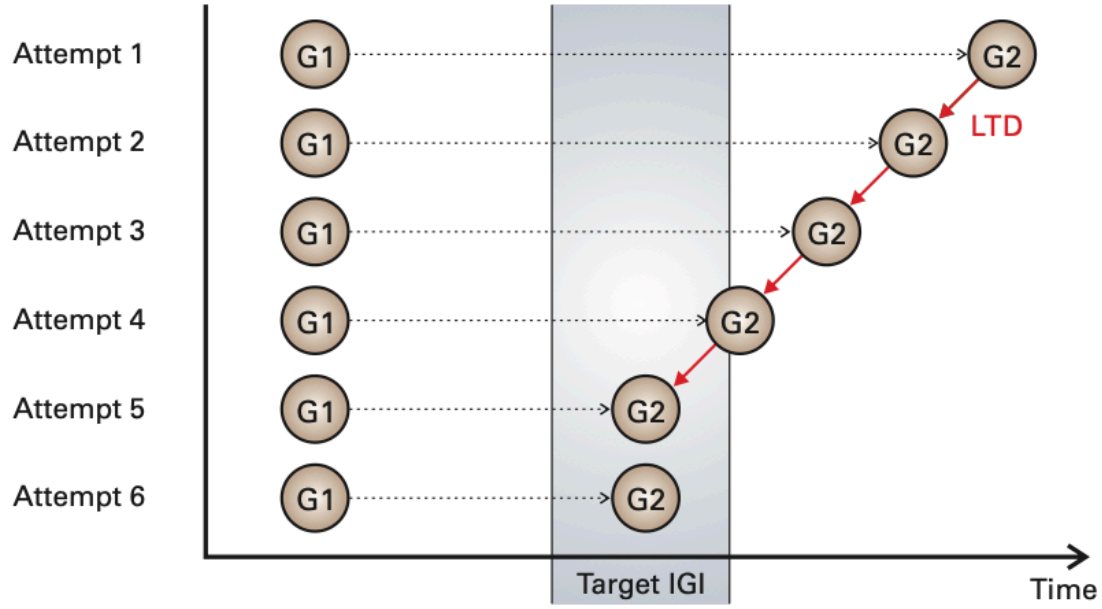


Figure Caption: Slide and Latch Model from Rhodes & Bullock (2002). Figure reprinted from Guenther (2006). Two speech gestures, G1 and G2, are locked into a target intergestural interval (IGI) through long term depression (LTD) which is mediated by Purkinje cells in the cerebellum. Error signals from G2 firing outside of the IGI cause LTD. This causes G2 to slide closer and closer to the target IGI with each attempt. Once it achieves the correct target IGI, G2 latches onto this proper IGI range for following attempts.

According to the Recurrent Slide and Latch Model, this "slides" the firing of a "punished" Purkinje cell closer to an acceptable interstimulus interval for a given sequenced movement until it "latches" onto an interstimulus range that does not result in long-term depression between it and afferent parallel fibers (Rhodes & Bullock, 2002).

The efferents from the inferior olive that mediate error-based learning in the cerebellum are climbing fibers (De Zeeuw et al., 1998; Rhodes & Bullock, 2002). Climbing fibers from the inferior olive are excitatory and cause complex spikes in the Purkinje cell consisting of many action potentials when activated. Complex spikes cause long-term depression in synapses between Purkinje and parallel fibers (e.g., De Zeeuw et al., 1998).

Climbing fibers also excite the deep cerebellar nuclei, where cells exit the cerebellum. Deep cerebellar nuclei receive afferents from a few sources, the excitatory climbing fibers from the inferior olive, excitatory mossy fibers that project from the pons, and inhibitory afferents from Purkinje cells. During long-term depression, the inferior olive's climbing fibers excite deep cerebellar nuclei to overcome the inhibition of Purkinje cells. In return, the nuclei send feedback to the inferior olive to stop this signal. Reciprocal inputs from the deep cerebellar nuclei help the error signal from the inferior olive to operate in a burst and terminate promptly to enhance learning.

Error signals from the inferior olive to the deep cerebellar nuclei are intense and increase output from the cortico-cerebellar loop to the ventral thalamus and motor cortex via efferent signals that leave the cerebellum at the level of the superior cerebellar peduncle. Over time, these strong signals degrade, likely due to further modulation from feedback into the inferior olive from the deep cerebellar nuclei (Rhodes & Bullock, 2002). This signal degradation may be because, at first, the strong output from the deep cerebellar nuclei, as a result of error detection from the inferior olive, increases the force of the resultant movements (e.g., Guenther, 2016). This explanation is in

line with other research that suggests that at the beginning of learning motor movements, cerebellar activity and the force of movements are greater but wane as the movements become well-learned (Doyon et al., 2002, 2003; e.g., Guenther, 2016).

These studies demonstrate that through the cellular structures in cortico-cerebellar loops, we learn forward models for movement. However, the cerebellum has ample connections and participates in closed loops with cerebral and subcortical areas. Closed loops likely allow the cerebellum and cerebrum to reciprocally influence the behavior of the other (Figure 4; for a discussion, see Bostan et al., 2013; Bostan et al., 2010; Bostan & Strick, 2010). Many regions likely influence the activity between structures in this loop, altering its ability to learn internal models and activate other cortical areas, such as the ventral motor area, essential for speech motor control.

Figure 4: Demonstration of closed loop pathways between the cerebellum and cerebrum

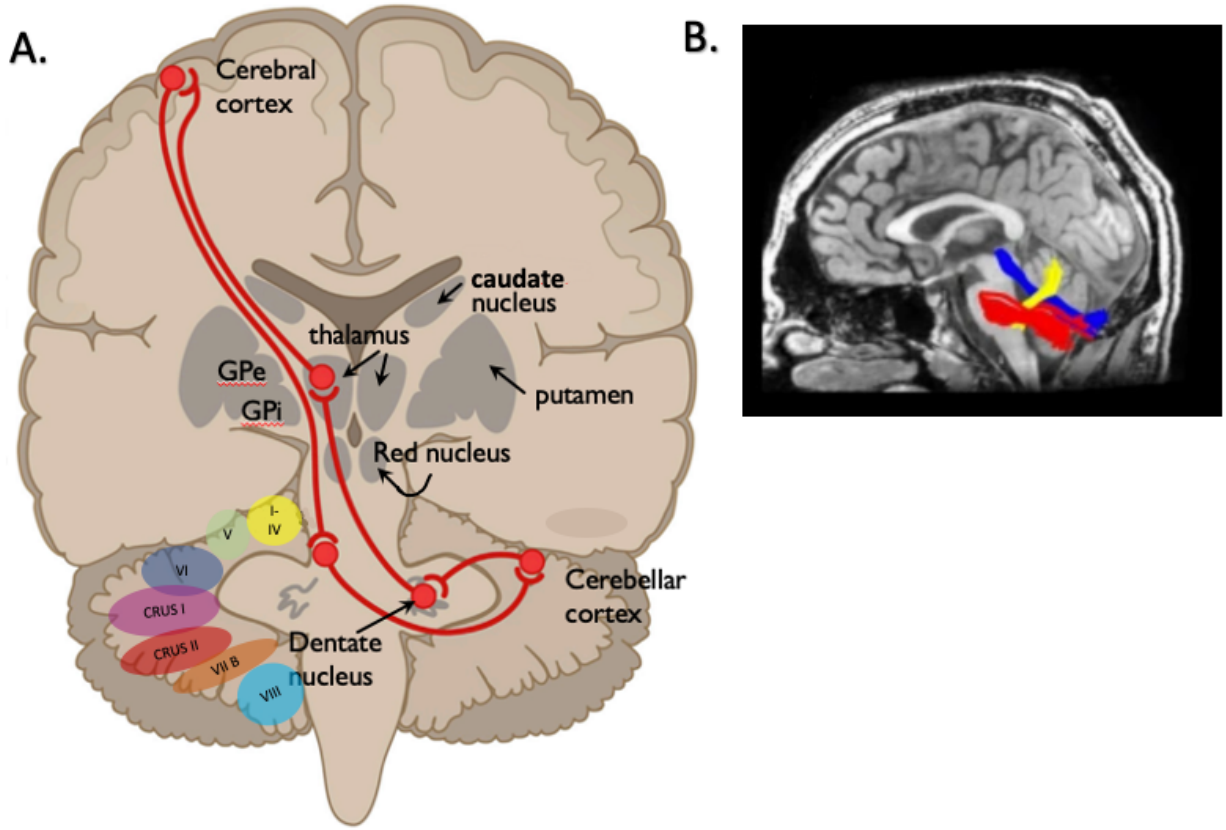


Figure Caption: A. Cerebellar lobules overlaid on the original figure. Reprinted from Buckner et al., (2013). B. Cerebellar peduncles reprinted from Johnson et al., (2022). Superior cerebellar peduncle, blue; Middle cerebellar peduncle, red; Inferior cerebellar peduncle, yellow.

Some of these areas may also lie in the initiation circuit of the feedforward control system (Figure 5). The initiation circuit involves the speech sound map in the ventral premotor cortex, the initiation map in the supplementary motor area, putamen, globus pallidus, and substantia nigra pars reticulata of the basal ganglia (Tourville & Guenther, 2011). This pathway is essential for selecting and initiating motor programs for speech. According to Mink (1996), the supplementary motor area, ventral premotor cortex, and the motor cortex support action initiation. Through connections with the subthalamic nucleus in the basal ganglia via the hyperdirect pathway, these cortical areas give the basal ganglia crucial contextual information to quickly inhibit cortical activation for movements that are not relevant to the planned sequence (Nambu et al., 2002).

While the cerebellum is not part of the initiation circuit of the DIVA model, malfunctioning of cortico-cerebellar loops is associated with motor control disorders involving the basal ganglia, such as Parkinson's disease. However, the differences in this system in Parkinson's appear to be secondary to basal ganglia disfunction as disordered cerebellar function worsens as the disease progresses (e.g., O'Callaghan et al., 2016). Although the reason for poor cerebellar functioning over time in disorders such as Parkinson's is unknown, this may be due to the cerebellum's closed-loop connections with other cortical areas (Figure 4).

The cerebellum is influenced by the subthalamic nucleus in the basal ganglia and contributes to movement pathologies in disorders associated with the basal ganglia, such as tremor in Parkinson's patients (for a discussion, see Bostan & Strick, 2010; e.g., O'Callaghan et al., 2016). Studies that track the transport of virus particles in non-human primates have reported connectivity between the subthalamic nucleus's cognitive and motor areas and the cerebellar cortex (Bostan et al., 2010; Bostan & Strick, 2010). Some have suggested that tremor in Parkinson's patients could be due to atypical functioning between the inferior olive and cerebellar structures, such as the

dentate nucleus (for a discussion, see Deuschl et al., 2000). Although the literature is still unclear about how the subthalamic nuclei interact with the cerebellum, modulated activity in cortical areas that receive projections from the subthalamic nuclei could influence closed loops associated with the cerebellum.

While the indirect pathway inhibits motor activity, the direct pathway of the basal ganglia activates to promote the initiation of movements consistent with the current motor plan (for a discussion, see Guenther, 2016). The striatum is the first stop on the direct pathway and receives afferents from the cortex. Interestingly, the striatum also receives input from both motor and cognitive efferent pathways originating from the cerebellum's dentate nucleus (Hoshi et al., 2005). This evidence suggests that the cerebellum's motor and nonmotor related input could interface with cortical afferents in the striatum.

Although it is still unclear how these connections influence behaviors, the striatum and the cerebellum are associated with different learning systems. This evidence may give us some clues as to how the cerebellum and basal ganglia interact. For example, the basal ganglia participate in both motor and nonmotor learning, particularly reward learning (e.g., Doya, 2000). While the error-based learning controlled by the cerebellum and the basal ganglia's reward-based learning may be largely separate, connectivity studies such as Hoshi et al. (2005) and Bostan & Strick (2010) suggest that these areas potentially communicate with each other for motor and nonmotor tasks. Unfortunately, the role of reward learning in speech motor control is debated and not well understood, so hypotheses about how it could interact with error-based learning are also not known.

Alm (2004) has suggested that there may be a relationship between reward learning and acquiring motor programs in developmental stuttering. He argued that stuttering, or even the

prediction of future stuttering, could be an adverse experience, causing less dopamine release in reward systems that could support the learning of speech motor commands (Alm, 2004; e.g., Schultz, 1998). However, while some studies have found that people who stutter have low dopamine metabolism in areas associated with reward (Wu et al., 1995), this theory appears to be largely unsupported by any current evidence related to stuttering and speech motor control. More research is needed to connect reward-based learning to the neurostructural bases of stuttering to better understand how reward-based learning may be involved with stuttering. Interestingly, the idea that reward and error-based learning interact is somewhat accepted (Bostan et al., 2013; Doyon et al., 2003). The connections between these two systems make the argument from Alm (2004) very compelling considering the number of studies that have connected the basal ganglia and cerebellum to developmental stuttering. More research is needed to understand how the cerebellum and basal ganglia mediate the interaction between these learning systems to support speech motor control.

### 2.1.3 The feedback control system

The DIVA model's feedback control system supports the integration of auditory and somatosensory feedback that results from produced speech into predictive motor commands from the feedforward system. Two different subsystems comprise the feedback control system, one which uses auditory feedback involving the posterior auditory cortex and another which uses somatosensory information via the ventral somatosensory cortex. Both subsystems include cortico-cerebellar loops. Additionally, the auditory and somatosensory information from the subsystems converge on the feedback control map in the right ventral premotor cortex that sends

direct and indirect efferents to the ventral motor cortex via another cortico-cerebellar loop (Tourville & Guenther, 2011).

The feedback control system corrects any detected errors from the speech stream through sensory-motor integration. However, there is a lag between speech production and when sensory information from speech becomes available. Because of this problem, projections from the feedforward control system, which include two cortico-cerebellar loops, are essential. This pathway provides the feedback control system with forward models that can cancel out sensory feedback if they fall within an accepted range of predicted sensory feedback as a result of the movements. The suppression of one's sensory information from movements is why, for example, one cannot tickle oneself (Blakemore et al., 2001; Blakemore et al., 2000). If efferent copy information is consistent with the current sensory context, the next movement's predictions take precedence over feedback from completed actions. Because of the delay in sensory feedback, feedforward control is the most efficient form of speech motor control, if the predicted and actual sensory feedback fall within an accepted range of agreement/matching.

The cortico-cerebellar loop leading from the feedback control map in the right ventral premotor area to the motor cortex uses inverse models to correct the speech movement (Tourville & Guenther, 2011). Given the sensory information from the feedback control system, the cerebellum uses the efference copy to refine motor commands that will produce the desired correction. Several studies have connected cerebellar lobule VIII with auditory and somatosensory perturbations during speech (Golfinopoulos et al., 2011; Tourville et al., 2008). Lobule VIII of the cerebellum is involved with integrating sensory consequences from the feedback control system and the new motor plans from the feedback control map.

Inverse models support learning, especially early in development. During the babbling phase of speech acquisition, babbling produces sensory feedback that slowly becomes associated with the motor commands used. This association between motor output and sensory information is a form of learning what ideal sensory outcomes should be for motor commands so that sensory outcomes map onto appropriate movements through inverse modeling (Tourville & Guenther, 2011). Each speech production further refines predictions to produce a feedforward control system, which includes target maps for auditory and somatosensory output from speech during the imitation period of speech development (for a discussion, see Guenther, 2016). The cerebellum uses inverse modeling to correct speech errors during the babbling phase and refines the target regions in the auditory and somatosensory target maps in the imitation phase. Thus, the cerebellum is an important region that mediates error-based learning during many stages of development. Although it is not well-understood how specific areas of the cerebellum are involved in inverse modeling, emerging evidence suggests that cerebellar lobules in posterior regions of the cerebellum, such as VII and VIII, are involved (for a discussion, see Guenther, 2016, p. 214).

## 2.2 FUNCTIONS OF DISTINCT CEREBELLAR LOBULES AND THEIR RELATION SPEECH MOTOR CONTROL

### 2.2.1 Introduction

As stated previously, there is currently only one lobule of the cerebellum mentioned explicitly in the DIVA model, lobule VI (Tourville & Guenther, 2011). However, many lobules of the cerebellum could play a role in different aspects of speech motor control. Although more research is still needed to bridge the gaps in the DIVA model regarding the cerebellum, the DIVA model does suggest that the unnamed areas of the cerebellum in their model are likely in the posterior lobe, also referred to as the cognitive cerebellum. Notably, the posterior lobe of the cerebellum has gained some interest in its functions related to several cognitive tasks (for a discussion, see Stoodley, 2012). Other studies have suggested that lobules I-V, VI, and VIII have many connections with cortical areas that support sensorimotor tasks. In contrast, lobules VI, VII, and IX are involved with cortical areas that support limbic and association functions that modulate both cognition and emotion (e.g., Hoover & Strick; for a discussion, see Stoodley & Schmahmann, 2010). While lobule VI is currently the only lobule officially included in the DIVA model, speech is arguably the most intricate and complex motor action humans complete. Several cognitive processes, including working memory, language, and basic attentional systems, likely contribute uniquely to speech motor control. Therefore, it is worth discussing how cognitive functions, especially those supported by the posterior lobe of the cerebellum, contribute to speech motor control.

### 2.2.2 The anterior lobe and speech motor control

Although this dissertation focuses mainly on the role of the posterior lobe of the cerebellum in stuttering neurophysiology, the anterior lobe should also be discussed in the context of developmental stuttering. The anterior lobe, also called the spinocerebellum, includes lobules I-V. This area is well known for its somatotopic representation of the body (Bushara et al., 2001; Grodd et al., 2001; Nitschke et al., 1996). Many of the anterior lobe's somatotopic areas also participate in closed loops with the primary motor area, M1 (Kelly & Strick, 2003). Anterior lobe areas have also been shown to strongly correspond with lobule VI and premotor and motor cortical regions (Palesi et al., 2015). Premotor and motor cortical areas have been connected to neurophysiology associated with stuttering (for a discussion, see Chang et al., 2019), as well as lobule VI, which is also the only area of the cerebellum officially included in the DIVA model (for a review, see Brown et al., 2005; Tourville & Guenther, 2011). Importantly, anterior paravermal regions of the cerebellum have also been connected to feedforward pathways in the DIVA model (Tourville & Guenther, 2011). This evidence suggests that anterior lobe regions of the cerebellum may work in tangent with posterior lobe areas, such as lobule VI, to support efference copy mechanisms that predict the sensory and articulatory responses needed for a planned speech movement.

### 2.2.3 Lobules VI, VII, VIII in the context of the DIVA model

The efference copy is a duplicate signal of feedforward commands in the DIVA model. Using this information, the cerebellum updates and refines predictions from the ventral premotor area (Brodal & Bjaalie, 1992; Miall & Wolpert, 1996). As discussed, the cerebellum also uses efference copy information to learn important speech motor control gestures and their sensory consequences using error-based learning.

Figure 5: The Directions into Velocities of Articulators Model

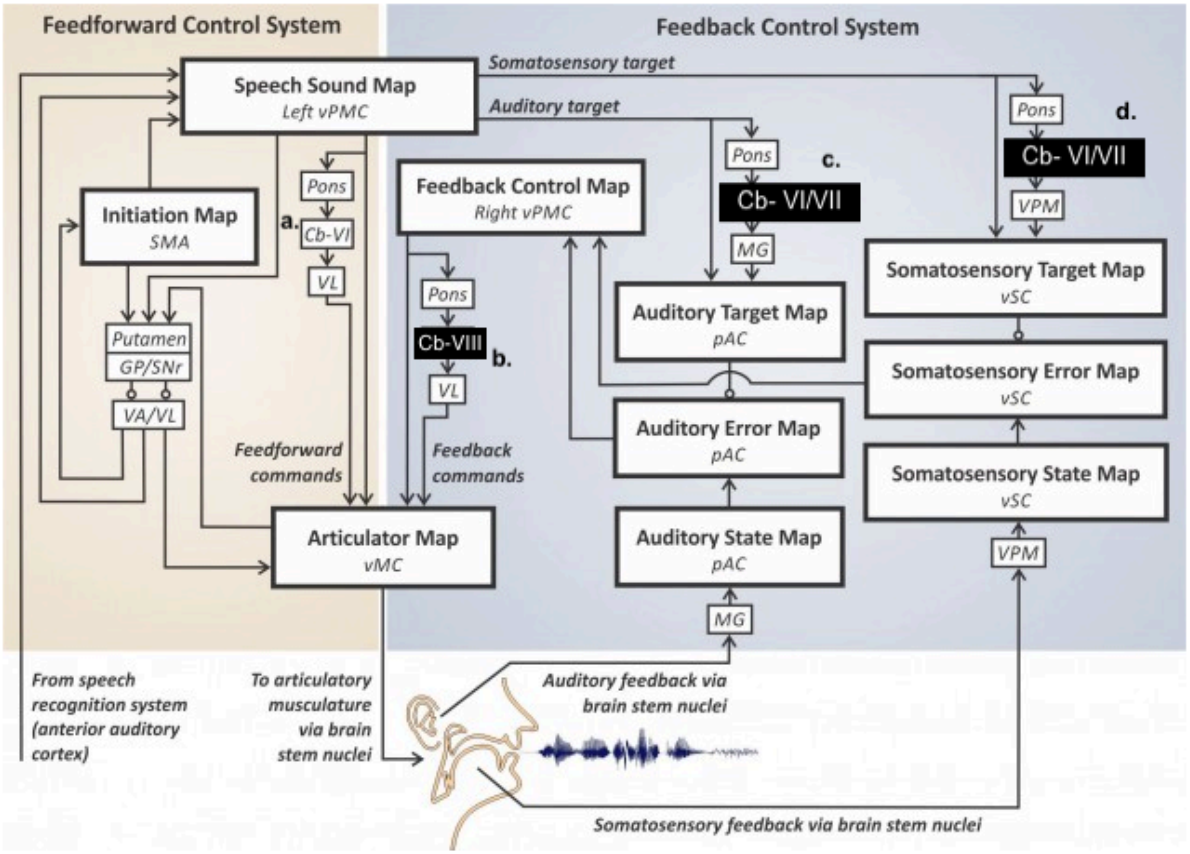


Figure Caption: The Directions into Velocities of Articulators Model (DIVA; adapted from Guenther, 2016) and predictions of cerebellar areas involved. Black boxes indicate lobules of the cerebellum that the author predicts may be part of that pathway (explanation of these hypotheses in the main text). Cb-VI, cerebellar lobule VI; Cb-VI/VII, cerebellar lobules VI and VII; Cb-VIII, cerebellar lobule VIII; GP, globus pallidus of the basal ganglia; MG, medial geniculate nucleus of the thalamus; pAC, posterior auditory cortex including the planum temporale, posterior superior temporal gyrus, and sulcus; SMA, supplementary motor area; SNr, substantia nigra pars reticular of the basal ganglia; VA, ventral anterior nucleus of the thalamus; VL, ventral lateral nucleus of the thalamus; vMC, ventral motor cortex; VPM, ventral posterior medial nucleus of the thalamus; vPMC, ventral premotor cortex which includes the rostral precentral gyrus, posterior inferior frontal gyrus, and anterior portions of the insula; vSC, ventral somatosensory cortex.

As discussed, only one area of the cerebellum, lobule VI (Figure 5a), has been officially attributed to one of the four cortico-cerebellar loops of the DIVA model. However, ample evidence for lobule VIII's inclusion between the right premotor cortex and the ventral motor cortex is emerging from empirical studies (Figure 5b; Golfinopoulos et al., 2011; Tourville et al., 2008; Tourville & Guenther, 2011). For example, lobule VIII is more active during perturbed speech feedback, which suggests that it processes corrective efference copy information (Golfinopoulos et al., 2011; Guenther, 2016; Tourville et al., 2008). DIVA neural modeling studies also suggest that Lobule VIII is most associated with correcting speech errors, not auditory-motor integration (Golfinopoulos et al., 2011; Tourville et al., 2008). Therefore, using inverse modeling, lobule VIII refines and updates new motor plans from the right ventral premotor cortex's efference copy. As previously discussed, lobule VIII likely uses inverse models to support learning early in development during the babbling phase (Tourville & Guenther, 2011).

However, lobule VIII consists of two subsections, lobules VIIIa and VIIIb. Whether cerebellar lobules VIIIa or VIIIb are most important for inverse modeling is not well understood. Generally, while lobule VIII is associated with motor control in studies, VIIIb is more often associated with sensorimotor tasks than VIIIa. For example, while both VIIIa and VIIIb activated during a motor task, somatosensory functions were observed in VIIIb (Stoodley & Schmahmann, 2009). VIIIb has also been connected to somatosensory intrinsic connectivity networks, suggesting that this area may participate in larger neural systems that support sensorimotor functions (Buckner et al., 2011). Cognitive aspects of tasks are often associated with activity in VIIIa, such as verb generation tasks (Stoodley, 2012; Stoodley et al., 2012). However, the separate function of VIIIa and VIIIb are still largely debated (for a discussion, see Stoodley & Schmahmann, 2009), primarily because they may function together to support many different functions such as verbal working

memory or certain attention networks of the brain (e.g., Brissenden & Somers, 2019; Chen & Desmond, 2005).

Interestingly, VIIIa is often associated with cerebellar lobule VIIb while supporting cognitive-linguistic aspects of tasks as well as a large range of cognitive processes. For example, activation of both VIIb and VIIIa was greater during semantic fluency and verb activation tasks (Nagels et al., 2012; Stoodley, 2012). The morphology of these areas is also important for language development. Gray matter volume of right VIIb and VIIIa in infants was later associated with receptive language skills at 12 months (Can et al., 2013). These studies give weight to the idea that these two lobules work together to support performance on certain linguistic tasks and even promote the development of some linguistic skills, which sets VIIIa apart from its more somatosensory-driven counterpart, VIIIb.

Other studies have suggested that VIIb and VIIIa form a network that contributes to the dorsal attention network and have noted that the activity of these cerebellar areas supports sustained attention and working memory and fluctuates based on the load of the task like other cortical nodes of this network (for a discussion, see Brissenden & Somers, 2019). While the role of attention in the DIVA model is not well understood, executive functioning processes are connected to speech planning. Specifically, the Gradient Order DIVA (GODIVA) model suggests that executive functioning processes such as verbal working memory underlie the feedforward processes in the DIVA model (Bohland et al., 2010). The dorsal attention network is consistently associated with working memory tasks, including verbal working memory (for a discussion, see Majerus et al., 2018). Because lobules VIIb and VIIIa are connected to dorsal attention processes and verbal working memory (see discussion below in 2.2.4), they likely support various speech planning aspects of feedforward control.

The definition of the two cortico-cerebellar loops in Figure 5c and Figure 5d are open for the most debate. The two cortico-cerebellar loops arise from the left premotor cortex and end in the feedback control system's sensory target maps. These cortico-cerebellar loops are two of the most crucial because they are involved in learning speech targets and processing the efference copy that suppresses incoming sensory information if speech predictions are within these target regions. This review proposes two primary substrates in the cerebellum for these two loops: lobules VI and VII. This prediction hangs on a few main points. Lobule VI is likely involved in all feedforward projections. Metanalyses of speech production have found that lobule VI is involved in the typical production of speech and coarticulation (Brown et al., 2005; Turkeltaub et al., 2002). Damage to lobule VI results in speech ataxia, which suggests that lobule VI is also involved with the timely production of smooth speech movements (Spencer & Slocomb, 2007; Tourville & Guenther, 2011).

The cortico-cerebellar loops in Figure 5c and Figure 5d project to sensory areas that serve to update the efference copy and perform higher-level cognitive functions. The efference copy in this pathway is subtracted from the sensory consequences of speech to answer the question: are corrective motor commands needed due to perceived mistakes? Tourville & Guenther (2011) state that superior aspects of the lateral cortex of the cerebellum are involved in these loops. The two most superior areas of the lateral cortex of the cerebellum are lobules VI and VII. Because processing efference information, as well as sensory feedback, is accomplished by these loops, this dissertation hypothesizes that lobule VI may also recruit other cerebellar lobules to support these processes, specifically lobule VII. Lobule VII is likely another substrate in this pathway because it has robust connectivity with lobule VI (van Baarsen et al., 2016). Empirical evidence also suggests that both lobules VI and VII activate to suppress sensory feedback. However, the

only available human study currently involves touch, not speech (Kilteni & Ehrsson, 2020). Some more speech-related studies support that these areas often work together during speech motor control processes. Lobules VI and VII work together to support similar verbal working memory aspects, for example (Bohland & Guenther, 2006; Chen & Desmond, 2005a). This working memory function is involved in efficient auditory-motor integration, which these corticocerebellar loops support (Figure 5c-d), also lending support to this theory (Guo et al., 2017).

### 2.2.4 Verbal working memory

The DIVA model requires feedforward commands to produce sequences of syllables. To have these sequences readily available during speech production as predicted in the DIVA model, we need to utilize our verbal working memory. Verbal working memory involves the phonological store, which is limited to a few phonological items held during short periods. With help from the phonological loop's articulatory process, the phonological store updates continuously until the current phonological loop changes again for the following phonological sequence (Baddeley & Hitch, 1994).

Different lobules of the cerebellum are involved in distinct stages of the Baddeley & Hitch (1994) model of verbal working memory. The articulatory process of the phonological loop maps onto cerebellar lobules VII/CRUS I and VI (Bohland & Guenther, 2006; Chen & Desmond, 2005). Phonological storage of verbal working memory involves lobule VIII (Bohland & Guenther, 2006; Chen & Desmond, 2005; Desmond et al., 1997; Marvel & Desmond, 2010). In these studies, areas of the cerebrum are also activated during distinct verbal working memory stages with other cortical regions. The prefrontal cortex supports articulatory control while the inferior parietal lobule guides the phonological store. Desmond et al. (1997) suggest that the cerebellum's role in connectivity

with these areas reflects a comparison of the actual and intended phonological output that updates feedforward models before feeding back into the cortex. These studies suggest that disruptions to posterior lobe lobules of the cerebellum, such as VII/CRUS I and VI, may cause disturbances in one's abilities to update working memory, and more inferior areas of the cerebellum, such as lobule VIII, could then interfere with one's ability to maintain new information in the phonological loop. Overall, interruptions in the verbal working memory system would disrupt one's ability to have speech sequence plans available for speech production.

### 2.2.5 Cognitive neural networks and cerebellar lobules

The cerebellum functions to support many cognitive processes (for a review, see Stoodley & Schmahmann, 2010). Emerging evidence suggests that these functions are associated with the cerebellum's, particularly the posterior cerebellum's (see Figure 1), involvement in several intrinsic functional connectivity networks that support executive functioning. This finding is notable because these same cerebellar areas associated with high cognitive functional connectivity networks also likely support speech motor control processes (see Table 2 for a summary of the areas discussed below).

Table 2: Summary of the discussed posterior cerebellar lobules and relevant cognitive and speech motor control processes

| Lobule | Lobe | Cognitive functions | Speech motor control functions |
|---|---|---|---|
| VI | Posterior | Spatial processing tasks, working memory, executive functioning, and emotional processing (for a discussion, see Stoodley, 2012); orofacial somatotopic representations (Bohland & Guenther, 2006; Grodd et al., 2001; Nitschke et al., 1996); Working memory (Chen & Desmond, 2005); salience detection and memory (Habas et al., 2009) | Feedforward pathway of the DIVA model (Tourville & Guenther, 2011); Activates during the production of syllable sequences (Bohland & Guenther, 2006; Grodd et al., 2001; Nitschke et al., 1996); General production of speech and coarticulation (Brown et al., 2005; Spencer & Slocomb, 2007; Tourville & Guenther, 2011; Turkeltaub et al., 2002); Suppresses sensory feedback in favor of forward models (Kilteni & Ehrsson, 2020) |
| VIIa (CRUS I) | Posterior | Executive functioning, language (Stoodley & Schmahmann, 2009); orofacial somatotopic representations (Bohland & Guenther, 2006; Grodd et al., 2001; Nitschke et al., 1996); verbal working memory (Baddeley & Hitch, 1974; Bohland & Guenther, 2006; Chen & Desmond, 2005); Working memory (Stoodley et al., 2010); Learning sequenced movements (Lehericy et al., 2005); Dorsal attention network: top-down attentional control (Brissenden et al., 2016; Buckner et al., 2011; Corbetta et al., 2008; Sonuga-Barke & Castellanos, 2007; Stephen et al., 2018); Associated with default mode network activity (Buckner et al., 2011); salience detection and memory (Habas et al., 2009) | Activates during the productions of syllable sequences (Bohland & Guenther, 2006; Grodd et al., 2001; Nitschke et al., 1996); Suppresses sensory feedback in favor of forward models (Kilteni & Ehrsson, 2020) |
| VIIa (CRUS II) | Posterior | Language (Stoodley & Schmahmann, 2009); verbal working memory (Baddeley & Hitch, 1974; Bohland & Guenther, 2006; Chen & Desmond, 2005); Associated with default mode network activity (Buckner et al., 2011); salience detection and memory (Habas et al., 2009) | Suppresses sensory feedback in favor of forward models (Kilteni & Ehrsson, 2020) |

Table 2 (cont'd)

| | | | |
|---|---|---|---|
| VIIb | Posterior | Language (Stoodley & Schmahmann, 2009); Verbal working memory (Baddeley & Hitch, 1974; Bohland & Guenther, 2006; Chen & Desmond, 2005); Spatial navigation (Iglói et al., 2015); Associated with Default mode network activity (Buckner et al., 2011); salience detection and memory (Habas et al., 2009) | Suppresses sensory feedback in favor of forward models (Kilteni & Ehrsson, 2020) |
| VIII | Posterior | Dorsal attention network: top-down attentional control (Brissenden et al., 2016); Verbal working memory (Becker et al., 1999; Chen & Desmond, 2005; Ravizza et al., 2004) | Monitoring and adjusting speech or reaching movements after detected errors (Diedrichsen, 2005; Golfinopoulos et al., 2011; Schlerf et al., 2012; Tourville et al., 2008); Timing movements (Habas & Cabanis, 2006) |

Lobule VI, which is officially included in the DIVA model, has been linked to language and spatial processing tasks, working memory, executive functioning, and emotional processing (for a discussion, see Stoodley, 2012). Evidence that demonstrates that lobule VI's connectivity with several functional neural networks that aid cognitive control and its prominent role in learning indicates that lobule VI is a hub supporting various cognitive functions. Lobule VI has robust connectivity with the anterior lobe, making it a bridge between motor tasks and higher-level cognitive processes involving movement, such as learning that supports speech motor control. However, the most substantial connectivity seen with lobule VI and another cerebellar area is with lobule VII (Bernard et al., 2012). Projections to association regions of the cerebrum arise primarily in lobules VI and VII of the cerebellum (Kelly & Strick, 2003; Stoodley & Schmahmann, 2010). Many of these higher-level cognitive areas of the cerebrum are also often associated with VI and VII activity (Krienen & Buckner, 2009; O'Reilly et al., 2010). Right-lateralized areas of lobules VI and VII coactivate to aid language tasks as well (Stoodley & Schmahmann, 2009).

Lobule VII includes a few subdivisions, VIIa, including CRUS I and CRUS II, and VIIb. These divisions were formed based on functional studies and studies showing that the projections to the cerebrum from VII differ between VIIa and VIIb. Whereas more medial pontine nuclei that receive frontal cortex input project to VIIa, lateral pontine nuclei that receive parietal and temporal input communicate with VIIb (e.g., Chen & Desmond, 2005). However, both lobule VIIb and other regions of lobule VII have high resting-state functional connectivity with large portions of the prefrontal cortex, suggesting that lobule VII areas function together for many tasks (for a review, see Stoodley, 2012).

The more superior regions of VII, located in VIIa, have the most functional evidence to support their role in different aspects of cognition. Chen & Desmond (2005) have suggested that this may be due to the relative size of the two lobules because VIIa is larger than VIIb. CRUS I and CRUS II in lobule VIIa are also likely to activate together, which could skew results (Stoodley & Schmahmann, 2010). Additionally, lobules VIIa and VIIb may also be involved with many of the same tasks. For example, each lobule was associated with a working memory task, although each could support different aspects of the task (Chen & Desmond, 2005).

When considering how these areas of the cerebellum are involved with speech and language, it is important to note that any disruption in the superior cerebellar artery that supplies these areas causes ataxic dysarthria (Ackermann et al., 1992). CRUS I is also similar to VI as it tends to be more active during the production of syllable sequences and represents part of the orofacial somatotopic representation of the body (Bohland & Guenther, 2006; Grodd et al., 2001; Nitschke et al., 1996). Significantly, simultaneous activity in both VI and CRUS I has been associated with articulatory control during verbal working memory tasks and both of these areas activate in tangent with frontal regions of the cortex (Chen & Desmond, 2005). These cerebellar

areas may work with frontal cerebral regions during the phonological loop's articulatory process to refresh the phonological store's content (Baddeley & Hitch, 1974; Bohland & Guenther, 2006; Chen & Desmond, 2005). VI and CRUS I are highly involved in updating the limited storage of verbal working memory, discussed in more detail under lobule VIII.

CRUS I may support tasks that utilize cognitive processes outside of verbal working memory. CRUS I has been associated with executive functioning (Stoodley & Schmahmann, 2009), working memory outside of the verbal domain (Stoodley et al., 2010), and the learning of finger movements in sequence (Lehericy et al., 2005). Many of these skills converge in two tasks, spatial navigation using sequential directions or place-based strategies. Different hippocampus areas activate for each approach, either the left hippocampus for the serial sequential direction task or the right hippocampus for spatial representations using the place-based strategy (Igloi et al., 2010). Right CRUS I was associated with higher activation in the left hippocampus and medial prefrontal cortex during sequence-based learning. The left hemisphere of CRUS I was active with the right hippocampus and medial prefrontal cortex during place-based navigation strategies (Iglói et al., 2015). This study supports that at least two distinct nonmotor pathways are associated with CRUS I that likely use the basic executive functioning, working memory, and sequential learning processes related to it in unique ways. Complementary to this idea, CRUS I is also a node in the dorsal attention network, which mediates top-down, goal-driven attention (Buckner et al., 2011; Corbetta et al., 2008; Sonuga-Barke & Castellanos, 2007; Stephen et al., 2018).

The default mode network is also associated with CRUS I, CRUS II, and VIIb (Buckner et al., 2011). The default mode network is active during mind-wandering and supports internally-focused cognition such as autobiographical memory and theory of mind (Andrews-Hanna, 2012; Buckner et al., 2008; Spreng et al., 2008). Interestingly, the default mode network interacts with

attention networks, like the dorsal attention network. Changes in the default mode network during attentionally-demanding tasks negatively affect performance (Bonnelle et al., 2011; Poole et al., 2016; Singh & Fawcett, 2008; Zhang & Li, 2010). However, during this literature review, it was hard to find clear distinctions discussed in any publications regarding functionality between VIIa and VIIb, mainly because results group them. As previously stated, areas of VII may work together during many cognitive functions. CRUS I, CRUS II, and VIIb form an executive control network with lobule VI that participates in salience detection and memory (Habas et al., 2009). Overall, it is hard to predict the many ways lobule VII influences cognition, but, along with VI, it seems to be a hub that communicates with many higher-order areas.

Lobule VIII supports various aspects of speech motor control and executive functioning. Lobule VIII activates in response to unexpected sensory feedback during movement and is associated with movement prediction errors. For example, Golfinopoulos et al. (2011) unexpectedly inflated a balloon apparatus meant to block jaw movement during speech in an fMRI task. From this paradigm, they noted that bilateral activity in lobule VIII significantly increased during perturbation trials compared to trials with unperturbed speech. Because of these findings, Golfinopoulos and colleagues suggest that VIII is responsible for monitoring and adjusting articulatory movements when sensory feedback detects errors during speech production. This study is backed by others, which have also noted increased activity in VIII during reaching errors (Diedrichsen, 2005), prediction errors (Schlerf et al., 2012), as well as during formant frequency perturbations during speech production (Tourville et al., 2008).

Lobule VIII is usually associated with sensorimotor functions but may also participate in higher-order cognitive processes. For example, activation of the dorsal attention network often includes both lobule VIII and VII (Brissenden et al., 2016). Lobule VIII is essential for timing

movements that may also use top-down attention. For example, Habas & Cabanis (2006) examined which areas of the brain were more active during a finger touching task where the left and right-hand movements were either in time or out-of-phase with each other. During the out-of-phase conditions, lobule VIII activated bilaterally. These results suggest that timing circuits that responded to the higher complexity of the timing control needed for the out-of-phase bimanual task are involved with the VIII lobule of the cerebellum.

Another function of lobule VIII is supporting working memory. Lobule VIII activates more during the maintenance phase of verbal working memory tasks with the left inferior parietal lobule, which is associated with phonological memory rehearsal and storage (Becker et al., 1999; Chen & Desmond, 2005; Ravizza et al., 2004). This activation was in contrast to lobules VI and CRUS I and prefrontal areas that activated during the experiment's encoding phase (Chen & Desmond, 2005). Overall, the two systems of the phonological loop involve distinct cerebellar and cortical areas, lobules VI/ CRUS I and the prefrontal cortex, which reflect the articulatory control portion that updates the phonological store, represented by activity in lobules VIII and the inferior parietal lobule (Chen & Desmond, 2005; Desmond et al., 1997; Marvel & Desmond, 2010). Cerebellar activity that corresponds with the verbal working memory systems of the neocortex may represent the comparison between actual and intended phonological output in the cerebellum, allowing for internal models to update before leaving the cerebellum again to feed into corticocerebellar closed loops to correct any errors (for a discussion, see Desmond et al., 1997). Cerebrocerebellar lobules VI, CRUS I, and VIII may update internal models that help coordinate and plan speech.

## 2.3 THE CEREBELLUM IN STUTTERING RESEARCH

### 2.3.1 Stuttering efference copy theories involving the cerebellum

While the cerebellum is an area of the brain that continually appears across stuttering neurophysiology studies, its role in the onset and persistence is not well understood. Stuttering arises from several cognitive processes combining dynamically in individuals who stutter, but atypical speech motor control is often considered the hallmark disruption leading to stuttering (Smith & Weber, 2017). The DIVA model is often used to map out where disruptions in speech motor control may reside in developmental stuttering (Tourville & Guenther, 2011). The cerebellum is one of the major structures within the DIVA model; however, it is unclear if specific parts of the cerebellum are atypical in people who stutter. Additionally, no studies to date have examined whether specific cerebellar lobules area are associated with age differently in populations of people who stutter, such as those who recover and persist into adulthood.

Brown et al. (2005) use a hypothesis that relies upon efference copy mechanisms to interpret their meta-analysis of neuroimaging studies. Their ALE review noted that one of the hallmark findings in stuttering included an under activation of the auditory region and overactivation of motor areas, including cortical areas and the vermal part of cerebellar lobule VI. They argue that stuttering is due to atypical activations of the efference copy signal that projects to sensory feedback control areas. The efference copy is used by error maps in the DIVA model's feedback control system to help predict if sensory information falls outside of the target region (Guenther, 2016; Tourville & Guenther, 2011). If the sensory input from speech falls within the target range, efference information suppresses the signals from sensory feedback, limiting their integration into our speech plans (Blakemore et al., 2001; Blakemore et al., 2000). In support of Brown et al. (2005), many studies of adults and children who stutter have noted atypical auditory suppression during speech tasks (Beal et al., 2010, 2011; Daliri & Max, 2018; Liotti et al., 2010;

Toyomura et al., 2020). Efference copy information may fail to efficiently suppress the incoming sensory feedback from people who stutters' speech. The idea that the efference copy in people who stutter is atypical and may result in inefficient use of sensory feedback control is a common theme across many of these theories. However, the extent to which sensory feedback is used (too much or too little) and how this may result in disfluencies differs between them. For example, Brown et al. (2005) predict that the timing and frequency of the efference copy signal are atypical in people who stutter, resulting in an intensified suppression of auditory areas.

Other mentions of the efference copy concerning stuttering usually suggest too much reliance on feedback control. One such example is Max et al. (2004), although, in their paper, they report two different hypotheses. The first hypothesis suggests that people who stutter have unstable or insufficiently activated internal models (*Unstable Internal Model Hypothesis*), which leads to disfluencies. The second hypothesis is that an overreliance on feedback control is what causes disfluencies (*Overreliance on Feedback Control Hypothesis*).

The *Unstable Internal Model Hypothesis* predicts that people who stutter rely on feedback control because signals from areas that support internal models that give rise to efference copies to sensory regions that support sensory-motor integration are atypical. If the internal models are unstable, the consequences of a movement can't be predicted, and the speech system will detect an error whether or not the movement was generated accurately, leading to activation of feedback control. In this view, speech errors occur due to an inability to predict sensory outcomes with internal models during feedforward control, as well as an inability of the feedback control system to form corrective commands due to poor internal model input. Specifically, unstable internal model information hinders the creation of inverse models due to the feedback system's inability to perform sensory-motor integration processes accurately.

Max et al. (2004) suggest that the *Unstable Internal Model* hypothesis is also supported by studies that indicate that people who stutter have less automatic speech motor control, as evidenced by studies such as De Nil et al. (2001), which shows that the cerebellum is more active in people who stutter. As discussed in this dissertation (see sections 2.1.2 and 2.1.3), the cerebellum supports error-based learning in speech, which is also crucial to the development of internal models. Therefore, early in development, the feedback control system uses sensory information to slowly learn the associations between speech motor commands and their sensory outcomes. If internal models are stable, speech is more automatic and doesn't require careful monitoring of sensory results. Additionally, Kim et al. (2020) have given some support for this theory as they have been the first study to connect poor auditory-motor learning to children and adults who stutter. Increased activity in the cerebellum that supports error-based learning through monitoring of the sensory results of speech may indicate less automatic speech in people who stutter and unstable internal models. De Nil et al. (2001)'s finding that the cerebellum is overactive in people who stutter compared to children who do not stutter has been corroborated across several studies since Max et al. (2004). As summarized in Brown et al. (2005), increased cerebellar activity in people who stutter is a common finding. However, its exact role in developmental stuttering is still contested (for a discussion, see sections 2.3.2 and 2.3.3 below).

The *Overreliance on Feedback Control Hypothesis* from Max et al. (2004) predicts that increased disfluencies in people who stutter are due to an overreliance on feedback control. This hypothesis differs from the first in that the overreliance on feedback control is not secondary to unstable internal models. The overreliance on feedback control is not due to atypical internal model information but an inability of the system to use feedforward pathways to transmit internal model information to articulation maps in the motor cortex. In this hypothesis, the feedback control

system is also directly causing disfluencies due to the nature of the feedback pathway needing to wait for sensory feedback. Speech is a rapid process, so when relying on the slow sensory input in the feedback pathway, this causes sensorimotor errors.

The *Overreliance on Feedback Control Hypothesis* has been supported through various lines of evidence. For example, increased gain of feedback control was connected to disfluency production using neurocomputational modeling within the DIVA model (Civier et al., 2010). Additionally, it is well-known that auditory feedback masking decreases the prevalence of disfluencies of people who stutter. It is hypothesized that auditory-feedback masking also supports this hypothesis. The masking of auditory feedback prevents the feedback system from detecting errors and reduces the prevalence of erroneous corrections that lead to disfluencies (for a discussion, see Bradshaw et al., 2021).

Significantly, all these theories predict that function of the efference copy, supported by cortico-cerebellar loops in the DIVA model, is affected in people who stutter. These theories also indicate that an imbalance between feedback and feedforward control influences stuttering severity in different ways. Cortico-cerebellar loops connect the feedforward and feedback control system. Therefore, all these theories predict that the cerebellum is involved in stuttering neurophysiology and likely stuttering severity. They differ in their prediction of whether reliance on feedback control leads to more disfluencies or is a compensatory strategy that promotes more typical speech fluency. Examining different cerebellar lobules linked specifically to efference copy function could help clarify these questions.

Importantly, theories that rely on efference copy mechanisms currently lack discussions regarding how balances between feedforward and feedback control change over development in people who stutter. The significance of these discussions has recently become apparent due to

several behavioral studies of children and adults who stutter, which alter the online feedback of speech. By changing the online auditory or sensory input from one's speech, researchers can measure changes in compensatory speech patterns to assess differences in different populations' speech motor control (for a discussion, see Kearney & Guenther, 2019). While adults who stutter have altered both the pitch and the timing of their voice differently as compared to adults who do not stutter in many studies, so far, studies of children who stutter have varied in their conclusions (Cai et al., 2012, 2014; Daliri et al., 2017; Daliri & Max, 2018; Kim et al., 2020; Loucks et al., 2012; Sares et al., 2018). However, adults who stutter compensate less to changes in auditory feedback than adult children who do not stutter across these studies.

Daliri et al. (2017) and Kim et al. (2020) are the only studies of auditory perturbation in children who stutter to date. They did not consider whether the children in their sample would persist or recover from stuttering. In Kim et al. (2020), they differentiated their group of children who stutter into two age groups, a 3-6-year-old and a 7-9-year-old group. It is widely known that younger children who stutter have a higher probability of recovery than those over 6 years of age. In their data, as children aged, the compensatory perturbation response decreased. While there is no way to know the composition of the youngest group of children who stutter in Kim et al. (2020), it is within reason to tentatively assume that the older group will continue to stutter into adulthood. Additionally, some evidence from neurophysiological studies in children who stutter supports the idea that processes and structures which support speech motor control change over development in persistent and recovered children who stutter.

Cortical areas associated with recognizing the proper sensorimotor contexts for articulation have comparable morphology in persistent children who stutter close to stuttering onset but develop differently over time (Garnett et al., 2018). For example, cortical thickness growth of the

superior temporal sulcus of persistent children who stutter slowly decreases with time compared to recovered children who stutter and children who do not stutter. This area maps onto the DIVA model in the auditory target and error maps (Figure 1; Tourville & Guenther, 2011). As discussed previously, efference copy information "cancels out" the sensory input in these areas of the DIVA model. The Atypical efference copy signaling, which slowly progresses throughout development in persistent people who stutter because of white matter integrity issues in the cerebellar peduncles, may also influence the results of Daliri et al. (2017). Efference copy signals potentially also explain the dip in speech compensatory behavior in the oldest group of children in Kim et al. (2002). Namely, anomalous auditory-motor integration function may develop over time, especially in persistent people who stutter.

Using the ERP component N100 to measure the amount of auditory suppression of one's speech, adults who stutter suppressed the auditory feedback from their speech to a lesser degree than adult children who do not stutter (Daliri & Max, 2015, 2018). The amount of suppression in adults who stutter was also significantly associated with compensation during a speech perturbation task. Still, in adult children who do not stutter, there was no relationship between these measures (Daliri & Max, 2018). Daliri & Max (2018) suggest that this might be due to auditory modulation playing a more vital role during speech development. Consistent with Max et al. (2004), unstable internal models could influence adults who stutter to use auditory feedback differently than other adults. Delayed auditory feedback (DAF) also increased auditory modulation in adults who stutter but decreased modulation in adults who do not stutter. The amount of auditory modulation in this condition was also positively associated with stuttering severity (Daliri & Max, 2018). These studies further suggest an imbalance between feedback and feedforward control mechanisms in adults who stutter.

From these studies, one can form hypotheses about a few possible mechanisms. The first may involve learning auditory/sensory targets using cortico-cerebellar loops. Atypical development of internal models influences the target region's specificity within the feedback control system (the auditory and somatosensory target maps) (Tourville & Guenther, 2011). Potentially, the target region of people who stutter accepts greater variation than that of people who do not stutter. It takes an extreme change, such as that caused by DAF, or other factors involved with explicit strategies, to finally "trick" the system to be more similar to people who do not stutter. Because speech perturbation studies mean to alter speech motor control implicitly, insufficiently developed target maps in adults who stutter may "miss" these errors across the many studies of this group. This hypothesis may also be generalized to the results from Kim et al. (2020) if their assumptions that their perturbation process was more implicitly driven than Daliri et al. (2017) are correct. Both the atypical target region and the error response from speech feedback that falls outside of speech targets are partially mediated by cortico-cerebellar loops that lead to the target maps in the feedback control system. The efference copy signals from these cortico-cerebellar loops are also involved in the auditory suppression process (Tourville & Guenther, 2011).

However, Daliri et al. (2017) suggest that in light of no significant differences between children who stutter and children who do not stutter in their compensatory responses to auditory perturbations, the lack of response from adults who stutter to feedback perturbations could be a compensatory response. This theory needs to be scrutinized considering the new data from Kim et al. (2020). As predicted by many stuttering studies, atypical learning of internal models that strengthen internal timing predictions may be a core feature of the disorder. Perturbation studies that alter the time of auditory responses instead of changing spectral aspects of the speech signal,

as in Daliri et al. (2017), found more robust differences between adults who do and do not stutter (Cai et al., 2014). Published data regarding how children who stutter might perform on this kind of perturbation task involving auditory timing perturbation isn't available yet. Still, some evidence suggests that the timing of auditory-motor integration modulation responses during speech, not the magnitude of the response, is what differentiates children who do and do not stutter (Beal et al., 2011). Overall, these data may mean that over time, efference copy mechanisms break down further due to atypical feedback and updating of internal model representations in persistent adults who stutter, leading to atypical auditory information usage beyond that related to timing. Further studies are needed to examine how this may change in childhood stuttering to confirm this hypothesis.

It is currently challenging to make any explicit theories about how the cerebellum's function is involved with the onset of stuttering due to the lack of studies of children who stutter close to stuttering onset. Notably, data that describes how the cerebellum may develop differently across childhood close to stuttering onset and into adulthood are needed to understand how cerebellar structures may be involved with developmental stuttering (See Tables 3 and 4 for a summary of current findings). Evidence from speech perturbation studies of children and adults who stutter particularly point to the importance of closing this gap in the literature.

### 2.3.2 How the cerebellum may decrease stuttering in developmental stuttering

While studies of children who stutter are lacking in comparison, many investigations have examined how the cerebellum supports various aspects of speech in adults who stutter. Notably, a significant area of discussion in the field of stuttering is how the cerebellum serves to either thwart typical speech motor control mechanisms that do not lead to stuttering or is used to compensate

for other systems that may be aberrant in people who stutter to decrease stuttering. From this review, cerebellar connectivity with areas outside of speech motor control, involved with high-level cognitive functioning, appears to be negatively associated with stuttering severity. In contrast, anomalous cerebellar connectivity with areas related to speech motor control may lead to more disfluencies. One can infer from this pattern that areas not classically thought to be primary areas of speech motor control could be a compensatory mechanism that does not totally amend atypical connectivity patterns between cortical areas and cerebellar structures.

A pathway that seems to be discussed the most across stuttering publications is between the cerebellum and the orbitofrontal cortex. Less severe stuttering is usually associated with greater connectivity between the left orbitofrontal cortex and the superior cerebellum (Kell et al., 2018; Sitek et al., 2016). The orbitofrontal cortex supports flexible learning based on stimuli-reinforcement, such as role reversals (e.g., Tsuchida et al., 2010). Sitek et al. (2016) have suggested that the orbitofrontal cortex and the superior cerebellum may work together to overcome deficiencies of feedforward systems mediated by the DIVA feedforward control system's initiation circuit. Connectivity between the left cerebellum and the left orbitofrontal cortex was also slightly stronger in adults who stutter than children who do not stutter. This result may suggest that this pattern is compensatory but does not successfully mitigate disfluencies to lead to recovery. For example, other studies have also noted decreased activity in the left orbitofrontal gyrus preceding a block (Sowman et al., 2012). It may be that the superior aspects of the cerebellum, such as the posterior lobe, also associated with higher-level cognitive systems, work to activate higher-order cerebral areas to process cognitive strategies that may decrease disfluencies (for a review of the superior cerebellum and cognition, see Stoodley, 2012). However, a significant limitation of these results is that no specific lobule data is available to understand how the orbitofrontal cortex may

connect to distinct superior cerebellar structures. This added information could help elucidate, for example, if these connections were more associated with the feedforward control system, as Sitek et al. (2016) suggest, or another system in the DIVA model.

Another compensatory relationship between the cerebellum and the cerebrum is between left lobule VI and the lingual gyrus. As connectivity increases between left lobule VI and the left lingual gyrus, stuttering severity decreases (Yang et al., 2016). While the lingual gyrus is involved with visual word recognition (Mechelli et al., 2000), this area may be part of visual imagery processes in general (Bogousslavsky et al., 1987), including motor imagery (Malouin et al., 2003). Typically, this area is not associated with speech motor control, but the lingual gyrus comes up often in stuttering literature (for a review, see Brown et al., 2005). As one may guess from its connection with several visual functions, the lingual gyrus is a hub of the visual intrinsic connectivity network (Yeo et al., 2011). This network has also shown decreased intrinsic and extrinsic connectivity with other executive functioning networks, the default mode, and dorsal attention networks in children who stutter (Chang et al., 2018). While it may be difficult to make any direct connections between how visual processing could influence stuttering, learning speech movements may also utilize visual information with the help of cerebellar areas (Venezia et al., 2016). The lingual gyrus and the cerebellum may facilitate learning speech motor commands. If this hypothesis holds, it would also fit well with efference copy theories of stuttering that predict that some kind of maldevelopment internal models used for efference copies are core to stuttering. Perhaps increased connectivity between the cerebellum and the lingual gyrus supports development that leads to less severe stuttering through more stable internal models (Yang et al., 2016). The connection between executive functioning networks and the visual network in childhood might indicate atypical learning patterns supported by these networks, for example

(Chang et al., 2018). However, the interpretation of intrinsic connectivity results in childhood in the context of adult studies is very tentative at best. Further studies are needed to understand how visual systems may support the development of speech motor control systems in people who stutter.

Greater connectivity between the vermis of lobule III and the left anterior cingulate is associated with lower stuttering severity as well (Yang et al., 2016). Overactivity of the anterior cingulate is another common finding across stuttering literature (for a review, see Brown et al., 2005). Connections between the cerebellum and the anterior cingulate may facilitate the proper ordering of sequences during sensorimotor learning (Ruiz et al., 2017). The cerebellar vermis and anterior cingulate are also associated with an inhibitory control system for error-related responses that develops into adulthood (Rubia et al., 2007). Rubia et al. (2007) suggest that pathways between frontal areas, the cingulate, and the cerebellum form an inhibitory control network, and recruitment of the cerebellum in this network increases with age. It could be that lack of connectivity in this pathway leads to more disfluencies because the cerebellum cannot properly communicate with areas such as the anterior cingulate cortex to inhibit errors during speech sequencing. However, more research is needed to understand the connections between the anterior cingulate and cerebellum, especially since it may change over development. Additionally, while differences in lobule III morphology are associated with childhood and adulthood stuttering (reviewed above), little is known about its exact function in the condition of stuttering. Due to its inclusion of somatotopic representations, one idea could be that lobule III's representations of the body may be disrupted in people who stutter, although lobule III is usually associated with gait and the lower portions of the body (Cavanagh et al., 1997; Grodd et al., 2001; Nolte, 2009; Schoch et al., 2006).

From these studies, higher cognitive areas likely play a role in reducing disfluencies in adults who stutter. However, many open questions remain. Most importantly, many of these cerebral areas are not part of essential systems for speech motor control, so their exact functions are somewhat unknown. Additionally, to the author's knowledge, these patterns have not yet been replicated in children who stutter. Therefore, it may be that some of these connectivity patterns seen in adults who stutter are the result of living with stuttering for a lifetime and not the core etiology of the disorder.

### 2.3.3 Disfluency-supporting features of the cerebellum in developmental stuttering

Heightened connectivity between cerebellar areas and motor regions may support a higher frequency of stuttering. For example, Kell et al. (2018) noted that the uncoupling of activity between the left cerebellum and the speech production network was associated with a reduction in stuttering severity. The uncoupling between the cerebellum and the rest of the motor regions also increased with stuttering therapy. Kell et al. (2018)'s results are complemented by other studies that have also noticed decreases in cerebellar activity or resting-state connectivity after stuttering therapy, especially of left-lateralized lobules VI and VII (De Nil et al., 2003; Kell et al., 2018; Lu et al., 2012). Others associate greater activity in the cerebellum's left hemisphere with higher stuttering severity, especially VI/VII (Fox et al., 2000; Wymbs et al., 2013). However, others have still noted the opposite pattern. For example, right-lateralized cerebellar activity is decreased due to therapy or was associated with fewer disfluencies, although these studies did not provide brain coordinates (De Nil et al., 2001; Sitek et al., 2016).

The studies that provided coordinates show that stuttering severity is linked to increased lobule VI and VII activity in the left cerebellum. In the stuttering field, many studies find atypical

morphology or activity of the right homologues of speech motor control areas (for a review, see Chang et al., 2019). Because the cerebellum communicates with contralateral regions of the cortex, this may indicate that the cerebellum's connection with the right-sided speech motor control areas in adults who stutter leads to increased disfluencies. However, whether the right-lateralized results in adults who stutter are compensatory or serve to promote disfluencies is still highly debated in the stuttering literature. Overall, all these studies indicate that increased cerebellar activity, especially in the left hemisphere, is associated with higher stuttering severity. This observation is supported by meta-analyses that indicate that the cerebellum is hyperactive in people who stutter as compared to children who do not stutter (e.g., Brown et al., 2005; Budde et al., 2014).

Several studies find greater connectivity between the bilateral inferior frontal gyrus and bilateral lobule VI in people who stutter as well (Chang et al., 2011; Yang et al., 2016). Congruent with the above results, greater activity of VI could also indicate miscommunication between areas that support feedforward control, leading to disfluencies. Stuttering severity is also positively associated with connectivity between lobule VI and other cerebellar regions, lobules VIII and CRUS I (Yang et al., 2016). Across all these studies, overactivation of lobule VI is consistently associated with greater stuttering severity. During speech tasks, covert and overt, people who stutter have increased lobule VI activity, regardless of the number of disfluencies during these tasks (De Nil et al., 2003; Lu et al., 2009; Lu et al., 2010). This suggests that lobule VI of the cerebellum is overactive in people who stutter and has increased connectivity with motor areas, especially those related to feedforward control. This overactivity may support an increased frequency of stuttering in people who stutter.

### 2.3.4 Morphological differences associated with childhood stuttering

Structural studies of the cerebellum and its connections with the cerebrum are available in children who stutter. The cerebellum's anterior and portions of the posterior lobe have an upside-down somatotopic representation of the body, such that areas V-VIIa represent orofacial areas (e.g., Grodd et al., 2001). Children who stutter have increased white matter integrity in the left hemisphere (IV/V) and decreased in the right hemisphere (V) (Chang et al., 2015). Persistent children who stutter tended to have higher gray matter volume in lobule III than recovered children (Chang et al., 2008). Although it is difficult to interpret how the anterior lobe is involved with stuttering at the moment, it is worth noting that lobules IV and V participate in closed loops with the primary motor area and could be involved with error signaling during motor errors (Kelly & Strick, 2003; Schlerf et al., 2012). This function could be associated with cortico-cerebellar loops involving lobule VI because lobule VI's activity is strongly correlated with the anterior lobe's (Bernard et al., 2012). Atypical morphology in these areas could indicate disruptive error signals to critical motor areas such as the primary motor cortex.

Consistent with DIVA model predictions of lobule VI being part of the feedforward control cortico-cerebellar loop, this lobule consistently appears as an area associated with childhood stuttering neurophysiology. The cerebellum communicates with contralateral motor cortical areas. Because language areas are left-lateralized in the brain, this would mean that areas of the cerebellum that support language and speech are also largely right-lateralized in the cerebellum (e.g., Scott et al., 2001). Therefore, right lobule VI may be of most interest to speech production. Findings from stuttering literature support this claim. For example, children who stutter have significantly less white matter integrity in the right hemisphere of lobule VI as compared to children who do not stutter (Chang et al., 2015).

Additionally, the activity of the right lobule VI had adverse effects on rhythm discrimination in children who stutter. Higher activation of right lobule VI in children who stutter was associated with lower rhythm discrimination abilities (Chang et al., 2016). These two results could mean that signaling within VI is aberrant in children who stutter due to altered morphology. This pattern may result in atypical processing of efference copy information in the feedforward system resulting in speech errors. A negative relationship seen between fractional anisotropy in the bilateral lobule VI of the cerebellum and stuttering severity supports this theory as well as results that suggest that decreased connectivity exists between the left lobule VI and the left supplementary motor area in children who stutter (Chang et al., 2015; Chang & Zhu, 2013).

Developmental patterns of lobule VI also differ between recovered children who stutter and children who do not stutter. Results suggest that there is lower gray matter volume in the right hemisphere in recovered children who stutter as compared to persistent children who stutter as well as decreased growth rate of white matter integrity in the left lobule VI of recovered children (Chang et al., 2008; Chow & Chang, 2017). These studies also connect lobule VI's morphology to persistence and recovery, particularly changes in the morphology of specific hemispheres of lobule VI. As discussed, this may impact the development of internal models through projections to feedback control areas and the updating of the internal model through efference copy mechanisms in the feedforward system. Perhaps the morphology changes in children who recover from stuttering protect them against progressively divergent feedforward control systems with age, priming them to recover in childhood naturally.

Lobule VII, particularly lobule VIIa, which houses CRUS I and CRUS II, has most frequently been reported across studies of children who stutter. Anomalous connectivity patterns between the left and right posterior superior temporal gyrus and CRUS I and II are associated with

childhood stuttering (Chang & Zhu, 2013). The posterior superior temporal gyrus is essential for processing sensory feedback in the DIVA model (Tourville & Guenther, 2011). Maldeveloped connectivity between VII and the posterior superior temporal gyrus could lead to aberrant auditory-motor integration and reduced feedback control system efficiency.

It is also interesting to think about how VII may result in atypical development in stuttering because lobule VII is involved in many executive functioning processes (e.g., Stoodley, 2012). The left supplementary motor area has increased and decreased connectivity with different VII regions (Chang & Zhu, 2013). Because of the supplementary motor area's role in gating the incoming motor commands from other regions included in the DIVA model, connectivity with VII, which is involved in executive functioning, could alter this area's abilities to accomplish this efficiently. Like lobule VI, the activity of left CRUS I is negatively associated with rhythm discrimination in children who stutter (Chang et al., 2016). Perhaps anomalous connectivity between the left supplementary motor area and VII leads to atypical timing predictions during speech production in children who stutter. Again, more research is needed to confirm these claims. Persistence and recovery from stuttering may also be associated with the morphology of this area (Chang et al., 2008; Chow & Chang, 2017).

Lobule VIII may play a vital role in the feedback control system's pathway from the right premotor cortex to the ventral motor cortex (Golfinopoulos et al., 2011; Tourville et al., 2008; Tourville & Guenther, 2011). The right lobule VIII has greater white matter integrity in kids who stutter as compared to children who do not, but in persistent children who stutter, the white matter integrity growth rate of this area may be less than in recovered children (Chang et al., 2015; Chow & Chang, 2017). These results could involve how feedback control may differ in adults who stutter, as demonstrated by perturbation studies (Cai et al., 2012, 2014; Daliri et al., 2017; Daliri & Max,

2018; Loucks et al., 2012; Sares et al., 2018). In adults who stutter, the white matter integrity of lobule VIII is also lower than that of adults who do not stutter (Lu et al., 2010). VIII activity is associated with error-related responses from motor tasks and the timing of complex movements (Diedrichsen, 2005; Golfinopoulos et al., 2011; Habas & Cabanis, 2006; Schlerf et al., 2012; Tourville et al., 2008). Perhaps lobule VIII is associated with improper updating of efference copy processes during corrective motor responses, controlled by the feedback system, leading to less speech compensation in persistent people who stutter.

Table 3: Summary of current lobular neurophysiological findings of the left and right cerebellum in children who stutter

| Lobule | White Matter Morphology | | Gray Matter Morphology | | Stuttering Severity | |
|---|---|---|---|---|---|---|
| | Left | Right | Left | Right | Left | Right |
| I | | | | | | |
| II | | | | | | |
| III | | | GMV CWS-P<CWS-R(Chang et al., 2008) | | | |
| IV | FA CWS>CWNS (Chang et al., 2015) | | | | | |
| V | FA CWS>CWNS (Chang et al., 2015) | FA CWS<CWNS (Chang et al., 2015) | | | | |
| VI | GR FA CWS-R<CWNS(Chow & Chang, 2017) | FA CWS<CWNS (Chang et al., 2015) | | GMV CWS-P>CWS-R (Chang et al., 2008) | Negative relation with FA (Chang et al., 2015) | Negative relation with FA (Chang et al., 2015) |
| VII | | GR FA CWS-P<CWNS (Chow & Chang, 2017) | | GMV CWS-P> CWS-R(Chang et al., 2008) | | |
| VIII | | GR FA CWS-P<CWS-R (Chow & Chang, 2017) | | | | |
| IX | | | | | | |
| X | | | | | | |

*Note*. FA= fractional anisotropy; CWS= children who stutter; CWNS= children who do not stutter; CWS-P= persistent children who stutter; CWS-R= recovered children who stutter; GMV= gray matter volume; WMV= white matter volume; GR= growth rate.

Table 4: Summary of current lobular neurophysiological findings of the left and right cerebellum in adults who stutter

| Lobule | White Matter Morphology | | Gray Matter Morphology | | Stuttering Severity | |
|---|---|---|---|---|---|---|
| | Left | Right | Left | Right | Left | Right |
| I | | | | | | |
| II | | | | | | |
| III | | | | | | |
| IV | | | | | | |
| V | | | | | | |
| VI | | FA AWS<AWNS(Watkins et al., 2007) | | | | |
| VII | FA AWS<AWNS(Watkins et al., 2007) | FA AWS<AWNS(Watkins et al., 2007) | GMV AWS<AWNS (Song et al., 2007) | GMV AWS<AWNS (Song et al., 2007) | | |
| VIII | | | | | | |
| IX | | FA AWS<AWNS(Watkins et al., 2007) | GMV AWS<AWNS (Song et al., 2007) | GMV AWS<AWNS (Song et al., 2007) | | |
| X | | | | GMV AWS>AWNS (Beal et al., 2007) | | |

*Note*. FA= fractional anisotropy; AWS= adults who stutter; AWNS= adults who do not stutter; GMV= gray matter volume; WMV= white matter volume.

Overall, many lobules in the cerebellum participate in speech motor control. Some of these same lobules could be atypical in children who stutter and differ between children with different recovery outcomes (for a summary, see Tables 2-4). Atypical morphology and connectivity with other speech areas, especially in lobules VI, VII, and VIII, support efference copy theories, which predict an imbalance between feedback and feedforward control in stuttering that may also lead to persistence into adulthood.

Like in children who stutter, distinct lobules of the cerebellum have morphological differences in adults who stutter compared to adults who do not stutter. From this review, the majority of the areas that are involved with persistent adult stuttering are consistent with those seen in children: lobules of the anterior lobe, VI, VII, and VIII (Lu et al., 2010, 2012; Song et al., 2007; Watkins et al., 2008). However, perhaps because of the higher number of studies of adults who stutter, differences in lobules IX and X also appear in some studies (See Table 4; Beal et al., 2007; Lu et al., 2010; Song et al., 2007; Watkins et al., 2008). These results could be due to a lifetime of stuttering as well. Lobules IX and X are involved with error detection as well as emotional processing, so they may represent further degradation of error detection signals related to speech motor control, or even affective systems, which are also associated with stuttering (e.g., Ide & Li, 2011; Schmahmann, 1996; Toyomura et al., 2018)

### 2.3.5 Summary: cerebellum and stuttering

Regarding the theories that posit that an imbalance between the feedforward and feedback systems of speech motor control results in developmental stuttering, the overwhelming number of results across studies that involve lobule VI give the most evidence to atypical efference processing feedforward control pathways in people who stutter. This conclusion supports both Brown et al.

(2005) and Max et al. (2004). However, how people who stutter use feedback control due to this breakdown has much less empirical evidence to support definite conclusions. Even less understood is how the relationships between these DIVA systems differ in children who stutter who recover or persist.

Evidence from an fNIRS study suggests that left-lateralized premotor areas deactivate during speech in young children who stutter (Walsh et al., 2017). Suppose these assumptions are correct regarding lobules VI and VII as the main cerebellar areas of the cortico-cerebellar loops leaving this area. In that case, aberrant signaling due to these deactivations of the left premotor regions could also influence the activity of lobules VI and VII. This relationship could, in turn, alter the development of these cerebellar lobules over time, as seen in the studies that found that the right lobule of VI had reduced white matter integrity in children who stutter (Chang et al., 2015). The lack of communication between the left premotor cortex and lobule VI could also result in atypical updating of efference copy information, leading to breakdowns such as atypical rhythm perception (Chang et al., 2016). The reduction of gray matter volume in recovered children and decreased white matter integrity growth trajectories could also be adaptive under this interpretation (Chang et al., 2008; Chow & Chang, 2017).

To make better predictions about how the cerebellum is involved in stuttering and stuttering persistence and recovery, large longitudinal studies of children who stutter need to examine how cerebellar developmental trajectories differ in these groups. Currently, this review supports that the cerebellum is involved in both adaptive strategies that decrease the number of disfluencies in speech of people who stutter and disfluency-supporting aspects of developmental stuttering neurophysiology. Many of the theories in this review also support that the cerebellum may alter how people who stutter use different speech motor control systems. Further studies will help us

elucidate the nature of this relationship.

## 2.4 RESEARCH QUESTIONS, HYPOTHESES, AND INTERPRETATIONS

This study focuses on applying voxel-based morphometry and specialized template tools for the cerebellum to evaluate how regional cerebellar volume differs in developmental stuttering and how developmental trajectories in cerebellar regional volumes differentiate children who continue to stutter compared to those who recover. The literature reviewed above substantial rationale to further investigate the cerebellum in the context of speech control and its structure and function in relation to developmental stuttering. Adequate speech adaptation in response to auditory feedback perturbation during speech production is supported by a well-established efference copy mechanism linked to cerebellar function. Multiple investigations that examined speech adaptation to auditory perturbations have reported attenuated speech compensations to sensory perturbations in adults who stutter (Cai et al., 2012, 2014; Daliri et al., 2017; Daliri & Max, 2018; Kim et al., 2020; Loucks et al., 2012; Sares et al., 2018). Though findings have been more consistent in adults, where adults who stutter show delayed and attenuated speech adaptations to sensory perturbations, this has not been the case for all studies of children who stutter (Daliri et al., 2017; Kim et al., 2020). A careful examination of developmental changes in the cerebellum in childhood is likely to provide much-needed clues to whether and how differences in adaptive speech control, influenced by efference copy mechanisms, might be a trait difference in stuttering, as opposed to a difference accrued over many years of stuttering.

This dissertation's central research question pertains to how cerebellar morphology differs in children who stutter relative to age-matched children who do not stutter and whether any structural differences in the cerebellum predict later persistence or recovery in children who stutter. Prior research has shown that the balance of speech motor control systems (i.e., feedback and feedforward control systems) may be altered as children who persist in stuttering continue into

adulthood. The cerebellum connects the two main subsystems of speech motor control (the feedback and feedforward systems, as outlined in the DIVA model) and may play a role in the development of both. Therefore, studying how cerebellar lobular anatomy differs in children who stutter will further our understanding of how the neural substrates that mediate speech motor control development in the cerebellum lead to pathways of persistence into adulthood or predispose children to begin stuttering.

Understanding which cerebellar areas are associated with stuttering persistence and recovery may also contribute new knowledge of which neural systems of the brain guide these diverging neural trajectories. For example, areas of the cognitive cerebellum, the posterior lobe, are involved in orofacial motor control and complex cognitive functions such as executive control. Additionally, a better understanding of the laterality of any morphological differences within the cerebellum between persistent or recovered children who stutter may also help us understand how these relate to cerebral laterality shifts observed in adults who stutter. Detailed data of regional cerebellar anatomy could also provide mechanistic insights related to the above aspects of stuttering neurophysiology and how they could be associated with processing efference copy information. Potentially, these clues to the mechanisms of stuttering could further our understanding of how the cerebellum fits into a larger neural picture that leads to the onset and/or persistence of stuttering.

This study applies current VBM techniques to probe morphological aspects of functionally distinct structures of the cerebellum in the largest sample of cerebellar data to date of children who stutter and age-matched peers. The aims of this study are two-fold: 1) Examine group differences in volumetric measures of the cerebellum among children who stutter and children who do not stutter, 2) Examine gray-matter volume differences in the cerebellum that differentiate persistent

and recovered children who stutter, and 3) Examine age-related associations of gray matter volume based on a group of preschool-age and school-age children who stutter and who do not stutter. In line with these aims, the current study seeks to answer the following questions:

1. What morphological differences in the gray matter of specific functional areas of the cerebellum are linked to childhood stuttering?
2. Do morphological differences in the cerebellum differentiate persistent versus recovered children who stutter?
3. How do age-related cerebellar morphology differences characterize children who do not stutter, persistent and recovered children?

It is hypothesized that children who stutter will differ from children who do not stutter in the right cerebellar lobule VI. Children who stutter are expected to have less gray matter in lobule VI. Because language areas are left-lateralized at the level of the cerebrum and given that the cerebellum primarily has contralateral connectivity with the cerebrum, this means that areas of the cerebellum that support language and speech are largely right-lateralized (e.g., Scott et al., 2001). Thus, it is expected that children who stutter will have less gray matter than children who do not stutter in the right lobule VI. Lobule VI is the only cerebellar lobule currently included in the DIVA model of speech production and is thus of greatest interest to speech production and highly relevant to stuttering.

Additionally, influential stuttering theories supported by several behavioral studies also suggest that sensorimotor learning, mediated by lobule VI, is central to stuttering neurophysiology (Cai et al., 2012, 2014; Daliri & Max, 2018; Kim et al., 2020; Loucks et al., 2012; Sares et al., 2018). Differences in the structure and functioning of the right lobule VI are also the most commonly reported cerebellar findings in empirical studies of childhood stuttering (Chang et al.,

2015; Chang et al., 2008, 2016). In addition, cerebellar lobule VI was also reported to have atypical connectivity patterns with the left supplementary motor area (Chang et al., 2015; Chang & Zhu, 2013), which could be an essential link to the many efference copy theories of stuttering.

Cerebellar morphology examined close to stuttering onset could help us predict recovery outcomes of stuttering. Thus, the second hypothesis that will be tested in this dissertation is that differences in gray matter volume in the right lobule VI will be associated with persistent stuttering. Currently, only one peer-reviewed study has compared static volumetric differences in children who stutter who are persistent or recovered (Chang et al., 2008). This study found that persistent children who stutter had greater gray matter volume in the right lobule VI than recovered children. However, no study has looked at cerebellar morphology associated with childhood stuttering close to stuttering onset and used these data to predict associations with later stuttering recovery status. The evidence from Chang et al. (2008) supports theories that predict that the feedforward system of speech motor control is overactive in people who stutter (Brown et al., 2005). Data from Brown et al. (2005) focuses on adults who stutter, i.e., persistent people who stutter, however. While the first hypothesis of this study predicts that children who stutter, regardless of recovery status, will have lower gray and white matter volumes than children who do not stutter, recovered and persistent children who stutter have different developmental patterns that lead to differential cerebellar development.

While Chang et al. (2008) found that persistent children who stutter have greater gray matter volume in the right cerebellar lobule VI, many adult studies of persistent people who stutter have found that gray matter volume is typically lower in key cerebellar lobules important to speech (see Table 4). One time point of data from the fifteen kids who stutter nearing their teenage years in Chang et al. (2008) may lead to results that do not adequately describe the nature of stuttering

neurophysiology associated with predictive factors of persistence at stuttering onset. Importantly, synaptic pruning, which alters gray matter morphology, continues well into one's early 20s. At the average age of persistent children who stutter in Chang et al. (2008), age 11 years, cerebellar volume peaks (e.g., Tiemeier et al., 2010). Therefore, more data from younger children is needed to understand the cerebellar development that contributes to the onset of stuttering. Using newer analysis techniques specialized for the cerebellum on a younger, larger cohort of childhood data may provide results that are more indicative of the nature of the cerebellum that brings about the onset of stuttering and what kind of patterns may predict stuttering outcomes in the future.

Because of these reasons, it is hypothesized that children who eventually persist in stuttering have lower gray matter volume in right lobule VI of the cerebellum as compared to control and recovered children. The right cerebellum supports the detection of mismatches between expected and unexpected sensory feedback during motor sequence learning (e.g., Blakemore et al., 2001; Gryga et al., 2012). Anomalous structural development here may lead to atypical functioning of predictive, feedforward systems in stuttering speakers, as suggested by Brown et al. (2005). Additionally, the cerebellum is crucial for learning internal model representations during development (for a discussion, see Guenther, 2016). Atypical morphology of the right cerebellum could lead to developing atypical internal models, which others have proposed as a key cause of disfluencies during the speech of people who stutter (Brown et al., 2005; Max et al., 2004). However, cerebellar evidence in children who stutter, which supports these theories, is sorely lacking. This study seeks to bridge the gap in the understanding of how efference copy theories could be supported by critical structural differences in children who stutter close to stuttering onset.

Importantly, a closer examination of age-related differences of cerebellar volume will help

us better understand how cerebellar volume varies at different ages in persistent and recovered children who stutter. We hypothesize that the right lobules VI and VII will be areas of the cerebellum that correspond with age differently in persistent and recovered children who stutter. In addition to lobule VI, VII is relevant to stuttering because of its connection with stuttering morphology in several studies (Chang et al., 2008; Chow & Chang, 2017; Song et al., 2007; Watkins et al., 2007), atypical connectivity with other important speech-motor control areas (Chang & Zhu, 2013; Lu et al., 2012), and associations with rhythm discrimination accuracy in children who stutter (Chang et al., 2016). As discussed in an earlier section, auditory perturbation studies have consistently reported reduced speech compensations in response to the auditory perturbations in adults who stutter relative to adults who do not stutter; however, in childhood, this difference may be less distinct or even nonexistent (Cai et al., 2012, 2014; Daliri et al., 2017; Daliri & Max, 2018; Kim et al., 2020; Loucks et al., 2012; Sares et al., 2018). We expect that children who recover will have greater gray matter volume differences with age in the right side of lobules VI and VII compared to children who stutter that persist into adulthood and children who do not stutter.

Growth trajectories of the cerebellar peduncles that contain the cerebellum's efferent and afferent fibers may also differentiate children who eventually recover versus persist in stuttering. Previous studies have reported that adults who stutter have lower fractional anisotropy, a measure associated with white matter integrity, in the cerebellar peduncles compared to adults who do not stutter. While some studies have suggested that all three peduncles have lower fractional anisotropy in persistent adults who stutter (Connally et al., 2014), other studies have only found the right middle peduncle to be different (Watkins et al., 2007). Still, other studies have found that the cerebellar peduncles do not have microstructural differences as compared to adults who do not

stutter; however, fractional anisotropy of the right inferior cerebellar peduncle is associated with speech rate in adults who stutter (Jossinger et al., 2021). In secondary analyses, Connally et al. (2014) found that the left inferior cerebellar peduncle had the lowest white matter integrity and that all three left peduncles had less white matter integrity than the right peduncles, which also decreased with age in adults who stutter. The inferior and middle peduncles are important for afferent signals from the cortex and brainstem. Given the current evidence, mechanisms behind how the disruptions to white matter in the cerebellar peduncles may affect stuttering are unclear. However, disruptions to white matter in the cerebellum could be highly relevant to many stuttering theories. These structures influence the timing and integrity of signals necessary for supporting efference copy signals (as suggested by Brown et al., 2005; Max et al., 2004).

Distinguishing which, if any, of the peduncles differ in pediatric cases of developmental stuttering has implications for how we continue to think about the efference copy in stuttering. For example, Max et al. (2004) propose two main theories associated with internal models, both of which could heavily involve the cerebellum. One hypothesis posits that internal model information is unstable due to atypical development of these programs (the *Unstable Internal Model Hypothesis*). Because of this difference, the motor system is unable to use both feedforward and feedback systems typically. Feedforward pathways are compromised due to their inability to predict sensory outcomes, and feedback pathways that receive the unstable and incorrect internal models are unable to predict errors based on this information. Several cerebellar peduncles could be impacted due to these differences. The inferior cerebellar peduncles would likely differ under this hypothesis. The inferior cerebellar peduncles have been associated with sensorimotor adaptation (Jossinger et al., 2020) and detecting errors in motor commands (for a review, see Shadmehr, 2017), which are both reliant on feedback control. If the feedback control system uses

internal models to decide if there are speech errors and to adapt to any errors, which would be affected if internal models were unstable. Lastly, the superior cerebellar peduncles carry efferent information to the cortex. Signaling from the cerebellum would differ if the processing of internal models deviated in either system.

The *Overreliance on Feedback Control Hypothesis* in Max et al. (2004) is that signaling from the feedforward pathway to the feedback pathway differs in people who stutter, leading to an overreliance on feedback control. However, due to speech being rapid and feedback control being too slow to support rapid speech motor control, disfluencies occur. Unlike the first theory, internal model information is not compromised, just the transmission of this information. Because the middle cerebellar peduncles receive information from the ventral premotor cortex where internal models are stored (see Figure 2), structural differences in these peduncles might indicate atypical signaling from important cortical motor areas that house internal model information. This theory also differs from the first in that the feedback control system can detect errors in speech typically; however, it is not sufficient to support speech in a typical manner as when it can work with the feedforward system. Therefore, I predict that the inferior cerebellar peduncle's role would not differ. Lastly, due to the heightened signaling from the feedback control system, the superior cerebellar peduncles would likely be affected under this hypothesis.

Pediatric studies of the cerebellar peduncles in developmental stuttering have found that the cerebellar peduncles differ over time in children who stutter. Additionally, one key peduncle, the inferior cerebellar peduncle, was associated with overall differences between the groups. Johnson et al. (2022) found that children who stutter have lower white matter coherence in the right inferior cerebellum than children who do not stutter. The white matter measures were also negatively associated with the frequency of stuttering in children who stutter. Differences in the

inferior cerebellar peduncles in children who stutter may suggest that the development of internal model information is supported by atypical usage of sensory information supplied by the inferior cerebellar peduncles, described by Max et al. (2004)'s first hypothesis. However, more studies are needed to confirm that the inferior cerebellar peduncles are a signature area of childhood developmental stuttering.

The growth rate of several cerebellar peduncles has been associated with childhood stuttering and recovery outcomes. For example, persistent children who stutter may have a decreased growth rate in various cerebellar peduncles' white matter than children who do not stutter (Chow & Chang, 2017; Connally et al., 2014; Garnett et al., 2018). In addition, because the fractional anisotropy of the cerebellar peduncles decreases with age in persistent people who stutter, this may indicate that inefficient communication between the cerebellum and the cerebrum begins in childhood for persistent people who stutter and further degrades well into adulthood (Chow & Chang, 2017; Connally et al., 2014; Garnett et al., 2018). This may mean that pathways that feed information from the cortex to the cerebellum, as well as vise versa, develop differently over time in childhood stuttering to support continued stuttering into adulthood.

In association with the decreased gray matter volume in older ages of children who stutter of important speech-motor control areas such as lobules VI and VII, the growth rate in the cerebellar peduncles would also lend some credibility to the idea that learning processes that support speech motor control do not develop typically in persistent children who stutter. Altered gray matter volume in older populations of children who stutter in lobules VI and VII may be associated with gray matter changes in interconnected cortical areas that support motor control in the cerebrum (e.g., Gryga et al., 2012). Therefore, studying how white matter differs in critical areas of the cerebellum, such as the peduncles, may help us better understand how systems that

support speech motor control may function differently in children who stutter. Differences in the white matter areas of the cerebellum would also support different hypotheses related to efference copies, as discussed above.

The cerebellum's contralateral connectivity with the cerebrum could support theories of how laterality shifts in motor areas such as the inferior frontal gyrus may support persistence or recovery from stuttering. For example, predicted changes in right-lateralized cerebellar cortex areas such as VI and VII might indicate that connectivity with left-sided cerebral areas plays a role in persistence and recovery pathways. While previous studies have focused on the cerebrum, accruing empirical and theoretical perspectives underscore the importance of investigating the role of the cerebellum, as it participates in closed loops with critical cortical areas linked to stuttering. A detailed examination of cerebellar anatomy in childhood stuttering will pave the way for a much-needed breakthrough in understanding the cerebellar-cortical loops, speech motor control, and a mechanistic understanding of stuttering onset and persistence.

## 3.0 METHODS

### 3.1 PARTICIPANTS

Planned statistical tests include between groups, independent sample t-tests for demographic and background speech and language data, general linear models to compare cerebellar regions of interest, and linear regressions for gray matter volume, Stuttering Severity Instrument (SSI) score and age. An a priori power analysis was conducted using G*Power (Faul et al., 2009). Power estimation to estimate the sample size with an alpha=.05, effect size= .5, and a moderate beta of .80 was used to compute the two-tailed independent sample tests. The results of this power estimation predict that a sample size of at least 64 children per experimental group is needed.

A power analysis was performed to estimate sample sizes based on data from Beal et al. (2013), who compared total gray and white matter cerebral volume between children who do (N= 11) and do not stutter (N=11) using VBM methods. With an alpha of 0.05 and power = 0.80, the estimated sample size needed to achieve the effect size from Beal et al. (2013) is N=12 in each group to detect group differences in gray matter volume and white matter volume across groups.

The second a priori power analysis was based on data from Chow & Chang (2017), who compared fractional anisotropy of white matter structures across the brain of children who do (N=35) and do not stutter (N=43) using diffusion tensor imaging methods. With an alpha of 0.05 and power = 0.80, the estimated sample size to achieve the effect size of Chow & Chang (2017) of 0.63 is at least N=37 per group to detect structural differences across groups.

Children who do and do not stutter were recruited as part of an ongoing longitudinal study. Participants were recruited through social media advertisements, community flyers, letters to physicians' offices, speech-language pathologists, daycare centers in the area, and email communications with parent groups. Children between the ages of 3-6 years were chosen for year-

one data collection due to approximate correspondence with typical stuttering onset (Bloodstein & Bernstein Ratner, 2008). A total of 485 children were screened as part of the longitudinal study. Before enrolling in the longitudinal study, families were asked to complete a phone interview to determine their eligibility status. All recruitment and study methods were approved by Michigan State University's Institutional Review Board.

## 3.2 INCLUSION CRITERIA

During the phone screening, children were screened for the following inclusion criteria before entering the study: monolingual English speakers, no history of concussions, or certain concomitant developmental disorders. Children with comorbid attention-deficit hyperactivity disorder diagnoses were included in the main longitudinal study to produce a more naturalized sample representing typical groups of people who stutter (e.g., Arndt & Healey, 2001; Conture, 2001; Riley & Riley, 2000). Children who do not stutter who had relatives who stutter were not enrolled in the study.

If the child met the inclusion criteria during the phone screening, they were brought in for study visits once a year for up to four years (up to 3 years in the case of a second, later wave of recruited participants). During these campus visits, children may have also been excluded if they had a previous history of articulation of phonological disorders and standardized language test scores that fell below 2 standard deviations of the mean, full-scale IQ scores below 1 standard deviation of the mean or were unable to tolerate MRI scanning procedures. Some children who stutter who could not tolerate the MRI scanning were still included in the longitudinal study to examine developmental trajectories associated with language and cognitive development outside of the main MRI study. Children who do not stutter were included if they had never been diagnosed with stuttering, had no family history of stuttering, there was no expressed parental concern of stuttering, and if the percentage of stuttering-like disfluencies was below 3%. Results from behavioral testing are described in tables 6 and 7.

Children were considered to be children who stutter based on three criteria during their first visit for the study: (a) expressed concern from the parent regarding stuttering, and a speech-language pathologist confirmed stuttering, (b) Stuttering Severity Instrument (SSI; Riley, 2009) scores exceeded a score of 10 (very mild or greater), (c) the child exhibited at least 3% of stuttering-

like disfluencies during a spontaneous conversation sample with a certified speech-language pathologist during their visit. The reliability of SSI scores was assessed using an intraclass correlation coefficient (ICC) calculation from two independent judges. The analysis indicated high reliability between the two judges, with a score of .98. Of the 211 children who passed the phone screening and attempted an MRI scan, 23 children did not meet the inclusion criteria for this project. A total of 188 unique children were included (children who stutter= 94, children who do not stutter= 94). Detailed additional demographic data are provided below. Figure 6 details the inclusion factors that led to the final number of children included in this study.

Children who stutter were retrospectively determined to be persistent after the final study visit of the longitudinal study based on the following criteria: (a) continued expressed concern from the parent regarding stuttering; (b) clinical impression of speech-language pathologist confirming persistent status based on direct assessment; (c) SSI score higher than "very mild" (composite score equal or greater than 10); (d) minimum of 3% of stuttering-like disfluencies identified during spontaneous speech sample comprising narrative and conversational speech. Children who stutter were considered to be recovered based on the following factors: (a) the composite SSI score was below a "very mild" score at the second annual visit and maintaining in future years; (b) the percentage of stuttering-like disfluencies was lower than 3% in the speech sample; (c) confirmation from speech-language pathologist based on direct assessment indicating recovery; and (d) parent confirmation that child had recovered.

Figure 6: Detailed inclusion determination tree for study participants

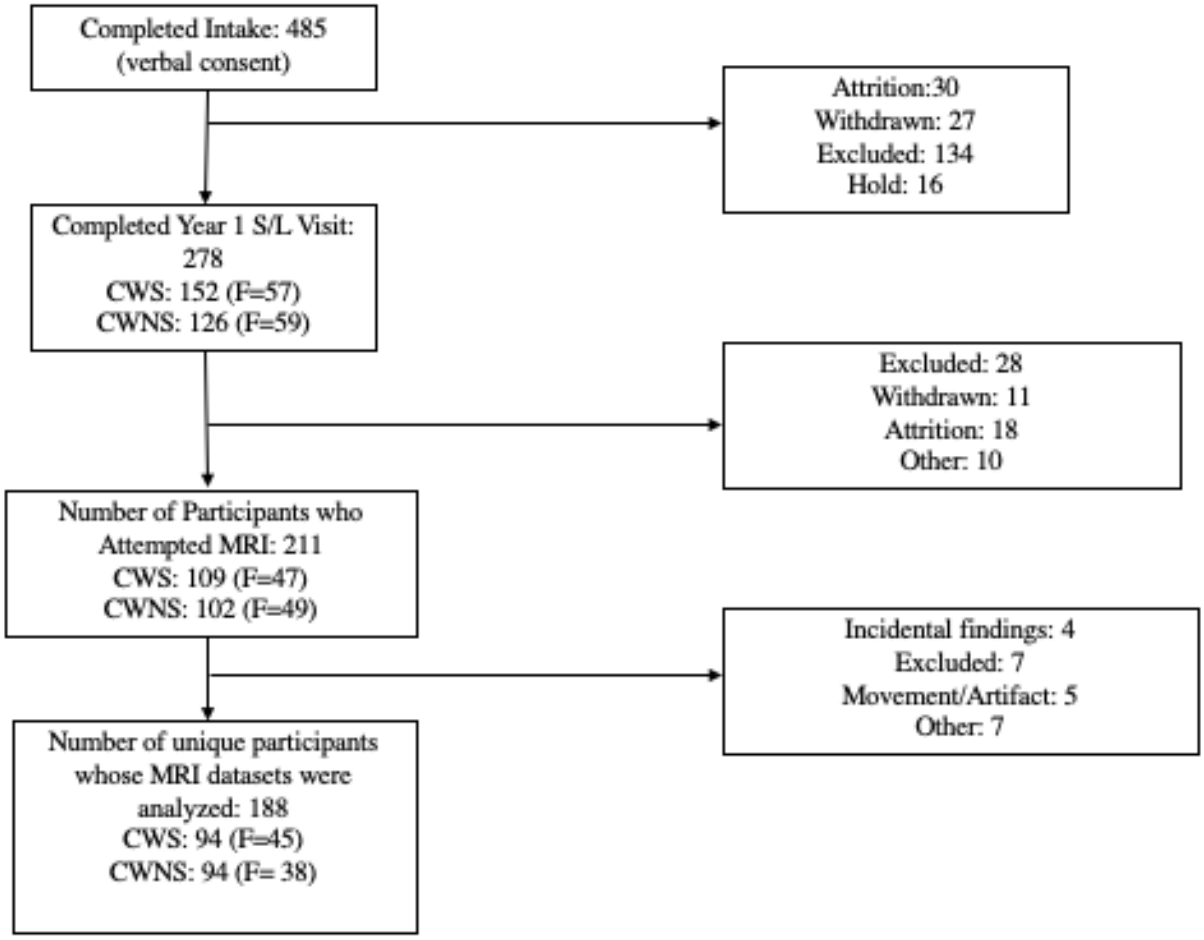

Table 5: Standardized assessments administered to all children participating in the longitudinal study

| Questionnaires & Assessments | Citation | Purpose |
|---|---|---|
| **Parent** | | |
| Four Factor Index of Social Status (SES) | (Hollingshead, 1975) | Maternal education indexed using this instrument for the study |
| Children's Behavior Questionnaire (CBQ) | (Rothbart, 2000) | Temperament assessment of children in the study |
| **Child** | | |
| Edinburgh Handedness Inventory | (Oldfield, 1971) | Determination of left or right-handedness |
| Purdue Pegboard Test | (Tiffin, 1968) | Measurement of manual dexterity and coordination of bimanual movements |
| Weschler Preschool and Primary Scale of Intelligence (WPPSI-III) | (Wechsler, 2003) | Used to determine participants' eligibility during the first year of the study; measurement of visual, performance, and full-scale intelligence quotient of children between the ages of 2:6-7:3 years |
| Goldman Fristoe Test of Articulation (GFTA-2) | (Goldman & Fristoe, 2000) | Determination of articulatory abilities of children in the main study |
| Communication Attitude Scale for Pre-K & Kindergarten Children Who Stutter (KiddyCAT) | (Vanryckeghem & Brutten, 2007) | Measurement of children's awareness or attitudes associated with stuttering in children 3-6 years of age |
| Test of Childhood Stuttering (TOCS) | (Gillam et al., 2009) | Identifies children who stutter and determines stuttering severity using four unique speech tasks |

Table 5 (cont'd)

| | | |
|---|---|---|
| Stuttering Severity Instrument (SSI-4) | (Riley, 2009) | Measures stuttering severity using norm-referenced assessment of the frequency and duration of stuttering, physical concomitants, and naturalness of speech. |
| Clinical Evaluation of Language Fundamentals (CELF-P:2 & CELF-5) | (Wiig et al., 2004, 2013) | Used in year 1 of the main study to assess eligibility. The CELF measures language abilities across six domains: sentence structure, word structure, expressive vocabulary, sentence comprehension, formulated sentences, and recalling sentences. From these domains, a Core Language Score is calculated. |

Table 6: Shapiro-Wilk test of normality by group & total sample

| **Variables** | **Children Who Stutter** | | **Children Who Do Not Stutter** | | **Total** | |
|---|---|---|---|---|---|---|
| | ***W*** | ***p-value*** | ***W*** | ***p-value*** | ***W*** | ***p-value*** |
| Age (MRI session) | 0.92 | <.001* | 0.93 | <.001* | 0.93 | <.001* |
| Age of Onset | 0.86 | <.001* | N/A | N/A | N/A | N/A |
| Full-Scale IQ | 0.98 | 0.34 | 0.98 | 0.60 | 0.99 | 0.35 |
| Performance IQ | 0.97 | 0.05* | 0.98 | 0.41 | 0.98 | 0.03* |
| Verbal IQ | 0.98 | 0.98 | 0.99 | 0.79 | 0.99 | 0.48 |
| GFTA | 0.88 | <.001* | 0.83 | <.001* | 0.86 | <.001* |
| Maternal Education | 0.90 | <.001* | 0.86 | <.001* | 0.88 | <.001* |
| SSI Score | 0.93 | <.001* | N/A | N/A | N/A | N/A |
| %SLDs Clinician Sample | 0.80 | <.001* | 0.93 | <.001* | 0.76 | <.001* |
| Total Cerebellar Volume | 0.96 | 0.03* | 0.86 | <.001* | 0.98 | 0.02 |

*Note.* GFTA= Goldman Fristoe Test of Articulation; SSI= Stuttering Severity Instrument; %SLDs= Percent stuttering-like disfluencies; * indicates statistically significant results

Table 7: Participant demographic information & behavioral test results

| Variables | Children Who Stutter | | Children Who Do Not Stutter | | Test Statistic | *df* | *p-value* | Cohen's *d* |
|---|---|---|---|---|---|---|---|---|
| | ***M*** | ***SD*** | ***M*** | ***SD*** | | | | |
| Age (MRI session) | 68.73 | 22.92 | 68.17 | 21.15 | 4406[2] | N/A | 0.97 | N/A |
| Age of Onset | 34.04 | 11.68 | N/A | N/A | N/A | N/A | N/A | N/A |
| Full-Scale IQ | 106.99 | 13.92 | 111.34 | 13.08 | 2.19[1] | 184 | 0.02* | 13.51 |
| Performance IQ | 105.43 | 15.29 | 108.49 | 15.23 | 3688.50[2] | N/A | 0.10 | N/A |
| Verbal IQ | 108.27 | 13.33 | 113.57 | 14.59 | 2.58[1] | 184 | 0.01* | 13.97 |
| GFTA | 101.84 | 11.79 | 102.48 | 11.43 | 4083[2] | N/A | 0.43 | N/A |
| Maternal Education | 6.10 | 0.77 | 6.24 | 0.73 | 3770[2] | N/A | 0.18 | N/A |
| SSI Score | 19.09 | 6.82 | N/A | N/A | N/A | N/A | N/A | N/A |
| %SLDs Clinician Sample | 6.82 | 5.12 | 1.16 | 0.87 | 301[2] | N/A | <.001* | N/A |
| Total Cerebellar Volume | 29458.57 | 3343.13 | 29562.22 | 2910.18 | 4169[2] | N/A | 0.50 | N/A |

*Note.* 1= independent samples t-test; 2= Mann-Whitney U test; GFTA= Goldman Fristoe Test of Articulation; SSI= Stuttering Severity Instrument; %SLDs= Percent stuttering-like disfluencies; Age values reported in months; Total cerebellar volume reported in $mm^3$; * indicates statistically significant results

## 3.3 MEASURES

### 3.3.1 Speech, language, and cognitive measures

Children visited the lab 2-3 times for behavioral testing, mock MRI training, and MRI scans. A parent or legal guardian signed an informed consent form, and children who participated in our study gave verbal assent, which was reviewed and approved by the Institutional Review Board at Michigan State University (IRB #09-810 LEGACY). During the first visit, children and their guardians completed a series of speech, language, and other cognitive tests to assess the child's cognitive abilities (see list of assessments in Table 5) and stuttering status. Additionally, children participated in MRI desensitization procedures ("mock scanning") to increase the probability of success in the scanning environment. During MRI desensitization training, children practiced staying still, viewed clear vs. blurry MRI images (to demonstrate the effects of movement during scanning), and laying in a mock MRI scanner (for a description of MRI desensitization procedures, see Theys et al., 2014). Trained research assistants working with the children would assess a child's readiness to participate in an MRI scan and if repeat desensitization appointments were needed.

The Institutional Review Board at Michigan State University reviewed and approved all the procedures. Families were compensated for their time and efforts. Children were remunerated $20 for the first hour and an additional $15.00 per hour during the behavioral testing sessions. For participating in MRI, children were paid an additional $30. If a family traveled to their appointments from a location greater than 60 miles away from the lab space, they were remunerated an additional $0.50/mile. All children were given small toys and stickers and a picture of their brain for participating.

### 3.3.2 MRI data collection

All MRI scans were collected using a GE 3T Signa HDx MR Scanner (GE Healthcare) using an 8-channel head coil. A pair of 180 T1-weighted 1-mm3 isotropic volumetric inversion recovery fast spoiled gradient-recalled sagittal images (about 5-minute scan time) were used during each session, with the cerebrospinal fluid (CSF) suppressed. This measure was collected to cover the entire brain using the parameters: TE = 3.8 ms, TR of acquisition = 8.6 ms, time of inversion (TI) = 831 ms, TR of inversion = 2332 ms, flip angle = 8°, FOV = 25.6 cm × 25.6 cm, matrix size = 256 × 256, slice thickness = 1 mm, and receiver bandwidth = ± 20.8 kHz, and parallel acceleration factor = 2.

Children were instructed to stay still while in the MRI scanner. During the session, children viewed a movie using headphones and a projection screen compatible with MRI. Children wore earplugs to dampen the sound of the scanner. Head cushions and a strap across the child's forehead were used to reduce movement. A researcher sat next to the child in the scanner room throughout the scan session to ensure that subjects were comfortable and tolerating the scanning procedures. The first available MRI scan (typically acquired during the first year visit) was entered into analyses for each participant in the current investigation. Namely, MRI data in this dissertation is from the first year of the longitudinal study only. Behavioral data, including age, was also from the same year of the study as the MRI scan entered into analyses. One scan per child was entered for each of the 188 participants included in this study.

### 3.3.3 Data preprocessing

Voxel-based morphometry (VBM) was performed on individual T1-weighted MRI data (SPGR) that covered the whole cerebrum and cerebellum. A visual representation of a typical VBM preprocessing pipeline is shown in Figure 8. The Spatially Unbiased Atlas Template of

the Cerebellum (SUIT) toolbox running on SPM12 was used to improve the normalization of the cerebellum (Diedrichsen, 2006). A higher-resolution template of the human cerebellum and brainstem is used in SUIT processing, which has been shown to significantly enhance the reliability and accuracy of anatomical measurements within cerebellar structures (Figure 7; Diedrichsen, 2006). For instance, SUIT preserves more cerebellar anatomical detail than the widely used Montreal Neurological Institute (MNI) International Consortium for Brain Mapping (ICBM 152) template. The SUIT atlas improves the alignment of cerebellar features between subjects and has a higher correlation with anatomical features of the cerebellum (.97) compared to ICBM152 (.87; Diedrichsen, 2006). See figure 7 for a representation of alignment accuracy of the primary fissure and intrabiventer fissure using the SUIT atlas compared to a whole-brain template, the ICBM152.

Figure 7: Better alignment between native images for the two fissures is achieved using the SUIT atlas

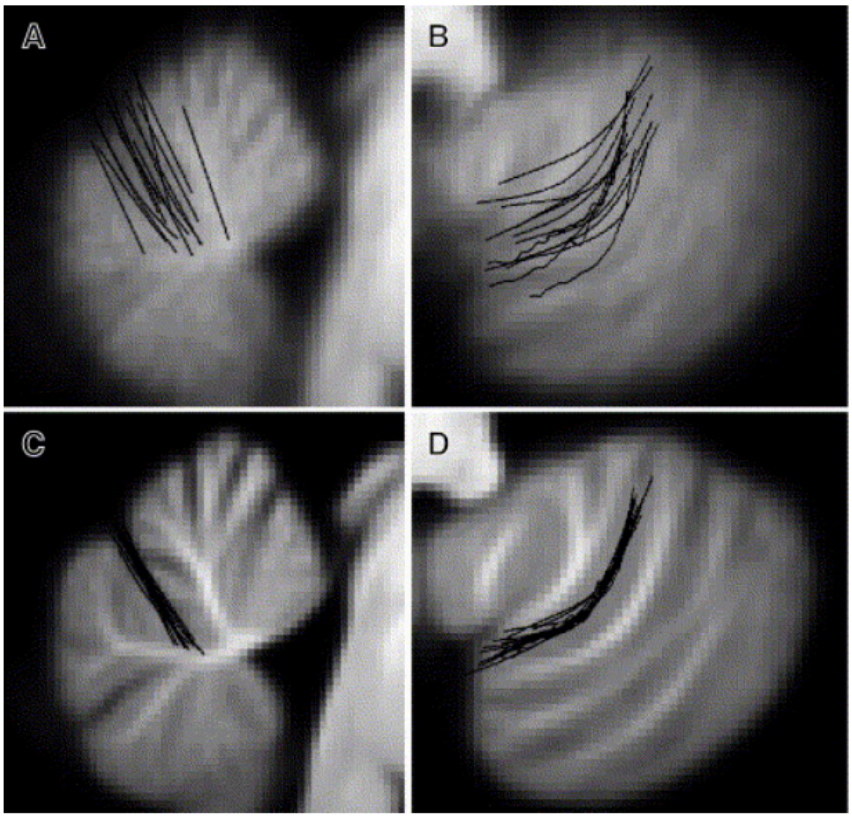


Figure Caption: Column 1 (A, C) represents data concerning the primary fissure of the cerebellum, and column 2 (B, D) displays data related to the alignment of the intrabiventer fissure. Black lines across the boxes represent the respective fissure locations on individual native images and are laid on normalized cerebellar images. The top row (A, B) are cerebellar images normalized using the whole-brain template, ICBM152, and the bottom row (C, D) are normalized images using SUIT. Reprinted from Diedrichsen (2006).

VBM is a well-established structural MRI technique that allows objective whole-brain analysis of gray and white matter volume. It relies on automatized steps that do not require manual tracing or expert anatomical knowledge, making VBM a powerful tool to efficiently analyze anatomical features of the brain over the entire brain, including the entire cerebellum (Ashburner & Friston, 2001). Gray and white matter volumes between study groups can be compared by normalizing individual raw structural MRI images to a standardized space, allowing comparisons of gray or white matter volume in comparable anatomical regions across subjects (Mechelli et al., 2005). Namely, VBM is a powerful tool to compare morphology between subjects while discounting global structural differences. Specifically, optimized VBM procedures were used in this study to calculate the volume of cerebellar gray and white matter, which preserves the absolute amount of gray and white matter tissues in analyses (see Figure 9 for optimized VBM steps). Modulation during optimized VBM is vital because, during normalization, brains are scaled to fit into the template image, which may change the shape of the structures being studied during further analyses. Optimized VBM preserves the absolute volume, or volume that is proportional to the native image, by performing calculations that consider the amount of change that happens during normalization.

Additionally, optimized VBM segments gray and white matter structures before normalization processes to reduce potential errors from low-frequency deformation fields, which are used in the normalization process (Mechelli et al., 2005). This process ensures that all data entering gray or white matter analyses are indeed associated with the structure in question, as they are the only structures included in each segmentation map after this step. For example, data related to gray matter would only include the gray matter segmentation maps, ensuring that gray matter is only considered in gray matter analyses. Segmentation of tissue types was calculated

using the statistical parametric mapping (SPM12) segmentation algorithm (Ashburner & Friston, 2000, 2005). Bayesian priors, which use priori probability maps, encode a general mathematical understanding of tissue distribution in the brain. These priors are then used in combination with voxel intensity information, the contrast between tissues in the anatomical images, to parse gray and white matter structures into separate spaces.

Segmented images were normalized into standard space using the diffeomorphic image registration algorithm (DARTEL; Ashburner, 2007) in SPM 12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). DARTEL takes the native images' segmentation map of both gray and white matter and rigidly aligns them to one another to create a mean of all the images. This mean of the images is used to create a template. The template image is considered a normalized representation of the data, where the structures of the brain are more representative of the global brain structure across the sample than one native scan may be alone. Deformation fields, which hold information about the stretched or squeezed locations of brains while mapping them to the template, are computed as a result of fitting the native images into the new template during DARTEL. This process of aligning native images to the emerging template image is repeated many times. The iterative process of aligning and creating a template through DARTEL increases subject alignment accuracy (Ashburner, 2007).

Once a template image is created for both the white and gray matter of the images, modulation is performed using Jacobean determinates of the deformation fields computed from the DARTEL normalization step. As mentioned previously, modulation preserves the absolute volume of the cerebellum. If modulation is not performed, the data would only represent relative gray and white matter differences to other areas of the template images, meaning the concentration of gray or white matter in voxels across brain areas of the template image is being

measured. Modulation ensures that the compression and warping of the native images are accounted for after normalization so that the proportional volume of the native images is preserved after normalization.

Modulated segmentation maps from the template images were then smoothed using a 4 x 4 x 4- mm full width at half maximum (FWHM) Gaussian smoothing kernel. Smoothing adjusts the intensity of each voxel in the template image so that a voxel's intensity is weighted based on the intensity of the voxels that surrounds it. This step of VBM is crucial because it makes the data more normal, which is an assumption of VBM. Additionally, smoothing reduces the variability between subjects (Ashburner & Friston, 2000). These changes due to smoothing increase the sensitivity of further tests to detect change by reducing variance across subjects (Whitwell, 2009). After DARTEL normalization, the new template image was sliced in the SUIT atlas space using the same DARTEL process. Reslicing the template images into the SUIT atlas space allows for parametric statistics to be run on the data in SUIT space. The last preprocessing step that reslices the template images into SUIT is important to take advantage of the higher subject alignment of the cerebellum shown to be a result of using the SUIT atlas as compared to more common atlases which are not specialized to the cerebellum (Diedrichsen, 2006).

Figure 8: Visual representation of the classic VBM approach to extract volume measures

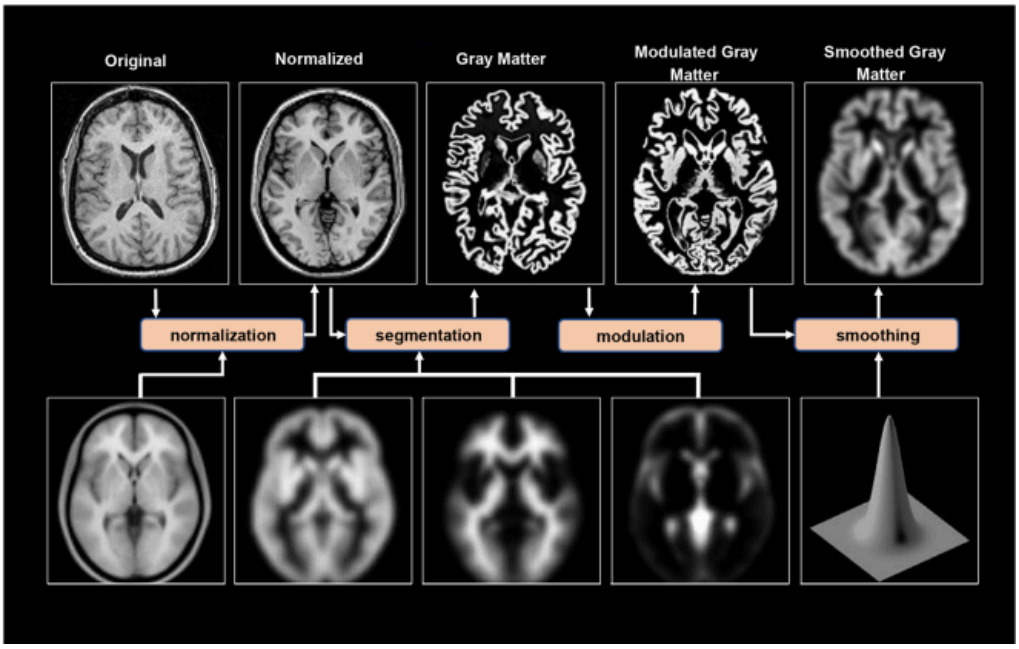


Figure Caption: Optimized procedures and DARTEL are not represented in the above figure. First, the brain is normalized to the template image. From the template, gray and white matter segmentations are completed. Deformation fields extracted from the normalization process are then used to modulate the gray and white matter data to calculate volumetric information. Lastly, the data are normalized using Gaussian kernels through smoothing. Reprinted from Gao et al. (2020).

Figure 9: Optimized voxel-based morphometry procedures used to calculate white and gray matter volumes of the cerebellum

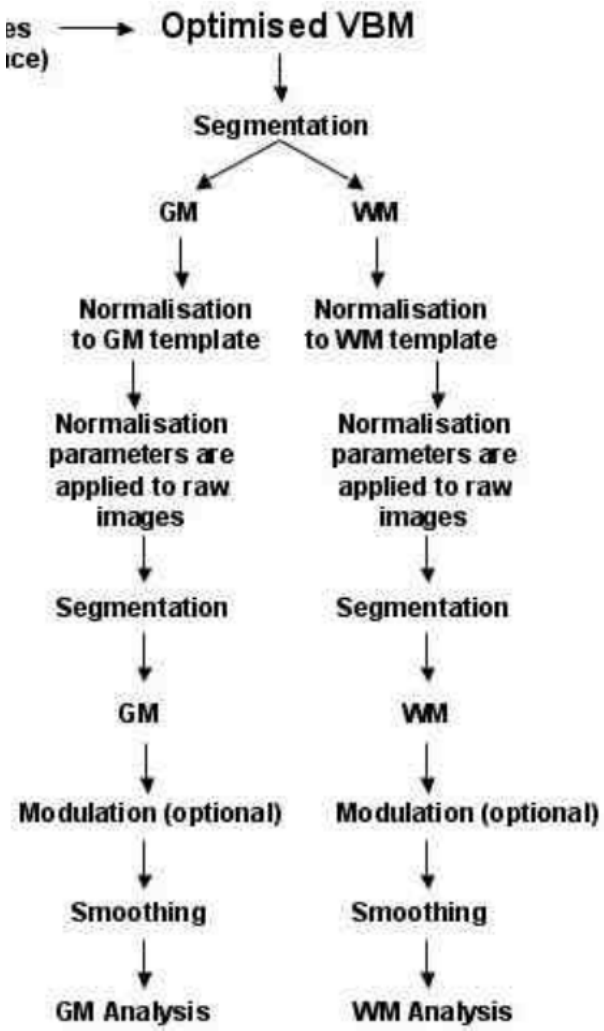


Figure Caption: Reprinted from Mechelli et al. (2005).

### 3.4 ANALYSES

Two different age-based groups of children were examined: a preschool-age group and a school-age group. For these groups, two sets if analyses were run, one with both children who do and do not stutter, and another with only children who stutter to examine the effects of SSI score on gray matter volume. The separate analyses based on smaller, age-restricted samples were conducted to capture any subtle but distinct differences expected to occur within the two developmental periods that may be washed out if combining them into a sample with a wider age range. Specifically, it was expected that any group differences observed in the preschool-age sample would capture early occurring neurostructural differences in young children who stutter that may be linked to structural changes contributing to the onset of stuttering. On the other hand, studying cerebellar morphology of school-age children may elucidate later occurring cerebellar structural differences that may be associated with continued stuttering over several years post-onset, and potentially better reveal bases for persistence and/or compensatory development associated with stuttering.

In both the preschool- and school-age datasets of children, the effect of stuttering status on gray matter volume was examined by a voxel-by-voxel basis throughout the cerebellum using a general linear model in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/) with sex, age, IQ, total cerebellar volume, and maternal education as covariates. These covariates were included to control for potential confounding influence of these variables. Cluster size thresholds were estimated using AFNI 3dClustSim procedures (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html). Several contrasts were computed including persistent and recovered children who stutter combined compared to children who do not stutter, persistent and recovered groups contrasted separately with children who do not

stutter, and the persistent and recovered groups compared to each other. From these voxel-wise analyses, gray matter volume was extracted to complete post hoc region of interest analyses. Proportional gray matter volume was extracted from each individual's smoothed, modulated gray matter segmentation maps by creating a 5mm mask around each significant cluster derived from group analysis. The average gray matter volume from each of the clusters corresponding with the regions of interest were extracted using 3dmaskave (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dmaskave.html). These region of interest data were used to create scatterplots and to perform the post hoc analyses. The first post hoc analyses included independent samples t-tests, which were used to compare gray matter volume between groups. Additionally, different relationships with gray matter volume and age as well as gray matter volume and Stuttering Severity Instrument score (SSI score; Riley 2004) were compared between groups using Pearson correlation.

The preschool-age sample included a total of 57 children who stutter and 59 who do not stutter. A voxel-wise height threshold of $p<.005$, and cluster size $k> 365$, was applied to correct for multiple comparisons, which corresponded to a corrected $p<.05$. Post hoc analyses were completed using the region of interest derived from the voxel-wise analysis. Pearson bivariate correlation analyses were completed between gray matter volume and age within the groups. Whole-cerebellar comparison of gray matter volume between groups was conducted using two-sample t-tests. Bonferroni correction was used to correct for multiple comparisons (0.05/4; $p=0.01$).

In the preschool-age group, a separate general linear model was used to examine the effect of stuttering status, persistent or recovered, and SSI score on gray matter volume in children who stutter. A voxel-wise threshold of $p<.005$, and cluster size $k > 351$, was applied to correct for

multiple comparisons, which corresponded to a corrected p<.05. Post hoc analyses were completed using the region of interest derived from the voxel-wise analysis. Associations between gray matter volume and SSI score were examined separately for persistent (N=41) and recovered (N=16) preschool-age children who stutter. Pearson bivariate correlation analyses were completed between gray matter volume and SSI score within the groups of persistent and recovered children who stutter. Bonferroni correction was used to correct for multiple comparisons (0.05/2; p=0.025).

The next dataset included 72 school-age children who do (N= 37) and do not stutter (N= 35). A general linear model was used to calculate the effect of stuttering status on gray matter volume in school-aged children. Sex, age, IQ, total cerebellar volume, and socio-economic status were used as covariates. Additionally, the effect of stuttering status and age on gray matter volume was also examined using a general linear model with sex, IQ, total cerebellar volume, and socio-economic status as covariates. A voxel-wise threshold of p< .005, and cluster size k > 368, were used to correct for multiple comparisons, which corresponded to a corrected p<.05. Whole-cerebellar comparison of gray matter volume between groups was conducted using two-sample t-tests. Post hoc analyses were completed using the region of interest derived from the voxel-wise analysis. Pearson bivariate correlation analyses were completed between gray matter volume and age within the school-age groups. Bonferroni correction was used to correct for multiple comparisons (0.05/4; p=0.01). Due to the low sample size of recovered school-age children who stutter in this study (N=4), an additional analysis of the effect of stuttering status, persistent or recovered, and SSI score on cerebellar gray matter volume was not conducted.

## 4.0 RESULTS

The current study compared gray matter volume in children who stutter relative to children who do not stutter in preschool-age and school-age groups. It was hypothesized that children who stutter would have lower gray matter volume than children who do not stutter in right lobule VI, and persistent children who stutter will have lower gray matter volume in right lobule VI than children who do not stutter and recovered children who stutter. Older recovered children who stutter were also hypothesized to have greater average gray matter volume in right cerebellar lobules VI and VII compared to persistent children who stutter and children who do not stutter.

## 4.1 MORPHOLOGICAL DIFFERENCES OF THE CEREBELLUM IN CHILDHOOD STUTTERING

### 4.1.1 Children who stutter do not exhibit significant cerebellar gray matter differences from children who do not stutter across different age groups

Regional gray matter volume for each of the 10 cerebellar lobules was calculated across children who stutter, recovered and persistent children who stutter, and children who do not stutter. Gray matter differences across groups were compared separately by age group: Preschool-age and school-age groups.

For the preschool age group, gray matter volume was compared between 116 preschool-aged children who do (N= 57) and do not stutter (N= 59). No significant differences were observed in gray matter volume across the ten cerebellar lobules between children who do or do not stutter in the preschool-age group or between persistent and recovery groups (recovered children who stutter N=16).

For the school age group, gray matter volume was compared between 72 school-age children who stutter (N= 37) and children who do not stutter (N= 35). No significant differences were observed in gray matter volume across the ten cerebellar lobules between children who do or do not stutter in the school-age group. A comparison between persistent and recovery groups was not conducted due to the low sample size of the recovered group (recovered children who stutter N=4).

Overall, these results indicated that there are no significant group differences in overall cerebellar gray matter volume across the 10 lobules of the cerebellum between stuttering and control groups. Furthermore, no significant overall gray matter volume differences were found between children with persistent stuttering versus those who recovered from stuttering.

Additionally, this pattern was consistent across all age-specific datasets: the preschool-age and school-age groups.

## 4.2 MORPHOLOGICAL DIFFERENCES OF THE CEREBELLUM THAT DIFFERENTIATE PERSISTENT AND RECOVERED CHILDREN WHO STUTTER

### 4.2.1 SSI score was associated with gray matter volume in cerebellar right lobule VI in persistent preschool-age children who stutter

Post hoc analyses of examining the relationship between SSI score and gray matter volume were completed after extracting gray matter volume from regions of interests. Preschool-age children who stutter (N=57) exhibited an association between right cerebellar lobule VI and SSI score ($x$= 24.5, $y$= -65.5, $z$= -34.5). These associations between gray matter volume and SSI score were examined in a correlation model of persistent and recovered children who stutter using Pearson bivariate analysis (Table 9). Persistent preschool-age children who stutter (N=41) were found to have a negative association between right cerebellar lobule VI gray matter volume and SSI score. No such significant relationships were found in the recovered stuttering group (Figure 10, Table 8, Table 9).

Table 8: Significant relationships between Stuttering Severity Instrument score and gray matter volume of preschool-aged children who stutter

| **Regions** | **Cluster Size** | **Max *Z*** | **x** | **y** | **z** |
|---|---|---|---|---|---|
| *Persistent children who stutter* | | | | | |
| Right VI | 369 | -3.89 | 24.5 | -65.5 | -34.5 |

Table 9: Relationships between Stuttering Severity Instrument score and gray matter volume of preschool-aged children

| | **Right VI** | |
|---|---|---|
| | ***B*** | ***p*-value** |
| Intercept | -8.888e-02 | 0.34 |
| CWS-R | -7.065e-02 | 0.07 |
| Age | -1.346e-04 | 0.84 |
| SSI | -4.1000e-03 | <.001* |
| SSI x CWS-R | 3.923e-03 | 0.06 |
| CIV | 2.061e-05 | <.001* |
| Sex | -1.779e-02 | 0.14 |
| VIQ | -2.308e-04 | 0.65 |
| Adjusted R-Square | 0.7075 | |
| Model ANOVA | F(7,49)=20.35 (*p*=<.001)* | |

*Note*. The reference group is persistent children who stutter across the model; CWS-R=Recovered children who stutter; CIV= Total cerebellar volume; VIQ= Verbal Intelligence Quotient; SSI= Stuttering Severity Instrument; * indicates statistically significant results

Figure 10: Significant association between the gray matter volume of right cerebellar lobule VI and Stuttering Severity Instrument score in preschool-age persistent children who stutter

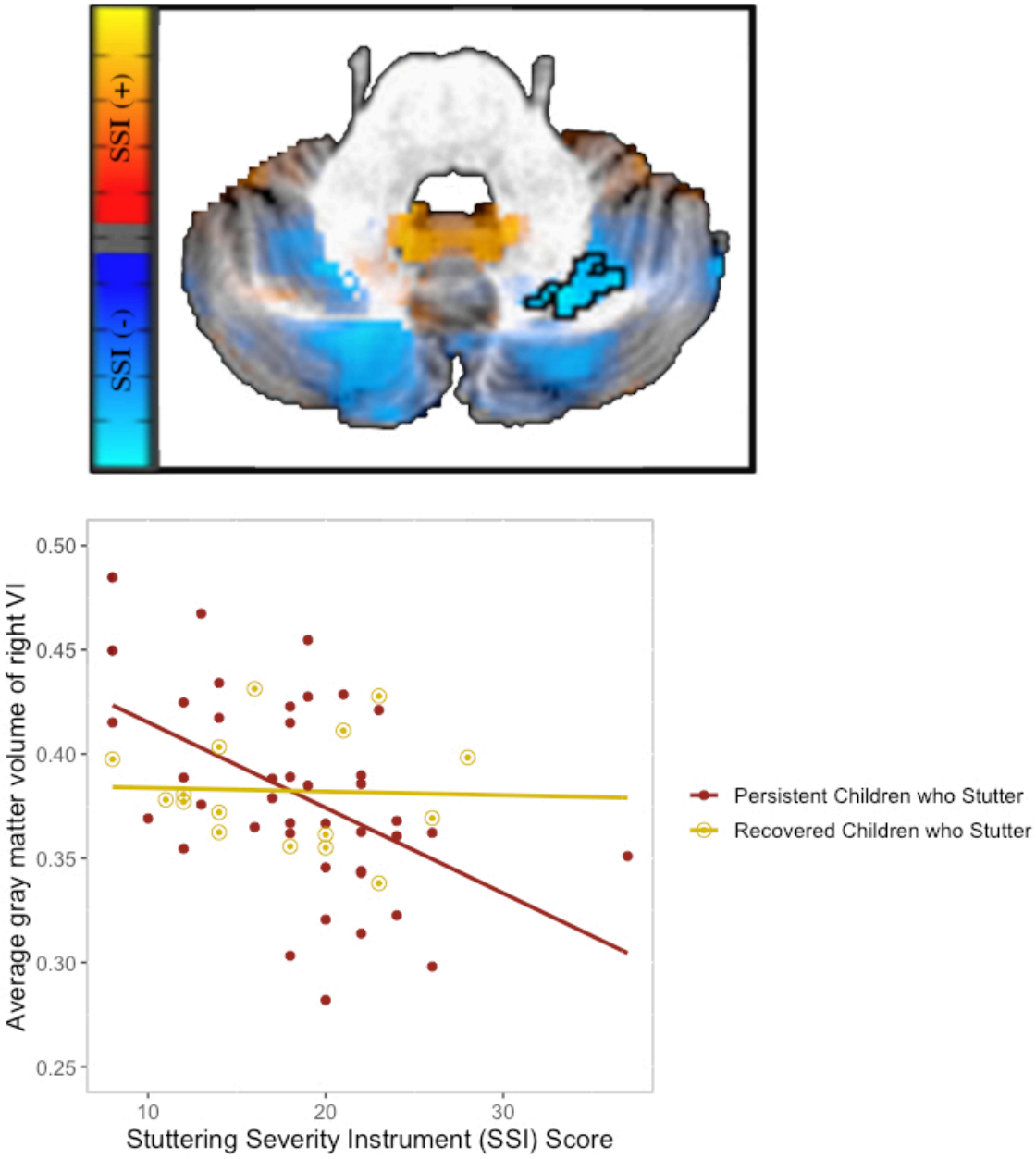


Figure Caption: SSI= Stuttering Severity Instrument score.

## 4.3 AGE-RELATED DIFFERENCES IN CEREBELLAR MORPHOLOGY THAT DIFFERENTIATE CHILDREN WHO STUTTER AND CHILDREN WHO DO NOT STUTTER

It was hypothesized that cross-sectional, age-related differences in gray matter volume in cerebellar lobules right VI and VII would differentiate children who stutter from children who do not stutter and, furthermore, differentiate persistent from recovered children who stutter. Specifically, stuttering children as a group, and persistent children, were hypothesized to exhibit attenuated age related variation of gray matter volume of these lobules compared to children who do not stutter. On the other hand, recovered children who stutter were expected to exhibit greater average gray matter volume in these two lobules particularly in older ages compared to persistent children who stutter and children who do not stutter. The results showed that older recovered children, specifically in the preschool-age group, showed greater average gray matter volume in left lobule VIIb relative to children who do not stutter. The hypothesis that this pattern of gray matter volume results would be associated with right lobule VI was not supported. Instead, the gray matter volume of bilateral lobule VIII was found to be associated with age in children who stutter. In this study, lobules VI, VII, and VIII were significant areas of interest. However, lobule IV was also significantly associated with age. Gray matter in right lobule IV was also associated with age differently in preschool-age children who stutter. These results are expanded upon in the following sections.

4.3.1 In preschool- age, gray matter volume in several cerebellar lobules differentiate children who stutter from children who do not stutter and between persistent and recovered children who stutter

Post hoc analyses of age-related gray matter volume variation were completed after gray matter volume extraction. Preschool-aged children who stutter differed from children who do not stutter in their associations between age and gray matter volume of lobules left VIIIb ($x$= -5.5, $y$= -65.5, $z$= -45) and right IV ($x$= 14, $y$= -46, $z$= -16.5; Table 11). Preschool-age children who stutter showed greater correlation between average gray matter volume and age in left cerebellar lobule VIIIb compared to children who do not stutter (Figure 11, Table 10, Table 11) and an association of lower gray matter volume with older children who stutter in right cerebellar lobule IV compared to children who do not stutter (Figure 12, Table 10, Table 11). Recovered preschool-aged children who stutter had different associations between left VIIb and left VIIIa ($x$= -32.5, $y$= -62.5, $z$= -49.5) and age than children who do not stutter (Table 12). Recovered children who stutter had an association of greater average gray matter volume in older groups of children in left VIIb/VIIIa compared to children who do not stutter (Figure 13, Table 10, Table 12).

Table 10: Significant relationships between age and gray matter volume of preschool-aged children

| **Regions** | **Cluster Size** | **Max *Z*** | **x** | **y** | **z** |
|---|---|---|---|---|---|
| *Children who stutter > Children who do not stutter* | | | | | |
| Left VIIIb | 377 | 3.6 | -5.5 | -65.5 | -45 |
| *Children who stutter < Children who do not stutter* | | | | | |
| Right IV | 373 | -3.49 | 14 | -46 | -16.5 |
| *Recovered children who stutter > Children who do not stutter* | | | | | |
| Left VIIb/ VIIIa | 677 | 3.98 | -32.5 | -62.5 | -49.5 |

Table 11: Relationships between age and gray matter volume of preschool-aged children

| | **Left VIIIb** | | **Right IV** | |
|---|---|---|---|---|
| | ***B*** | ***p*-value** | ***B*** | ***p*-value** |
| Intercept | 4.539e-02 | 0.52 | 1.217e-01 | 0.20 |
| CWS | 1.670e-03 | 0.03 | -1.827e-01 | 0.01 |
| Age | 1.670e-03 | 0.02 | -2.547e-03 | 0.01 |
| Age x CWS | -2.227e-03 | 0.02 | 3.246e-03 | 0.01 |
| CIV | 1.873e-05 | <.001* | 2.456e-05 | <.001* |
| Sex | -1.253e-02 | 0.20 | 8.878e-05 | 0.99 |
| VIQ | -3.629e-04 | 0.29 | -4.771e-04 | 0.31 |
| Adjusted R-Square | 0.586 | | 0.552 | |
| Model ANOVA | F(6,109)=28.13 (*p*=<.001)* | | F(6,109)=24.64 (*p*=<.001)* | |

*Note*. The reference group is children who do not stutter across the model; CWS= children who stutter; CIV= Total cerebellar volume; VIQ= Verbal Intelligence Quotient; * indicates statistically significant results

Table 12: Relationships between age and gray matter volume of preschool-aged children who persist and recover from stuttering

| | **Left VIIb/VIIIa** | |
|---|---|---|
| | ***B*** | ***p*-value** |
| Intercept | 1.966e-01 | 0.13 |
| CWS-P | 1.789e-02 | 0.85 |
| CWS-R | -5.347e-01 | 0.001* |
| Age | -5.309e-04 | 0.64 |
| Age x CWS-P | -5.539e-04 | 0.75 |
| Age x CWS-R | 1.090e-02 | <.001* |
| CIV | 1.935e-05 | <.001* |
| Sex | 2.160e-02 | 0.19 |
| VIQ | -1.746e-04 | 0.76 |
| Adjusted R-Square | 0.394 | |
| Model ANOVA | F(8,107)=10.38 (*p*=<.001)* | |

*Note*. The reference group is children who do not stutter across the model; CWS-P= Persistent children who stutter; CWS-R= Recovered children who stutter; CIV= Total cerebellar volume; VIQ= Verbal Intelligence Quotient; * indicates statistically significant results

Figure 11: Significant group differences between preschool-age children who stutter and children who do not stutter in the association between the gray matter volume of left cerebellar lobule VIIIb and age

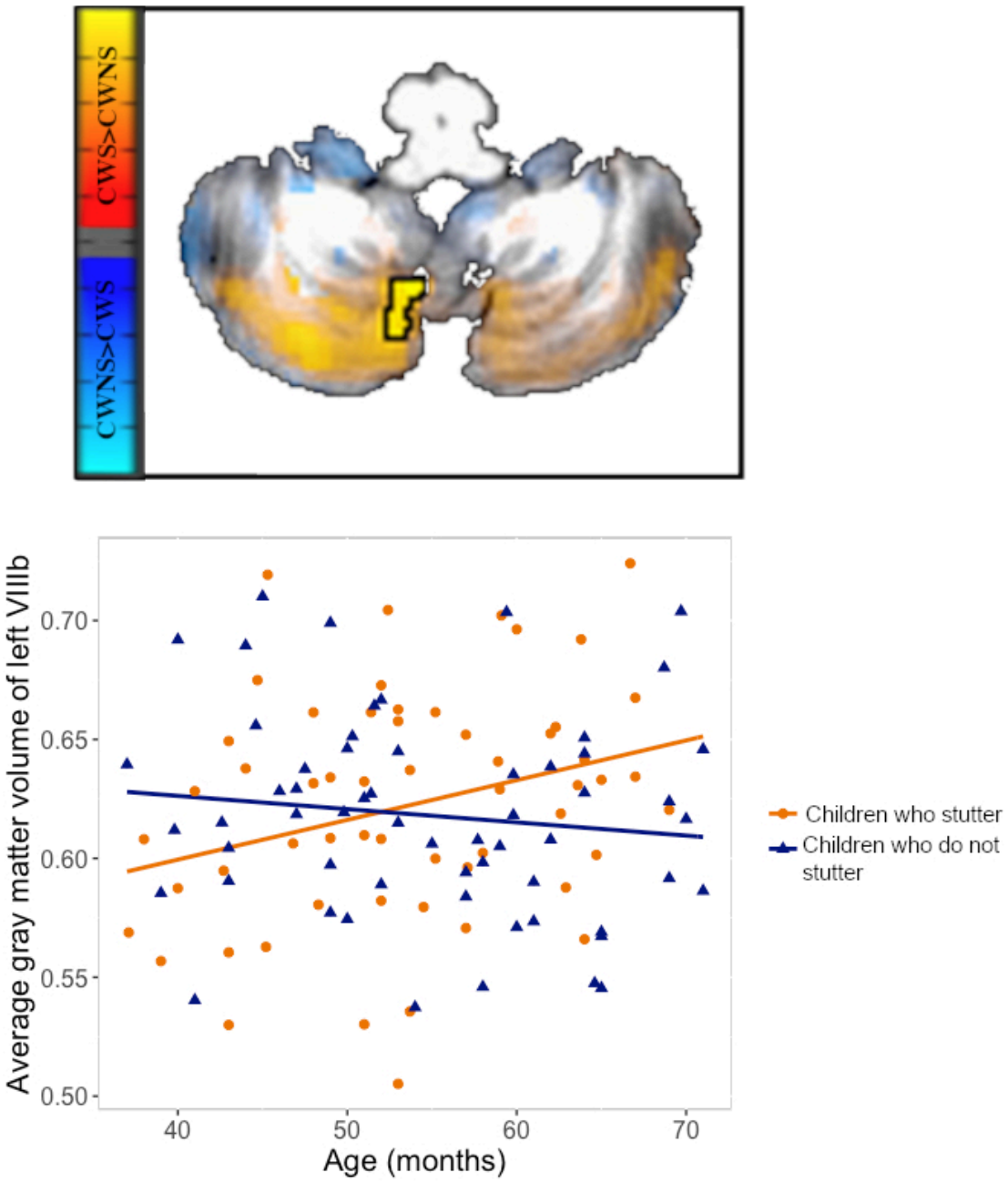


Figure Caption: CWS= children who stutter; CWNS= children who do not stutter

Figure 12: Significant group differences between preschool-age children who stutter and children who do not stutter in the association between the gray matter volume of right cerebellar lobule IV and age

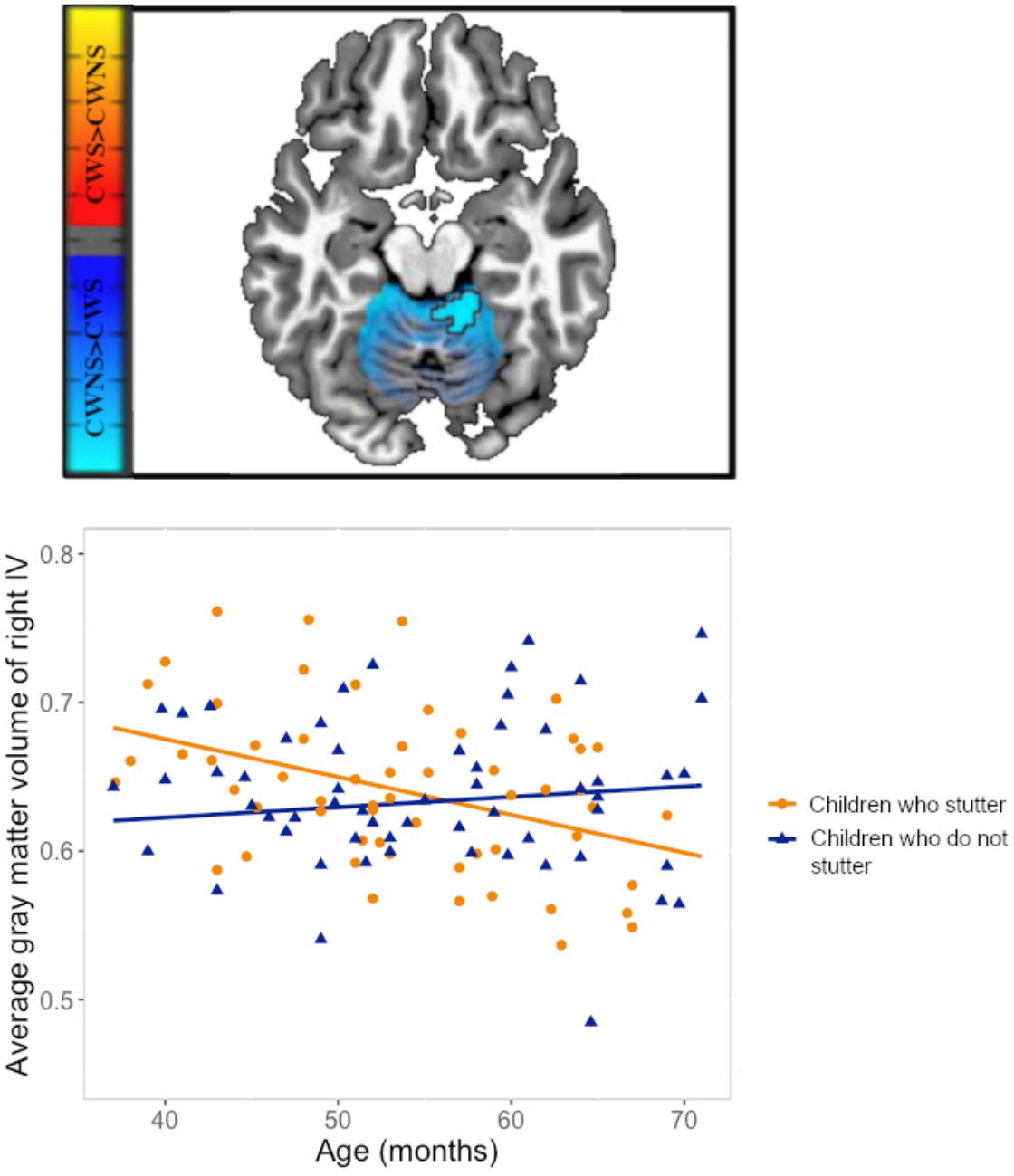


Figure Caption: CWS= children who stutter; CWNS= children who do not stutter

Figure 13: Significant group differences between preschool-age recovered children who stutter and children who do not stutter in the association between the gray matter volume of left cerebellar lobules VIIb/VIIIa and age

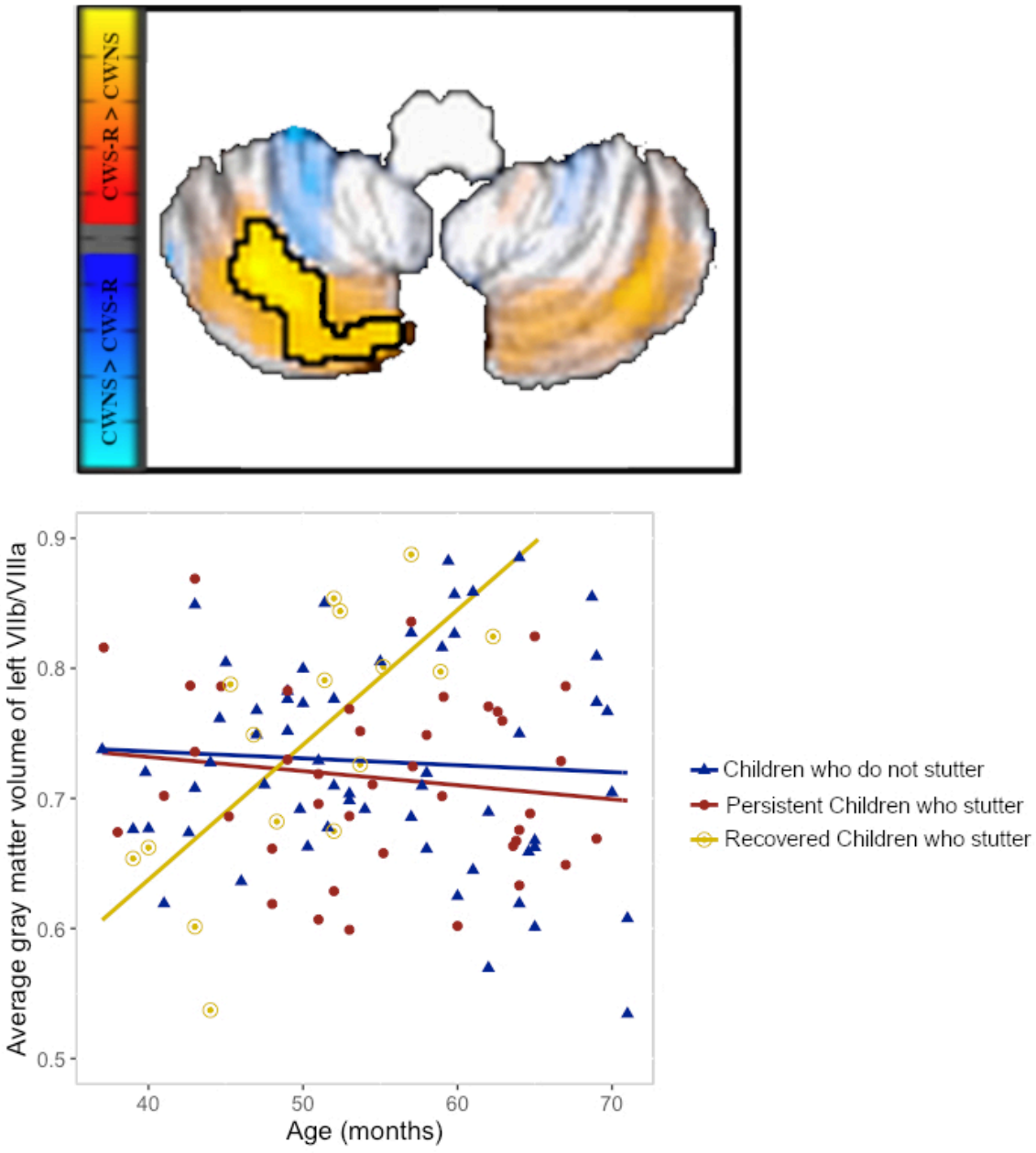


Figure Caption: CWS-R= recovered children who stutter; CWNS= children who do not stutter

4.3.2 In school-age, persistent children who stutter are differentiated from other groups in age-related gray matter volume development

Post hoc analyses of examining the relationship between age and gray matter volume were completed after extracting gray matter volume from regions of interests. School-age children who stutter exhibited different associations between right lobules VIIIa and VIIIb ($x$= 18.5, $y$= 62.5, $z$= -54; Table 13) and age compared to children who do not stutter. There were no significant differences between the groups of children who do and do not stutter, or between persistent and recovery groups. However, there was a significant age association observed in persistent school-age children who stutter (Table 14). Older school-age persistent children who stutter had greater gray matter volume than children who do not stutter in right cerebellar lobules VIIIb and VIIIa (Figure 14, Table 13, Table 14).

Table 13: Significant relationships between age and gray matter volume of school-aged children

| **Regions** | **Cluster Size** | **Max *Z*** | **x** | **y** | **z** |
|---|---|---|---|---|---|
| *Persistent children who stutter > Children who do not stutter* | | | | | |
| Right VIIIb/Right VIIIa | 740 | 4.42 | 18.5 | 62.5 | -54 |

Table 14: Relationships between age and gray matter volume of school-aged children

| | **Right VIIIa/VIIIb** | |
|---|---|---|
| | ***B*** | ***p*-value** |
| Intercept | 3.244e-01 | 0.001* |
| CWS-P | -4.057e-01 | <0.001* |
| CWS-R | -3.650e-01 | 0.18 |
| Age | -2.703e-03 | <.001* |
| Age x CWS-P | 4.531e-03 | <.001* |
| Age x CWS-R | 3.585e-03 | 0.19 |
| CIV | 2.13e-05 | <.001* |
| Sex | 3.258e-02 | 0.07 |
| VIQ | 3.339e-05 | 0.51 |
| Adjusted R-Square | 0.609 | |
| Model ANOVA | F(8,63)=14.86 (*p*=<.001)* | |

*Note*. The reference group is children who do not stutter across the model; CWS-P=persistent children who stutter; CWS-R=recovered children who stutter; CIV= Total cerebellar volume; VIQ= Verbal Intelligence Quotient; * indicates statistically significant results

Figure 14: Significant group differences between school-age persistent children who stutter and children who do not stutter in the association between the gray matter volume of right cerebellar lobules VIIIa/VIIIb and age

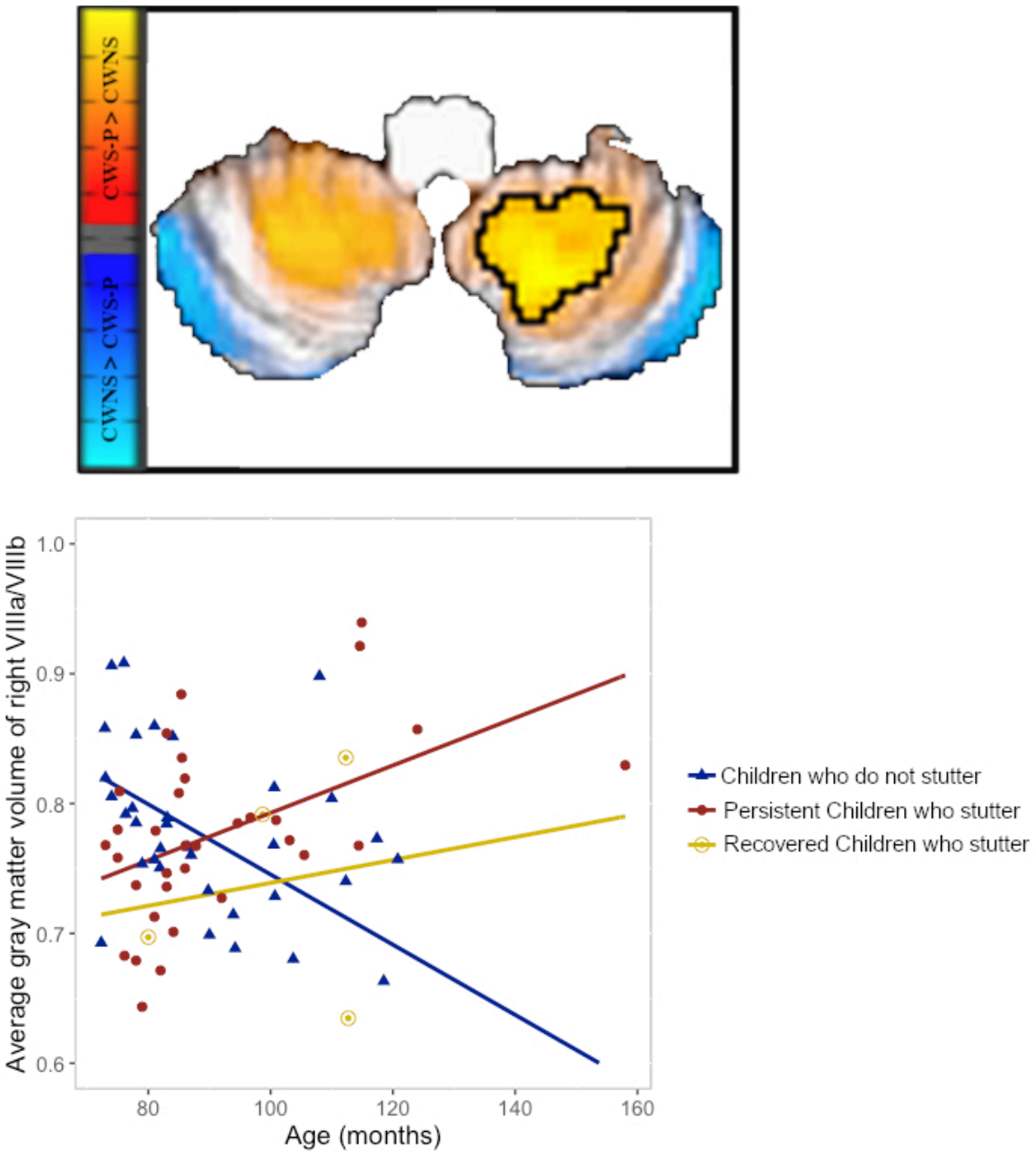


Figure Caption: CWS-P= persistent children who stutter; CWNS= Children who do not stutter

## 5.0 DISCUSSION

The overall aim of this study was to examine how regional gray matter volume of the cerebellum differs in children who stutter compared to children who do not stutter, whether cerebellar gray matter volume differentiates children who eventually persist versus recover from stuttering, and how associations between cerebellar gray matter volume and age differ between the groups. Results reported in this dissertation highlight group differences and age-related associations in gray matter volume that are present specifically in two age ranges: preschool-age and school-age children.

The *first aim* of this study was to compare gray matter volume of the cerebellum between children who stutter and children who do not stutter (Section 5.2). Lobule VI was one of the main regions of interest for this aim among the ten cerebellar lobules. Lobule VI is an area linked to fine-tuning of articulatory control and coordination of speech movements. It is the only cerebellar lobule labeled explicitly in the Directions into Velocities of Articulators (DIVA) model of speech production (Brown et al., 2005; Spencer & Slocomb, 2007; Tourville & Guenther, 2011; Turkeltaub et al., 2002). Additionally, computational simulations of the DIVA model have found that lobule VI supports feedforward control and sensorimotor learning processes (Guenther et al., 2006).

Previous empirical investigations and theoretical perspectives have pointed to differences in sensorimotor learning, mediated by lobule VI, as central to stuttering neurophysiology (Cai et al., 2012, 2014; Daliri & Max, 2018; Kim et al., 2020; Loucks et al., 2012; Sares et al., 2018). Lobule VI is also the most reported cerebellar lobule to differ in structure or function across studies of childhood stuttering (Chang et al., 2015; Chang et al., 2008, 2016; Table 3, 16). Apart from these few exceptions, most cerebellar gray matter morphology data reported in stuttering is from

adults who stutter. From these studies, key cerebellar lobules have been reported to exhibit lower gray matter volume in adults who stutter than children who do not stutter (Beal et al., 2007; Song et al., 2007; see Table 4). While the data available that examines cerebellar gray matter specifically in children who stutter is limited (e.g., Chang et al., 2008; Table 3), this dissertation predicted based on the extant evidence primarily based on adults who stutter; children who stutter would have less gray matter volume than children who do not stutter in the right lobule VI.

The *second aim* of this study was to examine gray matter volume variations in the cerebellum that differentiate persistent and recovered children who stutter (Section 5.3). Previously, the only study of childhood gray matter morphology that included examination of the cerebellum reported that persistent children who stutter had greater gray matter volume in the right lobule VI than recovered children who stutter (Chang et al., 2008). However, the children in this study did not include a preschool-age cohort, and the sample size was small, which limits deriving solid conclusions from the study (see Section 2.4 for a discussion). In addition, several studies of adults who stutter have found that gray matter volume in the cerebellum is lower in adults who stutter than in children who do not stutter (See Table 4). The results of this dissertation did not indicate significant group differences in cerebellar gray matter volume based on contrasts involving either the preschool-age group or school-age group. However, we found that specific cerebellar lobule gray matter volume was significantly correlated with SSI score in preschool-age persistent children who stutter.

The *third aim* of this study was to examine age-related cross-sectional differences in gray matter volume in preschool-aged and school-aged children who do and do not stutter (Section 5.4). Describing how cerebellar gray matter varies in different age groups of children who stutter was expected to provide new insights into how cerebellar function may contribute to differing speech

motor control systems and stuttering frequency at varying stages of the disorder. Cerebellar gray matter changes observed at age ranges relatively close to stuttering onset may provide insights on early age-related differences that lead to persistence or recovery from stuttering. On the other hand, results from school-age children might indicate later variations of cerebellar morphology associated with compensatory processes acquired over years of stuttering that may be linked to continued stuttering since early childhood.

The right lobule VI was a prominent region of interest for this age-related aim. It was hypothesized to develop differently in children who stutter over time compared to children who do not stutter. Along with right lobule VI, lobule VII was also a region of interest, given reports of its morphology differing in people who stutter in previous neurostructural studies (Chang et al., 2008; Chow & Chang, 2017; Song et al., 2007; Watkins et al., 2007), its atypical connectivity with cortical speech motor control areas in developmental stuttering (Chang & Zhu, 2013; Lu et al., 2012), and its associations with rhythm discrimination tasks in children who stutter (Chang et al., 2016).

Additionally, in this dissertation, lobules VI and VII were hypothesized to be critical cerebellar structures that are posited to interconnect the speech sound map (a significant component within the DIVA model that is involved in both feedforward and feedback control pathways localized to the left ventral premotor/inferior frontal cortex) to sensory cortical regions that allow feedback control (see Figure 5). Several behavioral perturbation studies have suggested that the balance between feedback and feedforward control systems is atypical (see Section 5.5.4) in children and adults who stutter (Cai et al., 2012, 2014; Daliri et al., 2017; Daliri & Max, 2018; Kim et al., 2020; Loucks et al., 2012; Sares et al., 2018).

For the above reasons, I posited that gray matter volume in cerebellar lobules VI and VII would differ with age in recovered children who stutter. In this dissertation, I tested the hypothesis that older children who recover would have greater gray matter volume in right lobules VI and VII compared to children who do not stutter and children who stutter that persist into adulthood. While the current study did not find group differences in age-related associations of cerebellar gray matter of lobule VI, gray matter volume of lobules VII and VIII were differently associated with age in preschool- and school-age children who stutter relative to that of children who do not stutter, along with lobule IV of the anterior lobe.

## 5.1 SUMMARY OF MAIN FINDINGS

The current study examined gray matter morphology in children who do and do not stutter between 3-13 years. Separate analyses were conducted in sub-cohorts comprising preschool-age (3–5-year-olds) and school-age (6–13-year-olds) children. Findings from this investigation do not support the hypothesis that regional cerebellar gray matter volume differs significantly between children who do and do not stutter (*Aim 1*). In addition, the results also did not support the hypothesis that there are significant differences in cerebellar gray matter volume between persistent and recovered children who stutter (*Aim 2*). However, a negative relationship between stuttering severity (SSI score) and gray matter volume was observed in persistent preschool-age children who stutter. In addition, age-related gray matter volume differences of the left VIIIb and right IV were found in preschool-age children who stutter and children who do not stutter (*Aim 3*). Lastly, older recovered preschool-age children had greater gray matter volume in lobules left VIIb/VIIIa with age than children who do not stutter. In the school-age group, older persistent children who stutter had greater gray matter volume than children who do not stutter in right lobules VIIIa and VIIIb.

Table 15: Summary of findings by cerebellar lobules pertinent to each study aim

| | IV | VI | VIIb | VIIIa | VIIIb |
|---|---|---|---|---|---|
| **Aim 1: Differences between CWS and CWNS** | No significant differences | | | | |
| **Aim 2: Differences between pCWS and rCWS** | | Preschool: Sig corr (-) with SSI in pCWS (Right) | | | |
| **Aim 3: Age-related differences among groups** | Preschool: CWS<CWNS w/age (Right) | | Preschool: rCWS>CWNS w/age (Left) | Preschool: rCWS> CWNS w/age (Left) | |
| | | | | School-age: pCWS>CWNS w/age (Right) | Preschool: CWS>CWNS w/ age (Left)<br><br>School-age: pCWS > CWNS w/ Age (Right) |

*Note*. Dark grey boxes indicate findings associated with feedforward control. White boxes indicate findings associated with feedback control. Light grey boxes indicate findings that may be associated with both feedforward and feedback control. Corr= correlation; CWS= Children who stutter; CWNS= Children who do not stutter; pCWS =Persistent children who stutter; rCWS = Recovered children who stutter.

Table 16: Summary of functional and structural neuroimaging findings involving people who stutter reporting differences in the cerebellar lobules that were also found in the current study

| | | |
|---|---|---|
| IV | Left | Dis(Braun et al., 1997)* |
| | Right | Speech(Brown et al., 2005) [1]<br><br>Dis(Braun et al., 1997)* |
| VI | Left | Speech(Brown et al., 2005; Chang et al., 2009; De Nil et al., 2003; Lu et al., 2009)<br><br>Speech(Brown et al., 2005)*<br><br>Speech Planning(Chang et al., 2009)<br><br>Trait(Connally et al., 2018)<br><br>Resting(Ingham et al., 2012)<br><br>Dis(Fox et al., 2000; Ingham et al., 2012; Lu et al., 2012; Wymbs et al., 2013) |
| | Right | **Rhythm(Chang et al., 2009)**<br><br>Speech(Brown et al., 2005; De Nil et al., 2003; Lu, Chen, et al., 2010; Lu et al., 2009)<br><br>Speech Perception(Chang et al., 2009)<br><br>Resting(Ingham et al., 2012)<br><br>Dis(Fox et al., 2000; Ingham et al., 2012) |
| VIIb | Left | Trait(Connally et al., 2018) |
| | Right | Dis(Ingham et al., 2012) |
| VIIIa | Left | Trait(Connally et al., 2018)<br><br>Speech(Watkins et al., 2008) |
| | Right | Speech(Watkins et al., 2008) |
| VIIIb | Left | |
| | Right | Trait(Connally et al., 2018) |

*Note.* Bolded text indicates findings in children who stutter. Dis= Active during disfluencies in speech or associated with stuttering severity/ rate; *=Vermal area; 1= Lobules III and IV;

Table 16 (cont'd)

Speech= Speech production task (covert or overt); Resting= Resting measurements; Trait= Speech without disfluencies

The findings reported in this dissertation bolsters the idea that anomalous structure of areas of the cerebellum that support functions that can be attributed to specific cerebellar pathways of the Directions into Velocities of Articulators (DIVA) model is associated with developmental stuttering. These variations could lead to atypical feedback and feedforward speech motor control which may be associated with the observed neuroanatomical changes related to childhood stuttering. Below, an argument is made regarding which cerebellar pathways of the DIVA model may be involved in the onset of developmental stuttering (see Figure 5) and which cerebellar areas related to age in distinct periods are linked to persistence and recovery of developmental stuttering.

Specifically, the main results reported in this dissertation show that children who do and do not stutter did not exhibit significant differences in regional cerebellar gray matter volume. The results of this dissertation instead support the claim that the cerebellum is part of larger neurological systems of stuttering due to its variation over age in specific periods of childhood stuttering (Section 5.2). For example, gray matter volume of cerebellar areas likely involved in both feedback control and feedforward control functions of the DIVA model were shown to develop differently with age in groups of children who stutter relative to children who do not stutter (Section 5.4). The results also back the argument that gray matter volume of cerebellar areas associated with pathways in the feedforward control system of the DIVA model are linked to SSI score (Section 5.3). Finally, these findings are discussed in the context of several prominent stuttering theories (Section 5.5).

## 5.2 MORPHOLOGICAL DIFFERENCES OF THE CEREBELLUM IN CHILDHOOD STUTTERING

### 5.2.1 Children who stutter and children who do not stutter exhibit comparable cerebellar gray matter volume

The results from the cross-sectional dataset that encompassed both preschool- and school-age children suggest that cerebellar gray matter morphology variations are associated with specific periods of development of children who stutter. Namely, a consistent pattern of volume difference between children who do and do not stutter was not seen in both preschool- and school-age children who stutter. For example, in this study, one cerebellar lobule did not always have lower volume in preschool- and school-age children who stutter than children who do not stutter. Overall, the results did not support the hypothesis that gray matter volume differs significantly between children who stutter and children who do not stutter in the hypothesized cerebellar lobule VI.

When examining preschool-age children separately, cerebellar gray matter volume differences with age and SSI score are associated with childhood stuttering (see Sections 5.3 and 5.4). These results suggest that atypical structure of the cerebellum may not be a primary difference related to stuttering. Instead, the cerebellum may be involved in developmental changes triggered by initial changes in other brain areas. These cerebellar changes may aid larger patterns that lead to stuttering persistence or differing developmental outcomes (for a discussion, see Chang & Guenther, 2020). This interpretation may mean that differences in the cerebellum alone are insufficient to lead to developmental stuttering. Still, the cerebellum could be involved with developmental patterns that begin very early in children who stutter and participate in networks of brain areas to produce the condition of developmental stuttering, such as feedforward and feedback

control pathways from the DIVA model. Additionally, these data suggest that cerebellar anatomy is associated with structural differences that lead to variations in stuttering frequency.

The cerebellum is a hub area of the brain that participates in closed-loop circuits, where connectivity is reciprocal with nearly every area of the cerebrum (for a discussion, see Bostan et al., 2013; Bostan et al., 2010; Bostan & Strick, 2010). Because of the connectivity with many cerebral areas, it has been predicted that the cerebellum can influence the development of many cortical systems (for a discussion, see Wang et al., 2014). These cortical areas may, in turn, affect the development and function of the cerebellum (for a discussion, see Caligiore et al., 2017; Kishore et al., 2014). Interestingly, most structural cerebellar findings in children who stutter are associated with white matter microstructure (see Table 3). Cerebellar white matter, such as the peduncles or areas surrounding deep cerebellar nuclei, are primarily afferent and efferent tracts carrying signals traveling to and from the cerebellum. Therefore, differences in white matter areas of the cerebellum could mean that signals leading to and from the cerebellum are more likely related to the functional differences seen in developmental stuttering.

Extended findings in white matter areas of the cerebellum in adults who stutter could indicate that signal disruptions from other cortical areas are core to cerebellar stuttering neurophysiological patterns. The findings from this study do not include significant group differences in gray matter but associations with age, suggesting that the cerebellum may not play a part in the initial neurostructural differences that lead to developmental stuttering. However, this does not mean that the cerebellum is not involved in neural circuits near the onset of stuttering. While the cerebellum is likely affected by a larger, dynamic system to produce the condition of stuttering, age-related differences occurring in the cerebellum at the earliest stages (captured via the youngest, preschool-age group) differentiated children who stutter from children who do not

stutter (Table 10). Therefore, the cerebellum appears to be a vital, albeit not the primary, structure relevant to developmental patterns close to stuttering onset.

Currently, stuttering theories centered around speech motor control support the idea that differences in cerebellar function or anatomy may not be sufficient to cause the condition. Many accounts predict that internal timing systems within the basal ganglia and supplementary motor area are central to developmental stuttering (Alm, 2004; Chang & Guenther, 2020; Etchell et al., 2014). Researchers have proposed that heightened involvement of the cerebellum may be a compensatory mechanism to ameliorate any aberrant activity of internal timing systems supported by the basal ganglia-thalamocortical network. For example, several studies posit that external timing rhythm processing supported by the cerebellum may compensate for the primary divergent development within the internal timing system in stuttering (see Section 5.3.1 for a further discussion). Again, the lack of group differences in this study supports claims like the above and are discussed in further detail below in the context of specific stuttering theories (see Section 5.4).

## 5.3 MORPHOLOGICAL DIFFERENCES OF THE CEREBELLUM THAT DIFFERENTIATE PERSISTENT AND RECOVERED CHILDREN WHO STUTTER

### 5.3.1 Relationship between SSI score and cerebellar gray matter volume differentiates children who stutter who persist and recover from stuttering

The results reported in this dissertation did not support significant group differences in cerebellar gray matter associated with persistence or recovery from stuttering. However, there were associations between the gray matter volume of specific cerebellar lobules and age (discussed in Section 5.4) as well as with SSI score that differentiated persistent preschool-age children who stutter (Table 15). This evidence suggests that areas of the cerebellum that support feedforward control functions attributed to specific pathways of speech motor control differ over time in children who stutter. Additionally, gray matter volume of lobule VI, a cerebellar substrate of feedforward control, differs in its relationship to SSI score for persistent children who stutter .

Overall, these results support the predictions based on the DIVA model, where projections from the left ventral premotor cortex in the feedforward control pathway that includes the cerebellum as an intermediary structure, play a role in the neurostructural bases of developmental stuttering. The cerebellar pathways, however, not only encompass those that interconnect the ventral premotor cortex and motor cortex via the cerebellum and other subcortical structures within the feedforward control system (Figure 5a) but also include those that interconnect the auditory and somatosensory cortices with motor cortical areas that originate in the ventral premotor cortex and lead to the feedback control pathway (Figure 5c, 5d). Below, I posit that differences in these cerebellar pathways could support external timing mechanisms or error monitoring that modulate the frequency of stuttering in people who stutter (Section 5.3.1.1). In later sections of this dissertation, age-related gray matter volume associations of cerebellar lobules more directly linked

to feedback control functions were those that differentiated preschool-age children who stutter and persistent school-age children who stutter from children who do not stutter (Section 5.4).

5.3.1.1 Cerebellar pathways linked to the feedforward control system are associated with SSI score

In preschool-age persistent children who stutter, right cerebellar lobule VI gray matter volume was negatively correlated with SSI scores (Figure 10, Table 8). As stated previously, lobule VI is essential for feedforward control (Guenther et al., 2006). Across studies of stuttering neurophysiology, cerebellar lobule VI is most often connected to stuttering (see Table 3, 4, 16). Cerebellar lobule VI supports feedforward projections that control coarticulation and the smooth production of speech movements (Brown et al., 2005; Spencer & Slocomb, 2007; Tourville & Guenther, 2011; Turkeltaub et al., 2002). An association of gray matter volume with SSI score in right cerebellar lobule VI may reflect greater involvement of several cerebellar pathways that originate in the feedforward control system or support feedforward control, leading to decreased stuttering.

In this dissertation, I proposed that atypical morphology in lobule VI could be involved in three different pathways in the DIVA model (see Figure 5; Section 2.2). The pathways of the DIVA model that include lobule VI all involve the left ventral premotor cortex that houses internal models in the feedforward control system (see Figure 5a, 5c, 5d). The first concerns projections within the feedforward system (Figure 5a), and the last two are in pathways that project from the ventral premotor cortex to the feedback control system (Figure 5c, 5d). The first pathway is within the feedforward subsystem (see Figure 5a). This projection in the feedforward system works to update internal model information based on the current state of the system (reviewed in Section 1.0.1).

Variations in the feedforward control system are often marked as the primary element that leads to developmental stuttering (for a review, see Bradshaw et al., 2021).

Feedforward control houses networks that support internal timing. Specifically, researchers have posited that internal timing systems that support rhythm processing differ in people who stutter, leading to disfluencies. For example, children who stutter have been found to have altered rhythm discrimination abilities compared to children who do not stutter (Chang et al., 2016; Wieland et al., 2015). One way the cerebellum may play a part in the production or reduction of disfluencies is through rhythm and external timing processes in the feedforward control pathway. This idea is a well-accepted theory involving cerebellar functioning in stuttering (for a discussion, see Chang et al., 2019).

The internal timing network in the feedforward control system involves the basal ganglia, posited to be a critical substrate in developmental stuttering (See Section 5.5; for a review, see Chang & Guenther, 2020; Kotz et al., 2009; Tourville & Guenther, 2011). Growing evidence suggests that a network involving the cerebellum, supplementary motor area, and thalamus is used in response to atypical functioning within the basal ganglia circuit (Kotz et al., 2009). Cerebellar lobule VI has also been shown to have atypical connectivity with internal timing structures (Chang & Zhu, 2013). This evidence supports the idea that the cerebellum responds to functional differences in internal timing circuits. Connectivity between initiation circuit areas, such as the supplementary motor area, and cerebellar lobule VI could suggest that cerebellar networks are being recruited differently in people who stutter because of aberrant basal ganglia functioning (e.g., Chang & Zhu, 2013). Notably, it has also been proposed that a cerebellar-lateral premotor connection may compensate for atypical internal timing supported by basal ganglia circuitry (Alm, 2004).

It is well-established that externally driven sources of rhythm decrease the frequency of stuttering in people who stutter—for example, talking synchronously with a metronome is widely known to reduce the frequency of stuttering in people who stutter. The negative relationship between SSI score and gray matter volume in preschool-age persistent children who stutter in this dissertation may indicate a greater reliance on externally driven neural systems that involve the cerebellum. This pattern may indicate that feedforward control pathways that involve the cerebellum are associated with mechanisms that mediate the frequency of disfluencies, specifically in children who stutter that do not recover in childhood.

However, the function of cerebellar externally driven timing in stuttering frequency and persistence and recovery is still debatable. As Chang et al. (2019) argue, it may be that externally driven timing systems of the cerebellum are insufficient to rectify anomalous internal timing in feedforward control in developmental stuttering to support recovery. This theory may also explain why increased activity in cerebellar lobule VI has been associated with decreased rhythm discrimination performance in children who stutter (Chang et al., 2016), and circuits within the feedforward system, including the cerebellum, were associated with atypical planning and production processing in adults who stutter (Lu et al., 2010). Additionally, decreased cerebellar activity corresponded with completing stuttering therapy in adults who stutter but not overall recovery from stuttering (De Nil et al., 2001). This evidence indicates that the connection between SSI score and gray matter volume in the cerebellum in this study is not enough to decrease stuttering levels for recovery from stuttering but could be generally associated with the frequency of stuttering in persistent people who stutter. It may be that an increase in cerebellar activity is not enough to modify functional differences of other circuits in the brain working atypically in people who stutter. The lack of significant cerebellar gray matter volume group differences between

recovered and persistent children who stutter in the current investigation also supports this conclusion.

The last two projections leave the speech sound map and connect to sensory cortical areas. These areas include the auditory and somatosensory target maps that help the feedback control system detect timing errors from sensory feedback (see Figures 5c, 5d). The cerebellum is essential for detecting the sensory consequences of speech as part of this pathway. Specifically, this dissertation predicted that lobules VI and VII are part of the projections from the ventral premotor cortex to the auditory and somatosensory target maps. This is because the projections from the ventral premotor cortex to the auditory and somatosensory target map cancel out signals from the auditory or somatosensory error maps if the sensory feedback from speech is within an acceptable range (see Guenther, 2016, pages 164-165). Lobules VI and VII have been associated with this process (e.g., Kilteni & Ehrsson, 2020). In this way, the feedback control pathway actively monitors speech feedback to detect errors, and the findings in lobule VI may be relevant to this process.

Interestingly, many stuttering theories predict that people who stutter have different error detection or monitoring abilities compared to people who do not stutter. For example, the *Vicious Cycle Hypothesis* (Vasic & Wijnen, 2005) predicts that people who stutter over-monitor their speech plans, resulting in needless over-modification of motor plans to bring about stuttering. Differences in error signaling in this pathway of the DIVA model (Figure 5c, 5d) may also contribute to speech monitoring differences in people who stutter, such as those described in the *Vicious Cycle Hypothesis*. For example, perhaps the method of correction, an overly active error signal from error maps in the DIVA model, leads to disfluencies.

Several experiments involving “fluency-inducing” conditions (e.g., metronome timed speech, choral speech) have been shown to heighten activity in the auditory cortex in people who stutter, which may represent activity fluctuations in the auditory target or auditory error maps of the DIVA model (Toyomura et al., 2011). These strategies rely on manipulating auditory feedback during ongoing speech production. For example, playing a masking noise during speech, shifting the frequency of feedback, or delaying auditory feedback from speech has been used to reduce stuttering (e.g., Foundas et al., 2013; Ingham et al., 2012; Kalinowski et al., 1993; van de Vorst & Gracco, 2017), and also heightens the lower-than-average activity of the auditory cortex in people who stutter (Braun et al., 1997; Fox et al., 1996; Toyomura et al., 2011, 2020). Across the stuttering literature, this pathway is posited to be a critical variation that leads to stuttering (e.g., Beal et al., 2011; Brown et al., 2005; Budde et al., 2014), and the above studies all point to the feedback control pathway's involvement in the stuttering frequency.

Specifically, altering the sensory feedback from speech could mean that error monitoring is also manipulated in people who stutter to decrease disfluencies. If, as predicted by this dissertation, lobule VI is involved in projections to the feedback control pathway that help detect errors in speech feedback, lobule VI could be involved in the compensation response provided by auditory manipulation strategies in developmental stuttering. This explanation may also lead to the association between gray matter volume in lobule VI and SSI score in this study.

The association of lobule VI gray matter volume and SSI score in children who stutter was posited to be involved in pathways that support external timing processes (Figure 5a) or those involved in error monitoring and detection (Figure 5c, 5d). All these functions are associated with projections from the ventral premotor cortex. Greater gray matter volume in the right lobule VI was associated with less severe stuttering among persistent preschool-age children who stutter.

This result indicates that greater gray matter volume in this cerebellar lobule may modulate SSI score in children who do not recover. Due to no significant group differences in this area, however, it does not seem to be a primary structure involved in contributing to persistence or recovery from stuttering.

## 5.4 AGE-RELATED DIFFERENCES IN CEREBELLAR MORPHOLOGY THAT DIFFERENTIATE CHILDREN WHO STUTTER AND CHILDREN WHO DO NOT STUTTER

### 5.4.1 Summary of age-related findings

This dissertation used cross-sectional analyses to examine age x group effects in preschool- and school-age children who stutter. Results from these analyses were performed to determine how age-related variation of cerebellar volume differs close to stuttering onset in preschool years and after stuttering for some time in school-age children. The results did not support the hypothesis that children who recover from stuttering exhibit significantly greater age-related gray matter volume differences in right lobules VI and VII compared to children who do not stutter and persistent children who stutter.

In the preschool-age group of children who stutter, age x group interactions were found in left VIIIb (Figure 11), right IV (Figure 12), and left VIIb/VIIIa (Figure 13; Table 11; Table 12). These results indicate that cerebellar lobules associated with functions related to feedforward and feedback control vary differently by age in preschool-aged children who stutter compared to children who do not stutter. In the school-age group of children who stutter, persistent children who stutter had greater age-related gray matter volume variation than children who do not stutter in right cerebellar lobules VIIIb/VIIIa (Figure 14; Table 14). I argue that the results from school-age children who stutter indicate that cerebellar feedforward and feedback control pathways differ most significantly in older children who stutter compared to older children who do not stutter.

5.4.2 In preschool-age children, the development of cerebellar lobules IV and VIIIb differentiated children who stutter from children who do not stutter, and lobules VIIb/VIIIa differentiated persistent children who stutter from children who do not stutter

The findings in preschool-age children who stutter highlight that cerebellar substrates of feedback as well as feedforward control functions differ with age. Specifically, it was posited previously that lobule VIIIb is associated with inverse modeling in the feedback control pathway, lobule IV may be associated with motor responses during feedforward control, and lobules VIIb/VIIIa support cognitive control functions subserving feedforward control.

First, older preschool-age children who stutter had *greater* gray matter volume than older children who do not stutter in the left cerebellar lobule VIIIb (Figure 11, Table 10). Lobule VIIIb exhibits greater activity during jaw perturbation trials (e.g., Golfinopoulos et al., 2011), indicating that this lobule is involved in processes that update corrective motor commands using inverse models (see Figure 5b; Table 1) in the feedback control system of speech. This result may suggest that inverse modeling processing in the feedback control system differs with age in the early stages of stuttering in children who stutter. Age-related differences in lobule VIIIb in children who stutter, especially those close to stuttering onset in the preschool period, could have an impact on the development of inverse model processing compared to that of typical children during this sensitive developmental period in children who stutter.

Second, older preschool-age children who stutter exhibited *decreased* gray matter volume than older children who do not stutter in the right cerebellar lobule IV (Figure 12; Table 10), which was an unexpected finding. Superior, anterior areas of the cerebellum, which may include lobule IV, have been associated with feedforward control (for a review of lobule IV functions, see Section 2.2.2; Tourville & Guenther, 2011). While this dissertation focused on lobule VI's role in

feedforward control, lobule IV may interact with lobule VI to support feedforward control and contribute to distinct feedforward control functions. For example, lobule IV has been shown to have robust connectivity with lobule VI of the cerebellum, which has been officially connected to feedforward control functions (Bernard et al., 2012). Finally, lobule IV has been shown to have connections to the motor cortex along with lobule VI as well (Hoover & Strick, 1999; Kelly & Strick, 2003).

Unlike lobule VI, which has been connected to error-based learning (for a review, see Section 1.0.2, 2.1.2, 2.3.1), and whose activity decreases over time during motor-learning trials (e.g., Doyon et al., 2002; Imamizu et al., 2000; Lehericy et al., 2005), lobule IV activity remains consistent and is associated with motor execution regardless of the stage of learning across practice trials (Lehericy et al., 2005). Lobule IV has also been associated with the speech and accuracy of motor execution during learning tasks (Lehericy et al., 2005). These studies show that lobule IV supports timely and accurately planned movements and may support non-learning functions of feedforward control, in contrast with lobule VI. Thus, the results showing less gray matter volume in lobule IV in older ages compared to children who stutter may suggest aberrant development of motor control functions in the feedforward control pathway in children who stutter.

Another age x group result in preschool-age children who stutter was observed in lobules VIIb and VIIIa, which may indicate that cognitive functions that bolster feedforward control differ with age to support recovery from stuttering. Older recovered preschool-age children who stutter had *greater* gray matter volume in left lobules VIIb and VIIIa than older children who do not stutter (Figure 13, Table 10). While VIIIa is sometimes connected to sensorimotor functions (Golfinopoulos et al., 2011; Guenther, 2016; Tourville et al., 2008), it is also recruited for cognitive functions, especially with lobule VIIb (Stoodley, 2012; Stoodley et al., 2012). Lobules VIIb and

VIIIa often coactivate to support linguistic tasks such as verbal working memory (Chen & Desmond, 2005), verb activation (Stoodley, 2012; Stoodley et al., 2012), semantic fluency (Grogan et al., 2009; Nagels et al., 2012), phonemic fluency (Grogan et al., 2009), receptive vocabulary (Can et al., 2013), and expressive vocabulary (Moore et al., 2017).

Differences in VIIb/VIIIa may also indicate atypical executive functioning processes that support motor control. For example, lobules VIIb and VIIIa also support top-down attentional control via the dorsal attention network (for further discussion, see Section 5.4.1.3 below; Habas, 2021), which is important for verbal working memory (Bohland & Guenther, 2006; Brissenden & Somers, 2019; Chen & Desmond, 2005; Desmond et al., 1997; Marvel & Desmond, 2010). In addition, verbal working memory abilities support speech motor control by supplying feedforward pathways with planned motor programs (Bohland et al., 2010). The findings from this dissertation involving greater gray matter volume increases with age in VIIb/VIIIa could indicate variable verbal working memory processing with age in recovered preschool-age children who stutter. Potentially, recovered children who stutter strengthen their capabilities to plan motor gestures that support feedforward control as part of recovery in childhood.

In conclusion, preschool-age age x group results indicate that morphology of cerebellar structures linked to both feedback and feedforward control may vary differently with age within this early period in young children who stutter. For example, a key cerebellar substrate for inverse modeling in the feedback control system, lobule VIIIb, showed greater gray matter volume in older children who stutter relative to older children who do not stutter. Additionally, three cerebellar lobules necessary for feedforward control functions, lobules IV and VIIb/VIIIa, were also associated with age differently in preschool children who stutter. This may also indicate that motor

execution and cognitive support for feedforward control planning differ with age in the early stages of developmental stuttering.

5.4.3 In school-age, persistent children who stutter are differentiated from other groups in age-related gray matter volume development

Similar to what was seen in the preschool-age sample, in this school-age sample, the gray matter volume of lobule VIII varied differently with age in children who stutter relative to children who do not stutter. Here the age x group interaction was specific to persistent children who stutter. Persistent school-age children who stutter exhibited *greater* gray matter volume than children who do not stutter in right cerebellar lobules VIIIb and VIIIa (Figure 14; Table 14), particularly at older ages. While the distinct functional roles of VIIIa and VIIIb are still not well-understood (for a review, see Section 2.2), lobule VIII itself is typically connected to motor control (for a review, see Section 2.1.3, 2.2; see also, Table 2). In addition, several cognitive tasks have been linked to VIIIa. As reviewed in Section 5.4.1.2, lobule VIIIa has been attributed to several cognitive-linguistic functions and top-down attentional control in the dorsal attention network (Habas, 2021). As previously mentioned, lobules VIIIa/VIIIb may contribute to feedback control processes associated with motor control functions. In contrast, lobule VIIIa is connected to executive functioning that may contribute to mitigating atypical feedforward control in developmental stuttering.

Lobule VIIIb is considered to have reciprocal connections with the somatomotor networks in the cerebrum. Thus, it is often considered a more motor-focused structure than lobule VIIIa, which has often been linked to cognitive tasks (Buckner et al., 2011; Stoodley & Schmahmann, 2009). That said, speech perturbation studies have found that activity in both VIIIa and VIIIb are

associated with performing corrective motor responses due to altered auditory or somatosensory feedback (Golfinopoulos et al., 2011; Tourville et al., 2008). Whether differences in VIIIa and VIIIb are associated with motor control or potentially some of the cognitive aspects of VIIIa in these data is difficult to interpret with the available evidence.

However, the inclusion of both VIIIa/VIIIb in association with persistent school-age developmental stuttering does suggest that areas of the cerebellum associated with corrective motor responses in the feedback control pathway have different age-related variation in this group (e.g., both lobules are associated with perturbation studies; Golfinopoulos et al., 2011; Tourville et al., 2008). Additionally, this result is complementary to the age-related results in lobules VIIIa and VIIIb in preschool-age children who stutter (Section 5.4.1.2). The pattern of results between these two groups of children who stutter has important implications for how feedback control differs in different ages of children who stutter with different recovery statuses (for a discussion, see Section 5.5.2).

Additionally, the age x group findings in school-age children who stutter could implicate feedforward control functions. Specifically, the result of different age-related gray matter volume variation in the right VIIIa in school-age persistent children who stutter, and in the left VIIIa in recovered preschool-age children who stutter compared to children who do not stutter, may also suggest that cerebellar structures involved in attentional control are relevant to recovery or persistence from stuttering. Many studies associating attentional control with developmental stuttering align with this idea (for a review, see Ofoe et al., 2018). However, attention's role in stuttering recovery outcomes is still unclear. Notably, an imbalance between the connectivity of the dorsal attention network and the speech motor control network, the somatomotor network, has been associated with developmental stuttering, regardless of recovery (Chang et al., 2018).

However, connectivity within and between attention networks is also associated with recovery from stuttering. For example, anomalous connectivity linked to both the dorsal attention network and the ventral attention network that supports bottom-up attentional control are associated with developmental stuttering and persistence into adulthood (e.g., Chang et al., 2018; Xuan et al., 2012). These findings may indicate that children who stutter that have atypical deployment or use of attentional resources may be predisposed to continue to stutter into adulthood.

One possibility of how the cerebellum may contribute to attentional functions in people who stutter may be that cerebellar lobule VIIIa is part of a pattern of imbalance between attentional systems used to support speech motor control in people who stutter (for a discussion, see Frankford et al., 2021). In Frankford et al. (2021), adults who stutter were shown to have decreased connectivity between lobule VIIIa and frontal cortical regions, which typically have strong connections with ventral attention network areas, during a rhythmic reading condition (Buckner et al., 2011; Frankford et al., 2021; Yeo et al., 2011; Vossel et al., 2014). Due to the cerebellum's strong connection to timing control in speech (e.g., Ackermann et al., 2007), Frankford et al. (2021) posit that adults who stutter rely less on bottom-up attentional systems controlled by the ventral attention network to help support speech timing using top-down control strategies.

The theory that cerebellar lobule VIIIa is part of a larger pattern of anomalous attentional control from Frankford et al., (2021) is also supported by findings of differential connectivity between the speech-motor control somatomotor network and the ventral/dorsal attention networks in children who stutter (Chang et al., 2018). In addition, as reviewed above (see Section 2.3.2, 2.3.3), connectivity between higher-order cognitive areas and the cerebellum is also related to stuttering frequency (e.g., Sitek et al., 2016; Yang et al., 2016).

Overall, the evidence may indicate that top-down cognitive strategies involving the cerebellum decrease disfluencies and support recovery. Under this view, the current findings concerning lobule VIIIa align with studies such as these that indicate that atypical attentional control systems are associated with developmental stuttering as well as development that leads to continued stuttering into adulthood (Chang et al., 2018; Frankford et al., 2021.; Xuan et al., 2012). Additionally, the argument from Frankford et al. (2021) suggests that feedforward control speech motor control is altered because of variable attentional control. In the context of these previously reported findings, the current results support the proposal that atypical development of feedforward control functions may be present in persistent school-age children who stutter compared to children who do not stutter.

In conclusion, age-related results from school-age children who stutter indicate two potential systems develop differently in this group of children who stutter of different ages. The first proposed explanation is that feedback control differs in children who stutter at different ages, and this change may contribute to persistent stuttering. Second, cerebellar lobules linked to executive functioning pertinent to feedforward control may also be differently associated with age in persistent children who stutter.

## 5.5 IMPLICATIONS FOR NEUROANATOMICAL THEORIES OF STUTTERING

This dissertation primarily examines neurostructural measures of the cerebellum relevant to speech motor control processes associated with developmental stuttering (Table 15). The results suggest that cerebellar gray matter volume of lobule VI, linked to feedforward control, is negatively associated with SSI score in persistent, preschool-aged children who stutter. Cerebellar areas of the feedforward control system were the only neurostructural aspects related to SSI score in this study. Additionally, the age-related variation of cerebellar lobules that support feedforward control functions were observed in this study, and group differences in these age-related results also differentiated persistent and recovery groups from children who do not stutter. Overall, the findings imply that a notable neurostructural difference contributing to developmental stuttering is cerebellar morphology of functional areas that may support feedforward control processes that were outlined in the DIVA model. Lastly, cerebellar substrates predicted to subserve feedback control were connected to age differently in children who stutter.

Therefore, the results from this study provide support for theories that implicate feedforward control as a core variation of developmental stuttering, such as the *Unstable Internal Model* hypothesis (Max et al., 2004; Section 5.5.1 & 5.5.2) and the *Left Hemisphere Basal Ganglia Motor Loop Theory* (Chang & Guenther, 2020; Section 5.5.3). Specifically, the *Left Hemisphere Basal Ganglia Motor Loop Theory* appears to be the best overall fit for these cerebellar results as it may also explain the development of feedback control over time.

### 5.5.1 Cerebellar feedforward control substrates are associated with SSI score in children who stutter

This dissertation supports theories of developmental stuttering that posit that feedforward pathways of speech motor control are highly relevant to the occurrence of disfluencies in people who stutter (Chang & Guenther, 2020; Civier et al., 2010; Max et al., 2004). Cerebellar lobule VI was the only lobule that was associated with SSI score and has been confirmed as the area of the cerebellum that leads from the ventral premotor cortex to the motor cortex in the feedforward control system of the DIVA model (Tourville & Guenther, 2011). Specifically, persistent preschool-age children who stutter were observed to have a negative correlation between right lobule VI and SSI score in this study (Table 9).

Gray matter volume is often associated with experience-related changes in neurological structures. The association between gray matter volume in lobule VI and SSI score in the children who stutter in this study may mean that feedforward pathways in the articulation circuit are associated with activity that leads to disfluencies in children who stutter. Max et al. (2004) predicted that either unstable internal models, the *Unstable Internal Model* hypothesis, or an inability to transmit internal models to the feedback pathway leads to an overreliance on feedback control, the *Overreliance on Feedback Control* hypothesis, leads to disfluencies in people who stutter. The current evidence supports Max et al. (2004)'s first hypothesis due to the lack of connection between lobule VIII, predicted to be associated with feedback control, to SSI score.

Unstable learning and maintenance of internal model information in developmental stuttering leads to stuttering under the *Unstable Internal Model* hypothesis (Max et al., 2004). Unstable internal models result in incorrect prediction of the sensory outcomes of speech,

impeding the timely control of feedforward systems, as well as the inability of the feedback system to create corrective responses to any perceived error. The *Unstable Internal Model* hypothesis is also supported by studies that found that left frontal cortical and subcortical areas that are part of the feedforward pathway are commonly linked to developmental stuttering (e.g., Alm, 2004; Chang et al., 2019; Chang & Guenther, 2020). Additionally, emerging evidence from speech perturbation studies has shown that sensorimotor learning differs in children and adults who stutter compared to children who do not stutter (for a review, see Bradshaw et al., 2021; e.g., Kim et al., 2020). Reduced speech adaptation in children who stutter suggests that feedforward control learning mechanisms that support these tasks are also seen in childhood.

Age-related variation of gray matter volume in cerebellar lobules predicted to subserve feedforward control processes differed in children who stutter compared to children who do not stutter in this study (Table 15). These results demonstrate that cerebellar structures that support feedforward control are associated with age differently in children who stutter compared to children who do not stutter. However, this interpretation of the data may not have a clear justification from other literature sources. Currently, a significant area of debate within the stuttering field is how feedforward control could change over time in people who stutter due to a lack of replication of childhood stuttering data in adults who stutter. For example, Chow & Chang (2017) observed that persistent children who stutter have a decreased growth rate of a tract that connects prefrontal areas with the cortico-basal ganglia loop. This finding was also linked to SSI score. However, this finding has yet to be replicated in adults who stutter (for a discussion, see Chang & Guenther, 2020), leaving a major gap in the field. Currently, no clear evidence connects the development of feedforward control areas and disfluencies in adults who stutter. If future studies support that adults who stutter have a similar relationship between

stuttering frequency and feedforward frontal areas, it could mean that connectivity affecting feedforward control areas of the brain is part of the mechanisms behind continued stuttering into adulthood. This dissertation adds to evidence such as Chow & Chang (2017) that has linked neural feedforward control structures to developmental changes that underlie persistent childhood stuttering.

Specifically, age-related differences in cerebellar morphology associated with feedforward control pathway functions were found in preschool-age children who stutter depending on recovery status (Table 12) and, potentially, in school-age children who stutter (Table 14). This finding supports the idea that feedforward control is differently associated with age to support recovery from stuttering. Additionally, other cerebellar lobules predicted to be associated with feedforward control were also associated with preschool-age childhood stuttering regardless of recovery status (Table 11). In combination with the results that related SSI score to cerebellar lobule VI (Table 8), these results could indicate that cerebellar feedforward pathways support both the condition of being a person who stutters, stuttering frequency in people who stutter, and neuroanatomical patterns that lead to persistence or recovery from stuttering.

As discussed in Section 5.4.1.2 & 5.4.1.3, divergent cerebellar age-related differences from children who do not stutter in lobules IV,VIIb/VIIIa, and VIIIa could indicate that feedforward systems have fluctuating age-related variations in children who stutter. Specifically, lobule IV is predicted to support motor execution (e.g., Lehericy et al., 2005; Section 5.4.1.2). Lobules VIIb/VIIIa could be associated with speech motor planning that bolsters feedforward control (Bohland et al., 2010; Guenther, 2016, pg. 241; Section 5.4.1.2), or potentially, lobule VIIIa could be associated with attentional control of speech motor timing in the feedforward pathway (see discussion in Frankford et al., 2021; Section 5.4.1.3).

Several of these lobules, VIIb, VIIIa, VIIIb, were also associated with persistence and recovery from stuttering. It may be that the mechanisms provided by this dissertation involved with feedforward control also support developmental trajectories that lead to persistence or recovery from stuttering in childhood. For example, recovered children who stutter may use verbal working memory (proposed to be linked to lobules VIIb/VIIIa; Section 5.4.1.2) to bolster speech planning that feeds into the feedforward control system. This strategy may further alleviate unstable feedforward control that leads to recovery from stuttering. Alternatively, an imbalance in top-down and bottom-up attentional control may be a signature pattern of persistent stuttering due to anomalous feedforward control (proposed to be linked to VIIIa; Section 5.4.1.3).

In conclusion, this dissertation's results support the argument that age-related variations in gray matter volume in cerebellar lobules linked to feedforward control may differ in children who stutter, leading to different persistence or recovery outcomes. Furthermore, I have proposed several hypotheses of potential mechanisms that involve the cerebellum that may explain how feedforward control is conducive to developmental stuttering, disfluencies, and persistence or recovery from stuttering in childhood. Overall, due to the association of both SSI score and age to cerebellar substrates that may be involved with feedforward control, the findings support the *Unstable Internal Model Hypothesis* as an explanation of how aberrant speech motor control contributes to developmental stuttering.

5.5.2 Cerebellar substrates of feedback control develop differently over age in children who stutter but are not associated with the frequency of disfluencies

Only cerebellar lobule VI was associated with SSI score in this study. Therefore, this dissertation cannot provide evidence that cerebellar systems of feedback control are associated with the disfluencies in people who stutter, as predicted by the *Overreliance on Feedback Control Hypothesis*. However, this dissertation asserts that gray matter volume of cerebellar lobule VIII, part of the feedback control system, has altered age-related variations in children who stutter. Specifically, cerebellar lobules VIIIa and VIIIb were linked to age differently in children who do and do not stutter.

The age x group results in this dissertation also contribute to larger discussions of how the laterality of morphological differences is related to persistence and recovery from stuttering. For example, in older *preschool-age children who stutter*, greater gray matter volume in *left* VIIIb was observed relative to older children who do not stutter (Figure 11). In comparison, greater gray matter volume in *right* VIIIb was observed in older *persistent school-age children who stutter* (Figure 14). Additionally, in older *preschool-age recovered children who stutter*, greater gray matter volume in *left* VIIIa was observed (Figure 13). Finally, in older *school-age persistent children who stutter*, greater gray matter volume in *right* VIIIa was observed (Figure 14). Therefore, age-related gray matter volume differences in feedback control pathways that involve lobule VIII could be associated with developmental trajectories that support persistence and recovery from stuttering at different ages. Specifically, left lobule VIII may be related to developmental patterns that support recovery in preschool years, while right lobule VIII could play a role in persistent school-age developmental stuttering. These findings are important in the

context of how the laterality of important speech motor control structures contributes to developmental stuttering.

While laterality findings are still contested in the stuttering field (for a review, see Chang et al., 2019), several results indicate that the morphology of left-lateralized areas important for speech and language either fail to develop over time to be similar to children who do not stutter (e.g., the left arcuate fasciculus; Chow & Chang, 2017), or are overall significantly different in persistent children who stutter compared to children who do not stutter (Garnett et al., 2018). These findings suggest that left-lateralized cortical areas are disrupted in persistent children who stutter. Additionally, in another study of older children who stutter (ages 7-11 years), deactivations over left-lateralized areas of in the inferior frontal cortex and premotor cortex were associated with childhood stuttering, in contrast to activations of these left hemisphere areas in children who do not stutter (Walsh et al., 2017). After age 5, recovery rates of stuttering decrease, so it is reasonable to assume that the children from Walsh et al. (2017) are also persistent children who stutter (e.g., Howell & Davis, 2011; Yairi & Ambrose, 1999). With this caveat in mind, these studies demonstrate that morphological and functional differences in left-lateralized speech and language areas of children who stutter corroborate persistence of stuttering.

While considering the results from this dissertation, the right cerebellum would have ample connections with left cortical areas affiliated with persistent developmental stuttering in all these studies. Therefore, right cerebellar lobule VIII findings associated with persistent school-age stuttering (Table 14; Figure 14) could be linked to the cortical findings that connect left cortical areas for speech and language functions to persistence. Potentially, right cerebellar

regions may also work to account for any functional deviations from the left speech and language cortical areas to help support speech.

Additionally, the mechanism behind the findings that suggest that gray matter volume in left cerebellar lobule VIII is linked to recovery from stuttering may also be associated with connectivity to important speech and language areas in the cerebrum. Kell et al. (2018) argue that the key to recovery from stuttering is uncoupling the left cerebellum from a left-lateralized speech production network. In combination with weaker connectivity between the left supramarginal gyrus and the left inferior frontal gyrus in recovered speakers who stutter, this finding was interpreted as a shift away from sensory processing during speech. Therefore, Kell et al. (2018) propose that the change in connectivity in recovered people who stutter reflects a shift in the balance of feedforward and feedback control. Overall, interpreting Kell et al. (2018) and the results from this dissertation could imply that the feedback control gain is lower in recovered people who stutter.

While the *Overreliance on Feedback Control* hypothesis may align with the idea that reduced gain of feedback control may alleviate stuttering, which may be associated with recovery, cerebellar substrates of feedback control were not associated with SSI score in this study. And while the evidence from previous discussions of cerebellar substrates suggests that the *Unstable Internal Model* hypothesis is the most fitting interpretation of the results, there are still several issues with both of Max et al. (2004)'s hypotheses that provide cause for consideration of other stuttering theories.

For example, both the *Unstable Internal Model* and *Overreliance on Feedback Control* hypotheses from Max et al. (2004) are lacking in their ability to describe the potential mechanisms behind cerebellar lobule VIII in developmental stuttering. This is central to the issue

that inverse modeling and feedback control development are not included in Max et al. (2004). Neither the *Unstable Internal Model* nor *Overreliance on Feedback Control* hypotheses include inverse modeling that is part of the feedback control system in the DIVA model (Max et al., 2004).

Under the DIVA model framework, it could be argued that unstable internal models, associated with the *Unstable Internal Model* hypothesis, would also result in inaccurate translation of errors from sensory feedback into corrective motor commands. For example, atypical internal model information from the feedforward system would then prime feedback control pathways to the wrong state of the system. This inaccurate signal from feedforward control pathways would also impede the feedback control system's ability to create correct inverse models to correct errors. This idea would also support the findings across many motor perturbation studies that find that people who stutter have atypical sensorimotor adaptation abilities in a variety of perturbation paradigms (Cai et al., 2012, 2014; Daliri et al., 2017; Daliri & Max, 2018; Kim et al., 2020; Kim & Max, 2020; Loucks et al., 2012; Sares et al., 2018) that involve both feedforward and feedback control (e.g., Daliri, 2021; Kearney et al., 2020). Overall, the role of cerebellar substrates of feedback control in developmental stuttering remains elusive, and the hypotheses by Max et al. (2004) may not be able to properly predict how the cerebellum is involved in the feedback control pathway of the DIVA model.

### 5.5.3 Feedforward control may be central to developmental stuttering, while feedback control is associated with age differently in children who stutter

As reviewed extensively, the *Unstable Internal Model* hypothesis from Max et al. (2004) predicts that variability in feedforward control is the prominent cause of disfluencies in people

who stutter. However, as stated above (Section 5.5.2), this theory is limited in its ability to describe developmental changes that correspond with stuttering. Notably, several findings from this dissertation indicate that age-related morphological associations of functional areas of the cerebellum that support feedforward and feedback control are associated with persistence and recovery from childhood stuttering. Another theory that predicts that feedforward control is the most crucial difference in developmental stuttering and that feedback control changes over development is by Chang & Guenther (2020), referred to as the *Left Hemisphere Basal Ganglia Motor Loop Theory* in the current investigation. Under the *Left Hemisphere Basal Ganglia Motor Loop Theory*, stuttering is due to disruptions in the initiation circuit's basal ganglia motor loop.

The *Left Hemisphere Basal Ganglia Motor Loop Theory* of stuttering predicts that feedback control system is suppressed in people who stutter to prevent the erroneous detection of errors that result from atypical feedforward control. Chang & Guenther (2020) support this idea through the number of studies that have found that people who stutter have reduced auditory cortical activity (for a review, see Brown et al., 2005; Budde et al., 2014). Suppressing feedback pathways would allow the basal ganglia to initiate the following motor command; however, people who stutter can then not detect speech errors that may need to be corrected. In this way, the feedback pathway also leads to disfluencies in people who stutter. In their review of stuttering theories that rely on the balance of feedforward and feedback control systems, Bradshaw et al. (2021) point out that the *Left Hemisphere Basal Ganglia Motor Loop Theory* is unlike others (e.g., Max et al., 2004) in that a gradual reduction in the gain of the feedback control system is proposed as a strategy to try to reduce the frequency of stuttering.

This study has found that cerebellar areas that could support feedforward control are associated with disfluencies in children who stutter (VI; See Section 5.5.1) and that cerebellar areas supporting functions of feedback control pathways are related to age differently in children who stutter and may also lead to persistence or recovery from stuttering (VIII; See Section 5.5.2). Therefore, these results most strongly support the *Left Hemisphere Basal Ganglia Motor Loop Theory* of stuttering. However, one limitation of the basal ganglia-centric *Left Hemisphere Basal Ganglia Motor Loop Theory* is that the cerebellum is not part of the basal ganglia-thalamocortical loop.

This dissertation provides evidence that the associations between the basal ganglia and the cerebellum are crucial to understanding and delineating the systems that underlie developmental stuttering. For example, the cerebellum and basal ganglia have been shown to have several connections between them (Bostan et al., 2010; Bostan & Strick, 2010; Hoshi et al., 2005; Middleton & Strick, 2000). Furthermore, these connections form an interconnected network of cerebral and subcortical circuitry between the cerebellum and basal ganglia (for a discussion, see Bostan & Strick, 2018). Therefore, atypical activity at one node of this network could cause disfunction at another within it, and the cerebellum should not be excluded from discussions of how the brain functions over time in developmental stuttering.

## 5.6 LIMITATIONS

This dissertation is the first to use a specialized cerebellar VBM toolbox in a large group of children who do and do not stutter. The Spatially Unbiased Atlas Template of the Cerebellum (SUIT) toolbox running on SPM12 was used to improve normalization of the cerebellum (Diedrichsen, 2006). SUIT has also been found to significantly enhance the reliability and accuracy of anatomical measurements within cerebellar structures (Diedrichsen, 2006). However, SUIT has been available for over ten years, and other, newer cerebellar methods may perform better. For example, newer multi-atlas methods, such as the CERES (CEREbellum Segmentation), have been shown to have better parcellation across pediatric populations than SUIT (Carass et al., 2018; Romero et al., 2017). Future studies of pediatric samples of people who stutter should explore these newer cerebellar methods.

Another limitation of this study is the size of the recovery group in children who stutter. While results involving recovered and persistent children who stutter were presented in this dissertation, group sizes were small in the recovered group (preschool-age N=16; school-age N=4). This likely increases the probability of both type I and II errors. There may be differences between recovered children who stutter and the other study groups that would be revealed in larger samples of people who stutter. On the other hand, lower sample sizes can also lead to higher sampling variability (for a discussion, see Szucs & Ioannidis, 2019), leading to exaggerated effect sizes. This variability may mean that the averages captured in the small sample size of children who stutter would differ from another sample size of a similar size. This leads to greater chances of type I errors, where spurious findings are reported, to increase (for a discussion, see Szucs & Ioannidis, 2016, 2019).

The power analysis in this study was based on sample sizes from Beal et al. (2013), who compared total gray and white matter cerebral volume between children who do and do not stutter using VBM methods. With an alpha of 0.05 and power = 0.80, the estimated sample size needed to achieve the effect size based on Beal et al. (2013) was N=12 in each group. The number of participants in our school-age group of recovered school-age children who stutter did not meet these criteria (N=4). Therefore, gray matter volume findings in the school-age model, particularly those involving recovered children who stutter, are tentative and should only be used as preliminary findings for further analyses that can capture cerebellar data from a larger group of recovered children who stutter. These results will need to be replicated in studies that include more recovered children who stutter.

Lastly, although this dissertation hypothesized the role of the cerebellum in several speech motor control functions of the DIVA model, only one of these lobules has been officially attributed to a specific pathway within the feedforward pathway, lobule VI. This dissertation predicted that cerebellar lobules VI (Figure 5a, 5c, 5d), VII (Figure 5c, 5d), and VIII (Figure 5b) are most likely to be part of functions attributed to aspects of the DIVA model. These hypotheses need to be confirmed with further investigations to verify the predictions about the cerebellum's role in developmental stuttering.

Additionally, there are likely several cognitive functions outside of motor control relevant to developmental stuttering that could also be attributed to the observed cerebellar differences. While the current discussion focuses on speech motor control, stuttering is a multifactorial condition that may involve additional factors outside of motor control (Smith & Weber, 2017). Cerebellar structures have also been attributed to many cognitive functions (e.g., Habas, 2021; Stoodley, 2012; Stoodley & Schmahmann, 2010). However, this dissertation focuses on motor

control features of the cerebellum to provide arguments for potential actions that the cerebellum takes in speech motor control processes to describe one significant aspect of developmental stuttering. Future studies are needed to examine the associations between cognition and cerebellar activity of people who stutter to elucidate other cerebellar processes relevant to the condition.

## 5.7 CONCLUSION

This study examined cerebellar gray matter volume in children who do and do not stutter. In addition, this dissertation used specialized VBM techniques for the cerebellum to enhance the accuracy of anatomical measurements of cerebellar structures compared to previous VBM techniques using templates developed for the cerebrum ( Chang et al., 2008; Diedrichsen, 2006). The aims of this investigation were to 1) Examine group differences in volumetric measures of the cerebellum among children who do and do not stutter, 2) Examine gray matter volume differences in the cerebellum that differentiate persistent and recovered children who stutter, and 3) Examine age-related variations in gray matter volume based on a group of preschool-age children and school-age children who do and do not stutter. In line with these aims, this study did not find that the overall gray matter volume of the cerebellum was different between groups. Instead, gray matter volume in certain cerebellar lobules was associated with SSI score and age in groups of preschool-age and school-age children who stutter.

Overall, the significant findings of this dissertation indicate that: 1) Cerebellar gray matter does not differentiate groups of children who stutter, 2) Cerebellar gray matter in the feedforward control pathway's lobule VI is associated with SSI score in children who stutter, and 3) Cerebellar gray matter in areas that are related to both feedforward and feedback control functions have different age-related variations in children who stutter compared to children who do not stutter as well as persistent and recovered children who stutter. Specifically, early age-related differences in primarily feedforward, and later age-related variations in feedback control pathways correspond with the condition of developmental stuttering and recovery and persistence in childhood. These findings support stuttering theories that predict that the atypical feedforward control is a prominent contributor to disfluencies in people who stutter, such as the

*Unstable Internal Model* hypothesis and the *Left Hemisphere Basal Ganglia Motor Loop Theory* (Chang & Guenther, 2020; Max et al., 2004).

As mentioned above, this dissertation made several predictions about the roles of the cerebellum in both speech motor control and developmental stuttering. However, a significant limitation to these hypotheses is the lack of detailed examination of the cerebellum in developmental stuttering. While the cerebellum is vital to motor learning, control of articulation, and fine control of movements and has been known as such for a long time (for a review, see Glickstein et al., 2009), current investigations often do not include imaging techniques that are sufficient to describe smaller functional areas of the cerebellum (e.g., Diedrichsen, 2006; Schlerf et al., 2014) or fail to acknowledge the cerebellum altogether. Therefore, the accuracy of past lobular results needs to be reexamined in future studies.

The cerebellum comprises more than half of the neurons in the central nervous system and participates in reciprocal connectivity with nearly every area of the cerebrum. The need for a better understanding of the cerebellum in the development of speech motor control is crucial to comprehending the intricate relationships of many networks that come together as developmental stuttering. Future studies of stuttering neuroanatomy need to examine the cerebellum with the same focus as the cerebrum has previously received. The work and discussion included in this investigation seek to provide reasons for future studies that concentrate on studying the "little brain." Our comprehension of development, speech motor control, and developmental stuttering is seriously precluded without a better understanding of the cerebellum.

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