5-18-2021

The Cerebellum's Relationship to Language Function Following Perinatal Stroke

Carolina Alexis Vias

Florida International University, cvias001@fiu.edu

Recommended Citation

Vias, Carolina Alexis, "The Cerebellum's Relationship to Language Function Following Perinatal Stroke" (2021). *FIU Electronic Theses and Dissertations*. 4813.
https://digitalcommons.fiu.edu/etd/4813

FLORIDA INTERNATIONAL UNIVERSITY

Miami, Florida

THE CEREBELLUM'S RELATIONSHIP TO LANGUAGE FUNCTION FOLLOWING PERINATAL STROKE

A dissertation submitted in partial fulfillment

of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

PSYCHOLOGY

by

Carolina Alexis Vias

2021

To: Dean Michael R. Heithaus
College of Arts, Sciences and Education

This dissertation, written by Carolina Alexis Vias, and entitled The Cerebellum's Relationship to Language Function Following Perinatal Stroke, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

Angela Laird

Robert Lickliter

Eliza Nelson

Anthony Steven Dick, Major Professor

Date of Defense: May 18, 2021

The dissertation of Carolina Alexis Vias is approved.

Dean Michael R. Heithaus
College of Arts, Sciences and Education

Andrés G. Gil
Vice President for Research and Economic Development
and Dean of the University Graduate School

Florida International University, 2021

DEDICATION

I dedicate my dissertation to my family, with a special appreciation to my mother, Martha Victoria Gonzalez, my father, Antonio Vias, my husband, Marcos Felipe Urra Hoyos, and Pacquiao, my petit prince. Your love supported me throughout and makes the accomplishment so much sweeter.

ACKNOWLEDGMENTS

I would like to thank my supervisor, Dr. Anthony Steven Dick, for his mentorship throughout my graduate school career. From the beginning, he insisted on each of us taking the initiative to accomplish our own goals and encouraged me to constantly set higher goals, which led to confidence in my ability to achieve. While he constantly promoted independent thinking, I always felt I had the support and assistance I needed. While there were moments in my career where the burden of life felt heavy, he let me know I had the support and challenged me when he knew I was capable of more. I truly appreciate the knowledge and confidence he has instilled to take me to the next step of my career.

My gratitude goes to my committee members, Drs. Angela Laird, Robert Lickliter, and Eliza Nelson. Thank you for contributing your knowledge in developmental science and cognitive neuroscience towards the success of this project through your feedback. Thank you to Dr. Jörn Diedrichsen for sharing his data, which contributed to the creation of the semi-automated cerebellar atlas. This work was supported by the National Institute of Child Health and Human Development under Grant #P01HD040605.

A special thank you to my friends and colleagues Drs. Iris Broce and Dea Garic for their assistance and support through graduate school. The knowledge and laughs that we shared made the journey a delight. Also, I would like to thank my undergraduate research assistants for all of their time and effort in processing my dissertation data, especially Jefferson Salan, Jairo Munoz, Alexarae Bryon, Cynthia Goldberg, Arnaldo

Morales, Ania Suros, and Sophia Tchir. I know the manual parcellation of cerebellar lobules required patience and dedication, which I greatly appreciate.

ABSTRACT OF THE DISSERTATION

THE CEREBELLUM’S RELATIONSHIP TO LANGUAGE FUNCTION FOLLOWING PERINATAL STROKE

by

Carolina Alexis Vias

Florida International University, 2021

Miami, Florida

Professor Anthony Steven Dick, Major Professor

While recent studies have demonstrated the association between the cerebellum and higher-order cognitive functioning, it is still unclear how volumetric differences of specific regions of interests within the cerebellum across typical and atypical development are related to language function. We have done so by measuring the volume of cerebellar subregions of healthy controls, and compared the volume to behavioral measures of language function. We then followed with an analysis of the cerebellum’s relationship to language function following perinatal stroke, which provides us with a greater knowledge of the impact of a cortical injury on cerebellar development and the cognitive outcomes of such changes by again measuring and comparing the volume of cerebellar subregions to language measures. We report several novel findings that contribute to the growing understanding of the cerebellum’s relationship to language function. We found that greater right laterality of lobules IV and VIIb predicted performance on expressive language measures in typical development. We also found that following an early injury to the cerebral cortex's left hemisphere, there was a bilateral association of cerebellar lobules to language measures. Specifically, we found greater right laterality of the cerebellar cortex, lobule IV, and Crus I predicted higher scores on the Expressive Vocabulary Test. While greater left lateralization of lobule VI predicted expressive language and lobule VIIIa predicted grammatical judgment, especially early in development, and greater left lateralization of lobule IX predicted receptive vocabulary. Implications of the findings of volumetric association to language function and post-stroke development within the cerebellum are discussed.

TABLE OF CONTENTS

CHAPTER PAGE

LIST OF TABLES

TABLE PAGE

LIST OF FIGURES

I. INTRODUCTION

Developing language is supported by a distributed network of brain regions that includes cortical as well as subcortical structures, including the cerebellum. The cerebellum has received significant attention recently for its potential to contribute to cognitive as well as sensorimotor development, including in the domain of language (Lesage, Hansen, & Miall, 2017; Mariën et al., 2014; Moberget, Gullesen, Andersson, Ivry, & Endestad, 2014; Moberget & Ivry, 2016; Schmahmann, 2001; Stoodley, 2012; Vias & Dick, 2017). As language develops at the phonological, grammatical, and lexical levels throughout childhood and adolescence, the cerebellum also undergoes morphological changes that may impact the maturation of these skills (E, Chen, Ho, & Desmond, 2014; Fiez, 2016; Stoodley, 2012). In the present study, we address whether morphological changes of specific subregions are related to the development of specific linguistic skills in typical children and adults. We also address the role the cerebellum plays in language development following disrupted neural development in early life, specifically in the case of pre/perinatal stroke.

Cerebellar Anatomy and Connectivity

The basis for the cerebellum's involvement in the language network is its underlying structural and functional connectivity with the cortical regions involved in language function. The cerebellum is unlike the cerebral cortex in terms of its cytoarchitecture and myeloarchitecture. In the cerebral cortex, cyto- and myelo-architecture is heterogeneous across the cortical sheet. The well-known Brodmann Areas (Brodmann & Garey, 1999) display these regional differences across the cerebral cortex's cortical sheet. However, in the cerebellum, the cytoarchitecture is composed consistently of three distinct layers across the cerebellar cortex. Throughout the cerebellar cortex, the most superior level is the molecular level composed of basket cells and stellate cells, which are located near the Purkinje cell bodies. This layer is followed by a layer of large Purkinje cells, which is then followed by a dense granule cell layer. It is because of the most inferior layer of compacted small granule cells that the cerebellum has the distinction of containing four times as many neurons as the cerebral cortex (Andersen, Korbo, & Pakkenberg, 1992). Given the consistency of the cerebellar cortex's cytoarchitecture, the cerebellum cannot be defined as the cerebral cortex with Brodmann areas. Rather than its cellular composition, the cerebellum's connectivity to cortical and subcortical regions determines the function of each region of the cerebellum (Andersen et al., 1992; Naidich et al., 2009). Thus, subregions connected to sensorimotor regions will play a specific computational role for sensorimotor processing. Likewise, cerebellar regions that connect to cortical language regions are likely to perform similar computations to those regions involved in sensorimotor processing, but they will do so on linguistic content, not sensorimotor content.

Studies using classical neuroanatomy methods, as well as diffusion-weighted imaging, have revealed a structural connectivity and contralateral lateralization between the cerebellum and association areas in the frontal lobe and posterior parietal cortex. The fibers that form these connections travel mainly through two of the three large cerebellar peduncles. While the inferior cerebellar peduncle carries several spinocerebellar fibers associated with proprioceptive and sensory function, it is the superior and middle cerebellar peduncles that compose the primary afferent and efferent connections with the cerebral cortex that form the cortico-cerebellar loop that is the basis for the cerebellum's involvement in cognitive function (Keser et al., 2015; Naidich et al., 2009; Salamon et al., 2007).

The cerebellum receives cortical information mainly from the middle cerebellar peduncle. These fibers receive information from motor and association areas of the cerebral cortex, which then project to the ipsilateral pontine nuclei. From the pontine nuclei, the fibers cross through the middle cerebellar peduncle to the contralateral cerebellar cortex. It is this cortico-ponto-cerebellar pathway that allows the cerebellum to receive information from regions involved in cognitive functioning. The cerebellum sends information to the cortex through the superior cerebellar peduncle. The majority of the fibers of the superior cerebellar peduncle project to the midbrain, where they cross and pass to the contralateral red nucleus to the thalamus. From the thalamus, fibers send information to motor and association areas in the cerebral cortex (see Figure 1) (Naidich et al., 2009). Therefore, the middle and superior cerebellar peduncles are the main cerebellar components of the cortico-cerebellar-cortical loop, which is the basis for the cerebellum's involvement in higher-order cognitive functioning, such as language. While classical neuroanatomy methods inform this understanding of cortico-cerebellar connectivity, studies using diffusion-weighted imaging of cerebellar fiber pathways have supported the anatomical findings (Keser et al., 2015; Salamon et al., 2007).

Tract-tracing studies in nonhuman primates support the cerebellum's structural connectivity to regions involved in higher-order cognitive functioning. For example, similar to human connectivity studies, tract-tracing studies in nonhuman primates show a cortico-cerebellar-cortico loop that sends and receives information from regions that perform higher-order cognitive functioning. Specifically, area 46 of the primate prefrontal cortex, which is involved in working memory, receives information from and sends information to, Crus II of the cerebellum (Ramnani, 2006; Ramnani et al., 2006; Schmahmann, 1996). This connectivity provides a foundation for the evolutionary development of the cerebello-cortical loop that supports cognitive functioning, and this knowledge can provide some information about how internal cerebellar models may contribute to language and its development.

Similarly to the cerebral cortex, the cerebellum's cortical surface is anatomically demarcated by deep fissures that organize the cerebellum's cortex into defined folia (Schmahmann et al., 1999). These fissures form the three main lobes (anterior, posterior, and flocculonodular) that are further defined into 13 lobules. The anterior lobe consists of lobules I through V, which are divided by the precentral, preculminate, intraculminate, and primary fissures. It is the primary fissure that divides the anterior lobe from the posterior lobe. The posterior lobe consists of lobules VI through X, which are divided by the superior posterior, horizontal, ansoparamedian, prepyramidal, intrabiventer, secondary, and posterolateral fissures. The posterolateral fissure divides the posterior lobe from the flocculonodular lobe, which only consists of lobule X. Thus, the cerebellum's hemispheres and vermis are anatomically defined into the 13 lobules I, II, III, IV, V, VI, Crus I (VIIAf), Crus II (VIIAt), VIIB, VIIIA, VIIIB, IX, X (Schmahmann et al., 1999).

While the cerebellum cannot be defined functionally by its cytoarchitecture as in the cerebral cortex, there are known functional divisions determined by its connectivity. There are three major longitudinal divisions along a medial to lateral axis, and these are the median, intermediate, and lateral zones. The median zone includes the vermis and flocculonodular lobe of the cerebellum, which receives information from the spinal cord and is related to proprioceptive and sensory function. The intermediate and lateral zones comprise the cerebellar hemispheres, where the intermediate zone includes the medial portion, while the lateral zone includes the lateral portion. These zones receive information from cortical regions through the cortico-ponto-cerebellar pathways and were historically known for their relation to motor function. The intermediate zone is related to movement execution, and the lateral zone is related to movement planning. However, with known cerebellar inputs from cortical association areas, and an increased interest in the cerebellum's role in higher-order cognitive functions, the intermediate and lateral zones are increasingly becoming associated with cognition as well (Naidich et al., 2009). The functional connectivity noted is supported by resting-state functional magnetic resonance imaging (rsfMRI) studies, as well as diffusion-weighted imaging findings, revealing significant functional connectivity between the intermediate and lateral zones of the cerebellum and association areas in the frontal lobe and posterior parietal cortex, which is the basis for the lateral cerebellum's relation to language function (Bernard et al., 2012; Buckner, Krienen, Castellanos, Diaz, & Thomas Yeo, 2011).

The research reviewed above suggests that the cortico-cerebellar connectivity establishes the particular function of specific cerebellar regions. Thus, the extant evidence suggests a functionally organized cerebellum, where higher-order association cortices are connected to the posterior-lateral regions of the cerebellum, as opposed to cortical motor regions that are connected to the more anterior cerebellum. Specifically, posterior-lateral regions of the right cerebellar lobules VI, Crus I, Crus II, and VIIb receive connections from the prefrontal, posterior parietal, and superior temporal cortices known to be involved in language function (see Figure 2) (Bernard et al., 2012; Buckner et al., 2011; E et al., 2014; Stoodley & Schmahmann, 2009).

Cerebellar Contributions to Cognitive Development

The anatomical explanations, which we review above, contribute to hypotheses about how the cerebellum might contribute to typical language development, and language development following early insult. The cerebellum undergoes a significant change in structure and function over the course of development, which has direct implications for cognitive development. Studies of cerebellar development and volume size suggest that the cerebellum's total volume continues to increase until around age 12 for females and 16 for males, and then starts to decrease (Tiemeier et al., 2010).

Notably, subregions within the cerebellum have different developmental trajectories, and the age at which volume increases reach an asymptote differs by region. For example, Tiemeir and colleagues (2010) conducted a morphometric analysis where they parsed the cerebellum into gross subregions, the anterior lobe (lobules III, IV, and V), superior posterior lobe (VI and Crus I), and inferior posterior lobe (Crus II, VIIb, VIII, and IX), and compared cerebellar volume in these regions over time. The results of the analysis suggested that the superior posterior lobe was the latest to peak, and it did so at age 16 for females age 18 for males. In contrast, the growth of the anterior lobe peaked earlier for both females and males, where age at peak volume was 14 for females and 16 for males. Finally, the inferior posterior lobe peaked at the earliest, at age 11 for females, and age 14 for males (Tiemeier et al., 2010). These findings improve our understanding of the cerebellum's developmental trajectory and its differences across gender and subregions. However, they tell us little about the cognitive functions associated with these changes.

Some progress has been made regarding understanding the relationship between volumetric differences in the cerebellum and cognition. For example, Pangelinan and colleagues (2011) reported a positive relationship between the volume of the cerebellum in children and IQ (Pangelinan et al., 2011). However, this study focused more generally on cognition—the specific relation of cerebellar volume to language function in typical children was not investigated. In a similar study, Moore and colleagues (2017) reported a positive relationship between the volume of cerebellar subregions in the posterior lobe and tasks relating to working memory, language, reading, and executive function. Specifically, there was a positive relationship between the Picture Vocabulary Test and increased grey matter in left lobule VI, bilateral Crus II, VIIB, VIIIA, and vermal VIIIA, VIIIB, IX, X. Higher scores on Oral Reading Recognition Test were associated with increased grey matter in bilateral lobules VIIB, VIIIA, VIIIB, and IX. Higher scores on the List Sorting Working Memory Test were associated with increased grey matter in right Crus I, Crus II, VIIB. Higher scores on the Dimensional Change Card Sort Test were associated with increased grey matter in bilateral VIIB and VIIIA, and left Crus II (Moore, D'Mello, McGrath, & Stoodley, 2017). While the results of this study demonstrate how the volume of specific cerebellar subregions has a positive relationship with a wide range of cognitive functions, including receptive vocabulary and reading, it focuses on cognition as a whole, and only deals with rather coarse language functions (e.g., vocabulary). More specific studies of the relationship between cerebellar function and language have involved not just structural imaging, but also functional neuroimaging.

The Cerebellum’s Relationship to Language: Functional Neuroimaging

Much of the information about the cerebellum’s relationship to language has come from functional neuroimaging studies, which have provided valuable information about the linguistic functions that elicit cerebellar activation. A number of neuroimaging studies report cerebellar activation during linguistic tasks such as verbal fluency, word generation, semantic processing, phonological processing. This has been the case even when controlling for or excluding the confounding motor aspects of speech (Stoodley & Schmahmann, 2009).

For example, several studies have used a silent verbal fluency paradigm, which asks the participant to generate words based on a phonemic or semantic cue silently in their mind. Generating the word silently ensures that the cerebellum's involvement in the task was genuinely related to language function and not the motor aspect of the articulation of words, which would speak more to the well-known association between the cerebellum and motor function. Studies using this paradigm have consistently shown that along with activating the left fronto-parietal cortex, activation is regularly noted in the cerebellum’s right posterior hemisphere for right-handed individuals (Hubrich-Ungureanu, Kaemmerer, Henn, & Braus, 2002; Weiss et al., 2003). When analyzing left-handed individuals, Hubrich-Ungureanu and colleagues (2002) showed that the same regions are involved but in opposite hemispheres, with activations instead in the right fronto-tempro-parietal cortical regions and the left cerebellar posterior hemisphere. Studies with patients who have focal cerebellar lesions have supported the results seen in healthy adults, showing that those with a cerebellar lesion in the right hemisphere performed significantly worse than those with left hemisphere lesions and controls

(Schweizer, Alexander, Gillingham BA, Cusimano, & Stuss, 2010). These findings are consistent with what is known about the crossed cortico-cerebellar connections that are the basis for understanding the functionally compartmentalized cerebellum (Naidich et al., 2009).

A number of meta-analyses have revealed the extent to which the cerebellum is functionally compartmentalized, with distinct regions for sensorimotor and cognitive functions. Specifically, the anterior lobe is related to general sensorimotor functions, and the posterior lobe is related to cognitive functions. However, each of the gross classifications can be further subdivided to further localized regions for specific functions. For example, cognitive functions are further localized into specific regions in the posterior lobe, such as the right posterior-lateral lobules VI, Crus I, and Crus II are related to language function (E et al., 2014; Riedel et al., 2015; Stoodley & Schmahmann, 2009). However, the relationship between individual volumetric differences in the cerebellum and language function is unknown, or how this relationship differs across development, which is the focus of the current study.

While limited studies focus on typical cerebellar development in relation to language function, there is one study that fills a gap in knowledge on how the size of certain cerebellar regions early in development predicts later language outcomes. Deniz Can, Richards, and Kuhl (2013) found that greater grey and white matter in the right posterior cerebellum at seven months predicted later receptive language ability at 12 months. Specifically, they found that greater grey matter in the right posterior lobules VIIB and VIII, and, greater white matter in the right inferior cerebellar peduncle, had predicted greater performance on a receptive language measure (Deniz Can et al., 2013).

This study shows how in early development, greater grey and white matter in specific regions and pathways of the cerebellum can predict later language outcomes. The results are consistent with what is known about cortico-cerebellar connectivity, implicating some of the regions we would expect to be associated with language function. Moving forward, this study provides a base for understanding how volumetric differences in the cerebellum across development can impact language outcomes.

Several studies in atypically developing children, such as children with autism or dyslexia, have also suggested that the volume of specific cerebellum subregions is associated with deficits in language function. For example, in comparison to typical children, one of the most replicable findings is that children with autism have reduced cerebellar volumes relative to neurotypical controls. Specifically, the reduced cerebellar volumes include less cerebellar grey matter and a smaller ratio of grey to white matter (Courchesne et al., 2001). With respect to language, comparisons among children with autism, children with language impairment, and those without language impairment are illustrative. The findings from these studies have shown that in children without a language impairment and typical controls, the right cerebellar volume VIIIA is larger than its counterpart on the left. However, for children with a language impairment, there was a smaller volume of right lobule VIIIA. These volumetric brain differences between those with a language impairment and those without a language impairment also correlated with language measures as measured by the Clinical Evaluation of Language Fundamentals (CELF), where higher scores on the language measures were related to larger VIIIA in the right hemisphere (Hodge et al., 2010). More recently, D'Mello and colleagues found that volumetric differences in the left cerebellar Crus I and Crus II differentiated children with autism who had an early language delay from those who did not have early language delay and typical controls (D’Mello, Moore, Crocetti, Mostofsky, & Stoodley, 2016). These findings suggest that volumetric differences in the cerebellum in those with autism spectrum disorder affect language function. However, more studies are needed in a typically developing population to understand the cerebellum’s role in the broader language network and clarify the specific subregions and language functions involved.

Cerebellar and Language Development Following Perinatal Stroke

The above-reviewed information may be particularly important when attempting to understand the cerebellum's involvement in language development following early cortical insult (early stroke). According to Raju, Nelson, Ferriero, and Lynch's (2007), perinatal stroke is defined as “a group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of fetal life through the 28th postnatal day, confirmed by neuroimaging or neuropathologic studies” (p. 5614). There are two major types of strokes, ischemic and hemorrhagic. Ischemic stroke is the most common type, which occurs when the blood vessel is obstructed, versus hemorrhagic stroke occurs when a blood vessel ruptures. However, it is not always possible to determine whether the lesions are initially hemorrhagic or ischemic, and patients may have many vascular pathologies that are difficult to parse. Given the heterogeneity of the population, cognitive and behavioral outcomes have shown to vary significantly depending on the lesion's size and location (Lynch, 2009; Raju et al., 2007).

This is an interesting population to study in order to address the central question about cerebellar contributions to language development because although the cerebellum is not directly affected by the stroke, its development is affected because of its direct anatomical connectivity with cortical regions that support language development. Thus, the stroke's indirect effects can be used to understand how the cerebellum develops in the face of damage to cortical regions and how that contributes to language function. This approach takes advantage of a known phenomenon termed crossed-cerebellar diaschisis, which describes the secondary effects of loss of function in the cerebellum from cortical damage. Prior studies have noted this cortico-cerebellar functional disconnection with positron emission tomographic (PET) scans, noting decreased blood flow in regions in the cerebellum connected to the lesioned cortical regions. The proposed mechanism for diaschisis of the cerebellum is a disruption of the cortico-ponto-cerebellar (CPC) pathway via a process of transneuronal degeneration. This process describes the degeneration of the projecting axons secondary to a lesion in a neuron in the afferent or efferent connections. A similar phenomenon is known as Wallerian degeneration involves the degeneration of the lesioned neuron. Wallerian degeneration would affect cortical neurons projecting to the pons, which could then cause transneuronal degeneration to the projecting neurons to the cerebellar cortex (Strother et al., 2016; Tien & Ashdown, 1992; Uchino, Takase, Nomiyama, Egashira, & Kudo, 2006; Yamada et al., 1998).

The structural changes noted in the process of transneuronal degeneration have been supported via diffusion tensor imaging (DTI) studies that demonstrate decreased fractional anisotropy (FA) of the descending white matter tracts (Kim, Lee, Lee, Kim, & Kim, 2005; Thomalla, Glauche, Weiller, & Röther, 2005; Yamada et al., 2003).

Similarly, structural changes to the projecting neurons in the cerebellar cortex have been noted via MRI studies that have found cortical atrophy in the cerebellar hemisphere contralateral to the supratentorial lesion (Strother et al., 2016; Tien & Ashdown, 1992; Uchino et al., 2006; Yamada et al., 1998). For example, Uchino and colleagues (2006) showed that months after a cortical lesion, Wallerian degeneration of the fronto-ponto tract leads to atrophy of the brainstem. After a year, the contralateral cerebellar hemisphere atrophies due to the transneuronal degeneration of the pontocerebellar tract. Similarly, authors have shown evidence of a reduction in cerebellar volume in children who suffer cortical lesions (Mah, DeVeber, Wei, Liapounova, & Kirton, 2013; Srinivasan et al., 2006). However, a number of studies have noted that the crossed cerebellar atrophy that develops after cortical stroke is more often noted in children and young adults than older adults (Tien & Ashdown, 1992; Uchino et al., 2006). Given the structural changes associated with the functional loss, the measurement of cerebellar atrophy can be used as a tool for understanding crossed-cerebellar diaschisis.

Relevant to the current study, it would thus be expected that rather than leading to global cerebellar atrophy, lesions to specific regions of the cortex would have an effect on specific subregions of the cerebellum associated with higher-level cognitive function, provided the lesion occurs in regions of the cortex associated with that function. Using the knowledge of cerebellar anatomy and connectivity allows us to make predictions about which regions of the cerebellum would be associated with specific language outcomes, based on the known cortical organization for language function. Further, the cortico-cerebellar connectivity establishes a basis for predicting developmental changes in the cerebellum following cortical injury.

The literature on cognitive outcomes following perinatal stroke is less straightforward, and research is currently attempting to parse out the factors contributing to the variability in outcomes following perinatal stroke. Most studies show that when comparing perinatal stroke patients with a typically developing sample, the perinatal group scores are significantly lower on cognitive functioning measures compared to controls (Westmacott, Askalan, Macgregor, Anderson, & Deveber, 2010). However, the extent to the differences in cognition across groups has varied across studies. For example, Westmacott and colleagues' (2010) noted that although the scores on Full-Scale IQ, Verbal IQ, Verbal Comprehension, and Working Memory were all significantly lower for perinatal stroke patients than the typical controls, the scores for the perinatal group still fell within the low end of the average range (Westmacott et al., 2010). These findings are consistent with a number of other studies that have previously reported normal or near-normal performance on language measures for children with early brain injury (Bates et al., 2001; Beharelle et al., 2010; Dick, Beharelle, Solodkin, & Small, 2013). However, in contrast, Ballantyne and colleagues' (2007) study assessed language-specific measures in those with perinatal stroke in comparison to typical controls and found that those in the perinatal group scored in the below-average range, where scores on all three language indices (Receptive, Expressive, and Total Language) were below the 14th percentile, while the control group scored in the average range (Ballantyne, Spilkin, & Trauner, 2007).

Some factors seem to impact cognitive and language development far less than might be expected. For example, several studies have found that the lesion size is not significantly associated with cognitive function (Ballantyne et al., 2007; Beharelle et al., 2010; Carlson, Sugden, Brooks, & Kirton, 2019). However, there are inconsistencies in whether the laterality of the damage occurred in perinatal stroke (right hemisphere versus left hemisphere) affects language outcomes across development. A number of studies have shown that whether the lesion is on the right or left hemisphere, there are no significant differences between them in cognitive and language measures (Ballantyne et al., 2007; Bates et al., 2001; Dick, Wulfeck, Krupa-Kwiatkowski, & Bates, 2004; Trauner, Eshagh, Ballantyne, & Bates, 2013; Westmacott et al., 2010). However, evidence to the contrary was found in an analysis of school-age children's and adolescents' language outcomes as they mature. Reilly and colleagues (2013) found that when analyzing a number of linguistic factors in the personal narratives of school-age children (ranging in age from 7 to 12) and adolescents (ranging in age from 13 to 17), there were differences across those with left hemisphere lesions and those with right hemisphere lesions in their performance in these areas when compared to typical controls. Those in the perinatal group who sustained damage to the left hemisphere scored significantly worse than typical controls in the Rate of Morphological Errors, Rate of Complex Syntax, Syntactic Depth, and Setting. In contrast, those who sustained damage to the right hemisphere differed significantly with the typical controls on only the Rate of Complex Syntax (Reilly, Wasserman, & Appelbaum, 2013). One reason for the inconsistencies seen in the results of studies analyzing the effects of laterality of cortical damage in relation to cognitive outcomes following perinatal stroke may have to do with the complexity and specificity of the language measures.

Another factor that is inconsistently related to language outcomes following perinatal stroke is the age at testing. One study analyzing preschool (mean age of 8-years) and school-age children's (mean age of 11-years) cognitive abilities following perinatal stroke resulted in no significant differences across time-points. This finding led the researchers to conclude that age at testing is not a significant factor contributing to language outcomes and that the brain's plasticity allows for stable cognitive development (Ballantyne, Spilkin, Hesselink, & Trauner, 2008). In contrast, Westmacott and colleagues found a significant negative correlation with time since stroke and scores on measures of IQ, Verbal IQ, and Verbal Comprehension (Westmacott et al., 2010).

A possible explanation for the inconsistencies in factors contributing to cognitive outcomes following perinatal cortical stroke may be that it is less about the initial damage, including the size and laterality, and more so about the subsequent development and the integrity of the structural and functional connectivity with the damaged region. Dependent on the cognitive tests, studies have shown that increased intra- and inter-hemispheric functional connectivity is associated with higher performance on cognitive and language measures (Beharelle et al., 2010; Carlson et al., 2019; Dick et al., 2013). For example, increased functional interhemispheric connectivity between the left and right posterior superior temporal gyrus predicted higher scores on the receptive language measures of Listening to Paragraphs, Verbal Comprehension, Newport Grammaticality Index, and the CELF Receptive Language (Dick et al., 2013). Additionally, increased intrahemispheric functional connectivity between the left inferior frontal gyrus and the left superior temporal gyrus was significantly related to better verbal comprehension (Carlson et al., 2019). Given that it is the integrity of the connectivity with regions that support language function that may determine post-stroke outcomes, it is expected that increased structural connectivity measured by the degree of atrophy in the cerebellum would be related to the efficacy of language function following perinatal stroke.

Cerebellar Mechanisms Supporting Language Function

The preceding review of anatomical connectivity, and functional and structural imaging evidence, provides strong support for the cerebellum's involvement in higher-order cognitive function, including language. There are also mechanistic explanations, based on the analysis of the computational contributions of the cerebellum to motor function, that lead to this expectation. The mechanistic explanations, which we review below, also contribute to hypotheses about how the cerebellum might contribute to typical language development, and language development following early insult.

Neuroimaging studies have long indicated the cerebellum’s involvement in the broader language network (Lesage, Hansen, & Miall, 2017; Mariën et al., 2014; Moberget, Gullesen, Andersson, Ivry, & Endestad, 2014; Moberget & Ivry, 2016; Stoodley, 2012). However, the exact role of the cerebellum in this network is unknown. Recently, the internal models theory that has been applied to the cerebellum’s involvement in motor function has been applied to language processing, with a number of studies reporting the contribution that the cerebellum plays in prediction, timing, error-detection, and adaptation in language production and comprehension.

Emerging evidence supports the internal models theory and the hypothesis that the cerebellum contributes to predictive processing during language comprehension. This theory proposes that dependent on its connectivity with the cortex, that the cerebellum establishes neural representations comprised of input-output associations called "internal models.” The cerebellum uses these internal models in the service of prediction via "forward model" representations, in which the cerebellum contributes to the organism's best guess about the next item in the sequence of an action, or potentially in the sequence of thoughts. When there is incongruence with the real-time occurrence and the internal model, the cerebellum uses error-based feedback to adapt the internal model, i.e., learning. Because the cerebellum has a consistent cytoarchitecture across its structure, this role in prediction and adaptation is the same across domains (e.g., motor, cognitive, affective) This can easily be seen to apply to motor sequences, which is historically how the cerebellum was conceived (i.e., as a motor structure). Thus, when attempting to sequence a movement, the cerebellum is involved in making predictions about the possible outcomes of each component of the motor sequence. It then updates, in an online fashion, the future predictions in response to sensory feedback about the consequences of prior motor components (Bellebaum & Daum, 2011; Ito, 2008; Moberget & Ivry, 2016; Sokolov, Miall, & Ivry, 2017).

The cerebellum's involvement in the language network has a similar role in prediction and adaptation. For example, in an fMRI study, Moberget and colleagues (2014) showed that the right cerebellum was engaged in a semantic prediction task, specifically when reading a sentence where the context made the final words predictable. The authors argued that if the internal models theory applies to language processing, then the cerebellum would be involved when there is a semantic association between presented words because the cerebellum is involved in making predictions about the semantic content of words presented in the future. Indeed, they found evidence for this. The right posterolateral cerebellum (Crus I/II) showed increased activation when the target word was highly predictable compared to a string of words with no semantic relation (Moberget et al., 2014). These findings add support to the cerebellum's internal models theory by demonstrating the cerebellum's involvement in predictive acts, and in this case specifically, regarding semantic relations in language processing.

Bellebaum and Daum argue that the internal models that the cerebellum encodes have information that not only allows it to predict *what* will come next in the sequence but also *when* (Bellebaum & Daum, 2011). This aspect of timing in prediction is noted in the cerebellum’s role in speech perception and speech production. The temporal role of the cerebellum is especially notable in those with cerebellar disorders, who show deficits in temporal aspects of speech production and perception. Specifically, in regard to deficits associated with speech perception, it has been noted that those with cerebellar disorders show impaired temporally-dependent phoneme categorization.

Consistent with internal models theory, when the actual outcome is incongruent with the predicted model, the cerebellum is involved in detecting the error. In Moberget and colleagues (2014) study of semantic predictability, when the target word was highly predictable but incongruent with the prediction given the context, the cerebellum showed wide bilateral activation in comparison to both the semantically congruent condition and the scrambled condition, which was a random string of words with no semantic relation (Moberget et al., 2014). Similarly, Lesage and colleagues found that the right lateral Crus II region showed more activation during an unexpected outcome than a highly predicted outcome (Lesage et al., 2017). These results are consistent with the theory that the cerebellum uses internal models to make predictions and detect an error in the prediction when the actual outcome is incongruent with the model. This online detection and feedback allows for error correction with the adaptation of the internal model, i.e., learning, and the cerebellum contributes to this adaptation process during speech production and perception.

Research Aims

The current dissertation aimed to acquire a deeper understanding of the cerebellum's relationship to language function. Specifically, we aimed to answer whether volumetric differences of specific regions of interests within the cerebellum are related to expressive and receptive language measures. We have done so by measuring the volume of the subregions of the cerebellum of healthy controls, specifically the grey matter of each cerebellar lobule, and compared the volume to behavioral measures of language function. We then followed with an analysis of the cerebellum's relationship to language function following perinatal stroke, which provides us with a greater knowledge of the impact of a cortical injury on cerebellar development and the cognitive and behavioral outcomes of such changes, by again measuring and comparing the volume of cerebellar subregions to language measures.

II. STUDY 1

Research Question

The present study focused on the structural volumetric analysis of the grey-matter of cerebellar subregions in typical development and how the individual subregions' volume compares to expressive and receptive language outcomes. We identified the main lobules following Schmahmann and colleagues' (1999) Three-Dimensional MRI Atlas of the Human Cerebellum in Proportional Stereotaxic Space and calculated the volume of each region. We investigated the relationship between each region's grey matter volume size to a battery of language measures, including measures of expressive and receptive language, grammar, and IQ.

Prior structural analyses of cerebellar grey matter volume in relationship to cognitive functioning have revealed a positive relationship to volume size and general measures of cognitive abilities (Moore et al., 2017; Pangelinan et al., 2011). However, there is a gap in knowledge regarding specific cognitive functions, especially specific aspects of language function, in structural analyses. Conversely, functional imaging studies have consistently shown cerebellar activations during a number of language tasks, including semantic fluency, phonemic fluency, and word generation. These studies have typically shown the posterior lateral regions of the cerebellum, lobules VI, Crus I, Crus II, and VIIb, as the regions associated with language function (E et al., 2014; Frings et al., 2006; Riedel et al., 2015; Schweizer et al., 2010; Stoodley & Schmahmann, 2009; Vias & Dick, 2017). On the basis of the reviewed literature, we predicted that greater cerebellar grey matter volume, specifically in the right posterior-lateral regions (VI, Crus I, Crus II, VIIb), will be related to better performance on the language measures.

Method

Participants. Analyses were carried out on previously collected behavioral and imaging data for deidentified participants. The data include demographics, structural MRIs, as well as several behavioral measures from 27 typically developing participants. The ethnicity of the complete sample is comprised of White (77%); African American (11%); Latino (5%); Asian American (1%); More than one ethnicity (3%); Other (3%).

Characteristics of the typical control group. Siblings of the perinatal stroke patients, which are the focus of Study 3, comprise our typically developing participant group. The ages at testing are *M*=195 months (16.27 years), *SD*=94.13 months (7.84 years), Range=102–467 months (8.50–38.92 years). There are 11 males and 16 females (*N*=27) in the typical sample.

Neuroimaging and Behavioral Data Acquisition. Structural T_1-weighted MRI was used to examine neural structures of interest. Behavioral measures collected outside the scanner were used to relate structural neuroimaging findings to behavior.

MR imaging parameters. Structural images consisted of a whole-brain T_1-weighted image for each participant using sagittal 3-D spoiled gradient recall (SPGR) sequence (124 slices, voxel size = $1.5mm^3$).

Behavioral Measures of Language and Cognition. All participants received several behavioral measures outside the scanner, within two weeks of scanning, to measure language function and intelligence. These included the Clinical Evaluation of Language Fundamentals (CELF-III), which can be further divided into Receptive Language and Expressive Language subtests that measure fundamental elements of language such as sentence structure, word structure, concepts and directions, formulated sentences, recalling sentences, and semantic relationships (Semel, Wiig, & Secord, 1995). Participants were also given the Peabody Picture Vocabulary Test (PPVT), which measures receptive vocabulary and hearing comprehension (Dunn, 1997), and the Expressive Vocabulary Test (EVT), which measures their expressive vocabulary and word retrieval (Williams, 1997). Additionally, participants were administered the Johnson–Newport Grammaticality Judgment task, which tests their knowledge of English rules of grammar (Johnson & Newport, 1989). Lastly, participants also completed the Wechsler Adult Intelligence Scale (WAIS-III) if they were over 16 years (Wechsler, 1997), or the Wechsler Intelligence Scale (WISC-III) if they were under 16 years (Wechsler, 1991). From the WAIS-III, a Verbal Comprehension Index and a Perceptual Organization Index were derived. The Verbal Comprehension Index was composed of the Comprehension, Vocabulary, Similarities, and Comprehension subtests, while the Perceptual Organization Index was composed of the Block Design, Picture Completion, and Matrix Reasoning subtests.

Quantification of Cerebellar Grey Matter Volumes. We manually parcellated each participant's cerebellum following Schmahmann and colleagues' (1999) Three-Dimensional MRI Atlas of the Human Cerebellum in Proportional Stereotaxic Space (see Figure 3). For each cerebellum, with reference to Schmahmann et al. (1999), we identified the primary fissures (intraculminate, primary, superior posterior, horizontal, ansoparamedian, prebiventer, intrabiventer, secondary and posterolateral). Using these as boundaries and FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/), we manually drew in the lobules over anatomical scans. For the regional parcellation, following Diedrichsen, we grouped lobules I-III into one mask, and separately parcellated IV, V, VI, Crus I, Crus II, VIIb, VIIIa, VIIIb, IX, and X across both hemispheres (see Figure 4). Once the lobules were segmented with the manual drawings, statistics from the segmentation were extracted using the FreeSurfer software. FreeSurfer *mri seg_stats* was used to compute the segmented volumes, providing the number of voxels and volume in each region of interest.

Relation of Cerebellar Volumes to Behavioral Outcomes. We used robust statistical procedures to predict the outcome measures in order to control the effect of and be less influenced by outliers. Specifically, we used robust regression, which can be interpreted in the same way as the ordinary least square regression. The robust method, however, downweighs the influence of outlying values. We calculated 95% confidence intervals (CIs) and standard errors (SEs) to gauge reliability using the bootstrap to estimate the standard error of the parameters. Laterality measures for each region of interest were used as the predictor for each cerebellar lobule, which was calculated using the formula (left - right)/(left + right). If the laterality measure was positive, that indicated left laterality.

Other Covariates. In addition to regional volume, predictors in the regression included age in months, sex, and intracranial volume to control for head size. Because of the large number of regressions, we balanced Type I and Type II error control by reporting 95% confidence intervals for all parameters.

Power to Detect Effects of Interest. Assuming a modest effect, power analysis suggests we will require $n \sim 30$ in each group (effect size $r = .5$, power = .82, alpha = .05; R package *pwr*) to detect relations between predictors and outcomes. Our sample size (27 control) is sufficient based on this analysis. Power to detect effects of interest are improved by using bootstrap methods to determine SEs, and by focusing on particular cerebellar regions, which will reduce noise from other regions not thought to be involved in language.

Results

To relate the grey matter volume of the specific cerebellar lobules to expressive and receptive language measures, we conducted robust regressions using the laterality of cerebellar lobules as predictors and the specific submeasures of language as our outcome variables, while controlling for age, sex, and intracranial volume. Two findings are reported for those 95% CIs that do not cover zero. First, the laterality measure of lobule IV predicted expressive vocabulary in the Expressive Vocabulary Test (*b* = -48.20, $\beta = -0.39$, *t*(22) = -2.16, *p* = .04, 95% CI of *b* = -91.99 to -4.71), where greater right laterality predicted higher scores on the expressive vocabulary measure. Second, the laterality measure of VIIb predicted expressive language in the CELF-E (*b* = -44.25, $\beta = -0.35$, *t*(22) = -2.10, *p* = .05, 95% CI of *b* = -85.31 to -2.87), where greater right laterality predicted higher scores on the expressive language measure (see Table 1).

Discussion

In this study, we focused on the volumetric differences of specific cerebellar regions across development in relation to a battery of language measures. In analyzing the volume size of each cerebellar lobule in comparison to language function, we predicted the right posterior-lateral regions (VI, Crus I, Crus II, VIIb) would be related to better performance on the language measures. In general, our findings supported our predictions, with two posterior lateral right hemisphere lobules being related to two different measures of expressive language. Specifically, we found that greater volume of the right lobule IV predicted higher scores on the Expressive Vocabulary Test, while greater volume of the right posterior-lateral lobule VIIb predicted higher scores on the CELF-E.

While a detailed discussion of the Study 1 findings will occur in the General Discussion to make comparisons with the other findings from these studies, we will briefly note how these findings are consistent with prior research. Specifically, the finding relating the right posterior-lateral lobule VIIb to higher scores on the CELF-E is consistent with the findings of prior studies regarding the laterality of language in the cerebellum, the general regions associated with language function, and the relationship between grey matter volume and cognitive functioning. This finding is consistent with the idea that language is lateralized in the cerebellum based on the crossed cortico-ponto-cerebellar connections that connect the fronto-tempro-parietal cortical language regions to the right posterior-lateral region of the cerebellum (Naidich et al., 2009). This finding is also consistent with the findings from functional neuroimaging studies and meta-analyses that note the general regions associated with language function, specifically the right posterior-lateral regions VI, Crus I, Crus II, VIIb (E et al., 2014; Riedel et al., 2015; Stoodley & Schmahmann, 2009). Lastly, this finding contributes to the growing understanding that cerebellar volume measurement can have a reliable association to measured cognitive functioning (Moore et al., 2017; Pangelinan et al., 2011).

With respect to the finding related to lobule IV, this lobule is frequently examined in conjunction with lobules I-III as a result of the small size of the anterior lobe structures. Those findings consistently relate those cerebellar regions to sensorimotor regions and functions. Although it was not predicted *a priori*, the finding of our current study that demonstrated a relationship between lobule IV to an expressive vocabulary task is consistent with the task's engagement of speech production, and the region's association with motor regions and the motor execution of speech (Bernard & Seidler, 2013; Bernard et al., 2012; E et al., 2014; Marvel & Desmond, 2010; Naidich et al., 2009; Riedel et al., 2015; Turkeltaub, Eden, Jones, & Zeffiro, 2002). The cerebellum's structural connectivity to the sensorimotor network has long been established with classical anatomy studies (Naidich et al., 2009). These findings have been supported by functional connectivity studies revealing connectivity between lobules I-IV of the cerebellum to cortical motor and somatosensory regions (Bernard & Seidler, 2013; Bernard et al., 2012; Riedel et al., 2015). Furthermore, neuroimaging studies have revealed a functionally topographical cerebellum, with the medial anterior cerebellum, including lobule IV is consistently involved in motor functions, including the motor execution of overt speech (Marvel & Desmond, 2010; Riedel et al., 2015; Turkeltaub et al., 2002).

With a limited number of prior studies showing how volumetric differences in a neuro-typical population are related to differences in cognitive functioning and performance on language tasks, this study provides novel findings in a broad age group. These results fill a gap in knowledge and help us understand how volumetric differences across development are related to language functioning, showing how greater volume in the right posterior-lateral lobules of IV and VIIb predicts greater expressive language function.

III. STUDY 2

Research Question

With an increased interest in the cerebellum calling for inspection of focal regions, accurate identification and volumetric measurement of cerebellar sub-regions has become essential for assessing the cerebellum. Currently, there are atlases available for parcellating the cerebellum after spatial warping to a standard stereotactic space. Specifically, Schmahmann and colleagues created an MRI atlas of the human cerebellum that was warped to the Talairach space (Schmahmann et al., 1999), and Diedrichsen and colleagues created an MRI atlas of the human cerebellum, which used Schmahmann's landmarks and nomenclature, that was warped to the MNI space (Diedrichsen, Balsters, Flavell, Cussans, & Ramnani, 2009). While these atlases are useful in making group comparisons after warping to a template, the distortion of the images that occurs during spatial warping eradicates subtle individual differences that can be important in the phenomenon of interest. However, current atlases for individual identification of cerebellar regions are limited and supply only a gross parcellation of the cerebellum into "cerebellar white matter" and "cerebellar grey matter." Therefore, if the research interests call for keeping the brains in their natural space to assess individual differences, currently, the only option is to manually parcellate each brain, which is a complicated and time-consuming process that requires precise knowledge of cerebellar anatomy. Therefore, our aim for Study 2 was to create an MRI atlas of the human cerebellum that can be applied in the individual subject space. Using the brains from our manual parcellations in Study 1, we developed a semi-automated cerebellar atlas, which will facilitate accurate identification of cerebellar sub-regions on an individual basis, and which will be very useful for the neuroimaging community. These individual atlases will be tested against the manual parcellation in Study 2 and will be used to parcellate the cerebellum of the perinatal stroke sample for analysis in Study 3.

Method

Developing the Group Atlas. FreeSurfer software provides tools to apply atlas conventions to individual brains processed through its pipeline. Specifically, FreeSurfer employs a proprietary file format (Gaussian Classifier Atlas) that encodes voxel label information based on probabilistic information estimated from a training set (Fischl et al., 2002, 2004). We supplied the training set, which was taken from our manual parcellations of the typical control group. As described in Study 1, each voxel in the 27 control group participants' cerebellum was manually labeled based on the nomenclature and noted landmarks from the Schmahmann atlas (Schmahmann et al., 1999). We also added 20 brains manually parcellated by, and kindly made available by, Diedrichsen for a total of 47 brains to comprise the newly developed atlas (note that the standard FreeSurfer cortical atlas uses 40 brains (Diedrichsen et al., 2009). Since both manual parcellations were created using Schmahmann’s nomenclature, it was possible to combine the two datasets seamlessly. The Gaussian Classifier Atlas (GCA) used the training set provided to calculate a number of probabilities about the tissue class, anatomical class, and relative spatial patterns. Specifically, it measured the voxel intensity to determine the probability that the voxel represents a specific type of tissue. Also, given the information provided in the atlas, it computed the probability that a voxel was a given label on the basis of its location in space. Lastly, the GCA calculated the probability that a voxel is a particular label depending on the labels in the surrounding voxels (Fischl et al., 2002, 2004). The output provided is a probabilistic map that takes into account the probabilities noted above and can be applied to future datasets with accuracy relative to manual parcellation.

Testing the Atlas. To establish the accuracy of the semi-automated parcellation, the performance of the semi-automated cerebellar parcellation was compared to a manual parcellation conducted on the same brains. A standard quantitative metric for accuracy of ROI identification is the Dice coefficient, which measures the overlap between two ROI sets, $(2|S_1 \cap S_2|)/(|S_1 + S_2|)$ where $|.|$ denotes the area of the ROI (Dice, 1945). We computed an average Dice similarity coefficient (DSC) and standard deviation for each brain, as well as for each lobule of the cerebellum, to compare the semi-automated with the manual labeling. The DSC value ranges from 0 to 1, with 0 indicating 0 overlap, and 1 indicating an exact match. In addition, we conducted t-tests to test the statistical significance of the dice coefficients relative to a null of zero.

Results and Discussion

The average DSC for the total cerebellar cortex is 0.98 ± 0.02. The average DSC of each of the 22 lobules ranges from 0.80 to 0.96 (see Table 2). The dice coefficients of all 22 lobules and the total cerebellum were all statistically different from zero at $p < .001$ (see Figure 5). The results indicate that the semi-automated atlas segments the cerebellum into its lobules with very high accuracy. Given that the total cerebellum's DSC between the manual and semi-automated parcellation is of 0.98 ± 0.02, and the parcellation of each lobule is at minimum a 0.80 ± 0.13 DSC, the final result of the semi-automated parcellation reaches a level of accuracy where little manual edits are needed. In fact, although all brains were inspected, manual edits were not required (see Figure 6).

The use of the semi-automated atlas enhances the efficiency of the segmentation of individual cerebellums into their 22 lobules by decreasing the time it requires to segment each brain. With a more efficient process, it provides the resource to segment large volumes of brains while keeping the image in its original dimensions. While currently it is possible to segment the cerebellum into its lobules after warping the images to a template, a disadvantage to doing so is the loss of individual differences when distorting the original image to match a stereotaxic space. Warping to a template is also not ideal in cases where the brain is lesioned, or in cases investigating pediatric populations, as standard templates are developed on unlesioned, adult brains. The current semi-automated atlas eliminates this issue and allows for the segmentation of a large number of subjects in their individual anatomic space.

IV. STUDY 3

Research Question

The present study focused on the structural volumetric analysis of the grey- and white- matter of cerebellar subregions following a perinatal stroke, and how the volume of the individual subregions compares to expressive and receptive language outcomes.

Grey Matter Analysis. Similar to Study 1, we identified the main lobules based on the nomenclature of Schmahmann and colleagues' (1999) Three-Dimensional MRI Atlas of the Human Cerebellum in Proportional Stereotaxic Space and calculated the volume of each region. We investigated the relationship between each region's grey matter volume size to a battery of language measures, including measures of expressive and receptive language, grammar, and IQ.

Based on the reviewed literature, we predicted that similar to typical controls, greater cerebellar grey matter volume, specifically in the right posterior-lateral regions (VI, Crus I, Crus II, VIIb), will be related to better performance on the language measures. We predicted that the perinatal stroke patients would show smaller cerebellar volumes compared to typical controls that negatively correlate to language outcomes. Given that language processing is generally left-lateralized in the cerebral cortex, and the crossed cortical-cerebellar pathways, we expected that those patients with left cortical lesions would show greater atrophy in the right cerebellar hemispheres, which would result in a more significant effect of the results.

Myelin Content Analysis. For the myelin content analysis, we identified the cerebellar lobules and calculated each region's myelin content. We investigated the relationship between the volume of each region's myelin content to a battery of language measures, including measures of expressive and receptive language, grammar, and IQ.

Based on the reviewed literature, we predicted that similar to the grey matter analysis, greater cerebellar myelin content in the regions typically associated with language function, specifically right posterior-lateral regions (VI, Crus I, Crus II, VIIb), will be related to better performance on the language measures. Given that language processing is generally left-lateralized in the cerebral cortex, and the crossed cortical-cerebellar pathways, it was expected that those patients with left cortical lesions would show atrophy in the right cerebellar hemispheres, which would result in a more significant effect of the results.

Method

Participants.

Participants include 19 children and adults with a documented history of perinatal stroke, diagnosed by developmental history, neurological examination, and either CT or MRI. Information about demographics and neurological status includes the following:

Demographics. There is a wide age range in the sample: *M*=190.74 months (15.89 years); *SD*=82.93 months (6.91 years); range=86–358 months (7.17–29.83 years). There are 7 males (36.84%) and 12 females (63.16%).

Lesion Location/Type. The side of injury is determined based on the side of the predominant injury. Given general left hemisphere lateralization of cortical regions associated with language function, all analyses have focused on the 19 patients that have predominantly left hemisphere lesions. The type of injuries are heterogenous, which is common with pre- and perinatal stroke (see Table 3).

Lesion Size. Fractional volume loss (FVL) was calculated on the T1 scan as our measure for lesion size. FVL = [(VN – VL)/VN] * 100, where VN is the volume of the intact hemispheric, and VL is the volume of the hemisphere containing the lesion. In this sample, FVL values range from 0.04% to 48.6% (*M*=16.83%; *SD*= 15.05%).

Neuroimaging and Behavioral Data Acquisition. Structural T_1- and T_2-weighted MRI were used to examine neural processes and structures of interest. Behavioral measures collected outside the scanner were used to relate structural neuroimaging findings to behavior.

MR imaging parameters. Structural images consist of a whole-brain T_1-weighted image for each participant using sagittal 3-D spoiled gradient recall (SPGR) sequence (124 slices, voxel size = 1.5mm^3), and a whole-brain T_2-weighted fluid-attenuated inversion-recovery (FLAIR) sequence image for each participant (18 axial slices, voxel size = 7.5 mm x 0.43 mm x 0.43 mm).

Behavioral Measures of Language and Cognition. The acquisition of behavioral data was the same as Study 1 (*see Table 4 for Group Performances on Behavioral Measures*).

Quantification of Cerebellar Grey Matter Volumes. Quantification of cerebellar grey matter was accomplished by applying the atlas created in Study 2 to T_1-weighted MR images of participants with brain lesions. The atlas segmented the cerebellum into its lobules based on the nomenclature of Schmahmann’s atlas (Schmahmann et al., 1999), as was done in Study 1. Once the atlas was applied and the cerebellum was segmented into its lobules, two separate researchers conducted a visual inspection of each cerebellum. Following the visual inspection, statistics from the segmentation were extracted using the FreeSurfer software. FreeSurfer *mri seg_stats* was used to compute the segmented volumes, providing the number of voxels and volume in each region of interest. The volume of each ROI was calculated based on the number of voxels in the mask, which was then compared to behavioral measures of language.

Quantification of Myelin in Cerebellar Subregions. We quantified the myelin content in the cerebellar lobules using the ratio of the T_1- /T_2-weighted MRI method from Glasser and Van Essen (2011). A benefit of this method is that it has shown to enhance the contrast to noise ratio between high and low myelin levels and eliminates the MR image intensity bias related to the sensitivity of the radio frequency receiver coils, which is present in both types of images. The dependent measure derived from this method is $(T_1w/T_2w) = x^2$ (Glasser & Van Essen, 2011). Although Glasser and Van Essen's method calls for the T_2-weighted image, Bajaj and colleagues found that the T_2-weighted FLAIR image can be used as a supplement showing that it provides a similar contrast as the T_1-/T_2-weighted MRI method (Bajaj, Pine, & Winkler, 2019). Therefore, we used this modified method of the ratio of T_1/T_2-weighted FLAIR to calculate x^2 in the cerebellar lobules for each participant, which was then compared to behavioral measures of language.

Relation of Cerebellar Volumes to Behavioral Outcomes. To mitigate concerns about the brains' heterogeneity with perinatal injuries, we used robust statistical procedures to predict the outcome measures. Robust procedures are less influenced by outliers and increase the precision of parameter estimates when there are outliers. Specifically, we used robust estimates regression, which can be interpreted in the same way as the least square regression. We calculated 95% confidence intervals (CIs) and standard errors (SEs) to gauge reliability using bootstrap methods to estimate the parameters. Laterality measures for each region of interest were used as the predictor, which was calculated using the formula (left - right)/(left + right). If the laterality measure was positive, that indicated left laterality.

Other Covariates. In addition to regional volume, predictors in the regression included age in months, sex, FVL (as a covariate to control for lesion size), and intracranial volume to control for head size.

Power to Detect Effects of Interest. Assuming a modest effect, power analysis suggests we will require *n* ~ 30 in each group (effect size *r* = .5, power = .82, alpha = .05; R package *pwr*) to detect relations between predictors and outcomes. Our sample size (27 control, 19 perinatal stroke patients) is sufficient based on this analysis. Power to detect effects of interest will be improved by using bootstrap methods to determine SEs, and by focusing on particular cerebellar regions, which will reduce noise from other regions not thought to be involved in language.

Results

Grey Matter Analysis. Due to typical left hemisphere lateralization of language function, the following grey matter analyses were conducted on those with left hemisphere lesions, to test for developmental changes to the language network following perinatal stroke. To relate the grey matter volume of the specific cerebellar lobules to expressive and receptive language measures, we conducted robust regressions using the laterality of cerebellar lobules as predictors and the specific submeasures of language as our outcome variables, while controlling for age, sex, lesion size (FVL) and intracranial volume. There were 3 significant findings within the perinatal stroke sample all relating expressive vocabulary to greater volume in three regions on the right hemisphere of the cerebellum. The laterality measure of the cerebellar cortex (*b* = -300.01, $\beta = -0.35$, $t(13)$ = -2.29, *p* = .03, 95% CI of *b* = -553.98 to -39.69), lobule IV (*b* = -184.59, $\beta = -0.47$, *t*(13) = -2.63, *p* = .02, 95% CI of *b* = -323.15 to -49.02), and Crus I (*b* = -328.40, $\beta = -0.61$, *t*(13) = -3.10, *p* = .01, 95% CI of *b* = -540.40 to -125.47) predicted expressive vocabulary in the Expressive Vocabulary Test, where greater right laterality predicted higher scores on the expressive vocabulary measure (see Table 5).

To understand how the age of participants at testing moderates the relationship between regional volume and language measures, we conducted robust regressions using the laterality of cerebellar lobules with the interaction of age as predictors and the specific submeasures of language as our outcome variables, while controlling for sex, lesion size (FVL) and intracranial volume. Two regions' association to language measures were impacted by the age of testing. Specifically, the interaction of the laterality measure of lobule IV and age at testing predicted verbal IQ (*b* = -0.78, $\beta = -0.05$, *t*(13) = -2.48, *p* = .01, 95% CI of *b* = -1.4 to -0.16), where greater left laterality predicted higher scores on the Verbal IQ measure at the age of 8.98 years, but greater right laterality predicted higher scores at the age of 22.8 years. Also, the interaction of the laterality measure of lobule VIIIa and age at testing predicted grammaticality (*b* = -0.31, $\beta = -0.03$, *t*(13) = -2.43, *p* = .02, 95% CI of *b* = -0.56 to -0.06), where greater left laterality predicted higher scores on the Johnson-Newport Grammaticality Judgement task at the age of 8.98 years, but greater right laterality predicted higher scores at the age of 22.8 years (see Table 6).

To test the difference between typical controls and perinatal stroke patients' relation of grey matter volumes to language measures, we conducted robust regressions using the interaction of the laterality of cerebellar lobules and group as predictors and the specific submeasures of language as our outcome variables, while controlling for age, sex, and intracranial volume. There was a significant interaction effect between the laterality of five regions and group to the language measures. The interaction of the laterality measure of lobule Crus I and group predicted expressive vocabulary (b = -364.03, $\beta = -18.62$, $t(39)$ = -2.98, p = .01, 95% CI of b = -603.08 to -124.98), where greater right laterality predicted higher scores on the EVT for patients following perinatal stroke, but there was no relationship between the laterality measure and expressive vocabulary in typical controls. Also, the interaction of the laterality measure of the cerebellar cortex and group predicted expressive vocabulary (b = -322.62, $\beta = -16.5$, $t(39)$ = -2.14, p = .04, 95% CI of b = -617.84 to -27.4), where greater right laterality predicted higher scores on the EVT for patients following perinatal stroke, but there was no relationship between the laterality measure and expressive vocabulary in typical controls.

However, the following three results presented contrasting outcomes, showing greater left laterality predicted higher scores on the language measures for patients following perinatal stroke. Specifically, the interaction of the laterality measure of lobule VI and group predicted expressive language (b = 174.69, $\beta = 10.47$, $t(39)$ = 2.31, p = .03, 95% CI of b = 26.34 to 323.04), where greater left laterality predicted higher scores on the CELF-Expressive test for patients following perinatal stroke, but there was no relationship between the laterality measure and expressive language in typical controls. The interaction of the laterality measure of lobule VIIIa and group predicted grammaticality (b = 80.07, $\beta = 6.58$, $t(39)$ = 3.62, p = .001, 95% CI of b = 36.77 to

123.37), where greater left laterality predicted higher scores on the Johnson-Newport Grammaticality Judgement task for patients following perinatal stroke, but there was no relationship between the laterality measure and expressive language in typical controls. Lastly, the interaction of the laterality measure of lobule IX and group predicted receptive vocabulary (*b* = 126.91, $\beta = 8.69$, *t*(39) = 2.01, *p* = .05, 95% CI of *b* = 3.14 to 250.67), where greater left laterality predicted higher scores on the PPVT for patients following perinatal stroke, but there was no relationship between the laterality measure and receptive vocabulary in typical controls (see Table 7).

Myelin Content Analysis. Similar to the grey matter analyses, due to typical left hemisphere lateralization of language function, the following myelin content analysis was conducted on those with left hemisphere lesions, to test for developmental changes of the myelin content in cerebellar lobules following perinatal stroke. To relate the myelin content volume in the specific cerebellar lobules to expressive and receptive language measures, we conducted robust regressions using the laterality of T_1/T_2-FLAIR ratio in cerebellar lobules as predictors and the specific submeasures of language as our outcome variables, while controlling for age, sex, lesion size (FVL) and intracranial volume.

Within the anterior lobe of the cerebellum, the laterality measure of lobule I-III predicted grammaticality (*b* = -97.32, $\beta = -7.72$, *t*(10) = -2.98, *p* = .01, 95% CI of *b* = -161.30 to -33.35) and verbal IQ (*b* = -112.59, $\beta = -7.18$, *t*(10) = -2.99, *p* = .01, 95% CI of *b* = -186.51 to -38.67), with greater right laterality predicting higher scored on both the Johnson-Newport Grammaticality Judgement task and the verbal submeasure of the IQ test. However, within the posterior lobe, greater left laterality of lobule VIIIa predicted higher scores on the EVT (*b* = 39.65, $\beta = 1.88$, *t*(10) = 2.84, *p* = .02, 95% CI of *b* =

12.28 to 67.01) and VIQ ($b = 37.39$, $\beta = 2.39$, $t(10) = 2.35$, $p = .04$, 95% CI of $b = 6.22$ to 68.57). Also, greater left laterality of lobule VIIIb predicted higher scores on the EVT ($b = 58.28$, $\beta = 2.76$, $t(10) = 2.42$, $p = .04$, 95% CI of $b = 11.08$ to 105.49) (see Table 8).

Discussion

In this study, we focused on post-stroke developmental outcomes in relation to language function. Specifically, similar to Study 1, we analyzed the volumetric differences of specific cerebellar regions across development in relation to a battery of language measures. In analyzing the volume size of each cerebellar lobule in comparison to language function, we predicted that greater atrophy of right posterior-lateral regions (VI, Crus I, Crus II, VIIb) would be related to worse performance on the language measures. Our findings show mixed results in terms of lateralization of language function within the cerebellum when comparing post-stroke development to typical development. These findings partially support our prediction by associating greater volume size of right hemisphere regions IV, Crus I, and the right cortex to better performance on an expressive language measure. However, post-stroke developmental outcomes also revealed a greater left lateralization of cerebellar lobules VI, VIIIa, and IX to be associated with higher scores on expressive and receptive language, with no association of the laterality measure to language measures in typical development. These results demonstrate developmental changes following early brain injury to language processing. In the following discussion, we'll briefly note how the current study results are consistent with prior research. A more detailed discussion comparing the results of this study and Study 1 will occur in the General Discussion. The current findings present several novel findings with a significant bilateral relationship to language function, including the continued right laterality of language in the cerebellar regions typically associated with language function following damage to the cerebral cortex's left hemisphere, and the relationship between grey matter volume of specific regions in both hemispheres of the cerebellum with language function.

The findings associating the right hemisphere regions of IV, Crus I, and the right cortex with expressive vocabulary support the theory that regions involved in the typical language network are still critical for language function even with cortical damage to the left hemisphere following perinatal stroke. Indeed, prior studies of post-stroke outcomes following damage to the left hemisphere note the significance of left cortical regions for language function (Beharelle et al., 2010; Carlson et al., 2019). These findings denote the early lateralization of language function and the significance of the structural and functional connectivity from the damaged regions in the cerebral cortex's left hemisphere to the other areas within the language network, including right cerebellar regions. Specifically, the finding relating the right posterior-lateral lobule Crus I to higher scores on the EVT is consistent with the functional neuroimaging studies and meta-analyses that note the general regions associated with language function are the right posterior-lateral regions VI, Crus I, Crus II, VIIb (E et al., 2014; Riedel et al., 2015; Stoodley & Schmahmann, 2009). While those meta-analyses focus on a healthy population, the finding continues to be true following perinatal stroke affecting left supratentorial regions, suggesting the continued functional connectivity of cerebellar right posterior-lateral regions to the typical language network. Lastly, the finding supports our prediction that greater atrophy of the right cerebellar region would relate to poorer performance on the language measures. Indeed, greater volume of the right hemisphere was associated with higher performance on the expressive language measure, adding support to the relation of cerebellar volume to measured cognitive functioning (Moore et al., 2017; Pangelinan et al., 2011).

However, while prior studies consistently link the right posterior regions of the cerebellum to language function, including the right Crus I, the current study's results demonstrate post-stroke developmental changes. Specifically, the laterality measure of Crus I showed no association to language measures in typical development but a significant association between greater right laterality and expressive vocabulary following perinatal stroke. Not only does there seem to be a greater reliance on cerebellar regions typically involved in the language network following a perinatal stroke, but the results show post-stroke developmental changes linking left hemisphere cerebellar regions to language measures. The plasticity of the brain following damage to left cortical regions results in a partial reorganization, with prior studies showing the significance of some right hemisphere cortical regions and interhemispheric connectivity for improved language function (Dick et al., 2013; Guzzetta et al., 2008; Jacola et al., 2006; Tillema et al., 2008). Given the crossed cortico-ponto-cerebellar connectivity, increased reliance on right cortical regions for language function would then link left hemisphere regions of the cerebellum to the language network following early brain injury. The current study results linking greater left laterality of lobules VI, VIIIa, and IX to expressive and receptive language measures fit with these post-stroke developmental changes.

The functional association of language function to the cerebellar regions VI, VIIIa, and IX are consistent with prior literature noting the regions’ association to cognitive function and language. Prior functional neuroimaging studies and meta-analyses in typically developing samples show a consistent association with the right VIIIa and word generation and sensorimotor functions, while the left hemisphere is typically linked with spatial processing, and has a bilateral association with working memory, specifically the maintenance and storage of information (Chen & Desmond, 2005a; Kirschen, Chen, Schraedley-Desmond, & Desmond, 2005; Stoodley, 2012; Stoodley, Valera, & Schmahmann, 2010). Our finding associating greater left laterality of lobule VIIIa with grammaticality fits with the literature showing the relationship between verbal working memory and the acquisition of grammar (Bosma, Heeringa, Hoekstra, Versloot, & Blom, 2017) and greater performance on a grammatical judgment task (Zhou, Rossi, & Chen, 2017). Similarly, prior studies link the right hemisphere of lobule VI with word generation and sensorimotor functions, the left hemisphere with spatial processing, and bilateral activation with working memory, executive function, and emotional processing (Stoodley, 2012; Stoodley et al., 2010). Our finding associating greater left laterality with expressive language fits with the current literature's findings of the region's involvement in word generation and cognitive processing. Lastly, prior studies analyses of lobule IX's activation patterns show a bilateral association to sensorimotor functions (Stoodley, 2012), where the right hemisphere is associated with verbal working memory and emotional processing (E et al., 2014). Our finding associating greater left laterality of lobule IX with a receptive vocabulary measure fits with the literature showing an associating between the region and verbal working memory. However, the focus of the prior literature reviewed above has been on typically developing samples, and therefore some of the differences in lateralization of function may be a result of post-stroke plasticity in lateralization. Even so, the findings of the current study are consistent with the regions’ association to language processing and cognitive functions and demonstrate the continued distribution of functional processing across an anterior to posterior axis following early brain injury, with certain regions continued association to language processing, however with some differences in lateralization due to post-stroke developmental changes.

V. GENERAL DISCUSSION

Summary

The overall goal of the current dissertation was to better understand the region-specific morphological changes in the cerebellum across typical and atypical development, and how these changes are associated with language function. With the manual parcellations of Study 1, we also sought to create a cerebellar atlas that would provide a semi-automated parcellation of the cerebellar grey matter lobules and apply it to future datasets for a more efficient approach to studying lobule specific relation to cognition. With the utilization of this new cerebellar atlas, we also sought to understand region-specific morphological changes in the cerebellum following perinatal stroke and the effects these changes may have on language development. The framework for our approach was the known cortico-cerebellar connectivity, which guided our reasoning as to the regions within the cerebellum that may be related to language function, and the regions in the cerebellum that would likely be the target of secondary effects to cortical injury. The following summary will review the findings of the current dissertation and how they relate to past research. The discussion will end with the theoretical implications of the present dissertation, methodological limitations, and the future directions needed to better understand the cerebellum’s relationship to language.

Study 1: The cerebellum’s relation to language function in typical development. In Study 1, we investigated the association between the volume of specific cerebellar regions across typical development with a number of language tasks. We manually parcellated the structural T1-weighted MRIs of the cerebellum of each of the 27 participants ranging in age from 8 to 40 years. We used Schmahmann and colleagues'

(1999) Three-Dimensional MRI Atlas of the Human Cerebellum in Proportional Stereotaxic Space as a guide to manually create the demarcations between lobules. We then assessed each cerebellar region to see if the volume size related to measures of expressive and receptive language, as well as general cognition. Those tasks included the Clinical Evaluation of Language Fundamentals (CELF-III) (Semel et al., 1995), Expressive Vocabulary test (Williams, 1997), Johnson–Newport Grammaticality Judgment task (Johnson & Newport, 1989), and the Wechsler Adult Intelligence Scale (WAIS-III) if they were over 16 years (Wechsler, 1997), or the Wechsler Intelligence Scale (WISC-III) if they were under 16 years (Wechsler, 1991). We found that greater volume in two regions in the right hemisphere of the cerebellum were related to higher performance on language measures. Specifically, lobule IV predicted expressive vocabulary in the Expressive Vocabulary Test, where greater right laterality predicted higher scores on the expressive vocabulary measure. Second, the laterality measure of VIIb predicted expressive language in the CELF-E, where greater right laterality predicted higher scores on the expressive language measure.

Our finding of the relation of the right cerebellar lobule IV with expressive vocabulary is consistent with the long-standing view of the cerebellum's role in coordinating motor function, especially the anterior regions of the cerebellum (Stoodley & Schmahmann, 2009; Stoodley, Valera, & Schmahmann, 2012). Past research has consistently linked the cerebellum with regulating motor aspects of speech production, which is applicable in the case of an expressive vocabulary task and consistent with the literature associating single-word utterances with right-hemisphere anterior regions of the cerebellum (Ackermann, Mathiak, & Riecker, 2007). This finding is also compatible with the known crossed cortico-cerebellar connectivity, linking right hemisphere regions of the cerebellum to the left cortical motor cortex (Ackermann, Wildgruber, Daum, & Grodd, 1998). Furthermore, clinical studies have shown several functional abnormalities in speech production following damage to the cerebellum, such as ataxic dysarthria and transient cerebellar mutism (Ackermann et al., 2007). Thus, the result of the current study linking the right cerebellar lobule IV with expressive vocabulary is consistent with the literature given what is known about the long-standing view of the anterior portions of the cerebellum's relationship with motor planning, the known crossed cortico-cerebellar connectivity, and the clinical findings demonstrating language function impairments following damage and disorders affecting the cerebellum (Ackermann et al., 2007, 1998; Stoodley & Schmahmann, 2010).

The second finding relating right lobule VIIb with expressive language supports prior research demonstrating a general right laterality for cognitive function, including language (Argyropoulos, 2016; Ashida, Cerminara, Edwards, Apps, & Brooks, 2019; Chen & Desmond, 2005b; E et al., 2014; Lesage et al., 2017; Mariën & Manto, 2018; Salmi et al., 2010; Schmahmann, 2010; Stoodley, 2012; Stoodley & Schmahmann, 2009; Stoodley et al., 2012). Specifically, past research has associated activation in the posterior lateral region of the right lobule VIIb with a verb generation task (Stoodley et al., 2012) and verbal working memory tasks (Chen & Desmond, 2005b; Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997; Ng et al., 2016; Salmi et al., 2010), specifically during the encoding and maintenance phases (Chen & Desmond, 2005b). Past research also links the activation of the right lobule VIIb with the left hemisphere of the pons (Chen & Desmond, 2005b), and the left hemisphere of cortical temporal and parietal regions known to be involved in language functions (Ng et al., 2016). These findings are consistent with the known crossed cortico-ponto-cerebellar pathways (Naidich et al., 2009), and adds support to the notion that the specific function of each cerebellar region is dependent on the afferent and efferent connections. With regards to language function, the current findings support the association of the right cerebellar lobule VIIb with the rest of the language network. However, as Chen and Desmond (2005) demonstrate in their study of verbal working memory, understanding the cerebellum's specific contribution to language function requires an in-depth analysis of each phase of a language task, and the mechanistic functions required during each phase to understand where exactly the cerebellum provides its contribution and how exactly it is doing so.

Study 2: The development of the cerebellum atlas. The goal of Study 2 was to develop the cerebellum atlas and utilize it to study region specific relations to language function. We created a cerebellar atlas that parcellates the cerebellum into the lobules based on the nomenclature and noted landmarks from the Schmahmann atlas (Schmahmann et al., 1999), using the 27 manual parcellations from Study 1 combined with 20 brains manually parcellated by Diedrichsen (Diedrichsen et al., 2009). The combined dataset totaled 47 brains (note that the standard FreeSurfer cortical atlas uses 40 brains), which compromised the training set that was then used to create a probabilistic map using the tools in the FreeSurfer software. Specifically, the Gaussian Classifier Atlas encoded voxel information based on probabilities about the tissue class, anatomical class, and relative spatial patterns. We tested the accuracy of the semi-automated parcellation by comparing the results to a manual parcellation conducted on the same brains and found a statistically significant level of accuracy with a high average dice coefficient (0.98 ± 0.02). Indeed, although we inspected each brain, we found no significant errors that required manual intervention.

The availability of a semi-automated tool to increase the efficiency of segmenting the cerebellum has a number of effects on the study of the cerebellum, including the continued understanding of the functional role of the specific regions in the cerebellum. Currently, a large number of studies have a vague representation of regions that are associated with certain functions, associating certain motor and cognitive functions to gross regions such anterior/posterior and lateral/medial. Given the large number of tasks and functions the cerebellum is associated with, and the continued implication of a functional topographical map within the cerebellum (Stoodley & Schmahmann, 2010), the ability to efficiently and effectively segment the cerebellum is a necessary and advantageous tool to understanding each region's role.

The enhanced ability to segment the cerebellum into its structural subdivisions can also contribute to the advancement of studies in disorders that impact the cerebellum. Understanding how specific regions in the cerebellum are associated with certain functions can provide much-needed information on potential targets for cerebellar stimulation in the treatment of both acquired and developmental disorders in the cerebellum. A number of studies have demonstrated the success in cerebellar stimulation for enhanced motor recovery following stroke (Cooperrider, Momin, Baker, & Machado, 2020; Koch et al., 2019; Machado & Baker, 2012; Wathen, Frizon, Maiti, Baker, & Machado, 2018). The success in post-stroke motor recovery following cerebellar stimulation can indicate the possibility of targeting the cerebellum for treatments in cognitive disorders. With a semi-automated atlas that segments the cerebellum into its structural subdivisions, we can better understand each region’s role and their potentiality for treatment targets in cognitive domains such as language function.

Study 3: The cerebellum’s relation to language development following perinatal stroke. Study 3 aimed to better understand the cerebellum’s morphological changes following a perinatal stroke and whether cortical injury leads to atrophy of the contralateral cerebellar hemisphere. We also sought to understand how these developmental changes following perinatal stroke affect the cerebellum’s relation to language function and how the cerebellum’s relation to language function differs between typical participants and perinatal stroke patients. To do so, we applied our newly created cerebellar atlas to the structural T1-weighted MRIs of the cerebellum of each of the 19 children and adults ranging in age from 7 to 30 years with a documented history of perinatal stroke with left hemisphere cortical lesions. Similar to Study 1, once we segmented each participant's cerebellum into its structural lobules, we then assessed each cerebellar region to see if the volume size related to measures of expressive and receptive language and general cognition. Those tasks were the same as those used in Study 1, which included the Clinical Evaluation of Language Fundamentals (Semel et al., 1995), Expressive Vocabulary Test (Williams, 1997), Peabody Picture Vocabulary Test (Dunn, 1997), Johnson–Newport Grammaticality Judgment task (Johnson & Newport, 1989), and the Wechsler Adult Intelligence Scale (WAIS-III) if they were over 16 years (Wechsler, 1997), or the Wechsler Intelligence Scale (WISC-III) if they were under 16 years (Wechsler, 1991).

In our analysis of the regions associated with language function following perinatal stroke, we found that greater volume in three regions in the right hemisphere of the cerebellum were related to higher performance on expressive language measures. Specifically, greater right laterality of the cerebellar cortex, lobule IV, and Crus I predicted higher scores on the Expressive Vocabulary Test. These findings for the atypically developing sample included right hemisphere regions that are typically associated with language function in a healthy population. As mentioned in the general discussion of Study 1, right hemisphere regions of the cerebellum are structurally and functionally connected to the language network in a healthy population, where anterior regions are associated with motor planning and posterior regions with prediction and error detection in cognitive functioning. Following a perinatal stroke, some of the same regions involved in language function in a healthy population continue to be significantly involved in language function, as measured by each lobule's comparative volume size across hemispheres.

One of the findings was the same result as Study 1, associating greater right laterality of the motor region lobule IV with expressive language. As was previously mentioned with the healthy controls, this finding is consistent with prior studies associating the cerebellum's anterior regions with coordinating motor function, including motor aspects of speech (Stoodley & Schmahmann, 2009; Stoodley et al., 2012). A novel finding for the sample of atypically developing participants following perinatal stroke is our finding associating greater right laterality of lobule Crus I and the right cortex with expressive language. While this finding is consistent with the literature that frequently associates right lateral posterior regions of the cerebellum, including the right Crus I, with language function (Frings et al., 2006; Mariën et al., 2014; Stoodley & Schmahmann, 2009; Stoodley et al., 2010, 2012), results of the current study did not find an association between the laterality measure of Crus I and the cortex with language function within the typically developing sample. These findings highlight post-stroke developmental patterns and how greater right lateralization following perinatal stroke may be more necessary for language outcomes than in typical development. Instead of a total functional reorganization of the language network taking place due to the damage of the connecting language regions, as has been theorized, structures typically involved in the language network continue to be necessary for optimal functioning. Given that these right hemisphere regions within the cerebellum are the regions typically associated with the left cerebral cortex regions through the crossed cortico-ponto-cerebellar pathways, these findings within left hemisphere stroke patients may indicate that language functioning following perinatal stroke may rely on the subsequent development of the typical language network and the integrity of the structural and functional connectivity with the damaged region.

However, group comparisons also found a novel organization of language function following perinatal stroke, with an association between greater left laterality of posterior regions and language measures. Specifically, our results found greater left lateralization of lobule VI predicted expressive language, lobule VIIIa predicted grammatical judgment, and lobule IX predicted receptive vocabulary. These findings are partially consistent with the literature related to the typical function of those regions. Meta-analyses of the functional mapping of the cerebellum in typical development have found that the left hemisphere of lobules VI and VIIIa are associated with spatial processing, with bilateral activation during verbal working memory tasks, while the right hemisphere of these lobules are typically associated with word generation. Similarly, the right hemisphere of lobule IX is associated with verbal working memory and emotional processing, with bilateral activation during sensorimotor functions (E et al., 2014; Stoodley, 2012; Stoodley et al., 2010). While the current results may be explained by the association between the cognitive processes the regions are typically is involved with, it may also be related to post-stroke developmental changes in lateralization. Prior studies focused on post-stroke outcomes have noted the changes in connectivity and laterality following early brain damage, with increased interhemispheric connectivity as well as a right hemisphere association to language function. Given that the right hemisphere of all three regions is typically associated with language measures, the findings of our current results may speak to a switch in lateralization of those language functions.

The switch in lateralization may be especially true early in development, given the current results' age effects. Specifically, our findings showed that early in development, there is an association between greater left lateralization of lobules IV predicted verbal IQ, and greater left lateralization of lobule VIIIa predicted grammatical judgment. Later in development, the association of both regions' laterality to language function flipped to right lateralization. These novel findings shed light on post-stroke developmental changes, demonstrating the brain's plasticity across development, with some compensation early in development from contralateral regions typically involved in the language network, some reorganization permanent across development, and also maintaining some typical developmental patterns with regions consistently involved in language function.

Implications, Limitations, and Future Directions

Structural Boundaries for Functional Map. The cerebellum's structural boundaries are useful given the consistent evidence for functional association to general regions (E et al., 2014; Stoodley & Schmahmann, 2009). We are able to consistently predict that specific neighboring lobules are associated with activations related to general language functions. Specifically, lobules VI, Crus I, Crus II, and VIIb have consistently been associated with tasks that target language function such as verbal fluency, verbal working memory, and verb generation (E et al., 2014; Stoodley & Schmahmann, 2009). However, there are two issues to our current mapping of structural regions of the cerebellum to functional tasks. The first issue involves our method of defining cerebellar structures. The structures of the cerebellum are divided into 10 lobules in each hemisphere based on deep fissures between each lobule (Schmahmann et al., 1999). While these deep sulci provide consistent landmarks within the cerebellum to compare and discuss findings within the cerebellum, a more detailed parcellation method is required. If compared to the structural demarcations within the cerebral cortex, even the cortical gyri are further subdivided based on consistent folds across brains. For instance we know that the inferior frontal gyrus is consistently divided in three general parts, the *pars opercularis*, *pars triangularis*, and *pars orbitalis*, and each of those parts are associated with different functions (Hartwigsen, Neef, Camilleri, Margulies, & Eickhoff, 2019; Molnar-Szakacs, Iacoboni, Koski, & Mazziotta, 2005). While the cerebral cortex also contains Brodmann areas based on differences in cytoarchitecture that structurally define regional differences in functional associations (Korbinian Brodmann, 1909), which similar differences within the cerebellum are just surfacing in research (De Zeeuw, Lisberger, & Raymond, 2020), the detailed map of the cerebral cortex based on consistent folding patterns across brains provides the specificity and the language to discuss structural boundaries for functional associations and that aspect could be the same for the cerebellum. Known cortico-cerebellar connectivity patterns have already demonstrated that we should be further subdividing cerebellar lobules into lateral functional zones of medial, intermediate, and lateral zones (Naidich et al., 2009). A detailed look at the consistent folding across brains could provide the demarcations within cerebellar lobules to note the boundaries of those lateral zones. With a more detailed structural parcellation of the cerebellum, including the lateral functional zones based on the cortico-cerebellar connectivity patterns, we would be able to create a functional map within the cerebellum using structural boundaries.

The second issue is our lack of consideration of the complexity of specific tasks, and the multiple cognitive processes that each of those tasks requires. Most studies looking at language function in the cerebellum combine a number of tasks, such as verb generation, verbal fluency, and verbal working memory, among others (E et al., 2014; Stoodley & Schmahmann, 2009), that each requires their own set of specific cognitive functions to complete the tasks. However, even if one only looks at the activation patterns of a single task, such as a verb generation task, one is still combining and confounding multiple cognitive processes that would reasonably activate multiple regions. Some of the cognitive processes associated with a verb generation task include executive function and linguistic processes such as generating semantically related words, choosing an appropriate word from the proper syntactic category, and inhibiting competing words (Del Missier & Crescentini, 2011). When looking at the activation patterns of a verb generation task within the cerebral cortex, activation is consistently noted within the left inferior frontal gyrus and left superior temporal gyrus (Frings et al., 2006; Stoodley, 2012). Known cortico-cerebellar structural and functional connectivity provides evidence for the cerebellum's association with a large portion of the cerebral cortex, so therefore it would be expected that regions in the cerebellum that connect to the cerebral cortex would co-activate (Kamali, Kramer, Frye, Butler, & Hasan, 2010; Naidich et al., 2009; Riedel et al., 2015; Salmi et al., 2010; Smits, Jiskoot, & Papma, 2014). That is confirmed by activation patterns within the cerebellum that show a number of cerebellar lobules associated with verb generation, including lobules VI, Crus I, VIIb, VIIIa (Stoodley et al., 2010, 2012), which would be expected given the number of cognitive processes that are required for a verb generation task, and the number of regions the cerebellum is connected to that co-activate during the task. To say that the structural boundaries of the cerebellum does not demarcate specific functions does not take into account the literature that consistently associates certain regions within the cerebellum to particular functions, the complexity of the computations involved in each task, nor the known cortico-connectivity patterns. If our understanding of the divisions of the cerebellum also took into account the lateral zones based on known connectivity, and our understanding of functions took into account the complexities of the computations involved in the tasks, we would more likely be able to map specific functional computations with medial, intermediate, and lateral regions of specific lobules.

Structural demarcations that are consistent across brains give us the labels and landmarks to discuss general regions of functional association, especially when those functions are consistently associated with specific regions. The findings of the current study can be reanalyzed in light of these factors. The regions associated with the language and cognitive measures in our study are partially consistent with the regions that are constantly associated with the same or similar language measures across other studies. This consistency notes the usefulness of referring to specific lobules within the cerebellum in association with general tasks. However, in order to better map regions with specific functions, it would require tasks that target specific computations. The current study, like many of the studies that target language function, used a range of tasks that confound many motor and cognitive functions. Therefore, it is understandable that a number of regions were associated with these tasks that target multiple motor and cognitive computations, such as the finding associating the right IV that is generally a motor region with expressive vocabulary, and the finding associating the right lobule VIIb that is frequently associated with language function with the expressive language measure. With improved parcellation methods that include functional zones, and more specific tasks that target precise computation, we could predict that the numerous specific computations involved in language function are individually associated with specific regions within certain lobules in certain lateral zones, better defining cerebellar functional maps based on structural boundaries.

Mechanistic Role of Cerebellum in Language Function Historically, the cerebellum's cytoarchitecture is shown to be consistent across the cortical sheet, and this consistency has led to the theory of the cerebellum providing similar computations across functions. There are three cellular levels throughout the cerebellar cortex, including the superior molecular level composed of basket cells and stellate cells, followed by the Purkinje cells, and the inferior level of dense granule cells. Understanding the activation of the cells during motor function has led to the theory that the cerebellum plays a role in prediction, timing, error-detection, and adaptation. Furthermore, given the noted consistency of the three cellular levels across the cortical sheet, the same theory has been applied to and supported in language production and comprehension, noting the same role the cerebellum plays in prediction, timing, error-detection, and adaptation in language function tasks (Bellebaum & Daum, 2011; Ito, 2008; Lesage et al., 2017; Moberget & Ivry, 2016; Sokolov et al., 2017). However, recent literature has provided evidence towards differences in how the cells communicate with each other within and across those levels in various regions across the cerebellum (De Zeeuw et al., 2020), and those differences may speak to computational differences in how the cerebellum learns language and other cognitive processes, versus other functions.

For instance, regional differences in firing patterns of Purkinje cells have been noted within the cerebellum based on aldolase C enzyme expression. The regional differences in gene expression are related to olivo-cerebellar connectivity, which leads to differences in resting-state firing rates. One of the functional consequences of these differences is the tendency for those regions with a higher firing rate to degenerate in progressive ataxia. These different zones based on the aldolase C enzyme expression also show differences in how cellular levels communicate with each other, showing activation pattern differences in how climbing fibers communicate with Purkinje cells, and parallel fibers with Purkinje cells (Cerminara, Lang, Sillitoe, & Apps, 2015; De Zeeuw et al., 2011, 2020; Sokolov et al., 2017). These findings speak to the complexity of the cerebellum’s communication patterns due to differences in molecular composition based on connectivity that are still vastly unknown across the cortical sheet. These differences can impact our understanding of regional differences based on connectivity patterns and the underlying complexities of how the cerebellum is contributing to learning within each network of function.

As previously noted, prior studies have focused on the cerebellum's role in error-based learning, with the ability to predict the next item in a sequence of an internal model and detect error when the internal model is incongruent with the event. When the model is incongruent with the actual outcome, the cerebellum is involved in signaling the incongruity and inhibiting the response dictated by the model in order to update the model by encoding a new response to the prior item in the sequence, i.e., learning. This function has been noted in motor and cognitive domains in typical development, and with noted deficits following damage to the cerebellum (Argyropoulos, 2016; Fiez, Petersen, Cheney, & Raichle, 1992; Herzfeld, Kojima, Soetedjo, & Shadmehr, 2018; Sokolov et al., 2017). Specifically, in language studies, results demonstrate an association between activation in the cerebellum and linguistic prediction and prediction error at the phonological, syntactic, and semantic levels (Argyropoulos, 2016; Lesage et al., 2017; Moberget et al., 2014), and learning semantic associations within language function (Lesage, Nailer, & Miall, 2016). Studies analyzing damage, or disruption in function, to the cerebellum have similarly shown a decreased ability to predict the next item in a sequence (Lesage, Morgan, Olson, Meyer, & Miall, 2012), detect errors, and learn (Fiez et al., 1992; Sokolov et al., 2017). To further understand the cerebellum's role in language acquisition and function, future work needs to focus on tasks that are able to measure the learning of language and the cerebellum's role in prediction, error detection, and error-based learning.

Post-Stroke Development of the Cerebellum The post-stroke outcomes across development noted in our study's results in patients following perinatal stroke compared to typical development are consistent with and provide a deeper understanding of the brain's development and its relation to language function. Prior research indicates a partial reorganization of language function across the brain, with significant activation in regions across both hemispheres relating to language measures (Beharelle et al., 2010; Carlson et al., 2019; Dick et al., 2013; Szaflarski et al., 2014). Following early damage to left cortical regions typically involved in language function, developmental changes include a reorganization of language to involve increased interhemispheric connectivity and engagement of right hemisphere regions for optimal language function (Dick et al., 2013; Heller et al., 2005; Jacola et al., 2006; Szaflarski et al., 2014). However, post-stroke developmental outcomes also show continued activation across the typical language network (Beharelle et al., 2010; Carlson et al., 2019). The regions involved in the language network may be related to the time of testing, with structural and functional changes occurring across development. Specifically, structural abnormalities such as atrophy of regions connected to the damage region noted early in development, and a reorganization of laterality of function, that trends towards normal in specific regions within the brain later in development. However, a permanent reorganization is noted in more posterior regions, with increased interhemispheric connectivity and activation in contralateral, posterior regions of both the cortical and cerebellar regions leading to better language performance.

Prior studies have supported the significance of left supratentorial regions following perinatal stroke for language function, including some of the same regions that are significant in a healthy population (Beharelle et al., 2010; Carlson et al., 2019). Specifically, Beharelle and colleagues (2010) found that the left inferior frontal gyrus was significantly associated with better language functioning in both patients following perinatal stroke and typical controls. However, their findings also showed an association between bilateral activation in superior temporal and inferior parietal regions with better outcomes in language measures than unilateral activation in either of those regions (Beharelle et al., 2010). Similarly, Carlson and colleagues (2019) found similar functional connectivity patterns within and across hemispheres between children following perinatal periventricular stroke and typical controls, but lower functional connectivity in children following perinatal ischemic stroke, with results indicating a positive relationship between functional connectivity and language outcomes (Carlson et al., 2019). While early stroke has shown to involve greater post-stroke plasticity, including the involvement of right hemisphere regions and interhemispheric connectivity (Dick et al., 2013; Szaflarski et al., 2014), regions involved in typical language function are still critical, including right posterior-lateral regions in the cerebellum as seen in the results of the current study.

Our study's outcomes with patients following perinatal stroke fit with the literature that indicates that the brain does not undergo a complete reorganization compared to the typical development patterns, with the right hemisphere compensating for the damaged function left hemisphere. Instead, the connectivity with the damaged region continues to impact the function typically associated with that network. Based on crossed cortico-ponto-cerebellar pathways, it is the right posterior-lateral regions of the cerebellum that are consistently associated with language function in typical development. Our findings show that even following early damage to the left hemisphere of the cerebral cortex, the right cerebellum continues to be associated with language function. The results of the current study showing greater right laterality of volume in regions typically associated with language function are consistent with past findings of language function following an early cortical injury.

However, the post-stroke plasticity found in prior studies has also been found in the current study. Our result of greater left lateralization of grey-matter volume and myelin content in posterior regions of the cerebellum fit with prior studies showing interhemispheric connectivity and right cortical regions compensating for language processing following early damage to the cerebral cortex’s left hemisphere, especially in posterior regions (Beharelle et al., 2010; Dick et al., 2013). However, the age effects noted in some of the regions where left lateralization was associated with language function may demonstrate that lateralization partially normalizes later in development. Studies analyzing the structural changes following perinatal stroke have noted atrophy in the contralateral cerebellar hemisphere following cortical injury, but only early in development. As perinatal stroke patients age, the structural differences cease, with a normal structural volume of connecting regions later in development (Tien & Ashdown, 1992; Uchino et al., 2006). These volumetric changes across time to regions connected to lesioned portions of the brain demonstrate the brain's plasticity. The age effects noted in lateralization of language function in our study are consistent with these developmental changes. In our study, some of the cerebellar regions that showed early left lateralization of language function switched to right lateralization as patients aged, matching typical developmental patterns of regions association to language. This may indicate that early in development, the brain compensates for structural deficiencies with the recruitment of contralateral regions typically associated with language function, and as the brain develops, some typical patterns of structure and function return. Together, these findings demonstrate post-stroke developmental patterns, with early right lateralization of language functioning in the cerebellum, even following damage to left cortical regions, and the compensation of the damaged portions of the network with bilateral structural and functional connectivity of posterior regions, especially early in development.

REFERENCES

Ackermann, H., Mathiak, K., & Riecker, A. (2007). The contribution of the cerebellum to speech production and speech perception: Clinical and functional imaging data. *Cerebellum*, *6*(3), 202–213. https://doi.org/10.1080/14734220701266742

Ackermann, H., Wildgruber, D., Daum, I., & Grodd, W. (1998). Does the cerebellum contribute to cognitive aspects of speech production? A functional magnetic resonance imaging (fMRI) study in humans. *Neuroscience Letters*, *247*(2–3), 187–190. https://doi.org/10.1016/S0304-3940(98)00328-0

Andersen, B. B., Korbo, L., & Pakkenberg, B. (1992). A quantitative study of the human cerebellum with unbiased stereological techniques. *Journal of Comparative Neurology*, *326*(4), 549–560. https://doi.org/10.1002/cne.903260405

Argyropoulos, G. P. D. (2016). The cerebellum, internal models and prediction in 'non-motor' aspects of language: A critical review. *Brain and Language*, *161*, 4–17. https://doi.org/10.1016/j.bandl.2015.08.003

Ashida, R., Cerminara, N. L., Edwards, R. J., Apps, R., & Brooks, J. C. W. (2019). Sensorimotor, language, and working memory representation within the human cerebellum. *Human Brain Mapping*. https://doi.org/10.1002/hbm.24733

Bajaj, M., Pine, D., & Winkler, A. (2019). T1/FLAIR as a surrogate for T1/T2 in the assessment of myelination. *Organization for Human Brain Mapping*, 0–4. Rome, Italy.

Ballantyne, A. O., Spilkin, A. M., Hesselink, J., & Trauner, D. A. (2008). Plasticity in the developing brain: Intellectual, language and academic functions in children with ischaemic perinatal stroke. *Brain*, *131*(11), 2975–2985. https://doi.org/10.1093/brain/awn176

Ballantyne, A. O., Spilkin, A. M., & Trauner, D. A. (2007). Language outcome after perinatal stroke: Does side matter? *Child Neuropsychology*, *13*(6), 494–509. https://doi.org/10.1080/09297040601114878

Bates, E., Reilly, J., Wulfeck, B., Dronkers, N., Opie, M., Fenson, J., … Herbst, K. (2001). Differential effects of unilateral lesions on language production in children and adults. *Brain and Language*, *79*(2), 223–265. https://doi.org/10.1006/brln.2001.2482

Beharelle, A. R., Dick, A. S., Josse, G., Solodkin, A., Huttenlocher, P. R., Levine, S. C., & Small, S. L. (2010). Left hemisphere regions are critical for language in the face of early left focal brain injury. *Brain*, *133*(6), 1707–1716. https://doi.org/10.1093/brain/awq104

Bellebaum, C., & Daum, I. (2011). Mechanisms of cerebellar involvement in associative learning. *Cortex*, *47*(1), 128–136. https://doi.org/10.1016/j.cortex.2009.07.016

Bernard, J. A., & Seidler, R. D. (2013). Relationships between regional cerebellar volume and sensorimotor and cognitive function in young and older adults. *Cerebellum*, *12*(5), 721–737. https://doi.org/10.1007/s12311-013-0481-z

Bernard, J. A., Seidler, R. D., Hassevoort, K. M., Benson, B. L., Welsh, R. C., Lee Wiggins, J., … Peltier, S. J. (2012). Resting state cortico-cerebellar functional connectivity networks: A comparison of anatomical and self-organizing map approaches. *Frontiers in Neuroanatomy*, *6*(AUG 2012), 1–19. https://doi.org/10.3389/fnana.2012.00031

Bosma, E., Heeringa, W., Hoekstra, E., Versloot, A., & Blom, E. (2017). Verbal Working Memory Is Related to the Acquisition of Cross-Linguistic Phonological Regularities. *Frontiers in Psychology*, *8*. https://doi.org/10.3389/fpsyg.2017.01487

Brodmann, K., & Garey, L. J. (1999). Brodmann's 'Localisation in the Cerebral Cortex.' In *Brodmann's 'Localisation in the Cerebral Cortex.'* https://doi.org/10.1142/p151

Brodmann, Korbinian. (1909). Vergleichende Lokalisationslehre der Grosshirnrinde (The Principles of Comparative Localisation in the Cerebral Cortex). In *Barth*. Leipzig, Germany.: Barth.

Buckner, R. L., Krienen, F. M., Castellanos, A., Diaz, J. C., & Thomas Yeo, B. T. (2011). The organization of the human cerebellum estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(5), 2322–2345. https://doi.org/10.1152/jn.00339.2011

Carlson, H. L., Sugden, C., Brooks, B. L., & Kirton, A. (2019). Functional connectivity of language networks after perinatal stroke. *NeuroImage: Clinical*, *23*(November 2018), 101861. https://doi.org/10.1016/j.nicl.2019.101861

Cerminara, N. L., Lang, E. J., Sillitoe, R. V., & Apps, R. (2015). Redefining the cerebellar cortex as an assembly of non-uniform Purkinje cell microcircuits. *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn3886

Chen, S. H. A., & Desmond, J. E. (2005a). Cerebrocerebellar networks during articulatory rehearsal and verbal working memory tasks. *NeuroImage*, *24*(2), 332–338. https://doi.org/10.1016/j.neuroimage.2004.08.032

Chen, S. H. A., & Desmond, J. E. (2005b). Temporal dynamics of cerebro-cerebellar network recruitment during a cognitive task. *Neuropsychologia*, *43*(9), 1227–1237. https://doi.org/10.1016/j.neuropsychologia.2004.12.015

Cooperrider, J., Momin, A., Baker, K. B., & Machado, A. G. (2020). Cerebellar Neuromodulation for Stroke. *Current Physical Medicine and Rehabilitation Reports*. https://doi.org/10.1007/s40141-019-00253-4

Courchesne, E., Karns, C. M., Davis, H. R., Ziccardi, R., Carper, R. A., Tigue, Z. D., … Courchesne, R. Y. (2001). Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. *Neurology*, *57*(2), 245–254. https://doi.org/10.1212/WNL.57.2.245

D'Mello, A. M., Moore, D. M., Crocetti, D., Mostofsky, S. H., & Stoodley, C. J. (2016). Cerebellar gray matter differentiates children with early language delay in autism. *Autism Research*, *9*(11), 1191–1204. https://doi.org/10.1002/aur.1622

De Zeeuw, C. I., Hoebeek, F. E., Bosman, L. W. J., Schonewille, M., Witter, L., & Koekkoek, S. K. (2011). Spatiotemporal firing patterns in the cerebellum. *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn3011

De Zeeuw, C. I., Lisberger, S. G., & Raymond, J. L. (2020). Diversity and dynamism in the cerebellum. *Nature Neuroscience*. https://doi.org/10.1038/s41593-020-00754-9

Del Missier, F., & Crescentini, C. (2011). Executive control of retrieval in noun and verb generation. *Cognitive Systems Research*, *12*(1), 45–55. https://doi.org/10.1016/j.cogsys.2010.01.001

Deniz Can, D., Richards, T., & Kuhl, P. K. (2013). Early gray-matter and white-matter concentration in infancy predict later language skills: A whole brain voxel-based morphometry study. *Brain and Language*, *124*(1), 34–44. https://doi.org/10.1016/j.bandl.2012.10.007

Desmond, J. E., Gabrieli, J. D. E., Wagner, A. D., Ginier, B. L., & Glover, G. H. (1997). Lobular patterns of cerebellar activation in verbal working-memory and finger-tapping tasks as revealed by functional MRI. *Journal of Neuroscience*, *17*(24), 9675–9685. https://doi.org/10.1523/jneurosci.17-24-09675.1997

Dice, L. R. (1945). Measures of the Amount of Ecologic Association Between Species. *Ecology*, *26*(3), 297–302. https://doi.org/10.2307/1932409

Dick, A. S., Beharelle, A. R., Solodkin, A., & Small, S. L. (2013). Interhemispheric functional connectivity following prenatal or perinatal brain injury predicts receptive language outcome. *Journal of Neuroscience*, *33*(13), 5612–5625. https://doi.org/10.1523/JNEUROSCI.2851-12.2013

Dick, F., Wulfeck, B., Krupa-Kwiatkowski, M., & Bates, E. (2004). The development of complex sentence interpretation in typically developing children compared with children with specific language impairments or early unilateral focal lesions. *Developmental Science*, *7*(3), 360–377. https://doi.org/10.1111/j.1467-7687.2004.00353.x

Diedrichsen, J., Balsters, J. H., Flavell, J., Cussans, E., & Ramnani, N. (2009). A probabilistic MR atlas of the human cerebellum. *NeuroImage*, *46*(1), 39–46. https://doi.org/10.1016/j.neuroimage.2009.01.045

Dunn, L. M. (1997). PPVT: Peabody Picture Vocabulary Test - 3rd Edtion. *Summary*.

E, K.-H., Chen, S.-H. A., Ho, M.-H. R., & Desmond, J. E. (2014). A meta-analysis of cerebellar contributions to higher cognition from PET and fMRI studies. *Human Brain Mapping*, *35*(2), 593–615. https://doi.org/10.1002/hbm.22194

Fiez, J. A. (2016). The cerebellum and language: Persistent themes and findings. *Brain and Language*, *161*, 1–3. https://doi.org/10.1016/j.bandl.2016.09.004

Fiez, J. A., Petersen, S. E., Cheney, M. K., & Raichle, M. E. (1992). Impaired non-motor learning and error detection associated with cerebellar damage: A single case study. *Brain*, *115*(1), 155–178. https://doi.org/10.1093/brain/115.1.155

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., … Dale, A. M. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355. https://doi.org/10.1016/S0896-6273(02)00569-X

Fischl, B., Salat, D. H., Van Der Kouwe, A. J. W., Makris, N., Ségonne, F., Quinn, B. T., & Dale, A. M. (2004). Sequence-independent segmentation of magnetic resonance images. *NeuroImage*, *23*(SUPPL. 1), 69–84. https://doi.org/10.1016/j.neuroimage.2004.07.016

Frings, M., Dimitrova, A., Schorn, C. F., Elles, H. G., Hein-Kropp, C., Gizewski, E. R., … Timmann, D. (2006). Cerebellar involvement in verb generation: An fMRI study. *Neuroscience Letters*, *409*(1), 19–23. https://doi.org/10.1016/j.neulet.2006.08.058

Glasser, M. F., & van Essen, D. C. (2011). Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. *Journal of Neuroscience*, *31*(32), 11597–11616. https://doi.org/10.1523/JNEUROSCI.2180-11.2011

Guzzetta, A., Pecini, C., Biagi, L., Tosetti, M., Brizzolara, D., Chilosi, A., … Cioni, G. (2008). Language organisation in left perinatal stroke. *Neuropediatrics*, *39*(3), 157–163. https://doi.org/10.1055/s-0028-1085465

Hartwigsen, G., Neef, N. E., Camilleri, J. A., Margulies, D. S., & Eickhoff, S. B. (2019). Functional Segregation of the Right Inferior Frontal Gyrus: Evidence from Coactivation-Based Parcellation. *Cerebral Cortex*, *29*(4), 1532–1546. https://doi.org/10.1093/cercor/bhy049

Heller, S. L., Heier, L. A., Watts, R., Schwartz, T. H., Zelenko, N., Doyle, W., & Devinsky, O. (2005). Evidence of cerebral reorganization following perinatal stroke demonstrated with fMRI and DTI tractography. *Clinical Imaging*, *29*(4), 283–287. https://doi.org/10.1016/j.clinimag.2004.09.003

Herzfeld, D. J., Kojima, Y., Soetedjo, R., & Shadmehr, R. (2018). Encoding of error and learning to correct that error by the Purkinje cells of the cerebellum. *Nature Neuroscience*. https://doi.org/10.1038/s41593-018-0136-y

Hodge, S. M., Makris, N., Kennedy, D. N., Caviness, V. S., Howard, J., McGrath, L., … Harris, G. J. (2010). Cerebellum, language, and cognition in autism and specific language impairment. *Journal of Autism and Developmental Disorders*, *40*(3), 300–316. https://doi.org/10.1007/s10803-009-0872-7

Hubrich-Ungureanu, P., Kaemmerer, N., Henn, F. A., & Braus, D. F. (2002). Lateralized organization of the cerebellum in a silent verbal fluency task: A functional magnetic resonance imaging study in healthy volunteers. *Neuroscience Letters*, *319*(2), 91–94. https://doi.org/10.1016/S0304-3940(01)02566-6

Ito, M. (2008). Control of mental activities by internal models in the cerebellum. *Nature Reviews Neuroscience*, *9*(4), 304–313. https://doi.org/10.1038/nrn2332

Jacola, L. M., Schapiro, M. B., Schmithorst, V. J., Byars, A. W., Strawsburg, R. H., Szaflarski, J. P., … Holland, S. K. (2006). Functional magnetic resonance imaging reveals atypical language organization in children following perinatal left middle cerebral artery stroke. *Neuropediatrics*, *37*(1), 46–52. https://doi.org/10.1055/s-2006-923934

Johnson, J. S., & Newport, E. L. (1989). Critical period effects in second language learning: The influence of maturational state on the acquisition of English as a second language. *Cognitive Psychology*. https://doi.org/10.1016/0010-0285(89)90003-0

Kamali, A., Kramer, L. A., Frye, R. E., Butler, I. J., & Hasan, K. M. (2010). Diffusion tensor tractography of the human brain cortico-ponto-cerebellar pathways: a quantitative preliminary study. *Journal of Magnetic Resonance Imaging : JMRI*, *32*(4), 809–817. https://doi.org/10.1002/jmri.22330

Keser, Z., Hasan, K. M., Mwangi, B. I., Kamali, A., Ucisik-Keser, F. E., Riascos, R. F., … Narayana, P. A. (2015). Diffusion tensor imaging of the human cerebellar pathways and their interplay with cerebral macrostructure. *Frontiers in Neuroanatomy*, *9*(APR), 1–13. https://doi.org/10.3389/fnana.2015.00041

Kim, J., Lee, S. K., Lee, J. D., Kim, Y. W., & Kim, D. I. (2005). Decreased fractional anisotropy of middle cerebellar peduncle in crossed cerebellar diaschisis: Diffusion-tensor imaging-positron-emission tomography correlation study. *American Journal of Neuroradiology*, *26*(9), 2224–2228.

Kirschen, M. P., Chen, S. H. A., Schraedley-Desmond, P., & Desmond, J. E. (2005). Load- and practice-dependent increases in cerebro-cerebellar activation in verbal working memory: An fMRI study. *NeuroImage*, *24*(2), 462–472. https://doi.org/10.1016/j.neuroimage.2004.08.036

Koch, G., Bonnì, S., Casula, E. P., Iosa, M., Paolucci, S., Pellicciari, M. C., … Caltagirone, C. (2019). Effect of Cerebellar Stimulation on Gait and Balance Recovery in Patients with Hemiparetic Stroke: A Randomized Clinical Trial. *JAMA Neurology*. https://doi.org/10.1001/jamaneurol.2018.3639

Lesage, E., Hansen, P. C., & Miall, R. C. (2017). Right lateral cerebellum represents linguistic predictability. *Journal of Neuroscience*, *37*(26), 6231–6241. https://doi.org/10.1523/JNEUROSCI.3203-16.2017

Lesage, E., Morgan, B. E., Olson, A. C., Meyer, A. S., & Miall, R. C. (2012). Cerebellar rTMS disrupts predictive language processing. *Current Biology*, *22*(18), R794–R795. https://doi.org/10.1016/j.cub.2012.07.006

Lesage, E., Nailer, E. L., & Miall, R. C. (2016). Cerebellar BOLD signal during the acquisition of a new lexicon predicts its early consolidation. *Brain and Language*, *161*, 33–44. https://doi.org/10.1016/j.bandl.2015.07.005

Lynch, J. K. (2009). Epidemiology and classification of perinatal stroke. *Seminars in Fetal and Neonatal Medicine*, *14*(5), 245–249. https://doi.org/10.1016/j.siny.2009.07.001

Machado, A., & Baker, K. B. (2012). Upside down crossed cerebellar diaschisis: Proposing chronic stimulation of the dentatothalamocortical pathway for post-stroke motor recovery. *Frontiers in Integrative Neuroscience*, *6*(MAY 2012), 1–9. https://doi.org/10.3389/fnint.2012.00020

Mah, S., DeVeber, G., Wei, X. C., Liapounova, N., & Kirton, A. (2013). Cerebellar atrophy in childhood arterial ischemic stroke: Acute diffusion MRI biomarkers. *Stroke*, *44*(9), 2468–2474. https://doi.org/10.1161/STROKEAHA.111.000744

Mariën, P., Ackermann, H., Adamaszek, M., Barwood, C. H. S., Beaton, A., Desmond, J., … Ziegler, W. (2014). Consensus paper: Language and the cerebellum: An ongoing enigma. *Cerebellum*, *13*(3), 386–410. https://doi.org/10.1007/s12311-013-0540-5

Mariën, P., & Manto, M. (2018, October 25). Cerebellum as a Master-Piece for Linguistic Predictability. *Cerebellum*, *17*(2), 101–103. https://doi.org/10.1007/s12311-017-0894-1

Marvel, C. L., & Desmond, J. E. (2010). Functional Topography of the Cerebellum in Verbal Working Memory. *Neuropsychology Review*, *20*(3), 271–279. https://doi.org/10.1007/s11065-010-9137-7

Moberget, T., Gullesen, E. H., Andersson, S., Ivry, R. B., & Endestad, T. (2014). Generalized role for the cerebellum in encoding internal models: Evidence from semantic processing. *Journal of Neuroscience*, *34*(8), 2871–2878. https://doi.org/10.1523/JNEUROSCI.2264-13.2014

Moberget, T., & Ivry, R. B. (2016). Cerebellar contributions to motor control and language comprehension: Searching for common computational principles. *Annals of the New York Academy of Sciences*, *1369*(1), 154–171. https://doi.org/10.1111/nyas.13094

Molnar-Szakacs, I., Iacoboni, M., Koski, L., & Mazziotta, J. C. (2005). Functional segregation within pars opercularis of the inferior frontal gyrus: Evidence from fMRI studies of imitation and action observation. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhh199

Moore, D. M., D'Mello, A. M., McGrath, L. M., & Stoodley, C. J. (2017). The developmental relationship between specific cognitive domains and grey matter in the cerebellum. *Developmental Cognitive Neuroscience*, *24*, 1–11. https://doi.org/10.1016/j.dcn.2016.12.001

Naidich, T., Duvernoy, H., Delman, B., Sorensen, A., Kollias, S., & Haacke, E. (2009). Duvernoy's Atlas of the Human Brain Stem and Cerebellum. In *American Journal of Neuroradiology* (Vol. 30). https://doi.org/10.3174/ajnr.a1550

Ng, H. B. T., Kao, K. L. C., Chan, Y. C., Chew, E., Chuang, K. H., & Chen, S. H. A. (2016). Modality specificity in the cerebro-cerebellar neurocircuitry during working memory. *Behavioural Brain Research*, *305*, 164–173. https://doi.org/10.1016/j.bbr.2016.02.027

Pangelinan, M. M., Zhang, G., VanMeter, J. W., Clark, J. E., Hatfield, B. D., & Haufler, A. J. (2011). Beyond age and gender: Relationships between cortical and subcortical brain volume and cognitive-motor abilities in school-age children. *NeuroImage*, *54*(4), 3093–3100. https://doi.org/10.1016/j.neuroimage.2010.11.021

Raju, T. N. K., Nelson, K. B., Ferriero, D., & Lynch, J. K. (2007). Ischemic perinatal stroke: Summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. *Pediatrics*, *120*(3), 609–616. https://doi.org/10.1542/peds.2007-0336

Ramnani, N. (2006). The primate cortico-cerebellar system: Anatomy and function. *Nature Reviews Neuroscience*, *7*(7), 511–522. https://doi.org/10.1038/nrn1953

Ramnani, N., Behrens, T. E. J., Johansen-Berg, H., Richter, M. C., Pinsk, M. A., Andersson, J. L. R., … Matthews, P. M. (2006). The evolution of prefrontal inputs to the cortico-pontine system: Diffusion imaging evidence from macaque monkeys and humans. *Cerebral Cortex*, *16*(6), 811–818. https://doi.org/10.1093/cercor/bhj024

Reilly, J. S., Wasserman, S., & Appelbaum, M. (2013). Later language development narratives children with perinatal stroke. *Developmental Science*, *16*(1), 67–83. https://doi.org/10.1111/j.1467-7687.2012.01192.x

Riedel, M. C., Ray, K. L., Dick, A. S., Sutherland, M. T., Hernandez, Z., Fox, P. M., … Laird, A. R. (2015). Meta-analytic connectivity and behavioral parcellation of the human cerebellum. *NeuroImage*, *117*, 327–342. https://doi.org/10.1016/j.neuroimage.2015.05.008

Salamon, N., Sicotte, N., Drain, A., Frew, A., Alger, J. R., Jen, J., … Salamon, G. (2007). White matter fiber tractography and color mapping of the normal human cerebellum with diffusion tensor imaging. *Journal of Neuroradiology*, *34*(2), 115–128. https://doi.org/10.1016/j.neurad.2007.03.002

Salmi, J., Pallesen, K. J., Neuvonen, T., Brattico, E., Korvenoja, A., Salonen, O., & Carlson, S. (2010). Cognitive and motor loops of the human cerebro-cerebellar system. *Journal of Cognitive Neuroscience*, *22*(11), 2663–2676. https://doi.org/10.1162/jocn.2009.21382

Schmahmann, J. D. (2001). The cerebellar cognitive affective syndrome: Clinical correlations of the dysmetria of thought hypothesis. *International Review of Psychiatry*, *13*(4), 313–322. https://doi.org/10.1080/09540260120082164

Schmahmann, J. D. (1996). From movement to thought: Anatomic substrates of the cerebellar contribution to cognitive processing. *Human Brain Mapping*, *4*(3), 174–198. https://doi.org/10.1002/(SICI)1097-0193(1996)4:3<174::AID-HBM3>3.0.CO;2-0

Schmahmann, J. D. (2010). The role of the cerebellum in cognition and emotion: Personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy. *Neuropsychology Review*, *20*(3), 236–260. https://doi.org/10.1007/s11065-010-9142-x

Schmahmann, J. D., Doyon, J., McDonald, D., Holmes, C., Lavoie, K., Hurwitz, A. S., … Petrides, M. (1999). Three-Dimensional MRI Atlas of the Human Cerebellum in Proportional Stereotaxic Space. *NeuroImage*, *10*(3), 233–260. https://doi.org/10.1006/nimg.1999.0459

Schweizer, T. A., Alexander, M. P., Gillingham BA, S., Cusimano, M., & Stuss, D. T. (2010). Lateralized cerebellar contributions to word generation: A phonemic and semantic fluency study. *Behavioural Neurology*, *23*(1–2), 31–37. https://doi.org/10.3233/BEN-2010-0269

Semel, E., Wiig, E. H., & Secord, W. A. (1995). *The Clinical Evaluation of Language Fundamentals* (Third Edit). San Antonio: The Psychological Corporation.

Smits, M., Jiskoot, L. C., & Papma, J. M. (2014). White matter tracts of speech and language. *Seminars in Ultrasound, CT and MRI*, *35*(5), 504–516. https://doi.org/10.1053/j.sult.2014.06.008

Sokolov, A. A., Miall, R. C., & Ivry, R. B. (2017). The Cerebellum: Adaptive Prediction for Movement and Cognition. *Trends in Cognitive Sciences*, *21*(5), 313–332. https://doi.org/10.1016/j.tics.2017.02.005

Srinivasan, L., Allsop, J., Counsell, S. J., Boardman, J. P., Edwards, A. D., & Rutherford, M. (2006). Smaller cerebellar volumes in very preterm infants at term-equivalent age are associated with the presence of supratentorial lesions. *American Journal of Neuroradiology*, *27*(3), 573–579. https://doi.org/27/3/573 [pii]

Stoodley, C. J. (2012). The cerebellum and cognition: Evidence from functional imaging studies. *Cerebellum*, *11*(2), 352–365. https://doi.org/10.1007/s12311-011-0260-7

Stoodley, C. J., & Schmahmann, J. D. (2009). Functional topography in the human cerebellum: A meta-analysis of neuroimaging studies. *NeuroImage*, *44*(2), 489–501. https://doi.org/10.1016/j.neuroimage.2008.08.039

Stoodley, C. J., & Schmahmann, J. D. (2010). Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex*, *46*(7), 831–844. https://doi.org/10.1016/j.cortex.2009.11.008

Stoodley, C. J., Valera, E. M., & Schmahmann, J. D. (2010). An fMRI study of intra-individual functional topography in the human cerebellum. *Behavioural Neurology*, *23*(1–2), 65–79. https://doi.org/10.3233/BEN-2010-0268

Stoodley, C. J., Valera, E. M., & Schmahmann, J. D. (2012). Functional topography of the cerebellum for motor and cognitive tasks: An fMRI study. *NeuroImage*, *59*(2), 1560–1570. https://doi.org/10.1016/j.neuroimage.2011.08.065

Strother, M. K., Buckingham, C., Faraco, C. C., Arteaga, D. F., Lu, P., Xu, Y., & Donahue, M. J. (2016). Crossed cerebellar diaschisis after stroke identified noninvasively with cerebral blood flow-weighted arterial spin labeling MRI. *European Journal of Radiology*, *85*(1), 136–142. https://doi.org/10.1016/j.ejrad.2015.11.003

Szaflarski, J. P., Allendorfer, J. B., Byars, A. W., Vannest, J., Dietz, A., Hernando, K. A., & Holland, S. K. (2014). Age at stroke determines post-stroke language lateralization. *Restorative Neurology and Neuroscience*, *32*(6), 733–742. https://doi.org/10.3233/RNN-140402

Thomalla, G., Glauche, V., Weiller, C., & Röther, J. (2005). Time course of wallerian degeneration after ischaemic stroke revealed by diffusion tensor imaging. *Journal of Neurology, Neurosurgery and Psychiatry*, *76*(2), 266–268. https://doi.org/10.1136/jnnp.2004.046375

Tiemeier, H., Lenroot, R. K., Greenstein, D. K., Tran, L., Pierson, R., & Giedd, J. N. (2010). Cerebellum development during childhood and adolescence: A longitudinal morphometric MRI study. *NeuroImage*, *49*(1), 63–70. https://doi.org/10.1016/j.neuroimage.2009.08.016

Tien, R. D., & Ashdown, B. C. (1992). Crossed cerebellar diaschisis and crossed cerebellar atrophy: correlation of MR findings, clinical symptoms, and supratentorial diseases in 26 patients. *American Journal of Roentgenology*, *158*(5), 1155–1159. https://doi.org/10.2214/ajr.158.5.1566683

Tillema, J. M., Byars, A. W., Jacola, L. M., Schapiro, M. B., Schmithorst, V. J., Szaflarski, J. P., & Holland, S. K. (2008). Cortical reorganization of language functioning following perinatal left MCA stroke. *Brain and Language*, *105*(2), 99–111. https://doi.org/10.1016/j.bandl.2007.07.127

Trauner, D. A., Eshagh, K., Ballantyne, A. O., & Bates, E. (2013). Early language development after peri-natal stroke. *Brain and Language*, *127*(3), 399–403. https://doi.org/10.1016/j.bandl.2013.04.006

Turkeltaub, P. E., Eden, G. F., Jones, K. M., & Zeffiro, T. A. (2002). Meta-Analysis of the Functional Neuroanatomy of Single-Word Reading: Method and Validation. *NeuroImage*, *16*(3), 765–780. https://doi.org/10.1006/nimg.2002.1131

Uchino, A., Takase, Y., Nomiyama, K., Egashira, R., & Kudo, S. (2006). Brainstem and cerebellar changes after cerebrovascular accidents: Magnetic resonance imaging. *European Radiology*, *16*(3), 592–597. https://doi.org/10.1007/s00330-005-0014-3

Vias, C., & Dick, A. S. (2017). Cerebellar Contributions to Language in Typical and Atypical Development: A Review. *Developmental Neuropsychology*, *42*(6), 404–421. https://doi.org/10.1080/87565641.2017.1334783

Wathen, C. A., Frizon, L. A., Maiti, T. K., Baker, K. B., & Machado, A. G. (2018). Deep brain stimulation of the cerebellum for poststroke motor rehabilitation: From laboratory to clinical trial. *Neurosurgical Focus*. https://doi.org/10.3171/2018.5.FOCUS18164

Wechsler, D. (1991). Wechsler intelligence scale for children. - Third edition. In *San Antonio: Psychological Corporation*.

Wechsler, D. (1997). Wechsler Adult Intelligence Scale (WAIS-3R). *The Psychological Corporation.*

Weiss, E. M., Siedentopf, C., Hofer, A., Deisenhammer, E. A., Hoptman, M. J., Kremser, C., … Delazer, M. (2003). Brain activation pattern during a verbal fluency test in healthy male and female volunteers: A functional magnetic resonance imaging study. *Neuroscience Letters*, *352*(3), 191–194. https://doi.org/10.1016/j.neulet.2003.08.071

Westmacott, R., Askalan, R., Macgregor, D., Anderson, P., & Deveber, G. (2010). Cognitive outcome following unilateral arterial ischaemic stroke in childhood: Effects of age at stroke and lesion location. *Developmental Medicine and Child Neurology*, *52*(4), 386–393. https://doi.org/10.1111/j.1469-8749.2009.03403.x

Williams, K. T. (1997). *EVT-2: Expressive Vocabulary Test* (2nd ed.). Pearson Assessments.

Yamada, K., Kizu, O., Ito, H., Nakamura, H., Yuen, S., Yoshikawa, K., … Nishimura, T. (2003). Wallerian degeneration of the inferior cerebellar peduncle depicted by diffusion weighted imaging. *Journal of Neurology Neurosurgery and Psychiatry*, *74*(7), 977–978. https://doi.org/10.1136/jnnp.74.7.977

Yamada, K., Patel, U., Shrier, D. A., Tanaka, H., Chang, J. K., & Numaguchi, Y. (1998). MR imaging of CNS tractopathy: wallerian and transneuronal degeneration. *American Journal of Roentgenology*, *171*(3), 813–818. https://doi.org/10.2214/ajr.171.3.9725322

Zhou, H., Rossi, S., & Chen, B. (2017). Effects of Working Memory Capacity and Tasks in Processing L2 Complex Sentence: Evidence from Chinese-English Bilinguals. *Frontiers in Psychology*, *8*. https://doi.org/10.3389/fpsyg.2017.00595

TABLES

Table 1

Relation of Laterality Measure of Cerebellar ROI Grey-Matter Volume to Language Measures

Predictor → Outcome	*b* (SE)	95% CI	*p* - value
Lobule IV → EVT	-48.20 (22.27)	-91.99 to -4.71	0.042
Lobule VIIb →CELF-E	-44.25 (21.03)	-85.31 to -2.87	0.047

Note. Effects reported for robust linear models after controlling for age, sex, and intracranial volume. Only results in which 95% confidence interval did not cover zero are reported. ROI = region of interest. If the laterality measure was positive, that indicated left laterality. EVT = Expressive Vocabulary Test. CELF-E = Clinical Evaluation of Language Fundamentals - Expressive Language subtest.

Table 2

Average Dice Similarity Coefficient (DSC) between Manual and Automated Segmentations per Cerebellar Region

Region	Hemisphere	DSC Mean ± SD
I-III	Left	0.82 ± 0.13
I-III	Right	0.82 ± 0.13
IV	Left	0.88 ± 0.10
IV	Right	0.88 ± 0.09
V	Left	0.87 ± 0.09
V	Right	0.92 ± 0.08
VI	Left	0.94 ± 0.06
VI	Right	0.94 ± 0.05
Crus I	Left	0.95 ± 0.03
Crus I	Right	0.96 ± 0.03
Crus II	Left	0.92 ± 0.05
Crus II	Right	0.93 ± 0.07
VII-b	Left	0.92 ± 0.07
VII-b	Right	0.92 ± 0.08
VIII-a	Left	0.92 ± 0.06
VIII-a	Right	0.92 ± 0.07
VIII-b	Left	0.88 ± 0.08
VIII-b	Right	0.90 ± 0.08
IX	Left	0.90 ± 0.09
IX	Right	0.91 ± 0.08
X	Left	0.80 ± 0.13
X	Right	0.84 ± 0.11
Total Cerebellum	N/A	0.98 ± 0.02

Note. The average DSC of each of the 22 lobules ranges from 0.80 to 0.96. The dice coefficients of all 22 lobules and the total cerebellum were all statistically different from zero at $p < .001$

Table 3

Lesion Location and Type Per Subject

Subject ID	Hemisphere	Lesion Time	Type	FVL
103	Left	Perinatal	Ischemic	0.4166
104	Left	Prenatal	Ischemic	0.3792
107	Left	Prenatal	Periventricular	0.0869
108	Left	Prenatal	Ischemic	0.4863
114	Left	Perinatal	Periventricular	0.0148
117	Left	Perinatal	Ischemic	0.1857
119	Left	Prenatal	Periventricular	0.0663
121	Left	Perinatal	Ischemic	0.4245
124	Left	Pre- or Perinatal	Ischemic	0.1790
130	Left	Prenatal	Periventricular	0.0484
132	Left	Prenatal	N/A	0.0665
133	Left	Pre- or Perinatal	Periventricular	0.0078
134	Left	Prenatal	Periventricular	0.0870
135	Left	Prenatal	Ischemic	0.0004
137	Left	Perinatal	Periventricular	0.1933
147	Left	Perinatal	Ischemic	0.0418
152	Left	Postnatal	Ischemic	0.0600
156	Left	Perinatal	Periventricular	0.2623
157	Left	N/A	Ischemic	0.0102

Note. FVL = Fractional Volume Loss, where FVL = [(VN – VL)/VN], where VN is the volume of the intact hemispheric, and VL is the volume of the hemisphere containing the lesion.

Table 4

Group Performances on Behavioral Measures of Language and Cognition

	Typical Controls		Perinatal Stroke			
Measure	*M*	*SD*	*M*	*SD*	Difference (SE)	*95% CI*
PPVT	104.96	12.53	95.00	15.66	9.96 (4.16)	1.56 to 18.37
EVT	101.44	13.02	85.05	23.33	16.39 (5.38)	5.52 to 27.26
VIQ	105.81	14.19	91.53	17.90	14.29 (4.73)	4.72 to 23.85
PIQ	106.81	13.68	89.11	16.97	17.71 (4.53)	8.57 to 26.85
Full IQ	106.85	13.04	89.16	17.47	17.69 (4.50)	8.61 to 26.78
CELF-R	99.11	20.32	84.63	21.06	14.48 (6.18)	2.00 to 26.96
CELF-E	97.78	12.22	86.32	19.96	11.46 (4.75)	1.87 to 21.05
CELF-T	102.67	20.56	84.47	20.88	18.19 (6.20)	5.68 to 30.71
Newport	130.37	7.14	122.21	15.98	8.16 (3.47)	1.14 to 15.18

Note. PPVT = Peabody Picture Vocabulary Test. EVT = Expressive Vocabulary Test. VIQ = Verbal Comprehension Index of the Intelligence Scale. PIQ = Perceptual Organization Index of the Intelligence Scale. CELF-R = Clinical Evaluation of Language Fundamentals – Receptive Language submeasure. CELF-E = Clinical Evaluation of Language Fundamentals – Expressive Language submeasure. CELF-T = Clinical Evaluation of Language Fundamentals – Total score. Newport = Johnson-Newport Grammaticality Judgement task.

Table 5

Relation of Laterality Measure of Cerebellar ROI Grey-Matter Volume to Language Measures in Patients with Perinatal Stroke

Predictor → Outcome	*b* (SE)	95% CI	*p* - value
Cortex → EVT	-300.01 (131.20)	-553.98 to -39.69	.035
Lobule IV → EVT	-184.59 (69.93)	-323.15 to -49.02	.018
Lobule Crus I → EVT	-328.40 (105.85)	-540.40 to -125.47	.007

Note. Effects reported for robust linear models after controlling for age, sex, lesion size, and intracranial volume. Only results in which 95% confidence interval did not cover zero are reported. If the laterality measure was positive, that indicated left laterality. ROI = region of interest. EVT = Expressive Vocabulary Test.

Table 6

Relation of Laterality Measure of Cerebellar ROI Grey-Matter Volume by Age Interaction to Language Measures in Patients with Perinatal Stroke

Predictor → Outcome	*b* (SE)	95% CI	*p* - value
Lobule IV → VIQ	-0.78 (0.31)	-1.4 to -0.16	.017
Lobule VIIIa → Newport	-0.31 (0.13)	-0.56 to -0.06	.020

Note. Effects reported for robust linear models after controlling for age, sex, lesion size, and intracranial volume. Only results in which 95% confidence interval did not cover zero are reported. ROI = region of interest. VIQ = Verbal Comprehension Index of the Intelligence Scale. Newport = Johnson-Newport Grammaticality Judgement task.

Table 7

Relation of Laterality Measure of Cerebellar ROI Grey-Matter Volume by Group Interaction to Language Measures

Predictor → Outcome	*b* (SE)	95% CI	*p* - value
Cortex → EVT	-322.62 (150.63)	-617.84 to -27.40	.039
Lobule VI → CELF-E	174.69 (75.69)	26.34 to 323.04	.026
Lobule Crus I → EVT	-364.03 (121.97)	-603.08 to -124.98	.005
Lobule VIIIa → Newport	80.07 (22.09)	36.77 to 123.37	.001
Lobule IX → PPVT	126.91 (63.15)	3.14 to 250.67	.051

Note. Effects reported for robust linear models after controlling for age, sex, lesion size, and intracranial volume. Only results in which 95% confidence interval did not cover zero are reported. If the laterality measure was positive, that indicated left laterality for the patients following perinatal stroke. ROI = region of interest. EVT = Expressive Vocabulary Test. CELF-E = Clinical Evaluation of Language Fundamentals – Expressive Language submeasure. Newport = Johnson-Newport Grammaticality Judgement task. PPVT = Peabody Picture Vocabulary Test.

Table 8

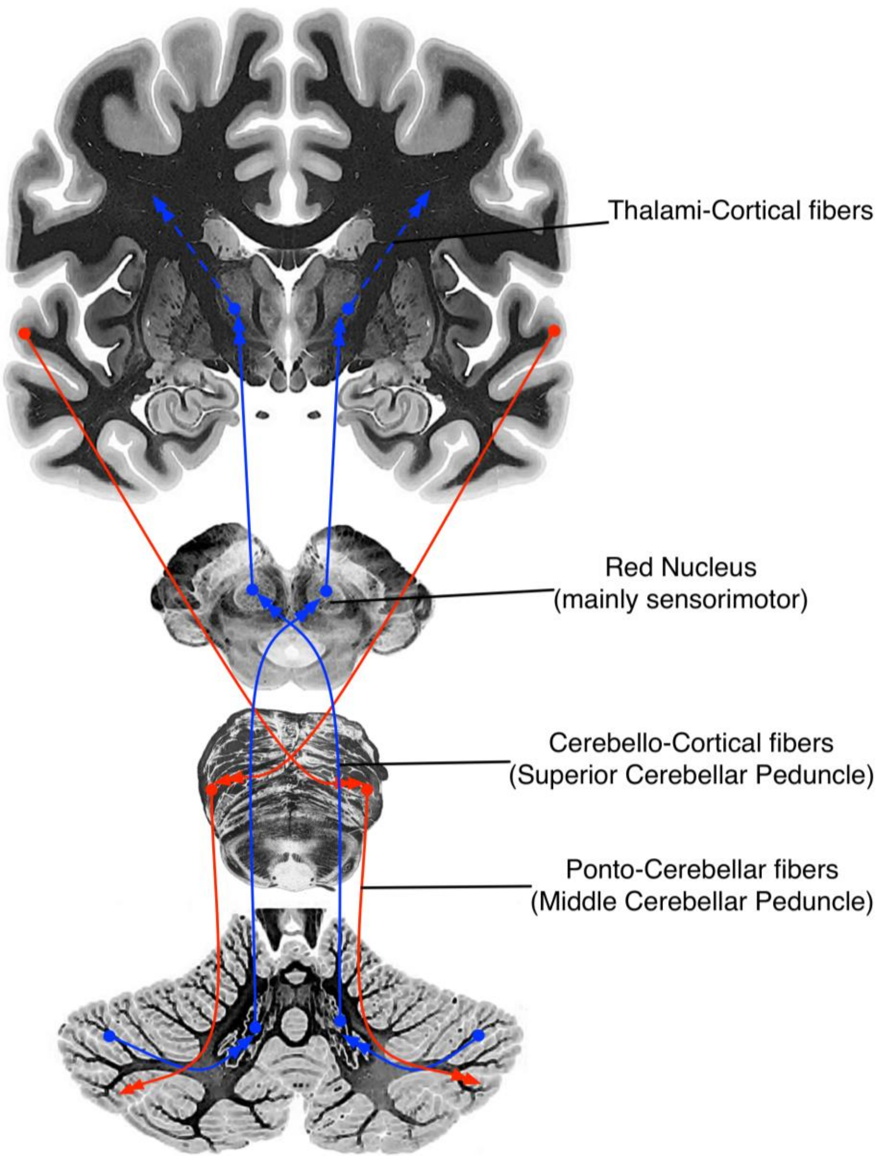
Relation of Laterality Measure of Cerebellar T_1/T_2-FLAIR Ratio to Language Measures

Predictor → Outcome	*b* (SE)	95% CI	*p* - value
Lobule I-III → Newport	-97.32 (32.64)	-161.30 to -33.35	.014
Lobule I-III → VIQ	-112.59 (37.72)	-186.51 to -38.67	.014
Lobule VIIIa → EVT	39.65 (13.96)	12.28 to 67.01	.018
Lobule VIIIa → VIQ	37.39 (15.91)	6.22 to 68.57	.041
Lobule VIIIb → EVT	58.28 (24.08)	11.08 to 105.49	.036

Note. Effects reported for robust linear models after controlling for age, sex, lesion size, and intracranial volume. Only results in which 95% confidence interval did not cover zero are reported. If the laterality measure was positive, that indicated left laterality for the patients following perinatal stroke. ROI = region of interest. Newport = Johnson-Newport Grammaticality Judgement task. VIQ = Verbal Comprehension Index of the Intelligence Scale. EVT = Expressive Vocabulary Test.

Figure 1

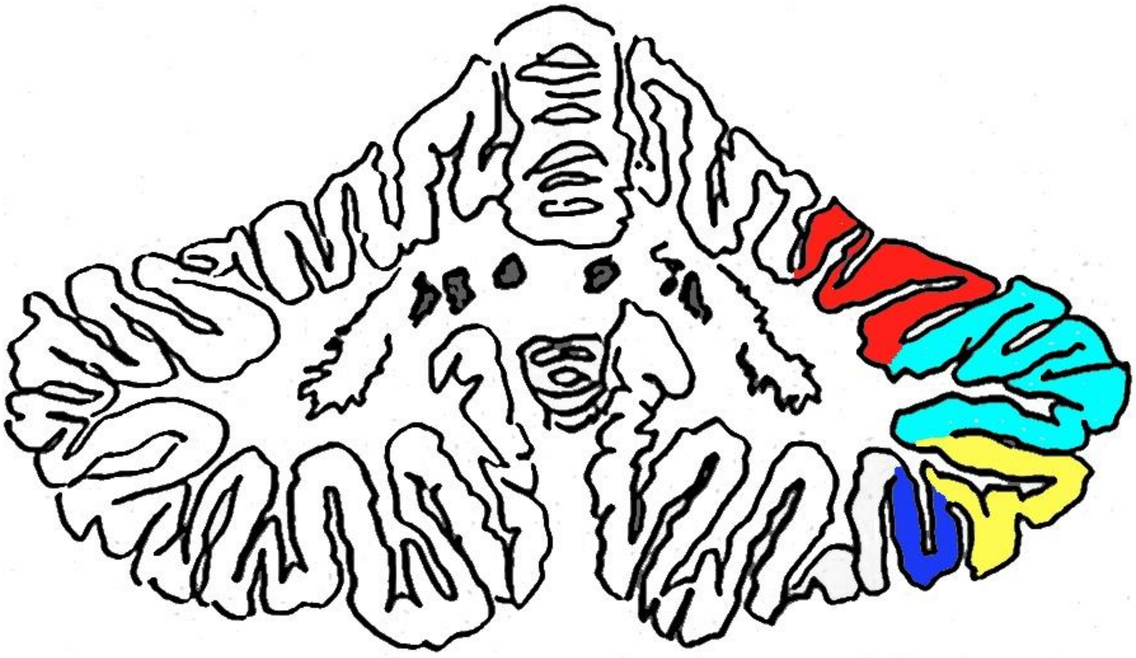
Cortico-Cerebello-Cortical Connections



Note. The red line notes the descending cortico-ponto-cerebellar pathway that originates in motor and association regions of the cerebral cortex. From the cerebral cortex, the fibers project to the ipsilateral pontine nuclei and then cross through the middle cerebellar peduncle to the contralateral cerebellar cortex. The blue line notes the ascending cerebellar-thalamic-cortico pathway that sends information from the cerebellar cortex through the superior cerebellar peduncle to the midbrain, where they cross and pass to the contralateral red nucleus to the thalamus. From the thalamus, fibers send information to motor and association areas in the cerebral cortex.

Figure 2

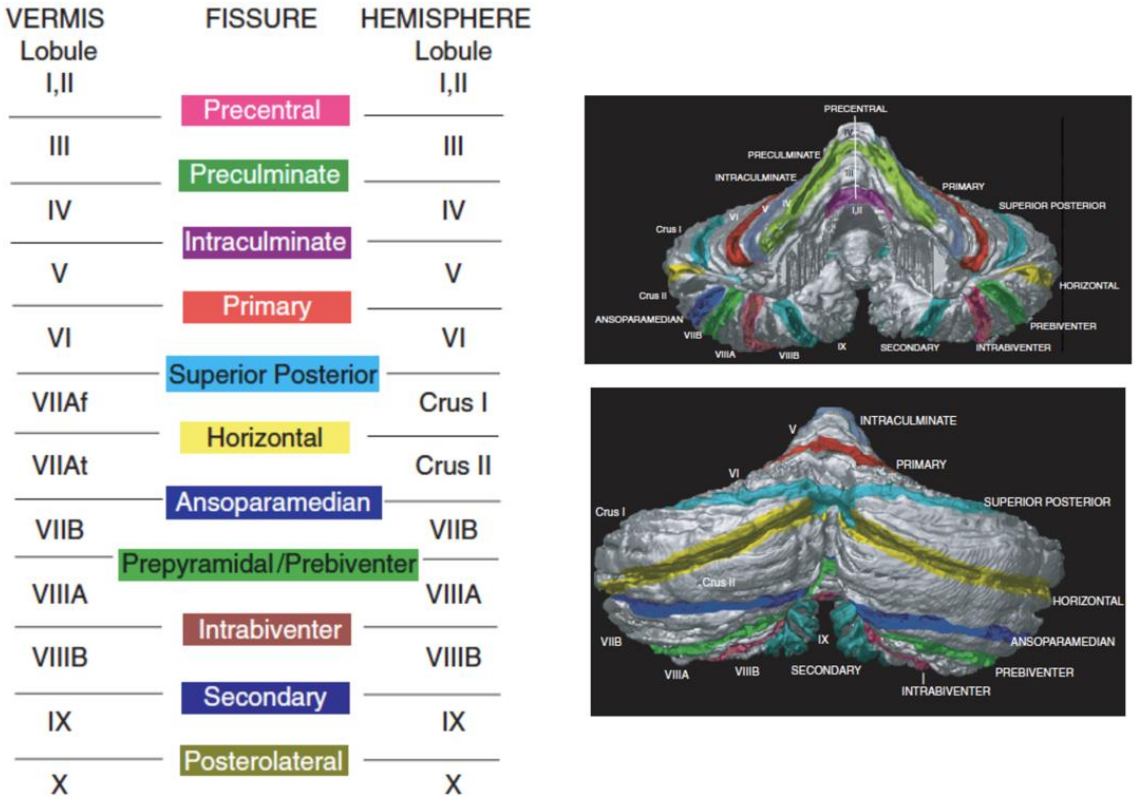
Language Regions of the Cerebellum



Note. The four lobules highlighted note the regions within the right hemisphere that are frequently associated with language function. Specifically, the right hemisphere lobules VI in red, Crus I in cyan, Crus II in yellow, and VIIb in blue are frequently activated during language tasks, and receive connections from the prefrontal, posterior parietal, and superior temporal cortices known to be involved in language function.

Figure 3

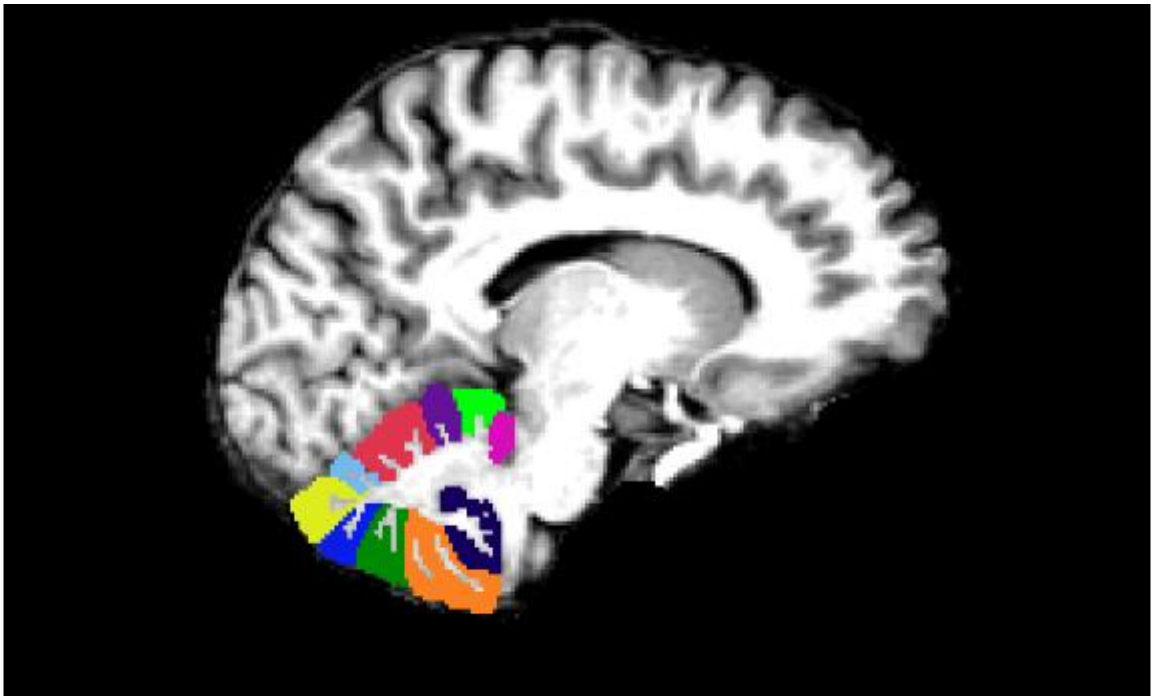
Schmahmann et al.'s (1999) Three-Dimensional MRI Atlas of the Human Cerebellum in Proportional Stereotaxic Space



Note. The atlas used to guide the manual parcellation of the cerebellar cortex.

Figure 4

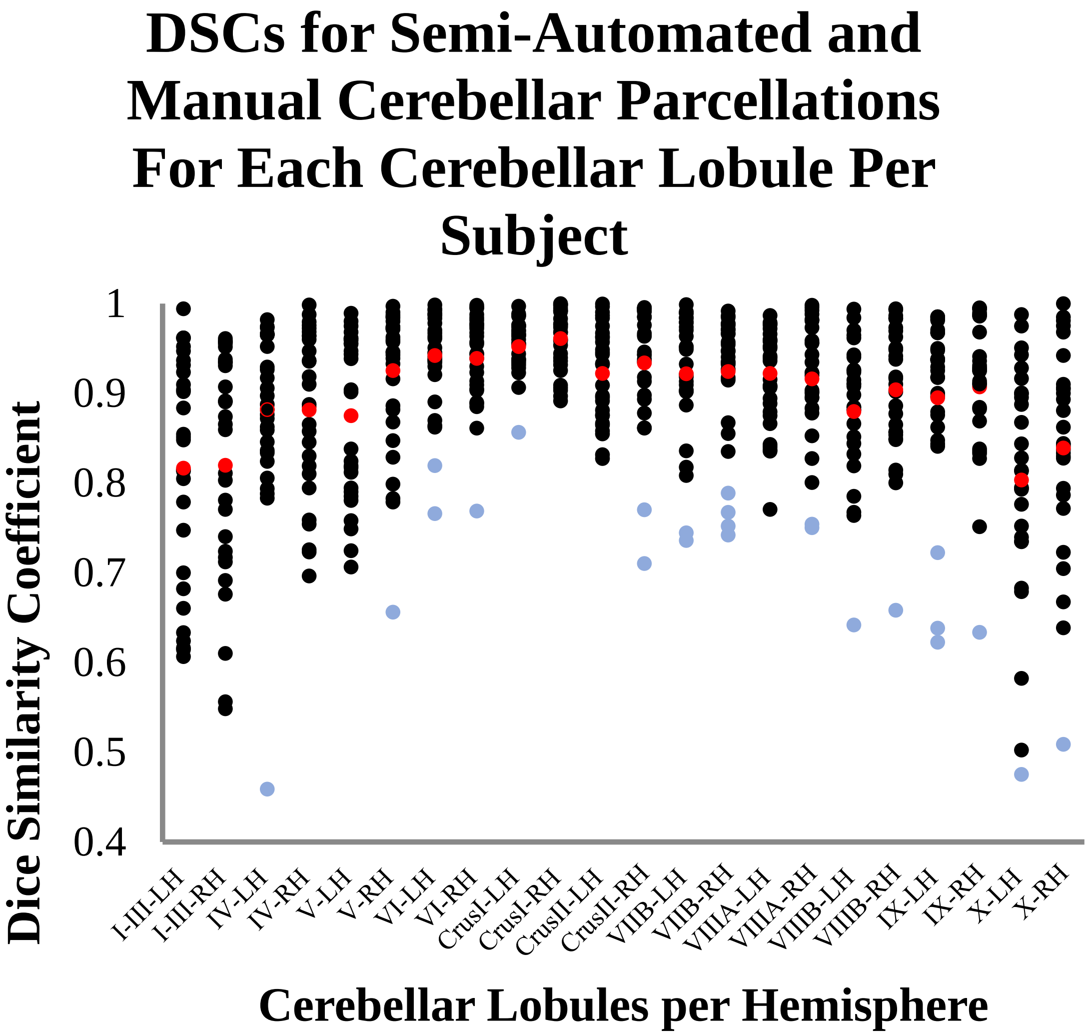
Manual Parcellation of Cerebellar Cortex



Note. Sagittal view of one of the 27 T_1-weighted MRIs that were manually segmented using the FreeSurfer software. Lobules I-III were grouped into one mask, followed by individual segmentations of lobules IV, V, VI, Crus I, Crus II, VIIb, VIIIa, VIIIb, IX, and X across both hemispheres.

Figure 5

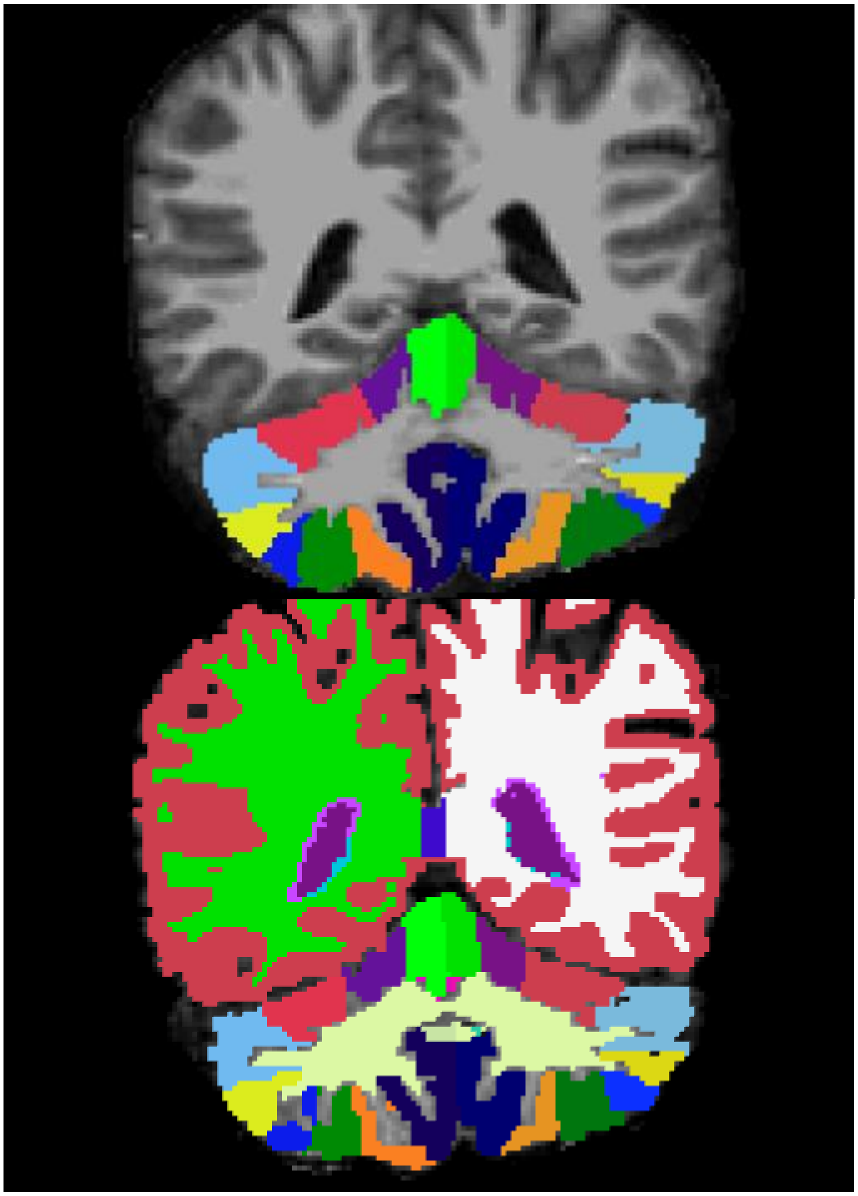
DSCs for Semi-Automated and Manual Cerebellar Parcellations for Each Cerebellar Lobule Per Subject



Note. Plotted are each individual subject's dice similarity coefficient (DSC) for each lobule. The average DSC per region is annotated in red, while the outliers calculated using the following formula, quartile 1- (1.5 * interquartile range) is annotated in blue.

Figure 6

Manual and Semi-Automated Parcellation of Cerebellar Cortex of the Same Subject



Note: Coronal view of one of the 27 T_1-weighted MRIs that were segmented using the FreeSurfer software. Top photo is of manual parcellation, bottom photo is of semi-automated parcellation. Lobules I-III were grouped into one mask, followed by individual segmentations of lobules IV, V, VI, Crus I, Crus II, VIIb, VIIIa, VIIIb, IX, and X across both hemispheres.

VITA

CAROLINA ALEXIS VIAS

2007 – 2012	B.A., Psychology Florida International University, Miami, FL
2013 – 2016	M.S., Psychology Florida International University, Miami, FL
2013 – 2021	Doctoral Candidate, Psychology Florida International University, Miami, FL

PUBLICATION AND PRESENTATIONS

Vias, C., Solodkin, A., Small, S. L., Dick, A. S. (2019, October). Cerebellar contributions to language recovery following early stroke. Poster presented at the Society for the Study of Human Development, Portland, OR.

Vias, C., & Dick, A. S. (2017). Cerebellar Contributions to Language in Typical and Atypical Development: A Review. *Developmental neuropsychology*, *42*(6), 404-421.

Vias, C., Munoz ,J., Tchir, S., Salan, J., Lopez, G., Suros, A., Grudny, M., Solodkin, A., Small, S. L., Dick, A. S. (2017, April). The cerebellum’s relationship to expressive language. Poster presented at the Society for Research in Child Development, Austin, TX.

Vias, C., Munoz, J., Tchir, S., Salan, J., Lopez, G., Suros, A., Grudny, M., Solodkin, A., Small, S. L., Dick, A. S. (2016, August). The cerebellum’s relationship to language function. Poster presented at the Society for Neurobiology of Language meeting, London, England, UK.

Munoz, J., Vias, C., Tchir, S., Salan, J., Lopez, G., Suros, A., Grudny, M., Dick, A. S. (2016, April). The cerebellum's role in language recovery following perinatal stroke. Poster presented at the 2016 Conference for Undergraduate Research at Florida International University, Miami, Florida.

Salan, J., Vias, C., Munoz, J., Tchir, S., Lopez, G., Suros, A., Grudny, M., Dick, A. S., Small, S. L., Solodkin, A. (2016, March). Development of a Semi-Automated Cerebellar Atlas for Brain Imaging Research. Poster presented at the Florida International University Undergraduate Research Conference, Miami, Florida.

Munoz, J., Vias, C., Tchir, S., Salan, J., Lopez, G., Suros, A., Grudny, M., Dick, A. S. (2016, February). The cerebellum's role in language recovery following perinatal stroke. Poster presented at the annual Florida Undergraduate Research Conference, Tampa, Florida.

Vias, C., Bryon, A., Morales, A., Goldberg, C., Dick, A. S., Solodkin, A., Small, S. L. (2015, March). Cerebellar contributions to language development following perinatal stroke. Poster presented at the biennial Society for Research in Child Development meeting, Philadelphia, Pennsylvania.

Vias, C., Bryon, A., Morales, A., De Feria, A., Medina, J., Dick, A. S., Solodkin, A., Small, S. L. (2014, April). Cerebellar contributions to language recovery following pre- or perinatal stroke. Poster presented at the annual Cognitive Neuroscience Society meeting, Boston, Massachusetts.

Bryon, A., Vias, C., Dick, A. S., Solodkin, A., & Small, S.L. (2014, March) Development of a Semi-Automated Cerebellar Atlas. Poster presented at the Advanced Research and Creativity in Honors, Miami, Florida.

Bryon, A., Vias, C., Dick, A. S., Solodkin, A., & Small, S.L. (2014, February) Development of a Semi-Automated Cerebellar Atlas. Poster presented at the Florida Undergraduate Research Conference, Miami, Florida.

DeFeria, A., Vias, C., Byron, A., Morales, A., Medina, J., Dick., A.S., Solodkin, A., Small, S.L. (2013, December) Cerebellar Contributions to Language Recovery Following Pre- or Perinatal Stroke. Poster presented at the 22nd Annual Neuroscience Research Day at the University of Miami Leonard M. Miller School of Medicine.