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Atypical development of the cerebellum : impact on language function

Lynette M. Silva

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**ATYPICAL DEVELOPMENT OF THE CEREBELLUM: IMPACT ON
LANGUAGE FUNCTION**

By

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B.A., English, Stanford University, 1996
M.S., Psychology, University of New Mexico, 2009

DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

**Doctor of Philosophy
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Dedication

For my parents, extended family, and valued friends, because it took a village.

And for Martin Rodriguez, who served as my Virgil, and showed me the way.

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ABSTRACT

Children born very low birth weight (VLBW; <1800 grams) and/or preterm (<33 weeks gestation) frequently have cerebellar hypoplasia, and a constellation of cognitive deficits. The cerebellum, now shown to be involved in many non-motor functions, has a protracted maturation process similar to the frontal lobes, and new evidence suggests the cerebellum may be more vulnerable to environmental factors than subject to genetics. However, relationships between specific cerebellar structures and cognitive functions have not been extensively investigated. We examined relationships between the volume of four cerebellar regions of interest (ROI) and language performance in two age samples: 27 participants between 16 and 20 months of age and 20 participants between 3 and 4 years old. Language performance was significantly different between VLBW and control groups in both age samples. No significant relationships were evident between language performance and ROI volume in the 18-month-old sample. Anterior vermis volume was significantly correlated with VIQ scores in only the 3-year-old VLBW group, in the absence of a significant group difference in anterior vermis volume. This correlation remained significant

in the VLBW group, even when controlling for number of days on ventilation. In terms of predicting group membership, VIQ was the most significant predictor in the 3-year-old sample, with increased specificity when adding right dentate nucleus volume. In terms of predicting VIQ scores, ethnicity was the most significant predictor for the control group, but days of ventilation along with anterior vermis volume best predicted VIQ in the VLBW group. The possibility of a differential relationship between anterior vermis volume and language ability in VLBW children, possibly emerging between 18 months and 3 years of age, may have implications for development of interventions, particularly given environmental vulnerability and the protracted cerebellar maturation process.

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Introduction

For more than a century the cerebellum was generally considered to be solely involved in motor control and balance coordination, and nothing more. Over the past two decades, interest in the role of the cerebellum in cognition, emotion, and non-motor behavior has begun to grow, resulting in a small but increasing body of research focused on the possible roles of the cerebellum in cognition. Much of this newer literature proposes a wide range of possible cerebellar function and involvement in various cognitive processes. The implication of factors such as evolution, development, and cytoarchitecture has been reconsidered, resulting in new, non-motor theories of the cerebellum. Recent hypotheses of cerebellar involvement in cognition encompass nearly all cognitive domains, such as attention, affect, language, memory, and executive function. Deficits in these areas commonly seen in various psychopathologies and some developmental disorders have begun to be examined in the context of these newer cerebellar theories. Given the cognitive functions now thought to be subject to cerebellar influence, and the possible involvement of the cerebellum in various psychological and developmental disorders, the development of this particular brain structure may play a key role in determining the level of functioning across many domains beyond motor and coordination.

One area of non-motor function now thought to have cerebellar involvement is language. Beyond ataxic dysarthria, there is mounting evidence that the cerebellum plays a role in a variety of language abilities including lexical retrieval, syntax, verbal fluency and grammar production (Leggio, Silveri, Petrosini & Molinari, 2000; Marien, Engleborghs, Fabbro & De Deyn, 2001; Paquier & Marein, 2005; Salman, 2002; Schlosser, et al., 1998; Silveri & Misciangna, 2000; Vokaer, et al., 2002). Several developmental disorders

consistently include evidence of atypical cerebellar structure concurrent with a variety of language deficits. However, these developmental disorders often have varying or unknown etiology (i.e. autism) or specific teratogenic effects (i.e. fetal alcohol syndrome). As the developing cerebellum appears to be particularly vulnerable to any interruption in development (Geidd, Schmitt & Neale, 2007; O'Hearn & Molliver, 2001), children born preterm and/or very low birthweight (VLBW) are the ideal population in which to examine the relationship between the cerebellum and language function.

Background

The Cerebellum. Though only one-tenth of total brain weight is accounted for by the cerebellum, it contains more neurons than the cerebral cortex (Andersen, Korbo & Pakkenberg, 1992). The cellular composition, or cytoarchitecture, of the cerebellum is very uniform and contains some of the largest neurons in the nervous system, with the fullest, most elaborate dendrites: Purkinje cells (Diamond, 2000; Leiner, Leiner & Dow, 1991). Each Purkinje cell in the cerebellum receives information from two types of fibers: parallel fibers, which are many per Purkinje cell, and climbing fibers, which are only one per Purkinje cell (Andersen, Korbo & Pakkenberg, 1992; Leiner, Leiner & Dow, 1991). During early development, each Purkinje cell has several climbing fibers that are pruned out as the cerebellum matures, leaving one climbing fiber per Purkinje cell (Andersen, Korbo & Pakkenberg, 1992; Leiner, Leiner & Dow, 1991). Despite each Purkinje cell receiving information from only one climbing fiber, the input from that climbing fiber is extremely strong and excitatory (Andersen, Korbo & Pakkenberg, 1992). Purkinje cells themselves are inhibitory, therefore, excitatory input from the single climbing fiber results in an inhibitory Purkinje response (Kreitzer & Regehr, 2001).

Most output fibers of the cerebellum originate in the four deep cerebellar nuclei, which are embedded in the cerebellar white matter, and these fibers project to and receive information from specific areas of the cerebral cortex (Hoppenbrouwers, Schutter, Fitzgerald, Chen & Daskalakis, 2008; Ito, 2008; Strick, Dum & Fiez, 2009). These fibers form closed circuits, allowing the cerebellum to influence or modulate the functions localized to various areas of the brain, as well as receive feedback from those areas (Hoppenbrouwers, Schutter, Fitzgerald, Chen & Daskalakis, 2008; Ito, 2008; Paquier & Marien, 2005; Strick, Dum & Fiez, 2009). Because the cerebellar cortex has homogenous cytoarchitecture, theories that the cerebellum performs uniformly across domains have arisen, and because it is connected to many different areas of the cerebral cortex, an emerging theory is that the cerebellum acts on non-motor functions as it acts on motor functions: by modulation and coordination (Bellebaum & Daum, 2007; Hoppenbrouwers, Schutter, Fitzgerald, Chen & Daskalakis, 2008; Ito, 2008; Marien, Engelborghs, Fabbro & De Deyn, 2001; Schmahmann, 2001). The prevailing theories of cerebellar involvement in cognition are those of indirect influence, as opposed to localized function.

Theories of cerebellar involvement in non-motor functions have been developed in part by looking back through human evolution, to a period of time when both the cerebellum and the prefrontal cortex underwent structural and functional changes. Not only did the human cerebellum evolve in tandem with the prefrontal cortex, it developed reciprocal connectivity with various areas of the cerebral cortex, as well (Andersen, Korbo & Pakkenberg, 1992; Leiner, et al., 1993). It has been theorized that the cerebellum and the prefrontal cortex expanded in structure and function simultaneously to work together in the

human brain and not other primates' brains due to environmental changes requiring higher-order cognition of humans (Andreasen & Pierson, 2008; Casini & Ivry, 1999).

Cerebellar involvement in language. From the traditional view of the cerebellum, one solely concerned with motor function, language deficits resulting from cerebellar damage would be limited to ataxic dysarthria (Ackerman, Mathiak & Riecker, 2007; Darley, Aronson & Brown, 1969; Holmes, 1922). While ataxic dysarthria is associated with cerebellar damage because motor control is necessary to physically produce speech, patients with intact language areas but lacking cerebellar input have shown impaired language functions including lexical retrieval, syntax, and language dynamics (Marien, Engleborghs, Fabbro & De Deyn, 2001). Theorists in this area have proposed that the cerebellum may not play a direct role in language, but may influence language indirectly through reciprocal connections with known language areas (Paquier & Marein, 2005). For example, damage to the cerebellum may not directly impact language generation, but distortion or disruption of signals from the cerebellum may result in an inability to impose syntactic rules. Another theory is that because the cerebellum is involved with timing, cerebellar damage may result in a slowing or disruption of the timing required for communication, which may be expressed as a language deficit (Salman, 2002).

Studies on patients with right cerebellar damage have been shown to experience a decrease in verbal fluency, or consistently finding the appropriate word to use (Leggio, Silveri, Petrosini & Molinari, 2000; Schlosser, et al., 1998; Silveri & Misciangna, 2000; Vokaer, et al., 2002). Several imaging studies have shown activation in the right cerebellum, which projects to the left hemisphere of the cerebral cortex (O'Hearn & Molliver, 1999), during verbal fluency tests and cognitive word association tasks (Marien, Engleborghs,

Fabbro & De Deyn, 2001; Ravnkilde, Videbech, Rosenberg & Gjedde, 2002; Videbech, et al., 2003). This right cerebellar activation was simultaneous with activation in Broca's area, suggesting the cerebellum and Broca's area are working together to accomplish verbal tasks (Ballieux, De Smet, Paquier & Marien, 2008; Martin, Haxby, Lalonde, Wiggs & Ungerleider, 1995; Paquier & Marien, 2005; Raichle, Fiez, Videen, MacLeod & Pardo, 1994). Another type of language deficit associated with cerebellar dysfunction is agrammatism (Justus, 2004; Leggio, Silveri, Petrosini & Molinari, 2000; Paquier & Marien, 2005; Zettin, et al., 1997). Agrammatism has been likened to Broca's Aphasia, and is characterized by telegraphic speech, a simplified style of speech that can lack tense, articles, pronouns, and contain incorrect verbs (Justus, 2004; Marien, Engelborghs, Fabbro & De Deyn, 2001). As with the deficits in word finding and word generation, agrammatism appears to be related to damage in the right hemisphere of the cerebellum, which is interconnected with the left hemisphere of the cerebral cortex, where the language centers are typically located (Leggio, Silveri, Petrosini & Molinari, 2000; O'Hearn & Molliver, 1999; Strick, Dum & Fiez, 2009; Zettin, et al., 1997).

While word finding, word generation, and grammar production and perception appear to be the most studied aspects of language connected with the cerebellum, they are not the only language deficits to arise as a result of cerebellar damage. Dyslexia (Nicolson & Fawcett, 1999), verbal working memory deficits (Desmond & Marvel, 2009), speech perception deficits (Ackermann, Mathiak & Riecker, 2007), mutism, and atypical prosody (Marien, Engelborghs, Fabbro & De Deyn, 2001) have been found to be associated with cerebellar damage in the absence of cerebral cortex abnormalities. The cerebellum may not

be a language center, but it appears to work in conjunction with language areas to accomplish many aspects of verbal communication.

Atypical cerebellar development. Many aspects of motor control as well as complex cognition have the longest maturation process, continuing to develop into adolescence (Diamond, 2000). This development is mirrored neurologically by the protracted maturation of both the prefrontal cortex and the neocerebellum, the evolutionarily newer lateral area of the cerebellar hemispheres (Diamond, 2000). In addition to a longer maturation process, there is evidence that the cerebellum may be less subject to genetic influences and more vulnerable to environmental factors than other areas of the brain (Geidd, Schmitt & Neale, 2007). Given the various cognitive domains theorized to be modulated or coordinated in some way by the cerebellum, it is possible that atypical development of the cerebellum might result in a wide variety of cognitive deficits. Likewise, interrupted development of the cerebellum, as seen in various developmental disorders, may result in a shared constellation of deficits. The frequent pattern of interaction, influence, and cooperation between the cerebellum and areas of the cerebral cortex has caused some researchers to hypothesize that concurrent cerebellar and frontal lobe abnormalities may be common to many developmental and acquired disorders of early childhood (Ciesielski, Harris, Hart & Pabst, 1997).

Fetal Alcohol Syndrome (FAS). FAS is the most prevalent, and most preventable, cause of mental retardation (Murthy, Kudlur, George & Mathew, 2009). The effects of maternal alcohol use during pregnancy have a wide range, and FAS does not encompass all alcohol related birth defects. A broader term, Fetal Alcohol Spectrum Disorder (FASD), is used to encompass the various physical, mental, and behavioral deficits resulting from

maternal alcohol use during pregnancy. Facial dysmorphism, growth retardation, and neurocognitive deficits, all caused by maternal alcohol use during pregnancy, must be present for the diagnosis of FAS (Murthy, Kudlur, George & Mathew, 2009). While varied, behavioral characteristics of individuals with FAS include impairments in sustained attention, verbal learning, working memory, spatial processing, visual-motor integration, and executive function (Carmichael Olson, Feldman, Streissguth, Sampson & Bookstein, 1998; Kodituwakku, Handmaker, Cutler, Weathersby & Handmaker, 1995; Mattson & Riley, 1998). While FAS has been shown to impact the entire nervous system, the focus here will be on how FAS impacts cerebellar development, and what role this atypical cerebellar development might play in the resulting neurocognitive and behavioral symptoms associated with FAS.

Exposure to alcohol *in utero* has been shown to result in incomplete development of the cerebellum, resulting in cerebellar hypoplasia, or a relatively smaller cerebellum. Cerebellar hypoplasia has been consistently found throughout the FAS research, though very few studies quantify the difference in volume (Archibald, et al., 2001; Goodlett, Marcussen & West 1990; Sowell, et al., 1996). This characteristic reduction in cerebellar volume supports the theory that the cerebellum may be particularly vulnerable to alcohol exposure *in utero* (O'Hearn & Molliver, 2001), and thus may play a role in some of the deficits associated with FAS. Cerebellar hypoplasia has been shown to result not only in psychomotor delay, but also cognitive impairment, developmental disorders, ataxia, attentional deficits (e.g., slowed orienting of attention), and mental retardation (Parmeggiani, Posar, Scaduto, Chiodo & Giovanardi, 2003; Segarra, et al., 2008; Singer Harris, 1998; Tavano, et al., 2007; Ventura, Presicci, Perniola, Campa & Margari, 2006). The

underdevelopment of the cerebellum in FAS may result in one or all of these effects of cerebellar hypoplasia.

The cerebellar vermis, the narrow median between the hemispheres of the cerebellum, appears to be an area most affected by prenatal alcohol exposure (Archibald, et al., 2001; O'Hare, et al., 2005; O'Hearn & Molliver, 2001; Riley, McGee & Sowell, 2004). Vermal hypoplasia, or reduced size of the vermis, has been found to be associated with FAS, particularly hypoplasia of the anterior vermis (Goodlett, Marcussen & West, 1990; O'Hare, et al., 2005). Hypoplasia of the anterior vermis has been shown to be associated with lower IQ scores (Nopoulos, Ceilley, Gailis & Andreasen, 1999; Segarra, et al., 2008). O'Hare, et al. (2005), found that not only is the cerebellar vermis smaller in individuals with FAS compared to controls, but the anterior vermis was also displaced, with the magnitude of displacement showing a negative correlation with verbal cognitive performance.

Purkinje cells, the neurons unique to the cerebellum, are thought to play a major role in modulating output from the cerebellum to regions of the cerebral cortex (Andreasen & Pierson, 2008), and are the only neurons sending output from the cerebellum (Lujan, 2007). Along with reduced total cerebellar volume in FAS, there is also a decrease in number of Purkinje cells (Kern, 2003; West & Goodlett, 1990). Either these Purkinje cells fail to develop or are lost prenatally. Research on the function of surviving Purkinje cells present in individuals with FAS is limited. Initial research seems to indicate that prenatal exposure to alcohol does result in Purkinje cell dysfunction ranging from increased spontaneous Purkinje cell firing, like that seen in ataxia (Servais, et al., 2007), to dendritic abnormalities (Abel, 1996), to altered amplitude of calcium currents (Gruol & Parsons, 1994; Servais, et al., 2007). Further research is needed to establish specific FAS behavioral correlates to these

differences in cellular structure and function, but all alcohol-induced Purkinje cell dysfunctions implicate motor learning deficits as one result. One point upon which the current research appears to agree is that Purkinje cells are particularly vulnerable to any insult, including prenatal alcohol exposure (Ramados, Lunde, Chen, West & Cudd, 2007; West, Goodlett, Bonthius, Hamre & Marcussen, 2006).

Autism. Autism is a pervasive developmental disorder, usually apparent within the first three years of life, characterized by delayed cognitive development, impaired social awareness, limited communication, and restricted and repetitive behavior (Amaral, Schumann & Nordahl, 2008). While the prevalence of the disorder has increased over the last twenty-five years, little is known regarding etiology, though there does appear to be a strong genetic component (Abrahams & Geschwind, 2008). In the abundance of autism research, various parts of the brain have been shown to be associated with the disorder, but no single structure, area, mechanism, or cause has been discovered (Penn, 2006). However, as with FAS, cerebellar hypoplasia has also been consistently shown to be present in autism (Ciesielski, Harris, Hart & Pabst, 1997; Courchesne, 1997). Another structural abnormality shared between FAS and autism is loss of Purkinje cells, the cells responsible for outgoing signals to the rest of the brain (Courchesne, 1997; Vargas, Nascimbene, Krishnan, Zimmerman & Pardo, 2005). In autism, the surviving Purkinje cells appear to be smaller in size compared to controls (Allen, 2005; Fatemi, et al., 2002; Ito, 2008). Smaller and fewer Purkinje cells may result in erroneous modulation of signals to other brain regions in those with autism. FAS and autism share a number of structural abnormalities, which perhaps accounts for some of their shared symptoms, including psychomotor delay, cognitive impairment, attentional deficits, language impairments, and mental retardation (Parmeggiani,

Posar, Scaduto, Chiodo & Giovanardi, 2003; Singer Harris, et al., 1999; Tavano, et al., 2007; Ventura, Presicci, Perniola, Campa & Margari, 2006).

As with FAS, hypoplasia of the cerebellar vermis is present in autism, however, where the vermal hypoplasia in FAS is most pronounced in the anterior region of the vermis, it is most pronounced in the posterior region of the vermis in autism (Ciesielski, Harris, Hart & Pabst, 1997; Courchesne, et al., 2001; Hashimoto, et al., 1995; Levitt, et al., 1999; Schaefer, et al., 1996). In a study of patients diagnosed with mental retardation and with partial vermal agenesis, or absence of the posterior vermis, many of the resulting symptoms are shared with those of autism: language was impaired or absent, cognitive abilities were delayed, social interaction was lacking, and the participants were described as “uncooperative” (Tavano, et al., 2007). Pierce and Courchesne (2001) found that the magnitude of hypoplasia of the posterior vermis in autistic children significantly correlated with measures of decreased exploration. The same study found frequency of stereotypic behavior to be negatively correlated with posterior vermis volume and positively correlated with frontal lobe volume. One possible explanation for this second finding is that the vermal hypoplasia results in production of fewer cerebellar inhibitory signals, causing the frontal lobe to overreact, and to repeat itself due to the feedback loop with the cerebellum (Pierce & Courchesne, 2001).

Autism studies have also found evidence that cerebellar abnormalities may influence how other circuitry develops, which can impact the functioning of other brain regions (Allen, 2005). Many of the symptoms of autism (e.g., impaired social interaction, attention, executive function) are commonly associated with the frontal cortex, and in fact, an early hypothesis had autism localized there (Damasio & Maurer, 1978). However, as research on

autism as progressed, the cerebellum has been the structure most consistently implicated in the disorder, and frontal structural abnormalities associated with autism are both less evident and less prevalent (Carper & Courchesne, 2000). A newer hypothesis suggests frontal atypical development may be a result of, or occur in tandem with, the cerebellar hypoplasia found throughout autism literature (Carper & Courchesne, 2000). There appears to be an inverse relationship between frontal and cerebellar volume in autism: the frontal cortex appears enlarged, the cerebellum is disproportionately small, and the extent of frontal abnormality correlates with the extent of cerebellar abnormality (Bailey, et al., 1998; Carper & Courchesne, 2000). The reduced number of Purkinje cells and their resulting atypical cell behavior could influence not only how circuitry develops, but also how other brain regions, like the frontal cortex, develop as well.

Born Preterm and/or Very Low Birth Weight (VLBW). The designations of preterm and very low birth weight (VLBW) both apply to individuals born prematurely, but “preterm” is used in the literature to describe those born before 33 weeks of gestation or with a weight less than 1800 grams (Van Braeckel, et al., 2008), and “VLBW” applies to individuals born with a weight less than 1500 grams (Gaddlin, Finnstrom, Wang & Leijon, 2008). While differences exist between these two conditions, they share some resulting cognitive, emotional, and behavioral symptoms. The exact causes or combination of causes of spontaneous preterm labor are poorly understood. Maternal factors known to be associated with premature labor and/or low birthweight include but are not limited to the following: infection, stress, substance use, pre-eclampsia, vascular disease, uterine overdistension, intrauterine growth restriction, low maternal body-mass index, short cervical length,

nutritional status, and immunological processes (Goldenberg, Culhane, Iams & Romero, 2008).

Preterm and VLBW conditions share some of those symptoms with both FAS and autism. Atypical cerebellar development has been seen in those born preterm (Allin, et al., 2001; Limperopoulos, et al., 2005), but for the most part the cerebellum has been overlooked in this population. While only a very few preliminary studies on preterm and VLBW have examined the associated state of the cerebellum, because the cerebellum appears to be particularly vulnerable to prenatal insult (O'Hearn & Molliver, 2001), and because of the shared symptoms with FAS and autism, perhaps hypotheses can be made regarding the role of the cerebellum in preterm or VLBW conditions.

The predominant neurocognitive deficits shared between FAS and autism include impaired ability to sustain attention, delayed cognitive development or mental retardation, impaired language and communication, and impulsivity. Likewise, those born VLBW have been shown to have a range of attention problems, developmental delay or mental retardation, language deficits, and impulsivity (Allin, et al., 2001; Aylward, 2002; Davis, Burns, Snyder & Robinson, 2007; Dezoete, MacArthur & Tuck, 2003; Nosarti, et al., 2008; Parker, et al., 2008; Pyhala, et al., 2009; Rickards, Kelley, Doyle & Callahan, 2001; Skranes, et al., 2007; Stolt, Haataja, Lapinleimu & Lehtonen, 2009; Taylor, Minich, Klein & Hack, 2004; Weisglas-Kuperus, Koot, Baerts & Fetter, 1993). While the cerebellum has only very seldom been explicitly examined in the VLBW population, because of the shared constellation of symptoms between FAS and autism, and because of the relationship between those symptoms and cerebellar abnormalities, and because the cerebellum appears to be

particularly subject to environmental influences, it is possible the symptoms shared with the VLBW population may have a cerebellar explanation, as well.

While there is no cerebellar hypothesis to explain the deficits seen in those born preterm or VLBW, some of the more recent studies have found evidence that the cerebellum may at least play a role (Hart, Whitby, Griffiths & Smith, 2008; Nosarti, et al., 2008; Skranes, et al., 2007). One preterm study found an association between reduced cerebellar volume and lower IQ scores (Parker, et al., 2008). This association is one that has been made with FAS and autism as well (Parmeggiani, Posar, Scaduto, Chiodo & Giovanardi, 2003; Segarra, et al., 2008; Singer Harris, 1998; Tavano, et al., 2007; Ventura, Presicci, Perniola, Campa & Margari, 2006). Allin, et al. (2001), found an association between decreased overall cerebellar volume and increased impulsivity in adolescents born preterm. The same group (Allin, et al., 2005) found reduced volume of the vermis in adolescents born preterm specifically to be related to reduced language, executive, and visuo-spatial function. Nosarti, et al. (2008) found decreased cerebellar gray and white matter to be associated with impulsivity, which suggests diminished or disorganized communication between the cerebellum and the frontal lobes, where executive functions like inhibition of behavior tend to be localized. Other than these studies, cerebellar involvement in the deficits associated with being born VLBW and preterm has not been specifically examined.

Purpose of This Study

Population and cognitive function. Neurocognitive deficits shared between FAS, autism, and VLBW and the preterm-born have been shown to include impaired ability to sustain attention, delayed cognitive development or mental retardation, impaired language and communication, and impulsivity. How and why this constellation of symptoms is shared

has not been extensively examined, and while preliminary investigation into a possible cerebellar explanation has begun in each of these three populations, the atypical developmental trajectory of the cerebellum and its implications has yet to be fully examined. A focused examination of one of the shared neurocognitive deficits and its relationship with the cerebellum might begin to lay the foundation for a unified cerebellar theory of interrupted cerebellar development. The VLBW and preterm-born may make up the ideal population for such a study, as the specific effects of alcohol, as in FAS, and unknown etiology, as in autism, are eliminated from the cerebellum-neurocognitive deficit relationship. An investigation on this population might be more informative regarding general interrupted development.

The shared impacted cognitive area that might be most informative to examine initially may be that of language. Impulsivity and impaired ability to sustain attention can both arguably fall under the category of “executive functions,” which are not universally defined or measured (Elliott, 2003; Rabbit, 1997). While executive function has historically been thought to be localized to the frontal lobes, there is increasing evidence that a distributed network model may be more accurate (Elliott, 2003). Mental retardation is defined as having an IQ below 70, deficits in adaptive skills, with the onset occurring before age 18 (American Psychiatric Association, 1994). Like executive function, mental retardation encompasses a wide variety of possible cognitive deficits, and is not thought to be localized to a specific area or hemisphere of the brain. Language function, while not as localized as once believed, is still thought to be lateralized to the left cerebral hemisphere for the majority of the population. Thus, investigating language deficits associated with cerebellar abnormalities allows for examination of more specific and discrete brain and cerebellar areas, as well as more specific and discrete measurable behavior. Likewise, while the VLBW

research does not focus on the cerebellum as it relates to language, several preterm studies have shown a relationship between cerebellar volume and language deficits (Allin, et al., 2001; Allin, et al., 2005; Parker, et al., 2008), suggesting the need for more specific investigation.

Cerebellar regions of interest. Four areas of the cerebellum appear to be good candidates for investigating cerebellar involvement in language function. One preterm study showed hypoplasia and displacement of the anterior vermis to have a negative correlation with verbal cognitive performance (O'Hare, et al., 2005). However, this particular relationship has yet to be fully investigated. Studies focusing on the anterior vermis are largely non-human or postmortem human studies, therefore the relationship with language function was not examined (Albert, Dempsey & Sorenson, 1985; Supple, 1993; Weinberger, et al., 1980). Based on preliminary information (O'Hare, et al., 2005), there may be a relationship between the anterior vermis and language function. The dentate nucleus is the largest of the deep cerebellar nuclei, projecting contralaterally to the cerebrum via the superior cerebellar peduncle and the ventrolateral thalamus (Habas, 2010). Because this is the output channel of the cerebellum to the cerebrum, examining the condition of the right dentate nucleus might be useful in determining the quality of the messages being sent to the left hemisphere of the cerebrum. Likewise, the middle cerebellar peduncle is the input channel for projections from the auditory cortex to the cerebellum (Okugawa, et al., 2004); therefore, examining the condition of the right middle cerebellar peduncle might be useful in determining the quality of the incoming messages to the cerebellum. The fourth area, the superior semilunar lobule, or lobule VII, crus I, is the evolutionarily newer area of the cerebellum, and has been shown to be involved in non-motor aspects of cognition

(Schmahmann & Sherman, 1998). Because it is newer, and hypothesized to have evolved to handle newer aspects of cognition, and because it is contralaterally connected with the left, eloquent hemisphere of the cerebrum, it bears investigating as it relates to language function.

Hypotheses. Based on the shared language deficits between FAS, autism, and those born VLBW, along with the cerebellar correlates found between those deficits in FAS and autism, and the emerging scientific support for cerebellar involvement in language function in general, the following hypotheses are made:

Hypothesis I. The VLBW group will have reduced volume in the anterior vermis, the right dentate nucleus, the right middle cerebellar peduncle, and the right superior semilunar lobule, or lobule VII, crus I, as compared to controls at both 18 months and 3 years old.

Hypothesis II. This decreased volume in the above mentioned areas of the cerebellum will be correlated with lower verbal functioning in the VLBW group at both 18 months and 3 years old, with the 3-year-old experimental group showing the strongest relationship.

Hypothesis III. Decreased volumes of these four cerebellar regions of interest will predict VLBW group membership, with the strongest prediction in the 3-year-old experimental group.

Methods

Participants

This study is part of a larger study examining neural correlates of cognitive function in VLBW participants at 18 months and three years of age. Data collection for the larger study is ongoing, and has been collected from April 2008. The data used in this study was collected and used as the pilot for the larger study. For the present study, the experimental group consists of children born with very low birth weight (VLBW), or less than 1500 grams, and/or with a gestational age less than 34 weeks ($n = 31$; 12 female). The control group consists of healthy children born full-term, or with a gestational age between 37 and 42 ($n = 20$; 2 female). The two groups are further subdivided by age, into 18-month-olds (18 experimental, 9 controls) and 3-year-olds (12 experimental, 8 controls). An additional 26 subjects were attempted (13 experimental, 13 controls), but could not complete the imaging portion of the study. All children in the experimental group were admitted to the Children's Hospital of New Mexico, Newborn Intensive Care Unit (NICU) at birth. Exclusion criteria were as follows: hearing or visual impairment; exposure to teratogenic substances *in utero*; and/or positive for a known genetic abnormality.

Study Procedure

The experimental group was recruited by pediatric research nurses and a graduate student through the University of New Mexico Hospital General Research Center (UNMH GCRC). These pediatric nurses reviewed lists of infants admitted to the Children's Hospital of New Mexico's Newborn Intensive Care Unit (NICU) to determine which met criteria for the study. The parents of eligible infants who were in the appropriate age window were then contacted, given a brief overview of the study, and asked if they would like more detailed

information. If parents expressed interest, they were contacted with more information, and if they agreed to participate in the study, appointments were scheduled for developmental testing and magnetic resonance imaging (MRI). The control group was recruited through fliers posted in public places in the community. Interested parents contacting experimenters were given information about the study, and if they decided to participate, appointments were scheduled for developmental testing and MRI. All parents completed consent forms prior to participation, and to ensure their comprehension of the consent forms, the forms were read aloud and reviewed with the parents.

Developmental data were collected at either the University of New Mexico Pediatric Clinic; the Mind Research Network; or in the participating family's home. Developmental testing took approximately two hours to complete. The research coordinator of the study administered the Bayley Scales of Infant Development to children in the 18-month-old age group, and the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) to children in the 3-year-old age group. The experimenter then administered additional developmental assessments appropriate to the central hypotheses of the larger study.

Magnetic resonance imaging (MRI) was performed at night during natural sleep for the control group. Natural sleep was attempted with the experimental group, and if it did not occur, light chloral hydrate sedation was administered orally (50 mg/kg). The scanning protocol was approximately an hour long, though total time in the scanner varied (i.e., if the child woke up, and how long it took for the child to go back to sleep). All scans were performed using a Siemens 3T Trio TIM scanner, with 12-channel phased array head coils standard to the system. Images obtained included sagittal T1-weighted images, using a multi-echo 3D MPRAGE sequence [TR/TE/TI=2530/1.64, 3.5, 5.36, 7.22, 9.08/1200 ms, flip

angle=7°, field of view (FOV)=256 x 256mm, matrix=256 x 256, 1mm thick slice, 192 slices, GRAPPA acceleration factor=2]. FreeSurfer was then used to process the raw images (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures have been extensively detailed elsewhere (see Dale et al., 1999, Dale and Sereno, 1993, Fischl and Dale, 2000; Fischl et al., 2001, Fischl, et al., 2002, Fischl et al., 2004, Fischl et al., 1999a, Fischl et al., 1999b, Fischl et al., 2004b, Han et al., 2006, Jovicich et al., 2006, Segonne et al., 2004). The FreeSurfer image processing methods removed images of non-brain tissue using a hybrid watershed/surface deformation procedure, performed an automated Talairach transformation, segmented the subcortical white and deep gray matter volumetric structures, tessellated gray matter/white matter boundaries, performed automated topology correction, and surface deformation following intensity gradients to optimally position the boundaries between gray and white matter and gray matter and cerebrospinal fluid. Due to the age of the participants, the Talairach atlas used by FreeSurfer in automatic transformations can result in inaccurate segmentations. Therefore, this population requires visual inspection of each participant's imaging data, and manual correction if needed, to ensure accurate segmentation.

Once visually assessed for accuracy, each set of MPRAGE files was opened with Freeview, an editing tool similar in functionality to FreeSurfer's tkmedit and tksurfer tools, chosen over the latter due to inclusion of the cerebellum. Each region of interest (ROI) was hand-traced for each subject twice, to ensure reliable segmentation, and volumes calculated through Freeview. Both versions of a traced volume were simultaneously loaded and examined for reliability. Any region with a volumetric difference of 10mm^3 or more was hand-traced a third time ($n = 6$). Established segmentation guidelines for ROIs were used

(Deoni & Catani, 2007; Okugawa, Sedvall & Agartz, 2003; Pierson, et al., 2002). An example of final ROIs hand-traced for a single subject can be seen in Figure 1.

Measures

Magnetic resonance imaging data. Using the MRI volumetric data, volumes of the following cerebellar structures were obtained through FreeSurfer and Freeview: the anterior vermis, the right dentate nucleus, the right middle cerebellar peduncle, and the right crus I. Preliminary analyses revealed no significant difference in total cerebellar volume between control and VLBW groups. Additionally, the hypotheses of the present study include non-cerebellar areas, as well as the overall developmental trajectory. Therefore, analyses were performed on regional volume data normalized to total intracranial volume.

Language measures. The Bayley Scales of Infant Development-Third edition (BSID-III), a standardized assessment of developmental status in infants (from 0 to 3 years old), assesses functions on three scales: cognitive, motor, and language. The score used for this study from The BSID-III is the composite language score, which measures receptive communication skills, or the extent to which the infant understands verbal words or directions, through quantifying recognition responses to people, sounds, and objects in the infant's environment. For toddlers, receptive communication is assessed with tasks involving following simple verbal commands and identifying pictures. The language scale also measures expressive communication skills, or the extent to which the infant can communicate with others. Expressive language in infants is observed in physical expressions and vocal nonverbal behavior (i.e., babbling), whereas toddlers are asked to name pictures and verbally answer basic questions. These two components yield a composite language score.

The Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) is a standardized developmental assessment for use with children between the ages of two years six months to seven years three months. Subtests of the WPPSI-III involve assembling blocks, completing visual puzzles, picture naming, pointing at pictures, and answering basic verbal questions. Subtest scores on the WPPSI-III yield Full Scale IQ, Performance IQ, and Verbal IQ scores. The proposed score for use in this study is the Verbal IQ composite score. The subtest batteries are divided into two groups, the younger of which (two years six months to three years eleven months) were used for both experimental and control groups.

Statistical Analyses

To assess whether ROI volume group differences existed and were statistically significant, two-tailed t-tests between each age group's experimental and control groups were used. Individuals born preterm and VLBW are susceptible to a number of illnesses that may contribute to language and other cognitive deficits, including hydrocephalus, intraventricular hemorrhage, periventricular leukomalacia, respiratory distress, and infection (Siva Subramanian, Barton & Montazami, 2009). Also, weeks of gestation and post-natal environment may also be important factors in language development. Therefore, an ANCOVA was performed to test whether cerebellar ROI volume has an effect on VIQ after removing the variance for which gestational age, ethnicity, illness severity (days of post-natal ventilation), and socio-economic status (family income level) account.

To examine the relationship between volumes of ROIs and language ability, correlational analyses, utilizing Spearman and Pearson correlations, were performed between volumes of cerebellar ROIs and language scores for each age group. To examine if decreased volume in the anterior vermis, the right dentate nucleus, the right middle cerebellar peduncle,

and/or the right crus I predicted experimental group membership, a stepwise linear regression was performed first to determine the significant predictors. A logistical regression was then performed to determine if the established predictors predicted group membership.

Results

Descriptives

The sample of subjects used in this study was generally representative of the New Mexico population in ethnicity (see Tables 1a and 1b). The mean BSID-III Cognitive scaled score for the 18-month-old sample was 96.5 (SD = 11.5) (see Table 2), which approximates the average standard score of 100 (± 15). The BSID-III Cognitive scaled score for the total sample represents a mean of 101.5 (SD = 8.8) for the control group and a mean of 93.4 (SD = 12.1) for the VLBW group, with less than one standard deviation between the group means. The mean BSID-III Language Composite scaled score for the total sample was 90.0 (SD = 11.5), representing a mean of 96.5 (SD = 8.4) for the control group and 85.9 (SD = 11.5) for the VLBW group. Independent samples t-tests showed a significant difference between groups on BSID-III Language Composite scaled score ($t(24) = 2.52, p < 0.01$), and on the Expressive Language component of that score ($t(24) = 2.80, p = 0.01$). Additionally, Cohen's effect size values ($d = -0.9, d = 1$, respectively) suggested high practical significance. The difference between groups on the BSID-III Cognitive scaled score approached significance ($t(24) = 1.96, p = 0.06$). However, while the difference was not statistically significant, Cohen's effect size value ($d = -0.7$) suggested moderate to high practical significance.

The mean WPPSI-III full-scale IQ (FSIQ) score for the 3-year-old sample was 95.7 (SD = 14.3) (see Table 3), which approximates the average standard score of 100 (± 15). This represents a mean FSIQ of 106.4 (SD = 10.5) for the control group and 88.5 (SD = 12.1) for the VLBW group. The mean VIQ of the total sample was 97.9 (SD = 14.8); representing a mean VIQ of 108.8 (SD = 10.6) for controls and 90.6 (SD = 12.7) for VLBW participants. Two-tailed independent samples t-tests showed FSIQ scores ($t(18) = 3.41, p < 0.1$) and VIQ

scores ($t(18) = 3.34, p < 0.01$) were significantly different between the control and VLBW groups ($t = 3.34, p < 0.01$). Additionally, Cohen's effect size values ($d = -1.3, d = -1.2$, respectively) suggested high practical significance.

All ROI volumes were normalized to total intracranial volume (see Tables 4a and 4b for raw values). Independent samples t-test showed that the normalized ROI volumes of the right dentate nucleus ($t(24) = 3.76, p < 0.01$) and the right middle cerebellar peduncle ($t(24) = 3.18, p < 0.01$) were significantly different between the 18-month-old controls and VLBW participants, with high practical significance, as well ($d = -1.3, d = -1.2$, respectively). Likewise, right dentate nucleus volume in the 3-year-old sample was also significantly different between groups ($t(18) = 3.03, p = 0.01$), with high practical significance ($d = -1.1$). Total intracranial volumes in both age groups were not significantly different between controls and VLBW participants, with low practical significance (18-month-old $d = -0.4$; 3-year-old $d = 0.1$).

Thus, the first hypothesis, which posited that compared to controls, the VLBW groups would evidence significantly reduced volume in the four cerebellar ROIs, was proven only in the case of the right cerebellar peduncle of the 18-month-old group, and the right dentate nucleus in both age groups.

Correlation Analyses

Preliminary correlation analyses revealed the possible presence of an outlier in the 3-year-old VLBW sample, with one correlation between anterior vermis volume and VIQ appearing to be an extreme data point. Casewise diagnostic results of a linear regression revealed the data point to be a univariate outlier in anterior vermis volume, but not in VIQ score. A Mahalanobis distance was calculated to investigate whether or not the correlation

between anterior vermis volume and VIQ was a bivariate outlier. As the Mahalanobis distance was determined not to have significant influence on the slope or coefficients of the regression equation ($p > 0.001$), justification for excluding the case could not be established, and the case was included in all the following analyses.

No significant relationships were found between cerebellar ROI volumes and BSID-III Language composite scores in the total 18-month-old sample, only total intracranial volume showed a significant relationship ($r = 0.76$, $p = 0.01$) (see Table 5a). The relationship between the volume of the right dentate nucleus and the BSID-III Language composite scaled score in controls showed the strongest positive trend. When examined further, this relationship appears largely due to the BSID-III Receptive Language scaled score, as the relationship with the volume of the right dentate nucleus approached significance ($r = 0.63$, $p = 0.051$) in the control group only. No significant relationships were found between cerebellar ROI volumes and any language score in the 18-month-old VLBW group. However, it is worth noting that one possible contributing factor to this absence of significant correlations may be insufficient sensitivity of the BSID-III. While the most frequently used assessment of infant development, and preferred research tool for the same, there is a dearth of information on sensitivity and specificity, and the younger age groups have been shown to have steep item gradients (Strauss, Sherman & Spreen, 2006).

In the total 3-year-old sample, anterior vermis volume was significantly correlated with both VIQ ($r = 0.595$, $p < 0.05$) (see Figure 2; Table 5b) and FSIQ ($r = 0.627$, $p < 0.05$) (see Figure 3). However, neither score showed a significant relationship with anterior vermis volume in the control group. There was a significant correlation between anterior vermis volume and both FSIQ ($r = 0.72$, $p < 0.05$) and VIQ scores ($r = 0.64$, $p < 0.05$) in the VLBW

group. The significance of the relationship between FSIQ and anterior vermis volume did not persist when controlling for VIQ score. No significant correlations were found between cerebellar ROI volumes and VIQ in the 3-year-old control group, though the negative relationship between right dentate nucleus and VIQ approached significance in controls ($r = -0.70$, $p = 0.06$) (see Figure 4).

Table 5b presents the associations between VIQ and cerebellar ROI volume in both groups of the 3-year-old sample. As hypothesized, these results suggest a relationship between at least one of the proposed cerebellar ROI volumes, the anterior vermis, and language ability, with the only significant, and thus the strongest, relationship demonstrated in the 3-year-old VLBW group. To evaluate the significance of the difference between these correlation coefficients, Pearson coefficients were standardized using Fisher's Z transformations. The result supported the trend, but failed to reach significance ($Z = 1.09$). Sample sizes of 24 participants in each group would be required to demonstrate a significant difference between these correlation coefficients.

Table 5c presents the associations between ROI volumes by group. As with the relationships between ROI volumes and language scores, the significance and direction of various relationships between ROIs differs between groups, though there is a high incidence of significant relationships. Examination of these relationships is beyond the scope of the current study, but these findings suggest future examination of these relationships is warranted.

Analyses of Variance

An analysis of variance (ANOVA) was used to covary other factors that may influence VIQ scores in the 3-year-old samples. As no significant relationships were found in

the 18-month-old samples, these relationships were not analyzed (summarized in Table 6). Based on theories proposed in the literature, gestational age, days of ventilation, family income, ethnicity, and erithropoietin use were used as covariates in the 3-year-old VLBW group. In accounting for the variance in VIQ, only number of days of ventilation contributed significantly ($F(1, 11) = 11.85, p < 0.01$). Partial correlation analysis determined that the relationship between VIQ and anterior vermis volume remained significant when accounting for days of ventilation ($r = 0.57, p = 0.01$).

Regression analyses were used to determine the contribution of significant predictors of VIQ between the two 3-year-old groups (see Table 7). For the control group, of gestational age, family income, and ethnicity entered in the first step, only ethnicity significantly predicted VIQ scores ($\beta = 0.72, t(6) = 2.52, p < 0.05$), explaining a significant proportion of variance ($R^2 = 0.51, F(1, 6) = 6.35, p < 0.05$). However, in predicting VIQ scores, neither of the two cerebellar ROI volumes with the strongest relationships to VIQ (anterior vermis and right dentate nucleus) were significant in either step 2 or the full model for the control group. For the VLBW group, of gestational age, family income, ethnicity, days of ventilation, and erithropoietin use entered in the first step, only days of ventilation significantly predicted VIQ scores ($\beta = 0.75, t(10) = 3.14, p < 0.05$), and accounted for a significant proportion of the variance in VIQ ($R^2 = 0.53, F(1, 10) = 15.15, p < 0.05$). In step 2, of all four ROI volumes entered, only anterior vermis volume significantly predicted VIQ scores ($\beta = 0.64, t(10) = 2.61, p < 0.05$), explaining a significant proportion of variance beyond that accounted for by days of ventilation ($R^2 = 0.41, F(2, 9) = 6.81, p < 0.05$).

Anterior vermis volume accounted for a significant proportion of the variance in 3-year-old VLBW VIQ scores, consistent with the first hypothesis. However, no other cerebellar ROI volume accounted for significant variance in VIQ in any group, inconsistent with the first hypothesis.

Significant Predictors

Logistical regression was used to determine the contribution of significant predictors of group membership, using the variables shared between groups (i.e., days of ventilation is only a variable for the VLBW group, and thus was not used to predict group membership). VIQ scores significantly predicted group membership, with 75% correctly predicted in the control group and 83.3% correctly predicted in the VLBW group. While not significantly predictive of group membership by itself, using the right dentate nucleus volume in step 2 predicted the remaining members of the control group correctly, and an additional 8.4% of the VLBW group were also predicted correctly, for a total of 91.7% of the VLBW group (see Table 8).

While decreased ROI volumes did not predict group membership overall, as hypothesized, right dentate nucleus volume along with VIQ scores proved to have significant combined predictive power.

Discussion

This study investigated the associations between regional volumes of the developing cerebellum and language ability in both very low birthweight (VLBW) and healthy control 18-month- and 3-year-old children. We used performance on standardized cognitive ability tests, the Bayley Scales of Infant Development-Third Edition (BSID-III) for the younger group and the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III VIQ) for the older group, to assess language ability. The correlation between WPPSI-III VIQ scores and the volume of the anterior vermis in the 3-year-old VLBW group supports the hypothesis of cerebellar involvement in language ability in this population. That no such relationship was found in either the 3-year-old control group, or in either 18-month-old group, suggests that this relationship is part of an atypical neurodevelopmental trajectory. Additionally, while ethnicity was the best predictor of VIQ in the 3-year-old control group, consistent with previous literature, when controlling for days of ventilation, anterior vermis volume was the best predictor in the 3-year-old VLBW group.

Group Differences

Consistent with the hypothesis that the VLBW groups will have reduced volume in the cerebellar ROIs as compared to controls, the volumes of the right dentate nucleus and right middle cerebellar peduncle were significantly lower in the 18-month-old VLBW group compared to controls. Inconsistent with this hypothesis, no significant volume differences were found between the VLBW and control groups in the 3-year-old sample. It is possible that between the ages of 18 months and 3 years, these regions in the VLBW population increase enough in volume to be equivalent to the control group. However, this increase in volume does not speak to the function of these regions.

One possible explanation for these volume differences of cerebellar regions in the VLBW group at 18 months, as well as the seemingly rapid increase assumed to take place between 18 months and 3 years is interrupted neurodevelopment. The environment the developing brain is typically exposed to prior to 34 weeks' gestation differs from the neonatal environment. The "younger" cerebellum may have lower regional volumes at birth. The time period between 18 months and 3 years of age involves the processes of myelination and synaptic overgrowth, followed by selective pruning, or cell death. These processes are thought to result in more efficient neural processing. As previously discussed, the cerebellum appears to be particularly vulnerable to environmental influences, and being exposed to the neonatal environment earlier may result in various regions of the cerebellum developing either more slowly, more quickly, or similar in volume but diverse in function and/or connections with the rest of the brain. This latter possibility might also explain the increased variability in both volume and cognitive functioning seen in the VLBW groups. Additionally, it may also explain the directional differences in relationships between language function and ROI volume found during this time of myelination and synaptic overgrowth and selective pruning. For example, we found anterior vermis volume to have a negative relationship with language function in the 18-month-old control group, but a positive relationship in the VLBW group. In the 3-year-old groups, this relationship was positive for both, with a stronger relationship seen in the VLBW group. Similar trends can be seen in the right dentate nucleus and the right middle cerebellar peduncle. It is possible that, despite the lack of significant regional volume differences, this pattern represents a different developmental trajectory for the VLBW group, and that this may involve the functions of the regions, or connections with other brain areas.

While the overall Cognitive Composite scaled score was not significantly different between VLBW and control 18-month-olds, the Language Composite scaled scores were significantly different, largely due to a significant difference in the Expressive component of that composite score. Consistent with expectations and the body of literature, the 3-year-old groups were significantly different on both FSIQ and VIQ, with the VLBW group scoring lower than controls. These differences suggest a widening gap in language abilities between 18 months and 3 years old, possibly impacting overall estimates of IQ. Additionally, the VLBW groups of both ages evidenced more variability in language performance than controls. This is consistent with the pattern noted above in the cerebellar ROIs: it is possible the increased variability of regional neurodevelopment plays a role in the increased variability of language performance. Additionally, if the developmental trajectory of the cerebellum is atypical, and it influences development of regions with which it is reciprocally connected, it is possible that atypical connections or atypical development of associated brain regions may also explain the differences in language ability. Given atypical development, it is possible the areas reciprocally connected to the cerebellum may differ between groups, as well.

Correlations

It was hypothesized that decreased volume in the cerebellar ROIs would be correlated with lower verbal functioning in the VLBW group at both 18 months and 3 years old, with the 3-year-old VLBW group showing the strongest relationship. Inconsistent with this hypothesis, no significant relationships were found between regional volumes and language ability in the 18-month-old sample. The relationship between the volume of the right dentate nucleus and the BSID-III Receptive Language scaled score showed the strongest positive

trend. In the total 3-year-old sample, anterior vermis volume had a significant positive relationship with VIQ. When comparing groups, this relationship did not persist in the control group, but remained significant in the VLBW group.

Additionally, relationships between cerebellar ROIs and language ability were not always consistent in direction, even within age groups. In the 18-month-old sample, the relationship between anterior vermis volume and the BSID-III Language Composite scaled score showed a negative trend for controls, and a positive trend for the VLBW group. Conversely, the relationship between right dentate nucleus volume and the BSID-III Language Composite scaled score evidenced a positive trend in the control group, and a negative trend in the VLBW group. In the 3-year-old group, the relationship between VIQ and right dentate nucleus volume showed a strong negative trend in the control group, and a slight positive trend in the VLBW group. One possibility is that the developmental trajectory, hypothesized to be atypical in the VLBW group, has different timing in neurogenesis and pruning. Again, this may represent differences in developmental trajectory between groups, but does not speak to the functions of these cerebellar regions.

Consistent with our hypothesis, the relationship between one cerebellar ROI volume, the anterior vermis, was correlated with lower VIQ, and the relationship was stronger in the 3-year-old group than in the 18-month-old group. However, it is worth noting that the relationship showed a strong negative trend in the 18-month-old control group, and a positive trend in the the VLBW group. This suggests that if the developmental trajectories differ between groups, the relationship between anterior vermis volume and verbal ability may also differ between groups. However, as VIQ was significantly lower for the VLBW group than

the control group, it is possible the two groups have different neural processes, and also different outcomes as measured by the standardized assessment.

Significant Predictors in the Older Sample

We predicted that decreased volumes of the four cerebellar ROIs would predict VLBW group membership. While the anterior vermis was the only ROI volume with a significant relationship with VIQ, volume was not significantly different between groups, and did not predict group membership. The strongest predictor of group membership was VIQ, which, along with right dentate nucleus volume, accurately predicted 91.7% of the VLBW group.

In terms of predicting language performance, days of ventilation was shown to best predict VIQ in the VLBW group. When controlling for days ventilation, anterior vermis volume was the best predictor of VIQ in the VLBW group. Ethnicity was shown to be the best predictor of VIQ in controls. Historically, performance on standardized measures of cognitive ability has been shown to have a very strong relationship with ethnicity, and a stronger relationship with anterior vermis volume than with ethnicity in the VLBW group was not expected. Overall, these results suggest different factors may influence verbal ability in the VLBW group, and the underlying neural processes may differ between groups, as well.

Limitations

Some possible limitations of this study include an over-representation of males in the 3-year-old sample, though preliminary analyses did not reveal any effect of gender on the variables of interest. The size of our total sample may have been another limiting factor in examining the relationships between language ability and cerebellar ROI volumes. As the larger study upon which this investigation is based continues to be ongoing, opportunities

may be available to examine these relationships in a larger sample. As mentioned above, a minimum of 24 participants per group in the 3-year-old sample would increase the statistical power of future similar investigations.

Another possible influence on statistical power is the precision of ROI volume measurement. While FreeSurfer functions are frequently used to transform volumetric data, and each subject was visually inspected for accuracy, the brain atlas used is based on an adult brain. Once accurate and reliable pediatric atlases have been developed, the raw data of this study might be transformed based on a pediatric brain of appropriate age, and re-analyzed. Additionally, volumetric analyses of cerebellar ROIs currently require hand-tracing of discrete regions. Attempts were made to minimize the impact of this limitation, and each region was traced a minimum of two times according to established guidelines outlined in the literature. This limitation may also be overcome in the future, with the development of an automated parcellation feature for regions of the cerebellum.

As previously mentioned, the causes of spontaneous preterm labor and very low birthweight are poorly understood. While participating mothers were screened for substance use, the many maternal factors shown to be associated with preterm/VLBW, such as infection, immunological processes, nutrition, etc., may have been contributing factors in the VLBW sample. Thus, any effects discovered in the experimental groups may also be influenced by neurodevelopment impacted by the same maternal factors that contributed to early labor and/or very low birthweight.

Finally, the present study represents a cross-section of participants, but aims to investigate developmental trajectories. A longitudinal study would be more appropriate to

examine these initial differences, and follow how they evolve over time. Again, as the current study is ongoing, this type of investigation may be possible in the future.

Cultural Factors

One possible limitation of the results of the present study is the inclusion of 12 bilingual children (2 VLBW 3-year-olds, 9 VLBW 18-month-olds, and 1 18-month-old control). Parental bilingualism has been associated with slower cognitive development in VLBW infants (Walch, Chaudhary, Herold & Obladen, 2009). Exposure to two languages has also been shown to impact neurodevelopment, particularly the development of white matter tracts (Mohades, et al., 2012). An established body of research has supported the hypothesis that bilingual infants recruit cortical regions that are both shared by each language in functionality, as well as cortical regions that are dedicated to one of their two languages, resulting in a distributed language network beyond the traditional left-hemisphere language regions. In terms of assessment, previous studies have indicated that standardized assessments, such as the WPPSI-R, predecessor to the instrument used in this study, lack sufficient construct validity for bilingual populations (diSabio & Whalen, 2000). Together these findings suggest atypical neurodevelopment in bilingual children, with different underlying cognitive processes measured on standardized assessments. While the present study did not find a significant contribution of bilingualism to the variance in language scores, a possible effect of bilingualism cannot be discounted in or beyond this study.

Bilingualism is not the only cultural factor thought to impact cognitive development and the resulting performance on standardized measures. Socioeconomic status (SES) and parental level of education have also been shown to be associated with cognitive performance on standardized assessments (Lee, Kawachi, Berkman & Grodstein, 2003).

Bilingualism, lower SES, and lower parental educational attainment have been associated more frequently with minority populations, and the contribution of these factors to cognitive test performance has been debated for decades, and is beyond the scope of this study.

However, these factors may result in lower validity with minority populations with the instruments used, as has been suggested in previous studies regarding the WPPSI-R (diSibio & Whalen, 2000). While the BSID-III was revised in 2006 to include a greater percentage of ethnic minorities and children of lower SES in the normative sample, similar questions regarding its validity with these populations persist (Duncan, et al., 2012).

Implications and Importance

The present study showed the 3-year-old control and VLBW groups did not differ significantly in anterior vermis volume, but did significantly differ in correlations between anterior vermis volume and VIQ scores. The relationship between anterior vermis volume and verbal ability has been found in adolescents born VLBW (Allin, et al., 2005). While this is consistent with our finding in the 3-year-old VLBW group, this relationship was not found to be significant in the 18-month-old group. Taken together, this suggests a possible difference in developmental trajectory for the anterior vermis emerging in the VLBW population between 18 months and 3 years of age, and persisting into adolescence.

Additionally, VIQ, but not anterior vermis volume, is significantly different between groups in the 3-year-old sample. Despite this, anterior vermis volume is a stronger predictor of VIQ in the VLBW group than the more established predictor of cognitive performance, ethnicity. It is possible the developmental trajectory in the VLBW group differs in the timing or amount of neurogenesis and pruning. While the anterior vermis volumes are not significantly different, this reveals nothing regarding the connections between the vermis and

other brain areas, or the characteristics of those connections. There may be differences in the organization of those connections, or the connections themselves. For example, hypotheses regarding neural organization in autism include those of over-connectivity: Too much white matter may result in disorganized signals and impaired modulation of various functions (Allen, 2005); and those of under-connectivity: Reduction of cerebellar white matter (McAlonan, et al., 2005) may result in weak signal transmission. It is possible the connections between the anterior vermis and other areas of the brain are likewise atypical, and increased volume in this population may compensate for the quality or number of the connections. This hypothesis appears to be consistent with our finding that anterior vermis has a positive correlation with language ability in both VLBW groups, but a negative relationship for controls at 18 months, and a positive relationship for controls at 3 years old. Future research, ideally longitudinal, investigating the integrity and organization of white matter associated with the anterior vermis utilizing diffusion-tensor imaging (DTI) may help clarify what the maturation process differences may between the VLBW population and healthy controls.

There may also be important implications of anterior vermis volume as a stronger predictor of VIQ in the VLBW group than ethnicity. While a full discussion of the various theories on the relationship between ethnicity and IQ is beyond the scope of this study, a prevailing, if contentiously debated, hypothesis holds that IQ is more strongly influenced by genetics (ethnicity) than environmental factors (Herrnstein & Murray, 1994). If the cerebellum is as involved in cognitive function as is now hypothesized, and if environmental factors more strongly influence both the cerebellum and cognitive performance under certain circumstances or during a specific window of neural development, the theory of genetically-

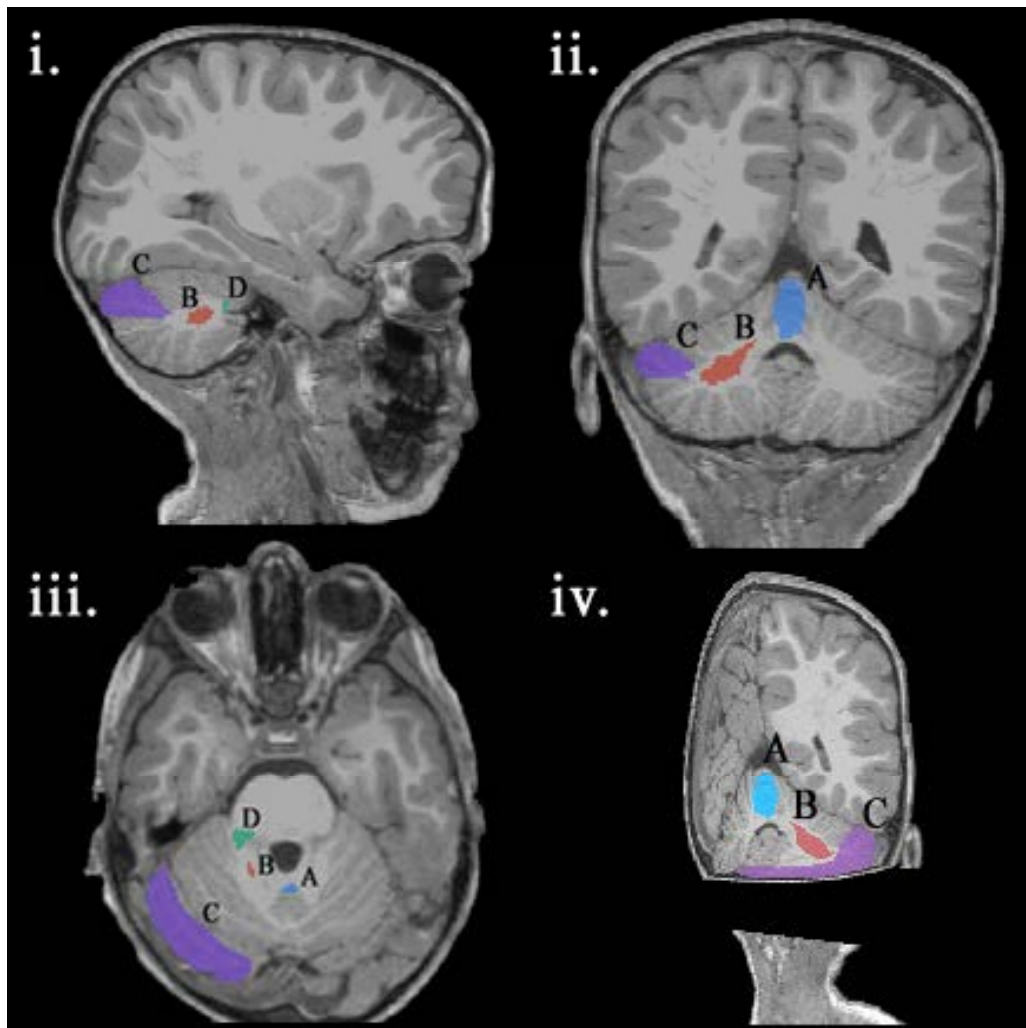
based intelligence may prove to be inaccurate, or at least incomplete. By further studying the neural development of this population, if specific developmental processes or periods can be identified, effective early interventions for the typically-developing brain may be developed to improve cognitive performance and IQ. Additionally, in investigating the interaction of neurodevelopmental factors and environmental influences not previously studied, the underlying mechanisms for the historical ethnic differences on standardized intelligence tests may be clarified, more fully elucidated, and understood.

The relationship between verbal ability or other cognitive abilities and the dentate nucleus volume bears further investigation as well, particularly as the relationship with verbal abilities appears to be negative for the VLBW group and positive for controls in the 18-month-old sample, and the reverse in the 3-year-old sample. A larger sample size may reveal a stronger relationship, as may DTI investigations, as the dentate nucleus is located within the deep cerebellar white matter. Also worth noting is that the right dentate nucleus was consistently significantly different between VLBW groups and controls. Additionally, the strongest trend in the 18-month-old group was the relationship between the right dentate nucleus and the Receptive component of the BSID-III composite Language score. One possibility for this is that receptive language development is already in progress at this stage of development. It is possible that further along the developmental trajectory, the relationship between expressive language and the right dentate nucleus could become stronger, weaker, or change direction. Likewise, this may explain the lack of correlation between expressive language and any ROI, as receptive language abilities develop first.

If increased anterior vermis volume can influence verbal ability, it may be possible for the population born VLBW to improve verbal ability with interventions aimed at

increasing the volume of this region, possibly involving motor tasks. The results of the current study suggest there may exist different neurological maturation processes for the VLBW population, and therefore any interventions based on healthy full-term populations may not be as effective. Further research is required to elucidate the developmental trajectory of the VLBW cerebellum, and develop interventions based on the specific neural development of that population. The protracted development of the cerebellum, its vulnerability to environmental influences, and its influence over the development of brain regions to which it is reciprocally connected make the cerebellum an ideal region to investigate and target for intervention.

Figures



A = Anterior Vermis; B = Right Dentate Nucleus; C = Right Crus I; D = Right Middle Cerebellar Peduncle; i. Saggital view, ii. Coronal view, iii. Axial view, iv. 3D view

Figure 1. Cerebellar ROIs Hand-Traced in 3 Planes

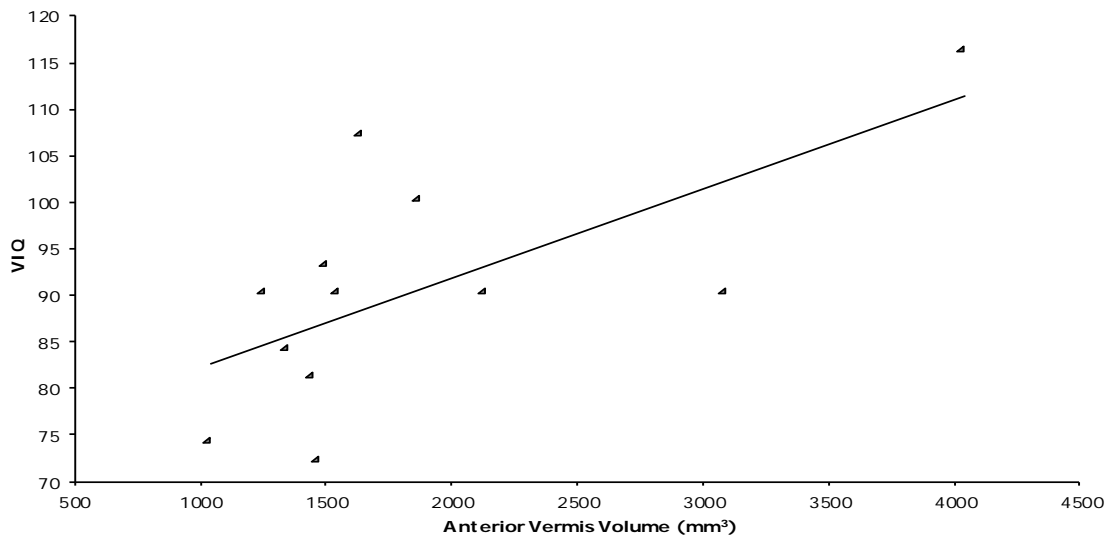


Figure 2. Anterior Vermis Volume & Verbal IQ (VIQ) for 3-year-old VLBW Group

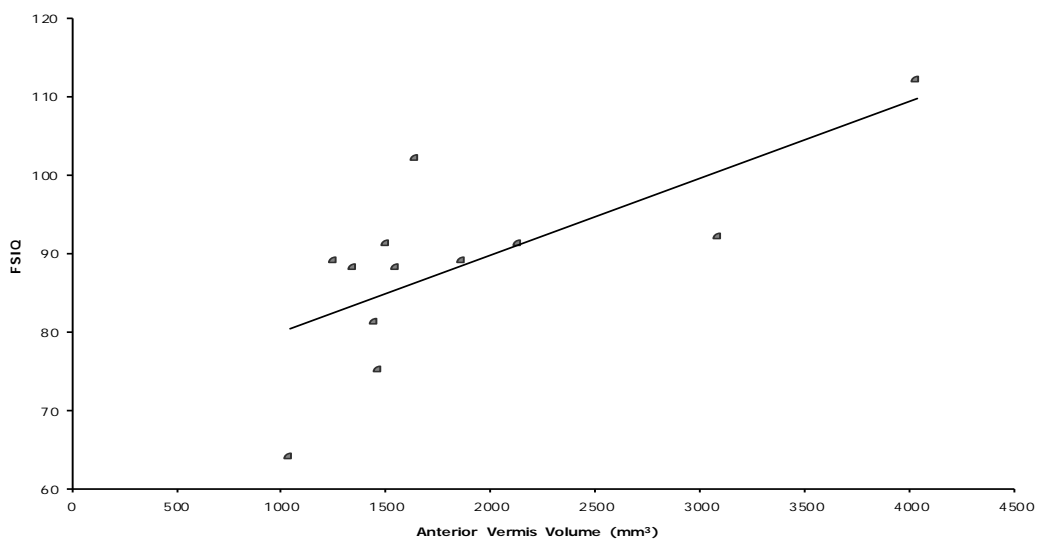


Figure 3. Anterior Vermis Volume & Full-Scale IQ (FSIQ) for 3-year-old VLBW Group

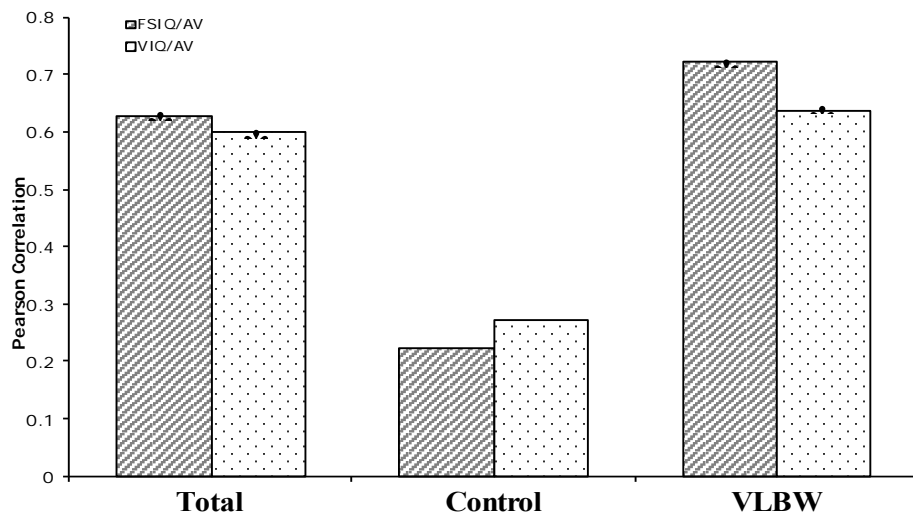


Figure 4. Correlations between Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition (WPPSI-III) Scores and Anterior Vermis Volume in the 3-year-old Sample

Tables

Table 1a. Demographic Information of the 18-month-old Sample

Variable	M/% Total	M/% Control	M/% VLBW
N	26	10	16
Age (in months)	20.6	21.4	20.2
Sex (female, %)	53.8%	60.0%	50.0%
Primary Ethnicity (N)			
European American	7.0	4.0	3.0
Hispanic	14.0	5.0	9.0
Native American	4.0	1.0	3.0
African American	1.0	0.0	1.0
Family Annual Income (thousands of dollars)	25.4	49.0	10.6
Gestational Age (weeks)	32.5	39.4	28.1
Days of Ventilation (VLBW group)			13.9
English as a First Language (%)	65.4%	90.0%	50%

Table 1b. Demographic Information of the 3-year-old Sample

Variable	M/% Total	M/% Control	M/% VLBW
N	20	8	12
Age (in months)	42.8	43.4	42.5
Sex (female, %)	10.0%	12.5%	8.3%
Primary Ethnicity (N)			
European American	9.0	4.0	5.0
Hispanic	10.0	4.0	6.0
Native American	1.0	0.0	1.0
African American	0.0	0.0	0.0
Family Annual Income (thousands of dollars)	37.5	42.5	34.2
Gestational Age (weeks)	33.4	38.8	29.7
Days of Ventilation (VLBW group)			10.5
English as a First Language (%)	90.0%	100%	83.3%

Table 2. Bayley Scales of Infant Development, 3rd Edition (BSID-III) Language and Cognitive Scaled Scores for the 18-month-old Sample

Variable	M Total	SD	M Control	SD	M VLBW	SD
N	26		10		16	
Receptive Scaled Score	8.7	2.2	9.6	1.9	8.1	2.3
Expressive Scaled Score	7.9	2.1	9.2	1.6	7.1	2.0
Language Composite Scaled Score	90.0	11.5	96.5	8.4	85.9	11.5
Cognitive Scaled Score	96.5	11.5	101.5	8.8	93.4	12.1

Table 3. Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition (WPPSI-III) FSIQ and VIQ Scores for the 3-year-old Sample

Variable	M Total	SD	M Control	SD	M VLBW	SD
N	20		8		12	
VIQ	97.9	14.8	108.8	10.6	90.6	12.7
FSIQ	95.7	14.3	106.4	10.5	88.5	12.1

Table 4a. Cerebellar ROI Volumes in the 18-month-old Group (mm³)

Variable	M Total	SD	M Control	SD	M VLBW	SD
N	26		10		16	
Total Intracranial Volume	1247435.6	194740.2	1291847.8	175492.6	1219677.9	206375.5
Anterior Vermis	1926.3	697.7	1961.0	721.4	1904.6	705.5
Right Dentate Nucleus	539.0	238.3	722.3	245.6	424.4	148.6
Right Crus I	7707.4	2532.0	7895.1	2019.2	7590.2	2863.7
Right Middle Cerebellar Peduncle	517.2	135.9	617.6	113.0	454.4	110.4

Table 4b. Cerebellar ROI Volumes in the 3-year-old Group (mm³)

Variable	M Total	<i>SD</i>	M Control	<i>SD</i>	M VLBW	<i>SD</i>
N	20		8		12	
Total Intracranial Volume	1397852.4	141674.1	1388232.0	171180.8	1404266.0	126133.2
Anterior Vermis	2063.8	789.3	2360.3	591.3	1866.2	864.4
Right Dentate Nucleus	813.4	262.0	989.1	243.0	696.25	208.6
Right Crus I	8993.5	2379.3	8983.7	2429.8	9000.0	2453.8
Right Middle Cerebellar Peduncle	673.8	149.5	732.4	147.2	634.8	143.8

Table 5a. Correlations between Cerebellar ROIs and Language Scores for the 18-month-old Sample

Region of Interest	Total (r)	Sig. (2-tailed)	Control (r)	Sig. (2-tailed)	VLBW (r)	Sig. (2-tailed)
N	26		10		12	
Total Intracranial Volume	0.207	0.310	0.760*	0.011*	0.089	0.742
Anterior Vermis	0.060	0.770	-0.366	0.299	0.281	0.292
Right Dentate Nucleus	0.246	0.227	0.498	0.143	-0.336	0.204
Right Crus I	0.208	0.307	0.058	0.875	0.312	0.239
Right Middle Cerebellar Peduncle	0.015	0.941	-0.304	0.393	-0.317	0.232

* p < 0.5

Table 5b. Correlations between Cerebellar ROIs and VIQ for the 3-year-old Sample

Region of Interest	Total (r)	Sig. (2-tailed)	Control (r)	Sig. (2-tailed)	VLBW (r)	Sig. (2-tailed)
N	20		8		12	
Total Intracranial Volume	0.021	0.930	0.380	0.352	0.148	0.646
Anterior Vermis	0.595*	0.006*	0.272	0.515	0.636*	0.260*
Right Dentate Nucleus	0.284	0.225	-0.696	0.055	0.137	0.671
Right Crus I	-0.157	0.509	-0.476	0.233	-0.091	0.778
Right Middle Cerebellar Peduncle	0.196	0.408	-0.108	0.799	0.027	0.935

* p < 0.5

Table 5c. ROI Correlations by Group

18-month-old Control Group	Total Intracranial Volume	Anterior Vermis	Right Dentate Nucleus	Right Crus I	Right Middle Cerebellar Peduncle
Total Intracranial Volume	--	-0.196	0.783*	0.534	0.669*
Anterior Vermis	-0.196	--	-0.365	-0.728*	-0.243
Right Dentate Nucleus	0.783*	-0.365	--	0.576	0.788*
Right Crus I	0.534	-0.728*	0.576	--	0.380
Right Middle Cerebellar Peduncle	0.669*	-0.243	0.788*	0.380	--
18-month-old VLBW Group					
Total Intracranial Volume	--	-0.164	0.263	0.506*	0.389
Anterior Vermis	-0.164	--	-0.136	-0.274	-0.081
Right Dentate Nucleus	0.263	-0.136	--	0.108	0.437
Right Crus I	0.506*	-0.274	0.108	--	0.056
Right Middle Cerebellar Peduncle	0.389	-0.081	0.437	0.056	--

* p < 0.5

Table 5c Continued

3-year-old Control Group	Total Intracranial Volume	Anterior Vermis	Right Dentate Nucleus	Right Crus I	Right Middle Cerebellar Peduncle
Total Intracranial Volume	--	0.171	0.708*	0.776*	0.442
Anterior Vermis	0.171	--	-0.270	-0.297	0.108
Right Dentate Nucleus	0.776*	-0.270	--	0.844*	0.287
Right Crus I	0.708*	-0.297	0.844*	--	0.427
Right Middle Cerebellar Peduncle	0.442	0.108	0.427	0.287	--
3-year-old VLBW Group					
Total Intracranial Volume	--	-0.078	0.014	0.160	-0.006
Anterior Vermis	-0.078	--	-0.150	-0.333	-0.115
Right Dentate Nucleus	0.014	-0.150	--	0.573*	0.603*
Right Crus I	0.160	-0.333	0.573*	--	0.320
Right Middle Cerebellar Peduncle	-0.006	-0.115	0.603*	0.320	--

* p < 0.5

Table 6. Separate Regression Models Predicting Language Scores for 18-month-olds

A.

<i>Lang SS</i>	<i>Step</i>	<i>R² Change</i>	<i>Model F</i>	<i>Df</i>	<i>p</i>
<i>Controls</i>	1 (ethn, gest age, income)	0.21	0.52	3,6	0.68
	2 (AV vol, RD vol, RCI vol, RMP vol)	0.28	0.41	4,2	0.85
		<i>Beta</i>	<i>t</i>	<i>Sig</i>	<i>Partial</i>
	<i>Model</i>				
	Ethnicity	0.13	0.32	0.76	0.13
	Income	0.45	1.18	0.28	0.43
	Gestational Age	-0.13	-0.33	0.76	-0.13
		<i>Beta In</i>	<i>t</i>	<i>Sig</i>	<i>Partial</i>
	<i>Excluded Variables</i>				
	Anterior Vermis	-0.01	-0.32	0.98	-0.14
	Right Crus I	0.31	0.74	0.50	0.31
	Right Dentate	0.58	1.45	0.21	0.54
	Rt Mid Peduncle	0.31	0.80	0.46	0.34

B.

<i>Lang SS</i>	<i>Step</i>	<i>R² Change</i>	<i>Model F</i>	<i>Df</i>	<i>p</i>	
<i>VLBW</i>	1 (ethn, gest age, income, days vent, epo)	0.12	0.36	4,11	0.83	
	2 (AV vol, RD vol, RCI vol, RMP vol)	0.35	0.77	4,7	0.64	
		<i>Model</i>	<i>Beta</i>	<i>t</i>	<i>Sig</i>	<i>Partial</i>
		Ethnicity	0.64	1.14	0.54	0.19
		Income	-1.69	-0.59	0.57	-0.18
		Gestational Age	-0.36	-0.13	0.90	-0.04
		Days Ventilation	0.06	0.28	0.79	0.08
		Epo	0.46	0.45	0.67	0.12
		<i>Excluded Variables</i>	<i>Beta In</i>	<i>t</i>	<i>Sig</i>	<i>Partial</i>
		Anterior Vermis	0.12	0.39	0.71	0.12
		Right Crus I	0.30	0.99	0.35	0.30
		Right Dentate	-0.34	-0.95	0.36	-0.29
		Rt Mid Peduncle	-0.47	-1.69	0.12	-0.47

Notes: Step 1 of each included significant covariates (ethnicity, gestational age, and family income for both groups, with days ventilation and erithropoietin use added for the VLBW group only) in the preliminary analyses with the BSID-III Language Scores as the dependent variable. Step 2 added the all ROI volumes (anterior vermis, right crus I, right middle cerebellar peduncle, and right dentate nucleus) with R² change representing the amount of Language score variance over and above that accounted for by the Step 1 variables. Ethn = ethnicity; gest age = gestational age; AV vol = anterior vermis volume; RD vol = right dentate nucleus volume; RCI vol = Right Crus I volume; RMP vol = Right Middle Cerebellar Peduncle volume.

Table 7. Separate Regression Models Predicting VIQ Scores for 3-year-olds

A.

<i>VIQ</i>	<i>Step</i>		<i>R² Change</i>	<i>Model F</i>	<i>Df</i>	<i>p</i>
Controls	1 (ethn)		0.51	6.35	1,6	0.045
	2 (AV vol, RD vol, RCI vol, RMP vol)		0.28	5.27	5,2	0.167
	<i>Excluded Variables</i>		<i>Beta In</i>	<i>t</i>	<i>Sig</i>	<i>Partial</i>
	Income		0.18	0.25	0.81	0.11
	Gestational Age		-0.29	-0.81	0.46	-0.34
	Anterior Vermis		0.52	2.46	0.06	0.74
	Right Crus I		-0.19	-0.63	0.56	-0.27
	Right Dentate		-0.30	-1.08	0.33	-0.44
	Rt Mid Peduncle		-0.17	-0.50	0.64	-0.22

B.

<i>VIQ</i>	<i>Step</i>		<i>R2 Change</i>	<i>Model F</i>	<i>Df</i>	<i>p</i>
<i>VLBW</i>	1 (vent)		0.53	17.15	5,6	0.002
	2 (AV vol)		0.41	6.81	2,9	0.015
	<i>Excluded Variables</i>		<i>Beta In</i>	<i>t</i>	<i>Sig</i>	<i>Partial</i>
	Income		0.03	0.12	0.91	0.15
	Gestational Age		-0.08	-0.26	0.81	-0.10
	Ethnicity		0.33	1.19	0.28	0.24
	Epo		-0.27	-0.87	0.42	0.44
	Right Crus I		0.36	1.12	0.31	0.45
	Right Dentate		0.75	4.11	0.12	0.58
	Rt Mid Peduncle		0.24	0.68	0.53	0.29

Notes: Step 1 of each included significant covariates (ethnicity, gestational age, and family income for both groups, with days ventilation and erithropoietin use added for the VLBW group only) in the preliminary analyses with the VIQ Scores as the dependent variable. Step 2 added the appropriate ROIs (anterior vermis and right dentate nucleus) with R² change representing the amount of VIQ score variance over and above that accounted for by the Step 1 variables. Ethn = ethnicity; gest age = gestational age; AV vol = anterior vermis volume; RD vol = right dentate nucleus volume; RCI vol = Right Crus I vol; RMP vol = Right Middle Cerebellar Peduncle volume.

Table 8. Logistic Regression Analysis of Group Predictors in 3-year-olds

<i>Predictor</i>	β	<i>SE</i> β	<i>Wald's</i> X^2	<i>Df</i>	<i>p</i> Δ	e^β
<i>VIQ</i>	0.127	0.055	5.35	1	0.002	0.881
<i>Rt Dentate Nucleus Volume</i>	49303	78336	0.396	1	0.001	0.00

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