DEVELOPMENTAL DYSLEXIA: VOLUMETRIC ANALYSIS OF REGIONAL VARIABILITY IN THE CEREBELLUM

A Thesis

Presented to

The Faculty of the Department

of Psychology

University of Houston

In Partial Fulfillment

of the Requirements for the Degree of

Master of Arts

By

Vindia G. Fernandez

May, 2012

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ABSTRACT

Previous research has suggested that cerebellar deficits and subsequent impairment in procedural learning explain motor difficulties and reading impairment in dyslexia. This study investigated the role of regional variation in cerebellar anatomy in children with single-word decoding impairments (N = 23), children with impairment in fluency alone (N = 8), and typically developing children (N = 16). Results indicated that children with dyslexia demonstrated no statistically significant differences in overall gray and white matter volumes, cerebellar asymmetry, and reduced volume in the anterior lobe of the cerebellum relative to typically developing children. The study lacked enough power to detect any statistically significant differences in the group of children with impairment in fluency. These results implicate cerebellar involvement in dyslexia, and establish an important foundation for future research on the connectivity of the cerebellum and cortical regions that are typically associated with reading impairment.

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Developmental Dyslexia: Volumetric Analysis of Regional Variability in the Cerebellum

Dyslexia is a common developmental disorder affecting between 5% and 15% of school-aged children. By definition dyslexia is characterized by difficulties acquiring accurate and fluent single word reading skills (Pennington, 2009). Almost 50% of all children that receive special education services do so for reading problems in the U.S. (Fletcher, Lyon, Fuchs, & Barnes, 2007). Given that reading is a fundamental skill required for learning other academic material, individuals with dyslexia often perform poorly in school (Lyon, 1998), are more likely to drop out of school, and are more likely to experience adjustment difficulties than youth with typical reading skills (Daniel et al., 2006).

Various studies have attempted to determine the neural correlates of dyslexia by focusing on anatomical differences between the brains of individuals with and without reading difficulties. Although findings are as variable as the methodologies employed, a pattern of differences in brain structures has emerged from the literature implicating the inferior frontal gyrus, temporal-parietal region, medial occipital lobe, and cerebellar anterior and posterior lobes (Eckert, 2004). Some of these findings are not surprising given the demands of reading on the brain's visual processing, language comprehension, and working memory capacities. Cerebellar findings, however, have generated a great deal of interest in the role of implicit learning on reading acquisition, particularly given the processing speed and motor deficits that are often observed in children with dyslexia and other learning and attention disorders (Denckla et al., 1985).

Cerebellar Theory of Dyslexia

Proponents of the cerebellar theory of dyslexia argue that the cerebellum is active during early stages of skill acquisition (Nicolson & Fawcett, 2005, 2007), a process with which some children with dyslexia appear to struggle (Reynolds, Nicolson, & Hambly, 2003). According to the cerebellar theory, the resulting procedural learning deficits prevent automatization of accurate word decoding and phonological processing. This theory has been evaluated by comparing children with dyslexia and controls on neuropsychological and cognitive tasks presumably associated with the cerebellum (Nicolson & Fawcett, 1994, 1999). However, the results are controversial because the children with dyslexia were defined in part by performance on these tasks. In addition, there have been efforts to train the cerebellum through exercises, with claims that reading and cerebellar functions improved (Reynolds et al., 2003; Reynolds & Nicolson, 2006). However, these findings have been controversial because of questions about the methods (Bishop, 2007). Finally, anatomical studies have been interpreted to show support for the cerebellar theory. As we see in the next sections, support for this hypothesis is not consistent and reflects variations in how dyslexia is defined and in the methods for assessing brain structure.

Cerebellar Anatomy in Adults with Dyslexia

Post-mortem studies. Early anatomical studies of developmental dyslexia were likely influenced by extensive postmortem studies conducted by Galaburda and his colleagues via the Orton International Dyslexia Society brain bank (Finch, Nicolson & Fawcett, 2002). These early, small-sample studies (5 with dyslexia, 7 controls) found abnormalities in the medial (Galaburda, Menard, & Rosen, 1994) and lateral geniculate nuclei (Livingstone, Rosen, Drislane, & Galaburda, 1991), auditory cortex (Galaburda & Kemper, 1979), and primary visual cortex (Jenner, Rosen, & Galaburda, 1999; Eckert, 2004). Finch et al. (2002) investigated the morphology of the cerebellum in the same group of specimens, focusing specifically on the olivo-cerebello-dentate pathway, which is thought to play a role in language related tasks. They found that the brains of these individuals with a history of dyslexia had fewer smaller and more larger cells in the anterior and posterior lobes of the cerebellum. Similar differences were observed in the inferior olive, while no differences were found in the flocculonodular lobe or dentate nucleus. Difficulties collecting behavioral and clinical histories made it difficult to tie these findings speciffically to the reading problem. Studies conducted with adult populations using assessment of anatomical MRIs since then have not reliably replicated these postmortem studies.

Structural imaging studies. Early structural MRI studies provided some support for the involvement of the cerebellum in dyslexia. Leonard et al. (2001) employed a manual tracing method to estimate cerebellar volume in 15 college students and 15 controls. They found leftward asymmetry of the anterior lobe of the cerebellum in the group with reading and language difficulties, which the investigators hypothesized was to be due to reduced grey matter volume in the right anterior lobe of the cerebellum. This finding was replicated by Rae et al. (2002) using an automated approach to quantitative volumetric analysis of each cerebellar hemisphere. Furthermore, the Rae et al. study determined that the degree of symmetry correlated with the severity of the decoding deficit.

Additional support for cerebellar abnormalities has been found in posterior and medial regions. Brown et al. (2001) reported decreased grey matter in the semilunar lobules of the cerebellum using an automated procedure for voxel-based analyses which compared the signal intensities of each voxel in a normalized brain to identify changes in tissue density. Brambati et al. (2004) found regional reductions in grey matter volume bilaterally in the cerebellar nuclei using voxel-based morphometry. Notably, this group of participants was aged 13-57 and recruited based on a family history of dyslexia, but did not show deficits on standardized tests.

Other studies have found no differences in cerebellar volume between adults with and without dyslexia using similar methods (Menghini et al., 2008; Pernet, Poline, Demonet, & Rousselet, 2009; Laylock, 2008). Pernet et al. (2009) reported that 100% of the participants with dyslexia were out of the normal range on the right cerebellar declive and right lentiform nucleus based on a 95% confidence interval constructed from the images collected from a control group. It is important to note that these abnormalities represented either increased or decreased volumes and that a statistical test did not meet conventional levels of significance ($p < .05$). Nevertheless, Pernet et al. also found that reduced reaction time on a phoneme deletion task was associated with decreased right cerebellar volume. Finally, Laylock et al. (2008) also failed to identify any regional reductions in grey matter. However, the group with dyslexia in this study had a larger volume of white matter in both cerebellar hemispheres, a finding which remained significant after controlling for total cerebellar volume.

Results from the adult literature seem to support cerebellar involvement in people with reading and language difficulties. However, the results are variable and highlight a few important problems with methodology. First, the studies varied with respect to age of participants, gender composition (i.e. some excluded females), and inclusion criteria. While some studies required that participants meet criteria for dyslexia as set forth in the Diagnostic and Statistical Manual of Mental Disorders, 4^{th} ed. (DSM-IV) or International Classification of Diseases (ICD), others included participants that only had a familial history of dsylexia and demonstrated no normative deficits. Second, the approach to the estimation of regional volumes of the cerebellum was variable. Some studies used manual approaches while others used automated methods for volmetric analysis. Few studies segmeted multiple regions of the cerebellum in favor of obtaining hemispheric volumes, often failing to separate grey matter from white matter.

Cerebellar Anatomy in Children with Dyslexia

One of the first studies of children with dyslexia was conducted to replicate cerebellar findings in college students (Eckert et al., 2003; Leonard et al., 2001). This study aimed to determine the probability of a dyslexia diagnosis for multiple anatomical measures, including a measure of the inferior frontal gyrus (pars triangularis), and to examine the relation between anatomical measures and measures of reading, spelling, verbal intelligence and language skills. Eighteen children with dyslexia in grades 4-6 were examined. Sagittal images (1.2 mm) were acquired using a 1.5 Tesla scanner. The volume of the anterior lobe of the cerebellum was measured manually using a single mid-sagittal slice. Participants with dyslexia had a smaller right anterior cerebellar lobe, right and left pars triangularis, and whole brain volume. The right anterior cerebellar lobe and right pars triangularis made unique contributions in predicting group membership even with cerebral volume and asymmetry included in the regression (Eckert et al., 2003).

Noting potential weaknesses in methodology, this group of researchers conducted a study to determine if an automated approach using voxel based morphometry (VBM) would identify anatomical differences in the right anterior cerebellar lobe and right and left pars triangularis in the same group of children. The VBM approach revealed grey and white matter estimates for the right anterior cerebellar lobe that were smaller for the group with dyslexia. However, these findings were no longer statistically significant after correcting for multiple comparisons and total grey and white matter was controlled in an ANCOVA (Eckert et al., 2005). These discrepant findings may reflect reduced power in the second study.

Based on previous findings, Leonard, Eckert, Given, Berninger, and Eden (2006) developed and utilized a quantitative anatomical risk index (ARI) in an attempt to predict behavioral profiles in a heterogeneous sample of children with reading and language impairments. The index was based on an asymmetry profile of the planum temporale, anterior cerebellar lobe, cerebral volume, and surface area of Heschl's gyrus. Children were categorized as having a positive or negative index, where a positive index score represented children with more leftward asymmetry of the planum temporale and anterior cerebellar lobe. Twenty-two children 11-16 years old identified by the school system as having reading and language impairments were scanned using a 1.5 Tesla scanner and 1mm thick slices. Blind raters traced every 4th sagittal image for cerebral hemispheres and every slice for cerebellar hemispheres. While children with negative risk indices had more deficits in general and were more likely to have deficits in both expressive and receptive oral language, children with positive risk indices (relatively smaller volume of the anterior lobe of the cerebellum) were more likely to have word reading deficits with comprehension relatively spared. Notably, there was no relation between rapid naming speed and anterior cerebellar lobe measures or the anatomical risk index, a relationship one might expect to see if the cerebellar hypothesis were correct (Leonard et al., 2006).

The cerebellar deficit hypothesis was further studied by examining the morphology of the cerebellum and its relation to cognition in a heterogeneous group of children between the ages of 8-12 years with dyslexia and Attention-Deficit/Hyperactivity Disorder (ADHD) (Kibby & Hynd, 2008). An MRI was obtained with a 0.6 Tesla scanner with 3.1mm slices. The cerebellar hemispheres were manually traced on the coronal plane using every other slice. The vermis and anterior and posterior lobes were traced using the midsagittal slice and one slice lateral to it on either side. The group of typical readers displayed greater rightward asymmetry than those with dyslexia. In this group, cerebellar hemisphere volume was associated with phonological awareness (Reversals) and short term memory (Digit Span), while the anterior vermis was correlated with phonological awareness (both Reversals and Elision). Rapid naming speed was also related to asymmetry. In the children with dyslexia, rapid naming errors correlated with left and right hemispheric volumes of the cerebellum (Kibby & Hynd, 2008).

Based on this body of research, it appears that a reduced volume in the right anterior lobe of the cerebellum can be reliably identified in heterogeneous groups of reading impaired children. These findings are corroborated by fMRI research in which the right hemisphere of the cerebellum has been linked to the speed-accuracy trade off in cue dependent decision-making (Vallesi, McIntosh, Crescentini, & Stuss, 2011). The anterior portion of the cerebellum is concerned with precise motor function and timing (Juranek, Dennis, Cirino, El-Messidi, & Fletcher, 2010). Furthermore, the finding that measures of phonological awareness, rapid naming (although not consistently), and short term memory are associated with this pattern of asymmetry is compelling and lends support to the cerebellar hypothesis. However, the strength of the association appears to vary based on the methodology used and in terms of how the groups of children with dyslexia were identified.

Evidence for Cerebellar Plasticity

The identification of differences in cerebellar anatomy in school aged children with and without difficulties reading does not imply a causal relationship between cerebellar size and/or asymmetry and reading ability. In order to determine whether grey matter alterations can be observed in pre-reading children with a family history of dyslexia, Raschle, Chang, and Gaab (2010) studied 20 children ages 5-6 years with a 1st degree relative with a clinical diagnosis of developmental dyslexia. This group of children was scanned around the beginning of kindergarten. A T1 weighted MPRAGE was collected in a 3T scanner. Voxel-based morphometry revealed significantly reduced grey matter volumes for pre-reading children with a family history in left occipital, bilateral parietotemporal regions, left fusiform gyrus and right lingual gyrus. Notably, no differences were observed in frontal or cerebellar regions. Furthermore, correlations with rapid naming speed were significant for the left temporoparietal and left occipitotemproal regions. No correlations were significant for phonological processing (Raschle et al., 2010). This research supports the idea that structural differences in developmental dyslexia may not be experience dependent, but may in fact be present before the onset of reading instruction. However, these changes were not observed in the cerebellum which raised the question of whether the differences observed in the cerebellum in children with reading instruction are experience-dependent and alterable with instruction.

This question was addressed by Krafnick, Flowers, Napoliello, and Eden (2010). An 8-week training program in cognitive and sensorimotor tasks focusing on imagery, articulation and tracing of letters, groups of letters and words was provided to 11 children with dyslexia from 7-11 years old, followed by an 8-week period of no intervention. Anatomical scans were obtained at baseline, post-intervention (8 weeks), and post-null period (16 weeks). In this study, 3T scanners were used with 1mm slices. The best images were selected for analysis and were processed using Statistical Parametric Mapping 2 (Good et al., 2001). Post hoc t-tests showed that the left anterior fusiform gyrus, left precuneus, right hippocampus, and right anterior cerebellum increased significantly in volume between the first and second scans (pre- and post-training). The amount of change in phonemic awareness (LAC-3) correlated positively with grey matter volume changes in the left precuneus and Word Attack correlated with changes in the right cerebellum. However, this correlation did not survive correction for multiple comparisons (Krafnick et al., 2010).

These findings provide some evidence in support of cerebellar plasticity. However, it is important to note that children with a familial history of dyslexia may or may not develop reading problems upon receiving instruction. Nevertheless, that changes in the cerebellum were observed with intervention is telling, although it is unclear whether all children would experience changes in cerebellar measurement with additional instruction as no control group that did not receive this instruction was utilized.

Furthermore, it is important to realize that that the cerebellum is only part of a network of structures in which differences were observed.

Rationale for the Present Study

Research on the anatomical features of dyslexia is marked by a clear distinction between child studies that generally focus on elementary school-aged children, and adult studies that include participants from broad age groups. Few anatomical studies include middle school-aged children and none to date target this group specifically. Middle-school aged children are expected to be able to learn from reading to a much larger degree than are elementary school-aged children and may be at greater risk considering the lack of reading instruction available at the middle school level.

Leonard et al. (2006) used children between the ages of 11 and 16 for their work on the quantitative anatomical risk index, representing the only known study to examine the brains of adolescents in this age range. However, this heterogeneous group of children included adolescents with reading and/or oral language impairments, many of which would not have met formal criteria for either dyslexia or specific language impairment (SLI). Brambati et al. (2004) studied 10 participants with a familial history of dyslexia between the ages of 13-57. Many of the participants may not have met criteria for dyslexia and the small size of the sample precluded drawing conclusions that pertained specifically to adolescents with dyslexia. Studying children in this age-range is critical for bridging the age gap in the dyslexia literature. The proposed study aims to address this area of need by focusing on older children with dyslexia in middle school (approximately between the ages of 11 and 14).

Research in the field also lacks a consistent or precise definition of dyslexia and utilizes a variety of methods for participant inclusion. While some studies, such as Brambati et al. (2004), required only a familial history of dyslexia, others required a discrepancy between verbal IQ and at least one measure of word reading or spelling (Eckert et al. 2003; 2005). As a result, researchers may be addressing different reading problems that have little to do with dyslexia, which should be defined by decoding and spelling difficulties. The proposed project intends to study adolescents that demonstrate a clear and persistent normative deficit in decoding and differentiate these students from those with reading fluency deficits but accurate decoding.

Discrepant methodology has also plagued the quantitative analysis of cerebellar anatomy, making it difficult to compare the outcomes of one study to one another. Semi-automated approaches and manual approaches alike have been utilized to produce separate estimates of volume for each cerebellar hemisphere, anterior and posterior regions, and at times white matter versus grey matter. However, few studies have adopted segmentation procedures that produce quantitative volumetric data for each of the primary subdivisions of the cerebellum: corpus medullare, anterior lobe, superior–posterior lobe, and inferior–posterior lobe (Juranek et al., 2010; Pierson et al., 2002) in addition to separate white and grey matter estimates. This study proposes to use methods outlined by Pierson et al. (2002) that were further modified by Juranek et al. (2010). These methods utilize both contemporary terminology and surface-landmark-based identification of two-dimensional slices developed exclusively for MR images (Schmahmann et al., 2000). A manual tracing procedure will be employed using every slice of T1-weighted images to ensure that intra-individual variations are captured. This methodology will facilitate the correlation of carefully divided subregions of the cerebellum with assessments of decoding and reading fluency.

Hypotheses

If the cerebellum theory is correct, children with decoding problems would be expected to differ from children with reading fluency problems and typical readers on at least some facets of cerebellar anatomy. Available research suggests that children with dyslexia should exhibit (1) no statistically significant differences in cerebellar grey matter volume, but increased white matter volume relative to typically developing children, (2) decreased cerebellar asymmetry (right – left hemisphere volume), and (3) reduced volume in the right anterior lobe of the cerebellum. An alternative hypothesis is that these abnormalities will be apparent in children with reading fluency deficits even when decoding is accurate, but not necessarily in children with word reading/decoding difficulties or dyslexia. This alternative hypothesis reflects the view that cerebellar abnormalities are related to the automaticity of word-reading.

Methods

Participants

Participants in this study were part of a large-scale, middle-school reading intervention study (Vaughn et al., 2010). During the spring of the year prior to the beginning of the study, students in grades 5-7 were randomly selected from groups of typical and struggling readers to participate in the study during grades 6-8 of the following year. Students were excluded from the study if: (a) they were enrolled in a special education life skills class; (b) their State-Developed Alternative Assessment (SDAA) Reading performance levels were equivalent to a 3rd grade reading level or lower; (c) they presented a significant sensory disability; or (d) were classified as English as Second Language by their middle school. These children were assessed on a variety of reading measures pre- and post-intervention. Additionally, archival data was used on a portion of the typically developing children.

A subset of 53 children volunteered for the MRI component of the study. The children completed a structural MRI at baseline prior to intervention as part of their participation in the functional imaging study. From these children, three groups were formed. Children in the group with *decoding impairment* [N= 23 (11f, 12m), mean age= 13.7] scored below the 26th percentile on a measure of single word decoding. Most of these children also had fluency deficits. Children in the group with *fluency impairment* [N=8 (6f, 2m), mean age =13.7] scored above the 25th percentile on the decoding measure, but below the 26th percentile on the fluency measure. *Typically developing children* [N=16 (5f, 11m), mean age = 11.7] did not show impairment on either measure and had no history of reading difficulties. The 25th percentile was selected because it has been commonly employed in studies of people with learning disabilities (Fletcher et al., 1994). All children had a composite IQ score of at least 70 on the Kaufman Brief Intelligence Test-2nd (KBIT-2) edition (Kaufman & Kaufman, 2004) to be included in the study.

Table 1 provides a summary of group characteristics on IQ and reading measures. A set of planned *t*-tests revealed that, on average, the typical readers were younger than the children in the group with dyslexia by 1.96 years, t (1, 37) = 4.06, $p < 0.001$, and younger than the children with impairments by 1.95 years, t (1, 22) = 2.70, $p < 0.05$.

Table 1

Descriptive Data (Standard Scores)

	FSIQ		VIQ		PIQ		LWID		TOWRE	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Dyslexia N=23 (11f, 12m)	88	11	85	10	93	16	79	10	83	13
Fluency* N=8 (6f, 2m)	100	10	98	12	101	6	96	5	85	4
Typical* N=16 (5f, 11m)	104	11	100	13	109	17	111	14	97	16

Note. A subset of these children received the Stanford Binet and WJ Reading Fluency measures instead of the KBIT-2 and TOWRE Fluency.

Measures

Decoding. Word reading accuracy was assessed with the Woodcock-Johnson III Letter-Word Identification (LWI). This measures has been widely used in studies of dyslexia (e.g., Fletcher et al., 1994) and has excellent reliability (LWI $r = 0.918$) (Woodcock & Mather, 1990).

Fluency. A composite score combining the Sight Word Efficiency (SWE) and Phonemic Decoding Efficiency (PDE) subtests from the Test of Word Reading Efficiency (TOWRE) was used to assess real and pseudowords. Reliability for these measures is also excellent (SWE $r = .91$, PDE $r = .90$, Total WRE $r = .93$) (Torgesen, Wagner, & Raschotte, 1999). A portion of the group of typical readers with archival data received the Reading Fluency measure of the Woodcock Johnson-III (Woodcock & Mather, 1990).

Intelligence. The KBIT-2 is an individually administered intellectual function measure used primarily for descriptive purposes. The Matrices subtest was administered pre-intervention and Verbal Knowledge subtest was administered post-intervention and prorated for the verbal domain score. The reliability of the Verbal ($r = 0.90$) and

Nonverbal (*r* = 0.86) scores is high among children and adolescents aged 4-18 and excellent for the IQ Composite among ages 10 to 18 (*r* = 0.93) (Kaufman & Kaufman, 2004). The subgroup of typically developing children with archival data received the Stanford-Binet Intelligence Scales-4; Reliabilities range from .94 to .96 for children under age 17 (Becker, 2003).

MRI Acquisition

T1-weighted MR images were utilized for this study. These images were collected on a 3T Philips Intera system with a SENSE (Sensitivity Encoding) technology head coil. Images are 256x256 pixels collected at .9375 x .9375 x 1 mm with full brain coverage. TR and TE vary by scan date as parameters were modified. A TE of between 3.9 and 4.0 and a TR between 8.5 and 8.6 with a flip angle of 6.0 is most common. Image slices were 1.5mm thick for the portion of the typically developing children with archival data.

MR Image Analysis

The methods for analyzing the acquired MR images, obtaining cerebellum parcellation units, and co-localization of anatomical landmarks were based on the procedures outline in Juranek et al. (2010), although some modifications were necessary. All procedures were administered by a rater blind to the adolescent's group membership

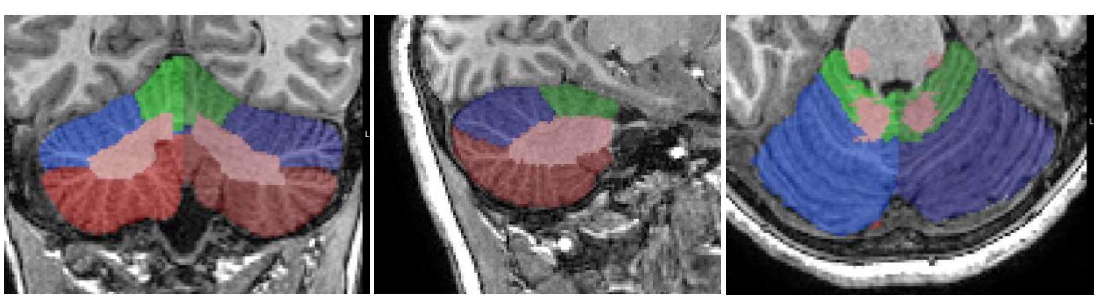
Cerebellar Parcellation Units

A four-compartment model (one WM and three principally GM) was used to parcellate the cerebellum into the following regions: corpus medullare, anterior lobe, superior–posterior lobe, and inferior–posterior lobe. As described by Pierson et al. (2002), each cerebellar parcellation unit was defined according to the following anatomical features: (1) corpus medullare: central white matter and output nuclei; (2) anterior lobe: lobules I–V, bounded by the most posterior point of the fourth ventricle, corpus medullare, and primary fissure; (3) superior–posterior lobe: lobe VI and crus I of VIIA, bounded by the primary fissure, corpus medullare, and horizontal fissure; and (4) inferior–posterior lobe: crus II of VIIA, VIIB, VIII, IX, and X, bounded by the most posterior point of the fourth ventricle, corpus medullare, and horizontal fissure. Localization of anatomical landmarks in each individual brain was guided by the cerebellum atlas published by Schmahmann et al. (2000). Nevertheless, inter-individual variation in cerebellar topography (e.g., fissures and lobes) was preserved as no spatial transformations to a standardized template were implemented. This procedure was completed for both the left and right cerebellar regions to obtain separate volumetric data for each region by hemisphere. Figures 1a-c illustrate the masks created for each of these regions.

Figure 1a-c

Parcellation Units

1a: Coronal plane 1b: Sagittal plane 1c: Axial plane



Anterior lobe
Posterior/Superior Lobe
Posterior/Inferior Lobe
Corpus Medullare

Co-localization of Anatomical Landmarks and Manual Fissure Tracings

Primary and horizontal fissures were manually delineated in the plane that optimized our ability to follow the entire trajectory of each fissure (e.g., sagittal plane for horizontal fissure and para-sagittal and axial planes for primary fissure). Each fissure marker was readily visible in all three cardinal planes, independent of the plane selected for tracing. This process facilitated the manual tracing of the boundaries of each parcellation unit which was then assigned to a new unique mask overlying the T1-weighted image.

Statistical Analyses

Analysis of covariance (ANCOVA) was utilized to test each of the hypotheses, controlling for age, gender, and cerebellar volume as needed. To test the first set of hypotheses that a) cerebellar white matter volume is greater for the group with impaired decoding and b) that there is no difference in cerebellar grey matter volume, the models had a single between-subjects factor (group) with three levels (typical readers, decoding impairment, and fluency impairment) and a single dependent variable (cerebellar WMV and GMV respectively).

To test the second hypothesis that asymmetry in cerebellar GM volume would be greater in the typical readers relative to the dyslexia group, an estimate of asymmetry was obtained by summing regional level volume for each of the hemispheres and calculating a difference (left hemisphere - right hemisphere) score for each participant. This model also had a single between-subjects factor (group) with the three levels mentioned above and a single dependent variable (difference score).

Finally, ANCOVA was used to test the third hypothesis that the group with decoding impairments (dyslexia) would demonstrate a reduced volume in the right anterior lobe of the cerebellum. The model included a single between-subjects factor (group) and a single within-subjects factor (anterior lobe volume). Post-hoc regression analysis was used to conduct a linear contrast between the dyslexia and typical reader groups. The relation between regional volumes and behavioral data were analyzed with a Pearson correlation matrix using volumes corrected for cerebellar volume.

Results

Table 2 presents descriptive statistics for estimated volume of each cerebellar region of interest by group. Pearson correlations were performed to determine if age and gender were related to the anatomical measures. Gender was moderately related to total cerebellar volume, $r = 0.41$, $p < 0.01$. Males had larger cerebellar volumes than females, $t\ (1, 45) = -3.00$, $p < 0.01$. Age, $r = -0.40$, $p < 0.01$, and gender, $r = 0.42$, $p < 0.01$, were moderately related to degrees of asymmetry. Age was also moderately related to the left anterior lobe of the cerebellum, $r = -0.36$, $p < 0.05$, although not to our primary region of interest (the right anterior lobe), r =-0.18, p >0.05.

Table 2

Neuroanatomical Means and Standard Deviations by Group (mm3)

		Dyslexia (n= 23)		Fluency (n=8)		Typical (n=16)	
		Mean	SD	Mean	SD	Mean	SD
Anterior	Left	7302.03	1578.94	8188.20	1509.85	9271.35	2224.31
	Right	7587.96	1768.88	8216.09	2839.27	8913.58	1872.23
Superior	Left	23555.56	3286.17	23748.65	5659.04	23435.78	2918.17
	Right	23638.17	3013.26	24765.26	5312.05	22878.27	3971.77
Inferior	Left	31039.45	3928.25	30494.56	6253.00	33166.14	4086.74
	Right	30648.53	3961.52	30175.87	6112.59	32223.13	4638.29
WMV*	Total	18219.92	1901.68	19134.17	3548.31	19156.88	1123.98
GMV**	Total	123771.69	12163.12	125588.64	25971.20	129888.26	14314.87

Note. White matter volume includes volume from right and left corpus medullare. Grey matter volume includes volume from right and left anterior lobe and the supreior and inferior regions of the posterior lobe

Hypothesis 1: Cerebellar Grey and White Matter Volume

ANCOVA, controlling for gender, was used to test hypothesis that children with decoding problems would demonstrate increased white matter volume relative to typically developing children and no differences in grey matter volume. No statistically significant differences in grey matter volume emerged among children with decoding impairments, fluency impairments, and typically developing children, F (2, 43) < 1. Additionally, no group differences were noted in total cerebellar white matter volume F (2, 43) = 1.57, $p > 0.05$, d= -0.39, again controlling for gender. Nor were there differences when analysis was conducted separately for left and right hemisphere white matter, F (2, 43) = 1.39, $p > 0.05$, d = -0.18 and F (2, 43) = 2.09, $p > 0.05$, d = -0.54 respectively.

Hypothesis 2: Index of Asymmetry

A similar model was used to test the hypothesis that the children with decoding impairments would demonstrate less asymmetry than the group of typical readers. It was hypothesized that the typically developing children would demonstrate greater right (vs. left) cerebellar hemisphere volume. However, the data showed that all groups of readers had greater left hemisphere volume. Results of the anatomical asymmetry index are summarized in Table 3. No statistically significant differences were found in degree of asymmetry among the three groups controlling for age and gender, F (2, 42) < 1, p > 0.05. However, group differences in cerebellar asymmetry were noted when controlling for total cerebellar volume, F (2, 43) = 4.52, p < 0.05, d = -0.8055, with the group of children with decoding and fluency impairments demonstrating reduced asymmetry

Table 3

Asymmetry Index

	N	Mean diff (mm3)	SD
Dyslexia	23	21618.65	3616.62
Fluency	8	19950.63	4453.71
Typical	16	24342.66	4058.61

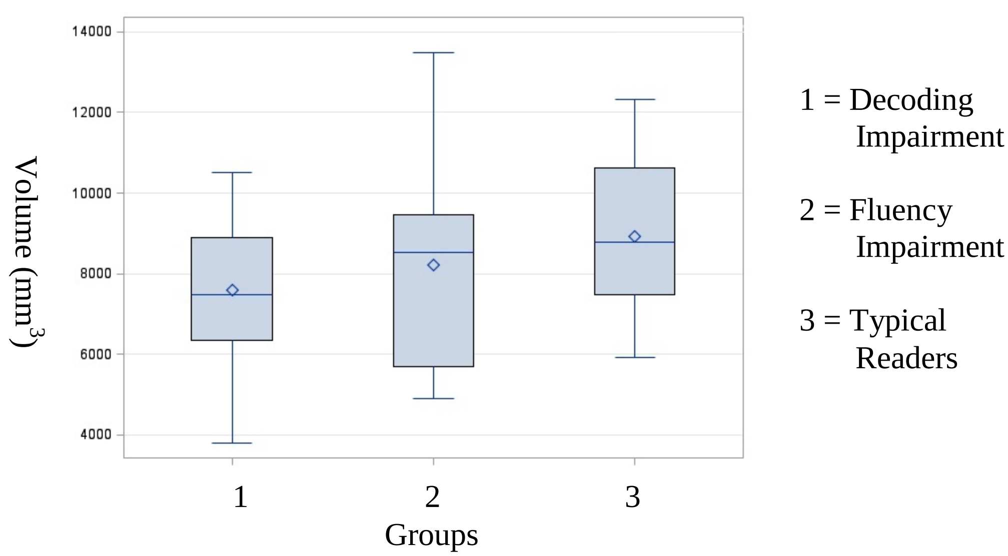
Note. Left - right grey matter unadjusted raw volume(mm3)

Hypothesis 3: Right Anterior Lobe Volume

Figure 2 illustrates the distribution of right anterior lobe of the cerebellum by group, and shows that the group with decoding impairment demonstrates the hypothesized reduction in the right anterior region. The hypothesis that the right anterior lobe of the cerebellum was reduced in the group with decoding impairment was tested with a regression model using one between subjects factor (group) with three levels and one dependent variable (right anterior lobe volume). Statistically significant results were found in the hypothesized direction, $t = 2.04$, $p < 0.05$, $d = -0.8210$. However, analysis with ANCOVA did not survive correction for cerebellar volume, $t = 1.55$, $p > 0.05$, $d = -1.6401$. Given the large effect size and to avoid a Type II error, post-hoc analyses were conducted to test the specific hypothesis that the volume of the anterior lobe was reduced in the group with decoding impairments relative to the typical readers. A t-test revealed a statistically significant difference between the two groups, $t = -2.25$, $p < 0.05$, $d = -0.7325$. However, the hypothesis was not supported when a regression model with a linear contrast controlling for cerebellar volume was utilized, $t = 1.55$, $p > 0.05$, $d = -0.6956$. Given the moderate effect size, it may be that the present study lacked sufficient power to detect a statistically significant difference between the two groups.

Figure 2

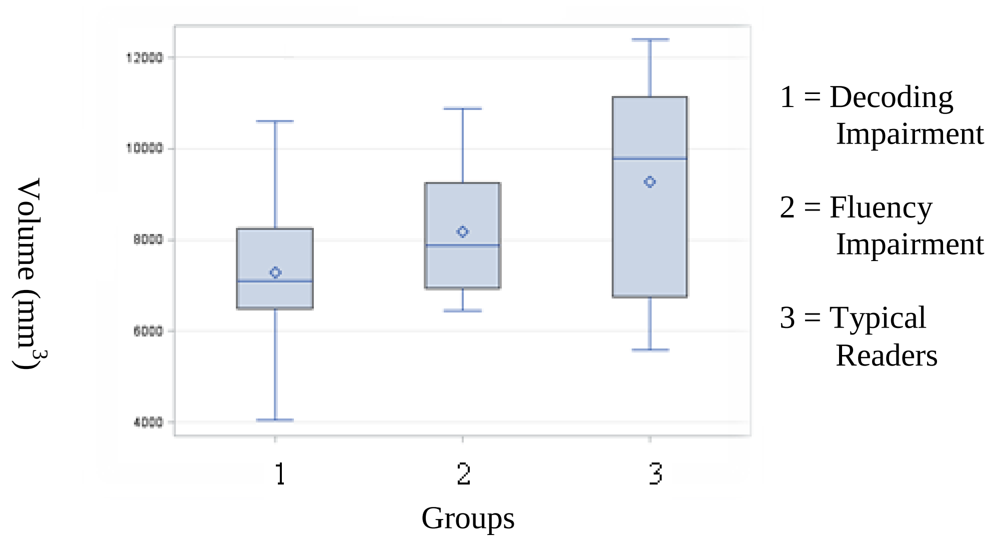
Distribution of volume in right anterior lobe of cerebellum by group



Notably, the data revealed an unexpected difference in the left anterior cerebellum. ANCOVA controlling for cerebellar volume revealed a statistically significant difference in volume for the left anterior cerebellum for the three groups, F (2, 43) = 4.69, p < 0.05, d = -0.9544.

Figure 3

Distribution of volume in left anterior lobe of cerebellum by group



Post-hoc Analysis: Anatomical Relation to Behavioral Reading Measure

In a post-hoc analysis, it was predicted that the decoding measure would account for the anatomical differences in the anterior cerebellum despite group structure. Given the fact that the standard score is calculated with respect to age, age was not used as a covariate. Pearson correlations of regional volumes corrected for cerebellar volume are summarized in Table 4. These analyses revealed a significant relation between LWI and left anterior lobe of the cerebellum, $r = 0.4113$, $p = < 0.01$.

Table 4

Pearson Correlates of Behavioral Measures and Cerebellar Regions

		LWI	Fluency
Anterior	Right	0.2160	0.0902
	Left	0.4113**	0.2246
Superior-Posterior	Right	-0.2105	-0.1767
	Left	-0.2098	-0.2586
Inferior-Posterior	Right	-0.0286	0.1572
	Left	0.0426	0.1046

Note. Fluency scores include those of both the TOWRE and WJ Fluency subtests
** p < 0.01

Additional analyses revealed that the relation between left anterior lobe volume and LWI varied by group. As illustrated in Figure 4 and Table 5 below, the group of children with fluency impairment demonstrated the most robust and only statistically significant relation between LWI and left anterior lobe volume $r = 0.78$, $p < 0.05$.

Table 5

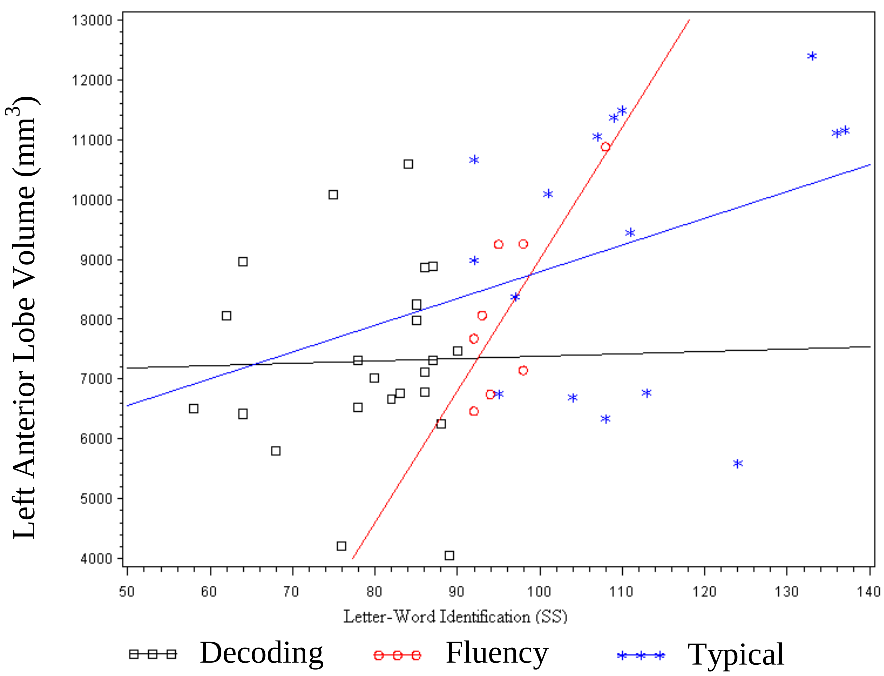
Pearson Correlates of Left Anterior Lobe and Behavioral Data by Group

Group	LWI	TOWRE
Decoding	0.0240	-0.1410
Fluency	0.7753*	-0.0909
Typical	0.4080	0.2085

* p < 0.05
= this analysis was conducted using dat from the Woodcock Johnson-III Reading Fluency subtest

Figure 4

Scatter Plot of Left Anterior Lobe and Behavioral Data by Group with Regression Lines



Discussion

The cerebellar theory of dyslexia has proposed an explanation for the diverse impairments observed in individuals with dyslexia by suggesting that cerebellar abnormalities contribute to ineffective procedural learning of both word reading and motor skills. This study examined the hypothesis at three levels of morphology: total cerebellar grey and white matter volume, degree of asymmetry, and regional variability among children with dyslexia, those with fluency impairments, and typically developing children. Results suggested children with dyslexia differed significantly from typically developing children in degree of cerebellar asymmetry and regional volume. Based on these findings, the hypothesis that word reading ability would be associated with right anterior lobe volume was not supported. However, there was a significant difference in the left anterior lobe of the cerebellum of typically developing children and those with decoding impairment. Given the size of the effects and the power to detect statistically significant differences at the critical level of alpha adopted for this study ($p \leq .05$), the difference in anterior cerebellum is most likely bilateral. Little evidence was found in support of an alternative hypothesis that the group of children with fluency impairment would represent a unique subgroup group of children with cerebellar abnormalities.

Cerebellar Grey Matter and White Matter Volume

These results were consistent with those of Menghini et al. (2008), who found that no general structural abnormalities were found in the grey matter of adults with dyslexia. They were also consistent with those of Raschle et al. (2010), who found no differences in cerebellar volume among pre-reading children with a family history of dyslexia. Interpretation of these data is limited by the lack of information available on how children were identified with dyslexia. Also, many studies of cerebellar morphology in dyslexia fail to report data on total cerebellar grey matter volume; although most studies accounted for individual variations in cerebellar volume in their analysis. The only statistically significant difference in grey matter volume in the present study was found with regard to sex, with males having larger cerebellar volume than females. When controlling for this variable, no statistically significant differences were noted. Furthermore, results were consistent with those of Rae et al. (2002), who found white matter to be symmetrical between groups of adult males with and without a history of dyslexia; they were inconsistent with those of Laylock et al. (2008), who reported that adult males with dyslexia demonstrated larger bilateral white matter volumes than controls.

Index of Asymmetry

The group of children with decoding impairment demonstrated less asymmetry than the typically developing children when controlling for cerebellar volume. This finding was consistent with previously published studies in children (Kibby & Hynd, 2008) and adults (Rae et al., 2002; Leonard et al., 2001). The Kibby and Rae studies, however, were limited by the poor image resolution (3.1 mm and 5mm slices respectively) and a resulting inability to examine the nuances of cerebellar volume that contribute to hemispheric differences. Therefore, interpretation of this finding is tempered by the fact that hemispheric differences can be accounted for by regional variations in volume (e.g. anterior lobe), rather than global differences in hemispheric volume. Whether or not asymmetry continues to be a useful index in the future will depend on whether measurements of asymmetry provide information above and beyond that of known regional correlates.

Regional volume

These findings are inconsistent with the findings of Eckert et al. (2003) and Leonard et al. (2001), who studied children and college students with reading disabilities respectively. These studies reported reduced right anterior lobe volume in individuals with dyslexia relative to typically developing individuals using a manual tracing technique similar to the one employed in this study. In contrast, the present study found a statistically significant reduction in the left anterior lobe and a moderate effect size for right anterior cerebellum volumes. Consistent with the findings of Eckert et al. (2005), the present study found a statistically significant reduction in the volume of the right anterior lobe that did not survive correction for cerebellar volume.

Interpretation of this finding is limited by the emerging literature on specific functions of the cerebellum at a regional level. Evidence that the cerebellum is relevant for cognitive function above and beyond motor timing, precision, and balance continues to grow, particularly in the direction of motor learning. However, research continues to be primarily correlational. The present study cannot prove a causal relation between regional cerebellar dysfunction and reading impairment, and the mechanism by which such dysfunction contributes to reading is still unknown. However, evidence from Kranfrick et al. (2010) demonstrated changes in the right anterior cerebellum following intervention. This finding lends support to the idea that the relation between anatomical correlates and dyslexia may be bidirectional and malleable rather than fixed.

Results are only somewhat consistent with those of Leonard et al. (2006) who utilized a positive risk index defined by leftward asymmetry of the anterior lobe among other variables to evaluate relations with poor word reading skills. The use of the anatomical risk index was used with a heterogeneous group of children with reading and specific language impairment. These results are therefore difficult to compare, because many of those children may not met criteria for dyslexia.

Relations to Behavioral Data

Based on the previous findings, it was hypothesized that word-reading would be associated with right anterior cerebellum. This hypothesis was not supported, and was found to be inconsistent with previous research on children with dyslexia. Eckert et al. (2003) found that the right anterior lobe among other cortical regions significantly correlated with real word reading, pseudoword reading, spelling, and rapid-automatic naming (RAN). Kibby and Hynd (2008) found a moderate correlation between left and right hemisphere volume and rapid naming errors. In adults, a cerebellar symmetry ratio was correlated with nonsense word reading time (Rae et al., 2002), an anatomical risk index that included a measure of asymmetry of the anterior lobe of the cerebellum predicted short- and long-term phonological memory (Leonard et al., 2001). Right cerebellar volume was associated with reaction time for phoneme deletion (Pernet et al., 2009). The present study found that singe-word reading was more related to left anterior lobe volume and found no significant relations between a direct assessment of word reading fluency and cerebellar morphology.

Notably, Menghini et al. (2008) found that adults with dyslexia were impaired on a task of implicit learning. Although an abnormal pattern of fMRI activation was found in the cerebellum of the participants with dyslexia, their analysis did not reveal structural changes at the anatomical level. The availability of implicit learning tasks represents a valuable opportunity to test the cerebellar theory of dyslexia more directly. Evidence of procedural learning impairment in children with dyslexia and cerebellar abnormalities could elucidate the mechanism of action that has eluded researchers thus far. Preliminary evidence has shown that children with dyslexia are impaired on the Serial Reaction Time test and Mirror Drawing Test (Vicari, Finzi, Marotta, Baldi, & Petrosini, 2005). However, no imaging data is available on these children. While the use of these tests informs motor learning, it fails to address the cognitive demands associated with learning to read.

Limitations and Improvements

The manual tracing approach utilized in the present study and some of the aforementioned studies have notable limitations, including difficulty replicating findings among research groups because of subtle and sometimes arbitrary differences in designated boundaries of certain regions (Eckert et al., 2003). A shortcoming of cerebellar research in general is that highly variable terminology and definitions of regional boundaries often prevented direct comparisons of grey and white matter volume differences altogether. This study addressed these limitations by using well-defined, anatomical landmarks found in the atlas published by Schmahmann et al. (2000). However, comparisons could not be reliably made between studies that reported various cerebellar abnormalities in the semilunar lobules (Brown et al., 2001), cerebellar nuclei (Brambati et al., 2004), cerebellar declive and right lentiform nucleus (Pernet et al., 2009).

A further limitation of the manual tracing technique is that regions that are not included in the *a priori* analysis and that may contribute to the understanding of the theory or construct under investigation may be overlooked. A limitation of this present study is that no cortical regions were analyzed in relation to cerebellar abnormalities. Because these data are available, relating cerebellar abnormalities to known cortical markers of dyslexia represents an important opportunity for future investigation.

Like many imaging studies, one of the limiting factors of the present study is sample size. Due to our small sample size, power was likely insufficient to detect some of the more subtle differences in regional cerebellar anatomy. Unfortunately, the group of children with fluency impairments was particularly small (n = 8) and likely contributed to the lack of unique findings for this group. It may be worthwhile to replicate this study with a larger sample and additional children that meet criteria for fluency impairments alone.

Additionally, the discrepancy in ages between the group of impaired children and the typically developing children resulted in paradoxical and unexpected results. With a slightly older group of children with dyslexia, one might expect to see increased cerebellar volume due simply to the effects of maturation, recognizing that the effects of maturation are attenuated by selective pruning of axons. Not only were there no significant differences in cerebellar grey and white matter volumes, but the volume of the right anterior lobe was smaller than that of the younger control group. It is possible, therefore, that this age discrepancy masked more robust findings.

An important improvement in the present study is that the IQ-discrepancy model was not used, as this criterion can be too stringent. Because children with reading impairments often have lower verbal IQ, some researchers believe that children with lower verbal IQs represent a more impaired group of children with broad language impairment. However, it has been hypothesized that children with dyslexia benefit less from the verbal material to which they are exposed and fail to make expected gains in verbal IQ. In other words, low verbal IQ is not necessarily causal to reading impairment. Furthermore, the IQ discrepancy model can be overly inclusive as children with high IQ and average reading abilities would technically qualify for inclusion based on this model. Therefore, aside from excluding those children with intellectual disability, verbal IQ was not used to select children for inclusion in the present study.

Future Directions

Future research should investigate connectivity of the right anterior cerebellum with cortical regions typically associated with reading including the inferior frontal gyrus, temporal-parietal regions, and medial occipital lobe (Eckert, 2004). Fronto-striatal connectivity has also been suggested (Vicari et al., 2005). Laylock et al. (2008) suggested that the changes in white matter they detected in addition to an abnormal ratio of metabolites in the right cerebellar hemisphere may indicate either excessive connectivity or abnormal myelination. In addition, relations with reading and other cognitive skills should be evaluated. If the cerebellar theory of dyslexia is correct, research ought to be able to demonstrate a direct link between cerebellar anatomy and the procedural learning of cognitive tasks rather than simple motor tasks.

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