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Abnormal Subcortical Components of the Corticostriatal System in Young Adults with DLI: A Combined Structural MRI and DTI Study

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Abstract

Developmental Language Impairment (DLI) is a neurodevelopmental disorder affecting 12% to 14% of the school-age children in the United States. While substantial studies have shown a wide range of linguistic and non-linguistic difficulty in individuals with DLI, very little is known about the neuroanatomical mechanisms underlying this disorder. In the current study, we examined the subcortical components of the corticostriatal system in young adults with DLI, including the caudate nucleus, the putamen, the nucleus accumbens, the globus pallidus, and the thalamus. Additionally, the four cerebral lobes and the hippocampus were also comprised for an exploratory analysis. We used conventional magnetic resonance imaging (MRI) to measure regional brain volumes, as well as diffusion tensor imaging (DTI) to assess water diffusion anisotropy as quantified by fractional anisotropy (FA). Two groups of participants, one with DLI ($n=12$) and the other without ($n=12$), were recruited from a prior behavioral study, and all were matched on age, gender, and handedness. Volumetric analyses revealed region-specific abnormalities in individuals with DLI, showing pathological enlargement bilaterally in the putamen and the nucleus accumbens, and unilaterally in the right globus pallidus after the intracranial volumes were controlled. Regarding the DTI findings, the DLI group showed decreased FA values in the globus pallidus and the thalamus but these significant differences disappeared after controlling for the whole-brain FA value, indicating that microstructural abnormality is diffuse and affects other regions of the brain. Taken together, these results suggest region-specific corticostriatal abnormalities in DLI at the macrostructural level, but corticostriatal abnormalities at the microstructural level may be a part of a diffuse pattern of brain development. Future work is suggested to investigate the relationship between corticostriatal connectivity and individual differences in language development.

Keywords

Developmental language impairment; Corticostriatal system; Structural magnetic resonance imaging; Diffusion tensor imaging

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1. Introduction

Developmental Language Impairment (DLI) is a neurodevelopmental disorder, which occurs in 12% to 14% of the school-age children in the United States (Tomblin et al., 1997). This common childhood disorder is characterized by difficulty acquiring and using language, in particular the morphosyntactic components of language, without identifiable causes (Leonard, 1997). A range of different terms has been used to describe this population, and *Specific Language Impairment* (SLI) is the most common usage in the literature. In the current study, we use the term DLI to acknowledge that deficits in individuals with DLI are not confined to language alone, but include general cognitive functioning, such as procedural memory (Ullman & Pierpont, 2005), phonological working memory (Archibald & Gathercole, 2006), reinforcement learning (Lee & Tomblin, 2012), statistical learning (Evans, Saffran, & Robe-Torres, 2009), and executive function (Henry, Messer, & Nash, 2011).

1.1. A Domain-general Approach: Corticostriatal System as One of the Neuroanatomical Mechanisms Underlying DLI

It has been widely accepted that DLI is a multifactorial disorder involving both biological and environmental factors. However, there is no consensus to date on what these might be. Numerous studies have examined the linguistic characteristics of DLI, along with studies of plausible perceptual and cognitive factors. We have joined others in exploring the hypothesis that language development and disorders are grounded in general purpose learning systems (e.g., Ullman & Pierpont, 2005; Lum et al., 2012). We are particularly interested in the procedural learning system and the closely related reinforcement learning system, and have found empirical support for their possible involvement in DLI (Tomblin, Mainela-Arnold, & Zhang, 2007; Lee & Tomblin, 2012, under review).

In the literature, both procedural learning and reinforcement learning are strongly mediated by the corticostriatal system. With respect to procedural learning, different types of procedural learning (e.g., motor skill learning, sequential learning) rely on different components of the corticostriatal system. For example, some studies showed a positive correlation between motor skill learning and neural activity of the motor corticostriatal loop (e.g., Grafton et al., 1994), while others reported a significant right-lateralized activation in both the anterior putamen and the head of the caudate nucleus in sequential learning (e.g., Kim et al., 2004; Rauch et al., 1997). Despite different types of procedural learning, all findings indicate that the corticostriatal system, particularly the caudate and the putamen, plays an important role in supporting procedural learning. Concerning reinforcement learning, the basal ganglia function as a reinforcement learning center, learning about consequences of one's actions, and then conveying prediction error signals (i.e., discrepancy between actual results and expected results) to guide action selection (Badre & Frank, 2012; Daw & Doya, 2006; Daw & Shohamy, 2008; Doya, 1999; Frank & Badre, 2012; Niv & Schoenbaum, 2008). In other words, the basal ganglia modulate activations in the cortex based on learned reinforcement history. Imaging findings support this view, showing that individual differences in performance on reinforcement learning are highly correlated with striatal blood oxygen-level dependent (BOLD) activities (Schonberg, Daw, Joel, & O'Doherty, 2007), and moreover, the occurrence of predication errors is closely related to increased activity in the nucleus accumbens and the putamen (Berns, McClure, Pagnoni, & Montague, 2001; McClure, Daw, & Montague, 2003; O'Doherty et al., 2003).

Given that individuals with SLI demonstrate impaired procedural and reinforcement learning that rely on the corticostriatal system, the basal ganglia in particular, this neuroanatomical system has become a good candidate for further study in the etiology of

DLI. To the best of our knowledge, no studies have directly examined brain structures in DLI with an a priori hypothesis of structural abnormalities in the corticostriatal system.

1.2. Previous Studies of Brain Structure in DLI

Very few researchers examined brain structures in *DLI per se*, and the findings are inconsistent. Most investigations focused on volume and asymmetry of classic cortical language areas in DLI. Results include atypical patterns of asymmetry, as well as reduced volumes of the perisylvian regions, the frontal regions (e.g., Broca's area and pars triangularis), and the parietal lobes (Badcock et al., 2012; De Fosse et al., 2004; Herbert et al., 2005; Jernigan et al., 1991; Plante et al., 1991), although non-significant structural differences between individuals with and without DLI were also reported (e.g., Gauger et al., 1997; Preis et al., 1998). It should be noted that the classic language areas were derived from adult patient studies (e.g., Broca, 1865; Wernicke, 1874). Given that DLI is a *developmental* language disorder, its anatomical correlates may not fully conform to the focal neuroanatomical basis of language that was built upon *acquired* language disorders (Johnson, Halit, Grice, & Karmiloff-Smith, 2002).

There were limited findings regarding global brain abnormalities in DLI. By using the conventional MRI, some researchers showed decreased white matter volumes in both motor- and language-related cortex of individuals with DLI (Jancke et al., 2007), whereas others showed global increases in total brain volumes driven by white matter enlargement (Herbert et al., 2004). Soriano-Mas et al. (2009) further pointed out that global volumetric increases in white and gray matter were more prominent in young children with DLI than in older children with DLI, indicating a trend toward normalization with age.

Kim et al. (2006) was the first to use diffusion tensor imaging (DTI) to examine white matter pathways in DLI. They found decreased anisotropy in the genu of corpus callosum of children with DLI whose brains looked normal on the magnetic resonance imaging (MRI) scans. This finding indicates a poor integrity of the corpus callosum in DLI, which may lead to abnormal integration of information between the left and right hemispheres. In addition, it also suggests that individuals with DLI may have structural brain abnormalities at the microstructural level, which cannot be observed by conventional MRI. DTI, on the other hand, provides microstructural information based upon the movement of water molecules in the brain (Basser, Mattiello, & LeBihan, 1994; Basser & Pierpaoli, 1996), and therefore can be a promising method to identify abnormal brain regions in DLI at a microscopic scale.

1.3. The Current Study

The aim of the current study was to examine the subcortical components of the corticostriatal system in young adults with DLI by using a combined volumetry and DTI method. The subcortical structures of the corticostriatal system included the caudate nucleus, the putamen, the nucleus accumbens, the globus pallidus, and the thalamus. In addition, we also looked into the structures of the four cerebral lobes and the hippocampus for an exploratory analysis.

In this study, we used a combination of anatomical and diffusion tensor imaging, along with language measurements, to develop a deeper knowledge of the brain-behavior relationship in DLI. Conventional MRI measures tissue volumes of anatomical structures, while DTI measures motions of water molecules in the brain (i.e., brain water diffusivity) to highlight subtle alterations in the tissue microstructure. These two techniques provide complementary information of volumetric and microstructural changes within the subcortical areas. Although DTI has been used to investigate regional white matter changes and connectivity of white matter, it can be also utilized to highlight microstructural alterations of subcortical

gray matter, as demonstrated by previous studies on psychiatric disorders (e.g., Spoletini et al., 2011), neurodegenerative disorders (e.g., Cherubini et al., 2010; Magnotta et al., 2009), and neurodevelopmental disorders (e.g., Makki et al., 2008; Neuner et al., 2011). Hence, by combining the study of abnormalities in MR volumetry with the potential of DTI in highlighting microstructural alterations, it should be possible to describe in detail subcortical abnormalities in DLI.

2. Methods

2.1. Participants

Participants were recruited from prior participation in another behavioral study (Lee & Tomblin, 2012), wherein their language and nonverbal IQ scores were obtained (see Section 2.2). The original sample included 48 participants (DLI: $n = 25$; Normal: $n = 23$). We paired them on age and gender, and excluded those who 1) were left-handed, 2) were pregnant, and 3) moved to other states and could not come back for participation. In the end, 24 participants, 12 from the DLI group and 12 from the control group, joined the current study. There was no significant difference in gender ratio (male: female = 4: 8) or in age, $t(22) = .15$, $p = .89$, between the two groups (see Table 1).

This research was approved by the institutional review board (IRB) at the University of Iowa. All participants provided consent in accord with the Declaration of Helsinki after having been informed of the study procedures and purpose. All participants were compensated for their time.

2.2. Behavioral Measures

Participants' language and nonverbal intelligence quotient (IQ) scores were collected from their prior participation in the prior study (Lee & Tomblin, 2012), and the time gap between the current study and the prior one was approximately six months. To summarize the behavioral measures, we included two performance IQ measures and three language tasks to assess participants' current nonverbal IQ and language skills respectively. The two nonverbal IQ measures are Block Design and Matrix Reasoning, which are subtests from Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999). The three language tasks include: 1) Word Derivations, a subtest from The Test of Adolescent and Adult Language, Fourth Edition (TOAL-4; Hammill, Brown, Larsen, & Wiederholt, 2007) to assess knowledge of derivational morphology, 2) Peabody Picture Vocabulary Test, Fourth Edition (PPVT-4; Dunn & Dunn, 2007) to assess receptive vocabulary, and 3) a modified version of the Token Test (de Renzi & Faglioni, 1978; Morice & McNicol, 1985) to assess sentence comprehension. Table 1 summarizes demographic information and measure scores by group.

2.3. Image Acquisition

All MRI scans were obtained at the University Hospital and Clinics of Iowa using the Siemens 3T Trio scanner. The standard imaging protocol was used to collect high-resolution anatomical images and a diffusion tensor sequence.

2.3.1. Anatomical Image—The high-resolution anatomical images consisted of a T1 weighted volume and proton density (PD/T2) images collected with a dual echo fast spin-echo two-dimensional (2D) sequence. The T1 weighted images were acquired in the coronal plane using a 3D MP-RAGE sequence with the following parameters: echo time (TE) = 2.8 ms, repetition time (TR) = 2530 ms, inversion time = 900 ms, flip angle = 10°, number of excitations (NEX) = 1, field of view (FOV) = 256 × 256 × 256 mm, slice thickness = 1.5

mm, and matrix = $256 \times 256 \times 256$. The total estimated time of image acquisition was ten minutes.

The T2 weighted images were acquired in the sagittal plane using a 3D SPACE sequence with the following parameters: TE = 406 ms, TR = 4000 ms, NEX = 1, FOV = $260 \times 260 \times 176$ mm, slice thickness: 3.0 mm, matrix = $260 \times 260 \times 176$, and turbo factor = 121. The total estimated time of image acquisition was five minutes.

2.3.2. Diffusion Tensor Image—The diffusion tensor data were acquired with the following parameters: TE = 82 ms, TR = 8700 ms, FOV = 256×256 mm, Matrix = 128×128 , slice thickness = 2.0 mm, the number of diffusion directions = 30, and *b*-values = 1000 s/mm² with one non-diffusion weighted baseline images (*b* = 0 s/mm²). The total estimated time of image acquisition was ten minutes.

2.4. Image Preprocessing and Processing

2.4.1. Anatomical MRI—All of the anatomical scans were processed using AutoWorkup, an automated procedure implemented in the software package Brain Research: Analysis of Images, Networks, and Systems (BRAINS, Magnotta et al., 2002). The BRAINS image analysis software has been in development for over 20 years and a recent reliability study has shown the fully automated method to be substantially more reliable than manual raters, and produces reliable data across scanners, scanner vendors, and across sequences (Pierson et al., 2011).

The standard image analysis pipeline was used for data processing, including anterior commissure (AC)-posterior commissure (PC) alignment of T1 volume, co-registration of T2 weighted images to AC-PC aligned T1, defining of Talairach parameters to warp the Talairach grid onto the raw space of each subject, tissue classification of white matter, gray matter, and cerebrospinal fluid (CSF) by employing a discriminant analysis method of tissue segmentation (Harris et al., 1999), and skull stripping using an artificial neural network (ANN; Magnotta et al., 1999). The ANN also provides a reliable way to automatically delineate regions of interest (ROI) for the caudate, the putamen, the globus pallidus, the nucleus accumbens, the hippocampus, and the thalamus in subject space (Powell, 2008). After completion of AutoWorkup, all scans were individually inspected by technicians blind to subject identity for quality control. The total tissue volume of each region is calculated by a summation of gray matter and white matter.

2.4.2. DTI—The diffusion tensor data were analyzed using the Guided Tensor Restore Anatomical Connectivity Tractography (GTRACT) software (Cheng et al., 2006). Details of image preprocessing and processing have been described in Magnotta et al. (2009). To summarize, the diffusion weighted images were first co-registered to the B0 image to correct for motion and distortions caused by eddy current artifacts. The diffusion tensor was estimated from the diffusion weighted images after applying a $3 \times 3 \times 3$ voxel median filter to the B0 and diffusion weighted images. The B0 image was then co-registered with the AC-PC aligned T1 weighted anatomical image from BRAINS2 using a rigid-body transformation and a non-linear B-spline transformation. The resulting transforms were then applied to the scalar maps, placing them within the space of the anatomical image. Fractional anisotropy (FA) measures were obtained for the subcortical structures as well as the four cerebral lobes for all subjects utilizing Talairach parameters (Collins et al., 1994; Andreasen et al., 1996). These regions contained both gray matter and white matter. The mean FA for each ROI represents the average FA within the defined region, and therefore FA for gray and white matter was not calculated separately.

2.5. Statistical Analysis

All statistical analyses were performed with SPSS software. We did not control for age and gender in statistical analyses because these two potentially confounding variables have been taken into account in the study design by matching participants on them. The Student's *t* test was used to compare brain measures between the DLI group and the control group in the ROIs. The primary analysis was concerned with testing hypotheses concerning the subcortical components of the corticostriatal system (i.e., the basal ganglia and the thalamus) and thus the alpha level for each hypothesis was .05 or lower. We also examined differences in the cerebral lobes and in the hippocampus. This portion of the analysis was exploratory and therefore emphasized the effect size. Effect sizes were reported as Cohen's *d*. Cohen (1988) suggested that *d* values of 0.2, 0.5, and 0.8 represent small, medium, and large effect sizes respectively.

3. Results

3.1. Anatomical MRI

3.1.1. Volumetric Analysis—Table 2 summarizes the absolute volumes by group. When compared with the control group, the DLI group showed smaller bilateral caudate nucleus, $t(22) = 2.97, p = .007$, smaller left globus pallidus, $t(22) = 2.44, p = .02$, smaller bilateral thalamus, $t(22) = 3.83, p = .001$, as well as smaller cerebral lobes, including the occipital lobes, $t(22) = 3.77, p = .001$, the parietal lobes, $t(22) = 3.61, p = .002$, the temporal lobes, $t(22) = 3.23, p = .004$, and the frontal lobes, $t(22) = 3.68, p = .001$.

However, the intracranial volume (ICV) was significantly different between the DLI group ($M = 1247.10, SD = 167.26$) and the control group ($M = 1504.51, SD = 181.76$), $t(22) = 3.61, p = .002$. To avoid potential confounding of the general effects of ICV differences with tests for specific regional differences, absolute volumes were transformed into relative volumes, obtained by dividing absolute volumes by ICV and multiplying by 100. Table 3 displays the relative volumes by group. The DLI group was significantly larger than the control group in the relative volumes of the putamen, $t(22) = 2.70, p = .01$, of the right globus pallidus, $t(22) = 3.19, p = .004$, and of the nucleus accumbens, $t(22) = 2.69, p = .01$. These findings remain significant even with alpha correction for multiple comparisons. Regarding exploratory analysis, the DLI group was significantly larger than the control group in the relative volumes of the hippocampus, $t(22) = 3.49, p = .002$. No significant difference was found in any of the relative volumes of the cerebral lobes ($ps > .7$). It is important to note that the relative volumes of these statistically significant ROIs (i.e., the putamen, the right globus pallidus, the nucleus accumbens, and the hippocampus) were in the direction of larger volumes in the DLI group than in the control group after adjusting for ICV.

3.1.2. Correlation Analysis between Relative Volumes and Language Scores

In the prior between-group comparisons, language status was treated as a dichotomous variable. Clearly, however, the relationship between individual differences in brain measures and language could be continuous. Therefore, the aim of the correlation analysis was to determine whether relative volumes of the brain were correlated with individual differences across a range of language ability (i.e., language as a continuous variable instead of a dichotomous variable).

The correlations between brain measures and language composite scores are summarized in Table 4. Results showed that language composite scores were inversely correlated with relative volumes of the nucleus accumbens, $r = -.52, p = .009$, of the globus pallidus, $r = -.54, p = .006$, of the putamen, $r = -.53, p = .008$, and of the hippocampus, $r = -.62, p = .001$.

That is, the larger the relative volumes of these structures, the worse the language performance. Language was not correlated with any of the cortical relative volumes. Indeed, these effects were more robust than those found using group comparisons.

3.2. DTI

3.2.1. FA Analysis—We use FA as the primary measure of directional diffusivity of water, and decline in FA values suggests poor microstructural integrity. Table 5 displays the results of the between-group FA analysis. Regarding the hypothesis-driven tests, the DLI group showed significantly lower FA values than the control group in the thalamus, $t(22) = 3.57$, $p = .002$, and in the globus pallidus, $t(22) = 2.37$, $p = .027$. FA values in the caudate nucleus, in the putamen, and in the nucleus accumbens were not significant between the two groups. Regarding the exploratory analysis, the DLI group showed significantly lower FA values than the control group in all cerebral lobes, including the occipital lobes, $t(22) = 5.37$, $p < .001$, the parietal lobes, $t(22) = 4.22$, $p < .001$, the temporal lobes, $t(22) = 3.71$, $p = .001$, and the frontal lobes, $t(22) = 5.49$, $p < .001$. No significant difference was found in the hippocampus between the two groups, $t(22) = 1.47$, $p = .16$. It should be mentioned that significant differences in those ROIs were driven by low FA values in the DLI group, indicating poor microstructural integrity of those regions in DLI.

However, given that the DLI group had significantly lower whole-brain FA value than the control group, $t(22) = 6.82$, $p < .001$, we performed an ANCOVA analysis with the whole-brain FA value as the covariate to test whether these FA abnormalities mentioned above are region-specific (i.e., proportionally abnormal FA values in the ROIs after correction of the whole-brain FA value). Results showed non-significant differences in the FA values in the ROIs after the whole-brain FA value was controlled.

3.2.2. Correlation Analysis between the whole-brain FA value and Language

Scores—Based on the ANCOVA analysis shown above, we argue that the FA abnormalities in the brains of individuals with DLI were diffuse, not regionally specific. Therefore, we conducted a correlation analysis between the language composite scores and the whole-brain FA value, aiming to see if the global diffuse abnormality were associated with language treated as a continuous variable. The results showed that the language composite scores are significantly correlated with the whole-brain FA value, $r = .58$, $p = .003$. That is, the better the language skills, the higher the whole-brain FA value.

4. Discussion

The aim of the current study was to examine structural differences in the subcortical components of the corticostriatal system between individuals with and without DLI. The four cerebral lobes and the hippocampus were also included for an exploratory analysis. Before we summarize the results, it should be noted that one of the main findings is significant difference in ICV between the two groups, with a large effect size of $d = 1.79$. Given that brain growth is the primary force for increasing ICV during early development and maturation (Nopoulos et al., 2011), smaller ICV is generally considered as an indicator of abnormal brain growth, which will be discussed in the following sections.

Our results showed that participants with DLI not only had smaller ICV than control participants, but they also revealed increased relative volumes of several subcortical components of the corticostriatal system after controlling for the ICV, including the bilateral putamen, the right globus pallidus, and the bilateral nucleus accumbens, indicating region-specific brain volume abnormalities. In addition, the DLI group also showed increased relative volumes of the hippocampus after controlling for the ICV. With regard to the DTI findings, participants with DLI had significantly lower whole-brain FA value than control

participants. Significantly different FA values in the cerebral and subcortical regions disappeared after controlling for the whole-brain FA value, suggesting that microstructural abnormality in the brains of individuals with DLI is diffuse, affecting almost every region of the brain. Taken together, these preliminary results suggest corticostriatal abnormalities in DLI at the macrostructural level, but corticostriatal abnormalities at the microstructural level may be a part of a diffuse pattern of brain development.

4.1. Abnormality in Subcortical Components of Corticostriatal System in DLI

Previous imaging studies showed that individuals with DLI had abnormal volumes of the caudate nucleus (Badcock et al., 2012; Herbert et al., 2003; Jernigan et al., 1991; Soriano-Mas et al., 2009; Watkins et al., 2002) and of the putamen (Watkins et al., 2002). However, none of the studies, except for Watkin et al. (2002), took into account of group difference in ICV, which confounds the results (e.g., Eritaia et al., 2000; Whitwell et al., 2001). Given that ICV provides a stable normalizing factor for estimating volume changes (Sahin et al., 2007), it is important to adjust for ICV to obtain region-specific volumetric information.

In the current study, we found increased relative volumes of the basal ganglia substructures in the DLI group. These findings are consistent with those reported by Watkin et al. (2002), who showed increased relative volumes of the putamen in the affected members of the KE family exhibiting severe forms of DLI. However, the findings were in contrast with those reported by Badcock et al. (2012), who found decreased volumes of the caudate nucleus and relatively normal volumes of the putamen in children with DLI. It should be noted that Badcock et al.'s did not report ICV adjustment in their paper, so it is possible that adjusting for ICV may change their results. Indeed, if we used the absolute volumes as dependent variables (see Table 2), our results would resemble those by Badcock et al. (i.e., non-significant difference in the putamen but significant difference in the caudate nucleus). Controlling for ICV is important to gain regionally specific information and discriminate people with neurological impairments from normal populations (e.g., Buckner et al., 2004; Pell et al., 2008); therefore, future studies are necessary to take into account of ICV adjustment while replicating the current findings.

We found structural abnormalities in the putamen, which are in line with prior research (e.g., Watkin et al., 2002). We also showed abnormal relative volumes of the globus pallidus and of the nucleus accumbens. To the best of our knowledge, there is only one study reporting abnormalities of the globus pallidus in DLI by using single-photon emission computed tomography (SPECT; Hwang et al., 2006), and no studies have shown abnormalities of the nucleus accumbens in DLI. Given that substantial research has shown the role of the nucleus accumbens in reinforcement learning processes (e.g., Ikemoto & Panksepp, 1999; Salamone & Correa, 2002), structural abnormalities of the nucleus accumbens may explain, in part, poor reinforcement learning in individuals with DLI (Lee & Tomblin, 2012).

However, we did not find evidence for structural differences in the caudate nucleus of individuals with DLI. Age differences may account for discrepancy in findings across studies. For example, Soriano-Mas et al. (2009) showed an increased volume of the caudate nucleus in young children with DLI (age range from 5 to 11), but this anatomical alteration was not found in older children with DLI (age range from 12 to 17). In the current study, participants with DLI were young adults with an age range from 19 to 22. Therefore, it is possible that abnormalities in the caudate nucleus of these language-impaired participants have normalized with age, although we could not explain why this normalization process does not occur in other subcortical regions.

In contrast with neurodegenerative brains, the relative volumes of the basal ganglia were *increased* in individuals with DLI. Brain volume increase is not uncommon to individuals

with neurodevelopmental disorders (e.g., Brieber et al., 2007; Mostofsky et al., 2007). One interpretation is that increased volumes of the basal ganglia substructures can be seen as a product of compensatory plasticity (Kalia, 2008). That is, synaptic density in the basal ganglia increases due to decreased functional activities in other brain areas. Another interpretation is that the process leading to the larger basal ganglia *per se* is indeed pathological. In our correlation analysis, the relative volumes of the basal ganglia substructures (i.e., the putamen, the globus pallidus, and the nucleus accumbens) were directly related to individual differences in language, with larger volumes of these basal ganglia substructures associated with poor language scores. This inverse correlation result suggests that this regional enlargement should be pathological, rather than compensatory in nature (see Moore et al., 2000; Nopoulos et al., 2010; Paulsen et al., 2005; Shriver et al., 2006, for similar discussions regarding *pathological enlargement*). Otherwise, a positive correlation between language performance and relative volumes of the basal ganglia would be expected.

4.2. Hippocampal Enlargement in DLI

The hippocampus is not a component region of the corticostriatal system. We included it in our exploratory analysis because the hippocampus plays a significant role in language development (e.g., Breitenstein et al., 2005; Davis & Gaskell, 2009; Ullman, 2004). In addition, examining the structure of the hippocampus addresses the current hypothesis of DLI, stating that the hippocampus (and related medial temporal lobes) in DLI is relatively normal, and therefore will take over certain functions from the impaired corticostriatal system as a way of brain compensation during development (Procedural Deficit Hypothesis; Ullman & Pierpont, 2005).

In the current study, the relative volume of the hippocampus was significantly larger in the DLI group than in the normal group, and it was strongly correlated with individual differences in language, with larger hippocampal volumes associated with poor language scores. These results were in contrast to the Procedural Deficit Hypothesis, indicating that the hippocampal enlargement is not likely a compensatory strategy for the brain. Or else, its volumetric increase should be positively correlated with language ability.

This is the first study reporting structural abnormalities in the hippocampal region of individuals with DLI. Given that the hippocampus is one of the key structures supporting declarative memory and word learning (Eichenbaum, 2004; Ullman, 2004), our results are in line with recent behavioral findings showing poor verbal declarative memory as well as difficulty with initial word learning in individuals with DLI (Alt, Plante, & Creusere, 2004; Gray, 2004; Lum et al., 2012). However, a combination of behavioral and functional MRI methods will be necessary to test whether a reciprocal relationship between BG and hippocampus exists as suggested by the Procedural Deficit Hypothesis, and to further examine the role of the hippocampus in DLI.

4.3. Small ICV in DLI: Indicator of Abnormal Brain Growth

ICV is a measure of the total tissue and cerebrospinal fluid (CSF) volumes within the calvarium, and this trait characteristic reflects maximal brain growth obtained during maturation (Nopoulos et al., 2011). The rate of increase in ICV is not linear along the developmental continuum. ICV reaches 90% of its adult size at approximately the age of seven, and then grows to the full adult cranial capacity very slowly by early adolescence (Giedd, 2004; Sgouros, Goldin, Hockley, Wake, Natarajan, 1999). Once the size of the cranial vault is fixed, the skull capacity remains stable with age (Giedd et al., 1996).

In our sample, the DLI group has smaller ICV than the control group, indicating abnormalities in brain maturation during development in individuals with DLI. Abnormal ICV has also been reported in individuals with other developmental disorders, such as autism spectrum disorders (e.g., Hardan et al., 2001), attention deficit/hyperactivity disorders (e.g., Durston et al., 2004), and dyslexia (e.g., Hasan et al., 2012). Given that ICV is correlated with general cognitive performance (e.g., Farias et al., 2012, MacLulich et al., 2002), it is not surprising to observe subtle differences in global cognitive functioning in individuals with DLI when compared with normal language learners.

It should be noted that in the current study, ICV is strongly correlated with the whole-brain FA value, $r = .72$, $p = .00$. We are not able to explain the close association between the two brain parameters at this point given the limited data available; however this high correlation could reflect a common developmental mechanism. Several studies have shown genetic influences on the growth of cranial capacity (e.g., Baare et al., 2001; Gilmore et al., 2010) and development of microstructural integrity in the brain (e.g., Chiang et al., 2011; Jahanshad et al., 2010). Future research is necessary to better understand the contribution of genetic and environmental factors to individual variation in human brain structure along the developmental continuum, and how these risk factors play a role in cognitive development, including language.

5. Future Work

The current study provides preliminary imaging findings of corticostriatal abnormalities in DLI. However, it does not provide information pertaining to the direction of the causal pathways. Therefore, it remains unclear whether these abnormalities are one of the primary causes of language impairments, or these brain differences are, at least partly, due to differences in participants' language use or their effect on language environment. To address this issue, longitudinal research beginning in early childhood with larger samples is a promising method. In addition, a combination of empirical experiments, multiple experimental modalities (e.g., functional MRI, genetics), and advanced imaging techniques (e.g., diffusion tensor tractography) will further elucidate the understanding of the neural basis of DLI.

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Highlights

- Examination of subcortical components of corticostriatal system in DLI.
- Use of anatomical magnetic resonance imaging and diffusion tensor imaging.
- Corticostriatal abnormality in DLI at macrostructural level.
- Corticostriatal abnormality at microstructural level as a diffuse pattern of brain development.
- Substantial reduction in intracranial volumes in participants with DLI.

Table 1

Age, language scores, and nonverbal IQ scores by group. Test scores were reported in standard scores with a mean (*M*) of 100 and a standard deviation (*SD*) of 15. These scores were converted from *z* scores based on local norms (the Token Test) or national norms (PPVT-4, Word Derivations, Nonverbal IQ). The nonverbal IQ composite scores were based on Block Design and Matrix Reasoning of the Wechsler Abbreviated Scale of Intelligence (WASI), and the language composite scores were the average standard scores of PPVT-4, Token Test, and Word Derivations. **PPVT-4**: Peabody Picture Vocabulary Test, Fourth Edition; **Token Test**: the modified Token Test of Language Comprehension; **Word Derivations**: A subtest from the Test of Adolescent and Adult Language, Fourth Edition (TOAL-4).

		DLI Group (<i>n</i> =12)		Control Group (<i>n</i> =12)		
		<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>p</i>
Age (year)		21.99	1.56	22.06	.51	.89
Nonverbal IQ Composite Scores		91.25	13.59	112.50	10.03	< .001
Language Measures	PPVT-4	84.00	7.50	105.17	13.10	< .001
	Token Test	45.33	44.66	99.99	15.00	= .001
	Word Derivations	70.00	5.22	95.00	15.67	< .001
	Language Composite Scores	66.44	16.43	100.05	11.85	< .001
Gender Ratio (Male: Female)		4:8		4:8		

Table 2

Absolute volumes of ROIs by group.

	DLI Group (<i>n</i> = 12)		Control Group (<i>n</i> = 12)		Analysis with <i>t</i> test (<i>df</i> = 22)		
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>t</i>	<i>p</i>	<i>d</i>
Intracranial Volume (ICV)	1259.32	163.40	1550.61	161.83	4.01	.001*	-1.79
<i>Hypothesis-driven Analysis</i>							
Caudate Nucleus	6.02	.73	7.12	1.06	2.97	.007*	-1.21
Putamen	8.95	.95	9.69	1.28	1.62	.12	-.66
Nucleus Accumbens	.56	.11	.54	.15	-.47	.64	.15
Globus Pallidus	2.80	.38	3.08	.51	1.52	.14	-.62
Thalamus	10.25	1.25	12.00	.96	3.83	.001*	-1.57
<i>Exploratory Analysis</i>							
Occipital Lobe	105.45	14.10	127.33	14.33	3.77	.001*	-1.54
Parietal Lobe	215.68	28.73	261.22	32.92	3.61	.002*	-1.47
Temporal Lobe	212.42	33.69	255.67	31.91	3.23	.004*	-1.32
Frontal Lobe	381.12	51.12	461.80	56.24	3.68	.001*	-1.50
Hippocampus	3.27	.39	3.17	.48	-.56	.58	.23

Table 3

Relative volumes of ROIs by group.

	DLI Group (n = 12)		Control Group (n = 12)		Analysis with <i>t</i> test (df = 22)		
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>t</i>	<i>p</i>	<i>d</i>
<i>Hypothesis-driven Analysis</i>							
Caudate Nucleus	.49	.06	.47	.04	.62	.54	.39
Putamen	.72	.06	.65	.07	2.70	.01*	1.07
Nucleus Accumbens	.05	.01	.04	.01	2.69	.01*	1.00
Globus Pallidus	.23	.03	.21	.03	1.79	.09	.67
Thalamus	.83	.08	.80	.09	.63	.54	.35
<i>Exploratory Analysis</i>							
Occipital Lobe	8.47	.41	8.48	.40	.08	.94	-.03
Parietal Lobe	17.30	.44	17.36	.66	.28	.78	-.11
Temporal Lobe	16.99	.55	16.99	.47	.01	.99	<.001
Frontal Lobe	30.56	.96	30.70	.88	.37	.71	-.15
Hippocampus	.27	.04	.21	.03	3.49	.002*	1.70

Table 4

Correlations between relative volumes of the brain and language composite scores.

Relative Volumes of ROIs	Language Composite Scores
Caudate Nucleus	– .22
Nucleus Accumbens	– .52 **
Globus Pallidus	– .54 **
Putamen	– .53 **
Thalamus	– .02
Occipital lobes	.15
Parietal lobes	– .04
Temporal lobes	.12
Frontal lobes	– .19
Hippocampus	– .62 **

** Correlation is significant at the 0.01 level (2-tailed).

Table 5

FA values in ROIs by group.

DLI Group (n = 12)		Control Group (n = 12)		Analysis with <i>t</i> test (df = 22)		
<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>t</i>	<i>p</i>	<i>d</i>
Whole-brain FA	.28	.01	.30	.01	6.82	< .001*
<i>Hypothesis-driven Analysis</i>						
Caudate Nucleus	.145	.017	.150	.017	.69	.50
Putamen	.201	.014	.208	.012	1.38	.18
Nucleus Accumbens	.140	.027	.142	.016	.14	.89
Globus Pallidus	.238	.019	.261	.028	2.37	.03*
Thalamus	.228	.015	.246	.010	3.57	.002*
<i>Exploratory Analysis</i>						
Occipital Lobe	.204	.008	.222	.008	5.37	< .001*
Parietal Lobe	.281	.011	.302	.013	4.22	< .001*
Temporal Lobe	.265	.011	.284	.013	3.71	.001*
Frontal Lobe	.285	.011	.310	.011	5.49	< .001*
Hippocampus	.133	.011	.140	.011	1.47	.16