Published in final edited form as:

Lang Cogn Neurosci. 2016 ; 31(9): 1098–1114. doi:10.1080/23273798.2015.1089359.

Examining Procedural Learning and Corticostriatal Pathways for Individual Differences in Language: Testing Endophenotypes of *DRD2/ANKK1*

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Abstract

The aim of the study was to explore whether genetic variation in the dopaminergic system is associated with procedural learning and the corticostriatal pathways in individuals with developmental language impairment (DLI). We viewed these two systems as endophenotypes and hypothesized that they would be more sensitive indicators of genetic effects than the language phenotype itself. Thus, we genotyped two SNPs in the *DRD2/ANKK1* gene complex, and tested for their associations to the phenotype of DLI and the two endophenotypes. Results showed that individuals with DLI revealed poor procedural learning abilities and abnormal structures of the basal ganglia. Genetic variation in *DRD2/ANKK1* was associated with procedural learning abilities and with microstructural differences of the caudate nucleus. The association of the language phenotype with these *DRD2/ANKK1* polymorphisms was not significant, but the phenotype was significantly associated with the two endophenotypes. We suggest that procedural learning and the corticostriatal pathways could be used as effective endophenotypes to aid molecular genetic studies searching for genes predisposing to DLI.

Keywords

Developmental Language Impairment; *DRD2/ANKK1*; Endophenotype; Procedural Learning; Corticostriatal Pathways

Introduction

Developmental Language impairment (DLI) is a complex neurodevelopmental disorder that affects approximately 7–14% of school-aged children, depending on how nonverbal IQ is incorporated in the diagnosis (Tomblin et al., 1997). It is characterized by difficulty in acquiring language in the absence of other developmental or sensory impairments, and in the face of adequate language experience and educational opportunities (Leonard, 1998). Individuals with DLI represent a highly heterogeneous group, and deficits can occur across a wide range of linguistic domains, including morphology (Rice & Wexler, 1996), syntax (Nippold, Mansfield, Billow, & Tomblin, 2009), phonology (Shriberg, Tomblin, & McSweeney, 1999), and vocabulary (McGregor, Newman, Reilly, & Capone, 2002),

Genetic basis of DLI

A large body of empirical research has demonstrated that DLI is a multifactorial disorder involving both biological and environmental factors (see Leonard, 1998, for a review). Family, twin, and adoption studies indicate substantial heritability with h^2 up to 0.6 (Logan et al., 2011), suggesting both genetic and environmental contributions to individual differences in language. The past decade has seen numerous studies aimed at identifying different chromosomal locations (i.e., genetic loci) underlying language phenotypes, including some genome-wide linkage and association scans (Bartlett et al., 2002; Bartlett et al., 2004; Eicher, Powers, Miller, et al., 2013; Gialluisi et al., 2014; Luciano et al., 2013; Nudel et al., 2014; The SLI Consortium, 2002, 2004). Results from these studies are mixed; with findings replicated within, as opposed to between, research groups. Thus, a clear pattern of findings has yet to emerge.

In classic Mendelian genetics (i.e., single-gene disorders), there is a straightforward relationship between an organism's biology (i.e., genetic variation or genotype) and its observable characteristics or behaviour (i.e., phenotype). One of the difficulties in investigating a complex trait like language is that this degree of genetic certainty does not exist, and environmental factors should not be ignored. Most common complex traits are likely to be highly polygenic; that is, the genetic basis of complex traits consists of several relatively frequent ($> 5\%$) alleles (i.e., genetic variants) at a very large number of different genetic loci. Furthermore, many of these variants may be in systems that control levels of gene expression rather than lead to differences in protein products. Thus, the lack of overlap in findings from genome-wide linkage and association studies of language traits supports the emerging consensus that the genetic architecture of language phenotypes is typically due to a large number of loci with individually small allelic effects, and the language phenotype is more likely to arise from the cumulative effect of multiple gene-gene and gene-environment interactions (Lander & Schork, 1994). This complexity within the genome is amplified by the fact that genetic effects on language are indirect. Between genetic actions and language behaviors lie extensive causal networks that support language acquisition, such as neural development and function as well as emergent brain-based cognitive learning systems constantly interacting with the environment. Therefore, the cascade from genetics to a language phenotype, entailing multiple interactive biological, developmental, and environmental systems, is likely what contributes to individual differences in language ability in the general population (Tomblin & Christiansen, 2010).

What are endophenotypes?

In an attempt to reduce some of the complexity and heterogeneity associated with complex traits, investigators in the studies of neurobiological disorders (e.g., schizophrenia, bipolar disorder) have begun to consider the *intermediate systems* that serve to link distal genetic factors and complex behaviors. These intermediate systems are termed *endophenotypes*. In studies of complex behavioral traits, endophenotypes elucidate the mechanistic processes that connect variations in gene function to variation in behavior, serving as quantifiable entities that mediate the gene-behavior relationship. Endophenotypes can be measured at different levels of analysis. For example, at a cognitive level, poor procedural learning, which has been associated with poor grammatical ability, might be operationalized by the

implicit learning trajectory shown during a laboratory test. Alternatively a more fundamental level could be brain structures involving the corticostriatal or corticocerebellar pathways that give rise to procedural learning.

Neurocognitive and brain-based endophenotypes that index liability for DLI offer several important advantages in terms of identifying genes likely to be involved in the etiology of the disorder. First, because endophenotypes represent the intermediate systems between biology and behavior, they should relate more directly to the underlying genetic etiology of the disorder. Second, the number of genes required to produce variations in this system is hypothesized to be fewer than those involved in the overall diagnostic entity (Gottesman & Gould, 2003). Both have the potential to add power to genetic analyses, thus enabling the search for genetic susceptibility loci. Finally, employing an endophenotype allows for a mechanistic process-based approach to the investigation of individual differences in language development and disorders.

To summarize, endophenotypes not only provide insight into the cascade of action leading from genes to the language phenotype, but they should also be more powerful in genetic analyses due to their hypothetical proximity to genes in the pathway from genes to language behaviors (Gould & Gottesman, 2006).

Endophenotypes for DLI

The use of endophenotypes in the study of neurobiological disorders is not novel (Flint & Munafo, 2007; Glahn et al., 2003; Hasler et al., 2006). Within the field of DLI, phonological working memory has been studied intensively as an endophenotype for DLI via the non-word repetition test (Bishop, 2006). Consistent with the view that endophenotypes may be more robust for discovery of gene-behavior development, the majority of genetic loci associated with DLI have also been linked to phonological working memory (Falcato et al., 2008; Newbury et al., 2009; The SLI Consortium, 2002, 2004; Vernes et al., 2008). Working memory capacity is considered as an emergent property of complex interactions among three specialized brain areas, including the corticostriatal pathways, the corticohippocampal pathways, and the posterior cortex (see Hazy, Frank, & O'Reilly, 2006, for details). In other words, there is substantial overlap between the neural networks supporting procedural learning and working memory. In the current study, we are more interested in procedural learning because of its close relationship with *DRD2/ANKK1* (e.g., Klein et al., 2007; Jocham et al., 2009). Thus, we proposed procedural learning and the corticostriatal pathways as two potential endophenotypes that have promise in revealing genetically-influenced neurocognitive pathways underlying individual differences in language. It should be noted that procedural learning and the corticostriatal pathways are not independent; instead, they represent different levels of analysis of the intermediate systems between genes and language behavior.

Procedural learning as a cognitive endophenotype for DLI—Procedural memory is one of several non-declarative memory systems underlying the encoding, storage, and retrieval of habits and skills (Gabrieli, 1998; Squire, 2004). Learning through procedural memory (i.e., procedural learning) is gradual, with the acquisition and storage of skills based

upon repetition, practice, and incremental changes in behavior. Procedural learning is usually associated with the acquisition of rule- or pattern-based skills that follow a structured sequence, such as riding a bike or playing an instrument. Once acquired, procedural skills can be executed quickly and automatically, without direct access to consciousness (Schacter & Tulving, 1994). For this reason, procedural learning is also referred to as a type of implicit learning.

Procedural learning and language. Procedural learning has been proposed as one of the fundamental learning mechanisms underlying language acquisition, grammatical acquisition in particular (Gupta & Dell, 1999; Ullman, 2001, 2004). Procedural learning is a slow and gradual process, particularly suited to encoding sequentially and statistically structured information (Conway & Pisoni, 2008; Squire & Zola, 1996). Likewise, language acquisition is an implicit and incremental process, wherein repetitive exposures to language are important for learners to track statistical structures of language (Kidd, 2012; Saffran, Aslin, & Newport, 1996). In addition, given the sequential nature of language processing, language learners need to figure out the rules or patterns underlying language (Christiansen, Conway, & Onnis 2012; Conway & Pisoni, 2008). In the literature, procedural learning has been simulated within the connectionist models to demonstrate that the ability to encode and manipulate sequentially or statistically structured information can explain the emergence of many rule-like behaviors observed in language, such as phonology (e.g., the sequencing of sounds), morphology (e.g., the regular past tense *-ed*), and syntax (e.g., the combining of words to form sentences)(see Westermann, Ruh, & Plunkett, 2009, for a review).

Procedural Learning and DLI. It is now nearly a decade since Ullman and Pierpont (2005) proposed the Procedural Deficit Hypothesis (PDH) of developmental language disorders. This stems from observations that individuals with DLI are impaired in their acquisition of rule- or pattern-based components of language. According to the PDH, a fundamental, but not exclusive, cause of DLI can be attributed to impaired procedural memory. The PDH has received considerable attention because it accounts for a wide array of linguistic and cognitive impairments that are characteristic of DLI, at the neural level.

The PDH has been tested and supported by several studies, showing that variance in language abilities is associated with performance on different domains of procedural memory, including the motor domain (as shown in the pursuit rotor task and the serial reaction time (SRT) task), the cognitive domain (as shown in the weather prediction task), and the linguistic domain (as shown in the artificial grammar learning task) (Adi-Japha, Strulovich-Schwartz, & Julius, 2011; Evans, Saffran, & Robe-Torres, 2009; Kemeny & Lukacs, 2010; Lee & Tomblin, 2014; Lum, Conti-Ramsden, Page, & Ullman, 2012; Tomblin, Mainela-Arnold, & Zhang, 2007). However, other studies have not replicated these findings, particularly those related to poor learning in the SRT task (Hedenius et al., 2011; Gabriel et al., 2011; Mayor-Dubois et al., 2012). Gabriel et al. (2011) found that children with DLI were able to learn sequential information in the SRT task as well as the comparison peers. However, they did a follow-up study with increased complexity of sequences, showing a significant learning effect between the language-impaired group and the comparison group (Gabriel et al., 2013). This suggests that complexity of the to-be-

learned sequence affects procedural learning in individuals with DLI. In addition, Hedenius et al. (2011) found comparable sequential learning in the SRT task between children with and without DLI. However, poor consolidation of sequence learning was found in the DLI group only, indicating a possible lack of learning saturation.

In sum, although findings concerning poor procedural learning in individuals with DLI are not uniform at this point, the collective evidence is supportive of depressed procedural learning being associated with DLI.

Corticostriatal pathways as a neuroanatomical endophenotype for DLI—

In addition to procedural learning, the corticostriatal pathways are the other potential endophenotype we propose as providing quantifiable characteristics that reflect genetic liability for DLI. The corticostriatal pathways are re-entrant loops connecting the basal ganglia with the cerebral cortex in the brain, wherein the basal ganglia play an important role in exerting modulatory influence on cortical representations, making decisions about which information should be returned to the cortex (Alexander & Crutcher, 1990; Atallah et al., 2004; Frank et al., 2001).

Corticostriatal pathways and language. Initial evidence for the role of the corticostriatal pathways in language came from patient studies with neurodegenerative basal ganglia disorders, for example, Parkinson's disease or Huntington's disease (De Diego-Balaguer et al., 2008; Teichmann et al., 2006, 2008). More recent brain imaging studies indicate involvement of the corticostriatal pathways in various aspects of language, including phonological processing (Tettamanti et al., 2005), syntactic processing (Chan et al., 2013), and semantic processing (Crosson, Benjamin, & Levy, 2007). Collectively, these studies suggest a significant role for the corticostriatal pathways in rule- or pattern-based computational processes that cut across a range of linguistic domains. In addition, computational modeling indicates that language is supported by distributed neural networks similar to those found in the corticostriatal loops, instead of specific cortical regions as proposed by the traditional Broca-Wernicke model of language (Blank et al., 2002; Lieberman, 2002; Mesulam, 1990).

Corticostriatal pathways and DLI. Several researchers have suggested the corticostriatal pathways as being crucial to DLI given their role in procedural learning (Ullman & Pierpont, 2005; Lee & Tomblin, 2014) and in reinforcement learning (Lee & Tomblin, 2012); however, few brain-imaging studies have been conducted to directly examine the corticostriatal pathways in individuals with DLI. In functional neuroimaging studies, Im et al. (2007) showed abnormalities in children with DLI on positron emission tomography (PET) scans, and most of the abnormal regions were confined to the corticostriatal pathways, including the thalamus, the basal ganglia, and the frontal lobes. Ors et al. (2005) and Hwang et al. (2006) used single photon emission computed tomography (SPECT) to examine brain functions in individuals with and without DLI, showing a decreased perfusion in the basal ganglia as well as other cortical regions (e.g., the right inferior parietal lobe), suggesting that abnormal development of the corticostriatal pathways should be considered in DLI. In terms of structural neuroimaging studies, individuals with DLI showed 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), the putamen (Lee, Nopoulos, & Tomblin, 2013; Watkins et al., 2002), the nucleus accumbens, and the right globus pallidus (Lee et al., 2013), indicating a role of the basal ganglia in the etiology of DLI. As far as we know, no studies have examined the structural and functional connectivity of the corticostriatal pathways in DLI.

The dopamine hypothesis: Linking DLI, procedural learning, and the corticostriatal pathways

Dopamine neurotransmitters playing a role in cognitive learning—Activity within the corticostriatal pathways is dynamically modulated by expression of the neurotransmitter dopamine (DA), which acts in gating the flow of information to and from the cortex via direct excitatory pathways (a.k.a. the “Go” pathway) and indirect inhibitory pathways (a.k.a. the “No Go” pathways). Several key findings support the notion that dopaminergic projections to the corticostriatal pathways influence cognitive function important for learning, including procedural learning and reinforcement learning (see Cohen, 2008, for a review). First, the close associations between abnormal dopamine receptor signaling and procedural learning and reinforcement learning behaviors have been implicated in several neuropsychiatric disorders, such as Attention-Deficit/Hyperactivity Disorder (ADHD) and Parkinson’s disease (Frank, Santamaria et al., 2007; Surmeier, Graves, & Shen, 2014). Second, studies in both animals and humans indicate that altering DA activity via pharmacological manipulation (e.g., via DA agonists and/or antagonists) results in changes in procedural learning behaviors (de Vries, Ute, Zwitserlood, Szymanski, & Knecht, 2010; Wise, 2004). Finally, genetic variation in dopaminergic activity has been linked to individual differences in reinforcement learning (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007).

DRD2/ANKK1: Gene complex regulating dopamine signaling in the brain—The *DRD2/ANKK1* gene complex, located on chromosome 11q22–23, influences the density and synthesis of dopamine receptors in the corticostriatal pathways (Lee et al., 2011; Neville, Johnstone, & Walton, 2004). Recent studies have shown that several single nucleotide polymorphisms (SNPs) within the *DRD2/ANKK1* gene complex are associated with cognitive learning behaviors, including procedural learning (Huertas, Bühler, Echeverry-Alzate, Giménez, & López-Moreno, 2012; Jocham et al., 2009; Klein et al., 2007) and language ability (Beaver, DeLisi, Vaughn, & Wright, 2010; Eicher, Powers, Cho, et al., 2013; Wong, Ettlinger, & Zheng, 2013). Beaver et al. (2010) reported a significant association between the Taq1 polymorphism (also known as rs1800497 (C/T)) in *DRD2/ANKK1* and performance on an abbreviated form of the Peabody Picture Vocabulary Test-Revised (PPVT-R; Dunn & Dunn, 1981). The minor A1 allele (rs1800497(T)) has fewer DA receptor binding sites, and is thereby postulated to decrease DA activity in the brain (Thompson et al., 1997). More recently, Wong et al. (2013) reported an association between this locus (i.e., rs1800497) and grammar learning. In addition, Eicher, Powers, Cho, et al. (2013) found an association between language impairment and a haplotype block stretching across *DRD2/ANKK1*, that included SNPs rs1800497 and rs2734849.

Although limited, these findings suggest the hypothesis for an association between dopamine-related genetic variation and individual differences in language.

The Current Study

The aim of the current study was to employ a multiple systems framework to examine the distal and proximal relationships among the *DRD2/ANKK1* genotype, the neurocognitive and brain-based endophenotypes, and the language phenotype, as illustrated in Figure 1. It is clear that it would be an oversimplification to suggest that Figure 1 could explain the systematic interactions among phenotype, endophenotype, genotype, and environment, and we did not aim to disentangle the complexity of these relationships in the current study. Instead, we think it is important to raise the possibility that the endophenotype approach is a feasible and promising method to study the genetics of individual differences in language. It should also be noted that we did not employ the genome-wide association analysis (GWAS) approach (i.e., an agnostic, large-scale approach to genetic investigation). This is an exploratory study with the hypothesis-driven testing of two targeted genetic loci in *DRD2/ANKK1*. Genetic data, brain-imaging data, and procedural learning data were collected from the same sample selected for language ability. This complexity of data collection led to small sample size in the current study.

Three specific questions were asked: 1) regarding the distal relationship between genotype and phenotype, is genetic variation within the candidate gene complex *DRD2/ANKK1* directly associated with language status? 2) Regarding the proximal relationship between phenotype and endophenotypes, do individuals with and without DLI show significant difference in procedural learning abilities and the subcortical structures of the corticostriatal pathways, and 3) regarding the proximal relationship between genotype and endophenotypes, does genetic variation within the candidate gene complex *DRD2/ANKK1* contribute to individual differences in procedural learning and the subcortical structures of the corticostriatal pathways?

We hypothesize that the proximal relationships between endophenotypes and phenotype and between genotype and endophenotypes will be stronger than the distal relationship between genotype and phenotype. Thus, the strength of the proximal associations of either language status and genetic variation in *DRD2/ANKK1* will be stronger with performance on the procedural learning tasks or structural differences in the subcortical components of the corticostriatal pathways, than will be the more distal relationship between genes and language. This does not rule out the presence of a gene-language relationship, however. Due to a relatively small sample size in this study, it is likely that we did not have sufficient power to test this relationship. Evidence for such a relationship between genetic variation in *DRD2/ANKK1* and group differences in language have been shown in Eicher, Power, Cho et al. (2013) where greater power was available. Indeed, such null findings highlight the value of the endophenotype approach to studying genetics of complex traits such as language.

Methods

Participants

Participants were originally ascertained as part of an epidemiological study on the prevalence of language disorders in kindergarten (Tomblin, et al., 1997). Methods for assessing language abilities and diagnosing DLI in this sample have been described extensively elsewhere (Tomblin & Nippold, 2014). A subset of participants were followed longitudinally, through the school years and into adulthood (Tomblin, 2008, 2010). From this sample, two groups of young adults (age: 19–25 years) were recruited for the current study: one with persistent poor language abilities (i.e., the DLI group; $n=21$) and the other with typical language abilities (i.e., the comparison group; $n=20$). All participants for this study were Caucasian.

To assess their current nonverbal IQ and language skills for the purpose of group status confirmation, participants completed three language assessments and two performance IQ tests. Details of these tests were described in Lee and Tomblin (2012). Briefly, these tasks comprised the Peabody Picture Vocabulary Test, Fourth Edition (PPVT-4; Dunn & Dunn, 2007), the Token Test (Morice & McNicol, 1985), and Word Derivations (Hammill et al., 2007) as measures of language ability, and the Block Design and Matrix Reasoning subscales of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) as measures of nonverbal IQ. Standard scores were combined to form composite measures in each domain. Individuals with a history of DLI, and a composite language score -1.25 standard deviations (SD) below the mean, were classified as DLI. Those with scores greater than -1.25 SD were assigned to the comparison group. All participants reported negative for a history of ADHD or autism spectrum disorders (ASD). Table 1 summarizes the current demographic information and measure scores for the participants. It should be noted that participants with DLI were not required to have nonverbal IQ above 85 (i.e., the traditional diagnostic cut-off for Specific Language Impairment (SLI)) for two reasons. First, longitudinal studies show there is no significant difference in the patterns of language deficits between language-impaired children with nonverbal IQ above and below 85 (Tomblin & Zhang, 1999). Other longitudinal research found a significant fall of over 20 nonverbal IQ points from kindergarten to adolescence in individuals with SLI. Both studies challenge the discrepancy-based approach to SLI research (Botting, 2005 and Rice et al., 2004). Therefore, we think that matching IQ scores will end up having two unrepresentative groups: either the DLI group will have higher nonverbal IQs than the population with DLI, or the healthy comparison group will have nonverbal IQs below normative expectations (Dennis et al., 2009).

Endophenotype Measures I: Procedural Learning Tasks

Participants completed three procedural learning tasks across different domains of procedural memory: the pursuit rotor task (i.e., the motor domain), the SRT task (i.e., the motor-perceptual domain), and the weather prediction task (i.e., the cognitive domain). Detailed descriptions of the materials and procedures for each of these tasks were provided in Lee & Tomblin (2014). Table 2 gives a summary of these measures.

Endophenotype Measures II: Corticostriatal Pathways

A subgroup of participants (DLI: $n=11$; comparison: $n=10$) also took part in a magnetic resonance imaging (MRI) brain scan. The time duration between procedural learning measures and brain measures was approximately six months. Both anatomical MRI and diffusion tensor imaging (DTI) were used to examine the subcortical structures of the corticostriatal pathways, including the caudate nucleus, the putamen, the globus pallidus, the nucleus accumbens, and the thalamus. Compared to conventional MRI, which measures tissue volumes of anatomical structures in cubic centimeters, DTI measures motions of water molecules in the brain (i.e., brain water diffusivity). The fractional anisotropy (FA) value is a widely used measure to quantify diffusion properties, describing the directional preference of diffusion processes in the brain, ranging from 0 (i.e., isotropic) to 1 (anisotropic) (Alexander, Lee, Lazar, & Field, 2007). FA is a sensitive biomarker of subtle alterations in the tissue microstructure, and the higher the FA value the more structured the region. These two neuroimaging techniques provide complementary information of macrostructural (i.e., regional volumes) and microstructural changes (i.e., FA values) within the regions of interest (ROIs).

Details of image acquisitions, pre-processing, and processing were described in Lee et al. (2013). The anatomical scans were processed using BRAINS2 (Magnotta et al., 2002). 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 ROI for the caudate, the putamen, the globus pallidus, the nucleus accumbens, and the thalamus in subject space (Powell et al., 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 was calculated by a summation of gray matter and white matter. Given the significant difference in intracranial volume (ICV) between the DLI group and the comparison group, $t(19)=3.83$, $p=.001$, each participant's absolute volumes were transformed into relative volumes, obtained by dividing absolute volumes by his/her ICV and multiplying by 100. FA values were obtained for the subcortical structures for all subjects utilizing Talairach parameters (Collins et al., 1994 and Andreasen et al., 1996). These regions contained both gray matter and white matter. Given that the mean FA for each ROI represents the average FA within the defined region, FA for gray and white matter was not calculated separately.

Genotyping and Quality Control Measures

Samples—DNA was obtained from blood, buccal swabs, and saliva, and processed using standard protocols. Briefly, DNA was extracted from buccal swabs using procedures described in Richards et al. (1993), and from whole blood using a modified version of Qiagen's DNA Blood Maxi kit (Qiagen, Inc., Valencia, CA). Samples derived from saliva

were processed using Oragene's standard 0.5mL and 4mL protocols (DNA Genotek, Ontario, Canada).

Genotyping—Two SNPs in *DRD2/ANKK1*, rs1800497 and rs2734849, were selected on the basis of previous studies linking the Taq1 polymorphism and cognition (e.g., Beaver et al., 2010; Wong et al., 2013) and on the basis of findings by Eicher, Power, Cho et al. (2013). The majority of samples (DLI: n=13; Comparison: n=19) were genotyped on the Sequenom platform (San Diego, CA) at the Yale Center for Genome Analysis (Orange, CT), following the manufacturer's guidelines. The remainder (DLI: n=9) was genotyped at the University of Iowa using Taqman Pre-designed Genotyping Assays under standard reaction conditions (Applied Biosystems, Foster City, CA). Allelic variation was determined via the Sequence Detection Systems 2.2 software (Applied Biosystems). Genotype data was uploaded into a Progeny database (Progeny Software, LLC, South Bend, IN) and integrated with phenotypic data using Microsoft Access.

Quality Control—Heterozygosity can be indicative of sample contamination or of inbreeding. The observed heterozygosity of markers was .63 and .66, compared to .50 and .49 expected. These differences were not statistically significant ($p < .05$). Both SNPs were in Hardy-Weinburg Equilibrium ($p < 1 \times 10^{-6}$).

Statistical Analyses—Linkage disequilibrium within the *DRD2/ANKK1* locus was then used to determine which of the two alleles in rs2734849 should be denoted as A1 vs. A2 (The International HapMap Project, <http://www.hapmap.org>). As with rs1800497, participants were then classified into two groups based on the presence of the A1 allele (i.e., the A1/A1 and A1/A2 group, and the A2/A2 group). Only one participant was homozygous for the A1 allele at this locus, which is consistent with previous reports (Beaver et al., 2010; Wong et al., 2013). Table 3 summarizes the sample means, standard deviations, and genotype distribution of participants.

Single marker analysis was performed under the dominant model (e.g., the A1/- group vs. the A2/A2 group) on the basis of previous literature on rs1800497, which shows that, in contrast to carriers of the A2 allele, carriers of the A1 allele have fewer receptor binding sites (Berman & Noble, 1995; Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991) and exhibit reduced dopamine activity in the central nervous system (Berman & Noble, 1995). Because rs1800497 and rs2734849 are in high linkage disequilibrium, we hypothesized that carriers of the A1 allele at both loci would show poorer performance on the endophenotypic measures.

Chi-squared analyses were used to examine the relationship between the two candidate SNPs in *DRD2/ANKK1* and the phenotype of language status as an overt phenotype (i.e., individuals were classified according to presence or absence of DLI). In addition, Independent-samples *t*-tests were carried out to examine the proximal relationship of the genetic variation in *DRD2/ANKK1* with the proposed endophenotypes (i.e., procedural learning and subcortical structures of the corticostriatal pathways).

Results

Relationship between Genotype and Phenotype

In the first analysis, we were interested in whether the two SNPs in *DRD2/ANKK1* (i.e., rs1800497 and rs2734849) were associated with group differences in language status. Chi-squared analyses showed no statistically significant relationship between genotype and phenotype for either SNP: rs1800497, $\chi^2=1.12$, $p=.57$; rs2734849, $\chi^2=2.19$, $p=.33$. In other words, the distal relationship between these genetic polymorphisms and individual differences in language was not demonstrated.

Relationship between Phenotype and Endophenotypes

In the following analyses, we used language status (i.e., either the DLI group or the comparison group) as the phenotype of interest. Two endophenotypes are: 1) procedural learning performance on the pursuit rotor task, the SRT task, and the weather prediction task, and 2) volumes and FA values of the subcortical structures of the corticostriatal pathways.

Individual Differences in Language and Procedural Learning—A multivariate analysis of variance (MANOVA) was performed to examine the effect of language on procedural learning, with language status as the dichotomous independent variable and performance on the SRT task, the pursuit rotor task, and the weather prediction task as the continuous dependent variables¹. Results showed that the language status has a significant effect on procedural learning performance as a whole, $F(3,36)=6.01$, $p<.002$. To determine the independence of the three procedural learning tasks and, therefore, the necessity of conducting multiple independent t -tests, a correlation analysis was conducted¹. This showed no significant inter-correlations among the three procedural learning tasks ($ps>.50$). In other words, it is likely that performance on the three procedural learning tasks (i.e., the pursuit rotor task, the SRT task, the weather prediction task) represents different domains of procedural learning abilities. As a result, we continued to examine the effect of language status on each procedural learning task.

Figure 2 illustrates the results of three procedural learning tasks between the two groups. In the pursuit rotor task, participants use a stylus to follow a moving target on a circular path on a computer screen. With time, they typically improve at following the target, as reflected by the target on time (TOT), which increases. Procedural learning is reflected by changes in mean percentage TOT across the six trial blocks. Data from one of the participants in the DLI group were missing due to technical problems. A 6 (Block: 1–6) x 2 (Group: DLI, Comparison) ANOVA revealed a significant main effect of Block, $F(5, 190)=27.63$, $p<.001$, and a significant Group by Block interaction, $F(5, 190)=2.48$, $p=.03$. The Group main effect was not significant, $F(1, 38)<.001$, $p=.99$. Post-hoc analyses for the interaction effect

¹Definitions of variables used in MANOVA and correlation analysis were described below. The index of performance on the SRT task: Difference of median reaction times between random blocks and pattern blocks. The index of performance on the pursuit rotor task: Difference of TOT between the first and the last block. The index of performance on the WP task: Difference of percent accuracy between the first and the last block.

showed that the DLI group did not reveal reliable changes across blocks, $F(5, 120)=.63$, $p=.681$, whereas the comparison group did, $F(5, 108)=2.47$, $p=.037$.

In the SRT task, procedural learning is reflected by the reaction time discrepancy between random blocks and pattern blocks (i.e., the learning effect). Independent samples t -test showed that the learning effect was not significantly different between the two groups in our study, $t(39)=-.13$, $p=.90$.

In the weather prediction task, participants make decisions to predict rain or shine on the basis of four distinct cue cards presented either individually or in combinations of up to three cards, and received feedback on their decisions. Procedural learning is reflected by significant improvement of response accuracy across blocks. A 5 (Block: 1–5) $\times$ 2 (Group: DLI, Comparison) ANOVA was performed to see whether there was a significant difference in response accuracy between the DLI group and the comparison group. Results showed a significant Group effect, $F(1, 39)=11.54$, $p=.002$, and Block effect, $F(4, 156)=3.10$, $p=.02$. The interaction effect was not significant, $F(4, 156)=.85$, $p=.50$. One-sample t -tests were employed to determine at which block procedural learning began (i.e., performance on response accuracy above chance levels) in each group. The comparison group showed significant learning effect, beginning at the first block ($p<.024$). In contrast, the DLI group did not show significant above-chance learning until the fourth block.

In sum, the DLI group showed poorer performance than the comparison group on the pursuit rotor task and the weather prediction task, but not on the SRT task. This finding indicates inefficient functioning of individuals with DLI in procedural learning across the motor and cognitive domains.

Individual Differences in Language and Subcortical Structures of Corticostriatal Pathways

Table 6 illustrates descriptive statistics for differences in subcortical structures of the corticostriatal pathways between the two groups. Results of anatomical MRI showed that the DLI group was significantly *larger* than the comparison group in the relative volumes of the whole putamen, $t(19)=2.53$, $p=.021$, of the right globus pallidus, $t(19)=3.00$, $p=.007$, and of the right thalamus, $t(19)=2.14$, $p=.045$. The difference in the relative volume of the nucleus accumbens approached significance, $t(19)=2.02$, $p=.057$.

In terms of the DTI findings, the DLI group showed significantly *lower* FA values than the comparison group in the globus pallidus, $t(19)=2.70$, $p=.014$, and in the thalamus, $t(19)=2.82$, $p=.011$. Between-group differences in the FA values in the right putamen approached significance, $t(19)=2.02$, $p=.058$. However, the DLI group also had significantly lower whole-brain FA value than the comparison group, $t(19)=5.89$, $p<.001$. We therefore performed an ANCOVA analysis with the whole-brain FA value as covariate in order to determine whether these FA abnormalities were region-specific (i.e., proportionally abnormal FA values in the ROIs after correction of the whole-brain FA value). After the whole-brain FA value was controlled, results were non-significant. This suggests that the microstructural abnormality seen in the brains of individuals with DLI is diffuse, affecting almost every region of the brain.

Relationship between Genotype and Endophenotypes

We have proposed procedural learning and the corticostriatal pathways as two endophenotypes mediating the biological pathway between genetic variation in *DRD2/ANKK1* and language ability. Therefore, the following analyses examined the association between 1) two SNPs in *DRD2/ANKK1* (i.e., rs2734849 and rs1800497) and procedural learning, and 2) the same two SNPs and the subcortical structures of the corticostriatal pathways. We assumed a dominant model because of previous findings that the A1 allele is linked to with poorer performance in tests of language and cognition (Beaver et al., 2010; Eicher, Powers, Cho, et al., 2013; Wong et al., 2013).

Genetic Variation in *DRD2/ANKK1* and Procedural Learning—Three procedural learning tasks were used to index different domains of procedural memory, including the pursuit rotor task (i.e., the motor domain), the SRT task (i.e., the motor-perceptual domain), and the weather prediction task (i.e., the cognitive domain). Descriptive statistics are shown in Table 4. Independent-samples *t*-tests revealed no significant association between rs2734849 and the SRT task, $t(39)=-.67$, $p=.51$, the pursuit rotor task, $t(38)=-.93$, $p=.36$, or the weather prediction task, $t(39)=-1.08$, $p=.29$. In contrast, a significant association was found between rs1800497 and the pursuit rotor task, $t(38)=2.10$, $p=.04$. These results suggest that allelic variation in *DRD2/ANKK1* affects motor-based procedural learning, as indexed on the pursuit rotor task.

Genetic Variation in *DRD2/ANKK1* and Subcortical Structures of Corticostriatal Pathways—The next set of analyses examined the relationship between allelic variation in *DRD2/ANKK1* and subcortical structures in the corticostriatal pathways. Again, we assumed a dominant model (see Table 5 for descriptive statistics). We found that rs2734849 was significantly associated with the relative volume of the left nucleus accumbens, $t(19)=2.35$, $p=.03$, while rs1800497 was not significantly associated with volumetric differences in any of the subcortical structures we investigated ($ps > .18$). In terms of FA values, we did not find significant associations between rs2734849 and FA values in any of ROIs, but we did find significant associations between rs1800497 and FA values in the caudate nucleus as a whole, $F(1,19)=7.299$, $p=.014$. These results suggest that allelic variation in *DRD2/ANKK1* affects the microstructure of the basal ganglia, the caudate nucleus in particular.

Discussion

Summary of the Current Study

The aim of the current study was to employ an endophenotype approach to the genetic investigation of language development and disorders. We were particularly interested in the *DRD2/ANKK1* gene complex, the genetic variation at SNPs rs2734849 and rs1800497 in particular, because of their known association with individual differences in procedural learning and language ability (e.g., Beaver et al., 2010; Eicher, Power, Cho et al., 2013; Eicher, Powers, Millers et al., 2013; Wong et al., 2012, 2013). It should be noted that this is an exploratory study with a relatively small sample size for the detection of genetic associations. Although the findings are consistent with our expectations, they are

preliminary and await replication with larger samples before further interpretations can be made.

To summarize the results, first, genetic variation in *DRD2/ANKK1* was not directly associated with individual differences in language ability. In other words, the distal relationship between genotype and phenotype appeared to be relatively weak, and thus within the power provided by the current study, we were not able to show such a relationship. Another study has demonstrated this association using a population-based sample (n=5579), with orders of magnitude larger than ours (Eicher, Powers, Cho, et al., 2013).

Second, we showed that individuals with DLI revealed structural abnormality in the brain, in particular the abnormally increased volumes of multiple subcortical regions of the corticostriatal pathways. In addition, their language performance was related to their procedural learning abilities. In other words, the proximal relationship between phenotype and endophenotypes was demonstrated. It is interesting to note that DLI is associated with *increased* volumes of the subcortical regions, indicating a role of poor synaptic pruning in individual differences in language development (see also Nation, 2014).

Finally, we showed that allelic variation in *DRD2/ANKK1* affects the motor domain of procedural memory, as well as the macrostructure and the microstructure of the basal ganglia. Again, a proximal association was revealed between the *DRD2/ANKK1* genotype and the neurocognitive and brain-based endophenotypes.

We found that rs1800497 was specifically associated with performance on procedural learning in the motor domain (as indexed by the pursuit rotor task), as well as with the FA values in the caudate nucleus. This finding is consistent with recent research showing that carriers of the A1 ‘risk’ allele perform more poorly on motor learning tasks than individuals homozygous for the A2 allele (Pearson-Fuhrhop, Minton, Acevedo, Shahbaba, & Cramer, 2013). Although a significant association between rs1800497 and the caudate nucleus volume has been found in the literature (e.g., Bartres-Faz et al., 2002), no studies have been conducted pertaining to the association between rs1800497 and the microstructure of the caudate nucleus (e.g., FA values in the caudate nucleus). At this point, we cannot explain why rs1800497 did not associate with caudate nucleus-dependent procedural learning abilities in the current study (e.g., performance on the SRT task or the weather prediction task). One of the possibilities is that FA is a measure of brain microstructure, and thus it does not reveal the functioning of the caudate nucleus directly.

With regard to rs2734849, we found a significant association between this marker and the relative volumes of the left nucleus accumbens. However, it was not significantly associated with any procedural learning abilities. One of the possible reasons for that is the nucleus accumbens is known for its role in the process of reward and reinforcement (Salamone & Correa, 2002), but none of our procedural learning tasks directly involved the component of reward or reinforcement.

Given the exploratory nature of the current study, we did not correct for multiple tests. And an obvious limitation to this study is the size of the sample. It should be noted that large

sample sets are not typical in brain imaging studies. In part, this is because the technology required to undertake this line of research (i.e., DTI, low-cost genotyping...etc.) has not existed until recently. It is also because this type of cross-disciplinary research is intrinsically difficult, requiring a high level of conceptual knowledge derived from a number of disparate fields (i.e., linguistics, psychology, and computer sciences) combined with technical skills in a number of different experimental paradigms (i.e., behavioural, neuroanatomical, and genetic). Despite the small sample size, nominally significant associations were found, and the number of subjects is indeed comparable to that reported in previous studies.

Collectively, findings from this study confirm our hypothesis, indicating that procedural learning and the corticostriatal pathways could be used as effective endophenotypes to aid molecular genetic studies searching for genes predisposing to DLI. Furthermore, our findings also suggest that changes in dopamine function may lead to changes in both behavioural and neuroanatomical phenotypes in individuals with DLI, although the neurochemical mechanisms underlying dopamine-dependent learning behaviors in the DLI population are not yet well understood (Wong et al., 2012). This is the first empirical study to demonstrate the link between genes, brain, and learning behavior in the same sample selected for language ability.

Endophenotype Approach to Developmental Language Disorders

In the current study, we proposed procedural learning ability and the corticostriatal pathways as two possible endophenotypes for DLI. That procedural learning is important for language acquisition and processing is not a new concept (Christiansen et al., 2012; Gupta & Dell, 1999; Ullman, 2004). Previous studies have shown poor learning of rules and patterns over time in individuals with DLI, including the SRT and the weather prediction task (e.g., Kemeny & Lukacs, 2009; Lee & Tomblin, 2014; Lum et al., 2012; Tomblin et al., 2007). Based on this research, several researchers have implicated a role of the corticostriatal pathways in the etiology of DLI (Lee & Tomblin, 2012, 2014; Lum et al., 2012; Ullman & Pierpont, 2005). This hypothesis has not been directly tested in the brains of people with DLI until recently. Lee et al. (2013) did a study to examine the subcortical structures of the corticostriatal pathways in a small sample of individuals with DLI. They found that individuals with DLI did show abnormalities in the putamen, the nucleus accumbens, the globus pallidus, and the thalamus at either the macrostructural or the microstructural level. However, to the best of our knowledge, linking evidence from procedural learning to empirical data indexing neurobiological *and* genetic differences in the idiopathy of DLI is novel.

Thus, in the current study, we attempted to integrate the procedural learning findings (Lee & Tomblin, 2014), the brain imaging findings (Lee et al., 2013), and novel genetic data into a multifactorial model of DLI, with the aim to improve our understanding of the pathways from gene to brain to behavior underlying individual differences in language. These results are exploratory, and await replication in larger samples. Given the extant literature on the association between *DRD2/ANKK1* and corticostriatal pathways in both humans and animals (Jönsson et al., 1999; Nelson et al., 2012), a better understanding of the

corticostriatal pathways in individuals with DLI may shed light on fundamental processes that are disrupted as a consequence of the inherited genetic susceptibility.

DRD2/ANKK1: Important for language, but not THE gene for language

Given this study's positive findings, it would be convenient to describe *DRD2/ANKK1* as a gene *for* language. However, as pointed out in the Introduction, all complex traits/disorders have a highly polygenic component to their variance. Although DLI tends to run in families and is considered highly heritable (Logan et al., 2011), only rarely does it follow a monogenic pattern of inheritance (Newbury & Monaco, 2010). This suggests that no one single major gene is likely involved in the aetiology of the disorder.

Indeed, findings from our study do not support the notion of a simple linear relationship between genes and behaviour: associations between genetic variation in *DRD2/ANKK1* and language status as an overt phenotype were null. One possible reason for this is that we were simply underpowered to detect such an association. In the main, genes associated with DLI are characterized by small *p*-values that would not stand the magnitude of significance currently expected for GWAS research. And studies that have demonstrated a straightforward relationship between genotype and language phenotypes have the order of magnitude larger than ours (e.g., Eicher, Powers, Cho et al., 2013; Eicher, Powers, Millers et al., 2013).

The fact that there is very little overlap in findings from genome-wide linkage and association studies of DLI admits of two explanations to why *DRD2/ANKK1* is not *the* gene for language. On the one hand, studies to date suggest that there may be numerous genetic variants in multiple chromosomal loci contributing to individual differences in language. Therefore, if *DRD2/ANKK1* is relevant for language development, this is alongside a collection of other genes, which cumulatively affects the manifestation and severity of the phenotype. Since intermediate phenotypes are more tractable to genetic mapping, we assume they represent an important tool in this discovery process. On the other hand, the importance of environmental influences for individual differences in language is not well understood. The relationship between genotype and phenotype is complex, and it is plausible that a single genotype may produce different phenotypes and vice versa, depending on the environment wherein language acquisition and learning occur over time. Although not a focus of the current study, the impact of the interplay between genetic and environmental factors on language development may offer a window of opportunity for early intervention with at-risk language learners before severe long-term consequences occur.

Endophenotype approach: Shedding light on the comorbidity between DLI and ADHD

Comorbid behavioral problems are common in children with DLI (Tomblin, Zhang, Buckwalter, & Catts, 2000), and one such example is ADHD. A recent population-based study estimated that having DLI increases the risk for ADHD threefold (Mueller & Tomblin, 2012; see also Sciberras et al., 2014). One possible explanation for this is that the comorbidity between the two disorders reflects shared etiology or risk factors. Studies on ADHD have shown aberrant dopaminergic neurotransmission as one of the underlying pathological mechanisms (Coccaro et al., 2007). Clinically, psychostimulant drugs are

commonly used in ADHD treatments to target dopamine reuptake in the brain (Roman et al., 2002). Our current findings that dopamine function may play an important role in language development are in line with the dopamine hypothesis of ADHD, and therefore, have broader clinical implications for explaining the high comorbidity of DLI with ADHD. In addition, the endophenotype approach may help elucidate different pathophysiological mechanisms underlying similar symptoms in DLI and ADHD. The value of the endophenotype approach for DLI and ADHD lies in the deconstruction of the diagnosis into its component parts by using biological and behavioral markers (e.g., the corticostriatal pathways or procedural learning skills), which lie closer to the genetic substrates than the full-blown clinical syndromes *per se* (Gottesman & Gould, 2003).

Future Directions

Neurocognitive and brain-based endophenotypes that index liability offer several advantages in terms of identifying genes likely to be involved in the etiology of DLI. As our study demonstrates, endophenotypes allow for a mechanistic process-based approach to the investigation of individual differences in language development and disorders. Given a wide variety of endophenotypes associated with the same behavioural outcome in between genes and phenotypes, future research is suggested to examine different aspects of cognitive or neural abnormalities in DLI, which may present as plausible endophenotypes contributing to the elucidation of the genetic effects on individual differences in language, as well as providing insights for new interventions.

Acknowledgments

This work was supported by the National Institute of Health (NIH) under Grant R01DC007643–05 awarded to Dr. J. Bruce Tomblin.

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Figure 1.
Conceptual illustration of complex relationships among genotype, endophenotypes, phenotype, and environment.

Figure 2.
Summary of performance on procedural learning tasks by the comparison and the DLI group.

Table 1.

Age, language scores, and nonverbal IQ composite scores. Test scores were reported in standard scores with a mean (M) of 100 and a standard deviation (*SD*) of 15. Independent samples *t*-tests were performed to compare the means between the DLI and the comparison groups, and *p* values were illustrated below.

Participants Performing the Procedural Learning Tasks					
	DLI Group (n=22)		Comparison Group (n=19)		
	M	(SD)	M	(SD)	<i>p</i>
Age (months)	264.09	16.13	266.32	6.63	.58
PPVT-4	84.05	7.16	101.16	13.96	<.001
Token Test	56.65	29.15	100.36	14.85	<.001
Word Derivations	72.05	8.2	93.42	13.85	<.001
Nonverbal IQ	92.76	11	108.80	13.87	<.001
Participants Undergoing Brain Imaging Scans					
	DLI Group (n=11)		Comparison Group (n=10)		
	M	(SD)	M	(SD)	<i>p</i>
Age (months)	262.46	18.96	264.50	6.10	.75
PPVT-4	83.91	7.85	104.30	14.14	.001
Token Test	62.97	29.71	101.30	13.71	.001
Word Derivations	70.46	5.22	94.50	16.24	<.001
Nonverbal IQ	92.73	13.20	113.30	10.83	.001

Table 2.

Summary of Procedural Learning Tasks.

Task	Task Description	Domain
Pursuit Rotor Task	Participants learn to maintain contact between a stylus and a small circular target on a touch screen over time.	Motor
Serial Reaction Time (SRT) Task	A neutral visual stimulus pops up in one of the four boxes on the computer screen. Participants need to press the button associated with the location of the visual stimulus as quickly and accurately as possible.	Motor-Perceptual
Weather Prediction Task	Participants learn the probabilistic association between two equally occurring outcome variables (i.e., RAIN or SUN) and combinations of four cue cards via trial and error.	Cognitive

Table 3.

Summary of genotype distribution of participants, with means (M) and standard deviations (*SD*) of language scores.

SNP		A1/A1	A1/A2	A2/A2
rs 2734849	Genotype	C/C	C/T	T/T
	Count	7	26	8
	M	91.06	81.38	84.34
	SD	10.25	16.58	26.31
rs 1800497	Genotype	T/T	T/C	C/C
	Count	1	12	28
	M	71.98	80.55	85.34
	SD	0	19.07	17.78

Table 4.

Summary of performance on procedural learning tasks by genotype. Learning effect for each task was defined below: 1) Pursuit rotor: difference of average time on target (TOT) between the last block and the first block, 2) Serial reaction time (SRT): difference of median reaction times between random blocks and pattern blocks, and 3) Weather prediction: Average percent accuracy across blocks.

SNP: rs2734849	C/C & C/T (n=33)		T/T (n=8)	
Procedural Learning Tasks	M	SD	M	SD
Pursuit rotor	12.60	9.44	9.06	10.59
SRT	19.64	24.62	13.31	20.64
Weather Prediction	64.98	10.99	69.27	17.67
SNP: rs1800497	C/C (n=28)		C/T & T/T (n=13)	
Procedural Learning Tasks	M	SD	M	SD
Pursuit rotor	13.90	9.33	7.19	9.05
SRT	18.34	23.56	18.54	25.27
Weather Prediction	65.65	11.60	63.62	14.60

Table 5.

Summary of relative volumes and fractional anisotropy (FA) values of the regions of interest (ROIs) by genotype.

SNP: rs2734849	C/C & C/T (n=17)		T/T (n=4)		C/C & C/T (n=17)		T/T (n=4)	
	Relative Volumes				FA Values			
ROI	M	SD	M	SD	M	SD	M	SD
Caudate Nucleus	.476	.046	.526	.057	.147	.018	.144	.012
Putamen	.677	.075	.696	.108	.206	.012	.195	.015
Nucleus Accumbens	.039	.010	.049	.007	.140	.024	.137	.010
Globus Pallidus	.214	.021	.207	.044	.253	.029	.248	.022
Thalamus	.793	.078	.858	.081	.235	.014	.240	.020
SNP: rs1800497	C/C (n=15)		C/T & T/T (n=6)		C/C (n=15)		C/T & T/T (n=6)	
	Relative Volumes				FA Values			
ROI	M	SD	M	SD	M	SD	M	SD
Caudate Nucleus	.491	.058	.473	.026	.152	.016	.133	.008
Putamen	.683	.077	.673	.092	.205	.013	.200	.013
Nucleus Accumbens	.039	.009	.044	.013	.142	.023	.135	.021
Globus Pallidus	.214	.026	.211	.027	.254	.028	.248	.027
Thalamus	.811	.086	.792	.071	.235	.014	.238	.017

Table 6.

Summary of relative volumes and fractional anisotropy (FA) of subcortical structures of the corticostriatal pathways in participants with and without DLI. M=mean; *SD*=standard deviation; ROI=region of interest.

	Comparison (n=10)		DLI (n=11)	
	Relative Volumes			
ROI	M	SD	M	SD
Caudate Nucleus	.484	.038	.487	.062
Putamen	.640	.078	.717	.063
Nucleus Accumbens	.036	.008	.044	.010
Globus Pallidus	.204	.027	.221	.022
Thalamus	.780	.073	.829	.083
	FA Values			
ROI	M	SD	M	SD
Caudate Nucleus	.147	.017	.145	.018
Putamen	.208	.011	.200	.142
Nucleus Accumbens	.140	.139	.140	.285
Globus Pallidus	.267	.027	.239	.020
Thalamus	.244	.009	.229	.015