CORTICAL THICKNESS AND GYRIFICATION IN CHILDREN WITH DEVELOPMENTAL DYSLEXIA

A Dissertation

Presented to

The Faculty of the Department

Of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

Victoria J. Williams

May, 2015

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ABSTRACT

Prior research has demonstrated a pattern of atypical neural structure and function within regions of the left hemisphere reading network in individuals with dyslexia compared to controls. However, studies of pediatric dyslexia are sparse, demonstrate variability in dyslexia classification, and yield inconsistent associations between cortical metrics and reading ability. This study investigated cortical metrics in typically developing readers (n=39) and children with dyslexia (n=37) as determined by deficient single word reading ability. Whole-brain vertex-wise analyses, performed using FreeSurfer, evaluated cortical thickness and local gyrification between reading groups, controlling for age. Following multiple comparison correction, readers with dyslexia demonstrated reduced cortical thickness within previously identified critical reading areas including: bilateral inferior-temporal, inferior-frontal, and occipito-parietal regions, along with left anterior cingulate cortex. In readers with dyslexia, thinner cortex was accompanied by increased gyrification in the cuneus and left inferior temporal cortex. The convergence of thinner and more gyrified cortex within the left inferior temporal region in children with dyslexia may reflect its early temporal role in processing word forms, and highlights the importance of the ventral stream for successful decoding. Reading fluency scores demonstrated a positive association with cortical thickness in right inferior frontal and bilateral inferior temporal cortices, while reading comprehension was significantly correlated with thickness across all regions.

Keywords: developmental dyslexia, gyrification, cortical thickness, single word reading, structural neuroimaging, developmental disorder

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INTRODUCTION

Reading is a relatively recent function of the human brain, with the first evidence of writing systems surfacing around 5000 years ago (Dehaene, 2009). Even then, illiteracy was frequently the norm prior to Industrialization in the early 1900's in which the advent of mass printing technology delivered an influx in accessibility to printed materials. Developing nations have subsequently provided a greater emphasis on educational attainment and literacy through standardized educational curriculums and equal access to education and reading instruction.

As a form of communication, reading is defined as the ability to process written symbols to derive meaning or comprehension from text. Reading thus provides an avenue to access the language system from visual rather than auditory stimuli. English is an alphabetic language system in which 26 letters can be arranged to form 44 possible phonemes or speech sounds (ex. /k/). Phonemes can then be combined to form a variety of morphemes– the smallest combination of speech sounds that portray meaning (ex. non- or -ing). The learned correspondence of graphemes (written text) to phonemes provides a framework for both reading and writing development, as the reader becomes familiar and forms a working knowledge of the relation between text and speech sounds. A metacognitive awareness of the internal structures of speech is therefore a fundamental prerequisite for assessing print in the developing reader, and allows for subsequent mastery of word recognition and spelling (Liberman & Shankweiler, 1991). Although word recognition increases rapidly with adequate phonological awareness, reading comprehension and fluency/automaticity skills are acquired gradually with increased exposure to print and reading practice.

Dyslexia

Various factors may contribute to poor reading acquisition. Environmental factors include limited access to print and poor academic instruction that may thwart reading development. Intrinsic deficits may also impede successful reading acquisition, such as poor attention and learning, hearing impairments, visual deficiencies, or low intellectual ability. Yet even in the absence of such adverse factors to reading acquisition, 6-17% of children struggle with reading proficiency within the context of standard didactic instruction and appropriate opportunities to learn (Vellutino, Fletcher, Snowling, & Scanlon, 2004), often with severe reading and spelling problems persisting into adulthood (Eden & Zeffiro, 1998; Fletcher, 2009; Shaywitz, 1998).

Dyslexia is a reading disability characterized by impaired decoding and encoding at the single word level (Snowling, 2000). This impairment is predominately associated with difficulties in phonological processing, which includes poor phonological awareness, delayed lexical retrieval, and difficulties with verbal short-term memory (Ramus, 2004). Poor decoding skills ultimately function as a bottleneck, limiting fluent and accurate word recognition, and often hampering effective reading comprehension as semantic knowledge cannot be easily gained from print. The International Dyslexia Association (IDA) currently defines dyslexia as "difficulties with severe and/or fluent word recognition and by poor spelling and decoding abilities," drawing on research identifying neuropsychological deficits grounded in brain based dysfunction (Lyon, Shaywitz, & Shaywitz, 2003). This more recent classification criteria for dyslexia serves to replace an outdated reliance on exclusionary criteria in defining reading disability (such as IQ and SES), which may be nonspecific to dyslexia (Fletcher, 2009; Rutter, 1982). Further supporting a neurologic basis for dyslexia,

family studies consistently demonstrate a genetic risk for the development of reading disabilities, with heritability estimates as high as 54-84% (Astrom, Wadsworth, & DeFries, 2007; DeFries, Fulker, & LaBuda, 1987).

In alphabetic languages, orthography is defined as the patterns of letters and letter strings that make up words based on the sounds of a language. Proficient reading occurs at the level of rapid processing of orthographic patterns. The manifestation of dyslexia can vary based on orthographic depth of a given language, often reflecting the transparency of the phonological and orthographic patterns (Ziegler & Goswami, 2006). In shallow orthographies like Spanish or German, the phonological and orthographic relations are closely linked, so that words look like the way they are pronounced. In deep orthographies such as English, there are many irregular relations (e.g., rough, plough, dough). Reading difficulties may be compounded by frequently encountered irregularities in phoneme to grapheme correspondence (e.g. the exceptional pronunciation of "ache" or "rough"), which leads to inaccurate word reading. In more transparent languages like German and Spanish, accuracy is less of a problem due to fewer irregular pronunciations. In these shallow orthographies reading impairment is alternatively characterized by slow and laborious reading and spelling difficulties (Richlan, 2014). Nonetheless, difficulties with single-word reading- accuracy and fluency- and spelling and phonological awareness are apparent cross culturally, providing additional support to the neural basis of developmental reading deficits (Paulesu, et al., 2001; Simos, Rezaie, Fletcher, & Papanicolaou, 2013; Wimmer, et al., 2010).

Reading in the Brain

Reading is a learned skill acquired through formal and informal instruction in grapheme to phoneme correspondence. As such, the underlying neural network that supports reading is particularly interesting in that it requires neuroplasticity and evolved specialization of brain regions for functions not designed through evolution (Dehaene, 2009; Dehaene, et al., 2010). Furthermore, reading exemplifies an impressive convergence of brain areas supporting auditory, visual, and language functions. Cognitive models of reading highlight at least three distinct components: a) orthographic processing of visual letter sequences, b) phonological awareness linking orthographic input to speech sounds, and c) semantic access of word meaning to encountered orthographic input. A fourth neural component is required to articulate the phonological representations of visually encountered word forms when articulating speech sounds.

In the brain, reading is accomplished through a complex neural network, predominately in the left (dominant) hemisphere as modeled through both early lesion studies, as well as by more recent investigations utilizing functional neuroimaging in vivo. This network commonly involves occipital temporal regions that are involved in processing word forms, posterior temporal and inferior parietal regions involved in phonological processing, inferior temporal regions supporting semantic access to word meaning, and the inferior frontal regions necessary for articulating speech. Using MEG, the temporal propagation of neural activity involved in phonological decoding of written text was investigated in a sample of typically developing children (Simos, et al., 2013). Results indicated a progression of onset and peak latency of regional activity in lateral to ventral occipitotemporal regions followed by temporoparietal activation. Neural activity subsequently appears within the inferior frontal region following a significant delay. Thus,

reading processes tend to follow a posterior to anterior trajectory in the brain, with specific contributions of each region discussed below.

Inferior Occipitotemporal Region. After initial activation of the primary visual cortex, the process of reading involves regions of the inferior occipital lobe supporting visual processing, with specific contributions of the visual word form area. This region of the brain typically supports visual and attentional processing. In reading, these regions are trained to process the graphical and orthographic components of written text. Subjacent to visual areas involved in object recognition, the visual word form area (VWFA) is a secondary association area first identified by Cohen (Cohen, et al., 2000; Cohen, et al., 2002; Dehaene, Le Clec, Poline, Le Bihan, & Cohen, 2002). Representing an adaptation of a more primitive visual area subserving object recognition, the introduction of reading instruction and learning promotes selectivity and specialization of this region in processing orthographic symbols (letter forms) (Cohen, et al., 2002) .

Inferior occipitotemporal regions have demonstrated reliable activity during skilled reading (Jobard, Crivello, & Tzourio-Mazoyer, 2003; Price & Mechelli, 2005), regardless of orthographic depth (Richlan, 2014). Furthermore, the contribution of the VWFA to reading is a universal construct, with functional imaging studies showing convergent evidence of activation of this area in reading, regardless of language (Cohen, et al., 2002; Richlan, 2014). Acquired damage to the left occipitotemporal cortex results in pure alexia (word blindness), as well as dysfluent letter by letter reading if there is also a lesion to the splenium of the corpus callosum (Cohen, et al., 2003).

Previous neuroimaging studies have identified differences in brain structure and function between children and adults identified with developmental dyslexia and proficient

readers. Voxel-based studies have identified reduced gray matter volume in individuals with dyslexia in bilateral occipitotemporal cortex (Kronbichler, et al., 2008). Additionally, fMRI studies have demonstrated consistent reduction in functional activation when engaged in reading tasks in left occipitotemporal regions, with the level of activation correlating with level of reading skill (Hoeft, Ueno, et al., 2007; Specht, et al., 2009; Temple, 2002). In proficient readers, the visual form area supports automatic recognition of words based on orthographic patterns that the brain learns to recognize through experience.

Temporoparietal Junction. Subsequent to letter identification in the VWFA, orthographic input is further processed via two routes serving text decoding and reading comprehension. The dorsal route involves cortical regions of the temporoparietal junction including the posterior superior temporal gyrus, the supramarginal gyrus, and the angular gyrus to support phonological processing. Subjacent to auditory processing areas, the dorsal route provides grapheme to phoneme conversion, and has been postulated as the site for the convergence of auditory and orthographic components in reading. Critical to decoding novel and pseudowords (phonologically plausible words with no meaning), temporoparietal regions link orthographic to phonemic conversion based on previously learned rules inherent to language structure (Shaywitz, et al., 2002; Simos, Breier, Wheless, et al., 2000). In the developing reader, this area is particularly salient in the acquisition and "sounding out" of new or unfamiliar words and brain activation in this region correlates with pre-reading skills prior to literacy (Raschle, Zuk, & Gaab, 2012). Functional neuroimaging studies of both children and adults with dyslexia demonstrate decreased activation of temporoparietal regions during phonological processing and reading-related tasks (Eden & Zeffiro, 1998;

Shaywitz, et al., 2002; Shaywitz, 1998; Simos, Breier, Fletcher, Bergman, & Papanicolaou, 2000).

Inferior Temporal Region. In parallel to the dorsal route involving temporoparietal regions supporting phonological decoding, direct connections between the visual word form area and cortex within the middle and inferior temporal gyrus form the ventral route, allowing for whole-word recognition and semantic processing of language. Frequently encountered and over-learned words within the lexicon often bypass letter-by-letter phonological decoding carried out within temporoparietal regions, as the word can be identified automatically through visual recognition of the word form in its entirety. Evidence of functional co-activation between occipitotemporal regions and semantic areas within the inferior temporal lobe have been hypothesized to allow for a direct association between word shape and meaning (Jobard, et al., 2003). Furthermore, the ventral reading route allows for fluent processing of words with irregular spellings, in which case the visual representation of the word is further identified through semantic associations.

Inferior Frontal Region. The functional contributions of the posterior reading network are often complemented by engagement of the inferior frontal cortex, an area that has been associated with naming and articulatory representations of language (such as phonological recoding necessary to produce speech sounds when reading aloud) (Fiez & Petersen, 1998; Mainy, et al., 2008; Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008). Additionally, functional imaging studies have implicated this region in silent reading and sub vocal rehearsal (Smith & Jonides, 1999), and in the extraction of phonological elements of speech (Gandour, et al., 2002). In studies of dyslexia, there is inconsistent evidence for both under-activation and over-activation of the inferior frontal region

(Richlan, Kronbichler, & Wimmer, 2011; Wimmer, et al., 2010), with over-activation in individuals with dyslexia largely interpreted as a compensatory mechanism for the reduced functional activation commonly observed in left temporoparietal areas (Demonet, Taylor, & Chaix, 2004; Pugh, et al., 2000; Sandak, et al., 2004; Shaywitz & Shaywitz, 2005). In a structural imaging study, Lu et al. (2007) found that cortical thickening in the left inferior frontal region was associated with greater development of phonological processing skills in typically developing children followed over a two-year period, which dissociated from regional cortical thinning in motor areas.

The Dual-Route Framework of Reading

Early lesion studies proposed distinct pathways of reading processes through a dissociation of reading related components that may break down at various observable levels. Although perhaps overly simplistic given the vast connections within neural networks, a dual-route cascading (DRC) hypothesis was postulated to account for differences in phonological versus semantic processes involved in reading (Castles & Coltheart, 1993; Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001). The DRC is characterized as a symbolic model, based on the assumptions that two information-processing routes are involved in reading, and that information processing is cascaded in nature.

The origins of this model stem from findings that the regularity and frequency of encountered words predict correct pronunciation (Waters & Seidenberg, 1985). Given the quasi-regular structure of English, depending on the difficulty/transparency of orthography, two information-processing routes may be employed to aid in word recognition. In

proficient readers, the dorsal (phonological) and ventral (semantic) routes work indistinguishably in parallel to accomplish fluent reading. However, through lesion studies of acquired alexia, the unique contributions of the temporoparietal and inferior temporal regions can be clearly identified. Isolated lesions to the dorsal route lead to deficient phonological decoding. Referred to as deep or phonological dyslexia, such patients demonstrate difficulties with rapid and accurate spelling to sound conversion. Manifested as a breakdown between learned orthographic and phonemic principles, infrequent words that cannot be compensated through the ventral semantic processing route become unreadable. In addition, reading deficits in the context of temporoparietal lesions are particularly salient in the phonological decoding of pseudo-words, as phonological awareness between text and sound is impaired with semantic knowledge offering no compensatory cues. Interestingly, some patients exhibit confusion of written words with semantically related words. For example, reading "pig" as "ham". This type of error clearly demonstrates the intact semantic route preserves access to word meaning for over-learned word forms, even when phonological conversion of text to speech renders impaired pronunciation.

Conversely, damage to the ventral route contributes to a different type of impairment referred to as surface or semantic dyslexia. In this case, phonological decoding is intact for both real words and pseudo-words, but reading breaks down when encountered with irregular words that do not follow standard orthographic to phonemic conversion rules. When faced with an irregular word (such as “though”), patients with a temporal lesion fail in its irregular pronunciation, and are unable to recognize the word visually as part of their lexicon with semantic significance.

While most words can be decoded into phonemes based on serial letter strings following spelling to speech conversion rules supported through temporoparietal functions, occasional irregular words rely on additional contributions of the ventral semantic route to resolve certain ambiguities in word reading. As reading becomes more automatic with experience, these two systems interact seamlessly to allow fluent and rapid reading ability. In children, the correspondence of these two systems gradually becomes more efficient over time with increased exposure to print, an expanding vocabulary, and adequate instruction. While this may be an overly simplistic model, it does provide a useful framework for understanding reading in the brain.

The Connectionist Model of Reading

As an alternative to the dual-route cascading framework of reading, the connectionist approach, utilizes computational theories to model reading in the brain based on weighted contributions of distributed reading areas and processes (Foorman, 1994; Plaut, McClelland, Seidenberg, & Patterson, 1996; Seidenberg & McClelland, 1989; Van Orden, Pennington, & Stone, 1990). Similar to the dual-route perspective, connectionists agree on separate neural pathways for phonological decoding and semantic representations. However, the main divergence between theories is that the connectionist approach employs a single, rather than dual, mechanism for processing words. In this way, word forms are processed simultaneously in parallel across distributed reading networks through bottom-up processing. Unlike the DRC model, the connectionist approach utilizes computationally derived models, are biologically inspired to mimic neural contributions at the cellular level, have no a priori assumptions as to how information is represented in the brain, and possess

the capacity to learn through the process of back-propagations during training sets. Learning within the system occurs through adjustments of connection weights of hidden 'units' (rather than symbolic rules in the DRC approach), which encode distributed properties and computational rules derived from the training data, and ultimately mediate both input and output from the system. Therefore, through extensive training and feedback, patterns of activation are encoded, forming the basis of the model's emergent 'knowledge'. Thus, connectionist models attempt to explain the formation of a functional reading network based on exposure to relevant stimuli, which is subsequently coded as distributed representations containing multiple units of 'knowledge' to inform future novel pronunciations. While the DRC model does a good job of simulating patters of both acquired and developmental dyslexia, the connectionist models have evidenced little success. Moreover, it is not obvious that the two models are truly distinct (Foorman, Francis, Fletcher, & Lynn, 1996).

Structural Correlates of Reading in the Brain

Following from deviant brain function observed both in behavioral phenotypes of those with dyslexia, as well as more directly through functional neuroimaging studies, a major question concerns the anatomical correlates underlying such observations. Prior to the development of contemporary neuroimaging techniques, attempts to gain insight into possible neural substrates of dyslexia were accomplished through histological post-mortem examinations of the brain. Most notably, Galaburda and colleagues published several case studies of dyslexic individuals with findings of reduced cortical asymmetry of the planum temporale (a region posterior to auditory cortex within the superior temporal gyrus) (Galaburda & Kemper, 1979), as well as several reports of neuronal ectopias and

architectonic dysplasias in perisylvian regions lateralized to the left hemisphere (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; Humphreys, Kaufmann, & Galaburda, 1990). Although these early studies paved the way for our current understanding of dyslexia as a brain-based disorder, concerns have arisen regarding the diagnostic criteria of dyslexia adopted in these studies, as well as methodological issues potentially biasing dyslexic samples (Heim & Keil, 2004). Nonetheless, neurostructural differences in individuals with dyslexia have continued to surface using more contemporary structural neuroimaging techniques.

Subsequent to Galaburda's research highlighting gray matter abnormalities in dyslexia, a large body of research has focused on cortical associations with reading skill. In addition, recent studies utilizing diffusion tensor imaging (DTI) to examine white matter integrity have also demonstrated neurostructural differences between typical readers and those with dyslexia (Vandermosten, Boets, Wouters, & Ghesquiere, 2012). As dyslexia is heritable, how such genetic variation result in the observed behavioral phenotype of impaired reading is mediated by neurostructural properties selective to the reading network. Genetic research has isolated several dyslexia risk genes, posing to influence subsequent reading ability through aberrant neurostructural development. Many of the dyslexia risk genes identified are related to neuronal migration and proliferation during development (Eicher & Gruen, 2013). Convergent with Galaburda's early pathological findings of neurostructural malformations within cortical reading areas, such gene variants in dyslexia may generate cortical ectopias resultant from incomplete neuronal migration. Thus, research associating gray matter structure and reading ability is of particular interest in understanding the nature of dyslexia.

Gray Matter Volume in Dyslexia

The development of in vivo neuroimaging techniques (including computed tomography and magnetic resonance imaging) facilitated an influx of studies targeting structural correlates of dyslexia allowing for increased sample size compared to the early histological studies. With early MRI investigations being limited by poor image resolution, and crude manual tracings of brain regions leading to variability in defined areas of interest, the development of voxel-based morphometry (VBM) in the early 2000's overcame these limitations through segregation of gray matter followed by statistical comparison of normalized images co-registered into stereotactic space on a single voxel basis across subjects (Ashburner & Friston, 2000). Improvements to voxel-based approaches have been refined to include semi-automated segmentation of various brain tissue types (gray matter, white matter, and cerebrospinal fluid), surface-based approaches to examine cortical properties, advanced non-linear co-registration techniques, along with the development of various anatomical reference atlases. To date, studies of neurostructural correlates of developmental dyslexia reveal variable regions of cortical differences in dyslexic readers compared to controls.

To address such variable findings, a recent meta-analysis of voxel-based morphometry studies (Richlan, Kronbichler, & Wimmer, 2013) aimed to objectively quantify the convergence of gray matter anomalies observed in dyslexic readers compared to typically reading controls. Meta-analysis implemented an Activation Likelihood Estimation approach in which peak voxels indicating gray matter differences between reading groups were identified across all studies, aligned into a common space, and statistically analyzed for

significantly converging effects. The adoption of a quantitative meta-analytic approach improved on an earlier qualitative review of VBM studies in dyslexia by Richardson and Price (Richardson & Price, 2009), largely evaluating the same body of literature. In the Richlan meta-analysis, inclusion criteria specified the use of VBM methodology with multiple comparison correction, a direct group comparison of typical readers and dyslexic readers constrained to an alphabetic language structure, with results reported in standardized stereotactic space. Nine studies were identified as satisfying such prerequisites, with participants largely consisting of adolescents and adults with a historical diagnosis of dyslexia.

Overall, a wide distribution of regions differing in gray matter volume between dyslexic and typical readers across studies have been reported across both hemispheres (Richlan, et al., 2013). Several factors may contribute to the heterogeneity of results between studies, including the selection criteria used to define dyslexia, the non-homologous age ranges across studies, as well as variations in the VBM methodologies implemented. Although two of the studies reported select regions in which gray matter volumes were increased in individuals with dyslexia, these effects were not reliable and most studies report reduced gray matter volume. Convergent regions of gray matter reductions in readers with dyslexia compared to non-impaired readers were identified in the left hemisphere superior temporal sulcus, as well as a reliable cluster in the right superior temporal gyrus proximal to the temporoparietal junction (which was spatially 3 times larger than the left hemisphere region). Although failing to meet the meta-analytic significance threshold, an additional region of reduced gray matter in the left ventral occipitotemporal region (including fusiform gyri and inferior temporal cortex) was also identified in four of the nine studies (Brambati,

et al., 2004; Brown, et al., 2001; Eckert, et al., 2005; Kronbichler, et al., 2008). Other commonly reported regions demonstrating reduced gray matter in dyslexia include posterior temporal and temporoparietal regions (Brambati, et al., 2004; Hoeft, Meyler, et al., 2007; Silani, et al., 2005; Steinbrink, et al., 2008) and cerebellar gray matter (Brown, et al., 2001; Eckert, et al., 2005; Kronbichler, et al., 2008).

Findings of reduced gray matter in left superior temporal sulcus and ventral occipitotemporal regions correspond to regions within the left hemisphere reading network as identified through both lesion and functional neuroimaging studies. Involvement of the left superior temporal sulcus in language functioning was previously implicated in the classic lesion study defining Wernicke's area, highlighting the role of this region in speech comprehension. Although Wernicke's area extends beyond the region delineated in the meta-analysis distinguishing gray matter volumetric differences between typical readers and those with dyslexia, the superior temporal sulcus has been shown to specifically contribute to aspects of phonological processing. In functional neuroimaging studies of developmental dyslexia, the left superior temporal sulcus is reliably underactivated during reading tasks (Blau, et al., 2010; Meyler, et al., 2007; Paulesu, et al., 2001).

Based on early reports of decreased planum temporale symmetry in developmental dyslexia, as well as a general consensus of a left hemisphere lateralization of reading processes, the meta-analysis findings of reduced gray matter volume in right hemisphere temporoparietal regions in readers with dyslexia may appear unexpected. However, evidence of an association between planum temporale asymmetry and reading skills are mixed, with some recent studies failing to show continued support of a left hemisphere gray matter thickness bias within this region across both poor and proficient readers (Leonard,

Eckert, Given, Virginia, & Eden, 2006; Welcome, Leonard, & Chiarello, 2010), while others have demonstrated global hemispheric asymmetries in cortical thickness (Frye, et al., 2010). Additionally, VBM studies of children with a high genetic risk of dyslexia reveal bilateral reductions in gray matter volume within temporoparietal regions when assessed in both pre-readers (Raschle, Chang, & Gaab, 2011) and 5 to 6 year old beginning readers (Black, et al., 2012), suggesting that gray matter abnormalities in both left and right temporoparietal regions may contribute to poor reading acquisition ability.

Although the majority of cortical morphology studies show decreased gray matter volume and thickness in children with dyslexia, a recent study by Ma et al. reported contrary findings of thicker cortex within the left fusiform and supramarginal gyrus compared to typical readers matched on age, sex, handedness, and IQ (Ma, et al., 2015). Although this study evaluated a similar age range as the present study, inclusion criteria only specified a historical diagnosis of dyslexia; two thirds of individuals within the dyslexia group had undergone formal reading remediation resulting in word reading scores on par with controls. Given that cortical thickness differences did not reach a level of significance between controls and the un-remediated dyslexia subgroup (only a trend was noted), the main study findings of increased cortical thickness appears to be largely driven by the possibility that the majority of participants had been remediated for dyslexia. In other words, the null results may be secondary to targeted and enhanced reading experience and instruction.

Gray Matter: Surface Area versus Cortical Thickness

Despite the heterogeneity of gray matter differences between individuals with dyslexia and typical readers, the conceptualization of dyslexia as a brain-based disorder with

observable anomalies in neuronal structure localized within the reading network is clear. However, all of the studies included in the VBM meta-analysis reported solely on differences in gray matter volume. Although volume within a single voxel is constrained by data acquisition parameters defining scan resolution, regional volume of brain regions averaged over a set of voxels is a product of both cortical surface area and cortical thickness, which may vary independently from one another. Thus, differences in volume may be a product of variable surface area, or alternatively, differences in cortical depth. Recent neuroimaging endeavors have attempted to clarify this distinction in dyslexia by performing surface-based cortical analysis to offer further insight into gray matter volume differences.

In a study of typical adult readers, Blackmon and colleagues evaluated associations between cortical thickness and reading proficiency on an exception word pronunciation task (Blackmon, et al., 2010). Results indicated that irregular word pronunciation performance correlated with thicker cortex within left the intraparietal sulcus, and bilaterally in the angular gyrus, posterior superior temporal gyrus, and the anterior superior temporal gyrus. Increased reading skill was also associated with thinner cortex in the left posterior fusiform gyrus, inferior frontal gyrus, and the central sulcus. Although this study did not examine individuals with dyslexia, reading ability is best characterized on a continuum (Ellis, 1984). By definition dyslexia is determined by an arbitrary cut point of reading scores distinguishing individuals whose reading difficulties are unexpected and severe. Findings of cortical thickness associating with reading ability speaks to the fact that variations in reading skill and proficiency may be rooted in structural variations within known reading networks in the brain, thus highlighting the importance of cortical thickness as an indicator of neuronal function.

An additional study evaluated group differences in cortical thickness among a sample of college-aged participants classified as poor, resilient, or proficient readers (Welcome, Chiarello, Thompson, & Sowell, 2011). Although this study revealed no significant differences in cortical thickness between the three groups, several methodological concerns may have influenced results. First, poor readers were defined by performance on Word Attack and Passage Comprehension subtests of the Woodcock Reading Mastery Test-Revised below a scaled score of 95, which is only a third of a standard deviation below the age-based norm. As a university-based sample, adults whose reading impairments may have significantly impacted academic achievement are likely underrepresented, as these individuals may be less likely to pursue higher education. Second, cortical thickness measurements were calculated as averages from six coarsely defined ROIs at the lobar level (with the frontal lobe partitioned into ventral and dorsal divisions, and the creation of an additional temporoparietal ROI). Such spatially large parcellations require the averaging of cortical thickness measurements across an extensive cortical area, which may be insensitive to more subtle variations in neuronal structure within specific regions associated with reading ability.

With the aim to parse the unique contributions of surface area and cortical thickness to gray matter volumetric changes observed in dyslexia, Frye et al. (2010) implemented a vertex-wise approach to evaluate differences in both cortical thickness and surface area in adults with and without a history of phonological dyslexia. Average thickness and surface area measurements were constrained to a priori regions of interest previously identified as contributory to reading processes: inferior frontal gyrus, fusiform gyrus, angular gyrus and supramarginal gyrus. Results indicated that regional gray matter volumetric differences

between readers with dyslexia and typical readers were largely the result of variations in surface area, not cortical thickness. Regional analyses indicated that gray matter volume and surface area, but not thickness, were associated with a history of reading disability and reading-related skills in the inferior frontal and fusiform gyri. However, the group with dyslexia did demonstrate increased cortical thickness within the right supramarginal gyrus when compared to typical readers. A whole-brain thickness analysis revealed a reading group by hemisphere interaction, such that typical readers showed greater thickness in the left hemisphere compared to the right, while readers with dyslexia demonstrated equivalent thickness across both hemispheres. Regional differences in gray matter volume were predominately driven by variations in surface area between groups, which was interpreted as resulting from aberrant gyrification patterns during development, contributing to variations in surface area of regional measurements, as well as a structural basis for poor reading skill development.

Several limitations to the Frye et al. study are worthy of discussion. Primarily, participants in the dyslexia group were identified by a historical report of dyslexia in grade school, with current reading scores at the time of study ranging from impaired to well within the range of proficient reading skills. Thus, despite a history of dyslexia in distant childhood, reading ability for some participants in the dyslexic group was on par with non-impaired readers. The inclusion of readers with no current reading difficulty within the dyslexic group (regardless of history) negates the notion that the acquisition of reading proficiency is accompanied by structural alterations in the brain subserving such abilities. Arguably, the amelioration of childhood reading impairments to that of typical reading ability in adulthood, likely correspond to underlying neurostructural plasticity supporting such

improvement in reading network function. This principle can be observed both in morphological studies of adult illiterates, as well as in reading intervention studies of individuals with dyslexia. To illustrate, several reading intervention studies have been conducted tracking improvements in reading with associated variations in regional brain structure and function. (Fletcher, Lyon, Fuchs, & Barnes, 2006; Simos, et al., 2002). Furthermore, a comparison of adult illiterates with closely matched literate controls demonstrate differences in volume and lateralization of both gray and white matter within the inferior parietal region (Castro-Caldas, Petersson, Reis, Stone-Elander, & Ingvar, 1998), with such anatomical differences posited to reflect the effects of developing literacy on the brain (Castro-Caldas, et al., 1999; Petersson, Silva, Castro-Caldas, Ingvar, & Reis, 2007).

Finally, although cortical thickness was determined by a vertex-wise procedure along the entire cerebral mantle, regional thickness measurements were determined by averaging data within predetermined ROIs. Although defining a region of interest is necessary to delineate the borders for surface area calculations, utilizing an ROI approach for cortical thickness analyses reduces regional specificity of group differences. Depending on the size of ROI employed, potential group differences in sub-regions may be minimized because of these averaging methods. An alternative voxel-wise approach compares cortical thickness at each vertex within the cortical mesh, allowing for the emergence of smaller and more specific regional differences between groups, as well as providing an overall account of cortical thickness patterns across the whole brain.

Another recently published study also distinguished between cortical thickness and surface area measurements while assessing the topological properties of structural brain networks involved in reading. Hosseini et al. (2013) identified beginning readers at-risk for

dyslexia through reported family history of reading difficulties. Using graph-theoretical analysis, separate structural correlation networks were identified based on co-occurring regional fluctuations in surface area and cortical thickness measurements. Briefly, this method entails extracting brain regions in which topological properties (cortical thickness and surface area) significantly covaried with one another, which is subsequently interpreted as an indicator of functional connectedness between such regions. Similar to previous findings by Frye et al. (2011), alterations in topological properties were revealed in brain regions preferentially implicated in dyslexia (left supramarginal gyrus, left inferior frontal gyrus) in the group with a positive family history for dyslexia, largely in the network formed through surface area measurements. However, network maps derived from thickness measurements also demonstrated unique findings, specifically a greater centrality and interaction of right hemispheric hubs with left language areas in the reading risk group, aligning with functional MRI studies identifying potential compensatory activity in right hemispheric regions in individuals with reading difficulties. Despite clear statistical differences between groups, a family history of dyslexia does not imply that included individuals will subsequently demonstrate reading impairments, as most of the reading standard scores in this group fell within the average range.

Specific Aims, Rationale, and Hypotheses for the Present Study

The present study attempts to build upon the previous body of research by utilizing contemporary vertex-wise whole brain analysis to examine cortical metrics in children with dyslexia compared to typical readers.

Aim I: To investigate regional differences in cortical thickness between children with dyslexia and typical readers using a whole brain approach.

Overall, previous studies addressing gray matter variations in developmental dyslexia vary in their regional findings, although some areas of convergence can be reliably identified within brain regions crucial to reading function. In the Richlan et al. (2013) quantitative meta-analysis assessing gray matter volumes in dyslexic versus typical adult readers, the right superior temporal gyrus and left superior temporal sulcus were the only regions surviving statistical thresholds across studies. These findings only partially overlap with regions identified as functionally atypical in a separate meta-analysis addressing correspondence between functional MRI studies (Maisog, et al., 2008; Richlan, et al., 2011). Although gray matter volumes are consistently reduced among individuals with dyslexia, volumetric studies are insensitive to the independent contributions of cortical thickness and surface area (or gyrification) – each driven by unique neurostructural properties and mechanisms. Few studies to date have examined these independent cortical properties that may underlie reading impairment, especially in children. Furthermore, prior studies that have evaluated cortical thickness in children with dyslexia are limited by selection criteria: those with a familial risk of dyslexia (who may or may not develop a significant reading impairment given the low penetrance of the genes involved in dyslexia), intellectual discrimination that may not adequately reflect the overall population of children with reading impairment (selecting children with dyslexia with IQ scores matched to controls), and studies of non-English speaking children that may not adequately generalize to English due to differences in orthographic depth (e.g., a prior study of Norwegian children).

Hypothesis I. Based on a general pattern of reduced gray matter volume observed in prior studies, it is hypothesized that children with dyslexia will demonstrate reduced cortical thickness within regions contributing to the left hemisphere reading network, as well as RH homologous structures.

Aim 2: To investigate differences in gyrification between children with dyslexia and typical readers using a contemporary 3-dimensial local gyrification index approach.

Recent evidence has suggested that variations in surface area best account for previously identified reductions of gray matter volume within cortical reading areas observed in individuals with dyslexia (Frye, et al., 2010). Cortical surface area is a function of both the width of sulci, as well as the number of gyrifications within a given area (Im, et al., 2008). Although surface area provides an indirect indicator of gyrification, no known studies have specifically examined cortical folding patterns in children with dyslexia. In particular, it is unknown whether regional differences in gyrification exist among brain regions implicated within the reading network. In adults with dyslexia, Casanova and colleagues (2004) demonstrated globally reduced gyrification indices, although these measurements relied on manual 2-D tracings (an unreliable measure due to sensitivity to slice orientation), and results were partially explained by overall smaller temporal lobe volume. Advancements in semi-automated image analysis software (such as FreeSurfer) allow for more reliable gyrification calculations utilizing 3D surface information based on a whole-brain approach. Unlike earlier gyrification methods relying on calculations of folding patterns through manual tracings on 2D image planes, these newer methods stand to contribute a greater understanding of cortical development in children with reading

impairment. Furthermore, the gyrification process is particularly sensitive to developmental factors given that the bulk of gyral/sulcal formations appear during the third trimester of neonatal development and that gyrification patterns remaining relatively stable throughout post-natal maturation. Thus, atypical gyrification in children with dyslexia may suggest a more developmental mechanism underlying reading impairment, as opposed to changes in brain morphology (such as cortical thickness) that have been previously linked to experiential factors including reading experience.

Hypothesis II. Children with dyslexia will have reduced LGI compared to typical readers. These differences are expected to occur in LH regions sub serving reading, along with homologous RH regions.

Aim 3: To delineate whether regional variations in cortical thickness correlate with additional reading fluency and comprehension measures.

In a clinical context, dyslexia is defined as deficient single word reading. In deep orthographies (such as English), reading accuracy is dependent on adequate phonological awareness that provides access to written text. Although word recognition increases rapidly with adequate phonological awareness, reading comprehension and fluency/automaticity skills are acquired gradually following from increased exposure to print and vocabulary expansion. Impaired single word decoding thus functions as a bottleneck to efficient reading fluency and comprehension. Empirical studies of dyslexia often vary in the selection criteria utilized to identify reading impairment. Although poor decoding and deficient single word reading skills most accurately characterize dyslexia, some studies have adopted other reading measures to classify reading impairment (such as reading fluency and

comprehension scores). Therefore, it is of interest to evaluate whether regionally specific neurostructural differences that emerge between reading groups defined by single word reading accuracy also correlate with alternative reading measures. No known studies to date have contrasted the differential relations between cortical metrics and additional reading measures in individuals with dyslexia.

Hypothesis III. Within neuroanatomical regions of interest identified as significantly different between individual with dyslexia and typical readers in Hypothesis I, it is expected that additional reading measures (reading fluency and comprehension) will demonstrate a positive correlation with cortical thickness, such that higher reading scores will associate with thicker cortex. It is further predicted that significant associations will occur preferentially in the left hemisphere.

METHODS

Participants

Participants were recruited from a series of large-scale reading intervention studies conducted in the Houston area (Denton, et al., 2011; Vaughn, et al., 2010). The first study randomly selected both typical and struggling readers to participate in a yearlong intervention study across grades 6-8. Individuals were excluded from the study based on enrollment in special education life skills, a reading score on the State-Developed Alternative Assessment at or below a 3rd grade level, a sensory disability, or if classroom instruction was not primarily in English. Children meeting criteria were administered various reading measures pre- and post-intervention; 27 of these children met criteria for the present study. The second study identified first grade children with poor reading skills at-

risk for a reading disability who were followed longitudinally in an intervention program (Denton, 2012); 26 met criteria for inclusion. A third math intervention study recruited third grade students with both math and reading difficulties, 6 of which were included as part of the present sample meeting criteria for reading disability (Fuchs, et al., 2008). Finally, 17 typical readers were included in the present sample from a study of children with spina bifida who were collected as a sample of typically developing controls (Fletcher, et al., 2005). All studies yielded comparable measures of single-word reading ability and demonstrated equivalent selection criteria for participation and imaging protocols. Anatomical MRIs were obtained from a subset of 76 children 6 to 15 years of age as part of a voluntary component within each of the studies described above. All children had an absence of acquired neurological conditions or formally identified attention deficit/hyperactivity disorder. For the imaging studies, written informed consent was obtained from all children and their legal guardian in accordance with regulations of the Committees for the Protection of Human Subjects (CPHS) at the University of Texas Health Science Center at Houston and The University of Houston.

Cognitive Measures

Decoding. The majority of participants received the Woodcock-Johnson III (Woodcock, McGrew, & Mather, 2001) Letter-Word ID subtest as a measure of single word decoding skills and reading accuracy. This is a common measure used in the identification of dyslexia, with excellent reliability (r=0.918). The six children from the math study were identified as reading impaired based on performance on the reading subtest of the Wide Range Achievement Test, Third Edition (WRAT-III). This measure also has excellent

reliability, with an alternate form correlation of 0.92. The classification of dyslexia was based on an age-based standard score below 90 (< 25th percentile) on either reading measure, indicating problems with single word reading. Based on these criteria, 37 children with dyslexia and 39 typical readers were identified.

Intelligence. Intellectual ability was assessed using either the Kaufman Brief Intelligence Test – Second Edition (KBIT-2), the Stanford-Binet Intelligence Scales-4 (SB-4), or the Weschler Abbreviated Scale of Intelligence (WASI) (Kaufman, 1990; Woodcock, et al., 2001). The KBIT-2 was used primarily for descriptive purposes within the intervention studies, with high reliability within the Verbal (r = 0.90) and Nonverbal (r = 0.86) scores among children between the ages of 10-18. All children selected for inclusion in the study demonstrated IQ scaled scores greater than 70 to rule out intellectual disabilities. In the case of participants missing either the verbal (n=3) or non-verbal (n=1) IQ composite score, the available composite score was substituted for full scale IQ.

In this study, IQ was obtained to screen for individuals at or below the level associated with intellectual disability. It was not utilized as a covariate in any of the subsequent analyses based on prior work demonstrating that the IQ construct does not meet requirements as a covariate in developmental disorders, and that when IQ is included in models, it often leads to overcorrected and erroneous findings in regards to neurocognitive abilities in children (Dennis, et al., 2009). Furthermore, similar patterns of reduced functional activation in poor readers have been observed when children with dyslexia were classified by low reading achievement with and without a discrepancy in IQ scores (Tanaka, et al., 2011).

MRI Data Acquisition

Whole-brain high-resolution T1-weighted scans were obtained for each participant on a Philips 3.0-T Intera scanner with SENSE (Sensitivity Encoding) using a 3D turbo fast echo sequence (TR= 8.4-8.6 ms; TE= 3.90-4.0 ms; flip angle = 6°; 0.94 mm slice thickness; square field of view=24 cm; matrix =256x256; in-plane pixel dimensions (*x,y*)=0.94, 0.94; number of excitations (NEX)=2). These T1-weighted, spoiled gradient-echo scan protocols were optimized for high contrast between gray and white matter, as well as gray matter and cerebrospinal fluid (CSF) to allow for optimal structural and surface segmentation for structural analyses.

T1-Weighted Imaging Analysis

High resolution, T1-weighted images were processed to obtain cortical thickness measures using the FreeSurfer version 5.3.0 image analysis suite, which is documented and fully available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl, et al., 2002; Fischl, Salat, et al., 2004; Fischl, Sereno, & Dale, 1999; Fischl, van der Kouwe, et al., 2004; Segonne, et al., 2004). Briefly, this process includes motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne, et al., 2004), automated Tailarach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (Fischl, et al., 2002; Fischl, van der Kouwe, et al., 2004; Segonne, et al., 2004), intensity normalization (Segonne, et al., 2004; Sled, Zijdenbos, & Evans, 1998), tessellation of the

gray matter/white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/CSF fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale, et al., 1999; Fischl & Dale, 2000; Segonne, et al., 2004). Once the models outlining cortical boundaries are complete, several deformable procedures can be performed for further data processing and analysis including surface inflation (Fischl, Sereno, & Dale, 1999), registration to a spherical atlas which optimizes individual cortical folding patterns to match cortical geometry across participants (Fischl, Sereno, Tootell, & Dale, 1999), and the creation of a variety of surface-based data including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl & Dale, 2000). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. Also, the maps are not restricted to the voxel resolution of the original data and are thus capable of detecting sub-millimeter differences between groups.

Cortical Thickness. Thickness measurements were mapped on the "inflated" surface of each participant's reconstructed brain (Dale, et al., 1999; Fischl, Sereno, & Dale, 1999). This procedure allows visualization of data across the entire cortical surface (i.e., both the gyri and sulci) without interference from cortical folding. Maps were subsequently smoothed using a circularly symmetric Gaussian kernel across the surface with a standard deviation of 20 mm and averaged across participants using a non-rigid high-dimensional

spherical averaging method to align cortical folding patterns (Fischl, Sereno, & Dale, 1999). This procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy while minimizing metric distortion, resulting in a mean measure of cortical thickness at each point on the reconstructed surface. Statistical comparisons of surface maps were generated by computing a general linear model of the effects of diagnostic group on thickness at each vertex in the cortical mantle, controlling for age. Maps were created using statistical thresholds of p=0.01 and were smoothed to a full width half maximum (FWHM) level of 20.

Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas, et al., 2002) and manual measurements (Kuperberg, et al., 2003; Salat, et al., 2004). In addition, FreeSurfer morphometric procedures have demonstrated good test-retest reliability across scanner manufacturers and field strengths (Han, et al., 2006), and across various sequence parameters (Hagler, Saygin, & Sereno, 2006; Jovicich, et al., 2006; Wonderlick, et al., 2009).

Local Gyrification Index (LGI). Within the FreeSurfer processing stream, a fully automated algorithm was also implemented to calculate 3-dimensional local gyrification index (LGI), a metric quantifying the ratio of visible gyral cortex to cortex hidden with the sulci (Schaer, et al., 2008). In this manner, a highly folded cortex would contribute to a large gyrification index, while a smoother cortex would demonstrate a smaller gyrification index. Once the pial and white matter surfaces were automatically generated and smoothed within the FreeSurfer processing stream, local gyrification indexes were calculated at each vertex along the 3D cortical mesh (using successive circular estimates at each vertex). This procedure resulted in a scalar output file aligned in standard space (similar to cortical

thickness) that was fed into general linear models to compare gyrification metrics between reading groups at each vertex along the cortical mesh. Maps were created using statistical thresholds of p=0.01 (equivalent to cortical thickness analyses) and were smoothed to a full width half maximum (FWHM) level of 5. The reduced group-level smoothing FWHM was necessitated due to prior smoothing at the individual level during algorithms implemented during the LGI procedure, resulting in a combined total FWHM of 26.

Clusterwise Correction for Multiple Comparisons

Following whole-brain regression analyses, multiple comparison correction was performed using a clusterwise procedure described previously (Hagler, et al., 2006; Segonne, et al., 2004) and adapted for cortical surface analysis. This procedure, which is available as part of the FreeSurfer processing stream, utilizes a simulation to obtain a measure of the distribution of the maximum cluster size under the null hypothesis. To accomplish this, a pre-cached normal distribution z-map was synthesized with the smoothing (FWHM) and thresholding parameters matched to original analysis ($p<0.01$). Areas of maximum clusters were recorded under these specifications, and the procedure was repeated for 10,000 iterations. Only clustered vertices are retained under the assumption that false positive vertices (i.e., vertices in which a significant relationship between group and thickness is only due to chance) would not appear next to each other. Once the distributions of the maximum cluster size were obtained, correction for multiple comparisons was accomplished by finding clusters in the original statistical maps using the same clustering threshold as was given in the simulation procedure. For each cluster, the p-value is the probability of seeing a maximum cluster of that size, or larger, during the simulation.

Remaining clusters (with a similar number of significant vertices to the multiple comparison simulation maps) would indicate that the result is not likely due to chance.

Statistical Analyses

All whole-brain vertex-wise regression analyses on the cortical surface were performed using "mri_glmfit," a general linear model tool within FreeSurfer. Significant group differences in cortical thickness and local gyrification index between reading groups, controlling for the effects of age, were thresholded at $p < 0.01$ prior to clusterwise correction procedures (described above). For ROIs surviving the multiple comparison correction procedure, mean cortical metric values were extracted per participant from each ROI and imported into SPSS version 18.0 to conduct all follow-up analyses.

RESULTS

Demographics

Demographic data is presented in **Table 1**. Prior to analysis, all demographic variables were examined for normality and the presence of outlying values (+/- 3 SD). The participants ranged in age from 6 to 15 years. The group of children with dyslexia was significantly older (M = 12.0 years, SD = 2.5) than the group of typical readers (M = 10.3 years, SD = 2.4), $t(74) = 3.12$, $p < 0.01$, although this difference is not large in terms of developmental differences. The groups did not differ in their distribution of handedness, $\chi^2(1) = 0.01$, $p = 0.93$, sex, $\chi^2(1) = .05$, $p = 0.82$, or ethnicity, $\chi^2(3) = 3.75$, $p = 0.29$. Because sex was equally distributed between the two reading groups, it was not included as a predictor in vertex-wise whole-brain analyses, but was examined as a between-

subjects factor in follow-up ROI-based analyses below. ANCOVA results confirmed there were no significant main effects of sex or interactions between sex and group in any of the resulting cortical ROIs.

All continuous measures of decoding, fluency, comprehension and IQ demonstrated equal variance between groups based on Levene's Test for Equality of Variances, except for the Verbal IQ measure, $p < 0.05$, in which case equal variances were not assumed and analysis utilized the Welch t-test. As expected, typical readers demonstrated higher Composite IQ, $t(74) = -5.12$, $p < 0.001$, Verbal IQ, $t(63.9) = -4.32$, $p < 0.001$, and Nonverbal IQ, $t(73) = -3.30$, $p < 0.01$, scores than the group of children with dyslexia. Typical readers also performed significantly higher (by definition) on all reading-related measures of single word decoding $t(74) = 11.27$, $p < 0.001$, reading fluency $t(51) = 6.26$, $p < 0.001$, and reading comprehension $t(68) = 9.59$, $p < 0.001$.

Supplementary Analysis of Attention

To determine if attention problems contributed to poor reading performance in the dyslexia group, children were classified based on a score of 6 or greater on either the inattention or hyperactivity subscales of the SWAN (a teacher report form), indicating a significant degree of inattention or hyperactivity symptoms. Of the children with dyslexia, 11/36 (1 missing data) scored at or above the cutoff on the hyperactivity subscale; 5 of these children also scored above cutoff on the inattention subscale. Independent sample t-tests between dyslexic children with and without attention difficulties revealed no significant differences on measures of single word reading, $t(35) = -0.81$, $p = 0.42$, reading fluency, $t(29) = -0.37$, $p = 0.71$, or reading comprehension, $t(29) = 0.75$, $p = 0.46$. Post-hoc

ANCOVA analyses within the dyslexia subgroup demonstrated that attention symptoms did not account for additional variance in resulting ROI cortical metrics ($p > 0.16$ for all regions), controlling for age.

Hypothesis I: Cortical Thickness Analysis

To address the hypothesis that children with dyslexia will have reduced cortical thickness compared to typical readers, a whole-brain vertex-wise regression analysis was conducted per hemisphere using the FreeSurfer general linear model regression tool (mri_glmfit). All participants' brains were co-aligned into a common stereotactic space and linear regression was performed at each vertex to assess regional differences in cortical thickness between groups across the entire cerebral mantle. Age was included as a covariate to control for expected age-related differences in cortical development.

Figure 1 shows results from the whole-brain analysis (thresholded at an alpha of $p < 0.01$) with the significance clusters surviving multiple comparison correction outlined in green. In support of Hypothesis I, regression results showed thinner cortex in individuals with dyslexia compared to typical readers in bilateral occipital-parietal, bilateral inferior frontal, and bilateral inferior temporal regions, as well as a cluster in the left anterior cingulated, controlling for age.

Table 2 reports the size (mm^2) of each cluster and corresponding cluster-wise p-value (CWP), the MNI coordinates for the location of maximum significance, and the effect size per cluster based on Cohen's d (ranging from 1.13 to 1.44).

Figure 2 depicts an enlarged view of the ventral occipitotemporal regions demonstrating the spatial distribution of thinner cortex found in children with dyslexia

overlayed with the Destrieux Atlas within FreeSurfer, a surface-based standard atlases distinguishing sulcal and gyral patterns. Significant effects included **inferior temporal regions** that spanned the middle temporal gyrus, inferior temporal sulcus and gyrus, collatoral transverse sulcus, and the occipito-temporal sulcus extending into the lateral aspect of the fusiform gyrus. The right hemisphere label also extended into the superior temporal sulcus and gyrus. Bilateral **parieto-occipital label** included the occipital pole, middle and superior occipital sulci and gyri, and occipital gyrus. The left hemisphere label extended superiorly into the intraparietal sulcus and superior parietal gyrus, while the right hemisphere label included a posterior section of the superior temporal sulcus Bilateral **inferior frontal** labels were mostly isolated to the orbital sulcus and gyrus. The left hemisphere **anterior cingulate** label (shown in Figure 1) included anterior and middle-anterior sulci and gyri.

Table 3 summarizes results from follow-up analyses of covariance (ANCOVA) for each of the cortical thickness ROIs with group (dyslexics, controls) and sex (male, female) as between-subjects factors, and age as a covariate. All 2-way and 3-way interactions were tested, with only the left hemisphere inferior frontal ROI showing a significant group-by-age interaction, $F(1,71) = 4.96$, $p < 0.05$. In this region, similar cortical thickness metrics were observed between younger reading groups, while older children with dyslexia revealed significantly reduced cortical thickness compared to typical readers. For the remaining cortical thickness ROIs, no other significant interactions emerged ($p > 0.13$) and interaction terms were subsequently dropped from the models. The predicted main effects of gender or age were not significant within any of the ROIs ($p > 0.05$). The main effect of group was significant and accounted for the majority of model variance such that children with dyslexia

showed thinner cortex than typical readers ($p < 0.001$ for all regions).

Follow-up Analyses of Non-linear Age Effects. A series of regression analyses were run to evaluate whether the inclusion of a quadratic age term significantly improved model fit when compared to the reduced model of age and group. **Table 4** shows the univariate statistics and regression weights for the full model including a quadratic age term, as well as the R^2 change between the full and reduced models. Of the seven cortical thickness clusters, three demonstrated a significantly improved model fit ($p < 0.01$) when including a quadratic age term in the full model: LH anterior cingulate (R^2 change = 0.108), LH occipital-parietal (R^2 change = 0.079), and RH inferior temporal (R^2 change = 0.086). Scatterplots demonstrating the relation of age and thickness measures by group are shown in **Figure 3**.

Hypothesis II: Local Gyrification Index Analysis

In order to address the hypothesis that children with dyslexia will have reduced gyrification compared to typical readers, linear regression analyses were performed at each vertex per hemisphere using the statistical tools as part of FreeSurfer. Age was included in the model as a covariate to control for age-related differences in regional gyrification indices. Cluster-wise multiple comparison correction was performed as described in the methods above.

Figure 4 shows LGI results from the whole-brain vertex wise analysis (thresholded at $p < 0.01$). In opposition to Hypothesis II, increased gyrification in children with dyslexia compared to typically developing readers were observed in several regions isolated to the left hemisphere, controlling for age. The clusters surviving multiple comparison correction are outlined in green: left cuneus and inferior occipito-temporal cortex.

Table 2 reports the size of each resulting cluster, the MNI coordinates for the location of maximum significance, and the effect size of each cluster based on Cohen's d. Significant group differences in left cuneus and inferior temporal LGI metrics demonstrated medium to large effect sizes (Cohen's d of 0.63 and 0.86 respectively).

Table 3 summarizes results from follow-up ANCOVAs for each of the LGI ROIs specifying group and sex as between-subjects factors, and age as a covariate. There were no significant 2-way or 3-way interactions for either ROI, and interaction terms were subsequently dropped from the models. The predicted main effect of gender was not significant for either ROI. In the left cuneus the predicted main effect of group was significant, $F(1,72) = 13.15$, $p < 0.001$, such that children with dyslexia showed increased gyrification than typically developing children. Age was also significant, $F(1,72) = 9.69$, $p < 0.01$, such that LGI values decreased with increasing age. Similarly, the predicted main effects of age, $F(1,72) = 7.82$, $p < 0.01$, and group, $F(1,72) = 22.23$, $p < 0.001$, were also significant, explaining a significant amount of variance in mean left inferior temporal LGI metrics.

Hypothesis III: Relation of Cortical Thickness to Reading Performance

Table 5 summarizes the bivariate correlations between mean cortical metrics and continuous indicators of age-standardized reading fluency and comprehension measures. **Figure 5** depicts ROIs from the whole-brain thickness analysis in which age-standardized reading measures significantly correlated with mean cortical thickness ($p < 0.05$). Reading fluency positively correlated with cortical thickness within right hemisphere inferior frontal and inferior temporal ROIs ($p < 0.05$). Reading comprehension positively correlated with

cortical thickness across all ROIs (bilateral inferior frontal, bilateral inferior temporal, bilateral occipito-parietal, and left anterior cingulate).

DISCUSSION

I examined cortical thickness and local gyrification via whole-brain vertex wise analyses in a large pediatric sample with identified dyslexia compared to typically developing readers. Overall, children with dyslexia demonstrated thinner cortex bilaterally within occipital-parietal, inferior frontal, and inferior temporal regions, as well as a lateralized cluster in the left anterior cingulate cortex. Reduced cortical thickness was accompanied by increased gyrification in the left cuneus and occipitotemporal cortex.

Areas of cortical differences in children with dyslexia partially align with previously identified circuits involved in reading, demonstrate regional correlations with reading fluency and comprehension measures, and support the concept of dyslexia as a reading disorder grounded in brain-based dysfunction. The following discussion will contrast the present results with previous neuroimaging studies of dyslexia and their convergence with contemporary neural reading models. In particular, findings of thinner and more gyrified cortex in the occipitotemporal cortex among children with dyslexia, in conjunction with a lack of cortical differences in temporoparietal regions, are of particular interest. Finally, cross-sectional neuroimaging studies of children and adolescents are challenging in that they capture brain morphology within a dynamic period of rapid neural development and skill acquisition. Thus, a consideration of typical brain maturation and experience-dependent neural plasticity will be presented to establish a context for interpreting present results.

Reading in the Brain

Revisiting the neural circuits that underlie reading, crucial contributions of several left hemisphere cortical regions converge to accomplish literacy. Written text is initially processed visually within the occipital lobe, with more complex visual features activating ventral occipitotemporal regions along an anterior gradient within a cortical area coined the visual word form area. Following the visual recognition of letter forms, a dual-route cascading model speculates a convergence of dorsal and ventral route processing to accomplish fluent reading. The dorsal route involves the left temporoparietal cortex (including the posterior superior temporal gyrus, supramarginal gyrus and angular gyrus) and mediates phonological decoding as a hypothesized site of integration between orthography and phonology. As reading skills develop, the ventral route (inferior temporal and fusiform gyri) is subsequently engaged in retrieving learned whole-word forms, thereby increasing reading speed and fluency and bypassing the slower process of letter-by-letter decoding, leading to the automaticity of word recognition that is central to proficient reading. An additional anterior reading circuit (comprised of the left inferior frontal gyrus) allows for recoding of written text into speech sounds. Functional over-activation in this area has been frequently observed in fMRI studies of dyslexia, generally interpreted as compensatory activation to offset dysfunction in posterior reading networks (Shaywitz, et al., 2002). However, the role of the inferior frontal gyrus as compensatory in reading is controversial, although its role in speaking words is clear.

The spatial distribution of reduced cortical thickness in children with dyslexia observed in the present study only partially overlaps with anatomical regions comprising the classic left hemisphere reading network. Most notably, there were no observed differences

in cortical metrics between typical and poor readers that remained after multiple comparison correction in temporoparietal regions, while the reduced thickness in inferior frontal regions centered on orbitofrontal cortex as opposed to Broca's area. In contrast, significant findings of reduced cortical thickness and increased gyrification in bilateral inferior occipitotemporal areas are spatially consistent with ventral reading network regions.

The Role of Temporoparietal Cortex in Reading

The relative importance of the temporoparietal region within the reading network (hypothesized to underlie sight-sound convergence) is supported by atypical functional activation within this area during reading tasks in children with dyslexia, as well as the observation that poor phonological awareness is a hallmark deficit of poor readers (Shaywitz & Shaywitz, 2005). Thus, the lack of structural differences in temporoparietal areas observed in the present study is somewhat unexpected. However, meta-analyses of fMRI studies of dyslexia show inconsistent functional results within dorsal stream temporoparietal regions; while adult studies largely demonstrate functional MRI underactivations in the left superior temporal gyrus in dyslexia, empirical syntheses of fMRI studies of children fail to show functional differences (Richlan, et al., 2011). In addition, magnetoencephalography (MEG) studies with higher temporal resolution consistently reveal underactivation of temporoparietal regions in children with dyslexia (Simos, Breier, Fletcher, et al., 2000). Despite mixed findings across functional studies of dyslexia, relatively few studies to date have assessed children with well-defined dyslexia so it is clear more work is needed in this area. Yet based on the present results in combination with prior studies of dyslexia, neural

correlates of disordered reading in children may differ from those of adults, possibly stemming from accumulated reading experience across the lifespan.

Due to the emerging evidence of generally null findings within temporoparietal areas in pediatric samples of dyslexia using fMRI, several authors have proposed revised models of reading to accommodate this unexpected observation. Although the cortical areas comprising the reading network are preserved, new models significantly differ in how such regions interact to accomplish fluent reading. In particular, less emphasis has been placed on temporoparietal regions as a primary site of phoneme-grapheme conversion, although it's role in phonological awareness is maintained. Instead, dysfunction of the ventral occipitotemporal cortex is proposed as a site of central disruption to reading network proficiency (Dehaene & Cohen, 2011; Kronbichler, et al., 2007; Price & Devlin, 2011; Schurz, et al., 2010).

Ventral Occipitotemporal Cortex in Reading

A recent meta-analysis of structural voxel-based morphometry studies show consistent occipitotemporal cortical differences in children with dyslexia compared to typical readers within the left fusiform gyrus, extending into the left inferior temporal gyrus (Linkersdorfer, Lonnemann, Lindberg, Hasselhorn, & Fiebach, 2012). In the present study, the concurrent observation of both thinner and more gyrified cortex in poor readers within the left ventral occipitotemporal (vOT) region is of particular interest.

Within the basic framework of a dual-route cascading model, Cohen and colleagues (2000) suggested that primary deficits in word reading may occur prior to phonological integration, particularly during early stage visual processing of orthographic information

within the visual word form area (VWFA). Anatomically, the VWFA largely encompasses the occipito-temporal sulcus, but also extends into areas within the fusiform gyrus and the inferior temporal gyrus (see **Figure 2**). The VWFA is reliably found adjacent and lateral to visual field maps, well situated to receive direct connections from primary ventral visual field areas V1 and V2. Although V1 and V2 respond to various contrast maps, they selectively activate when distinguishing the invariant visual properties of word forms, with increasing involvement of neurons as the signal progresses anteriorly across the cortical surface (Cohen, et al., 2000; Cohen, et al., 2002; Rauschecker, et al., 2011). This information is then combined to recognize word-forms within the VWFA, where functional activations in this area positively correlate with reading skill (Maisog, et al., 2008; Wandell, Rauschecker, & Yeatman, 2012), and behavioral reading improvement predicts increased neural response (Ben-Shachar, Dougherty, Deutsch, & Wandell, 2011). Moreover, the role of vOT cortex in word form recognition and processing are universally observed across languages as well as across varying orthographic depths (Richlan, 2014). More anteriorly within basal temporal language regions, functional activation of the vOT increases in response to previously encountered perceptual stimuli (visual, auditory, and tactile), especially during tasks that involve language processing (Price & Devlin, 2011).

The VWFA is also directly connected to distant cortical language areas including the temporoparietal junction and inferior frontal lobe via the ventral occipital fasciculus (Yeatman, Rauschecker, & Wandell, 2013). Thus, the VWFA serves a privileged role in communicating orthographic information to higher-level areas associated with phonological processing and articulating text. Dysfunction either within the VWFA, or emanating white matter pathways, would thus disturb adequate reading ability.

In line with the present findings of thinner cortex in vOT among poor readers, prior studies of individuals with dyslexia have reported consistent anomalies within this region including reduced gray matter volume (Kronbichler, et al., 2008; Raschle, et al., 2011), thinner cortex (Altarelli, et al., 2013), as well as altered functional activations during reading-related tasks (Richlan, Kronbichler, & Wimmer, 2009; Richlan, et al., 2010). In addition, a case study of selective damage to the left vOT area from stroke initially resulted in pure alexia with later recovery of short (3-5 letters) familiar words (Seghier, et al., 2012). When evaluated during an fMRI reading task, this patient demonstrated functional activation of the dorsal reading route involving the occipital cortex, the left superial temporal sulcus, and frontal premotor regions while reading, as well as behaviorally showed declining reading performance with increasing word length.

Thus, although deficient phonological processing is a classic hallmark of dyslexia, evidence for a primary dysfunction within vOT regions is also supported. As brain networks involved in reading are extensively interconnected yet spatially distinct, understanding the temporal engagement of these areas may provide insight into reading dysfunction. The use of MEG in reading studies allows high temporal resolution of reading-induced neural activation (observable even at the single word level), and offers clarity to fMRI studies in which the slow hemodynamic response yields poor discriminability between the relative timing of activations in response to single word reading. Reading in typical children initiates with early activation of the ventral occipitotemporal cortex, with subsequent involvement of the superior temporal cortex and angular gyrus, and ultimate activation of inferior frontal regions in a “feed forward” manner (Simos, et al., 2013).

However, children with dyslexia demonstrate atypical patterns in both intensity and latency of activations between regions. *Increased* activation was shown in vOT regions, while *decreased* activation occurred in posterior temporal regions (Rezaie, et al., 2011). Furthermore, readers with dyslexia tended to demonstrate simultaneous activation across the left hemisphere when reading, while typical readers showed separated peaks of neural activity temporally progressing across regions. Of note, fMRI studies consistently demonstrate reduced functional activation of the vOT during reading tasks, contrary to recent MEG findings. However, these differences may be reconcilable given the temporal delay of the hemodynamic response and that vOT activation occurs within the early stages of word processing. Furthermore, the temporal resolution of MEG studies distinguishes neural activity on a word-by-word basis during phonological decoding (as opposed to an averaged comparison between contrast levels in fMRI studies). This is important when considering that individuals significantly vary in their familiarity and automaticity when decoding some words compared to others, and these effects may be washed out when averaging a neural response across single word presentations.

The Interactive Account of reading

Given the mounting evidence of anomalous vOT structure and function in poor readers, this area was highlighted within an Interactive Account reading model (Price & Devlin, 2011). This model situates the vOT as an important integration site for perceptually acquired bottom-up inputs (orthography) and associated top-down "predictions" automatically supplied by higher-level cognitive input (i.e. phonological rules and semantics). In beginning readers with emerging phonological awareness, the functional

activations of the vOT are minimal as top-down connections from temporoparietal regions have yet to be established and strengthened. However, once a reader gains mastery of sight-sound convergence principles facilitated by temporoparietal regions (which is further strengthened by reading experience), this information contributes to top-down predictions when bottom-up stimuli are "word-like" in nature. Distinct visual information unique to specific words thus elicits coherent activations in phonological and semantic regions (generating prediction errors in word recognition), which in turn project back to the vOT for integration. According to the model, this integration "represents the intimate association between visual inputs and higher level linguistic representations that occurs automatically and is modulated by attention and task demands. Interpreting activation in vOT therefore requires consideration of the stimulus, experience-dependent learning, and context."

It is thus suggested that in typical beginning readers, vOT activation is elevated due to less-honed phonological or semantic predictions from higher order cortex. This results in increased neural demands and time reconciling these imprecise prediction errors, and ultimately laborious word identification. When applied to dyslexia, the model postulates that abnormally low vOT functional activation (consistently observed across prior fMRI studies of dyslexia) results from impoverished connectivity between vOT and top-down left hemisphere language regions. It is further postulated that a failure to form such connections between the vOT and higher-order modulatory regions stems from poorly developed phonological awareness in dyslexia. These deficits ultimately limit the backwards, top-down word recognition predictions, consequently leading to greater prediction errors.

Principles of the Interactive Account model in conjunction with recent MEG findings of poor discriminability in temporal activation peaks between the vOT and temporoparietal

areas provide an interesting perspective on reading dysfunction in the brain. As noted, poor phonological awareness in individuals with dyslexia may lead to increased prediction errors from top-down processing areas in the temporoparietal cortex. Poor resolution of grapheme-phoneme conversion (i.e. word decoding) is thus perpetuated, leading to cyclic and simultaneous co-activation of these two reading networks. In light of *increased* functional vOT activity among dyslexic readers in MEG studies, over-activation of the vOT may be an attempt to assimilate these decoding ambiguities that are not being efficiently predicted by phonological strategies, or may be due to an over-reliance on ventral stream processing. Alternatively, based on the present findings of atypical structural morphology (thinner and more gyrified cortex), inherent structural inefficiencies in this region may introduce a confound to proficient reading, providing an inherent mechanism for inefficient vOT word processing apart from (or in addition to) poor phonological awareness.

Finally, despite a predominate focus on structural and functional differences in the cortex of dyslexic readers, the integrity of white matter pathways interconnecting all of these spatially disparate regions cannot be neglected. Several studies have thus far demonstrated clear reductions in white matter integrity among pathways connecting cortical reading areas within the frontal, temporal, and parietal cortex in individuals with dyslexia (Steinbrink, et al., 2008; Vandermosten, et al., 2012; Yeatman, Dougherty, Ben-Shachar, & Wandell, 2012). In children, those demonstrating longitudinal increases in FA within the left inferior longitudinal fasciculus and left arcuate fasciculus performed better on reading measures than did children with decreasing FA over time. Furthermore, the association of white matter and behavioral reading scores were specific to left hemisphere reading pathways, with no association of reading scores and white matter development in right hemisphere homologous

pathways, or within non-reading related pathways. (Yeatman, et al., 2012). In adults, a positive correlation between arcuate fasciculus FA and cortical thickness within frontal and parietal regions was observed, preferentially in the left hemisphere (Phillips, et al., 2011). Reduced FA within frontotemporal white matter was also observed in a small sample of adults with dyslexia (Richards, et al., 2008). Morphologically, there is a strong developmental relation between white matter integrity and cortical metrics. In particular, the mechanisms by which white matter development influences cortical thickness and gyrification patterns are highlighted as a later point in the discussion.

Reduced Cortical Thickness in the Frontal Lobes

Several functional neuroimaging studies have identified functional over-activation corresponding to the inferior frontal gyrus (Broca's area) in both children and adults with dyslexia. As this area has been associated with subvocal rehearsal and articulation during reading tasks, it has been debated that such over-activation in impaired readers serves as a compensatory strategy during word reading resulting from poor phonological processing in temporoparietal cortices. Results of the present study did not show differences in cortical metrics between reading groups in the inferior frontal gyrus, although reduced cortical thickness in dyslexic readers was identified in bilateral orbitofrontal regions. A longitudinal study relating cortical thickness change and phonological skills in children found the strongest correlation of positive thickness growth and reading skills in left frontal perisylvian regions, but also observed a trend approaching significance within the left ventral orbitofrontal regions (Lu, et al., 2007); ventral frontal activations were spatially similar to the current findings of reduced thickness. The orbitofrontal cortex has been

previously implicated in affective reinforcement (reward/punishment) and decision-making (Kringelbach, 2005).

While the orbitofrontal cortex is not directly implicated in reading per se, this region has been identified as serving a cognitive role in conflict resolution and in flexible learning from probabilistic feedback (Tsuchida, Doll, & Fellows, 2010). Especially in light of the Interactive Account of reading in the brain, both of these skills are likely instrumental in the development of top-down predictions guiding effective decoding in beginning readers. In the macaque, extensive connections exist between the orbitofrontal cortex and cortical areas within the ventral visual stream (emanating from inferior temporal areas) as well as temporoparietal cortex within the dorsal stream (Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000). Given that dyslexia is defined as a *learning* disorder, findings of aberrant cortical metrics in higher-level executive areas in poor readers may contribute to the poor and inefficient acquisition of reading-related skills (such as learning strategies in developing phonological awareness and complex irregular phoneme-grapheme convergence rules).

Alternatively, atypical cortical thickness in bilateral orbitofrontal cortex in poor readers may be secondary to motivational and emotional vulnerability experienced by poor readers in the school setting that has been associated with early difficulty with reading and spelling when poor readers compare themselves to peers (Poskiparta, Niemi, Lepola, Ahtola, & Laine, 2003). Indeed, a recent pilot MEG study supports this perspective as children with dyslexia demonstrate abnormal cortical activity associated with performance goals with a focus on normative evaluations (Sideridis, Antoniou, & Simos, 2013).

Finally, the reliability and subsequent interpretation of cortical thickness measurements in the orbitofrontal cortex may be limited due to particular vulnerability of this region to susceptibility artifacts in MRI. Given their proximal location to the air-filled sinus cavity, signal contrast is often reduced. However, this phenomenon systematically affects all images, and thus would not explain observed group differences in thickness.

Similar to inferior frontal findings, reduced cortical thickness within the left anterior cingulate may also reflect poor learning specific to the development of reading skills in dyslexia. An early PET study revealed associations between reduced metabolism in the middle anterior cingulate and both attentional control and response monitoring during speech production (Paus, Petrides, Evans, & Meyer, 1993). A recent voxel-based study also identified reduced anterior cingulate gray matter volume in children with dyslexia when compared to age-matched typical readers (Krafnick, Flowers, Luetje, Napoliello, & Eden, 2014). Furthermore, thinner cingulate cortex was observed in a sample of pre-readers who later received a diagnosis of dyslexic (Clark, et al., 2014). Overall, resulting frontal areas of observed cortical thinning in poor readers in the present study coincide with frontal regions that potentially mediate reading development by inefficient response monitoring and conflict resolution, despite a lack of findings within the classic Broca's area involved in speech production.

Reduced Cortical Thickness in Parietal-Occipital Cortex

While the intra-parietal sulcus has been implicated in some reading studies, it lacks specificity to reading tasks, instead functioning more generally within the domain of attention and mental effort as evidenced by marked deactivation in dyslexic compared to

typical readers (Shaywitz & Shaywitz, 2008). In a recent fMRI meta-analysis of pediatric dyslexia studies, children with reading disorders showed bilateral inferior parietal under-activation compared to baseline, attributed to a failure to disengage default mode network when engaged in the task (Richlan, et al., 2011). However, more ventral occipito-parietal lesions have also been associated with selective deficits in processing relative letter order during word encoding, suggesting an additional role of visual encoding that may impact reading ability (Friedmann & Gvion, 2001). While the present study does not demonstrate differences in reading performance among poor readers with and without significant attention difficulties, co-morbidities of ADHD and learning disabilities are common and additional research in this area is warranted.

Reading Fluency and Comprehension

In the present study, age-standardized reading fluency and reading comprehension scores showed variable associations with cortical thickness across the ROIs. Reading fluency was minimally associated with cortical thickness, such that thicker cortex correlated with better performance in the right inferior frontal region. Alternatively, reading comprehension was more globally associated with cortical thickness, where all ROIs demonstrated significant positive correlations. A widespread association between cortical thickness and reading comprehension is not surprising. As dyslexia is a reading difficulty at the single word level, impaired decoding functions as a bottleneck to text comprehension. Thus, individuals who scored below cutoff on the single-word reading measure used to differentiate the two reading groups expectedly struggle with reading comprehension. For poor decoders, reading comprehension is likely further exacerbated by reduced vocabulary

from impoverished reading development, and by difficulty integrating text due to laborious single-word decoding. While effective and efficient reading comprehension is the ultimate goal of literacy, recent work has shown that the sub-processes that contribute to reading comprehension vary as to their effects on reading rate, accuracy, or comprehension. Although phonological and orthographic recognition skills contribute to single word reading accuracy, phonological awareness does not predict reading rate (Katzir, et al., 2006).

The right-lateralized correlations between cortical thickness and reading fluency performance are also interesting. Given that reading fluency requires speeded verbal output, its correlation with right prefrontal regions is in line with prior work demonstrating right functional activations during a similar verbal fluency task (Brown, et al., 2005), as well as atypical activation in right prefrontal areas associated with stuttering (De Nil, Kroll, Lafaille, & Houle, 2003). Finally, the lack of significant correlations between reading fluency and cortical thickness illustrates the important point that classification of dyslexia by reading fluency criteria may not adequately capture the essence of the underlying reading dysfunction.

The Human Cortex: Ontology and Development

Cortical Thickness. This study demonstrated largely bilateral reductions in cortical thickness among individuals with dyslexia compared to typical readers. Cortical thickness metrics have been consistently related to brain changes accompanying developmental, experiential, aging, and disease processes, where structural differences in relation to a typically developing comparison group are often interpreted as indicators of neuronal health and integrity. Cortical thickening is often conceptualized as increased dendritic arborization

from newly formed connections between existing neurons, or alternatively as increased myelination of existing axons extending within (or between) cortical layers (Benes, Turtle, Khan, & Farol, 1994; Paus, 2010). Increased cortical volume and thickness correlate with skill acquisition, and are often attributed to learning-dependent neuroplasticity.

In the context of literacy, increased cortical thickness in left perisylvian regions associate with reading acquisition in adult illiterates (Carreiras, et al., 2009). In children, gray matter volume increases are noted in cortical reading areas following experience-dependent behavioral improvement (Krafnick, Flowers, Napoliello, & Eden, 2011), and in dyslexic children following intensive reading interventions (Shaywitz, et al., 2004). On the other hand, cortical thinning is often conceptualized as secondary to either synaptic pruning, or neuronal loss. In adults, cortical thinning is often associated with poorer cognitive function and compromised neuronal health or degeneration due to disease or aging processes. In children however, cortical thinning is an expected stage of cortical maturation.

Cortical thickness demonstrates an inverted U-shaped developmental trajectory implicating early cortical thickening, followed by an extended period of gray matter loss. Several studies have demonstrated mild cortical thickness increases in early childhood, peaking between ages 8-11 (depending on brain region), followed by a period of accelerated cortical thinning throughout adolescence and young adulthood that stabilizes around age 30 (Lyall, et al., 2014; Schnack, et al., 2014; Sowell, et al., 2004; Zhou, Lebel, Treit, Evans, & Beaulieu, 2015). Other studies have reported a much earlier peak in cortical thickness trajectories, with a longitudinal study of infants finding maximal cortical thickness at 2 years of age (Lyall, et al., 2014) and a second study demonstrating steady declines in cortical thickness from age 4 onward (Brown & Jernigan, 2012). Furthermore, regional variations in

cortical growth and reduction are apparent, such that increasing cortical thickening in left inferior frontal and bilateral posterior perisylvian regions is often accompanied by simultaneous thinning in right frontal and bilateral parieto-occipital cortices. Interestingly, regions that demonstrate substantial cortical thickening throughout childhood correspond well to reading networks, and left lateralized gray matter thickening predicts vocabulary development over time (Sowell, et al., 2004). Furthermore, higher mean fractional anisotropy of the arcuate fasciculus (an important white matter pathway in reading) is strongly associated with increased cortical thickness along its entire trajectory, encompassing Broca's area, prefrontal cortex, the temporo-parietal junction, inferior parietal cortex, and superior/middle/inferior temporal cortex, proximately in the left hemisphere (Phillips, et al., 2011). Overall, cortical development is a complex process, incorporating both age-dependent cortical reduction effects with neuroplasticity and cortical growth secondary to experience-dependent skill acquisition. Observed widespread reductions of cortical thickness reflect typical age-dependent brain maturation, with a consensus of prolonged thinning of the cortex throughout childhood and adolescence into adulthood.

Several mechanisms of developmentally driven cortical thinning have been suggested. As the brain matures throughout childhood, selective pruning minimizes less utilized and arbitrary connections between neurons – leaving behind connections with the most functional relevance and utility. Alternatively, cortical thinning may follow from the conversion of gray matter into white matter as axonal myelination expands into the lower cortical layers, supported by an inverse relation between gray and white matter volumes across brain maturation (Giedd, et al., 1999; Jernigan, Trauner, Hesselink, & Tallal, 1991; Sowell, et al., 2004). The present findings demonstrate thinner cortex in readers with

dyslexia compared to typical readers controlling for both linear and nonlinear age effects. Although lag hypotheses have been previously suggested to account for behavioral discrepancies in poor and skilled readers (Beech & Harding, 1984), longitudinal studies examining the growth slopes of reading development have not supported this trend and instead are more consistent with a deficit model (Francis, Shaywitz, Stuebing, Bennet, & Fletcher, 1996). Therefore, the present findings of reduced cortical thickness and gyrification are not likely due to a delay in cortical development, especially given the specificity of cortical effects within reading circuits and the persistence of neuroanatomical differences into adulthood.

From a deficit viewpoint, findings of reduced cortical thickness may alternatively arise from a complex interaction between genetic predisposition that place the brain at risk and environmental influences related to the capacity to access the printed word. Upon reading acquisition, this genetically influenced risk (possibly affecting only one or more particular components of the network) then instigates a cascading effect on connectivity with related areas, ultimately leading to a pattern of aberrant structural/functional integrity throughout the network. As previously highlighted, the primary site of dysfunction in dyslexia has long been centered within the temporoparietal junction given its role in phonological processing. Yet ventral occipitotemporal cortex has also demonstrated consistent gray matter structure/function abnormalities and more uniquely, demonstrates reduced cortical thickness accompanied by increased gyrification within the present study.

Gyrification. The process of gyrification allows for increased cortical surface area within the static confines of intracranial volume. Increased gyral patterns are more pronounced in cognitively advanced species in order to accommodate the cerebral expansion

of tertiary association areas that support evolutionarily advanced cognitive abilities (Kaas, 2013). In humans, early gyral and sulcal formations manifest between 10-16 weeks of gestation with cortical folding increasing substantially during the third trimester to resemble a pattern consistent with the adult brain (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995). Following birth, the gyrification index declines by 18% throughout development and into early adulthood (Armstrong, et al., 1995; Klein, et al., 2014). Proposed mechanisms for developmental gyrification reductions include increasing gyral width following increased input/output fiber connectivity and myelination of underlying white matter (Kochunov, et al., 2005).

Late postnatal gestation periods are particularly vulnerable to disruptions in the gyrification process; specific events during this developmental period have been linked to anomalous cortical folding and subsequent adverse behavioral outcomes (Dubois, et al., 2008). For example, increased left-lateralized gyrification of the Sylvian fissure is related to better language function, with asymmetries observed as early as 20-40 gestational weeks (Sun & Hevner, 2014). Premature birth increases risk for the development of a learning disability later in life (Guarini, et al., 2010; Wocadlo & Rieger, 2007). In accordance with accelerated gyrogensis in late pregnancy, preterm infants demonstrate greater bilateral temporal lobe gyrification compared to children reaching full-term gestation, with the extent of cortical folding negatively related to reading scores (Kesler, et al., 2006). Finally, as temporal and frontal lobes are last to develop, these areas may be particularly vulnerable to even mild disruptions in late gestational development. Although prenatal and birth variables were not assessed in the present study, even minor variations in gestational length and birth weight have been associated with increased risk of reading disorders (Kirkegaard, Obel,

Hedegaard, & Henriksen, 2006), as well as increased vulnerability for atypical temporal lobe gyrification (Kesler, et al., 2006). This would be an interesting direction for future studies as little is known regarding the mechanisms of atypical sulcal and gyral formations in developmental disorders.

To date, few studies have examined localized gyrification in children with dyslexia. Partially consistent with the present findings, children with dyslexia, as well as a pre-reading group with positive family history, both demonstrate atypical gyrification patterns (more sucli of smaller size) in left occipitotemporal and temporoparietal regions (Im, Raschle, Smith, Ellen Grant, & Gaab, 2015). Although early studies demonstrated reduced gyrification in dyslexic adult males calculated by a 2-dimensional gyrification index (ratio of manually drawn outlines of pial surface to perimeter of convex hull), these results are limited as calculated folding patterns are quite sensitive to slice orientation in this method (Casanova, Araque, Giedd, & Rumsey, 2004).

Research into the ontology of cerebral gyrification has provided several mechanisms of gyrogenesis in utero. Although allowing for distinct mechanistic pathways to the formation of gyri and sucli, the varied contributions demonstrated by each perspective are complex and may not be mutually exclusive. One hypothesis postulates differential growth rates among cortical layers, where outer cortical layers expand at a faster rate than inner sheets, leading to a buckling of the cortical mantle. Alternatively, the 'axon tension' hypothesis proposes that axons mechanically influence gyral formation by pulling together functionally interconnected cortical areas constrained by short cortico-cortical pathways (Van Essen, 1997). This process supports neural efficiency by minimizing axonal distance between communicative brain areas, thus enhancing neural signal transduction speed.

Primate studies demonstrate a correspondence of white matter development and changes in gyrification, adding support to the axon tension hypothesis. In humans, gyrification is greatest in parieto-occipito-temporal and prefrontal regions, consistent with preferentially dense cortico-cortical connections in this areas (Zilles, Armstrong, Schleicher, & Kretschmann, 1988). The high regional density of connections within the vOT is supported by a recent DTI study revealing extensive short and long-range white matter connectivity emanating from vOT cortex, including the inferior longitudinal fasciculus, the inferior frontal occipital fasciculus, and the ventral occipital fasciculus (Yeatman, et al., 2013).

While intrinsic vulnerabilities in cortical morphology may underlie poor reading development, reading is also an acquired cognitive skill dependent on both language development and experiential neuronal plasticity. While reading acquisition certainly stands to influence cortical development through experience-dependent learning, genetic and maturational processes may facilitate or impede the initial acquisition of reading skills. Considering the observed pattern of cortical differences between typical readers and those with dyslexia, a chicken versus egg problem emerges. Are these anatomical differences due to aberrant structural development, or are they secondary changes from an impoverished reading experience? Even if the underlying reading difficulty does have an intrinsic or maturational basis, would this fully explain the extent of cortical differences? Recent neuroimaging studies of pediatric dyslexia have attempted to disentangle the relative contributions of these developmental and experience-driven effects.

Mechanisms for Cortical Differences in Dyslexia

Reading Experience. Children who struggle to read don't have access to print. By the end of first grade, high achieving readers were exposed to approximately three times as many words as low achievers (Allington, 1984). These effects are apparent as early as midway through first grade between poor and efficient readers (Biemiller, 1977-1978). This gap continues to widen throughout education advancement and is difficult to remediate (Torgesen, et al., 2001).

A recent study investigated this phenomenon of experience-dependent differences by comparing gray matter volume between children with dyslexia and two separate control groups; matched on age and reading level (Krafnick, et al., 2014). When compared to *age-matched controls*, children with dyslexia demonstrated reduced gray matter volume in the middle temporal gyrus bilaterally, left anterior cingulate gyrus, right precentral gyrus, right middle frontal and right anterior superior temporal areas. However, when mean gray matter volume in the dyslexic group was contrasted against a control group of younger children *matched on reading level* (within the same ROIs identified in the age-matched sample), reduced gray matter volume in the dyslexia group was only found in the left middle temporal gyrus. The authors interpret the lack of cortical volume differences between dyslexics and reading-matched controls as evidence for reading experience accounting for significant cortical variance that has been demonstrated in prior studies with age-matched samples.

Although Krafnik's reading-matched design attributed many cortical effects between good and poor readers to reading experience, it was limited in that the reading-matched comparison analyses were two-sample t-tests without controlling for age-expected cortical changes between the younger (mean age of 7.4 years) and older (mean age of 9.8 years)

reading groups. Although the reading-matched design did not demonstrate differences in vOT regions, volumetric differences may be obscured based on findings of reduced thickness in conjunction with increased gyrification in this area (as demonstrated in our results), an interaction that may result in comparable volume but overlooks significant differences in morphology. Indeed, a similar study design evaluated cortical thickness within a experimentally defined region of vOT cortex that selectively responded in a fMRI design to respond selectively to words, as opposed to faces or houses (Altarelli, et al., 2013). Results from two independent datasets found that dyslexic readers had reduced cortical thickness in the area of the left vOT that specifically activated to words, compared to age-matched controls. In a reading-matched design using the same region of interest, dyslexic readers again showed a thinner cortex compared to younger intact readers, just to a smaller spatial extent.

In adults, experience-dependent gray matter differences have been observed. In a unique study comparing brain volumes between individuals with literacy acquired as adults with carefully matched illiterates (Carreiras, et al., 2009), reading skill acquisition resulted in increased gray matter volume within areas of the left temporo-parietal junction, as well as in bilateral angular, dorsal occipital, and middle temporal gyri. Comparable to the pediatric age-matched designs above, a study comparing reading skill and cortical morphology in an adult sample may be better suited to differentiate learning-dependent changes outside of a dynamic stage of cortical growth. Goldman and Manis (2013) evaluated the relations between regional metrics of cortical thickness, reading skill, and print exposure in adults. Overall, reading skill positively predicted cortical thickness among all regions within the left hemisphere reading network. Furthermore, increased print exposure significantly accounted

for additional variance in thickness within the left hemisphere reading network beyond reading skill alone. In pediatric developmental studies of reading, an interaction of cortical growth secondary to reading experience and developmental global cortical thinning is likely. As cross-sectional designs only show age-related variability and are only proxies of change, future studies employing longitudinal study designs are needed.

Innate Brain Vulnerability in Dyslexia. While the process of learning to read undoubtedly accounts for some variance in brain morphology between typical and disabled readers, experience alone cannot account for the deficits in initial reading acquisition among dyslexic children. The extent of morphological changes dependent on reading experience in pediatric dyslexia is challenged by findings in pre-readers and those with a genetic predisposition for reading impairment. Pre-reading children with a positive family history of developmental dyslexia had reduced gray matter volume in left occipitotemporal areas, left fusiform gyrus, bilateral temporoparietal regions, and the right lingual gyrus (Raschle, et al., 2011). Reduced gray matter volume in occipitotemporal and temporoparietal regions correlated with poor rapid automatized naming (a robust predictor of later reading skill), and demonstrated reduced functional activations during a phonological processing task (Raschle, et al., 2011; Raschle, et al., 2012). Children with a genetic predisposition to dyslexia also show stronger cortical thickness co-variations between left language areas and homologous right hemisphere regions compared to children with no family history of dyslexia (Hosseini, et al., 2013).

In addition, results from a longitudinal study of 6-7 year old children learning to read a shallow orthography (Norwegian) suggest that children who were later identified with developmental dyslexia in adolescence had thinner cortex prior to reading acquisition in left

hemisphere lingual gyrus, Heschl's gyrus, middle cigulate and medial frontal regions, as well as right orbitofrontal cortex (Clark, et al., 2014). Longitudinal analyses revealed overall stable cortical thickness in dyslexic children within these regions over time, while typical readers start out with a thicker cortex that gradually thins to match that of dyslexic readers. Many of the pre-reading differences in cortical thickness at ages 6-7 resolved by ages 11-12 revealing a different cross-sectional pattern of thinner cortex in dyslexic readers post-literacy. These late identified differences consisted of cortical thinning in the left hemisphere temporoparietal cortex, fusiform region, visual word form area, and inferior frontal gyrus, as well as right hemisphere anterior cingulate cortex and Heschl's gyrus. Unfortunately, the authors did not specify whether these post-literacy differences occurred due to longitudinal thinning in dyslexic readers, or thickening in typical readers following reading acquisition. In all, overlap between cortical thinning in individuals at risk for dyslexia (particularly in ventral occipitotemporal regions), likely suggests a neural vulnerability affecting reading acquisition that persists post-literacy.

While compelling evidence supports several ontological mechanisms for differences in cortical morphology between dyslexic and typical readers, most likely environmental effects (such as reading exposure) and biological effects (genetically determined variations/disadvantages of cortical structure) share reciprocal causation. While inherent vulnerability of reading related structures (either through genetic influence or disruptions in typical brain development in utero) impede early and efficient reading acquisition. Subsequent poor and laborious reading, characteristic of individuals with dyslexia, contributes to an impoverished overall reading experience with less reading exposure.

Conversely, less reading exposure adversely limits further development of reading skill and efficiency.

Limitations and Future Directions

Limitations. Although advances in brain imaging techniques have provided a novel and insightful methodology for examining correlates of brain tissue in vivo, these methodologies are far from being irreproachable. While structural imaging protocols were selected to minimize distortions, certain anatomical regions are more susceptible to unavoidable artifacts and signal degradation based on proximity to the air-filled cavities. Further, linear transformations of raw data are necessary for standard-space alignment of volumes to perform vertex-wise analyses. While this process inherently results in some alignment error, contemporary spherical alignment and transformation techniques based on cortical sulcal/gyral patterns utilized in FreeSurfer aim to minimize these issues and provide good registration between subjects.

A second imaging concern is the large number of statistical tests required to perform a vertex-wise analysis across the entire cerebral mantle leading to an inherent limitation to cortical thickness studies, introducing a significant multiple comparison problem. Given the relative novelty of neuroimaging techniques, statistical approaches are not well developed. However, targeted statistical solutions addressing such limitations are gradually improving in the field. While correcting for roughly 150,000 vertex-based analyses across the cortical mesh for each hemisphere presents as a daunting task, it is important to keep in mind that vertex-based cortical metrics are not independent observations within subject, and instead significantly co-vary with neighboring measurements across large regions. Monte Carlo

simulation approaches as utilized in the present study are widely adopted as a standard approach for multiple comparison correction. This technique does not solely rely on thresholding z statistics at each vertex as standard practice in independent statistical analysis. Instead, the resulting cluster-size of contiguous vertices demonstrating significance above a certain threshold in the initial vertex-wise analysis, are compared to a simulated z-distribution consistent with both the significance level and smoothing parameters of the initial analysis. Thus, a second threshold is determined to define clusters that are spatially either the same size or larger compared to a distribution of resulting cluster sizes observed in simulations. This study employed particularly conservative thresholding criteria, adopting a vertex-wise threshold of $p<0.01$ and a cluster-wise threshold of $p<0.05$.

A third limitation is introduced by combining participants from three different studies. In regards to imaging limitations, FreeSurfer morphometric procedures have demonstrated good test-retest reliability across scanner manufacturers and field strengths (Han, et al., 2006), and across various sequence parameters (Hagler, et al., 2006; Jovicich, et al., 2006; Wonderlick, et al., 2009). Additionally, T1 acquisition parameters were similar across studies due to prospective intentions of merging these data. Thus, the effects of combining differing study samples is likely minimal, especially in light of the large effect sizes and observed power that was observed in resulting analyses. However, despite imaging sequences being closely matched, different behavioral measures were employed between studies introducing additional variance in identification of participants on reading and IQ measures.

Finally, IQ scores were obtained to exclude individuals on the basis of intellectual disability, and were not utilized as predictor variables in any subsequent models assessing

cortical metrics and/or reading skill. While many previous studies utilize IQ as a covariate to control for general cognitive ability, this practice is strongly debated (see (Dennis, et al., 2009). Although IQ scores significantly differed between typical and poor readers in the present study, the inclusion of dyslexic readers across a full range of IQ scores enhances the generalizability and external validity of findings. In individuals with poor reading (and subsequent poor vocabulary development), IQ scores tend to underestimate cognitive ability as this measure relies heavily on verbal processing. Furthermore, IQ-achievement discrepancy models commonly used to classify dyslexia are increasingly unsupported. A large-scale behavioral reading study did not support the validity of discrepancy classification in dyslexia (Francis, et al., 1996). Functional neuroimaging studies using distinct modalities (fMRI and MEG), also fail to demonstrate any differences in neural activation within reading areas as a function of IQ (Simos, Rezaie, Papanicolaou, & Fletcher, 2014; Tanaka, et al., 2011).

Future Directions. Early studies of familial occurrence and reading dysfunction in monozygotic twins have suggested a substantial genetic basis for dyslexia that may be related to brain development. Thus far, 9 loci have been identified and replicated as dyslexia susceptibility genes (DYX1 - DYX9). Although the combined genetic effects of these loci fail to explain the strength of dyslexia heritability rates, they have demonstrated various roles in subtle cortical and white matter disruptions, particularly in the period of neonatal brain formation. As discussed in several reviews of molecular genetics in developmental dyslexia, dyslexia susceptibility genes have been shown to influence: neurite outgrowth and density in cortical layers, axonal guidance, neuronal positioning and connectivity, and dendritic growth and differentiation (Eicher & Gruen, 2013; Gabel, Gibson, Gruen, &

LoTurco, 2010; Kere, 2014). In genetic neuroimaging studies, variants of these genes influence white matter volume in temporoparietal regions, particularly along pathways connecting the middle temporal gyrus with the inferior parietal lobe (Darki, Peyrard-Janvid, Matsson, Kere, & Klingberg, 2012), as well as cross-callosal fibers connecting hemispherically homologous regions within the superior parietal and lateral occipital cortex, and the fusifurm gyrus (Scerri, et al., 2012). Genetically linked variations in cross-callosal fibers may therefore provide a mechanism underlying the hemispherically symmetric findings of reduced thickness in the present study. While additional studies are needed fully explain the heritability of developmental dyslexia, converging evidence points to a genetic component. The identification of developmental mechanisms underlying gross structural findings presently observed in neuroimaging studies of dyslexia is of great interest. In particular, studies that bridge levels of inference (genes, micro/macro structures, cellular activations and behavioral expression or experience) would be increasingly informative. One example includes a recent study demonstrating negative correlations between choline and glutamate concentrations (implicated in learning) and reading skill in emergent readers (Pugh, et al., 2014). Another interesting future direction may include studies evaluating the complex interaction between genetics and prenatal environmental factors to gain insight into additional mechanistic factors of developmental disabilities.

Conclusions

In conclusion, children with dyslexia demonstrate a pattern of thinner cortex in several regions previously associated with the reading network. In the left inferior temporal and cuneus regions, thinner cortex is accompanied by increased gyrification. These cortical

effects are apparent even when controlling for both linear and non-linear developmental age effects, are similar for boys and girls, and do not vary based on the co-occurrence of significant attention symptoms. The left ventral occipitotemporal region has been consistently identified in both functional and structural neuroimaging pediatric studies of developmental dyslexia, gaining support as a key region underlying disordered reading. Since successful reading depends on interaction between several distant cortical regions, the relative strength and contribution of each area within the network has been debated. One perspective highlights dysfunction in the visual word form area (situated in ventral occipitotemporal cortex) as the primary cause of deficit in dyslexia, interrupting subsequent cascaded information to down-stream phonological integration areas. In the Interactive Association model, the ventral occipitotemporal cortex is designated as the site of grapheme-phoneme integration, although reading deficits are postulated to follow from impaired phonological awareness leading to inefficient predictions from top-down nodes in the temporoparietal junction. Thus, future explorations into white matter connectivity between distant areas in the reading circuit are of importance.

While there have been support for induced changes in brain morphology related to reading experience and print exposure, these differences cannot adequately explain dyslexia when appropriately characterized by an initial deficit in reading acquisition. Dyeslxia shows a strong genetic component, with atypical cortical metrics observed in those with a family history of reading impairment, as well as in pre-readers who were subsequently diagnosed with dyslexia. Most likely, there is an interaction between genetics and environmental factors or experience, illustrating the challenge and complexity in identifying underlying mechanisms of disordered reading. This is especially true during a period of dynamic brain

change typical of childhood neural development, where longitudinal studies are necessary. However, genetic research has identified several mechanisms for presently observed differences in cortical metrics, particularly effecting neuronal migration and proliferation, along with dendritic growth between gray matter layers and axonal long-range white matter connectivity. Thus, aberrant gyrification findings are of particular interest given their susceptibility to genetic influence and adverse prenatal factors in the late phase of gestation.

Overall, this is the first known large-scale cross-sectional examination employing vertex-wise whole-brain analysis to measure cortical thickness and gyrificaiton in children with dyslexia. In particular, this is the only known study applying contemporary 3-dimensional local gyrification index procedures in this population. Results indicate that children with dyslexia have thinner cortex in bilateral inferior temporal, occipito-parietal, and orbitofrontal cortex, as well as a region within the left anterior cingulate. Increased gyrification was observed in the left cuneus and inferior temporal cortex. While classification criteria of dyslexia are variable across studies (possibly explaining some between-study result variance), this study identified children with reading disability using single word decoding performance consistent with contemporary definitions. As demonstrated by variable associations between cortical thickness and reading fluency/comprehension performance across ROIs, cortical regions contributing to secondary reading skills may not overlap with reading circuits dedicated to accurate whole word decoding. Finally, although this study successfully demonstrated regional differences in cortical metrics in developmental dyslexia, longitudinal studies utilizing multi-modal imaging techniques incorporating reading-related behavior and genetics are needed to fully grasp the neural basis of developmental dyslexia.

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Table 1. Demographic and behavioral variables

	Dyslexic Readers (n=37)	Typical Readers (n=39)	Effect Size (Cohen's D)
Years of Age at MRI*	12.02 (2.51)	10.27 (2.40)	0.71
Sex (% Male)	51	49	
Ethnicity (% of group)			
Hispanic	43	38	
African American	54	46	
Caucasian	3	13	
Other	0	3	
Handedness (# Left Handed)	5	5	
IQ Total Composite**	88 (11)	102 (11)	1.27
IQ Non-Verbal Composite*	93 (16)	104 (15)	0.70
IQ Verbal Composite**	86 (10)	99 (16)	0.97
Single Word Decoding**	79 (10)	108 (13)	2.50
Reading Comprehension**	78 (12)	104 (11)	2.25
Reading Fluency**	83 (13)	102 (8)	1.76

*$p<0.01$; **$p<0.001$; Continuous variables presented as mean(std dev.); Data unavailable: Comprehension (Dys=6); Fleuncy (Dys=6; Con=17) IQ Verbal (Dys=2; Con=1); IQ Non-Verbal (Dys=1): IQ Total (missing verbal subscale for 3 participants and non-verbal subscale for 1 participant); All reading measures and IQ data presented as age-corrected standard scores

Table 2. Descriptive report of resulting corrected clusters showing between-group cortical differences.

	Cluster Size	**CWP**	**MNI Coordinates**			**Mean Metric (SD)**		**Effect Size**	**Brodmann**
	(mm^2)	*(p-value)*	X	Y	Z	Dyslexia	Control	(Cohen's d)	**Area**
Cortical Thickness									
LH Anterior Cingulate	1953	<0.001	-11	12	45	2.97(0.19)	3.20(0.19)	1.27	24,32
LH Inferior Frontal	1096	0.016	-23	43	-12	2.93(0.19)	3.18(0.25)	1.13	11
LH Inferior Temporal	4276	<0.001	-54	-38	-17	2.93(0.14)	3.16(0.18)	1.43	20,21,22,37
LH Occipito-parietal	6223	<0.001	-19	-85	37	2.13(0.11)	2.32(0.21)	1.13	17,18,19,
RH Inferior Frontal	2395	<0.001	31	41	-12	2.75(0.14)	2.99(0.19)	1.44	10,11
RH Inferior Temporal	3030	<0.001	45	-28	-4	2.89(0.13)	3.09(0.16)	1.37	21,22,37
RH Occipito-parietal	5488	<0.001	19	-100	8	2.03(0.12)	2.22(0.20)	1.15	17,18,19
Local Gyrification Index									
LH Cuneus	1016	0.010	-9	-88	19	3.00(0.18)	2.89(0.17)	0.63	18,19
LH Inferior Temporal	1802	<0.001	-45	-22	-25	2.69(0.13)	2.59(0.10)	0.86	20,21,37

Table 3. ANCOVA results for between-subjects effects of ROI mean cortical metrics.

	Overall Model Fit		**Gender**		**Age**		**Group**	
	$F_{(3,72)}$	Adjusted R^2	$F_{(1,72)}$	η^2	$F_{(1,72)}$	η^2	$F_{(1,72)}$	η^2
Cortical Thickness								
LH Anterior Cingulate	10.74**	0.280	2.47	0.033	2.95	0.039	17.84**	0.199
LH Inferior Frontal	*11.18***	*0.289*	*0.04*	*0.001*	*6.78*	*0.086*	*15.85***	*0.180*
LH Inferior Temporal	12.50**	0.315	3.28	0.044	0.13	0.002	31.93**	0.307
LH Occipito-parietal	9.10**	0.245	3.04	0.041	0.80	0.011	18.51**	0.205
RH Inferior Frontal	10.80**	0.282	0.57	0.008	4.22	0.055	17.71**	0.197
RH Inferior Temporal	9.11**	0.245	1.34	0.018	0.26	0.004	21.40**	0.229
RH Occipito-parietal	8.56**	0.232	3.28	0.044	0.15	0.002	18.96**	0.208
Local Gyrification Index								
LH Cuneus	6.13**	0.170	1.34	0.018	9.69*	0.119	13.16**	0.154
LH Inferior Temporal	7.95**	0.217	0.01	<0.001	7.82*	0.098	22.23**	0.236

* $p<0.01$; ** $p<0.001$; η^2 = partial eta-squared.
LH inferior frontal region showed a significant age by group interaction ($F(1,69)=4.60$, $p=0.036$).

Table 4. Comparisons between reading groups using linear (reduced) versus non-linear (full) ANCOVA models.

	Full Model: $y = \alpha + \beta(group) + \beta(age) + \beta(age^2) + \varepsilon$					Model Comparison
	Overall Model Fit		Beta Weights of Predictors			
	$F_{(3,72)}$	Adjusted R^2	*Group*	*Age*	*Age²*	R^2 Change
Cortical Thickness						
LH Anterior Cingulate	15.55**	0.368	0.44**	3.23*	-3.49*	0.108**
LH Inferior Frontal	11.47**	0.295	0.41**	0.54	-0.81	0.006
LH Inferior Temporal	12.30**	0.311	0.57**	1.77	-1.73	0.026
LH Occipito-parietal	11.48**	0.295	0.45**	2.89*	-2.99*	0.079**
RH Inferior Frontal	11.13**	0.288	0.44**	0.95	-1.17	0.012
RH Inferior Temporal	12.78**	0.320	0.49**	3.05*	-3.11*	0.086**
RH Occipito-parietal	8.63**	0.234	0.46**	1.95	-2.00	0.035
Local Gyrification Index						
LH Cuneus	7.00**	0.194	-0.40	-2.38	2.05	0.037
LH Inferior Temporal	7.97**	0.218	-0.51	-0.54	0.24	0.001

*$p<0.01$; **$p<0.001$

Table 5. Spearman's rho correlations between cognitive variables and ROI cortical metrics.

	Reading Measure			Intellectual Quotient (IQ)		
	Decoding	**Fluency**	**Comprehension**	**Verbal**	**Non-Verbal**	**Full-Scale**
	(N=76)	*(N=53)*	*(N=70)*	*(N=73)*	*(N=75)*	*(N=76)*
	rho (ρ)	rho (ρ)	rho (ρ)	rho (ρ)	rho (ρ)	rho (ρ)
Cortical Thickness						
LH Anterior Cingulate	0.472**	0.201	0.424**	0.278*	0.190	0.267*
LH Inferior Frontal	0.464**	0.087	0.381**	0.230	0.080	0.212
LH Inferior Temporal	0.514**	0.246	0.434**	0.285*	0.100	0.232*
LH Occipito-parietal	0.549**	0.233	0.493**	0.297*	0.197	0.274*
RH Inferior Frontal	0.549**	0.364**	0.513**	0.257*	0.169	0.260*
RH Inferior Temporal	0.451**	0.282*	0.363**	0.346**	-0.008	0.182
RH Occipito-parietal	0.521**	0.110	0.432**	0.210	0.199	0.240*
Local Gyrification Index						
LH Cuneus	-0.263*	-0.230	-0.299*	-0.314**	-0.045	-0.259*
LH Inferior Temporal	-0.306**	-0.054	-0.294*	-0.252*	-0.049	-0.201

*$p<0.05$; **$p<0.01$

Reading fluency scores were unavailable for 23 participants (17 controls, 6 dyslexics)

Reading comprehension scores were unavialbel for 6 participants in the dyslexic group

Figure 1. Results from whole-brain vertex-wise analysis of cortical thickness between reading groups, controlling for age (thresholded at $p<0.01$). Regions that survived a cluster-based multiple comparison correction procedure are outlined in green (cluster-wise threshold $p<0.05$).

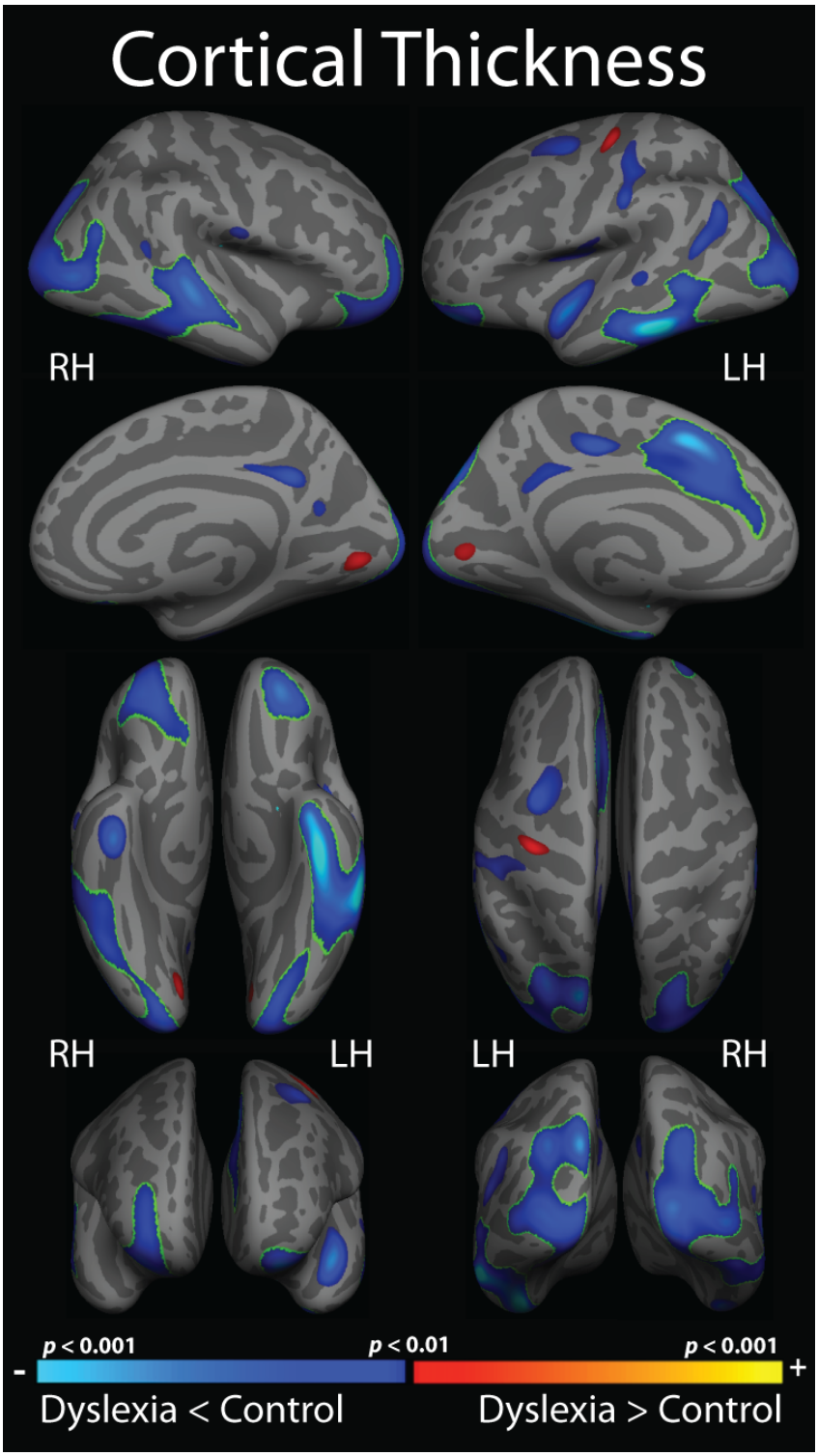

Figure 2. Corrected results from vertex-wise analysis of cortical thickness between reading groups, controlling for age. Anatomical segmentations correspond to Destrieux atlas, a surface-based anatomical parcellation based on sulcal and gyral patterns available within the FreeSurfer processing stream.

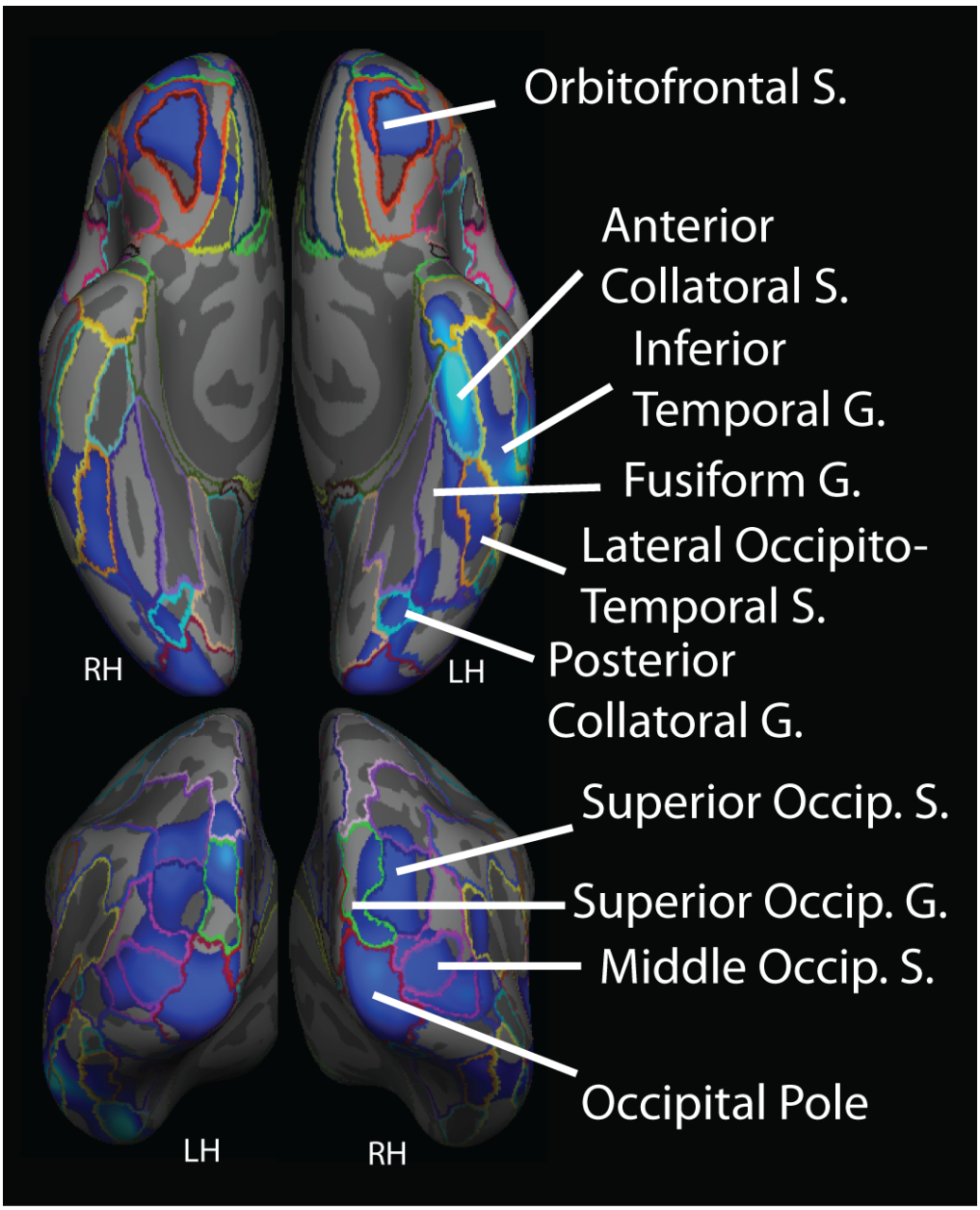

Figure 3. Scatterplots demonstrating the association between cortical thickness metrics and age. The left hemisphere inferior frontal ROI demonstrated a significant age by reading group interaction. The left hemisphere anterior cingulate, left occipital-parietal, and right inferior temporal ROIs demonstrated improved model fit when including a non-linear age prediction term (see table 4). LH=left hemisphere; RH=right hemisphere; ROI=region of interest.

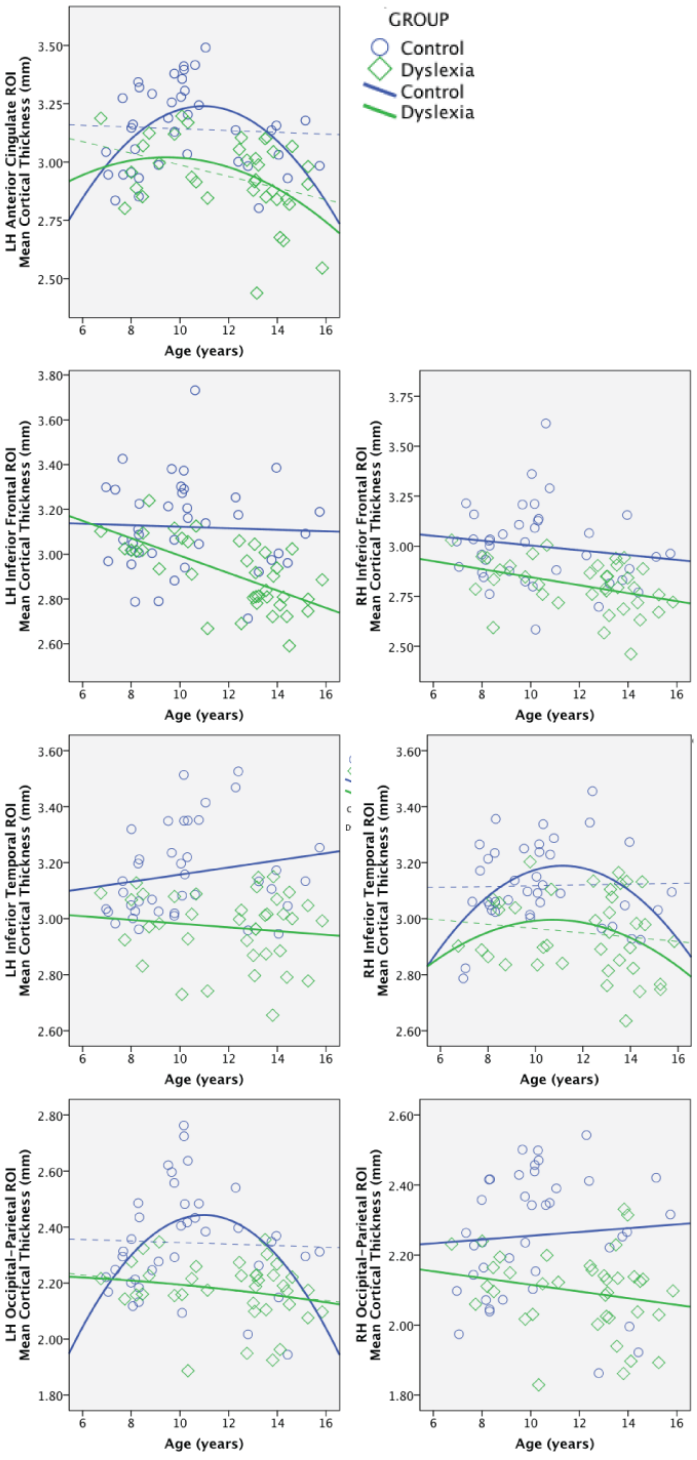

Figure 4. Results from whole-brain vertex-wise analysis of local gyrification index between reading groups, controlling for age (p<0.01). Regions that survived a cluster-based multiple comparison correction procedure are outlined in green (cluster-wise threshold p<0.05).

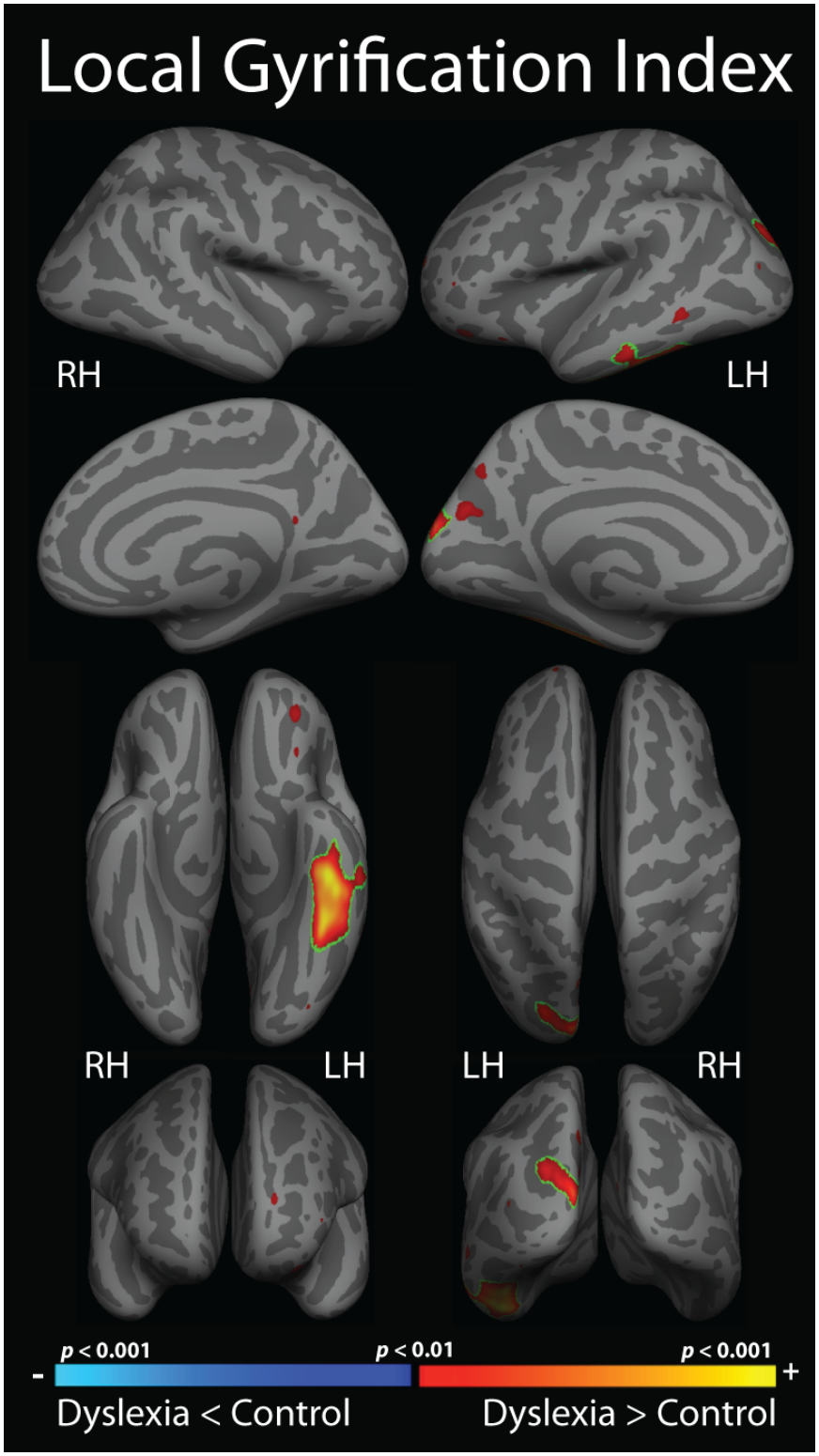

Figure 5. Map of spatial overlap (purple) between reduced cortical thickness (blue) and increased local gyrification index (red) in children with dyslexia compared to typical readers.

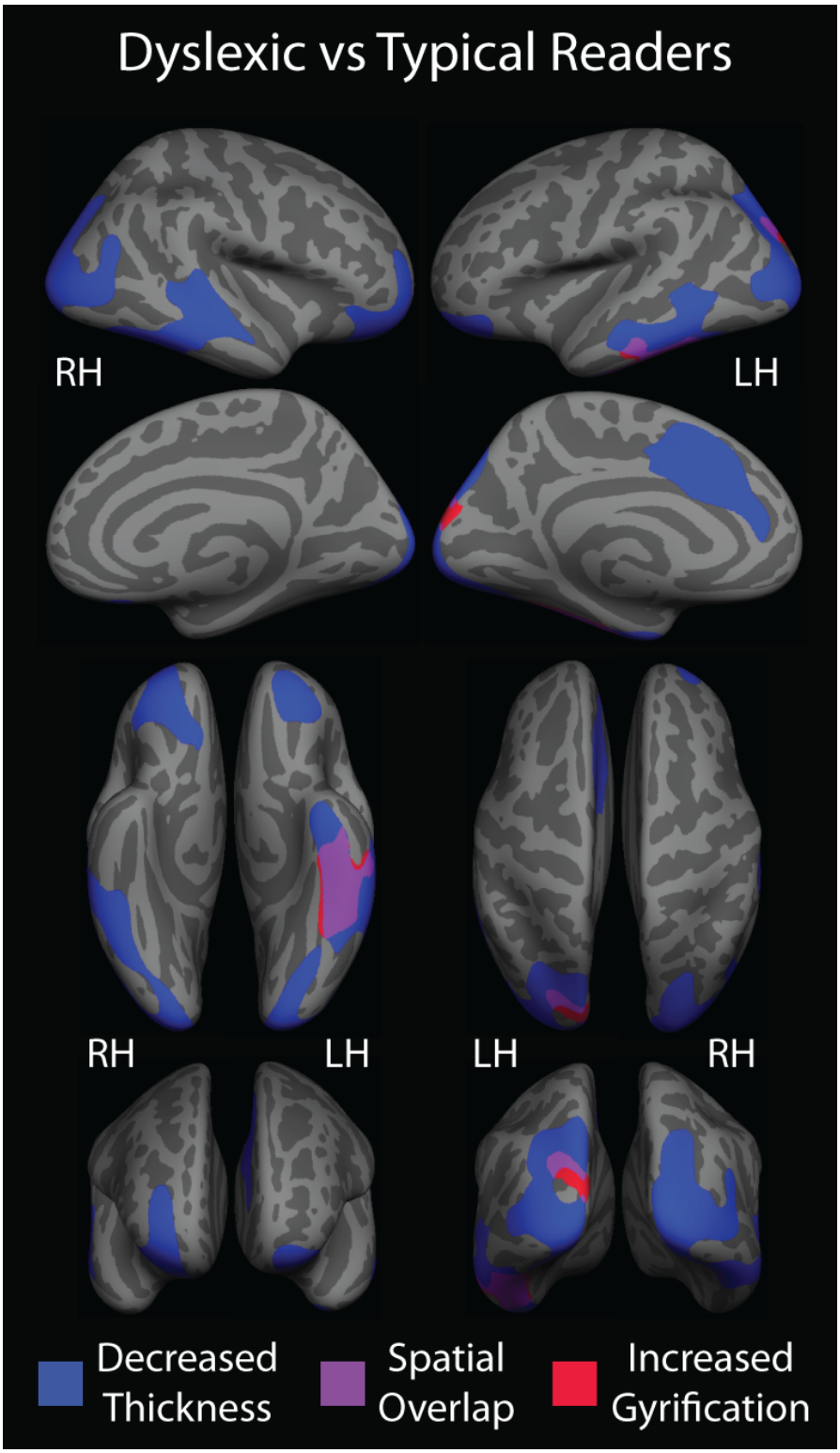

Figure 6. Map of cortical regions demonstrating a significant association (Spearman's rho) between mean cortical thickness and reading performance (reading fluency and reading comprehension age-corrected standard scores). All correlations were positive, such that higher reading scores were associated with increased thickness. Regions of interest were derived from cortical thickness differences between typical and dyslexic readers (controlling for age).