

Surface Area Accounts for the Relation of Gray Matter Volume to Reading-Related Skills and History of Dyslexia

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It is unknown whether the abnormalities in brain structure and function observed in dyslexic readers are congenital or arise later in development. Analyzing the 2 components of gray matter volume separately may help in differentiating these possibilities. Gray matter volume is the product of cortical surface area, determined during prenatal brain development, and cortical thickness, determined during postnatal development. For this study, 16 adults with a history of phonological dyslexia and 16 age- and gender-matched controls underwent magnetic resonance imaging and an extensive battery of tests of reading-related skills. Cortical surface area and gray matter volume measures of the whole brain, the inferior frontal gyrus, and the fusiform gyrus were similarly related to phonological skills and a history of dyslexia. There was no relationship between cortical thickness and phonological skills or history of dyslexia. Because cortical surface area reflects cortical folding patterns determined prenatally, this suggests that brain differences in dyslexia are rooted in early cortical development and are not due to compensatory changes that occur during postnatal development and would be expected to influence cortical thickness. This study demonstrates the importance of examining the separate components of gray matter volume when studying developmental abnormalities.

Keywords: cortical morphology, cortical surface area, cortical thickness, dyslexia, gray matter volume, reading

Introduction

Developmental dyslexia is the most common learning disorder worldwide, affecting children and adults with a prevalence ranging up to 17.5% (Shaywitz 1998). Several lines of evidence suggest that early brain development is altered in dyslexic readers. Neuropathological evidence implicates developmental cortical dysplasias (Galaburda et al. 1985; Kaufmann and Galaburda 1989; Humphreys et al. 1990), whereas genetic studies implicate genes associated with neuronal migration and axonal guidance (Galaburda et al. 2006), and electrophysiological data suggest that a deficit in the perception of speech sounds is present in infants who become dyslexic readers (Molfese 2000).

Functional neuroimaging studies of dyslexic readers have reported atypical activation in 3 cortical regions: the temporoparietal area, the inferior frontal gyrus, and the fusiform gyrus. The significance of this atypical activation is difficult to interpret because it is not known whether such atypical activation is a direct consequence of congenital brain abnormalities or whether this activity develops later as part of

a compensatory neural network. For example, abnormal lateralization of activity in the temporoparietal area may begin in early childhood (Simos et al. 2002), or it may be associated with a compensatory pathway (Simos et al. 2000; Shaywitz et al. 2003). The inferior frontal gyrus manifests greater activity in dyslexic as compared with typical readers, but the onset and role of this activity in reading in dyslexia is not known. Such activity has been reported to increase with age (Brunswick et al. 1999), the degree of compensation (Milne et al. 2002), remediation (Richards et al. 2002; Temple et al. 2003), and phonological task difficulty (Milne et al. 2002). A third region involved with reading, the fusiform area, is in and around the so-called visual word form area. During reading, brain activity in the fusiform area increases from childhood into adulthood in both dyslexic and typical readers, albeit with slightly different lateralization and anatomical localization (Shaywitz et al. 2007).

Structural imaging studies have used a variety of analysis methods to localize anatomical atypicalities in dyslexic readers. The examination of lobar or local gray matter volume using voxel-based morphometry (VBM) has yielded inconsistent results (Ashburner and Friston 2000; Silani et al. 2005; Hoefft et al. 2007; Kronbichler et al. 2008; Steinbrink et al. 2008). For instance, 2 studies attempted to independently validate the significance of their anatomical findings by correlating gray matter volume and functional atypicalities in dyslexic readers, but across these studies, findings were inconsistent (Silani et al. 2005; Hoefft et al. 2007). One reason for these inconsistencies could be related to the fact that cortical gray matter volume is the combination of 2 morphological measurements, cortical surface area and cortical thickness, each of which can change independently of the other. Therefore, the interpretation of changes in gray matter volume is difficult without examining its individual components.

Surface area and thickness are the 2 components of gray matter volume that are influenced by different factors during development. Cortical surface area dramatically increases during late fetal development as a consequence of cortical folding (Kapellou et al. 2006). Children born prematurely have reduced surface area, relative to whole-brain gray matter volume, as a result of attenuation in cortical folding (Kapellou et al. 2006). Accordingly, cortical folding measurements are starting to be recognized as markers for neurodevelopmental disorders that originate prenatally. For example, atypical cortical folding patterns have been described in child- and adolescent-onset schizophrenia (White et al. 2003) and in autism and Asperger syndrome (Nordahl et al. 2007). On the other hand, cortical thickness changes dynamically across the

life span as a consequence of development and disease. For instance, cortical thinning may reflect the absence of specific cortical neurons due to neurodegenerative diseases (Seo et al. 2007; Im, Lee, Won Seo, Hyung Kim, et al. 2008; Im, Lee, Won Seo, Yoon, et al. 2008). In addition, fluctuations in thickness vary with stage of development as a consequence of different phases of laminar growth as well as pruning of cortical connections (Landing et al. 2002; Shaw et al. 2008).

In this study, we aimed to examine the origin of dyslexic gray matter volume abnormalities by examining the 2 independent components of gray matter volume. We used a well-validated algorithm to calculate surface-based cortical gray matter volume, surface area, and thickness (Fischl et al. 2002; Makris et al. 2006) in 4 cortical regions: the inferior frontal gyrus; the fusiform gyrus; and 2 subdivisions of the temporoparietal area, the angular gyrus and supramarginal gyrus. We have targeted these areas for several reasons. First, as pointed out above, these are key regions that have been shown to manifest differences in functional activation between dyslexic and typical readers in both children and adults. Second, these areas represent key brain regions responsible for both phonological and orthographical processing, the 2 systems essential for reading (Eckert 2004). This study will not address anatomical changes in noncortical regions such as the cerebellum, which appear to also demonstrate differences between dyslexic and typical readers (Eckert 2004).

To best represent the complete range of reading-related skills, we recruited adults with a history of dyslexia who varied widely in their current reading-related skills. This was possible because some dyslexic readers slowly develop adequate phonological word decoding skills by adolescence or adulthood while others never achieve normal phonological word decoding skills (Miller-Shaul 2005; Svensson and Jacobson 2006). Although some have suggested that there are multiple groups of dyslexic readers with distinct deficits in phonological and/or orthographic skills (Berninger et al. 2001, 2008; Richards et al. 2006), distinct groups of dyslexic readers have been difficult to define (Fletcher et al. 2007). Indeed, reading ability for dyslexic readers has been argued to be best represented on a continuum of severity with multiple genetic and environmental risk factors interacting to result in the phenotype known as dyslexia (Snowling 2008). For example, children considered at-risk for dyslexia due to a family history of reading disability may develop average reading skills. However, when these individuals are compared with their peers who do not have a family history of dyslexia, subtle deficits in reading, fluency, and spelling can be uncovered (Pennington and Lefly 2001; Snowling 2008). Thus, the natural history of developmental phonological dyslexia and our selection of dyslexic readers have facilitated our ability to examine variations in the development of language skills in dyslexic readers.

The ability to read is based on phonological awareness—the ability to perceive and manipulate sounds which make up spoken words. This is believed to be the key deficit in dyslexia (Boets et al. 2007, 2008; Murphy and Schochat 2009). Phonological awareness skills are used to translate print into its equivalent auditory representation, a process known as orthographic decoding. Sublexical orthographic decoding skills involve breaking down (i.e., segmenting) words into small pronounceable units (i.e., graphemes) and translating such units into their auditory equivalents (i.e., phonemes). Sub-

lexical decoding skills are used to “sound out” new words and are believed to be deficient in phonological dyslexia. In contrast to sublexical decoding skills, lexical skills involve processing words as wholes without breaking them down into parts. Lexical skills do not necessarily require phonological awareness and can simply use a memory pathway (Shaywitz et al. 2003).

Although the cognitive process involved in word reading are well established in typical readers, the exact cognitive processes utilized by dyslexic readers may be different and are only beginning to be understood. For example, some dyslexic readers may use a memory-based orthographic word recognition system, analogous to lexical reading, that may or may not depend on phonological awareness ability (Shaywitz et al. 2003). Thus, to address phenotypic variability in both orthographic and phonological skills within the dyslexic and typical groups, we linked specific reading-related skills to anatomical brain differences across reading groups in order to demonstrate brain-behavior relationships. In this study, we used measures of pure auditory phonological awareness, sublexical decoding, lexical skills, and pure orthographic skills. Using this approach, we hoped to gain insight into whether changes in cortical morphology develop as a consequence of compensatory pathways or originate during early brain development.

Materials and Methods

Participants

Dyslexic readers in this study consisted of 16 young adults (age range 20–42 years) with a history of phonological dyslexia. The dyslexic readers performed several reading-related skill tests and underwent a structural magnetic resonance imaging (MRI) scan. Age- (within 2 years of age) and gender-matched controls without phonological dyslexia were recruited and also underwent the same protocol. Thirty-one percent of each cohort was female. Phone interviews eliminated nonnative English speakers and individuals with a history of attention deficit disorder, psychiatric and neurological illness, prematurity, birth complications, psychoactive medication use, abnormal hearing or vision, implanted ferromagnetic metal or device, claustrophobia, or pregnancy. Upon arrival to the laboratory, the study protocol was described to the participant. Once the participant's questions were answered adequately, written informed consent was obtained in accordance with our Institutional Review Board regulations for the protection of human subjects. Right handedness was confirmed by a laterality index as assessed by the Edinburgh Handedness Inventory (Oldfield 1971) score greater than 50 (Dragovic 2004).

All dyslexic readers had a history of phonological dyslexia during grade school, defined as below expected reading ability with normal intelligence and a deficit in the ability to phonologically decode words. We verified that participants manifested the typical residual deficits in fluency and spelling skills seen in adults with a childhood history of reading disability (Brosnan et al. 2002; Shaywitz et al. 2003; Kemp et al. 2008). The “Test of Variables of Attention” (TOVA) and the “Comprehensive Test of Nonverbal Intelligence” (CTONI) ruled out attention and intelligence deficits in all participants. All participants demonstrated a scaled score of 85 or greater on the omission and commission subscales of the TOVA and on the global nonverbal intelligence scale of the CTONI. As seen in Table 1, nonverbal intelligence was higher for typical as compared with dyslexic readers, even though the nonverbal intelligence scores for dyslexic readers were normal. Greater than average intelligence is not unusual in control participants in studies of adult dyslexia (Shaywitz et al. 2003). Others have shown that the intelligence quotient is correlated with reading ability throughout childhood and adolescence (Ferrer et al. 2007; Frye, Landry, et al. 2009).

Participants were tested on carefully selected reading-related skills (Table 1). Orthographic lexical and sublexical decoding was measured

Table 1

Participant characteristics

	Typically developing Mean (SE)	Dyslexic readers Mean (SE)	t-Test
Age, mean (years)	29.0 (1.6)	28.8 (1.7)	0.06
TOVA: commissions	105.6 (5.3)	104.0 (5.0)	0.83
TOVA: omissions	104.9 (0.7)	101.0 (1.9)	1.92
CTONI	109.3 (2.6)	99.4 (2.6)	2.66*
Reading-related phonological skills			
LWID	104.8 (1.6)	86.8 (2.6)	4.23‡
WA	103.2 (2.7)	83.6 (2.9)	4.94‡
Phoneme awareness composite (PA)	110.3 (1.5)	91.4 (2.6)	5.89‡
Alternate phoneme awareness composite (APA)	103.4 (2.9)	87.9 (2.4)	4.06‡
Rapid naming composite (RNC)	105.8 (2.9)	86.3 (3.5)	4.23‡

Note: All scores in tests above were standardized.

* $P < 0.05$.† $P < 0.01$.‡ $P < 0.001$.

with WJ3 “letter–word identification” (LWID) and “word attack” (WA), respectively. Auditory phonological awareness was assessed using the Comprehensive Test of Phonological Processing (CTOPP) “phonological awareness” (PA) composite and “alternate phonological awareness” (APA) composite. These 2 composites are complimentary as they represent the ability to analyze and synthesize words and nonwords, respectively. Additionally, a measure of orthographic skills was measured using the CTOPP “rapid naming” composite (RNC). Performance on reading-related skills varied from normal to subnormal values in dyslexic readers and varied throughout the normal range for typical readers. This prevented significant linear correlations from arising simply due to large intergroup differences. Table 1 provides t -test results representing the differences in these reading-related skills across reading groups.

MRI Protocol

A 3-D T_1 -weighted (time echo = 4.03 ms, time repetition = 8.6 ms, flip angle = 8°, field of view = 256 mm, 256 contiguous 1 mm slices, matrix = 256 × 256) magnetization-prepared 180° radio frequency pulses and rapid gradient echo sequence optimized for gray–white matter contrast differentiation were used to collect 2 sets of high-resolution structural MRIs on a 3.0-T Phillips Achieva scanner with Dual Quasar gradients (62 mT/m) and all-digital radio frequency acquisition system.

MRI Processing

Each participant’s brain was processed separately using an automated processing stream that required no manual user intervention. Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>). First, the 2 T_1 MRI volumes were corrected for participant motion during the acquisition and averaged together. Next, nonbrain tissue was removed using a hybrid watershed/surface deformation procedure (Segonne et al. 2004), followed by segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl et al. 2002, Fischl, Salat, et al. 2004). Next, the gray–white matter border was identified and tessellated. This process created a polygonal mesh model of the cortical surface. This mesh was made up of adjacent triangles, each with 3 edges and 3 vertices, creating a mesh with ~150 000 vertices per hemisphere (Dale and Sereno 1993; Dale et al. 1999; Fischl et al. 1999; Fischl and Dale 2000). A number of deformation procedures were then performed on the cortical model, and defects in the cortical surface model were automatically corrected using manifold surgery (Fischl et al. 1999, 2001; Segonne et al. 2007). Additional surfaces, such as the pial surface, were created, and cortical topographical characteristics, including surface curvature, were defined during these deformation procedures (Dale and Sereno 1993; Dale et al. 1999; Fischl et al. 1999; Fischl and Dale 2000).

A variety of surface-based topographical measures were derived from cortical maps produced from this stream. Cortical thickness, cortical

surface area, and gray matter volume were calculated for each vertex of the cortical mesh. Measures of cortical thickness have been validated and demonstrated to show good test–retest reliability across scanner manufacturers and across field strengths (Han et al. 2006). Cortical surface area was calculated as the total area of the triangles connected to a vertex (Fischl and Dale 2000; Pienaar et al. 2008). Total cortical surface area defined by this method is in agreement with surface area derived from postmortem studies and has been validated on several brain phantoms and compared with other surface-based analysis packages (Lee et al. 2006; Makris et al. 2006; Eskildsen and Ostergaard 2007). This processing stream parcellates the cerebral cortex into gyral and sulcal structures using a validated first-order anisotropic non-stationary Markov random field model algorithm that incorporates both global and local positions as well as surface curvature information (Fischl, van der Kouwe, et al. 2004; Desikan et al. 2006). Cortical topographical measures, including average thickness, total surface area, and gray matter volume, were calculated for each parcellated unit from the topographical maps created.

Analysis of Regional Cortical Characteristics

Analysis of covariance, using the mixed procedure of SAS 9.1 (SAS Institute Inc., Cary, NC), was used to investigate the relationships of whole-brain and regional gray matter volume, surface area, and thickness to reading group and hemisphere. For regional measurements, a covariate was used to control for corresponding whole-brain measurement. These factors, along with their interactions, were examined for significance, and the model was simplified by removing the highest order nonsignificant interaction, or effect if no interaction existed, and recomputing the model. This simplification procedure was repeated until all effects and interactions in the model were significant with the exception that nonsignificant effects remained in the model if they were dependent effects of a significant interaction. This procedure has been widely used by ourselves and others (Landry et al. 2001; Frye et al. 2007, 2008; Frye, Hasan, et al. 2009; Frye, Landry, et al. 2009). Initial models included both age and nonverbal intelligence, but these factors were not found to be significant in any model.

Next, each reading-related skill covariate was added to each model separately. These models were recalculated and simplified, as described above. Interactions were further analyzed using orthogonal contrasts. Because multiple comparisons were made using the same morphological measures (i.e., 5 behavioral performance variables), the alpha was set to 0.01 for the main analysis (in order to correct for an inflated alpha). Alpha was 0.05 for the orthogonal contrast because these follow-up tests were used to confirm already identified differences.

Results

Whole-Brain Surface Area and Gray Matter Volume Are Similarly Related to Phonological Skills and a History of Dyslexia

Gray Matter Volume

Reading-related task performance. Greater whole-brain gray matter volume was related to better phonological awareness performance for both dyslexic and typical readers ($F_{1,31} = 8.69$, $P < 0.01$) (Fig. 1A).

Group effects. Whole-brain gray matter volume was greater in the right, as compared with the left, hemisphere ($F_{1,31} = 23.78$, $P < 0.001$) and greater for dyslexic as compared with typical readers ($F_{1,31} = 7.48$, $P = 0.01$) (Fig. 2A).

Surface Area

Reading-related task performance. Greater whole-brain surface area was related to better phonological awareness

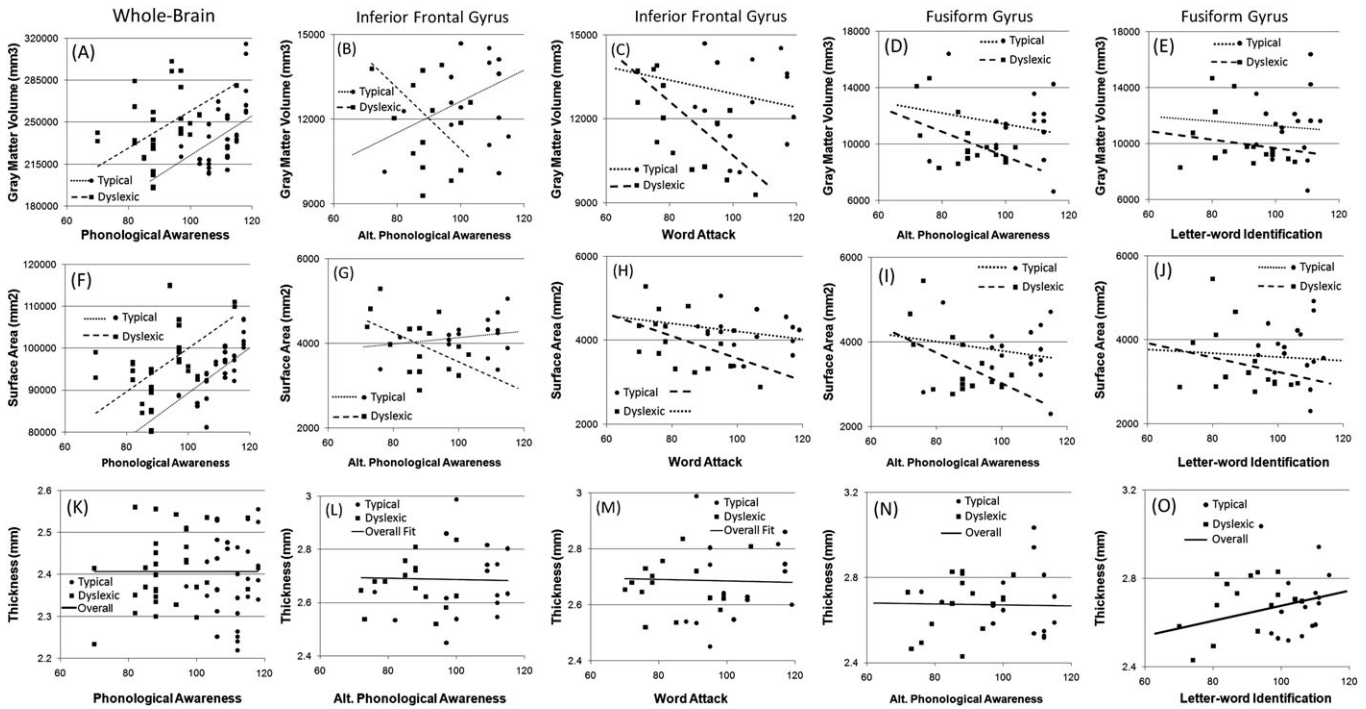


Figure 1. Relations between reading-related tasks and cortical gray matter volume (A–E), surface area (F–J), and thickness (K–O) for whole brain (A, F, K), the inferior frontal (B–C, G–H, L–M), and fusiform (D–E, I–J, N–O) gyri. Relations are depicted for dyslexic and typical readers separately for gray matter volume and surface area to demonstrate the effect of both the group difference and influence of the whole-brain covariate for the inferior frontal and fusiform gyri. Note that also the relations between reading-related skills and regional gray matter volume and surface area are the same across reading groups (except for the relationship between alternative phonological awareness and inferior frontal gyrus gray matter volume and surface area); the influence of the whole-brain covariate influences these relations. Relations between reading-related tasks and cortical morphology were not different across hemispheres, so each data point is averaged across the 2 hemispheres.

performance for both dyslexic and typical readers ($F_{1,32} = 12.77, P = 0.001$) (Fig. 1F).

Group effects. Whole-brain surface area was greater for dyslexic as compared with typical readers ($F_{1,32} = 8.25, P < 0.01$) (Fig. 2B).

Thickness

Reading-related task performance. None.

Group effects. The right hemisphere was found to be thicker than the left hemisphere ($F_{1,31} = 7.31, P = 0.01$) (Fig. 2C).

Angular Gyrus Surface Area and Gray Matter Volume Are Greater in the Right Hemisphere

Gray Matter Volume

Reading-related task performance. None.

Group effects. Angular gyrus gray matter volume was greater in the right hemisphere as compared with the left hemisphere ($F_{1,30} = 43.21, P < 0.0001$) (Fig. 2D).

Whole-brain covariate. Greater angular gyrus gray matter volume was associated with greater whole-brain gray matter volume ($F_{1,30} = 32.57, P < 0.0001$).

Surface Area

Reading-related task performance. None.

Group effects. Angular gyrus surface area was greater in the right as compared with the left hemisphere ($F_{1,30} = 72.87, P < 0.0001$) (Fig. 2E).

Whole-brain covariate. Greater angular gyrus surface area was also related to greater whole-brain surface area ($F_{1,30} = 34.52, P < 0.0001$).

Thickness

Reading-related task performance. None.

Group effects. Angular gyrus was thicker in the left as compared with the right hemisphere ($F_{1,30} = 32.20, P < 0.0001$) (Fig. 2F).

Whole-brain covariate. Greater angular gyrus thickness was associated with greater whole-brain thickness ($F_{1,30} = 56.94, P < 0.0001$).

The Right Supramarginal Gyrus Is Thicker for Dyslexic as Compared with Typical Readers

Gray Matter Volume

Reading-related task performance. None.

Group effects. Supramarginal gyrus gray matter volume was greater in the left as compared with the right hemisphere

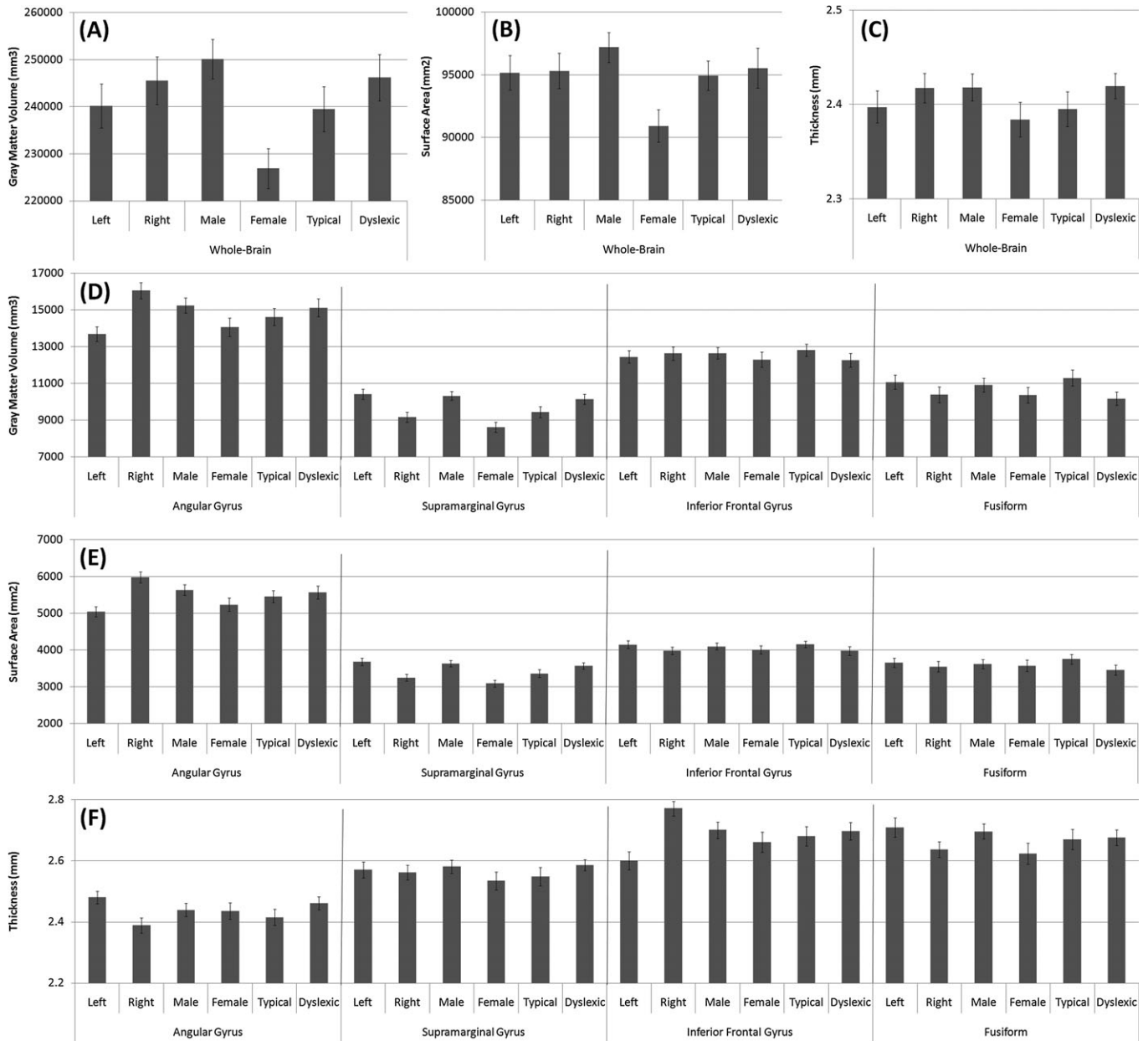


Figure 2. Average gray matter volume, surface area, and thickness differences across hemisphere, gender, and reading groups for whole brain (A–C) and regional brain areas (D–F).

($F_{1,31} = 23.96$, $P < 0.0001$) and greater in men as compared with women ($F_{1,31} = 16.46$, $P < 0.001$) (Fig. 2D).

Whole-brain covariate. None.

Surface Area

Reading-related task performance. None.

Group effects. Supramarginal gyrus surface area was greater in the left as compared with the right hemisphere ($F_{1,31} = 28.38$, $P < 0.0001$) and greater in men as compared with women ($F_{1,31} = 11.62$, $P < 0.005$) (Fig. 2E).

Whole-brain covariate. None.

Thickness

Reading-related task performance. None.

Group effects. The difference between thickness across the left and right hemispheres was different for dyslexic and typical readers resulting in a reading group by hemisphere interaction ($F_{1,29} = 7.60$, $P < 0.01$). This interaction arose due to the fact that the left hemisphere [2.58 (0.05)] was thicker than the right hemisphere [2.52 (0.04); $F_{1,14} = 10.48$, $P < 0.01$] for typical readers but that thickness was similar across the left [2.57 (0.03)] and right [2.61 (0.02)] hemispheres for dyslexic readers.

Whole-brain covariate. Greater supramarginal gyrus thickness was associated with greater whole-brain thickness ($F_{1,29} = 86.39, P < 0.0001$).

Inferior Frontal Gyrus Surface Area and Gray Matter Volume Are Similarly Related to Phonological Skills and a History of Dyslexia

Gray Matter Volume

Reading-related task performance. Inferior frontal gyrus gray matter volume was related to alternative phonological awareness performance with this relation different across reading groups ($F_{1,31} = 6.77, P = 0.01$). To further analyze this interaction, we examined the relation between inferior frontal gyrus gray matter volume and alternative phonological awareness performance for each reading group separately. Lesser inferior frontal gyrus gray matter volume was found to be related to better alternative phonological awareness performance for dyslexic readers ($F_{1,15} = 18.59, P < 0.001$) (Fig. 1B). No relation was found between inferior frontal gyrus gray matter volume and alternative phonological awareness for typical readers. Lesser inferior frontal gyrus gray matter volume was related to better WA performance ($F_{1,31} = 12.96, P = 0.001$) (Fig. 1C).

Group effects. For both analyses, inferior frontal gyrus gray matter volume was greater for typical as compared with dyslexic readers ($F_{1,31} = 9.63, P < 0.01; F_{1,31} = 15.30, P < 0.001$, respectively) (Fig. 2D).

Whole-brain covariate. For both omnibus analyses, greater inferior frontal gyrus gray matter volume was related to greater whole-brain gray matter volume ($F_{1,31} = 33.35, P < 0.0001; F_{1,31} = 39.88, P < 0.0001$, respectively) (Fig. 1B,C).

Surface Area

Reading-related task performance. The interaction between alternative phonological awareness and reading group was near significance ($F_{1,31} = 4.65, P < 0.05$). To further analyze this interaction, we examined the relation between inferior frontal gyrus surface area and alternative phonological awareness performance for each reading group separately. Lesser inferior frontal gyrus surface area was associated with better alternative phonological awareness performance for dyslexic readers ($F_{1,15} = 6.07, P < 0.05$), although, again, this relationship did not reach significance for our corrected alpha (Fig. 1G). No relation was found between surface area and alternative phonological awareness performance for typical readers. Lesser inferior frontal gyrus surface area was related to better WA performance ($F_{1,31} = 8.68, P < 0.01$) (Fig. 1H).

Group effects. For both analyses, inferior frontal gyrus surface area was greater for typical as compared with dyslexic readers ($F_{1,31} = 4.65, P < 0.05; F_{1,31} = 8.94, P < 0.01$, respectively) (Fig. 2E).

Whole-brain covariate. For both analyses, greater inferior frontal gyrus surface area was related to greater whole-brain surface area ($F_{1,31} = 13.48, P < 0.001; F_{1,31} = 17.63, P < 0.001$, respectively) (Fig. 1G,H).

Thickness

Reading-related task performance. None.

Group effects. The right inferior frontal gyrus was significantly thicker than the left inferior frontal gyrus ($F_{1,30} = 34.89, P < 0.0001$) (Fig. 2F).

Whole-brain covariate. Inferior frontal gyrus thickness increased as average whole-brain thickness increased ($F_{1,30} = 86.14, P < 0.0001$) (Fig. 1L,M).

Fusiform Gyrus Surface Area and Gray Matter Volume Are Similarly Related to Phonological Skills and a History of Dyslexia

Gray Matter Volume

Reading-related task performance. Lesser fusiform gyrus gray matter volume was related to better alternative phonological awareness performance ($F_{1,31} = 8.36, P < 0.01$) (Fig. 1D).

Group effects. Fusiform gyrus gray matter volume was greater for typical as compared with dyslexic readers ($F_{1,31} = 12.61, P = 0.001$) (Fig. 2D).

Whole-brain covariate. Greater fusiform gyrus gray matter volume was associated with greater whole-brain gray matter volume ($F_{1,31} = 13.08, P = 0.001$) (Fig. 1D,E).

Surface Area

Reading-related task performance. Greater fusiform gyrus surface area was related to poorer LWID ($F_{1,31} = 7.69, P < 0.01$) (Fig. 1I) and alternative phonological awareness ($F_{1,31} = 8.36, P = 0.01$) (Fig. 1J).

Group effects. In the analyses above, fusiform gyrus surface area was greater for typical as compared with dyslexic readers ($F_{1,31} = 12.61, P = 0.001; F_{1,31} = 9.41, P < 0.01$, respectively) (Fig. 2E).

Whole-brain covariate. In all analyses, greater fusiform surface area was related to greater whole-brain surface area ($F_{1,31} = 13.08, P = 0.001; F_{1,31} = 26.07, P < 0.0001$, respectively) (Fig. 1I,J).

Thickness

Reading-related task performance. None.

Group effects. Left fusiform gyrus was thicker than the right fusiform gyrus ($F_{1,30} = 14.53, P < 0.001$) (Fig. 2F).

Whole-brain covariate. Greater fusiform gyrus thickness was associated with greater whole-brain thickness ($F_{1,30} = 27.58, P < 0.0001$) (Fig. 1N,O).

Discussion

Our goal was to determine whether whole brain or regional differences in cortical gray matter volume between dyslexic and

typical readers were due to either one or both morphological components that combine to produce cortical gray matter volume, namely, cortical thickness and surface area. Overall, we found that almost all reading group differences in gray matter volume and all relationships between gray matter volume and reading-related skills were paralleled by similar changes in surface area, but not thickness. Due to their parallelism, we will first discuss surface area and gray matter volume findings on the whole brain and regional level, their implications for the origins and mechanisms underlying dyslexia, and new directions inspired by these results. Then we will review and interpret the isolated findings related to cortical thickness. Finally, we will address why it is important to covary for total cortical volume when undertaking this research.

Whole-Brain Gray Matter Volume and Surface Area, but not Thickness, Were Significantly and Similarly Related to a History of Reading Disability and Reading-Related Skills

Both whole-brain gray matter surface area and volume were greater in dyslexic as compared with typical readers. This may be surprising in light of the fact that several studies have found a lower whole-brain volume in dyslexic as compared with typical readers (Eckert et al. 2003; Casanova et al. 2004). Most of these studies, however, included subcortical areas as well as both white and gray matter in their whole-brain volume measurements; we specifically measured cortical gray matter. This is an important difference, as the ratio of gray-to-white matter volume has been shown to be larger in dyslexic and typical readers (Sandu et al. 2008), suggesting that a comparison between whole-brain volumes may not be accurate in this population and that white matter and gray matter volumes need to be analyzed separately. Additional analysis of our data did, in fact, reveal that our dyslexic reading group [0.92 (0.01)] demonstrated a significantly higher gray-to-white matter ratio ($F_{1,32} = 6.29, P = 0.02$) as compared with the typical reader group [0.86 (0.01)]. In our analysis, this ratio was not found to differ across gender or hemisphere.

Our results suggest that the greater whole-brain gray matter volume in the dyslexic readers, as compared with typical readers, is driven by greater surface area. Surface area is related to the pattern of cortical folding in a complex manner (Im, Lee, Lyttelton, et al. 2008). Specifically, surface area is known to increase with both a greater number of cortical folds (i.e., greater gyrification) and larger separation between cortical folds (i.e., larger sulci). An increase in surface area in dyslexic readers due to a larger separation between cortical folds would be consistent with previous whole-brain analysis studies that demonstrated that dyslexic readers have wider, deeper sulci (Casanova et al. 2010) and a reduced gyrification index (Casanova et al. 2004).

The formation and wiring of cortical folds, which occur during gestation, is referred to as the tension-based theory of morphogenesis. This theory posits that cortical folds develop as a result of mechanical tension along axons connecting cortical regions (Van Essen 1997). Highly connected regions are pulled together to form gyri, whereas weakly connected regions drift apart with sulci developing between them (Hilgetag and Barbas 2005, 2006). In the context of the tension-based theory framework, our findings suggest that there is weaker whole-brain intercortical connectivity in dyslexic as compared with typical readers. Weaker than normal intercortical connectivity

in dyslexia is supported by the large base of both functional and anatomical neuroimaging studies that suggest abnormal connectivity between language areas in individuals with reading disability (Paulesu et al. 1996; Klingberg et al. 2000; Pugh et al. 2000; Beaulieu et al. 2005; Deutsch et al. 2005; Niogi and McCandliss 2006; Dougherty et al. 2007). In addition, cortical dysplasias (Galaburda et al. 1985; Kaufmann and Galaburda 1989; Humphreys et al. 1990) are associated with white matter disorganization (Jenner et al. 2000). Similarly, genes associated with dyslexia may regulate neural migration and axonal growth (Galaburda et al. 2006). A second implication of our findings is that because cortical folding is established during gestation, the origin of dyslexia is probably prenatal.

The Gray Matter Volume and Surface Area, but not the Thickness, of Both the Inferior Frontal Gyrus and the Fusiform Gyrus Were Significantly and Similarly Related to a History of Reading Disability and Reading-Related Skills

Our finding of decreased gray matter volume as well as surface area, but not cortical thickness, in the inferior frontal gyrus of dyslexic but not typical readers is consistent with our claim that differences between dyslexic and typical brains are related to cortical folding.

Although previous studies have not looked at cortical surface area and thickness, many have used a wide variety of methods to measure regional brain volume in dyslexics. Some of their findings are consistent with ours. For example, Kronbichler et al. (2008) found lesser fusiform gyrus gray matter volume in dyslexic adolescents as compared with nonimpaired readers, using VBM. In addition, Eckert et al. (2003) found a smaller pars triangularis bilaterally in older children with reading disability as compared with age-matched children without reading disability, using a manual tracing method. Yet, others have suggested that the total prefrontal volume is larger, as a percentage of whole-brain volume, particularly in the superior frontal area (Zadina et al. 2006). Even so, many studies have not found any differences in frontal or fusiform areas using lobar (Eliez et al. 2000) or VBM (Hoeft et al. 2007; Phinney et al. 2007; Menghini et al. 2008) methods.

Reading-related skills were similarly related to surface area in the inferior frontal and fusiform areas; better performance was related to a lower surface area. This trend suggests that better reading-related performance is associated with less space between gyri, potentially as a result of stronger connections in and out of these regions to other brain areas. The alternative phonological awareness composite was related to inferior frontal gyrus surface area for dyslexic, not typical, readers. The association of inferior gyrus surface area with the alternative phonological composite, a set of tests that specifically targets the manipulation of nonwords, for dyslexic but not typical readers, is consistent with the notion that this area is overused, potentially as an area for compensatory processing, during phonological tasks (Shaywitz et al. 2003).

We also found that gray matter volume and surface area of the fusiform gyrus differed between reading groups. The activity in and around the fusiform area has been found to change from childhood to adulthood, with at least one report of a change in laterality between dyslexic and typical readers (Shaywitz et al. 2007). It is generally thought that "postnatal" developmental changes in gray matter are primarily reflected

by changes in cortical thickness (Landing et al. 2002; Shaw et al. 2008). In contrast, the most rapid changes in cortical folding occur during late gestation, with these changes peaking at term gestation (Pienaar et al. 2008; Rodriguez-Carranza et al. 2008). Therefore, it might be surprising that the performance on reading-related tasks was related to fusiform gyrus surface area, not thickness. It is possible that cortical folding may continue to change with cognitive development as local and distance connections are strengthened and pruned. Future longitudinal studies will need to examine this question. In the mean time, there is evidence that small changes in cortical folding can occur during postnatal development as a consequence of cortical atrophy related to aging and neuropsychiatric disorders (Pienaar et al. 2008; Mirakhor et al. 2009); but our participants were young and those with neurological or psychiatric illness were excluded.

There was only one exception to the rule that cortical volume and surface area differences occurred together; in the fusiform gyrus, surface area but not gray matter volume was found to be related to LWID.

There Are Some Isolated Differences between Reading Groups in Terms of Cortical Thickness, but They Are Not Paralleled by Differences in Gray Matter Volume

Right supramarginal gyrus thickness is greater for dyslexic as compared with typical readers, whereas there was no group difference in supramarginal gyrus gray matter volume. In particular, a lack of asymmetry in thickness, primarily driven by greater right supramarginal gyrus thickness, was related to a history of dyslexia. This is an example of an isolated finding for cortical thickness that is not paralleled by gray matter volume.

The fact that reading group differences in cortical thickness were only found in the supramarginal gyrus confirms the importance of this region for reading. The supramarginal gyrus has been hypothesized to be involved in processing subsegmental aspects of speech and in translating between the acoustic and motor representations of speech. These processes underlie the perception of individual phonemes and syllables, which is the basis for phonological awareness (Poepfel et al. 2008). The supramarginal and angular gyri have been shown to demonstrate abnormal right hemisphere activity in dyslexic readers (Simos et al. 2000), which may lead to a lack of pruning in the right hemisphere, thereby leading to an increased thickness in this region.

The presence of a reading group difference in thickness and the absence of a difference in surface area in the supramarginal gyrus might seem to contradict previous studies that have examined surface area differences in certain “subregions” of the supramarginal gyrus (Rumsey et al. 1997; Green et al. 1999; Leonard et al. 2001). Several of these studies measured the symmetry of the planum “plus”—a measure of the surface area of the caudal infrasyllian fissure, including the planum temporale and the planum parietale (Leonard et al. 2001). Although some studies have shown differences in the symmetry of this region, others have not been able to confirm this finding, and one study in particular found a larger absolute surface area of the planum plus (Green et al. 1999). We should note that our study did find that supramarginal gyrus surface area was larger in the left hemisphere as compared with the right and that this difference was dependent on gender. The results from this study and others suggest that it is of the utmost importance to control for gender

differences across reading groups (Schultz et al. 1994). In addition, it should be noted that our analysis technique was not designed to examine subregions of supramarginal gyrus. Indeed, surface-based topographic techniques that are sensitive to local changes in surface area and thickness should be used to complement our findings.

VBM studies have examined gray matter volume in regions of interest, which have included the supramarginal gyrus, but they have measured a variety of subregions with different methods, and none have reported thickness. Two studies reported smaller gray matter volume in the left temporoparietal area in childhood dyslexic as compared with typical readers (Eckert et al. 2005; Hoeft et al. 2007), and one study reported decreased gray matter volume in the right temporoparietal area in adult dyslexic compared with typical readers (Kronbichler et al. 2008). Although these results seem contrary to ours, several methodological issues must be addressed. In the first study, some gray matter differences disappeared when younger performance-matched children were used as controls instead of age-matched controls (Hoeft et al. 2007). In the second study, the effect disappeared when total gray matter volume was taken into account (Eckert et al. 2005). In the third study, no correction for total gray matter volume was performed (Kronbichler et al. 2008). In addition, differences in techniques can contribute to the variability of the results. For example, VBM studies are sensitive to the degree of smoothing, differences in registration, and the choice of normalization templates (Bookstein 2001; Park et al. 2004; Eckert et al. 2005; Jones et al. 2005).

The angular gyrus results provide another example where surface area and volume were different between hemispheres in a parallel manner, but cortical thickness manifested an asymmetry in the opposite direction. Although this was not a group difference, it is another example of a finding, which was isolated to the measure of cortical thickness.

The Importance of Accounting for Whole-Brain Morphology

This study has demonstrated that whole-brain morphology is important in 2 respects. First, measures of whole-brain morphology may be different across reading groups and may be related to performance measures. Second, regional morphological measurements may be related to whole-brain morphology, suggesting that if the relation between region morphology and whole-brain morphology is not taken into account, it will not be known if relations found in region morphology across birth group and performance are specific for the region or are a reflection of whole-brain morphology. This is not the only study to demonstrate this point. For example, Schultz et al. (1994) found that the surface area and symmetry of the planum temporale between dyslexic and typical readers disappeared when gender and brain size were taken into account. Similarly, others have shown that VBM findings related to dyslexic reading disappeared when total gray matter volume was taken into account (Eckert et al. 2005).

Conclusions

This study illustrates that changes in gray matter volume associated with dyslexia and reading-related abilities may be accounted for by changes in surface area and not thickness. The changes in key areas found in this study are similar

to those found in previous studies (for review, See Eckert 2004). Interpretation of our results is limited by the fact that surface area is related to cortical folding in a complex manner (Im, Lee, Lyttelton, et al. 2008). For example, a greater number of cortical folds (i.e., greater gyrification) or a larger separation between cortical folds (i.e., larger sulci) may both increase surface area. In addition, there is evidence that small changes in cortical folding can occur during postnatal development and as a consequence of cortical atrophy related to aging and neuropsychiatric disorders (Pienaar et al. 2008; Mirakhor et al. 2009). Future studies need to carefully consider differences in surface area and its relation to cortical folding in dyslexic readers. In addition, the cross-sectional nature and limited age variability in our sample may have prevented us from detecting changes in cortical morphology associated with postnatal development. Further studies need to address how changes in cortical morphology are associated with the development of compensatory circuits in dyslexic readers.

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