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Sex-specific Gray Matter Volume Differences in Females with Developmental Dyslexia

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Abstract

Developmental dyslexia, characterized by unexpected reading difficulty, is associated with anomalous brain anatomy and function. Previous structural neuroimaging studies have converged in reports of less gray matter volume (GMV) in dyslexics within left hemisphere regions known to subserve language. Due to the higher prevalence of dyslexia in males, these studies are heavily weighted towards males, raising the question whether studies of dyslexia in females only and using the same techniques, would generate the same findings. In a replication study of men we obtained the same findings of less GMV in dyslexics in left middle/inferior temporal gyri and right postcentral/supramarginal gyri as reported in the literature. However, comparisons in women with and without dyslexia did not yield left hemisphere differences and instead we found less GMV in right precuneus and paracentral lobule/medial frontal gyrus. In boys, we found less GMV in left inferior parietal cortex (supramarginal/angular gyri), again consistent with previous work, while in girls differences were within right central sulcus, spanning adjacent gyri, and left primary visual cortex. Our investigation into anatomical variants in dyslexia replicates existing studies in males, but at the same time shows that dyslexia in females is not characterized by involvement of left hemisphere language regions but rather early sensory and motor cortices (i.e. motor and premotor cortex, primary visual cortex). Our findings suggest that models on the brain basis of dyslexia, primarily developed through the study of males, may not be appropriate for females and suggest a need for more sex-specific investigations into dyslexia.

Keywords

dyslexia; sex differences; MRI; anatomy; morphometry

Introduction

Developmental dyslexia is a specific learning disability affecting five to twelve percent of the English-speaking population (Katusic et al. 2001; Rutter et al. 2004). It is characterized by reading deficits, specifically for word decoding, which cannot be explained by lack of

intellectual ability or limited access to instruction (Lyon et al. 2003; Peterson and Pennington, 2012). Dyslexia is highly heritable (Olson et al. 1989), and two to three times more prevalent in males compared to females (Flannery et al. 2000; Katusic et al. 2001; Rutter et al. 2004; Liederman et al. 2005). This imbalance is poorly understood, and discovering the factors causing a higher incidence in males could help elucidate the etiology of this common reading disability. Importantly, the predominance of males with dyslexia frequently results in studies conducted in male-only or male-dominated samples, yet the interpretation of results are often generalized to dyslexia in both sexes.

Single word reading is supported by a network of regions in the left hemisphere, including dorsal (temporal-parietal), ventral (occipitotemporal) and inferior frontal circuits, which are altered in developmental dyslexia (for review see Pugh et al. 2000; Sandak et al. 2004; Gabrieli, 2009). Historically, a biological basis for dyslexia was first investigated by Geschwind and colleagues who found upon *post mortem* examination of healthy brains that the left *planum temporale* was larger than its right hemisphere homologue (Geschwind and Levitsky, 1968); this asymmetry was found to be absent in a male case with a history of dyslexia during his lifetime (Galaburda and Kemper, 1979). Further, investigations of four male dyslexics reported cytoarchitectonic anomalies (ectopias), especially in the left hemisphere perisylvian region, attributed to anomalies in neuronal migration (Galaburda et al. 1985). A follow-up in three female dyslexics also reported these ectopias, however there were fewer and their distribution was wider and not constrained to the perisylvian region (Humphreys et al. 1990).

Non-invasive anatomical *in vivo* studies using Magnetic Resonance Imaging (MRI) have given some support for these original findings through identification of gross structural anomalies in left perisylvian cortex in dyslexic individuals. Earlier MRI studies followed up on *postmortem* results, examining the *planum temporale in vivo* (e.g. Hynd and Semrud-Clikeman, 1989). Later research expanded the scope, reporting differences in dyslexia in a variety of aspects of temporal, inferior parietal and inferior frontal regions primarily in the left hemisphere, as well as cerebellum (for review see Eckert, 2004). In addition to structural findings, functional neuroimaging studies have identified physiological anomalies in dyslexic readers, revealing hypoactivity compared to typical readers within the language network during reading or phonological processing tasks (Flowers et al. 1991; Démonet et al. 1992; Ingvar, 1993; Paulesu et al. 1996; Rumsey et al. 1997; Shaywitz et al. 1998; Brunswick et al. 1999; Shaywitz et al. 1998; Eden et al. 2004). More recent work has combined these techniques, explicitly linking this hypoactivation with atypical brain morphology in similar regions (Hoeft et al. 2007; Siok et al. 2008; Linkersdörfer et al. 2012).

While earlier studies examining brain anatomy with MRI relied on manual tracing techniques, standardization of analysis tools has provided more methodological consistency for recent studies. Specifically, Voxel-Based Morphometry (VBM), employing fully- or semi-automated algorithms (Ashburner and Friston, 2000), has been used in approximately ten studies of dyslexia. We next review the findings of less gray matter volume (GMV) in dyslexia, focusing on investigations implementing whole-brain VBM analysis (rather than those that limited analysis to regions of interest) in adults (Brown et al. 2001; Brambati et al.

2004; Vinckenbosch et al. 2005; Steinbrink et al. 2008) and children (Eckert et al. 2005; Hoeft et al. 2007).

Beginning with studies in adults, Brown et al. (2001) found less GMV in 16 male dyslexics relative to 14 male controls in left temporal lobe (inferior, middle and superior gyri) and bilateral temporal-parietal-occipital junction, frontal lobe, caudate, thalamus and cerebellum. Similarly, Vinckenbosch et al. (2005) reported less GMV in left middle and inferior temporal gyri in their sample (10 male dyslexics, 14 male controls). Steinbrink et al. (2008) studied mostly male participants (8 dyslexics: 6 male, 8 controls: 6 male), again revealing less GMV in left middle/superior temporal gyrus, and right superior temporal gyrus. The only VBM study to include nearly equal numbers across gender (10 dyslexics: 5 male, 11 controls: 5 male) was conducted by Brambati et al. (2004). While this investigation offers convergence with Brown et al.'s and Steinbrink et al.'s reporting of less GMV in left superior temporal gyrus, and Brown et al.'s and Vinckenbosch et al.'s findings in left inferior temporal gyrus, they also reveal right hemisphere GMV differences in middle temporal gyrus, bilateral *planum temporale*, fusiform and cerebellar nuclei. Together, these findings suggest the most reliable differences in dyslexia are in bilateral temporal lobe structures (inferior, middle and superior gyri), confirmed by recent meta-analyses (Linkersdörfer et al. 2012; Richlan et al. 2012), a logical finding given the roles of left temporal lobe in spoken and written language.

To date, only two whole-brain investigations employing VBM have been conducted on pediatric samples: one with males, the second with a mixed group. Eckert et al. (2005) identified less GMV in dyslexics in left supramarginal gyrus, lentiform nucleus and posterior cerebellum, as well as bilateral lingual gyri in a group of boys (13 dyslexics, 13 controls). Consistent with this, Hoeft et al. (2007) reported reduced GMV in left inferior parietal lobe and lentiform nucleus in a mixed group of male and female adolescents with dyslexia compared to controls (19 dyslexics: 10 male, 19 controls: 10 male). In addition, Hoeft et al. reported less GMV in left inferior frontal gyri and anterior cingulate, bilateral insula, precentral, postcentral and superior temporal gyri, as well as right inferior parietal lobe and middle temporal gyrus. The number of pediatric studies is limited, but even so, there are noticeably more regions reported outside of the temporal lobe and instead in frontal and parietal regions (i.e. insula, precentral, postcentral gyri and inferior parietal lobe) in the mixed group (Hoeft et al. 2007), suggesting that introducing females may change the nature of findings in studies of brain morphometry in dyslexia.

Considering the prevalence of dyslexia is two to three times higher in males than females (Flannery et al. 2000; Katusic et al. 2001; Rutter et al. 2004; Liederman et al. 2005; however see Shaywitz et al. 1990), it may not be surprising that the VBM studies discussed above are heavily weighted towards males. However, this means that the results obtained cannot be generalized to females with dyslexia. Further, any inconsistencies in the results reported, may in part depend on the number of females included in any given sample (Schultz et al. 1994). Importantly, in the typical population there are male/female differences in anatomy (Good et al. 2001; Peper et al. 2009; Witte et al. 2010), as well as in brain activity during language tasks (Shaywitz et al. 1995; Jaeger et al. 1998). This raises the possibility that when only females with dyslexia are studied in comparison to female controls, the

neuroanatomical findings characterizing dyslexia may be different from those reported to date in the male-dominated studies. The importance of sex-specific differences in research on dyslexia was noted over three decades ago when Norman Geschwind drew attention to the fact that the higher incidence of dyslexia in males suggests either the etiology for dyslexia is different for males and females, or that the etiology is the same, but females are “protected” from manifesting a reading disability because of unknown sex-specific mechanisms (Geschwind, 1981). Here we address the question of sex-specific differences in brain anatomy of dyslexia by comparing GMV between dyslexic and non-dyslexic males as has been done numerous times in the published literature, and then, using the same methodology, for the first time test for GMV differences in female dyslexics compared to female controls. This approach offers consistency with previously employed methods and also avoids any ambiguity as to whether any between-group differences should be attributed to dyslexia or sex (as would be the case if male dyslexics were directly contrasted to female dyslexics). Finally, we extended the study to children, allowing us to draw conclusions about morphometric differences in dyslexia for each sex at different stages of development.

Material and Methods

Participants

Anatomical MRI data were drawn from different studies on developmental dyslexia and typical readers within our laboratory involving functional MRI, where structural scan acquisition constituted part of the study protocol. Subjects with dyslexia had a documented childhood record of developmental dyslexia. Control subjects had no history of a learning disability, did not have a first degree relative with a learning disability and were within normal range on standardized measures of reading (see below).

Our adult dyslexic subjects were drawn from either a cohort of a longitudinal study of dyslexia at Wake Forest University North Carolina (Meyer et al. 1998) or a cohort of dyslexic adults who grew up and reside in North Carolina and whose childhood records on reading and cognitive skills were available through a historical archive accessed by investigators at Wake Forest University (Flowers et al. 1991; Eden et al. 2004). For subjects drawn from either source, reading problems during childhood were documented in each subjects' childhood testing records. Adult non-dyslexic controls were recruited from North Carolina and the Washington, DC area. Scans of 27 adult dyslexic subjects and 27 typical adult readers were available and we conducted comparisons of male adults with and without dyslexia (n=14 per group) as well as female adults with and without dyslexia (n=13 per group).

The dyslexic children were recruited from a private school specialized in learning disabilities in Maryland and the control children were recruited from the general population within the same geographical region, including the DC metropolitan area. Scans of 32 dyslexic children and 32 typical readers were available and we conducted comparisons of boys with and without dyslexia (n=15 per group) as well as girls with and without dyslexia (n=17 per group).

All participants in the study were monolingual English speakers and in good physical health. All participants had a Full Scale IQ score above 80 based on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). None had neurologic, severe language or psychiatric disorders, a history of traumatic brain injury with loss of consciousness, or clinical abnormality on MRI. Other exclusion criteria included any use of medications that could affect brain function or cerebral blood flow at the time of scanning, pregnancy, or history of substance use. Individuals who had cardiac or neural pacemakers, surgical clips in the brain or blood vessels, implanted metal objects in their body, or other contraindications for MRI were not eligible for the study. All studies were approved by the Institutional Review Board of Georgetown University Medical Center. Written informed consent was obtained. All adult participants were paid for their participation and children were given toy prizes or bookstore giftcards.

All subjects underwent testing to specifically characterize their reading skills and their phonological coding ability (these measures are presented in Table 1). For all subjects, pseudoword reading was measured with the Word Attack subtest of the Woodcock Johnson III Tests of Achievement (Woodcock et al. 2001). Pseudoword reading requires reading of nonwords that follow English pronunciation rules and assess a person's decoding skills (i.e., how good subjects are in applying knowledge of letter-sound relationships and letter patterns to the correct pronunciation of written words). Pseudoword reading skills are often used in assessing dyslexia. Single real word reading was also measured. The Letter-Word Identification subtest of the Woodcock Johnson III Tests of Achievement (Woodcock et al. 2001) was used in all children and for 22 of the 54 adults to gauge real word reading. For the other 32 adults, real word reading was evaluated using the Wide Range Achievement Test-3 Reading subtest (Wilkinson, 1993). Both tests are normed measures of untimed, single real word reading and provide an age-referenced standardized score with a mean of 100 and a standard deviation of 15. For the adults, the group means presented in Table 1 was derived from using single real word reading scores obtained from either test. Finally, we administered tests to determine phonemic awareness, a skill known to support reading (Wagner and Torgesen, 1987) and thought to be the primary impediment to dyslexics' ability to acquire reading skills (Stanovich, 1988). Phonemic awareness (the ability to understand and manipulate the sound structure of language at the phoneme level) was measured with the Test of Auditory Analysis Skills (TAAS; Rosner, 1975) in adults. The Lindamood Auditory Conceptualization Test-3 (LAC-3; Lindamood and Lindamood, 2004) was used in 51 of the pediatric subjects, while the remaining 13 pediatric subjects' phonemic awareness was evaluated using the Comprehensive Test of Phonological Processing (CTOPP; Wagner et al. 1999). As both measures used for the children are standardized, Table 1 combines these two measures into one mean. Handedness was determined by the Edinburgh Handedness Scale in all subjects (Oldfield et al. 1971).

Acquisition of Magnetic Resonance Images

MRIs were acquired on a Siemens Vision Magnetom 1.5-Tesla scanner (14 male adult dyslexics, 14 male adult controls, 5 female adult dyslexics and 5 female adult controls) and a 3.0-Tesla Siemens Trio scanner (8 female adult dyslexics, 8 female adult controls, 15 male pediatric dyslexics, 15 male pediatric controls, 17 female pediatric dyslexics, 17 female

pediatric controls). The number of subjects who received MRI scans with the higher field strength did not differ between the dyslexic and their respective control groups. To be conservative, however, we added field strength (1.5 or 3.0) as a covariate of no interest in the data analysis (Pernet et al. 2009). We used a circularly polarized head coil equipped with foam padding to restrict head motion. Multiple high-resolution T1-weighted 3D sagittal MPRAGE images (FOV read: 256; phase: 256; Slices: 173 on 1.5T, 160 on 3.0T; Slice Resolution: 1 mm) were acquired for each participant yielding images with a voxel size of $1 \times 1 \times 1$ mm. A blind, independent two-rater system was used to select one of the structural images acquired from each subject. This system allowed us to identify images of sufficient quality for data analysis, especially in the pediatric sample where an anatomical scan is often compromised by a single, large head movement that occurred during the scan.

Voxel-Based Morphometry (VBM) Analysis

Statistical Parametric Mapping (SPM8, Wellcome Trust Centre for Neuroimaging, London) was used for preprocessing and analysis. Specifically, MRI data was processed according to the optimized protocol described by Good et al. (2001). Non-brain tissue (skull, scalp, etc.) was removed, and initial gray matter, white matter, and cerebral spinal fluid segmentations were spatially normalized with the DARTEL toolbox and resampled to the Montreal Neurologic Institute (MNI) space. These deformation parameters were applied to the original images, which were subsequently segmented. Finally, Jacobian modulation was applied to gray matter to restore the original absolute volume altered by the normalization process, and images were smoothed using an 8mm, full-width, half-maximum isotropic Gaussian kernel. FSL 4.1 (FMRIB Software Library, Oxford, UK) was used to set an absolute intensity threshold of 0.2 to remove voxels of low gray matter intensity.

To determine clusters that significantly differed across groups with and without dyslexia, we applied a two-sample t-test. Scanner field strength was included as a regressor of no interest. We also calculated total brain volume (gray and white matter) for each group, and ensured no significant differences between each sample of individuals with dyslexia compared to their respective control group. For statistical map generation, a height threshold of $p < .001$ uncorrected was utilized. We used the VBM toolbox for SPM to implement a $p < 0.05$ extent threshold utilizing a non-stationary correction (Hayasaka et al. 2004) that allows for cluster-level statistics on VBM data and has been previously implemented in studies in the lab (Krafnick et al. 2011). Those clusters that also survived a more conservative FWE correction ($p < 0.05$) are indicated via asterisks in Table 2. Clusters less than 5 voxels are not reported. Coordinates were converted from MNI to Talairach coordinate space utilizing the Brett transform mni2tal (<http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/mni2tal.m>).

Results

Profile of Participants

As can be seen in Table 1, all four of the dyslexic groups (adult males, adult females, pediatric males, and pediatric females) were matched for age and Performance IQ to their respective non-dyslexic control groups of the same sex. As would be expected based on their

diagnostic history of a reading disability, each dyslexic group demonstrated significantly lower scores on measures of pseudoword reading, real word reading and phonemic awareness than their respective control groups. The four dyslexic groups were also similar to one another in their average performance IQ, with most subjects falling well within the normal range. Subjects were right handed, except two adult dyslexic participants (1 male, 1 female), four pediatric dyslexic (3 male, 1 female) and two pediatric control (1 male, 1 female) participants, who were determined to be not strongly right-handed.

Gray Matter Volume Between-Group Differences: Adults

Male Adults—As shown in Table 2 and Figure 1, men with dyslexia demonstrated less GMV than their non-dyslexic male controls in the left middle temporal gyrus (BA 21) extending into inferior temporal gyrus (BA 20). This result survived a more stringent statistical threshold (FWE correction $p < 0.05$) and is consistent with previous studies reporting differences in left temporal cortex. The adult dyslexic males also showed less GMV in the right postcentral sulcus (BA 2) with the cluster extending posteriorly into the supramarginal gyrus of the parietal lobe (BA 40).

Female Adults—As can also be seen in Table 2 and Figure 1, women with dyslexia demonstrated significantly less GMV than the non-dyslexic female adults in the precuneus of the right parietal lobe (BA 7) and in the paracentral lobule of the right frontal lobe (BA 4), extending into the medial frontal gyrus portion of the supplementary motor cortex (BA 6). Surprisingly, this analysis revealed no differences in the temporal lobe of females with dyslexia.

Gray Matter Volume Between-Group Differences: Children

Male Children—Boys with dyslexia compared to their matched controls demonstrated relatively less GMV in a cluster located in left supramarginal gyrus (BA 40) extending into angular gyrus (BA 39) (see Table 2 and Figure 1). These results are consistent with earlier reports on GMV differences in dyslexic children and once again support the idea of anatomical aberrations in left hemisphere brain regions that support language.

Female Children—Girls with dyslexia showed less GMV in multiple right hemisphere regions: the central sulcus extending into the adjacent postcentral gyrus (BA 3) and precentral gyrus (BA 4). An additional cluster was located in the right precentral gyrus (BA 4/6) and survived a more stringent statistical threshold (FWE correction $p < 0.05$). Girls with dyslexia also had less GMV in the cuneus (BA 17) of the left occipital lobe (see Table 2 and Figure 1).

Figure 2 provides a brain rendering for visualization of the results of these four between-group comparisons (Controls > Dyslexics). To summarize, men (blue), and boys (green) with dyslexia exhibit less GMV than their respective male control groups in the lateral aspects of the bilateral middle temporal and inferior parietal cortices. However, findings for the females are located in bilateral sensory and motor cortices in frontal, parietal and occipital lobes. A single focus in the left hemisphere in the medial occipital cortex (BA 17) emerged from the pediatric comparison (yellow). Other differences observed for females

with dyslexia are in the right hemisphere, notably posterior parietal cortex (BA 7) and medial aspects of the frontal lobe (BA 4/6) in women (red) and lateral aspects of the frontal lobe (BA 3/4/6) in girls (yellow).

Discussion

Our study reports the first direct investigation into neuroanatomical differences in dyslexia in females. Critically, we conducted parallel studies in females and males, comparing groups of dyslexics with age and IQ matched controls for each sex separately, yet using the same methods as those employed in publications on male only and male dominated samples that have led to the field's current understanding of the differences in GMV in dyslexia. Our findings in adult males were consistent with the anomalies reported in previous studies within the left hemisphere language network and homologous regions in the right hemisphere. While findings based on male dyslexics are accounted for through theories of left hemisphere, language-based dysfunction, our findings in females represent a notable departure from this framework. Adult females with dyslexia did not differ from their female controls within the left temporal-parietal cortex. Instead, between-group differences are located primarily in sensory and motor cortices of the frontal and parietal lobes (precuneus and paracentral lobule extending into medial frontal gyrus, inclusive of SMA) and primarily in the right hemisphere. Our investigation also included children allowing us to ask the same questions specific to dyslexia in females at a younger age. Boys with dyslexia compared to their male pediatric control group had relatively less GMV in left supramarginal/angular gyri, again replicating prior work in male children (Eckert et al. 2005) and in support of the language-based learning problems encountered by dyslexic children. However, our findings in female children once again departed from prior published reports and from the observations in our own male children: Girls with dyslexia had less GMV than the controls in right precentral gyrus and left cuneus, again regions involved not in language but in sensory and motor processing.

Our results demonstrate that anatomical differences observed in adult dyslexics to date may largely be unique to males, and females with dyslexia exhibit distinct anatomical variants compared to typical readers. Further, the sexual dimorphism for GMV in dyslexia in our pediatric sample suggests sex-specific differences exist across the lifespan. These results raise important questions about the yet unknown etiology of dyslexia. They also have important implications for practice and research. For example, studies on GMV in dyslexia evaluated via meta-analytical methods (for recent examples see Richlan et al. 2012; Linkersdörfer et al. 2012) are based on dyslexic participants that contain less than 20% females, yet conclusions are typically generalized to all dyslexics. Our findings suggest that new brain-based models may have to be adopted to best characterize female dyslexia. Perhaps even diagnosis and treatment approaches may have to take sex into consideration.

Our findings raise the question whether differences in brain morphology in males and females with dyslexia are the end product of two entirely different etiologies, or do they represent a sex-specific variation at the end of a complex biological cascade that has at its core a common etiology. We discuss this here in the context of prior work. First, we examine studies in typically-developing populations reporting sex-based differences in brain

anatomy. It might be that sex-specific findings in dyslexia are related to the anatomical differences that exist between males and females in the normal population. Neuroimaging studies contrasting males and females have also examined brain function through positron emission tomography (PET) and functional MRI (fMRI), making it possible to relate our anatomical findings to sex-specific activity underlying language processing in typical subjects. We also discuss research examining the role of sex hormones in early brain maturation, considering the possibility that our findings represent the end product of a sex-specific divergence beginning prenatally, rendering the brains of males more vulnerable to dyslexia. We then examine behavioral studies suggesting differentiation between males and females with dyslexia, and genetic work in dyslexia focused on gender differences. Finally, we consider our findings in light of competing theoretical frameworks put forth to explain dyslexia. We entertain the possibility that the more prevalent theory, a phonological deficit attributed to the left hemisphere, explains dyslexia in males, while dyslexia in females might be better accounted for by dysfunction and in domains subserving sensory processing.

Sex-specific differences in GMV in the normal population

Several studies have explored sex-specific differences in brain anatomy of typical subjects using the same methodological approach employed in the present study and have revealed striking sex-specific differences (Good et al. 2001; Peper et al. 2009; Witte et al. 2010; Takahashi et al. 2011; Lombardo et al. 2012). Most relevant to our findings are results from a large (n=465) study of typical adults conducted by Good et al. (2001), who identified, among other things, greater GMV in females compared to males in regions adjacent to the depths of left and right central sulci. A related study by Amunts and colleagues (2000) using a non-VBM-based approach found that females exhibit symmetry in the depth of the central sulci, while males show leftward asymmetry. In our study, we observed dyslexia-specific reduced GMV in the posterior aspects of the right postcentral sulcus in men, suggesting that whatever mechanism leads to relatively smaller GMV around this region in typical males may be accentuated in dyslexic males. Similarly, reduced GMV in right pre- and postcentral gyri in our girls suggests dyslexic females do not attain the same GMV in a region typically associated with higher volumes for females. This is somewhat speculative since the study by Good and colleagues was conducted in adults, and neuroanatomical profiles are known to vary across the lifespan (Giedd et al. 1997). Nevertheless, it is clear from our results that the organization of right sensory and motor cortices may vary for individuals with dyslexia. Further support comes from a third finding in the present study, in right hemisphere motor cortex in women, albeit more medial (BA 4/6), suggesting again that right hemisphere motor systems might play a role in dyslexia among females.

Females display symmetry not only in anatomy of a variety of brain regions (see Amunts et al. 2000), but also in functional organization of language, while males, again, appear to be asymmetric. During a rhyme-judgment task, typically-reading men revealed left lateralized activation in IFG, while women activated bilateral IFG (Shaywitz et al. 1995). Similarly, Jaeger and colleagues (Jaeger et al. 1998) found that women activated a bilateral network of perisylvian regions during past tense verb generation, in contrast to left-lateralized findings in men. These studies clearly demonstrate sexual dimorphism for the functional specialization of language (however see Sommer et al. 2004; Sommer et al. 2008; Kaiser et

al. 2009), and explain why the incidence of aphasia in males may be higher than in females following insult to the left hemisphere (McGlone, 1977; for discussion see Tallal et al. 2012). Interestingly, sex-specific differences in brain lateralization are not unique to humans. Behavioral work in rats has shown that male rats show a right over left ear advantage for the discrimination of tone sequences and that this advantage is stronger than in female rats (Fitch et al. 1993). Similarly, more recent work in bats has demonstrated sex-dependent hemispheric asymmetries for processing frequency-modulated sounds (Washington and Kanwal, 2012), together suggesting that sexual dimorphism in lateralization is not unique to humans. Given these biological constraints, it is easy to see how perturbations caused by dyslexia would affect brain function differently in males and females. In fact, it has been proposed that a bilateral distribution of language function across two hemispheres in females may be one reason that dyslexia is less prevalent, because females effectively have a “reserve” in the right hemisphere that is called upon when aberrations underlying language function occur in the left hemisphere. Our results provide a different and simpler explanation, instead suggesting that women with dyslexia do not have the severe temporal-parietal anomalies that somehow disrupt the phonological abilities thought to be critical to reading. Whether this means they have a milder form of the reading disability or a different form (e.g. due to sensory/motor dysfunction) remains to be investigated.

These sex-specific differences in anatomy also emphasize the importance of our methodological approach: not only does the comparison of female dyslexics with age and IQ matched controls provide consistency with the studies published to date on male or male dominated samples for both the adult and pediatric work, but it also avoids the ambiguity that would be present if dyslexic males were directly contrasted to dyslexic females, making it impossible to attribute differences to sex versus dyslexia. While not the primary objective of this work, it is obvious that our results in children with dyslexia look quite different than those in adults, even though our analysis protocols were identical. The shifts in GMV differences in both males and females with dyslexia suggest age-dependent anatomical differences in individuals with dyslexia, serving as a reminder that the phenotype of dyslexia changes throughout the lifespan.

Male and Female Sex Hormones and Development

A significant limitation of MRI based *in vivo* studies is that the cellular mechanisms underlying these differences remain elusive. Interestingly, founding neuroanatomical work by Galaburda and colleagues in individuals with dyslexia at *post mortem* describing first gross (Galaburda and Kemper, 1979) and then fine-grained cortical abnormalities such as neuronal ectopias and architectonic dysplasias (Galaburda et al. 1985) have led these investigators to advance a theory of improper migration of neurons during cortical development. To test this model, rodents are subjected to conditions (application of a freezing probe to the cortex) that result in cortical ectopias much like those observed in the tissue of humans with dyslexia at *post mortem* (Humphreys et al. 1991). Male animals showed more anatomical change in response to this interference than did females, as did androgenized (testosterone treated) females, suggesting that the hormonal disposition of males may make them more vulnerable to perturbations during early neuronal development (Rosen et al. 1999). This theory is consistent with the neuroprotective properties of estrogen

(Brann et al. 2007) and other accounts of a female advantage in recovery to cerebral insult (Goldman et al. 1974; Loy and Milner, 1980; Raz et al. 1995). Improper migration of cortical neurons during development may produce these ectopias in the human, and (directly or indirectly) may be the source of interference for skills that support reading (Ramus, 2004). While the above research suggests that disruption of typical cortical migration may have sex-specific responses, it is unknown whether the patterns of ectopias among males and females with dyslexia diverge. Future studies could test this prediction. Further investigation is also needed into the relationship between macro- and microstructural anatomical findings that have been described above (using MRI in humans and microscope in the animal) to determine if there is a link between observations at these two levels of inquiry.

The sex hormones estrogen and progesterone have noteworthy neuroprotective and cognitive effects (see Dumitriu et al. 2010 for review). Monthly fluctuation in estrogen positively correlates with CA1 spine density in rodent hippocampus (Woolley et al. 1990). Decreases in spine density following ovariectomy are reversible with immediate estrogen treatment (Gould et al. 1990), and accompanied by new synapse formation (Woolley and McEwen, 1992). In humans, verbal memory varies with the ovarian cycle, and timely estrogen replacement protects against post-menopausal decline (see Sherwin, 2012 for review). Interestingly, for the present study, oral reading and verbal memory skills are significantly stronger in post-menopausal women taking estrogen supplements compared to controls (Shaywitz et al. 2003). Further, estrogen intake (compared to a placebo) results in greater brain activity during the verbal storage component of a verbal working memory task in bilateral frontal and inferior parietal lobes, and right occipital cortex (Shaywitz et al. 1999). While these regions do not overlap directly with brain areas reported here, hormonally driven effects may nevertheless impact anatomy and function elsewhere in the female brain and in ways that result in dyslexia manifesting differently than it does in males.

Sex hormones have also been linked to neuroanatomical differences. Peper et al. (2009) found a positive correlation between global GMV and testosterone levels in boys, and a negative correlation between global GMV and estradiol level in girls. Witte et al. (2010) examined young men and women, finding positive correlations between GMV estradiol levels in left IFG, and negative correlations between GMV and testosterone levels in left IFG. The left IFG is involved in reading and GMV in this region has been correlated with phonological awareness (Lu et al. 2007). Lombardo and colleagues (2012) recently identified a direct link between fetal testosterone levels and subsequent gray matter volume in pediatric boys (ages 8–11): Greater testosterone levels predicted greater GMV in bilateral somatosensory, motor and premotor cortices, and less GMV in bilateral *planum temporale* and left middle/superior temporal cortex. These observations are especially interesting in light of our results of less GMV in dyslexic males in bilateral temporal-parietal cortex, and less GMV in dyslexic females in sensory and motor cortices. This suggests that brain regions regulated by sex hormones in typical individuals could be vulnerable to fluctuations in these hormones with the resulting effect of atypical neural development and cognitive function (e.g. high fetal testosterone might be a cause of dyslexia in males). These studies provide interesting connections between sex, hormones and brain anatomy and potential

differences between males and females with dyslexia on the grounds of anatomical and hormonal differences and their interaction, a prediction that was made by Norman Geschwind over three decades ago (Geschwind, 1981).

Sex-specific behavioral performance of dyslexics

One might also expect sex differences in behavioral performance of dyslexics on measures of spoken and written language. Divergence in behavior does not necessarily mean a different etiology for dyslexic males and females (for review see Vogel, 1990); however, researchers have been interested in sex-specific differences, especially since they too are expressed in typical readers. Among normal readers there is the tendency for girls to acquire reading more rapidly than boys due to their advantage in rate of linguistic processing and basic word recognition (Wolf and Gow, 1986). School-identified female students with learning disabilities (LDs), including but not specific to reading disability, demonstrate lower intelligence than males (Bradbury et al. 1975; Holowinsky and Pascale, 1972; Lawson et al. 1987) and Vogel and Walsh (1987) found the same in college-aged students. They also reported that relative to males with LD, females with LD displayed strengths in verbal conceptualizations. Consistent with the observed strength in language skills in females is another study (Berninger et al., 2008) examining children with dyslexia, finding boys to have lower scores in working memory and orthographic coding compared to the girls. These results all indicate a more typical language-based dyslexic phenotype in males, going hand in hand with GMV differences observed in left hemisphere language areas of males.

Genetics

Dyslexia is a highly heritable and genetically heterogeneous condition (for review see Paracchini et al. 2007). Candidate genes have roles in brain development, axonal growth and neural migration, providing further evidence in support of the model of anomalous neuronal migration discussed above (Galaburda et al. 2006). The higher incidence of dyslexia has prompted genetic studies to address whether the same genetic mechanisms are at work for males and females with dyslexia. Qualitative sex differences in genetic studies would imply that the two sexes are influenced by different environmental and genetic factors. For example, Harlaar and colleagues (2005) found evidence for qualitative sex differences in almost four thousand twins, concluding that reading problems may occur as a function of sex. However, another study could not replicate these results (Hawke et al. 2007). Quantitative sex differences have also been entertained, whereby genetic and environmental factors are the same for both sexes, but the impact is thought to be stronger in males. A sex-influenced polygenic threshold model was put forward by DeFries (1989) based on data indicating that the presence of dyslexia is higher in relatives of female dyslexics compared to male dyslexics (Vogler et al. 1985). This model posits that females have a higher risk threshold for dyslexia than males and explains both the lower rate in prevalence of dyslexia in females and the higher number of relatives with reading disability found for female dyslexics compared to male dyslexics (DeFries, 1989). Unfortunately, studies to date investigating these various models have not converged, possibly due to varying methodological approaches and limited sample sizes. Future research combining neurogenetics and cognitive neuroscience will help expand on observations like the one demonstrating that GMV in Broca's and Wernicke's language areas are genetically

influenced (Thompson et al. 2001) and help address questions about sex-specific differences in the relationship between genes, brain and behavior (Ramus, 2006).

Language versus non-language based theories about dyslexia

There is strong consensus that dyslexia is the consequence of temporal-parietal speech-sound processing (e.g. phonemic awareness) deficits (for review see Gabrieli, 2009; Peterson and Pennington, 2012). Interventions targeting this weakness successfully remediate dyslexia (for review see Alexander et al. 2004). In parallel, the notion of right hemisphere dysfunction in dyslexia, specifically involving parietal cortex, has emerged and needs to be considered in light of our findings of less GMV in dyslexic women in right parietal cortex. Dyslexics have deficits in visual-spatial tasks subserved by right parietal cortex such as mental rotation (Rüsseler et al. 2005; Karádi et al. 2001; however see Corballis et al. 1985; Lachmann et al. 2009). These and other parietal functions, including visual attention (Facoetti et al. 2000; Facoetti et al. 2003) and visuospatial judgment (Eden et al. 1996) might contribute to dyslexia, prompting investigators to draw analogies between these weaknesses and those exhibited by patients with lesions to posterior parietal cortex (Stein and Walsh, 1997), such as left neglect syndrome (Facoetti and Turatto, 2000; Facoetti and Molteni, 2001; Hari et al. 2001; Eden et al. 2003). Our findings of less GMV in right parietal cortex in women with dyslexia would predict differences in brain function in female dyslexics for visuospatial tasks, a hypothesis that has not yet been tested.

While there is strong agreement that poor phonological awareness is at the core of dyslexics' reading problems, the origins of poor phonemic awareness are still unknown. In light of our findings, it is interesting to note that one theory posits rapid nonverbal auditory processing as the cause of poor phonological awareness and hence reading disability (for review see: Fitch and Tallal, 2003). Pivotal to this theoretical framework is the observation that there are gender differences in the hemispheric lateralization underlying rapid auditory processing as demonstrated in behavioral studies of humans (Brown et al. 1999) and animals (Fitch et al. 1993) as well as lesion studies in animals (Fitch et al. 1997) and clinical cases in humans (Tallal and Newcombe, 1978). As mentioned above, studies in rats have shown that males but not females show greater lateralization to the left hemisphere (as demonstrated by a right ear advantage) for rapid auditory processing (Fitch et al., 1993); rapid auditory processing may be evolutionary precursors to the left-hemisphere language specialization observed in humans, with sex-specific differences in the degree of lateralization. Further, animal models of dyslexia examining rats with cortical ectopias (like those seen in humans with dyslexia at *postmortem*), reveal impairments on tasks of rapid auditory processing only in males and not females, despite comparable lesions leading to ectopias and microgyria (Fitch et al. 1997). This work suggests that male dyslexics may have auditory processing-based deficits that lead to phonological impairments while female dyslexics have deficits not inclusive of auditory processing; however, both may have anomalies that originate within sensory domains. Future studies could be performed to make a more direct connection between this work and the current anatomical findings.

Our adult female dyslexics also showed less GMV in right SMA; together with the right parietal cortex finding, this replicates a report by Menghini et al. in primarily female

dyslexic adults (10 dyslexics: 9 female; 2008). This GMV analysis was constrained by regions of interest derived from between-group differences (dyslexics versus controls) from an implicit learning fMRI study (Menghini et al. 2006), thus not included in the review of existing GMV studies of dyslexia in the introduction confined to whole-brain analyses. Of note is that this report (Menghini et al. 2008) contains the largest number of women to date, and is highly consistent with those regions reported for our female adult dyslexics (for example, the right parietal lobe/precuneus is within one cm of the one reported here). In their study, Menghini and colleagues also showed implicit learning deficits on a serial reaction time task in dyslexia and less brain activity during this task in SMA, inferior parietal areas and cerebellum. This work, along with ours, lends support to the notion that visuomotor learning, integration of visual information with motor commands, plays a role in females with dyslexia. In girls with dyslexia, right hemisphere findings were closer to primary motor cortex (BA 4), suggesting that in younger females the differences are more prominently aligned with earlier sensorimotor cortex. Interestingly, it has also been pointed out that motor and cognitive development may be fundamentally intertwined (Diamond, 2000), suggesting perhaps that aberrations in motor system development may affect cognition. Early sensory system differences were also seen in left primary visual cortex in the girls with dyslexia. Of note here is that neurons in primary visual cortex have been shown to differ between dyslexics and non-dyslexics at *post mortem*, where the normal asymmetry seen in controls in favor of the left hemisphere is absent in dyslexics (Jenner et al. 1999). While these are early sensory regions, they do relate to higher linguistic function related to reading. That is, left visual cortex GMV correlates positively with spelling of irregular words in dyslexic adults but negatively in controls, and positively with pseudoword reading performance for both groups (Pernet et al. 2009). However, the debate about the relationship between sensorimotor performance and reading in dyslexia has been contentious. While some propose a variety of sensorimotor impairments in dyslexia (e.g. Nicolson et al. 2001), others argue these impairments are only found in a subset of dyslexics and are not the cause of reading disability *per se*, but nonspecific markers of dyslexia (White et al. 2006). Investigating the role of sex in this matter might go a long way to resolve this issue since existing work has again been largely performed in groups of dyslexics containing more males than females.

Conclusion

This is the first investigation of gray matter volume in females with dyslexia, conducted in both adults and children. In pure male samples, we replicated previous findings of relatively less GMV in left middle/inferior temporal gyri and right postcentral gyrus in men with dyslexia and in left supramarginal/angular gyri in boys with dyslexia compared to age and IQ matched typically reading controls of the same sex. In females however, our findings did not conform to the left-hemisphere deficit model of dyslexia. Women with dyslexia had less GMV in the right precuneus and paracentral lobule/medial frontal gyrus and girls with dyslexia had less GMV in the right central sulcus and adjacent gyri as well as left cuneus relative to non-dyslexic controls. Results in our pure female samples stand in stark contrast to previous reports in the literature for all-male or male dominated samples, and suggest a different pathophysiology for dyslexia in females. Given the disproportionately higher

prevalence of dyslexia in males (Flannery et al. 2000; Katusic et al. 2001; Rutter et al. 2004; Liederman et al. 2005), sex differences and hormone involvement reported in anatomical studies of typically developing individuals (Good et al. 2001; Peper et al. 2009; Witte et al. 2010; Lombardo et al. 2012), and functional imaging studies of typical language processing (Shaywitz et al. 1995; Burman et al. 2008), sex is likely to play a critical role in furthering our understanding of the etiology of dyslexia. Future studies need to include and isolate female dyslexics and their respective control groups when examining behavior, brain structure and brain function in dyslexia.

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Fig. 1.

Between-group statistical maps (Controls > Dyslexics) from the whole-brain gray matter VBM analysis in adults and children of both sexes, demonstrating reduced GMV for dyslexics relative to typical reading controls. In the men, clusters were found in left middle/inferior temporal gyri (BA 21/20) and right postcentral sulcus extending into supramarginal gyrus (BA 2/40). In the women, clusters were found in right precuneus (BA 7) and paracentral lobule/medial frontal gyrus (BA 4/6). In the boys, a cluster was found in left supramarginal/angular gyri (BA 40/39). In the girls, two adjacent clusters are found in right precentral gyrus (BA 4/6) and central sulcus extending into precentral and postcentral gyri (BA 3/4). Another was found in left cuneus (BA 17). Horizontal slices are shown for these peak coordinates

Fig. 2.

Overlay of results reported in Table 2 rendered on a brain for visualization purposes: Men (blue), Women (red), Boys (green) and Girls (yellow) with dyslexia showed less GMV in these regions compared to their respective control groups of the same sex. While males demonstrated differences in left hemisphere regions associated with language and their right hemisphere homologues, females show differences in right hemisphere regions within primary motor cortex and posterior parietal cortex, as well as left hemisphere primary visual cortex. More medial ($x > 10$) clusters are indicated by black horizontal hash lines

Table 1

Behavioral/Demographic Profile of All Subjects

	Men			Women			Boys			Girls										
	<i>Dyslexia (n=14)</i>			<i>Dyslexia (n = 13)</i>			<i>Dyslexia (n=15)</i>			<i>Dyslexia (n=17)</i>										
	Mean	SD	Typical (n=14)	Mean	SD	Typical (n = 13)	Mean	SD	Typical (n=15)	Mean	SD	Typical (n=17)								
Age	42.9	10.4	41.1	9.0	34.0	11.6	27.9	9.7	9.6	1.3	8.3	2.1	10.1	2.1	9.1	3.0				
Performance IQ	108.0	14.7	114.1	7.3	99.6	13.9	109.2	9.2	101.7	9.5	110.9	14.7	101.9	11.1	107.2	10.4				
Pseudoword Reading	92.0	10.1	111.8	11.4	**	84.5	7.4	109.5	10.0	**	92.2	7.4	116.8	11.1	**	90.1	5.5	115.3	11.9	**
Real Word Reading	89.1	10.0	111.8	5.6	**	83.5	10.4	111.7	7.0	**	76.9	8.1	119.8	11.6	**	78.8	9.3	121.7	12.9	**
Phonemic Awareness	9.9	3.3	12.7	1.1	*	8.9	4.6	13.0	0.0	*	98.7	8.5	114.9	11.2	**	96.8	8.7	111.7	14.2	*

Behavioral scores for the male and female adult and pediatric groups: All four dyslexics groups were matched to their respective control groups on age and Performance IQ; all dyslexic groups differed significantly from their control groups in their performance on measures of Real Word Reading, Pseudoword Reading and Phonemic Awareness. All scores are standardized scores with the exception of the measure of Phonemic Awareness in the adults. See text for further details.

SD = standard deviation, Sig = significance of t-test,

* p < 0.01,

** p < 0.001.

Table 2

Gray Matter Volume: Dyslexic Readers < Typical Readers

Hemisphere	Lobe	Anatomical Region	Talairach Coordinates			Z-score	Volume (voxels)
			x	y	z		
Adults							
Men							
L	temporal	middle (BA 21)/inferior temporal (BA 20) gyri *	-50	-30	-11	4.23	91
R	parietal	postcentral sulcus (BA 2)/supramarginal gyrus (BA 40)	38	-27	35	3.74	23
Women							
R	parietal	precuneus (BA 7)	20	-48	50	4.3	12
R	frontal	paracentral lobule (BA 4)/medial frontal gyrus (BA 4/6)	8	-27	62	3.7	16
Children							
Boys							
L	parietal	supramarginal (BA 40)/angular gyri (BA 39)	-44	-46	30	3.59	11
Girls							
L	occipital	cuneus (BA 17)	-10	-91	5	3.61	68
R	frontal	precentral gyrus (BA 4/6) *	36	-16	40	4.07	20
R	fronto-parietal	central sulcus/precentral/postcentral gyri (BA 3/4)	33	-15	46	3.57	20

Location of peak Talairach coordinates, Z-scores, and volumes identified by two-sample t-tests (Control > Dyslexic) for Men (14 Controls, 14 Dyslexics), Women (13 Controls, 13 Dyslexics), Boys (15 Controls, 15 Dyslexic), and Girls (17 Controls, 17 Dyslexic), p < 0.001 height and p < 0.05 non-stationary cluster extent thresholds,

* FWE correction p < 0.05.