Developmental Cognitive Neuroscience 36 (2019) 100636

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: www.elsevier.com/locate/dcn

Relationships between gray matter volume and reading ability in typically developing children, adolescents, and young adults

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ARTICLE INFO

Keywords:
Voxel-based morphometry
Reading
Dyslexia
Gray matter volume
Neuroimaging
NIH
Normative database

ABSTRACT

Reading is explicitly taught and foreshadows academic and vocational success. Studies comparing typical readers to those with developmental dyslexia have identified anatomical brain differences in bilateral temporo-parietal cortex, left temporo-occipital cortex, and bilateral cerebellum. Yet, it is unclear whether linear relationships exist between these brain structures and single real word reading ability in the general population. If dyslexia represents the lower end of the normal continuum, then relationships between gray matter volume (GMV) and reading ability would exist for all reading levels. Our study examined this question using voxel-based morphometry in a large sample (n = 404) of typically developing participants aged 6–22 derived from the NIH normative database. We tested correlations between individual GMV and single word reading and found none. After dividing this sample into groups based on age and on sex, we only found results in the group aged 15–22: positive correlations between GMV in left fusiform gyrus and reading, driven by females; and in right superior temporal gyrus in males. Multiple regressions also yielded no results, demonstrating that there is no general linear relationship between GMV and single real word reading ability. This provides an important context by which to interpret findings of GMV differences in dyslexia.

1. Introduction

Reading is a skill that is integral to communication, pivotal to educational and vocational achievement in many societies. Reading acquisition is hampered in 5–12% of children due to the reading disability developmental dyslexia (Katusic et al., 2001). Dyslexia is a neurologically-based learning disability attributed to deficits in phonological processing that lead to difficulty in reading words accurately and fluently (Lyon et al., 2003; Shaywitz, 1998). While the brain bases of dyslexia are widely accepted, the role of the reported anatomical differences in dyslexia are difficult to interpret and would benefit from a deeper understanding about the relationship between brain anatomy and reading ability in the general population.

Specifically, studies comparing groups with and without dyslexia have revealed differences in gray matter volume (GMV) in numerous brain regions (Brown et al., 2001; Brambati et al., 2004; Eckert et al., 2005; Silani et al., 2005; Vinckenbosch et al., 2005; Hoeft et al., 2007; Kronbichler et al., 2008; Menghini et al., 2008; Steinbrink et al., 2008; Pernet et al., 2009; Raschle et al., 2011; Evans et al., 2013; Krafnick et al., 2014; Jednoróg et al., 2015). The main findings from this research are summarized by two meta-analyses (Linkersdörfer et al., 2012; Richlan et al., 2013). The meta-analysis by Linkersdorfer and colleagues (2012) included nine studies conducted in children and adults (combined) with and without dyslexia and reported less GMV in the bilateral supramarginal gyrus, right superior temporal gyrus, left inferior temporal gyrus, left fusiform gyrus, and bilateral cerebellum in dyslexia. The meta-analysis by Richlan and colleagues (2013), which also used nine studies and overlapped with seven of the studies used by Linkersdorfer and colleagues, revealed less GMV in left superior temporal sulcus and right superior temporal gyrus in adolescents and adults (combined) with dyslexia compared to controls.

The interpretation of these findings in dyslexia would be facilitated by knowing whether there is a linear relationship between GMV and reading ability in groups that represent a wide spectrum of reading skills. If such a relationship exists in the brain regions that are known to differ in dyselxia, it would suggest that the findings in dyslexia reflect a brain-behavioral relationship that exists in the general population, with dyslexics representing the lower end of the spectrum (with low GMV and low reading scores). On the other hand, if there is no linear relationship in the general population between GMV and reading in these specific areas, one would conclude that dyselxia represents a unique group. The picture is likely to be more complex, with some brain regions found to differ in GMV in dyselxia showing a correlation with reading ability, but others not. Regions showing a correlation betweeen

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https://doi.org/10.1016/j.dcn.2019.100636
Received 7 August 2018; Received in revised form 6 March 2019; Accepted 8 March 2019
Available online 12 March 2019

GMV and reading would suggest that GMV in these brain areas is tightly yolked with reading abiliy in *all* children, whereas regions showing no such correlation are those that are altered in dyslexia, indicative of pathology. These findings could be used to better understand the etiology of dyslexia, refine models on the brain basis of reading, and make predicitions about which areas are likely to change through treatment (i.e. those that are correlated with reading ability) versus those that may be more resistant to change (i.e. those unique to dyselxia).

There have been prior efforts investigating whether there is a linear relationship between GMV and reading ability, often in the context of dyslexia. One such study in children by Jednoróg and colleagues (2015) tested for linear correlations between GMV and reading ability in a group with dyslexia (n = 130) and typical readers (n = 106). This study was conducted in a diverse linguistic sample (monolingual speakers of French, German, or Polish). They found no positive relationships within the dyslexic group. They did, however, observe a relationship within the control group: a positive correlation between GMV in the left supramarginal gyrus (SMG) with reading accuracy (using language-appropriate standardized tests of single real word reading). There have also been studies examining relationships between GMV and reading ability in adults. For instance, Pernet and colleagues (2009) tested for correlations between GMV and reading ability in a sample of native French-speaking adults with dyslexia (n = 38) and typical readers (n = 39). Here too no correlations were observed in the dyslexic group alone. Pernet et al. reported significant positive correlations when both groups were combined, this time between GMV and measures of pseudoword reading in left STG, fusiform gyrus (FG), and bilateral cerebellum. Importantly, the correlations within left STG and FG were also found when testing the control group alone. There are also studies conducted in adult typical readers only, and these report positive correlations between GMV and reading ability in the left STS and left SMG in 39 native English speaking adults (Johns et al., 2017) and for the left SMG in 253 native Chinese speaking adults with strong English reading proficiency (He et al., 2013). Taken together, the results of these studies suggest a positive linear relationship between GMV and reading ability in left SMG in typically reading children (Jednoróg et al., 2015) and adults (He et al., 2013; Johns et al., 2017), as well as in left STG, STS, and FG in adults (Pernet et al., 2009; Johns et al., 2017). Interestingly, the left SMG and FG regions have been reported to have less GMV in a meta-analysis study of dyslexia (Linkersdörfer et al., 2012).

The goal of the present study was to examine a large representative sample of children, adolescents, and young adults to test for linear relationships between GMV and single real word reading ability in those brain regions implicated in dyslexia. The results will allow for better interpretation of the reported GMV anomalies in dyslexia. Specifically, it is unclear whether the differences revealed by between-group comparisons of dyslexic participants and their age-matched controls are due to (i) a linear relationship between GMV (in specific brain areas) and reading ability in the population, or (ii) a unique anatomical profile in the dyslexic population relative to typical readers. The latter would be consistent with the view that dyslexia represents a “hump” at the low end of the population’s distribution (Rutter and Yule, 1975). This model suggests that dyslexia is a specific disability that occurs at a rate above what would be expected if the full spectrum of reading was normally distributed. This model also implies that dyslexic children exist in addition to, and are distinct from, other children with low reading performance who are not diagnosed with dyslexia, i.e. garden-variety poor readers (Stanovich, 1988). On the other hand, others have conceptualized dyslexia as representing the distribution’s lower tail (Shaywitz et al., 1992). This model would therefore predict that a relationship between GMV and reading performance exists in those brain regions identified to differ in dyslexia when looking across the spectrum of all reading abilities.

Consistent with previous work, our study used voxel-based morphometry (VBM). Because it is well known which brain regions differ in GMV in dyslexia, the present study narrowed the investigation to these specific regions (bilateral temporo-parietal cortex, left temporo-occipital cortex, and bilateral cerebellum) to test for a linear relationship between GMV and reading performance in a large US-based sample of children, adolescents, and young adults taken from the National Institutes of Health (NIH) normative database. The group of 404 subjects selected from the database was first studied as a whole and then divided into three age groups for consistency with prior studies. Further, these three groups were divided by sex, given that some of the brain regions implicated in reading and dyslexia have also been reported to show sex-specific differences in brain structure (Good et al., 2001), and there is evidence that some of the previously reported VBM differences in dyslexia may be influenced by sex (Evans et al., 2013).

While the main focus of this study is on simple linear correlations so as to be consistent with prior work (Pernet et al., 2009; Jednoróg et al., 2015), we also conducted multiple regression analyses to include the factors of sex, IQ, and socioeconomic status (SES) in the model due to their potential significant influences in the relationship between brain structure and reading ability. We hypothesized that if there is a relationship between GMV and reading ability in all readers (even when accounting for sex, IQ, and SES), this would suggest that GMV differences in any brain region in dyslexia are observed because GMV is yoked to reading ability, and that reading ability in dyslexia is low. However, if there is no linear relationship between GMV and reading ability, this would suggest that for this brain region dyslexia represents a unique group by exhibiting low GMV.

2. Materials and methods

2.1. Participants

All data were acquired by the Brain Development Cooperative Group (at six different sites in the US) as part of a larger longitudinal study of typical development, the National Institutes of Health (NIH) normative database (A. C. Evans and Brain Development Cooperative Group, 2006). All participants were healthy, native English-speaking and typically reading participants without learning or language disorders.

2.2. Behavioral measures

Participants completed a large battery of tests, and from this battery, the present study used the only measure of reading that was available, the Letter-Word Identification (LW-ID) subtest of the Woodcock-Johnson III Tests of Achievement (Woodcock and Johnson, 2011) for single real word reading. It also used the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) for IQ, providing Performance IQ (PIQ) and Verbal IQ (VIQ). PIQ was comprised of scores on Matrix Reasoning and Block Design, and VIQ was comprised of scores on Vocabulary and Similarities. SES was captured by the Brain Development Cooperative Group using a survey including measures of Income (adjusted for family size and the Metropolitan Statistical Area of residence at the time of interview) and Parental Educational (average of the highest level of education attained by both mother and father).

The Brain Development Cooperative Group exclusion criteria relevant to our study were: No children of parents with limited English proficiency; no history of inherited neurological disorder or mental retardation; no current or past treatment for psychiatric or language disorders; and no Woodcock-Johnson III or WASI standard subtest scores < 70. The behavioral testing battery also served “to exclude Learning Disability" (The MRI Study of Normal Brain Development, Study Protocol, Version: November 2006). Specifically, they noted that "Any Standard Scores < 70 would be exclusionary" or "2 SD below the mean." Also, their screening interview included the following: "Has [name] ever been diagnosed as having a learning or language

Table 1
Demographics and Behavioral Measures for Full Sample. Mean, standard deviation, and range of reading ability, IQ, and SES for full group of 404 participants. Reading ability and IQ represent standardized measures, where 100 is the mean and 15 points represent one standard deviation.

	Mean (SD)	Range
N	404	
Age	12.0 (*3.8*)	6–22
Single Real Word Reading (Standard)	108.2 (*10.9*)	71–151
Single Real Word Reading (Raw)	57.5 (*13.0*)	15–76
Full Scale IQ	111.3 (*11.4*)	77–160
Verbal IQ	109.6 (*13.1*)	74–156
Performance IQ	110.6 (*13.1*)	72–157
Adjusted Family Income	69,743.4 (*30,842.2*)	2257–144,750
Average Parental Education (years)	14.9 (*2.2*)	7–18

disorder?" (The MRI Study of Normal Brain Development, Procedure Manual, Objective 1, Version Public Release 1.0). The goal of our study was to have a wide range of reading skills (considering that children scoring between 70 and 130 represent 95 percent of all readers), including garden-variety poor readers.

We restricted our selection to individuals who were 6 years of age and older so as not to include pre-readers. The MRI images for these 431 participants were inspected and rated for quality (scale of 1–5) by two blind scorers from our lab. For each subject, the scan with the highest quality (out of three scans) was used; 27 participants were discarded entirely due to an average quality rating lower than 3 on all of their scans. Altogether, these steps resulted in using scans from 404 participants (avg. age 12 years; age range 6–22 years) of the 554 participants in the database. Of these, 211 were females and 193 were males.

Following the correlation analyses of the whole sample, the sample was further grouped by age: (1) 6–9, (2) 10–14, and (3) 15–22 years, roughly corresponding to elementary, middle, and high-school/college ages. All demographic info listed in Tables 1 and 2. A one-way ANOVA was conducted for reading, IQ, and SES across the three age groups and indicated differences for reading only ($F = 8.303$, $p < .001$; one-way ANOVA). A post-hoc *t*-test revealed that the youngest groups (ages 6–9 and 10–14) were significantly better at reading compared to the oldest group (ages 15–22) ($p < .001$, $T = 3.96$; unpaired *t*-tests for standard reading).

2.3. Imaging measures

2.3.1. MRI data acquisition

Images acquired by the Brain Development Cooperative Group used a General Electric or a Siemens 1.5 T scanner located at six different pediatric study sites. For this study we included 52 scans from Site 1, 78 from Site 2, 81 from Site 3, 73 from Site 4, 47 from Site 5, and 73 from Site 6. The scans chosen for this study did not differ across the six sites for subjects' sex, age, reading, IQ, and SES (one-way ANOVAs, n = 404; main effect of site was nonsignificant; $p > 0.05$ for all five measures). Images were collected using a 3D T1-weighted spoiled gradient recalled (SPGR) echo sequence (TR (ms) = 22–25, TE (ms) = 10–11, FOV (mm) = 256, 1–1.5 mm slice thickness, voxel size = 1mm isotropic). For more detail, see www.pediatricmri.nih.gov.

2.4. MRI data analyses

2.4.1. Preprocessing

Structural MRI scans were pre-processed and analyzed using the automated voxel-based morphometry (VBM) technique in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) via the methods outlined by Ashburner and Friston, 2000. First, each participant's image was manually aligned to the anterior commissure to decrease variability and then co-registered to the SPM12 white matter template. Next, images were segmented into gray matter, white matter, and CSF using the New Segment toolbox (Ashburner & Friston, 2005). Next, the DARTEL (Diffeomorphic Anatomical Registrations Through Exponentiated Lie Algebra) tool was used to register each image to a custom, study-specific template derived from all of the subjects' images (n = 404). This template was used for all analyses. The template file generated by DARTEL was affine registered to more closely align and spatially normalize the images to Montreal Neurological Institute (MNI) space. Normalized images were then smoothed using an 8 mm full-width at half-maximum Gaussian kernel. We used an intensity threshold of 0.2 to remove voxels of low intensity from the analysis to prevent possible edge effects prior to statistical analyses. Finally, total intracranial brain volume (TIV) was calculated by adding gray matter, white matter, and CSF for each participant for use as a covariate of no interest in statistical analyses.

2.4.2. Regions of interest

This study was focused on brain regions previously identified to differ in dyslexia compared to typically reading groups. Regions of interest were derived from two VBM meta-analysis studies, both of which found relatively less (but not more) GMV in groups with dyslexia. Each of the meta-analyses used nine VBM studies (7 of which overlapped) from the published literature of comparisons between groups with and without dyslexia to identify the studies' converging findings (Linkersdörfer et al., 2012; Richlan et al., 2013). Studies included by Linkersdorfer et al. ranged in age from 5 to 31 years, while those included by Richlan et al. ranged from 15 to 40 years. The six regions revealed by Linkersdorfer et al. (bilateral supramarginal gyrus, left inferior temporal gyrus, left fusiform gyrus, and bilateral cerebellum) and the two regions revealed by Richlan et al. (left superior temporal sulcus and right superior temporal gyrus) were used in our investigation (See Table 3). We created masks of these regions of interest (ROIs) using the MarsBaR toolbox (http://marsbar.sourceforge.net/) in SPM12 by growing a 10 mm diameter around the reported local maxima. GMV in

Table 2
Demographics and Behavioral Measures for Age-Specific Subgroups. Mean, standard deviation, and range of reading ability, IQ, and SES for the same 404 subjects, this time divided into subgroups by age. Reading ability and IQ represent standardized measures, where 100 is the mean and 15 points represents one standard deviation. Last column shows result from one-way ANOVA.

	Ages 6–9 Mean (SD)	Range	*Ages 10–14* Mean (SD)	Range	*Ages 15–22* Mean (SD)	Range	*p*-value
N	125		164		115		
Age	7.8 (*.97*)	6–9	12.2 (*2.2*)	10–14	16.9 (*1.8*)	15–22	< .001***
Single Real Word Reading (Standard)	110.6 (*11.9*)	84–148	108.5 (*11.3*)	71–151	105.0 (*9.8*)	76–134	< .001***
Single Real Word Reading (Raw)	43.3 (*12.0*)	15–66	60.5 (*7.2*)	28–75	68.5 (*3.9*)	56–76	< .001***
Full Scale IQ	112.0 (*14.0*)	77–156	111.6 (*11.9*)	79–160	110.1 (*10.7*)	85–133	.462
Verbal IQ	110.4 (*14.7*)	74–149	110.6 (*12.5*)	85–156	107.5 (*11.9*)	84–137	.116
Performance IQ	111.0 (*14.8*)	79–157	110.4 (*13.6*)	72–149	110.5 (*10.5*)	77–129	.945
Adjusted Family Income	66,900.0 (*31,580.0*)	8546–144,750	72,980.0 (*31,004.0*)	7964–142,500	68,210.0 (*29,560*)	2257–135,400	.208
Average Parental Education (years)	15.0 (*1.9*)	8–18	15.0 (*2.2*)	8–18	14.8 (*2.4*)	8–18	.700

Table 3
Regions of Interest (ROIs) Used in Analyses. MNI coordinates and Brodmann's areas of ROIs selected from VBM meta-analyses. ROIs were selected on the basis of showing significant GMV differences in dyslexia.

	MNI Coordinates			Brodmann's areas
	x	y	Z	
Linkersdorfer et al. (2012)				
L supramarginal gyrus	−54	−34	30	40
L inferior temporal gyrus	−56	−64	−10	37
L cerebellum	−26	−50	−32	n.a.
L fusiform gyrus	−38	−66	−14	19
R cerebellum	26	−54	−34	n.a.
R supramarginal gyrus	48	−40	26	40
Richlan et al. (2013)				
L superior temporal sulcus	−57	−51	6	21
R superior temporal gyrus	51	−37	16	22

each of the eight ROIs was extracted and entered as a dependent variable in JASP software (https://jasp-stats.org) (Fig. 1).

To test our hypothesis that GMV has a positive linear relationship with reading in regions identified to have reduced GMV in dyslexia, correlations between GMV for each ROI and standardized reading scores (Letter-Word Identification) were conducted. This approach was motivated by prior publications (e.g. Pernet et al., 2009; Jednoróg et al., 2015). First, we tested the entire sample of 404 participants. Second, the correlations were repeated for the subgroups derived by age (6–9, 10–14, and 15–22 years). Third, this test was repeated separately for females and males in the entire sample and again within each of the three age-specific subgroups. This encompassed 96 tests in total (12 correlations x 8 ROIs), which was corrected for in all analyses using the Holm-Bonferroni correction method (Holm, 1979).

For the analysis of the entire sample (n = 404), age, sex, and TIV were entered as covariates of no interest, as in prior studies (Pernet et al., 2009; Jednoróg et al., 2015). For the analyses of the age-specific subgroups, these same three covariates of no interest were entered (age was included given the subgroups range in age). When the sample was split by both age and sex, only age and TIV were entered as covariates of no interest.

2.4.3. Whole-Brain

In addition to the region of interest approach, we also conducted exploratory whole-brain analyses to examine whether there are any relationships between GMV and reading ability outside these ROIs. When looking at the entire sample (n = 404) and when looking at the three age-specific subgroups, age, sex, and TIV were entered as covariates of no interest. Finally, when the sample was split by both age and sex, only age and TIV were entered as covariates of no interest. We used a threshold of $p < .05$, corrected for multiple comparisons using familywise-error (FWE) correction.

2.4.4. Multiple regression model

While the simple linear correlation analyses described above were aligned with the approach used in prior studies, we also submitted the data to a multiple regression analysis given the number of factors that potentially contribute to reading. The independent variables in the model included standard scores for Letter-Word ID, VIQ, and PIQ, as well as scores for Income and Parental Education. Dependent variables were GMV from each of the ROIs. The model was considered significant at a threshold of $p < .001$ and statistical contributions to variance were considered significant at a threshold of $p < .05$. We report the adjusted R^2 value, which adjusts for the number of predictors (independent variables). Results were visualized using the Mango software package with the Colin brain template in MNI space (Holmes et al., 1998).

2.4.5. Correlations of behavioral data

While the focus of our tests was on the relationship between GMV and reading, we also provide data on the relationships between all behavioral measures, namely Letter-Word ID, VIQ, PIQ, Income, and Parental Education. We used Pearson's correlations at a threshold of $p < .05$ and applied a Holm-Bonferroni correction for multiple comparisons (taking into account also the additional correlations computed when the sample was divided into three age groups and again by sex). Consistent with the analyses for the MRI data, we computed correlation values first for the entire sample of 404, and then again for the sample divided into three groups based on age and based on sex. For brevity, we report only on the whole group and the age-specific subgroups, but not on the age-specific subgroups divided again based on sex.

3. Results

3.1. Regions of interest

3.1.1. Whole group

When testing for correlations (both positive and negative) between GMV and reading ability across the entire sample of 404 participants, we had no findings in any of the eight ROIs. When the entire group was further divided by sex, there again were no significant correlations in any of the eight ROIs.

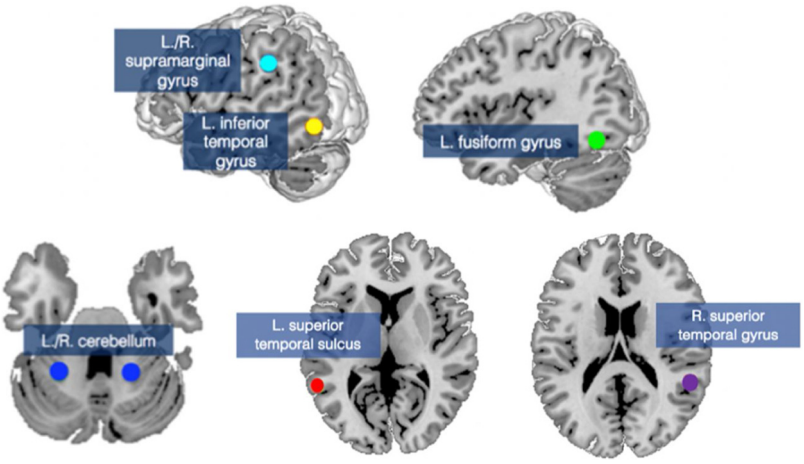

Fig. 1. Regions of Interest (ROIs) Used in Analyses. 10 mm diameter spheres centered on the local maxima (MNI coordinates) of regions identified in two meta-analyses studies as showing GMV differences in dyslexia.

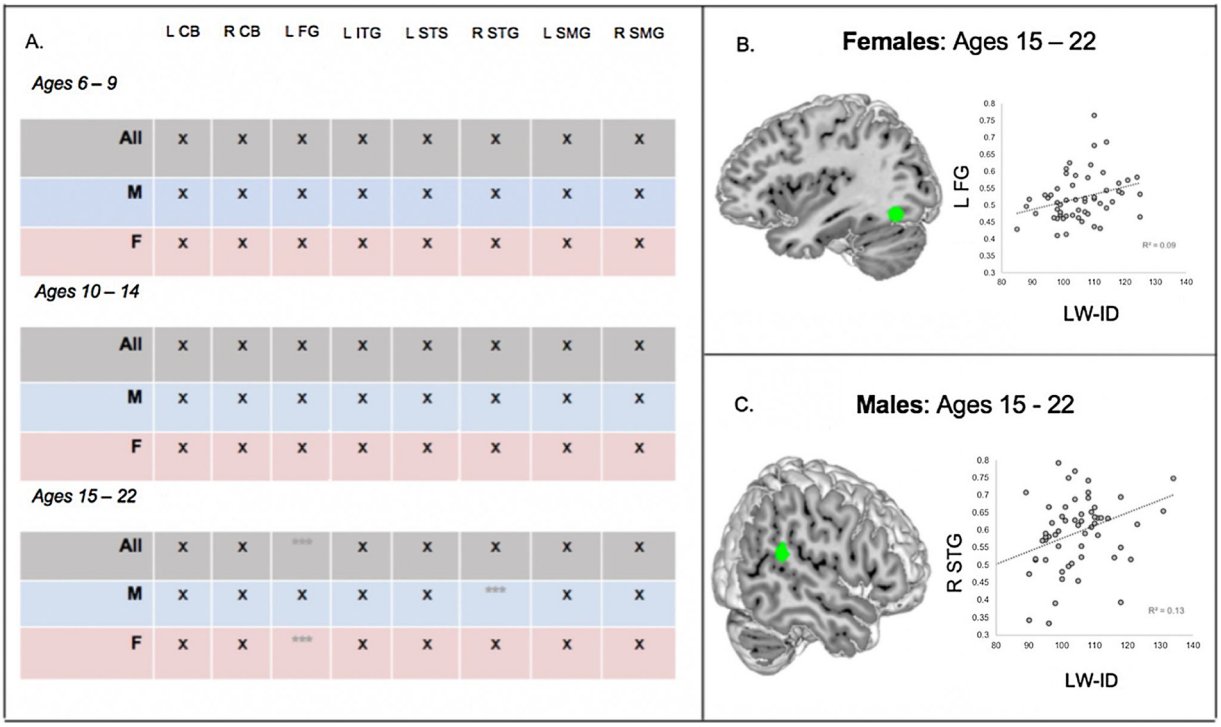

Fig. 2. Results of Correlations between GMV and Reading Ability. (A) Correlations between GMV and Single Real Word Reading within each age group. X indicates no significant results. Correlations were considered significant at $p < .05$, using Holm-Bonferroni correction for multiple comparisons as indicated by ***. (B) GMV in the L FG was positively associated with LW-ID in the group aged 15–22 years (n = 115). When divided further, there was no correlation for males, but only for females (n = 56). (C) GMV in the R STG was positively associated with LW-ID in males ages 15–22 (n = 59), but not females or males and females combined.

3.1.2. Age-specific subgroups

When testing for correlations between GMV and reading ability for the groups aged 6–9 and 10–14, we found no significant correlations in any of the eight ROIs. When these subgroups were further divided based on sex, there again were no significant correlations (see Fig. 2A). However, for the oldest group, aged 15–22, we observed a significant positive correlation between GMV in the left fusiform gyrus (FG) and reading ability ($p = .002$; T = 3.20). When this subgroup was further divided based on sex, females (but not males) showed this region to be significantly correlated with reading ability ($p = .001$; T = 3.43) (see Fig. 2B). Splitting this older age group based on sex also revealed a relationship between GMV in the right superior temporal gyrus (STG) and reading ability in males ($p = .004$; T = 3.02) (see Fig. 2C). There was no finding here in the females (and also not when males and females were combined).

When repeating all analyses using raw measures of single real word reading (controlling for age), we obtained the same results described above.

3.2. Whole-Brain

When conducting whole-brain analyses at the level of the full sample and at the levels of grouping by sex and age, there were no significant clusters ($p < .05$, FWE-corrected).

3.3. Multiple regression model

When examining whether reading ability predicts GMV in any of the eight ROIs for the entire sample of 404 using a model that incorporated effects of age, sex, IQ, and SES, it was found that reading did not contribute any significant variance (see Table 4). However, there were some significant relationships. First, VIQ was a significant predictor of GMV in the bilateral SMG, and PIQ contributed significant variance to GMV in bilateral SMG, L FG, and R STG. Second, sex contributed unique variance to GMV in bilateral SMG, L FG, and R STG. Lastly, age was a significant predictor of GMV in the L SMG and R STG.

3.4. Correlations of behavioral data

Whole Group: Pearson correlation tests showed significant relationships between most of the behavioral measures (reading ability, VIQ, PIQ, Income, and Parental Education). Specifically, reading ability was significantly correlated to both measures of IQ and SES; and measures of IQ and SES were significantly correlated with each other (see Table 5 for statistical values).

Age-Specific Subgroups: When dividing the entire sample into three separate age groups, Pearson correlation tests again showed significant correlations between reading ability and both measures of IQ for all three age groups. Also, reading ability was significantly correlated with at least one measure of SES in each age group (see Table 5 for details).

While the correlations in the entire group divided by sex, and the three age-specific subgroups divided by sex were similar. For space constraints they are not reported here.

3.5. Summary of results

In a large number (n = 404) of participants combining children, adolescents, and young adults, we found no linear relationships between gray matter volume and a measure of single real word reading in our predefined regions of interest. The same was true for younger children and adolescents when examining the age-specific subgroups. Only in the oldest group (15–22 years), GMV in two of the eight regions of interest showed a positive correlation with reading, but sex was a driving factor in these relationships. The left FG was specific to females and the right STG was specific to males. Consistent with these observations, the regression model, which accounted for age, sex, IQ, and SES, revealed no relationships between GMV and reading ability. In sum, our results demonstrate that there is not a general linear

Table 4
Results of Multiple Regression Model of GMV and Reading, IQ, SES, Sex, and Age. Multiple regression models to test the unique contributions of reading, IQ, SES, sex, and age to GMV in the ROIs identified four models to be significant (shown above: L SMG, r^2 = .170; R SMG, r^2 = .070; L FG, r^2 = .160; R STG, r^2 = .163; p < .001). However, for none of these did reading contribute significant unique variance (p < .05) when also accounting for other variables.

L SMG		Unstandardized	Standard Error	Standardized	*t*	*p*
	intercept	0.426	0.056		7.660	< .001
	Single Real Word Reading	−0.001	0.000	−0.075	−1.376	0.170
	Parental Education	−0.000	0.002	−0.007	−0.132	0.895
	Adjusted Family Income	0.000	0.000	0.022	0.411	0.681
	Performance IQ	0.001	0.000	0.103	2.017	0.044
	Verbal IQ	0.001	0.000	0.132	2.295	0.022
	Sex	0.053	0.008	0.295	6.327	< .001
	Age	−0.005	0.001	−0.222	−4.691	< .001
R SMG		Unstandardized	Standard Error	Standardized	*t*	*p*
	intercept	0.337	0.041		8.281	< .001
	Single Real Word Reading	−0.000	0.000	−0.067	−1.169	0.243
	Parental Education	0.001	0.002	0.018	0.322	0.748
	Adjusted Family Income	0.000	0.000	0.029	0.524	0.600
	Performance IQ	0.000	0.000	0.046	0.840	0.401
	Verbal IQ	0.001	0.000	0.160	2.621	0.009
	Sex	0.023	0.006	0.183	3.696	< .001
	Age	−0.001	0.001	−0.049	−0.975	0.330
L FG		Unstandardized	Standard Error	Standardized	*t*	*p*
	intercept	0.407	0.057		7.191	< .001
	Single Real Word Reading	0.000	0.000	0.042	0.764	0.445
	Parental Education	−0.002	0.002	−0.042	−0.781	0.435
	Adjusted Family Income	0.000	0.000	0.102	1.926	0.055
	Performance IQ	0.001	0.000	0.120	2.321	0.021
	Verbal IQ	0.000	0.000	0.065	1.121	0.263
	Sex	0.057	0.008	0.314	6.680	< .001
	Age	−0.002	0.001	−0.081	−1.693	0.091
R STG		Unstandardized	Standard Error	Standardized	*t*	*p*
	intercept	0.397	0.064		6.250	< .001
	Single Real Word Reading	0.000	0.001	0.023	0.419	0.675
	Parental Education	0.003	0.003	0.070	1.305	0.193
	Adjusted Family Income	0.000	0.000	0.049	0.928	0.354
	Performance IQ	0.001	0.000	0.133	2.596	0.010
	Verbal IQ	0.000	0.000	0.038	0.665	0.506
	Sex	0.051	0.010	0.253	5.389	< .001
	Age	−0.005	0.001	−0.198	−4.174	< .001

relationship between GMV and reading ability in the general population of typical readers.

4. Discussion

The overarching goal of this study was to investigate whether there is a linear relationship between gray matter volume and reading ability in the general population, with the aim of providing a context by which to interpret findings of GMV differences in dyslexia. We found no relationship between GMV and single real word reading ability in those regions known to differ in dyslexia when testing a sample of 404 healthy participants aged 6–22. The same was true when examining subgroups of younger children and younger adolescents. However, in the oldest age group, aged 15–22, one region was positively correlated to reading ability (the left FG) but this was driven by sex, because it held up only in the female but not the male subgroup. Examination of the male and female subgroups in this older age group also revealed that the right STG was correlated to reading only in males. Consistent with these findings, a multiple regression analysis of the entire group incorporating the effects of age, sex, IQ, and SES also showed that none of the eight regions of interest had a relationship with reading ability. Overall, we conclude that there is no general linear relationship between this measure of brain structure and single real word reading ability in the general population. These findings suggest that previously observed GMV differences in dyslexia are specific to this reading disorder and likely not driven by a relationship between GMV and reading ability that exists across all people.

4.1. Relationships between GMV and reading

Prior work suggests a linear positive relationship in typically reading children between GMV and reading ability in the left SMG (Jednoróg et al., 2015); and in typically reading adults in left STG and left FG (Pernet et al., 2009), as well as SMG (He et al., 2013; Johns et al., 2017) and STS (Johns et al., 2017). In the current study, we did not find such a relationship, or any other relationships in the groups with children or young adolescents. For the oldest group, which included late adolescents and adults and thereby represents the group with the most reading experience, we did find a relationship in one region, the left FG, similar to the report by Pernet and colleagues. But when examining males and females separately, it became clear that the finding in this subgroup was driven by the females (Pernet et al. did not take sex into consideration). Pernet and colleagues also reported the left STG, which we did not replicate in our whole-brain analysis. Others have reported on the left SMG (He et al., 2013; Johns et al., 2017) and one group has reported on the left STS (Johns et al., 2017), which we did not find in our ROI or whole-brain analyses. However, our findings are consistent with these adult studies in that they did not, like us, find relationships between GMV and reading in regions outside of the left STG, FG, SMG, and STS. While we did find that the GMV in the right STG correlated to reading in the male group of older participants, this was not the case in the females or in the group of males and females

Table 5
Behavioral Correlations. Pearson correlations between behavioral variables for the whole group of participants and within each age group confirmed that reading was behaviorally correlated with measures of IQ and SES.

Full sample	1	2	3	4	5
1 Letter Word-ID (Standard)	–				
2 Verbal IQ	.490***	–			
3 Performance IQ	.287***	.382***	–		
4 Adjusted Family Income	.163**	.302***	.193***	–	
5 Parental Education	.229***	.381**	263***	.509***	–
Ages 6–9	1	2	3	4	5
1 Letter Word-ID (Standard)	–				
2 Verbal IQ	.430***	–			
3 Performance IQ	.344***	.434***	–		
4 Adjusted Family Income	.244***	.303***	.135	–	
5 Parental Education	.225***	.311***	.317***	.468***	–
Ages 10–14	1	2	3	4	5
1 Letter Word-ID (Standard)	–				
2 Verbal IQ	.509***	–			
3 Performance IQ	.251**	.312***	–		
4 Adjusted Family Income	.125	.331***	.255***	–	
5 Parental Education	.240**	.404***	.312***	.519***	–
Ages 15–22	1	2	3	4	5
1 Letter Word-ID (Standard)	–				
2 Verbal IQ	.537***	–			
3 Performance IQ	.281**	.442***	–		
4 Adjusted Family Income	.129	.253**	.209*	–	
5 Parental Education	.200*	.407***	.081	.360***	–

combined. Taken together, there are no strong positive (or negative) linear relationships between GMV and single real word reading ability, except for two positive correlations in late adolescence/early adulthood that are sex-specific.

Our findings in participants without reading disability can be used to inform models of dyslexia. Our observations align with the conceptualization of dyslexia by Rutter and Yule, which describes dyslexia as a distinct bump at the low-end tail of the continuum of reading ability and a unique population. Under this model, a linear relationship between gray matter and reading across the population would not seem likely. In contrast, a model put forward by Shaywitz et al. suggests that dyslexia represents the lower end of the normal distribution. Under this model, one would expect the anomalies in GMV in dyslexia to be the product of a correlation between GMV and reading ability in the entire population, with poor readers having low GMV in the ROIs investigated in the current study. Interestingly, not one of the eight ROIs showed such a relationship.

While all eight ROIs were considered candidates, one might have envisioned a scenario in which some but not all regions showed significant correlations. This would have informed models of dyslexia, where there is an ongoing discussion about areas that represent the primary deficit in dyslexia and areas that represent secondary consequences. For example, one model argues for the primary deficit in dyslexia (phonological decoding) to be in temporo-parietal cortex, and with the difference in the occipito-temporal cortex—especially the visual word form area (VWFA), thought to underlie word form recognition—to be considered secondary to the decoding problem (Pugh et al., 2001). Under this scenario, one might expect to see a linear relationship between reading and GMV in the VWFA but not temporo-parietal cortex. An alternative suggestion has been that the VWFA is primarily compromised in dyslexia and should not be considered a secondary consequence (Richlan, 2012). However, since none of the regions showed a relationship, we unequivocally conclude that dyslexia should be considered as a unique group rather than the lower end of the normal distribution.

As our goal was to study a wide range of reading skills, our sample included readers with a standard score between 70 and 85 (representing 13.5% of the population). While learning disabilities were ruled out during the data collection phase, one may wonder about the children reading this poorly; however, when removing the seven subjects in this range, the results were not altered in any way. One question of interest is whether GMV and reading have a linear relationship for individuals at the lower end of the continuum, but not for those at the higher end. To address this, we conducted a *post hoc* test for a linear relationship between GMV and reading ability in individuals with a standard reading score of < 92 ($n = 23$), but there were none. Additionally, a between-group whole-brain comparison between this group with the next highest group of 23 readers showed no significant differences, suggesting that the poor readers in our sample are garden-variety poor readers. This lends further support to the idea that dyslexia represents a distinct distribution that is not captured by the normal continuum.

Our investigation included all of the brain regions reported in the adult correlation studies by Pernet et al. (e.g. STG and FG) and the left SMG reported by He et al. and Johns et al., yet our findings do not support a relationship for any of the regions at any age group (again, unless sex is taken into consideration, in which case two of the eight regions were significant in the oldest age group for one of the two sexes). However, there could be concerns about the reliability of the ROIs used, especially since the two meta-analyses, even though conducted largely using the same prior publications, did not converge in their findings. Yet our whole-brain analysis explored relationships between GMV and reading ability outside the regions of interest at a standard threshold, and this also showed no significant relationships. Another concern could be our conservative approach to statistical corrections, but when applying a less stringent threshold to our ROI-based primary analyses of interest (correlations at the level of the full sample and at the age- and sex-group levels), no additional regions emerged as significant. It should be noted that we did find a relationship between GMV and IQ, which will be discussed later, suggesting that specific brain-behavioral relationships do exist in this sample, just not for single word reading ability.

While we did not find positive (or negative) linear correlations between GMV and single real word reading, our findings do not rule out the possibility of a more complex relationship between these variables. Such non-linear relationships have been demonstrated in other domains. For example, it has been suggested that polynomial models best describe the relationship between cortical structure and IQ throughout development (Shaw et al., 2006). Our study does not preclude the possibility that GMV and reading ability may share a non-linear relationship, though a test for the line of best fit between the GMV data and reading measure confirmed that a linear regression was the best fit for most regions of the brain across the full sample and its age-specific subgroups. Our rationale for a simple linear approach was based on the prevalent use of simple correlations in prior studies of brain structure with reading. Further, linear relationships between behavioral measures not involving GMV and reading were been found in this dataset in our analyses (discussed below) and also by prior reports using this database (Lange et al., 2010; Pangelinan et al., 2011). For instance, Lange et al. (2010) observed positive linear associations between gray matter in the bilateral temporal lobe with Full IQ, and Pangelinan et al. (2011) reported a linear relationship between bilateral frontal and parietal gray matter with Full IQ. Neither of these investigations examined the relationship between GMV and reading ability.

It is important to address potential limitations of examining only single real word reading. Reading is complex, involving explicit phonological decoding or sight word recognition for the reading of single words or connected text. Reading can be measured in terms of accuracy, fluency and comprehension. The only measure provided by the database was the Letter-Word Identification subtest of the Woodcock-Johnson III Tests of Achievement (Woodcock and Johnson, 2011). Albeit a widely used test, it is not timed and thus has no information about fluency. Further, there was no measure of pseudoword reading, a test that is especially useful for gauging grapheme-to-phoneme mapping. In our sample, single real word reading accuracy was significantly lower in the oldest subgroup, despite the investigators' effort to create a normative sample. This is due to a paucity of participants with scores at the higher range relative to the two younger groups, perhaps suggesting that older adolescents/young adults are less likely to participate in research studies if they have strong reading skills. Yet our overall findings did not change when we repeated all of our analyses after removing 27 participants to more closely match the three age groups.

Our results speak to the relationship between GMV and reading in an English-speaking population. English is characterized by having a deep orthography, or opaque grapheme-to-phoneme mapping. Learning to read in English takes longer than some other languages (Seymour et al., 2010), and the incidence of dyslexia is higher in the UK and the US compared to countries with a shallow orthography (e.g. Germany) (Landerl et al., 1997). Future studies in languages with a shallow orthography using similar methods as the current study will be important.

While our overall finding suggests that there is no linear relationship between GMV and reading ability in typical children and young adolescents, we observed two standalone relationships when accounting for age and sex in our oldest subgroup. First, we found that GMV in the left FG positively correlated with reading ability in males and females aged 15–22, but when the sample was divided based on sex, the finding was maintained only in the females. The left FG contains the visual word form area (VWFA), which has been shown to be especially responsive to visual word stimuli (Mccandliss et al., 2003; Dehaene et al., 2010), making this region a strong candidate for structural plasticity following reading experience. Notably, Pernet and colleagues identified the left FG to be correlated with reading ability in adults, while no such relationship emerged in the pediatric study by Jednoróg et al. (2015). Findings of a relationship between GMV in the left FG and single word reading observed specifically in the older adolescent/young adult group and not in the two younger groups suggest that such a relationship may be formed through experience with reading. For example, neuroimaging studies have examined GMV following skill training (Draganski and May, 2008), showing increases in medical students' GMV after preparations for exams (Draganski et al., 2006). In the VWFA, functional brain imaging studies of illiterate adults compared to adults who learned to read later in life suggest that this region is trained by reading acquisition (Dehaene et al., 2010). Though this offers a likely explanation of a potential relationship between GMV and reading ability in adults, it remains unclear why this would be observed in females but not males, which we discuss next.

4.2. Sex-specific relationships between GMV and reading

Previous research in children has shown that cortical thickness in the left FG is thicker in age-matched and reading-matched typically reading children compared to children with dyslexia, but only for girls and not boys (Altarelli et al., 2013), suggesting a sex-specific effect in children with reading disability. The fact that this difference in dyslexia was observed when comparing children with dyslexia to both chronological age and reading age-matched control groups indicates that the difference in brain structure is not likely attributable to reading experience. As such, brain structure in the left FG may play a causal role in female children with dyslexia, whereas in typical adult female readers, GMV in this region is correlated with reading ability, most likely invoked by reading experience. Our observation was specific to the left FG, as a *post hoc* analysis of the homotopic ROI in the right hemisphere did not reveal a relationship between GMV and reading in females of the oldest group. We also found a positive correlation between GMV and reading in the right STG in the group of males aged 15–22. There is prior evidence to suggest that this relationship may also evolve from the acquisition of reading experience: Carreiras and colleagues showed that previously illiterate adults, after reading acquisition, exhibited more gray matter in the right STG when compared to adults who did not learn to read (Carrieras et al., 2009). However, unlike their results, which were observed in both males and females, our result was found only in males. These two sex-specific relationships could be based on biological predisposition, which facilitates learning to read, or learning-induced plasticity, which is experience-dependent—or even a combination of both. These sex-specific findings warrant further study.

It should also be noted that our regions of interest were taken from two meta-analysis studies which relied on existing literature, and the original studies were skewed towards males. For instance, the studies included in the meta-analyses of VBM differences in dyslexia by Linkersdorfer et al. are comprised of less than 20% females. As such, our ROIs are biased to findings in males. Indeed, research on females with and without dyslexia shows results that are somewhat different from those reported in males, with less GMV in the right precuneus and middle frontal gyrus (Evans et al., 2013). However, our whole-brain analysis conducted solely in females provided an opportunity to test these regions, but they did not emerge as significant. Nevertheless, the issue of GMV in the context of sex remains an important issue. For example, studies comparing GMV in male versus female adults (e.g. Good et al., 2001) have suggested that males possess relatively more GMV in the bilateral cerebellum, whereas females have more GMV in the left STS and IFG. Further, female sex hormones are positively associated with GMV in the left IFG, and when testing regional sex differences, males have shown greater GMV in the left FG and bilateral cerebellum (Witte et al., 2009). In consideration of the sex-specificity of our findings in the older group and given that these areas are implicated in dyslexia, our study emphasizes the importance of considering sex in future studies of reading and dyslexia. Another notable result from our study is that a significant contribution was found for sex (as well as for PIQ and age) to GMV in the right STG in our multiple regression model. This result raises the question of whether it was these variables rather than reading *per se* that drove the results of the right STG finding in the prior studies of dyslexia.

4.3. Relationships between GMV and IQ, and GMV and SES

Other aspects we considered in our multiple regression analysis were IQ and socioeconomic status (SES), as each could potentially contribute to relationships between brain structure and reading ability. Speaking first to IQ, the GMV differences reported in dyslexia are in large part in the same brain regions as those that have been published in studies correlating gray matter with IQ in the general population. FIQ has been shown to correlate positively with GMV in left STG, bilateral SMG, and left FG in adults (Haier et al., 2004) and with gray matter in frontal, parietal, and cerebellar regions in children (Pangelinan et al., 2011). Research focusing more specifically on VIQ and PIQ has shown that the gray matter changes observed in adolescents' left hemisphere language areas correlate to changes in VIQ over that same time period, while gray matter changes over time in the left cerebellum correlate with changes in PIQ (Ramsden et al., 2011). Of the studies included in the VBM meta-analyses of dyslexia, only two (Hoeft et al., 2007; Pernet et al., 2009) explicitly reported controlling for or regressing effects of IQ. Our multiple regression analysis revealed that VIQ contributed unique variance to GMV in the bilateral SMG, which is consistent with an observation by Haier et al., who examined FIQ only and found a relationship between this and GMV in the left SMG in groups of both young and older adults (Haier et al., 2004), and with Colom et al., who found that scores on vocabulary—a test that contributes to VIQ—is related to GMV in the right SMG (Colom et al., 2006). Our multiple regression analysis also showed that PIQ contributed unique variance to GMV in the left FG, left SMG, and right STG, which is in part consistent with previously observed relationships between FIQ in the left FG and left SMG (Haier et al., 2004). Importantly, these results demonstrate that there are relationships between measures of behavior, in this case IQ, with GMV in this sample, and the nature of these findings are consistent with prior reports. Given this, the absence of any relationships between GMV and reading is all the more striking.

SES has also been shown to correlate with GMV in the left perisylvian regions of the brain that are of relevance to VBM differences dyslexia (Raizada et al., 2008). Of the studies included in the meta-analyses of dyslexia, none controlled or regressed for effects of SES. Surprisingly, we did not find that measures of SES contributed unique variance to GMV.

4.4. Implications for dyslexia

The differences reported in the literature comparing groups of participants with dyslexia and their controls could be explained in two ways: There is less GMV in dyslexia, leading to two discrete distributions of GMV (low and high) when examining the dyslexic and control groups' individual differences. Or, both groups have a relationship between GMV and reading, and as such, when the groups are divided based on reading ability, they are also observed to have differences in GMV. In this latter case, however, individual differences in GMV are distributed across a continuum rather than within discrete clusters representing the two groups. Our results indicate that the latter scenario is not likely, given that there is no linear relationship or continuum between GMV and reading in the normal population. Our findings in this large sample provide an important context through which prior observations of GMV differences in developmental dyslexia may be interpreted. Future work is needed to better understand the GMV differences observed in dyslexia (Ramus et al., 2018).

5. Conclusions

Our study investigated whether there are relationships between brain structure and reading ability in children, adolescents, and young adults in the general population. We showed that, in brain regions known to be reduced in GMV in dyslexia, there is no linear relationship between GMV and reading ability that manifests, independent of age and sex, in the general population. Our study revealed only two relationships, but these were sex-specific and unique to the oldest age group, ages 15–22. A multiple regression analysis taking age, sex, IQ, and SES into account revealed no relationship between GMV and single real word reading ability. Together these results suggest that differences reported in GMV in dyslexia are due to dyslexia representing a unique group.

Declarations of interest

None.

Acknowledgments

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Mental Health or National Institutes of Health. Data employed in the preparation of this article were obtained from the Pediatric MRI Data Repository created by the NIH MRI Study of Normal Brain Development, Release 5. These data derive from a multi-site, longitudinal study of typically developing children, from ages newborn through young adulthood conducted by the Brain Development Cooperative Group and supported by the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke (Contract #s N01-HD02-3343, N01-MH9-0002, and N01-NS-9-2314, -2315, -2316, -2317, -2319 and -2320). A listing of the participating sites and a complete listing of the study investigators can be found at http://www.bic.mni.mcgill.ca/nihpd/info/participating_centers.html. GE and GAT are supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (R01 HD081078). We thank Anna Matejko for her input on the manuscript.

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