Behavioral/Cognitive

DCDC2 Polymorphism Is Associated with Left Temporoparietal Gray and White Matter Structures during Development

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Three genes, *DYX1C1*, *DCDC2*, and *KIAA0319*, have been previously associated with dyslexia, neuronal migration, and ciliary function. Three polymorphisms within these genes, rs3743204 (*DYX1C1*), rs793842 (*DCDC2*), and rs6935076 (*KIAA0319*) have also been linked to normal variability of left temporoparietal white matter volume connecting the middle temporal cortex to the angular and supramarginal gyri. Here, we assessed whether these polymorphisms are also related to the cortical thickness of the associated regions during childhood development using a longitudinal dataset of 76 randomly selected children and young adults who were scanned up to three times each, 2 years apart. rs793842 in *DCDC2* was significantly associated with the thickness of left angular and supramarginal gyri as well as the left lateral occipital cortex. The cortex was significantly thicker for T-allele carriers, who also had lower white matter volume and lower reading comprehension scores. There was a negative correlation between white matter volume and cortical thickness, but only white matter volume predicted reading comprehension 2 years after scanning. These results show how normal variability in reading comprehension is related to gene, white matter volume, and cortical thickness in the inferior parietal lobe. Possibly, the variability of gray and white matter structures could both be related to the role of *DCDC2* in ciliary function, which affects both neuronal migration and axonal outgrowth.

Key words: **ciliary function; developmental dyslexia; neuroimaging; reading ability; single nucleotide polymorphism; SNP; supramarginal and angular gyrus**

Introduction

Developmental dyslexia, or reading disability, is one of the most common learning disorders among children (Shaywitz et al., 1990; Katusic et al., 2001). A different pattern of activation in the left temporoparietal, inferior parietal, and occipitotemporal cortical regions has been observed in impaired compared with normal readers (Shaywitz et al., 2002, 2004; Richlan et al., 2011; Richlan, 2012). Dyslexia has also been associated with structural deviations of gray and white matter in corresponding regions (Klingberg et al., 2000; Deutsch et al., 2005; Silani et al., 2005; Vinckenbosch et al., 2005; Niogi and McCandliss, 2006; Kronbichler et al., 2008; Altarelli et al., 2013). These differences could rather be seen as the end distribution of a continuum in the general population, without any diagnosis of dyslexia (Klingberg et al., 2000; Nagy et al., 2004; Beaulieu et al., 2005; Deutsch et al., 2005; Niogi and McCandliss, 2006; Darki et al., 2012).

A small number of candidate genes, such as *DYX1C1*, *DCDC2*, and *KIAA0319*, have been associated with increased risk for reading impairment (Taipale et al., 2003; Cope et al., 2005; Meng et al., 2005; Schumacher et al., 2006; Eicher et al., 2014) as well as with neuronal migration during cortical development (Wang et al., 2006; Gabel et al., 2010; Peschansky et al., 2010; Szalkowski et al., 2012). At the cellular level, *DYX1C1* and *DCDC2* have been implicated in regulating ciliary growth and function (Massinen et al., 2011; Chandrasekar et al., 2013). Impaired ciliary function may lead to misplacement of neurons in the cerebral cortex and may hinder the axonal outgrowth (Higginbotham et al., 2012). Thus, genetic polymorphisms associated with ciliar functioning may lead to disturbances in both white and gray matter in the brain.

Gray matter volume alterations in association with single nucleotide polymorphisms (SNPs) in or near the *DYX1C1*, *DCDC2*, and *KIAA0319* genes have been reported in some genetic imaging assessments (Meda et al., 2008; Jamadar et al., 2011). Functional MRI studies have also detected an association of genetic variants

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in *KIAA0319* and *DCDC2* with brain activation in superior temporal sulcus, as well as the left anterior inferior parietal and right temporal gyrus and lateral occipital cortex (LOC; Cope et al., 2012; Pinel et al., 2012).

Three SNPs, rs3743204 (*DYX1C1*), rs793842 (*DCDC2*), and rs6935076 (*KIAA0319*), showed significant effects on the normal variability of white matter volume in left temporoparietal regions in which the white matter pathways connect the middle temporal gyrus (MTG) to the angular gyrus (AG) and the supramarginal gyrus (SMG; Darki et al., 2012). These cortical regions have been reported to be functionally and structurally different in individuals in whom dyslexia has been diagnosed compared with normal readers (Paulesu et al., 2001; McCandliss et al., 2003; Carreiras et al., 2009).

Knowing the involvement of the dyslexia susceptibility genes *DYX1C1*, *DCDC2*, and *KIAA0319* in neuronal migration and ciliary function, we aimed to assess whether the individual genotypes of the SNPs rs3743204, rs793842, and rs6935076 have any significant effect on the normal variability of cortical thickness in the temporal and parietal associated regions during development.

Materials and Methods

Participants

Seventy-six typically developing children and young adults, already included in our previous study (Darki et al., 2012), were scanned for the third time as a part of a longitudinal study (Söderqvist et al., 2010). The participants (41 males and 35 females) were in nine different age groups (6, 8, 10, 12, 14, 16, 18, 20, and 25 years of age) with no reports of any neurological or psychological disorders. This study was approved by the ethics committee of the Karolinska University Hospital. Informed consent was provided by the participants or the parents of children <18 years of age.

Genotyping

Thirteen SNPs located in or in close vicinity to three dyslexia susceptibility genes (*DYX1C1*: rs3743204, rs3743205, and rs17819126; *DCDC2*: rs793842, rs793862, rs807701, rs2328819 rs2792682, rs7751169, and rs9460974; *KIAA0319*: rs4504469, rs6935076, and rs2143340) were genotyped with matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry with iPLEX Gold assays, as previously described (Darki et al., 2012).

We previously (Darki et al., 2012) reported that three of these SNPs, rs3743204 (*DYX1C1*), rs793842 (*DCDC2*), and rs6935076 (*KIAA0319*) showed significant effects on the normal variability of white matter volume for two imaging rounds (i.e., the first two time points of the longitudinal dataset). Here, we analyzed the structural MRI data from all three time points to investigate the association of these SNPs with white matter structure and the cortical thickness. The association between these SNPs and behavior measures was also assessed.

Behavioral assessment

All subjects were assessed with a reading comprehension task using narrative and expository texts from the Progress in International Reading literacy Trend Study (PIRLS 2001 T) and The International Association for the Evaluation of Educational Achievement Reading Literacy Study 1991. Reading comprehension tests included 77 items for four age groups including individuals ranging in age from 8 to 25 years and were administered either individually or in groups of 2–20 participants in a classroom (Söderqvist et al., 2010). Different age groups thus received different, but overlapping, sets of items. An item response theory analysis (Bond and Fox, 2003) was then used to achieve a reading ability *z*-score for each subject, which was used for further analysis.

Additionally, a word decoding task called "word chains" was tested. This is similar to the English Woodcock Johnson Word-ID test, in which the subjects had 72 sets of written words, each consisting of three words without spaces in between. The task was to read as many words as possible during 2 min and mark with a pencil where the spaces should occur. The score is based on the number of words that has been marked correctly (Woodcock, 1987).

Structural brain imaging and analysis

T1-weighted spin echo scans were collected with a 1.5 T Avanto scanner (Siemens Medical System) using a 3D magnetization-prepared rapid acquisition gradient echo sequence with TR = 2300 ms, TE = 2.92 ms, 256×256 matrix size, 176 sagittal slices, and 1 mm^3 isotropic voxel size.

Voxel-based morphometry, which segmented the brain into gray matter, white matter, and CSF, was performed on structural data collected across all three rounds of data collection using SPM5, Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox (Ashburner, 2007). The structural data of all individuals were first segmented into gray matter, white matter, and CSF using a mixture–model cluster analysis, which identifies the voxels by matching their intensities to the tissue types and combines this information with a priori knowledge from probability maps of these three tissues. Next, the tissue-segmented images were iteratively registered to each other to create a template. Then the images were subjected to a nonlinear modulation by multiplying the registered images with the Jacobian determinants. The modulation reflects the probability of being locally expanded or contracted to fit to the template. The modulated white matter segmented images were registered to Montreal Neurological Institute (MNI) space by affine transformation and then smoothed with an 8 mm Gaussian kernel for further statistical analysis.

SNP genotypes and white matter volume

All white matter segmented images were analyzed by second-level SPM analysis, using a flexible factorial design in SPM8, to assess the variation of white matter volume with respect to genotype variability. Flexible factorial design allowed specifying the participants and it considered the repeated measures for all individuals by including subjects and testing rounds as factors. The SNPs rs3743204 (*DYX1C1*), rs793842 (*DCDC2*), and rs6935076 (*KIAA0319*) were entered separately as a main factor in the model. The sample sizes by genotype are as follows: rs3743204 (GG, $n = 53$; GT/TT, $n = 23$); rs793842 (CC, $n = 21$; CT, $n = 41$; TT, $n = 14$); and rs6935076 (CC, $n = 30$; CT, $n = 39$; TT, $n = 7$). Age, sex, handedness, and total white matter volume were used as covariates, and the interaction of SNP, as the main factor, with age and sex was also added. This part of the analysis was repeated in the same way as the analysis previously published (Darki et al., 2012), but this time considering all three time points of the longitudinal data. We aimed to assess whether the effect of the previously published SNPs remains significant when adding the image data from the third time point. The exploratory analysis was performed on the cluster level with nonstationary cluster extent correction at $p = 0.05$ (Hayasaka et al., 2004) to find the main effect of SNPs. We then corrected for multiple comparisons of three SNPs and set the threshold of significance at $p = 0.016$ (Bonferroni correction of three tests). The significant regions were then saved as regions of interest (ROIs) and their overlapping area was used as a seed region for white matter tractography.

Diffusion tensor imaging and fiber tracking

Diffusion tensor imaging (DTI) with a field of view of 230×230 mm^2, a 128×128 matrix size, 40 slices, 2.5 mm slice thickness, and a b value of 1000 s/mm^2, and was performed in 64 gradient directions with one b0 image collected in the beginning. Eddy current and head motions were corrected with affine registration to the reference volume (b0 image) using FSL software. The diffusion tensor parameters were then estimated, and subsequently the DTI and fractional anisotropy (FA) data were constructed. Nonlinear registration was performed using Tract-Based Spatial Statistics (TBSS) version 1.2 (Smith et al., 2006), in FSL (Smith et al., 2004) to align all FA images to the mean FA image. TBSS back projection was used to map the significant ROI to the FA image of all individuals. Deterministic fiber tracking was then applied by ExploreDTI version 4.7.3 (Leemans et al., 2009), with 1 mm step size, considering an FA threshold of 0.15 and an angular difference of 30°, to find the white matter fibers passing through the significant ROI on individual DTI space. The traced white matter pathways of all individuals were then transformed to the mean FA template using the TBSS method for

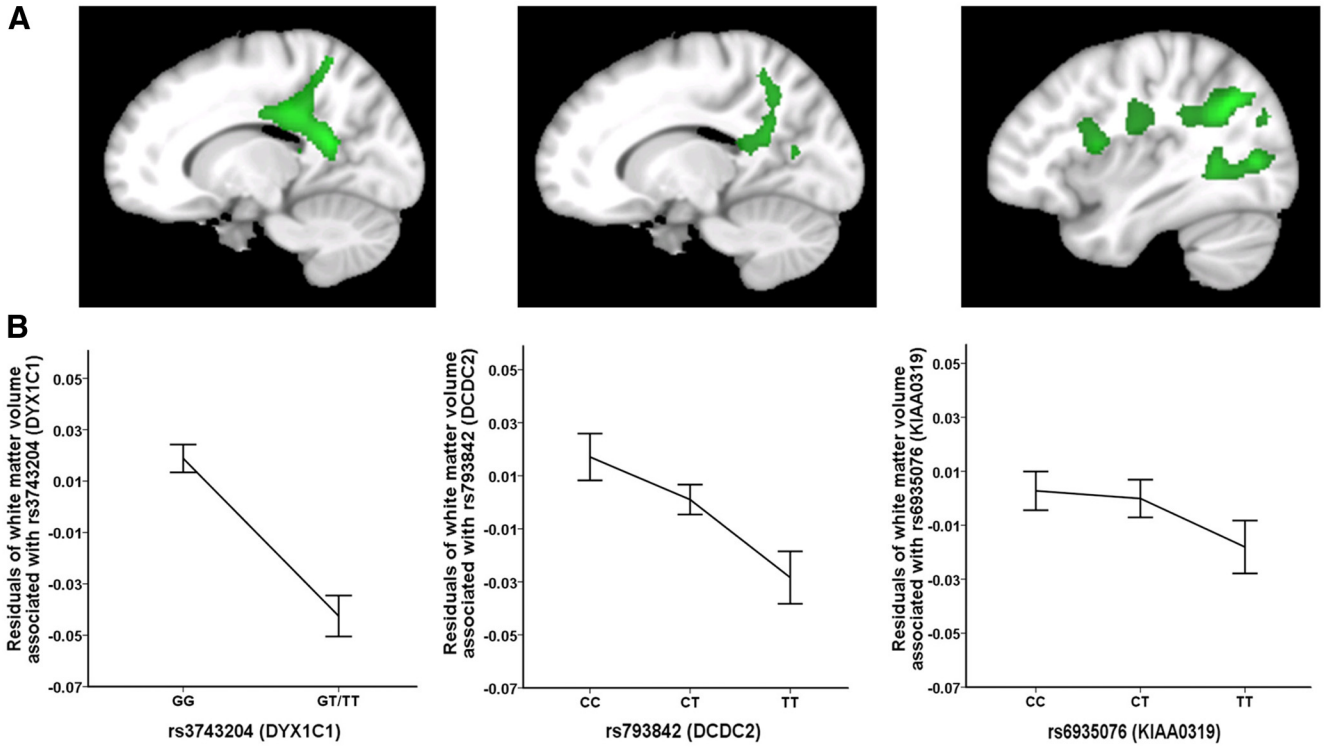

Figure 1. Main effect of three SNPs from the *DYX1C1*, *DCDC2*, and *KIAA0319* genes on white matter structure. ***A***, White matter clusters showing significant association between SNPs and white matter volume in sagittal sections. ***B***, Distribution of residuals of mean white matter volume in each significant region across different genotypes after correction for age, sex, and handedness. Error bars indicate ±1 SEM.

non-FA images in which the corresponding nonlinear transformation matrices for FA images was used to register the traced white matter pathways to template. The aligned white matter pathways were then binarized and averaged across all subjects. The averaged map of white matter pathways was then overlapped with the Harvard-Oxford cortical structural atlas to find the cortical regions connected by white matter pathways.

Cortical thickness measurement

The cortical thickness of the structural images was estimated using an automatic longitudinal stream in Freesurfer (Reuter et al., 2012) by constructing models for the boundary between gray and white matter. First, a within-subject template was created for each subject using inverse consistent registration of the T1-weighted images (Reuter et al., 2010; Reuter and Fischl, 2011). Then, several processing steps (Dale et al., 1999; Fischl and Dale, 2000), including skull removal, template transformation, and atlas registration, were performed. Images were later segmented to white matter, gray matter, and pia, based on intensity and neighborhood voxel restrictions. The distance between the white matter and the pia was computed as the thickness at each location of cortex.

To investigate our main hypothesis regarding the effect of the SNPs on cortical thickness, we first identified the cortical regions connected by white matter pathways and then we extracted their cortical thickness using the workflow described in http://surfer.nmr.mgh.harvard.edu/fswiki/VolumeRoiCortical Thickness.

Statistical analyses

SNP genotypes and cortical thickness. To assess the effect of the SNPs on the cortical thickness of the corresponding regions, the cortical thickness of the particular ROIs was analyzed using a mixed linear model in SPSS version 21.0. The model was set for three repeated measures, and the "unstructured" type was chosen for repeated covariance. The measures of cortical thickness were entered separately as dependent variables, and the SNP genotypes were set as a factor. Age, sex, and their interactions by the SNPs, as well as handedness were entered as covariates. The main effect of the SNPs on the thickness of the cortex was tested for each ROI separately.

SNP genotypes and reading ability. The association of all three SNPs with reading scores was assessed using a mixed linear model considering three repeated measures of reading ability. The reading scores were entered as dependent variables, and the SNP genotypes were set as a factor. Age, sex, and handedness were considered as covariates. The main effect of the SNPs on the reading ability was assessed for each SNP separately. We later entered the SNP interaction by age and sex as covariates to assess for interaction possibility in the model.

Brain structure and behavior measures. The white matter volume in the SNP-associated regions as well as the thickness of the cortical areas were set separately as covariates of interest in the mixed linear model and were tested for a significant relationship to reading ability, including all three repeated measures (sex and handedness were covariates). Next, we entered age as a covariate to find the brain–behavior relationships after the effect of covariates were removed.

In another set of analyses, we assessed which brain measures can predict future reading ability. Round 1 and 2 brain measures were set as covariates, and they were analyzed to predict round 2 and 3 reading scores using a mixed linear model considering two repeated measures with sex and handedness as covariates. The model was then corrected for the effect of either age or reading at baseline to see which relationship would stay significant age independently.

Results

Genetic associations to white matter volume

In the assessment of the association of three dyslexia-related SNPs, rs793842 (*DCDC2*), rs6935076 (*KIAA0319*), and rs3743204 (*DYX1C1*), on white matter volume now including all three rounds of imaging of the longitudinal data, we found the same significant association with white matter volume for these SNPs, as already reported based on data from the first two time points (Darki et al., 2012). Figure 1*A* shows the clusters found to be significant for the association of each SNP. The clusters associated with these SNPs overlapped mainly with superior longitudi-

Table 1. Coordinates for the effect of SNPs on white matter

SNP	Gene	FDR-corrected cluster-level *p* value	Cluster size	Peak voxel			
				z-score	MNI coordinates		
					x	*y*	*z*
rs3743204	*DYX1C1*	1.28×10^{-10}	9804	4.11	−16	−54	18
rs793842	*DCDC2*	8.19×10^{-5}	3353	4.24	−28	−70	33
rs6935076	*KIAA0319*	3.33×10^{-10}	8195	5.32	−34	−58	31
		3.32×10^{-10}	8285	4.01	36	−28	37

nal fasciculus and the posterior part of corpus callosum based, on the Johns Hopkins probabilistic atlas. The rs6935076 and rs3743204 clusters were bilateral, while the significant region associated with rs793842 was located only in the left hemisphere. The peak MNI coordinates, the size of the clusters, and the false discovery rate (FDR)-corrected *p* values at cluster level are listed in Table 1. All three significant regions ($p < 8.19 \times 10^{-5}$) survived a more restricted significant threshold at multiple-comparison correction [e.g., correction for 13 SNPs (Darki et al., 2012), $p < 0.0038$] and were overlapped in left temporoparietal area (Fig. 2*A*) in the same location found earlier (Darki et al., 2012). Figure 1*B* illustrates the residual distribution of the mean white matter volume in each significant region for the related genotypes after correction for age, sex, and handedness.

Fiber tracking

An overlapping region of all three clusters was found in the left temporoparietal area (Fig. 2*A*) and was used as the seed region for fiber tracking. Using streamline fiber tracking, the tracts passed through this ROI were traced on all individuals DTI space separately, and then binarized and averaged across all subjects. Fiber tracking on one subject as well as the group-averaged map of the tracts across all individuals are shown in Figure 2, *B* and *C*, respectively. Figure 2*D* shows the white matter pathways reached to cortex after 10% thresholding. This was done to remove the uncertain voxels with the probability of having fibers in <10% of the subjects. The averaged map of white matter pathways was then overlapped with the Harvard-Oxford cortical structural atlas and subsequently labeled with different colors (Fig. 2*E*). We found the white matter pathways; passed through the SNP-associated region; and connected to the left MTG, SMG, and AG, as well as to the bilateral LOC, superior parietal lobules, precuneus, and cingulate gyrus.

rs793842 (*DCDC2*) associated with cortical thickness

The main effects of the three SNPs on the thickness of cortical areas were assessed for the left lateral regions identified by the tract tracing (Fig. 2*D*) as well as their homologous areas in right hemisphere. The only significant association was between rs793842 (*DCDC2*) and the left lateral cortical region ($F_{(2,83.99)} = 9.39$, $p = 2.09 \times 10^{-4}$, partial $\eta^2 = 0.140$). There was a trend for this SNP also for the right hemisphere ($p = 0.037$), but it did not survive the correction for multiple comparisons of six tests ($p_{corrected} < 0.008$). Next, to anatomically localize the associated regions in the left hemisphere, we tested the association of rs793842 with the thickness of each of the five segmented cortical areas (Fig. 2*E*). We found significant associations (Fig. 3*A*) between rs793842 (*DCDC2*) and the cortical thickness of left SMG ($F_{(2,86.96)} = 5.05$, $p = 2.68 \times 10^{-4}$, partial $\eta^2 = 0.152$), left AG ($F_{(2,88.78)} = 5.12$, $p = 7.87 \times 10^{-3}$, partial $\eta^2 = 0.112$), and left LOC ($F_{(2,84.21)} = 11.96$, $p = 2.70 \times 10^{-5}$, partial $\eta^2 = 0.165$). The cortex was significantly thicker for T-allele carriers, who also had lower white matter volume (Fig. 1*B*). There was also a significant interaction (Fig. 3*B*) between rs793842 and age on the thickness of left SMG ($F_{(2,114.78)} = 7.61$, $p = 7.88 \times 10^{-4}$) and left LOC ($F_{(2,110.38)} = 7.77$, $p = 6.94 \times 10^{-4}$). (The mixed linear model used here did not provide the effect size or the partial η squared. The partial η^2 values reported above are therefore the effect sizes from the analyses performed on time point 1 only.)

Rs793842 (*DCDC2*) associated with reading ability

Rs793842 (*DCDC2*) was the only SNP that showed significant association with reading comprehension scores ($F_{(2,50.02)} = 4.66$, $p = 0.014$) with lower reading scores for T-allele carriers who had significantly lower white matter volume in the left temporoparietal area, and thicker cortex in the left SMG, AG, and LOC. The SNP interaction by age was not significant. No genetic association was found for a test of single-word reading, the word chain test ($p = 0.608$).

Brain measures correlated with reading ability

The reading comprehension scores were positively correlated with white matter volume in all three white matter regions ($p < 5.00 \times 10^{-5}$), also after correction for age ($p < 0.001$). Reading comprehension scores were also associated with cortical thickness in parietal regions, including left SMG ($F_{(1,128.28)} = 8.45$, $p = 4.32 \times 10^{-3}$), right SMG ($F_{(1,152.68)} = 16.14$, $p = 9.2 \times 10^{-5}$), left AG ($F_{(1,137.73)} = 8.59$, $p = 3.95 \times 10^{-3}$), right AG ($F_{(1,144.97)} = 21.72$, $p = 7.0 \times 10^{-6}$), as well as the left and right LOC ($F_{(1,111.81)} = 7.51$, $p = 7.15 \times 10^{-3}$; and $F_{(1,130.28)} = 20.41$, $p = 1.4 \times 10^{-5}$, respectively). In contrast to the white matter associations, the gray matter correlations did not remain significant when age was included as a covariate.

The word chain scores were associated with the white matter volumes ($p < 10^{-6}$) as well as the cortical measures in all three bilateral regions ($p < 0.036$ for MTG, $p < 0.001$ for SMG, $p < 1.64 \times 10^{-4}$ for AG, and $p < 1.0 \times 10^{-5}$ for LOC). The cortical measures did not remain significant after entering age as a covariate, but the relationships between white matter volumes and word chain scores did remain significant ($p < 0.010$).

White matter volume predicted reading ability 2 years later

The white matter volumes in the SNP-associated regions were the only brain measures that significantly predicted future reading comprehension ($p < 4.60 \times 10^{-5}$) and word chain scores ($p < 0.003$). The volumes of white matter remained a significant predictor for reading comprehension 2 years later, even after correcting for age ($p < 0.001$) or reading ($p < 0.041$) at baseline.

To quantify the amount of information gained from genetic markers and brain measures compared with information gained from knowing the baseline reading comprehension score in predicting future reading ability, we compared the following two models: Model 1: $\text{Reading2} = \beta_1 \times \text{age} + \beta_2 \times \text{sex} + \beta_3 \times \text{handedness} + \beta_4 \times \text{Reading1}$, $r^2 = 0.617$ ($r = 0.785$); Model 2: $\text{Reading2} = \beta_1 \times \text{age} + \beta_2 \times \text{sex} + \beta_3 \times \text{handedness} + \beta_4 \times \text{gene} + \beta_5 \times \text{white matter} + \beta_6 \times \text{cortical thickness}$, $r^2 = 0.613$ ($r = 0.783$). The results show that genetic information and brain measures at baseline ($r^2 = 0.613$) are approximately as informative as knowing the baseline reading ability ($r^2 = 0.617$) in predicting future reading comprehension.

In another analysis, we aimed to assess how much of the variance in reading scores can be explained by the brain measures. Using three different models, we showed that reading at baseline explained 8.4% more variance than the model predicted by age, sex, and handedness ($r^2 = 0.533$). Adding genetic and structural

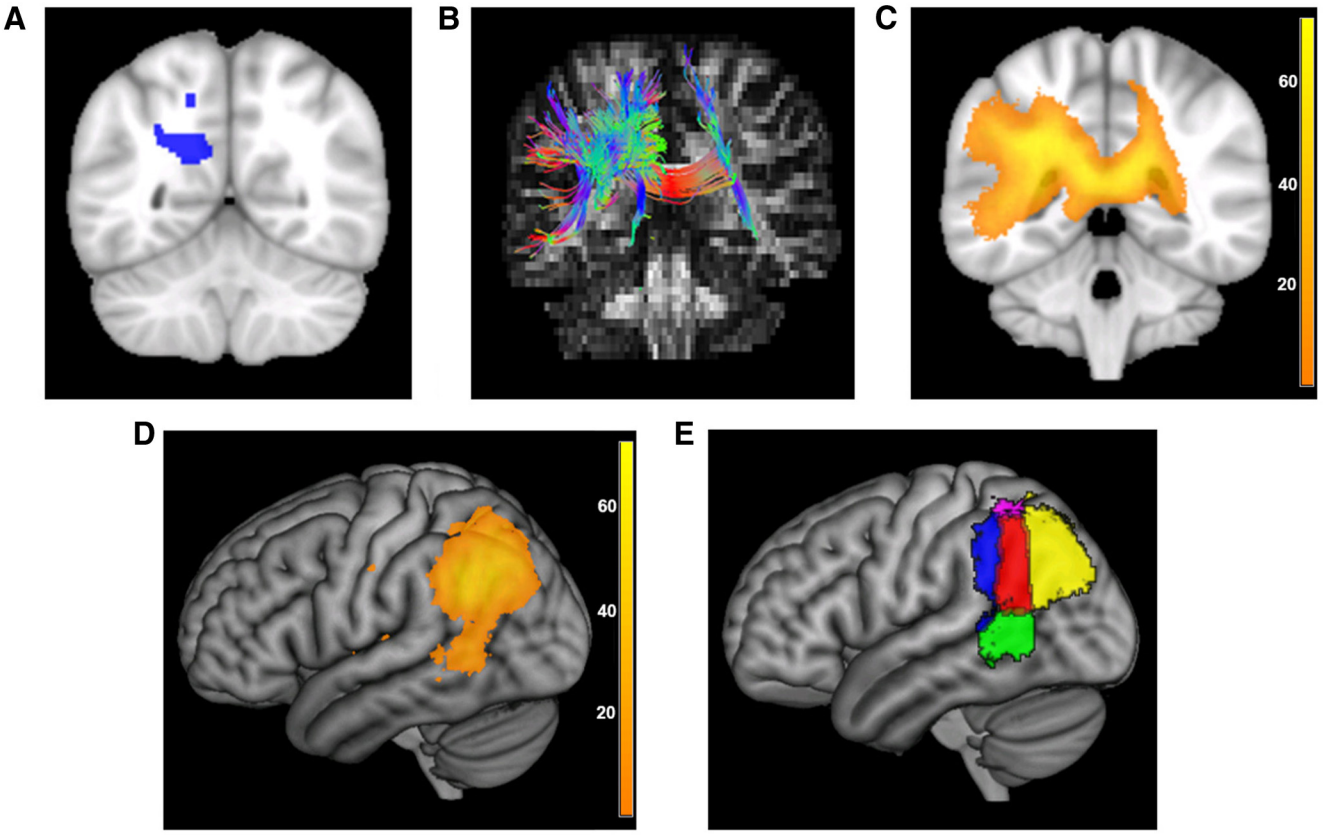

Figure 2. ***A***, Overlap region between the significant white matter areas associated with the three dyslexia-related SNPs: rs3743204 (*DYX1C1*), rs793842 (*DCDC2*), and rs6935076 (*KIAA0319*). ***B***, Example of fiber tracking of one individual (red, green, and blue fibers show left–right, anterior–posterior, and inferior–superior directions, respectively). ***C***, Probability map of traced fibers across all individuals. ***D***, The cortical regions most consistently connected are the middle temporal gyrus, supramarginal and angular gyri, as well as the lateral occipital cortex. The color bars correspond to the number of subjects with available white matter pathways. ***E***, Overlapped white matter pathways with Harvard-Oxford cortical structural atlas are labeled with different colors; red for left angular gyrus, blue for left supramarginal gyrus, green for left middle temporal cortex, yellow for lateral occipital parietal cortex, and purple for superior parietal cortex.

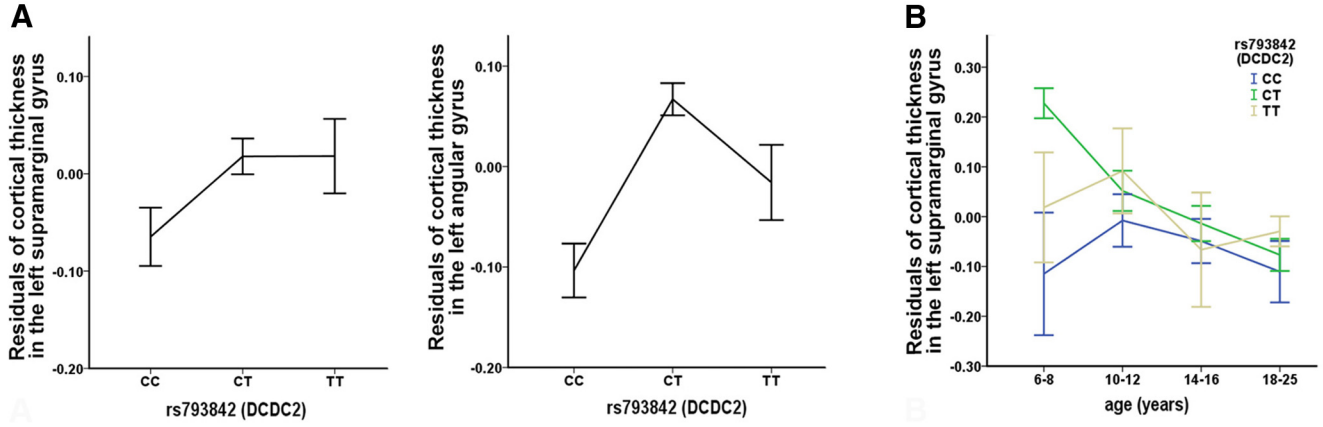

Figure 3. ***A***, Cortical thickness of left supramarginal and angular gyri across rs793842 (*DCDC2*) genotypes, after correction for age, sex, and handedness. All three time points are collapsed together. ***B***, rs793842 interaction by age for the residuals from the mean cortical thickness of left supramarginal gyrus across four different age groups after correction for sex and handedness. Error bars indicate ±1 SEM.

information explained another 5.9% of unique variance about future reading comprehension.

White matter volume and cortical thickness

The white matter volume of left temporoparietal pathways negatively correlated with the cortical thickness of left AG ($p = 0.004$), SMG ($p = 0.048$), and MTG ($p = 0.039$) after correcting for the effect of sex and handedness. We did not correct for the effect of age to keep the developmental aspect of brain maturation. In another analysis, we corrected for the effect of age to see whether the link between white matter and gray matter structures are age dependent. After correcting for age, the correlation was not significant. The associations of *DCDC2* polymorphism with white matter volume and cortical thickness were also significant after the effect of age was removed. This suggests that the genetic associations are not de-

pendent on the developmental relationship between brain white and gray matter measures, and that they are related to the interindividual differences.

Discussion

Here we expanded our previous analysis of the associations of three dyslexia candidate genes with brain structural measures and found that variation in *DCDC2* (rs793842) affected the cortical thickness in left SMG and AG. By including three rounds of the longitudinal imaging data, we replicated our previous findings of the effect of all three SNPs (rs3743204 of *DYX1C1*, rs793842 of *DCDC2*, and rs6935076 of *KIAA0319*) on white matter volume in left temporoparietal region (Darki et al., 2012). Both white and gray matter structures were associated with reading ability.

The white matter pathways passing through the overlapping area of the SNP-associated regions connected to the left SMG, AG, posterior MTG, and the bilateral LOC. The parietal and temporal cortical areas have been reported to be hypoactive in dyslexic subjects (Paulesu et al., 2001; McCandliss et al., 2003; Richlan et al., 2011; Richlan, 2012). Moreover, these regions showed volumetric differences in late literates relative to illiterates (Carreiras et al., 2009). The role of these cortical regions in language comprehension and semantic processing has also been established in several functional neuroimaging studies (Chertkow et al., 1997; Binder et al., 2009; Turken and Dronkers, 2011; Noonan et al., 2013).

Based on the temporoparietal white matter region, our fiber tracking was restricted to temporoparietal pathways, and they did not terminate at occipitotemporal cortical regions, which were reported to be structurally different in dyslexic individuals compared with normal control subjects (Kronbichler et al., 2008; Altarelli et al., 2013). We found connections to the LOC with the fibers extending from the posterior part of corpus callosum. LOC has been previously associated with functional and structural abnormalities in dyslexia (Pernet et al., 2009; Danelli et al., 2013). The white matter volume in the posterior part of the corpus callosum and cingulum, with the connection to the parietal, occipital, and temporal lobes, has also been associated with the other dyslexia candidate locus, MRPL19/C2ORF3 (Scerri et al., 2012), suggesting that this locus is associated with visual perception and possibly general cognitive abilities such as recognition and imagination (Danelli et al., 2013).

In the present study, the white matter volume in the SNP-associated regions as well as the cortical thickness of the parietal ROIs were significantly correlated with reading comprehension and word chain scores. This is consistent with previously published studies, which have assessed the associations between reading and white and gray matter structures (Klingberg et al., 2000; Nagy et al., 2004; Deutsch et al., 2005; Ben-Shachar et al., 2007; Blackmon et al., 2010; Welcome et al., 2011; Vandermosten et al., 2012; Wandell and Yeatman, 2013). Here, we also showed that white matter volume in the left temporoparietal tract predicted future reading ability. This emphasizes the role of white matter in driving cognitive development in children, as was previously shown for working memory (Darki and Klingberg, 2014; Ullman et al., 2014).

rs793842 within the *DCDC2* gene was also significantly associated with reading ability, with lower reading scores for T-allele carriers. We did not find this association in our previous study (Darki et al., 2012) where we had two rounds of the longitudinal data. T-allele carriers had significantly lower white matter volume in left temporoparietal area, and thicker cortex in left SMG, AG, and LOC. Previously, the genetic markers of *DCDC2*, *KIAA0319*, and *DYX1C1* genes have been associated with variations in general reading ability (Luciano et al., 2007; Bates et al., 2010; Lind et al., 2010). To our knowledge, rs793842 from DCDC2 has not previously been associated with dyslexia, but it is in linkage disequilibrium with previously associated markers.

The genomic distance between *DCDC2* and *KIAA0319* is only ~130 kb; however, this interval is relatively rich in recombinations, and thus there is no linkage disequilibrium between the markers for both genes (Schumacher et al., 2006). Thus, any associations detected are likely to be specific for the gene implicated and not reflect a genetic effect of the other gene. The *DCDC2* SNP rs793842, which showed association with cortical thickness, happens to be highly informative, with a minor allele frequency of 0.47, which may yield optimal power for detecting associations, given that the functional haplotype covaries with this marker. Because of the more limited power for the other polymorphisms with lower frequencies, we cannot exclude the effects that the other gene might have on cortical thickness.

All three dyslexia susceptibility genes studied in this article have been associated with dyslexia (Paracchini et al., 2008; Couto et al., 2010; Newbury et al., 2011; Scerri et al., 2011; Venkatesh et al., 2013), neuronal migration (Wang et al., 2006; Gabel et al., 2010; Peschansky et al., 2010; Szalkowski et al., 2012), and ciliary function (Massinen et al., 2011; Chandrasekar et al., 2013) in developing neocortex. Another study (Rosen et al., 2007) reported neocortical and hippocampal malformations in *Dyx1c1* knock-down rat brains. Similar to *Dyx1c1* and *Kiaa0319*, the knock-down expression of *Dcdc2* in rats disturbed the migration of neuronal precursors (Meng et al., 2005; Adler et al., 2013). Furthermore, it has been shown that the expression of *DCDC2* regulates the cilia length and signaling in primary rat hippocampal neurons, suggesting that *DCDC2* affects the structure and function of primary cilia (Massinen et al., 2011). The essential role of the other dyslexia candidate gene, *DYX1C1*, for cilia growth and motility in zebrafish has also been reported (Chandrasekar et al., 2013). Interestingly, the proteins produced by *DYX1C1* and *DCDC2* form protein–protein complexes in a neuroblastoma cell line, suggesting that they relate to interactions at the cellular level, perhaps in cilia function (Tammimies et al., 2013).

Besides the animal models, neuroimaging studies have tried to find the link between genetic markers in dyslexia susceptibility genes and structural and functional phenotypes in human brain. Alteration in gray matter distribution has been related to a 2.4 kb deletion within *DCDC2* with higher gray matter volume in the superior and middle temporal gyri, the occipitoparietal and intraparietal areas, and the inferior and middle frontal gyri for the heterozygous healthy subjects (Meda et al., 2008). *DCDC2* has also been associated with brain activation during phonological processing tasks in the superior anterior and posterior cingulate gyrus, and the left inferior frontal gyrus (Pinel et al., 2012). These studies suggest a wider cortical association with *DCDC2*, not only a link to parietal and temporal cortex as in the present study.

While the white matter pathways studied here were correlated with the thickness of the anatomically connected cortical areas during development, they did not reveal any significant correlation between each other after the effect of age was removed. This suggests that *DCDC2* has an independent effect on white matter structure and cortical thickness, and that the relationship between these brain measures has not driven the genetic associations.

In summary, we attempted to find the link between dyslexia genes, gray matter structure, and reading ability. Knowing the

role of these genes (*DCDC2*, *KIAA0319*, and *DYX1C1*) in neuronal migration and ciliary function as well as considering the association of these genes with variations in general reading ability (Luciano et al., 2007; Bates et al., 2010; Lind et al., 2010), we assessed whether these genetically coded molecular and neuronal mechanisms influence the brain changes, and subsequently behavior. The findings also suggest that neuroimaging can provide intermediate phenotypes as a bridge between genetic markers and behavior outcome.

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