

Metadata of the article that will be visualized in OnlineFirst

1	Article Title	Polymorphism of <i>DCDC2</i> Reveals Differences in Cortical Morphology of Healthy Individuals—A Preliminary Voxel Based Morphometry Study	
2	Journal Name	Brain Imaging and Behavior	
3		Family Name	Meda
4		Particle	
5		Given Name	Shashwath A.
6	Corresponding	Suffix	
7	Author	Organization	Institute of Living at Hartford Hospital
8		Division	Olin Neuropsychiatry Research Center
9		Address	200 Retreat Ave., Hartford 06106, CT, USA
10		e-mail	smeda01@harthosp.org
11		Family Name	Gelernter
12		Particle	
13		Given Name	Joel
14		Suffix	
15		Organization	Yale University School of Medicine
16		Division	Department of Psychiatry
17		Address	New Haven , CT, USA
18	Author	Organization	Yale University School of Medicine
19		Division	Department Neurobiology
20		Address	New Haven , CT, USA
21		Organization	VA CT Healthcare Center
22		Division	
23		Address	West Haven , CT, USA
24		e-mail	
25		Family Name	Gruen
26		Particle	
27		Given Name	Jeffrey R.
28		Suffix	
29		Organization	Yale University School of Medicine
30	Author	Division	Department of Genetics
31		Address	New Haven , CT, USA
32		Organization	Yale University School of Medicine
33		Division	Department of Pediatrics, Yale Child Health Research Center
34		Address	New Haven , CT, USA
35		e-mail	

36		Family Name	Calhoun
37		Particle	
38		Given Name	Vince D.
39		Suffix	
40		Organization	Institute of Living at Hartford Hospital
41		Division	Olin Neuropsychiatry Research Center
42		Address	200 Retreat Ave., Hartford 06106, CT, USA
43		Organization	Yale University School of Medicine
44	Author	Division	Department of Psychiatry
45		Address	New Haven , CT, USA
46		Organization	The MIND Institute
47		Division	
48		Address	Albuquerque , NM, USA
49		Organization	University of New Mexico
50		Division	Department of ECE
51		Address	Albuquerque , NM, USA
52		e-mail	
<hr/>			
53		Family Name	Meng
54		Particle	
55		Given Name	Haiying
56		Suffix	
57	Author	Organization	Yale University School of Medicine
58		Division	Department of Pediatrics, Yale Child Health Research Center
59		Address	New Haven , CT, USA
60		e-mail	
<hr/>			
61		Family Name	Cope
62		Particle	
63		Given Name	Natalie A.
64		Suffix	
65	Author	Organization	Yale University School of Medicine
66		Division	Department of Pediatrics, Yale Child Health Research Center
67		Address	New Haven , CT, USA
68		e-mail	
<hr/>			
69		Family Name	Pearlson
70		Particle	
71		Given Name	Godfrey D.
72	Author	Suffix	
73		Organization	Institute of Living at Hartford Hospital
74		Division	Olin Neuropsychiatry Research Center

75	Address	200 Retreat Ave., Hartford 06106, CT, USA
76	Organization	Yale University School of Medicine
77	Division	Department of Psychiatry
78	Address	New Haven , CT, USA
79	e-mail	
80	Received	15 June 2007
81	Schedule Revised	
82	Accepted	19 October 2007
83	Abstract	<p>Objective: The purpose of this investigation was to determine whether there is an association between the putative reading disability (RD) susceptibility gene Doublecortin Domain Containing 2 (<i>DCDC2</i>), and gray matter (GM) distribution in the brain, in a sample of healthy control individuals.</p> <p>Method: Fifty-six control subjects were genotyped for an RD-associated deletion in intron 2 of <i>DCDC2</i>. Voxel based morphometry (VBM) was used to examine structural magnetic resonance imaging (MRI) scans to assess GM differences between the two groups.</p> <p>Results: Individuals heterozygous for the deletion exhibited significantly higher GM volumes in reading/language and symbol-decoding related brain regions including superior, medial and inferior temporal, fusiform, hippocampal/parahippocampal, inferior occipito-parietal, inferior and middle frontal gyri, especially in the left hemisphere. GM values correlated with published data on regional <i>DCDC2</i> expression in a lateralized manner.</p> <p>Conclusions: These data suggest a role for <i>DCDC2</i> in GM distribution in language-related brain regions in healthy individuals.</p>
84	Keywords separated by ' - '	Structural imaging - Polymorphism - VBM - Dyslexia - Language
85	Foot note information	Presented at The Joint Annual Meeting International Society for Magnetic Resonance in Medicine—European Society for Magnetic Resonance in Medicine and Biology 2007, Berlin, Germany.

1 Brain Imaging and Behavior
2 DOI 10.1007/s11682-007-9012-1

4 Polymorphism of *DCDC2* Reveals Differences in Cortical 5 Morphology of Healthy Individuals—A Preliminary Voxel 6 Based Morphometry Study

7 Shashwath A. Meda · Joel Gelernter · Jeffrey R. Gruen ·
8 Vince D. Calhoun · Haiying Meng · Natalie A. Cope ·
9 Godfrey D. Pearlson

10 Received: 15 June 2007 / Accepted: 19 October 2007
11 © Springer Science + Business Media, LLC 2007

14 Abstract

15 *Objective* The purpose of this investigation was to determine
16 whether there is an association between the putative reading
17 disability (RD) susceptibility gene Doublecortin Domain
18 Containing 2 (*DCDC2*), and gray matter (GM) distribution
19 in the brain, in a sample of healthy control individuals.

20 *Method* Fifty-six control subjects were genotyped for an
21 RD-associated deletion in intron 2 of *DCDC2*. Voxel based
22 morphometry (VBM) was used to examine structural
23 magnetic resonance imaging (MRI) scans to assess GM
24 differences between the two groups.

25 *Results* Individuals heterozygous for the deletion exhibited
26 significantly higher GM volumes in reading/language and
27 symbol-decoding related brain regions including superior,
28 medial and inferior temporal, fusiform, hippocampal/para-
29 hippocampal, inferior occipito-parietal, inferior and middle

frontal gyri, especially in the left hemisphere. GM values 30
correlated with published data on regional *DCDC2* expres- 31
sion in a lateralized manner. 32

Conclusions These data suggest a role for *DCDC2* in GM 33
distribution in language-related brain regions in healthy 34
individuals. 35

Keywords Structural imaging · Polymorphism · VBM · 36
Dyslexia · Language 37

Introduction 38

Reading disability (RD) is a common, cognitive, neurolog- 39
ical disorder in which twin studies have demonstrated that 40
genes play a significant etiologic role (Meng et al. 2005). 41
Heritability estimates have been reported to range between 42
44 and 75% (DeFries et al. 1987). More recent estimates of 43
heritability assessed through a composite-reading measure 44

Presented at The Joint Annual Meeting International Society for
Magnetic Resonance in Medicine—European Society for Magnetic
Resonance in Medicine and Biology 2007, Berlin, Germany.

S. A. Meda (✉) · V. D. Calhoun · G. D. Pearlson
Olin Neuropsychiatry Research Center,
Institute of Living at Hartford Hospital,
200 Retreat Ave.,
Hartford, CT 06106, USA
e-mail: smeda01@harthosp.org

J. Gelernter · V. D. Calhoun · G. D. Pearlson
Department of Psychiatry, Yale University School of Medicine,
New Haven, CT, USA

J. R. Gruen
Department of Genetics, Yale University School of Medicine,
New Haven, CT, USA

J. Gelernter
Department Neurobiology, Yale University School of Medicine,
New Haven, CT, USA

J. R. Gruen · H. Meng · N. A. Cope
Department of Pediatrics, Yale Child Health Research Center,
Yale University School of Medicine,
New Haven, CT, USA

V. D. Calhoun
The MIND Institute,
Albuquerque, NM, USA

V. D. Calhoun
Department of ECE, University of New Mexico,
Albuquerque, NM, USA

J. Gelernter
VA CT Healthcare Center,
West Haven, CT, USA

45 in a large sample of twins show that greater than 50% of the
46 group deficit is attributable to genetic influences (Raskind
47 et al. 2000). Analysis of the cognitive components of
48 reading (phonological decoding, orthographic representa-
49 tion/coding and phoneme awareness) also revealed similar
50 results (Raskind et al. 2000).

51 Linkage and association studies have to date identified
52 four risk genes for dyslexia, including, Doublecortin
53 Domain Containing 2 (*DCDC2*), KIAA0319, DYX1C1
54 and ROBO1 (Paracchini et al. 2007). Two candidate genes
55 are encoded on the short arm of chromosome 6 (6p22),
56 *DCDC2* and KIAA0319, which have been reported to be
57 in tight linkage disequilibrium and share many similar
58 characteristics (Harold et al. 2006). The 6p22 locus is one
59 of the most well characterized and replicated quantitative
60 trait loci in linkage studies of RD (Harold et al. 2006).
61 *DCDC2* was the most recently identified candidate gene for
62 RD (Meng et al. 2005; Paracchini et al. 2007; Schumacher
63 et al. 2006). Specifically, a deletion in intron 2 was shown
64 to be associated with RD in a family based sample of
65 individuals from the USA (Meng et al. 2005).

66 Compared to other genes encoded within the 6p22 RD
67 locus, quantitative RT-PCR on healthy post-mortem human
68 brain, shows relatively high *DCDC2* expression in hippo-
69 campus, entorhinal cortex, hypothalamus and amygdala. In
70 inferior and medial temporal cortex, the anatomical location
71 of the major reading centers of the brain, *DCDC2* is the
72 most highly expressed of these genes (Meng et al. 2005;
73 Paracchini et al. 2007).

74 Variation in human language regions has been shown to
75 be under strong genetic control; therefore, direct associa-
76 tions with anatomic features in the brain may be measur-
77 able. (Thompson et al. 2001). In this study, we used voxel
78 based morphometry (VBM) data from MRI scans of healthy
79 control subjects, to determine whether the deletion is
80 associated with GM volume, given that previous reports
81 suggest GM volumetric anomalies in poor readers (Brambati
82 et al. 2004; Casanova et al. 2005; Kronbichler et al. 2007;
83 Silani et al. 2005; Vinckenbosch et al. 2005).

84 Materials and methods

85 Fifty-six right-handed healthy volunteer individuals under-
86 went a physical examination and were screened using psy-
87 chiatric and health questionnaires. Persons were excluded
88 if they reported a history of cardiovascular, neurological or
89 psychiatric disorders, (including learning disabilities), head
90 trauma (loss of consciousness >30 min), central nervous
91 system (CNS) disease, or drug or alcohol abuse or
92 dependence. Subjects were free from medications known
93 to affect the CNS. Forty three subjects (age range (years):
94 20–85 Mean/SD (years): 41.69/18.18 Male/Female: 19/24)

were homozygous for no deletion and were described as
genotype 1/1. Thirteen subjects (age range (years): 19–82,
Mean/SD (years): 38.23/21.12, Male/Female: 9/4) were
heterozygous for the deletion and described as genotype
1/2. Individuals homozygous for the deletion (genotype
2/2) were infrequent and were omitted from the study.
Groups were age ($t(df)$: 0.58(54), $p=0.57$) and sex
matched (χ^2 =1.603, $p=0.26$). Further, groups were
also found to be age matched ($p=0.86$) using a non-
parametric Kolmogorov–Smirnov (KS) statistic. The insti-
tutional review board of Hartford Hospital approved the
project and participants provided written informed consent.

Scans were performed on a 3T Siemens Allegra scanner
(Siemens, Erlangen Germany) at the Olin Neuropsychiatry
Research Center. High resolution 3D MPRAGE images
were acquired on all subjects (FOV=176×256 mm², matrix
size=176×256, slice thickness 1 mm, yielding a resolution
of 1×1×1 mm³, echo time (TE) of 2.74 ms, repetition time
(TR) of 2,500 ms, inversion time (TI) of 900 ms, flip angle
of 8°).

The intron 2 deletion of *DCDC2* was genotyped by
allele-specific PCR as previously described (Meng et al.
2005). Images were analyzed with the optimized VBM
approach (Good et al. 2001) using SPM2 software (<http://www.fil.ion.ucl.ac.uk/spm/software/spm2/>) running on
MATLAB version 6.5. We created customized gray matter,
white matter and CSF templates using data from all 56
subjects. Customized templates were created to better match
sample contrast and demographics. As part of the optimized
VBM protocol, all images were run through an iterative
segmentation and normalization protocol as detailed in
Good et al. 2001. The optimized approach aims to reduce
misclassification of gray matter and thus improves the
utility of segmented images towards a voxel-wise compar-
ison approach. Jacobian Modulation was applied during
VBM to preserve the absolute volume of GM. Images were
then smoothed with a 12 mm FWHM isotropic Gaussian
kernel before performing a voxel-wise group comparison.

A two-sample t -test within the general linear model
framework in SPM2 was used to investigate group differ-
ences in GM volume. Statistical parametric maps were
created seeking volumetric differences for both genotype1/
1>genotype1/2 and genotype1/2>genotype1/1. No voxels
survived the correction for multiple comparison (FDR at
 $p<0.05$). All results are therefore reported at the $p<0.01$
($t=2.4$; $df=54$) uncorrected level with a cluster threshold of
 $k=20$ voxels corrected for non-stationarity (Hayasaka et al.
2004). Corresponding peak coordinates for each significant
region is reported in Montreal Neurological Institute (MNI)
space. Related effect sizes were computed using the VBM2
toolbox (<http://dbm.neuro.uni-jena.de/vbm/vbm2-for-spm2/>).

A Spearman rank correlation analysis was performed
between published regional *DCDC2* expression levels in

148 the normal, post-mortem human brain (Meng et al. 2005)
 149 and the suprathreshold GM volumes from this study (See
 150 Fig. 1). *DCDC2* expression levels were ranked relative to
 151 thalamus, which was set to a value of 1. Derived suprathres-
 152 hold volumes were clustered together based on Brodmann
 153 areas to match the published regions. The correlation was
 154 performed for multiple brain regions including inferior (BA
 155 21, 20, 38), medial and superior (BA 22) temporal cortex,
 156 frontal (BA 44, 45) and prefrontal (BA 9, 10, 11, 46) cortex
 157 and posterior and superior parietal (BA 7) cortex. Masks
 158 were created for the above regions using the WFU pickatlas
 159 utility ([http://www.fmri.wfubmc.edu/cms/software#WFU_](http://www.fmri.wfubmc.edu/cms/software#WFU_PickAtlas)
 160 [PickAtlas](http://www.fmri.wfubmc.edu/cms/software#WFU_PickAtlas)). Further, custom Matlab scripts were used to
 161 calculate the extent of suprathreshold voxel volume within
 162 each of the above listed region of interest. Table 1 depicts
 163 the GM suprathreshold volume measure and *DCDC2*
 164 expression values that were used as part of the Spearman
 165 rank correlation analysis.

166 Masks corresponding to the above brain regions were
 167 also used to perform a small volume correction (SVC) on
 168 the main effect results to investigate regions surviving a
 169 FDR correction for multiple comparisons within the volume
 170 of interest (Salgado-Pineda et al. 2003).

171 To determine laterality differences, we computed later-
 172 ality indices (LI) for the above mentioned language cortices
 173 using a laterality index toolbox, provided as an extension to
 174 SPM2 (Wilke and Lidzba 2007). Data clustering and
 175 variance weighting was performed to consider the effects
 176 of smoothing and residual data variance in computing the
 177 LI. LIs were computed based on un-thresholded *t*-map
 178 values to reduce thresholding bias (Holland et al. 2001).

179 **Results**

180 Genotype frequencies were consistent with Hardy–Weinberg
 181 equilibrium expectations ($p < .025$). Further, the frequency

of the deletion was consistent with previous reports (Meng
 et al. 2005). Volumetric differences in GM were observed
 in multiple frontal and temporal regions (Fig. 2). Higher
 GM volume was observed in subjects with genotype 1/2 in
 regions including superior, medial and inferior temporal
 gyri, fusiform gyrus, hippocampus, uncus and parahippo-
 campal, inferior occipito-parietal, inferior and middle
 frontal gyri (Fig. 2; Table 2). For several regions this was
 more marked in the left hemisphere.

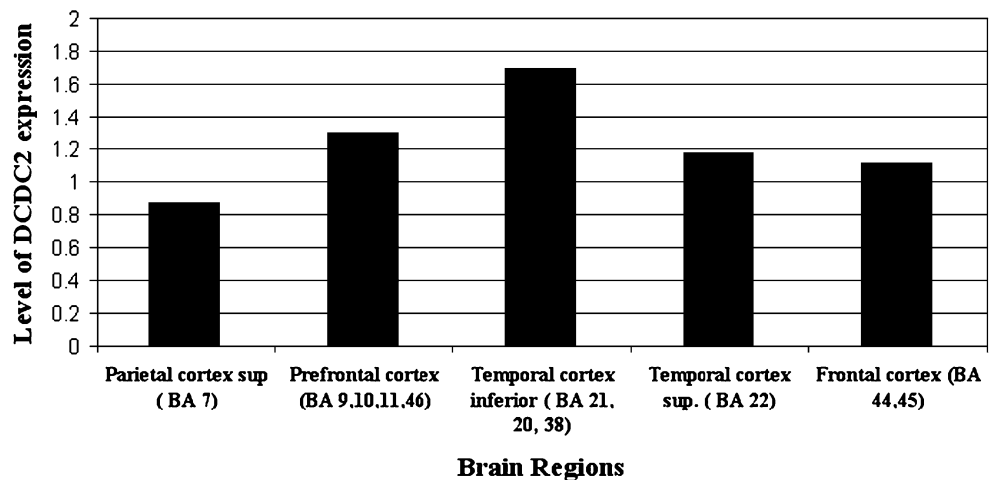
Correlation analysis, revealed a positive correlation
 between total suprathreshold volume (right and left com-
 bined) and expression levels of *DCDC2* ($r=0.6$; $p=0.28$).
 Analyzing the left and right hemispheres separately (see
 Table 1) also yielded positive correlations. However, the
 correlation was markedly stronger and significant in the left
 hemisphere ($r=0.9$; $p=0.03$) and was much weaker in the
 right hemisphere ($r=0.3$; $p=0.62$).

Left and right inferior temporal cortices demonstrated
 significantly increased GM volume in the genotype 1/2
 group (FDR corrected; $p=0.05$) when a SVC was per-
 formed. Also, regions including, right superior parietal ($p <$
 0.15) and left superior temporal cortex ($p < 0.15$) demon-
 strated a trend towards significance. Further, based on the
 laterality indices computed, superior temporal (LI: 0.04),
 inferior temporal cortices (0.10) and posterior/superior
 parietal cortices (LI: 0.13) were found to be left-lateralized
 and frontal (LI: -0.20) and prefrontal (LI: -0.10) were
 found to be right-lateralized for GM differences.

Discussion

This pilot study is the first to investigate the relationship
 between *DCDC2* and brain structure and indeed the first
 study to undertake this analysis for any RD susceptibility
 genes, although abnormalities in neuronal migration have
 recently been investigated with respect to *DCDC2*

Fig. 1 RT-PCR results for *DCDC2* expression from Meng et al. (2005), in five areas of anonymous donor human brain regions (normalized to thalamus = 1)



t1.1 **Table 1** Table shows the level of *DCDC2* expression in each anatomical region from published results (scaled to thalamus = 1) along with corresponding regional suprathreshold voxels in the left hemisphere, right hemisphere and combined hemispheres used towards the spearman correlation analysis

	Language regions (Brodmann areas)	<i>DCDC2</i> expression levels	Suprathreshold voxel volume within region of interest Left (CC)	Suprathreshold voxel volume within region of interest Right (CC)	Suprathreshold voxel volume within region of interest Total (CC)
t1.2					
t1.3					
t1.4	Parietal cortex sup (BA 7)	0.87	0.03	1.73	1.76
t1.5	Prefrontal cortex (BA 9,10,11,46)	1.3	0.44	1.72	2.16
t1.6	Temporal cortex inferior (BA 21, 20, 38)	1.7	12.72	10.77	23.49
t1.7	Temporal cortex sup. (BA 22)	1.17	0.01	0	0.01
t1.8	Frontal cortex (BA 44,45)	1.11	0	1.18	1.18

216 embryonic rat brains (Meng et al. 2005). However, given
 217 the preliminary nature of the current study, it might be
 218 crucial to replicate and extend our results in the future
 219 involving both behavior and imaging.

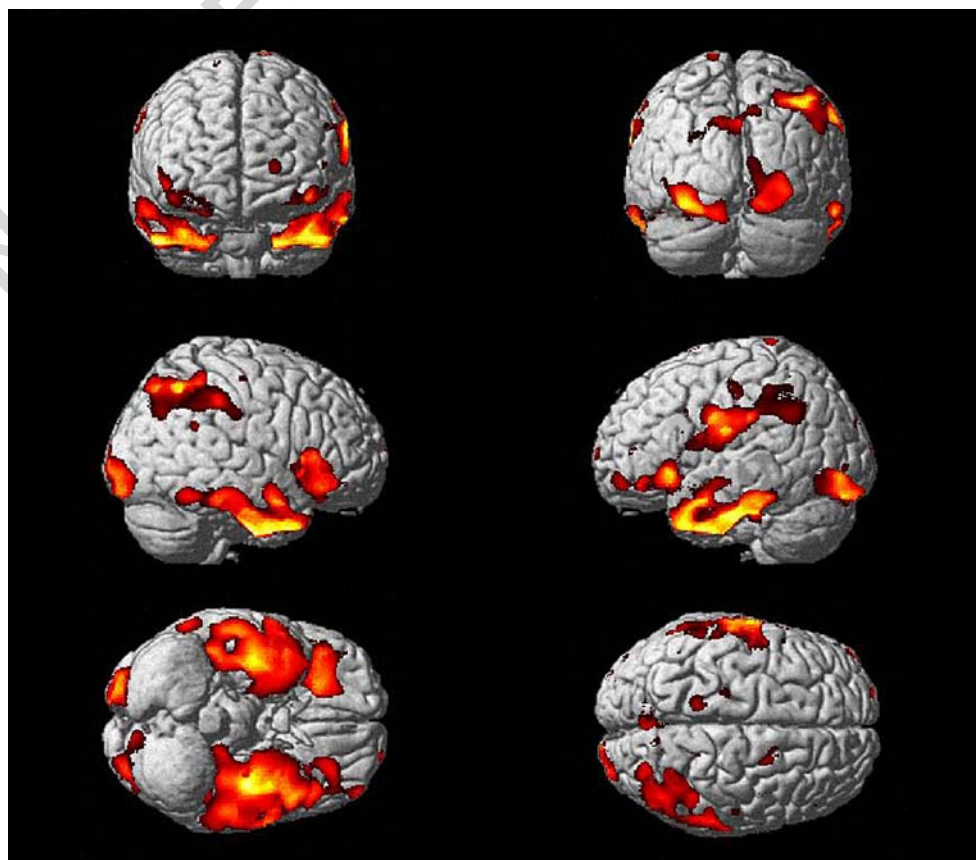
220 While *DCDC2* is associated with RD, it is also likely
 221 that genes affecting RD will also be responsible for normal
 222 variation in reading ability, thus differences in *DCDC2*
 223 effects will be observed in control individuals as studied
 224 here. Given this hypothesis and that disruption of *DCDC2*

regulatory regions may affect *DCDC2* activity and conse-
 quently brain structure, we used VBM to determine
 whether there was an association between a deletion in
DCDC2 and GM volume in the brain.

Individuals carrying the 1/2 genotype (deletion present)
 had increased GM volume in brain regions compared to the
 group carrying the 1/1 genotype (no deletion). These
 included cortical regions of the superior, middle and inferior
 temporal gyrus, inferior, middle and superior frontal gyrus,

225
 226
 227
 228
 229
 230
 231
 232
 233

Fig. 2 Volumetric differences (genotype1/2>genotype1/1) between groups, represented as color intensity with yellow depicting the largest difference between groups, and surface rendered on a 3D brain. Results displayed are at the $p < 0.01$ uncorrected level



Print will be in black and white

t2.1 **Table 2** Columns depict anatomical label, MNI coordinate for peak activation voxel in each brain region, *t*-scores and effect size from random effects analysis

t2.2	Regions	Left vol (CC)	MNI coordinates (x,y,z)	Max <i>t</i> value	Effect size (d)	Right vol (CC)	MNI coordinates (x,y,z)	Max <i>t</i> value	Effect size (d)
t2.3	Inferior temporal gyrus	5.8	-50.5, -3.3, -41.9	3.04	0.82	7.7	46.4, -13.6, -41.3	3.07	0.83
t2.4	Superior temporal gyrus	5.8	-43.4, 22.2, -36.8	3.32	0.9	2.1	50.5, 16.1, -38.4	2.72	0.74
t2.5	Uncus	5.3	-21.2, 2.8, -41.5	2.97	0.81	2	37.3, -10.6, -39.9	3.17	0.86
t2.6	Middle temporal gyrus	3.6	-37.3, -6.9, -30.2	2.93	0.79	4.5	50.5, 13.0, -39.7	3.24	0.88
t2.7	Postcentral gyrus	2.7	-68.6, -17.8, 28.4	2.5	0.64	0.2	62.6, -30.9, 44.0	2.6	0.7
t2.8	Fusiform gyrus	2.6	-38.3, -12.2, -29.3	3.05	0.83	2.3	45.4, -37.4, -16.4	3.53	0.96
t2.9	Lentiform nucleus	2.5	-29.2, -19.7, 2.2	2.91	0.8	0.6	32.3, -20.6, 0	2.56	0.7
t2.10	Caudate	2.1	-18.1, -11.4, 23.3	2.65	0.73	NS	NS	NS	NS
t2.11	Parahippocampal gyrus	1.9	-34.3, -16.4, -25.9	2.96	0.8	0.6	41.4, -36.6, -12.8	2.9	0.78
t2.12	Inferior occipital gyrus	1.6	-34.3, -80.2, -5.8	2.96	0.8	0.6	29.2, -92.5, -7.7	2.64	0.72
t2.13	Inferior frontal gyrus	1.2	-47.4, 25.0, -6.8	2.77	0.75	5.6	41.4, 25.3, 8.9	3.32	0.9
t2.14	Sub-gyral	1.1	-38.3, -13.3, -25.8	3.12	0.85	0.3	45.4, -42.7, -14.3	2.83	0.77
t2.15	Inferior parietal lobule	1	-67.6, -26.2, 31.2	2.58	0.7	2.9	31.3, -55.6, 41.6	3.16	0.86
t2.16	Middle frontal gyrus	1	-45.4, 56.1, -9.8	2.43	0.67	1.8	34.3, 34.4, -9.9	3	0.82
t2.17	Supramarginal gyrus	0.8	-63.6, -55.2, 32.9	2.58	0.7	<0.1	62.6, -46.1, 37.8	2.42	0.66
t2.18	Middle occipital gyrus	0.7	-31.3, -81.2, -5.8	2.96	0.81	0.6	30.3, -94.7, -5.4	2.65	0.72
t2.19	Insula	0.7	-40.4, -28.9, 0.6	2.81	0.76	NS	NS	NS	NS
t2.20	Lingual gyrus	0.7	-33.3, -75.9, -9.1	2.68	0.73	0.3	17.1, -96.2, -17.4	2.56	0.7
t2.21	Precuneus	0.3	-11.1, -71.9, 36.4	2.43	0.67	0.4	30.3, -75.8, 53.6	2.8	0.76
t2.22	Superior frontal gyrus	0.2	-22.2, 70.8, 8.0	2.69	0.74	0.1	16.1, 6.7, 75.4	2.5	0.68
t2.23	Superior parietal lobule	1.3	27.2, -58.7, 42.6	2.42	0.66	1.8	27.2, -55.6, 41.6	3.37	0.91
t2.24	Angular gyrus	NS	NS	NS	NS	0.3	30.3, -58.5, 38.2	2.98	0.81
t2.25	Cuneus	NS	NS	NS	NS	0.2	27.2, -94.6, -6.6	2.62	0.71

t2.26 Regions show significant increases in gray matter volume for subjects with genotype1/2 compared to genotype1/1.

234 inferior parietal lobule, fusiform gyri, extrastriate visual
 235 cortices (inferior/middle occipital gyrus), lingual gyrus and
 236 supramarginal gyrus. Differences in non-cortical regions
 237 included the hippocampus/parahippocampus, amygdala,
 238 globus pallidus and putamen. These brain regions correlate
 239 with areas identified previously as being involved in reading
 240 and/or symbol decoding either structurally or functionally
 241 (Kronbichler et al. 2007; Brambati et al. 2006; Cao et al.

2006; Casanova et al. 2005; Silani et al. 2005; Vinck- 242
 243 enbosch et al. 2005; Aylward et al. 2003; Eckert et al. 2003;
 244 Ruff et al. 2003; Brown et al. 2001; Eliez et al. 2000;
 245 Rumsey et al. 1999).

246 Compared to structural imaging studies before 2005
 247 (Brambati et al. 2004; Eckert et al. 2003; Brown et al. 2001;
 248 Eliez et al. 2000), several recent studies, using more
 249 optimized and contemporary imaging techniques, have 249

250 reported mixed patterns of increased and decreased gray
 251 matter volumes in dyslexia. More specifically, these studies
 252 show increases in GM volume in several cortical areas
 253 pertaining to language including, posterior, medial and
 254 inferior temporal gyri, precentral and postcentral gyri,
 255 superior and medial frontal gyri and precuneus (Kronbichler
 256 et al. 2007; Silani et al. 2005; Vinckenbosch et al. 2005).
 257 These new data suggest that gray matter changes observed
 258 in dyslexia are not merely associated with decreases in gray
 259 matter alone and have a more complex genetic etiology.

260 Consistent with expectations based on known laterality
 261 differences in cortical language representation, correlation
 262 analyses between GM volume and *DCDC2* expression yielded
 263 both significant and higher results in the left hemisphere.

264 This study provides the first evidence that a deletion in
 265 *DCDC2* correlates with GM volume and suggests that it
 266 may exert its effects across the whole reading ability
 267 spectrum. In addition, brain regions implicated in this study
 268 concur with previous VBM reading studies and structural
 269 and functional neuroimaging methods. The higher and
 270 significant correlation between *DCDC2* gene expression
 271 levels and GM volume in the left hemisphere, suggest that
 272 *DCDC2* is acting in language-related brain systems given
 273 the laterality hypothesis of language. In the context of other
 274 VBM studies of reading and RD, where better reading is
 275 associated with increased GM volume, the deletion may
 276 have a protective effect, being associated with increased GM
 277 volume. However, we did not assess reading ability in our
 278 subjects, which awaits further study in a replication sample.

279 Further studies with a larger sample size are required to
 280 increase detection power. Also, it might be very important
 281 to conduct studies including RD individuals and individuals
 282 homozygous for the deletion to further investigate the
 283 effects of *DCDC2* on brain anatomy.

285 **Acknowledgements** The authors would like to thank Ann Marie
 286 Lacobelle and Greg Kay for technical assistance. This research was
 287 supported in part by grants from the National Institutes of Health,
 288 under RO1 grants MH60504, MH43775, MH52886 and an NIMH
 289 MERIT award (to GP) 1 R01 EB 000840 and 1 R01 EB 005846, R01
 290 DA12690, R01 DA12849, K24 DA15105; 1 R01 NS43530 to JRG;
 291 the U.S. Department of Veterans Affairs (the VA Connecticut-
 292 Massachusetts Mental Illness Research, Education and Clinical Center
 293 [MIRECC]) to JG; a Hartford Hospital Open Grant Award, and a
 294 National Association for Research in Schizophrenia and Affective
 295 Disorders Young Investigator Award to VC.

296 Support for HM is from a General Grant Award of the International
 297 Dyslexia Association.

298 **References**

299 Aylward, E. H., Richards, T. L., Berninger, V. W., Nagy, W. E., Field,
 300 K. M., Grimme, A. C., et al. (2003). Instructional treatment
 301 associated with changes in brain activation in children with
 302 dyslexia. *Neurology*, 61(2), 212–219.

Brambati, S. M., Termine, C., Ruffino, M., Danna, M., Lanzi, G.,
 303 Stella, G., et al. (2006). Neuropsychological deficits and neural
 304 dysfunction in familial dyslexia. *Brain Research*, 1113(1), 174–
 305 185. 306
 Brambati, S. M., Termine, C., Ruffino, M., Stella, G., Fazio, F.,
 307 Cappa, S. F., et al. (2004). Regional reductions of gray matter
 308 volume in familial dyslexia. *Neurology*, 63(4), 742–745. 309
 Brown, W. E., Eliez, S., Menon, V., Rumsey, J. M., White, C. D., &
 310 Reiss, A. L. (2001). Preliminary evidence of widespread
 311 morphological variations of the brain in dyslexia. *Neurology*, 56
 312 (6), 781–783. 313
 Cao, F., Bitan, T., Chou, T. L., Burman, D. D., & Booth, J. R. (2006).
 314 Deficient orthographic and phonological representations in
 315 children with dyslexia revealed by brain activation patterns.
 316 *Journal of Child Psychology and Psychiatry*, 47(10), 1041–1050. 317
 Casanova, M. F., Christensen, J. D., Giedd, J., Rumsey, J. M., Garver,
 318 D. L., & Postel, G. C. (2005). Magnetic resonance imaging study
 319 of brain asymmetries in dyslexic patients. *Journal of Child*
 320 *Neurology*, 20(10), 842–847. 321
 DeFries, J. C., Fulker, D. W., & LaBuda, M. C. (1987). Evidence for a
 322 genetic aetiology in reading disability of twins. *Nature*, 329
 323 (6139), 537–539. 324
 Eckert, M. A., Leonard, C. M., Richards, T. L., Aylward, E. H.,
 325 Thomson, J., & Berninger, V. W. (2003). Anatomical correlates
 326 of dyslexia: Frontal and cerebellar findings. *Brain*, 126(2), 482–
 327 494. 328
 Eliez, S., Rumsey, J. M., Giedd, J. N., Schmitt, J. E., Patwardhan, A.
 329 J., & Reiss, A. L. (2000). Morphological alteration of temporal
 330 lobe gray matter in dyslexia: An MRI study. *Journal of Child*
 331 *Psychology and Psychiatry*, 41(5), 637–644. 332
 Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston,
 333 K. J., & Frackowiak, R. S. (2001). A voxel-based morphometric
 334 study of ageing in 465 normal adult human brains. *Neuroimage*,
 335 14(1 Pt 1), 21–36. 336
 Harold, D., Paracchini, S., Scerri, T., Dennis, M., Cope, N., Hill, G.,
 337 et al. (2006). Further evidence that the KIAA0319 gene confers
 338 susceptibility to developmental dyslexia. *Molecular Psychiatry*,
 339 11, 1085–1091 1061. 340
 Hayasaka, S., Phan, K. L., Liberzon, I., Worsley, K. J., & Nichols, T.
 341 E. (2004). Nonstationary cluster-size inference with random field
 342 and permutation methods. *Neuroimage*, 22, 676–687. 343
 Holland, S. K., Plante, E., Weber Byars, A., Strawsburg, R. H.,
 344 Schmithorst, V. J., & Ball Jr., W. S. (2001). Normal fMRI brain
 345 activation patterns in children performing a verb generation task.
 346 *Neuroimage*, 14(4), 837–843. 347
 Kronbichler, M., Wimmer, H., Staffen, W., Hutzler, F., Mair, A., &
 348 Ladurner, G. (2007). Developmental dyslexia: Gray matter
 349 abnormalities in the occipitotemporal cortex. *Human Brain*
 350 *Mapping*. 351
 Meng, H., Smith, S. D., Hager, K., Held, M., Liu, J., Olson, R. K.,
 352 et al. (2005). *DCDC2* is associated with reading disability and
 353 modulates neuronal development in the brain. *Proceedings of the*
 354 *National Academy of Sciences of the United States of America*,
 355 102(47), 17053–17058. 356
 Paracchini, S., Scerri, T., & Monaco, A. P. (2007). The genetic lexicon
 357 of dyslexia. *Annual Review of Genomics and Human Genetics*,
 358 8(1), 57. 359
 Raskind, W. H., Hsu, L., Berninger, V. W., Thomson, J. B., &
 360 Wijsman, E. M. (2000). Familial aggregation of dyslexia
 361 phenotypes. *Behavior Genetics*, 30(5), 385–396. 362
 Ruff, S., Marie, N., Celsis, P., Cardebat, D., & Demonet, J. F. (2003).
 363 Neural substrates of impaired categorical perception of phonemes
 364 in adult dyslexics: An fMRI study. *Brain and Cognition*, 53(2),
 365 331–334. 366
 Rumsey, J. M., Horwitz, B., Donohue, B. C., Nace, K. L., Maisog, J. M.,
 367 & Andreason, P. (1999). A functional lesion in developmental
 368

- 369 dyslexia: Left angular gyral blood flow predicts severity. *Brain*
370 *and Language*, 70(2), 187–204.
- 371 Salgado-Pineda, P., Baeza, I., Perez-Gomez, M., Vendrell, P., Junque, C.,
372 Bargallo, N., et al. (2003). Sustained attention impairment
373 correlates to gray matter decreases in first episode neuroleptic-
374 naive schizophrenic patients. *Neuroimage*, 19(2 Pt 1), 365–375.
- 375 Schumacher, J., Anthoni, H., Dahdouh, F., Konig, I. R., Hillmer, A. M.,
376 Kluck, N., et al. (2006). Strong genetic evidence of DCDC2 as a
377 susceptibility gene for dyslexia. *American Journal of Human*
378 *Genetics*, 78(1), 52–62.
- 379 Silani, G., Frith, U., Demonet, J. F., Fazio, F., Perani, D., Price, C.,
380 et al. (2005). Brain abnormalities underlying altered activation
in dyslexia: A voxel based morphometry study. *Brain*, 128(Pt 10), 381
2453–2461. 382
- Thompson, P. M., Cannon, T. D., Narr, K. L., van Erp, T., Poutanen, 383
V. P., Huttunen, M., et al. (2001). Genetic influences on brain 384
structure. *Nature Neuroscience*, 4(12), 1253–1258. 385
- Vinckenbosch, E., Robichon, F., & Eliez, S. (2005). Gray matter 386
alteration in dyslexia: Converging evidence from volumetric and 387
voxel-by-voxel MRI analyses. *Neuropsychologia*, 43(3), 324– 388
331. 389
- Wilke, M., & Lidzba, K. (2007). LI-tool: A new toolbox to assess 390
lateralization in functional MR-data. *Journal of Neuroscience* 391
Methods, 163(1), 128–36. 392

UNCORRECTED PROOF

AUTHOR QUERY

AUTHOR PLEASE ANSWER QUERY.

Q1. Meng et al was changed and was linked to Meng et al. (2005). Please check if appropriate.

UNCORRECTED PROOF