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Developmental trajectories of grey and white matter in dyscalculia

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ABSTRACT

Developmental dyscalculia is a significant neural deficit with broad social impact. A number of techniques have been used to identify the brain basis of dyscalculia, and many of these have highlighted the role of the intraparietal sulci and a left fronto-parietal network in the representation of core number skills. These studies offer conflicting explanations of the neurobiological deficits associated with dyscalculia, and to date few studies have elucidated the timeline of cortical changes involved.

Here we report a volumetric study comparing well-characterized dyscalculic learners aged from 8 to 14 years with tightly matched controls. Using automated cortical parcellation of anatomical MRI, we show that the posterior parietal and fronto-parietal systems in dyscalculia may undergo abnormal development during the pre-teenage and teenage years. As a result, the present study more clearly characterizes the underlying neural basis of dyscalculia than previous studies have hitherto achieved.

1. Introduction

Developmental dyscalculia (DD) is a congenital disability in learning about numbers and arithmetic. A recent review of prevalence studies across many countries suggests that it affects between 3% and 6% of the population [1], a prevalence comparable with dyslexia [2]. Like dyslexia, DD is a serious handicap for individual sufferers, affecting their employment and health [3,4], and therefore constitutes a significant burden on national economies [5,6].

The core deficit in DD is now generally agreed to be a disability in processing numerosities – the number of objects in a set [7,8] ([9] for slightly different methodology). It is possible to identify this deficit in kindergarten simply by the speed and accuracy of naming the number of dots in a visual array (up to nine dots). Moreover, a longitudinal study using this method, was able to predict age-appropriate arithmetical attainment up to the age of 11 years [10].

Just as specialized teaching is required for dyslexics that focuses on their core deficit in phonology [11], it is now recognized that DDs also need specialized teaching that focuses on their core deficit in numerosity processing and which the teaching schedule carefully adapts to the learner's current level of competence [7,12,13].

Several studies have shown that learners identified as DD have abnormalities in brain regions known to be critical for number processing [14–16]. Many of these highlight the intraparietal sulci, either unilaterally or bilaterally, as well as a larger fronto-parietal arithmetic network, typically in the left hemisphere (see [17] for a recent review).

Despite this progress in describing the dyscalculic brain, the current body of literature fails to distinguish brain changes occurring over time from brain changes occurring over space. It is now quite clear that cortical grey and white matter development varies both temporally and regionally during childhood and the early teenage years [18], and this changing cortical landscape presents a unique problem to the study of cognitive development in children: baseline regional changes will vary by group (DD vs. controls) and by age. Such regional shifts in developmental trajectories may reflect longer-term influences on cortical maturation than are typically examined in functional activation studies.

A morphometric analysis of such shifting trajectories requires careful phenotypic characterization of DD learners. While a variety of criteria for classifying learners as DD can be found in the literature [19], the first study comparing brain structure in DDs and matched controls, performed by our group, used a discrepancy between measured and predicted performance on the Numerical Operations subtest of the WOND [20]. The subjects in this study were drawn from a population of low-birthweight adolescents who had normal or superior IQs when tested [21]. The study found reduced grey-matter density in the left intraparietal sulcus (IPS). However, one study of 9 year olds, using an unspecified clinical

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diagnosis, found reduced grey-matter density in the *right* IPS [22]. Another study of 7–9 year olds, identified as DD if they scored at or below 95 on one of two subscales of the WIAT-II (Numerical Operations Score or Math Composite Score), found reduced grey matter bilaterally in superior parietal lobule, intra-parietal sulcus, as well as the fusiform gyrus, parahippocampal gyrus and the right anterior temporal cortex in children with DD as compared with controls [23].

Another potentially useful way of identifying grey matter regions that may be implicated in DD is to consider those areas that are active in the development of arithmetical abilities. An recent meta-analysis [24] suggests that the network active in arithmetical development comprised: bilaterally the inferior and superior parietal cortex (BA40), including the precuneus (BA7) the inferior frontal gyrus (BA9), premotor cortex (BA6), the insula (BA47, BA13); also, the right angular gyrus (BA39), and the left inferior temporal gyrus (BA20), along with striate and extrastriate cortex bilaterally (BA18, BA19). (p776-777)

This meta-analysis also confirmed that DDs showed lower activations in left precuneus (BA 7), right inferior parietal lobe (BA 40), left frontal paracentral lobe (BA 6), left fusiform gyrus (BA 37), left superior frontal gyrus (BA 10) and right middle frontal gyrus (BA 9).

In addition to grey matter (GM) differences, more recent work has also reported differences in white matter (WM) [23]. White matter differences may be even more critical in the description of dyscalculia, since white matter changes are known to be associated with learning. For example, structural changes in white matter are correlated with learning a motor skill in both humans [25] and monkeys [26], and in learning to read [27] (see [28] for a recent review). Furthermore, voxel-based morphometric techniques have been used to demonstrate reduced white matter (WM) volume in right temporo-parietal cortex of DD learners, while diffusion-tensor imaging revealed reduced fractional anisotropy (FA) in this WM region. This reduction in white matter integrity in DD learners correlated in turn with their performance on a standardized test of simple arithmetic [23].

In order to describe the brain basis of dyscalculia with validity, both the morphometric and functional aspects of the dyscalculic brain must be characterized by age. The present study examines regional variation in cortical grey and white matter morphology in dyscalculics and carefully matched controls over a range of ages between 8 and 14 years. See Table 1.

The aim of this study was to describe in detail the differences in regional cortical anatomy that characterize the dyscalculic brain, and to establish how those regional differences might vary during cortical development. We used, Freesurfer, a method of automatic parcellation of brain regions that provides measures of the area, thickness and volume of GM and the volume of WM [29–32].

We argue that both temporal and regional changes in cortical surface parameters might account for the phenotype of developmental dyscalculia.

2. Results

Using data processed using Freesurfer 5.1.0, we were able to compare grey-matter (GM) volume, area and thickness, and white-matter (WM) volume between the DDs and matched controls.

2.1. Main effects

2.1.1. Grey-matter

There was a main effect of group on a number of cortical structures; these are illustrated graphically in Fig. 1 and summarized in Table 2. The largest group differences in cortical surface area were seen in the bilateral subcentral gyri (BA43); dyscalculics had significantly reduced cortical surface area in these regions compared to matched controls. Cortical thickness was also reduced in the dyscalculic group, most prominently in the left temporal (BA22) and right inferior frontal lobes (BA44). Finally, dyscalculics had large reductions in grey matter volume in the right parahippocampal gyrus (BA36) and the right inferior and posterior parietal lobe (BA39, BA40).

2.1.2. White matter

In addition to these grey matter deficits, dyscalculics had reduced white matter volume in the right inferior parietal lobe, the right temporal pole and transverse temporal lobe, and the right pars orbitalis. See Table 3.

2.2. Age effects

To describe the effect of age on cortical morphology, we performed a regional ANCOVA in dyscalculics and matched controls.

2.2.1. Grey matter

We found significant age-related increases in GM area in left frontal cortex in controls only, depicted anatomically in Fig. 2, the trends are depicted graphically in Fig. 4; see also Table 3. The largest effect on cortical surface area was in the left supramarginal gyrus (BA40), where dyscalculics gained area more slowly over the age range than controls. Relative to controls, grey matter volume in dyscalculics increased as they grew older in the left lateral frontal cortex (dorso-lateral prefrontal cortex, essentially BA 46) and the right superior occipital lobe (BA19), but decreased slightly in the left primary motor cortex. Cortical thickness was minimally decreased around the right cingulate cortex.

2.3. White matter

Dyscalculics had notable delays in white matter development relative to controls, with changes seen broadly in the left frontal and parietal cortices, with additional effects seen in right superior and medial frontal cortex. These effects were typically characterized by an age-related increase in WM in the control subjects, while in DDs WM volume remained stable or even decreased. Significant differences were observed in the left precuneus, left supramarginal gyrus, and bilaterally in the superior frontal lobes. These results are depicted anatomically in Fig. 3 and the trends are depicted graphically in Fig. 5, and tabulated in Table 4.

By contrast, in the posterior corpus callosum there was a *decrease* in volume in controls, compared to a relatively unchanged volume over time in DDs (see Fig. 5)(Table 5).

Table 1
DD and Control Demographics.

	N	Age at test (years)	Gestational age	FSIQ	VIQ	WOND NOp
Dyscalculics	11	8–14	36.4 weeks (15 days)	111 (16)	110 (16)	91 (18)
Matched controls	11	8–14	36.5 weeks (15 days)	111 (16)	114 (14)	113 (14)

DDs were paired with controls matched for chronological age, gestational age, Full Scale IQ, and Verbal IQ. Independent *t*-tests of each of these variables confirmed that there were no group differences (all *p*-values > 0.05). SDs given in parentheses.

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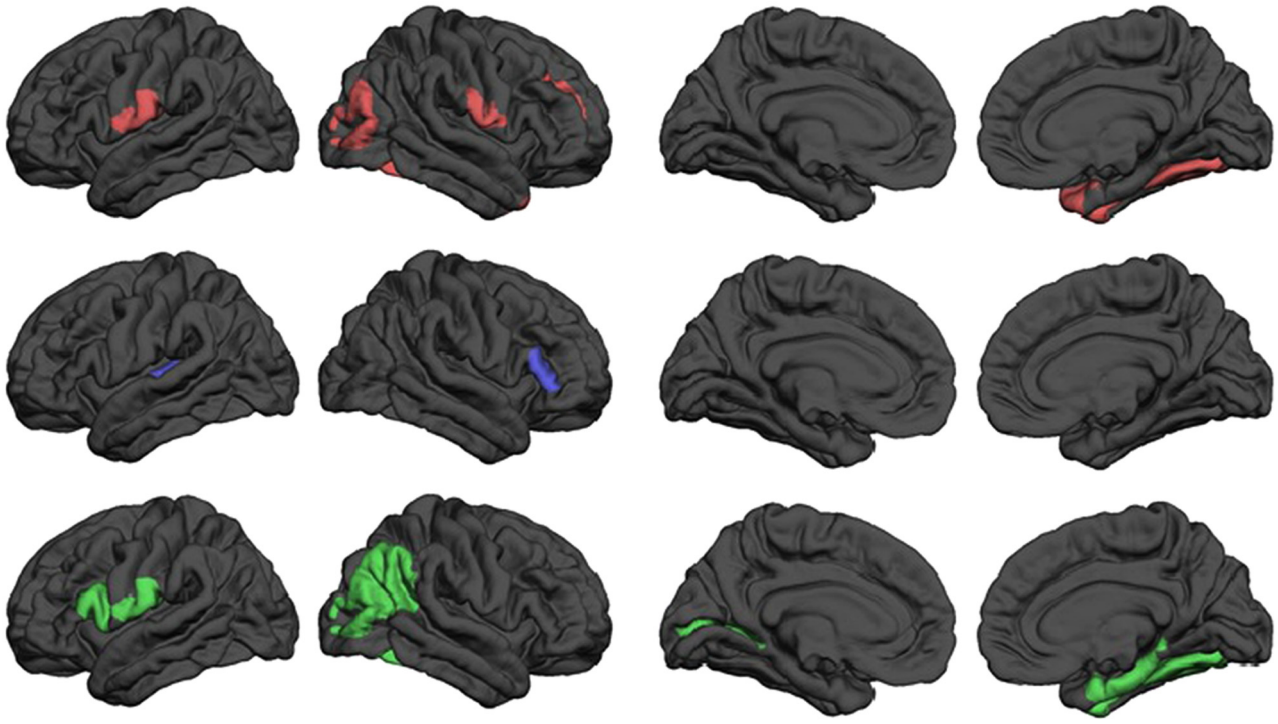

Fig. 1. Regional grey matter differences. Automatically measured morphometric statistics were obtained and compared in groupwise *t*-tests between dyscalculics and matched controls. Several regions were significantly different in terms of cortical surface area (*red*), thickness (*blue*), and volume (*green*). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Regional Grey-matter differences.

Region	DD	Controls	*t*	*r*
A. Area				
L subcentral gyrus	2309.73 (80.04)	1850.3 (79.13)	−4.08	0.68
R subcentral gyrus	1876.45 (92.76)	1606.9 (56.28)	−2.48	0.53
R middle occipital	2993.82 (213.25)	3689.6 (195.17)	2.41	0.48
R lateral fusiform	2086.82 (124.92)	2646.8 (148.65)	2.88	0.56
R frontal middle sulcus	3387.64 (174.97)	2865.1 (145.27)	−2.30	0.47
R fusiform	5516.45 (271.89)	6420.2 (304.55)	2.21	0.46
R temporal pole	640 (49.46)	814.2 (53.4)	2.39	0.48
B. Thickness				
L superior temporal gyrus	2.97 (0.2)	3.51 (0.11)	2.37	0.52
L transverse temporal	2.96 (0.15)	3.43 (0.1)	2.58	0.53
R inferior frontal triangle	3.53 (0.08)	3.82 (0.1)	2.31	0.48
C. Volume				
L subcentral gyrus	10,345.64 (472.95)	8459.7 (432.13)	−2.94	0.56
L calcarine sulcus	7973.82 (405.59)	6799.1 (360.21)	−2.17	0.45
L pars opercularis	13,241 (795.28)	15,840.9 (773.55)	2.34	0.47
R middle occipital	14,462.36 (1499.04)	18,573.5 (1139.45)	2.18	0.46
R lateral fusiform	9926.36 (820.74)	12,594.5 (477.13)	2.81	0.57
R medial parahippocampal	7899.18 (380.97)	10,576.1 (724.81)	3.27	0.66
R fusiform	20,547.18 (1558.04)	25,339.5 (1009.16)	2.58	0.53
R inferior parietal	39,388.45 (2434.15)	46,267.8 (941.48)	2.64	0.59

Automatically measured morphometric statistics were obtained and compared in groupwise *t*-tests between DD and controls. Each subtable gives the group mean values in mm^2 (area), mm (thickness) and mm^3 (volume). Standard errors are in parentheses. The tabulated *t*-values are all significant at $p < 0.05$, and the effect sizes are measured with *r* values. Using traditional categories, $r=0.1$ represents a small effect, $r=0.3$ is a medium effect, and $r=0.5$ is a large effect.

3. Discussion

The present study is an analysis of three different cortical parameters (thickness, area, and volume) across a range of ages. It is important, therefore, to consider the meaning of these three parameters.

During foetal development, cortical neurons migrate along a cellular scaffolding to form the six layers of neocortex [33]. Delays

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or disruptions in this process of cortical layering might result in abnormally thin cortex, with potentially few effects on cortical surface area.

While cortical thickness is an index of developmental integrity and lifetime health [34], from an evolutionary point of view, surface area may be a better measure of functional capacity. The rapid expansion of neocortex in higher primates is characterized by an increase in surface area with relative preservation of cortical thickness [35], suggesting that expansion of cortical area rather than thickness is important for long-term species-level functional change. Furthermore, both functional neuroimaging volumes and the voxel based morphometry studies that have informed the present work use anatomic measures more highly correlated with cortical surface area than with cortical thickness, suggesting that on an individual level too, surface area is a predictor of functional status [36].

The third anatomic parameter we considered was volume. Geometrically, volume is a reflection of both thickness and area, but in our hands as in previous studies, volumetric measurements tend to correlate more strongly with area (although volumetric measurements also tend to have greater variability). We include this parameter both to preserve direct comparisons with previous work as well as to enable comparison of grey matter and white matter regions; the latter of which cannot be meaningfully parcelled with any measurement other than volume.

All three parameters shed light on the ontogeny and ongoing development of cerebral cortex in our subjects. There is clear evidence that cortical thickness and surface area are under independent genetic control [36], and that cortical volume has some independence from both of these. For the purposes of this study, and from a theoretical perspective only, we argue that cortical thickness is reflective of the perinatal and environmental factors affecting brain development, that cortical surface area is reflective of regional variations in functional capacity, and that cortical volume is a non-linear combination of these two properties.

Given that background, the main effects of the present study confirm previous findings of less GM in the parietal lobes of DDs [21,22], the critical areas for the representation of numerical magnitude [15,37–39]. Comparison (Table 6) with the regions identified in the meta-analysis of activation studies [24] is laid out in Table 4.

Our findings also extend previous studies in showing less GM volume and thickness in DD brain areas associated with setting up and monitoring ongoing tasks. It is perhaps not coincidental that neurons in these areas demonstrate magnitude sensitivity in monkeys [40]. We also found decreased GM volume in the right parahippocampal gyrus and entorhinal cortices of DD subjects, areas known to be associated with learning and memory (e.g. [41,42] for reviews).

Table 3
Regional white-matter differences.

Region	DD	Controls	*t*	*r*
R inferior parietal	22,968.64 (1046.09)	26,389.00 (927.47)	2.45	0.49
R pars orbitalis	2163.18 (131.8)	2637.60 (141.20)	2.46	0.49
R temporal pole	1186.91 (102.12)	1741.90 (208.06)	2.39	0.55
R transverse temporal	1038.09 (89.06)	1517.60 (138.80)	2.91	0.59

As before, automatically measured morphometric statistics were obtained and compared in groupwise *t*-tests between DD and controls. For white matter parcels, only volume (mm^3) was calculated. Standard errors are in parentheses. The tabulated *t*-values are all significant at $p < 0.05$, and the effect sizes are measured with r values. Using traditional categories, $r = 0.1$ represents a small effect, $r = 0.3$ is a medium effect, and $r = 0.5$ is a large effect.

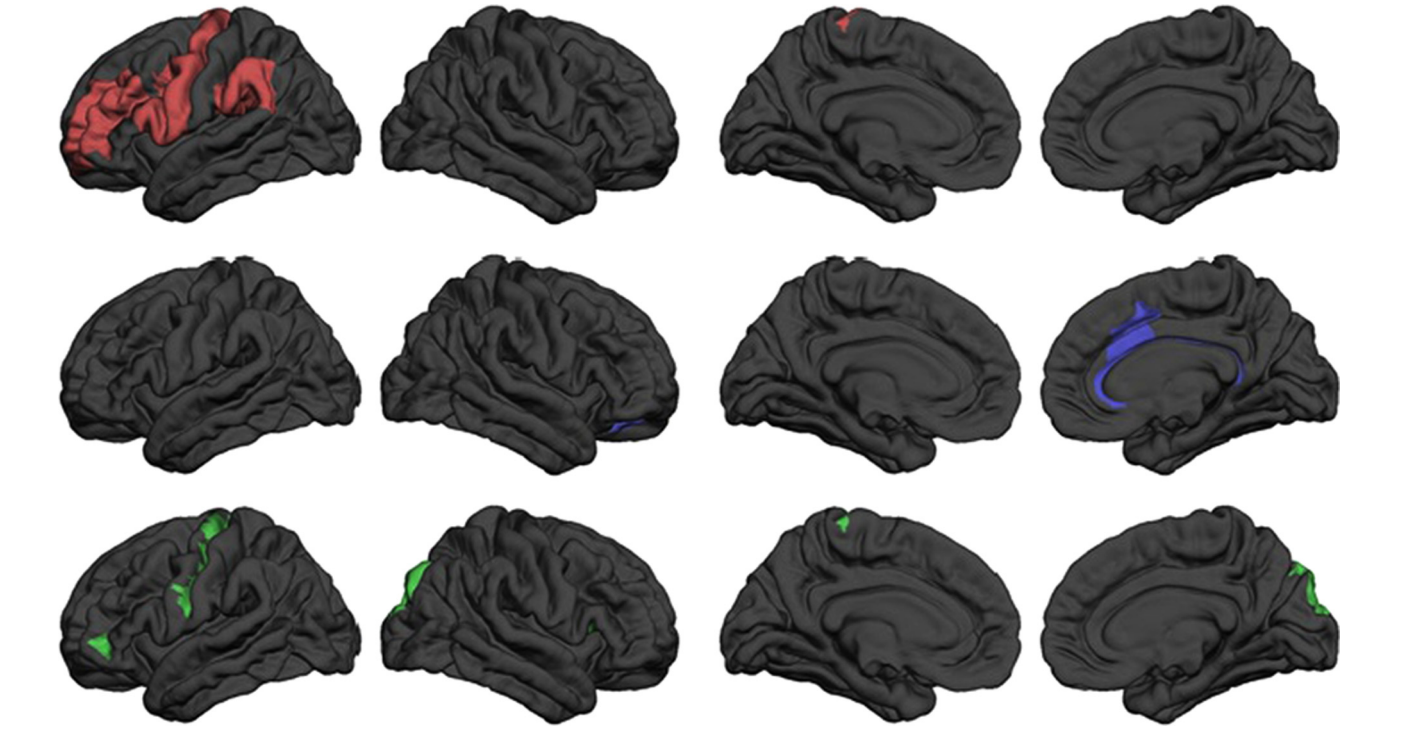

Fig. 2. Age trends in grey matter. Regional parcellation data were compared in an ANCOVA, with the morphometric statistics as the dependent variable and both age and group as independent predictors. Significant age × group interactions are depicted for GM area (*red*), thickness (*blue*), and volume (*green*). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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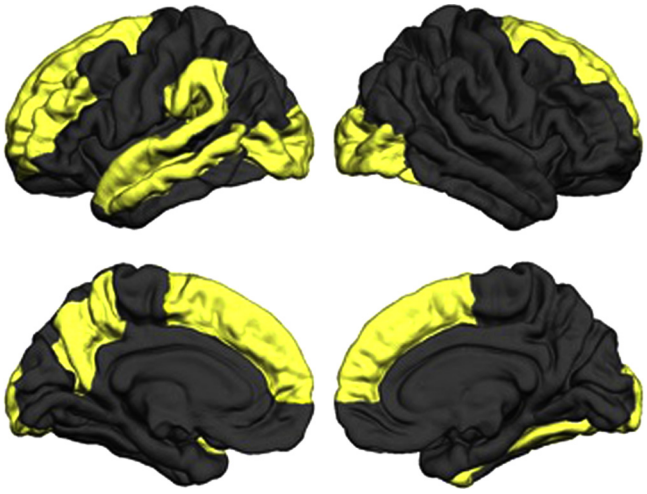

Fig. 3. Age trends in white matter. Regional WM parcellation data were compared in an ANCOVA, with the morphometric statistics as the dependent variable and both age and group as independent predictors. Significant age × group interactions are depicted.

Of particular interest are the contrasting developmental trajectories of WM in controls and DDs. It was clear that WM volumes *increased* with age in the controls but not in DDs, most notably in the left frontal lobe. The control results are consistent with previous large-scale studies on brain development in the pre-adolescent brain [18]. Typical neuro-development is characterized by a modest decrease in GM volume simultaneous with an increase in WM volume. To the extent that this morphological change reflects both genetic development and experience-dependent learning, the present results may reflect the neural basis of DDs failure to learn.

Two developmental changes are particularly striking. First, significant increases in WM in the frontal lobes in controls, but not in DDs, suggests that the frontal lobes may be connecting increasingly to parietal areas in the fronto-parietal network known to be involved in arithmetic [16,43]. Second, and consistent with this, are the increases of parietal WM in controls only, especially in the angular gyrus and in the supramarginal gyrus, known to be implicated in retrieval of arithmetical facts [44–48] and in the left inferior parietal lobe, associated with representation of numerosities and numerical magnitudes [15,37,49–52]. Given the stringent

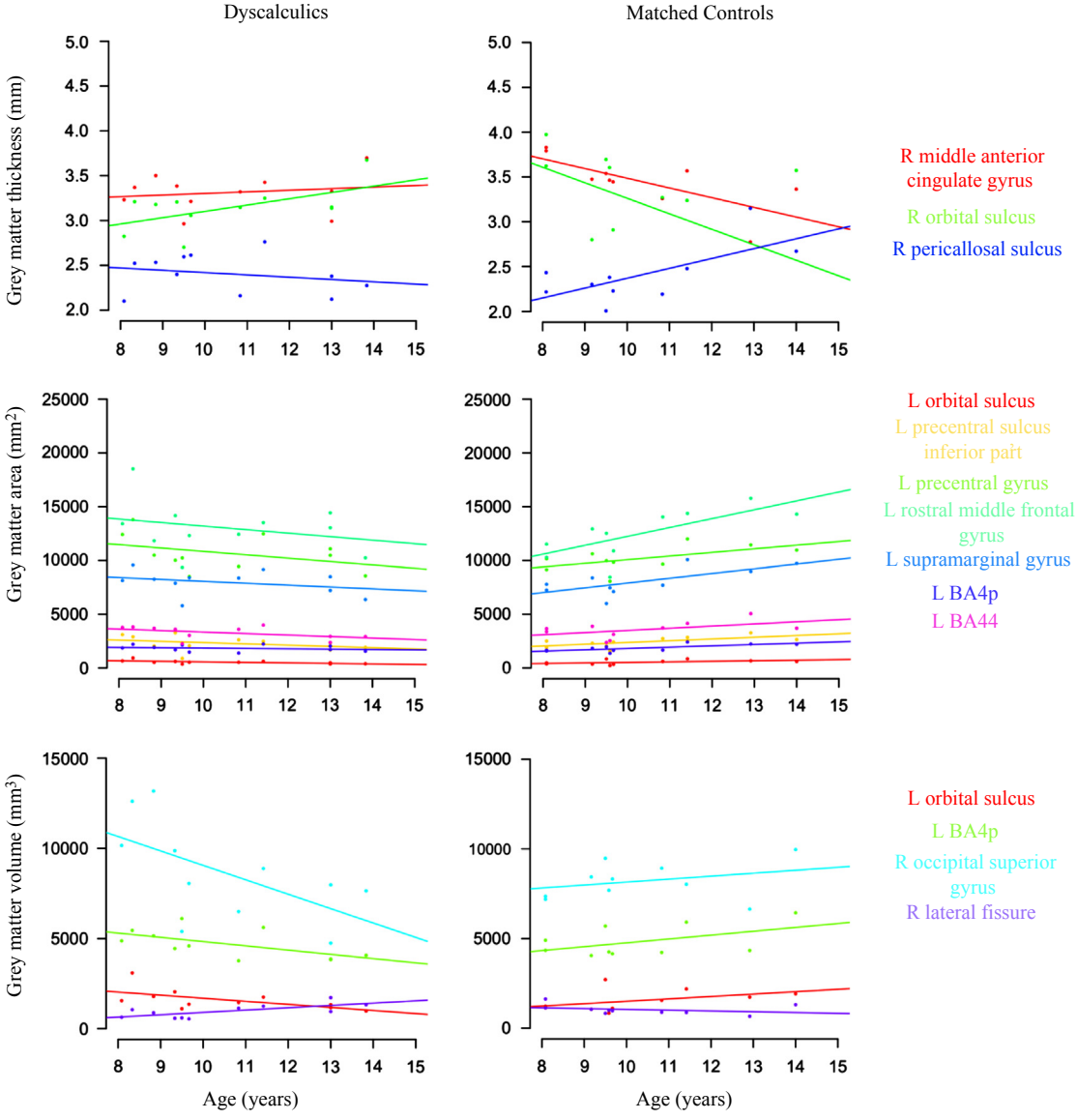

Fig. 4. Age trends in grey matter. Linear representations of the independent ANCOVAs demonstrate the changes in GM morphology with age, in both DDs (*left graphs*) and matched controls *(right graphs)*. All depicted age × group interactions are significant at $p < 0.05$.

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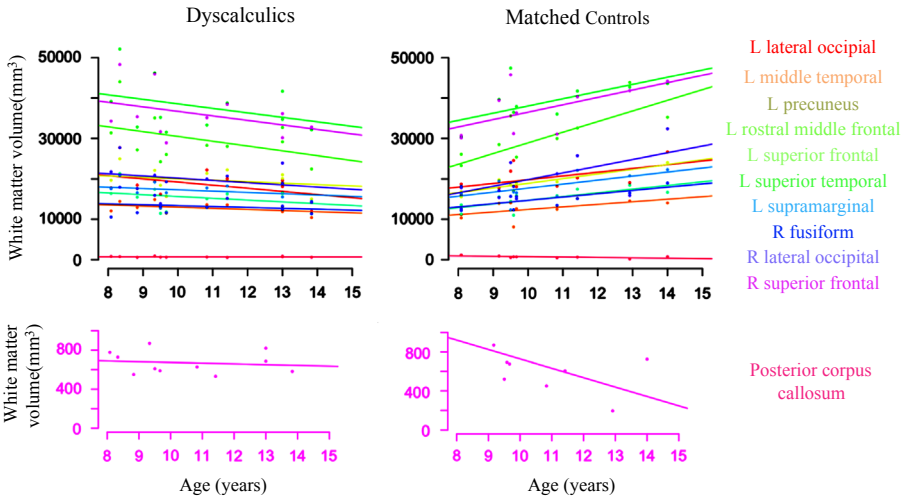

Fig. 5. Age trends in white matter. Linear representations of the independent ANCOVAs demonstrate the changes in WM morphology with age, in both DDs (*left graphs*) and matched controls (*right graphs*). All depicted age × group interactions are significant at $p < 0.05$. Because of the small callosal volumes, that result is depicted separately in the lower graphs.

Table 4
Age trends in grey matter.

Region	DD	Controls	*F*	ω^2
A. Area				
L orbital lateral sulcus	541.36 (48.82)	532.9 (67.56)	6.55	0.31
L precentral inferior	2301.82 (207.32)	2425.9 (155.26)	4.63	0.20
L precentral gyrus	10,676.36 (499.69)	10,180.5 (360.22)	4.35	0.19
L rostral middle frontal	13,018.36 (722.09)	12,503.4 (706.5)	5.70	0.26
L suparmarginal	7961.64 (338.1)	8040.8 (396.89)	6.51	0.31
L BA4p	180.36 (89.24)	1856.7 (106.46)	5.90	0.27
L BA44	3271.82 (180.37)	3558.1 (244.84)	5.47	0.25
B. Thickness				
R mid-anterior cingulate	3.31 (0.06)	3.45 (0.09)	6.27	0.29
R orbital sulcus	3.14 (0.07)	3.21 (0.23)	4.44	0.19
R pericallosal sulcus	2.4 (0.07)	2.41 (0.1)	6.18	0.29
C. Volume				
L lateral orbital sulcus	1600.36 (177.59)	1543.4 (187.94)	6.21	029
L BA4p	4705 (241.54)	4830.1 (274.39)	7.01	0.33
R superior occipital	8637.91 (810.66)	8206.4 (329.41)	5.41	0.25
R lateral fissure, anterior	967.82 (113.02)	1030.5 (86.52)	7.31	0.35

Regional parcellation data were compared in ANCOVAs, with the morphometric statistics as the dependent variable and both age and group as independent predictors. Each subtable gives the group mean values in mm^2 (area), mm (thickness) and mm^3 (volume). Standard errors are in parentheses. The tabulated *F*-values are for age × group interaction, and all significant at $p < 0.05$, and the effect sizes are measured with omega-squared values.

Table 5
Age trends in white matter.

Region	DD	Controls	*F*	ω^2
Corpus callosum, mid-post.	670.18 (34.38)	697.1 (90.52)	4.64	0.20
L lateral occipital	18,818.73 (1202.96)	20,112.7 (1054.04)	4.58	0.20
Lmiddle temporal	12,820.27 (392.25)	12,619.4 (697.96)	6.11	0.28
L precuneus	19,837.36 (899.9)	19,288.6(813.55)	7.72	0.37
L rostral frontal	29,873 (1791.39)	29,760.3 (2373.29)	8.33	0.41
L superior frontal	37,979.36 (1969.82)	38,621.7 (1766.71)	4.92	0.22
L superior temporal	15,388 (892.55)	14,997.5 (779.16)	5.72	0.26
L supramarginal	17,115.36 (695.52)	18,029.9 (1001.83)	5.36	0.24
R fusiform	13,248.27 (672.55)	14,933.1 (724.54)	4.84	0.21
R lateral occipital	19,898 (1200.3)	20,387.7 (1757.38)	4.76	0.21
R superior frontal	3611.64 (1846.2)	37,100.4 (1897.36)	5.24	0.24

Regional parcellation data were compared in ANCOVAs, with the morphometric statistics as the dependent variable and both age and group as independent predictors. Each subtable gives the group mean values in mm^3 (volume). White matter volumes are projected on to the cortical surface using Freesurfer conventions. Standard errors are in parentheses. The tabulated *F*-values are for age *x* group interaction, and all significant at $p < 0.05$, and the effect sizes are measured with omega-squared values.

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Table 6
Previous findings.

Region	Kaufmann, 2011	This study
Left precuneus	More activity in controls	More WM gain over time in Controls
Right inferior parietal lobule	More activity in controls	More GM volume in controls
Left frontal paracentral lobe	More activity in Controls	More WM gain over time in controls
Left fusiform gyrus	More activity in Controls	No significant results
Left superior frontal gyrus	More activity in controls	More WM gain over time in controls
Right middle frontal gyrus	More activity in controls	No significant results
Left postcentral gyrus	More activity in dyscalculics	No significant results
Right inferior parietal lobule	More activity in dyscalculics	More GM volume in controls (see above)
Left superior frontal lobe	More activity in dyscalculics	More WM gain over time in controls (see above)
Left red nucleus	More activity in dyscalculics	Not analyzed
Right paracentral frontal lobe	More activity in dyscalculics	More WM gain over time in controls
Left inferior parietal lobe	More activity in dyscalculics	More GM area and WM gain over time in controls

Regions identified as structurally different in DDs in this study compared with those regions showing different activations in a meta-analysis of functional MRI studies by Kaufmann et al. [24].

definition of DD used in this study, the present results offer strong evidence for a neural basis of core numerosity that is disrupted during pre-adolescent cortical maturation.

The one exception to this trend was in a small posterior region of the corpus callosum that connects the parts of the parietal lobes implicated in number processing. One interpretation of these results is that the age-dependent reduction in posterior callosal fibres in controls reflects axonal pruning, and therefore an effect of normal maturation. Conversely, the relatively stable volume of posterior callosal fibres in DDs may be the manifestation of a transhemispheric system with reduced plasticity.

In general, the present results replicate a well-established pattern in control subjects: GM area and thickness tend to decline modestly with age, and WM volume tends to increase; in DD subjects however, the size of these effects is diminished or even reversed. These morphological changes may represent a long-term effect of learning and experience-dependent plasticity, though of course they may also reflect genetically determined individual differences.

As an aside, neither non-numerical markers of general performance (including performance IQ and processing speed) nor markers of verbal performance (including verbal IQ and vocabulary scores) exhibited regional or age specificity in regions of the brain previously associated with numerical cognition. The lack of significant results associated with these non-numerical tasks illustrates that the whole brain regression method we have employed here effectively tests task-relevant cortical anatomy.

The present study has several important limitations. First, this is a very small sample, and DD learners may be atypical in ways that were not observed here. The present results are suggestive of an important conjunction of temporal and regional changes that may characterize dyscalculia; it would be very useful to look at a larger sample with more individuals at each age point and across the ability spectrum to assess the typicality of DD brains apart from the differences noted in this study.

Second, we selected dyscalculic subjects from our larger sample using the WOND-NO criteria first described by Isaacs and colleagues [21]. However, recent evidence supports the hypothesis that dyscalculics share a core number deficit that is only crudely captured by untimed arithmetical tests, such as the WOND-Numerical Operations subtest [8]. Nevertheless, in this sample we were able to validate the WOND-NO classifier using individual core number tasks (timed dot enumeration): for number tasks, DDs were significantly impaired relative to control subjects. Furthermore we confirmed that non-numerical measures of general performance (processing speed and IQ) were not able to distinguish our dyscalculic sample from controls. We conclude that at least for the straightforward delineation we desired for this study, the WOND-NO was an effective and simple tool for identifying dyscalculics.

Finally, although we restricted our regional analysis to brain areas previously associated with dyscalculia [24] our analysis was not otherwise corrected for multiple comparisons. Although Type I errors in significance testing may occur, here we are concerned with patterns of network activation previously found to be abnormal in DD based on previous fMRI studies, and as will be seen from the tables, substantial effect sizes were observed. These effect sizes are a good guide to the relative strength of the results, and provide a better characterization of our findings than would null hypothesis testing alone.

In addition to the well-characterized involvement of the left IPS, functional studies of calculation have highlighted involvement of the left and right IPS, the rostral frontal cortices, and the left precuneus [18]. Our results are spatially consistent with previously described anatomy, and the effect sizes we report further bolster our conclusion that the present results are not spurious.

Overall, the present study gives a more comprehensive picture of the differences between DD and typical brains than had previously been available. Notably, the present results demonstrate that DD is well-characterized by core number deficits, that these deficits have a clear anatomical basis, and that regionally-specific developmental trajectories in both GM and WM are relevant to the development of arithmetical abilities.

Our results also raise questions about how best to help DDs acquire the numeracy skills required for a numerate society. As the brain changes with age, should teaching methods change as well?

4. Methods

4.1. Analysis

All statistical analyses were carried out in R, an open-source statistical programming environment (R Development Core Team, 2011).

4.2. Participants

Participants were recruited as a larger twin study of the genetic and neural basis of mathematical development, supported by the Multiple Births Foundation at Queen Charlotte's and Chelsea Hospital. The aims of the study were made clear to parents via study information sheets. The following exclusion criteria were applied: Autistic Spectrum Disorders; severe chronic disease (e.g. cerebral palsy); having received treatment at birth for acute twin-to-twin transfusion; children unwell on the study day. Information on birthweight and gestational age were obtained from parents and source-verified against notes for twins born at QCCH. All subjects took part

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in a battery of cognitive tests, including IQ testing and numerical assessment, as detailed below. Subjects in the present sample were twins at birth, although no twin pairs were included.

We used two convergent approaches to identify DDs. First, we used a discrepancy criterion such that DDs obtained significantly lower scores on a standardized arithmetic test [20] than the scores predicted by their full-scale IQ [53]. Twenty-one members of our original sample of 269 children satisfied this criterion. The dyscalculic subjects were then paired with controls from the sample population, matching for length of gestation, age, and IQ. To cross-validate our selection, we compared our subjects on core numerosity measures. Dyscalculic subjects showed impaired performance in timed estimation of the numerosity of dots ($F(1,32)=6.4$, $p<0.02$) and on timed arithmetic tasks ($F(1,34)=8.9$, $p<0.01$), but demonstrated normal performance in general processing speed ($F(1,39)=3.09$, $p>0.05$) and vocabulary tests ($F(1,39)=0.03$, $p>0.05$). These clear core number deficits validated and confirmed the discrepancy classification of DD [21].

4.3. Cognitive testing

In addition, to assessment of WISC III Full-Scale IQ, specific tests of numerical abilities were carried out to identify DDs using standard criteria:

1. **WOND**, specifically the Numerical Operations subtest was used to categorize learners as dyscalculic if their score was significantly different from Full Scale IQ, following the procedure of Isaacs et al. [21].
2. **Dot enumeration**. Arrays of two and nine dots were generated and presented on a computer display using a custom-designed computer programme. Subjects were asked to enumerate these displays and press the corresponding number key on a standard keyboard. Reaction times for correct trials, standardized from an age-matched sample, constituted the metric for comparing the two groups.

4.4. Imaging

4.4.1. Image acquisition

MRI studies were performed on a 1.5 T Siemens Vision system. Investigations included magnetization-prepared rapid acquisition gradient echo [54]; a three-dimensional volume acquisition with repetition time of 10 ms; echo time, 4 ms; inversion time, 200 ms; flip angle, 12°; matrix size, 256×256; field of view, 250 mm; partition thickness, 1.25 mm; 128 sagittal partitions in the third dimension; and acquisition time, 8.3 min producing high resolution T1-weighted volumetric scans.

Of the 21 DD we identified, seven did not have brain scans, and an additional three had invalid Freesurfer reconstructions. To keep numbers balanced, both the DDs who were missing scans and their normal counterparts were eliminated. The final Freesurfer sample had 11 dyscalculics, and 11 controls (Table 1).

4.4.2. Post-acquisition imaging processing

4.4.2.1. Cortical parcellation. The surface-based analysis utilized Freesurfer 5.1.0 and followed the procedures described by Fischl, Dale and colleagues [29,30,32]. After initial preprocessing of the T1-weighted images, surfaces corresponding to the white matter boundary and pia mater were obtained automatically by the software. The pial surface was segmented into 34 regions per hemisphere using the Desikan-Killiany atlas [29] and cortical thickness for each region was obtained as the mean distance between the pial and white matter surfaces. The area of segmented surface and total grey matter volume were obtained similarly for each region. This approach has the advantage of combining atlas-based information with subject-specific morphology.

4.4.3. Statistical analysis

Parcellation data from Freesurfer was imported into R for further analysis. Only regions consistent with prior activation studies were analyzed. Broadly defined, these were regions in the bilateral inferior parietal cortices, the superior and rostral frontal cortices, and the bilateral precuneate cortices. Reported p-values are uncorrected for multiple comparisons; given the possibility of Type I errors with a survey approach like this, we have reported effect sizes for every comparison. Main effects were examined with t-tests, and effect sizes were calculated as Pearson's r values:

$$r=\sqrt{\frac{t^2}{t^2+df}}$$

Pearson's r was chosen over Cohen's d because of the general utility and familiarity of the former, as well as the validity of both metrics in describing effects sizes for means testing [55]. Effect sizes were interpreted traditionally, with $r=0.1$ representing a small effect, $r=0.3$ a medium effect, and $r=0.5$ a large effect. Age by group interactions were examined with ANCOVA, with age, group, and their interaction as predictors. The reported effect size is omega-squared.

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