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Volumetric and surface characteristics of gray matter in adult dyslexia and dyscalculia

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ABSTRACT

Dyslexia, dyscalculia and their comorbid manifestation are prevalent disorders associated with well-documented behavioral manifestations. However, attempts to relate these manifestations to abnormalities in brain structure have yielded mixed results, with no clear consistency across a range of measures. In this study, we used a unique design including adults with dyslexia, dyscalculia, both disorders and controls, to explore differences in gray matter characteristics across groups. Specifically, we examined whether dyslexia, dyscalculia, or their comorbid manifestation could be related to volumetric and surface characteristics of gray matter, using voxel-based and surface-based morphometry. We demonstrate with Bayesian analyses that the present data favor the null model of no differences between groups across the brain, a result that is in line with recent findings in this field of research. Importantly, we provide detailed statistical maps to enable robust assessment of our findings, and to promote cumulative evaluation of the evidence. Together, these findings suggest that gray matter differences associated with dyslexia and dyscalculia might not be as reliable as suggested by previous literature, with important implications for our understanding of these disorders.

1. Introduction

Dyslexia and dyscalculia—characterized by impairments in reading and mathematical abilities—are associated with difficulties that often persist into adulthood. These include difficulties converting speech sounds into word representations (Habib, 2000), subitizing (Koontz, 1996; Schleifer and Landerl, 2011) and retrieving words or numbers from long-term memory (Vukovic et al., 2010; Wolf and Bowers, 1999). Yet beyond the behavioral manifestations, can these be related to abnormalities in brain structure? Several neuroimaging studies have investigated the structural and functional correlates of dyslexia and dyscalculia; in particular, several studies have reported differences in gray matter volume between dyslexics and typical readers (Brambati et al., 2004; Hoeft et al., 2007; Kronbichler et al., 2008; Silani et al., 2005), and between dyscalculics and controls (Rotzer et al., 2008; Rykhlevskaia et al., 2009), either across the whole brain or in specific brain regions. Despite the abundance of positive findings, however, the literature relating gray matter differences to dyslexia and dyscalculia is riddled with inconsistencies (for a review, see Ramus et al., 2018).

A number of limitations have also been identified, some of which can potentially help explain the mixed findings. For example, many studies reporting significant effects were shown to be underpowered, whereas studies with larger sample sizes are much more likely to report null findings (Eckert et al., 2016; Pernet et al., 2009; Tamboer et al., 2015). Interestingly, this pattern of results is the reverse of what one would expect if effects were real—in theory, larger sample sizes should be associated with a larger number of significant clusters (Ramus et al., 2018). Other limitations pertain to the specific techniques and analyses used to investigate gray matter differences—most of these studies employed voxel-based morphometry (VBM), a technique that remains extremely popular, but that has also been associated with important limitations in recent years. For example, apparently trivial decisions at each step of the preprocessing pipeline, such as specific choices of registration algorithms (Peelle et al., 2012) and smoothing kernel sizes (Henley et al., 2010), have been shown to greatly influence results. Furthermore, the interpretation of volumetric differences, even when following best practices, remains difficult, given that they can arise from both cortical thickness and cortical folding (Ramus et al., 2018). These potential limitations have not been left unanswered, however—surface-based morphometry (SBM) has been proposed to help circumvent some of the problems inherent to VBM, and has thus been used frequently in recent years to complement VBM results (Fischl et al., 2008).

Beside these statistical and technical limitations, the large majority

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of studies relating gray matter to dyslexia or dyscalculia has involved children. For example, a recent study by Skeide and colleagues (2018) used a design composed of children with low reading ability, low mathematical abilities, or both, to investigate VBM and SBM, and found no association between behavioral abilities and gray matter morphometry, except for cortical surface complexity assessed via fractal dimensional measures (Yotter et al., 2011). However, these studies might not allow reliable inferences to adult populations. In contrast with the developmental literature, it seems plausible that individuals who still suffer from reading or mathematical difficulties in adulthood are not representative of those who experience similar problems earlier in life. Even if the underlying causes are similar (Ramus et al., 2003), it remains the case that the impoverished reading or mathematical environment may have magnified some of the behavioral problems and their potential neural correlates by the time dyslexics or dyscalculics are adults (Butterworth et al., 2011; Goswami, 2015), or that, on the contrary, some of these difficulties may have been remediated, for example via compensation strategies (Temple et al., 2003). In addition, most studies have focused on either dyslexia or dyscalculia, with very little work investigating the comorbidity of the disorders (but see Moreau et al., 2018b; Peters et al., 2018; Skeide et al., 2018), despite the very high prevalence of their co-occurrence (about 40%, see Moll et al., 2014; Wilson et al., 2015). For these reasons, it appears important to study adult populations with one or both of the disorders, to be able to confirm or disprove the findings from developmental populations (Richlan et al., 2011). Yet, none of the previous studies on gray matter characteristics have investigated adult dyslexia, dyscalculia, and their comorbid manifestation in a single design, despite the hypothesized shared mechanisms and frequent comorbidity of the two disorders (Moreau et al., 2018b; Peters et al., 2018; Wilson et al., 2015).

Here, we attempted to identify neuroanatomical correlates of dyslexia and dyscalculia in adults with one or both of these disorders. In particular, we examined whether dyslexia, dyscalculia, or their comorbid manifestation could be related to volumetric and surface characteristics of gray matter in a sample of 48 adults. Importantly, we designed our experiment with the aforementioned limitations in mind. First, we recruited a balanced sample of dyslexics, dyscalculics, comorbid and control individuals, to allow direct group comparisons as well as contrasts collapsing groups. This factorial design allowed us to make multiple well-powered comparisons, in particular when combining groups sharing one of the two disorders. Second, we recruited adults exclusively, given that this population has been underrepresented in previous studies relating gray matter characteristics with either dyslexia or dyscalculia. Third, we used SBM, in addition to VBM, to refine our understanding of potential group differences. We could thus provide a fine-grained representation of group characteristics, including gray matter volume, but also cortical thickness, gyrification, sulcal depth and cortical complexity. Finally, we used both frequentist analyses as well as Bayesian methods, to allow comparisons with traditional statistics together with precise, probabilistic estimation of group differences. The use of these two complementary methods was especially relevant in the present study, given that we report null results.

2. Methods

2.1. Participants

Participants were recruited as part of the Auckland Comorbidity Study (Wilson et al., 2015). From the initial 85 adults participating in the larger behavioral study, 48 were selected for the present study based on resources available. The final sample (n = 48) included 12 dyslexics, 12 dyscalculics, 12 comorbids, and 12 controls, all right-handed. Note that different analyses (task fMRI, white matter tractography, and behavioral performance) on partly overlapping subsets of the present data have been reported elsewhere (Moreau et al., 2018b; Waldie et al., 2017; Wilson et al., 2015). All participants gave informed consent for all procedures. The study was approved by The University of Auckland Human Participants Ethics Committee.

2.2. Clinical Assessments

The criteria for dyslexia were at least one score ≤ 25th percentile on one of the reading and spelling tests (WJ Word ID and Word Attack, and WRAT spelling), plus at least one other of these scores ≤ 50th percentile (Wilson et al., 2015). The criterion for dyscalculia was a score ≤ 25th percentile on the WRAT mathematics. These were corroborated by a history of reading and/or mathematical difficulties. Exclusion criteria for all groups included fMRI contraindications, the presence of a neurological disorder, a history of major head injury or non-standard schooling, English as a second language, vision or hearing impairment, Full Scale Intelligence Quotient (FSIQ) < 85, and a clinical diagnosis of ADHD. The Adult Self Report Scale (Kessler et al., 2005) was used as a screening measure for ADHD, and above-threshold scores were followed up with a full diagnostic clinical interview. Note that we did not screen for specific learning impairment (SLI), though we should note that the extent to which SLI and dyslexia/dyscalculia are separable disorders continues to be debated: some researchers have proposed that they are disorders of varying severity on the same disorder continuum, while others maintain that they are more likely partially overlapping clusters of cognitive phenotypes in a multivariate space (Bishop and Snowling, 2004; Pennington and Bishop, 2009; Snowling and Melby-Lervåg, 2016). For a comprehensive description of the design and all measures included, please refer to Wilson et al. (2015). Sample characteristics are shown in Table 1.

2.3. Behavioral assessments

Behavioral assessments included three reading-related tests (Word ID, Word Attack, and Spelling) and one mathematical test. The Woodcock-Johnson Word ID involves reading words aloud from a list; the Woodcock-Johnson Word Attack requires participants to read nonsense words aloud to test phonological decoding skills; the Wide Range Achievement Test Spelling involves spelling words read by the test administrator. The Wide Range Achievement Test Mathematics requires participants to perform basic mathematical calculations. Reading and math scores, broken down by groups, are shown in Fig. 1.

2.4. MRI acquisition parameters

Sagittal T1-weighted images (voxel size = $1 \times 1 \times 1\,mm^3$) were acquired using a single shot 3D magnetization-prepared rapidly acquired gradient echo (MP-RAGE) sequence on a 1.5 T Siemens Avanto with a 12-channel head matrix coil, TE = 4.94 ms, TR = 11 ms, FA = 15°, matrix = 256 × 256, FOV = 256 mm, 176 slices.

Table 1
Sample characteristics, broken down by groups (control, dyslexia, dyscalculia, comorbid).

	Control	Dyslexia	Dyscalculia	Comorbid
n	12	12	12	12
Age (mean/sd)	28.6/6.14	30.1/6.70	31.5/7.19	33.2/5.78
Gender (M/F)	7/5	7/5	6/6	7/5
Education (mean yrs/sd)	15.3/1.91	15.5/1.68	14.9/2.02	14.8/2.13
Mother education (mean yrs/sd)	13.4/2.23	14.3/2.70	14.6/2.35	13.6/2.19
Father education (mean yrs/sd)	13.9/3.15	13.4/1.43	13.0/2.13	13.1/2.03
IQ (mean/sd)	120.1/6.35	122.1/8.73	115.7/8.48	109.8/8.47

Note: Only the last measure (IQ) showed significant differences, $F(3,44) = 5.44$, $p = 0.003$, $\eta_p^2 = 0.27$, between Comorbid and Control, $t(44) = 3.11$, $p_{bonf} = 0.02$, and Comorbid and Dyslexia, $t(44) = 3.72$, $p_{bonf} = 0.003$.

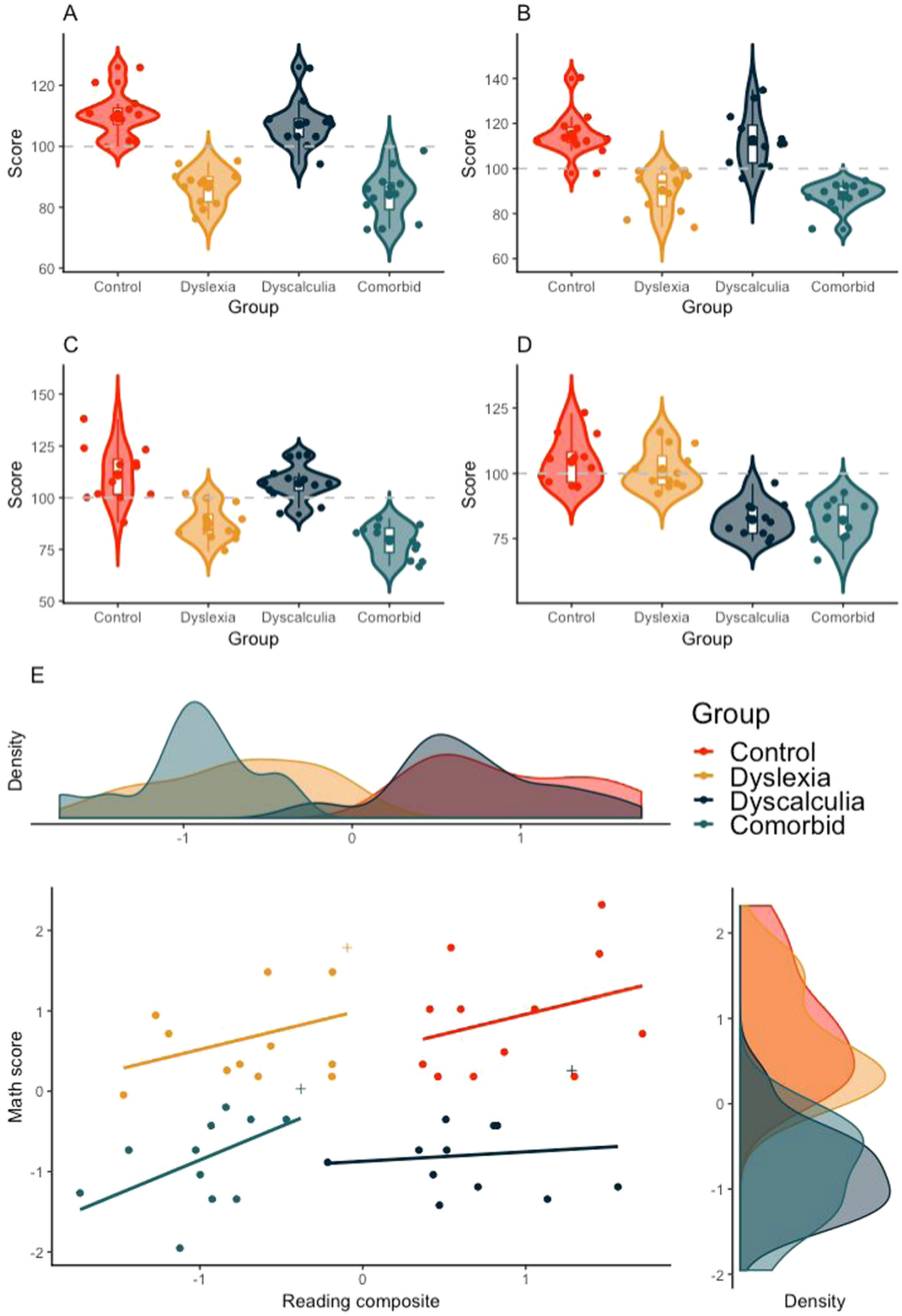

Fig. 1. (A-D) Violin and box plots, for Word ID (A), Word Attack (B), Spelling (C) and Math (D). The plots show the distribution of scores (violin) for each group, together with the mean (box central dot), median (box central line), first and third quartile (box edges), minimum and maximum (whiskers), and all individual data points. (E) Correlation and density plots for reading (Word ID, Word Attack, and Spelling) and Math (Wide Range Achievement Test Mathematics) performance across all subjects. Participants marked with a (+) were identified using a discrepancy criterion based on IQ (for details see Wilson et al., 2015).

2.5. Preprocessing

We used the Computational Anatomy Toolbox (CAT12, r1278; Gaser and Dahnke, 2016; Gaser and Kurth, 2016) in SPM12 (Penny et al., 2011) for preprocessing and analysis of the data. Images were segmented and registered to the high-dimensional DARTEL template provided with CAT12. We then smoothed the resulting gray matter images using an isotropic Gaussian kernel with 8 mm full width half maximum (FWHM). We also estimated cortical thickness, gyrification (Luders et al., 2006), sulcal depth and cortical complexity (Yotter et al., 2011), and smoothed these images using an isotropic Gaussian kernel with 15 mm (cortical thickness) and 20 mm (gyrification, sulcal depth, and cortical complexity) FWHM. All preprocessing scripts can be found at https://github.com/davidmoreau/VSBM/tree/master/scripts.

2.6. Image quality

We visually inspected all T1 images for MR or preprocessing artefacts and for anatomical abnormalities. In addition, we computed the Image Quality Rating (IQR) for all participants. Images had to be rated above 70 (corresponding to a satisfactory rating in the CAT manual, link here: http://www.neuro.uni-jena.de/cat/) to be included in our analyses. All images exceeded this threshold (IQR_{mean} = 79.27, IQR_{range} = 75.35–81.97), therefore no images were excluded from our analyses. Importantly, image quality did not significantly differ between groups, $F(3,44) = 1.19$, $p = 0.32$ (see https://github.com/davidmoreau/VSBM for the IQR values and a figure showing IQR across groups).[1]

2.7. Statistical analyses

To compare volumetric and surface measures (gray matter volume, cortical thickness, gyrification, sulcal depth, and cortical complexity) across groups, we modeled the data using 2 (*no dyslexia, dyslexia*) × 2 (*no dyscalculia, dyscalculia*) factorial ANOVAs,[2] resulting in the following design cells: control, dyscalculia, dyslexia, comorbid. For the gray matter volume model, we included total intracranial volume and age as covariates.[3] We were interested in 5 comparisons: the main effect of dyslexia (*F*-contrast: [1 1 −1 −1]), the main effect of dyscalculia (*F*-contrast: [1 −1 1 −1]), the main effect of comorbidity (*F*-contrast: [1 1 1 −3]), the interaction (*F*-contrast: [1 −1 −1 1]), as well as any differences between any of the four groups (*F*-contrast: [1 −1 0 0; 0 1 −1 0; 0 0 1 −1]).

As a mere absence of differences using a frequentist approach is largely uninformative—in the sense that it does not provide evidence for the absence of an effect—we complemented frequentist analyses by Bayesian model comparisons for all null results, conducted in R (RRID:SCR_001905; R Core Team, 2018). To this end, we calculated and extracted region of interest (ROI) mean values, using the Neuromorphometrics atlas (http://neuromorphometrics.com/) for gray matter volume, and the HCP_MMP1.0 atlas (Glasser et al., 2016) for the four surface measures. Using these extracted ROI values, we ran Bayesian linear models using the same contrasts as for frequentist analyses. We used prior scales on fixed effects set to 1, prior scales on random effects set to 1, and prior scales on covariates set to 0.354 (Rouder et al., 2012). All analyses were set at 10^4 iterations, with diagnostic checks for convergence. One chain per analysis was used for all analyses reported in the paper, with a thinning interval of 1 (i.e., no iteration was discarded).

3. Results

Using a frequentist factorial ANOVA, we first tested whether gray matter volume differed between individuals with dyslexia and those without, between individuals with dyscalculia and those without, between individuals with comorbid dyslexia and dyscalculia and those with either one or none of these disorders, as well as the interaction effect. In addition, we looked for differences between healthy controls, dyslexics, dyscalculics, or individuals with both disorders, that is, any differences between any of the groups. None of these analyses revealed any significant differences after FWE correction ($\alpha = 0.05$), using either standard parametric methods or nonparametric, permutation-based threshold-free cluster enhancement (TFCE; Smith and Nichols, 2009). We therefore complemented these frequentist analyses with their equivalent Bayesian analyses, to quantify the absence of robust volumetric differences for each ROI, and confirmed that evidence for any difference was limited across the whole brain (see Fig. 2A). Specifically, support for the null hypothesis of no differences between any of the groups ranged from $BF_{01} = 0.26$ to $BF_{01} = 36.93$ across the whole brain ($M = 14.95$; SD = 9.93).

We then extracted surface characteristics and tested whether any group differences could be observed in cortical thickness, gyrification, sulcal depth, or cortical complexity. Again, we found no evidence for systematic differences between any groups for any of the comparisons, using frequentist analyses. Bayesian hypothesis testing allowed us to demonstrate the absence of robust surface differences across the brain, and to specifically quantify these for each ROI (see Fig. 2B-E). For cortical thickness, support for the null hypothesis of no differences between any of the groups ranged from $BF_{01} = 0.28$ to $BF_{01} = 37.70$ across the whole brain ($M = 15.66$; SD = 9.29). For gyrification, support for the null hypothesis of no differences between any of the groups ranged from $BF_{01} = 0.09$ to $BF_{01} = 37.50$ across the whole brain ($M = 15.53$; SD = 9.95). For sulcal depth, support for the null hypothesis of no differences between any of the groups ranged from $BF_{01} = 0.23$ to $BF_{01} = 37.97$ across the whole brain ($M = 17.38$; SD = 9.91). For cortical complexity, support for the null hypothesis of no differences between any of the groups ranged from $BF_{01} = 0.02$ to $BF_{01} = 37.60$ across the whole brain ($M = 15.10$; SD = 9.61).

Importantly, we also provide complete statistical maps (frequentist and Bayesian) to enable fine-grained assessment of the lack of consistent group differences (see https://neurovault.org/collections/4145/ and https://github.com/davidmoreau/2018/VSBM for details). These allow the reader to explore volumetric and surface characteristics in an unbiased manner, enabling stronger, richer inferences from our results.

4. Discussion

In this study, we aimed to identify neuroanatomical correlates of dyslexia and dyscalculia in adults with one or both of these disorders. We specifically examined whether dyslexia, dyscalculia, or their comorbid manifestation could be related to volumetric and surface characteristics of gray matter in adults. Consistent with traditional neuroimaging analyses, we used a voxelwise frequentist approach to allow detecting localized group differences while adequately controlling for error rates (i.e., FWE = .05). However, because null findings remain largely inconclusive in this framework, we complemented these analyses with Bayesian methods to quantify changes of belief based on

[1] Nevertheless, we also ran all analyses with the addition of image quality as a covariate in all models. In all cases, our findings remain unchanged (F-maps can be found at https://github.com/davidmoreau/VSBM/tree/master/supplemental_analyses).

[2] Given recent concerns related to the discretization of reading and mathematical abilities, we also analyzed the data in a continuous way, correlating volume and surface characteristics with reading and math scores. The results were consistent with the analyses we report herein (F-maps can be found at https://github.com/davidmoreau/VSBM/tree/master/supplemental_analyses).

[3] There are a few reports that have found an association between either total gray matter volume (GMV) or local GMV and intelligence. In the present study, neither total nor local GMV correlated with either total IQ or subscales of it (collected as part of Wilson et al., 2015). Thus, IQ was not used as a covariate in our models.

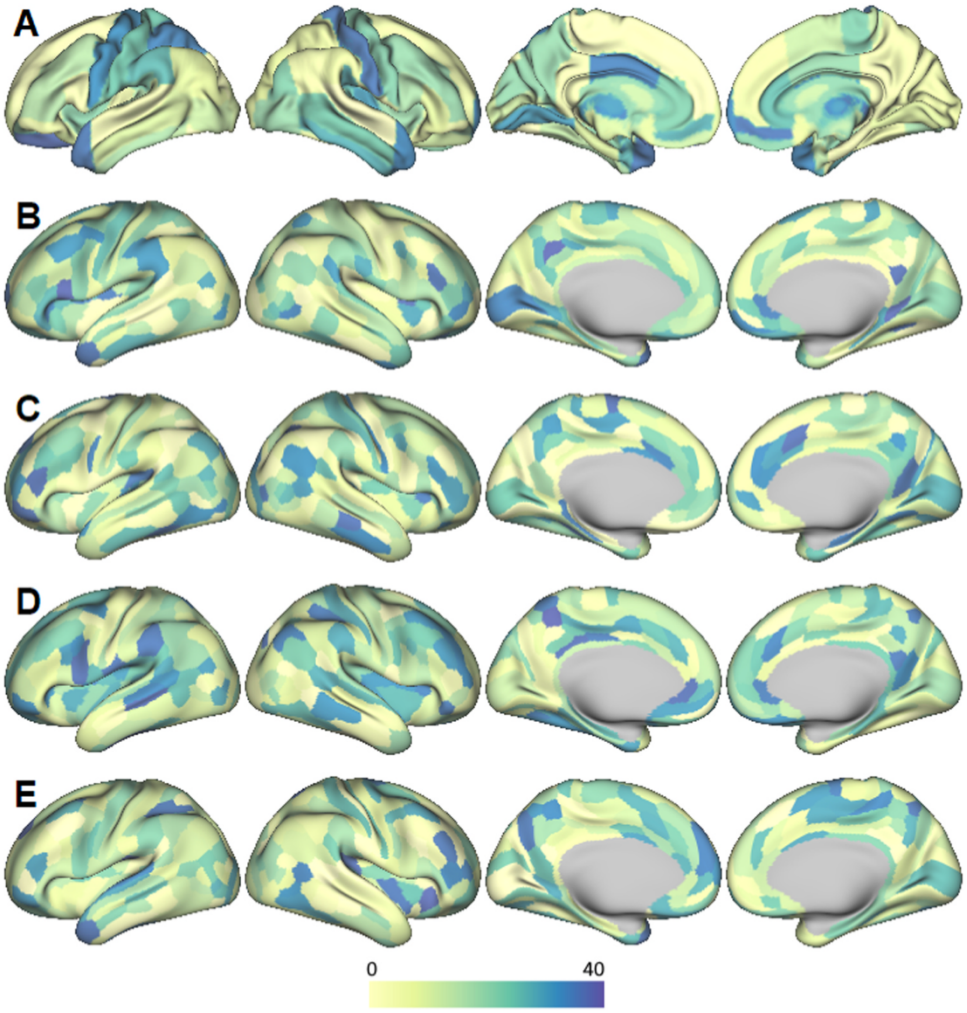

Fig. 2. (A-E) Bayes Factors quantifying evidence for the absence of structural differences for the contrast between all groups. (A) Gray matter volume; (B) Cortical thickness; (C) Gyrification; (D) Sulcal depth; (E) Cortical complexity. The volume map is based on the Neuromorphometrics atlas; the HCP_MMP1.0 atlas was used for all surface maps. All maps were visualized using the Connectome Workbench (Marcus et al., 2011). Complete maps for all contrasts reported are available at https://neurovault.org/collections/4145/ and https://github.com/davidmoreau/VSBM.

the present data, and therefore allow detailed assessments of the association between these disorders and gray matter characteristics. Together, this set of analyses enabled precise inferences while avoiding dichotomized claims about the neuroanatomical correlates of dyslexia and dyscalculia.

Overall, our results showed no evidence for differences in gray matter volumetric and surface characteristics associated with either dyslexia, dyscalculia, or their comorbid manifestation. Together, these findings contrast with a number of results reported in the literature (Hoeft et al., 2007; Rykhlevskaia et al., 2009). For example, they are inconsistent with studies that have found significant gray matter differences associated with either dyslexia (Brambati et al., 2004; Brown et al., 2001; Dole et al., 2013; Eckert et al., 2005, 2008; Evans et al., 2014; Hoeft et al., 2007; Jednoróg et al., 2015; Krafnick et al., 2014; Kronbichler et al., 2008; Menghini et al., 2008; Silani et al., 2005; Siok et al., 2008; Steinbrink et al., 2008; Tamboer et al., 2015; Vinckenbosch et al., 2005; Xia et al., 2016) or dyscalculia (Rotzer et al., 2008; Rykhlevskaia et al., 2009). More recently however, Skeide et al. (2018) reported structural differences associated with reading and mathematical difficulties—but not either of these in isolation—in only one of the three gray matter measures they reported (cortical complexity). Although our results did not show any reliable group difference associated with this specific measure, findings from these two studies are consistent in that they indicate that gray matter differences, provided they can be probed with the parameters of typical designs (MR resolution, statistical power, etc.), are subtle.

The present study also provides further support for recent calls to move away from unconstructive labels associated with screening for these disorders, given that they are based on arbitrary thresholds that do not reflect clear underlying structural differences (Elliott and Grigorenko, 2014). More generally, our results are also in line with recent, well-powered analyses, including meta-analytic investigations, at least with respect to dyslexia (Ramus et al., 2018). Specifically, the gray matter correlates of these disorders might not be as systematic as previously thought, both in terms of volumetric and surface differences. The present findings add to this literature with an unprecedented design combining both disorders and their comorbid manifestation in a single study of adults. It is also worth noting that the push toward the publication of null findings is recent, and that a number of previous studies showing the absence of associations between behavioral difficulties and gray matter characteristics may not appear in the literature, a point we have made elsewhere (e.g., Moreau et al., 2018a).

Importantly, we are not arguing that the behavioral manifestations associated with dyslexia and dyscalculia do not originate at the neural level. As we have mentioned previously, other findings have identified structural correlates of dyslexia and dyscalculia, and our findings are by no way definitive. Rather, we emphasize that (i) these structural differences are probably more subtle than has been reported in previous

literature, (ii) that these differences might not be as consistent within groups as previous studies suggest, and (iii) that adult populations might not present the same neural correlates as those widely reported in younger populations. Note that the present study does not allow differentiating between these possibilities, nor does it necessarily provide evidence for the combination of all, or a subset, of these hypotheses. Technical improvements—both in terms of acquisition and analyses—together with transparent, theoretically motivated experiments, will enable a finer understanding of the two disorders and of their comorbidity. The Bayesian statistical maps we report in the present study are a step in this direction, as they facilitate cumulative evidence, rather than arguing for definitive answers on this specific research question. Reporting all studies—irrespective of statistical significance—with statistical maps enables mega-analyses: meta-analyses that include all data points, rather than mere study averages (Costafreda, 2009), to improve precision and prevent erroneous assumptions (e.g., Moreau and Corballis, 2018). The results of these analyses provide a more detailed picture of a field of research, one that goes beyond central tendencies across studies, to refine our understanding of important moderators.

Finally, the absence of volume and surface differences between groups might be representative of broader disparities within this field of research (Ramus et al., 2018). For example, we recently reported evidence for the absence of systematic white matter correlates of dyslexia and dyscalculia (Moreau et al., 2018b), further corroborated by an activation likelihood estimation meta-analysis of the current literature (Moreau et al., 2018a). Although still underrepresented in the literature, these findings are not isolated, with multiple research groups worldwide reporting null findings from well-designed studies with large sample sizes (see for a review Ramus et al., 2018). Together, this body of evidence suggests that neuroanatomical differences associated with dyslexia and dyscalculia might not be as reliable as previously thought, or that they may not persist into adulthood.

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Author contributions

Study design and analyses: DM, KW, AJK, KEW; Writing: DM, KW; Funding acquisition: AJK, KEW. All authors approved the final version of the manuscript.

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