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Increased structural covariance in brain regions for number processing and memory in children with developmental dyscalculia

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Abstract

Developmental dyscalculia (DD) is a developmental learning disability associated with deficits in processing numerical and mathematical information. Several studies demonstrated functional network alterations in DD. Yet, there are no studies, which examined the structural network integrity in DD. We compared whole-brain maps of volume based structural covariance between 19 (4 males) children with DD and 18 (4 males) typically developing children. We found elevated structural covariance in the DD group between the anterior intraparietal sulcus to the middle temporal and frontal gyrus ($p < 0.05$, corrected). A hippocampus subfield analysis showed higher structural covariance in the DD group for area CA3 to the parahippocampal and calcarine sulcus, angular gyrus and anterior part of the intraparietal sulcus as well as to the lingual gyrus. Lower structural covariance in this group was seen for the subiculum to orbitofrontal gyrus, anterior insula and middle frontal gyrus. In contrast, the primary motor cortex (control region) revealed no difference in structural covariance between groups. Our results extend functional magnetic resonance studies by revealing abnormal gray matter integrity in children with DD. These findings thus indicate that the pathophysiology of DD is mediated by both structural and functional abnormalities in a network involved in number processing and memory function.

KEYWORDS

brain volume, children, developmental dyscalculia, magnetic resonance imaging, maturation, number processing, structural covariance

1 | INTRODUCTION

The term "developmental dyscalculia" (DD) was first introduced in 1968 (Cohn, 1968) to describe a learning disability in basic numerical and mathematical operations, such as addition or subtraction deficits. Similar to dyslexia, DD affects about 3%–6% of the population (Badian, 1999; Gross-Tsur et al., 1996; Kosc, 1974), and recent findings suggest that slightly more females are affected than males (Fischbach et al., 2013; Schulz et al., 2018). Individuals with DD cannot master mathematics despite normal cognitive abilities in other domains. Children with DD also show a persistent inability to commit basic arithmetic information to long-term memory, to

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understand, or access magnitudes associated with number words and Arabic numerals, as well as a delay in the learning of arithmetical procedures (Butterworth et al., 2011; Geary, 1993; Jordan et al., 2003; Mazzocco et al., 2011; Rousselle & Noel, 2007). Several behavioral and neuroimaging studies examined children with DD relative to typically developing (TD) children to identify the role of confounding behavioral factors and underlying neuronal substrates associated with DD. Behavioral studies predominantly focused on tasks involving arithmetic problems and showed that children with DD rely more on counting strategies relative to TD (Geary, 2004). It is also known that people with dyscalculia often retain some residual numerical abilities. For example, in a study by Cappelletti and Price (2014) it was shown that participants accurately performed semantic and categorical color-decision tasks with numerical and non-numerical stimuli, with adults with dyscalculia performing slower than controls in the number semantic tasks only (Cappelletti & Price, 2014). MRI studies revealed that DD showed reduced gray matter (GM) volume, particularly in the inferior and superior parietal cortex as well as in the fusiform gyrus, parahippocampal gyrus, anterior temporal cortex, and frontal cortex (Cappelletti & Price, 2014; Ranpura et al., 2013; Rotzer et al., 2008; Rykhlevskaia et al., 2009). For example, the study by Ranpura et al. (2013) demonstrated abnormal GM morphometry (cortical surface area, thickness, and volume) between 11 children and adolescents with DD compared to 11 matched controls (Ranpura et al., 2013). In addition, Rotzer and colleagues used optimized (related to spatial segmentation and normalization procedures) voxel-based morphometry (VBM) and reported lower GM volume in DD in the intraparietal sulcus (IPS), anterior cingulate cortex (ACC), inferior- and middle frontal gyri but also a reduction of white matter (WM) in the hippocampus (HC) and frontal lobe (Rotzer et al., 2008). The link between IPS abnormalities and DD was also demonstrated in a single-case study, revealing that a severe head injury, including a right parietal skull fracture and right temporal hemorrhage, can lead to the presence of dyscalculia and dyslexia despite normal intellectual functioning (Levin et al., 1996). In addition, Molko and colleagues (2003) demonstrated an abnormal length, depth, and sulcal geometry of the right IPS, in Turner syndrome, a genetic disorder associated with math learning problems (Molko et al., 2003). Brain regions are linked and communicate by a complicated network formed by short fiber connections among different cortical and subcortical regions. Successful cognitive performance relies on the development and establishment of such well-organized connections in the brain. The evidence to date provides additional support that DD may be also attributable to altered connection between areas important for number processing. Results highlighted a deficit of the superior longitudinal fasciculus, a fiber tract that connects parietal, frontal, and temporal areas. In particular, the superior longitudinal fasciculus seemed to be affected in parts that are adjacent to key areas for number processing, namely the intraparietal sulcus (Kucian et al., 2013). Rykhlevskaia et al. (2009) reported long-range white matter projection fibers linking the right fusiform gyrus with temporo-parietal white matter as a specific source of vulnerability in children with DD (Rykhlevskaia et al., 2009). Functional MRI studies in children demonstrate altered fMRI signal responses in fronto-parietal regions during arithmetic tasks (Ashkenazi et al., 2012; Berteletti et al., 2014; Dinkel et al., 2013; Kaufmann et al., 2009, 2011; Kucian et al., 2006, 2011; Molko et al., 2003; Morocz et al., 2012; Mussolin et al., 2010). Recently, it could be demonstrated that children (Rosenberg-Lee et al., 2015) and adults with DD (Bulthe et al., 2018) show functional hyperconnectivity compared to controls. This neuro-functional impairment could be normalized after behavioral training (Iuculano et al., 2015; Michels et al., 2018). In fact, the IPS was hyperconnected before intervention to parietal, frontal, visual, and temporal brain regions, including the HC. This result indicates that DD is related to alterations in brain regions associated with short-term as well as long-term memory. In addition, amygdala fMRI responses (and math fear) can be normalized through cognitive tutoring (Supekar et al., 2015). In summary, these findings suggest that people with DD demonstrate functional and structural deficits in the core region for number processing in the parietal lobe, which might be seen as a direct neuronal correlate of math difficulties (for review see Kucian, 2016).

Significance

Developmental dyscalculia characterizes a severe deficit in processing numerical and mathematical information. Our study indicates that developmental dyscalculia might be mediated by abnormalities in the communication between specific brain regions. This alteration was seen as group difference (i.e., compared to typically developing children) of inter-regional correlations of gray matter volume.

Structural covariance network (SCN) analysis allows the examination of brain networks arising from inter-regional correlations of anatomical measurements, for example GM volume. There is evidence that structural covariance (SC) partially reflects structural connectivity (Gong et al., 2012). Yet, also, functional networks are partially indicated by SC (Alexander-Bloch, Giedd, et al., 2013). Thus, information about connectivity patterns gained by SC is distinct from what can be yielded by investigations on structural connectivity or functional connectivity alone (Gong et al., 2012). A crucial advantage of investigations on SCN is the fact that functional networks can be detected even if they are not activated during data acquisition (Fornito et al., 2012), because SC can detect the structural imprint left by the functional networks' repeatedly synchronized activity. Age is a significant moderator of both anatomical (Collin & van den Heuvel, 2013; Hagmann et al., 2010) as well as functional (Chan et al., 2014; Dosenbach et al., 2010) connectivity. Some of the most extensive age effects occur in GM (Giorgio et al., 2010) and it is evident that GM organization undergoes significant structural change with age (DuPre & Spreng, 2017), including synaptic proliferation, pruning, and eventual atrophy (Fjell et al., 2010; Low & Cheng, 2006). Normative GM changes do not occur simultaneously, however, and show variation across cortex (Krongold et al., 2017;

Raz et al., 2005), yielding significant differences in age-related trajectories across SCN. There has therefore been substantial interest in the impacts of age on SCN, and how these age-related trajectories may differ across neurocognitive networks. Investigations of SC trajectories have largely focused on specific developmental periods, including childhood and adolescence (Zielinski et al., 2010) or aging (Montembeault et al., 2012). These studies have suggested the occurrence of increasing long-range SC across early development (Zielinski et al., 2010) and amplified local covariance with advancing age (Montembeault et al., 2012). Importantly, examining SCN in isolated developmental periods may limit our understanding of the normative life cycle of each of these networks (DuPre & Spreng, 2017; Zuo et al., 2017). Initial work examining trajectories over multiple developmental periods has found significant internetwork variation (Hafkemeijer et al., 2014). Current findings from neuroscience clearly illustrate that number processing and calculation require the integration of different co-activated brain networks (Arsalidou & Taylor, 2011; Dehaene et al., 2004). Because basic number processing and calculation depend on a large-scale network that includes different and widespread brain areas, deficits in brain function, brain structure, interconnections, or metabolism have been reported across almost the entire network as outlined above. Moreover, SCN analyses offer the unique opportunity to analyze alterations of brain networks arising from inter-regional correlations of anatomical measurements, which are independent of actual brain activation. To date, however, it is unclear whether local covariance differs in children with DD compared to TD. Findings will provide new insights in the neuronal underpinnings of DD and go beyond the mere localization of abnormalities, but will offer information on (structural) correlations between brain regions and how such networks differ between children with and without DD.

Based on previous functional imaging studies (Iuculano et al., 2015; Michels et al., 2018), we hypothesized that DD will show abnormally high SC originating areas involved in number processing and memory, that is, the IPS and HC.

2 | METHODS

2.1 | Participants

Participants were chosen from a former study including 20 TD and 23 DD children (Kucian et al. 2018). We selected a sub-sample of this original sample to carefully balance both groups for age by narrowing the age range within each group. In detail, we excluded all children above 15 years (one TD, two DD), plus the youngest of the TD group and the two oldest of the DD group. This resulted in a final sample of 18 TD (age range: 8.7–14.5 years, mean 11.1 years) and 19 DD children (age range: 9.4–14.3 years, mean 12 years). Accordingly, groups did not differ in age ($p = 0.21$, see Table 1). This sample size is similar to previously published studies of children with math learning disability or DD (Iuculano et al., 2015; Kaufmann et al., 2009; Kucian et al., 2011; Price et al., 2007; Rosenberg-Lee et al., 2015) but see below for a power analysis.

All children underwent detailed neuropsychological testing and MRI measurement. Due to the wide age range, different age-appropriate behavioral tests had to be conducted to identify children with DD. Children with DD below the age of 12 years fulfilled all the diagnostic criteria for DD according to the Neuropsychological Test Battery for Number Processing and Calculation in Children for grades 1–4 (ZAREKI-R) (von Aster et al., 2006). Children with DD older than 12 years did all not achieve basic mathematical competencies of the fourth grade according to the standardized test battery Basic Diagnostic in Mathematics for grades 4–8 (BASIS-Math) and fulfil according to this test battery the clinical criteria for dyscalculia in line to the WHO definition (Moser Opitz et al., 2010). None of the participants had neurological or psychiatric disorders, was on medication, or met exclusion criteria for MRI such as braces. Demographic and cognitive measures of all volunteers are provided in Table 1. Ethics approval was obtained from the Cantonal ethics-commission Zurich based on guidelines from the World Medical Association's Declaration of Helsinki (WMA, http://www.wma.net/en/30publications/10policies/b3/). The parents of all participants gave written informed consent prior to the study.

2.2 | Power analysis

We performed a power analysis. In particular, we applied a multiple regression power calculation, using an effect size (f^2) of 0.4 (corresponding to a large effect size), a power of 80%, and an alpha error of 0.05. This analysis revealed that a sample size of n (total) = 38 is required to "claim" effects statistically robust. In our study, we included an n (total) = 37. Thus, we believe that any reported group differences on structural covariance are not spurious.

2.3 | Cognitive assessment

2.3.1 | Mathematical performance

Two different age-appropriate test batteries were used to assess numerical and mathematical performance in children younger or older than 12 years, respectively: Numerical achievement in children younger than 12 years was assessed using the standardized Neuropsychological Test Battery for Number Processing and Calculation in Children (ZAREKI-R) (von Aster et al., 2006). This neuropsychological battery examines basic skills in calculation and arithmetic and aims to identify and characterize the profile of mathematical abilities in children with DD from the first to fourth grade level. It is composed of 11 subtests, such as reverse counting, subtraction, number reading, dictating, visual estimation of quantities, and digit span forward and backward. Criteria for DD were met if a child's performance in the ZAREKI-R was below the 10th percentile

TABLE 1 Behavioral data of children with developmental dyscalculia (DD) and typically developing children (TD)

	Total	DD	TD	Statistics
All children				
Subjects (*N*)	37	19	18	–
Age (years)				
Range	8.7–14.5	9.4–14.3	8.7–14.5	
Mean (*SD*)	11.5 (2.0)	12.0 (1.7)	11.1 (2.2)	0.207[U]
Gender (male/female)	8/29	4/15	4/14	1.000[F]
Handedness (right/ambidextrous/left)	31/3/3	16/1/2	15/2/1	0.710[L]
Number line performance[a] (%) *mean* (*SD*)	6.1 (2.5)	6.4 (2.9)	5.7 (2.0)	0.390
Addition[b] (%) *median* (*IQR*)	95 (7.5)	90 (15)	95 (15)	**0.00009[U]**
Subtraction[b] (%) *median* (*IQR*)	85 (23.8)	75 (25)	95 (9.4)	**0.00003[U]**
Arithmetic summary score (mean % of correctly solved addition and subtraction tasks)	85 (14.8)	77 (15.8)	95 (4.9)	0.00012
Intelligence[c] (IQ) *median* (*IQR*)	105 (16.9)	95.8 (10.8)	110.8 (7.2)	**0.0002 U**
Working memory[d] (total score) *mean* (*SD*)	5.4 (1.9)	5.2 (1.9)	5.7 (2.0)	0.380
Children < 12 years				
Subjects (*N*)	20	8	12	–
Mathematical performance[e] (PR) *median* (*IQR*)	40 (51)	6 (6.0)	55 (37.3)	**0.001[U]**
Arithmetical fluency[f] (*t*) *mean* (*SD*)	47.2 (8.2)	41 (6.4)	51.9 (6.4)	**0.002**
Reading[g] (*t*) *median* (*IQR*)	48.5 (9.0)	43.0 (4.3)	50.5 (4.5)	**0.018[U]**
Children > 12 years				
Subjects (*N*)	17	11	6	–
Mathematical performance[e] (total score) *mean* (*SD*)	58.4 (14.9)	50 (11.2)	73.8 (3.8)	**0.000**
Magnitude comparison[h] (*t*) *median* (*IQR*)	43 (9.0)	41 (8.0)	51 (7.8)	**0.001[U]**
Reading children[h] (PR) *mean* (*SD*)	20.7 (20.0)	24.2 (24.5)	15 (7.6)	0.291

Notes: Individual groups were first tested for normal distribution by the Kolmogorov–Smirnov test. For normal distributed data, mean, standard deviation (*SD*), and *p* values are indicated based on two-sample *t* tests. If in one or both groups the assumption of normality was violated, median and interquartile range (IQR) are listed and a Mann–Whitney *U* test was performed (indicated by U). For nominal data, the Fisher's exact test (indicated by F) was performed for gender and the likelihood ratio (indicated by L) for handedness.

$p = 0.000154$ indicates bold values.

[a]Number line performance of children younger than 12 years is based on the percentage error between indicated and correct location of an Arabic digit, the solution of an addition or subtraction problem, and estimated number of dots on a paper-and-pencil number line task 0–100 ($N = 20$, 8 DD and 12 TD). For children older than 12 number line performance is measured by a computerized number line task 0–100 on which 20 visually presented Arabic digits had to be located by mouse click ($N = 17$, 11 DD and 6 TD).

[b]Percentage of correctly solved addition and subtraction problems, respectively, in the number line task.

[c]Mean IQ of children younger than 12 years is based on the mean of the subtests similarities, block design, digit span, picture concepts, vocabulary, and arithmetic of the WISC-IV and of children older than 12 years is based on the mean of the subtests similarities, block design, digit span, and matrix reasoning of the WISC-IV.

[d]Working memory capacity is based on the number of correctly repeated blocks of the CORSI-Block Suppression test.

[e]Mathematical performance of children younger than 12 years ($N = 19$, 7 DD and 12 TD) is based on the total reached percentile rank (PR) in the ZAREKI-R test battery. Mathematical performance of children older than 12 years ($N = 17$, 11 DD and 6 TD) is assessed by the total score of the BASIS-Math test battery (maximum is 83 points, whereas scores below 67 indicate that basic mathematical competencies of the fourth grade are not achieved).

[f]Arithmetical fluency of children younger than 12 years is based on the mean of correctly solved addition, subtraction, multiplication, and division problems within 2 min each of the HRT test ($N = 20$, 8 DD and 12 TD).

[g]Reading skills of children younger than 12 years ($N = 20$, 8 DD and 12 TD) are based on the subtest reading of the BUEGA test battery (*t*-value) and of children older than 12 years ($N = 16$, 10 MD and 6 TD) on the mean percentile rank (PR) of correctly read words and pseudo-words of the SLRT-II.

[h]Magnitude comparison skills of children older than 12 years ($N = 15$, 9 DD and 6 TD) are based on the mean *t*-values of the subtest quantity of the KFT 4–8+R test battery.

on average in three subtests or in the total reached percentile rank. Numerical abilities of children older than 12 years were assessed using the German test battery Basic Diagnosis in Mathematics Education for Grades 4–8 (BASIS-MATH 4–8) (Moser Opitz et al., 2010). The test battery measures different numerical abilities at three difficulty levels such as counting, arithmetic, decimal system, text problems, and part–whole relationships. The BASIS-MATH test battery is a criterion-referenced test conceptualized to identify children with deficits in basic mathematical concepts from grades 4 to 8. In accordance to the WHO definition of developmental dyscalculia, the mathematical performance is measured by the criterion "not reaching mastery of the basic mathematical concepts." Criteria for DD are met if the performance falls under a total threshold score of 67 points (out of a total of 83 points), which indicates that mastery of basic mathematical concepts has not been reached. The BASIS-MATH is scaled according to the one-dimensional Rasch model (Rasch, 1980). The normative sample consists of 692 Swiss and German children from grades 4 to 8. The test has a high sensitivity (92%) and reliability (internal consistency Cronbach's alpha = 0.92).

2.3.2 | Number line performance

The spatial representation of numbers was measured by a paper-and-pencil number line task in children younger than 12 years a computerized version for children older than 12 years: Children below 12 years had to indicate with a pencil on a left-to-right oriented number line from 0 to 100 the location of 20 Arabic digits, results of 20 additions and 20 subtractions, or the estimated number of 10 different dot arrays. The error rate of the paper-and-pencil number line task was evaluated by measuring the distance in percent (% distance) relative to the position of the correct number for each trial. Mean percentage distance was then calculated over all trials (Arabic digits, additions, subtractions, dots), but only correctly calculated addition and subtraction problems were included. A detailed description of the task is described in a previous publication of our group (Kucian et al., 2011a). Children older than 12 years solved a computerized number line task 0–100 including 20 Arabic digits that had to be located on the number line by mouse click (Käser et al., 2013). Again, the mean distance between the correct and indicated location in percent was calculated.

2.3.3 | Arithmetic

Addition and Subtraction skills were measured in all children by the percentage of correctly solved addition or subtraction problems that had to be calculated in the number line task described above (Käser et al., 2013; Kucian et al., 2011a). Arithmetic fluency was additionally evaluated in children younger than 12 years using the addition, subtraction, multiplication, and division subtests of the "Heidelberger Rechentest (HRT)" (Haffner et al., 2005). In this test, a list of 40 addition/subtraction/multiplication/division tasks is presented to the child and he/she is asked to solve as many problems as possible within 2 min. Hence, in contrast to the assessment of addition and subtraction skills in the number line task, the present test puts children under time pressure. We also computed a summary score (mean % of correctly solved addition and subtraction tasks) for both groups.

2.3.4 | Magnitude comparison

Magnitude comparison skills of children older than 12 years were assessed by the subtest Quantity Comparison of the standardized Cognitive Abilities Test (KFT 4–8+R) (Heller & Perleth, 2000). Adolescents had 10 min time to solve as many magnitude comparison problems as possible of increasing difficulty of totally 25 different trials. Always two magnitudes had to be compared and decided which is the larger or if both are equal. Trials include non-symbolic comparison of number of items (e.g., dots), non-symbolic and symbolic calculation problems, different unities (e.g., time, money, weight, and liters), surface areas, and fractions.

2.3.5 | Intelligence

Estimated intelligence was measured by the mean of different subtest of the standardized test battery Wechsler Intelligence Scale for Children (WISC-IV) (Petermann & Petermann, 2007). Mean IQ of children younger than 12 years is based on four verbal (vocabulary, arithmetic, similarities, and digit span) and two performance subtests (picture arrangement and block design) of the WISC-IV. Mean IQ of children older than 12 years was assessed by the mean of the subtests similarities, block design, digit span, and matrix reasoning of the WISC-IV.

2.3.6 | Working memory

Spatial working memory was assessed by the Block Suppression Test (Beblo et al., 2004). This test is based on the CORSI-Block Tapping test (Schellig, 1997) and requires the subject to reproduce every second block in a given sequence of touched cubes on a wooden board as the examiner demonstrated. While the sequences gradually increase in length, the number of cubes last tapped in two consecutively correct sequences is defined as the maximum spatial working memory span.

2.3.7 | Reading skills

Reading skills were measured by standardized age-appropriate German reading tests. Reading in children younger than 12 years was assessed by the subtest reading of the test battery "Basisdiagnostik Umschriebener Entwicklungsstörungen im Grundschulalter" (BUEGA) (Esser et al., 2008). The subtest reading consists of two word lists (list 1 = 32 short words; list 2 = 24 longer words) that children had to read aloud while number of errors and time was measured and influenced the reached *t*-value. Reading performance in children older than 12 years was estimated by the reading task from the standardized Salzburg Reading and Orthography Test (SLRT-II) (Moll & Landerl, 2010), which assesses word and pseudo-word reading fluency of a 1-min-reading task. Because of lacking test norms in grades 7 and

8, values were obtained by interpolating the norms from the test manual (grade 6) and from Kronschnabel et al. (2013) (grade 9).

2.3.8 | Handedness

Handedness was determined by the Edinburgh Handedness Inventory (Oldfield, 1971).

2.4 | Behavioral data analysis

Behavioral data were analyzed by IBM SPSS Statistics 22 Version 2. The Kolmogorov–Smirnov test was used to assess normal distribution. For normal distributed data, mean and standard deviations are indicated and group differences were calculated by two-sample *t* tests. If in one or both groups the assumption of normality was violated, median and interquartile range (IQR) are listed and a Mann–Whitney *U* test was performed to compare groups. Nominal data input (gender, handedness) was compared between DD and TD by means of Fisher's exact test for gender, and by likelihood ratio for handedness.

2.5 | MR data acquisition

MRI data were acquired on a 3T General Electric Discovery 750 Scanner (GE Medical Systems, USA) using an eight-channel head coil. Three-dimensional anatomical images of the entire brain were obtained parallel to the anterior–posterior commissure line with a T1-weighted structural image using a spoiled gradient echo sequence (3D SPGR). Imaging parameters: number of slices = 172, slice thickness = 1 mm, matrix size = 256 × 256, field of view = 256 mm, FA = 8°, TE = 3 ms (n = 20) or 5 ms (n = 17), TR = 10 ms (n = 20) or 11 ms (n = 17), scan duration = 3 min 52 s. Cushions were placed around participants' heads to minimize head movement. Differences in TE and TR were due to a scanner software release upgrade, but these differences did not affect the image quality (see Results section).

2.6 | MR data pre-processing

Anatomical images were processed by FreeSurfer (v5.3.0, http://surfer.nmr.mgh.harvard.edu), running on a Linux operating system. Default settings were used to run the standard automated reconstruction pipeline "recon-all" (Dale et al., 1999; Fischl et al., 1999, 2002, 2004). Main steps of the pipeline include skull stripping (Segonne et al., 2004), affine registration with Talairach atlas (Talairach & Tournoux, 1988), signal intensity normalization (Sled et al., 1998), voxel-based GM and WM segmentation, volume calculation, inflation, and registration to a spherical surface atlas, allowing parcellation and labeling of subcortical (Fischl et al., 2002) and cortical regions (Destrieux et al., 2010). The quality of segmentation into GM and WM was visually inspected and corrected where necessary by the recommended instructions on the FreeSurfer Wiki webpage (https://surfer.nmr.mgh.harvard.edu/fswiki) using the integrated tool TKMEDIT. Manual correction was performed in three steps: (a) checking Talairach transformation, (b) GM corrections in the brain mask, and (c) WM corrections in the WM mask. Thus, before starting the "recon-all" pipeline, first Talairach alignment was adjusted. The second step included deletion of obvious non-gray matter classified as GM, for example, from a bad skull stripping, as well as, adding control points in the WM where WM was included into the GM mask. After these corrections, a part of the recon-all pipeline was rerun (autorecon2-cp). Third, obvious non-WM voxels classified as WM were deleted from the WM mask and lateral ventricles were filled where the automatic pipeline did not fill them entirely. Next, part of recon-all workflow was rerun (autorecon2-wm). The generated models of the cortical surfaces enable to calculate the cortical volume, that is, the product of the cortical thickness and the surface area, at each vertex of the whole cortex. "Vertex" denotes a "point" on the surface commonly used in 2D surface-based morphometry representing the smallest entity in this analysis, comparable to a "voxel" when applying a 3D voxel-based morphometric approach. The "volume of a vertex" is referring to the volume of the region around one vertex, specifically the product of the thickness and the surface surrounding this particular vertex (i.e., the area comprising one third of the area of all faces (triangles) meeting at this vertex) (Winkler et al., 2012).

2.7 | Region of interest (ROI) analysis

Corresponding to our hypothesis, we chose the left and right IPS and hippocampus as seed ROIs. Here we subdivided the IPS into an anterior and posterior ROI, allowing a locally specific analysis of the IPS. We performed this analysis also because it has been shown that the IPS is organizing visual spatial attention (Grefkes & Fink, 2005), which is known to be disturbed in DD (Bugden & Ansari, 2016; Szucs et al., 2013). Furthermore, the IPS consists of different subregions (Choi et al., 2006; Scheperjans et al., 2008), and thus, we were interested if SC was different with respect to anterior and posterior sub-regions. Hippocampal subfields were segmented using the FreeSurfer v6.0 automated tool (which is not available in FreeSurfer v5.3), which shows a high test–retest reliability, as recently demonstrated (Brown et al., 2020). Based on this reference, we only focused on volumetric subfields with a high cross-sectional and longitudinal test–retest reliability, that is, subfields with a mean intra-class correlation values > 0.77 (areas CA1 and CA3 as well as the subiculum). We also examined group differences in two cortical "control" ROIs, that is, the left and right primary motor cortex (M1), as no previous study revealed any structural abnormality in this region in DD. The volumes of the motor cortices were extracted from the Destrieux parcellation atlas (Destrieux et al., 2010) implemented in FreeSurfer.

2.8 | Statistical analysis

Analyses on the morphometric measures (i.e., cortical volume) were conducted for both hemispheres separately using FreeSurfer software 5.3.0 (http://surfer.nmr.mgh.harvard.edu). We first tested (*t* test within the framework of a general linear model analysis) for differences in cortical volume between groups controlling for age. These analyses were conducted vertex-wise across the whole cortex and corrected for multiple comparisons using Monte Carlo simulations with 10,000 iterations.

To assess differences in seed-based SC, we adopted a linear model at each vertex of the cortex comparing the slopes between groups, that is, "seed × group interaction." This interaction is also visualized in subsequent plots to indicate the sign of the group-specific slopes. The model comprised the group, age, IQ, reading ability, and the volume of the seed ROI residuals (corrected for age, IQ, reading ability) as independent variables and the volume of each tested vertex as the dependent variable:

$$\begin{aligned}\text{Volume (vertex at target region)} &= \text{intercept} + \beta 1(\text{group}) \\ &+ \beta 2(\text{age}) + \beta 3(\text{IQ}) + \beta 4(\text{reading ability}) \\ &+ \beta 5(\text{mean - centred seed volume residuals} \\ &(\text{corrected for age, IQ and reading ability}))\end{aligned}$$

All presented results were thresholded at $p < 0.05$ (two-tailed), corrected for age, IQ, and reading ability. We corrected for age, despite non-significant between group differences in age, because the age range within each group was relatively large (TD: 8.7–14.5 years; DD 9.4–14.3 years). In addition, we controlled for reading ability and IQ scores in all SC and correlation analyses in order to show the specificity of the results. We did not compare groups by sex, as the number of males and females was too low (<10) and unbalanced (see Table 1) to conduct a meaningful statistical comparison. Monte Carlo simulations with 10,000 iterations and a cluster-wise threshold of $p < 0.05$ were conducted in order to correct for multiple comparisons. We displayed the results on the average brain of the participants in our study sample.

For ROIs showing significant group differences, we performed a seed × summary score interaction term (the summary score corresponds to the mean percentage of correctly solved addition and subtraction tasks, see Table 1) to examine the interaction between SC and global mathematical skills across both groups. The following model was used to test the seed × summary score interaction:

$$\begin{aligned}\text{Volume (vertex at target region)} &= \text{intercept} + \beta 1(\text{group}) \\ &+ \beta 2(\text{age}) + \beta 3(\text{IQ}) + \beta 4(\text{reading ability}) + \beta 5(\text{seed residuals}) \\ &+ \beta 6(\text{summary score}) + \beta 7(\text{seed} \times \text{summary score}).\end{aligned}$$

Values of seed residuals, summary score, and interaction term were mean centered to minimize the multi-collinearity between these variables. In brain regions where the slope significantly differed from zero, the SC between the tested vertex and the interaction term are statistically associated. The presented results were thresholded at $p < 0.05$ (two-tailed), corrected for age, IQ, reading ability, the seed volume, and the summary score.

To confirm that any group difference was not caused by outliers, we show boxplots (Figure S1) per group for each ROI, illustrating the distribution of gray matter volume and occurrence of outliers. Values more than 1.5 times interquartile range greater than the 75th or lower than the 25th percentile, respectively, were defined as outliers. Furthermore, scatterplots with group-wise slopes between seed region and associated region were inspected (Figure S2). Furthermore, we tested for homoscedasticity of error variance across all subjects using a test for non-constant error variance and provide residual plots (Figure S3). Regression analyses with heteroscedastic error variance were remodeled after Box–Cox transforming the dependent variable.

3 | RESULTS

3.1 | Behavioral results

As expected, children with DD performed worse in tests measuring numerical competence in a wide range of skills from basic numerical abilities (magnitude comparison, counting, transcoding between magnitudes and Arabic digits etc.) to higher mathematical operations (e.g., arithmetic, word problems; see Table 1). Intelligence was in the normal range for all children, however, lower in children with DD. IQ measures are known not to be fully independent from measures of math ability, and the present sample therefore reflects the cognitive pattern typically observed in DD. Moreover, dyscalculic children below 12 years were less fluent readers compared to typically achieving children below 12. Taken together, differences in IQ and other domains, such as reading/writing or attention can be expected in a group of children with DD. In line, we found slightly lower levels compared to controls, but still in the normal range. Therefore, we controlled statistically in our subsequent analyses for IQ and reading. We based the diagnosis of DD on the ICD-10 F.81.2 and the S3 guidelines [1], which require mathematical performance below the age-appropriate range and IQ in the normal range. All children with DD clearly fulfilled these diagnostic criteria.

3.2 | MRI results

Performance of the Fisher's exact Test revealed that there was no significant difference in the distribution of TR/TE between groups (p value (two-sided) = 0.191). Thus, all participants were included in the subsequent analyses.

3.3 | Cortical volume

We did not observe significant group differences using a threshold of $p < 0.05$ (corrected; unpaired two-sample t test).

3.4 | SC results

Comparing groups (controlling for age, IQ, and reading ability), we observed increased SC in the DD group when using the anterior IPS and CA3 of the HC as a seed ROI (Figure 1, Table 2) and decreased SC in DD for the subiculum. Specifically, for the left anterior IPS, higher SC was seen in the DD group to the left middle temporal gyrus (MTG) ($p_{max} < 3.206e{-}04$, cluster-wise p value $p_{cluster} = 0.034$, corrected). This cluster extended to the superior temporal, angular gyrus, and anterior occipital sulcus.

In addition, increased SC was seen between left anterior IPS and the right rostral middle frontal gyrus (DLPFC) ($p_{max} < 3.214e{-}05$, $p_{cluster} = 0.019$, corrected) as well as the right MTG extending to the superior temporal gyrus (STG) ($p_{max} < 4.276e{-}04$, $p_{cluster} = 0.041$, corrected). No group differences were seen using the right anterior IPS or any of the posterior IPS ROIs as seed region. The right area

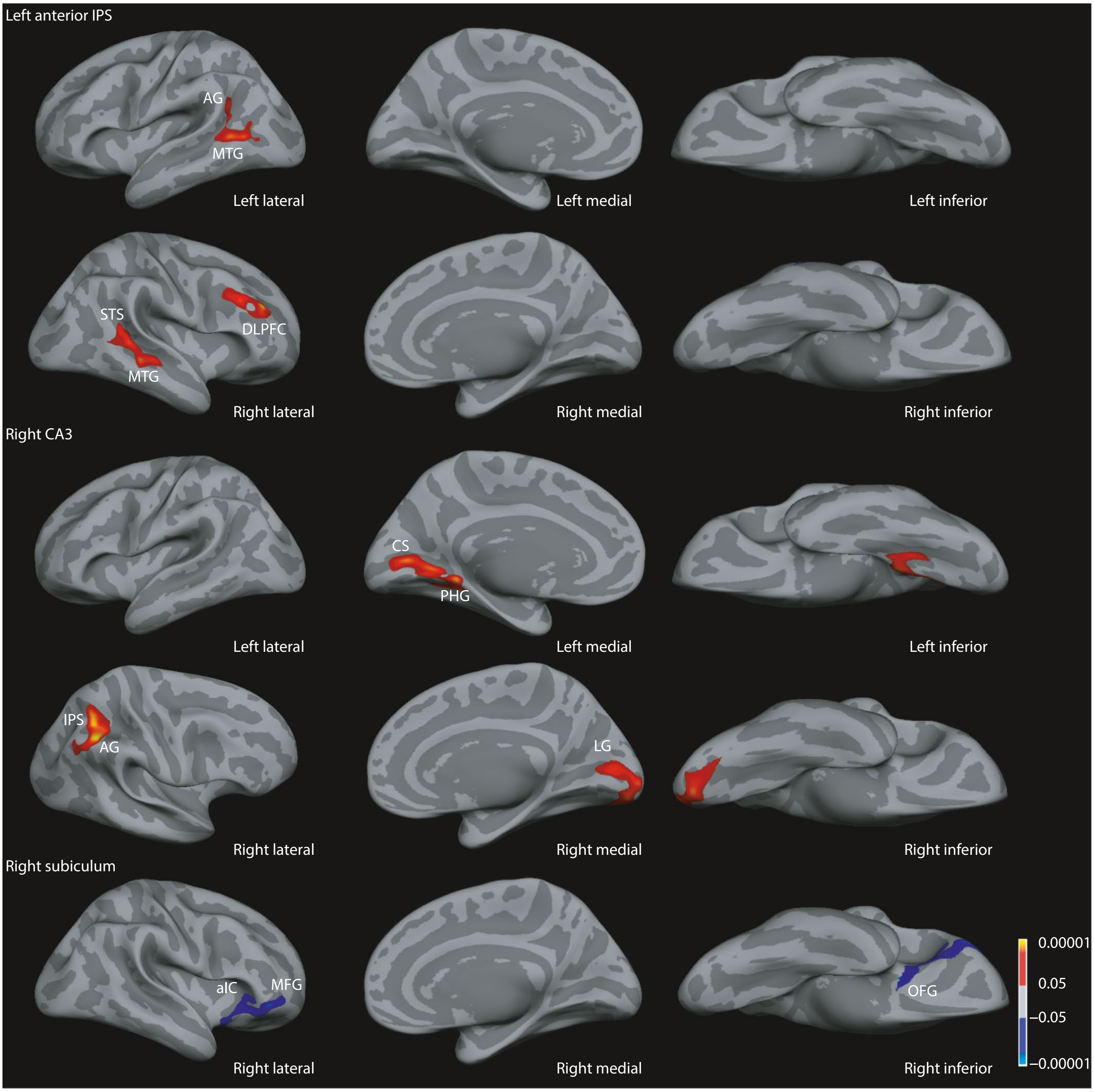

FIGURE 1 Results of the SC analyses for the left anterior IPS and right HC. Increased and decreased SC was seen in the DD compared to TD. Red highlights indicate increased SC in DD while blue represents decreased SC in DD compared to TD. All results are shown at $p < 0.05$ (corrected and controlled for age, IQ, and reading ability). For a full list of regions showing altered SC, we refer to Table 2

TABLE 2 Group differences in SC comparing TD and DD for significant ROIs. (a) DD > TD, (b) TD > DD

Left anterior IPS: DD > TD (*p* < 0.05, corrected and controlled for age, IQ, and reading ability)							
# Cluster no	**Max (−log10 (*p* value))**	**Size (mm²)**	**MNI X**	**MNI Y**	**MNI Z**	**# vertices**	**Anatomical label**
Left hemisphere							
1	−3.5	835.8	−55.3	−57.3	6.3	1,475	Middle temporal gyrus
			−51.5	−51.3	4.2		Superior temporal gyrus
			−52.7	−53.9	24.1		Angular gyrus
			−42.7	−70.3	3.8		Anterior occipital sulcus
Right hemisphere							
1	−4.5	946.4	35.9	37.8	26.2	1,463	Rostral middle frontal gyrus (dorso-lateral prefrontal cortex)
2	−3.4	860.7	57.1	−32.8	−6.6	1,887	Middle temporal gyrus
			43.6	−41.0	3.4		Superior temporal sulcus
Right CA3: DD > TD (*p* < 0.05, corrected and controlled for age, IQ, and reading ability)							
# Cluster no	**Max**	**Size (mm²)**	**MNI X**	**MNI Y**	**MNI Z**	**# vertices**	**Anatomical label**
Left hemisphere							
1	−3.8	1,397.9	−16.7	−43.7	−7	2,580	Parahippocampal gyrus
			−17.3	−80.0	5.8		Calcarine sulcus
Right hemisphere							
1	−5.5	1,253.9	44.4	−51.1	48.6	2,590	Angular gyrus
			30.0	−53.7	41.6		Anterior intraparietal sulcus
2	−3.3	1,532.7	14.3	−91.3	−8.0	1,868	Lingual gyrus
Right subiculum: TD > DD (*p* < 0.05, corrected and controlled for age, IQ, and reading ability)							
# Cluster no	**Max**	**Size (mm²)**	**MNI X**	**MNI Y**	**MNI Z**	**# vertices**	**Anatomical label**
Right hemisphere							
1	3.1	1,043.5	25.3	8.5	−15.1	1,691	Orbitofrontal gyrus
			32.5	26.9	−6.6		Anterior insular cortex
			45.5	39.1	−6.9		Lateral orbital sulcus
			40.2	49.6	−1.2		Middle frontal gyrus

Note: All results are shown at $p < 0.05$ (corrected and controlled for age, IQ, and reading ability).

CA3 demonstrated higher SC in the DD group to the left parahippocampal gyrus extending to the calcarine sulcus ($p_{max} < 1.718e{-}04$, $p_{cluster} = 0.001$, corrected) and to the right angular gyrus, extending to the anterior IPS ($p_{max} < 2.825e{-}06$, $p_{cluster} = 0.003$, corrected) and to the lingual gyrus ($p_{max} < 4.955e{-}04$, $p_{cluster} = 0.001$, corrected).

In contrast, the right subiculum revealed lower SC in DD to the border of the right orbitofrontal cortex ($p_{max} < 0.001$, $p_{cluster} = 0.010$, corrected). This cluster was extending to the anterior insula, lateral orbitofrontal cortex, and middle frontal gyrus.

Among all between-group differences, we observed a seed × summary score interaction between the right subiculum and right pericalcarine sulcus ($p_{max} = 0.002$, $p_{cluster} = 0.041$, corrected). However, inspection of the data point distribution (scatterplot, not shown) indicated that this interaction was probably caused by three outliers and we thus refrain to interpret this finding. For the control ROIs, that is, the left and right M1, no significant group differences in SC were detected.

Boxplots of seed ROIs are shown in Figure S1. The boxplots yielded that only one ROI (i.e., right CA3 but not the IPS or subiculum) contains an outlier. Figure S2 shows scatterplots, illustrating the group-specific slopes of each ROI and connected region(s). Regarding the CA3 ROI, SC appeared to be biased by the individual outlier seen in the boxplot presented in Figure S1. However, after excluding the outlier, the results did not differ (we thus report the analysis including the single outlier data point). The tests for homoscedasticity of error variance (Figure S3) revealed that the data of two models were not homoscedastic: First, the regression with the left anterior IPS ROI as predictor and the right inferior parietal region as a dependent variable and second, the regression model comprising the right CA3 ROI as a predictor and the right MTG as the dependent variable. Therefore, we Box–Cox transformed the values of the dependent variables. The models with the transformed data did still show different slopes (we thus report the original results without data point transformations).

4 | DISCUSSION

The main aim of the study was to examine SC in DD and TD children. After controlling for age, IQ, and reading ability, we found predominately stronger SC in DD of the anterior IPS and area CA3 seed ROIs. In contrast, the M1 control region did not show group differences.

The source of GM shared covariance patterns is unclear and has been hypothesized to reflect both genetic and plastic influences, including maturational timing (Alexander-Bloch, Raznahan, et al., 2013). In addition, SC analysis can identify the structural imprint left by the functional networks' repeatedly synchronized activity. Increased SC can also be caused by concurrent GM reductions (Alexander-Bloch, Giedd, et al., 2013) due to the fact that synchronized volume changes will increase the correlation of the respective volumes. As reduced GM volume was found in parietal, temporal, parahippocampal, and frontal regions (Cappelletti & Price, 2014; Rotzer et al., 2008; Rykhlevskaia et al., 2009), this could be a reasonable explanation for increased SC we found in these regions. However, our morphometric analyses did not reveal reduced GM in DD. Rather our results indicate the increased SC in DD could reflect abnormally high synchronization of GM volume.

Additionally, the fact that our discovery of increased SC in DD compared to TD is in line with reported evidence of altered intrinsic functional connectivity in DD (Jolles et al., 2016; Michels et al., 2018; Rosenberg-Lee et al., 2015) led to the assumption that altered SC might arise from aberrant functional connectivity: Functional hyperconnectivity of the IPS to prefrontal brain regions has been reported in two recent functional connectivity studies comparing children with DD to TD (Rosenberg-Lee et al., 2015) and/or math difficulties (Qin et al., 2016). This abnormal connectivity most likely reflects a cognitive impairment as behavioral intervention (Kucian et al., 2011b; Michels et al., 2018) and cognitive tutoring (Iuculano et al., 2015) led to neuroplastic effects, remediate brain function, and cognitive function in children with math learning disability. In addition, in children diagnosed with fetal alcohol syndrome the performance of simple number processing tasks resulted in broad range activations not only in the IPS and prefrontal cortex but also in additional parietal pathways, involving the angular gyrus and posterior cingulate/precuneus, which may entail verbally mediated recitation of numbers and/or subtraction to assess relative numerical distances (Meintjes et al., 2010). These observations underline the importance of the parietal cortex in number line processing but also demonstrate that number line processing does not only require the involvement of the IPS but also frontal brain regions, especially in the presence of clinical symptoms (for a review see Serra-Grabulosa et al., 2010).

Analogous to functional hyper-connectivity, we found increased SC between the left anterior IPS in children with DD and temporal as well as frontal brain regions, specifically bilateral MTG extending to the STG, angular gyrus and occipital sulcus and right rostral middle frontal gyrus (DLPFC). Rosenberg-Lee et al. (2015) reported functional hyper-connectivity while solving addition and subtraction problems between IPS and, among other regions, angular and right middle frontal gyrus. Furthermore, the direction of the increased connectivity was the same as in our analysis: Hyper-connectivity was the result of a positive correlation, rather than a negative (anti-correlation), the increased SC was seen as a positive slope in DD (Figure S2). The angular gyrus is—besides other function—involved in episodic and semantic memory, and is important for encoding and retrieval of math facts (Grabner et al., 2009; Qin et al., 2014). It appears that the left angular gyrus activation is modulated by inter-individual differences in arithmetic performance (for a review see Zamarian et al. (2009)).

Jolles and colleagues demonstrated predominantly hyperconnectivity in children with math difficulties of the bilateral IPS to the angular and supramarginal gyri and parietal brain regions but also to frontal and visual, using resting state fMRI (Jolles et al., 2016). In normally developing children and adults, the gain of arithmetic competence is reflected by a shift of activation from frontal brain areas to more parietal areas relevant for arithmetic processing (Kucian et al., 2008), which probably takes place in the age range from 9 to 13 years. Yet, our data suggest that increased SC between the left anterior IPS and the rostral middle frontal gyrus in DD could reflect the lack of this shift.

In addition, we observed altered SC between subfields of the HC and the angular gyrus, anterior IPS, lingual gyrus, as well as the parahippocampal and calcarine cortex (seed area CA3) and orbitofrontal, insular and middle frontal regions (seed right subiculum). The subiculum is the major output region of the HC and projects to several cortical and subcortical regions such as the entorhinal cortex, hypothalamus, perirhinal cortex, prefrontal cortex and parietal cortex, qualifying the subiculum as the major output structure of the HC (O'Mara et al., 2001; Witter & Groenewegen, 1990). It plays a role in spatial navigation, mnemonic processing, and control of the response to emotional stress. In fact, it has been shown that DD demonstrate problems with spatial navigation and spatial processing (e.g., visual crowing: identifying objects when surrounded by other simular items) related to memory and inhibition (Castaldi et al., 2020; Szucs et al., 2013), which appear to be still present after numerosity-based arithmetic training (Cheng et al., 2020). From our results and based on the recorded behavioral data, we cannot comment on why the subiculum shows lower SC in DD. This findings could be a result of disturbed efferent output to cortical and subcortical regions or to impaired input of the CA3 to the CA1 area or from CA1 to the subiculum. To examine this observation in more detail behavioral tests related to spatial navigation, mnemonic processing and control of the response to emotional stress would be beneficial to examine its interaction to SC in TD and DD. However, the observed increased SC between area CA3 and anterior IPS could rely on the tight interaction between these regions, for example, for the formation of a dynamic representation of spatial location (Whitlock et al., 2008) and for memorizing objects in space, which could potentially also be numbers on an internal representation (on a number line).

Our findings of altered HC-related structural integrity extend a previous study (Rotzer et al., 2008) that reported WM reductions in the right HC, as it is not only the volume, which is altered, but also the structural integrity of the HC. Yet, in contrast to replicable findings such as functional hyperconnectivity and GM volume reductions of the IPS, the evidence for WM alterations in DD is still a matter of debate. Moreau and colleagues compared individuals with dyslexia, dyscalculia, both disorders and controls, using diffusion tensor imaging (DTI). The authors focused on the corona radiata and the arcuate fasciculus, two tracts associated with reading and mathematics in a number of previous studies, and could not find differences between groups for these particular tracts (Moreau et al., 2018). Only two DTI studies have examined microstructural differences in white matter between children with DD and typically achieving children (Kucian et al., 2013; Rykhlevskaia et al., 2009). The results accentuate the evidence of impaired fiber tracts connecting different brain areas of the fronto-parietal network recognized to be responsible for number processing and calculation. Rykhlevskaia et al. (2009) reported long-range WM projection fibers linking the (right) fusiform gyrus with temporo-parietal WM as a specific source of vulnerability in children with DD. However, the authors performed specific analyses of fiber tracts only in regions that showed reduced WM volume in a prior analysis of brain structure. In summary, these studies indicate the importance of deficient fiber connections as “a” neurological correlate of DD, along with additional fiber tracts that might be affected. Kucian et al. (2013) examined the WM integrity on a whole-brain analysis of children with DD (Kucian et al., 2013). The authors found a deficit of the superior longitudinal fasciculus, a fiber tract connecting frontal, temporal and parietal brain areas. In particular, the superior longitudinal fasciculus seemed to be affected in parts that are adjacent to key areas for number processing, namely the IPS. The authors concluded that the development of axonal coherence and/or myelination projecting to/from the parietal lobe could be impaired or delayed in dyscalculia, leading to the possibility that DD might be seen as a dysconnection syndrome. In a similar vein, Ranpura et al. (2013) found increased WM in the frontal lobe in healthy controls but not in DDs, indicating that the frontal lobes may be connecting increasingly to parietal areas in the fronto-parietal network known to be involved in arithmetic (Dehaene et al., 2004; Zago et al., 2001). This could suggest that myelination processes are disrupted to some degree in children with DD, which might be seen in DD as abnormal SC between the IPS and, for example, frontal brain regions. In summary, our novel findings additionally suggest that DD is partially reflected by abnormal GM volume integrity between parietal, temporal, frontal, visual, and parietal brain regions.

In contrast to the IPS and HC, the M1 demonstrated no group differences between DD and TD, suggesting that this region does not show structural impairment in DD.

The studies by Ranpura et al. (2013) and Winkler et al. (2010) suggested that surface area is—from an evolutionary point of view—a better measure of functional capacity and predictor of functional status, compared to cortical thickness (Ranpura et al., 2013; Winkler et al., 2010). The latter appears to be rather an index of developmental integrity and lifetime health (Zarei et al., 2013) and both cortical thickness and surface area are under independent genetic control (Winkler et al., 2010). In contrast, cortical volume has some independence from both of these measures. We restricted our analysis to cortical volume as we could only extract the volume of hippocampal subfields but not thickness or surface area. Hence, a correlation between (hippocampal) value and (whole-brain) thickness would not be meaningful. Future studies should examine the change in SC between cortical areas in subjects with DD (compared to matched controls) over time using all three metrics: volume, cortical thickness, and surface area. By this, it would be possible to test for the sensitivity of SC capturing developmental trajectories related to functional status and structural brain integrity.

5 | LIMITATIONS

As this study only considers cross-sectional data, we could not test if alterations in SC can be normalized, for example, by behavioral intervention, or change during development into adulthood. Another study limitation is the inability for to study sex differences where they may exist, due to the low and unequal number of males and females in each group (TD and DD, respectively). Despite the reported power analysis, the sample remains small and the large effect size needs to be validated in a larger sample.

6 | CONCLUSION

In conclusion, our findings indicate that children with DD demonstrate elevated SC in GM. Particularly, children with DD showed increased volume correlations in a brain regions critically involved in number processing and memory function.

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

All authors have contributed and have approved the final manuscript. L.M. contributed to formal analysis and writing of the original draft as well as reviewing and editing of the draft. R.B. contributed to formal analysis and validation of results. In addition, he was involved with reviewing and editing of the draft. K.K. contributed to study conceptualization, data curation, formal analysis, investigation, project administration, resources, supervision and paper reviewing and editing.

ETHICAL STATEMENT

Parents gave informed consent and children received a voucher for their participation. The study was approved by the local ethics committee (Cantonal ethics commission Zurich) based on guidelines from the World Medical Association's Declaration of Helsinki (WMA 2002). All authors have read and agreed to the content of the manuscript.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/jnr.24998.

DATA AVAILABILITY STATEMENT

According to Swiss law, the researchers must assess whether the use of the data is within the primary scope of the informed consent. This also applies to coded data sets, which therefore cannot simply be made publicly available. Thus, subject level data are only available upon request and after the researchers have reviewed the purpose of the request. Requests about such data should be made directly to Dr. Lars Michels [Department of Neuroradiology, University Hospital Zurich, lars.michels@usz.ch], who will evaluate such requests.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

FIGURE S1 Distribution of grey matter volumes per group. The boxplots of the seed ROIs yielded that only one ROI (i.e., right CA3) contains an outlier. DD, developmental dyscalculia; ROIs, region of interests; TD, typically developing children

FIGURE S2 Scatterplots with group-wise slopes between seed region and associated region. We only present results from ROIs showing a group difference, i.e., anterior IPS, area CA3

FIGURE S3 Homoscedasticity of error variance. We tested across all subjects using a test for non-constant error variance. Regression analyses with heteroscedastic error variance were remodelled after Box-Cox transforming the dependent variable

Supplementary Material

Supplementary Material

Supplementary Material

Transparent Science Questionnaire for Authors

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