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ORIGINAL RESEARCH

Mathematical abilities in dyslexic children: a diffusion tensor imaging study

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Abstract Dyslexia is characterized by a deficit in language processing which mainly affects word decoding and spelling skills. In addition, children with dyslexia also show problems in mathematics. However, for the latter, the underlying structural correlates have not been investigated. Sixteen children with dyslexia (mean age 9.8 years [0.39]) and 24 typically developing children (mean age 9.9 years [0.29]) group matched for age, gender, IQ, and handedness underwent 3 T MR diffusion tensor imaging as well as cognitive testing. Tract-Based Spatial Statistics were performed to correlate behavioral data with diffusion data. Children with dyslexia performed worse than controls in standardized verbal number tasks, such as arithmetic efficiency tests (addition, subtraction, multiplication, division). In contrast, the two groups did not differ in the nonverbal number line task. Arithmetic efficiency, representing the total score of the four arithmetic tasks, multiplication, and division, correlated with diffusion measures in widespread areas of the white matter, including bilateral superior and inferior longitudinal fasciculi in children with dyslexia compared to controls. Children with dyslexia demonstrated lower performance in verbal number tasks but performed similarly to controls in a nonverbal number task. Further, an association between verbal arithmetic efficiency and diffusion measures was demonstrated in widespread areas of the white matter suggesting compensatory mechanisms in children with dyslexia compared to controls. Taken together, poor fact retrieval in children with dyslexia is likely a consequence of deficits in the language system, which not only affects literacy skills but also impacts on arithmetic skills.

Keywords Dyslexia · Diffusion tensor imaging · Mathematical ability · Mathematics disorder · Learning disorder

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Background

With a prevalence of 4–9 %, dyslexia is among the most common neurodevelopmental disorders and has a severe impact on a child's psychosocial development. Both the ICD-10 (World Health Organization 1992) and the DSM-5 (American Psychiatric Association 2013) describe dyslexia as a specific learning disorder. Dyslexia is characterized by deficits in accurate and fluent word decoding as well as by problems in word spelling, despite age-appropriate general cognitive abilities (for review see Schulte-Körne 2010). It is assumed that most of these difficulties result from a deficit in language

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processing (i.e., phonological processing), particularly given that those diagnosed with dyslexia show under-activation of the complex brain network responsible for word reading (for meta-analysis see Richlan et al. 2009). This network is mainly located in the left hemisphere and consists of the visual word form area, the superior temporal lobe, the parietal lobe, and the inferior frontal lobe (Richlan et al. 2009). Reading abilities are found to correlate positively with white matter microstructure in fiber tracts connecting these areas, including bilateral inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and arcuate fasciculus (AF) (Lebel et al. 2013).

While numerous studies have investigated the neurobiological correlates of deficits in reading and phonological processing, far less is known about the neurobiological correlates of arithmetic problems in those diagnosed with dyslexia. This is surprising, given that many children with dyslexia also experience problems with mathematics (Moll et al. 2014b). More specifically, epidemiological studies suggest that the overlap between reading disorder and mathematics disorder is as high as 20–70 % (e.g., Dirks et al. 2008; Moll et al. 2014b). Recent findings further suggest that many of those who are diagnosed with dyslexia, and who do not fulfill diagnostic criteria for mathematics disorder, nevertheless show problems in certain aspects of mathematics (Boets and De Smedt 2010; De Smedt and Boets 2010; Moll et al. 2014a). These studies show that children with dyslexia are mainly impaired in number tasks requiring verbal skills (e.g., counting, number naming, and fact retrieval), while their nonverbal number skills (e.g., estimation and number line) seem to be unimpaired (Boets and De Smedt 2010; De Smedt and Boets 2010; Moll et al. 2014a). This is in line with the fact that the core deficit in dyslexia is in the language system (Vellutino et al. 2004).

The association between the language system and verbal number tasks has also been demonstrated in a functional magnetic resonance imaging (fMRI) study (Prado et al. 2014) that reported an increase in activation with age in language-related regions in a verbal number task (multiplication) in typically developing children. This suggests that a dysfunction in language-related brain regions, which is known to occur in children with dyslexia (Norton et al. 2014), may lead to impaired verbal number skills. In fact, in a recent study by Evans and colleagues (Evans et al. 2014), findings showed a stronger activation in left hemisphere language areas during fact retrieval (addition) in typically developing children compared to children with dyslexia. In contrast, children with dyslexia showed stronger activation in right hemisphere parietal regions during tasks involving addition compared to controls. These findings support the hypothesis that children with dyslexia are less efficient in fact retrieval-based calculation tasks and need to recruit broader brain networks including those associated with procedural-based arithmetic to solve arithmetic problems. However, to date the structural correlates associated with poor verbal number skills in children with dyslexia have not been investigated and offer the possibility for developing a biological model of language processing related deficits in word reading and in arithmetic tasks.

Diffusion Tensor Imaging (DTI) is an advanced magnetic resonance imaging (MRI) technique that provides insight into the brain's white matter microstructure by measuring the magnitude and direction of the movement of water molecules (Pierpaoli et al. 1996). Within white matter, water molecules are more likely to diffuse along fiber tracts. The directionality of this diffusion is commonly measured using fractional anisotropy (FA) (Basser and Pierpaoli 2011). Higher FA values are found in well-organized and also in more mature fiber tracts (Basser and Pierpaoli 2011). Another diffusion parameter is trace, which is the sum of diffusion in all directions (Basser and Pierpaoli 2011; Pierpaoli et al. 1996). In poorly-organized tissues, the multidirectional diffusion of water molecules can occur with little resistance, resulting in high trace and low FA values (Basser and Pierpaoli 2011). Furthermore, diffusion parameters such as axial (AD) and radial (RD) diffusivity are acquired, which are sensitive to detecting variations in diffusivity, potentially reflecting axon size, axon number or myelin coating. DTI has also been shown to be sensitive for detecting white matter microstructural alterations in dyslexics (e.g., Boets et al. 2013; Lebel et al. 2013; Saygin et al. 2013) and has proven to be an appropriate tool to investigate the underlying structural deficits in learning disorders (e.g., Matejko and Ansari 2015; Vandermosten et al. 2012).

The aim of this study was to use DTI to investigate, for the first time, the structural correlates associated with verbal number skills in children with dyslexia, and to correlate white matter microstructure with measures of mathematical ability.

Methods

Participants

The local IRB approved the study design, and written informed consent was given by both children and parents prior to study participation. Fifty-five boys were recruited via flyers in doctors' offices and by emailing parents of 3rd graders in Munich, Germany. Inclusion criteria were: normal or corrected-to-normal vision, age-appropriate schooling, male, right handedness, and German as a first language. In addition, children's nonverbal IQ had to be within the normal range ($IQ \geq 85$). Exclusion criteria were any past or present neurological or psychiatric disorder assessed based on a clinical interview with the parents and based on a parental questionnaire using the German version of the Child-Behavior-Checklist (CBCL/4-18 (Achenbach et al. 1991)). In order to be included in the study, children also had to score below the clinical cutoff for the total score (T-value<60) and below a scaled score of 8 in the attention subscale of the CBCL. The latter ensured that children with symptoms of attention/ hyperactivity disorder were not included in the study.

Cognitive examination

Children were recruited into two groups based on their reading and spelling skills: a group with dyslexia (n=21) and a control group with age-adequate literacy development (n=34). All children in the dyslexic group had a documented history of reading and spelling problems. In addition to be considered as a subject with dyslexia, children had to show very low spelling and word reading skills (i.e., at least 1 SD below the mean in the respective tests) in a standardized word spelling test (Wirtz 2014) and in a single word reading test (Moll and Landerl 2010). All children with dyslexia were untreated. In order to have a clear distinction between the two groups, children in the control group had to score at or above a z-score of −0.7 in the word spelling and word reading test.

Measures and procedures

General cognitive abilities Non-verbal IQ was tested using the German version of the Cultural Fair Intelligence Test (CFT-20R; (Jacobs 2007)), including the subtests Matrices, Topology, Sequence Completion and Classification.

Literacy measures

Spelling A standardized spelling test for 3rd and 4th graders was administered (Wirtz 2014). Children were asked to spell single words that were dictated in a sentence frame. The test score was the number of correctly spelled words.

Reading fluency Word and pseudoword reading fluency was tested by using the standardized reading test of the 'Salzburger Reading and Spelling Test' (Moll and Landerl 2010). Children were asked to read out loud a list of words and a list of pseudowords as quickly and correctly as possible within a time limit of one minute each. The relevant scores were the number of correctly read words/pseudowords within one minute.

Reading comprehension In addition to word reading fluency, reading comprehension was assessed using a standardized word, sentence, and text passage reading comprehension test (ELFE 1-6 (Lenhard and Schneider 2006)).

Cognitive measures

Phoneme awareness Two tests were used to assess phoneme awareness: In the *phoneme deletion task* the child was asked to say a nonword presented by the examiner after dropping out a designated sound (e.g., say /ti:k/ without /k/). After five training trials the 27 test trial were presented. In the *phoneme segmentation task* the child was asked to break down a pseudoword in its constituting phonemes (e.g., folt - /f/ / /ɔ/ / l/ /t/). After seven practice trials ten test trails were presented. Corrective feedback was given for the practice trials, but not for the test trials. The mean percentage of correct items was calculated for the two subtests.

Rapid automatized naming (RAN) Naming speed was assessed by alphanumeric (digits and letters) and non-alphanumeric (colors and objects) versions of the RAN task (Denckla and Rudel 1976). For each of the four subtests, children had to name 50 items presented in 5 lines as quickly and accurately as possible. The mean number of items named correctly per minute was calculated for alphanumeric and non-alphanumeric naming speed.

Verbal short-term memory Verbal short-term and working memory was measured using the digit span subtest of the German version of the Wechsler Intelligence Scale for Children – 4th Edition (Petermann and Petermann 2010). The test requires repeating increasing sequences of single digits forward and backwards.

Number skills

In order to distinguish between verbal and nonverbal number skills we assessed both components:

Verbal number skills were assessed using four subtests (addition, subtraction, multiplication, and division) of a standardized arithmetic efficiency test (Haffner et al. 2005). In each subtest, children were asked to solve as many calculations as possible within two minutes. Items increased in difficulty for each subtest (e.g., item 1: 1+6; item 19: 13+8; item 35: 77+45). An efficiency score was calculated for each subtest based on the number of correctly solved items within the two-minute time limit. The efficiency score is a measure of fact retrieval; children who still rely on counting strategies will solve fewer items within the time limit compared to those who are able to directly access arithmetic facts. The difference between strategies is expected to be especially marked for multiplication and division subtests. The mean t-score of all subtests was built. Children who scored more than one standard deviation below the mean (composite t-score < 40) were considered to have impaired arithmetic skills (mathematics disorder). Based on this criterion, none of the boys in the control group and five boys in the group with dyslexia showed comorbid arithmetic problems. The composite arithmetic score as well as the single subtest scores were used for the analyses.

Nonverbal number skills were assessed using a *number line task* (Helmreich et al. 2011; Moeller et al. 2009): In this paper-and-pencil task children were asked to estimate and mark the position of a target number on a 10 cm (3.94 in.) number line presented on paper. The left end of the number line was labeled "0" and the right end was labeled "100". For each of the 18 target numbers a separate line was presented and the target number was printed centrally above the line in Arabic notation. For each item the absolute deviance from the correct position was calculated and the mean deviance score was used for the analyses.

MR imaging acquisition

Diffusion images were acquired on a 3 T whole-body-scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) with a 12-channel-headcoil. Two averages of 30 diffusion directions with a b-value of 1000 mm^2/s and one additional image with a b-value of 0 mm^2/s were acquired using the following parameters: TR=9600 ms, TE=110 ms. Sixty-five slices with 2 mm slice thickness were taken with a field of view (FOV) of 208 mm (104×104 matrix) and a voxel size of $2\times2\times2$ mm^3 was received. Additionally, a T1-weighted Magnetization Prepared Rapid Gradient Echo (MP-RAGE) sequence was acquired with the following parameters: TR=1800 ms, TE=3.06 ms, FOV=256 mm, voxel size=$1\times1\times1$ mm^3, iPAT acceleration factor 2.

Diffusion tensor imaging

Every diffusion direction was visually inspected for image quality using the 3DSlicer version 4.3.0 (Surgical Planning Laboratory, Brigham and Women's Hospital, Boston, USA). Correction for motion artifacts and eddy currents were done by using MCFLIRT and the eddy tools of FMRIB Software Library (FLIRT; FMRIB Software Library, FSL 4.1, The Oxford Centre for Functional MRI of the Brain, Oxford, UK (Smith et al. 2004)). Adjustment of the diffusion directions was performed by using the rotational component of the affine transformations. A relative-motion parameter was estimated from the transformation matrices (Ling et al. 2012). Outliers were identified using boxplot in MATLAB (Version 8.0.0.783, MATLAB and Statistics Toolbox Release 2012b, The MathWorks, Inc., Natick, MA, US) and only datasets with none or very minor artefacts were included in the analyses. A whole brain mask was then automatically created based on the b0 image and then manually edited where necessary using 3DSlicer.

Eigenvalues and eigenvectors were estimated for every voxel by applying a multivariate linear fitting algorithm on the diffusion tensor, the following four main scalar measures were calculated: Fractional Anisotropy (FA), trace, Radial Diffusivity (RD), and Axial Diffusivity (AD). FA provides information about the directionality of diffusion where a high value reflects well-organized tissue. Trace is the sum of all diffusion within a voxel. AD equals the main axis of diffusion whereas RD is the mean of the diffusion perpendicular to the main axis. Therefore, an association of RD with behavioral measures is expected to be in the opposite direction compared to an association of FA with behavioral measures.

Based on the quality check, 15 data sets had to be excluded due to motion artifacts, leaving a final cohort of 16 dyslexics (mean [SD] 117.06 months [4.63] (including five boys with comorbid arithmetic problems), IQ 108.44 [13.70]), and 24 healthy controls (118.38 months [3.42], IQ 110.04 [9.87]).

White matter analysis

Tract-Based Spatial Statistics (TBSS, FSL 5.0.4, FMRIB, The Oxford Centre for Functional MRI of the Brain, Oxford, UK) were used to examine the brain's white matter. The method is described in detail elsewhere (Smith et al. 2006). Briefly, all subjects' FA images were linearly aligned to their non-diffusion-weighted images to correct for head motion and to minimize the result of gradient coil eddy currents. Then, the subject who was closest to the whole cohort's average was chosen using tbss_2_reg –n. The rationale for not using the FMRIB58_FA target was that it is based on the data of 58 adults (20–50 years) from both sexes, which differs significantly from our cohort. After aligning all subjects' FA images to the automatically selected target, the whole data set was aligned to MNI152 (Montreal Neurological Institute) standard space. The average FA for all subjects was calculated for each voxel and projected to the mean FA image. This procedure was also used to create mean images for AD, RD, and trace. The mean FA image was then thinned to create the mean FA skeleton with a threshold of > 0.3 so as to only include the inner part of the main WM tracts.

Statistics

Within TBSS the mean FA skeleton was applied to the mean data of each of the four diffusion parameters, and voxelwise statistics were then performed. To test for brain regions with correlation between behavioral measures and diffusion parameters in the dyslexic group, compared to the controls, we used a two-sample t test with 10.000 random permutations and Threshold-Free-Cluster-Enhancement (TFCE). Results were corrected for multiple comparison using family-wise error and considered significant at a $p<0.05$ (Winkler et al. 2014). Next, diffusion parameters of those brain regions with significantly different correlation in the dyslexic group, compared to the controls, were extracted for each subject. These values were exported to Graphpad Prism (Version 5.0.336 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com) for further analyses and visualization. All data were tested for normal distribution using D'Agostino & Pearson omnibus normality test. Spearman's Rho was used to calculate the cluster-specific post-hoc correlation coefficients for the group of children with dyslexia and the control group.

Results

Cognitive evaluation

Table 1 shows the descriptive statistics for age, IQ, literacy, and numeracy measures for the two groups together with the group comparisons. Children with and without dyslexia did not differ in general cognitive abilities. In line with the classification criteria, children with dyslexia scored significantly poorer than typically developing children on all literacy measures and on the cognitive measures associated with literacy skills (phoneme awareness, RAN, and verbal memory). The dyslexic group also performed worse than controls in the standardized arithmetic efficiency tests (addition, subtraction, multiplication, division). In contrast, the two groups did not differ in the nonverbal number line task. Importantly, the pattern was the same when excluding the five children with mathematics disorder, with a clear group difference in arithmetic efficiency (Means: 43.93 versus 52.02, $F=15.86$, $p<.001$), but no group difference in the nonverbal number line task (Means: 4.37 versus 4.17, $F=0.08$, $p=.776$). These findings suggest that children with dyslexia score poorly on verbal number tasks, while their nonverbal number skills are unaffected.

Group difference in diffusion measures

Group comparison using TBSS did not reveal a significant difference in diffusion measures after correcting for multiple comparisons.

Group differences in correlation of diffusion parameters and behavioral measures

Arithmetic efficiency (HRT - Heidelberger Rechentest)

A significantly different correlation was observed between the total arithmetic efficiency score and FA, AD, and RD, between groups ($p<0.05$) (Fig. 1). In dyslexics, arithmetic efficiency correlated positively with FA in a cluster involving most of the

Table 1 Descriptive statistics and group comparisons between children with dyslexia and typically developing controls

Test	Dyslexics $n=16$		Controls $n=24$		Group difference	Effects size
	M	SD	M	SD	F-value p (uncorr.)	Cohen's d
Age in months	117.06	4.63	118.38	3.42	1.06[ns]	0.32
IQ	108.44	13.70	110.04	9.87	0.19[ns]	0.13
Word reading[a]	33.06	5.02	54.02	8.83	73.85 ***	2.92
Pseudoword reading[a]	38.38	3.84	53.29	8.67	41.66 ***	2.22
Spelling[a]	34.00	3.83	57.96	9.04	99.76 ***	3.45
Reading comprehension[a]	34.99	7.27	55.50	8.46	62.94 ***	2.60
Phoneme awareness[b]	70.47	14.97	81.86	10.72	7.88 **	0.88
Alphanumeric RAN[c]	102.83	17.84	123.14	13.54	16.74 ***	1.28
Non-alphanumeric RAN[c]	55.36	10.26	66.61	10.34	11.43 **	1.09
Verbal memory[a]	38.94	7.62	45.96	9.65	5.97 *	0.81
HRT total score[a]	40.89	5.56	52.02	6.27	33.04 ***	1.88
- Addition	39.81	5.74	51.91	6.74	34.75 ***	1.93
- Subtraction	43.38	7.19	55.83	7.49	27.39 ***	1.70
- Multiplication	40.19	7.46	51.17	8.55	17.48 ***	1.37
- Division	40.19	7.17	49.17	7.72	13.75 **	1.21
Number line[d]	5.25	2.07	4.17	2.11	2.56[ns]	−0.52

** $p<.01$; *** $p<.001$

[a] T-score

[b] Percentage correct

[c] Items correct/minute

[d] Raw score (mean deviance from the correct position on the number line)

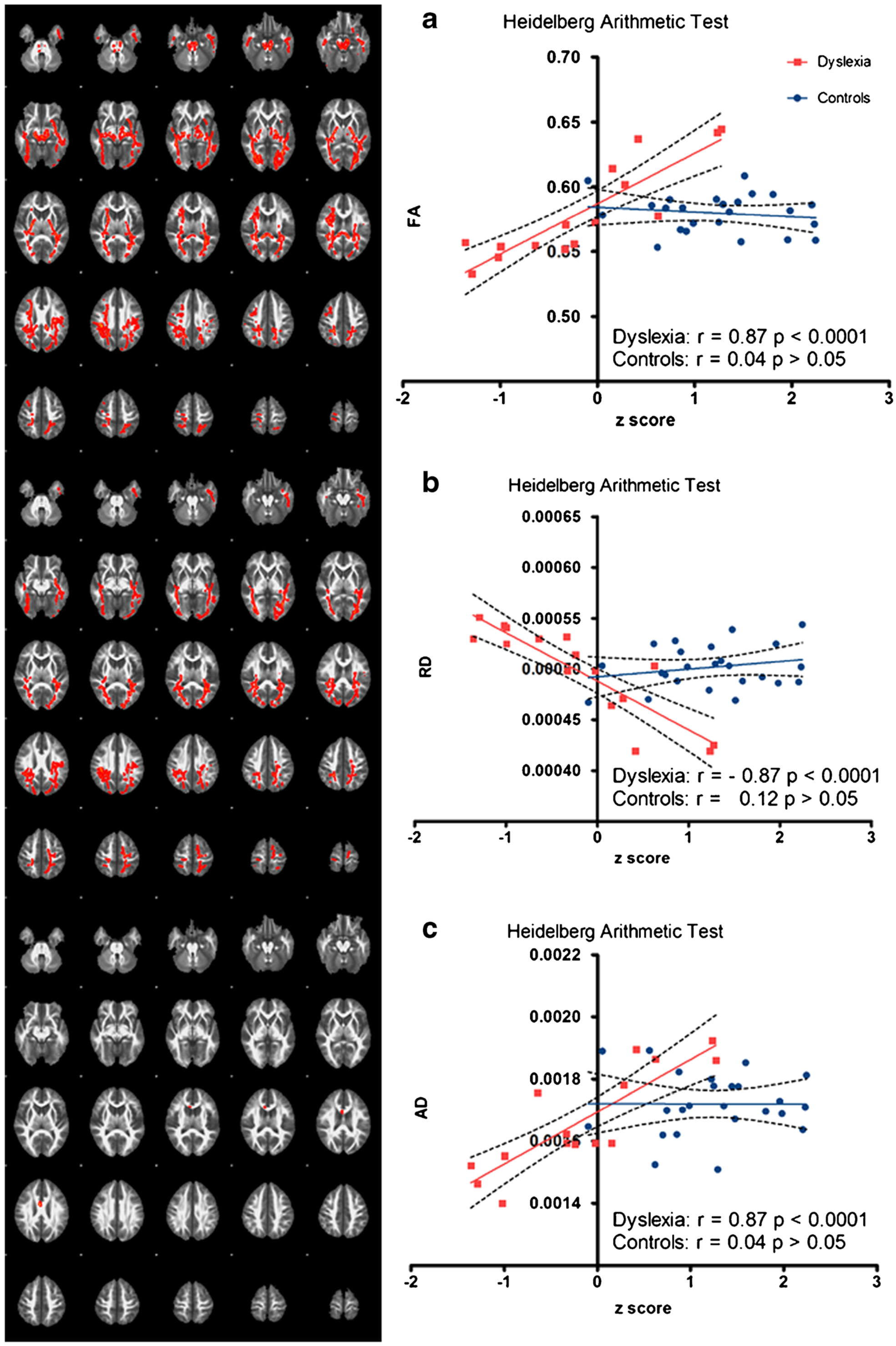

Fig. 1 *Left*: Voxel with significant correlation between HRT results and diffusion parameters ($p<0.05$, corrected for multiple comparisons) are shown in *red*. *Right*: Extracted mean values from the cluster for each subject, plotted against the z-score reached in the calculation test. *Red squares* = dyslexic group, *blue circles* = control group. *A*) results for the positive correlation between fractional anisotropy (FA) and the test results of the dyslexic group; *B*) negative correlation between the dyslexic test results and radial diffusivity (RD); *C*) results for the positive correlation between the dyslexic test results and axial diffusivity (AD). Post-hoc analysis of Spearman's rho and level of significance are shown

white matter of the parietal and temporal lobe in both hemispheres and parts of the brainstem. Arithmetic efficiency correlated negatively with RD in a cluster involving the whole parietal lobe and parts of both temporal lobes. Arithmetic efficiency correlated positively with AD in a small cluster in the anterior part of the corpus callosum. There was no significant correlation between arithmetic efficiency and trace.

Multiplication

Significantly different correlations between multiplication scores and FA, RD, and trace were found between groups (Fig. 2). In dyslexics, FA correlated positively with performance in multiplication in a cluster that included most of the white matter in the parietal, occipital, and temporal lobes, and

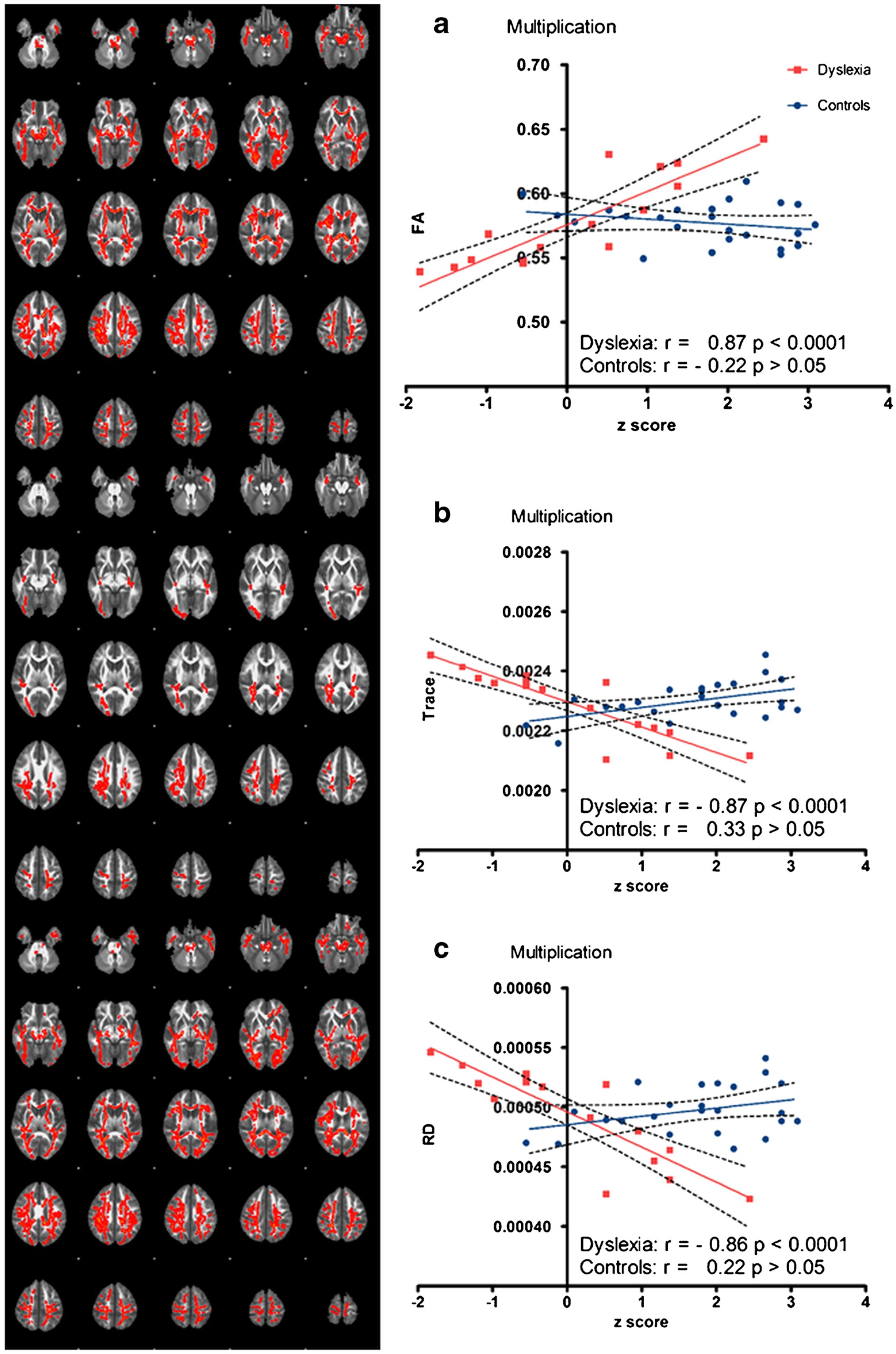

Fig. 2 *Left*: Voxel with significant correlation between multiplication and diffusion parameters ($p<0.05$, corrected for multiple comparisons) are shown in *red*. *Right*: Extracted mean values from the cluster for each subject, plotted against the z-score reached in the calculation test. *Red squares* = dyslexic group, *blue circles* = control group. *A*) positive correlation between the dyslexics' test results and fractional anisotropy (FA), *B*) negative correlation for the dyslexics' test results and trace and *C*) negative correlation between radial diffusivity (RD) and the dyslexics' test results. Post-hoc analysis of Spearman's rho and level of significance are shown

also in parts of the frontal lobes in both hemispheres, as well as in parts of the brainstem. Trace correlated positively with the subtest multiplication in a cluster involving both parietal lobes, parts of both temporal lobes, and smaller parts of the occipital lobes. RD correlated negatively with the subtest multiplication in most of the white matter in the parietal, occipital, temporal, and parts of the frontal lobes in both hemispheres, as well as in parts of the brainstem. No significant correlation was found for AD.

Division

Different correlations with the subtest division were found for FA, RD, and AD (Fig. 3). FA correlated positively in

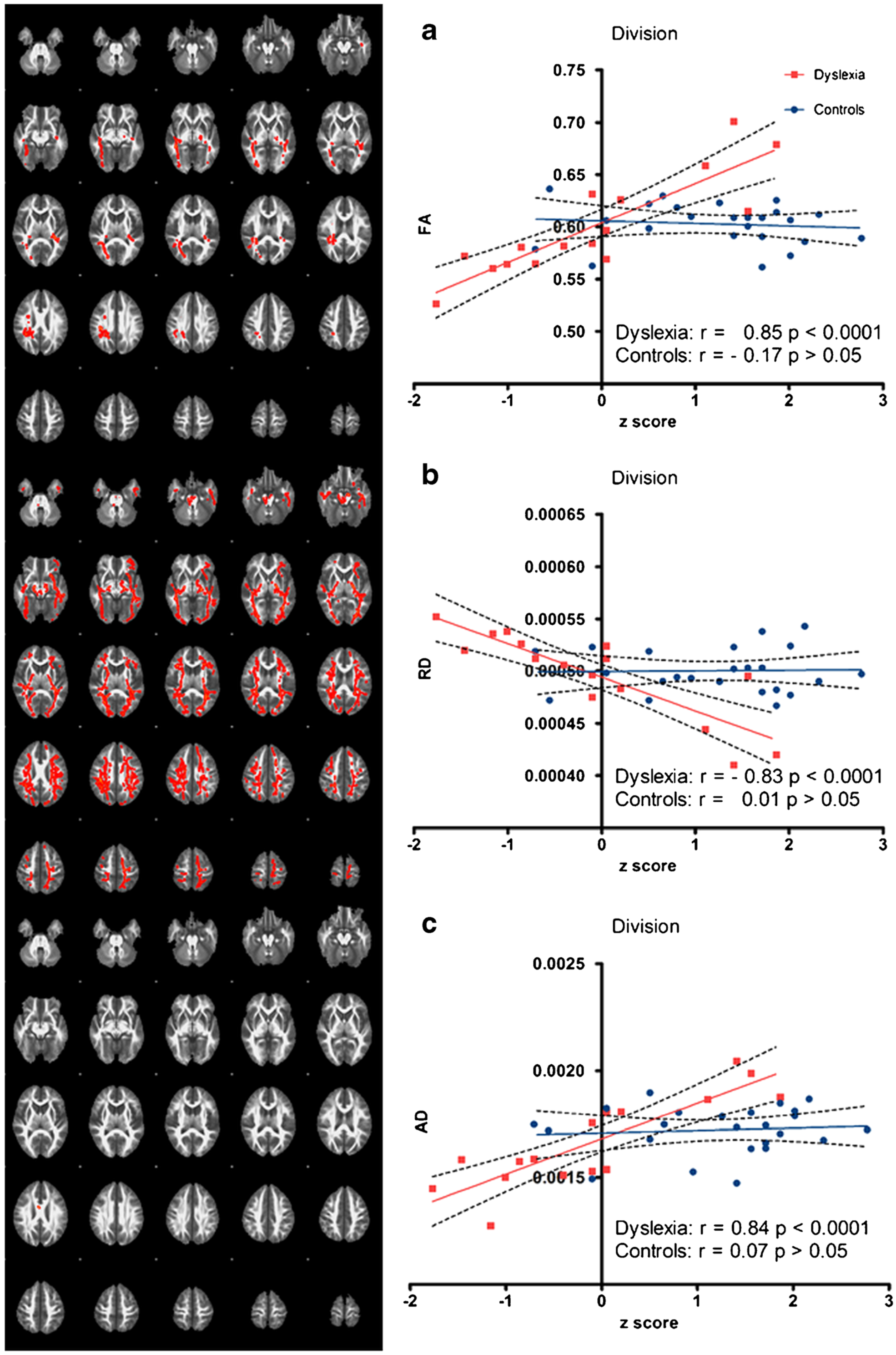

Fig. 3 Results for the correlations between the dyslexics' division score (z-score) and the diffusion parameter: FA (*A*), RD (*B*) and AD (*C*). The significant clusters are shown in *red* ($p<0.05$, corrected for multiple comparisons). Dyslexic children are marked in *red*, controls in *blue*. Post-hoc analysis of Spearman's rho and level of significance are shown

a cluster that included parts of the parietal and occipital lobes in both hemispheres. RD correlated negatively in a cluster that included both hemispheres' parietal and temporal lobes, as well as in parts of the brainstem. AD correlated positively in a small cluster located in the middle of the genu of the corpus callosum. There was no significant correlation between trace and the subtest division.

Importantly, all results remained statistically significant when excluding the five boys with mathematics disorder using post-hoc analysis. For the other two subtests of the HRT, subtraction and addition, there were no significant correlations between group and FA, RD, AD, and trace.

Discussion

This study used DTI to investigate, for the first time, the association between the brain's white matter microstructure and performance in number skills in children with dyslexia. First, our behavioral measures revealed significantly lower verbal number skills (arithmetic efficiency) in children with dyslexia compared to controls. As expected, there was no significant group difference between children with dyslexia and controls for the nonverbal number task (number line). Second, a correlation between arithmetic efficiency and diffusion measures in large parts of the white matter including bilateral SLF, AF, and ILF was found in children with dyslexia compared to controls. Further, and as expected, the largest white matter area was found for the correlation with the multiplication subtest, a measure of fact retrieval that is purported to rely on verbal skills.

To our knowledge, this is the first study to investigate white matter structural correlates of number skills in children with dyslexia. Previous imaging studies on mathematical abilities included either controls or children with mathematics disorder/dyscalculia (Grabner et al. 2013; Kucian et al. 2006; Rotzer et al. 2008). Rykhlevskaia et al. found reduced gray matter volume in both superior parietal lobes, intraparietal sulci (IPS), parahippocampal gyrus, fusiform gyrus, and in the right anterior temporal cortex in 7–9 year old dyscalculics compared to controls (Rykhlevskaia et al. 2009). This is in line with studies demonstrating the importance of bilateral IPS, as well as left angular gyrus, for quantity representation and calculation processes. Moreover, there is evidence that children with dyscalculia show a stronger activation in larger cortical areas than typically developing controls when performing simple addition tasks (Ashkenazi et al. 2012). In addition to functional and structural differences in gray matter there is also evidence for microstructural differences in white matter. Van Eimeren et al. found an association between FA of the left superior corona radiata and typically developing children's mathematical reasoning (Van Eimeren 2008). Additionally, children with dyscalculia showed a decrease in FA in the right parietofrontotemporal area, which was mainly related to numerical operations (Rykhlevskaia et al. 2009).

To date, there is only one study that has investigated the functional correlates of arithmetic skills in children with dyslexia (Evans et al. 2014). In this study, the investigators found that, compared to controls, children with dyslexia showed hypoactivation of the left supramarginal gyrus during fact retrieval, indicative of a left hemisphere based language deficit. In addition, they showed higher activation in right hemispheric parietal regions, suggesting the use of compensatory strategies using procedural-based mechanisms such as finger counting. To extend these findings further, we investigated arithmetic efficiency, in a cohort that represents the whole spectrum of arithmetic abilities in dyslexic children. Importantly, all results remained statistically significant in a post-hoc analysis when excluding the five boys who were affected the most and qualified for a diagnosis of mathematics disorder suggesting that this subgroup did not solely drive the results. These five boys did not differ on age, handedness, or IQ from other members of this cohort. Further, we focused on whole brain white matter microstructural characteristics, which have not been previously investigated.

In our study arithmetic efficiency correlated with diffusion measures in bilateral frontoparietal regions including SLF, ILF, and arcuate fasciculus in children with dyslexia. This was mainly driven by multiplication efficiency which is based on fact retrieval. Multiplication strongly relies on language-based skills and is therefore supposed to be impaired in individuals with dyslexia. Indeed, previous research has shown that individuals with dyslexia use fact retrieval less efficiently than typically developing controls (Boets and De Smedt 2010). Importantly, our results extend these behavioral findings by showing that the association between dyslexia and poor performance on arithmetic efficiency (i.e., multiplication) is also reflected by brain microstructural alterations in areas involved in reading. While acquiring mathematical abilities, typically developing children are known to initially use a combination of both procedural-based mechanisms, including counting strategies, and fact retrieval, including working memory and language processing, when performing multiplication tasks before they become proficient enough in fact retrieval (Prado et al. 2014). Our results suggest that children with dyslexia require higher FA values in widespread areas of the brain to solve arithmetic tasks, compared to typically developing controls. There is evidence for an initial increase in FA during learning of a new task followed by a decrease when reaching an advanced level (Scholz et al. 2009). In addition, a study by Hänggi et al. found lower FA in motor areas in female ballet dancers compared to controls, which the authors discussed as an effect of training (Hanggi et al. 2010). Similarly, Schmithorst and Wilke found lower FA values in musicians compared to non-musicians in brain regions specifically trained in musicians (Schmithorst and Wilke 2002). In this context, the positive correlations between FA values and arithmetic efficiency in our group of dyslexic children may be due to a relatively inexperienced use of fact retrieval strategies.

Further, the correlation between behavioral measures and white matter microstructure in widespread areas of the brain may reflect compensatory mechanisms resulting from a deficit in the language system associated with problems in fact retrieval. This may indicate that in order to solve arithmetic tasks, children with dyslexia may use additional strategies involving larger brain areas, i.e. procedural-based mechanisms. Future studies are needed to elucidate the role of the different anatomical and functional regions that are part of the widespread cluster.

There are limitations in our study that need to be taken into account when interpreting the data. First, the group size is relatively small. However, the study cohort is very homogeneous regarding age, sex, handedness, IQ, and the absence of comorbidity with attention disorders. Another limitation is the cross-sectional design. As the process of learning mathematics takes time and may change over time, future studies need to include longitudinal evaluations. We also note that a group comparison of diffusion measures using TBSS, without considering the behavioral data, did not reveal significant group differences. Although there are studies which report differences in diffusion measures (Vandermosten et al. 2012), results of our study are in line with previous studies using TBSS (Odegard et al. 2009). The latter study, which like our study also used TBSS, reported no significant difference between children with dyslexia and typical readers, which may be due to the more conservative statistical approach of TBSS that uses stringent criteria for multiple comparisons.

In summary, children with dyslexia demonstrated lower performance in verbal number tasks but performed similarly in a nonverbal number task compared to controls. Further, this study demonstrated for the first time an association between fact-retrieval based tasks and diffusion measures in widespread areas of the brain's white matter suggesting compensatory mechanisms in children with dyslexia compared to controls. Taken together, poor fact retrieval in children with dyslexia is likely a consequence of deficits in the language system which not only affects literacy skills but also impacts on arithmetic skills.

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Disclosures

Compliance with ethical standards All procedures performed in this study involving human participants were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1975, and the applicable revisions. Written informed consent was obtained from all study participants and their parents prior to inclusion in the study.

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Conflict of interest All authors declare that they have no conflict of interest.

References

Achenbach, T. M., Howell, C. T., Quay, H. C., Conners, C. K., & Bates, J. E. (1991). National survey of problems and competencies among four- to sixteen-year-olds: parents' reports for normative and clinical samples. *Monographs of the Society for Research in Child Development, 56*(3), 1–130. doi:10.2307/1166156.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders. 5th ed.

Ashkenazi, S., Rosenberg-Lee, M., Tenison, C., & Menon, V. (2012). Weak task-related modulation and stimulus representations during arithmetic problem solving in children with developmental dyscalculia. *Developmental Cognitive Neuroscience, 2*(Suppl 1), S152–S166. doi:10.1016/j.dcn.2011.09.006.

Basser, P. J., & Pierpaoli, C. (2011). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. 1996. *Journal of Magnetic Resonance, 213*(2), 560–570. doi:10.1016/j.jmr.2011.09.022.

Boets, B., & De Smedt, B. (2010). Single-digit arithmetic in children with dyslexia. *Dyslexia, 16*(2), 183–191. doi:10.1002/dys.403.

Boets, B., Op de Beeck, H. P., Vandermosten, M., Scott, S. K., Gillebert, C. R., Mantini, D., Bulthé, J., Sunaert, S., Wouters, J., & Ghesquiere, P. (2013). Intact but less accessible phonetic representations in adults with dyslexia. *Science, 342*(6163), 1251–1254. doi:10.1126/science.1244333.

De Smedt, B., & Boets, B. (2010). Phonological processing and arithmetic fact retrieval: evidence from developmental dyslexia. *Neuropsychologia, 48*(14), 3973–3981. doi:10.1016/j.neuropsychologia.2010.10.018.

Denckla, M. B., & Rudel, R. G. (1976). Rapid automatized naming (R.A.N): dyslexia differentiated from other learning disabilities. *Neuropsychologia, 14*, 471.

Dirks, E., Spyer, G., van Lieshout, E. C., & de Sonneville, L. (2008). Prevalence of combined reading and arithmetic disabilities. *Journal of Learning Disabilities, 41*(5), 460–473. doi:10.1177/0022219408321128.

Evans, T. M., Flowers, D. L., Napoliello, E. M., Olulade, O. A., & Eden, G. F. (2014). The functional anatomy of single-digit arithmetic in children with developmental dyslexia. *NeuroImage, 101*, 644–652. doi:10.1016/j.neuroimage.2014.07.028.

Grabner, R. H., Ansari, D., Koschutnig, K., Reishofer, G., & Ebner, F. (2013). The function of the left angular gyrus in mental arithmetic: evidence from the associative confusion effect. *Human Brain Mapping, 34*(5), 1013–1024. doi:10.1002/hbm.21489.

Haffner, J., Baro, K., Parzer, P., & Resch, F. (2005). HRT 1-4 - Heidelberger Rechentest—Erfassung mathematischer Basiskompetenzen im Grundschulalter. *Hogreffe*.

Hanggi, J., Koeneke, S., Bezzola, L., & Jancke, L. (2010). Structural neuroplasticity in the sensorimotor network of professional female ballet dancers. *Human Brain Mapping, 31*(8), 1196–1206. doi:10.1002/hbm.20928.

Helmreich, I., Zuber, J., Pixner, S., Kaufmann, L., Nuerk, H. C., & Moeller, K. (2011). Language effects on children's nonverbal number line estimations. *Journal of Cross-Cultural Psychology, 42*(4), 598–613. doi:10.1177/0022022111406026.

Jacobs, C. (2007). Testinformation: Grundintelligenz CFT 20—R von Hermann Weiß. *Diagnostica, 53*(2), 5.

Kucian, K., Loenneker, T., Dietrich, T., Dosch, M., Martin, E., & von Aster, M. (2006). Impaired neural networks for approximate calculation in dyscalculic children: a functional MRI study. *Behavioral and Brain Functions, 2*, 31. doi:10.1186/1744-9081-2-31.

Lebel, C., Shaywitz, B., Holahan, J., Shaywitz, S., Marchione, K., & Beaulieu, C. (2013). Diffusion tensor imaging correlates of reading ability in dysfluent and non-impaired readers. *Brain and Language, 125*(2), 215–222. doi:10.1016/j.bandl.2012.10.009.

Lenhard, W., & Schneider, W. (2006). Ein Leseverständnistest für Erst- bis Sechstklässler (ELFE 1-6). *Hogrefe*.

Ling, J., Merideth, F., Caprihan, A., Pena, A., Teshiba, T., & Mayer, A. R. (2012). Head injury or head motion? Assessment and quantification of motion artifacts in diffusion tensor imaging studies. *Human Brain Mapping, 33*(1), 50–62. doi:10.1002/hbm.21192.

Matejko, A. A., & Ansari, D. (2015). Drawing connections between white matter and numerical and mathematical cognition: a literature review. *Neuroscience and Biobehavioral Reviews, 48c*, 35–52. doi:10.1016/j.neubiorev.2014.11.006.

Moeller, K., Pixner, S., Kaufmann, L., & Nuerk, H. C. (2009). Children's early mental number line: logarithmic or decomposed linear? *Journal of Experimental Child Psychology, 103*(4), 503–515. doi:10.1016/j.jecp.2009.02.006.

Moll, K., & Landerl, K. (2010). Lese- und Rechtschreibtest (SLRT-II). Weiterentwicklung des Salzburger Lese- und Rechtschreibtests. *Verlag Hans Huber*.

Moll, K., Göbel, S. M., & Snowling, M. J. (2014a). Basic number processing in children with specific learning disorders: comorbidity of reading and mathematics disorders. *Child Neuropsychology*. doi:10.1080/09297049.2014.899570.

Moll, K., Kunze, S., Neuhoff, N., Bruder, J., & Schulte-Korne, G. (2014b). Specific learning disorder: prevalence and gender differences. *PLoS One, 9*(7), e103537. doi:10.1371/journal.pone.0103537.

Norton, E. S., Beach, S. D., & Gabrieli, J. D. (2014). Neurobiology of dyslexia. *Current Opinion in Neurobiology, 30C*, 73–78. doi:10.1016/j.conb.2014.09.007.

Odegard, T. N., Farris, E. A., Ring, J., McColl, R., & Black, J. (2009). Brain connectivity in non-reading impaired children and children diagnosed with developmental dyslexia. *Neuropsychologia, 47*(8–9), 1972–1977. doi:10.1016/j.neuropsychologia.2009.03.009.

Petermann, F., & Petermann, U. (2010). *HAWIK-IV.* Bern: Huber.

Pierpaoli, C., Jezzard, P., Basser, P. J., Barnett, A., & Di Chiro, G. (1996). Diffusion tensor MR imaging of the human brain. *Radiology, 201*(3), 637–648.

Prado, J., Mutreja, R., & Booth, J. R. (2014). Developmental dissociation in the neural responses to simple multiplication and subtraction problems. *Developmental Science, 17*(4), 537–552.

Richlan, F., Kronbichler, M., & Wimmer, H. (2009). Functional abnormalities in the dyslexic brain: a quantitative meta-analysis of neuroimaging studies. *Human Brain Mapping, 30*(10), 3299–3308. doi:10.1002/hbm.20752.

Rotzer, S., Kucian, K., Martin, E., von Aster, M., Klaver, P., & Loenneker, T. (2008). Optimized voxel-based morphometry in children with developmental dyscalculia. *NeuroImage, 39*(1), 417–422. doi:10.1016/j.neuroimage.2007.08.045.

Rykhlevskaia, E., Uddin, L. Q., Kondos, L., & Menon, V. (2009). Neuroanatomical correlates of developmental dyscalculia: combined evidence from morphometry and tractography. *Frontiers in Human Neuroscience, 3*, 51. doi:10.3389/neuro.09.051.2009.

Saygin, Z. M., Norton, E. S., Osher, D. E., Beach, S. D., Cyr, A. B., Ozernov-Palchik, O., Yendiki, A., Fischl, B., Gaab, N., & Gabrieli, J. D. (2013). Tracking the roots of reading ability: white matter volume and integrity correlate with phonological awareness in prereading and early-reading kindergarten children. *Journal of Neuroscience, 33*(33), 13251–13258. doi:10.1523/JNEUROSCI.4383-12.2013.

Schmithorst, V. J., & Wilke, M. (2002). Differences in white matter architecture between musicians and non-musicians: a diffusion tensor imaging study. *Neuroscience Letters, 321*(1–2), 57–60.

Scholz, J., Klein, M. C., Behrens, T. E., & Johansen-Berg, H. (2009). Training induces changes in white-matter architecture. *Nature Neuroscience, 12*(11), 1370–1371. doi:10.1038/nn.2412.

Schulte-Körne, G. (2010). The prevention, diagnosis, and treatment of dyslexia. *Deutsches Ärzteblatt International, 107*(41), 718–726. doi:10.3238/arztebl.2010.0718.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage, 23*(Suppl 1), S208–S219. doi:10.1016/j.neuroimage.2004.07.051.

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., Ciccarelli, O., Cader, M. Z., Matthews, P. M., & Behrens, T. E. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage, 31*(4), 1487–1505. doi:10.1016/j.neuroimage.2006.02.024.

Van Eimeren, L. (2008). White matter microstructures underlying mathematical abilities in children. *Neuroreport, 19*(11), 5.

Vandermosten, M., Boets, B., Wouters, J., & Ghesquiere, P. (2012). A qualitative and quantitative review of diffusion tensor imaging studies in reading and dyslexia. *Neuroscience and Biobehavioral Reviews, 36*(6), 1532–1552. doi:10.1016/j.neubiorev.2012.04.002.

Vellutino, F. R., Fletcher, J. M., Snowling, M. J., & Scanlon, D. M. (2004). Specific reading disability (dyslexia): what have we learned in the past four decades? *Journal of Child Psychology and Psychiatry, 45*(1), 2–40.

WHO World Health Organization. (1992). The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines.

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *NeuroImage, 92*, 381–397. doi:10.1016/j.neuroimage.2014.01.060.

Wirtz, M. A. (2014). Weingartener Grundwortschatz Rechtschreibtest (WRT 1+, WRT 2+, WRT 3+, WRT 4+). *Dorsch – Lexikon der Psychologie, 17*.