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ORIGINAL ARTICLE

Developmental dyscalculia: a dysconnection syndrome?

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Abstract Numerical understanding is important for everyday life. For children with developmental dyscalculia (DD), numbers and magnitudes present profound problems which are thought to be based upon neuronal impairments of key regions for numerical understanding. The aim of the present study was to investigate possible differences in white matter fibre integrity between children with DD and controls using diffusion tensor imaging. White matter integrity and behavioural measures were evaluated in 15 children with developmental dyscalculia aged around 10 years and 15 matched controls. The main finding, obtained by a whole brain group comparison, revealed reduced fractional anisotropy in the superior longitudinal fasciculus in children with developmental dyscalculia. In addition, a region of interest analysis exhibited prominent deficits in fibres of the superior longitudinal fasciculus adjacent to the intraparietal sulcus, which is thought to be the core region for number processing. To conclude, our results outline deficient fibre projection between parietal, temporal and frontal regions in children with developmental dyscalculia, and therefore raise the question of whether dyscalculia can be seen as a dysconnection syndrome. Since the superior longitudinal fasciculus is involved in the integration and control of distributed brain processes, the present results highlight the importance of considering broader domain-general mechanisms in the diagnosis and therapy of dyscalculia.

Keywords Developmental dyscalculia · Diffusion tensor imaging · Children · Calculation · Intelligence · Number processing · Discrepancy

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Introduction

There is a widespread misunderstanding of the importance of math in everyday life and a lack of appreciation of how important math learning is for young children. Not only the importance but also the complexity of number processing is underestimated. Even the mental calculation of a simple addition problem like $7 + 5$ requires the engagement of a broad, intact functionally integrated neuronal network. Brain imaging studies have revealed that in addition to the parietal lobes the prefrontal cortices, regions associated with the dorsal and ventral visual pathways, as well as subcortical areas play a significant role in numerical tasks (Arsalidou and Taylor 2011; Kaufmann et al. 2011). The disruption of key areas within this network has been related to specific learning deficits in math (Kucian et al. 2006,

2011a, b; Mussolin et al. 2010; Price et al. 2007; Kaufmann et al. 2009; Kovas et al. 2009). However, most of the studies published to date have focused on brain function or grey matter differences, and little is known about the white matter deficits linked to specific math learning disabilities. The goal of the present study was to examine the role of structural abnormalities in white matter integrity in children with developmental dyscalculia.

Developmental dyscalculia (DD) is a specific learning disability affecting the development of arithmetical skills. In every classroom there will be approximately one child that suffers from DD (Reigosa-Crespo et al. 2012; Shalev et al. 2000; Shalev and von Aster 2008; von Aster et al. 2007). The deficit comprises problems in the mastery of a wide range of numerical understanding such as counting skills, magnitude processing, arithmetical computations, transcoding between number words, digits and quantities, or the spatial number representation. These deficits are not explicable on the basis of general mental retardation, inadequate schooling or neurological injuries. Since mathematical skills are tremendously critical for success in school and employment, arguably more important than reading and writing abilities, the knowledge about neuronal underpinnings of this learning disability is of high relevance to provide adequate support for children with DD and thereby reduce the socioeconomic burden associated with this disorder (Duncan et al. 2007; Gross et al. 2009; Parsons and Bynner 2005).

To investigate white matter abnormalities in children with DD, we conducted diffusion tensor imaging (DTI), which is a magnetic resonance imaging (MRI) technique providing information about white matter microstructure non-invasively. Diffusion of water molecules is restricted by axons in white matter. This directional dependence of diffusion can be quantified by the fractional anisotropy (FA), which reflects both the size and number of myelinated axons and the coherence of axonal orientation. Reduced FA is a marker of decreased white matter integrity and can point to a disruption or disorganization of white matter tracts which has been demonstrated in a variety of diseases [details about DTI can be found e.g. in the review article by Le Bihan et al. (2001)].

To our knowledge, only one study has looked at DTI findings in children with DD (Rykhlevskaia et al. 2009). Results point to abnormalities in microstructure of white matter in the right temporo-parietal cortex in children with DD. However, differences in FA have only been evaluated in this area on the basis of a prior analysis, which indicated reduced white matter volume in the right temporo-parietal cortex. Accordingly, DD seems to be related to disruption of white matter integrity; however, the question remains open whether additional areas in the brain might be affected. Rykhlevskaia et al. (2009) reported not only reduced FA in children with DD, but also showed that diffusivity correlated positively with numerical operations related to fact retrieval and computation.

Similarly, two clinical studies demonstrated a positive link between white matter integrity and arithmetic levels in different patient groups (Till et al. 2011; Barnea-Goraly et al. 2005). Therefore, deficits in math performance due to DD or another clinical disease may relate to a disruption of white matter fibre connections.

Findings in typically achieving children also demonstrated a significant association between FA and mathematical abilities (Tsang et al. 2009; van Eimeren et al. 2008), leading some authors to suggest a role of white matter tracts in the left hemisphere for the development of mathematical competencies (Van Eimeren et al. 2008). In particular, the left superior corona radiata and inferior longitudinal fasciculus showed an association between white matter integrity and calculation abilities. Tsang et al. (2009) assessed the relation between diffusivity and arithmetic skills in the anterior portion of the superior longitudinal fasciculus (SLF), a fibre tract linking the frontal, parietal and temporal lobes. They also found a significant association between white matter integrity in this fibre tract on the right hemisphere and children's ability to perform approximate mental arithmetic. In the same vein, Holmes et al. (2010) reported a significant association between the direct measure of myelin integrity and mathematical abilities in children in a white matter region close to the right intraparietal sulcus (IPS), a region which is essential to number processing (Arsalidou and Taylor 2011; Kaufmann et al. 2011).

Some further information can be gained by the examination of white matter changes induced through intensive mathematical training. A recent study reported an enhancement of FA after a long-term abacus calculation training program (Hu et al. 2011). The authors concluded that the training might have affected brain development by increasing myelination of fibres responsible for motor and visuo-spatial processing, both capacities on which effective abacus calculation is based. Another learning study investigated white matter changes after participants learned the association of figures with a numerical value from 1 to 9 (Koch et al. 2010). Successful learning of this task was related to enhanced diffusivity in the SLF, cingulate bundle, and the corpus callosum that might reflect an increased connectivity to neighbouring, task-relevant regions.

Taken together, these results indicate that calculation is a demanding cognitive ability which is processed by a complex neuronal network. Successful development of mathematical skills is partly based on the construction of effective, fast and accurate connections between task-relevant brain areas. There is evidence that increased white matter integrity measured by DTI is related to calculation

skills, while a disruption of white matter fibre tracts has been associated with DD and other math problems. However, no consensus about which fibre connections are most critical for calculation has yet been achieved. In the present study, we aim to shed further light on possible white matter deficits in children with DD. We hypothesized that dyscalculia is associated with abnormalities in diffusion measurements due to aberrant myelination, axonal maturation, or coherence of fibre orientation. These diffusion abnormalities are hypothesized to arise in brain regions or related networks known to be essential for calculation.

Methods

Subjects

A total number of 47 children between 8 and 11 years participated in the present study, of whom 30 children had a clinical diagnosis of DD and 17 were age-matched controls showing age-appropriate calculation performance. All of these children underwent detailed neuropsychological testing and DTI-measurements. The diagnosis of DD was confirmed in all children from the DD sample. None of the participants had neurological or psychiatric disorders, were on medication, or had any contraindications for MRI.

Parents gave informed consent and children received a voucher for their participation. The study was approved by the local ethics committee based on guidelines from the World Medical Association's Declaration of Helsinki (WMA 2002).

After preprocessing of DTI-data and a thorough data-quality check, 24 subjects had to be excluded due to insufficient data quality (please see "Data analysis" section for further information), which resulted in a group of 15 dyscalculic children and eight controls. Due to the small number of controls, additional DTI data sets of ten age- and gender-matched control children were included from two other studies running at the Center for MR-Research of the University Children's Hospital Zurich. DTI-data of these children had been acquired with the identical scan-protocol on the same scanner. Three children had to be excluded since the data did not pass our data-quality criteria, resulting in a final sample of 15 dyscalculic children and 15 control children matched for gender, age and handedness entering statistical DTI analysis. Table 1 summarizes demographic and behavioural data of participants. Please note that complete behavioural data were only available for eight control children deriving from the original study. From the remaining seven control children, measures of handedness, age, gender and intelligence were available, but not for the ZAREKI-R and CORSI-test.

Behavioural testing

Handedness

Handedness was determined by the Edinburgh Handedness Inventory (Oldfield 1971). Results are shown in Table 1.

Mathematical performance

Numerical abilities were assessed using the Neuropsychological Test Battery for number processing and calculation in children [ZAREKI-R: (von Aster et al. 2006)]. This neuropsychological battery examines the progress of basic skills in calculation and arithmetic and aims to identify and characterize the profile of mathematical abilities in children with dyscalculia. It is composed of 12 subtests such as counting forward and backward, writing numbers, addition, subtraction, multiplication, reading numbers, number line (verbal and Arabic digits), digit span forward and backward, number comparison (words), perceptual and cognitive quantity judgement, story problem, and finally number comparison of Arabic digits. Criteria for DD were met if a child's performance in the ZAREKI-R was 1.5 standard deviations below the average in three subtests or in the total score.

Intelligence quotient (IQ)

Intelligence was measured with three verbal (vocabulary, arithmetic, similarities) and two performance subtests (picture arrangement, block design) of the Wechsler Intelligence Scale for Children (WISC-III) (Wechsler 1999). Table 1 shows estimated IQ of these subtests as well as the total estimated IQ which is corrected for differences in arithmetical thinking. Estimated total IQ was calculated by the mean of picture arrangement, block design, vocabulary, and similarities.

Data from seven control children were included from parallel studies at the Center of MR-Research of the University Children's Hospital Zurich. Neuropsychological measures of intelligence also acquired by the WISC-test battery were available from these seven children, which are summarized in Table 1.

Spatial working memory

The Corsi Block-Tapping test was conducted to assess the visual block span forward (Corsi 1972). The basic idea of the Corsi Block-Tapping test is, by usage of a plate with cubes, to reproduce a sequence previously tapped by the investigator. In addition, the Corsi Block-Suppression test has been performed (Beblo et al. 2004). In this test, subjects are asked to reproduce only every second block of a

Table 1 Demographic and testmetric data

	Dyscalculics		Controls		*p* value
N	15		15		n.s.
Gender (f/m)	11/4		11/4		n.s.
Handedness (r/a/l)	12/2/1		14/1/0		n.s.
Age (years) (SD)	10.0 (1.2)		10.1 (1.3)		n.s.
Numerical abilities	*N*	Mean (SD)	*N*	Mean (SD)	
ZAREKI-R 1 counting forward	15	80.7 (32.5)	8	82.1 (35.2)	n.s.[a]
ZAREKI-R 2 counting backward	15	68.9 (43.6)	8	92.6 (20.9)	n.s. [a]
ZAREKI-R 3 writing numbers	15	35.1 (43.5)	8	92.1 (22.3)	<0.01[a]
ZAREKI-R 4a addition	15	31.6 (37.6)	8	80.1 (30.6)	<0.01
ZAREKI-R 4b subtraction	15	9.4 (11.3)	8	75.8 (26.4)	<0.001
ZAREKI-R 4c multiplication	15	66.1 (47.2)	8	88.1 (33.6)	n.s.[a]
ZAREKI-R 5 reading numbers	15	49.0 (46.9)	8	77.4 (41.9)	n.s.[a]
ZAREKI-R 6a number line (with lines)	15	71.0 (40.6)	8	83.9 (30.5)	n.s.[a]
ZAREKI-R 6b number line (without lines)	15	50.4 (28.1)	8	63.3 (24.7)	n.s.
ZAREKI-R 7a digit span forward	15	34.1 (20.2)	8	75.5 (20.0)	<0.001
ZAREKI-R 7b digit span backward	15	43.8 (23.4)	8	66.3 (19.3)	<0.05
ZAREKI-R 8 number comparison (words)	15	44.6 (39.0)	8	82.9 (23.6)	<0.01
ZAREKI-R 9 perceptual quantity judgement	15	63.1 (36.9)	8	88.8 (22.5)	n.s.[a]
ZAREKI-R 10 cognitive quantity judgement	15	84.1 (31.8)	8	85.5 (27.9)	n.s.[a]
ZAREKI-R 11 story problem	15	41.4 (45.7)	8	73.6 (39.6)	n.s.
ZAREKI-R 12 number comparison (digits)	15	47.4 (42.5)	8	82.5 (34.1)	n.s.[a]
ZAREKI-R total	15	15.1 (21.1)	8	68.9 (16.3)	<0.001
Intelligence					
WISC-III similarities	15	109.7 (14.9)	8	113.8 (7.4)	n.s.
WISC-III vocabulary	15	104.7 (10.9)	8	108.8 (11.6)	n.s.
WISC-III picture arrangement	15	98.3 (13.5)	8	101.9 (11.6)	n.s.
WISC-III block design	15	98.0 (15.8)	8	116.3 (10.9)	<0.01
WISC-III arithmetical thinking	15	92.7 (8.6)	8	106.9 (10.0)	<0.01
WISC-III total (corrected for arithmetical thinking[b])	15	102.7 (7.9)	8	110.2 (7.6)	n.s.
WISC-III total[c]			7	115.2 (13.9)	–
Memory					
CORSI block-tapping	15	4.7 (0.8)	8	5.0 (1.2)	n.s.
CORSI block-suppression	15	1.9 (0.6)	8	2.9 (1.0)	<0.01[a]

[a] Non-parametric testing because normal distribution of one or both groups is not assumed

[b] Arithmetical thinking is not included in the mean of HAWIK-III total and statistical comparison is corrected for arithmetical thinking

[c] Seven control children were recruited from parallel running studies at the Center for MR-Research of the University Children's Hospital Zurich for whom intelligence was also determined by subtests of the WISC-III

previous demonstrated sequence. The visual block span forward is associated with retrieving visual short-term information, whereas the Corsi Block-Suppression test is thought to require storage and manipulation of visual information.

DTI-data acquisition

Brain images were acquired from all 57 children on a 3.0-T whole-body scanner (GE Medical Systems, Milwaukee, WI, USA) using a standard eight-channel head coil. Images were sampled along 21 different encoding directions with a diffusion-weighted single-shot double spin-echo sequence. An effective b value of 1,000 s/mm^2 was used for each of the 21 directions. Five additional b0 measurements with a b value of 0 s/mm^2 were interleaved with the diffusion encoding scans. Thirty-nine continuous 3.2-mm-thick axial slices were acquired parallel to the anterior–posterior commissural line with a measured and reconstructed resolution of $0.94 \times 0.94 \times 3.2$ mm. Further imaging

parameters were: repetition time TR = 10.725 s, echo time TE = 87.3 ms, acquisition matrix size = 128 × 128 pixels (resampled to 256 × 256 pixels), flip angle = 90°, and field of view FOV = 240 × 240 mm^2. Scan time was 4 min 50 s.

Data analysis

Software

Statistical analysis of behavioural data was analysed using Predictive Analytics Software 18 (PASW). Significance was assumed on the $p < 0.05$ level.

DTI-data analysis was performed by FMRIB (functional MRI of the brain) software library (FSL) of the University of Oxford (Smith et al. 2004; Woolrich et al. 2009) and Statistical Parametric Mapping (SPM8) (Wellcome Department of Cognitive Neurology, London, UK on MATLAB Version R2010a, The Math-Works, Natick, MA, USA) as well as in-house software.

DTI preprocessing

First, in order to improve the robustness of the registration, skull and other non-brain tissue were removed from the brain images by creation of an individually adapted binary mask which determines the voxels of pure brain tissue. After correcting distortion due to eddy current effects and head motion, a diffusion tensor model was fitted at each voxel. This resulted in maps including all necessary DTI-parameters, such as FA, $\lambda 1$ (axial diffusivity = AD), $\lambda 2$, $\lambda 3$, $\varepsilon 1$, $\varepsilon 2$, $\varepsilon 3$, and mean diffusivity (MD) for each voxel. Radial diffusivity (RD) was calculated by $[(\lambda 2 + \lambda 3)/2]$. FA is thought to be related to white matter coherence and integrity and a decline in FA is often used as an index of decreasing white matter health. AD reflects the primary eigenvector describing water diffusivity in the direction of the fibre tract, and increasing AD values are often associated with axonal maturation. RD is assumed to be linked to myelin content, such that the higher the RD, the lower the degree of myelination. MD itself is rather non-specific, albeit increased MD may represent alterations in white matter microstructure attributed to pathophysiological processes.

Since DTI acquisition is prone to noise, all FA-maps were carefully checked for data quality. This was done by colour-coding the FA-maps and manual screening of all 39 slices of each subject. Bad slices were quickly visible by distortions in the colour distribution. Data sets with more than one faulty slice were excluded. Based on this strict quality checks, 27 from our 57 subjects had to be excluded. The remaining 15 dyscalculic and 15 control children entered the next data analysis steps.

All individual FA-maps were normalized by non-linear registration to a reference image. FA-templates serving this purpose are currently only available for adult brain images. Therefore, a study-specific template was determined among all subjects by estimating the average amount of warping that was necessary to align all other images to it. The one with the smallest amount of warping was then used as the reference image. After non-linear normalization to the reference image, an affine transformation into MNI152 space was performed to enable the subsequent reporting of coordinates. Finally, FA-maps were smoothed with a Gaussian kernel of the full-with at half maximum (FWHM) of 9 mm.

For subsequent statistical DTI analysis, it is important to control for the influence of individual variability of the total brain microstructure. For this purpose, the mean FA of the total brain was computed for every subject using the MarsBaR software tool by Matthew Brett.

Statistical analyses of DTI-data

DTI-parameters (FA, MD, AD, and RD) were compared between groups in a second-level whole brain analysis. Individual mean FA served as a covariate of no interest in the two-sample t test design matrix of the FA comparison. An implicit mask threshold of 0.1 was applied, which means that voxels with an FA value below 0.1 were excluded from the analysis.

A whole brain multiple regression analysis was then conducted. All behavioural parameters (see Table 1) were correlated with FA values in every voxel, while mean FA of the whole brain served as nuisance covariate. Behavioural data were z-transformed before entering the analysis. Design matrices were calculated for each behavioural parameter separately as well as in combined groups (IQ, including all 5 IQ subtests and total IQ; math, including all ZAREKI-subtests and total score; IQ and math, including total IQ- and total ZAREKI-score; working memory, including both CORSI-Block and CORSI-Suppression score). All children from whom behavioural data were available were included in the regression analysis (15 children with DD and eight controls).

Multiple statistical comparisons increase the risk of detecting significant differences in some voxels between groups just by chance. The application of a family-wise error (FWE) correction can prevent this from happening. Further the problem of non-stationary cluster inference, which occurs due to non-isotropic (non-uniform) smoothness of data leads to invalid cluster size statistics and an over- or underestimation of cluster sizes (Hayasaka et al. 2004). To correct for both problems, we used the toolbox "VBM8" of SPM8 developed by Christian Gaser (http://dbm.neuro.uni-jena.de/author/admin/). Reported results

reach a statistical p value of 0.001, a cluster extent threshold of $p < 0.01$, FWE-corrected for multiple comparisons, and are also corrected for non-isotropic smoothness.

Results

Behavioural testing

According to group definition, data analysis revealed significant differences in math performance assessed by the ZAREKI-R and the arithmetical thinking subtest of the WISC-III (for details please see Table 1). In contrast, both children with and without DD showed average estimated intelligence. However, children with DD reached lower levels in the block design subtest of the WISC-III. The estimated IQ of the seven control children derived from parallel studies showed intelligence above 85 (mean estimated IQ based on WISC-III subtests = 115.2, SD 13.9). Finally, the visual–spatial memory span measured by the CORSI Block-Tapping task was comparable between groups, but visual–spatial working memory capacity (CORSI Block-Suppression) was reduced in children with DD.

Whole brain analyses

Group differences

Fractional anisotropy (FA), mean diffusivity (MD), axial (AD), and radial diffusivity (RD) were compared in a two-sample t test between dyscalculic children and controls with mean FA, MD, AD or RD values as covariate, respectively. Only FA revealed significant differences between groups at a statistical p value of 0.001, including a FWE cluster extent correction at $p < 0.01$ (minimum cluster extent 1,530 voxels) and a correction for non-stationarity of smoothness. Dyscalculic children showed significantly lower FA values in three clusters which are all part of the superior longitudinal fasciculus (see Table 2; Fig. 1). No cluster was found to show higher FA values in DD children.

In order to ascertain whether the group differences in FA arise from differences in axial or radial diffusivity a more liberal statistical threshold was applied of $p < 0.001$, uncorrected. Differences in MD, AD and RD were only calculated within regions that have shown significant group differences in FA. Therefore, the significant clusters from the whole brain FA analysis served as regions of interest (ROIs). Within these ROIs, dyscalculic children showed higher RD compared to controls in three clusters at $p < 0.001$, uncorrected (see Table 3). No cluster showed lower RD in dyscalculic children at $p < 0.001$. Regarding AD, dyscalculic children exhibited lower AD values compared to controls only in one small cluster in the left hemisphere at $p < 0.001$ (see Table 3). AD was not higher in any voxel in DD children. Therefore, reduced FA in dyscalculic children appears to be explained by differences in RD than AD. MD did not differ between groups within the ROIs showing FA differences.

Correlations with behavioural parameters

Multiple regression analysis of behavioural data and FA values revealed no significant correlation in any voxel that would survive correction for multiple comparisons.

Region of interest analysis

Group differences

Differences between dyscalculic and control children in FA, MD, AD, and RD were not only analysed on a whole brain level, but additionally in predefined ROIs representing the most important fibre tracts. The superior longitudinal fasciculi (SLF), the inferior longitudinal fasciculi (ILF), the cinguli (CI), and the uncinate fasciculi (UF) served as ROIs. These ROIs were derived from the JHU white matter tractography atlas, which is included in FSL (Mori et al. 2005; Hua et al. 2008; Wakana et al. 2007). The ROIs were thresholded by 33 % for the SLF and ILF. The thresholding assures that at least 33 % of all subjects contain fibres in the corresponding tract. The thresholding was performed by the image calculation tool (ImCal) of SPM. The CI and UF were thresholded at 15 % to gain a comparable number of fibres. Only the SLF showed significant differences. Since the SLF is a large fibre tract, we decided to further split our SLF ROI into an anterior, a posterior and inferior part. The splitting was performed in the middle of the longest dimension (anterior to posterior), resulting in an anterior SLF ROI and a posterior part of the SLF. The posterior part was the split further in the middle of the longest inferior to superior extension creating an inferior SLF ROI and a superior SLF ROI. For illustration please see Fig. 2. The most prominent differences were evident in the posterior SLF. Dyscalculic children showed significantly lower FA in this ROI at a Bonferroni corrected threshold level of $p < 0.008$. In addition, at an uncorrected p level of 0.05, dyscalculic children showed lower FA in the left anterior SLF, higher RD in the posterior SLF on both hemispheres, and a trend towards reduced MD in the right anterior SLF. Please see Table 4 for a summary of all differences in the SLF ROIs.

Table 2 Whole brain analysis of FA (control vs. dyscalculic children)

Fibre tract	Cluster size (voxels)	*T* value	MNI coordinates		
			x	*y*	*z*
(A) Left SLF near parietal lobe	2,523	7.02	−41	−34	27
(B) Left SLF near central operculum and secondary somatosensory cortex	2,433	6.37	−42	−7	17
(C) Right SLF near insula	1,991	4.10	38	−19	12

SLF superior longitudinal fasciculus

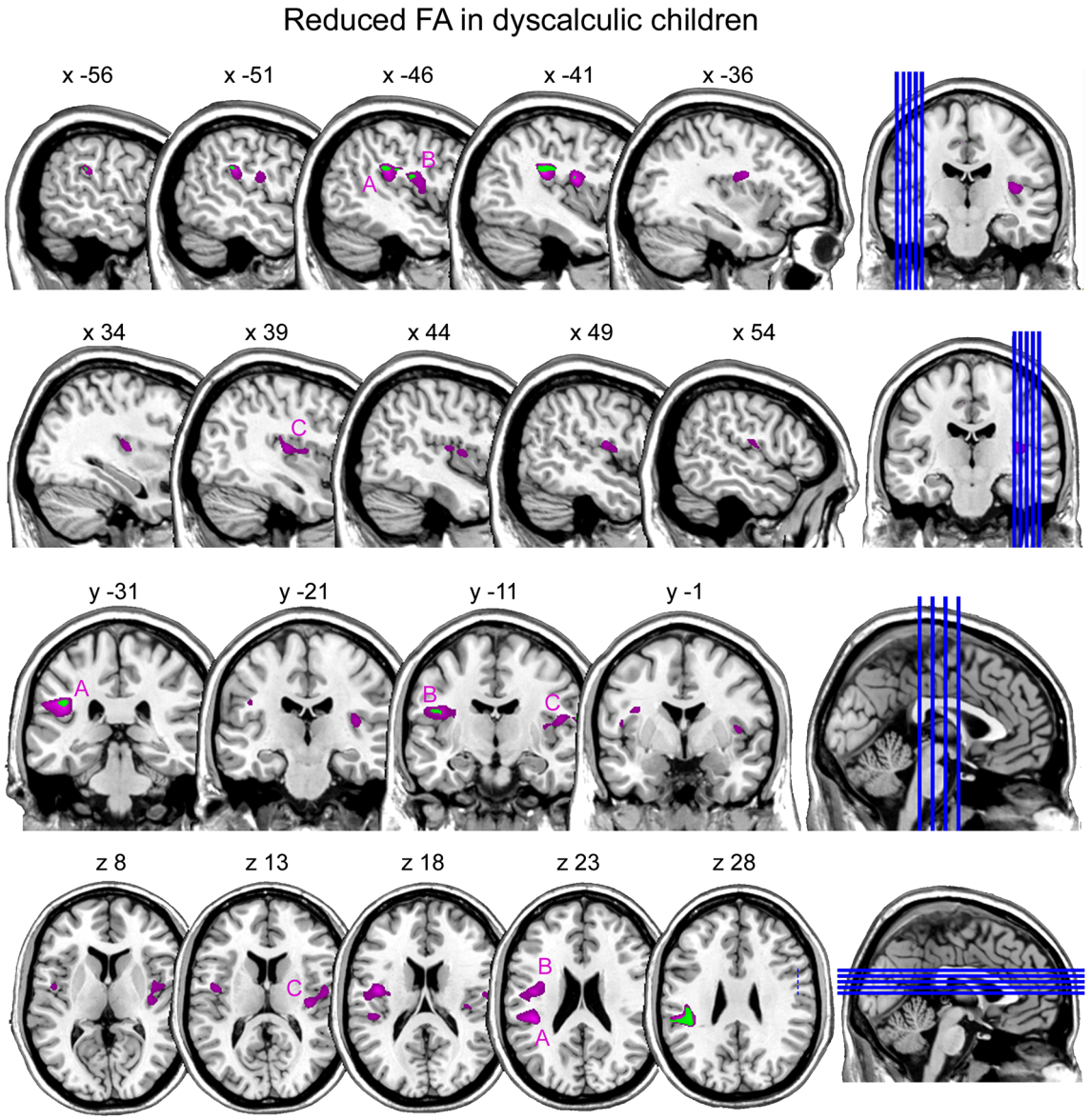

Fig. 1 Sagittal slices of the left and right hemisphere, coronal and axial slices illustrate regions in *pink* where children with DD show reduced fractional anisotropy (FA) compared to control children at $p < 0.001$ corrected for multiple comparisons: **a** left superior longitudinal fasciculus, close to parietal lobe; **b** left superior longitudinal fasciculus, close to central operculum and secondary somatosensory cortex; **c** right superior longitudinal fasciculus, close to insula. Within this pattern of reduced FA, dyscalculic children showed increased radial diffusivity (RD) at $p < 0.001$ uncorrected marked in *green*

Table 3 Analysis of radial (RD) and axial (AD) diffusivity within areas showing significant group differences in FA

DTI parameter	Contrast	Fibre tract	Cluster size (voxels)	*T* value	MNI coordinates		
					x	*y*	*z*
RD	DD > CC	(A) Left SLF near parietal lobe	531	4.24	−42	−31	28
		(B) Left SLF near central operculum and secondary somatosensory cortex	110	3.73	−46	−12	21
		(B) Left SLF near parietal operculum and secondary somatosensory cortex	10	3.65	62	−10	15
AD	CC > DD	(C) Left SLF near Brocca's area	37	4.52	−37	1	22

SLF superior longitudinal fasciculus

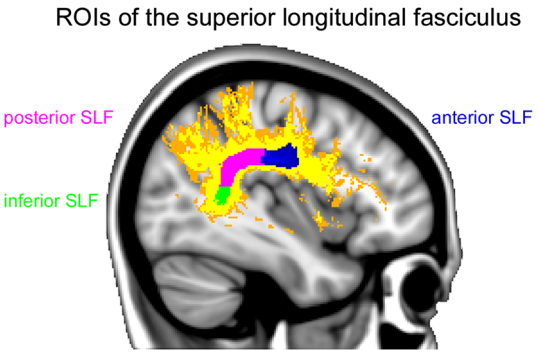

Fig. 2 The superior longitudinal fasciculus (SLF) shown in *yellow* was thresholded at 33 % probability and split into three different regions of interest (ROIs): an inferior (*green*), posterior (*pink*), and anterior (*blue*) part. The figure illustrates only the ROIs of the left hemisphere. Most prominent differences in fractional anisotropy (FA) and radial diffusivity (RD) between children with DD and controls were evident in the posterior (*pink*) ROI on both hemispheres

Table 4 ROI analysis in the segmented SLF comparing children with and without DD

ROIs	*p* values (one-tailed two-sample *t* test)			
	FA	MD	AD	RD
Anterior SLF				
Left	**0.038**	0.483	0.206	0.316
Right	0.195	0.092	0.070	0.245
Posterior SLF				
Left	**0.005**[a]	0.113	0.302	**0.010**
Right	**0.003**[a]	0.332	0.073	**0.021**
Inferior SLF				
Left	0.375	0.166	0.388	0.218
Right	0.178	0.350	0.095	0.328

Bold values are reaching significance

[a] Reaching Bonferroni correction of $p > 0.008$

Correlations with behavioural parameters

In order to evaluate the relationship between behavioural measures and FA values in ROIs that have shown significant group differences, a partial correlation was conducted. All subjects were included and the influence of individual differences in mean FA of the entire brain was measured with a correlation analysis. Table 5 summarizes significant correlation coefficients and *p* values. Most prominent correlations were found in the posterior SLF: on the left hemisphere FA correlated positively with the performance in the number line 6a subtests ($r = 0.484$, $p < 0.05$) and in both hemispheres with digit span forward 7a subtests (right: $r = 0.605$, $p < 0.01$; left: $r = 0.524$, $p < 0.05$) of the ZAREKI-R. Furthermore, multiplication abilities assessed in the ZAREKI-R 4c showed a significant correlation with FA in the inferior ROI of the SLF, only in the left hemisphere. Finally, FA of the anterior part of the SLF was significantly related to number line representation measured in the ZAREKI-R 6a and to more domain-general skills depicted in the WISC-III similarities subtest.

To examine whether the observed relations between behavioural measures and FA values are not only driven by group differences, we analysed the correlations within each group. Results indicated that most of the correlations over all subjects are mainly driven by children with DD, because control children performed at ceiling level and showed low variance in number processing and calculation tasks. This is the case in the left posterior SLF for the digit span forward 7a subtest of the ZAREKI-R (in DD: $r = 0.259$, $p = 0.393$; in CC: $r = 0.221$, $p = 0.633$), the left inferior SLF for the multiplication subtest of the ZAREKI-R (in DD: $r = -0.642$, $p = 0.018$; in CC: $r = 0.028$, $p = 0.952$), as well as in the left anterior SLF for the number line 6a subtest of the ZAREKI-R (in DD: $r = 0.722$, $p = 0.005$; in CC: $r = 0.093$, $p = 0.843$) and the similarities subtest of the WISC-III (in DD: $r = 0.684$, $p = 0.010$; in CC: $r = -0.442$, $p = 0.321$).

In contrast, the relation between FA values and performance of the number line 6a subtest of the ZAREKI-R in the left posterior SLF (in DD: $r = 0.363$, $p = 0.222$; in CC: $r = 0.723$, $p = 0.067$) and digit span forward skills measured in the ZAREKI-R 7a in the right posterior SLF (in DD: $r = 0.238$, $p = 0.434$; in CC: $r = 0.713$, $p = 0.072$) appear to be driven by control children.

Table 5 Partial correlation between behavioural parameters and FA values in ROIs corrected for mean FA

Behavioural tests	Fractional anisotropy (FA)									
	Posterior SLF				Anterior SLF				Inferior SLF	
	L		R		L		R		L	R
ZAREKI-R 4c multiplication									*r* −0.447	
									p 0.042	
ZAREKI-R 6a number line (with lines)	*r*	0.484			*r*	0.522				
	p	0.026			*p*	0.015				
ZAREKI-R 7a digit span forward	*r*	0.524	*r*	0.605						
	p	0.015	*p*	0.004						
WISC-III similarities					*r*	0.479				
					p	0.028				

r correlation coefficient, *p* *p* value, *L* left, *R* right, *SLF* superior longitudinal fasciculus

Discussion

The present study addressed the question of whether deficits in numeracy are rooted in neurobiological anomalies in white matter tracts, using the DTI brain imaging method to investigate white matter properties in children with and without a specific learning disability in math (developmental dyscalculia = DD). Findings revealed deficient white matter integrity in children with DD in the SLF, an important fibre tract connecting parietal and frontal brain regions. Most prominent differences were evident in white matter close to the intraparietal sulcus, the key region for number processing. Furthermore, dyscalculic and typical calculators both yielded significant correlations between the degree of FA in these regions and numerical abilities.

Group differences whole brain analysis

The present study revealed striking differences in white matter integrity between children with and without DD. FA as a quantitative indicator of white matter coherence and integrity was reduced in children with DD in three clusters, all belonging to the SLF. On the left hemisphere, cluster A is located near the parietal lobe at the tip of the intraparietal sulcus. In the elongation of the fibre tract towards the frontal lobe, cluster B appears which is in vicinity to the central operculum and secondary somatosensory cortex. The third cluster C is located close to the insula on the right hemisphere. Reduced FA is often associated with pathological processes and lower cognitive performance [for review please see Hüppi (2010)]. Similarly, there is growing evidence that deficits in reading (developmental dyslexia) are related to lower FA values [for review please see Vandermosten et al. (2012)]. Moreover, developmental studies report an increase of FA from childhood to adulthood [for review please see Hüppi and Dubois (2006)]. In general, FA is thought to be influenced by myelin-sheets around axons, axonal membrane, axon properties like the number and size of axons or axonal density and the parallel organization of fibres and filaments. All these properties restrict the diffusivity, and the main contribution to FA stems from the interaxonal space rather than restricted diffusion in the axoplasm [please see review article by Le Bihan et al. (2001)]. Further investigation indicated that group differences in FA were largely explained by differences in RD and AD. In a similar vein, research on dyslexia has suggested that the white matter abnormalities that underlie reading impairments are mainly rooted in atypical RD rather than in AD [for review please see Vandermosten et al. (2012)]. RD is assumed to be related to the degree of myelination whereas AD is thought to reflect axonal maturation. Therefore, reduced white matter integrity in children with DD might be due to deficient myelination of fibres rather than axonal development. However, since the neurophysiological underpinnings of FA, RD and AD are still unclear, interpretations are rather speculative and probably oversimplified (Wheeler-Kingshott and Cercignani 2009).

Our results indicate that the superior longitudinal pathway is atypical in children with DD. The SLF emanating from the parietal lobe can be seen as one of the major projection fibres according to the known functional neuroanatomy of numerical cognition in children and adults (Kaufmann et al. 2011; Kucian et al. 2008; Dehaene et al. 2003; Arsalidou and Taylor 2011). Similarly, Tsang et al. (2009) identified the SLF as the most relevant connection of the inferior parietal lobe/IPS with precentral and frontal regions involved in calculation. Moreover, they report a positive correlation of FA values in the left SLF with arithmetic approximation skills in typically achieving children. These results support our findings and strengthen the notion that the SLF plays a critical role in the development of numerical reasoning and might be impaired or developmentally retarded in dyscalculia. Similarly, van

Eimeren et al. (2008) also linked arithmetical abilities with white matter microstructure in the left SLF in typically achieving children, but only the inferior part of the fibre connection reached significance.

Consistent with these findings, Rykhlevskaia et al. (2009) identified abnormalities in white matter fibre tracts related to dyscalculia. However, they reported the ILF and fronto-occipital fasciculus to be mainly affected on the right hemisphere. In addition to these two pathways, five other tracts were identified that showed a reduced degree of FA in children with DD, including the SLF. Differences with respect to our results are most likely explained by the fact that Rykhlevskaia et al. restricted their analysis to a predefined region in the right temporo-parietal cortex where children with DD exhibited reduced white matter volume defined by voxel-based morphometry. Since FA seems more sensitive than volume loss, other fibre connections are expected to be impaired next to the ones included in the regions showing reduced white matter volume as reported by Rykhlevskaia (Hugenschmidt et al. 2008), given the relation between white matter volume and integrity. Therefore, our results provide important new insights into abnormalities of white matter integrity related to DD on an unbiased whole brain level.

ROI analysis

Atlas-based definition of major fibre tracts in the brain as ROIs supported our whole brain analysis by specifically identifying the SLF to be affected in children with DD. Since the SLF represents a wide-ranging fibre connection, we decided to split the tract into an inferior, posterior, and superior part. Comparison of mean FA in these parts between groups revealed prominent and highly significant deficits in the posterior SLF on both hemispheres in children with DD. The posterior part of the SLF is in closest proximity to the intraparietal sulcus. Interestingly, results from investigating the brains of rhesus monkeys showed projections of the SLF to the intraparietal sulcus (Schmahmann et al. 2007). In terms of DD, recent work has emphasized core structural and functional deficits in the parietal lobes including the IPS (Kucian et al. 2006, 2011a, b; Mussolin et al. 2010; Price et al. 2007; Kaufmann et al. 2009; Kovas et al. 2009). Furthermore, studies in patient groups with reduced numerical understanding also showed white matter aberrations close to the parietal lobes that contribute to their reduced arithmetic abilities (Barnea-Goraly et al. 2005; Till et al. 2011). Consistent with these findings, our results suggest that the fibres connecting the key region for numerical representation with other areas necessary for number processing and calculation are impaired or developmentally delayed in children with DD.

Relation to behavioural measures

Correlation of behavioural measures with mean FA values in predefined ROIs of the SLF revealed some interesting relations. The ability to identify the location of a spoken number on a number line is assumed to be a measure of the internal representation of the mental number line. This skill correlated positively with white matter integrity in the left posterior SLF. On a functional level, the IPS is thought to code the mental number line (Fulbright et al. 2003; Kucian et al. 2011a). Moreover, number line performance also correlated with the adjacent anterior part of the SLF. Therefore, not only the IPS but also the intact connection of parietal areas with the frontal lobe through the SLF in the left hemisphere seems to be essential for the spatial numerical representation.

Further, digit span forward test showed a significant relation to white matter integrity in the posterior SLF. Digit span forward represents the memory span of numbers and is therefore a measure of short-term memory capacities. It is known that parietal areas are not exclusively involved in processing numerical functions. Among others, memory capacities also rely on parietal activations (Knops et al. 2006). Hence, connection of parietal regions with the frontal lobe in both hemispheres seems to be important for efficient numerical memory span processes.

In addition to numeracy, domain-general capabilities like abstract and concrete verbal reasoning abilities also correlate significantly with white matter integrity in our ROIs, since the verbal reasoning skills measured by the similarities subtest of the WISC-III are linked to the degree of FA in the anterior part of the SLF. Fronto-parietal pathways in particular, including the SLF, are claimed to contribute to intelligence (Barbey et al. 2012; Deary et al. 2010; Gläscher et al. 2010). A recent study (Barbey et al. 2013) identified the dorsolateral prefrontal cortex as a region providing an integrative domain-general neural architecture for human intelligence, which may underlie our observed correlation with markers of intelligence in the anterior part of the SLF.

Finally, multiplication abilities were related to white matter integrity in the inferior part of the left SLF, which is close to the angular gyrus. Left lateralized activation of the angular gyrus has been observed in numerical fact retrieval tasks such as multiplication (Delazer et al. 2003; Grabner et al. 2011). In line with these observations, our results suggest that fibres projecting to or from this region may be relevant for multiplication competencies. However, in contrast to other findings, we observed a negative relation such that children with low FA values exhibited better multiplication skills. Studies examining white matter integrity in children with developmental dyslexia similarly reported inverse relations between FA and reading related

measures in some areas [for review please see Vandermosten et al. (2012)]. It seems that better performance is not always associated with higher FA, further illustrating that the relationship between diffusion measures and behaviour are still unclear and interpretation has to be taken with care.

Limitations

Some limitations have to be considered when evaluating the present study. First, due to the strict inclusion criteria with regard to the quality of the imaging data, we had to exclude 24 children out of the total sample of 47 kids. As a consequence, we were reliant on the inclusion of an additional seven control children from parallel studies. These seven control children underwent the identical MR-measurements and behavioural tests of intelligence. However, study-specific data of the ZAREKI-R and the CORSI tests were not collected from these children, so the correlation analyses could only be done in a reduced sample size. Second, control children performed at ceiling level in the numerical tasks, leading to a reduction of correlation strength. Third, the problem of multicollinearity has to be taken into account, which means that correlations can change erratically in response to small changes in the data. These factors might explain why most of the correlations did not reach significance when calculating them within the group of control children. Therefore, correlative results and their interpretation have to be taken with care and we suggest further investigation of these relationships in future studies in more detail.

Finally, DTI interpretation needs to be done with great caution. Current DTI analyses cannot determine the unique influence of neuroanatomical factors such as myelination or fibre properties on FA (Wheeler-Kingshott and Cercignani 2009). Moreover, since a high density of fibre crossings can also affect FA values in these areas, we cannot exclude the possibility that group differences in FA are explained by a different number of crossing fibres in these regions (Wheeler-Kingshott and Cercignani 2009).

Impact

The SLF represents one of the longest association fibre tracts and connects mainly the frontal cortex with the dorso-lateral parietal and temporal cortex. This important fibre connection has been reported to be involved in a range of cognitive functions including cognitive processing speed (Turken et al. 2008), spatial working memory (Vestergaard et al. 2011), reading (Rauschecker et al. 2009), and arithmetic (Tsang et al. 2009). Interestingly, the parieto-frontal integration theory of intelligence claims that general intelligence requires undisrupted information transfer among parietal and frontal regions (Jung and Haier 2007). To date, there is a growing consensus that intelligence does not reside in a single brain region. Intelligence seems to be best described by fast and accurate integration and control of information processing among different brain regions (Naghavi and Nyberg 2007; Deary et al. 2010). It is interesting to note that two lesion mapping studies pointed to the SLF as one of the major fibre tracts implicated in general intelligence (Barbey et al. 2012; Gläscher et al. 2010). In addition, studies examining white matter integrity in childhood support the notion that fronto-parietal connections are significantly involved in general intelligence (Deary et al. 2006; Schmithorst et al. 2005).

On these grounds, in the context of results presented in the current study, it seems not surprising that many children with DD might show additional impairments in domains contributing to measures of intelligence. For instance, in addition to numeracy children with DD also show problems in spatial working memory on behavioural and neural levels (Rotzer et al. 2009). It seems plausible that impairments in the fast and accurate transfer of information between parietal and frontal lobes via the SLF affect not only numeracy, but additionally hinder general fronto-parietal integration of information. Furthermore, standard neuropsychological test batteries assessing intelligence also include subtests reliant on numerical understanding and calculation. Both factors can affect measures of intelligence in children with DD. In addition, these results question the current principle of DD diagnosis which requires a discrepancy between numerical and general intellectual skills, and might be seen as neurobiological evidence for reconsidering the diagnostic criterion of DD relative to intelligence. Similarly in the research field of developmental dyslexia, brain imaging results converge with behavioural evidence indicating that, regardless of IQ, poor readers have similar kinds of reading difficulties in relation to phonological processing (Tanaka et al. 2011). We assume that comparable mechanisms might be observed in children with DD and we are looking forward to future research addressing this question specifically.

Conclusion

The present results highlight a connection deficit between parietal and frontal areas in children with DD. In particular, the SLF seems to be affected in parts that are adjacent to key areas for number processing, namely the IPS. The development of axonal coherence and/or myelination projecting to/from the parietal lobe might be impaired or delayed in dyscalculia, leading to the possibility that DD might be seen as a dysconnection syndrome. However, it cannot be clarified whether observed impairments in fibre tracts are a cause or consequence of generally deficient

activation in parietal regions in children with DD. Finally, since the SLF can be seen as a critical tract of a core system allowing integration and control of widespread information processes in the brain, additional problems in higher cognitive functions are likely and might underlie the behavioural deficits observed outside the numerical domain in dyscalculia.

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References

Arsalidou M, Taylor MJ (2011) Is 2 + 2 = 4? Meta-analyses of brain areas needed for numbers and calculations. Neuroimage 54(3):2382–2393

Barbey AK, Colom R, Solomon J, Krueger F, Forbes C, Grafman J (2012) An integrative architecture for general intelligence and executive function revealed by lesion mapping. Brain 135(Pt 4): 1154–1164

Barbey AK, Colom R, Grafman J (2013) Dorsolateral prefrontal contributions to human intelligence. Neuropsychologia 51(7): 1361–1369

Barnea-Goraly N, Eliez S, Menon V, Bammer R, Reiss AL (2005) Arithmetic ability and parietal alterations: a diffusion tensor imaging study in velocardiofacial syndrome. Brain Res Cogn Brain Res 25(3):735–740

Beblo T, Macek C, Brinkers I, Hartje W, Klaver P (2004) A new approach in clinical neuropsychology to the assessment of spatial working memory: the block suppression test. J Clin Exp Neuropsychol 26(1):105–114

Corsi PM (1972) Human memory and the temporal region of the brain. Diss Abstr Int 34(2-B):891

Deary IJ, Bastin ME, Pattie A, Clayden JD, Whalley LJ, Starr JM, Wardlaw JM (2006) White matter integrity and cognition in childhood and old age. Neurology 66(4):505–512

Deary IJ, Penke L, Johnson W (2010) The neuroscience of human intelligence differences. Nat Rev Neurosci 11(3):201–211

Dehaene S, Piazza M, Pinel P, Cohen JD (2003) Three parietal circuits for number processing. Cogn Neuropsychol 20(3): 487–506

Delazer M, Domahs F, Bartha L, Brenneis C, Lochy A, Trieb T, Benke T (2003) Learning complex arithmetic—an fMRI study. Brain Res Cogn Brain Res 18(1):76–88

Duncan GJ, Dowsett CJ, Claessens A, Magnuson K, Huston AC, Klebanov P, Pagani LS, Feinstein L, Engel M, Brooks-Gunn J, Sexton H, Duckworth K, Japel C (2007) School readiness and later achievement. Dev Psychol 43(6):1428–1446

Fulbright RK, Manson SC, Skudlarski P, Lacadie CM, Gore JC (2003) Quantity determination and the distance effect with letters, numbers, and shapes: a functional MR imaging study of number processing. AJNR Am J Neuroradiol 24(2):193–200

Gläscher J, Rudrauf D, Colom R, Paul LK, Tranel D, Damasio H, Adolphs R (2010) Distributed neural system for general intelligence revealed by lesion mapping. Proc Natl Acad Sci USA 107(10):4705–4709

Grabner RH, Ansari D, Koschutnig K, Reishofer G, Ebner F (2011) The function of the left angular gyrus in mental arithmetic: evidence from the associative confusion effect. Hum Brain Mapp 34(5):1013–1024

Gross J, Hudson C, Price D (2009) The long term costs of numeracy difficulties. Every Child a Chance Trust and KPMG, London

Hayasaka S, Phan KL, Liberzon I, Worsley KJ, Nichols TE (2004) Nonstationary cluster-size inference with random field and permutation methods. Neuroimage 22(2):676–687

Holmes RD, Mazabel S, Maedler B, Denk C, Siegel L, Beaulieu C, MacKay A (2010) Cerebral myelin content correlation with mathematical abilities in young children. In: ISMRM-ES-MRMB, Stockholm

Hu Y, Geng F, Tao L, Hu N, Du F, Fu K, Chen F (2011) Enhanced white matter tracts integrity in children with abacus training. Hum Brain Mapp 32(1):10–21

Hua K, Zhang J, Wakana S, Jiang H, Li X, Reich DS, Calabresi PA, Pekar JJ, van Zijl PC, Mori S (2008) Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. Neuroimage 39(1):336–347

Hugenschmidt CE, Peiffer AM, Kraft RA, Casanova R, Deibler AR, Burdette JH, Maldjian JA, Laurienti PJ (2008) Relating imaging indices of white matter integrity and volume in healthy older adults. 18(2):433–442. doi:10.1093/cercor/bhm080

Hüppi PS (2010) Growth and development of the brain and impact on cognitive outcomes. Nestle Nutr Workshop Ser Pediatr Program 65:137–149 (discussion 149–151)

Hüppi PS, Dubois J (2006) Diffusion tensor imaging of brain development. Sem Fetal Neonatal Med 11(6):489–497

Jung RE, Haier RJ (2007) The parieto-frontal integration theory (P-FIT) of intelligence: converging neuroimaging evidence. Behav Brain Sci 30(2):135–154 (discussion 154–187)

Kaufmann L, Vogel S, Starke M, Kremser C, Schocke M (2009) Numerical and non-numerical ordinality processing in children with and without developmental dyscalculia: evidence from fMRI. Cogn Dev 24(4):486–494

Kaufmann L, Wood G, Rubinsten O, Henik A (2011) Meta-analyses of developmental fMRI studies investigating typical and atypical trajectories of number processing and calculation. Dev Neuropsychol 36(6):763–787

Knops A, Nuerk HC, Fimm B, Vohn R, Willmes K (2006) A special role for numbers in working memory? An fMRI study. Neuroimage 29(1):1–14

Koch K, Wagner G, Dahnke R, Schachtzabel C, Gullmar D, Reichenbach JR, Schlosser RG (2010) Structure-function relationships in the context of reinforcement-related learning: a combined diffusion tensor imaging-functional magnetic resonance imaging study. Neuroscience 168(1):190–199

Kovas Y, Giampietro V, Viding E, Ng V, Brammer M, Barker GJ, Happe FG, Plomin R (2009) Brain correlates of non-symbolic numerosity estimation in low and high mathematical ability children. PLoS One 4(2):e4587

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. Behav Brain Funct 2:31

Kucian K, von Aster M, Loenneker T, Dietrich T, Martin E (2008) Development of neural networks for exact and approximate calculation: a FMRI study. Dev Neuropsychol 33(4):447–473

Kucian K, Grond U, Rotzer S, Henzi B, Schonmann C, Plangger F, Galli M, Martin E, von Aster M (2011a) Mental number line training in children with developmental dyscalculia. Neuroimage 57(3):782–795

Kucian K, Loenneker T, Martin E, von Aster M (2011b) Non-symbolic numerical distance effect in children with and without developmental dyscalculia: a parametric FMRI study. Dev Neuropsychol 36(6):741–762

Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriat H (2001) Diffusion tensor imaging: concepts and applications. J Magn Reson Imaging 13(4):534–546

Mori S, Van Zijl PC, Oishi K, Faria AV (2005) MRI atlas of human white matter. Elsevier, Amsterdam

Mussolin C, De Volder A, Grandin C, Schlogel X, Nassogne MC, Noel MP (2010) Neural correlates of symbolic number comparison in developmental dyscalculia. J Cogn Neurosci 22(5): 860–874

Naghavi HR, Nyberg L (2007) Integrative action in the fronto-parietal network: a cure for a scattered mind. Behav Brain Sci 30:161–162

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9(1):97–113

Parsons S, Bynner J (2005) Does numeracy matter more? National Research and Development Centre for adult literacy and numeracy. Institute of Education, London

Price GR, Holloway I, Räsänen P, Vesterinen M, Ansari D (2007) Impaired parietal magnitude processing in developmental dyscalculia. Curr Biol 17(24):R1042–R1043

Rauschecker AM, Deutsch GK, Ben-Shachar M, Schwartzman A, Perry LM, Dougherty RF (2009) Reading impairment in a patient with missing arcuate fasciculus. Neuropsychologia 47(1):180–194

Reigosa-Crespo V, Valdes-Sosa M, Butterworth B, Estevez N, Rodriguez M, Santos E, Torres P, Suarez R, Lage A (2012) Basic numerical capacities and prevalence of developmental dyscalculia: the Havana survey. Dev Psychol 48(1):123–135

Rotzer S, Loenneker T, Kucian K, Martin E, Klaver P, von Aster M (2009) Dysfunctional neural network of spatial working memory contributes to developmental dyscalculia. Neuropsychologia 47(13):2859–2865

Rykhlevskaia E, Uddin LQ, Kondos L, Menon V (2009) Neuroanatomical correlates of developmental dyscalculia: combined evidence from morphometry and tractography. Front Hum Neurosci 3:51

Schmahmann JD, Pandya DN, Wang R, Dai G, D'Arceuil HE, de Crespigny AJ, Wedeen VJ (2007) Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. Brain 130(Pt 3):630–653

Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK (2005) Cognitive functions correlate with white matter architecture in a normal pediatric population: a diffusion tensor MRI study. Hum Brain Mapp 26(2):139–147

Shalev RS, von Aster M (2008) Identification, classification, and prevalence of developmental dyscalculia. Encyclopedia of Language and Literacy Development, London, pp 1–9

Shalev RS, Auerbach J, Manor O, Gross-Tsur V (2000) Developmental dyscalculia: prevalence and prognosis. Eur Child Adolesc Psychiatry 9(Suppl 2):II58–II64

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23(Suppl 1):S208–S219

Tanaka H, Black JM, Hulme C, Stanley LM, Kesler SR, Whitfield-Gabrieli S, Reiss AL, Gabrieli JD, Hoeft F (2011) The brain basis of the phonological deficit in dyslexia is independent of IQ. Psychol Sci 22(11):1442–1451

Till C, Deotto A, Tipu V, Sled JG, Bethune A, Narayanan S, Arnold DL, Banwell BL (2011) White matter integrity and math performance in pediatric multiple sclerosis: a diffusion tensor imaging study. Neuroreport 22(18):1005–1009

Tsang JM, Dougherty RF, Deutsch GK, Wandell BA, Ben-Shachar M (2009) Frontoparietal white matter diffusion properties predict mental arithmetic skills in children. Proc Natl Acad Sci USA 106(52):22546–22551

Turken A, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JD (2008) Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. Neuroimage 42(2):1032–1044

van Eimeren L, Niogi SN, McCandliss BD, Holloway ID, Ansari D (2008) White matter microstructures underlying mathematical abilities in children. Neuroreport 19(11):1117–1121

Vandermosten M, Boets B, Wouters J, Ghesquière P (2012) A qualitative and quantitative review of diffusion tensor imaging studies in reading and dyslexia. Neurosci Biobehav Rev 36(6):1532–1552

Vestergaard M, Madsen KS, Baare WF, Skimminge A, Ejersbo LR, Ramsoy TZ, Gerlach C, Akeson P, Paulson OB, Jernigan TL (2011) White matter microstructure in superior longitudinal fasciculus associated with spatial working memory performance in children. J Cogn Neurosci 23(9):2135–2146

von Aster M, Weinhold Zulauf M, Horn R (2006) ZAREKI-R (neuropsychological test battery for number processing and calculation in children), revidierte version. Harcourt Test Services, Frankfurt

von Aster M, Schweiter M, Weinhold Zulauf M (2007) Rechenstörungen bei Kindern: Vorläufer, Prävalenz und psychische Symptome. Z Entwicklungspsychol Padagog Psychol 39(2):85–96

Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Perry M, Gollub RL, Hua K, Zhang J, Jiang H, Dubey P, Blitz A, van Zijl P, Mori S (2007) Reproducibility of quantitative tractography methods applied to cerebral white matter. Neuroimage 36(3): 630–644

Wechsler D (1999) WISC-III Wechsler Intelligence Scale for Children, 3rd edn. Hans Huber, Bern, Göttingen, Toronto, Seattle

Wheeler-Kingshott CA, Cercignani M (2009) About "axial" and "radial" diffusivities. Magn Reson Med 61(5):1255–1260

WMA (2002) The World Medical Association's Declaration of Helsinki: ethical principles for medical research involving human subjects. WMA General Assembly, Washington

Woolrich MW, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T, Beckmann C, Jenkinson M, Smith SM (2009) Bayesian analysis of neuroimaging data in FSL. Neuroimage 45(1 Suppl):S173–S186