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# Optimized voxel-based morphometry in children with developmental dyscalculia

S. Rotzer,[a,*,1] K. Kucian,[a,1] E. Martin,[a] M. von Aster,[a,c] P. Klaver,[a] and T. Loenneker[a,b]

[a] University Children's Hospital, MR-Center, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland
[b] Center for Integrative Human Physiology, University of Zurich, Switzerland
[c] Department of Child and Adolescent Psychiatry, German Red Cross Hospitals Westend, Berlin, Germany

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**Developmental dyscalculia (DD) is a specific learning disability affecting the normal acquisition of arithmetic skills. Current studies estimate that 3–6% of the school population is affected by DD. Genetic, neurobiological, and epidemiologic evidence indicates that dyscalculia is a brain-based disorder. Imaging studies suggest the involvement of parietal and prefrontal cortices in arithmetic tasks.**

**The aim of the present study was to analyze if children with DD show structural differences in parietal, frontal, and cingulate areas compared to typically achieving children.**

**Magnetic resonance imaging was obtained from 12 children with DD aged 9.3 ± 0.2 years and 12 age-matched control children without any learning disabilities on a 1.5 T whole-body scanner. Voxel-based morphometry analysis with an optimization of spatial segmentation and normalization procedures was applied to compare the two groups in order to find differences in cerebral gray and white matter.**

**Compared to controls, children with DD show significantly reduced gray matter volume in the right intraparietal sulcus (IPS), the anterior cingulum, the left inferior frontal gyrus, and the bilateral middle frontal gyri. White matter comparison demonstrates clusters with significantly less volume in the left frontal lobe and in the right parahippocampal gyrus in dyscalculic children.**

**The decreased gray and white matter volumes in the frontoparietal network might be the neurological substrate of impaired arithmetic processing skills. The white matter volume decrease in parahippocampal areas may have influence on fact retrieval and spatial memory processing.**

*Keywords:* Gray matter; White matter; Learning disability; Number processing; Working memory

## Introduction

Children with developmental dyscalculia (DD) show a significant discrepancy between specific math performance and general intelligence that cannot be explained by mental retardation, inappropriate schooling, or poor social environment. The prevalence of developmental dyscalculia is 3 to 6% in the school aged population. Unlike other learning disabilities, little is known about its underlying neural mechanisms (Schweiter et al., 2005; Shalev et al., 2000; Shalev and Gross-Tsur, 2001). Current data indicate that this learning disability is a brain-based disorder (Alarcon et al., 1997; Dellatolas et al., 2000; Kucian et al., 2006; Shalev and Gross-Tsur, 2001; Shalev et al., 2001).

The underlying brain processes of arithmetic performance in adults are well studied. Functional brain imaging (fMRI) studies with typically achieving adults have identified a number of brain regions involved in the performance of arithmetic tasks (Dehaene et al., 1999; Kawashima et al., 2004; Rivera et al., 2005; Rueckert et al., 1996). Dehaene et al. (2003) describe the horizontal segment of the intraparietal sulcus (HIPS) as the region most specifically involved in number representation. Activation of this region is observed in many different number processing tasks (Dehaene et al., 1999; Pinel et al., 2001), especially when nonverbal representation of numerical quantity, conceptualized as "mental number line", is required. However, the network of areas activated during number processing includes frontal and anterior cingulate components as well (Chochon et al., 1999). These areas are related to working memory and visuospatial attention (Corbetta et al., 1993; D'Esposito et al., 2000; Postle et al., 2000).

FMRI studies of numerical processing in typically achieving children revealed similar functional networks compared to adults (Cantlon et al., 2006; Kawashima et al., 2004; Rivera et al., 2005). However, children primarily engaged frontal regions, suggesting that children require comparatively more working memory and/or allocation of attentional resources to complete a calculation task. Adults, on the other hand, showed an increased activation in parietal areas referring to a functional specialization for the processing of mental arithmetic and numerical magnitude over age (Ansari and Dhital, 2006; Ansari et al., 2005; Rivera et al., 2005).

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* Corresponding author. Fax: +41 44 266 71 53.
*E-mail address:* stephanie.rotzer@kispi.uzh.ch (S. Rotzer).

[1] Shared first author.

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In contrast to the amount of knowledge about the neural underpinnings of number processing in typically performing adults and children, only few studies investigated brain functions in populations with impaired number processing capacities. Less activation in the frontoparietal network during number processing was reported in populations with chromosomal disorders and abnormal numerical representations (Molko et al., 2003).

Recently, Kucian et al. (2006) presented the first characterization of the neural underpinnings of developmental dyscalculia in affected children by means of fMRI. Results indicated weaker brain activation in almost the entire neuronal network for analog number processing in dyscalculic children. In general, dyscalculic and typically achieving children activated similar brain regions during number processing.

The investigation of children with DD poses a special challenge as the outcome of this disorder is very heterogeneous. This constitutes a serious problem in functional neuroimaging studies because one task is not able to address the whole spectrum of impairments. Indeed, a great variety of nonspecific problems, including slow speed of processing, poor working memory span, problems of attention, and deficits in the long-term storage of arithmetic facts have to be considered as an important factor, which may influence arithmetic performance (Temple and Sherwood, 2002).

Brain activation patterns demonstrated by fMRI are strongly task dependent, whereas voxel-based morphometry focuses on global structural differences independent of paradigm design or performance. Isaacs et al. (2001) used voxel-based morphometry to compare gray matter density in two groups of preterm-born adolescents. The target group suffered from arithmetical problems with otherwise normal IQ, while the control group showed calculation abilities consistent with IQ. The left intraparietal sulcus was the most prominent region with reduced gray matter density in the dyscalculia group. The authors concluded that this area is the neural correlate of arithmetical impairments in the examined adolescents. However, the degree to which this finding can be extended to children who were not born very prematurely still remains to be discovered (Dowker, 2006; Isaacs et al., 2001). To answer this question, we investigated term-born children with developmental dyscalculia and typically achieving children by using optimized voxel-based morphometry (OVBM), a voxel-wise comparison of local ratios of gray matter (GM), and white matter (WM). We expected structural differences in parietal areas, particularly in the IPS, in children with developmental dyscalculia according to the literature on calculation disabilities. Furthermore, we assumed the entire neuronal network for number processing, including parietal, frontal, and cingulate areas to be altered in dyscalculic children (Chochon et al., 1999; Kucian et al., 2006).

## Materials and methods

### Subjects

We used OVBM to analyze T1-weighted magnetic resonance images (MRI) of 12 healthy, right-handed children with DD (6 male, 6 female, mean age 9.3 ± 0.2 years). None of the children suffered from any other neurological, psychiatric, or learning disorders (e.g. dyslexia, ADHD) as determined by a detailed questionnaire and all were medication free. Children with dyscalculia were executed by a trained specialist from the psychological school services. Each child passed through a whole test battery, including tests to assess his/her mathematical, linguistic and spatial abilities as well as the IQ. Numerical abilities were assessed using the Neuropsychological Test Battery for Number Processing and Calculation (ZAREKI) (von Aster, 2001). Dyscalculia was clearly diagnosed in all of our subjects. The diagnosis was based on the definition of the ICD-10 (WHO, 2005), which uses the discrepancy between the individual's general intelligence and his or her mathematical performance that cannot be explained by inadequate schooling, sensory deficits, or other neurological, psychiatric, or medical disorders. An estimate of general intelligence was obtained by using either the K-ABC (Kaufman and Kaufman, 1994) or the HAWIK-III (Wechsler, 1999). IQ scores of all children indicated normal intellectual functioning. Since the testing was carried out by the psychological school services of the state of Zurich, it was not possible to obtain detailed information. Therefore, a table showing behavioral performance is missing. Twelve typically achieving children from public school (6 females, 6 males, mean age 9.7 ± 0.2 years) served as age- and gender-matched control group. Children were tested for number processing and calculation abilities (ZAREKI; von Aster, 2001) as well as for reading and spelling skills (Knuspel's Leseaufgaben; Marx, 1998; Salzburger Lese-und Rechtschreibtest; Landerl et al., 1997). All children showed normal age-related performance [ZAREKI: 147.5 (21.9); Knuspel's Leseaufgaben: 26.5 (2.9); Salzburger Lese-und Rechtschreibtest: 8.0 (1.7)] compared to a Swiss normative sample of 337 age-matched children [143.6 (27.7); 21.2 (8.6); 7.53 (4.2)].

Written, informed consent for the participation in this study was obtained from the legal guardians of the children. The study was approved by the local ethics committee based on the World Medical Association's Declaration of Helsinki (WMA, 2002).

### Image acquisition

MRI acquisition was performed on a 1.5 Tesla whole-body system (Signa Twinspeed Excite, GE Healthcare, Milwaukee, WI, USA). Three-dimensional anatomical images of the entire brain were obtained by using a T1-weighted gradient echo pulse sequence (TR = 25 ms; TE = 5 ms; FOV = 220 mm × 220 mm × 170 mm; image resolution = 1.72 mm × 1.72 mm × 1.70 mm).

### Optimized voxel-based morphometry

Data were analyzed using SPM2 (Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk) on MATLAB 6.5 (The MathWorks, Natick, MA, USA). Voxel-based morphometry as proposed by Ashburner and Friston (2000) involves a voxel-wise comparison of the local concentration of gray and white matter between two groups of subjects. This standard preprocessing protocol tends to result in misinterpretations of structural differences as a result of normalization, which are not directly related to gray or white matter volumes (Mechelli et al., 2005). We used the optimized VBM protocol, as described by Good et al. (2001) and a special-purpose scripting tool with modulation (http://dbm.neuro.uni-jena.de/vbm) to minimize this potential source of error by performing the normalization using the segmented gray and white matter volumes rather than the whole brain volumes. With this adjustment, VBM can be thought of as comparing the absolute volume of gray or white matter structures. We performed the OVBM in a two-stage process: (1) *creating templates*: customized GM and WM templates were created to reduce scanner- and population-specific biases. Images were linear spatially normalized

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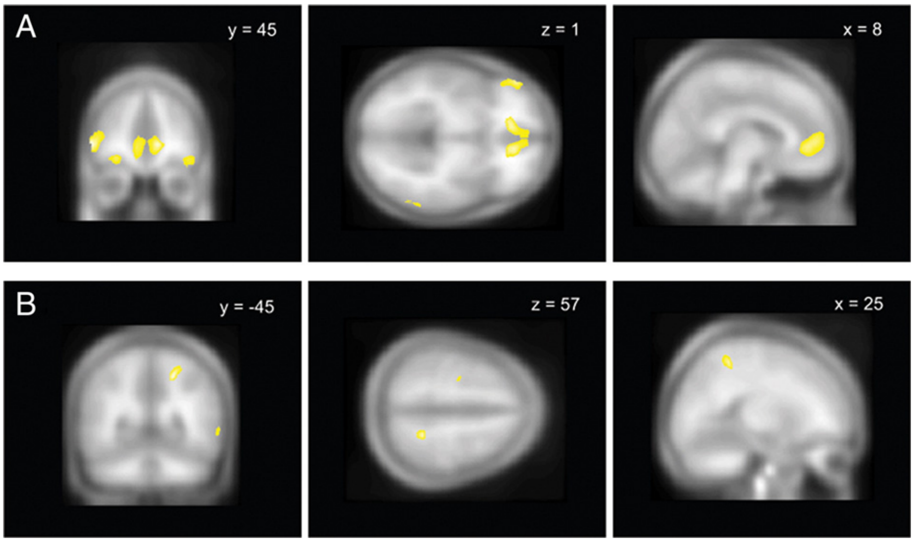

Fig. 1. (A) Frontal regions of decreased gray matter volume in children with DD compared to controls (cluster level corrected $p<0.001$). (B) Parietal region of decreased gray matter volume in children with DD compared to controls (cluster level corrected $p<0.001$).

to a standardized anatomical space using an age-matched brain template (CCHMC pediatric brain template, http://www.irc.cchmc.org/ped_brain_templates.htm) to further improve spatial normalization. Normalized brain volumes were segmented into GM, WM, and cerebrospinal fluid (CSF) volumes and smoothed with a full-width at half-maximum Gaussian kernel of 8 mm. (2) *Voxel-based morphometry*: each segmented volume was nonlinearly normalized to the customized template; resulting normalization parameters were applied to the original brain volumes. Nonlinearly normalized brain volumes were afterwards segmented and modulated for comparison of volume effects. Thereafter, GM and WM segments were spatially smoothed with a full-width at half-maximum Gaussian kernel of 12 mm, as recommended by Gaser (http://dbm.neuro.uni-jena.de/vbm). Finally voxel-wise between group comparisons of the smoothed GM and WM volumes were performed using a two-sample *t*-test within SPM2. Reported results represent uncorrected $p$ values of $<0.001$ on the voxel level ($p<0.001$ on corrected cluster-levels) restricted to clusters of $>70$ voxels.

## Results

### *Voxel-based morphometry*

#### *Gray matter*

Two-sample *t*-test comparisons demonstrated clusters with significantly less gray matter volume for dyscalculic children in frontal lobe regions: the bilateral anterior cingulum, the right and left middle frontal gyrus, and the left inferior frontal gyrus (Fig. 1A and Table 1), as well as in the right intraparietal sulcus (Fig. 1B and Table 1).

No cluster of increased gray matter volume was found in dyscalculic children when compared to control children.

#### *White matter*

Two-sample *t*-test white matter comparisons demonstrated clusters with significantly decreased white matter volume in the left frontal lobe and adjacent to the right parahippocampal gyrus for dyscalculic children (Fig. 2 and Table 2).

Dyscalculic children did not show regions of significantly increased white matter volume.

## Discussion

The aim of the present study was to identify differences in brain structures of dyscalculic children without any co-morbid diagnosis. A number of brain-imaging studies have implicated the frontal and parietal cortices in arithmetical processing (Chochon et al., 1999; Rickard et al., 2000). Therefore, we hypothesized that children with DD show structural differences in parietal and frontal areas when compared to typically achieving children.

In the present study, children with dyscalculia show decreased gray matter volume in the right IPS compared to the control group, while the left IPS shows no volume differences. The right parietal

Table 1
Gray matter volume changes in dyscalculic children

| Anatomical region | Hemisphere | Talairach coordinates | | | $p$ value corrected Cluster level | $T$ score voxel level | Number of voxels in cluster ($k_E$) |
|---|---|---|---|---|---|---|---|
| | | $x$ | $y$ | $z$ | | | |
| Anterior cingulum | Right | 11 | 43 | 2 | <0.001 | 5.09 | 5487 |
| Anterior cingulum | Left | −11 | 40 | 2 | <0.001 | 4.97 | 4660 |
| Middle frontal gyrus | Right | 45 | 41 | −11 | <0.001 | 3.98 | 1644 |
| Middle frontal gyrus | Left | −43 | 37 | −11 | <0.001 | 4.47 | 7476 |
| Inferior frontal gyrus | Left | −55 | 45 | 2 | <0.001 | 5.41 | 7476 |
| Intraparietal sulcus | Right | 22 | −45 | 55 | <0.001 | 5.25 | 766 |

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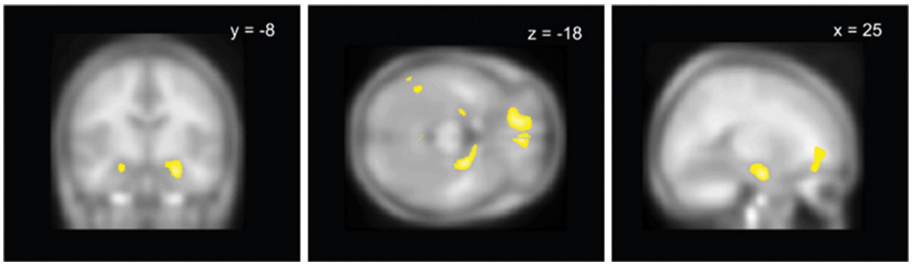

Fig. 2. Frontal and parahippocampal regions of decreased white matter volume in children with DD compared to controls (cluster level corrected $p < 0.001$).

region found to exhibit less gray matter volume in children with DD compared to typically achieving children is rather medial compared to right parietal regions, such as right intraparietal sulcus, typically found to be modulated in functional neuroimaging studies of numerical cognition (Dehaene et al., 2003). The IPS is a long, discontinuous sulcus (Kadosh et al., 2007) and shows a large intersubject variability both anatomically (Zilles et al., 2003) and functionally (Kadosh et al., 2007). Additionally, we examined a child population and our data are based on structural findings, which might differ from functional findings. Therefore, further investigation is needed to relate structural with functional studies.

The VBM study of Isaacs et al. (2001) identified only one region of decreased gray matter volume in the left intraparietal sulcus in preterm-born adolescents with calculation deficits. However, they discuss the possibility of a whole network of regions relevant for number processing being affected. These regions include the homologous area in the right parietal lobe as well as frontal areas. One study in patients with Turner Syndrome and arithmetic impairments demonstrated a morphologically abnormal length, depth, and sulcal geometry of the right IPS and reduced neural activation of this region as a function of number size (Molko et al., 2003).

Overall, reported laterality of parietal anomalies is inconsistent. This variation of affected hemispheres may be a result of differences between examined patient groups, used tasks, or the age of subjects.

The developmental study of Rivera et al. (2005) reports that brain activation during calculation changes with age. The authors conclude that their findings provide evidence for a process of increased functional specialization of the left inferior parietal cortex in mental arithmetic, a process that is accompanied by decreased dependence on memory and attentional resources with development (Rivera et al., 2005). Our morphological results support this assumption—gray matter volume differences in parietal regions between our two groups are not as distinctive as expected, there is only one region within the right IPS where typically achieving children show more gray matter than dyscalculic children. We assume, therefore, that the parietal brain areas are not fully developed in our pediatric population. This is in good accordance with the developmental fMRI study investigating adults and children during magnitude judgment (Ansari et al., 2005). Whereas numerical distance modulates parietal regions in adults, children primarily engage frontal regions. The authors conclude that the functional neuroanatomy underlying symbolic numerical magnitude processing undergoes an ontogenetic shift toward greater parietal engagement. Additionally, younger subjects require comparatively more working memory and attentional resources to achieve similar levels of mental arithmetic performance (Rivera et al., 2005). Based on the fact that children with arithmetical disability have a specific working-memory deficit in relation to processing numerical information (Siegel and Ryan, 1989) and that an important component in the development of arithmetical skill is the growth of working memory for numerical information, the gray matter volume differences found in our group at the bilateral middle frontal gyrus, the left inferior frontal gyrus, and bilateral anterior cingulum may be of major importance in the development of dyscalculia. These findings refer to possible prior subclinical impairments of the attentional and the working memory system, which might have a negative effect on the acquisition of number representation and number processing capacities. Besides, general brain development is not finished at the age of 7 to 9 years. Therefore, comparisons of morphological as well as fMRI data between children and adults should be drawn carefully (Wilke et al., 2007).

Furthermore, the right parietal area identified in this study has also been shown to be involved in working memory and attention (Shulman et al., 2002; Wager and Smith, 2003). Therefore, the parietal gray matter differences might be related to more domain-general factors such as working memory and attention. The question if the frontoparietal network in DD plays a specific, number related role (Nieder et al., 2002) or has to be considered in a more general way (Shuman and Kanwisher, 2004) is still matter of debate and further investigations are needed.

In addition to gray matter differences, we observed decreased white matter volume of the right parahippocampal gyrus, a region known to play a major role in fact retrieval and spatial memory processes (Stern et al., 1996). These white matter volume differences further support the assumption that deficits in neuronal networks important for fact retrieval might hamper the development of adaptive number representations in children with developmental dyscalculia.

In conclusion, our results provide new insights into the brain anatomy of dyscalculic children. Morphological differences in

Table 2
White matter volume changes in dyscalculic children

| Anatomical region | Hemisphere | Talairach coordinates | | | *p* value corrected Cluster level | *T* score voxel level | Number of voxels in cluster ($k_E$) |
|---|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | | |
| Parahippocampal gyrus – white matter | Right | 25 | −9 | −14 | <0.001 | 5.11 | 4579 |
| Frontal lobe – subgyral | Left | −16 | 43 | −19 | <0.001 | 5.06 | 5317 |

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frontal and parietal brain areas of children with DD point to missing auxiliary functions, like working memory, interference control, and strategic planning. These impaired processes might influence the development of dyscalculia.

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