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Mental number line training in children with developmental dyscalculia

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ABSTRACT

Developmental dyscalculia (DD) is a specific learning disability that affects the acquisition of mathematical skills in children with normal intelligence and age-appropriate school education (prevalence 3–6%). One essential step in the development of mathematical understanding is the formation and automated access to a spatial representation of numbers. Many children with DD show a deficient development of such a mental number line. The present study aimed to develop a computer-based training program to improve the construction and access to the mental number line.

Sixteen children with DD aged 8–10 years and 16 matched control children completed the 5-week computer training. All children played the game 15 min a day for 5 days a week. The efficiency of the training was evaluated by means of neuropsychological tests and functional magnetic resonance imaging (fMRI) during a number line task.

In general, children with and without DD showed a benefit from the training indicated by (a) improved spatial representation of numbers and (b) the number of correctly solved arithmetical problems.

Regarding group differences in brain activation, children with DD showed less activation in bilateral parietal regions, which reflects neuronal dysfunction in pivotal regions for number processing. Both groups showed reduced recruitment of relevant brain regions for number processing after the training which can be attributed to automatization of cognitive processes necessary for mathematical reasoning. Moreover, results point to a partial remediation of deficient brain activation in dyscalculics after consolidation of acquired and refined number representation.

To conclude, the present study represents the first attempt to evaluate a custom-designed training program in a group of dyscalculic children and results indicate that the training leads to an improved spatial representation of the mental number line and a modulation of neural activation, which both facilitate processing of numerical tasks.

Introduction

Developmental dyscalculia (DD) is a specific learning disorder of mathematical abilities presumed to be due to impairments in brain function (Cohen Kadosh et al., 2007; Kucian et al., 2006; Mussolin et al., 2010; Price et al., 2007; Shalev, 2004). Children with DD show a variety of fundamental deficits in number processing, including basic competences such as the representation of quantity and numbers (Bachot et al., 2005; Koontz and Berch, 1996; Landerl et al., 2004, 2009; Rousselle and Noel, 2007). This representation is thought to be similar to a number line on which we organize, arrange and classify numbers (Dehaene, 2003). The formation of such a mental number line constitutes a vital step in the development of mathematical skills (von Aster and Shalev, 2007). It is thought that children start to develop their internal representations of numbers long before formal schooling. With the entrance into school and the acquisition of the symbolic number system and arithmetical skills these representations become more precise and are expanded to an increasing numerical range (Barth et al., 2005; Berch et al., 1999; Schweiter et al., 2005). In agreement, a recent study showed that formal education and numerical enculturation sharpens magnitude representation specifically (Soltesz et al., 2010). Moreover, the authors claim that the development of symbolic number knowledge, acquired during the first years of school, develop independently of non-symbolic number comparison skills. The gain in precision of the mental number line is characterized by a shift from a logarithmic to a linear ruler representation (Berteletti et al., 2010; Siegler and Booth, 2004;

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Siegler and Opfer, 2003). Relative to a linear representation of numbers, a logarithmic representation exaggerates the distance between the magnitudes of numbers at the low end of the range and minimizes the distance between magnitudes of numbers in the middle and upper ends of the range (Siegler and Booth, 2004). The developmental trajectory of this number representation follows a continuing refinement throughout childhood, with adult-like levels of acuity attained surprisingly late (Halberda and Feigenson, 2008). Furthermore, the representational change to a linear fit was found to correlate positively with mathematical skills and the precision of the internal number representation correlates with math achievement scores (Halberda et al., 2008; Siegler and Booth, 2004), indicating that the nature and quality of number representation decisively influences the development of calculation capabilities.

A recent study examining the link between number representation and dyscalculia (Piazza et al., 2010) showed that number representation is severely impaired in dyscalculics, with 10-year-old dyscalculics scoring at the level of 5-year-old normally achieving children. This study also reported that the severity of the representational impairment predicts the defective performance on tasks involving the manipulation of symbolic numbers. Observed deficits of mental representation of numbers in children with DD are in line with neuro-imaging findings pointing to functional impairments and structural and microstructural alterations in parietal brain regions thought to represent the locus of the mental number line (Kaufmann et al., 2009; Kucian et al., 2006; Mussolin et al., 2010; Price et al., 2007; Rotzer et al., 2008; Rykhlevskaia et al., 2009; Soltesz et al., 2007). Therefore, it is hypothesized that targeted training to improve the representation of numbers in dyscalculic children will have a beneficial effect on mathematical competence in these children, which is reflected by changes in neuronal activation in math relevant brain regions.

Two previous studies have evaluated different approaches for training number representation in children (Siegler and Ramani, 2009; Wilson et al., 2006a). The first called "Number Race" by Wilson et al. (2006a) is an adaptive software game principally designed to enhance quantity representation. Evaluation of this training in children age 7–9 years with mathematical learning difficulties suggests that the remediation is successful in producing an improvement in basic numerical cognition (Wilson et al., 2006b). However, this study had some limitations, such as only a small sample size of children with mathematical difficulties ($n=9$) was examined and a control group was lacking.

The second approach is a linear number board game tested by Siegler and Ramani (2009) against a circular board in a group of low-income preschoolers. As predicted, playing the linear number board game increased numerical knowledge in these children significantly, and these children learned more from subsequent practice and feedback on addition tasks (Ramani and Siegler, 2008; Siegler and Ramani, 2009; Whyte and Bull, 2008). In contrast, playing with the circular number board did not result in any improvement in numerical understanding. The authors argue that the linear board game lead to greater learning than the circular game because the linear board more closely resembles the desired mental representation of numbers.

These two promising approaches lend support to the importance and efficacy of intervention programs with math tasks which aim to improve basic competences such as the representation of quantity and numbers. Both demonstrated promising improvements in fundamental numerical understanding, suggesting that children with developmental dyscalculia may benefit tremendously from such an intervention program.

The goal of the present study was to develop and evaluate a computer-based training program for dyscalculic children based on cognitive neuroscience and brain imaging findings. The intervention aims to improve number representation in a similar manner to the aforementioned intervention studies. In addition, the training should also strengthen the link between representations of numbers and space, which are known to be closely associated (Dehaene et al., 1993). The development of a precise spatial representation of numbers is crucial for the understanding of the principle of ordinality of numbers, which relates to the ability to rank numbers in order of magnitude. Moreover, the training aimed to improve both the ability to estimate a given quantity of dots, as a very basic aspect of number processing, as well as more demanding arithmetical skills.

Despite the high prevalence of dyscalculia of 3–6% (Gross-Tsur et al., 1996; von Aster et al., 2007), which is similar to that of dyslexia, dyscalculia research is generally under-represented and the scientific evaluation of appropriate intervention programs in dyscalculic children is missing, except of the initial study of Wilson et al. (2006b). Therefore, the present study attempts to evaluate a custom-designed training program in a group of dyscalculic children by means of behavioral outcome. Moreover, it represents the first evaluation of neuro-plastic changes in brain function in children with developmental dyscalculia, which will provide additional insides in neuronal correlates of dyscalculia and learning. Functional magnetic resonance imaging (fMRI) studies in dyslexia have demonstrated changes in brain activity after training (Eden et al., 2004; Simos et al., 2002; Temple et al., 2003). Therefore, we expect that children with developmental dyscalculia will improve their internal representation of numbers and consequently show better performance on mathematical tasks after completion of the training, since the more sophisticated spatial representation is assumed to rely on a linear number representation. Based on previous training studies, we hypothesize that our training will lead to a modification of brain activation patterns including frontal and parietal regions. On the one hand, the parietal lobe underpins domain-general mechanisms, like attention and working memory, and on the other hand, it hosts the most specific brain center for numerical understanding. The training is expected to influence both processes antithetically, inducing a general reduction of brain activation, but also fostering an increase in activation when an initially impaired activation can be assumed, such as in dyscalculic children.

In line with reported findings, main effects of training are expected to result in a relative decrease in blood oxygenation level dependent (BOLD) signal in the fronto-parietal activation pattern including mainly areas supporting domain-general cognitive processes in both groups (Delazer et al., 2003; Ischebeck et al., 2006, 2007; Pauli et al., 1994). In particular, deceased activation in the parietal lobule after training has been reported in the intraparietal sulcus (IPS), superior parietal lobules extending into the precuneus, and the inferior parietal lobe; in terms of the frontal lobe, reduced activation has been allocated to the superior and inferior frontal gyrus, the precentral gyrus, and supplemental motor area (Delazer et al., 2003; Ischebeck et al., 2006, 2007). Regarding neuronal correlates of the mental number line in children with developmental dyscalculia, reduced activation in areas playing a pivotal role, such as the intraparietal sulcus is anticipated. After completion of the training, a restoration of deficient brain activation in children with developmental dyscalculia is expected, facilitating an increase of activity in affected parietal regions in these children.

Methods

Study design

Children with dyscalculia and control children were evaluated by behavioral tests and fMRI before and after completion of the 5-week training program. Control children were evaluated three times during the study, firstly for neuropsychological testing, secondly for fMRI scanning and testing before the training and finally for fMRI scanning and testing after the 5-week training session. In contrast, dyscalculic children were evaluated after a 5-week rest period in addition to before and after the training period. During the rest period children received no intervention. Half of the dyscalculic children performed the training first, and then followed the training with a 5-week break, and the other half started the training after a 5-week rest period. This cross-sectional design was chosen to minimize the number of dyscalculic children to be tested. Fig. 1 summarizes the study design.

Participants

Twenty children with a diagnosis of DD (9.6 (SD 0.8) years) and 16 age-matched controls (9.5 (SD 1.1) years) with age-appropriate calculation performance participated in the study (Table 1). Subsequent testing confirmed the diagnosis of DD in all but three children who were excluded from the sample. None of the participants had neurological or psychiatric disorders, were on medication, or had exclusion criteria for MRI such as braces. All children completed the training successfully. However, one child with DD was excluded from data analysis concerning training effects since we did not receive the log file from this child. Therefore, behavioral data analysis is based on 16 children with and 16 children without DD. Demographic data of participants are summarized in Table 1.

For the fMRI analysis, children with less than a 50% accuracy rate within the scanner task or who moved more than 2 mm in *x*-, *y*-, or *z*-plane or rotated their head more than 1° in pitch, jaw or roll direction were excluded, resulting in 23 valid data sets for children with DD (12 pre-training/11 post-training) and 32 for the control group (16 pre-training/16 post-training).

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).

Behavioral testing

All children underwent a series of behavioral tests, detailed below. Both parents and children completed a questionnaire after the training, including questions on difficulty, motivation, problems and personal evaluation of the training.

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 11 subtests, such as reverse counting, subtraction, number reading, dictating, visual estimation of quantities, digit span forward and backward. Criteria for developmental dyscalculia were met if a child's performance in the ZAREKI-R was 1.5 SD below average in three subtests or in the total score.

Table 1
Demographic and clinical characteristics.

	Dyscalculic children (DD)	Control children (CC)	*t*-test
Subjects (*n*)	16	16	n.s.
Gender (f/m)	10/6	9/7	n.s.
Handedness (right/left/ambidextrous)	14/1/1	12/0/4	n.s.
Age (SD)	9.5 (0.8)	9.5 (1.1)	n.s.
Domain general cognitive abilities (WISC-III)			
Arithmetic (SD)	89 (9)	108 (11)	$p<0.001$
Vocabulary (SD)	101 (9)	110 (10)	$p<0.05$
Similarities (SD)	105 (10)	115 (7)	$p<0.01$
Picture arrangement (SD)	103 (14)	103 (14)	n.s.
Block design (SD)	97 (19)	114 (9)	$p<0.01$
Estimated general IQ (WISC-III) (SD)	99 (7)	110 (7)	$p<0.001$
Estimated general IQ (WISC-III) (SD) corrected for arithmetic	101 (14)	111 (12)	n.s.
Mathematical performance (ZAREKI-R) (SD)	17 (23)	75 (20)	$p<0.001$

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 all five subtests (Picture Arrangement, Block Design, Vocabulary, Arithmetic, Similarities), estimated General IQ based on these subtests, and estimated General IQ based on four subtests (Picture Arrangement, Block Design, Vocabulary, Similarities) without Arithmetic.

Handedness

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

Number line

The spatial representation of numbers was measured by a paper-and-pencil number line task. All children performed this task at each examination, immediately before starting the training and after

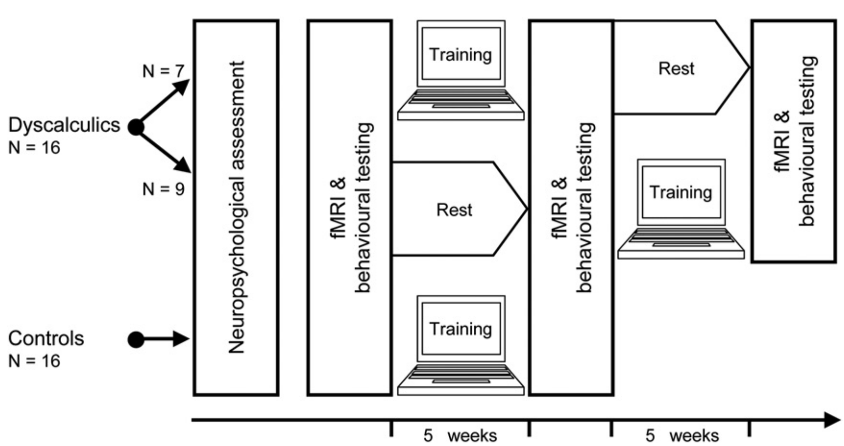

Fig. 1. Study design. Sixteen children with DD and 16 control children underwent first detailed neuropsychological assessment. Thereafter half of the DD children performed the 5-week training after the first fMRI and behavioral testings. The other half of the DD children performed the 5-week training after the second fMRI and behavioral testings. During the rest period, DD children had no intervention. Control children were only examined before and after the 5-week training.

finishing the training period of 5 weeks, as well as after rest period. Children had to indicate on a left-to-right oriented number line from 0 to 100 the location of Arabic digits, results of additions and subtractions, or the estimated number of dots. The number line was 16 cm in length and only the start and end points were marked with 0 and 100, respectively. A card (7 cm × 4.5 cm) with an Arabic digit (Times New Roman, font size 36) was shown and read aloud to the child. The child marked with a pencil the location of the number on the number line, at which point the next card was shown and the child indicated the location on the next number line template. In total, each child evaluated 20 Arabic digits. Afterwards, 20 cards with addition calculations were shown. The child had first to calculate the results of an addition and tell the examiner (who noted it on the evaluation sheet) and then indicate the location of the result on the number line. Addition tasks were followed by 20 subtraction problems. Finally, 10 cards were shown for only 3 s, which contained randomly arranged dots, all of the same size (diameter = 1 mm). The child had to estimate the number of dots, tell it to the examiner who noted it also on the evaluation sheet, and mark the location on the number line. Three different versions of this test consisting of different digits, calculation problems, and dot amounts were used. The three versions were matched for difficulty and each child solved a different version at every examination. Between subjects the versions were administered in a counter-balanced manner.

Spatial working memory

Spatial working memory capacity was assessed twice, before and after the training. Spatial working memory performance was measured with the Corsi-Block Tapping test (Schellig, 1997), a test assessing spatial working memory span. On a board with nine cubes, the examiner taps the cubes in a given sequence. Subjects are required to repeat the cube sequences in the same order immediately after the examiner has finished. While the sequences gradually increase in length, the number of cubes last tapped in two consecutively correct sequences is defined as the maximum span. Children were also tested with the Block Suppression Test (Beblo et al., 2004). This test is based on the Corsi-Block tapping test and requires the subject to reproduce every 2nd block in a given sequence. This task requires children to suppress irrelevant spatial information actively.

Training

A computer-based training "Rescue Calcularis" was developed and programmed with the capability to be installed and played on any home computer (see Fig. 2). The program aims to improve the spatial representation of numbers and automated access to the internal mental number line, including an improved association between representations of numbers and space, the understanding of ordinality of numbers, estimation, and arithmetical skills.

Children were instructed to train at home 15 min a day, 5 days a week for 5 weeks. A timer controls the daily training time, which is always visible during the game. After completing the 15 min training session, the program is automatically blocked until the next day. The training is embedded into a story game, in which the player aims to rescue his home planet, called "Calcularis", where the energy reserves are coming to an end. A brave astronaut flies with his spaceship to the planet "Heureka" to collect the super-energy-gas "Archim". Since Heureka is 30 light-years away, the astronaut has to make stopovers

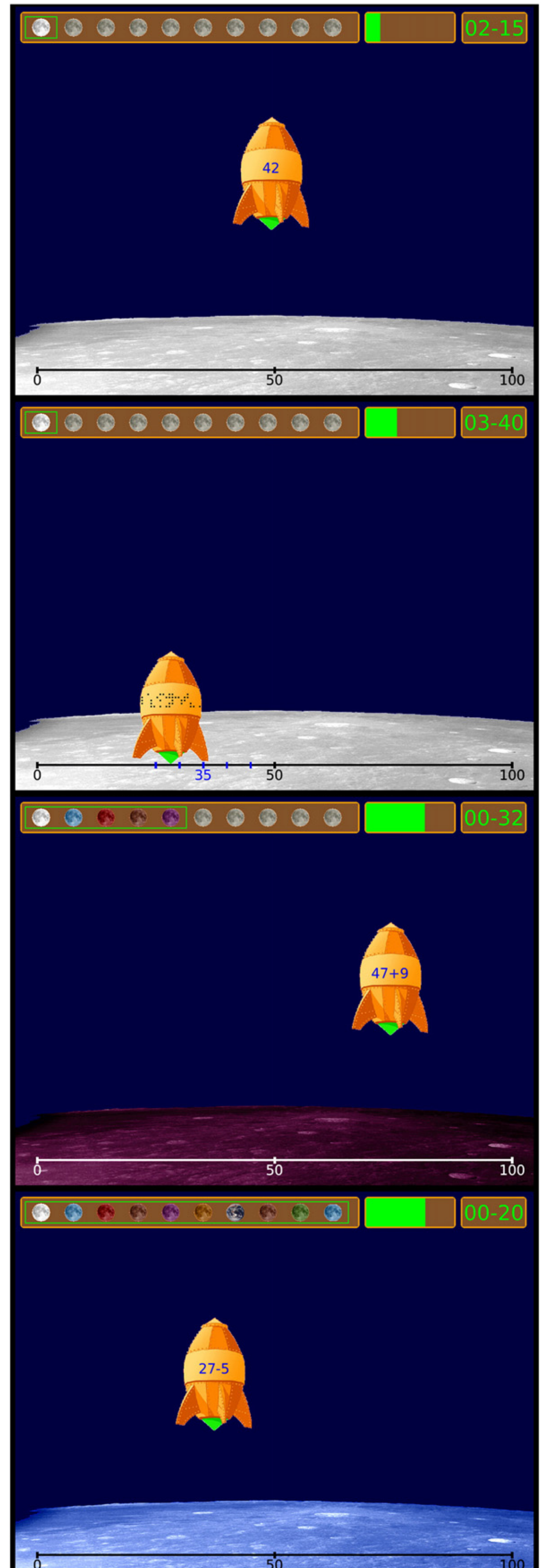

Fig. 2. Training program. The training software "Rescue Calcularis" is played daily 15 min, 5 days a week for 5 weeks. The player is asked to steer the spaceship to the exact location on the number line corresponding to the Arabic digit, the estimated number of dots, or the result of the addition or subtraction task displayed on it. After landing, the correct position and an interval of ± 10 is indicated as feedback (see 2nd screen from top). Ten different planets have to be approached. On which planet the player is can be seen on the top left. Daily playing time is counted from 0 to 15 min displayed on the top right. The energy tank of the spaceship is filled with each correct landing indicated by the green bar next to the timer. When the energy tank is full, the spaceship can fly to the next planet.

on 10 planets to refuel his spaceship. The 30 light-years correspond to 30 different levels with increasing difficulty. On each planet a left-to-right oriented number line from 0 to 100 is displayed and 3 levels have to be solved successfully before the player can fly to the next planet. Either an Arabic digit, an addition problem, a subtraction problem or a number of dots will appear on the spaceship, and the challenge is to land the spaceship at the corresponding location on the number line. The child has to steer the spaceship to the correct position on the number line, using a joystick which was loaned to all participants. If the astronaut lands within a range of ±10 of the correct position, the challenge is rated as successful and he gains fuel to fill up his tank. Immediately after landing, the exact position within the range of ±10 is given as feedback. The next level can be reached when each problem on the current level has been solved correctly. Each level consists of 75 trials, resulting in a total of 2250 trials for all levels. Incorrectly solved tasks are repeated until they are solved successfully to support learning. After solving all three levels for a particular planet, the tank of the spaceship is completely filled and the spaceship is ready to continue to the next planet. Thus, a major virtue of the training is that it works in an adaptive way and each child trains at her or his individual performance level and speed. To sustain motivation and focus attention, the rocket flies with a speed which can be accelerated or decelerated to the initial velocity, and motivating feedback appears when the child has performed very well or very badly. Moreover, an exciting story is built around the training, and sound effects and short video clips simulating the flight through the universe enhance the attractiveness of the program. All playing parameters such as training time, accuracy, speed etc. are saved in a log file.

Paradigm design

Before entering the scanner children were carefully instructed about the examination procedure and task. The paradigm is based on that of Fulbright et al. (2003) and is intended to map spatial number representation. In each trial, three single-digit Arabic numbers were presented simultaneously via video goggles (MRI Audio/Video System, Resonance Technology, Inc., USA). Children were instructed either to distinguish whether one of the digits was a “2” or not (control task) or judge whether the three numbers were in ascending or descending order or not in order (order condition) (see Fig. 3).

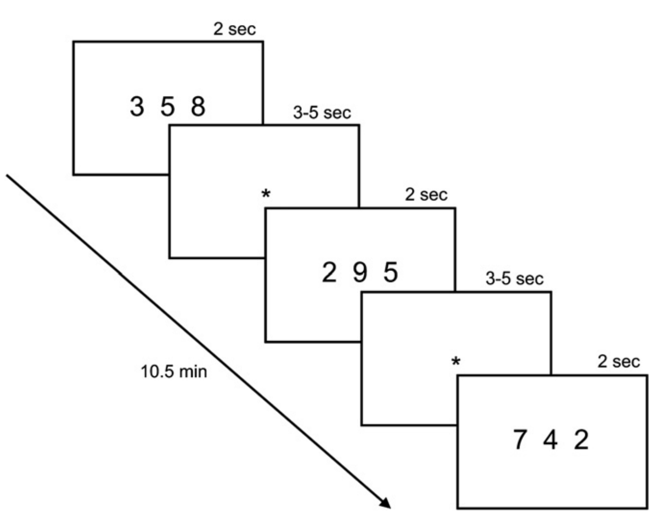

Fig. 3. Paradigm. The fMRI paradigm consisted of alternating epochs of experimental and control tasks. In the experimental condition, subjects hat to decide whether the three displayed Arabic digits are in ascending or descending order (order task). For instance, subject had to press “yes” in the first and last trial shown in the picture and “no” for the second one. In the control condition, subjects had to indicate if the number 2 was included.

Subjects had to press a button with their index finger for “yes” and another button for “no” with their middle finger of the right hand. The whole paradigm lasted 10.5 min and consisted of four epochs of the order condition and four epochs of the control task. Before the beginning of an epoch a short explanation indicated to the subjects which task they have to perform (2 s). Epochs of order representation and control tasks were presented in a counter-balanced manner between subjects, and between epochs a fixation cross was displayed for 20 s. Each epoch included 10 trials, each of which was presented for 2 s, followed by a blank screen. The inter-stimulus-interval was jittered between 3 and 5 s. The paradigm was programmed on E-Prime (E-Prime, Psychology Software Tools Inc.) and reaction time and accuracy rate was recorded by means of the response box (LUMINA, Cedrus Corporation, San Pedro, USA).

Image acquisition

Brain images were acquired on a 3.0 T whole-body scanner (GE Medical Systems, Milwaukee, WI, USA) using a standard eight-channel head coil. Thirty-six slices (NS) were acquired parallel to the AC–PC line, with a slice thickness (ST) of 3.4 mm, a matrix size (MS) of 64×64, a field of view (FOV) of 220 mm×220 mm, a flip angle (FA) of 45°, an echo time (TE) of 31 ms and a repetition time (TR) of 2100 ms. Three-dimensional anatomical images of the entire brain were obtained with a T1-weighted gradient echo pulse sequence (NS=172, ST=1.0 mm, TR=9.972 ms, TE=2.912 ms, FOV=240 mm×240 mm, FA: 20°, MS=256×192).

Data analysis

Behavioral data

Statistical analysis of behavioral data was performed with the “Statistical Package for the Social Sciences 14.0” (SPSS 14.0). A repeated-measures general linear model (GLM) analysis was conducted to evaluate training effects (pre-/post-training) as a within-subject factor and group (DD/CC) as a between-subject factor. Parametric *t*-tests were used to calculate post-hoc differences (paired-sample *t*-test for two related samples and independent sample t-tests for unrelated samples).

Number line. The error rate of the paper-and-pencil number line task was evaluated by measuring the distance in percent (% distance) relative to the position of the correct number for each trial. Mean % distance was then calculated over all trials (Arabic digits, additions, subtractions, dots), but only correctly calculated addition and subtraction problems were included. The percentage of correctly solved calculation tasks (additions, subtractions) was also determined.

For the evaluation of the linearity and variability of spatial representation of numbers only estimations of Arabic digits and estimation of number of dots were included in the analysis since error rates of addition and subtraction problems were often too high for further analyses.

Imaging data

Functional MRI data were analyzed using the Statistical Parametric Mapping (SPM5) software (Wellcome Department of Cognitive Neurology, London, UK) on MATLAB (Version 7 (R14), The Math-Works, Natick, MA, USA).

Pre-processing. The first three image volumes were discarded, thus allowing for the development of a steady-state magnetization. The functional scans from each subject were realigned, and only children with motion of less than ±2 mm in *x*, *y* or *z* direction and head rotation of less than ±1° in pitch, roll or yaw direction were included in the analysis. The individual T1-images were coregistered to the first motion-corrected functional image of each subject. The T1-images were then normalized to an age-matched pediatric template (CCHMC pediatric brain template, http://www.irc.cchmc.org/ped_brain_templates.htm) to minimize the amount of deformation during the spatial transformation (Wilke et al., 2002). The parameters of this transformation were then applied to the realigned functional images. Finally, the functional images were smoothed with a 6 mm Gaussian kernel.

Statistical analysis. To generate statistical maps for each subject, we modeled the expected hemodynamic response (HRF) for the experimental and control task with a canonical hemodynamic response function, and its temporal and dispersion derivatives. The HRFs were convolved with the event train of stimulus onsets for every trial in a general linear model. Parameter estimates for each covariate were obtained by maximum-likelihood estimation using a temporal high-pass filter (cut-off 318 s) and modeling temporal autocorrelations as an AR(1) process. For group analysis, we conducted the standard whole-brain second-level random effects analysis as implemented in SPM5.

An ANOVA with the factors group (DD/CC) and training (pre-/post-training) was computed for the order–control condition to determine effects for both groups, between groups, and the effects of training.

Paired-sample *t*-tests were also computed to reveal activation differences before and after the rest period in the group of dyscalculic children.

Significant voxels are reported either at $p<0.05$, corrected for multiple comparisons according to the false discovery rate (FDR) with a minimum of 29 voxels per cluster, or at $p<0.01$ uncorrected, but with a cluster-extent threshold corrected for multiple comparisons according to Monte Carlo simulations at $p<0.01$ including clusters of a minimum of 29 voxels. Monte Carlo simulations determine the cluster-extent threshold to correct for multiple comparisons in the analysis of neuro-imaging data. This cluster-extent threshold method effectively models the entire imaging volume, assumes a specific voxel type I error, smooths the volume with a Gaussian kernel, and then counts the number of voxel clusters of each size. After a number of iterations (1000 iterations in the present study), a probability associated with each cluster-extent (i.e., number of contiguous voxels) is calculated across runs, and the cluster-extent threshold yielding the desired correction for multiple comparisons can be derived (Slotnick et al., 2003).

Statistical results are reported in the Montreal Neurological Institute (MNI) coordinate space. Anatomical localization was performed by transformation of the MNI coordinates into the Talairach stereotactic system of coordinates using the MNI2TAL tool (MNI2TAL, Matthew Brett) and by the Talairach Client (Lancaster et al., 2000) and the Talairach atlas (Talairach and Tournoux, 1988).

ROI analysis. Region of interest (ROI) analysis has been conducted for further investigations. Maximum activation of all clusters showing an effect of task (order–control condition) in both groups calculated in the ANOVA ($p<0.01$, cluster-extend corrected) served as centers of spheres with a 10 mm radius: SFG: bilatral superior frontal gyrus (0, 18, 60); Right SPL_1: right superior parietal lobe (30, −66, 57); Right SPL_2: right superior parietal lobe (39, −45, 54); Left MFG: left middle frontal gyrus (−48, 0, 45); Right MFG: right middle frontal gyrus (48, 3, 39); Left CRBL: left cerebellum (−36, −63, −33). Since parietal areas are of special interest in the present study, we have also chosen the maximum activation of the left parietal activation cluster calculated in the ANOVA ($p<0.01$), but this has a slightly smaller cluster size of 18 voxels: Left SPL: left superior parietal lobe (−24, −69, 60). Please see illustrated ROIs in the supplementary data (Supplementary Fig. 1).

Spherical ROIs have been built by means of the wfu_Pickatlas toolbox and mean beta values of each ROI have been extracted by the REX-toolbox. Extracted beta values have been transferred to SPSS and statistically analyzed.

Results

Behavioral performance

Table 1 includes testmetric features and demographic data for all participants. The estimated general intelligence of all subjects was in the normal range, and no significant difference in estimated General IQ based on all subtests but Arithmetic was found between groups when correcting for Arithmetic. However, comparison of estimated General IQ including all five subtests and of single subtests revealed significantly lower parameters in DD children except for Picture Arrangement. This is not surprising since IQ-measures are known to be not independent from measures of numerical skills.

Analysis of the ZAREKI-R showed significantly different percentile ranges for children with DD compared to normally achieving children both for the total score and the different subtests ($p<0.001$).

Training effects on behavior

All children completed the training successfully and trained at least 20 days during the 5-week period, with a daily training period of 15 min (see Table 2). Control children reached higher difficulty levels, solved more trials and were faster relative to dyscalculic children.

Table 3 summarizes the mean and standard deviation of all behavioral measures before and after training for both groups, including calculated statistical results. Fig. 4 illustrates the main behavioral improvements due to the training.

Number line

The error in spatial representation in the number line task was measured by calculating the percentage distance between the correct location of the number and the indicated location on the number line. Repeated-measures GLM with mean percentage distance as within-subject factor (pre-/post-training) and group as between-subject factor (CC/DD) demonstrated significant training effects ($F(1, 30)=23.037$, $p<0.001$). The interaction between training and group was not significant ($p=0.25$). Both groups were able to locate the correct position on the number line more accurately after the training (DD $p<0.01$, CC $p<0.01$). Before and after training, groups differed significantly in error rate (pre-training $p<0.05$, post-training $p<0.05$).

Arithmetic

Repeated-measures GLM with percentage of correctly solved addition and subtraction problems as within-subject factors (pre-/post-training) and group as between-subject factor (CC/DD) revealed significant training effects ($F(1, 30)=12.474$, $p<0.01$) and no significant interaction between training and group. Post-hoc paired-sample *t*-test showed a significant improvement in both groups after training (DD $p<0.05$, CC $p<0.01$). In general, CC solved more calculation problems correctly than DD (pre-training $p<0.001$, post-training $p<0.01$).

Table 2
Training "Rescue Calcularis".

	Control children ($n=16$)	Dyscalculic children ($n=16$)	p value
Mean number of training days (days)	24.6 (2.0)	23.9 (2.1)	n.s.
Mean training time per day (min)	14.6 (2.0)	15.0 (0.5)	n.s.
Reached difficulty level (mean)	28	22	$p<0.01$
Mean number of trials	2558 (546)	2166 (412)	$p<0.05$
Accuracy (%)	86 (8)	79 (13)	n.s.
Mean time to land (s)	5.7 (1.9)	10.3 (1.7)	$p<0.001$

Table 3
Training effects on behavior.

	Pre-training	Post-training	Statistics
Number line, error (% distance)			
Dyscalculic children	10.2 (3.0)	7.4 (2.3)	$p<0.01$
Statistics	$p<0.05$	$p<0.05$	Interaction: n.s.
Control children	7.8 (2.0)	6.0 (1.1)	$p<0.01$
Arithmetic, accuracy of additions and subtractions (%)			
Dyscalculic children	64.2 (24.8)	72.2 (20.5)	$p<0.05$
Statistics	$p<0.001$	$p<0.01$	Interaction: n.s.
Control children	92.0 (4.3)	94.4 (6.0)	$p<0.01$
Linearity of Arabic digits, correlation coefficient of linear function (R^2)			
Dyscalculic children	0.83	0.95	$p<0.05$
Statistics	$p<0.01$	n.s.	Interaction: $p<0.05$
Control children	0.96	0.97	$p<0.05$
Linearity of estimation of dots, correlation coefficient of linear function (R^2)			
Dyscalculic children	0.86	0.88	n.s.
Control children	0.90	0.91	n.s.
Linearity of estimation of dots, correlation coefficient of logarithmic function (R^2)			
Dyscalculic children	0.83	0.84	n.s.
Control children	0.88	0.90	n.s.
Variability of Arabic digits, SD of accuracy (%)			
Dyscalculic children	14.8	5.5	$p<0.001$
Statistics	$p<0.001$	n.s.	Interaction: $p<0.001$
Control children	5.9	4.8	$p<0.05$
Variability of estimation of dots, SD of accuracy (%)			
Dyscalculic children	12.1	10.6	n.s.
Control children	18.5	16.7	n.s.
Spatial working memory, Corsi-Block tapping test			
Dyscalculic children	4.6 (0.7)	4.8 (0.7)	n.s.
Control children	4.9 (1.0)	5.2 (0.9)	n.s.
Spatial working memory, Corsi-Block supression test			
Dyscalculic children	2.1 (0.7)	2.2 (0.4)	n.s.
Control children	2.8 (0.9)	3.1 (0.9)	n.s.
fMRI Paradigm, accuracy rate (%)			
Dyscalculic children	60.8 (18.9)	71.4 (21.0)	$p<0.05$
Statistics	$p<0.001$	$p<0.05$	Interaction: n.s.
Control children	83.9 (12.2)	86.5 (9.9)	n.s.
fMRI Paradigm, reaction time (ms)			
Dyscalculic children	1708.4 (448)	1777.8 (426.8)	n.s.
Control children	1829.8 (327)	1790.0 (458)	n.s.

Linearity

We tested whether the spatial representation of Arabic digits is better explained by a linear or logarithmic function by calculating correlation coefficients between the actual and estimated numerical position on the number line. For both groups the spatial representation of numbers from 0 to 100 is better explained by a linear than a logarithmic fit (DD pre-training $p<0.05$, post-training $p<0.001$; CC pre-training $p<0.001$, post-training $p<0.001$). Comparing correlation coefficients of the linear fit between groups and before and after training indicates significant training effects (repeated-measures GLM ($F(1, 30)=9.992$, $p<0.01$)) and a significant interaction between group and training ($F(1, 30)=6.975$, $p<0.05$). Post-hoc analysis shows that spatial representation is more linear after training in both groups (DD $p<0.05$, CC $p<0.05$). At a group level, the spatial representation of control children is more linear compared to dyscalculic children before training ($p<0.01$). However, no differences in linearity between groups could be found after training, suggesting that children with DD catch up during the training period and benefit more from training than the control children (given the significant interaction between group and training).

Additionally, we have also evaluated whether spatial representation of estimation of dots is rather explained by a linear or logarithmic function. In general, no significant difference between correlation coefficients of the linear and the logarithmic fit could be found before and after training for both groups with one exception. After training, spatial representation of dyscalculic children was better described by a linear than a logarithmic function ($p<0.01$). Repeated-measures GLM analysis with correlation coefficients of the linear or logarithmic fit as within-subject factors (pre-/post-training) and group as between-subject factor (CC/DD) revealed no significant training effects and no significant interaction between training and group.

Variability

The variability (SD) of estimation of each Arabic digit and estimated number of dots was calculated and compared between groups and before and after training. Repeated-measures GLM analysis with variability before and after training (pre-/post-training) was defined as within-subject factor and group as between subject factor (DD/CC). Results for Arabic digits indicated significant training effects ($F(1, 78)=30.953$, $p<0.001$) and a significant interaction between training and group ($F(1, 78)=18.788$, $p<0.001$). Mean variability was shown to decrease in both groups after training (DD $p<0.001$, CC $p<0.05$), but this decrease is more pronounced in dyscalculic children such that no significant difference between groups is evident after training (pre-training $p<0.001$, post-training $p<$n.s.). The significant interaction between training and group indicates that the decrease in variability is significantly stronger in dyscalculics relative to controls.

Regarding number of dots estimation, repeated-measures GLM analysis showed no significant effects of training ($p=0.300$) and no interaction between training and group ($p=0.896$).

Corsi-block tapping test

Statistical analysis revealed no significant effects and interactions.

Corsi-block supression test

Statistical analysis revealed no significant effects and interactions.

fMRI paradigm – accuracy rate

The behavioral performance results are based on all 16 dyscalculic children and 16 control children. However, for the fMRI analysis only children who performed better than chance (> 50%) were included (11 out of 48 datasets of DD children had to be excluded and none of controls). Repeated-measures GLM analysis with mean accuracy rate as within-subject factor (pre-/post-training) and group as between subjects factor (DD/CC) shows significant training effects ($F(1, 29)=6.143$, $p<0.05$), but no interaction between training × group. Subsequent analysis demonstrated increased accuracy in children with DD after training ($p<0.05$), but no significant differences in control children. In general, control children performed better than dyscalculics (pre-training $p<0.001$, post-training $p<0.05$).

fMRI paradigm – reaction time

No training effects could be found in reaction time and no significant interaction between RT and group was evident.

Effects of rest period

Dyscalculic children were also measured following a 5-week rest period. No differences were found before and after the rest period for the error rate of the number line task (paired t-test $p=0.958$), the number of correctly solved arithmetical problems (paired t-test $p=0.749$), the accuracy level of the fMRI paradigm (paired t-test $p=0.553$), or the reaction time of the fMRI paradigm (paired t-test $p=0.956$). When analyzing both subgroups of DD children separately

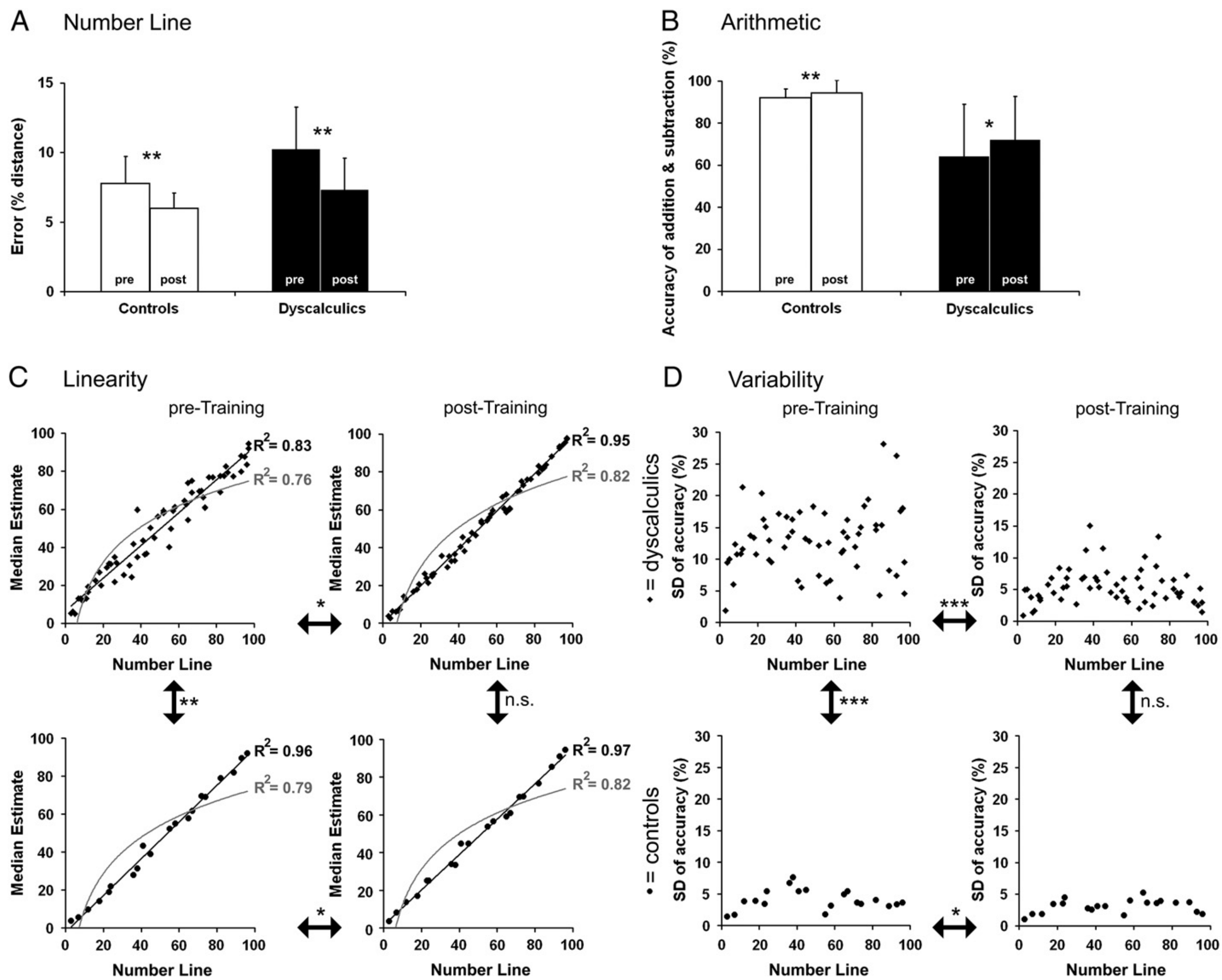

Fig. 4. Behavioral effects. Illustrated behavioral results come from the paper-and-pencil number line task and significant differences are indicated by asterisks (*$p<0.05$; **$p<0.01$; ***$p<0.001$). (A) The error of distance in percent to the exact location on the number line is displayed. (B) The number of correctly solved arithmetical problems in percent is illustrated in the bar plot. (C) Correlation coefficients are shown for the linear (black) and the logarithmic (gray) fit. Since both groups showed rather a linear representation, indicated differences in significance bear on linear fits. (D) Illustrates mean variability of accuracy for each presented Arabic digit. In C and D dots represent mean response across DD children and diamonds mean across controls.

(group 1: training first; group 2: rest first), no differences were evident in the error rate of the number line task (group 1: paired *t*-test $p=0.665$; group 2: paired *t*-test $p=0.802$) or the number of correctly solved arithmetical tasks (group 1: paired *t*-test $p=0.374$; group 2: paired *t*-test $p=0.659$).

fMRI results

Brain activation before training

Analysis of brain activation before training revealed activation of expected fronto-parietal areas used for number processing in control children. Dyscalculic children exhibited maximal activation in the superior frontal gyrus. Fig. 5 illustrates activation pattern for both groups and detailed information for the significant clusters is listed in Table 4.

Main effects of group

ANOVA of effects between groups independent of the training showed that dyscalculic children exhibited significantly less activation predominantly in bilateral parietal areas compared to controls ($p<0.01$, cluster-extent corrected). Furthermore, when restricting the calculation of group differences to clusters activated by control children by applying a mask corroborated that dyscalculic children show significantly reduced activation in pivotal task related areas that are typically activated by controls including bilateral intraparietal sulcus, superior parietal lobe, and cingulated gyrus (please see supplementary data for detailed results). Finally, ROI analysis also confirmed reduced activation of dyscalculic children compared to controls (for detailed results please see Supplementary Fig. 2). In contrast, no region was found to show stronger activation in dyscalculic children compared to controls at the same statistical threshold.

Main effects of training

The training led to a prominent decrease in activation in mainly frontal lobe areas including middle and superior frontal regions, but also in the left postcentral gyrus, left intraparietal sulcus, and the left insula ($p<0.05$, FDR-corrected) in both groups. In addition, activation decrease was also evident in subsequent ROI analysis (for detailed results please see Supplementary Fig. 2). Significant negative interaction between group and training indicates that the decrease after training is stronger in dyscalculic children ($p<0.01$, cluster-

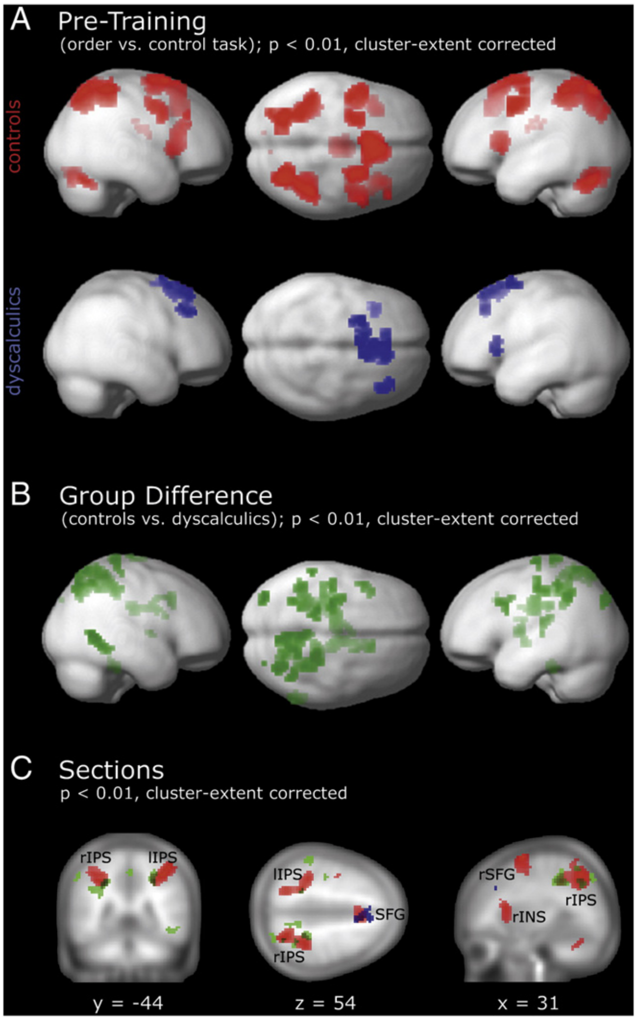

Fig. 5. Main effects of groups. (A) Brain activation recorded at the first session of control children (red) and dyscalculic children (blue) depicted on an averaged brain template of SPM is shown for the contrast order vs. control task at $p<0.01$, cluster-extent corrected. (B) Illustrates where children with dyscalculia showed less activation relative to control children at $p<0.01$, cluster-extent corrected. (C) Summary of results of A and B on brain sections of the pediatric template (CCHMC pediatric brain template, http://www.irc.cchmc.org/ped_brain_templates.htm). Brain activation at first session of controls are shown in red, of dyscalculics in blue and calculated group differences in green. rIPS = right intraparietal sulcus, lIPS = left intraparietal sulcus, rSFG = right superior frontal gyrus, SFG = superior frontal gyrus, rINS = right insula.

extent corrected). Regions showing an interaction between group and training mainly include brain areas which showed a decreased activation after training, such as superior and middle frontal areas, left precentral gyrus, left middle temporal gyrus, superior temporal gyri bilaterally, and left parietal areas including the angular gyrus and inferior parietal gyrus. The positive interaction between group and training was not significant reflecting no differences between groups in activation increase after training. No increase in activation after training was found when correcting for multiple comparisons by FDR, nor by administering an uncorrected statistical threshold ($p<0.01$) and correction for multiple comparisons on the cluster-level. Fig. 6 and Table 5 summarize training effects on brain activation.

Main effects of rest period

All dyscalculic children underwent additional fMRI studies before and after a rest period of 5 weeks. Paired-sample *t*-tests corrected for multiple comparisons with FDR showed no activation changes before and after the rest period. However, using an uncorrected p value of $p<0.01$ and cluster-extent correction by the Monte Carlo method

Table 4
Brain activation of control and dyscalculic children.

Location	MNI coordinates			Cluster size	*t* value	*p* value
Pre-training: control children (order vs. control task) $p<0.01$, cluster-extend corrected						
Right intraparietal sulcus	42	−45	60	623	5.13	0.001
Bilateral superior frontal gyrus	−3	18	60	678	4.99	0.001
Left cerebellum	−42	−63	−30	183	4.89	0.001
Left intraparietal sulcus	−30	−48	48	607	4.67	0.001
Right cingulate gyrus	3	−18	30	146	4.63	0.001
Bilateral cerebellum	−9	−75	−24	262	4.45	0.001
Left middle frontal gyrus	−45	3	45	211	4.10	0.001
Right insula	33	21	21	205	4.03	0.001
Left insula	−36	15	9	99	3.78	0.001
Right superior frontal gyrus	24	0	69	145	3.63	0.001
Right inferior frontal gyrus	51	6	36	136	3.62	0.001
Pre-training: dyscalculic children (order vs. control task) $p<0.01$, cluster-extend corrected						
Left superior frontal gyrus	−12	30	42	30	3.84	0.001
Right superior frontal gyrus	3	21	57	310	3.78	0.001
Left insula	−39	21	3	38	3.50	0.001
Right middle frontal gyrus	39	24	42	31	3.14	0.001
Group difference (control vs. dyscalculic children) $p<0.01$, cluster-extend corrected						
Left cingulate gyrus	−12	−18	36	459	4.11	0.001
Left inferior parietal gyrus	−63	−39	57	48	3.92	0.001
Right superior parietal gyrus	18	−63	48	279	3.81	0.001
Right middle temporal gyrus	63	−54	0	84	3.77	0.001
Left thalamus	−15	−3	9	161	3.65	0.001
Left postcentral gyrus	−24	−33	75	142	2.80	0.01
Left inferior parietal gyrus	−36	−84	36	29	3.46	0.01
Right intraparietal sulcus	30	−42	51	153	3.21	0.01
Right postcentral gyrus	21	−36	75	57	2.94	0.01
Left insula	−36	−27	15	30	3.14	0.01
Left pons	−12	−33	−27	76	3.09	0.01
Left inferior frontal gyrus	−45	9	30	31	2.90	0.01
Right cingulate gyrus	9	18	39	30	2.86	0.01

revealed a significant increase in activation mainly in the parietal lobule bilaterally after rest (see Fig. 7 and Table 6). No decrease in activation was evident. However, due to the cross-sectional study design, half of the children had finished the training before the rest period. Therefore, the effects of the rest period on brain activation were also analyzed separately for both dyscalculic groups (group 1:

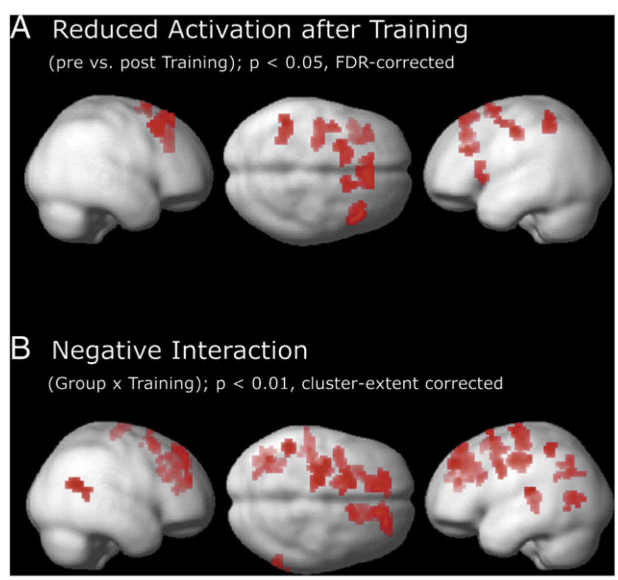

Fig. 6. Main effects of training. All illustrated results derive from the calculated ANOVA for the contrast order vs. control task. (A) Reduced brain activation for both groups after the training is shown at $p<0.05$, FDR-corrected with a cluster size of 29 voxels or more. (B) Brain areas that showed a negative interaction between group and training are shown at $p<0.01$, cluster-extent corrected.

Table 5
Training effects on brain activation.

Location	MNI coordinates			Cluster size	t value	p value
Reduced activation after training (pre- vs. post-training) $p<0.05$, FDR-corrected						
Right middle frontal gyrus	39	21	45	75	4.94	0.001
Left superior frontal gyrus	−9	30	42	32	4.44	0.001
Right superior frontal gyrus	9	36	54	241	4.42	0.001
Left middle frontal gyrus	−33	27	27	32	4.38	0.001
Left postcentral gyrus	−39	−15	45	86	3.28	0.001
Left intraparietal sulcus	−36	−48	48	98	4.32	0.001
Left superior frontal gyrus	−24	3	66	71	3.78	0.001
Left insula	−42	15	0	40	3.75	0.001
Negative interaction (Group × Training) $p<0.01$, cluster-extend corrected						
Left precentral gyrus	−27	−18	42	254	4.16	0.001
Left middle temporal gyrus	−39	−66	6	57	4.04	0.001
Left superior frontal gyrus	−12	39	39	205	3.76	0.001
Left middle frontal gyrus	−36	3	39	42	3.48	0.01
Left superior temporal gyrus	−51	−27	12	55	3.38	0.01
Left superior frontal gyrus	−18	3	54	114	3.36	0.01
Left angular gyrus	−36	−63	30	56	3.35	0.01
Right superior frontal gyrus	9	12	60	32	3.21	0.01
Right superior frontal gyrus	24	48	24	216	3.20	0.01
Right superior temporal gyrus	63	−66	21	51	2.91	0.01
Left inferior parietal gyrus	−48	−45	54	30	3.06	0.01

training first; group 2: rest first). Results showed that the increase in activation in parietal areas after rest arise from the group of dyscalculic children who have already completed the training. ROI analysis corroborated the significant increase in parietal areas in these children. ROIs in the right superior parietal lobe showed a significant increase (rSPL_2 $p<0.05$) or a trend for enhanced activation (rSPL_1 $p=0.85$) after rest. All the other ROIs showed no significant change in mean beta values after rest.

The other group of children without previous training, showed no increase in brain activation in any region.

Discussion

Despite the relatively high prevalence of developmental dyscalculia, few studies to date have attempted to develop or evaluate targeted interventions based on neuro-cognitive knowledge of this impairment. In the present study, we developed a custom computer-based training program and performed the first assessment of the efficacy and neuro-cognitive effects of this targeted training for remediation of dyscalculia by means of neuropsychological tests and fMRI examinations. The results obtained are promising and demonstrate an improvement in various aspects of spatial number representation and mathematical reasoning in children with and without developmental dyscalculia. Moreover, brain imaging results depict a general decrease in brain activation immediately after training in both groups and point to a partial restoration of normal activation in number processing after a consolidation phase in dyscalculic children.

Training

The Training "Rescue Calcularis" was designed on the basis of state of the art neuropsychological and neuro-imaging findings of dyscalculia and aims to specifically improve the spatial representation of numbers in children with DD. Feedback from children who have completed the training and from their parents confirms that the difficulty level is appropriate for children between the second and fourth grade. However, some older children suffering from more severe dyscalculia might also benefit from the training if their math level is comparable to that of a younger typically developing child. Evaluation of the feedback questionnaire also confirmed that all children liked to play the game and were able to train without the help of their parents. The popularity of the game among children represents an important benefit as training can only be successful

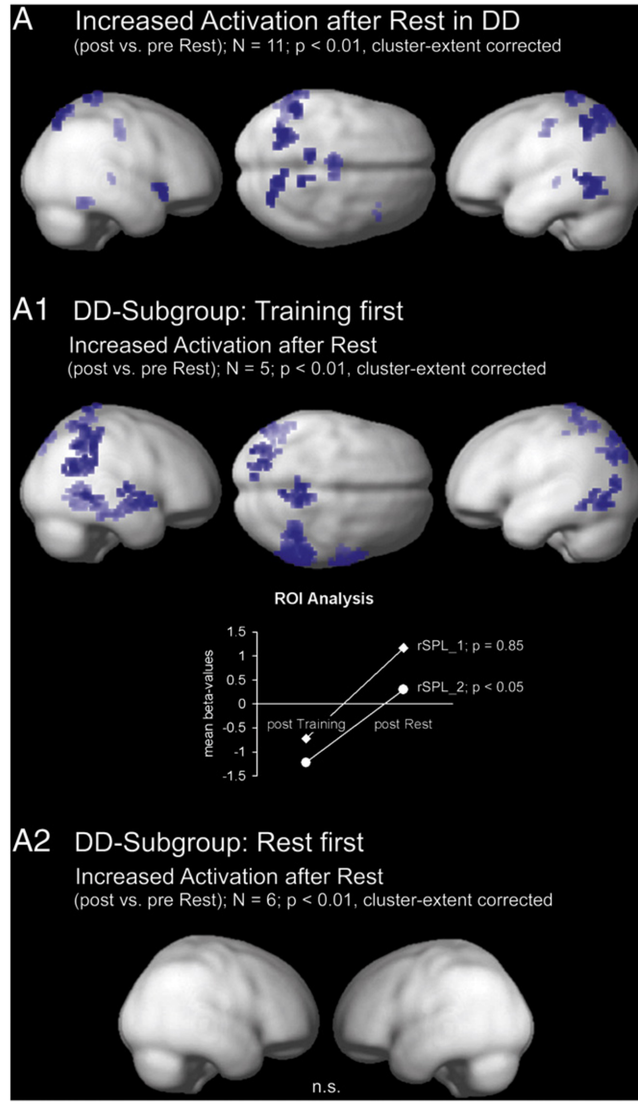

Fig. 7. Main effects of rest period. Effects of rest were calculated by paired-sample *t*-tests of the contrast order vs. control condition. (A) Activation increase after rest period including all dyscalculic children is displayed on an averaged brain template of SPM at $p<0.01$, cluster-extent corrected. Separate analysis of subgroups indicated an increase in activation after rest only in the subgroup of dyscalculic children who had accomplished the training prior to the rest period (A1). Furthermore, ROI analysis supported that mean beta values of the right superior parietal lobe increased significantly in this subgroup of dyscalculics (A1). No increase was evident in the subgroup which underwent first the rest period (A2).

when children are motivated to accomplish it. Furthermore, the software was designed in an adaptive manner to maintain the accuracy level at approximately 80% to create ideal learning stimulation, and the limited daily training time makes results directly comparable between subjects. A further benefit of "Rescue Calcularis" is the capability for installation on any home computer, with no further supervision or education required for the child to complete the training.

Behavioral effects

Behavioral results clearly demonstrate improvements in mathematical skills after completion of the training, not only in children with DD, but also in typically achieving children. However, the significant interactions observed between groups and behavioral performance indicate that dyscalculic children could benefit more from the training compared to controls (Linearity, Variability,

Table 6
Effects of rest period on brain activation.

Location	MNI coordinates			Cluster size	T value	p value
Increased activation after rest in DD (post- vs. pre-training) $p<0.01$, cluster-extend corrected; $n=11$						
Right cerebellum	12	−48	−18	29	5.45	0.001
Right inferior frontal gyrus	36	21	−12	43	5.10	0.001
Left postcentral gyrus	−12	−39	69	38	3.59	0.01
Left inferior parietal gyrus	−51	−51	42	75	4.75	0.001
Left medial frontal gyrus	−3	−18	54	48	4.67	0.001
Left superior parietal gyrus	−27	−63	57	105	4.66	0.001
Left inferior temporal gyrus	−60	−54	−12	98	4.63	0.001
Right postcentral gyrus	15	−45	75	29	4.51	0.01
Left thalamus	−6	−24	0	31	4.35	0.01
Right superior parietal gyrus	27	−72	51	99	4.07	0.01
Increased activation after rest: training first (post- vs. pre-training) $p<0.01$, cluster-extend corrected; $n=5$						
Right postcentral gyrus	9	−45	78	89	27.82	0.001
Right inferior parietal gyrus	54	−54	42	299	21.19	0.001
Left precuneus	−33	−87	33	34	15.06	0.001
Left middle temporal gyrus	−51	−78	9	81	13.52	0.001
Right parahippocampal gyrus	30	−24	−18	47	13.12	0.001
Right precuneus	27	−48	6	63	13.12	0.001
Left superior occipital gyurs	−12	−87	42	43	12.85	0.001
Right superior temporal gyrus	54	−6	−9	70	12.37	0.001
Right precuneus	3	−60	60	63	12.13	0.001
Right middle temporal gyrus	63	−48	0	49	11.91	0.001

Accuracy in fMRI Paradigm). In some aspects of numerical reasoning (Linearity, Variability), dyscalculic children were able to catch up with control children and showed no significant differences relative to their typically achieving peers after the training.

Specifically, children were able to locate a number, the result of addition or subtraction problems, or the estimated number of dots on a number line more accurately after the training. Better performance in such a number line task is associated with an improved understanding of the relationship between numerical magnitudes, increased comprehension of ordinality of the numerical system, and more accurate mapping of number representation. Moreover, improved performance in this task points to a potential refinement of the internal mental number line, as demonstrated by the increased linearity of Arabic number representation after the training. Moreover, the spatial representation of estimation of dots is rather explained by a linear than a logarithmic function after training in children with dyscalculia. This increase in linearity provides further evidence for a postulated developmental shift in numerical representation from logarithmic to linear, in a familiar number range shaped by the acquisition of cultural practices with numbers (Berteletti et al., 2010; Halberda and Feigenson, 2008; Halberda et al., 2008; Siegler and Booth, 2004; Siegler and Opfer, 2003). Our results also showed a substantial reduction in variability in children's estimates of Arabic digits after the training, further supporting an increase in precision of the mental number line. The training can therefore be seen to enhance or accelerate normal development of spatial number representation. However, it has to be mentioned that training effects regarding variability and linearity were not as evident when analyzing the spatial characteristics of dot estimation. This might be explained by the fact that children had to estimate the number of dots in a first step and thereafter indicate the analog location on the number line in a second step. Both can be erroneous, leading to higher variance and we cannot say whether children were less accurate in their estimation and correct in the localisation on the number line, vice versa, or poor in both steps. Furthermore, these results place emphasis against the misconception that mere training of non-symbolic number processing is leading to improved processing of digits. In contrast, it is highly important to train number processing using non-symbolic as well as symbolic modalities to achieve improved number representation and mathematical skills.

In accordance with developmental studies, the more accurate mental representation was accompanied by improved arithmetical performance (Berteletti et al., 2010; Halberda et al., 2008; Siegler and Booth, 2004) such that both groups solved more addition and subtraction problems correctly after the training. At present is not possible to establish whether this improvement in arithmetic skills arises solely from transfer effects between increased spatial representation and better arithmetical abilities, since some improvement may also result from the additional practice in solving addition and subtraction problems. However, it seems likely that the improved performance arises more from the combination of arithmetical training problems and practice in translating results into ordinal relations, rather than simple arithmetical practice, since children were never asked to calculate exact results of calculation problems or enter exact results before guiding the spaceship to the correct position on the number line. In contrast to the computer game, the observed improvement in arithmetic in the paper number line task may be influenced by practice effects as the solutions to this task were based on mentally calculated addition and subtraction problems.

These positive effects on number representation and arithmetic processing are plausibly attributed to the training and specific to the numerical domain, since no effects were evident after a 5-week rest period without training, and the training did not influence the performance in tasks of spatial working memory.

Furthermore, positive training effects seem to persist for at least 5 weeks following the training, since the performance of children increased significantly after training and was stably maintained to the subsequent follow-up testing session 5 weeks later. However, as these results are based on only six subjects further research will be required to verify the long-term effects of training.

In summary, behavioral outcome after training is promising and demonstrated a specific gain of spatial representation in children.

Brain imaging effects

The fronto-parietal brain activation pattern detected for number representation in control children is in line with that reported by Fulbright et al. (2003), who examined adult subjects with a similar task. Whereas control children showed the maximum activation in the intraparietal sulcus, dyscalculic children recruited mainly medial frontal areas. A former study, which examined distance effects in children with DD also reported a strong reliance on medial frontal regions in dyscalculic children reflecting rather domain-general processes of cognitive control and conflict processing (Kucian et al., in press). A direct comparison between groups indicated reduced activation in bilateral parietal lobules in dyscalculics. Moreover, masking group differences by the activation pattern of control children corroborates that dyscalculic children show significantly reduced activation in task related areas (bilateral intraparietal sulcus, superior parietal lobe, cingulated gyrus) which are typically activated. Besides, also ROI analysis showed reduced activation in dysalculic children compared to controls. Parietal areas, and the intraparietal sulcus in particular, are thought to represent the most specific locus for number processing in the brain and several studies have implicated deficits in these regions with developmental dyscalculia (Kaufmann et al., 2009; Kucian et al., 2006; Mussolin et al., 2010; Price et al., 2007). Our results lend further support to a deficient number representation in the parietal lobe associated with dyscalculia, causing stronger engagement of supporting frontal lobe functions such as working memory and attentional control to solve a numerical task.

Learning is associated with changes in functional circuitry within and between systems and more specific, targeted training can shape the corresponding brain activations, as seen in the present study. The 5-week intensive training of number representation altered brain function significantly. Conducting whole-brain analysis, as well as, ROI analysis demonstrated that both groups showed a clear reduction in the recruitment of relevant brain regions after the training, including mainly frontal areas, bilateral intraparietal sulci and the left fusiform gyrus, consistent with several previous neuro-imaging studies which examined learning processes in arithmetic have reported a similar decrease in the fronto-parietal activation pattern after training (Delazer et al., 2003; Ischebeck et al., 2006, 2007; Pauli et al., 1994). Interestingly, these studies demonstrated a decrease in brain activation after extensive practice over several weeks (Pauli et al., 1994), but also during the process of learning itself (Ischebeck et al., 2007). Reduction of brain activation in these regions and particularly of the frontal lobe is argued to reflect automatization of cognitive processes necessary for mathematical reasoning (Ischebeck et al., 2006, 2007; Pauli et al., 1994). Therefore, it seems that after completion of the training, the task puts less demand on quantity processing, executive functions, working memory, and requires less attentional effort. Moreover, the interaction between groups and training points to a stronger decrease in recruitment of these regions in children with dyscalculia, which is consistent with the more pronounced improvement of behavioral outcome in these children.

It should be noted that learning in general is associated with modulation of domain specific neural activations, which involve not only decreases but also increases. Existing training studies in the field of number processing describe a common and stable increase of brain activation in the left angular gyrus after training (Delazer et al., 2003; Ischebeck et al., 2006, 2007). In our study, we did not observe an increased activation in this region. However, this is not surprising, considering that activity in the left angular gyrus is thought to be related to numerical fact retrieval (Grabner et al., 2009a,b). Studies reporting stronger activation in this region after training compared over-learned arithmetical problems with novel ones, which could not be retrieved from memory. In contrast, in the present study, children were not asked to retrieve practiced problems from memory to solve the fMRI-order-task. Instead, children were trained on the understanding of a conceptual principle of numerosity, the spatial number representation.

Following results from intervention studies in dyslexic children, we expected a restoration of deficient brain activation in children with developmental dyscalculia. Specifically, the deficient activation in the parietal lobules in dyscalculics was hypothesized to ameliorate after training. However, we could not find an increase in BOLD signal in parietal areas immediately after training in children with DD, although a significant increase in bilateral parietal regions, including the intraparietal sulcus (IPS) bilaterally was found in a follow-up examination 5 weeks later. Interestingly, voxels showing an increased activation after rest in the IPS overlapped with the ones showing a main effect of activation decrease after training. Since the IPS is known to play a pivotal role in number representation, these results suggest that time for consolidation is needed after training to establish number representation. Consolidation is a category of processes that stabilize a memory trace after the initial acquisition (Dudai, 2004). Consolidation is distinguished into two specific processes, synaptic consolidation, which occurs within the first minutes to hours after learning, and system consolidation, where learned content undergoes reorganization to a more permanent form of storage over a period of weeks to years (Dudai, 2004; Roediger et al., 2007). Therefore, our results point to the need of system consolidation before being able to detect corresponding cortical activation. The increase in parietal activation in dyscalculic children in the present study after a suggested consolidation period is rather speculative due to the small sample size, so further research will be needed to elucidate the nature of the activation changes associated with learning and consolidation in this subject group. Nevertheless, we believe that these results shed an interesting light on potential learning processes in dyscalculia.

In contrast to plastic effects after training, no changes could be found after a 5-week rest period without training applying false-discovery rate correction, suggesting that observed neuro-plastic changes after training can be attributed to the intervention. However, when conducting an uncorrected p value and cluster-extend correction for multiple comparisons an increase in inferior and superior parietal, postcentral, and medial frontal regions bilaterally and right inferior frontal gyrus and left superior temporal gyrus was evident. Separate analysis of dyscalculic subgroups, indicated that this activation increase was based on the subgroup which had accomplished the training prior to the rest period. In contrast, no activation increases after rest could be found in the subgroup which performed the training subsequent to the 5-week rest period.

Taken together, neuro-imaging results lend support to the notion that developmental dyscalculia could be caused by deficient functioning of parietal areas. Further, the game software “Rescue Calcularis” evokes changes in brain activation necessary for number processing. In particular, reduced activation in fronto-parietal regions can be associated with reduction in the demands of executive functions. Finally, results hint to a partial remediation of deficient brain activation in dyscalculics after consolidation of acquired and refined number representation.

Limitations

Some limitations of the present study have to be considered regarding group matching, study design and interpretation of results. Firstly, although subjects were carefully selected, detailed examination revealed differences in estimated IQ between children with and without dyscalculia. IQ measures are known to be not at all fully independent from measures of math ability, which makes the IQ discrepancy criterion in dyscalculia diagnosis questionable. The subscale Arithmetic as part of the WISC intelligence test battery is highly intercorrelated with several other WISC subtests, including Similarities (correlation index .50), Vocabulary (correlation index .48), Picture Arrangement (correlation index .40) and Block Design (correlation index .45) (Wechsler, 1999). When comparing children with and without math disabilities these confounding factors have to be taken into account. Following, no group differences in estimated IQ were evident in the present study when controlling for performance differences in arithmetic, suggesting that our groups are matched for IQ, but differ significantly in tasks that are closely related to number processing.

Secondly, control children have not been measured after a rest period. Although, dyscalculic children have been examined additionally after a 5-week rest period, either before or after completion of the training, subsequent data analysis revealed lasting effects of the training on follow-up examinations. While the chosen cross-sectional study design hints at a possible learning trajectory in dyscalculic children following intervention, the sample size of subgroups are rather small to draw firm conclusions. Moreover, part of the dyscalculic children has completed the tasks after the training for the third time. In contrast, control children have only performed the tasks twice. However, no differences were found in performance before and after rest period, independent whether they have completed the task for the second or third time. This makes it rather implausible that results are mainly explained by the fact that some children have performed the task one time more. Additionally, confirmation of specific training effects will require results to be compared not only to a rest period, but also to another intervention.

Finally, we would like to point to a potential conflict in the brain activation changes seen in the parietal lobe. On the one hand, dyscalculic children showed reduced activation of parietal areas compared to matched peers, while on the other hand, a decrease of activity in parietal areas was found after training and was associated with increased performance. As outlined above, both results have been reported previously by other studies examining neural correlates of dyscalculia or training of arithmetical skills. Developmental studies of number processing, which demonstrate an increase in BOLD signal in task specific areas, such as the intraparietal sulcus and a decrease in regions of supporting functions, suggest that stronger engagement of parietal areas is associated with more experienced performance (Kucian et al., 2008; Rivera et al., 2005). We believe that our results provide a possible explanation for these apparently contradictory results, as learning is a complex process which is especially demanding when the mind acquires higher cognitive capabilities, like calculation. Our results indicate that neural correlates of learning do not follow a linear path. Instead, intensive training lead initially to a general activation decrease of relevant brain regions due to reorganization and fine-tuning processes, and subsequently to an increase in task-relevant areas after consolidation. Therefore, the results derived from training studies are crucially dependent on the time-point of measurement. However, the time course of neural correlates of learning has not yet been fully established and further research is needed to improve our understanding of influence of basic numerical training on parietal activity.

Despite these limitations, we believe the results obtained in this study, both for behavioral and neuro-plastic changes emphasize the efficacy of our training. To our knowledge, this is the first imaging study to examine effects of a specific intervention in children with developmental dyscalculia. This study also provides important insight into the manner in which educational software games may support learning efforts in affected children, further enhancing the prospects of linking changes in brain activity to educational experimental manipulations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.01.070.

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