



## SPECIAL ISSUE ARTICLE

# Parietal hyper-connectivity, aberrant brain organization, and circuit-based biomarkers in children with mathematical disabilities

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## Abstract

Mathematical disabilities (MD) have a negative life-long impact on professional success, employment, and health outcomes. Yet little is known about the intrinsic functional brain organization that contributes to poor math skills in affected children. It is now increasingly recognized that math cognition requires coordinated interaction within a large-scale fronto-parietal network anchored in the intraparietal sulcus (IPS). Here we characterize intrinsic functional connectivity within this IPS-network in children with MD, relative to a group of typically developing (TD) children who were matched on age, gender, IQ, working memory, and reading abilities. Compared to TD children, children with MD showed hyper-connectivity of the IPS with a bilateral fronto-parietal network. Importantly, aberrant IPS connectivity patterns accurately discriminated children with MD and TD children, highlighting the possibility for using IPS connectivity as a brain-based biomarker of MD. To further investigate regional abnormalities contributing to network-level deficits in children with MD, we performed whole-brain analyses of intrinsic low-frequency fluctuations. Notably, children with MD showed higher low-frequency fluctuations in multiple fronto-parietal areas that overlapped with brain regions that exhibited hyper-connectivity with the IPS. Taken together, our findings suggest that MD in children is characterized by robust network-level aberrations, and is not an isolated dysfunction of the IPS. We hypothesize that intrinsic hyper-connectivity and enhanced low-frequency fluctuations may limit flexible resource allocation, and contribute to aberrant recruitment of task-related brain regions during numerical problem solving in children with MD.

## Research highlights

- Mathematical disabilities (MD) have a negative life-long impact on professional success, employment, and health outcomes, yet little is known about the intrinsic functional brain organization that contributes to poor math skills in affected children.
- Intrinsic functional hyper-connectivity of the intraparietal sulcus (IPS) – a brain region critical for numerical cognition – is a distinguishing and behaviorally relevant neurobiological feature of children with MD.
- Childhood MD is also associated with higher levels of spontaneous low-frequency fluctuations in multiple frontal and parietal areas.
- Our findings advance the view that MD is best characterized as a network-level deficit; we hypothesize that IPS hyper-connectivity and high levels of spontaneous activity may limit flexible resource allocation in response to changing task demands.

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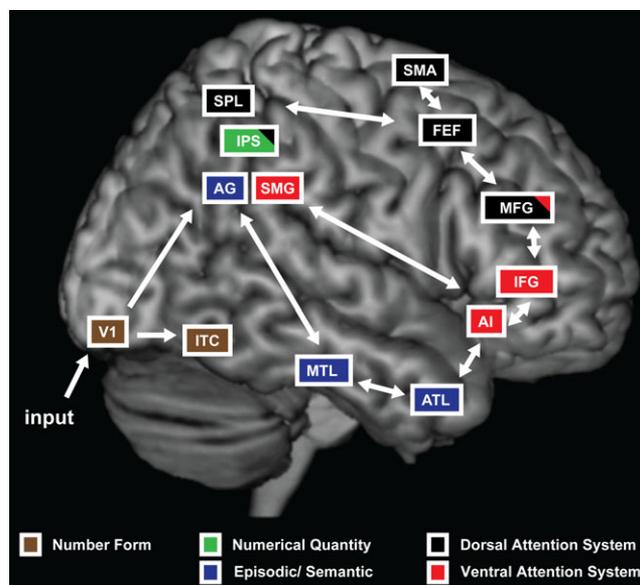
## Introduction

Strong foundational skills in mathematics are indispensable not only for educational and professional success, but also for quantitative reasoning in everyday life (Butterworth, Varma & Laurillard, 2011; Geary, Hoard, Nugent & Bailey, 2013; Parsons & Bynner, 2005). Critically, disabilities in numerical and mathematical problem solving, including developmental dyscalculia, are widespread (Butterworth *et al.*, 2011; Shalev, Auerbach, Manor & Gross-Tsur, 2000; Szucs & Goswami, 2013). Yet, despite its negative consequences for employability, academic performance, and socioeconomic well-being (Butterworth *et al.*, 2011; Parsons & Bynner, 2005), the etiology of mathematical disabilities (MD) and its neural underpinnings remain unclear.

It has been argued that MD originates from a core dysfunction in the representation of quantity and the inability to access numerical magnitude information conveyed by number symbols or words (Butterworth *et al.*, 2011; Noel & Rousselle, 2011). Converging evidence from adults, children and non-human primates suggests that the representation of approximate quantity is a foundational ability supported by the intraparietal sulcus (IPS) subdivision of the dorsal posterior parietal cortex (for reviews, see e.g. Ansari, 2008; Brannon, 2006; Cohen Kadosh, Lammertyn & Izard, 2008). An emerging body of research has led to the hypothesis that the IPS is a key locus of deficits in children with MD (e.g. Cohen Kadosh, Cohen Kadosh, Schuhmann, Kaas, Goebel *et al.*, 2007; Price, Holloway, Rasanen, Vesterinen & Ansari, 2007). However, while task-based functional MRI (fMRI) studies have consistently demonstrated aberrant IPS recruitment in children with MD (Ashkenazi, Rosenberg-Lee, Tenison & Menon, 2012; Kaufmann, Vogel, Starke, Kremser, Schocke *et al.*, 2009b; Kucian, Loenneker, Dietrich, Dosch, Martin *et al.*, 2006; Molko, Cachia, Riviere, Mangin, Bruandet *et al.*, 2003; Mussolin, De Volder, Grandin, Schlogel, Nassogne *et al.*, 2010; Price *et al.*, 2007; Rosenberg-Lee, Ashkenazi, Chen, Young, Geary *et al.*, 2015), it is the case that multiple distributed regions within posterior parietal, prefrontal and ventral temporal-occipital cortices show impairments as well (Ashkenazi *et al.*, 2012; Kaufmann, Wood, Rubinsten & Henik, 2011; Kucian, 2011; Mussolin *et al.*, 2010). Furthermore, children with MD show aberrant task-related functional connectivity between IPS and multiple brain systems during arithmetic problem-solving (Rosenberg-Lee *et al.*, 2015). These findings have led to the hypothesis that MD may involve an intrinsic network-level aberration,

rather than an isolated dysfunction of the IPS (Fias, Menon & Szucs, 2014).

There is growing evidence to suggest that numerical cognition relies on interactions within and between multiple functional brain systems, including those subserving quantity processing, episodic and semantic memory, working memory, and cognitive control (e.g. Arsalidou & Taylor, 2011; Fias *et al.*, 2014; Figure 1). While the IPS plays a key role in building representations of numerical quantity, it is also part of an intrinsically connected dorsal fronto-parietal system that includes the superior parietal lobe (SPL), frontal eye fields, supplementary motor area (SMA), insula, and middle frontal gyrus (MFG) (Corbetta, Patel & Shulman, 2008; Corbetta & Shulman, 2002; Menon & Uddin, 2010; Supekar & Menon, 2012; Uddin, Supekar, Amin, Rykhlevskaia, Nguyen *et al.*, 2010). This system is thought to be important for top-down goal-driven attention, including performance monitoring and manipulation of numerical



**Figure 1** Schematic diagram of math-related brain circuits. It is increasingly recognized that mathematical processing requires interaction within and between multiple interacting brain systems, including systems involved in processing lower-order visual information and number form (brown), numerical quantity (green), episodic and semantic memory (blue), and attentional control (red and black). Adapted from Fias *et al.* (2014). AG = angular gyrus, AI = anterior insula, ATL = anterior temporal lobe, FEF = frontal eye fields, IFG = inferior frontal gyrus, IPS = intraparietal sulcus, ITC = inferior temporal cortex, MFG = middle frontal gyrus, MTL = medial temporal lobe, SMA = supplementary motor area, SMG = supramarginal gyrus, SPL = superior parietal lobe.

information in working memory. In contrast, the ventral attention system, which includes the supramarginal gyrus (SMG), insula and inferior frontal gyrus, is thought to be involved in saliency processing and attentional filtering (Corbetta *et al.*, 2008; Corbetta & Shulman, 2002; Fox, Corbetta, Snyder, Vincent & Raichle, 2006; Menon & Uddin, 2010; Supekar & Menon, 2012). Finally, memory systems anchored in the medial and anterior temporal lobe, as well as in the angular gyrus, are important for encoding and retrieval of math facts (Grabner, Ansari, Koschutnig, Reishofer, Ebner *et al.*, 2009; Qin, Cho, Chen, Rosenberg-Lee, Geary *et al.*, 2014a). It is currently not known whether functional circuits associated with the IPS are aberrant in MD and, crucially, whether they impact the multiple dorsal and ventral fronto-parietal and memory circuits that are involved in numerical cognition.

Although most studies of numerical cognition in children with MD have found aberrations within the IPS, as well as multiple other parietal and prefrontal cortical areas, the exact profile of aberrations has varied considerably from study to study. For example, some studies have reported *hypo*-activity in IPS and associated fronto-parietal brain areas in children with MD (e.g. Kucian, 2011; Kucian *et al.*, 2006; Price *et al.*, 2007), while others have found *hyper*-activity (e.g. Davis, Cannistraci, Rogers, Gatenby, Fuchs *et al.*, 2009; Iuculano, Rosenberg-Lee, Richardson, Tenison, Fuchs *et al.*, 2015; Kaufmann *et al.*, 2009b; Rosenberg-Lee *et al.*, 2015). Such inconsistencies may arise from differences in the numerical tasks (e.g. non-symbolic number comparison, symbolic number comparison, addition, subtraction) and baseline ('control') conditions (e.g. fixation, mental rotation, manipulation of task complexity) used in various studies, as well as differences in task performance between the MD and typically developing groups (see Menon, 2015, for a detailed review). Intrinsic functional connectivity (e.g. Fox & Raichle, 2007) has the potential to address broader questions related to functional brain organization in MD and to circumvent methodological issues arising from differences in the type of numerical task and control conditions used, as well as confounding effects of task performance and strategy use (e.g. Church, Fair, Dosenbach, Cohen, Miezin *et al.*, 2009; Fair, Dosenbach, Church, Cohen, Brahmbhatt *et al.*, 2007; Finn, Shen, Holahan, Scheinost, Lacadie *et al.*, 2014; Koyama, Di Martino, Zuo, Kelly, Mennes *et al.*, 2011; Supekar, Uddin, Khouzam, Phillips, Gailard *et al.*, 2013b; Uddin, Supekar, Lynch, Khouzam, Phillips *et al.*, 2013).

Here we use task-free fMRI to address critical gaps in our knowledge of aberrant parietal networks in children with MD. Specifically, we investigated intrinsic

functional connectivity of the IPS in 7- to 9-year-old children with MD, and contrasted it with functional connectivity of a well-matched group of typically developing (TD) children, who differed on math achievement, but not on age, gender, IQ, reading abilities, or working memory. We hypothesized that functional circuits associated with the IPS would be aberrant in children with MD, and that IPS connectivity patterns could be used to discriminate children with MD from TD controls.

## Methods

### Participants

Data from two ongoing research projects (Project 1: Ashkenazi, Rosenberg-Lee, Metcalfe, Swigart & Menon, 2013; Ashkenazi *et al.*, 2012; Rosenberg-Lee *et al.*, 2015; Project 2: Iuculano *et al.*, 2015; Supekar, Swigart, Tenison, Jolles, Rosenberg-Lee *et al.*, 2013a) examining mathematical cognition in children with and without MD were included in the present study. Participants were recruited from a wide range of schools in the San Francisco Bay Area using mailings to schools, and postings at libraries and community groups. We included second and third grade children (7–9 years old) with no history of developmental disabilities and with a full-scale IQ above 80, assessed using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). In the absence of agreement about the exact definition and diagnostic criteria of MD (Kaufmann, Mazzocco, Dowker, von Aster, Gobel *et al.*, 2013; Szucs & Goswami, 2013), here MD was defined as mathematical achievement at or below the 25th percentile (Ashkenazi *et al.*, 2013; Ashkenazi *et al.*, 2012; Davis *et al.*, 2009; Swanson, Jerman & Zheng, 2009), which corresponds to 90 points on a standardized test scale. This is in line with cut-off criteria used in fMRI studies of developmental dyslexia (e.g. Finn *et al.*, 2014; Tanaka, Black, Hulme, Stanley, Kesler *et al.*, 2011).

Nineteen children (8.91 years (*SD* 0.60), 13 girls and 6 boys) who scored at or below 90 on the Numerical Operations subtest of the Wechsler Individual Achievement Test, Second Edition (WIAT-II; Wechsler, 2001) were included in the MD group. In addition, we performed follow-up analyses on a subset of 14 children with the most severe math disabilities, scoring at or below 85 on Numerical Operations (i.e. at least one standard deviation lower than the population average). MD children with co-morbid reading disabilities, i.e. children who scored at or below 90 on the Word Reading or Reading Comprehension subtests of the WIAT-II

(Wechsler, 2001) were excluded from the study, as were children with excessive head movement (for movement characteristics see below). The TD group consisted of 19 children (8.75 years (*SD* 0.75), 9 girls, 10 boys) who scored at or above 95 (37th percentile) on the Numerical Operations subtest of the WIAT-II. TD children were selected using a genetic algorithm (Uddin *et al.*, 2013) designed to ensure that the two groups did not differ on age, gender, full-scale IQ, and reading ability (based on the Word Reading subtest of the WIAT-II).

To control for variations in data acquisition and scan parameters across the two research studies, we ensured that the MD and TD groups included the same number of children from each study cohort – the MD and TD groups included 13 children from one cohort (Ashkenazi *et al.*, 2013; Ashkenazi *et al.*, 2012; Rosenberg-Lee *et al.*, 2015) and 6 children from the other (Iuculano *et al.*, 2015; Supekar *et al.*, 2013a). Furthermore, all analyses included ‘cohort’ as a covariate of no interest. To further examine the robustness of our findings, we performed additional region of interest (ROI) analyses in the two cohorts separately. Informed consent was obtained from the legal guardian of each child participant, and study protocols were approved by the Stanford University Institutional Review Board.

### *Standardized cognitive assessments*

#### Mathematical abilities

Mathematical abilities were assessed using the WIAT-II (Wechsler, 2001). This achievement battery includes nationally standardized measures of K-12 academic skills and problem-solving abilities, which are normed by grade and time of academic year (Fall, Spring, or Summer). The Numerical Operations subtest is a paper-and-pencil test that measures number writing and identification, rote counting, number production, and simple addition, subtraction, multiplication, and division problems. For example,  $4 - 2 = \underline{\quad}$  and  $37 + 54 = \underline{\quad}$  (presented horizontally and vertically, respectively) are two problems in the second and third grade range. The Mathematical Reasoning subtest is a verbal problem-solving test that measures counting, geometric shape identification, and single- and multi-step word problem-solving involving time, money, and measurement with both verbal and visual prompts. The child is required to solve problems with whole numbers, fractions or decimals, interpret graphs, identify mathematical patterns, and solve problems of statistics and probability. For example, a dime is presented and

the child is asked, ‘How many pennies does it take to equal the value of one dime?’ An example of a probability problem is: ‘If you flipped a coin ten times, how many times would the coin be most likely to land on heads?’

#### Reading abilities

The WIAT-II was also used to assess reading abilities. The Word Reading subtest involves reading individual words presented visually to the child, and was used for matching the MD and TD groups on reading ability. In addition, the Reading Comprehension subtest was administered, which involves reading passages and answering questions about them.

#### Working memory

Four subtests of the Working Memory Test Battery for Children (WMTBC) (Pickering & Gathercole, 2001) were used to assess working memory abilities: (1) Counting Recall and (2) Backward Digit Recall, which are thought to measure the central executive, (3) Digit Recall, which is thought to measure phonological loop, and (4) Block Recall, a variant of the Corsi block tapping test which is thought to measure the visuo-spatial sketch pad (Pickering & Gathercole, 2001).

### *fMRI data acquisition*

Functional imaging data were acquired at a 3T General Electric Signa Scanner at the Richard M. Lucas Center for Imaging at Stanford University. Participants were instructed to lay still with their eyes closed for the duration of the entire scan. For the first study cohort (13 MDs and 13 TDs), the resting-state scan contained 240 volumes and was acquired using a single-channel head-coil. Data for the second study cohort (6 MDs and 6 TDs) contained 180 volumes and was acquired using an 8-channel head-coil. All other scanning parameters were similar as noted below. Twenty-nine axial slices (4.0 mm thickness, 0.5 mm skip) were collected parallel to the AC-PC line, using a T2\* weighted gradient echo spiral in-out pulse sequence (Glover & Lai, 1998) (TR = 2000 ms; TE = 30 ms, flip angle = 80°, 1 interleave). Scans were acquired with a field of view of 20 × 20 cm and a matrix size of 64 × 64, providing an in-plane spatial resolution of 3.125 mm. To reduce blurring and signal loss from field in-homogeneity, an automated high-order shimming method based on spiral acquisitions was used before acquiring the functional MRI scan (Kim, Adalsteinsson, Glover & Spielman, 2002).

### Movement

Head movement was minimized during scanning by a comfortable, custom-built restraint. Before group matching, we excluded children with movement larger than 5 mm in either the x, y, or z directions. In the examined MD sample, the movement range was on average 0.41 (*SD* 0.27), 0.74 (*SD* 0.58), and 1.54 (*SD* 1.33) mm in the x, y, and z direction, with 0.71 (*SD* 0.50), 1.76 (*SD* 1.54), 0.68 (*SD* 0.64) degrees of roll, pitch, and yaw. In TDs, the movement range was on average 0.43 (*SD* 0.51), 0.69 (*SD* 0.63), 1.39 (*SD* 1.19) mm in the x, y, and z direction, with 0.80 (*SD* 0.74), 1.71 (*SD* 1.46), 0.70 (*SD* 0.63) degrees of roll, pitch, and yaw. There were no significant differences in movement between the groups on any of the six movement parameters (all *ps*  $\geq$  .649,  $\eta^2_p \leq$  .006). Mean frame-wise displacement did not exceed  $>$  .5, and was almost identical across groups (*p* = .955,  $\eta^2_p <$  .001).

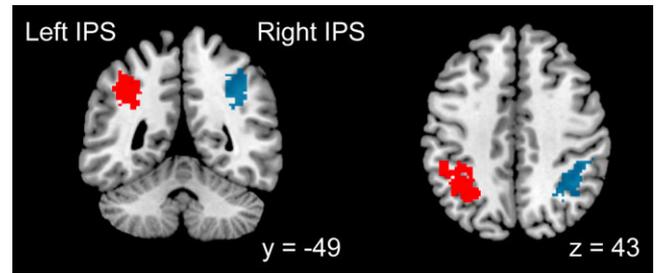
### fMRI data preprocessing

The first six volumes were not analyzed to allow for signal equilibration. A linear shim correction was applied separately for each slice during reconstruction using a magnetic field map acquired automatically by the pulse sequence at the beginning of the scan (Glover & Lai, 1998). fMRI data were preprocessed and analyzed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). Preprocessing procedures included slice time correction, normalization to the standard Montreal Neurological Institute (MNI) T1 template, and spatial smoothing using a Gaussian kernel (6 mm full-width at half-maximum). For the functional connectivity analyses, a bandpass filter (0.008 to 0.1 Hz) was applied to the smoothed data to remove high frequency artifacts.

### Functional connectivity analysis

#### Seed regions of interest

We defined the IPS seed ROIs using observer-independent cytoarchitectonic regions, combining the maximum probability maps of hIP1, hIP2, and hIP3 of the Anatomy Toolbox in SPM8. Detailed information about the anatomical boundaries of these maps has been published elsewhere (Caspers, Eickhoff, Geyer, Scheperjans, Mohlberg *et al.*, 2008; Caspers, Geyer, Schleicher, Mohlberg, Amunts *et al.*, 2006; Choi, Zilles, Mohlberg, Schleicher, Fink *et al.*, 2006). The MarsBar toolbox (<http://marsbar.sourceforge.net/>) was used to create a binary ROI from these maps (Figure 2).



**Figure 2** IPS seed regions of interest (ROIs). ROIs were defined based on unbiased observer-independent cytoarchitectonic regions (Caspers *et al.*, 2006, 2008; Choi *et al.*, 2006). IPS = intraparietal sulcus. Coordinates are in MNI space.

#### Whole-brain functional connectivity analysis

For the whole-brain functional connectivity analysis we used a seed-correlation approach similar to that described in Uddin *et al.* (2010). First-level analyses were performed on a subject-by-subject basis. For each ROI, we separately extracted the first eigenvector time course, and then calculated how strongly that time course fit the data at each voxel using a General Linear Model (GLM). The global mean signal, computed across all voxels of the brain, as well as six motion parameters were included as additional covariates of no interest in the model to take into account the effects of physiological noise and participant movement. Individual contrast images were then submitted to group-level analyses.

Group comparisons of functional connectivity were performed using two-sample *t*-tests, with study cohort as a covariate of no interest. In addition, to examine whether severity of MD was related to the level of aberrant brain connectivity, we performed regression analyses within the MD group using demeaned scores of math ability (WIAT-II Numerical Operations subtest) as a covariate of interest. Cohort was again included here as a covariate of no interest. This analysis addresses an important question regarding the neural correlates of heterogeneity and individual differences in MD. Note that performing this analysis across the entire sample would have been minimally informative, as we would have likely found results similar to the categorical MD versus TD analysis since these same math ability scores were used as an inclusion criterion for group membership.

Results were masked using a gray matter image and thresholded at *p* < .01 height, with family-wise error (FWE) corrections for multiple comparisons at the cluster level (*p* < .01, spatial extent 128 voxels). The cluster size was determined using Monte Carlo

simulations implemented in MatLab (see Rosenberg-Lee, Barth & Menon, 2011).

#### *Network-based classification of children with MD*

To examine whether children with MD could be discriminated from their TD peers based on IPS functional connectivity patterns, we used a linear, hard-margin SVM classifier implemented in the R package *e1071* (<http://cran.r-project.org/web/packages/e1071/>). Before running the classification analysis, connectivity maps were normalized, voxel-wise, within each cohort by subtracting the mean and then dividing by the standard deviation. Next, individual subject maps were masked to include only voxels that were significant at the group level ( $p < .01$  FWE correction at the whole-brain level, spatial extent 100 voxels; Supplementary Figure S1). A linear, hard-margin SVM with cost parameter  $C$  fixed to  $10e9$  was used to avoid over-fitting, which might occur in cases where the predictors (number of voxels) outnumber the observations (participants) (Uddin *et al.*, 2013). Classification accuracy was estimated using a leave-one-out cross-validation. The data were divided into  $N$  folds ( $N = 38$ ).  $N-1$  folds were used to build a classifier, and classification was tested on the left-out sample. This procedure was repeated  $N$  times, and the average classification accuracy was computed. We used permutation tests (10,000 permutations) to compute the  $p$ -values associated with the classification accuracy of each IPS-network by randomly assigning subjects into TD and MD groups. Further, confidence intervals for classification accuracy were computed via a bootstrapping procedure. For each of 10,000 iterations, 19 subjects from each group were sampled with replacement to generate a surrogate sample which was then submitted to the same cross-validation procedure outlined above. This produces an empirical distribution of classification accuracies from which we derived the 95% confidence interval.

#### *Fractional Amplitude of Low Frequency Fluctuations (fALFF) analysis*

To investigate group differences in regional low-frequency fluctuations, we performed voxel-wise analyses of fractional Amplitude of Low Frequency Fluctuations (fALFF), which provides a measure of the BOLD signal amplitude within a specific brain region, and is defined by the power of the signal in the low-frequency range relative to the power across all frequencies (Mennes, Zuo, Kelly, Di Martino, Zang *et al.*, 2011; Zang, He, Zhu, Cao, Sui *et al.*, 2007; Zou, Zhu, Yang, Zuo, Long *et al.*, 2008; Zuo, Di Martino, Kelly, Shehzad, Gee *et al.*, 2010). Unlike functional connectivity, which examines the interactions of

investigator-specified brain regions, fALFF is a regional measure that does not require a priori definition of specific ROIs, and can therefore be used to explore aberrant intrinsic brain dynamics outside our hypothesized IPS-network. Compared to ALFF (i.e. the power of the fluctuations in the low-frequency range, irrespective of the power in the other frequencies), fALFF is thought to have better sensitivity and specificity in detecting the spontaneous signal fluctuations because it is less affected by physiological noise (Zou *et al.*, 2008). Preprocessing procedures for the fALFF analyses involved the same steps as the functional connectivity analyses, including slice time correction, normalization to the MNI template, and spatial smoothing. Because fALFF involves computation of the power across the entire frequency spectrum, bandpass filtering was not applied to the time series. Following Zou *et al.* (2008), we computed the power spectrum at each voxel by transforming the time series to the frequency domain. Then we calculated the square root of the amplitude at each frequency (which is proportional to the power at that frequency). Finally, we divided the sum of the amplitude across the low frequencies (0.008 to 0.1 Hz) by the sum of the amplitudes across the entire frequency range.

Results were masked using a gray matter image and thresholded at  $p < .01$  height, with FWE corrections for multiple comparisons at the cluster level ( $p < .01$ , spatial extent 128 voxels).

## Results

### *Neuropsychological profile*

Table 1 shows standardized measures of math, reading, IQ, and working memory for the MD and TD groups. These groups were a priori matched on age, gender, full-scale IQ, and Word Reading. Beyond the difference in Numerical Operations by design, groups also differed on the Mathematical Reasoning subtest of the WIAT-II. None of the non-math measures showed a significant difference between groups, including working memory and Reading Comprehension, suggesting that the groups were very well matched for general cognitive abilities.

### *Children with MD show IPS hyper-connectivity compared to TD children*

Across the MD and TD groups, the IPS showed strong intrinsic functional connectivity with multiple bilateral prefrontal, parietal, and ventrottemporal occipital areas, including IPS, SPL, SMG, MFG, superior frontal gyrus (SFG), SMA, insula, and fusiform gyrus (Supplementary

**Table 1** Participant characteristics of the MD and TD groups

	MD	TD	
Age*	8.91 (0.60)	8.75 (0.75)	$p = .480, \eta^2_p = .014$
Gender*	13F/ 6M	9F/ 10M	$p = .325, \phi = .213$
<i>WASI</i>			
Performance IQ	103.1 (11.8)	106.6 (10.3)	$p = .334, \eta^2_p = .026$
Verbal IQ	104.9 (12.7)	100.8 (11.2)	$p = .292, \eta^2_p = .031$
Full-scale IQ*	104.1 (8.9)	104.5 (9.0)	$p = .900, \eta^2_p < .001$
<i>WIAT-II</i>			
Numerical Operations**	83.5 (4.4)	110.7 (8.1)	$p < .001, \eta^2_p = .821$
Mathematical Reasoning	94.3 (9.5)	106.2 (11.4)	$p = .001, \eta^2_p = .256$
Word Reading*	102.9 (8.2)	103.7 (5.8)	$p = .734, \eta^2_p = .003$
Reading Comprehension	103.6 (6.1)	104.1 (9.6)	$p = .841, \eta^2_p = .001$
<i>WMTB-C</i>			
Digit Recall	100.9 (17.2)	104.9 (19.1)	$p = .502, \eta^2_p = .013$
Block Recall <sup>§</sup>	91.6 (11.8)	97.6 (11.5)	$p = .125, \eta^2_p = .066$
Counting Recall <sup>§</sup>	81.8 (18.3)	83.3 (16.5)	$p = .789, \eta^2_p = .002$
Backward Digit Recall	92.4 (17.9)	91.2 (12.2)	$p = .809, \eta^2_p = .002$

Note: \*\*Used for group assignment; \*Used for matching; §For Block recall and count recall, data from one participant were lost. For all other analyses,  $N = 38$ . Gender differences were assessed using a chi-square test. All other differences were examined using univariate ANOVAs. MD = children with mathematical disabilities, TD = typically developing children.

Figure S1). Comparison of IPS connectivity patterns between the groups revealed greater functional connectivity in children with MD in a number of regions within this fronto-parietal network ( $p < .01$ , spatial extent 128 voxels; Tables 2 and 3; Figure 3A). Specifically, children with MD showed increased inter-hemispheric connectivity between left and right IPS, as well as between IPS and other dorsal fronto-parietal regions, including bilateral SPL/lateral occipital cortex and left SFG/MFG. In addition, both the left and right IPS showed greater functional connectivity with right SMG and superior temporal gyrus (STG). In addition to these regions, the right IPS also showed greater connectivity with right SFG, precentral gyrus, and SMA, while the left IPS showed greater connectivity with the left frontal pole and right putamen in children with MD. Only one cluster showed reduced IPS connectivity in children with MD compared to TD children (Tables 2 and 3; Supplementary Figure S2). Because of the close vicinity of this region to the lateral ventricle, this finding should be interpreted with caution.

Next, to examine IPS functional connectivity in children with the most severe math difficulties, we performed a follow-up analysis in a subset of 14 MD children who scored at or below 85 on the Numerical Operations subtest of the WIAT-II (i.e. at least one standard deviation lower than the population average), in comparison to the original TD sample ( $n = 19$ ). The MD and TD groups remained matched on age, gender, IQ, reading, working memory, and movement (all  $ps \geq .241, \eta^2_p \leq .044$ ). Results in the MD subgroup were in line with the original analysis (see Tables 2 and 3 and Figure 3B). As in the original analysis, children with the most severe MD showed greater functional connectivity

between IPS and regions of the dorsal fronto-parietal network, as well as right SMG and STG, compared to TD children. A notable difference between the results was the extension of the right SMG cluster to posterior middle temporal gyrus/lateral occipital cortex in the subsample of children with more severe MD. Taken together, our results reveal a consistent and robust pattern of hyper-connectivity in left and right IPS circuits in children with MD.

#### *IPS functional connectivity is negatively correlated with math ability in children with MD*

To further investigate the relation between IPS connectivity and math ability in MD children, we performed regression analyses within the MD group. For this purpose, we included demeaned scores of the WIAT-II Numerical Operations test as a covariate of interest in the whole-brain analysis. Study cohort was included as a covariate as well. In agreement with the results of the group comparison, we found a negative correlation between math ability and IPS functional connectivity (Figure 4). More specifically, in children with the lowest math abilities, bilateral IPS showed the highest functional connectivity with left SPL and anterior cingulate gyrus, extending into the SMA. In addition, children with the lowest math abilities showed highest connectivity between right IPS and two large right hemisphere clusters: one in the right temporal parietal junction (including SMG and middle temporal gyrus) and the other in right anterior STG and temporal pole. The patterns of brain-behavior correlations partially overlapped with the results of the group comparison in left

**Table 2** Group differences in functional connectivity of the left IPS

Local Maxima	Clustersize	Peak (T)	Coordinates		
			x	y	z
<b>MD &gt; TD</b>					
L frontal pole*	354	4.52	-34	50	16
L frontal pole		3.80	-48	42	12
L frontal pole		3.35	-36	52	24
R SMG, angular gyrus, SPL (IPS)*	760	4.27	42	-46	48
R SMG (IPS)		4.09	44	-36	44
R SMG (IPS)		3.84	52	-28	42
L SFG*	336	3.99	-12	4	70
L SFG, MFG		3.97	-28	6	62
L SFG		3.70	-16	0	56
L precuneous cortex, SPL, lateral occipital cortex*	391	3.91	-8	-58	66
L lateral occipital cortex		3.65	-18	-66	64
L precuneous cortex, lateral occipital cortex		3.40	-6	-72	52
R putamen*	376	3.55	28	-4	10
R putamen		3.48	30	-2	-6
R putamen		3.35	30	6	8
R Heschl's gyrus	141	3.41	54	-8	-2
R STG		3.36	58	0	-6
<b>TD &gt; MD</b>					
L precuneous/ posterior hippocampus*	268	4.10	-24	-42	10
L precuneous/ posterior hippocampus		3.82	-16	-42	18
L precuneous/ posterior hippocampus		3.74	-30	-48	8

Note: Results are reported at  $p < .01$ , 128 voxels. MNI coordinates are labeled according to the Harvard-Oxford atlas. IPS is defined based on the Juelich atlas. For each cluster, 3 sub-peaks are reported which are more than 8mm apart. \* = cluster also found in a subset children who scored at or below 85 on the Numerical Operations subtest of the WIAT-II compared with typically developing children. MD = children with mathematical disabilities, TD = typically developing children, IPS = intraparietal sulcus, MFG = middle frontal gyrus, SFG = superior frontal gyrus, SMG = supramarginal gyrus, SPL = superior parietal lobe, STG = superior temporal gyrus.

SPL, SMA, and right SMG. These results reveal greater hyper-connectivity in low functioning children with MD.

#### IPS-connectivity based classification of MD and TD children

Next, we used a linear hard-margin SVM classifier to examine whether IPS connectivity patterns could be used to distinguish MD status in children. IPS connectivity maps (which were masked to include only voxels that were significant at the group level) served as features in the classification analysis. Using leave-one-out cross-validation, the classifier was trained on  $N-1$  participants and tested on the remaining participant. We found that

**Table 3** Group differences in functional connectivity of the right IPS

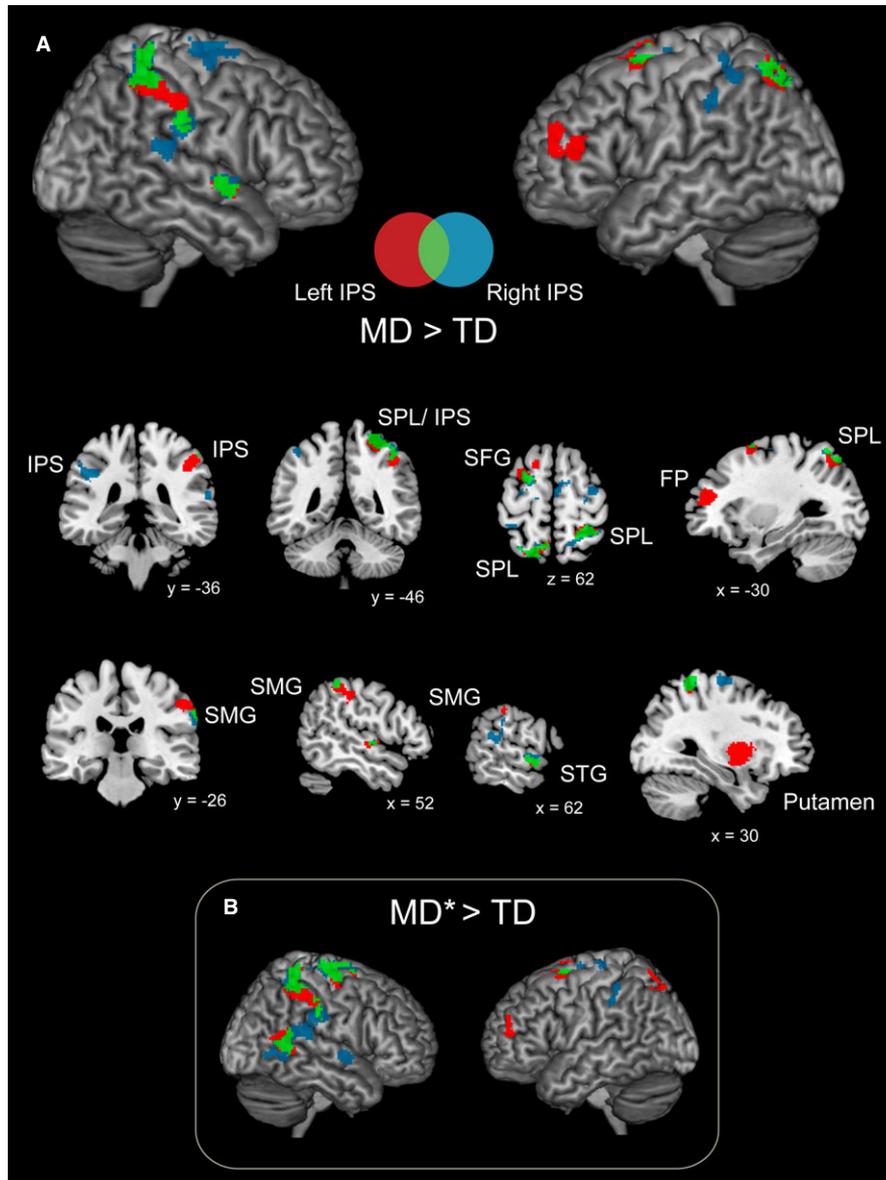
Local Maxima	Clustersize	Peak (T)	Coordinates		
			x	y	z
<b>MD &gt; TD</b>					
R SMG*	163	4.25	68	-22	30
R STG		3.56	64	-32	12
R SPL*	411	3.99	28	-46	64
R SPL, SMG, angular gyrus (IPS)		3.60	44	-46	56
R lateral occipital cortex, SPL		3.22	16	-58	62
R STG*	161	3.96	60	-2	-4
R precentral gyrus*	485	3.61	30	-18	68
R SFG, precentral gyrus		3.24	20	-8	72
R precentral gyrus		3.14	36	-10	64
L SMG (IPS)*	295	3.55	-50	-34	40
L SMG, SPL (IPS)		3.44	-44	-46	54
L SPL, postcentral gyrus		3.20	-34	-40	66
L SFG, MFG*	218	3.42	-26	8	64
L SFG		3.36	-24	0	64
L precentral gyrus, SFG		3.18	-16	-14	68
L precuneous cortex, SPL, lateral occipital cortex	186	3.16	-8	-58	62
L lateral occipital cortex, SPL (IPS)		3.10	-30	-62	60
L lateral occipital cortex		2.95	-28	-72	52
<b>TD &gt; MD</b>					
L precuneous cortex*	252	3.91	-20	-52	10
L precuneous cortex		3.58	-28	-54	8
L precuneous cortex		3.57	-18	-44	16

Note: Results are reported at  $p < .01$ , 128 voxels. MNI coordinates are labeled according to the Harvard-Oxford atlas. IPS is defined based on the Juelich atlas. For each cluster, 3 sub-peaks are reported which are more than 8mm apart. \* = cluster also found in a subset children who scored at or below 85 on the Numerical Operations subtest of the WIAT-II compared with typically developing children. MD = children with mathematical disabilities, TD = typically developing children, IPS = intraparietal sulcus, MFG = middle frontal gyrus, SFG = superior frontal gyrus, SMG = supramarginal gyrus, SPL = superior parietal lobe, STG = superior temporal gyrus.

left IPS connectivity-based classification yielded a significant cross-validation accuracy of 84.2% ( $p = .0098$ ). The 95% confidence interval of left IPS was 76.3–94.7% (Supplementary Figure S3). Cross-validation accuracy of right IPS connectivity-based classification was 76.3%, which did not reach significance ( $p = .0564$ ). The 95% confidence interval for right IPS was 76.3–94.7% (Supplementary Figure S3). These results reveal that aberrant IPS connectivity patterns can be used to discriminate children with MD from their TD peers.

#### Children with MD show increased fractional Amplitude of Low Frequency Fluctuations compared to TD children

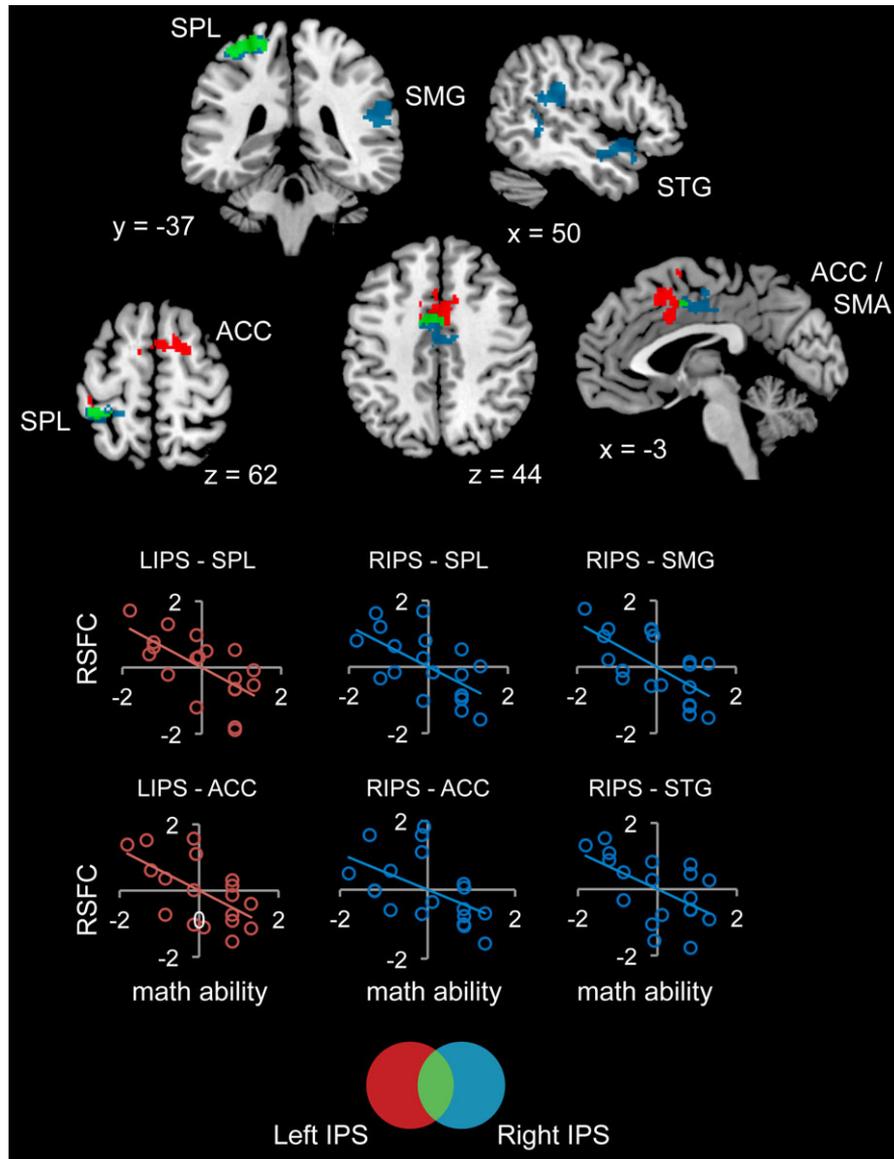
Finally, we investigated group differences in the amplitude of the low-frequency BOLD fluctuations. To measure BOLD signal fluctuation, we used fALFF,



**Figure 3** Brain areas that showed greater IPS connectivity in children with mathematical disabilities (MD) compared to typically developing (TD) children. (A) Children with MD showed hyper-connectivity between bilateral IPS and multiple dorsal frontal and parietal cortical regions, between bilateral IPS and right hemisphere SMG and STG, and between left IPS and right putamen. (B) Results were almost identical when examining a subset of 14 MD children who scored at or below 85 on the Numerical Operations subtest of the WIAT-II (MD\*). All results are thresholded at  $p < .01$  height, with family-wise error (FWE) corrections for multiple comparisons at the cluster level ( $p < .01$ , spatial extent 128 voxels). Greater connectivity for MD > TD in red (left IPS), blue (right IPS), and green (both left and right IPS). Coordinates are in MNI space. FP = frontal pole; IPS = intraparietal sulcus; SFG = superior frontal gyrus; SMG = supramarginal gyrus; SPL = superior parietal lobe; STG = superior temporal gyrus.

a regional measure that does not require a priori definition of seed ROIs. A two-sample  $t$ -test of group differences in fALFF indicated that children with MD show increased BOLD signal amplitude in multiple brain regions relative to their TD peers, particularly in the fronto-parietal network, including bilateral IPS, SPL/lateral occipital cortex, and MFG/SFG (Table 4;

Figure 5). Children with MD also showed elevated fALFF in right SMG and middle temporal gyrus, as well as in temporal occipital fusiform cortex, left inferior frontal gyrus/orbitofrontal cortex, and medial prefrontal cortex. Increased fALFF was also found in subcortical regions, including bilateral putamen, hippocampus, and amygdala.



**Figure 4** Negative correlation between IPS connectivity and math ability within the group of children with mathematical disabilities (MD). Results are thresholded at  $p < .01$  height, with family-wise error (FWE) corrections for multiple spatial comparisons at the cluster level ( $p < .01$ , spatial extent 128 voxels). Brain-behavior correlations are displayed in red (left IPS), blue (right IPS), and green (both left and right IPS). Coordinates are in MNI space. Graphs (created for illustrative purposes) depict the correlation between math ability (WIAT-II Numerical Operations) and functional connectivity measures, after scores were normalized across children within each cohort. RSFC = resting state functional connectivity; ACC = anterior cingulate gyrus; IPS = intraparietal sulcus; SMA = supplementary motor area; SMG = supramarginal gyrus; SPL = superior parietal lobe; STG = superior temporal gyrus.

To examine the relationship between intrinsic functional connectivity to the IPS and fALFF results, we performed ROI analyses based on the regions that showed increased functional connectivity with both left and right IPS. There were six clusters that showed overlap between left and right IPS connectivity of at least 30 voxels: right IPS/SPL, left SPL/lateral occipital

cortex, two clusters in left SFG, right STG and right SMG. Because the two SFG clusters were very close in space, only the largest cluster was examined. We found that, across the whole sample, there was a positive correlation between fALFF and functional connectivity in each of the five ROIs examined (all  $r_s \geq .371$ ;  $p_s \leq .024$ , controlling for cohort; Supplementary Table S1), indi-

**Table 4** Group differences in fALFF (MD > TD)

Local Maxima	Clustersize	Peak (T)	Coordinates		
			x	y	z
L MFG, SFG	569	5.51	-30	8	64
L precentral gyrus		3.97	-54	-8	52
L MFG		3.89	-32	26	52
R SMG	959	5.42	68	-24	38
R SMG (IPS)		4.15	50	-28	40
R SMG, angular gyrus		3.76	48	-40	56
R cerebellum	1547	5.26	18	-52	-30
R cerebellum		4.00	20	-70	-32
L cerebellum		3.65	-20	-70	-32
L central opercular cortex	831	5.03	-32	2	16
L putamen		4.35	-24	0	0
L hippocampus, parahippocampal gyrus		4.07	-18	-8	-32
L angular gyrus	716	4.56	-58	-56	44
L SMG, parietal operculum cortex		4.21	-60	-42	28
L SMG		4.19	-62	-46	44
R MTG, angular gyrus	345	4.41	58	-52	12
R MTG		4.27	62	-52	0
L lateral occipital cortex	401	4.31	-46	-78	34
L lateral occipital cortex		3.69	-40	-66	24
L lateral occipital cortex		3.36	-42	-70	16
L frontal operculum cortex, IFG pars triangularis, IFG pars opercularis	166	4.16	-48	18	-4
L frontal orbital cortex		3.36	-50	24	-12
L frontal operculum cortex, IFG pars triangularis, IFG pars opercularis		3.17	-44	18	6
L thalamus	262	3.79	-4	-22	-6
brain stem		3.60	0	-22	-14
R brain stem		2.97	4	-14	-16
L SPL, SMG, angular gyrus (IPS)	259	3.78	-40	-52	54
L lateral occipital cortex		3.32	-44	-62	56
L lateral occipital cortex		3.31	-22	-68	64
R MFG	146	3.77	28	14	48
R MFG		2.46	34	12	56
R temporal fusiform gyrus, temporal occipital fusiform cortex	233	3.73	40	-38	-20
R ITG		3.46	46	-28	-18
R ITG		3.45	54	-22	-24
L frontal orbital cortex	143	3.64	-30	18	-20
L temporal pole		3.30	-50	14	-18
L insular cortex		3.08	-28	14	-10
L frontal medial cortex	278	3.42	-10	50	-12
R frontal pole		3.41	18	50	-14
L frontal medial cortex		3.36	-10	42	-16
R putamen	161	3.37	30	4	-2
R amygdala, hippocampus		3.13	26	-8	-12

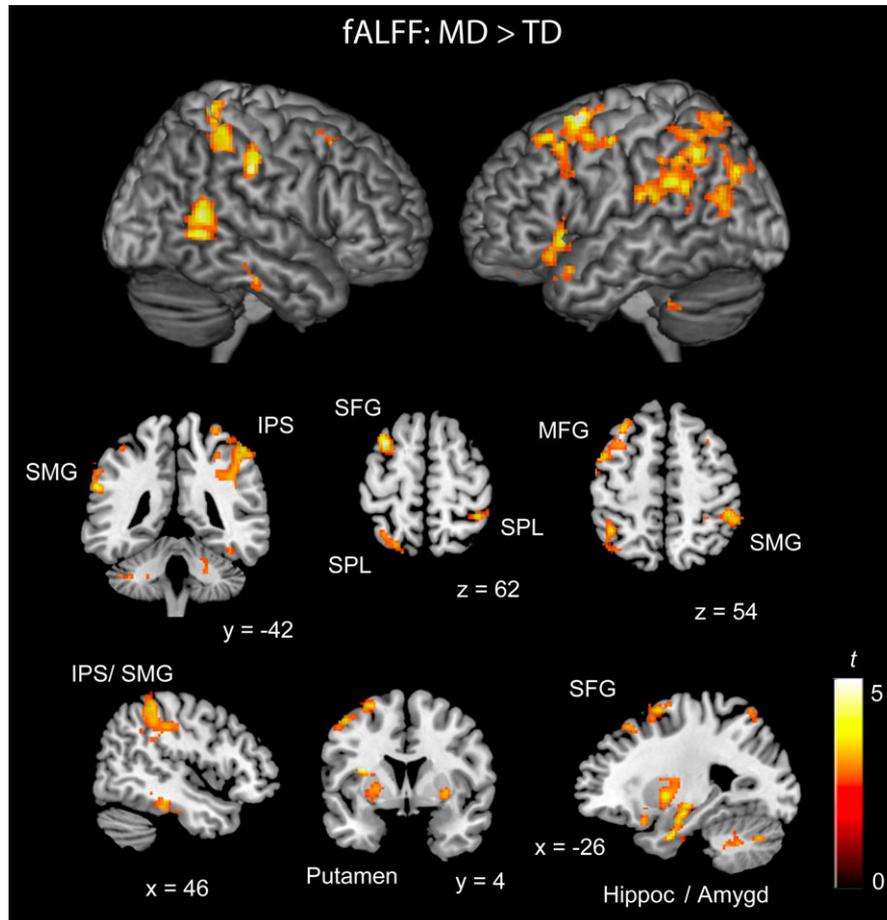
Note: Results are reported at  $p < .01$ , 128 voxels. MNI coordinates are labeled according to the Harvard-Oxford atlas. IPS is defined based on the Juelich atlas. For each cluster, 3 sub-peaks are reported which are more than 8mm apart. MD = children with mathematical disabilities, TD = typically developing children, IFG = inferior frontal gyrus, IPS = intraparietal sulcus, ITG = inferior temporal gyrus, MFG = middle frontal gyrus, MTG = middle temporal gyrus, SFG = superior frontal gyrus, SMG = supramarginal gyrus, SPL = superior parietal lobe.

cating an overlap and correspondence in brain areas that showed hyper-activity and hyper-connectivity. Next, to examine whether group differences in functional connectivity could be accounted for by differences in fALFF, we performed a set of ANCOVA analyses to examine functional connectivity differences, including regional fALFF and cohort as covariates. We found that for most ROIs, group differences in functional connectivity remained significant after covarying out fALFF (Supplementary Table S2). These results indicate that

IPS hyper-connectivity in children with MD cannot simply be explained by enhanced levels of low-frequency fluctuations.

#### *Additional analyses to demonstrate the robustness of our findings*

Although the motion parameters between the MD and TD groups were closely matched, we performed a number of additional analyses to examine the robust-



**Figure 5** Greater fALFF in children with mathematical disabilities (MD) compared to typically developing children (TD). Results are thresholded at  $p < .01$  height, with family-wise error (FWE) corrections for multiple spatial comparisons at the cluster level ( $p < .01$ , spatial extent 128 voxels). Coordinates are in MNI space. fALFF = Fractional Amplitude of Low Frequency Fluctuations; IPS = intraparietal sulcus; MFG = middle frontal gyrus; SFG = superior frontal gyrus; SMG = supramarginal gyrus; SPL = superior parietal lobe.

ness of our findings against potential head motion-related confounds. First, we excluded five participants (2 MD, 3 TD) who had head motion in excess of 3 mm and reran the functional connectivity and fALFF group analyses on data from the remaining 33 participants (17 MD, 16 TD). Second, we implemented a procedure recommended by Power and colleagues to compute framewise displacement (Power, Barnes, Snyder, Schlaggar & Petersen, 2012; Power, Mitra, Laumann, Snyder, Schlaggar *et al.*, 2014; Power, Schlaggar & Petersen, 2015). To control for head motion, we included framewise displacement as a covariate of no interest in the first-level functional connectivity analyses and reran the entire analysis. Results from these analyses (reported in Supplementary Figures S4 to S6 of the Supplementary Material)

were consistent with the results from the original analysis, suggesting that our findings are robust against motion-related confounds.

Next, to examine the robustness of our findings against potential cohort-related confounds, group means were plotted for the two study cohorts separately. For the functional connectivity data, we examined the five clusters that showed increased functional connectivity with both left and right IPS (as described in the previous section). For the fALFF data, we examined all 15 clusters that showed increased fALFF in MD > TD. Results from these analyses are reported in Figures S7 and S8 of the Supplementary Material. Briefly, for Cohort 1, mean connectivity of both left and right IPS seed ROIs was higher for MD > TD in all five clusters. Furthermore, the MD group showed higher fALFF in

all 15 clusters. For cohort 2, MDs showed higher right IPS connectivity in all five clusters and higher left IPS connectivity in four out of five clusters. Similar to cohort 1, MDs showed higher fALFF in all 15 clusters. Taken together, these results point to a consistent pattern of differences across the two cohorts.

## Discussion

While task-based fMRI studies of numerical cognition have provided important information about the neural correlates of MD, findings from these studies have been inconsistent with respect to the profile of IPS and fronto-parietal function in affected children (Ashkenazi *et al.*, 2012; Davis *et al.*, 2009; Kaufmann *et al.*, 2009b; Kaufmann *et al.*, 2011; Kucian, 2011; Kucian *et al.*, 2006; Molko *et al.*, 2003; Mussolin *et al.*, 2010; Price *et al.*, 2007). Moreover, little is known about intrinsic brain circuits that contribute to poor math skills in children with MD. Here, we investigated intrinsic functional connectivity and regional low-frequency signal fluctuations in a well-characterized group of 7–9-year-old children with MD. Importantly, the MD group did not have co-morbid reading difficulties or other developmental disabilities, which have been shown to have unique aberrations in intrinsic connectivity (e.g. Finn *et al.*, 2014; Koyama, Di Martino, Kelly, Jutagir, Sunshine *et al.*, 2013). Furthermore, children with MD were closely matched to a group of TD children on age, gender, IQ, reading ability, and working memory.

We demonstrate for the first time that, rather than being under-connected, functional circuits associated with the IPS are intrinsically hyper-connected in children with MD. Furthermore, novel machine learning algorithms revealed that aberrant IPS connectivity patterns could be used to discriminate children with MD from TD children with high levels of accuracy, suggesting that IPS connectivity is a distinguishing neurobiological feature of the disorder. Finally, we found evidence for spontaneous regional hyper-activity in the IPS as well as multiple other brain regions in children with MD. Our findings of aberrant IPS connectivity and widespread aberrations in low-frequency fluctuations advance the view that MD is best characterized as a network-level deficit, affecting the IPS and its functional circuits (Fias *et al.*, 2014). More generally, our findings are consistent with an interactive specialization model which suggests that neurodevelopmental disorders are likely to be characterized by dysfunction in multiple functional circuits, rather than isolated dysfunction of a particular brain area, as typically seen in adult patients with focal

brain injuries (Johnson, 2011; Menon, 2013; Rubinsten & Henik, 2009; Schlaggar & McCandliss, 2007).

### *Parietal hyper-connectivity in children with MD*

Compared to their TD peers, children with MD showed aberrant IPS connectivity with multiple regions, notably in frontal and parietal cortex. Specifically, children with MD showed greater functional connectivity between left and right IPS, as well as between IPS and other dorsal fronto-parietal regions, including bilateral SPL, SFG/MFG, and SMA. In addition, children with MD showed increased IPS connectivity with right temporo-parietal cortex, including the SMG and STG. Importantly, results were almost identical when more stringent criteria of MD were used, suggesting that the broad pattern of hyper-connectivity observed was not caused by the relatively lenient MD criteria used in this study. Additional analysis within the MD group revealed a negative correlation between IPS connectivity and individual math scores, particularly with the anterior cingulate cortex, SMA, left SPL, and right SMG and STG, further demonstrating the robustness of our findings of hyper-connectivity in childhood MD.

Many brain regions that showed aberrant connectivity in the MD group overlapped with prefrontal and parietal cortex regions typically engaged during numerical cognition (Arsalidou & Taylor, 2011; Kaufmann *et al.*, 2011). It is plausible that intrinsic hyper-connectivity in the fronto-parietal network in children with MD may underlie the increased activation and connectivity of these regions reported in several studies of numerical problem-solving (Iuculano *et al.*, 2015; Kaufmann, Vogel, Starke, Kremser & Schocke, 2009a; Kaufmann *et al.*, 2009b; Kaufmann *et al.*, 2011; Rosenberg-Lee *et al.*, 2015). Interestingly, not all studies have found greater fronto-parietal activation in children with MD, but discrepancies between studies may be explained by the type of baseline conditions used (Menon, 2015). Specifically, it has been suggested that MD is characterized by reduced *modulation* of brain responses with increasing task complexity, rather than reduced activation per se (Ashkenazi *et al.*, 2012). For example, children with MD show reduced activation in fronto-parietal regions for small versus large distances in number comparison tasks (Mussolin *et al.*, 2010; Price *et al.*, 2007; but see Kucian, 2011), and for complex versus simple problems in arithmetic tasks (Ashkenazi *et al.*, 2012). Moreover, multivariate representational similarity analyses have indicated that IPS response patterns are less differentiated between complex versus simple arithmetic problems in children with MD (Ashkenazi *et al.*, 2012), which is also indicative of reduced

task-complexity-related modulation of brain response. We suggest that in children with MD, IPS hyper-connectivity may limit their ability to flexibly and efficiently engage and modulate task-relevant fronto-parietal circuits.

Beyond their involvement in numerical cognition, prefrontal and posterior parietal regions identified as being hyper-connected in MD have also been associated with more general attention and cognitive control mechanisms (e.g. Corbetta & Shulman, 2002; Duncan, 2006; Niendam, Laird, Ray, Dean, Glahn *et al.*, 2012). Aberrant connectivity within these fronto-parietal areas in children with MD is consistent with deficits in spatial attention that have been reported in MD even in domains outside mathematical problem-solving (Ashkenazi & Henik, 2010; Szucs, Devine, Soltesz, Nobes & Gabriel, 2013). The dorsal frontal and parietal regions that typically show high functional connectivity with the IPS show close resemblance to the dorsal spatial network thought to be involved in top-down, goal-driven attention (Figure 1; Corbetta *et al.*, 2008; Corbetta & Shulman, 2002). It has been argued that this network can be distinguished from a ventral attention system anchored in the right hemisphere temporal parietal junction and inferior frontal gyrus, which plays a more prominent role in stimulus-driven reorienting (Figure 1; Corbetta *et al.*, 2008; Corbetta & Shulman, 2002; Fox *et al.*, 2006). Children with MD showed IPS hyper-connectivity not only with dorsal prefrontal and parietal cortex, but also with right temporo-parietal regions, including SMG, suggesting that their dorsal and ventral attention streams are less differentiated in affected children. Consistent with this hypothesis, a recent meta-analysis has found greater right SMG engagement in children with MD during numerical processing (Kaufmann *et al.*, 2011). Further studies with both intrinsic and task-based fMRI are needed to investigate how intrinsic hyper-connectivity in dorsal and ventral attentional systems may contribute to both mathematical difficulties and domain-general cognitive deficits.

#### *Hyper- as opposed to hypo-connectivity in children with MD*

Our findings of increased functional connectivity in MDs compared to TDs might seem contradictory with the notion that greater functional connectivity reflects greater neuronal efficiency (Van Den Heuvel & Hulshoff Pol, 2010). Studies in children with neurodevelopmental disorders, including autism (Supekar *et al.*, 2013b; Uddin *et al.*, 2013), anxiety disorders (Qin, Young, Duan, Chen, Supekar *et al.*, 2014b) and schizophrenia (Whitfield-Gabrieli, Thermenos, Milanovic, Tsuang, Faraone *et al.*, 2009) have, however, pointed to hyper-connectivity as a

prominent feature of aberrant functional circuits in children. We have suggested that hyper-connectivity may result in an inability to flexibly engage and disengage brain circuits in a context dependent manner (Uddin, Supekar, Lynch, Cheng, Odriozola *et al.*, 2015), thereby contributing to impaired cognition. Our finding of hyper-connectivity is also noteworthy in the context of fronto-parietal and parieto-temporal white matter deficits that have been reported in children with MD (Kucian, Ashkenazi, Hänggi, Rotzer, Jäncke *et al.*, 2014; Rykhlevskaia, Uddin, Kondos & Menon, 2009). The relation between structural connectivity and intrinsic brain dynamics is not, however, as straightforward as one might expect (Damoiseaux & Greicius, 2009; Horwitz, Hwang & Alstott, 2013). In a review of the literature on large-scale neural modeling of functional-structural relationships, Horwitz *et al.* concluded that weakening of a structural connection could lead to both decreases and increases of functional connectivity between brain regions that are not directly affected (Horwitz *et al.*, 2013). Furthermore, increased functional connectivity can also result from changes in alternative multi-synaptic pathways that link areas with structural deficits. Further research is needed to examine how white matter tract deficits influence functional connectivity in MD and how hyper-connectivity of intrinsic functional circuits disrupts math problem solving.

#### *IPS connectivity patterns discriminate MD and TD children*

Multivariate classification analyses demonstrated that brain connectivity can be used to discriminate TD children and children with MD. Using left IPS connectivity maps as features in an SVM classifier, MD status could be determined with greater than 80% accuracy. These results illustrate the robustness of IPS-related connectivity differences between the MD and TD groups, and suggest that functional connectivity could be used as a brain-based biomarker to predict learning disabilities such as MD in children. Critically, our findings provide the strongest evidence to date that IPS connectivity may be a distinguishing neurobiological feature of the disorder.

#### *Aberrant local signal fluctuations in children with MD*

Next, to investigate aberrant brain organization in local neural circuits, as measured at the individual voxel level, and its potential links to atypical IPS functional connectivity in children with MD, we performed fALFF analyses on the same task-free fMRI data (Mennes *et al.*, 2011; Zang *et al.*, 2007; Zou *et al.*, 2008; Zuo

*et al.*, 2010). fALFF is a voxel-wise measure of spontaneous BOLD signal fluctuations and can be used to examine intrinsic brain dynamics without a priori selection of ROIs. We found that compared to TD children, children with MD showed greater fALFF levels in multiple brain regions, most prominently in the IPS, SPL, MFG/SFG, and SMG, providing additional evidence for fronto-parietal circuit dysfunction extending beyond the IPS. fALFF differences partly overlapped with fronto-parietal areas that showed hyper-connectivity with the IPS. Convergent on these findings, we found a significant correlation between fALFF and functional connectivity in fronto-parietal cortex. Nevertheless, despite the relation between fALFF and functional connectivity, group differences in functional connectivity could not completely be accounted for by group differences in fALFF. Moreover, fALFF also identified additional abnormalities in subcortical regions, notably bilateral putamen and left anterior hippocampus. It is noteworthy, in this context, that memory-based fact retrieval, which relies in part on the hippocampus (Qin *et al.*, 2014a), is known to be weaker in children with MD (Geary, Hoard, Byrd-Craven, Nugent & Numtee, 2007). The extent to which aberrations in procedural and associative memory systems contribute to impaired fact retrieval in children with MD remains to be investigated. We suggest that extensive enhancements of spontaneous low-frequency fluctuations in children with MD reflects aberrations in multiple brain regions that extend beyond the IPS, which may limit their ability to flexibly and efficiently engage task-relevant brain areas and distributed circuits (see Supekar *et al.*, 2013b).

#### *Limitations and future directions*

One important challenge for future studies is addressing heterogeneity in the clinical profile of MD (Kaufmann *et al.*, 2013; Rubinsten & Henik, 2009). This heterogeneity may reduce the likelihood of finding robust neural deficits within a study sample of children with MD, and give rise to inconsistent findings between studies with different sample characteristics. In this study, we focused on a well-characterized group of children with MD without co-morbid reading difficulties or developmental disabilities, matched to TD children on IQ, reading, and working memory. By using strict selection and matching criteria, we hoped to identify an intrinsic connectivity and brain organization profile that could be specifically attributed to math difficulties. An important avenue of future research is to investigate whether the same neurobiological deficits are found in children across heterogeneous clinical profiles, e.g. in children with co-morbid reading disabilities (Menon, 2015). Moreover,

with regard to the practical applications of using functional connectivity as a brain-based biomarker, further studies are needed to examine whether classification is possible in a broader sample, including children of different ages and co-morbid learning disabilities.

It is also important to take into account the specific cut-off criteria that are used to define MD, as it has been argued that children who meet the most stringent criteria of MD (i.e. math scores below the 10th percentile) have a different etiology compared to children with less severe difficulties (Mazzocco, Feigenson & Halberda, 2011; Murphy, Mazzocco, Hanich & Early, 2007). Here, only a minority of children ( $n = 7$ ) scored at or below the 10th percentile, which precluded us from studying this subgroup separately. However, our brain-behavior analyses provide preliminary evidence that parietal hyper-connectivity is most evident in children with more severe math difficulties. Further studies are necessary to replicate our findings in larger samples, to examine similarities and differences in the functional network architecture of children with different learning profiles, and to investigate the influence of aberrant intrinsic functional circuits on cognitive information processing in affected children.

#### *Conclusions*

Our study reveals aberrant intrinsic functional brain organization in a well-characterized group of 7–9-year-old children with MD. Our findings provide novel insights into the neurobiology of the disorder, and open up new opportunities for using brain connectivity-based biomarkers of specific learning disabilities. Crucially, our findings demonstrate that, even in a relatively pure sample of children with math difficulties, aberrant brain organization is not confined to focal IPS regions. Rather, our findings indicate that the neurobiology of childhood MD is characterized both by aberrant regional signals and inter-regional functional connectivity. We hypothesize that high levels of spontaneous activity and IPS hyper-connectivity may make it difficult for children with MD to modulate brain circuits in a context-dependent manner, thereby limiting flexible resource allocation in response to changing task demands (see Supekar *et al.*, 2013b; Uddin *et al.*, 2015).

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1:** IPS connectivity in children from both groups combined.

**Figure S2:** Brain areas that showed reduced IPS connectivity in children with mathematical disabilities (MD) compared to typically developing (TD) children.

**Figure S3:** Cross-validation accuracy (cva) of classification based on left IPS connectivity (red) and right IPS connectivity (blue).

**Figure S4:** Brain areas that showed greater IPS connectivity in children with mathematical disabilities (MD) compared to typically developing (TD) children, after excluding five participants with head motion > 3 mm.

**Figure S5:** Greater fALFF in children with mathematical disabilities (MD) compared to typically developing (TD)

children, after excluding five participants with head motion > 3 mm.

**Figure S6:** Brain areas that showed greater IPS connectivity in children with mathematical disabilities (MD) compared to typically developing (TD) children, when including framewise displacement as a covariate in the first level analyses.

**Figure S7:** Brain areas that showed greater IPS connectivity in children with mathematical disabilities (MD) compared to typically developing (TD) children, plotted separately for each cohort.

**Figure S8:** Brain areas that showed greater fALFF in children with mathematical disabilities (MD) compared to typically developing (TD) children, plotted separately for each cohort.

**Table S1:** Partial correlations between fALFF and IPS functional connectivity

**Table S2:** Group differences in IPS functional connectivity, after correcting for fALFF