Check for updates

Received: 6 April 2024 | Revised: 23 August 2024 | Accepted: 27 August 2024

DOI: 10.1111/jon.13236

JOURNAL OF NEUROIMAGING
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF NEUROIMAGING
WILEY

CLINICAL INVESTIGATIVE STUDY

Alterations in functional brain connectivity associated with developmental dyscalculia

Roger Mateu-Estivill[1,2] | Ana Adan[1,2] | Sergi Grau[3] | Xavier Rifà-Ros[4] | Xavier Caldú[1,2] | Núria Bargalló[5] | Josep M. Serra-Grabulosa[1,2]

[1]Department of Clinical Psychology and Psychobiology, University of Barcelona, Barcelona, Spain

[2]Institute of Neurosciences, University of Barcelona, Barcelona, Spain

[3]Digital Care Research Group, University of Vic - Central University of Catalonia, Vic, Spain

[4]Cognition and Brain Plasticity Unit, Bellvitge Biomedical Research Institute, L'Hospitalet de Llobregat, L'Hospitalet de Llobregat, Spain

[5]Centre Diagnòstic per la Imatge, Hospital Clínic de Barcelona (CDIC), Barcelona, Spain

Correspondence
Josep M. Serra-Grabulosa, Department of Clinical Psychology and Psychobiology, University of Barcelona, Pg. Vall d'Hebron 171, 08035 Barcelona, Catalonia, Spain.
Email: jmserra@ub.edu

Funding information
Fundació La Caixa (Recercaixa program)

Abstract

Background and Purpose: In recent years, there has been a growing interest in the study of resting neural networks in different neurological and mental disorders. While previous studies suggest that the default mode network (DMN) may be altered in dyscalculia, the study of resting-state networks in the development of numerical skills, especially in children with developmental dyscalculia (DD), is scarce and relatively recent. Based on this, this study examines differences in resting-state functional connectivity (rs-FC) data of children with DD using functional connectivity multivariate pattern analysis (fc-MVPA), a data-driven methodology that summarizes properties of the entire connectome.

Methods: We performed fc-MVPA on resting-state images of a sample composed of a group of children with DD ($n = 19$, 8.06 ± 0.87 years) and an age- and sex-matched control group of typically developing children ($n = 23$, 7.76 ± 0.46 years).

Results: Analysis of fc-MVPA showed significant differences between group connectivity profiles in two clusters allocated in both the right and left medial temporal gyrus. Post hoc effect size results revealed a decreased rs-FC between each temporal pole and the DMN in children with DD and an increased rs-FC between each temporal pole and the sensorimotor network.

Conclusions: Our results suggest an aberrant information flow between resting-state networks in children with DD, demonstrating the importance of these networks for arithmetic development.

KEYWORDS
developmental dyscalculia, DMN, early childhood, fc-MVPA, mathematical difficulties, rs-FMRI, SMN

INTRODUCTION

Since the 1980s and with the emergence of new neuroimaging techniques, different studies have revealed the neural bases of number processing. Several studies showed that the intraparietal sulcus (IPS) and its adjacent areas are the neural substrate of number sense[1] and that the alteration of the IPS is a characteristic of developmental dyscalculia (DD), a learning disability affecting the acquisition of mathematical skills in children with normal intelligence and age-appropriate education.[2] In this sense, alteration of the IPS function has been observed in the pediatric population with DD.[3–8] In longitudinal studies,[9] it has been suggested that the development of number processing areas is slower in children with DD, and functional (f) MRI detected an alteration of regions in the parietal lobe and other areas of the brain and their connections,[3,4,9–12] thus reinforcing the heterogeneous view of DD.[13–15]

Resting-state functional connectivity (rs-FC) has proven to be a tool that facilitates a better understanding of functional networks in certain neurological disorders, without the constraint of task limitation.[16–18] However, the use of rs-FC to study functional connectivity (FC) of numerical skills, especially in childhood and more specifically in cases of DD, is scarce and relatively recent. Thus, little is known about brain networks at rest in atypical numerical development. In one of the first studies, results showed that the differences in the morphometry and connectivity between the hippocampus and the frontal and temporal areas were a very robust predictor of the acquisition of mathematical skills in children.[19] Later, a longitudinal study demonstrated that the patterns of rs-FC were predictors of the increase in numerical skills throughout the 6-year duration of the study.[20] More recently, IPS connections have been found to predict adult mathematical ability.[21] Together, these results make the analysis of FC even more important for establishing markers in DD. In this sense, a recent study considered the possibility of using the rs-FC of the IPS as a physiological marker in the diagnosis of DD, observing an aberrant hyperconnectivity in the IPS, which was partially corrected after training.[22,23] A more recent study suggested that a robust interhemispheric FC of the IPS is important for mathematical development.[24] Moreover, Jolles et al[22,23] suggested that the default mode network (DMN) may be altered in dyscalculia. Although the role of the DMN in DD is understudied in the literature, the specific involvement of the default network in numeracy in adults has been described in addition to the aforementioned study. In particular, a negative association has been found between the connections of the right middle frontal gyrus and the DMN with numerical ability.[25]

In these previous studies, the study of rs-FC in dyscalculia was carried out placing regions of interest (ROIs) in areas previously identified as critical in mathematical processing. However, in ROI approaches, a limited set of areas is selected for the study. To avoid this limitation, functional connectivity multivariate pattern analysis (fc-MVPA)[26] can be used. This method provides a data-driven analysis to detect putative abnormal intrinsic FC patterns at a full brain scale, with no bias as to the selection of any specific area.[1] Many authors suggest that the use of multivariate techniques would provide a greater and more precise understanding of the interaction and modulation between brain networks. A recent study, which found no differences in brain activation related to numerical tasks in children with DD, suggested the need to investigate the neural basis of DD using multivariate and network-based brain imaging approaches.[27] In this sense, an MVPA study showed a pattern of hyperconnectivity in visual brain regions in adults with dyscalculia. It concluded that dyscalculia is related to impaired number representations, as well as to altered connectivity in the brain, impairing access to such representations.[28]

The aim of this study is to explore cerebral network alterations associated with DD in early childhood. An fc-MVPA approach was used to facilitate a better understanding of brain connectivity dynamics. Recently, this procedure has been used to study FC alterations associated with literacy difficulties in early readers.[29] Based on the results of previous studies, we hypothesize that children with DD will have impaired rs-FC in the DMN. Specifically, and in accordance with the results of studies on children with DD, we expect to find a pattern of hyperconnectivity between IPS and DMN.

METHODS

Participants

Participants were right-handed, Catalan-speaking children in the first to third grades of primary school. Sample included a group of children with typical development but with DD (n = 19, DD group) (8.06 ± 0.87 years) (14 female and 5 male) and an age- and sex-matched control group of typically developing (TD) children (n = 23, TD group) (7.76 ± 0.46 years) (17 female and 6 male). Children in the DD group met the DSM-5 dyscalculia criteria. They had a school report of mathematical difficulties being substantially below the expected level; these mathematical difficulties persisted for at least 6 months, despite the provision of targeted interventions; there were no motor or sensorial deficits that might explain mathematical difficulties.[30] They scored below the 25th percentile[8] on the di-CALC[31] test (renamed as NeurekaCALC, available at: http://hdl.handle.net/2445/104756), with the median level at the 17th percentile. Exclusion criteria included having an intelligence quotient (IQ) below 85, a history of chronic disorders or mental illness, or not being fluent in Catalan. Participants completed an MRI session at the Hospital Clínic de Barcelona. Informed written and verbal consent was obtained from a parent, and affirmed assent was obtained from the children. The University of Barcelona (Spain) research ethics committee Institutional Review Board (IRB00003099) approved the study.

Neuropsychological assessment

All study participants were assessed individually by a trained neuropsychologist (JMSG), including the following.

IQ estimation

The WISC-IV[32] vocabulary subtest was used to estimate the verbal IQ, and the block design subtest was used to estimate the performance IQ.

Numerical abilities

Performance measures of mental calculation (correct responses), number line (distance), knowledge of base 10 system (correct responses in conceptual knowledge: correct responses in knowledge of units, tens, hundreds, and thousands; and correct responses in word problems), reading numbers (correct responses), and word problems (correct responses) were assessed using the di-CALC.[31]

Working memory

This measure was assessed using Digit span.[32] The task was to repeat digits (spanning from two to eight digits) backward in the correct order. Each correctly repeated span was scored.

Reading

Reading speed and accuracy measures were obtained from the pseudoword subtest of the PROLEC-R.[33]

Behavior

The Conners' Teacher and Parent Rating Scales[34] were used to assess behavior and signs of attention-deficit hyperactivity disorder (ADHD).

Image acquisition

All participants were examined by means of a 3 Tesla MRI scanner (Magnetom Trio Tim; Siemens Medical Systems), including the following sequences: a high-resolution 3-dimensional structural dataset (T1-weighted magnetization-prepared rapid gradient-echo, sagittal plane acquisition: repetition time [TR] = 2300 ms, echo time [TE] = 3 ms, 240 slices, slice thickness = 1 mm, field of view [FOV] = 244 mm, matrix size = 256 × 256) and a resting state fMRI sequence (T2*-weighted gradient-echo echo-planar imaging sequence: TR = 2500, TE = 29 ms, 40 slices per volume, slice thickness = 3 mm, FOV = 240 mm, matrix size = 80 × 80) that lasted 10 minutes 7 seconds (240 volumes).

Preprocessing

Image preprocessing was performed using the SPM12 software (SPM12, Welcome Trust Center for Neuroimaging, University College London, UK, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and the Conn-fMRI toolbox 15th (Boston, MA, https://web.conn-toolbox.org/home) for SPM.[35] Structural and functional images were normalized to the Montreal Neurological Institute (MNI) template, which was found to be appropriate for children aged 5 and above,[36] and spatially re-sliced into 2-mm isotropic voxels. Normalization, segmentation, and smoothing into 8-mm full width at half maximum Gaussian kernel were performed with the default parameters of the Conn toolbox. Scrubbing, a technique that excludes time points with excessive motion, was performed using ArtRepair toolbox (ArtRepair Toolbox v5b, Stanford University, Stanford, CA, USA, https://github.com/PAmcconnell/ArtRepair), with the following criteria: frame-wise displacement >0.5 mm or signal intensity changes >3 standard deviation.[37] These outlier volumes were also used as first-level nuisance covariates. Additionally, participants with more than 15.83% (38/240) of the volumes scrubbed were excluded. There were no differences between groups on scrubbed volumes ($p > .052$; average scrubbed volumes: TD = 3.65 ± 6.86, DD = 7.12 ± 12.63) or signal intensity change ($p > .29$; average signal intensity change: TD = 0.87 ± 0.12, DD = 0.87 ± 0.09).

rs-FC analysis

Resting-state data analysis was carried out using the Conn-fMRI toolbox 15th. Subject-specific regressors pertaining to white matter and cerebrospinal fluid signals were included as nuisance covariates, as well as six motion parameters.

To study rs-FC, we employed fc-MVPA.[26] This method follows a general searchlight procedure, which considers separately for each voxel the entire multivariate pattern of functional connections between this voxel and the rest of the brain to identify abstract multivariate representations. In detail, the first-level fc-MVPA analysis estimates the top 10 eigenpatterns and eigenvectors, characterizing the major axes of heterogeneity in FC between subjects and their whole-brain functional connectome status. Both were calculated separately for each individual seed voxel from a singular value decomposition (SVD) (group-level SVD) of the matrix of FC values between each seed voxel and the rest of the brain. SVD is the specific method by which the principal component analysis (PCA) was computed to reduce the dimensionality of our data, as it directly provides the principal components and their associated variances. Individual FC values were calculated from the bivariate correlation coefficient matrices between the blood-oxygen-level-dependent (BOLD) time series of each voxel pair, estimated by a *z*-score-normalized SVD of the BOLD signal (subject-level SVD) with 64 components separately for each subject. Next, group-level analyses were performed using a general linear model. For each individual voxel, an independent generalized linear model was estimated. Voxel-level hypotheses were evaluated using multivariate parametric statistics with between-subject random effects and estimation of sample covariance across multiple measurements. Inferences were performed at the level of individual clusters (groups of contiguous voxels). Cluster-level inferences were based on parametric statistics of Gaussian random field theory. Finally, as described, the resulting clusters were thresholded using a combination of a cluster formation threshold $p < .001$ at the voxel level and a cluster size threshold *p*-false discovery rate (FDR) <.05.

The resulting abstract multivariate representations (peak-level $p < .001$, cluster $p < .05$, family-wise error $k > 100$) were retained. Since it is an omnibus test, it needs post hoc analyses to determine specific connectivity patterns. For post hoc characterization, we used seed-to-voxel bivariate correlation to explore which aspects of FC differ across groups.

TABLE 1 Neuropsychological performance measures of typically developing and developmental dyscalculia groups.

	TD group	DD group	Student *t*-test	*p*
IQ estimation				
Verbal IQ	11.30 ± 2.12	11.26 ± 3.96	0.04[a]	.968
Performance IQ	10.13 ± 1.29	9.47 ± 1.39	1.59	.121
Math performance				
Mental calculation	56.61 ± 16.04	17.29 ± 21.85	6.71	<.001
Number line	54.34 ± 16.33	16.39 ± 11.39	8.54	<.001
Base ten system				
Conceptual knowledge	96.13 ± 3.48	33.65 ± 36.02	7.53[a]	<.001
Word problems	52.70 ± 14.05	17.69 ± 13.37	8.21	<.001
Reading numbers	93.04 ± 5.62	11.54 ± 18.21	20.36	<.001
Word problems	56.04 ± 15.85	11.78 ± 5.92	12.38[a]	<.001
Reading performance				
Speed reading	51.48 ± 5.75	52.53 ± 11.06	−0.37	.712
Reading accuracy	49.26 ± 6.81	52.68 ± 10.69	−1.20	.237
Working memory				
Correct responses	12.00 ± 2.97	10.74 ± 1.88	1.67[a]	.102

Note: All the data represent mean ± standard deviation unless otherwise indicated. Intelligence quotient (IQ) estimation and working memory scores are represented by scaled cores. All other variables are represented by percentile scores.
Abbreviations: DD, developmental dyscalculia; TD, typically developing.
[a]After correction (Levene's test $p < .05$).

Pearson's correlation coefficients between time courses of fc-MVPA-derived clusters and all other voxels were then converted to normally distributed *z*-scores using the Fisher transformation (voxel-wise height $p < .001$, FDR $p < .05$).[38]

In addition to the multivariate analysis, an additional analysis was carried out to test rs-FC patterns of the IPS in both hemispheres. For this purpose, an anatomical ROI was selected in the IPS of both hemispheres. To define the ROI, we combined the three IPS subdivisions from the Juelich histological atlas, 25% threshold,[39,40] following the same methodology described previously.[41]

RESULTS

Neuropsychological data

All participants had an estimated IQ in the normal range, and there were no differences between groups. The DD children had a significantly lower mathematical performance than the TD group (it scored above percentile 50 in all measures). Specifically, DD children scored below percentile 25 in mental calculation, number line performance, base 10 system (word problems), reading numbers, and word problems. However, the DD group scored above percentile 25 in the base 10 system (conceptual knowledge). Analysis of reading measures showed a performance in the normal range in the DD and the TD groups (Table 1). No signs of ADHD were detected neither in the TD nor in the DD group.

fc-MVPA results

In terms of connectivity profiles, a second-level analysis showed significant differences between both groups. Specifically, these significant differences were observed in component 1 (C1) ($p < .05$ FDR corrected, two-sided). Subsequent components were discarded due to their low level of explanation for the variance of global connectivity.

C1 included two clusters of interest. The first one (C1_1) was located on the right medial temporal gyrus ($p = .0021$ FDR, $k = 856$), while the second (C1_2) was on the left medial temporal gyrus ($p = .0202$ FDR, $k = 529$) (Figure 1).

Post hoc seed-to-voxel analysis of fc-MVPA-derived clusters of interest

Statistical comparisons between the DD and TD groups showed significant differences (Table 2). In this sense, the analysis of the cluster C1_1, located in the right middle temporal gyrus (MTG), showed that the DD group had a lower FC between this region and the areas of the DMN (precuneus/posterior cingulate cortex [pCC], medial frontal cortex [MedFC], anterior MTG, and angular gyrus [AG] of both hemispheres), in addition to subcallosal cortex/anterior cingulate cortex. Moreover, DD showed an increased FC between the right MTG and areas belonging to the sensorimotor network (SMN), such as the left precentral gyrus (preCG), postcentral gyrus (postCG), and the supplementary motor area (SMA).

FIGURE 1 Main resting-state functional connectivity multivariate pattern analysis results showing areas with significant developmental dyscalculia-related differences in functional connectivity.

TABLE 2 Significant effect size differences between groups in resting-state functional connectivity.

	x	*y*	*z*	Area	*K*	Cluster *p*-FDR
C1_1	52	4	−44	MTG	856	.002
TD > DD	12	−50	36	Prec/pCC	1814	<.001
	−10	−2	−10	SubCalC/Acc	486	<.001
	2	58	−6	FP/MedFC	451	<.001
	42	22	−36	aMTG	434	<.001
	−42	−50	30	AG/sLOC	433	<.001
	58	−64	32	AG/sLOC	281	.002
	−70	−16	−10	pMTG/aMTG	224	.006
DD > TD	−64	−2	8	postCG/preCG/CO	983	<.001
	6	8	58	SFG/SMA	328	.005
	−28	36	4	FO	198	.033
C1_2	−58	−32	−24	MTG	529	.020
TD > DD	−6	−50	22	Prec/pCC	2901	<.001
	−14	64	20	FP/MedFC	2028	<.001
	−48	−60	32	sLOC/AG	1847	<.001
	40	18	−30	pMTG/aMTG	1756	<.001
	−22	30	50	SFG/MFG	963	<.001
	46	−52	30	AG/sLOC	507	<.001
	−62	−28	−18	pMTG	443	<.001
	26	30	56	SFG	380	<.001
	16	−84	−24	Cereb1/Cereb2	277	.002
	−34	−24	−10	Hippocampus	222	.006
DD > TD	52	−10	26	postCG/preCG/IC	1005	<.001
	−62	−10	26	postCG/preCG/CO	607	<.001
	56	14	20	IFGop/PreCG	357	<.001
	16	40	−28	FP/Forb	304	<.001
	−28	−20	72	preCG/postCG	219	.001

Abbreviations: Acc, accumbens nucleus; AG, angular gyrus; aMTG, anterior pars of middle temporal gyrus; C1_1, component 1, cluster 1, on right medial temporal gyrus; C1_2, Component 1, cluster 2, on left medial temporal gyrus; Cereb, cerebellum; CO, central operculum; DD, developmental dyscalculia; FDR, false discovery rate; FO, frontal operculum; Forb, frontal orbital; FP, frontal pole; IC, insular cortex; IFGop, inferior frontal gyrus, pars opercularis; *K*, number of voxels; MedFC, medial frontal cortex; MedFC, medial frontal cortex; MFG, medial frontal gyrus; MTG, middle temporal gyrus; pCC, posterior cingulate cortex; pMTG, posterior pars of middle temporal gyrus; PostCG, postcentral gyrus; Prec, precuneus; preCG, precentral gyrus; SFG, superior frontal gyrus; sLOC, superior lateral occipital cortex; SMA, superior motor area; SubCalC, subcallosal cortex; TD, typically developing.

JOURNAL OF NEUROIMAGING THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF NEUROIMAGING WILEY

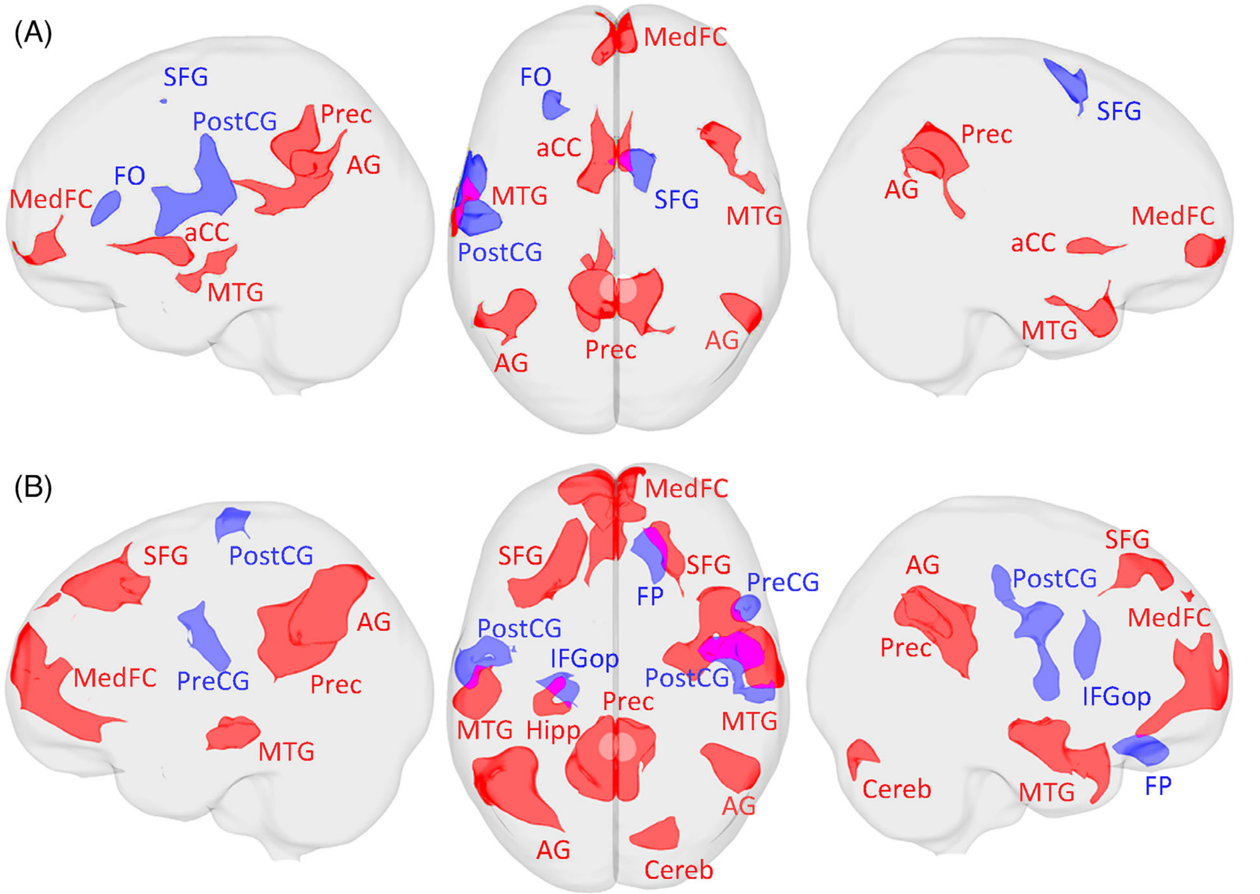

FIGURE 2 Effect sizes within main resting-state functional connectivity multivariate pattern analysis areas, which indicate the pattern of differences in connectivity with each area between groups. Top row: significant different functional connectivity with the middle temporal gyrus (MTG) of the right hemisphere. Bottom row: significant different functional connectivity with the MTG of the left hemisphere. Red color indicates higher connectivity in typically developing (TD) compared to developmental dyscalculia (DD) subjects. Blue color indicates higher connectivity in DD compared to TD subjects (p-false discovery rate <.05). Pink color is due to the superimposition of connectivity patterns of different axial levels. aCC, accumbens nucleus; AG, angular gyrus; Cereb, cerebellum; FO, frontal operculum; FP, frontal pole; Hipp, hippocampus; IFGop, inferior frontal gyrus, pars opercularis; MedFC, medial frontal cortex; PostCG, postcentral gyrus; Prec, precuneus; PreCG, precentral gyrus; SFG, superior frontal gyrus.

The analysis of the FC of the cluster C1_2 (left MTG) showed that the DD group had also a lower FC than the control group between the left MTG and areas of the DMN. In addition, the left MTG had a lower FC with the middle frontal gyrus and superior frontal gyri of both hemispheres, the hippocampus, and areas of the cerebellum (1 and 2). Moreover, and in line with the results of the C1_1 cluster, a higher FC in the DD group than the TD group was found in the areas making up the SMN, including the preCG and postCG of both hemispheres. Furthermore, the results also include a right orbital frontal pole area (Figures 2 and 3).

No significant correlations were found between the neuropsychological tests and the rs-FC patterns in any of the groups.

ROI analysis

ROI analysis indicates that the right IPS has shown greater rs-FC in TD children than in DD children between the right IPS and the left Insular cortex (−42, 6, −10) (p = .006 FDR; k = 444) (Figure 4).

DISCUSSION

The main objective of our study was to evaluate functional brain connectivity alterations in children with DD. Our results show differences in FC in resting-state brain networks, such as the DMN and the SMN. Likewise, there is an alteration of the FC between the right IPS and the precuneus.

Regarding the differences in the connectivity of the DMN, the DD group showed a lower rs-FC between the right MTG and the precuneus/pCC, MedFC, anterior MTG, AG, and the anterior cingulate area. The DD group also showed a similar pattern of lower rs-FC from the left MTG to areas of the DMN and between the left MTG and the medial frontal gyrus, the hippocampus, and the cerebellum. Moreover, DD showed an increased FC between the right and left MTG and areas belonging to the SMN (SMA and left preCG and postCG).

Alterations of the DMN in children with DD have already been described,[8] revealing a pattern of hyperconnectivity between the IPS and multiple brain systems, including the DMN. This was interpreted

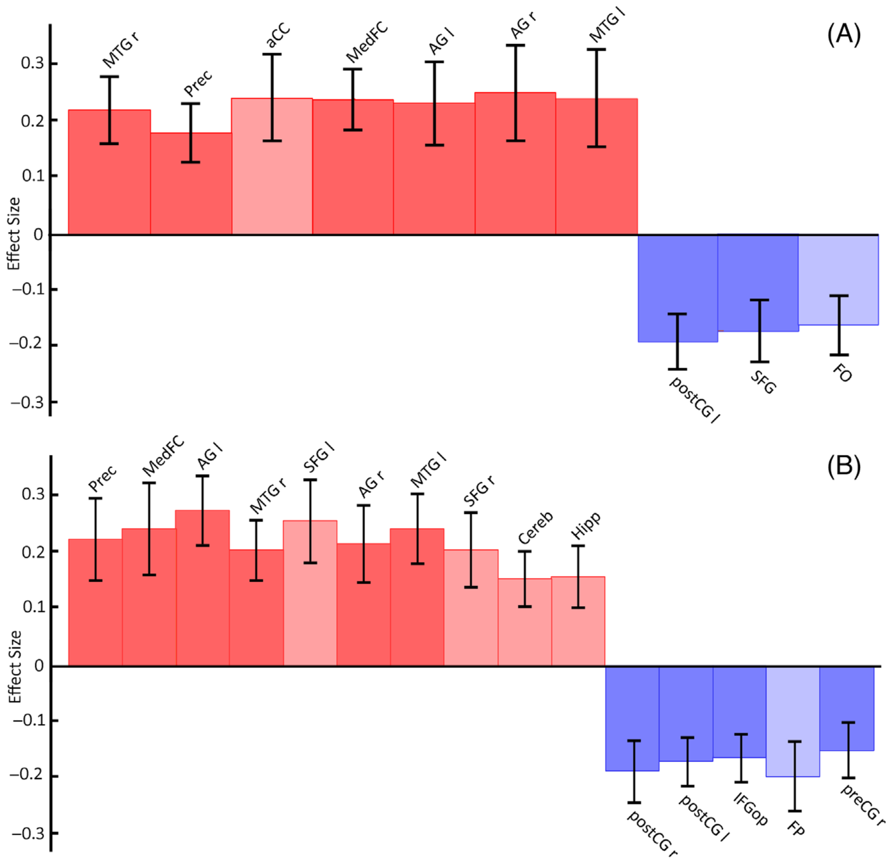

FIGURE 3 Effect sizes from the second-level seed-to-voxel resting-state functional connectivity (rs-FC) analysis for MVPA-selected clusters. (A) Right middle temporal gyrus seed. (B) Left middle temporal gyrus seed. Red color refers to TD > DD rs-FC contrast; blue color refers to DD > TD rs-FC contrast. Dark red color: Areas belonging to default mode network. Dark blue color: Areas belonging to sensorimotor network. aCC, accumbens nucleus; AG, angular gyrus; Cereb, cerebellum; FO, frontal operculum; FP, frontal pole; Hipp, hippocampus; IFGop, inferior frontal gyrus; l, left; MedFC, medial frontal cortex; MTG, middle temporal gyrus; Prec, precuneus; postCG, postcentral gyrus; preCG, precentral gyrus; r, right; SFG, superior frontal gyrus.

as an inability to successfully disengage the DMN from task-positive IPS regions. Since the MTG is related to number processing and calculation,[6,42,43] our results of lower rs-FC between the MTG and the areas of the DMN suggest that children with DD have an alteration of the DMN activation/deactivation that could interfere in their performance.

Likewise, our results show an rs-FC alteration of the precuneus with the MTG and the right IPS. Precuneus is a key area of the DMN implicated in numerical processing and calculation. In a recent study, dyscalculic children showed task-related hyperconnectivity between IPS and precuneus.[8] Interestingly, this hyperconnectivity was reduced after training.[15] In line with these results, our study showed a higher FC between the IPS and the precuneus, thus confirming that an aberrant FC of this area could be a marker for dyscalculia.

On the other hand, our study also observed lesser connectivity in the DD group between the MTG and the AG, a region that supports the numerical processing mediated by verbal components, such as the retrieval of overlearned numerical facts.[44] In line with it, previous studies have found functional alterations of AG in dyscalculic children, probably reflecting a dysfunctional DMN.[45]

Our study also showed FC alterations between the left MTG and the right cerebellum. The role of the cerebellum in number processing seems demonstrated by previous research in TD[46] and DD children.[47] Similar results were previously reported in children with reading difficulties, where the cerebellum showed an altered communication with the cortex in children with dyslexia.[48] This approach can be critical due to the similarities and comorbidity between both neurodevelopmental disorders.[2,49]

The last area with altered rs-FC with the left MTG was the left hippocampus. Connectivity between hippocampal areas and frontal and temporal areas is associated with learning and memory and is a very robust predictor of the acquisition of mathematical skills in children. Studies on rs-FC indicate that the pattern of connectivity with other regions involved in this learning would vary throughout neurodevelopment. In this sense, the relationship between hippocampal resting-state connectivity and math ability might shift from being positive during childhood (in agreement with our results) to negative in later stages of development. Specifically, left IPS has lower rs-FC with the hippocampus in DD than in TD children.[22] Moreover, it has been found that rs-FC of the hippocampus with the right MTG before

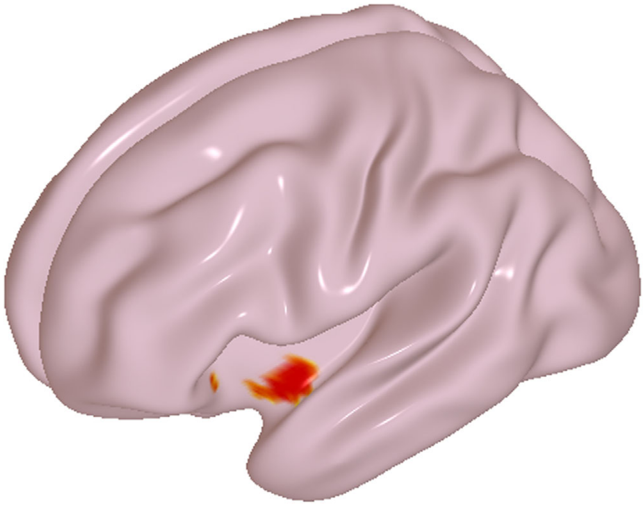

FIGURE 4 Results of the region-of-interest-to-voxel analysis between groups of both intraparietal sulcus (IPS) and the rest of the brain. Right IPS showed a larger resting-state functional connectivity with the left insular cortex in typically developing than the developmental dyscalculia group.

training tutoring shows a significant positive relation with changes in performance efficiency after training tutoring.[19,23] And in adolescence, the hippocampus shows hyperconnectivity with the preCG and insula, which is related to low mathematical ability.[41]

In terms of the SMN, we found that the DD group had an increased FC between the MTG and areas of the SMN. The SMN is made up of the preCG, postCG, and SMA. Its main function is the detection and processing of sensory information, as well as the preparation and execution of motor functions.[50] Also, the preCG and postCG have been related to number processing.[11] Specifically, the preCG would be related to both symbolic and nonsymbolic numerical processing. The right postCG, on the other hand, has been considered as an area of differential recruitment in children with DD, with a possible compensatory function. Other studies suggest that activations in the postCG and areas close to the anterior IPS may reflect a connection between finger counting and number processing, acting as compensatory mechanisms.[51] Thus, it could reflect sensorimotor requirements on behalf of certain tasks, such as the identification of Arabic numbers or the selection of the appropriate response.[52]

On the other hand, the SMA, together with the areas surrounding the superior parietal lobe, participates in attentional and cognitive control.[53] These areas are also part of the dorsal spatial network, whose function is believed to be involved in descending directed attention.[54] It has been suggested that an increased activity of SMA could be related to a deficient development of a spatial number representation in DD.[4] Together with the alteration of the DMN, these results suggest a dysfunction in the relationship between both networks, which would affect the correct distribution of attentional resources, as well as motor preparation.

In relation to the analysis performed to test the rs-FC patterns of the IPS in both hemispheres, our results also indicate that there is a greater rs-FC in TD children between the right IPS and the left insular cortex. This is congruent with the results of recent studies.[15] The role of the insula in numerical processing has been described in previous studies. In this sense, the functional and structural connectivity between the IPS and the insula has been highlighted, suggesting that this connection may help mediate the detection of visually salient stimuli.[12] Furthermore, it has been suggested that performance on arithmetic word problems relies on bilateral fronto-insular-parietal circuits.[55] This study showed that anterior insular circuits were more strongly coupled with IPS during arithmetic sentence judgments than nonarithmetic sentences. In another rs-FC study, authors showed that right anterior insula FC facilitates arithmetic performance.[56] More recently, it has been found that children with DD had reduced gray matter volume in the insula.[57] Taken together, these results would indicate that structural and/or functional alterations of the insula may be related to reduced performance in numerical processing and calculation.

Finally, and in line with previous studies,[8] our results suggest that arithmetic deficits in dyscalculia are unlikely to be in one single brain region. Rather, both local processing deficits in multiple areas of the brain as well as the coordination between multiple brain circuits are affected.

Our study has several limitations. The limited knowledge of neural interactions and their relation to individual skills in the rs-FC analysis should be noted. Additionally, we interpreted our results, in part, by comparing the data obtained using an rs-fMRI paradigm with data from previous studies using a task paradigm. Thus, results must be interpreted with caution. The sample size could also be considered a limiting factor in our research. It has been pointed out that the robustness of neuroimage results increases with the sample size.[58] This fact could also lead to correlations between clinical symptoms and the rs-FC in both the TD and DD groups. In summary, our results indicate that DD is associated with a pattern of brain FC that differs from TD children. This alteration affects the IPS, the precuneus, and the DMN and SMN. Furthermore, the use of an fc-MVPA approach facilitates a better understanding of brain connectivity, as it is not limited to a specific group of ROIs. Since we studied rs-FC in a group of children with mathematical difficulties at the early stages of the mathematical learning process, these rs-FC alterations could represent brain markers for dyscalculia. Further studies with larger samples are needed to confirm that.

ACKNOWLEDGMENTS

We thank all subjects and their parents for participating in this study. This study was supported by a grant from Fundació La Caixa (Recercaixa program) to J.M.S.G.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Josep M. Serra-Grabulosa https://orcid.org/0000-0002-4291-9432

REFERENCES

1. Peters L, De Smedt B. Arithmetic in the developing brain: a review of brain imaging studies. Dev Cogn Neurosci. 2018;30:265-79.
2. Kucian K, von Aster M. Developmental dyscalculia. Eur J Pediatr. 2015;174:1-13.
3. Kaufmann L, Vogel SE, Starke M, et al. Developmental dyscalculia: compensatory mechanisms in left intraparietal regions in response to nonsymbolic magnitudes. Behav Brain Funct. 2009;5:35.
4. Kucian K, Loenneker T, Martin E, et al. Non-symbolic numerical distance effect in children with and without developmental dyscalculia: a parametric fMRI study. Dev Neuropsychol. 2011;36:741-62.
5. Rotzer S, Loenneker T, Kucian K, et al. Dysfunctional neural network of spatial working memory contributes to developmental dyscalculia. Neuropsychologia. 2009;47:2859-65.
6. Ashkenazi S, Rosenberg-Lee M, Tenison C, et al. Weak task-related modulation and stimulus representations during arithmetic problem solving in children with developmental dyscalculia. Dev Cogn Neurosci. 2012;2:S152-66.
7. Berteletti I, Prado JÔ, Booth JR. Children with mathematical learning disability fail in recruiting verbal and numerical brain regions when solving simple multiplication problems. Cortex. 2014;57:143-55.
8. Rosenberg-Lee M, Ashkenazi S, Chen T, et al. Brain hyper-connectivity and operation-specific deficits during arithmetic problem solving in children with developmental dyscalculia. Dev Sci. 2015;18:351-72.
9. McCaskey U, Von Aster M, Maurer U, et al. Longitudinal brain development of numerical skills in typically developing children and children with developmental dyscalculia. Front Hum Neurosci. 2018;11:629.
10. Üstün S, Ayyıldız N, Kale EH, et al. Children with dyscalculia show hippocampal hyperactivity during symbolic number perception. Front Hum Neurosci. 2021;15:687476.
11. Kaufmann L, Wood G, Rubinsten O, et al. Meta-analyses of developmental fMRI studies investigating typical and atypical trajectories of number processing and calculation. Dev Neuropsychol. 2011;36:763-87.
12. Uddin LQ, Supekar K, Amin H, et al. Dissociable connectivity within human angular gyrus and intraparietal sulcus: evidence from functional and structural connectivity. Cereb Cortex. 2010;20:2636-46.
13. Rubinsten O, Henik A. Developmental dyscalculia: heterogeneity might not mean different mechanisms. Trends Cogn Sci. 2009;13:92-99.
14. Rosenberg-Lee M, Barth M, Menon V. What difference does a year of schooling make? Maturation of brain response and connectivity between 2nd and 3rd grades during arithmetic problem solving. Neuroimage. 2011;57:796-808.
15. Michels L, O'Gorman R, Kucian K. Functional hyperconnectivity vanishes in children with developmental dyscalculia after numerical intervention. Dev Cogn Neurosci. 2018;30:291-303.
16. Raichle ME, MacLeod AM, Snyder AZ, et al. A default mode of brain function. Proc Natl Acad Sci USA. 2001;98:676-82.
17. Martin A, Schurz M, Kronbichler M, et al. Reading in the brain of children and adults: a meta-analysis of 40 functional magnetic resonance imaging studies. Hum Brain Mapp. 2015;36:1963-81
18. Van Dijk KRA, Hedden T, Venkataraman A, et al. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. J Neurophysiol. 2010;103:297-321.
19. Supekar K, Swigart AG, Tenison C, et al. Neural predictors of individual differences in response to math tutoring in primary-grade school children. Proc Natl Acad Sci USA. 2013;110:8230-35.
20. Evans TM, Kochalka J, Ngoon TJ et al. Brain structural integrity and intrinsic functional connectivity forecast 6 year longitudinal growth in children's numerical abilities. J Neurosci. 2015;35:11743-50.
21. Skagerlund K, Bolt T, Nomi JS, et al. Disentangling mathematics from executive functions by investigating unique functional connectivity patterns predictive of mathematics ability. J Cogn Neurosci. 2018;31:560-73.
22. Jolles D, Ashkenazi S, Kochalka J, et al. Parietal hyper-connectivity, aberrant brain organization, and circuit-based biomarkers in children with mathematical disabilities. Dev Sci. 2016;19:613-31.
23. Jolles D, Supekar K, Richardson J et al. Reconfiguration of parietal circuits with cognitive tutoring in elementary school children. Cortex. 2016;83:231-45.
24. Price GR, Yeo DJ, Wilkey ED, et al. Prospective relations between resting-state connectivity of parietal subdivisions and arithmetic competence. Dev Cogn Neurosci. 2018;30:280-90.
25. Koyama MS, O'Connor D, Shehzad Z, et al. Differential contributions of the middle frontal gyrus functional connectivity to literacy and numeracy. Sci Rep. 2017;7:1-13.
26. Nieto-Castanon A. Brain-wide connectome inferences using functional connectivity Multivariate Pattern Analyses (fc-MVPA). PLoS Comput Biol. 2022;18:e1010634.
27. Kwok FY, Wilkey ED, Peters L, e al. Developmental dyscalculia is not associated with atypical brain activation: a univariate fMRI study of arithmetic, magnitude processing, and visuospatial working memory. Hum Brain Mapp. 2023;44:6308-25.
28. Bulthé J, Prinsen J, Vanderauwera J, et al. Multi-method brain imaging reveals impaired representations of number as well as altered connectivity in adults with dyscalculia. Neuroimage. 2019;190:289-302.
29. Mateu-Estivill R, Forné S, López-Sala A, et al. Functional connectivity alterations associated with literacy difficulties in early readers. Brain Imaging and Behav. 2021;15:2109-20.
30. Asociación Americana de Psiquiatría. Manual diagnóstico y estadístico de los trastornos mentales. 5ª ed. Madrid: Panamericana; 2013.
31. Camacho A, Grau S, Mateu R. et al. Di-Calc: Spanish digital test to evaluate mathematics learning disabilities (MLDs) in primary school. Presented at the 6th Scientific Meeting of the Federation of the European Societies of Neuropsychology (FESN), Maastricht, 13th to 15th September 2017.
32. Wechsler D. WISC-IV: escala de inteligencia Wechsler para niños IV. Madrid: TEA; 2005.
33. Cuetos F, Rodríguez B, Ruano E, et al. PROLEC-R: Batería de evaluación de los procesos lectores, revisada. Barcelona: TEA Ediciones; 2007.
34. Farré-Riba A, Narbona J. Conners' rating scales in the assessment of attention deficit disorder with hyperactivity (ADHD). A new validation and factor analysis in Spanish children. Rev Neurol. 1997;25:200-204.
35. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2012;2:125-41.
36. Altaye M, Holland SK, Wilke M, et al. Infant brain probability templates for MRI segmentation and normalization. Neuroimage. 2008;43:721-30.
37. Mazaika PK, Hoeft F, Glover GH, et al. Methods and software for fMRI analysis for clinical subjects. Hum Brain Mapp. 2009;47:S58.
38. Eklund A, Nichols TE, Knutsson H. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. Proc Natl Acad Sci USA. 2016;113:7900-7905.
39. Choi HJ, Zilles K, Mohlberg H, et al. Cytoarchitectonic identification and probabilistic mapping of two distinct areas within the anterior ventral bank of the human intraparietal sulcus. J Comp Neurol. 2006;495:53-69.
40. Scheperjans F, Hermann K, Eickhoff SB, et al. Observer-independent cytoarchitectonic mapping of the human superior parietal cortex. Cereb Cortex. 2008;18:846-67.
41. Abreu-Mendoza RA, Pincus M, Chamorro Y, et al. Parietal and hippocampal hyper-connectivity is associated with low math achievement in adolescence—a preliminary study. Dev Sci. 2022;25:e13187.

42. Wood G, Ischebeck A, Koppelstaetter F, et al. Developmental trajectories of magnitude processing and interference control: an fMRI study. Cereb Cortex. 2009;19:2755-65.
43. Prado J, Mutreja R, Zhang H, et al. Distinct representations of subtraction and multiplication in the neural systems for numerosity and language. Hum Brain Mapp 2011;32:1932-47.
44. Grabner RH, Ansari D, Koschutnig K, et al. The function of the left angular gyrus in mental arithmetic: evidence from the associative confusion effect. Hum Brain Mapp. 2013;34:1013-24.
45. Dinkel PJ, Willmes K, Krinzinger H, et al. Diagnosing developmental dyscalculia on the basis of reliable single case FMRI methods: promises and limitations. PLoS ONE. 2013;8:e83722.
46. Piazza M, Eger E. Neural foundations and functional specificity of number representations. Neuropsychologia. 2016;83:257-73.
47. Vandervert L. The origin of mathematics and number sense in the cerebellum: with implications for finger counting and dyscalculia. Cerebellum Ataxias. 2017;4:12.
48. Ashburn SM, Flowers DL, Napoliello EM, et al. Cerebellar function in children with and without dyslexia during single word processing. Hum Brain Mapp. 2000;41:120-38.
49. Branum-Martin L, Fletcher JM, Stuebing KK. Classification and identification of reading and math disabilities: the special case of comorbidity. J Learn Disabil. 2013;46:490-99.
50. Beckmann CF, DeLuca M, Devlin JT, et al. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci. 2005;360:1001-13.
51. Gracia-Bafalluy M, Noël MP. Does finger training increase young children's numerical performance? Cortex. 2008;44:368-75.
52. Mussolin C, De Volder A, Grandin C, et al. Neural correlates of symbolic number comparison in developmental dyscalculia. J Cogn Neurosci. 2010;22:860-74.
53. Niendam TA, Laird AR, Ray KL, et al. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. Cogn Affect Behav Neurosci. 2012;12:241-68.
54. Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to theory of mind. Neuron. 2008;58:306-24.
55. Chang TT, Lung TC, Ng CT, et al. Fronto-insular-parietal network engagement underlying arithmetic word problem solving. Hum Brain Mapp. 2019;40:1927-41.
56. Chang TT, Lee PH, Metcalfe AWS. Intrinsic insula network engagement underlying children's reading and arithmetic skills. Neuroimage. 2018;167:162-77.
57. McCaskey U, von Aster M, O'Gorman R, et al. Persistent differences in brain structure in developmental dyscalculia: a longitudinal morphometry study. Front Hum Neurosci. 2020;14:272.
58. Thirion B, Pinel P, Tucholka A, et al. Structural analysis of fMRI data revisited: improving the sensitivity and reliability of fMRI group studies. IEEE Trans Med Imaging. 2007;26:1256-69.

How to cite this article: Mateu-Estivill R, Adan A, Grau S, Rifà-Ros X, Caldú X, Bargalló N, et al. Alterations in functional brain connectivity associated with developmental dyscalculia. J Neuroimaging. 2024;34:694–703. https://doi.org/10.1111/jon.13236