SUPPLEMENTARY MATERIALS

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Title: Neural Connectivity in Developmental Dyscalculia: A Resting-State fMRI Study Using ROI-Based and Connectome-Based Approaches

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MRI Data Preprocessing. Functional data were realigned using SPM realign and unwarp procedures (Andersson et al., 2001), where all scans were coregistered to a reference image (first scan of the first session) using a least squares approach and a 6 parameter (rigid body) transformation (Friston et al., 1995), and resampled using b-spline interpolation to correct for motion and magnetic susceptibility interactions. Temporal misalignment between different slices of the functional data (acquired in interleaved Siemens order) was corrected following the SPM slice-timing correction (STC) procedure (Henson et al., 1999; Sladky et al., 2011), using sinc temporal interpolation to resample each slice BOLD timeseries to a common mid-acquisition time. Potential outlier scans were identified using ART (Whitfield-Gabrieli et al., 2009) as acquisitions with framewise displacement above 1.5 mm or global BOLD signal changes above 4 standard deviations (Nieto-Castanon, 2022; Power et al., 2014) and a reference BOLD image was computed for each subject by averaging all scans excluding outliers. One participant was removed at this stage due to a large amount of movement (greater than 20% of outlying volumes), leaving 67 participants (30 with DD and 37 who were TA) to proceed into the analyses. The average number of outlying volumes across participants was 2.31 volumes per run (1%). Functional and anatomical data were normalized into standard MNI space, segmented into grey matter, white matter, and CSF tissue classes, and resampled to 2 mm isotropic voxels following a direct normalization procedure (Calhoun et al., 2017; Nieto-Castanon, 2022) using SPM unified segmentation and normalization algorithm (Ashburner, 2007; Ashburner & Friston, 2005) with the default IXI-549 tissue probability map template. Last, functional data were smoothed using spatial convolution with a Gaussian kernel of 8 mm FWHM.

In addition, functional data were denoised using the standard denoising pipeline in CONN (Nieto-Castanon, 2020) including the regression of potential confounding effects characterized by white matter timeseries (5 CompCor noise components), CSF timeseries (5 CompCor noise components), motion parameters and their first order derivatives (12 factors) (Friston et al., 1996), outlier scans (below 25 factors) (Power et al., 2014), session effects and their first order derivatives (2 factors), and linear trends (2 factors) within each functional run, followed by bandpass frequency filtering of the BOLD timeseries (Hallquist et al., 2013) between 0.008 Hz and 0.09 Hz. CompCor (Behzadi et al., 2007; Chai et al., 2012). Noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. From the number of noise terms included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to range from 59.4 to 66.9 (average 66.2) across all subjects (Nieto-Castanon, 2022). Functional and anatomical data from one participant failed to normalize successfully based on visual inspection when preprocessed through the default CONN pipeline and was instead separately preprocessed using fmriprep version 20.2.3-2 without modification. All analyses in this study were repeated without this participant as part of a sensitivity check; results did not significantly change when this participant was excluded and are therefore reported in this paper with the inclusion of this participant.

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WBCC classification details. Functional connectivity data from the ROI-to-ROI matrices were fed into a nested cross-validation framework to evaluate and select a predictive model using logistic regression with elastic net regularization. Feature reduction using mutual information values (computed against the binary vector of those with and without DD) was used to reduce the number of edges to 200 to reduce the complexity of the regularized regression. The outer loop, defined by a 5-fold stratified cross-validation, divided the dataset into training and test splits, ensuring class balance across folds. 5-fold validation was selected for bias-variance trade off (Kohavi, 1995; Breiman & Spector, 1992; Hastie et al., 2009). Within each outer training fold, a 2-fold inner cross-validation performed a grid search over hyperparameters (the regularization strength, C, and L1 ratio for the L1/L2 regularization mix) using a pipeline that standardized the features and applied logistic regression. The best hyperparameter combination from the inner loop was selected, and the corresponding model's coefficients were used to identify the 20 most important predictors based on absolute coefficient values. These selected features were then used to train a simplified logistic regression model without regularization, which was evaluated on the held-out test set from the outer loop. Key metrics, including AUC (area under the ROC curve) and accuracy, were computed for each fold. Whereas accuracy is a metric of overall percentage correct, AUC analyzes the relationship between the true positive and false positive rate. Connectivity edges (i.e., node-to-node connections) that consistently appeared in at least 60% of the folds were retained as potentially important features and are reported in the results section. See https://osf.io/zxswg for archived Python scripts used for the current analysis.

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Supplementary Table S1. Group Differences in IPS connectivity between DD and TA

Seed ROI	Cluster Size (Voxels)	Mean T†	MNI x	y	z
Left Intraparietal Sulcus (hIP1)					
TA > DD					
Right superior lateral occipital cortex (91%)	150*	-4.38	50	-64	28
Right angular gyrus (6%)					
Right pars opercularis (49%)	113*	-4.49	58	10	16
Right precentral gyrus (45%)					
Right central opercular cortex (1%)					
Right middle frontal gyrus (98%)	61	-4.85	38	12	56
DD > TA					
No significant clusters					
Left Intraparietal Sulcus (hIP2)					
TA > DD					
Right superior lateral occipital and parietal cortex (86%); Right IPS hIP5 and hIP6	236*	-5.18	32	-68	38
Right precentral gyrus (69%)	68	-4.30	58	10	20
DD > TA					
No significant clusters					
Left Intraparietal Sulcus (hIP3)					
TA > DD					
No significant clusters					
DD > TA					
Right cerebellum crus I (88%)	74	4.30	20	-80	-30
Right cerebellum crus II (12%)					
Right Intraparietal Sulcus (hIP1)					
TA > DD					
Left middle frontal gyrus (68%)	184*	-4.83	-32	4	68
Left superior frontal gyrus (14%)					
Right middle frontal gyrus (74%)	131*	-5.06	32	0	56
Right precentral gyrus (5%)					
Right superior frontal gyrus (3%)					
Right precentral gyrus (52%)	69	-4.30	54	10	18
Right pars opercularis (43%)					
Left superior lateral occipital cortex (97%)	64	-4.40	-36	-68	18
DD > TA					
No significant clusters					
Right Intraparietal Sulcus (hIP2)					
TA > DD					
Left temporal pole (75%)	83	-5.12	-24	12	-38
Right precentral gyrus (64%)	81	-4.57	54	6	20
Right pars opercularis (26%)					
DD > TA					
No significant clusters					

Right Intraparietal Sulcus (hIP3)	
TA > DD	
No significant clusters	
DD > TA	
No significant clusters	

Note. All clusters present in the table are significant at FDR-adjusted $p < .05$. p-values for all t-statistics were less than 0.0001 after being FDR adjusted. Cluster †Positive t-values indicate DD > TA. Negative t-values indicate TA > DD. * indicates that the cluster survives a Bonferroni correction of the already FDR-adjusted cluster p-value based on 12 ROIs being test across the full analysis.

Supplementary Table S2. Group Differences in AG connectivity between DD and TA

Seed ROI	Cluster Size (Voxels)	Mean T†	MNI x	y	z
Left Angular Gyrus (Anterior)					
TA > DD					
Left precentral gyrus (30%) Left postcentral gyrus (6%)	81	-5.24	-12	-30	60
DD > TA					
No significant clusters					
Left Angular Gyrus (Posterior)					
TA > DD					
Left angular gyrus (50%) Left superior supramarginal gyrus (21%) Left superior parietal lobule (7%) Left superior lateral occipital cortex (1%)	72	-4.28	-44	-56	54
DD > TA					
Left cerebellum crus I (89%) Left cerebellum lobule VI (7%) Left fusiform cortex (5%)	61	4.49	-40	-52	-36
Right frontal pole (56%) Right frontal occipital cortex (14%)	50	4.43	40	36	-20
Right Angular Gyrus (Anterior)					
TA > DD					
No significant clusters					
DD > TA					
No significant clusters					
Right Angular Gyrus (Posterior)					
TA > DD					
Right posterior inferior temporal gyrus (47%) Right temporo-occipital inferior temporal gyrus (17%) Right cerebellum crus I (3%)	72	-4.43	50	-36	-26
DD > TA					
No significant clusters					

Note. All clusters present in the table are significant at FDR-adjusted $p < .05$. p-values for all t-statistics were less than 0.0001 after being FDR adjusted. Cluster †Positive t-values indicate DD > TA. Negative t-values indicate TA > DD. * indicates that the cluster survives a Bonferroni correction of the already FDR-adjusted cluster p-value based on 12 ROIs being test across the full analysis.

Supplementary Table S3. Group Differences in hippocampus connectivity between DD and TA

Seed ROI	Cluster Size (Voxels)	Mean T†	MNI x	y	z
Left Hippocampus					
TA > DD					
Left paracingulate gyrus (38%) Left superior frontal gyrus (22%) Left juxtapositional lobule cortex / SMA (10%) Right paracingulate gyrus (5%) Right superior frontal gyrus (1%)	102*	-4.41	-6	12	52
DD > TA					
No significant clusters					
Right Hippocampus					
TA > DD					
No significant clusters					
DD > TA					
No significant clusters					

Note. All clusters present in the table are significant at FDR-adjusted $p < .05$. p-values for all t-statistics were less than 0.0001 after being FDR adjusted. Cluster †Positive t-values indicate DD > TA. Negative t-values indicate TA > DD. * indicates that the cluster survives a Bonferroni correction of the already FDR-adjusted cluster p-value based on 12 ROIs being test across the full analysis.

Supplementary Table S4. WBCC Connections in which TA > DD

Node 1				Node 2			
Hemisphere	Location	Specific Anatomical Region	Network	Hemisphere	Location	Specific Anatomical Region	Network
Left	Inferior Frontal Gyrus	A45c, caudal area 45	Default	Left	Superior Temporal Gyrus	A38l, lateral area 38	Limbic
Left	Inferior Temporal Gyrus	A20iv, intermediate ventral area 20	Limbic	Left	Hippocampus	cHipp, caudal hippocampus	SCGM
Left	Inferior Temporal Gyrus	A20cv, caudoventral of area 20	Limbic	Left	Lateral Occipital Cortex	msOccG, medial superior occipital gyrus	Visual
Left	Precuneus	dmPOS, dorsomedial parietooccipital sulcus (PEr)	Visual	Left	Lateral Occipital Cortex	OPC, occipital polar cortex	Visual
Right	Middle Frontal Gyrus	A9/46d, dorsal area 9/46	Frontoparietal	Right	Postcentral Gyrus	A1/2/3tru, area 1/2/3 (trunk region)	Somatomotor
Right	Superior Temporal Gyrus	A22r, rostral area 22	Default	Right	Hippocampus	cHipp, caudal hippocampus	SCGM
Right	Superior Parietal Lobule	A7ip, intraparietal area 7(hIP3)	Dorsal Attention	Right	Cingulate Gyrus	A24cd, caudodorsal area 24	Ventral Attention
Left	Superior Frontal Gyrus	A9m, medial area 9	Default	Right	Superior Frontal Gyrus	A9m, medial area 9	Frontoparietal
Left	Superior Frontal Gyrus	A9m, medial area 9	Default	Right	Superior Frontal Gyrus	A10m, medial area 10	Default

Supplementary Table S5. WBCC Connections in which DD > TA

Node 1				Node 2			
Hemisphere	Location	Specific Anatomical Region	Network	Hemisphere	Location	Specific Anatomical Region	Network
Left	Middle Frontal Gyrus	A9/46v, ventral area 9/46	Frontoparietal	Left	Inferior Temporal Gyrus	A20iv, intermediate ventral area 20	Limbic
Left	Middle Frontal Gyrus	A8vl, ventrolateral area 8	Default	Left	Superior Parietal Lobule	A7c, caudal area 7	Dorsal Attention
Left	Precentral Gyrus	A4t, area 4 (trunk region)	Somatomotor	Left	Thalamus	cTtha, caudal temporal thalamus	SCGM
Left	Inferior Parietal Lobule	A39rd, rostrodorsal area 39 (Hip3)	Frontoparietal	Right	Middle Frontal Gyrus	A46, area 46	Frontoparieta l
Left	Cingulate Gyrus	A23v, ventral area 23	Default	Right	Superior Frontal Gyrus	A10m, medial area 10	Default