

Predicting Children’s Math Skills from Task-Based and Resting-State Functional Brain Connectivity

Andrew Lynn¹, Eric D. Wilkey² and Gavin R. Price^{1,3}

¹Department of Psychology and Human Development, Peabody College, Vanderbilt University, Nashville, TN 37212, USA

²Brain and Mind Institute, Western University, London, ON N6A 3K7, Canada

³Vanderbilt Brain Institute, Vanderbilt University, Nashville, TN 37232, USA

Address correspondence to Andrew Lynn, Department Psychology and Human Development, Vanderbilt University, 230 Appleton Place, Nashville, TN 37203, USA. Email: Andrew.Lynn.1@vanderbilt.edu

Abstract

A critical goal of cognitive neuroscience is to predict behavior from neural structure and function, thereby providing crucial insights into who might benefit from clinical and/or educational interventions. Across development, the strength of functional connectivity among a distributed set of brain regions is associated with children’s math skills. Therefore, in the present study we use connectome-based predictive modeling to investigate whether functional connectivity during numerical processing and at rest “predicts” children’s math skills ($N = 31$, $M_{\text{age}} = 9.21$ years, 14 Female). Overall, we found that functional connectivity during symbolic number comparison and rest, but not during nonsymbolic number comparison, predicts children’s math skills. Each task revealed a largely distinct set of predictive connections distributed across canonical brain networks and major brain lobes. Most of these predictive connections were negatively correlated with children’s math skills so that weaker connectivity predicted better math skills. Notably, these predictive connections were largely nonoverlapping across task states, suggesting children’s math abilities may depend on state-dependent patterns of network segregation and/or regional specialization. Furthermore, the current predictive modeling approach moves beyond brain–behavior correlations and toward building models of brain connectivity that may eventually aid in predicting future math skills.

Keywords: childhood, development, functional connectivity, math, predictive modeling

Introduction

A critical goal of cognitive neuroscience is to “predict” behavior from neural structure and function. One promising approach is “connectome-based predictive modeling” (CPM), in which an individual’s behavior is predicted from their brain connectivity patterns (e.g. Shen et al. 2017). CPMs derived from functional brain connectivity during attention tasks have proved useful in predicting severity of attention deficit hyperactivity disorder in childhood (Rosenberg et al. 2015). However, such predictive methods have not yet been applied in the domain of academic development. Early prediction of risk of low math achievement is crucial to providing insights into which children might benefit from clinical and/or educational interventions. Therefore, in the present study we use CPM to investigate whether functional connectivity during numerical processing and at rest predicts children’s math skills.

Predictive modeling leverages the relation between two variables (e.g. brain connectivity and behavior) in a dataset to make a prediction about novel data (Gabrieli et al. 2015; Rosenberg et al. 2018). In the present study, we refer to “prediction” as the output of a model when applied to a novel datapoint and “correlation” as the

statistical measure of association between two variables across a set of data. A key goal of developmental and educational neuroscience is to predict a future behavior from earlier brain and behavioral measures. However, predictive modeling may also be used to examine individual differences at a given time in development. We have focused on predicting third and fourth graders’ (8–10 year olds) math skills from their “concurrent” brain connectivity because this is a time in academic development when individual differences in math skills begin to emerge (Jordan and Hanich 2003; Geary and Hoard 2005).

The extant functional connectivity literature shows that an individual’s math skills are correlated with the strength of functional connectivity between a distributed set of frontal, parietal, and temporooccipital brain regions. Key math-related brain regions include the inferior frontal gyrus (IFG), intraparietal sulcus (IPS), and inferior temporal number area (ITNA) located in the inferior temporal gyrus (ITG) (Arsalidou and Taylor 2011; Yeo et al. 2017). Subdivisions of these regions are distributed across several canonical networks, including the frontoparietal, dorsal attention and ventral attention networks (Yeo et al. 2011), thus suggesting that several brain networks may be involved in the development of math skills. Across childhood, stronger

frontoparietal connectivity during symbolic number processing is associated with better math skills (Park et al. 2014). Some studies show that during calculation, stronger intraparietal functional connectivity is related to better math skills (Park et al. 2013; Battista et al. 2018), but others show that “weaker” intraparietal and frontoparietal connectivity is associated with better math skills (Rosenberg-Lee et al. 2015). Similarly, weaker temporooccipital functional connectivity during number processing is related to better math skills in adulthood (Bulthé et al. 2019). Across childhood, stronger resting-state connectivity within frontal and between frontal and parietal regions is correlated with better counting, numerical processing, and calculation skills (Zhang et al. 2019). Moreover, stronger intraparietal and weaker frontoparietal resting-state connectivity in the first grade is associated with children’s calculation skills in the second grade (Price et al. 2018). Across childhood, stronger resting-state connectivity between temporooccipital and frontal, as well as parietal regions is associated with better calculation skills (Evans et al. 2015; Nemmi et al. 2018). The extant literature, therefore, presents an inconsistent web of findings showing that both stronger and weaker functional connectivity support better math skills in childhood.

One possible explanation for this inconsistency is that the relation between functional connectivity and children’s math skills may differ depending on the functional connectivity task-state (Geerligs et al. 2015; Finn et al. 2017). Both behavioral and brain data suggest that nonsymbolic and symbolic magnitude comparison abilities support math skills across development (e.g. De Smedt et al. 2013), with nonsymbolic magnitude processing setting the foundation for symbolic magnitude processing abilities across childhood (Price and Fuchs 2016). It is, as yet, unclear whether patterns of functional connectivity differentially predict children’s math skills during nonsymbolic and symbolic number comparison tasks and at rest. If the same connectivity profile predicts math skills across tasks and rest, it would suggest that a stable pattern of functional connectivity, or trait-level neural architecture, may provide the foundation for each child’s math skills. On the other hand, if varying patterns of functional connectivity across these task- and rest-states predict math skills, it may reflect a flexibility in network organization that supports the acquisition of math skills.

Here, we used CPM (Rosenberg et al. 2015; Shen et al. 2017) to test whether functional connectivity during symbolic and nonsymbolic number comparison, and during rest, predicts children’s math skills measures outside the scanner. CPM leverages leave-one-out cross-validation (LOOCV) to 1) select all functional connections correlated with a behavior of interest (i.e. math skills), 2) train a linear model to fit the sum of connection strengths and behavioral variable, and 3) predict the behavior of a held-out participant from their functional connectivity values using the trained linear model. In using CPM, the present study moves beyond

brain-behavior correlation to predict children’s math skills from their functional connectivity during different task-states and at rest.

Materials and Methods

Participants

The final sample included 31 typically achieving 8- to 10-year-old children (14 female). Children completed a behavioral visit and a neuroimaging visit. An additional five children that completed the neuroimaging visit were removed from analyses due to excessive motion during resting-state. We defined excessive motion as at least half of the scan volumes (i.e. TRs) with temporal derivative of the root-mean-squared variance (DVARs) $> 3^\circ$ and/or framewise displacement (FD) > 0.5 mm. The current sample partially overlaps with a previously published sample (Wilkey and Price 2019), from which we include only children who had completed both symbolic and nonsymbolic number comparison task scans and resting-state scans. Children’s parents provided consent, and children provided their assent in accordance with our university IRB policies. Prior to neuroimaging, children were acclimated to a mock MRI scanner.

Experimental Design and Statistical Analyses

Behavioral Visit

Children first completed a behavioral visit in which they completed several tasks, including the Woodcock–Johnson III tests of achievement (WJ-III) (Woodcock et al. 2001) and the Kaufman brief intelligence test, second edition (KBIT) (Kaufman and Kaufman 2004). We derived separate composite math and reading scores from the WJ-III and full-scale IQ scores from the KBIT.

Math skills

We measured children’s math skills using the WJ-III applied problems, calculation and math fluency subtests. The applied problems subtest measures children’s ability to analyze and solve math problems in an untimed task in which they hear a math word problem and must correctly select the relevant numerical information and mathematical operation to find the answer. The calculation subtest measures children’s ability to perform math computations in an untimed task in which they complete as many calculation problems as possible, ranging from simple arithmetic to calculus and increased in difficulty with each consecutive problem. The math fluency subtest measures children’s ability to quickly solve calculation problems in a 3-min timed task in which they complete as many simple addition, subtraction, and multiplication problems as possible. Subtest scores were first normed to the child’s age and then averaged to create a composite math score for each child.

Reading skills

We measured children’s reading skills using the WJ-III letter–word identification and passage comprehension

subtests. The letter–word identification subtest measures children's ability to first identify target letters and words among distracting letters, words, and pictures, and then to read words of increasing difficulty. The passage comprehension subtest measures children's ability to first match pictures of common objects to symbols, then to read words or phrases and choose the matching picture, and finally to fill in missing words in sentences and paragraphs of increasing difficulty. Subtest scores were first normed to the child's age and then averaged to create a composite reading score for each child.

Intelligence quotient (IQ)

We calculated full-scale IQ estimates for each child based on the KBIT. Full-scale IQ is a composite score of verbal IQ and nonverbal IQ. Verbal IQ is measured using picture-based vocabulary and riddles, and nonverbal IQ is measured using matrix reasoning questions.

Neuroimaging Visit

Symbolic and nonsymbolic number comparison tasks

We instructed children to lay motionless while they completed a symbolic and nonsymbolic number comparison task during fMRI scanning. We counterbalanced symbolic and nonsymbolic number comparison tasks across all participants. We asked participants to indicate which of the two simultaneously presented Arabic digits (symbolic) or sets of dots (nonsymbolic) was larger in magnitude by responding with a button press on either a left-hand or right-hand button box (i.e., two button boxes were used). We presented target stimuli for 1250 ms followed by a fixation line for 3250–6250 ms (1000 ms steps, $M = 4750$ ms). We recorded reaction times (RTs) and error rates (ER) to calculate a “performance” metric, $P = RT / (1 + 2ER)$, which corrects children's RTs by their ER and controls for speed/accuracy trade-offs (Lyons et al. 2014). Thus, a “smaller” P metric corresponds to “better” performance. Note that accuracy on both the symbolic ($M = 91.7\%$, $SD = 5.8\%$) and nonsymbolic tasks ($M = 86.5\%$, $SD = 9.9\%$) was well above chance.

The numerosity ratio (smaller number divided by larger number) between the two stimuli varied from smaller and easier (0.286–0.375) to larger and harder (0.625–0.714). Arabic digits ranged from 1 to 9 and the number of dots in each set ranged from 5 to 21. Each task included a total of 80 trials (40 easy ratio, 40 hard ratio). On half of the trials, the physical size of the stimulus was congruent with the numerosity (large 7, small 3), and on the other half the size of the stimulus was incongruent (small 7, large 3). For the nonsymbolic number comparison task, the stimulus “size” was measured by convex hull, total surface area, and dot diameter (Gebuis and Reynvoet 2011).

Resting state

Children completed resting-state scans after having completed both number comparison tasks. Children

were instructed to lay motionless with their eyes open while a fixation cross was presented on the screen.

Image acquisition, preprocessing, and nuisance regression

We acquired all MR imaging with a Phillips Achieva 3 T MR scanner using a 32-channel head coil. Children watched a cartoon movie while we acquired high-resolution anatomical images using a T1-weighted magnetization prepared rapid gradient recalled echo sequence according to the following specifications: times repeated (TR) = 8.929 s; echo time (TE) = 4.61 ms; flip angle = 8°; 170 sagittal slices with no interslice gap; voxel size = $1 \times 1 \times 1$

mm; imaging matrix = 256×256 ; acquisition time = 264.8 s. We oriented scans in the anterior–posterior commissure plane.

We acquired whole-brain functional images using a multislice 2D SENSE T2* gradient-echo, with an echo planar imaging pulse sequence in the axial plane with the following parameters: slices = 40; TR = 2000 ms; TE = 25 ms; voxel size = $2.5 \times 2.5 \times 3$ mm with an interslice gap of 0.25 mm; field of view = $240 \times 129.75 \times 240$ mm; imaging matrix = 96×96 ; flip angle = 90°; SENSE factor = 2.5. Symbolic and nonsymbolic task scans were approximately 9 min in total (4.5 min per run), and the resting scan was approximately 7.5 min.

We preprocessed images using FreeSurfer v7.1.1 (Ségonne et al. 2007) and the CONN toolbox v20 (Whitfield-Gabrieli and Nieto-Castanon 2012) for SPM in MATLAB R2019b. We first segmented anatomical images using the FreeSurfer cortical reconstruction process (i.e. recon-all). We visually inspected and manually edited gray matter and white matter segmentations for common errors (e.g. skull strip errors). We then preprocessed functional imaging data using the CONN toolbox preprocessing pipeline for surface-based analyses. First, we aligned functional volumes and then corrected for slice-timing. Then, we coregistered each child's functional images to their anatomical image using nonlinear registration and then resampled to children's FreeSurfer structural cortical surface. Finally, we smoothed the surface data using iterative spatial diffusion smoothing with 40 iterations to approximate an 8 mm full width at half maximum kernel (Hagler et al. 2006).

Following preprocessing, we employed nuisance regression to correct for in-scanner motion and remove task activation effects using the CONN toolbox for SPM. We included the following parameters: 1) first five components and derivatives of both CSF and WM signals, 2) 24 movement parameters derived from children's realignment (i.e. x , y , z , roll, pitch, yaw, derivatives, quadratic expansion), 3) global signal, and 4) framewise displacement (FD). We also included task event onsets convolved with a canonical hemodynamic response function (HRF) to remove the effect of task activation. We then band-pass filtered ($0.008 < f < 0.09$ Hz) the functional surface data.

We chose short runs for each task so children could take breaks and therefore minimize the in-scanner motion (e.g. Meissner et al. 2020). As we had short runs, we also aimed to keep as much data as possible. Spike regression/scrubbing reduces temporal degrees of freedom and may bias functional connectivity estimates across the sample (Ciric et al. 2017). Therefore, we explored the impact of two temporal censoring approaches separately: “spike regression” (DVARs > 3° and/or FD > 0.5 mm) and “despiking” (prior to regression). There are several ways to define a successful denoising approach (see Ciric et al. 2017; Satterthwaite et al. 2019). One way is to determine which approach resulted in minimizing the relation between CONN toolbox quality control (QC) measures (i.e. mean/max motion, mean/max global signal change, number of TRs without motion, and mean FD) and functional connectivity (FC) values. Stronger QC–FC correlations at the group levels would indicate that a denoising approach did not adequately remove motion-related noise, but weaker QC–FC correlations would indicate that the approach adequately removed motion-related noise. Thus, a successful denoising approach would result in a distribution of QC–FC correlations centered around zero. A secondary benchmark was that an individual’s connectivity values were normally distributed around zero. Overall, visual inspection QC–FC correlation distributions and individual connectivity value distributions indicated that timeseries despiking, rather than spike regression, resulted in a better denoising (see [Supplementary Fig. 1](#)). Therefore, our complete motion correction pipeline included timeseries despiking followed by nuisance regression as outlined above.

Following preprocessing and nuisance regression, we utilized the CONN toolbox v20 to extract the raw signal timeseries from each of the 210 cortical regions of interest (ROIs) from the connectivity-derived and biologically plausible Brainnetome atlas (Fan et al. 2016). For each child, we then calculated the Fisher Z-transformed correlation coefficient between the timeseries of all regions, which resulted in a 210×210 functional connectivity matrix. These child-level Z-score connectivity matrices were then submitted to subsequent analyses. See [Supplementary Fig. 2](#) for surface-based Brainnetome atlas with Yeo et al. (2011) network labels.

Connectome-based predictive modeling (CPM)

We used separate CPMs to predict children’s composite math skills (measured outside the scanner) from connectivity during symbolic number comparison, nonsymbolic number comparison, and resting state (eyes open). CPM employs LOOCV to predict a held-out (novel) child’s behavior (e.g. math skills) from an independent set of connectivity values across three main steps: 1) feature selection, 2) model fitting, and 3) behavior prediction (Rosenberg et al. 2015; Shen et al. 2017). During feature selection, we selected connections correlated with composite math skills scores in the training set ($P < 0.01$),

controlling for children’s age and mean FD. Note that during the feature selection step, connection strength may be positively or negatively correlated with the behavior of interest. During the model fitting step, we therefore trained a general linear model (GLM) with one parameter for the sum of positive features and one for the sum of negative features. During behavior prediction, we used the fitted GLM to predict the held-out child’s composite math skills score. We repeated this process until every child was held out, yielding a “predicted” composite math score for each child.

To assess each model, we calculated the Pearson correlation between the predicted and observed composite math skills scores and followed up with permutation testing (iterations = 10 000). We report both standard P -values associated with the correlation distribution (corrected for multiple comparisons) and permutation test P -values. To calculate permutation P -values, we randomly permuted children’s composite math scores and ran the same CPM procedure 10 000 times to create a null distribution of r values. Then we divided the number of times the null r values were greater than or equal to the observed r value by the total number of permutations.

Results

Correlations among Behavioral Measures

We computed Pearson correlations to determine the relation between age (years), composite math score, composite reading score, full scale IQ, and motion for each task (mean FD). See [Table 1](#) for all statistics. Better math skills were associated with better reading skills and higher full-scale IQ. Better reading skills were also associated with higher full-scale IQ and less in-scanner motion across all three tasks. In-scanner motion among the three tasks was positively correlated.

Connectome-Based Predictive Modeling

We used CPM to determine whether functional connectivity during each task separately (i.e. symbolic, nonsymbolic, and rest) predicts children’s composite math skills (e.g. WJ-III). To account for the influence of age-related changes and in-scanner motion on functional connectivity, we include age (years) and mean FD as covariates during feature selection. It is important to highlight that because each child serves as the held-out participant across different LOOCV rounds, the exact connections that predict each children’s composite math skills likely vary. In other words, the set of connections whose strength is summed to predict child A may only partially overlap with the set of connections whose strength is summed to predict child B. To characterize which functional connections consistently predicted children’s composite math skills across the sample, we identified connections whose strength was selected by the model across all LOOCV rounds. This resulted in one set of “consistent connections” for each model. Note that these

Table 1. Correlations among behavioral measures and in-scanner motion.

Variable (n = 31)	M	SD	Min	Max	1.	2.	3.	4.	5.	6.	7.	8.
1. Age	9.21	0.65	8.24	10.67								
2. Math Skills	103.98	13.07	78.33	130.33	-0.234							
3. Reading Skills	107.97	11.36	82.50	127.50	-0.010	0.617***						
4. FSIQ	114.32	15.65	73.00	140.00	-0.089	0.56**	0.838***					
5. Symbolic Performance (P)	1124.14	179.48	792.71	1555.31	-0.351	-0.281	-0.462**	-0.387*				
6. Non-symbolic Performance (P)	1167.58	216.87	760.90	1649.19	-0.127	-0.229	-0.423*	-0.385*	0.465**			
7. Symbolic Mean FD	0.33	0.28	0.09	1.25	-0.051	-0.257	-0.456*	-0.335	-0.061	0.157		
8. Non-Symbolic Mean FD	0.27	0.20	0.09	0.82	-0.271	-0.165	-0.496**	-0.209	0.201	0.058	0.407*	
9. Rest Mean FD	0.33	0.27	0.08	1.07	-0.039	-0.274	-0.451*	-0.200	0.056	0.096	0.749***	0.484**

*P < 0.05 **P < 0.01 ***P < 0.001

connections are a subset of those identified across each LOOCV round and are selected for illustrative purposes.

To observe whether connectivity predicts composite math skills similarly or differently across each task state, we identify which consistent connections predict composite math skills across more than one task-state. If similar connections predict math scores across multiple task-state, then children's trait-dependent connectivity may underlie individual differences in children's composite math skills. However, if different connections predict composite math skills for each task-state, then state-dependent connectivity may underlie these individual differences.

Functional Connectivity During Symbolic Number Comparison Predicts Children's Math Skills

CPM revealed 14 positive and 59 negative consistent connections during symbolic number comparison that together significantly predicted children's composite math score (Fig. 1; $r=0.535$, Bonferroni-corrected $P=0.006$, permutation $P=0.01$). The most common connections whose strength was positively correlated with children's math skills were between the visual and default mode networks (29%). The regions with the largest number of positive connections were the R posterior superior temporal sulcus ($n=3$), R precuneus ($n=3$), and L precuneus ($n=3$). See Figure 2 for depictions of consistently predictive connections and their distribution across networks.

The most common connections whose strength was negatively correlated with children's math skills were also between the visual and default mode networks (19%) and between the dorsal attention and default mode networks (10%). The regions with the largest number of negatively correlated connections were the L middle frontal gyrus (MFG, $n=9$), L superior frontal gyrus (SFG, $n=9$), R SFG ($n=4$), R lateral occipital gyrus (LOC, $n=8$), L precentral gyrus (PrG, $n=6$), R middle temporal gyrus (MTG, $n=6$), L insula ($n=5$), L parahippocampal gyrus (PhG, $n=5$), R inferior parietal lobule (IPL, $n=5$), L IPL ($n=4$), L inferior frontal gyrus (IFG, $n=4$), R superior parietal lobule (SPL, $n=4$), R cingulate gyrus (CG, $n=4$), and the L

CG ($n=4$). See Supplementary Table 1 extended data for the detailed list of consistently predictive connections.

Using the same approach, we found that functional connectivity during symbolic number comparison did not predict children's composite reading skills ($r=0.245$, $P=0.183$, permutation $P=0.156$) or their full-scale IQ ($r=0.262$, $P=0.154$, permutation $P=0.138$).

Functional Connectivity During Non-symbolic Number Comparison Does Not Predict Children's Math Skills

During nonsymbolic number comparison, functional connectivity did not predict children's composite math score outside the scanner (Fig. 1; $r=0.154$, $P=0.407$, permutation test $P=0.237$). We also found that functional connectivity during nonsymbolic number comparison did not predict children's composite reading skills ($r=0.230$, $P=0.213$, permutation $P=0.152$) or their full-scale IQ ($r=-0.094$, $P=0.616$, permutation $P=0.561$). Thus, we found no evidence that whole-brain functional connectivity during nonsymbolic number comparison predicts children's math skills, reading skills, or IQ.

Functional Connectivity During Rest Predicts Children's Composite Math Skills

CPM revealed 6 positive and 38 negative consistent connections during resting state that together significantly predicted children's composite math scores (Fig. 1; $r=0.541$, Bonferroni-corrected $P=0.005$, permutation test $P=0.008$). The most common connections whose strength was positively correlated with children's math skills were between the visual and frontoparietal networks (33%). The region with the largest number of positively correlated connections was the R MFG ($n=3$). See Figure 3 for depictions of consistently predictive connections and their distribution across networks.

The most common connections whose strength was negatively correlated with children's math skills were within the frontoparietal network (13%) and between the frontoparietal and dorsal attention networks (13%). The regions with the largest number of negatively correlated connections were the R IFG ($n=10$), L IFG ($n=6$), L MFG ($n=6$), R MFG ($n=4$), R IPL ($n=5$), R insula ($n=5$), L inferior temporal gyrus (ITG, $n=5$), R ITG ($n=4$), R PrG ($n=5$),

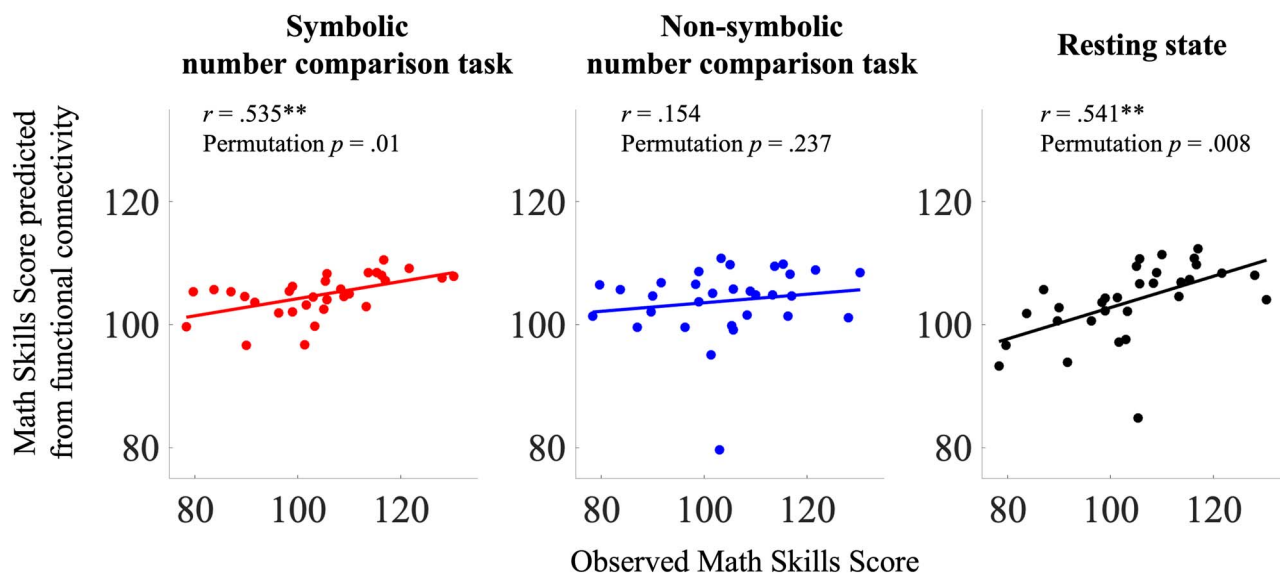


Figure 1. Connectome-based predictive model fits for each task. Scatter plots show the correlation between observed math skills scores outside the scanner and the math skills score predicted from functional connectivity during a given task. For each task separately, models were trained on connectivity data from $n - 1$ children and tested on the held-out child, n . Note that the CPM includes both positive and negative connections as separate terms in the GLM. Each model controls for age, IQ, and mean FD. $**P < 0.01$.

and L PrG ($n = 4$). See [Supplementary Table 2](#) extended data for the detailed list of consistently predictive connections.

Using the same approach, we found that functional connectivity during rest did not predict children's composite reading skills ($r = 0.191$, $P = 0.303$, permutation $P = 0.207$) or their full-scale IQ ($r = -0.238$, $P = 0.198$, permutation $P = 0.757$).

Predictive Connections Are Distinct across Different Tasks

So far, we have demonstrated that distributed sets of functional connections during symbolic number comparison and rest predict children's composite math scores. However, it is unclear whether the same or different connections are predictive of math skills across these task-states. Therefore, we identified consistent connections that negatively predicted children's math skills during more than one task and/or at rest.

We found only one connection, between the R CG and R insula, negatively correlated with children's math skills across both symbolic number comparison and rest. We found no positively correlated connections shared between symbolic number comparison and rest. Additionally, we found no connections whose relationship with children's math skills switched direction from one task to another (e.g. positively correlated during symbolic number comparison but negatively correlated during rest). The general lack of predictive connectivity overlap between tasks suggests math skills may be related to distinct patterns of cortical connectivity across different tasks.

Summary

Overall, we found that functional connectivity during symbolic number comparison and rest but not during

nonsymbolic number comparison, predicts children's math skills. Within the same task-state, we observed connections whose strength was positively correlated with children's math skills and those whose strength was negatively correlated with children's math skills. In both symbolic number comparison and resting state, we found more connections whose strength was negatively correlated with children's math skills than whose strength was positively correlated. During symbolic number comparison, we found that many of the negatively correlated connections were between the default mode and visual networks and between the default mode and dorsal attention networks. During rest, we found that many of the negatively correlated connections were within the frontoparietal network and between the frontoparietal and dorsal attention networks. Notably, these predictive connections were largely non-overlapping across task states.

Discussion

Here, we used CPM to show that functional connectivity during both symbolic number comparison and resting state predicts children's math skills. Each task revealed a largely distinct set of predictive connections distributed across canonical brain networks and major brain lobes. Most predictive connections were negatively correlated with children's math skills so that weaker connectivity predicted better math skills. Through the lens of canonical brain networks, most connections implicated the default mode, dorsal attention, and visual networks during symbolic number processing, and the frontoparietal and dorsal attention networks during resting state. Through the lens of individual brain regions, many predictive connections implicated key

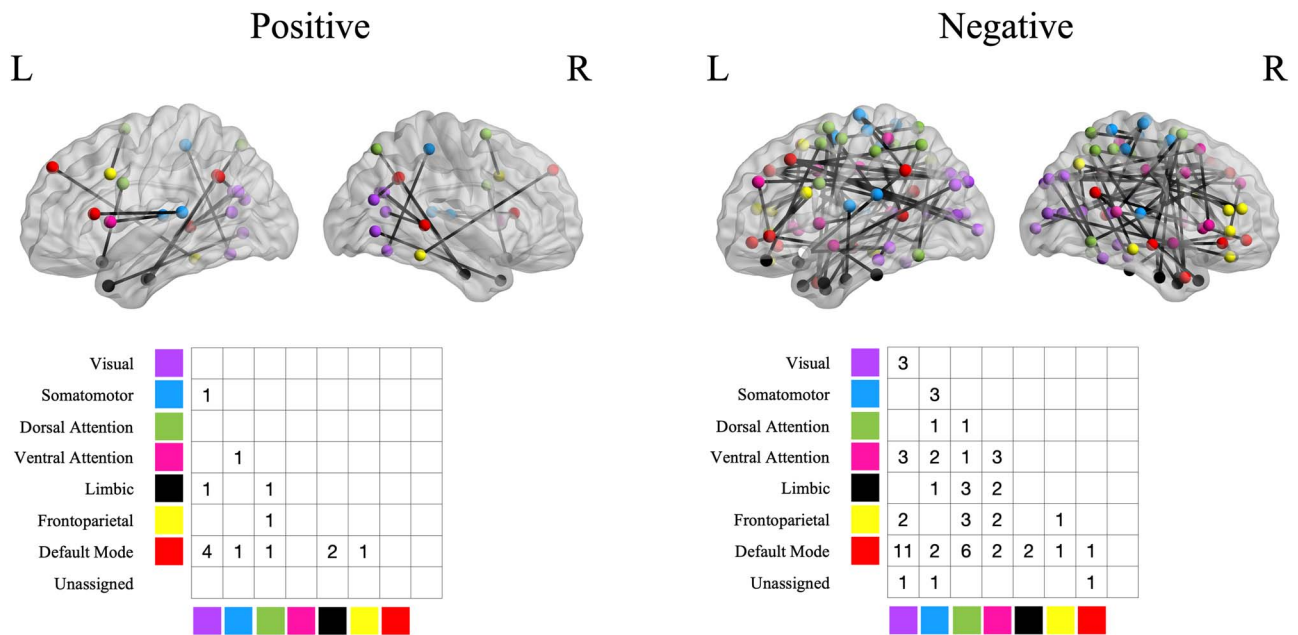


Figure 2. Connectome-based predictive model predicting math skills from functional connectivity during symbolic number comparison task. The left panel depicts connections with strengths that were positively correlated with children's math skills. The right panel depicts connections with strengths that were negatively correlated with children's math skills. Matrices represent the number of predictive connections within and between each canonical network as defined by Yeo et al. (2011). We display only consistent connections that correlated with math skills across all rounds of leave-one-out cross validation. Note that the CPM includes both positive and negative connections as separate terms in the GLM. Each model controls for age and mean FD.

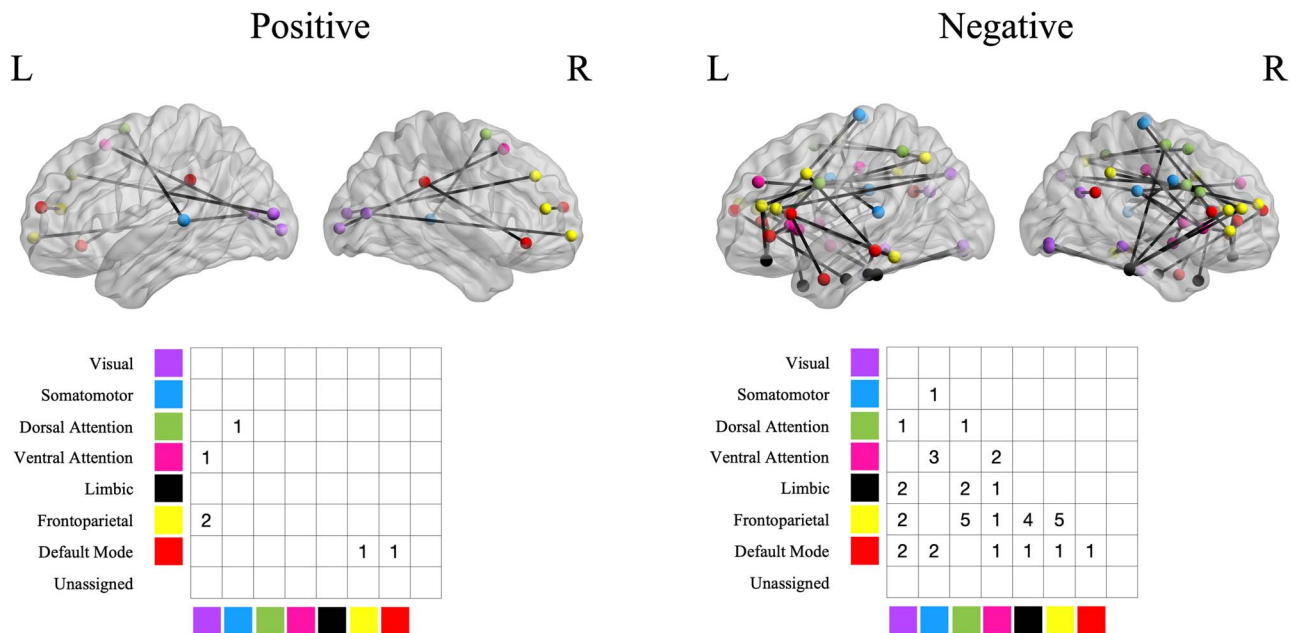


Figure 3. Connectome-based predictive model predicting math skills from functional connectivity during the resting-state. The left panel depicts connections with strengths that were positively correlated with children's math skills. The right panel depicts connections with strengths that were negatively correlated with children's math skills. Matrices represent the number of predictive connections within and between each canonical network as defined by Yeo et al. (2011). We display only consistent connections that correlated with math skills across all rounds of leave-one-out cross validation. Note that the CPM includes both positive and negative connections as separate terms in the GLM. Each model controls for age and mean FD.

regions typically associated with higher-order cognition and numerical processing, including among others, the IFG, MFG, IPL, and ITG.

This is first study to move beyond merely correlational measures of brain-behavior relationships and predict children's math skills from functional connectivity. The extant math-related functional connectivity literature

is "explanatory" rather than predictive. We are in no way suggesting that these approaches are not valuable. Descriptive and explanatory approaches have taught us much about the brain, development, and cognition, and continue to be valuable for answering certain types of questions. However, predicting individual differences in math skills is important to better inform educators and

clinicians about who may need intervention to remediate math skills across development. While our results suggest that a few minutes of resting-state fMRI data may be sufficient for predicting children's concurrent math skills, this is simply the foundation for constructing a generalizable model of functional connectivity that may eventually aide in predicting children's "future" math skills. It is important to note that in the current study children were in the third and fourth grades, a time when robust math skill differences begin to emerge (Jordan and Hanich 2003; Geary and Hoard 2005). Thus, it remains unclear whether this model will generalize to earlier points in development when there is less variability in individual differences in math skills. Future longitudinal studies should examine whether and "when" functional connectivity first becomes predictive of children's later math skills, which may in turn inform the timing of intervention for math disabilities.

Most work examining math-related functional connectivity identifies a few ROIs either functionally (e.g. activation across relevant task conditions) or anatomically (e.g. cytoarchitecturally) and then correlates activity patterns in each ROI with the rest of the brain (Park et al. 2014; Chang et al. 2016; Jolles et al. 2016; Battista et al. 2018; Nemmi et al. 2018; Price et al. 2018). This approach is valuable for initially identifying brain networks and circuits underlying math abilities. However, it also limits the scope of the functional connectivity space to only those connections with ROIs and makes it challenging to integrate findings because ROIs and the methods for defining them typically differ across studies. A few studies examine math-related connectivity among a circumscribed set of regions (Rosenberg-Lee et al. 2011; Emerson and Cantlon 2012; Zhang et al. 2019), but these regions are also inconsistent across studies. The current approach, which defines brain regions based on patterns of anatomical and functional connectivity (i.e. Brainnetome atlas) (Fan et al. 2016), effectively expands on the multiple ROI approach to consider connections between all brain regions as potential predictors of children's math skills, allowing for the possibility of revealing connections related to math skills that were not previously considered or tested. To the extent that future studies adopt the current approach, examining functional connectivity between an agreed upon set of brain regions will facilitate integrating findings across the literature to identify points of reproducibility and novelty. Note, however, that it is possible that our chosen brain atlas may mask additional predictive power available from other connectivity configurations. Future work should compare several brain atlases to identify those that uncover the most predictive power, especially those that consider structural and functional differences across development.

To that end, our findings are broadly consistent with previous research showing that weaker frontal and parietal functional connectivity is correlated with

better math skills (Rosenberg-Lee et al. 2015; Jolles et al. 2016; Price et al. 2018; Zhao et al. 2019). Across symbolic number comparison and resting state, we found that weaker connectivity within and between key regions associated with numerical cognition include the IFG, SPL, IPL, and ITG (Arsalidou and Taylor 2011; Yeo et al. 2017) and is predictive of better math skills during symbolic number comparison and at rest. Within our canonical network definitions, subdivisions of these regions were distributed across several networks, including the frontoparietal, dorsal attention, ventral attention, and default mode networks. During rest, many of the negatively predictive connections were between the IFG, MFG, IPL, and ITG, which connected regions within the frontoparietal network and between the frontoparietal and dorsal attention networks. However, our whole-brain ROI approach also revealed that, during symbolic number comparison, many of the negatively predictive connections occurred between the MFG and occipital cortex, which connected the default mode and visual networks.

The current approach is limited in its ability to provide insights into the neural mechanisms underlying math skills. However, a benefit of the current approach is that we have identified sets of connections whose strength is either positively or negatively predictive of children's math skills, which allow us to make mechanistic predictions that can be tested in future work. Stronger connectivity between visual regions and those spanning the frontal and parietal lobes may reflect network integration and stronger attentional regulation of sensory processing regions. Weaker connectivity between key math-related and domain-general regions may reflect network segregation, regional specialization, and/or a reduction in the required level of cognitive engagement for higher math achievers. Moreover, that we found largely distinct sets of these connections across several task states that are thought to support math skills suggests that brain states underlying basic numerical processing may aid in children's higher order math skills. Thus, the current study points to task-dependent network integration and segregation among math-related regions and domain-general regions (e.g. visual cortex) as possible neural mechanisms supporting children's math skills. Of course, future experimental work is needed to confirm these predictions.

The current study is the first to examine the relation between math skills and both task-based and resting-state connectivity in the same cohort of children. Although we found that the precise cortical connections that predicted math skills largely differed between symbolic number comparison and resting state, it remains unclear whether subcortical connections and subcortical-cortical connections predict math skills across different task states. Nevertheless, the utility of task-based CPM remains crucial for insight to mechanistic questions. That is, children's math skills may

depend on state-dependent, rather than trait-dependent, patterns of distributed whole-brain functional connectivity patterns. Moreover, this task-dependent variability may explain the disparate findings across the extant literature regarding which specific regional connections correlate with math skills. Whether and how “changes” in connectivity across task demands predict children's math skills remains an open question. Future work needs to consider changes in connectivity strength as input to the CPM model rather than connectivity strength per se to determine how reconfigurations in state-dependent functional network architecture predict children's math skills.

The predictive capacity of functional connectivity during symbolic number comparison and at rest seems to be specific to math skills. That is, functional connectivity did not also predict children's reading skills or general cognitive ability. We were surprised to find that resting-state functional connectivity did not predict children's reading skills and general cognitive abilities. It is worth noting, however, that resting-state data were collected following two numerical comparison tasks and a flanker task. Children also previously visited the lab in which they completed a battery of math-related tasks. Therefore, we speculate that children's resting-state functional connectivity may contain residual patterns of connectivity related to numerical processing, decreasing the predictive power of these functional connections for predicting reading skill and general cognitive ability (e.g. [Tung et al. 2013](#)). Future work should explore the role of reading-related task states in predicting reading skills by collecting resting-state data directly following both reading- and math-related tasks and comparing the predictive capacity of these two resting-state scans.

The present study has several limitations that need to be addressed to further develop the current predictive model of brain connectivity for children's math skills. First, we have only provided evidence for internal validation. Future work will use the currently established model to predict children's math skills in a novel dataset to assess model generalizability and provide external validation ([Gabrieli et al. 2015](#)). The limited number of developmental numerical cognition studies and lack of large numerical cognition fMRI datasets limits our ability to conduct such external validation analyses. Second, our sample size is relatively small for modeling of individual differences; however, previous predictive models have been derived from small sample sizes and show promise in generalizing across samples (e.g. [Rosenberg et al. 2015](#)). Future work should ideally include larger samples ($N > 100$) to increase power and allow for more complex models to be fit ([Dubois and Adolphs 2016](#)) although there are of course logistical obstacles to collecting such large samples. Future iterations of large-scale neuroimaging studies such as the adolescent brain and cognitive development (ABCD) and human connectome project—development (HCP-D) studies should consider including measures of math and reading skills.

Including measures of academic skills in these large studies will also work to address the first limitation because large samples may be split into test and replication samples to provide internal and external validity. Finally, our data are cross-sectional and can only speak to the predictive power of functional connectivity for children's concurrent math skills. If predictive models of brain connectivity are to provide value in diagnosing and identifying children in need of early intervention for dyscalculia and other math-related developmental disorders, future work must leverage longitudinal data to predict children's future math skills from earlier functional connectivity, ideally before robust individual differences emerge.

Conclusions

Our findings demonstrate that weaker functional connectivity distributed across the whole brain and weaker connectivity between key math-related brain regions and between domain-general brain regions predicts better math skills in childhood. Critically, predictive connections largely differed between tasks, suggesting that children's math abilities may depend on state-dependent (rather than trait-dependent) patterns of functional connectivity that tap into different canonical networks according to the task-state. These findings provide a framework to compare findings across future studies and form a foundation for constructing a generalizable model of functional connectivity that may eventually aid in predicting children's future math skills.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

Funding

National Science Foundation (NSF) (1660816 to G.P.); NSF (1750213 to G.P.).

Notes

We thank members of the Numerical Brain Lab at Vanderbilt University for recruitment and testing. We also thank Benjamin Conrad and Darren Yeo for feedback on this project. Finally, we thank the children and families that trusted us and made this research possible. *Conflict of Interest:* We have no known conflicts of interest to disclose.

Data Availability

Processed data are available at <https://osf.io/b4uej/>.

References

- Arsalidou M, Taylor MJ. 2011. Is $2+2=4$? Meta-analyses of brain areas needed for numbers and calculations. *NeuroImage*. 54(3): 2382–2393. <https://doi.org/10.1016/j.neuroimage.2010.10.009>.
- Battista C, Evans TM, Ngoon TJ, Chen T, Chen L, Kochalka J, Menon V. 2018. Mechanisms of interactive specialization and emergence of functional brain circuits supporting cognitive development in children. *NPJ Sci Learn*. 3(1):1. <https://doi.org/10.1038/s41539-017-0017-2>.
- Bulthé J, Prinsen J, Vanderauwera J, Duyck S, Daniels N, Gillebert CR, Mantini D, Op de Beeck HP, De Smedt B. 2019. Multi-method brain imaging reveals impaired representations of number as well as altered connectivity in adults with dyscalculia. *NeuroImage*. 190(June 2018):289–302. <https://doi.org/10.1016/j.neuroimage.2018.06.012>.
- Chang TT, Metcalfe AWS, Padmanabhan A, Chen T, Menon V. 2016. Heterogeneous and nonlinear development of human posterior parietal cortex function. *NeuroImage*. 126:184–195. <https://doi.org/10.1016/j.neuroimage.2015.11.053>.
- Ciric R, Wolf DH, Power JD, Roalf DR, Baum GL, Ruparel K, Shinohara RT, Elliott MA, Eickhoff SB, Davatzikos C, et al. 2017. Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. *NeuroImage*. 154(March):174–187. <https://doi.org/10.1016/j.neuroimage.2017.03.020>.
- De Smedt B, Noël MP, Gilmore C, Ansari D. 2013. How do symbolic and non-symbolic numerical magnitude processing skills relate to individual differences in children's mathematical skills? A review of evidence from brain and behavior. *Trends Neurosci Educ*. 2(2):48–55. <https://doi.org/10.1016/j.tine.2013.06.001>.
- Dubois J, Adolphs R. 2016. Building a science of individual differences from fMRI. *Trends Cogn Sci*. 20(6):425–443. <https://doi.org/10.1016/j.tics.2016.03.014>.
- Emerson RW, Cantlon JF. 2012. Early math achievement and functional connectivity in the fronto-parietal network. *Dev Cogn Neurosci*. 2(Suppl 1):S139–S151. <https://doi.org/10.1016/j.dcn.2011.11.003>.
- Evans TM, Kochalka J, Ngoon TJ, Wu SS, Qin S, Battista C, Menon V. 2015. Brain structural integrity and intrinsic functional connectivity forecast 6 year longitudinal growth in children's numerical abilities. *J Neurosci*. 35(33):11743–11750. <https://doi.org/10.1523/JNEUROSCI.0216-15.2015>.
- Fan L, Li H, Zhuo J, Zhang Y, Wang J, Chen L, Yang Z, Chu C, Xie S, Laird AR, et al. 2016. The human Brainnetome atlas: a new brain atlas based on connectional architecture. *Cereb Cortex*. 26(8):3508–3526. <https://doi.org/10.1093/cercor/bhw157>.
- Finn ES, Scheinost D, Finn DM, Shen X, Papademetris X, Constable RT. 2017. Can brain state be manipulated to emphasize individual differences in functional connectivity? *NeuroImage*. 160(March): 140–151. <https://doi.org/10.1016/j.neuroimage.2017.03.064>.
- Gabrieli JDE, Ghosh SS, Whitfield-Gabrieli S. 2015. Prediction as a humanitarian and pragmatic contribution from human cognitive neuroscience. *Neuron*. 85(1):11–26. <https://doi.org/10.1016/j.neuron.2014.10.047>.
- Geary DC, Hoard MK. 2005. Learning disabilities in arithmetic and mathematics: theoretical and empirical perspectives. In: Campbell JIDeditor. *The handbook of mathematical cognition*. New York, NY: Psychology Press, p. 253–267. <https://doi.org/10.4324/9780203998045-24>.
- Gebuis T, Reynvoet B. 2011. Generating nonsymbolic number stimuli. *Behav Res Methods*. 43(4):981–986. <https://doi.org/10.3758/s13428-011-0097-5>.
- Geerligs L, Rubinov M, Tyler LK, Brayne C, Bullmore ET, Calder AC, Cusack R, Dalgleish T, Duncan J, Henson RN, et al. 2015. State and trait components of functional connectivity: individual differences vary with mental state. *J Neurosci*. 35(41):13949–13961. <https://doi.org/10.1523/JNEUROSCI.1324-15.2015>.
- Hagler DJ, Saygin AP, Sereno MI. 2006. Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. *NeuroImage*. 33(4):1093–1103. <https://doi.org/10.1016/j.neuroimage.2006.07.036>.
- Jolles D, Supekar K, Richardson J, Tenison C, Ashkenazi S, Rosenberg-Lee M, Fuchs L, Menon V. 2016. Reconfiguration of parietal circuits with cognitive tutoring in elementary school children. *Cortex*. 83:231–245. <https://doi.org/10.1016/j.cortex.2016.08.004>.
- Jordan NC, Hanich LB. 2003. Characteristics of children with moderate mathematics deficiencies: a longitudinal perspective. *Learn Disabil Res Pract*. 18(4):213–221. <https://doi.org/10.1111/1540-5826.00076>.
- Kaufman AS, Kaufman NL. 2004. *Kaufman brief intelligence test*. 2nd ed. Circle Pines, MN: American Guidance Service.
- Lyons IM, Price GR, Vaessen A, Blomert L, Ansari D. 2014. Numerical predictors of arithmetic success in grades 1–6. *Dev Sci*. 17(5): 714–726. <https://doi.org/10.1111/desc.12152>.
- Meissner TW, Walbrin J, Nordt M, Koldewyn K, Weigelt S. 2020. Head motion during fMRI tasks is reduced in children and adults if participants take breaks. *Dev Cogn Neurosci*. 44:100803. <https://doi.org/10.1016/j.dcn.2020.100803>.
- Nemmi F, Schel MA, Klingberg T. 2018. Connectivity of the human number form area reveals development of a cortical network for mathematics. *Front Hum Neurosci*. 12(November):1–15. <https://doi.org/10.3389/fnhum.2018.00465>.
- Park J, Park DC, Polk TA. 2013. Parietal functional connectivity in numerical cognition. *Cereb Cortex*. 23(9):2127–2135. <https://doi.org/10.1093/cercor/bhs193>.
- Park J, Li R, Brannon EM. 2014. Neural connectivity patterns underlying symbolic number processing indicate mathematical achievement in children. *Dev Sci*. 17(2):187–202. <https://doi.org/10.1111/desc.12114>.
- Price GR, Fuchs LS. 2016. The mediating relation between symbolic and nonsymbolic foundations of math competence. *PLoS One*. 11(2):1–14. <https://doi.org/10.1371/journal.pone.0148981>.
- Price GR, Yeo DJ, Wilkey ED, Cutting LE. 2018. Prospective relations between resting-state connectivity of parietal subdivisions and arithmetic competence. *Dev Cogn Neurosci*. 30:280–290. <https://doi.org/10.1016/j.dcn.2017.02.006>.
- Rosenberg MD, Finn ES, Scheinost D, Papademetris X, Shen X, Constable RT, Chun MM. 2015. A neuromarker of sustained attention from whole-brain functional connectivity. *Nat Neurosci*. 19(1): 165–171. <https://doi.org/10.1038/nn.4179>.
- Rosenberg MD, Casey BJ, Holmes AJ. 2018. Prediction complements explanation in understanding the developing brain. *Nat Commun*. 9(1):1–13. <https://doi.org/10.1038/s41467-018-02887-9>.
- Rosenberg-Lee M, Barth M, Menon V. 2011. What difference does a year of schooling make?. Maturation of brain response and connectivity between 2nd and 3rd grades during arithmetic problem solving. *NeuroImage*. 57(3):796–808. <https://doi.org/10.1016/j.neuroimage.2011.05.013>.
- Rosenberg-Lee M, Ashkenazi S, Chen T, Young CB, Geary DC, Menon V. 2015. Brain hyper-connectivity and operation-specific deficits during arithmetic problem solving in children with developmental dyscalculia. *Dev Sci*. 18(3):351–372. <https://doi.org/10.1111/desc.12216>.

- Satterthwaite TD, Ciric R, Roalf DR, Davatzikos C, Bassett DS, Wolf DH. 2019. Motion artifact in studies of functional connectivity: characteristics and mitigation strategies. *Hum Brain Mapp.* 40(7):2033–2051. <https://doi.org/10.1002/hbm.23665>.
- Ségonne F, Pacheco J, Fischl B. 2007. Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Trans Med Imaging.* 26(4):518–529. <https://doi.org/10.1109/TMI.2006.887364>.
- Shen X, Finn ES, Scheinost D, Rosenberg MD, Chun MM, Papademetris X, Constable RT. 2017. Using connectome-based predictive modeling to predict individual behavior from brain connectivity. *Nat Protoc.* 12(3):506–518. <https://doi.org/10.1038/nprot.2016.178>.
- Tung KC, Uh J, Mao D, Xu F, Xiao G, Lu H. 2013. Alterations in resting functional connectivity due to recent motor task. *NeuroImage.* 78:316–324. <https://doi.org/10.1016/j.neuroimage.2013.04.006>.
- Whitfield-Gabrieli S, Nieto-Castanon A. 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect.* 2(3):125–141. <https://doi.org/10.1089/brain.2012.0073>.
- Wilkey ED, Price GR. 2019. Attention to number: the convergence of numerical magnitude processing, attention, and mathematics in the inferior frontal gyrus. *Hum Brain Mapp.* 40(3):928–943. <https://doi.org/10.1002/hbm.24422>.
- Woodcock RW, McGrew KS, Mather N. 2001. *Woodcock-Johnson III test*. Itasca, IL: Riverside Publishing.
- Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zöllei L, Polimeni JR, et al. 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol.* 106(3):1125–1165. <https://doi.org/10.1152/jn.00338.2011>.
- Yeo DJ, Wilkey ED, Price GR. 2017. The search for the number form area: a functional neuroimaging meta-analysis. *Neurosci Biobehav Rev.* 78(January):145–160. <https://doi.org/10.1016/j.neubiorev.2017.04.027>.
- Zhang H, Wee CY, Poh JS, Wang Q, Shek LP, Chong YS, Fortier MV, Meaney MJ, Broekman BFP, Qiu A. 2019. Fronto-parietal numerical networks in relation with early numeracy in young children. *Brain Struct Funct.* 224(1):263–275. <https://doi.org/10.1007/s00429-018-1774-2>.
- Zhao H, Li X, Karolis V, Feng Y, Niu H, Butterworth B. 2019. Arithmetic learning modifies the functional connectivity of the fronto-parietal network. *Cortex.* 111:51–62. <https://doi.org/10.1016/j.cortex.2018.07.016>.