Predicting children's math skills from task-based and resting-state functional brain connectivity

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Abstract

A critical goal of cognitive neuroscience is to predict behavior from neural structure and function, thereby providing crucial insight 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_{age} = 9.21 years, 14 Female). Overall, we found that functional connectivity during symbolic number comparison and rest, but not during non-symbolic 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, such that weaker connectivity predicted better math skills. Notably, these predictive connections were largely non-overlapping 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, math, functional connectivity, predictive modeling

A critical goal of cognitive neuroscience is to *predict* behavior from neural structure and function (Gabrieli et al., 2015; Rosenberg et al., 2018). 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 proven useful in predicting attention deficit hyperactivity disorder severity 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 providing insight 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.

The extant functional connectivity literature shows that individual's math skills are correlated with functional connectivity strength 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 & Taylor, 2011; D. J. Yeo et al., 2017). Subdivisions of these regions are distributed across several canonical networks, including the Frontoparietal, Dorsal Attention and Ventral Attention networks (B. T. Yeo et al., 2011), suggesting 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 (Battista et al., 2018; Park et al., 2013), 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 1st grade is associated with children's calculation skills in 2nd grade (Price et al., 2018). Across childhood, stronger resting-state connectivity between temporooccipital and frontal, and 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 *both stronger and weaker* functional connectivity supports 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 (Finn et al., 2017; Geerligs et al., 2015). It is, yet, unclear whether patterns of functional connectivity differentially predict children's math skills during different numerical processing tasks. If the same connectivity profile predicts math skills across tasks, 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 states predict math skills, it may reflect a flexibility in network organization across tasks 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 non-symbolic 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 5 children that completed the neuroimaging visit were removed from analyses due to excessive motion during resting-state (more than half of scan volumes contaminated). The current sample partially overlaps with a previously published sample (Wilkey & Price, 2019), from which we include only children whom completed both symbolic and non-symbolic 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 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 III (WJ-III) (Woodcock et al., 2001) and the Kaufman Brief Intelligence Test, second edition (KBIT) (Kaufman & Kaufman, 2004). We derived separate composite math and reading scores from the WJ-II 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 where 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 where 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-minute timed task where 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 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 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 non-verbal IQ. Verbal IQ is measured using picture-based vocabulary and riddles, and non-verbal IQ is measured using matrix reasoning questions.

Neuroimaging Visit

Symbolic and Non-symbolic Number Comparison Tasks. We instructed children to lay motionless while they completed a symbolic and non-symbolic number comparison task during fMRI scanning. We counterbalanced symbolic and non-symbolic number comparison tasks across

all participants. We asked participants to indicate which of two simultaneously presented Arabic digits (symbolic) or sets of dots (non-symbolic) 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 1250ms followed by a fixation line for 3250ms to 6250ms (1000ms steps, *M* = 4750ms). Performance on both the symbolic (M = 91.7%, SD = 5.8%) and non-symbolic 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 to 0.375) to larger and harder (0.625 to 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 non-symbolic number comparison task stimulus "size" was measured by convex hull, total surface area and dot diameter (Gebuis & 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 3T 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: TR = 8.929 s; TE = 4.61 ms; flip angle = 8°; 170 sagittal slices with no inter-slice gap; voxel size = 1 × 1 × 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, echo planar imaging pulse sequence in the axial plane with the following parameters: Slices = 40; Repetition Time (TR) = 2000 ms; Echo Time (TE) = 25 ms; voxel size = 2.5 × 2.5 × 3 mm with an inter-slice gap of 0.25 mm; field of view = 240 × 129.75 × 240 mm; imaging matrix = 96 × 96; flip angle = 90°; SENSE factor = 2.5. Symbolic and non-symbolic task scans were approximately 9 minutes in total (4.5 minutes per run), and the resting scan was approximately 7.5 minutes.

We preprocessed images using FreeSurfer v7.1.1 (Ségonne et al., 2007) and the CONN Toolbox v20 (Whitfield-Gabrieli & 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 grey matter and white matter segmentations edited 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 subsequently corrected for slice-timing. Then, we co-registered each child's functional images to their anatomical image using non-linear registration and then resampled to children's FreeSurfer structural cortical surface. Finally, we smoothed surface data using iterative spatial diffusion smoothing with 40 iterations to approximate 8mm FWHM kernel (Hagler et al., 2006).

Following preprocessing, we employed nuisance regression to correct for in-scanner motion and remove task activation effects using CONN Toolbox for SPM. We included the following parameters: 1) first 5 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<0.09Hz) functional surface data.

We also explored the impact of two additional motion-correction approaches: motion censoring ("scrubbing") (DVARS > 3 deg and/or FD > 0.5mm) and timeseries despiking *prior to regression*. We found that timeseries despiking, rather than motion censoring, resulted in a better improvement of the relation between functional connectivity values and quality control (QC) measures (*i.e.,* max motion). 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 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 by 210 functional connectivity matrix. These child-level *z-score* connectivity matrices were then submitted to subsequent analyses. See Supplementary Figure 1 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, non-symbolic number comparison, and resting state (eyes open). CPM employs leave-one-out cross-validation (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 ($p < .01$), 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 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.

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

Variable (N = 31)	*M*	*SD*	*Min*	*Max*	1.	2.	3.	4.	5.	6.
1. Age	9.21	0.65	8.24	10.67						
2. Math Skills	103.98	13.07	78.33	130.33	-.234					
3. Reading Skills	107.97	11.36	82.50	127.50	-.010	.617***				
4. FSIQ	114.32	15.65	73.00	140.00	-.089	.56**	.838***			
5. Symbolic Mean FD	0.33	0.28	0.09	1.25	-.051	-.257	-.456*	-.335		
6. Non-Symbolic Mean FD	0.27	0.20	0.09	0.82	-.271	-.165	-.496**	-.209	.407*	
7. Rest Mean FD	0.33	0.27	0.08	1.07	-.039	-.274	-.451*	-.200	.749***	.484**

*p < .05; **p < .01; ***p < .001

Connectome-based Predictive Modeling

We used CPM to determine whether functional connectivity during each task separately (*i.e.,* symbolic, non-symbolic, 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 likely that different sets of connections predict children's composite math skills across different LOOCV rounds. To characterize which functional connections *consistently* predicted children's composite math skills, 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.

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.

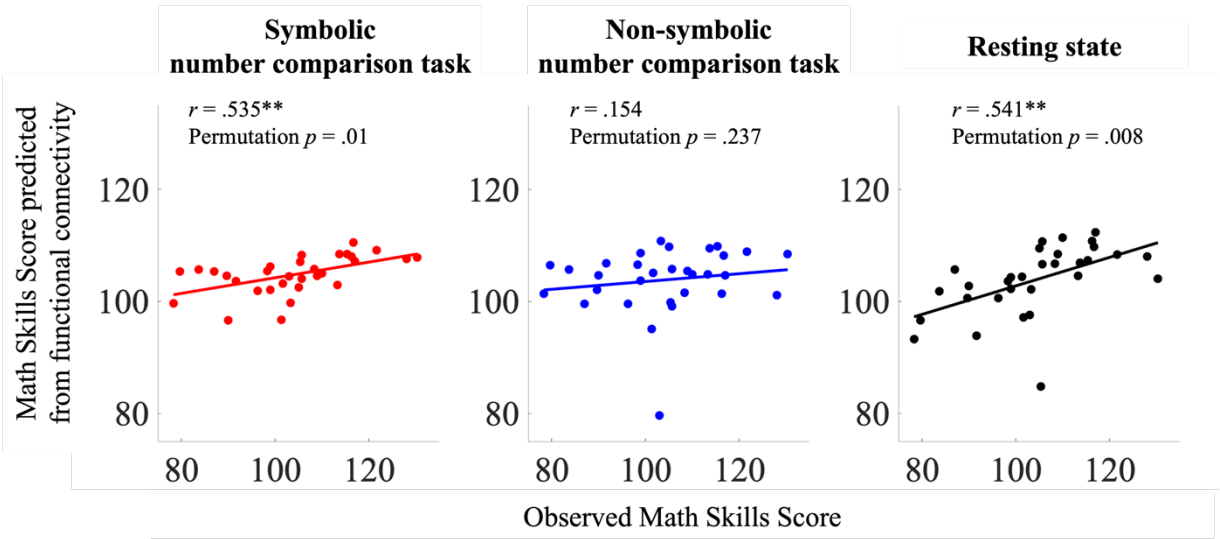

Figure 1. Connectome-based predictive models fit for each task. Scatter plots show the correlation between observed math skills scores outside the scanner and the math skills score predicted from functional connectivity during a given task. For each task separately, models were trained on connectivity data from $n - 1$ children and tested on the held-out child. 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. $^{**}p < .01$

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 (Figure 1; r = .535, Bonferroni-corrected p = .006, permutation p = .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), Left 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

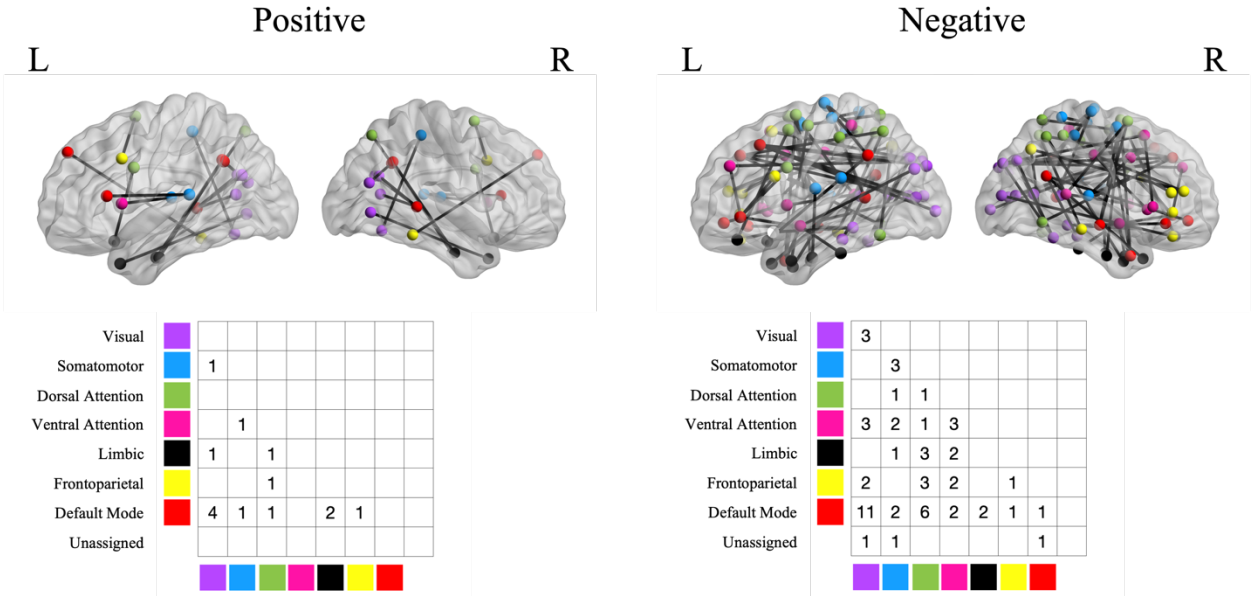

Figure 2. Connectome-based predictive model predicting math skills from functional connectivity during symbolic number comparison task. The left panel depicts connections with strengths that were positively correlated with children's math skills. The right panel depicts connections with strengths that 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.

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 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 = .245, p = .183, permutation p = .156) or their full-scale IQ (r = .262, p = .154, permutation p = .138).

Functional connectivity during non-symbolic number comparison does not predict children's math skills

During non-symbolic number comparison, functional connectivity did not predict children' composite math score outside the scanner (Figure 1; r = .154, p = .407, permutation test p = .237). We also found that functional connectivity during non-symbolic number comparison did not predict children's composite reading skills (r = .230, p = .213, permutation p = .152) or their full-scale IQ (r = -.094, p = .616, permutation p = .561). Thus, we found no evidence that whole-brain functional connectivity during non-symbolic 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 (Figure 1; r = .541, Bonferroni-corrected p = .005, permutation test p = .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 Middle Frontal Gyrus (n = 3). 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), and L PrG (n = 4). See Supplementary Table 2 extended data for detailed list of consistently predictive connections.

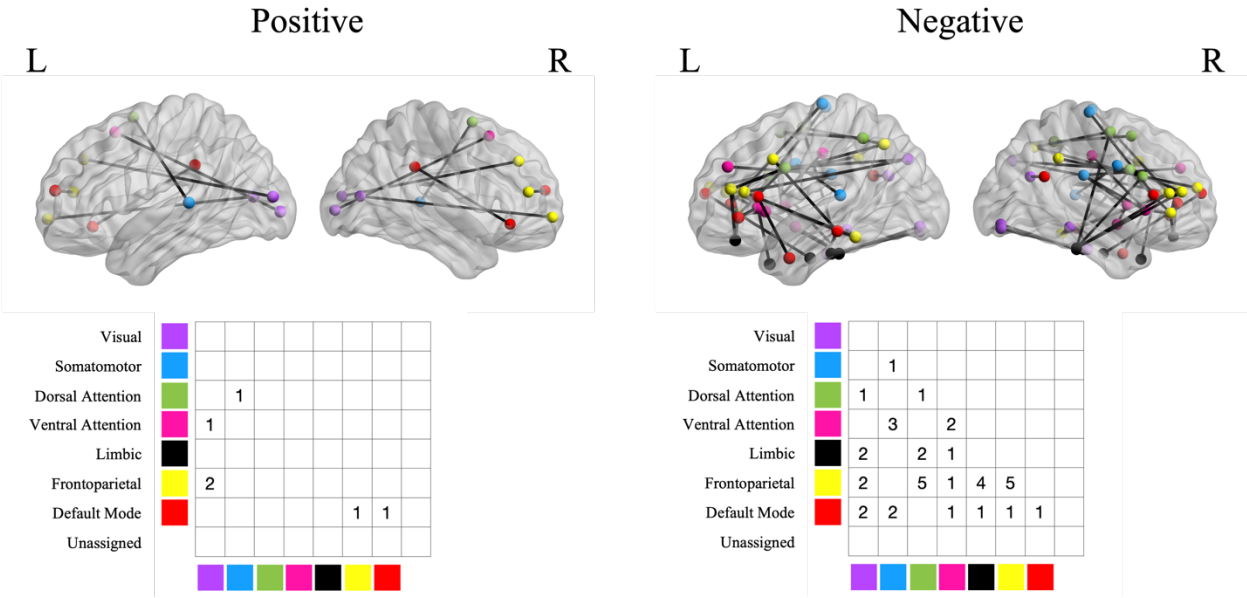

Figure 3. Connectome-based predictive model predicting math skills from functional connectivity during resting-state. The left panel depicts connections with strengths that were positively correlated with children's math skills. The right panel depicts connections with strengths that were negatively 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.

Using the same approach, we found that functional connectivity during rest did not predict children's composite reading skills (r = .191, p = .303, permutation p = .207) or their full-scale IQ (r = -.238, p = .198, permutation p = .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 cingulate gyrus 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 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 connectivity across different tasks.

Summary

Overall, we found that functional connectivity during symbolic number comparison and rest, but not during non-symbolic 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 were 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, such 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 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 3rd grade, a time when robust math skills differences begin to emerge (Geary & Hoard,

2005; Jordan & Hanich, 2003). 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 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 regions of interest (ROIs) either functionally (e.g., activation across relevant task conditions) or anatomically (e.g., cytoarchitectonically) then correlates activity patterns in each ROI with the rest of the brain (Battista et al., 2018; Chang et al., 2016; Jolles et al., 2016; Nemmi et al., 2018; Park et al., 2014; 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 an 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 (Emerson & Cantlon, 2012; Rosenberg-Lee et al., 2011; 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 (Jolles et al., 2016; Price et al., 2018; Rosenberg-Lee et al., 2015; 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 & Taylor, 2011; D. J. Yeo et al., 2017) 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. Weaker connectivity within and between these regions may reflect network segregation, regional specialization, and/or a reduction in the required level of cognitive engagement for higher math achievers. Our findings show that in addition to connectivity with regions commonly associated with math skills, additional domain general regions (e.g., visual cortex) may also be important for math skills.

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. Given that the precise

connections that predicted math skills largely differed between symbolic number comparison and resting state, 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. However, it remains unclear whether and how *changes* in connectivity across task demands predict children's math skills. 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 task and comparing the predictive capacity of these two resting-state scans.

While our current approach moves toward predicting children's math skills across several tasks, there are several limitations. First, 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 & Adolphs, 2016), although of course there are logistical obstacles to collecting such large samples. Second, we have only provided evidence for internal validation using leave-one-out cross-validation. While this provides protection against detecting false positives, the gold standard for model generalizability is external validation to a separate data set. The limited number of developmental numerical cognition studies and lack of large numerical cognition fMRI dataset limits out ability to conduct external validation analyses. Future work will use the currently established model to predict children's math skills in a novel data set. Finally, our data are cross-sectional and can only speak to the predictive power of functional connectivity for children's concurrent math skills. Future work will 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 grain regions predicts better math skills in childhood. Critically, predictive connections largely differed between tasks, suggesting 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 the foundation for constructing a generalizable model of functional connectivity that may eventually aid in predicting children's future math skills.

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