



## PAPER

# Neural connectivity patterns underlying symbolic number processing indicate mathematical achievement in children

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## Abstract

*In early childhood, humans learn culturally specific symbols for number that allow them entry into the world of complex numerical thinking. Yet little is known about how the brain supports the development of the uniquely human symbolic number system. Here, we use functional magnetic resonance imaging along with an effective connectivity analysis to investigate the neural substrates for symbolic number processing in young children. We hypothesized that, as children solidify the mapping between symbols and underlying magnitudes, important developmental changes occur in the neural communication between the right parietal region, important for the representation of non-symbolic numerical magnitudes, and other brain regions known to be critical for processing numerical symbols. To test this hypothesis, we scanned children between 4 and 6 years of age while they performed a magnitude comparison task with Arabic numerals (numerical, symbolic), dot arrays (numerical, non-symbolic), and lines (non-numerical). We then identified the right parietal seed region that showed greater blood-oxygen-level-dependent signal in the numerical versus the non-numerical conditions. A psychophysiological interaction method was used to find patterns of effective connectivity arising from this parietal seed region specific to symbolic compared to non-symbolic number processing. Two brain regions, the left supramarginal gyrus and the right precentral gyrus, showed significant effective connectivity from the right parietal cortex. Moreover, the degree of this effective connectivity to the left supramarginal gyrus was correlated with age, and the degree of the connectivity to the right precentral gyrus predicted performance on a standardized symbolic math test. These findings suggest that effective connectivity underlying symbolic number processing may be critical as children master the associations between numerical symbols and magnitudes, and that these connectivity patterns may serve as an important indicator of mathematical achievement.*

## Introduction

In most human cultures, children acquire a verbal count list and learn to identify written symbols for number. The capacity for count lists and symbolic mathematics is uniquely human, and its acquisition takes place slowly over human development (Fuson, 1988; Spelke & Kinzler, 2007; Wynn, 1992). One part of this developmental process includes associating, or mapping, acquired written number symbols (e.g. Arabic numerals) with evolutionarily and developmentally primitive non-verbal numerical magnitude representations (Feigenson, Dehaene & Spelke, 2004; Gallistel & Gelman, 1992).

The classic evidence for such a mapping is the symbolic numerical distance effect (Moyer & Landauer,

1967). When asked to compare two Arabic digits, participants take more time to make correct judgments when the numbers are numerically closer than when they are more distant. This pattern mirrors the numerical distance and ratio effects of non-symbolic numbers (i.e. those that are presented in dot arrays instead of digits), suggesting that Arabic digit comparison involves mapping the symbols onto their analog magnitudes and then comparing those non-symbolic magnitude representations. Children as young as 5 years of age show the symbolic distance effect, implying that this symbol-to-number mapping begins early in childhood (Duncan & McFarland, 1980; Sekuler & Mierkiewicz, 1977; Temple & Posner, 1998). Yet, children do not typically show numerical Stroop effects, whereby numerical values

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interfere with judging the physical size of two Arabic numerals, until about 7 years of age (Gebuis, Cohen Kadosh, de Haan & Henik, 2009; Girelli, Lucangeli & Butterworth, 2000; Rubinsten, Henik, Berger & Shahar-Shalev, 2002). This suggests that automaticity in associations between numerical symbols and magnitude representation emerges in this developmental window between 4 and 7.

How does the developing brain support symbol to magnitude associations? In this study, we evaluate the hypothesis that symbolic number acquisition, the process of mapping numerical symbols to their corresponding numerical magnitude representations, is subserved by communication between the neural systems that support numerical magnitude representations and other neural systems critical for symbolic number processing.

Research on the neural basis of the nonverbal numerical magnitude system implicates the parietal cortex, in and around the intraparietal sulcus (for reviews see Ansari, 2008; Nieder & Dehaene, 2009). For example, passive viewing adaptation studies in adults show that these parietal regions are selectively sensitive to changes in numerical magnitude (Jacob & Nieder, 2009; Piazza, Izard, Pinel, Le Bihan & Dehaene, 2004). Similar results are found in the developing brain and appear to be right lateralized. Event-related potentials in 3-month-old infants show sensitivity to changes in the number of dots in a visual array (i.e. numerosity) in right frontoparietal electrodes (Izard, Dehaene-Lambertz & Dehaene, 2008). Functional near-infrared spectroscopy measured in 6-month-olds shows right, but not left, parietal sensitivity to changes in numerosity (Hyde, Boas, Blair & Carey, 2010). Functional magnetic resonance imaging in 4-year-olds shows predominantly right parietal activation in response to changes in numerosity (Cantlon, Brannon, Carter & Pelphrey, 2006). These findings collectively suggest that the right parietal cortex is the primary brain region for the primitive number system.

Numerous neuroimaging studies in adults report that the parietal cortex is also recruited during symbolic number processing (e.g. Cohen Kadosh, Cohen Kadosh, Kaas, Henik & Goebel, 2007; Eger, Sterzer, Russ, Giraud & Kleinschmidt, 2003; Holloway, Price & Ansari, 2010; Piazza, Pinel, Le Bihan & Dehaene, 2007). Given that numerical symbols automatically evoke magnitude representations and given that newly learned symbol systems may exploit evolutionarily older neural circuits for processing number (Anderson, 2010; Dehaene & Cohen, 2007), it is plausible that symbolic and non-symbolic number processing share a common neural circuitry. Yet, other brain regions, such as the left ventral parietal cortex, show more selective involvement during

symbolic number processing. In particular, cortical stimulation in the left supramarginal gyrus (SMG) disrupts reading of Arabic numerals (Roux, Lubrano, Lauwers-Cances, Giussani & Demonet, 2008), and a patient with a lesion in the SMG was selectively impaired on symbolic but not non-symbolic numerical magnitude processing (Polk, Reed, Keenan, Hogarth & Anderson, 2001). Other neuroimaging studies have also shown left angular gyrus (AG) involvement during Arabic digit processing (Holloway *et al.*, 2010; G.R. Price & Ansari, 2011). In addition, some studies show frontal cortex involvement in symbolic number processing. After intensive training on the association between Arabic digits and dot arrays, prefrontal neurons, but not parietal neurons, in rhesus monkeys exhibited tuning to the same numerical values for numerosities and their associated symbols (Diester & Nieder, 2007). Along with neuroimaging findings showing greater symbolic distance effects in the precentral and inferior frontal gyrus (IFG) in children (Ansari, Garcia, Lucas, Hamon & Dhital, 2005; Kaufmann, Koppelstaetter, Siedentopf, Haala, Haberlandt, Zimmerhackl, Felber & Ischebeck, 2006), these findings have raised a possibility that prefrontal regions might mediate symbolic number learning.

Based on these findings, we hypothesized that, in brains that are actively establishing symbol-to-number mapping, symbolic number processing triggers neural communication between the right parietal cortex, the primary brain region for the primitive number system, and brain regions such as the left SMG/AG or the IFG, which show selective involvement in symbolic numerical thinking. We used functional magnetic resonance imaging (fMRI) with an effective connectivity approach (using psychophysiological interaction, or PPI, analysis) to test this hypothesis in children between 4.5 and 6.5 years of age. We selected children in this age range because they show understanding of numerical symbols (e.g. Duncan & McFarland, 1980; Temple & Posner, 1998), but their mapping process still seems to be solidifying (Gebuis, Cohen Kadosh, de Haan & Henik, 2009; Girelli *et al.*, 2000; Rubinsten *et al.*, 2002). The PPI analysis (Friston, Buechel, Fink, Morris, Rolls & Dolan, 1997; Gitelman, Penny, Ashburner & Friston, 2003) enables the assessment of effective connectivity, a modulation of the contribution of one brain region to another by a psychological context. In the current study, this approach was used to identify effective connectivity patterns specific to symbolic number processing as opposed to non-symbolic number processing (for examples in the numerical cognition studies, see Dormal, Dormal, Joassin & Pesenti, 2011; Park, Park & Polk, 2013).

Children compared the magnitude of two Arabic numerals, two sets of dot arrays, or two vertical lines

in an event-related design while undergoing fMRI scanning. In our first analysis, we identified right parietal activation selective to numerical stimuli (numerals and dots) compared to non-numerical stimuli (lines), replicating and extending previous studies. Then, using a PPI analysis, we looked for brain regions in which the contribution of the right parietal seed activity was modulated by whether the child processed symbolic versus non-symbolic number (i.e. effective connectivity from the seed to a target region underlying symbolic number processing). In particular, we expected significant effective connectivity from the right parietal seed to the left SMG/AG and IFG. Finally, we asked whether such effective connectivity has developmental implications by testing whether the degree of effective connectivity correlated with age and/or mathematical achievement.

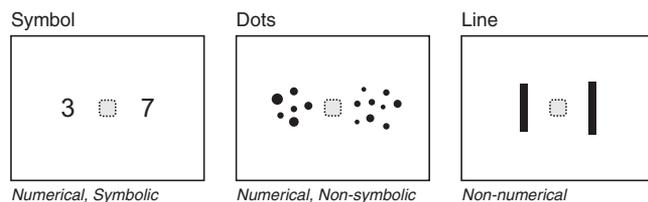
## Materials and methods

### Participants

Forty-one typically developing children between 4.5 and 6.5 years of age were recruited to participate. Five children were unable to either start or complete the study. An additional 15 children were excluded due to excessive motion ( $> 3.5$  mm [size of a voxel] of any translational or 3.5 degrees of any rotational movement during the two 7-minute runs). The remaining 21 children ( $N = 21$ ; 12 female; ages from 4.82 to 6.59 with mean age of 5.55) were included in the final analyses. Children were all right-handed by parental report. Parents provided written consent to a protocol approved by Duke University Institutional Review Board before their children's participation.

### Stimuli and task

Participants were asked to compare the magnitude of two stimuli presented side-by-side and equidistant from a cartoon character on the center of the screen. The two stimuli were from one of three categories: symbol, dot array, or line (Figure 1). Background color was black,



**Figure 1** Examples of the stimuli. A cartoon character was displayed as a fixation point in the center of the screen.

and stimuli color was constant within each trial but was randomized across trials to maintain children's engagement. The visual angle from the center of the screen to the center of one of the items was approximately 7 degrees. Children were instructed to press a button under their right thumb if they thought the item on the right side represented a larger magnitude and a button under their left thumb if they thought the item on the left side represented a larger magnitude. The three trial types were randomized in an event-related design.

In the symbol condition, two Arabic numerals ranging from 1 to 9 were presented on each trial. Half of the trials (i.e. *far* trials) had a numerical distance between the two numbers equal to or greater than four (1–5, 2–7, 3–7, 4–9, 5–9, and 2–8) and the other half (i.e. *close* trials) had a numerical distance equal to two (1–3, 2–4, 3–5, 5–7, 6–8, and 7–9). The font face was Arial, and the font size was constant within a trial but was randomized across trials from 56 to 97 points.

In the dots condition, two sets of dot arrays ranging from 4 to 18 were presented on each trial. On half of the trials (i.e. *far* trials), the ratio between the two numerosities was 1:3, and on the other half (i.e. *close* trials), the ratio was 2:3. These numerical ratios were determined based on a pilot study in which the behavioral performance at these ratios was roughly equated to those of the symbol condition. In order to discourage reliance on continuous variables, average dot size was equated between the two arrays on half of the trials, and the total surface area was equated on the other half. In addition, individual dot size was varied within a dot array in order to discourage making judgments solely on the size of the dots.

In the line condition, two vertical lines ranging in length from 76 to 399 pixels with a width of 31 pixels were presented on each trial. On half of the trials (i.e. *far* trials), the ratio between the two line lengths was 4:5, and on the other half (i.e. *close* trials), the ratio was 6:7. These ratios were again determined based on a pilot study to roughly equate behavioral performance across the symbol, dots, and line conditions. The vertical position of each line was jittered to discourage making the comparison solely based on the relative positions of one end of the lines. This line condition served as a control condition for the numerical (i.e. symbol and dots) conditions, as children were making the same magnitude comparison judgment but with non-numerical stimuli.

All visual stimuli were presented via Psychtoolbox (version 3.0.9) running on MATLAB (R2010a) displayed by a back-projection system. Non-differential auditory feedback was delivered through headphones when the participant made a button press.

### Experimental paradigm

The experiment consisted of two 7-minute runs in an event-related fMRI paradigm. Each run consisted of a total of 72 trials, with 24 trials of each of the three conditions presented in a random order. On each trial, a cartoon character appeared in the center of the screen for 200 ms to cue the presentation of the stimuli. The stimuli were presented for 2 seconds, followed by a variable intertrial interval ranging from 3 to 9 seconds. The cartoon character was replaced with a white square at the offset of the stimuli if a button press was made within 2 seconds; otherwise, it remained on the screen until a button press was made. Prior to the actual scanning session, children underwent a 30-minute training session in a mock scanner, during which they were trained to remain still and practiced performing the experiment.

### Image acquisition

Brain images were acquired with a GE MR750 3T scanner. Functional scans were acquired as 39 axial slices using an echo-planar imaging pulse sequence to measure blood-oxygen-level-dependent (BOLD) T2\* contrast. Other acquisition parameters were as follows: TR = 2000 ms, TE = 27 ms, flip angle = 77°, field of view = 22.4 cm, acquisition matrix = 64 × 64, and slice thickness = 3.8 mm. The first five volumes of each run were discarded to allow for scanner equilibrium. After the functional runs, low-resolution T1 contrast images that were co-planar to the functional images were acquired (TR = 7.7 ms, TE = 3.024 ms, flip angle = 12°, field of view = 25.6 cm, and acquisition matrix = 256 × 256, slice thickness = 3.8 mm). Then, high-resolution FSPGR T1 contrast images were acquired (TR = 8.096 ms, TE = 3.18 ms, flip angle = 12°, field of view = 25.6 cm, and acquisition matrix = 64 × 64, slice thickness = 1 mm).

### Image pre-processing and activation analysis

Functional and anatomical images were analyzed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) on MATLAB (R2012a). The functional images were slice-time corrected and realigned to the first image of the session. The T1 co-planar structural image was coregistered to the mean image of the functional images, and the T1 FSPGR structural image was coregistered to this T1 co-planar image. The FSPGR image was then segmented into gray matter, white matter, and cerebral spinal fluid. The gray matter was normalized into an age-specific pediatric brain template created from the Template-O-Matic Toolbox (Wilke, Holland, Altaye & Gaser, 2008). The acquired normalization parameters were used to normalize the

realigned functional images with a spatial resolution of 3 mm × 3 mm × 3 mm. The resulting functional images were smoothed with an 8 mm full-width-half-maximum Gaussian kernel.

Neural activations in response to stimulus categories (i.e. symbol, dots, line) in contrast to the baseline fixation were estimated using the standard general linear model (GLM) with a high-pass filter at 128 Hz and correcting for temporal autocorrelation with an AR(1) model. The model included separate regressors, convolved with a canonical hemodynamic response function, for each of the stimulus conditions separately for each ratio/distance level. Motion regressors including the linear, squared, time-shifted, and squared time-shifted transformations of the six rigid-body movement parameters were also included as nuisance covariates. Individual contrast maps from each participant were entered into a second-level random effects group analysis. As considerable developmental differences may be present within our group of children, a linear effect of chronological age was regressed out in this second-level analysis. Statistical significance of these activation maps was assessed using the AlphaSim clusterwise correction for multiple comparisons (implemented in AFNI, <http://afni.nimh.nih.gov/afni>) with a voxelwise threshold at  $p < .005$ . All coordinates are in the MNI (Montreal Neurological Institute) space.

The primary contrast of interest was numerical (symbol and dots) versus non-numerical (line) conditions. A region in the right parietal cortex identified in this contrast (see Figure 2a) served as a candidate seed region in the subsequent psychophysiological interaction analysis.

### PPI analysis

Effective connectivity patterns were identified using a psychophysiological interaction (PPI) analysis, which predicates a model of the influence that one neuronal system exerts over another (Friston *et al.*, 1997; Gitelman *et al.*, 2003). The seed region was defined in each participant first by identifying individual children's local peak voxel in the symbol + dots > line contrast closest to the group-level peak [21, -64, 49] and second by constructing a spherical volume of interest with a radius of 5 mm around this peak voxel (19 voxels). The first eigenvariate of the BOLD time series within this volume of interest was extracted, while this time series was adjusted using the F-contrast of all the task regressors in order to remove confounds in the BOLD signal that cannot be explained by task variables (e.g. motion). This time-series served as the physiological variable ( $y$ ).

Next, a PPI model was constructed to find effective connectivity patterns that showed a modulation of the

contribution of this right parietal seed region by the task contrast of symbol > dots. In each participant, the psychological variable ( $p$ ) was defined by the symbol > dots contrast, and the interaction variable ( $ppi$ ) was constructed by taking the product of  $p$  and deconvolved  $y$ . This interaction term tests whether the contribution of the seed activity on the target activity is modulated by the psychological context. In other words, it can be interpreted as the difference in the degree to which target activity is explained by seed activity in the symbol versus dots conditions. The parameter estimate of  $ppi$ , which represents this degree of modulation, is henceforth referred to as the PPI parameter estimate. The individual PPI parameter estimate images were entered into a second-level random effects analysis, again while removing a linear effect of age (centered around the average). As a result, group-level maps presented in the Results can be interpreted as a brain map of a hypothetical child with an average age (i.e. 5.55 years in this study). Statistical significance of the PPI maps was assessed using AlphaSim clusterwise correction for multiple comparisons with a voxelwise threshold at  $p < .005$ .

Note that in order to validate the robustness of this traditional PPI approach, an alternative PPI model was constructed which included a regressor representing [symbol + dots] and another representing [line] to capture the full task-related variance. The results from this model are not reported here because they were not qualitatively different from the traditional PPI model described above.

In addition, the nature of the significantly positive PPI estimates was examined with supplementary regression analyses to distinguish between three possibilities (see Friston *et al.*, 1997, for a similar approach). One possibility is that the positive PPI estimate resulted from a more positive regression slope of target activity on seed activity in the experimental condition compared to the control condition. A second possibility is that there was a positive regression slope of target activity on seed activity in the experimental condition with a negative regression slope in the control condition. A third possibility is that the regression slope was less negative in the experimental condition than in the control condition while both slopes were negative. To distinguish these three possibilities, we constructed four independent PPI models in each pair of seed and target. First, a  $ppi$  term was computed by taking the interaction between the seed BOLD series and a psychological variable [symbol] (with fixation as the implicit baseline). Second, another  $ppi$  term was computed by taking the interaction between the target (e.g. left SMG) BOLD series and the same psychological variable [symbol]. These  $ppi$  terms were considered as proxies for activities in the seed and

target regions during the symbol condition. We then regressed the target activity on the (mean corrected) seed activity to compute the regression slope. The third and fourth  $ppi$  terms were computed similarly except that the psychological variable was [dots] (with fixation as the implicit baseline), after which two regression slopes under two different conditions were computed. We then compared the sign and the magnitude of these regression slopes to understand the underlying nature of significantly positive PPI estimates from the main analysis.

#### *Motion-induced BOLD artifacts*

Head motion is known to disrupt the readout of the BOLD signal resulting in artificial intensity changes (Friston, Williams, Howard, Frackowiak & Turner, 1996; Wu, Lewin & Duerk, 1997) and may even result in systematic bias in resting state functional connectivity analyses (Power, Barnes, Snyder, Schlaggar & Petersen, 2012). As the contrast of the task conditions is a critical manipulation in the PPI analysis, we do not expect a systematic bias in the PPI results due to motion. Nevertheless, we assessed whether the results can be explained by BOLD intensity changes presumably induced by head motion and the number of sudden motion jumps in each child. A summary measure of BOLD intensity variability was obtained for each participant using the automated quality assurance protocol (Friedman & Glover, 2006). To be specific, we computed the standard deviation of the mean intensity measures of the difference volume computed by subtracting the mean volume from each volume. There was a non-significant negative trend between age and this BOLD intensity variability measure ( $r = -0.268$ ,  $p = .239$ ). Using the same automated quality assurance protocol, the number of sudden jumps was also computed by subtracting the mean intensity of each volume from the mean intensity of its subsequent volume and counting the number of times in which the mean intensity difference exceeded 1% of the baseline intensity. On average, there were 7.28 jumps across all children. This measure had a non-significant correlation with age ( $r = -0.333$ ,  $p = .141$ ).

#### *Behavioral assessment*

An average of 48.8 days (standard deviation of 31.9 days) after the scanning session, all participants except for one returned for a behavioral assessment session in which they were administered the Test of Early Mathematics Ability, 3rd Edition (TEMA-3; Ginsburg & Baroody, 2003). The TEMA-3 is a standardized test of mathematics ability for children between the ages of 3 years 0 months and 8 years

11 months. While the TEMA-3 mostly consists of symbolic mathematics problems (i.e. counting, recognizing Arabic numerals, simple written addition and subtraction), it also includes a small number of non-symbolic mathematical problems (i.e. comparing quantities of dots). All of the children in our study, however, performed at ceiling on the non-symbolic questions, except for one child who made a single error in the non-symbolic math portion. Thus, variability in TEMA-3 scores in our study can be attributed to differences in symbolic mathematics knowledge. Raw TEMA-3 score was taken to be a measure of each child's symbolic mathematics achievement. Total TEMA-3 administration time was approximately 40 minutes per child.

## Results

### Behavioral performance

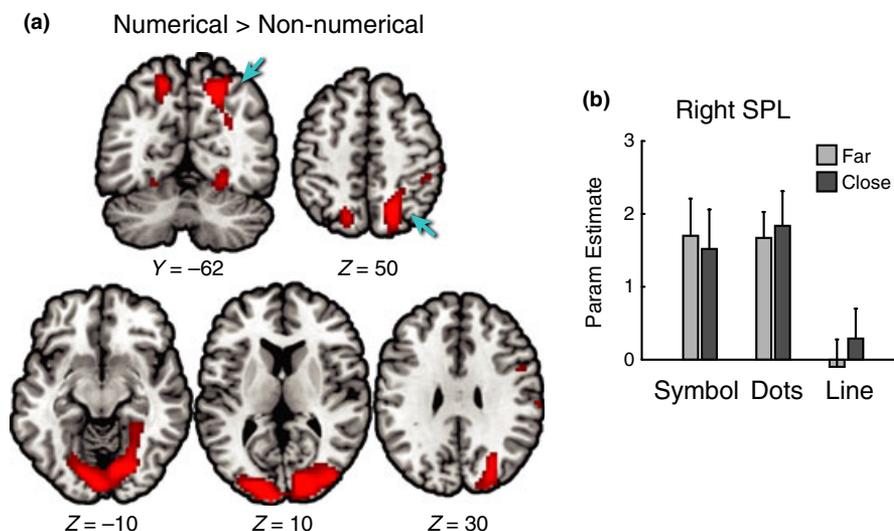
Accuracy and reaction time (RT) for correct trials in each condition (symbol, dots, line) at each ratio/distance level (close and far) are listed in Table 1. Two-way within-subject analysis of variance (ANOVA, when necessary Greenhouse-Geisser correction was used to adjust for sphericity violation) showed that there were significant differences in accuracy ( $F_{1,781, 35.612} = 7.214, p = .003$ ) and RT ( $F_{1,305, 26.093} = 23.075, p < .001$ ) across the three experimental conditions. Post-hoc contrast analyses

showed that this was due to the non-numerical line condition being more difficult than the two numerical conditions (accuracy,  $F_{1, 20} = 10.051, p = .005$ ; RT,  $F_{1, 20} = 26.674, p < .001$ ) while there were negligible differences between the two numerical conditions (accuracy,  $F_{1, 20} = 2.170, p = .098$ ; RT,  $F_{1, 20} = 0.010, p = .919$ ). There was a significant effect of ratio/distance on accuracy ( $F_{1, 20} = 40.097, p < .001$ ) and RT ( $F_{1, 20} = 52.784, p < .001$ ), but no significant interaction between experimental condition and ratio/distance (accuracy,  $F_{1,901, 38.019} = 1.044, p = .359$ ; RT,  $F_{1,746, 34.926} = 2.612, p = .094$ ). Across children, age showed a moderate correlation with RT (line:  $r = -0.444, p = .043$ ; dots:  $r = -0.384, p = .086$ ; symbol:  $r = -0.407, p = .067$ ) and accuracy (line:  $r = 0.575, p = .006$ ; dots:  $r = 0.375, p = .094$ ; symbol:  $r = 0.409, p = .066$ ).

The raw TEMA-3 scores, collected in a separate session, ranged from 12 to 51, with the mean of 33.95 and the standard deviation of 10.61. TEMA-3 score was significantly correlated with age ( $r = 0.567, p = .009$ ).

### Parietal activation selective to numerical comparison task

The main goal of this study was to test the hypothesis that symbolic number processing is subserved by the effective connectivity from the right parietal cortex to other brain regions previously implicated in numerical symbol processing. As a first step to achieve this goal, we



**Figure 2** Parietal activation selective to numerical comparison task. *a.* The group-level ( $N = 21$ ) contrast of the numerical processing (symbol and dots) conditions against the non-numerical processing (line) condition overlaid on a standard MNI template. The left hemisphere appears on the left in all cross sectional brain images. The peak in the right parietal cortex is highlighted with an arrow pointer. *b.* The mean (and its standard error) of the individual parameter estimates within a 5-mm radius spherical ROI around the right SPL peak at [21, -64, 49].

**Table 1** Mean accuracy and reaction time ( $\pm$  standard error) in each condition. Overall performance as well as performance in each ratio/distance level is reported

	Symbol		Dots		Line	
Accuracy (%)	88.3 ( $\pm$ 2.3)		91.0 ( $\pm$ 1.6)		82.8 ( $\pm$ 3.1)	
	Far	Close	Far	Close	Far	Close
	91.3 ( $\pm$ 2.4)	85.2 ( $\pm$ 2.9)	96.3 ( $\pm$ 1.7)	85.8 ( $\pm$ 2.0)	86.3 ( $\pm$ 3.1)	79.3 ( $\pm$ 3.4)
Reaction Time (ms)	1135 ( $\pm$ 63)		1137 ( $\pm$ 62)		1369 ( $\pm$ 98)	
	Far	Close	Far	Close	Far	Close
	1113 ( $\pm$ 50)	1156 ( $\pm$ 83)	1042 ( $\pm$ 70)	1231 ( $\pm$ 60)	1330 ( $\pm$ 106)	1407 ( $\pm$ 92)

identified regions that were selective to numerical processing (symbol and dots) compared to non-numerical processing (line). As illustrated in Figure 2a (see also Table 2), numerical comparison elicited a large swath of activation in the visual cortex, likely reflecting differences in the visual content of the stimuli in the contrasting conditions. More central to our hypothesis, this cluster of activation in the bilateral visual cortex extended to the right precuneus and to a robust peak in the right superior parietal lobule (SPL) at [21, -64, 49]. Activation peaks were also found in the left SPL and in the right IFG. Primarily right parietal involvement in the numerical tasks is consistent with previous reports in infants and children (Cantlon *et al.*, 2006; Hyde *et al.*, 2010; Izard *et al.*, 2008). Activation parameter estimates in this right SPL region indeed showed significant activation in the symbol and dots conditions but virtually no activation in the line condition (Figure 2b). Two-way within-subject ANOVA with condition and ratio/distance as the two factors along with contrast analysis resulted in no activation difference between the dots and symbol conditions ( $F_{1, 20} = 0.230$ ,  $p = .637$ ), no effect of ratio/distance ( $F_{1, 20} = 0.195$ ,  $p = .664$ ), and no interaction between ratio/distance and condition ( $F_{1, 768, 35.367} = 0.345$ ,  $p = .648$ ). This right SPL region served to define the seed in the subsequent PPI analysis. Given that we did not observe an effect of ratio/distance or its interaction with condition, the ratio/distance levels were collapsed in all further analyses.

Given that response selection processes may drive activation in the parietal cortex (Gobel, Johansen-Berg, Behrens & Rushworth, 2004), one might wonder if the current pattern of results is due to differences in task difficulty. Note, however, that the line condition was considerably harder, while the difficulty between the symbol and the dots conditions was matched. If task difficulty elevates the BOLD response in the parietal cortex (Gobel *et al.*, 2004), the line condition should exhibit the greatest activation in this region, which was clearly not the case. Nevertheless, we performed an additional analysis to rule out this alternative explanation. In repeated iterations, a random subset of the children was

sampled until there were no significant differences ( $p > .2$ ) in accuracy and RT measures across the three different conditions. A subset with eight children showed comparable accuracy ( $p = .438$ ) and RT ( $p = .213$ ). Importantly, these eight children still showed significantly greater activation in the symbol and the dots conditions compared to the line condition ( $t_7 = 4.409$ ,  $p = .003$ ), and there was no significant difference between the dots and symbol conditions ( $t_7 = 1.950$ ,  $p = .092$ ). Thus, it is unlikely that such stark differences in the parietal activation are due to differences in task difficulty across conditions.

Before describing the main effective connectivity analysis from the selected right parietal seed region, we report the whole brain standard activation patterns in other contrasts of interest (Figure 3 and Table 2). First, activation evoked by all task conditions with an implicit baseline of the intertrial intervals was examined. This contrast elicited large areas in the brain including the visual cortex, the bilateral parietal cortex, the bilateral motor cortex, and the anterior cingulate cortex. Second, a contrast of symbolic (symbols) versus non-symbolic (dots) numerical conditions revealed activations around the left angular gyrus, left inferior temporal area, and the right pre- and post-central gyri. Lastly, a ratio/distance effect was examined by contrasting close trials to far trials. This contrast, however, did not yield any supra-threshold activation at the clusterwise corrected significance level of  $\alpha < 0.05$ . With a more lenient threshold ( $\alpha < 0.10$ ), regions in the right IFG and anterior insula revealed significant activation.

#### *Right but not left SPL effective connectivity modulated by symbolic numerical processing*

Using a PPI analysis, we examined the effective connectivity arising from the right SPL region that was revealed to differentiate numerical (symbol and dots) from non-numerical processing (lines). This analysis revealed two brain regions that were effectively connected from the SPL seed region (Figure 4a): a left temporal parietal area mostly encompassing the supramarginal gyrus (SMG) ( $\alpha < 0.0001$ ) (peak at [-66, -22, 22]) and a

**Table 2** Suprathreshold clusters and local maxima information in each contrast

Contrast	Cluster size (voxel)	Peak Z	Peak MNI coordinate	Peak label		
All Tasks	8803	6.301	[6,-19,-11]	undefined		
		5.871	[33,-58,-14]	Fusiform_R		
		5.72	[-36,-64,-17]	Fusiform_L		
		5.657	[-36,-76,-14]	Fusiform_L		
		5.627	[36,-49,-17]	Fusiform_R		
		2682	5.051	[12,-1,58]	Supp_Motor_Area_R	
			4.878	[-3,8,55]	Supp_Motor_Area_L	
			4.759	[-45,-10,58]	Precentral_L	
		203	4.725	9,8,49]	Supp_Motor_Area_R	
	4.663			[-42,-22,67]	Precentral_L	
	3.902		[-30,20,13]	Insula_L		
	3.685		[-42,5,31]	Precentral_L		
	2.904		[-39,2,16]	Rolandic_Oper_L		
	113	3.49	48,5,19]	Frontal_Inf_Oper_R		
			80	3.216	[-33,-31,19]	Insula_L
	Numerical > Non-numerical	2373	2.999	[-42,-28,10]	Temporal_Sup_L	
			5.383	[27,-88,19]	Occipital_Mid_R	
		116	4.027	4.993	[-15,-94,16]	Occipital_Sup_L
				4.876	[-24,-91,13]	Occipital_Mid_L
4.81				[15,-88,4]	Calcarine_R	
4.689				[21,-64,49]	Parietal_Sup_R	
4.027				[-15,-67,55]	Parietal_Sup_L	
74				4.027	[51,8,22]	Frontal_Inf_Oper_R
Symbol > Dots		194	4.022	[-48,-76,25]	Angular_L	
			157	3.652	[-51,-67,7]	Temporal_Mid_L
		3.526		[-51,-28,-26]	Temporal_Inf_L	
		3.48		[-63,-34,-20]	Temporal_Inf_L	
	3.35	[-51,-49,-20]		Temporal_Inf_L		
	282	3.336		[39,-22,49]	Postcentral_R	
		3.314	[57,-22,43]	Postcentral_R		
3.116		[33,-10,52]	Precentral_R			
Close > Far	44	2.878	[36,-13,61]	Precentral_R		
		3.08	[51,5,13]	Rolandic_Oper_R		
		40	3.011	[36,20,4]	Insula_R	

*Note:* A maximum of 5 greatest local peaks at least 8 mm apart in each cluster are reported; anatomical brain regions are labeled according to the Anatomical Automatic Labeling (Tzourio-Mazoyer, Landeau, Papathanassiou, Crivello, Etard, Delcroix, Mazoyer & Joliot, 2002).

right superior precentral area (PreC) ( $\alpha = 0.0004$ ) (peak at [15, -16, 70]). The reverse contrast showed no significant regions in the whole brain.

The nature of the positive PPI parameter estimates was further examined by supplemental regression analyses (see Methods). The mean regression slope of the left SMG activity on the seed activity in the symbol condition ( $\beta = 0.357$ ) and the same mean regression slope in the dots condition ( $\beta = 0.266$ ) were both

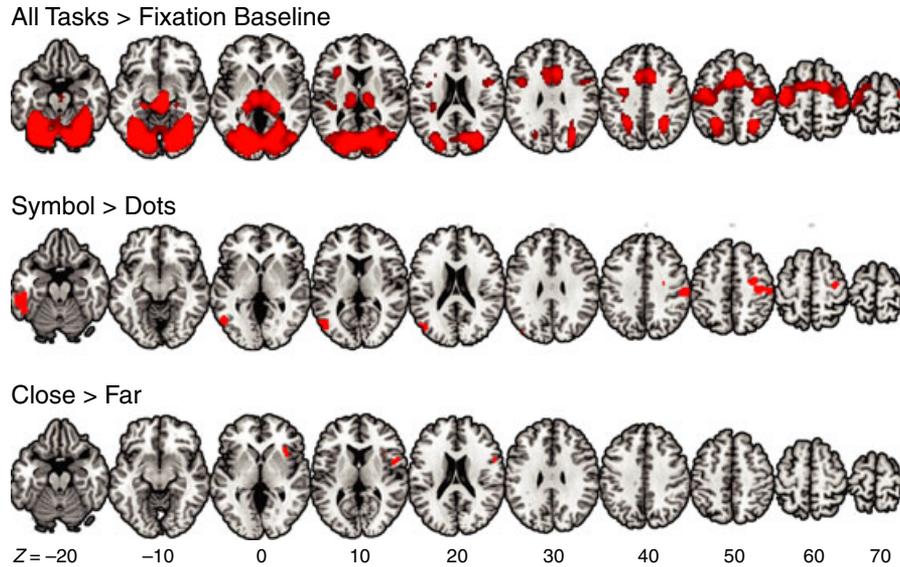
positive, suggesting that the significant effective connectivity in left SMG can be seen as an augmentation of the contribution of right SPL to left SMG activity by symbolic number processing. Likewise, the mean regression slope of the right PreC activity on the seed activity in the symbol condition ( $\beta = 0.396$ ) and the same mean regression slope in the dots condition ( $\beta = 0.248$ ) were both positive, also suggesting that the significant effective connectivity in right PreC can be seen as an augmentation of the contribution of right SPL to right PreC activity by symbolic number processing.

It should also be noted that there was no activation difference in the left SMG between the dots (mean parameter estimate =  $-0.624$ ) and symbol (mean parameter estimate =  $-0.443$ ) conditions ( $t_{20} = 0.608$ ,  $p = .550$ ) or in the right PreC between the dots (mean parameter estimate =  $-0.158$ ) and symbol (mean parameter estimate =  $0.090$ ) conditions ( $t_{20} = 1.038$ ,  $p = .312$ ). In addition, in an independent analysis, we examined the effective connectivity patterns arising from the left SPL found from the initial activation contrast of symbol + dots > line (see Figure 2a). Interestingly, no brain region showed a significant PPI effect.

#### *Developmental implications of the effective connectivity*

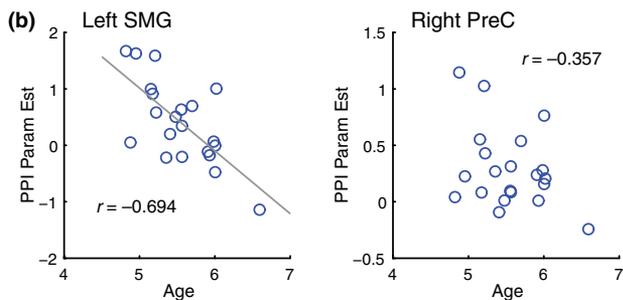
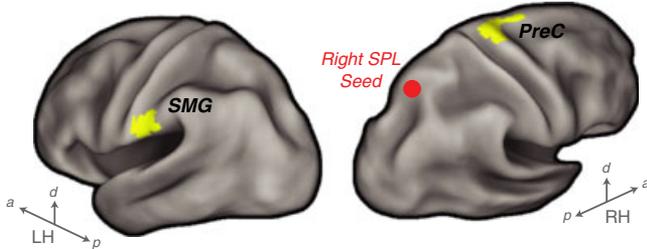
The findings so far suggest that the right superior parietal region is recruited for numerical as opposed to non-numerical processing. Furthermore, comparing numerical symbols involves effective connectivity from the right SPL to the left SMG and to the right PreC underlying symbolic number processing. These results suggest that such effective connectivity may be critical for symbolic representation of number during the developmental time window in which children are solidifying the meaning of numerical symbols.

To assess how effective connectivity underlying symbolic number processing develops, we first examined whether individual differences in the PPI parameter estimates could be explained by children's chronological age. While age did not significantly correlate with the PPI parameter estimate in the right PreC ( $r = -0.357$ ,  $p = .112$ ), it was a significant predictor of the degree of effective connectivity to the left SMG ( $r = -0.694$ ,  $p < .001$ ) (Figure 4b). Note that this association is unlikely to be due to head motion confounds as there was no correlation between BOLD intensity variability or the amount of sudden motion and age (see Methods). Supporting this conjecture, age was a significant predictor for the PPI parameter estimates in the left SMG even after controlling for BOLD intensity variability and the number of sudden motion jumps ( $t_{17} = -3.843$ ,  $p = .001$ ).

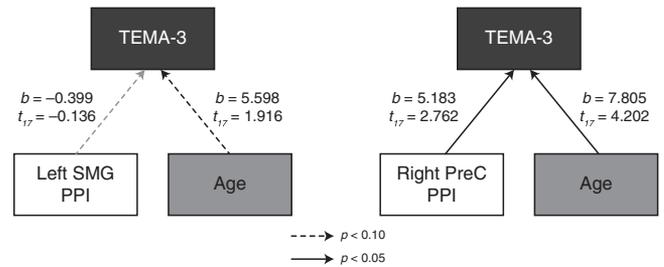


**Figure 3** Whole brain activation maps in other contrasts of interest overlaid on a standard MNI template (cluster size  $\alpha < 0.05$ ). As no suprathreshold activation was found in the contrast of close > far, a more liberal threshold was used (cluster size  $\alpha < 0.10$ ) to view the activation patterns.

**(a)** Effective Connectivity: Symbol > Dots



**Figure 4** Effective connectivity arising from the right SPL modulated by the task contrast of symbolic versus non-symbolic numerical processing. *a.* Regions showing significant PPI parameter estimates are overlaid onto an inflated human PALS atlas for visualization ([brainvis.wustl.edu/wiki/index.php/Caret:About](http://brainvis.wustl.edu/wiki/index.php/Caret:About)). LH: left hemisphere; RH: right hemisphere; a: anterior; p: posterior; d: dorsal. *b.* Scatterplots showing a correlation between age and the PPI parameter estimate. Grey line indicates a linear fit for a significant correlation.



**Figure 5** Regression models and results assessing the contribution of the PPI parameter estimate to mathematical achievement. Standardized *b* values and *t* values are listed.

We then assessed whether the degree of effective connectivity between the SPL and the two other brain regions is related to children’s symbolic mathematical abilities. If such effective connectivity supports the mapping between symbols and non-symbolic numerical magnitudes, then solving symbolic math problems might benefit from greater effective connectivity. In simultaneous multiple regression models, we examined whether the PPI parameter estimates predict the TEMA-3 scores while controlling for age (Figure 5). While the PPI parameter estimate in the left SMG did not predict the TEMA-3 score ( $t_{17} = -0.136$ ,  $p = .893$ ), the PPI parameter estimate in the right PreC was a significant predictor of the TEMA-3 score ( $t_{17} = 2.762$ ,  $p = .013$ ). The same pattern was true after BOLD intensity variability and the number of sudden motion jumps were entered as

covariates (SMG:  $t_{17} = -0.086, p = .932$ ; PreC:  $t_{17} = 3.489, p = .003$ ). These results suggest that the effective connectivity from the right SPL to the right PreC underlying symbolic number processing may be a functional underpinning of mathematical competence in 4- to 6-year-old children.

## Discussion

In this study, we investigated the neural underpinnings of symbolic number processing in 4–6-year-old children using an effective connectivity approach. Largely consistent with previous reports, numerical magnitude processing elicited robust activation in the right parietal cortex. Further PPI analysis revealed that symbolic numerical processing augmented the contribution of the right parietal seed activity to the left supramarginal activity and to the right superior precentral activity. Furthermore, the level of effective connectivity to the left SMG was highly correlated with chronological age, and the level of effective connectivity to the right PreC was a reliable predictor of symbolic mathematical achievement measured from a standardized test.

### *Number-selective activation in the superior parietal lobule*

Activation in the bilateral parietal cortex, particularly in the intraparietal sulcus (IPS), has been elicited repeatedly in response to numerical magnitude comparison in adults (for review see Dehaene, Piazza, Pinel & Cohen, 2003). In our study, however, we found regions more superior to the IPS for both symbolic and non-symbolic numerical processing compared to non-numerical processing. One possibility for this slight discrepancy may arise from differences in the subject population. In fact, a previous study that used an fMRI adaptation paradigm in 4-year-olds reported number-related activations primarily in the superior parietal lobule (Cantlon *et al.*, 2006). Thus, it is possible that the parietal activation pattern in young children is qualitatively different from that in adults. Alternatively, more superior parietal activity may result from the control contrast that we used. The numerical conditions were compared to a non-numerical line comparison condition. This kind of non-numerical magnitude comparison may recruit regions of the IPS that overlap with regions recruited for numerical magnitude judgments and thus may have been cancelled out by our contrast (Fias, Lammertyn, Reynvoet, Dupont & Orban, 2003; Pinel, Piazza, Le Bihan & Dehaene, 2004). To prevent any parietal activation due to response selection or time on task (Gobel *et al.*, 2004), we constructed this

non-numerical control task to be at least as difficult as the numerical task conditions, which has not been done in most previous studies (Cantlon, Libertus, Pinel, Dehaene, Brannon & Pelphrey, 2008; Holloway & Ansari, 2010). Thus, SPL activation in response to dots and symbol conditions in our task may reflect more selective activations to discrete quantity processing, while IPS activation may be related to general magnitude processing (Fias *et al.*, 2003; Pinel *et al.*, 2004; Walsh, 2003) in these children. Consistent with this idea, strong bilateral IPS activation was found when all task conditions were contrasted with baseline intertrial intervals (see Figure 3).

Another noteworthy observation is that the activation in the parietal regions was not modulated by ratio/distance of the two quantities. In fact, no region in the whole brain showed a significant main effect of ratio/distance (see Figure 3). Only with a liberal statistical threshold did inferior frontal regions show an effect of ratio/distance. This observation is in line with previous studies showing an absence of, or very little, neural ratio/distance effects in children (Cantlon *et al.*, 2008; Holloway & Ansari, 2010; Kaufmann *et al.*, 2006; Ansari & Dhital, 2006). Our results, consistent with previous studies, suggest that counting on the neural ratio/distance effect may not be a reliable approach to localize number-selective parietal regions in young children.

### *Effective connectivity patterns in the supramarginal gyrus*

Previous lesion studies, as well as one cortical stimulation study, have implicated the SMG as an important neural structure for Arabic numeral processing (Cipolotti, Warrington & Butterworth, 1995; Polk *et al.*, 2001; Roux *et al.*, 2008). Supporting these prior studies, we found that the left SMG was effectively connected from the right SPL during symbolic number processing in children. These results suggest that children who are actively strengthening the mapping between Arabic numerals and numerical magnitudes benefit from effective neural communication between brain regions subserving numerical quantity processing and symbolic number processing.

The supramarginal gyrus has been implicated in phonological storage and production (Henson, Burgess & Frith, 2000; Nakamura, Hara, Kouider, Takayama, Hanajima, Sakai & Ugawa, 2006; Paulesu, Frith & Frackowiak, 1993). One prevalent idea is that this region is associated with orthographic to phonological conversion (C.J. Price, 1998). Along this line of reasoning, the effective connectivity from the right SPL to the left SMG in 4- to 6-year-old children may represent verbal mediation of the visual Arabic numerals to their numerical quantities. Interestingly, the degree of effective connectiv-

ity to the left SMG was strongly negatively correlated with age. This pattern might indicate the reduction in verbal mediation with development. As children become more fluent in symbol-to-number mapping, they may rely less on verbal mediation. This interpretation is consistent with the idea that the representation of number in the Arabic form depends on the verbal system at the initial learning phase but quickly becomes independent of verbal coding (Fayol & Seron, 2005). It is also consistent with the idea that numerical symbols are more intentionally processed at younger ages and become more automatically processed at later ages (Gebuis *et al.*, 2009; Girelli *et al.*, 2000; Rubinsten *et al.*, 2002).

It seems less likely, however, that children were subvocally articulating the Arabic numerals to convert symbols to counting words. First, we see no evidence of greater activation in the symbol compared to dots condition in the left SMG or other areas related to verbal production, as shown in other studies that aimed to elicit subvocal articulation (Henson *et al.*, 2000; Lurito, Kareken, Lowe, Chen & Mathews, 2000; C.J. Price, Moore, Humphreys & Wise, 1997). Second, magnitude comparison using Arabic numerals is not influenced by language impairment and does not interfere with concurrent articulation in children as young as 5 years old (Donlan, Bishop & Hitch, 1998). Thus, the kind of verbal mediation supported by the connectivity between the left SMG and the right SPL may be beyond simple subvocalization. Further understanding of this connectivity presents a direction for future research.

#### *Effective connectivity patterns in the precentral gyrus*

In addition to the left SMG, the right PreC showed significant effective connectivity from the SPL specific to symbolic numerical comparisons as opposed to non-symbolic number processing. Interestingly, the degree of this effective connectivity was a strong predictor of symbolic mathematical competence measured by a standardized test. Previous neuroimaging studies in numerical cognition have revealed activation in the primary motor cortex, the premotor area, and the supplementary motor area during simple numerical processing tasks. For instance, the precentral gyrus shows increased regional blood flow changes when comparing or adding Arabic numerals (Pesenti, Thioux, Seron & Volder, 2000); is sensitive to numerical, size and luminance distance effects as well as number-size interference (Pinel *et al.*, 2004); and is specifically recruited during subtraction tasks (Chochon, Cohen, van de Moortele & Dehaene, 1999). Involvement of these motor areas is further supported by the change of corticospinal excitability induced by transcranial magnetic stimulation

of these areas during counting and numerical judgment (Andres, Seron & Olivier, 2007; Sato, Cattaneo, Rizzolatti & Gallese, 2007). A recent meta-analysis also reports reproducible activation in these motor areas during number and calculation tasks (Arsalidou & Taylor, 2011). Involvement of motor-related areas has often been interpreted as a remnant of finger counting habits when children are learning to count (Fischer, Kaufmann & Domahs, 2012). Accordingly, effective connectivity from the right parietal region to the precentral gyrus underlying Arabic numeral comparison may indicate that symbolic, but not non-symbolic, numerical processing is facilitated by neural communication between sites for numerical magnitude representation and finger use.

Alternatively, PreC involvement in numerical processing may be indicative of ordinal knowledge, as the dorsal precentral area is activated not only in number comparison but also when adult participants judge the ordinal position of two letters in the alphabet (Fias, Lammertyn, Caessens & Orban, 2007) and during random generation of both numbers and non-numerical materials from an ordered category (Ischebeck, Heim, Siedentopf, Zamarian, Schocke, Kremser, Egger, Streng, Scheperjans & Delazer, 2008). This interpretation is more in line with electrophysiology studies in monkeys that suggest that these motor-related areas might be one component of a network that encodes sequences (for review see Nieder, 2005). While children in our study were engaged in a relative magnitude task, it is possible that the symbol condition evoked more automatic processing of ordinal relationships. According to this interpretation, effective connectivity from the right parietal area to the precentral area may represent the need for combined quantity and ordinal processing in the symbol condition. Our findings may further suggest that effective processing of quantity and ordinal information in combination is one basis of symbolic mathematical competence in young children.

#### *Developmental and behavioral implications*

We found that while both SMG and PreC showed effective connectivity from the right SPL at the group level, the relationship between individual children's measures of effective connectivity and math achievement differed between the two regions. These results suggest that the effective connectivity to SMG and PreC may be subserving different aspects of symbolic number processing. On the one hand, the effective connectivity from SPL to PreC may represent not only the representation of symbolic numbers but also children's efficacy in retrieving symbols or their precise understanding of the

relations among symbols, which may drive the strong predictive relationship with math scores. On the other hand, the effective connectivity from SPL to SMG may be critical in representing quantity in a symbolic manner, independent of how proficient children are at symbolic representation. As stated above, this effective connectivity may be driven by the necessity of language or verbal processing in the symbolic condition, particularly more for those younger children who are just beginning to learn Arabic numerals. Language or verbal processing thus may be helpful for children to initially acquire Arabic numeral knowledge, but it does not give specific benefits to the proficiency of numeral knowledge thereafter.

#### *Other candidate brain regions*

While our results showed robust effective connectivity in two regions across the whole brain, we did not see similar connectivity patterns in other notable regions. The angular gyrus is thought to be critical in grapheme-to-phoneme transformations (Horwitz, Rumsey & Donohue, 1998; Joseph, Cerullo, Farley, Steinmetz & Mier, 2006; Pugh, Mencl, Jenner, Katz, Frost, Lee, Shaywitz & Shaywitz, 2001; Pugh, Mencl, Shaywitz, Shaywitz, Fulbright, Constable, Skudlarski, Marchione, Jenner, Fletcher, Liberman, Shankweiler, Katz, Lacadie & Gore, 2000) or in arithmetic fact retrieval (Grabner, Ansari, Koschutnig, Reishofer, Ebner & Neuper, 2009; Grabner, Ansari, Reishofer, Stern, Ebner & Neuper, 2007). Largely consistent with these findings, symbolic numbers often show greater activation (or less deactivation) than non-symbolic numbers or control stimuli in the angular gyrus (Holloway *et al.*, 2010; G.R. Price & Ansari, 2011), leading to the hypothesis that the left angular gyrus may be involved in symbol-to-number mapping. We did not, however, find enhanced PPI for symbolic number processing in this region. Similar to previous reports we found activation in the left angular gyrus peaking at  $[-48, -76, 25]$  ( $\alpha < 0.0001$ ) when the symbol condition was contrasted with the dots condition (see Figure 3) (Holloway *et al.*, 2010). This activation was due to less deactivation in the symbol condition (mean parameter estimate =  $-0.315$ ) than in the dots condition (mean parameter estimate =  $-2.487$ ) relative to baseline. However, the line condition elicited even greater activation (mean parameter estimate =  $0.878$ ) in this region of interest (pairwise *t*-test against the symbol condition,  $t_{20} = 1.297$ ,  $p = .210$ ; against the dots condition,  $t_{20} = 3.370$ ,  $p = .003$ ), which challenges the argument that the left angular gyrus activation is specific for symbolic number processing in the context of magnitude comparison tasks at least in 4- to 6-year-old children.

Previous studies have also implicated the prefrontal cortex as a mediator for symbolic acquisition of numerical values. Prefrontal neurons in monkeys were tuned to represent numerical values after extensive training, and this tuning was interpreted as establishing semantic associations between symbols and their referents (Diester & Nieder, 2007; Nieder, 2009). Also, greater neural distance effects were found in IFG in children than in adults (Ansari *et al.*, 2005; Cantlon *et al.*, 2008; Kaufmann *et al.*, 2006), which has often been interpreted as active semantic associations between numerals and numerical values in the child's brain (Nieder, 2009). We did not, however, observe effective connectivity patterns from the right SPL to any prefrontal regions. It is possible that such connectivity exists but the effect size is too small to be observed with our dataset. While one might argue that semantic association may be represented only by neural activation in the prefrontal region and not by its effective connectivity to the parietal region, this is not supported by our finding that the contrast of symbol > dots did not yield any activation in the prefrontal region (see Figure 3). Our findings are consistent with a meta-analysis reporting absence of prefrontal involvement in numerical and arithmetic processing in children (Kaufmann, Wood, Rubinsten & Henik, 2011). One plausible explanation is that prefrontal involvement in other developmental neuroimaging studies is more related to domain-general effortful processing rather than to symbol-to-number mapping (Kaufmann *et al.*, 2011).

In addition, significant effective connectivity patterns were only observed when the right, but not left, SPL was used as the seed in the PPI analysis. Numerous neuroimaging studies have so far shown a strong bilateral parietal activation during numerical tasks. More recently, however, it has been argued that there might be a functional distinction between the two hemispheres (e.g. Ansari, 2007; Cappelletti, Barth, Fregni, Spelke & Pascual-Leone, 2007; Park *et al.*, 2013). The right parietal cortex has been mostly associated with primitive understanding of numerical quantities (Holloway *et al.*, 2010; Piazza, Mechelli, Price & Butterworth, 2006; Prado, Mutreja, Zhang, Mehta, Desroches, Minas & Booth, 2011), whereas the left parietal cortex has been more associated with precise numerical values represented in symbols and learned arithmetic facts and operations (Bugden & Ansari, 2011; Chochon *et al.*, 1999; Notebaert, Nelis & Reynvoet, 2011; Pinel, Dehaene, Riviere & LeBihan, 2001). The idea that the right parietal cortex has a primary role in primitive numerical cognition is in line with developmental findings showing relatively greater involvement of the right parietal cortex in response to numerical stimuli (Cantlon *et al.*, 2006; Hyde *et al.*, 2010; Izard *et al.*, 2008). Our results are

consistent with these findings, as predominantly the right parietal cortex was selective to the numerical comparison task. Moreover, our findings show that the development of symbolic representations hinges on the functional role of the right, but not left, parietal cortex, further suggesting that the right parietal cortex is the primary locus of numerical cognition in young children. Investigating how the left parietal cortex becomes more associated with numerical symbols and their operations at later ages is an important avenue for future research.

### Summary

Research on the neural basis of the development of mathematical cognition has primarily focused on the commonalities in the neural pathway between symbolic and non-symbolic number representations in children (Cantlon *et al.*, 2008; Holloway *et al.*, 2010) and adults (Cohen Kadosh *et al.*, 2007; Cohen Kadosh & Walsh, 2009; Piazza *et al.*, 2007). However, symbolic acquisition of numerical knowledge is uniquely human (Wiese, 2003) and represents an important phase in development towards full-fledged mathematical achievement. For example, some studies suggest that the size of the symbolic, but not non-symbolic, distance effect predicts math competency in children of age 6 and 8 (Holloway & Ansari, 2009), and children with mathematics learning disabilities are impaired in symbolic, but not non-symbolic, number representations (De Smedt & Gilmore, 2011; Iuculano, Tang, Hall & Butterworth, 2008; but see Piazza, Facoetti, Trussardi, Berteletti, Conte, Lucangeli, Dehaene & Zorzi, 2010; Rousselle & Noel, 2007). Thus, investigating the neural basis of symbolic number processing in children who are actively establishing symbol-to-number mapping provides a unique way to understand this important developmental stepping stone. In the current study, we found that two brain regions, the supramarginal gyrus and the superior precentral gyrus, show effective connectivity from the right parietal cortex specific to symbolic number processing in young children. Our findings suggest that active numerical symbol learning is subserved by these connectivity patterns, which change with age and may serve as a basis for symbolic mathematical competence.

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### References

- Anderson, M.L. (2010). Neural reuse: a fundamental organizational principle of the brain. *Behavioral and Brain Sciences*, **33** (4), 245–266; discussion 266–313.
- Andres, M., Seron, X., & Olivier, E. (2007). Contribution of hand motor circuits to counting. *Journal of Cognitive Neuroscience*, **19**(4), 563–576.
- Ansari, D. (2007). Does the parietal cortex distinguish between ‘10’, ‘ten’, and ten dots? *Neuron*, **53**(2), 165–167.
- Ansari, D. (2008). Effects of development and enculturation on number representation in the brain. *Nature Reviews Neuroscience*, **9**(4), 278–291.
- Ansari, D., & Dhital, B. (2006). Age-related changes in the activation of the intraparietal sulcus during nonsymbolic magnitude processing: an event-related functional magnetic resonance imaging study. *Journal of Cognitive Neuroscience*, **18**(11), 1820–1828.
- Ansari, D., Garcia, N., Lucas, E., Hamon, K., & Dhital, B. (2005). Neural correlates of symbolic number processing in children and adults. *NeuroReport*, **16**(16), 1769–1773.
- Arsalidou, M., & Taylor, M.J. (2011). Is  $2 + 2 = 4$ ? Meta-analyses of brain areas needed for numbers and calculations. *NeuroImage*, **54**(3), 2382–2393.
- Bugden, S., & Ansari, D. (2011). Individual differences in children’s mathematical competence are related to the intentional but not automatic processing of Arabic numerals. *Cognition*, **118**(1), 32–44.
- Cantlon, J.F., Brannon, E.M., Carter, E.J., & Pelphrey, K.A. (2006). Functional imaging of numerical processing in adults and 4-y-old children. *PLoS Biology*, **4**(5), e125.
- Cantlon, J.F., Libertus, M.E., Pinel, P., Dehaene, S., Brannon, E.M., & Pelphrey, K.A. (2008). The neural development of an abstract concept of number. *Journal of Cognitive Neuroscience*, **21**(11), 2217–2229.
- Cappelletti, M., Barth, H., Fregni, F., Spelke, E., & Pascual-Leone, A. (2007). rTMS over the intraparietal sulcus disrupts numerosity processing. *Experimental Brain Research*, **179**(4), 631–642.
- Chochon, F., Cohen, L., van de Moortele, P.F., & Dehaene, S. (1999). Differential contributions of the left and right inferior parietal lobules to number processing. *Journal of Cognitive Neuroscience*, **11**(6), 617–630.
- Cipolotti, L., Warrington, E.K., & Butterworth, B. (1995). Selective impairment in manipulating Arabic numerals. *Cortex*, **31**(1), 73–86.
- Cohen Kadosh, R., Cohen Kadosh, K., Kaas, A., Henik, A., & Goebel, R. (2007). Notation-dependent and -independent representations of numbers in the parietal lobes. *Neuron*, **53** (2), 307–314.
- Cohen Kadosh, R., & Walsh, V. (2009). Numerical representation in the parietal lobes: abstract or not abstract? *Behavioral and Brain Sciences*, **32** (3–4), 313–328; discussion 328–373.
- De Smedt, B., & Gilmore, C.K. (2011). Defective number module or impaired access? Numerical magnitude processing in first graders with mathematical difficulties. *Journal of Experimental Child Psychology*, **108**(2), 278–292.

- Dehaene, S., & Cohen, L. (2007). Cultural recycling of cortical maps. *Neuron*, **56**(2), 384–398.
- Dehaene, S., Piazza, M., Pinel, P., & Cohen, L. (2003). Three parietal circuits for number processing. *Cognitive Neuropsychology*, **20**(3), 487–506.
- Diestler, I., & Nieder, A. (2007). Semantic associations between signs and numerical categories in the prefrontal cortex. *PLoS Biology*, **5**(11), e294.
- Donlan, C., Bishop, D., & Hitch, G.J. (1998). Magnitude comparisons by children with specific language impairments: evidence of unimpaired symbolic processing. *International Journal of Language & Communication Disorders*, **33**(2), 149–160.
- Dormal, V., Dormal, G., Joassin, F., & Pesenti, M. (2011). A common right fronto-parietal network for numerosity and duration processing: an fMRI study. *Human Brain Mapping*, **33**(6), 1490–1501.
- Duncan, E., & McFarland, C. (1980). Isolating the effects of symbolic distance, and semantic congruity in comparative judgments: an additive-factors analysis. *Memory & Cognition*, **8**(6), 612–622.
- Eger, E., Sterzer, P., Russ, M.O., Giraud, A.L., & Kleinschmidt, A. (2003). A supramodal number representation in human intraparietal cortex. *Neuron*, **37**(4), 719–725.
- Fayol, M., & Seron, X. (2005). About numerical representations: insights from neuropsychological, experimental, and developmental studies. In J.I.D. Campbell (Ed.), *Handbook of mathematical cognition* (pp. 3–22). New York: Psychology Press.
- Feigenson, L., Dehaene, S., & Spelke, E. (2004). Core systems of number. *Trends in Cognitive Sciences*, **8**(7), 307–314.
- Fias, W., Lammertyn, J., Caessens, B., & Orban, G.A. (2007). Processing of abstract ordinal knowledge in the horizontal segment of the intraparietal sulcus. *Journal of Neuroscience*, **27**(33), 8952–8956.
- Fias, W., Lammertyn, J., Reynvoet, B., Dupont, P., & Orban, G.A. (2003). Parietal representation of symbolic and non-symbolic magnitude. *Journal of Cognitive Neuroscience*, **15**(1), 47–56.
- Fischer, M.H., Kaufmann, L., & Domahs, F. (2012). Finger counting and numerical cognition. *Frontiers in Psychology*, **3**, 108.
- Friedman, L., & Glover, G.H. (2006). Report on a multicenter fMRI quality assurance protocol. *Journal of Magnetic Resonance Imaging*, **23**(6), 827–839.
- Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., & Dolan, R.J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage*, **6**(3), 218–229.
- Friston, K.J., Williams, S., Howard, R., Frackowiak, R.S.J., & Turner, R. (1996). Movement-related effects in fMRI time-series. *Magnetic Resonance in Medicine*, **35**(3), 346–355.
- Fuson, K.C. (1988). *Children's counting and concepts of number*. New York: Springer-Verlag.
- Gallistel, C.R., & Gelman, R. (1992). Preverbal and verbal counting and computation. *Cognition*, **44**(1–2), 43–74.
- Gebuis, T., Cohen Kadosh, R., de Haan, E., & Henik, A. (2009). Automatic quantity processing in 5-year olds and adults. *Cognitive Processing*, **10**(2), 133–142.
- Ginsburg, H.P., & Baroody, A.J. (2003). *Test of early mathematics ability* (3rd edn.). Austin, TX: Pro-Ed.
- Girelli, L., Lucangeli, D., & Butterworth, B. (2000). The development of automaticity in accessing number magnitude. *Journal of Experimental Child Psychology*, **76**(2), 104–122.
- Gitelman, D.R., Penny, W.D., Ashburner, J., & Friston, K.J. (2003). Modeling regional and psychophysiological interactions in fMRI: the importance of hemodynamic deconvolution. *NeuroImage*, **19**(1), 200–207.
- Gobel, S.M., Johansen-Berg, H., Behrens, T., & Rushworth, M.F.S. (2004). Response-selection-related parietal activation during number comparison. *Journal of Cognitive Neuroscience*, **16**(9), 1536–1551.
- Grabner, R.H., Ansari, D., Koschutnig, K., Reishofer, G., Ebner, F., & Neuper, C. (2009). To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving. *Neuropsychologia*, **47**(2), 604–608.
- Grabner, R.H., Ansari, D., Reishofer, G., Stern, E., Ebner, F., & Neuper, C. (2007). Individual differences in mathematical competence predict parietal brain activation during mental calculation. *NeuroImage*, **38**(2), 346–356.
- Henson, R., Burgess, N., & Frith, C. (2000). Recoding, storage, rehearsal and grouping in verbal short-term memory: an fMRI study. *Neuropsychologia*, **38**(4), 426–440.
- Holloway, I.D., & Ansari, D. (2009). Mapping numerical magnitudes onto symbols: the numerical distance effect and individual differences in children's mathematics achievement. *Journal of Experimental Child Psychology*, **103**(1), 17–29.
- Holloway, I.D., & Ansari, D. (2010). Developmental specialization in the right intraparietal sulcus for the abstract representation of numerical magnitude. *Journal of Cognitive Neuroscience*, **22**(11), 2627–2637.
- Holloway, I.D., Price, G.R., & Ansari, D. (2010). Common and segregated neural pathways for the processing of symbolic and nonsymbolic numerical magnitude: an fMRI study. *NeuroImage*, **49**(1), 1006–1017.
- Horwitz, B., Rumsey, J.M., & Donohue, B.C. (1998). Functional connectivity of the angular gyrus in normal reading and dyslexia. *Proceedings of the National Academy of Sciences, USA*, **95**(15), 8939–8944.
- Hyde, D.C., Boas, D.A., Blair, C., & Carey, S. (2010). Near-infrared spectroscopy shows right parietal specialization for number in pre-verbal infants. *NeuroImage*, **53**(2), 647–652.
- Ischebeck, A., Heim, S., Siedentopf, C., Zamarian, L., Schocke, M., Kremser, C., Egger, K., Strenge, H., Scheperjans, F., & Delazer, M. (2008). Are numbers special? Comparing the generation of verbal materials from ordered categories (months) to numbers and other categories (animals) in an fMRI study. *Human Brain Mapping*, **29**(8), 894–909.
- Iuculano, T., Tang, J., Hall, C.W., & Butterworth, B. (2008). Core information processing deficits in developmental dyscalculia and low numeracy. *Developmental Science*, **11**(5), 669–680.
- Izard, V., Dehaene-Lambertz, G., & Dehaene, S. (2008). Distinct cerebral pathways for object identity and number in human infants. *PLoS Biology*, **6**(2), e11.

- Jacob, S.N., & Nieder, A. (2009). Tuning to non-symbolic proportions in the human frontoparietal cortex. *European Journal of Neuroscience*, **30**(7), 1432–1442.
- Joseph, J.E., Cerullo, M.A., Farley, A.B., Steinmetz, N.A., & Mier, C.R. (2006). fMRI correlates of cortical specialization and generalization for letter processing. *NeuroImage*, **32**(2), 806–820.
- Kaufmann, L., Koppelstaetter, F., Siedentopf, C., Haala, I., Haberlandt, E., Zimmerhackl, L.B., Felber, S., & Ischebeck, A. (2006). Neural correlates of the number-size interference task in children. *NeuroReport*, **17**(6), 587–591.
- Kaufmann, L., Wood, G., Rubinsten, O., & Henik, A. (2011). Meta-analyses of developmental fMRI studies investigating typical and atypical trajectories of number processing and calculation. *Developmental Neuropsychology*, **36**(6), 763–787.
- Lurito, J.T., Kareken, D.A., Lowe, M.J., Chen, S.H.A., & Mathews, V.P. (2000). Comparison of rhyming and word generation with fMRI. *Human Brain Mapping*, **10**(3), 99–106.
- Moyer, R.S., & Landauer, T.K. (1967). Time required for judgements of numerical inequality. *Nature*, **215**(5109), 1519–1520.
- Nakamura, K., Hara, N., Kouider, S., Takayama, Y., Hanajima, R., Sakai, K., & Ugawa, Y. (2006). Task-guided selection of the dual neural pathways for reading. *Neuron*, **52**(3), 557–564.
- Nieder, A. (2005). Counting on neurons: the neurobiology of numerical competence. *Nature Reviews Neuroscience*, **6**(3), 177–190.
- Nieder, A. (2009). Prefrontal cortex and the evolution of symbolic reference. *Current Opinion in Neurobiology*, **19**(1), 99–108.
- Nieder, A., & Dehaene, S. (2009). Representation of number in the brain. *Annual Review of Neuroscience*, **32**, 185–208.
- Notebaert, K., Nelis, S., & Reynvoet, B. (2011). The magnitude representation of small and large symbolic numbers in the left and right hemisphere: an event-related fMRI study. *Journal of Cognitive Neuroscience*, **23**(3), 622–630.
- Park, J., Park, D.C., & Polk, T.A. (2013). Parietal functional connectivity in numerical cognition. *Cerebral Cortex*, **23**, 2127–2135.
- Paulesu, E., Frith, C.D., & Frackowiak, R.S.J. (1993). The neural correlates of the verbal component of working memory. *Nature*, **362**, 342–345.
- Pesenti, M., Thioux, M., Seron, X., & Volder, A.D. (2000). Neuroanatomical substrates of Arabic number processing, numerical comparison, and simple addition: a PET study. *Journal of Cognitive Neuroscience*, **12**(3), 461–479.
- Piazza, M., Facoetti, A., Trussardi, A.N., Berteletti, I., Conte, S., Lucangeli, D., Dehaene, S., & Zorzi, M. (2010). Developmental trajectory of number acuity reveals a severe impairment in developmental dyscalculia. *Cognition*, **116**(1), 33–41.
- Piazza, M., Izard, V., Pinel, P., Le Bihan, D., & Dehaene, S. (2004). Tuning curves for approximate numerosity in the human intraparietal sulcus. *Neuron*, **44**(3), 547–555.
- Piazza, M., Mechelli, A., Price, C.J., & Butterworth, B. (2006). Exact and approximate judgements of visual and auditory numerosity: an fMRI study. *Brain Research*, **1106**(1), 177–188.
- Piazza, M., Pinel, P., Le Bihan, D., & Dehaene, S. (2007). A magnitude code common to numerosities and number symbols in human intraparietal cortex. *Neuron*, **53**(2), 293–305.
- Pinel, P., Dehaene, S., Riviere, D., & LeBihan, D. (2001). Modulation of parietal activation by semantic distance in a number comparison task. *NeuroImage*, **14**(5), 1013–1026.
- Pinel, P., Piazza, M., Le Bihan, D., & Dehaene, S. (2004). Distributed and overlapping cerebral representations of number, size, and luminance during comparative judgments. *Neuron*, **41**(6), 983–993.
- Polk, T.A., Reed, C.L., Keenan, J.M., Hogarth, P., & Anderson, C.A. (2001). A dissociation between symbolic number knowledge and analogue magnitude information. *Brain and Cognition*, **47**(3), 545–563.
- Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., & Petersen, S.E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, **59**(3), 2142–2154.
- Prado, J., Mutreja, R., Zhang, H., Mehta, R., Desroches, A.S., Minas, J.E., & Booth, J.R. (2011). Distinct representations of subtraction and multiplication in the neural systems for numerosity and language. *Human Brain Mapping*, **32**(11), 1932–1947.
- Price, C.J. (1998). The functional anatomy of word comprehension and production. *Trends in Cognitive Sciences*, **2**(8), 281–288.
- Price, C.J., Moore, C.J., Humphreys, G.W., & Wise, R.J.S. (1997). Segregating semantic from phonological processes during reading. *Journal of Cognitive Neuroscience*, **9**(6), 727–733.
- Price, G.R., & Ansari, D. (2011). Symbol processing in the left angular gyrus: evidence from passive perception of digits. *NeuroImage*, **57**(3), 1205–1211.
- Pugh, K.R., Mencl, W.E., Jenner, A.R., Katz, L., Frost, S.J., Lee, J.R., Shaywitz, S.E., & Shaywitz, B.A. (2001). Neurobiological studies of reading and reading disability. *Journal of Communication Disorders*, **34**(6), 479–492.
- Pugh, K.R., Mencl, W.E., Shaywitz, B.A., Shaywitz, S.E., Fulbright, R.K., Constable, R.T., Skudlarski, P., Marchione, K.E., Jenner, A.R., Fletcher, J.M., Liberman, A.M., Shankweiler, D.P., Katz, L., Lacadie, C., & Gore, J.C. (2000). The angular gyrus in developmental dyslexia: task-specific differences in functional connectivity within posterior cortex. *Psychological Science*, **11**(1), 51–56.
- Rousselle, L., & Noel, M.P. (2007). Basic numerical skills in children with mathematics learning disabilities: a comparison of symbolic vs. non-symbolic number magnitude processing. *Cognition*, **102**(3), 361–395.
- Roux, F.E., Lubrano, V., Lauwers-Cances, V., Giussani, C., & Demonet, J.F. (2008). Cortical areas involved in Arabic number reading. *Neurology*, **70**(3), 210–217.
- Rubinsten, O., Henik, A., Berger, A., & Shahar-Shalev, S. (2002). The development of internal representations of magnitude and their association with Arabic numerals. *Journal of Experimental Child Psychology*, **81**(1), 74–92.
- Sato, M., Cattaneo, L., Rizzolatti, G., & Gallese, V. (2007). Numbers within our hands: modulation of corticospinal excitability of hand muscles during numerical judgment. *Journal of Cognitive Neuroscience*, **19**(4), 684–693.

- Sekuler, R., & Mierkiewicz, D. (1977). Children's judgments of numerical inequality. *Child Development*, **48**(2), 630–633.
- Spelke, E.S., & Kinzler, K.D. (2007). Core knowledge. *Developmental Science*, **10**(1), 89–96.
- Temple, E., & Posner, M.I. (1998). Brain mechanisms of quantity are similar in 5-year-old children and adults. *Proceedings of the National Academy of Sciences, USA*, **95**(13), 7836–7841.
- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., & Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, **15**(1), 273–289.
- Walsh, V. (2003). A theory of magnitude: common cortical metrics of time, space and quantity. *Trends in Cognitive Sciences*, **7**(11), 483–488.
- Wiese, H. (2003). *Numbers, language, and the human mind*. Cambridge and New York: Cambridge University Press.
- Wilke, M., Holland, S.K., Altaye, M., & Gaser, C. (2008). Template-O-Matic: a toolbox for creating customized pediatric templates. *NeuroImage*, **41**(3), 903–913.
- Wu, D.H., Lewin, J.S., & Duerk, J.L. (1997). Inadequacy of motion correction algorithms in functional MRI: role of susceptibility-induced artifacts. *Journal of Magnetic Resonance Imaging*, **7**(2), 365–370.
- Wynn, K. (1992). Children's acquisition of the number words and the counting system. *Cognitive Psychology*, **24**(2), 220–251.

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