Prospective relations between resting-state connectivity of parietal subdivisions and arithmetic competence

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ABSTRACT

The present study investigates the relation between resting-state functional connectivity (rsFC) of cytoarchitectonically defined subdivisions of the parietal cortex at the end of 1st grade and arithmetic performance at the end of 2nd grade.

Results revealed a dissociable pattern of relations between rsFC and arithmetic competence among subdivisions of intraparietal sulcus (IPS) and angular gyrus (AG). rsFC between right hemisphere IPS subdivisions and contralateral IPS subdivisions positively correlated with arithmetic competence. In contrast, rsFC between the left hIP1 and the right medial temporal lobe, and rsFC between the left AG and left superior frontal gyrus, were negatively correlated with arithmetic competence. These results suggest that strong inter-hemispheric IPS connectivity is important for math development, reflecting either neurocognitive mechanisms specific to arithmetic processing, domain-general mechanisms that are particularly relevant to arithmetic competence, or structural 'cortical maturity'. Stronger connectivity between IPS, and AG, subdivisions and frontal and temporal cortices, however, appears to be negatively associated with math development, possibly reflecting the ability to disengage suboptimal problem-solving strategies during mathematical processing, or to flexibly reorient task-based networks. Importantly, the reported results pertain even when controlling for reading, spatial attention, and working memory, suggesting that the observed rsFC-behavior relations are specific to arithmetic competence.

1. Introduction

Early math skills are a robust predictor of academic success, employment, physical and mental health, arrest, and incarceration (Bynner and Parsons, 1997, 2006; Duncan et al., 2007). However, many individuals are 'functionally innumerate', lacking the basic numerical and mathematical skills to function effectively in modern society (DfES, 2005; NCES, 2007).

Behavioral research suggests a set of core foundational competencies that underlie development of math skills, specifically, the processing of nonsymbolic (i.e., sets of dots) and symbolic (i.e., Arabic digits) numerical magnitude (Bugden and Ansari, 2011; De Smedt et al., 2009; Halberda et al., 2008). A reliable set of neural substrates are associated with these foundational competencies. First, the intraparietal sulcus (IPS) supports the processing of numerical magnitude in typically developing individuals (Cantlon et al., 2006; Holloway et al., 2010; Piazza et al., 2007) and is structurally and functionally atypical in individuals with math learning disabilities (Mussolin et al., 2009; Price et al., 2007; Ranpura et al., 2013). A number of studies suggest that the right hemisphere IPS is particularly involved in the processing of nonsymbolic magnitudes while the left IPS develops specialization for processing symbolic magnitudes (Ansari, 2008; Holloway et al., 2010). Second, the left angular gyrus (AG) appears to play a role in the processing of symbolic numbers (Ansari, 2008; Holloway et al., 2010; Price and Ansari, 2011) and the retrieval of arithmetic facts from memory (Delazer et al., 2005; Grabner et al., 2009a). Thus, two circumscribed regions of the parietal cortex have been reliably identified whose function during nonsymbolic/symbolic magnitude processing (IPS) and symbolic/arithmetic processing (AG) appears to be related to math development.

While structural and functional integrity of these regions is associated with the development of math competence, focus on isolated cortical regions may be insufficient for linking brain function to cognition. Instead, attention must be paid to the connectivity between brain regions (Bressler and Menon, 2010). Task-independent,

resting-state functional connectivity (rsFC) analyses can be advantageous over task-based functional connectivity for at least two reasons. Firstly, task-related connectivity patterns may be a product of incidental task demands (e.g., visual stimulation in a magnitude comparison task or response selection during mental arithmetic) that vary dramatically across experimental paradigms. rsFC, on the other hand, is thought to measure intrinsic connectivity of brain regions that have developed a functional relationship through a history of co-activation (Dosenbach et al., 2007; Fair et al., 2007). As such, rsFC can provide important insights into behaviorally relevant functional brain architecture independent of transient task demands. Secondly, individual differences in network connectivity during a task could be a function of intrinsic and task-specific behavioral differences in cognitive strategies, neural differences, or both. rsFC is particularly useful in avoiding these confounding factors, especially in the study of atypically developing individuals with learning difficulties, or even performance or test anxiety, when task administration might not be optimal. To the best of our knowledge, there is also no consensus on which numerical or mathematical task is optimal in capturing individual and group differences in functional brain organization.

A further advantage of rsFC is that being task-independent, it can be easily replicated methodologically and compared across studies. rsFC can provide important insights into the functional organization of the brain in ways that complement information yielded by investigating task-based functional connectivity (Cole et al., 2010; Fox and Raichle, 2007), and thus represents a potentially informative method to probe the neural mechanisms underlying math development. Recently, a large-scale analysis of task-based and resting-state fMRI data from over 400 subjects in the Human Connectome Project database, Shah et al. (2016) found systematic differences in group-mean functional connectivity between task and rest, but also across different tasks. Crucially, they also found preserved individual differences in functional connectivity during task and rest, and between different tasks (Shah et al., 2016). The utility of rsFC in elucidating possible biomarkers associated with reading difficulties has been demonstrated by several studies in individuals with (Schurz et al., 2015) and without dyslexia (Koyama et al., 2010, 2011, 2013; Zhou et al., 2015), suggesting a strong potential for rsFC studies to contribute to the understanding of typical and atypical development in alternative academic domains, such as math. These findings further support the validity of using rsFC measures as a complementary approach to task-based neuroimaging in the investigation of individual differences in behaviorally relevant functional connectivity.

Several studies have investigated task-based functional connectivity during numerical and mathematical processing (for a review see Moeller et al., 2015), indicating an important role for a network of frontal and parietal regions. Number related networks have also been identified using rsFC. For example, Abboud et al. (2015) used seed regions in the inferior temporal gyrus (ITG), derived from a number processing task to show rsFC between the right ITG and bilateral parietal and prefrontal cortices. In contrast, a letter-related region in the left ITG showed rsFC patterns with a left lateralized network of regions typically associated with language processing. Those results suggest that a functional network related to numerical processing can be identified using rsFC.

However, to the best of our knowledge, only four studies have examined the relation between rsFC and math development. Supekar et al. (2013) found that rsFC between the hippocampus and frontal and temporal brain regions predicted response to arithmetic tutoring in third grade children. In another sample of third grade children, Jolles et al. (2016b) found that rsFC between the IPS, prefrontal cortex, ventral temporal-occipital cortex, and hippocampus strengthened after arithmetic tutoring, and was correlated with individual performance gains. They also found that the rsFC of angular gyrus did not predict response to tutoring. Subsequently, Evans et al. (2015) showed that rsFC between regions in the fusiform gyrus, IPS, frontal, and prefrontal cortex predicted gains in math performance over a six year period. Most recently, Jolles et al. (2016a) reported hyper-connectivity between the IPS and bilateral frontal and parietal regions in children with mathematical learning difficulties. In sum, those studies which have investigated rsFC in the context of mathematical or numerical processing suggest an important role for multiple networks, often involving prefrontal, medial and inferior temporal, and parietal regions.

While the majority of neuroimaging studies investigating numerical and mathematical cognition refer to the IPS and AG as unitary cortical regions, cytoarchitectonic mapping studies suggest the IPS can be divided into hIP1, hIP2, and hIP3, and AG can be divided into anterior (PGa) and posterior (PGp) portions (Caspers et al., 2006; Choi et al., 2006), and that these subdivisions show distinct patterns of functional and structural connectivity (Uddin et al., 2010). Furthermore, a recent study suggests that these subdivisions are functionally heterogeneous during the performance of mental arithmetic (Wu et al., 2009). It is possible that treating the IPS and AG as unitary cortical areas masks nuanced patterns of functional connectivity that relate to math competence in differing ways. In summary, of the four studies relating rsFC to math performance, only two (Jolles et al., 2016a,b) used anatomically defined seed regions (left and right IPS), and no study to date has examined the relation between math achievement and rsFC of cytoarchitectonic subdivisions of key parietal regions.

To address this, the present study examines the relation between rsFC of cytoarchitectonically defined parietal subdivisions and the whole brain at the end of 1st grade, and calculation performance at the end of 2nd grade. We focus our analyses on subdivisions of the IPS and AG as two regions widely reported as being associated with the development of math competence (Ansari, 2016; Dehaene et al., 2003). We also further examine the extent to which our results are specific to arithmetic competence, given that the IPS is also involved in attention (Anderson et al., 2010) and working memory (Bray et al., 2015; Pessoa et al., 2002), and the angular gyrus is involved in reading and language (Church et al., 2011; Meyler et al., 2007; Price, 2000; Seghier, 2012). In so doing, this is the first study to our knowledge that investigates the prospective relation between intrinsic functional connectivity of anatomically defined parietal subdivisions and math achievement.

2. Methods

2.1. Subjects

The present study initially comprised 60 typically developing 1st grade children who were part of an ongoing longitudinal study on the development of reading skills, and for whom standardized measures of math achievement were available at the end of 2nd grade. Initial exclusion criteria included known and uncorrected visual impairment, hearing impairment of at least 25 dB loss in either ear, previous diagnosis of intellectual disability, history of neurological disorders including epilepsy, spina bifida, cerebral palsy, and traumatic brain injury, current or previous diagnosis of an autism spectrum disorder, parental report of significant symptoms of a severe psychiatric diagnosis including major depressive, bipolar, or conduct disorders, and treatment with any antipsychotic medication – with the exception of stimulant medications for attention-deficit hyperactivity disorder (ADHD). Two children in the current sample met the criteria for ADHD. No children met the criteria for oppositional defiant disorder, adjustment disorder, and mild depression.

Table 1
Standardized scores on IQ, math, and reading achievement for 1st and 2nd grade children.

Measure	1st Grade (N = 47)		2nd Grade (N = 47)	
	M (range)	SD	M (range)	SD
Males/Females	17/30		17/30	
Age (years)	7.46 (6.83–8.08)	0.31	8.45 (7.75–9.08)	0.33
WASI-II IQ	113.65 (78–144)[a]	16.82		
WISC-III Forward Spatial Span			10.00 (7–15)	2.14
WISC-III Backward Spatial Span			10.02 (4–15)	2.38
WCJ-III Calculation			103.30 (81–124)	11.05
WCJ-III Word Attack			107.04 (66–133)	11.40
WCJ-III Letter-Word Identification			109.43 (73–127)	12.11
WCJ-III Basic Reading			109.17 (73–128)	12.45

[a] WASI-II IQ score was unavailable for one subject, but all other measures were within 1SD of mean.

Neuroimaging and global IQ data were collected during the summer following 1st grade, while standardized math and reading achievement scores were collected during the summer following 2nd grade. No subjects were excluded based on IQ or reading achievement. One subject was missing an IQ score, but all other standardized achievement measures for that subject were within 1 standard deviation of the standardized test score means ($M = 100$, $SD = 15$). Two participants were excluded because their math achievement measures were greater than 2 standards deviations below the standardized mean, indicating a potential for math learning disability. A further 11 subjects were excluded based on excessive head motion during the resting-state scan (described below), resulting in a final sample of 47 subjects. 34 of these subjects were right-handed, 9 as ambidextrous, and 3 as left-handed, according to the Edinburgh Handedness Inventory (Oldfield, 1971). One subject had missing data on handedness.

Descriptive statistics of demographic and cognitive measures are presented in Table 1, and bivariate correlational analyses of the standardized test measures are presented in Table 2. One-sample Kolmogorov-Smirnov goodness-of-fit tests (K-S) showed that IQ and arithmetic competence were normally distributed ($p > 0.05$), suggesting a wide and representative range of scores. The control variables were not normally distributed. Letter-word Identification (K-S = 0.144, $p = 0.016$), the basic reading cluster scores (K-S = 0.175, $p = 0.001$), and backward spatial span (K-S = 0.149, $p = 0.011$) were negatively skewed. Forward spatial span (K-S = 0.202, $p < 0.001$) was positively skewed. Nonetheless, all regression residuals used in the rsFC-competence analyses were normally distributed.

2.2. Standardized cognitive measures

2.2.1. Iq

A two-subtest version of the Wechsler Abbreviated Scale of Intelligence (Second Edition) (WASI-II; Wechsler, 2011), which includes the vocabulary and matrix reasoning subtests, was administered at the end of 1st grade as a metric of global IQ.

2.2.2. Spatial attention and working memory

Nonverbal attention and working memory were assessed using standard scores from the Forward and Backward Spatial Span subtests from the Wechsler Intelligence Scale for Children (Third Edition) (WISC-III; Wechsler, 1991). The forward and backward subtests require the repetition of a sequence of tapping on an array of cubes in the given order or reversed order respectively.

2.2.3. Arithmetic competence

Arithmetic competence was assessed using the age-normed standard scores from the Woodcock-Johnson III Tests of Achievement Calculation subtest (WCJ-III; Woodcock et al., 2001). The Calculation subtest is an untimed, paper-and-pencil test that includes age-appropriate content to assess knowledge of cal-

culation procedures (e.g., $2 + 4 =$ __, presented horizontally and vertically) of increasing complexity.

2.2.4. Reading competence

The Word Attack and Letter-Word Identification subtests of the Woodcock-Johnson III Tests of Achievement (Woodcock et al., 2001) were used to assess basic reading competence. Word Attack measures an individual's skills in phonetic coding (e.g., sound of the letter 'k') and decoding of nonsense words of increasing complexity (e.g., sound of word 'zoop'). The Letter-Word Identification subtest measures an individual's ability to read isolated letters and a list of words of increasing difficulty. A basic reading cluster score was computed from both subtests.

2.3. Neuroimaging data acquisition and preprocessing

2.3.1. Image acquisition

Within a single session, participants performed a functional magnetic resonance imaging (fMRI) reading comprehension task, a resting-state fMRI scan, an anatomical scan, and a diffusor-tensor imaging scan, in that order. Given the focus of this study, only the parameters for the resting-state and anatomical scans are reported.

Magnetic resonance (MR) imaging was performed on a Philips Achieva 3T MR scanner with an 8-channel head coil. Resting-state functional T2*-weighted images were acquired using a field echo–echo planar imaging (FE-EPI) pulse sequence with the following parameters: 160 vols; Repetition time (TR) = 2200 ms; Echo time (TE) = 30 ms; flip angle = 75°; 40 axial slices; inter-slice gap = 1 mm; voxel size = $1.875 \times 1.875 \times 3$ mm³; Field of View = 240×240 mm²; imaging matrix = 128×128; acquisition time = 365.2 s. To allow for steady-state magnetization to be reached before acquiring the functional data, 5 dummy volumes were added at the beginning of each scan, which were subsequently discarded. Subjects were instructed to keep their eyes open, think of nothing in particular, and to look at the fixation cross presented in the center of the visual field during the single run of 6-min.

A high-resolution T1-weighted three-dimensional Magnetization Prepared Rapid Gradient Recalled Echo (MP-RAGE) sequence was acquired according to the following specifications: TR = 8.0457 ms; TE = 3.7 ms; flip angle = 7°; 170 sagittal slices with no inter-slice gap; voxel size = $1 \times 1 \times 1$ mm³; imaging matrix = 256×256; acquisition time = 391.8 s. Scans were oriented in the anterior-posterior commissure plane.

2.3.2. Data preprocessing

The Artifact Detection Toolbox (http://www.nitrc.org/projects/artifact_detect/) was first used to identify time points in each subject's functional data when the global mean signal fluctuated by more than 3 standard deviations from the mean signal of the entire scan or when the frame-to-frame composite (translational and rotational) subject motion exceeded 1 mm 10 subjects were identi-

Table 2
Bivariate correlation coefficients of standardized cognitive measures.

Measure	1	2	3	4	5
1. WASI-II IQ[a] (Grade 1)	–	0.049	0.239	0.434[**,b]	0.459[**]
1. WISC-III Forward Spatial Span (Grade 2)		–	0.277	0.078	−0.110
1. WISC-III Backward Spatial Span (Grade 2)			–	0.316[*]	0.131
1. WCJ-III Calculation (Grade 2)				–	0.233
1. WCJ-III Basic Reading (Grade 2)					–

[*] $p < 0.05$.

[**] $p < 0.01$.

[a] Pairwise correlations were excluded for one subject whose WASI-II IQ score was unavailable.

[b] Spearman's rho correlation coefficients were used as most cognitive variables were non-normally distributed. Pearson's r correlation coefficient was used for correlation between IQ and WCJ-III Calculation, which were both normally distributed.

fied with greater than 20% outlying time points and were excluded from subsequent analyses, resulting in a final sample of 47 subjects.

Both anatomical and functional data were then preprocessed and analyzed using BrainVoyager QX 2.8 (Brain Innovation, Maastricht, Netherlands) and NeuroElf toolbox version 1.0 (http://neuroelf.net) for MATLAB (MathWorks, Natick, MA, USA). Anatomical images were corrected for intensity inhomogeneity and the brain was segmented from surrounding head tissue. Preprocessing for functional data included slice-scan time correction using a cubic spline interpolation and head motion correction using a trilinear-sinc interpolation. Additionally, a band-pass filter was applied using a combination of (a) a high-pass temporal filter with a cut-off of 3 or fewer cycles per time course (equivalent to 0.0085 Hz) to remove linear trends and low-frequency non-linear drifts, and (b) a low-pass filter of full-width at half- maximum (FWHM) Gaussian kernel of 2.1 s (equivalent to 0.1486 Hz) to remove high-frequency fluctuations. The band-pass filter was applied as the frequency range of 0.008–0.15 Hz has been used in many studies to reveal meaningful resting-state functional connectivity (Biswal et al., 1995; Fox and Raichle, 2007; Fransson, 2005; Greicius et al., 2003). After these preprocessing steps, each subject's structural and functional scans were coregistered and spatially transformed into Talairach standard space (Talairach and Tournoux, 1988) using a 12-parameter affine transformation. Lastly, individual volume time courses were created and spatially smoothed with an 8-mm FWHM Gaussian kernel to accommodate inter-subject anatomical variability and decrease spatial noise, and resampled to an iso-voxel size of $3 \times 3 \times 3$ mm³.

To mitigate the influences of motion and physiological processes such as fluctuations to cardiac and respiratory cycles, each subject's preprocessed time course was then regressed on eight nuisance covariates – signals from white matter and cerebrospinal fluid (Birn et al., 2014), and six motion parameters (van Dijk et al., 2012) in a single-subject General Linear Model. Mean global signal was not regressed as it has been found to introduce spurious anti-correlated networks (Murphy et al., 2009; Saad et al., 2012). All predictors in the model were z-normalized within each subject to account for different baseline signal levels.

2.3.3. Seed regions-of-interest (ROIs)

ROIs were defined through the Jülich atlas' probability maps available within the Anatomy Toolbox v2.0 in SPM8 (Eickhoff et al., 2005). The IPS is divided into three distinct subdivisions – hIP1 on the posterior lateral bank, hIP2, which is anterior to hIP1 (Choi et al., 2006), and hIP3, which is posterior and medial to both subdivisions (Scheperjans et al., 2008a, 2008b). The AG is divided into two subdivisions – an anterior subregion, PGa, and a posterior subregion, PGp (Caspers et al., 2006, 2008).

Instead of directly using the non-overlapping ROIs from the maximum probability maps that Uddin et al. (2010) used, we created the ROIs from individual probability maps and thresholded them using SPM8′s Imcalc utility to increase their anatomical specificity such that only voxels with at least 50% probability of

Table 3
Seed ROIs in IPS and AG.

ROI	Center-of-Gravity Coordinates (Talairach)	
	x, y, z	Volume (mm³)
Left		
hIP1	−35, −55, 35	1027
hIP2	−45, −41, 39	1093
hIP3	−30, −55, 41	1370
PGa	−46, −59, 33	2571
PGp	−43, −72, 26	3460
Right		
hIP1	37, −49, 36	1663
hIP2	42, −41, 42	783
hIP3	32, −50, 46	1218
PGa	53, −54, 27	3159
PGp	44, −68, 29	4987

belonging to each subdivision were included (Eickhoff et al., 2006). Any overlapping voxels between each of those ROIs were also excluded. These thresholded ROIs were then imported into Brain-Voyager, and transformed from MNI space to Talairach space using the transformation matrix derived from the Talairach-transformed Colin27 brain (Holmes et al., 1998). These 10 ROIs (Fig. 1 and Table 3) were then used as seeds in the resting-state functional connectivity analyses described below.

2.4. Analyses

2.4.1. Subject-level rsFC analyses

For each seed, we extracted its mean time course by averaging the time courses across all voxels within the region. A whole-brain rsFC map was then created for each subject for each seed region by computing the bivariate correlation coefficient between the mean time course from a given seed region and the time course of every other voxel in the brain, resulting in ten maps per subject. Fisher's r-to-z transformation, $z' = 0.5*[\ln(1 + r) − \ln(1-r)]$, was then applied to convert the Pearson's r-values to normally distributed z-scores.

2.4.2. Dissociable rsFC of parietal subdivisions

To assess the extent to which our defined parietal subdivisions demonstrated that the dissociable rsFC patterns, we compared the functional connectivity of each seed ROI, independent of any behavioral measure. This allowed us to investigate whether children show dissociable connectivity within the IPS and AG as had been demonstrated in adults by Uddin et al. (2010). Specifically, we performed paired-samples t-tests on the following contrasts for the left and right hemispheric seeds separately: hIP1 and hIP2, hIP1 and hIP3, hIP2 and hIP3, and PGp and PGa.

2.4.3. Group-level rsFC and rsFC- arithmeticcompetence analyses

To examine the extent to which individual differences in arithmetic competence were related to rsFC of our seed regions, subject-level rsFC maps for each seed were correlated with resid-
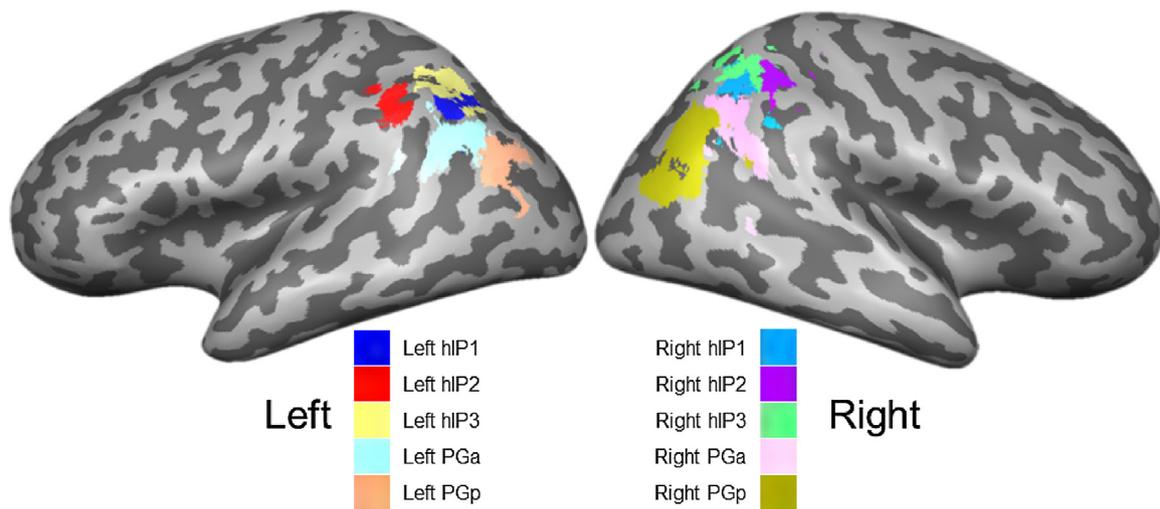
Fig. 1. rsFC seed regions shown on the inflated surfaces of a Talairach-transformed Colin27 brain.

ualized scores of arithmetic competence. These unstandardized residuals were obtained from a multiple regression of calculation on basic reading, spatial attention, spatial working memory, age at behavioral testing at Grade 2, and gender. Reading competence was included as a covariate to control for verbal ability. Spatial attention and working memory were included to control for domain-general abilities that have been found to underlie individual differences in math competence especially in children (Alloway and Passolunghi, 2011; Ashkenazi et al., 2013; Fias et al., 2013; McLean and Hitch, 1999; Raghubar et al., 2010; Simmons et al., 2012; Szucs et al., 2013), and have been associated with the activation and functional connectivity of the IPS (Bray et al., 2015; Pessoa et al., 2002). This resulted in a correlation map of voxels whose rsFC strength with each seed varied significantly as a function of arithmetic competence over and above other possible explanatory variables such as reading competence, attention, and working memory.

The group-level rsFC maps and rsFC- Arithmetic competence maps were masked with a grey matter mask obtained from the average, normalized T1 volume of all subjects, and corrected for multiple comparisons using voxel-wise thresholds of $p < 0.001$, and a cluster-wise threshold of $p < 0.05$ determined by an iterative Monte Carlo with 1000 iterations performed in BrainVoyager QX. This nonparametric statistical procedure estimates a minimum cluster size that yields a cluster-level false-positive rate of $\alpha = 0.05$ (Forman et al., 1995; Goebel et al., 2006). Anatomical locations of the peak voxels were predominantly labeled in Talairach space using the Talairach Client Version 2.4.3 (http://www.talairach.org/client.html), and also in Montreal Neurological Institute (MNI) space using the Nonlinear Yale MNI to Talairach Conversion Algorithm (http://bioimagesuite.yale.edu/mni2tal/; Lacadie et al., 2008) and the SPM8 Anatomy Toolbox v2.15 (Eickhoff et al., 2005) when it was necessary to localize subdivisions, particularly in the IPS and AG. The brain-behavior relations are illustrated in Fig. 2 using BrainNet Viewer (Xia et al., 2013).

3. Results

3.1. Contrasts of rsFC of IPS and AG subdivisions

3.1.1. hIP1 and hIP2

Left hIP1 showed greater rsFC than left hIP2 with other inferior parietal regions and the posterior cingulate. The left hIP2, however, showed greater rsFC more anteriorly with the pre- and post-central gyri extending to the paracentral lobules and medial

frontal regions, the anterior cingulate, as well as the insula than left hIP1 (Fig. S1a, Table S1). Highly similar patterns of rsFC were found for the right hIP1 and hIP2, although the right hIP1 showed greater rsFC than right hIP2 with the anterior prefrontal cortex.

3.1.2. hIP1 and hIP3

The left hIP1 showed greater rsFC with the inferior parietal, frontal, prefrontal and middle temporal regions, and the thalamus than left hIP3 (Fig. S1b, Table S1). Left hIP3, on the other hand, showed greater rsFC with the bilateral superior parietal lobules, frontal and middle occipital regions. Similar rsFC patterns were observed using the right hemisphere seeds.

3.1.3. hIP2 and hIP3

Left hIP2 showed greater rsFC than left hIP3 with the inferior parietal lobules, anterior cingulate, inferior frontal and superior temporal regions, and thalamus (Fig. S1c, Table S1). The left hIP3, on the other hand, showed greater rsFC with the superior parietal lobules extending posteriorly to the precuneus, and occipital/cerebellar regions. Similar rsFC patterns were observed in the right hemisphere seeds.

3.1.4. PGp and PGa

The left PGp showed greater rsFC with precuneus and occipital/cerebellar regions than left PGa. The left PGa, however, showed greater rsFC than the left PGp with superior and inferior parietal regions, frontal, prefrontal and temporal regions, anterior and posterior cingulate, as well as the insula (Fig. S1d, Table S1). The right seeds showed slightly different rsFC patterns than the left seeds. Specifically, the right PGp showed greater rsFC with the superior parietal lobules extending to the postcentral gyri, middle frontal regions, hippocampus and parahippocampal gyrus, temporal regions, and occipital/cerebellar regions than the right PGa. However, the right PGa showed greater rsFC than the right PGp with the inferior parietal lobules, precentral gyri extending to the insula and anterior cingulate.

3.2. Relations between rsFC and arithmetic competence

3.2.1. IPS subdivisions

Graphical illustrations and details of the relationship between the rsFC of each seed ROI in the IPS and arithmetic competence are shown in Figs. 2 and S2, and Table 4 respectively. The rsFC of all subdivisions in the left IPS showed a negative association
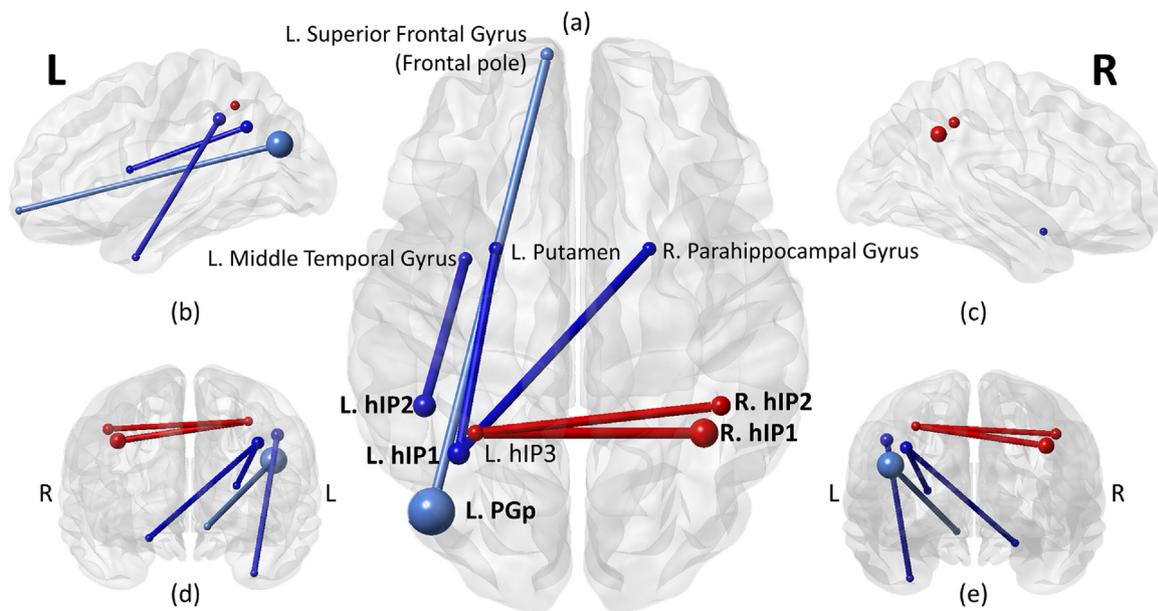
Fig. 2. Relations between rsFC at Grade 1 and arithmetic competence at Grade 2 for the IPS and AG ROIs in the (a) axial view, (b) sagittal view of the left hemisphere, (c) sagittal view of the right hemisphere, (d) coronal view from the front, and (e) coronal view from the back. Size of the nodes indicates the relative sizes of the seed and target regions. Line thickness indicates rsFC strength. Red represents a positive rsFC-competence relationship, and blue represents a negative relationship. Labels of seed regions are in bold and target clusters are not. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Significant rsFC – arithmetic competence relationships.

Seed ROI	Target Region(s)	Cluster Size (mm³)	Peak (Talairach) x, y, z	Peak r-value [a]	Mean r-value [a]
Left hIP1	Right parahippocampal gyrus (BA 34)	213	21, 5, −14	−0.59	−0.49
	Left putamen	252	−24, 5, 13	−0.57	−0.50
Left hIP2	Left middle temporal gyrus (BA 21)	216	−33, 2, −32	−0.60	−0.50
Right hIP1	Left hIP3 (BA 7)	468	−30, −49, 46	0.66	0.54
Right hIP2	Left hIP3 (BA 7)	302	−30, −49, 46	0.59	0.51
Left PGp	Left superior frontal gyrus/ frontal pole (BA 10)	170	−9, 62, −8	−0.62	−0.53

with arithmetic competence. Specifically, rsFC strength between the left hIP1 and right parahippocampal gyrus, as well as the left putamen, was negatively associated with arithmetic competence. Arithmetic competence was also negatively related to the rsFC strength between the left hIP2 and left middle temporal gyrus.

In contrast, the rsFC of most subdivisions in the right IPS showed a positive association with arithmetic competence. In particular, cross-hemispheric intraparietal rsFC strength between the right hIP1 and left hIP3 was positively correlated with arithmetic competence. The right hIP2 showed a similar connectivity-competence relationship with the left hIP3. Scatterplots of the IPS rsFC-competence relationships are illustrated in Fig. 3. rsFC strengths of the bilateral hIP3 subdivisions were not correlated with arithmetic competence in any region.

3.2.2. AG subdivisions

Graphical illustrations and details of the relationship between the rsFC of each seed ROI in the AG and arithmetic competence are shown in Figs. 2, 3, S2, and Table 4. The rsFC strength between the left PGp and left superior frontal gyrus, specifically the frontal pole (BA10), was negatively correlated with arithmetic competence. rsFC strengths of the bilateral PGa and right PGp subdivisions were not correlated with arithmetic competence in any region.

3.2.3. Specificity to arithmetic

To assess the extent to which our rsFC-arithmetic correlations were specific to arithmetic, we replicated the above analyses using basic reading and spatial working memory, rather than arithmetic,

as the dependent variables. Essentially, our main results report the correlation between rsFC and arithmetic while controlling for reading, attention, working memory, age, and gender, while our secondary results report the correlations between rsFC and reading while controlling for arithmetic, attention, working memory, age, and gender (Table S2), as well as the correlation between rsFC and working memory while controlling for arithmetic, reading, attention, age, and gender (Table S3). Both reading and working memory showed more extensive networks associated with IPS and AG than with arithmetic. Reading competence was positively correlated with predominantly fronto-parietal and temporo-parietal connections, whereas working memory was negatively correlated with predominantly intra-parietal and temporo-parietal connections. Importantly, most of the rsFC patterns with arithmetic, reading, and working memory did not overlap spatially. Only the right parahippocampal gyrus target clusters found for reading overlapped spatially with the parahippocampal gyrus cluster found in our main analyses with math. Even when similar target clusters were observed (e.g., the right parahippocampal gyrus, left superior frontal gyrus, and left middle temporal gyrus), the parietal subdivision origins were different, and directions of the relationship between rsFC and the cognitive measures were reversed. These findings provide further evidence that our main reported results are indeed specific to arithmetic competence and not reflective of simply domain general task positive mechanisms.
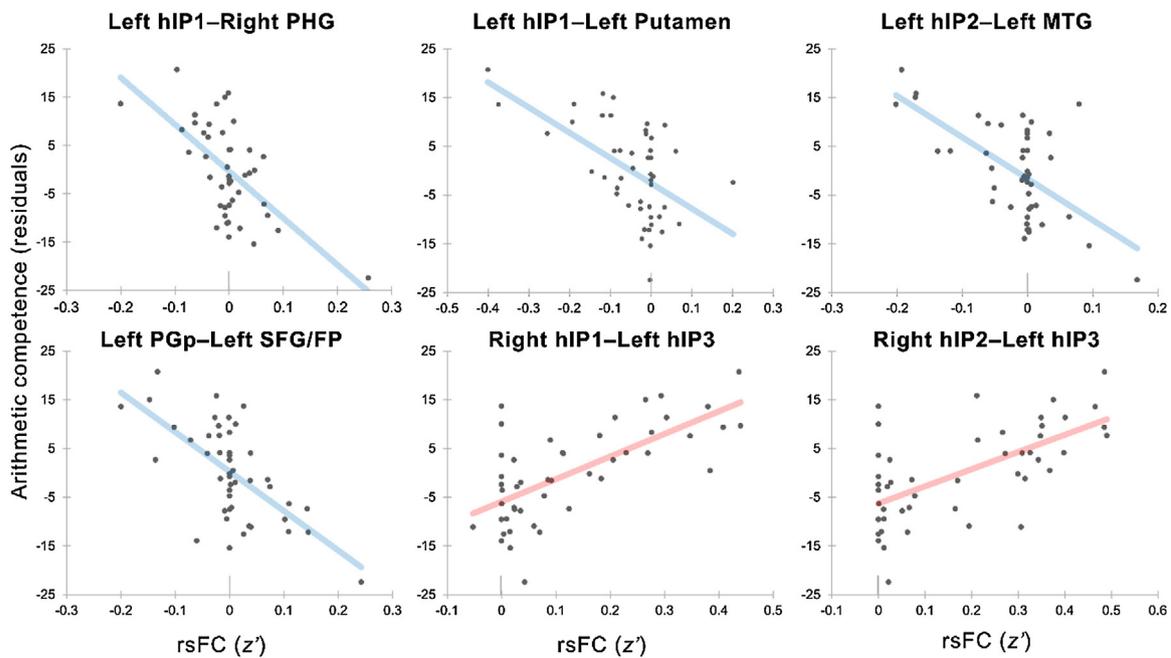
Fig. 3. Correlations between rsFC strength (Fisher's z-transformed, z') at Grade 1 and arithmetic competence (residuals) at Grade 2. PHG: Parahippocampal gyrus; MTG: Middle temporal gyrus; SFG: Superior frontal gyrus; FP: Frontal pole.

4. Discussion

The current study investigated the prospective relation between resting-state functional connectivity (rsFC) of cytoarchitectonically defined subdivisions of the parietal cortex and arithmetic competence in typically developing children.

Our results demonstrate a dissociable pattern of relations between rsFC and arithmetic competence among the subdivisions of IPS and AG. Firstly, we found that the strength of rsFC between right hemisphere IPS subdivisions and contralateral (i.e., left hIP3 with right hIP1 and right hIP2) IPS subdivisions at the end of first grade were positively correlated with arithmetic competence at the end of second grade. In contrast, the strength of connectivity between the left hIP1 and the parahippocampal gyrus, as well as the strength of connectivity between the left AG and the left frontal pole, was negatively correlated with arithmetic competence.

The observed positive associations between parietal connectivity are consistent with the findings of Park et al. (2013) who reported a concurrent relationship between the strength of cross-hemisphere functional connectivity of the IPS and individual differences in nonsymbolic arithmetic competence in a task-based functional connectivity study. This inter-hemispheric parietal connectivity could potentially reflect the importance of binding nonsymbolic and symbolic numerical representations for the development of arithmetic competence. Specifically, it has been suggested that the right hemisphere is particularly associated with nonsymbolic magnitude processing, while the left hemisphere is especially associated with symbolic magnitude processing (Ansari, 2008; Ansari, 2007; Holloway et al., 2010; Holloway et al., 2013; Vogel et al., 2015). In fact, a growing body of behavioral literature suggests that the strength of the mapping between Arabic digits and the magnitudes they represent is a critical foundation for the effective development of math skills, perhaps even more so than the representation of nonsymbolic magnitudes themselves (De Smedt et al., 2013; Mundy and Gilmore, 2009; Price and Fuchs, 2016). Thus, one possible interpretation of the current results is that they provide evidence for this 'mapping hypothesis' (De Smedt et al., 2013) by showing that the intrinsic coupling between key neural mech-

anisms for symbolic and nonsymbolic numerical processing is a significant precursor to the development of early math skills.

An alternative interpretation of these findings is that they may reflect individual differences in efficiency of recruiting and co-activating contralateral brain regions, irrespective of domain-specific cognitive function. Such efficiency, and in turn, our findings, may reflect 'cortical maturity' whereby structural connectivity between brain regions influences functional connectivity (Damoiseaux and Greicius, 2009; Supekar et al., 2010). In summary, our findings may reflect the action of neurocognitive mechanisms specific to numerical and arithmetic processing, or they may reflect the action of domain-general mechanisms that are particularly relevant to the development of arithmetic competence, or they may reflect structural 'cortical maturity', or some combination of all of these. It should be noted, however, that the relation between rsFC and task-based connectivity of these regions is yet to be empirically established. It is possible that increased rsFC relates to either increased or decreased potential for functional co-activation during numerical and mathematical processing.

The observed *negative* associations between parietal rsFC and arithmetic are also broadly consistent with a number of recent studies suggesting that strong functional connectivity between the IPS and regions in the frontal lobes and medial temporal lobes may be negatively associated with the development of math skills. Rosenberg-Lee et al. (2015) reported task-based hyperconnectivity between the IPS and a series of lateral frontal and parietal regions in children with development dyscalculia during both addition and subtraction. Similarly, Jolles et al. (2016a) reported a pattern of resting-state hyper-connectivity between the IPS and a number of frontal and parietal regions in children with mathematical learning difficulties. Although the specific target regions differ between studies, the results of the current study support and extend existing findings by showing analogous patterns in typically developing children whereby a high degree of coupling between parietal subdivisions and extra-parietal regions is negatively associated with math development. In other words, our findings are consistent with previous literature as in regards to hyperconnectivity as a principle, rather than replicating exact regional rsFC relations. A

possible explanation for this pattern of findings was suggested by Jolles et al. (2016a), such that increased functional connectivity at rest between the IPS and regions outside the parietal lobe may be associated with reduced ability to flexibly allocate cognitive resources during variable task situations. This is especially probable because the superior parietal lobe is a densely connected 'hub region', with a large number of connections to a wide variety of extra-parietal brain regions (Anderson et al., 2010). Reduced connectivity at rest may be advantageous for the flexible and efficient coupling of this regions across a wide variety of task contexts (Deco et al., 2012; Senden et al., 2016). This dimension of 'neurocognitive flexibility' in the case of the current study may relate to the need to disengage parietal magnitude processing mechanisms during the processing of basic calculations. This idea fits well with the findings of Rosenberg-Lee et al. (2015), who showed hyperconnectivity during addition and subtraction in children with low math achievement, as well as the results of Price et al. (2013) who showed that higher level math competence was negatively associated with engagement of the IPS during simple arithmetic. Similarly, the negative relations between strength of connectivity of the AG and left frontal pole (BA 10) and math competence may reflect a reduced ability to disengage domain general problem solving mechanisms such as exploratory decision-making (Daw et al., 2006; Koechlin et al., 2002; see Koechlin and Hyafil, 2007 for review), working memory (Boisgueheneuc et al., 2006; Owen et al., 2005; Yoo et al., 2004), relational integration (De Pisapia et al., 2007; see Ramnani and Owen, 2004, for review), and multitasking (Gilbert et al., 2006; Koechlin et al., 1999) in tasks during which pure memory retrieval is optimal (i.e., simple arithmetic). This is especially likely given the role of the AG in the processing and retrieval of highly learned arithmetic facts (Delazer et al., 2005; Grabner et al., 2009b, 2007). Thus, the present findings may reflect domain-general network properties that impact the action of more domain-specific networks that are relevant to the development of arithmetic competence.

In addition to differences between positive and negative associations between rsFC and arithmetic competence, our results also reveal differential patterns of rsFC related to arithmetic competence between cytoarchitectonically defined subdivisions of the parietal cortex. The specificity of the relation between hIP1/hIP3 rsFC and arithmetic competence is congruent with several studies that report greater involvement of the hIP1 and hIP3 than hIP2 in arithmetic tasks (De Smedt et al., 2011; De Visscher et al., 2015; Price et al., 2016; Rosenberg-Lee et al., 2015; Wu et al., 2009). Similarly, we observed slightly different patterns of rsFC associated with arithmetic competence between the subdivisions of the AG. Our results suggest greater importance for rsFC of the left than the right AG in relation to arithmetic competence, and are consistent with previous findings suggesting differential roles of the posterior and anterior AG in mental arithmetic (Grabner et al., 2011; Rosenberg-Lee et al., 2011; Wu et al., 2009).

By and large, our findings are qualitatively consistent with Uddin et al. (2010). Specifically, hIP1 demonstrated greater fronto-parietal connectivity than either hIP2 or hIP3, whereas hIP3 showed greater connectivity with the occipital regions than either hIP1 or hIP2. PGp demonstrated greater connectivity with the frontal and occipital regions, parahippocampal gyrus, and precuneus, whereas PGa showed greater connectivity with the frontal regions and cingulate than PGp. Nonetheless, whether children and adults demonstrate quantitatively similar rsFC patterns as adults remains an open question. For instance, Koyama et al. (2011) demonstrated significant, meaningful differences between children and adults in their rsFC-reading competence relationships that could be attributed to developmental changes.

Taken together, the full set of results from the present study suggests that strong inter-hemispheric intrinsic connectivity between IPS regions is important for math development, perhaps reflecting strong mapping between numerical symbols and their magnitude referents. Stronger connectivity between IPS and AG subdivisions and frontal and temporal cortices, however, appears to be negatively associated with math development, possibly reflecting a reduced ability to disengage suboptimal problem solving strategies during mathematical processing. Although our interpretations necessarily involve a degree of reverse inference, and so should be considered as hypotheses for future investigation, rather that statements of fact, our secondary analyses using basic reading and working memory as dependent variables suggest that the dissociable connectivity patterns in relation to arithmetic competence do not appear to be general to academic skills. The fact that they remain even when controlling for spatial attention and working memory suggests that they are also not general to cognitive processes also known to activate the IPS during task contexts. Moreover, our findings are consistent with Bray et al. (2015) who demonstrated that arithmetic, attention shift, and working memory tasks engaged distinct activation and connectivity patterns of the IPS visuotopic subdivisions. Thus, we believe it is reasonable to infer that our reported results are at least somewhat specific to arithmetic competence. It should be noted that the results reported here are open to a variety of interpretations, and that making inferences about the function of brain regions during resting-state scans comes with inherent challenges due to the lack of actual task performance, most notably, the challenge of 'reverse inference', whereby inferences about a brain region's function are made on the basis of that region's function in the extant literature (Poldrack, 2006). However, reverse inference can be a useful method of scientific reasoning and hypothesis generation, as it is essentially a form of adductive reasoning (Poldrack, 2011). Therefore, in the interpretations of the findings of the present study, we attempt to offer multiple possible interpretations, and note that these interpretations are suggested possibilities that require further empirical investigation.

It should be noted that although we employed standard motion correction using trilinear-sinc interpolation implemented in Brain-Voyager, excluded subjects with more than 20% outlying volumes as identified using the artifact detection toolbox, and utilized six parameters of motion as nuisance covariates in the GLM, it is still possible that motion of the remaining subjects may have influenced the data. This is specifically relevant to our current findings given that "many long-distance correlations are decreased by subject motion, whereas many short-distance correlations are increased" (Power et al., 2012, p. 2142). It should also be noted that rsFC values of zero are difficult to interpret, and may in of themselves be qualitatively different from negative or positive rsFC values, thus limiting to some extent the ability to interpret rsFC scores numerically on a continuum of phasic synchrony between regions.

The current results advance our understanding of the relation between inter-hemispheric connectivity of right parietal regions and the development of arithmetic competence in two crucial ways. First, our reported results are prospective as opposed to concurrent, suggesting that the integrity of the observed intraparietal networks precedes the acquisition of related math skills, and therefore may be part of a constellation of causal factors such as genetics and early environmental influences, rather than a consequence. Second, our findings suggest that the IPS and AG should not be considered as homogenous cortical entities with regards to its role in numerical and mathematical processing. Instead, consideration of functionally and structurally heterogeneous subdivisions is crucial for deepening and refining our understanding of the neurocognitive bases of math development. Future research should investigate the specific role of parietal subdivisions in numerical (e.g., numerical magnitude comparison) and mathematical (e.g., mental arithmetic) task contexts. Finally, our results suggest that resting-state fMRI is an effective tool for identifying math-relevant cortical networks.

This fact is important as it opens the door to studies of typical and atypical ontogenetic development of cortical networks that are not confounded by task performance or strategy use, and thus may provide a purer characterization of the relation between neural development and the acquisition of arithmetic competence.

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dcn.2017.02.006.

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