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ORIGINAL ARTICLE

Fronto-parietal numerical networks in relation with early numeracy in young children

Han Zhang[1,2] · Chong-Yaw Wee[1] · Joann S. Poh[2] · Qiang Wang[1] · Lynette P. Shek[2,6,7] · Yap-Seng Chong[2,8] · Marielle V. Fortier[3] · Michael J. Meaney[2,4,5] · Birit F. P. Broekman[2] · Anqi Qiu[1,2]

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Abstract

Early numeracy provides the foundation of acquiring mathematical skills that is essential for future academic success. This study examined numerical functional networks in relation to counting and number relational skills in preschoolers at 4 and 6 years of age. The counting and number relational skills were assessed using school readiness test (SRT). Resting-state fMRI (rs-fMRI) was acquired in 123 4-year-olds and 146 6-year-olds. Among them, 61 were scanned twice over the course of 2 years. Meta-analysis on existing task-based numeracy fMRI studies identified the left parietal-dominant network for both counting and number relational skills and the right parietal-dominant network only for number relational skills in adults. We showed that the fronto-parietal numerical networks, observed in adults, already exist in 4-year and 6-year-olds. The counting skills were associated with the bilateral fronto-parietal network in 4-year-olds and with the right parietal-dominant network in 6-year-olds. Moreover, the number relational skills were related to the bilateral fronto-parietal and right parietal-dominant networks in 4-year-olds and had a trend of the significant relationship with the right parietal-dominant network in 6-year-olds. Our findings suggested that neural fine-tuning of the fronto-parietal numerical networks may subserve the maturation of numeracy in early childhood.

Keywords School readiness test · Counting · Number relation · Resting-state functional magnetic resonance imaging · Fronto-parietal network

Introduction

Early numeracy refers to a set of operations performed by counting objects (i.e., counting skill) and number relations (i.e., number relational skill), such as number comparison and simple arithmetic (Raghubar and Barnes 2016). It is

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✉ Anqi Qiu
bieqa@nus.edu.sg

1 Department of Biomedical Engineering and Clinical Imaging Research Center, National University of Singapore, Singapore 117576, Singapore

2 Singapore Institute for Clinical Sciences, Singapore 117609, Singapore

3 Department of Diagnostic and Interventional Imaging, KK Women's and Children's Hospital, Singapore (KKH), Singapore, Singapore

4 Ludmer Centre for Neuroinformatics and Mental Health, Douglas Mental Health University Institute, McGill University, Montreal, Canada

5 Sackler Program for Epigenetics and Psychobiology, McGill University, Montreal, Canada

6 Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

7 Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore, Singapore

8 Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

the basis for number concept development in children and emerges before formal schooling (Piaget 1965; Gelman and Galistell 1978; Fuson 1988; Van de Rijt 1996). Lagged development of early numeracy can seriously affect the formation of children's number concept and subsequent development of higher-level mathematical skills, and can even cause dyscalculia or mathematical learning difficulties (Aunio and Niemivirta 2010; Kolkman et al. 2013; Bartelet et al. 2014; Toll et al. 2015). Understanding neural basis of early numeracy may offer insights on its assessment and intervention for children at risk for mathematical learning difficulties (Ansari and Karmiloff-Smith 2002; Raghubar and Barnes 2016).

Both parietal and frontal brain regions are identified as the key structures for numerical processing (Dehaene 2011; Zhang et al. 2012; Harvey et al. 2017). Nevertheless, different parietal and frontal regions may be involved in counting and number relational processing over the course of development (Nieder 2005; Nieder and Dehaene 2009; Lussier and Cantlon 2017). In adults, bilateral parietal cortex, especially the left inferior parietal lobule (IPL), is responsible for both counting and number relational processing (Chochon et al. 1999; Dehaene et al. 2003; Sokolowski et al. 2016). But, the brain activation of right IPL and prefrontal cortex (e.g., inferior frontal gyrus) is enhanced in number relational processing when task demand is high (Park et al. 2013; Feng et al. 2014; Menon 2014; Sokolowski et al. 2016). In school-age children, the activation strength of bilateral fronto-parietal regions is related to the development of mathematical skills in early life (Rosenberg-Lee et al. 2011; Metcalfe et al. 2013; Jolles et al. 2016b). This suggested that children, unlike adults, may recruit both parietal and prefrontal regions when performing basic counting. Compared with adults, the number relational processing in children shows dependence not only on the left IPL, but also on the right IPL (Rivera et al. 2005; Ansari and Dhital 2006; Vogel et al. 2015). In addition, school-age children show stronger activation in the prefrontal cortex during number comparison and arithmetic tasks than adults (Cantlon et al. 2009; Fias et al. 2013). We hence hypothesize that the fronto-parietal numerical networks, similar to that observed in adults and school-age children, might be formed in early childhood even before school-age. Common and distinct neural substrates in the parietal and prefrontal cortex may be involved in counting and number relational skills in preschoolers. However, preschoolers may involve frontal regions and bilateral parietal regions for both counting and number relational processing. As age increases, less frontal and parietal regions are involved for simple counting. However, the number relational processing would mainly depend on the right parietal cortex in early childhood.

This study aimed to unravel the neural mechanism of early numeracy in preschoolers using resting-state functional magnetic resonance imaging (rs-fMRI) and to examine associations of counting and number relational skills with the fronto-parietal numerical networks in children at age of 4 and 6 years. We conducted a meta-analysis of activation likelihood estimation (ALE) to identify neural substrates of numeracy based on existing functional imaging studies. Most of the existing functional imaging studies on numeracy were conducted in adults. This meta-analysis allows identifying relatively mature numerical functional networks and investigating their role in early numeracy development. The identified numerical functional networks (i.e., fronto-parietal numerical networks) were applied to elucidate neural substrates for counting and number relational processing in preschoolers. Finally, multivariate analysis was employed to examine the associations of the counting and number relational skills with the fronto-parietal numerical networks at age 4 and 6 years. The results of this study provide, to our knowledge, the first direct link between early numeracy (both counting and number relational skills) and numerical functional networks in early childhood.

Materials and methods

Participants

This study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB) and the Sing Health Centralized Institutional Review Board (CIRB). Written informed consent was obtained from mothers and oral informed consent was obtained from children prior to participation.

Children who participated in the prospective Growing Up in Singapore Towards healthy Outcomes (GUSTO) longitudinal birth cohort study were recruited for this neuroimaging study when they were 4 and 6 years old. The GUSTO cohort recruited pregnant Singapore citizens or permanent residents of Chinese, Malay or Indian ethnic backgrounds from two major birthing hospitals in Singapore at the first antenatal visit.

Birth outcomes, including gestational age, birth weight, appearance, pulse, grimace, activity, and respiration (APGAR) score, and gender were obtained from the hospital record. This study only included children with gestational age ≥ 34 weeks, birth weight ≥ 2 kg and a 5-min APGAR score ≥ 9 to avoid their potential impacts on brain development and behavioral performance.

School readiness test

The school readiness test (SRT) was used to assess early numeracy in this study in children at 4 years of age. School readiness is a multi-faceted construct that has gained increasing attention over recent years as an important determinant of later academic and developmental outcomes (UNICEF 2012). The SRT is designed to incorporate behavioral and socio-emotional functioning, early numeracy, literacy and cognitive development, as well as general knowledge domains (Jordan and Kaplan 2009; Fitzpatrick and Pagani 2012; Pratt et al. 2016). By age of 4, typically-developing children have achieved major developmental milestones in these areas. To evaluate the early numeracy, this study employed scores of Lollipop subtest 3 (Lollipop), and the number knowledge test level 1 (NKT1) and level 2 (NKT2) from the SRT.

Lollipop test (Lollipop)

The Lollipop is a well-validated diagnostic screening test of school readiness (Chew and Morris 1984). Subtest 3 examines the identification of numbers (e.g., look at this page with numbers; show me the number 4) and counting (e.g., count the red lollipops in this box). Among total 14 items, we only used scores from the last 5 items which are targeting the counting skill. All items are scored on a pass or fail basis. A child needs to complete all items regardless their performance. The full score for counting is 5 points. A higher score indicates better performance in counting.

Number knowledge test (NKT)

The NKT assesses the emergence and progressive integration of children's knowledge on numeracy (Okamoto and Case 1996; Forget-Dubois et al. 2007). In this test, children have to answer a series of questions regarding the understanding of the base 10 system of whole numbers. These questions are grouped in two levels, increasing in difficulty, based on the different abilities required to respond in a successful manner (Case et al. 2001; Purpura and Lonigan 2013). The first level (NKT1) consists of 5 items assessing counting skill. To comprehensively quantify the counting performance, a composite score was calculated via standardizing Lollipop and NKT1 scores and taking their average in 4-year-olds. A higher composite score indicates better performance of counting.

The second level (NKT2) consists of 13 items assessing number relational skill. It examines children's understanding of quantity corresponding to each number, the generative rule which relates adjacent numbers, and the relations between numbers such as number comparison (e.g., Which is bigger, 5 or 4?) and simple arithmetic (e.g., How much is 2 plus 4?). All items are scored on a pass or fail basis. The child has to get at least 3 successful items at the first level to reach the second level. The test is terminated after three consecutive failures. The full score of NKT1 is 5 points and the full score of NKT2 is 13 points. A higher score indicates better performance. Since children around age 4 may not be capable to fulfill NKT2 (Piaget 1965; Van de Rijt 1996), a categorical score NKT2-cat is defined based on whether the full score of NKT2 is above 0. Specifically, children with a score above 0 in NKT2 were categorized as pass and re-scored as 1 in NKT2-cat, while children with score 0 in NKT2 were categorized as fail.

Nonverbal IQ

The nonverbal IQ of 4-year-olds was evaluated using the subtest Matrices of Kaufman Brief Intelligence Test, Second Edition (K-BIT2) (Hildman et al. 1993; Kaufman and Kaufman 1993). K-BIT2 is a brief, individually administered standardized intelligence test. This nonverbal IQ was considered as a confounding factor for early numeracy (Alloway and Alloway 2010; Purpura et al. 2011; Bullard et al. 2013).

MRI acquisition and analysis

Children underwent MRI scans using a 3 T Siemens Skyra scanner with a 32-channel head coil at KK Women's and Children's hospital. The imaging protocols were: (i) high-resolution isotropic T1-weighted Magnetization Prepared Rapid Gradient Recalled Echo (MPRAGE; 192 slices, 1 mm thickness, in-plane resolution 1 mm, sagittal acquisition, field-of-view 192×192 mm, matrix = 192×192, repetition time = 2000 ms, echo time = 2.08 ms, inversion time = 877 ms, flip angle = 9°); (ii) isotropic axial rs-fMRI protocol (single-shot echo-planar imaging; 48 slices with 3 mm slice thickness, no inter-slice gaps, matrix = 64 × 64, field-of-view = 192×192 mm, repetition time = 2660 ms, echo time = 27 ms, flip angle = 90°, scan time = 5.27 min). The children were asked to close their eyes during the rs-fMRI scan.

The image quality was verified immediately after the acquisition through visual inspection while the children were still in the scanner. If the motion artifact was large, a repeat scan was conducted. The subject was dropped from the study if no acceptable image was obtained after three repetitions. After the data acquisition, the image quality was further visually inspected. After this screening step, T1-weighted MRI and rs-fMRI with good quality were included for the following MRI preprocessing.

Structural MRI

Anatomical segmentation into three tissue types, grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF), was performed using FreeSurfer (Fischl et al. 2002). Nonlinear image normalization was achieved by aligning individual T1-weighted MRI images to the atlas space via large deformation diffeomorphic metric mapping (LDDMM) (Du et al. 2011; Tan and Qiu 2016).

Rs-fMRI

The rs-fMRI scan was preprocessed using FSL with slice time correction, motion correction, skull stripping, and intensity normalization. The rs-fMRI scans with maximal framewise displacement (FD > 0.5 mm) of head motion were removed from the study at this stage (Power et al. 2012). Six motion parameters, whole brain, WM and CSF signals were further partialled out from rs-fMRI signals. Global signal regression was an appropriate preprocessing step particularly for studying pediatric, clinical and elderly populations to eliminate artifactual variance due to head motion (Power et al. 2014). Band-pass filtering (0.01–0.08 Hz) was then applied. Within subjects, the mean functional volume was aligned to the corresponding anatomical image via rigid body alignment. The functional data were finally transformed to the atlas space via LDDMM obtained based on the T1-weighted MRI.

Meta-analysis on shared and distinct networks supporting counting and number relational processing in adults

Meta-analysis was conducted to identify brain regions involved in counting and relational numerical processing. BrainMap Sleuth 2.4 (Laird 2009) was used to select fMRI or PET studies with experiments of counting (i.e., counting numbers or objects such as dots) and number relational processing (i.e., number magnitude comparison and arithmetic such as addition and subtraction) in healthy participants. Each experiment was limited to a sample size greater than 5, and only positive activation. ALE in GingerALE 2.3.6 (Eickhoff et al. 2012, 2017; Turkeltaub et al. 2012) was employed to identify brain regions that are activated during counting or number relational processing. The ALE map was thresholded at a cluster-forming (uncorrected) threshold of $p < 0.001$ and a cluster-level threshold of $p < 0.05$ based on 1000 permutations (Eickhoff et al. 2016, 2017), which was suggested by the developer to correct for false-positive clusters.

Conjunction analysis was then computed to examine the overlap of the ALE maps respectively corresponding to counting and number relational processing (Caspers et al. 2010; Sokolowski et al. 2016). The conjunction was considered to be significant at a voxel if both ALE maps showed significant activation in this voxel. The minimum value of the two ALE images was used to create the conjunction map. On the other hand, contrast analysis was computed to identify brain regions that were only involved in number relational processing but not in counting. The ALE contrast map was created by directly subtracting the ALE map associated with counting from the ALE map associated with number relational processing. GingerALE simulated null data to correct for unequal sample sizes by pooling foci and randomly dividing the foci into two groupings that were equal in size to the original datasets. One simulation dataset was subtracted from the other and compared to the true data. This produced a voxel-wise p value image that was then converted to z scores. The conjunction and contrast maps were thresholded at $p < 0.01$ based on 5000 permutations and with a minimum volume of 100 mm^3 (Eickhoff et al. 2012; Sokolowski et al. 2016). The conjunction and contrast maps were further parcellated based on the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al. 2002) and were considered as seeds for the following brain functional network analysis if the seed had more than 10 voxels (i.e., 80 mm^3).

Functional network construction

Three functional networks, including left parietal-dominant, right parietal-dominant, and bilateral fronto-parietal numerical networks, were constructed. The left parietal-dominant numerical network was comprised of the seeds in the conjunction map, while the right parietal-dominant numerical network consisted of the seeds in the contrast map. Rs-fMRI time series were computed by averaging the signal of all voxels within each seed. Pearson's correlation coefficients between the mean fMRI signals of any two seeds were calculated and transformed to z scores using Fisher's r-to-z transformation for subsequent multivariate statistical analysis.

Multivariate statistical analysis

Multivariate analysis was employed to examine associations between the three functional networks and the early numeracy skills. For this, the variance of functional connectivities in each functional network due to nonverbal IQ and the mean framewise displacement was first removed using linear regression. Nonverbal IQ as measured with K-BIT2 was included to minimize its possible effect on the numeracy performance of children (Kyttälä and Lehto 2008; Alloway and Alloway 2010; Purpura et al. 2011). The mean framewise displacement across all volumes was included to minimize possible effects of rs-fMRI head motion on the brain functional connectivity. Subsequently, minimum redundancy maximum relevance (mRMR) algorithm was used to select the subset of the functional connectivity that was best to describe the brain numerical networks of preschool children (Peng et al. 2005; Ghorai et al. 2011; Wee et al. 2012). To be specific, the full set of subjects was randomly divided into 10 different sets in a stratified manner to ensure that the distribution of behavioral score in each set was equivalent. One set was first left out and the remaining 9 sets were employed to reordering features (in our case, correlation values of the functional network) by minimizing the total relevance of each feature–feature pairs to achieve minimum redundancy and to simultaneously maximize the total relevance of each feature-label pairs (in our case, labels are the behavioural scores) to achieve maximum relevance condition. The highest ranked 5 functional connectivities were selected in each trial. This procedure was repeated 100 times, generating 1000 different optimal subsets of functional connectivities in each brain network. Selection frequency of all functional connectivities was determined and those with a frequency higher than chance level (i.e., 50%) were selected as features. Finally, a multivariate canonical correlation analysis (CCA) was used to examine the joint contribution of these selected functional connectivities to the counting and relational numerical skills. The feature selection and multivariate CCA were performed for each functional network (i.e., left parietal-dominant, right parietal-dominant, bilateral fronto-parietal networks) with each behavioral performance (i.e., counting composite score and NKT2-cat) at the individual time point (i.e., 4 and 6 years old). Finally, false discovery rate (FDR) was carried out to correct for multiple comparisons.

Results

Demographics and early numeracy skills

Among 709 children who underwent SRT, 123 and 146 children, respectively, had high-quality rs-fMRI scans at 4 (mean age 4.58 years; SD = 0.08) and 6 years of age (mean age 6.02 years; SD = 0.11). Among them, 61 children had rs-fMRI scans at both time points. All subjects were born at gestational age ≥ 34 weeks, birth weight ≥ 2 kg, and a 5-min APGAR score ≥ 9. Table 1 lists the demographics and SRT measures in the full SRT sample assessed at age 4 and the samples with SRT and rs-fMRI at age 4 and 6.

There were no significant differences in gestational age ($F_{(2, 975)} = 1.453$, $p = 0.234$), birth weight ($F_{(2, 975)} = 0.191$, $p = 0.826$), APGAR ($F_{(2, 975)} = 0.746$, $p = 0.475$), gender ($\chi^2_2 = 5.940$, $p = 0.051$) and non-verbal IQ ($F_{(2, 589)} = 1.077$, $p = 0.341$) among the full SRT sample and the samples with SRT and rs-fMRI at age 4 and 6. However, significant difference was found in maternal ethnicity ($\chi^2_4 = 12.303$, $p = 0.015$). Post-hoc pair-wise group comparisons revealed the group difference in maternal ethnicity between the full SRT sample and the sample with SRT and rs-fMRI of 4-year-olds ($\chi^2_1 = 4.331$, $p = 0.037$).

Brain functional networks for counting and relational skills via meta-analysis

Activation likelihood estimation was used to conduct meta-analysis to identify brain regions activated during counting and number relational processing in adults. ALE included 26 studies for counting skill (Supplementary Table 1; 347 subjects, 40 contrasts, 333 foci) and 44 studies for number relational skill (Supplementary Table 2; 633 subjects, 77 contrasts, 757 foci). Figure 1a, b shows the ALE maps for counting and number relational processing. Conjunction analysis (Fig. 1c; Table 2) revealed brain regions activated during both counting and number relational processing,

Table 1 Demographic characteristics and early numeracy skills

Characteristics	Age 4 sample with Rs-fMRI ($N = 123$)	Age 6 sample with Rs-fMRI ($N = 146$)	Full SRT sample ($N = 709$)
Gestational age (week), mean (s.d.)	38.73 (1.27)	38.96 (1.22)	38.91 (1.18)
Birth weight (gram), mean (s.d.)	3118.16 (416.75)	3104.32 (405.38)	3126.95 (410.88)
AGPAR score, mean (s.d.)	9.01 (0.09)	9.00 (0.00)	9.00 (0.05)
Gender, male/female	51/72	61/85	357/352
Maternal ethnicity, %*			
Chinese	43.90	45.89	56.28
Malay	37.40	35.62	25.95
Indian	18.70	18.49	17.77
Nonverbal IQ, mean (s.d.)	102.34 (13.99)	101.33 (14.74)	100.00 (14.67)
Lollipop, mean (s.d.)	3.37 (1.28)	3.50 (1.26)	3.45 (1.31)
NKT1, mean (s.d.)	3.50 (1.24)	3.66 (1.31)	3.67 (1.32)
Counting, mean (s.d.)	0.644 (0.195)	0.673 (0.198)	0.672 (0.200)
NKT2-cat, pass/fail	43/77	56/87	278/399

s.d. standard deviation, *APGAR* appearance, pulse, grimace, activity, and respiration, *Lollipop* subtest 3 of Lollipop test, *NKT1* level 1 of number knowledge test, *NKT2-cat* a categorical score with 1 indicating the pass of level 2 of number knowledge test and 0 representing the failure of level 2 of number knowledge test

*$p < 0.05$. Counting means the composite score by averaging standardized scores from Lollipop and NKT1

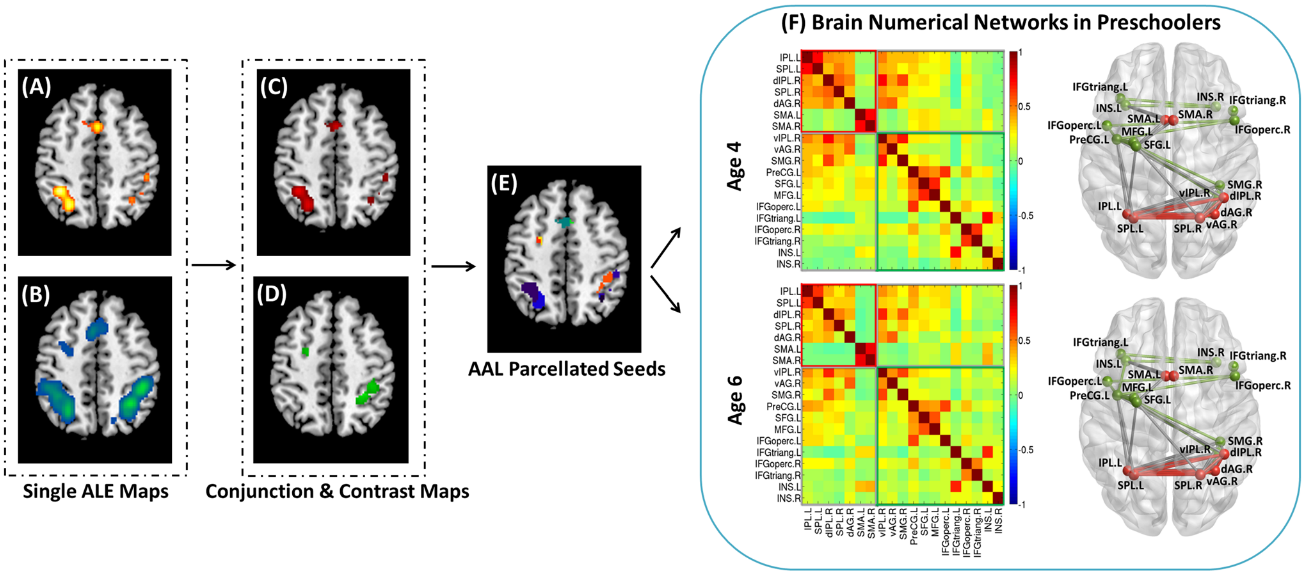

Fig. 1 Brain functional networks related to the counting and number relational processing. **a, b** Show the ALE maps for counting (orange) and relational numerical (blue) processing, respectively. **c, d** Show the conjunction (red) and contrast (green) maps between the ALE maps of the counting and number relational processing. **e** Indicates seeds on the conjunction and contrast maps parcellated by the AAL atlas. **f** Displays the brain functional networks built from the rs-fMRI data at 4 and 6 years of age, with values in each cell indicating the mean functional connectivity across all subjects. Brain slices are shown at the MNI coordinates ($Z=49$). The nodes are drawn on the centroid stereotaxic coordinates of the seed regions, and only edges with top 30% functional connectivity are displayed. The boxes, nodes, and edges in red, green, and grey, respectively, represent the left parietal-dominant, right parietal-dominant, bilateral fronto-parietal numerical networks. *R* right, *L* left, *A* anterior, *P* posterior, *dAG* dorsal portion of angular gyrus, *vAG* ventral portion of angular gyrus, *IPL* inferior parietal lobule, *dIPL* dorsal portion of IPL, *vIPL* ventral portion of IPL, *SPL* superior parietal lobule, *SMA* supplementary motor area, *IFGoperc* inferior frontal gyrus, opercular part, *IFGtriang* inferior frontal gyrus, triangular part, *MFG* middle frontal gyrus, *SFG* superior frontal gyrus, *INS* insula, *PreCG* precentral gyrus, *SMG* supramarginal gyrus

Table 2 Shared and distinct brain regions involved in counting and number relational processing

Hemisphere	Structure	BA	X	Y	Z	ALE	Vol (mm^3)
Left parietal-dominant network for counting and number relational skills							
L	Inferior parietal lobule	40	−36	−48	46	0.023	3120
R	Superior parietal lobule	7	24	−62	62	0.017	1432
L	Supplementary motor area	32	0	12	48	0.018	1320
Hemisphere	Structure	BA	X	Y	Z	*z* value	Vol (mm^3)
Right parietal-dominant network for number relational skill only							
R	Inferior parietal lobule	40	29.7	−48.1	42	3.719	3728
L	Inferior frontal gyrus	6	−48.5	2.8	25.5	3.719	1656
L	Insula	48	−36	18	10	3.719	1624
R	Inferior frontal gyrus	44	50	14	18	3.353	1352
L	Precentral gyrus	6	−26.4	−12	54.8	3.036	1000
R	Insula	47	36	18	−4	2.820	392

R right, *L* left, *BA* Brodmann area, *ALE* activation likelihood estimation, *X, Y and Z* the MNI coordinates of the maximum ALE values

including the left supplementary motor area (SMA), left inferior parietal lobule (IPL), and right superior parietal lobule (SPL). Contrast analysis (Fig. 1d; Table 2) revealed brain regions activated only during number relational processing, but not during counting processing, including the right IPL, bilateral inferior frontal gyrus (IFG), bilateral insula (INS), and left precentral gyrus (PreCG). Table 2 lists the MNI coordinates (X, Y, Z), the peak ALE values for the conjunction map, and *z* values for the contrast map.

In the above meta-analyses, the number of experiments on number relational processing was almost twice as large as that on counting processing, which may result in potential bias to the identification of brain regions only for number relational processing in the contrast analysis (Caspers et al. 2010). To evaluate the reliability of the findings obtained from the contrast analysis, half of the experiments related to the number relational skill were randomly selected each time to construct the ALE map and conduct the contrast analysis using the equivalent numbers of experiments for counting processing. The re-analysis was repeated ten times. A high correlation of the evaluation results was found with the contrast map in Fig. 1d ($r > 0.63$), suggesting little influence due to unequal numbers of the experiments for counting and number relational processing on the contrast analysis.

The conjunction and contrast maps were further parcellated based on the automated anatomical labeling (AAL) atlas, resulting in 7 and 12 seeds, respectively (Fig. 1e). In general, the parietal regions mainly associated with both counting and number relational skills and formed the left parietal-dominant network, while the right parietal-dominant network was mainly associated with number relational skills and constructed to the bilateral fronto-parietal network. Using rs-fMRI and the above-defined seeds, the left parietal-dominant, right parietal-dominant, and bilateral fronto-parietal networks in children at age of 4 and 6 years were constructed using rs-fMRI, which are respectively shown in red, green, and grey in Fig. 1f.

Associations between early numeracy and the brain numerical networks

Counting skill

CCA revealed the associations of the bilateral fronto-parietal network with counting (Table 3; $F_{(4, 80)} = 3.568$, $p < 0.05$, FDR corrected) among 4-year-olds. In particular, the significant relationship with counting was mainly due to the functional connections among left parietal and bilateral frontal regions, including connections between the left SPL and left PreCG, between the left IPL and the triangular segment of left IFG (i.e., IFGtriang), between the left IPL and the opercular segment of left IFG (i.e., IFGoperc), as well as between right IFGtriang and left SMA (see CCA coefficients in Figs. 2a, 3a). Nevertheless, there were no associations of counting in the left or right parietal-dominant networks among 4-year-olds (Table 3).

Unlike 4-year-olds, 6-year-olds showed the significant relationship of counting skills with the right parietal-dominant network rather than with the bilateral fronto-parietal network (Table 3; $F_{(5, 95)} = 4.851$, $p < 0.01$, FDR corrected). This significant relationship was mainly contributed by the functional connections among right parietal and frontal regions, including connections between the ventral portion of right IPL (vIPL) and left IFGtriang, between the right vIPL and right supramarginal gyrus (SMG), between the left superior frontal gyrus (SFG) and right IFGoperc, as well as between the left SFG and left IFGoperc (see CCA coefficients in Figs. 2b, 3b).

Nevertheless, the counting skill was not significantly associated with the developmental changes in the left parietal-dominant ($F_{(4,41)} = 0.616$, $p = 0.653$), right parietal-dominant ($F_{(3,42)} = 0.011$, $p = 0.999$), and bilateral fronto-parietal numerical networks ($F_{(5,40)} = 0.419$, $p = 0.832$) from 4 to 6 years of age.

Number relational skill

The capability of number relational processing (i.e., NKT2-cat) was significantly associated with both the right parietal-dominant (Table 3; $F_{(3, 80)} = 4.279$, $p < 0.05$, FDR corrected) and the bilateral fronto-parietal (Table 3; $F_{(2, 81)} = 11.848$,

Table 3 Associations between brain functional networks and early numeracy

	CCA *F* value (*p* value)					
	4-year olds			6-year-olds		
	Left parietal-dominant network	Right parietal-dominant network	Bilateral fronto-parietal network	Left parietal-dominant network	Right parietal-dominant network	Bilateral fronto-parietal network
Counting skill						
Counting	1.684 (0.177)	2.811 (0.045)	3.568 (0.010)*	1.561 (0.179)	4.851 (0.000)**	0.980 (0.435)
Number relational skill						
NTK2-cat	1.667 (0.153)	4.279 (0.008)*	11.848 (0.000)**	1.137 (0.344)	3.025 (0.033)	1.255 (0.293)

CCA canonical correlation analysis, *Lollipop* subtest 3 of Lollipop test, *NKT1* level 1 of number knowledge test, *NKT2-cat* a categorical score with 1 indicating the pass of the level 2 of number knowledge test and 0 representing the failure of the level 2 of number knowledge test

*$p < 0.05$ (FDR corrected); **$p < 0.01$ (FDR corrected). Counting means the composite score by averaging standardized scores from Lollipop and NKT1

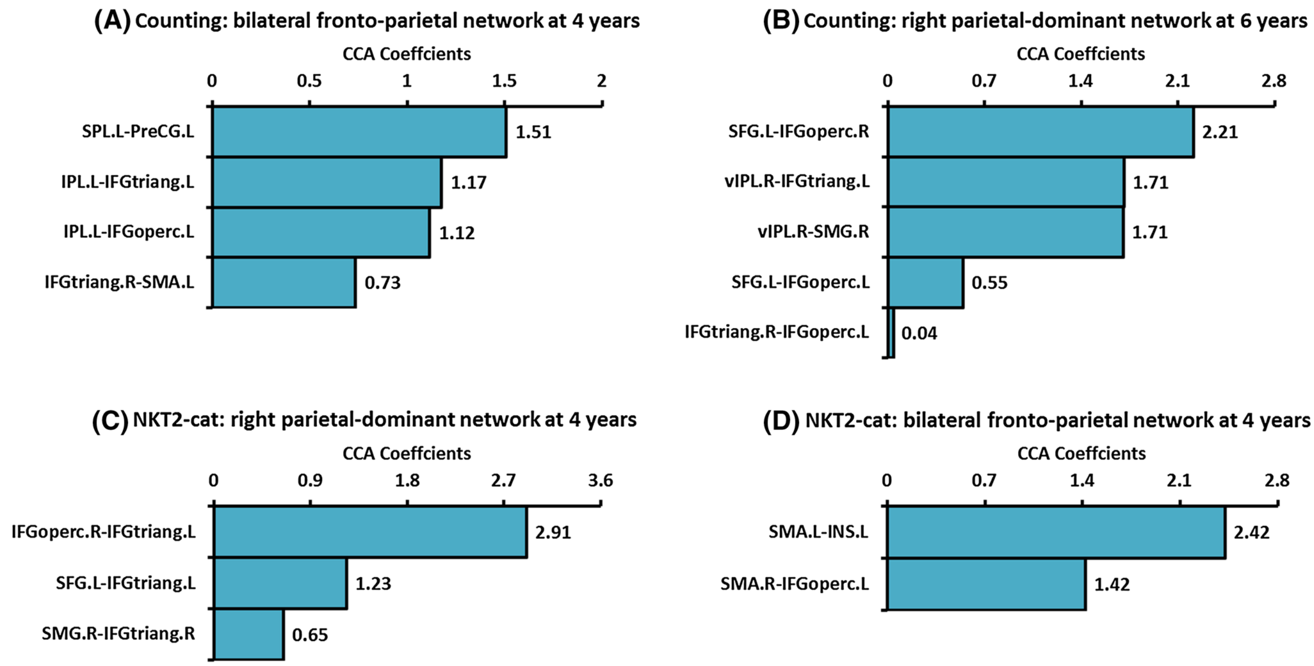

Fig. 2 CCA coefficients for associations between brain numerical networks and early numeracy. **a–d** Respectively show CCA coefficients for associations of counting with bilateral fronto-parietal network in 4-year-olds and with right parietal-dominant network in 6-year-olds, and associations of NKT2-cat with bilateral fronto-parietal network and right parietal-dominant network in 4-year-olds. *R* right, *L* left, *IPL* inferior parietal lobule, *dIPL* dorsal portion of IPL, *vIPL* ventral portion of IPL, *SPL* superior parietal lobule, *SMA* supplementary motor area, *IFGoperc* inferior frontal gyrus, opercular part, *IFGtriang* inferior frontal gyrus, triangular part, *MFG* middle frontal gyrus, *SFG* superior frontal gyrus, *INS* insular, *PreCG* precentral gyrus, *SMG* supramarginal gyrus, *CCA* canonical correlation analysis

$p < 0.01$, FDR corrected) networks in 4-year-olds. The contributing connections were anchored in the prefrontal cortex. In the right parietal-dominant network, NKT2-cat was associated with functional connections between the right IFGoper and left IFGtriang, between the left SFG and left IFGtriang, as well as between the right SMG and right IFGtriang (see CCA coefficients in Figs. 2c, 3c). In the bilateral fronto-parietal network, NKT2-cat was associated with functional connections between the left SMA and left INS, as well as between the right SMA and left IFGoperc (see CCA coefficients in Figs. 2d, 3c). Unlike 4-year-olds, there was a trend of significant association between NKT2-cat and the right parietal-dominant network in children of 6-year-old (Table 3; $F_{(3, 95)} = 3.025$, $p = 0.080$, FDR corrected).

Similar to the counting skill, NKT2-cat was also not significantly associated with the developmental changes in the left parietal-dominant ($F_{(5,39)} = 0.692$, $p = 0.633$), right parietal-dominant ($F_{(5,39)} = 0.815$, $p = 0.546$), and bilateral fronto-parietal numerical networks ($F_{(4,40)} = 3.226$, $p = 0.022$) from 4 to 6 years of age.

Discussion

This study provided the evidence that the fronto-parietal numerical networks, observed in adults, already exist in 4-year and 6-year-olds. It was in line with evidence that the functional intersection of number-related fronto-parietal regions had contribution to mathematical performance in 4–11-year-old children (Emerson and Cantlon 2012). The neural representation of number sense has been observed in the fronto-parietal cortex as early as 3-year-olds (Cantlon et al. 2006; Kersey and Cantlon 2016). Our study further revealed that the counting skills were associated with the bilateral fronto-parietal network in 4-year-olds and with the right parietal-dominant network in 6-year-olds. Moreover, the number relational skills were related to the bilateral fronto-parietal and right parietal-dominant networks in 4-year-olds and had a trend of the significant relationship with the right parietal-dominant network in 6-year-olds. These findings suggested that the

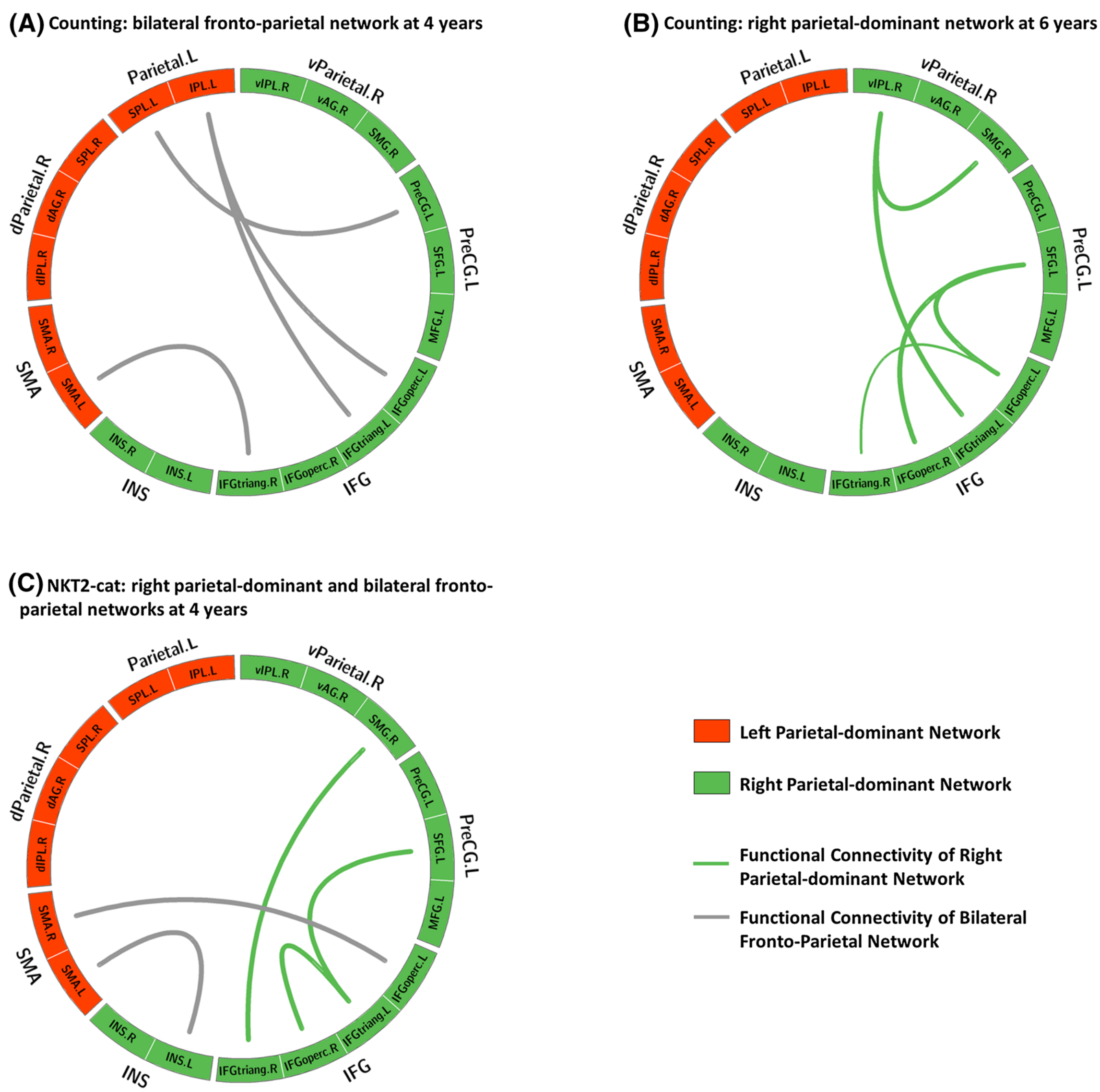

Fig. 3 Associations between brain numerical networks and early numeracy. Each circle represents 19 seeds in the fronto-parietal numerical networks. The seeds in red and green respectively represent the conjunction and the contrast results from our meta-analysis. The connections between seeds are drawn with lines. The width of the line indicates the strength of CCA coefficients, with values above 0.5 displayed with thicker lines. The connections in green and grey respectively represent connections of the right parietal-dominant and bilateral fronto-parietal numerical networks. *R* right, *L* left, *vParietal* ventral portion of parietal regions, *dParietal* dorsal portion of parietal regions, *IFG* inferior frontal gyrus, *dAG* dorsal portion of angular gyrus, *vAG* ventral portion of angular gyrus, *IPL* inferior parietal lobule, *dIPL* dorsal portion of IPL, *vIPL* ventral portion of IPL, *SPL* superior parietal lobule, *SMA* supplementary motor area, *IFGoperc* inferior frontal gyrus, opercular part, *IFGtriang* inferior frontal gyrus, triangular part, *MFG* middle frontal gyrus, *SFG* superior frontal gyrus, *INS* insular, *PreCG* precentral gyrus, *SMG* supramarginal gyrus, *CCA* canonical correlation analysis

interregional collaboration in the fronto-parietal numerical networks would be fine-tuned according to the development of numeracy.

Through the developmental course of counting, its brain functional support shifts from the widespread bilateral fronto-parietal network to the right parietal-dominant network, and to the left parietal-dominant network from childhood to adulthood. Our meta-analysis identified the left parietal-dominant network as a key circuitry associating with counting skills in adults. However, the bilateral fronto-parietal networks were critical to the counting skills in 4-year-olds. This is probably related to the specific developmental stage of the counting skills in preschoolers. At age of 4, preschoolers' counting skills are at an indexical stage (i.e., establishing the associations between numbers and their values) (Gelman and Galistell 1978; Fuson 1988). The bilateral prefrontal cortex and left parietal cortex of young children are usually activated during the task of the link between numbers and their values (Nieder 2009; Cantlon et al. 2009). Our results further revealed that the functional connectivities among left parietal and bilateral prefrontal regions (i.e, SPL.L-PreCG.L, IPL.L-IFGtriang.L, IPL.L-IFGoperc.L, and IFGtriang.R-SMA.L) could predict the counting skills in 4-year-olds, supporting the prior result on their role in the executive control and active retrieval of associative representations between discrete objects and numbers (Tomita et al. 1999; Nieder 2009). Nevertheless, our study indicated a shift from the bilateral fronto-parietal network to the right parietal-dominant network for counting from 4-year-olds to 6-year-olds. This shifting is likely due to the fact that the counting skills of 6-year-olds are developing from an indexical stage to a syntactic stage (i.e., counting based on the number-word sequence, or the syntax of numbers) (Reynvoet and Sasanguie 2016). In particular, the number-word sequencing task often activates the right inferior parietal lobule in children (Kaufmann et al. 2009). Compared to adults, 6-year-olds showed more activation in the inferior frontal regions during syntactic processing task (Brauer and Friederici 2007). Likewise, our findings identified that the counting skills of 6-year-olds were remarkably contributed by the connections among the right inferior parietal and bilateral inferior frontal regions (i.e., vIPL.R-IFGtriang.L, vIPL.R-SMG.R, IFG.operc.R- SFG.L, and IFGoperc.L-SFG.L). All together suggested that the fronto-parietal numerical networks for the counting process may work differently according to the development of counting skill at different times.

Similarly, the fronto-parietal networks were broader associated with the number relational skills in young children than in adults. Our meta-analysis showed that the right parietal-dominant network was uniquely associated with the number relational skill in adults. In contrast, the ability of 4-year-olds to conduct the number relational skills (i.e., NKT2-cat) was associated with both the right parietal-dominant and bilateral frontal–parietal numerical networks. NKT2-cat was mostly related to the connections among frontal regions (i.e., IFGtriang.L-IFGoperc.R, IFGtriang.L-SFG.L, IFGoperc.L-SMA.R, and SMA.L-INS.L). These results were consistent with the previous findings that young children may require more cognitive resources for the number relational processing than adults (Leibovich and Ansari 2016). In particular, the high cognitive demand involves the lateral prefrontal function in children (Crone and Steinbeis 2017). Moreover, Piaget's cognitive developmental theory suggests that the counting skill plays a cognitive readiness role in the development of the number relational skills in early life (Piaget 1965). Our study showed the bilateral fronto-parietal network involved in both the counting and number relational skills of 4-year-olds and provided the neural support for Piaget's cognitive developmental theory. Furthermore, the right inferior parietal lobule played a solid role in the number representation over the early childhood (Hyde et al. 2010; Emerson and Cantlon 2015; Edwards et al. 2016). The right inferior parietal lobule also exhibited a strong activation when children performed tasks about quantity (Price et al. 2007; Jolles et al. 2016a). Our study also highlighted a potential shift of neural support from the distributed fronto-parietal networks to the right parietal-dominant network for the number relational skills from age of 4 to 6 years. Hence, our findings on number relational processing further suggested that the fronto-parietal numerical networks would be fine-tuned according to the development of early numeracy.

Our study is best considered as exploratory providing new evidence on the adaptation of the fronto-parietal numerical networks to early numeracy. Our study only assessed early numeracy at 4 years of age. This is partly because of subjects' burden and high correlation of early numeracy between ages of 4 and 6 years (Purpura et al. 2011; Vanbinst et al. 2015). Hence, our findings could partially reflect the relation of early numeracy with the fronto-parietal numerical networks for 6-year-old children. Longitudinal assessment of early numeracy along with brain imaging will be required for future investigation. Moreover, due to a lack of numeracy-specific task-based fMRI in young children, especially at age of 4 and 6 years, our meta-analysis findings were concluded based on adult studies. The fronto-parietal networks in relation with numeracy in young children were thus best considered as being compared with the matured adult's brain, per se. There may be other neural networks and mechanisms contributing to the development of early numeracy, which need to be further explored. Moreover, we employed the AAL to label the brain anatomy, which may not be ideal for studying brain functional networks in children (Korhonen et al. 2017) and can be further improved based on rs-fMRI data. Last but not least, this neuroimage study was a part of a longitudinal cohort study, GUSTO. Imaging brain at age of 4 and 6 years was extremely challenging. Even though we had near 50% consent rate for MRI among eligible participants in GUSTO at each visit, usable imaging data were limited, especially across multiple visits. Hence, this study only had 61 children whose rs-fMRI data were usable for both 4- and 6-year visits. Nevertheless, we believed that this study provided an unique dataset for understanding the neural development in line with early numeracy in early childhood.

In summary, our study took an advantage of the meta-analysis on the existing knowledge on adult numeracy to define the fronto-parietal numerical networks and revealed the readiness of these networks to support the early numeracy in preschoolers. However, the involvement of the fronto-parietal numerical networks is fine-tuned through the course of early numeracy development in childhood.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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