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Original Article

ORIGINAL ARTICLE

Specialization of the Right Intraparietal Sulcus for Processing Mathematics During Development

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Abstract

Mathematical ability, especially perception of numbers and performance of arithmetics, is known to rely on the activation of intraparietal sulcus (IPS). However, reasoning ability and working memory, 2 highly associated abilities also activate partly overlapping regions. Most studies aimed at localizing mathematical function have used group averages, where individual variability is averaged out, thus confounding the anatomical specificity when localizing cognitive functions. Here, we analyze the functional anatomy of the intraparietal cortex by using individual analysis of subregions of IPS based on how they are structurally connected to frontal, parietal, and occipital cortex. Analysis of cortical thickness showed that the right anterior IPS, defined by its connections to the frontal lobe, was associated with both visuospatial working memory, and mathematics in 6-year-old children. This region specialized during development to be specifically related to mathematics, but not visuospatial working memory in adolescents and adults. This could be an example of interactive specialization, where interacting with the environment in combination with interactions between cortical regions leads from a more general role of right anterior IPS in spatial processing, to a specialization of this region for mathematics.

Key words: cortical thickness, development, DTI, interactive specialization, mathematics

Introduction

Mathematics requires a range of different skills and knowledge that rely on a broad network of regions in the occipital, parietal, and frontal lobes of the brain (Nieder and Dehaene 2009). Of these regions, the intraparietal sulcus (IPS) is particularly important for comparing numbers (Piazza et al. 2007; He et al. 2015), and performing arithmetical operations (Knops et al. 2009; Rosenberg-Lee et al. 2011). Recently, it has been shown that the structural gray matter properties of the IPS are predictive of future mathematical skills (Evans et al. 2015; Price et al. 2016). Aberrant functional and structural integrity of the IPS are also consistently found to be implicated in dyscalculia (Molko et al. 2003; Kaufmann et al. 2009; Rotzer et al. 2009; Rykhlevskaia et al. 2009). However, both the structure (Sowell et al. 2004; Tamnes et al. 2013; Darki and Klingberg 2015) and function (Klingberg et al. 2002; Crone et al. 2009; Darki and Klingberg 2015) of the IPS are also associated with nonverbal reasoning and visuospatial working memory, abilities for which performance is tightly linked to mathematics performance (Gathercole et al. 2004; Geary et al. 2004; Primi et al. 2010; Geary 2011; Fuchs et al. 2012).

Most studies looking at all these cognitive abilities, however, have used group averages, which can give the false suggestion that different cognitive abilities are localized in an overlapping area, although they are separate in each individual. This is especially problematic in highly anatomically variable brain regions, such as the IPS (Choi et al. 2006; Scheperjans et al. 2008a). Therefore, in order to determine if the strong associations between mathematics, nonverbal reasoning, and working memory are observed because they all rely on the same subregion of the IPS, it is necessary to examine the neural basis at the individual level.

Cytoarchitectonic studies of the IPS have identified 3 subregions within IPS (hIP1, hIP2, and hIP3) based on the cellular density of the different cortical layers (Choi et al. 2006; Scheperjans et al. 2008b), but the exact location of these subregions differs considerably between individuals (Choi et al. 2006; Scheperjans et al. 2008a). This could explain why studies using probabilistic regions of interest of hIP1, hIP2, and hIP3 (Eickhoff et al. 2005; Choi et al. 2006; Scheperjans et al. 2008a) to get a more precise understanding of the role of the IPS in different forms of mathematics have not found differential specialization of IPS subregions for different forms of mathematics (Wu et al. 2009; Rosenberg-Lee et al. 2011).

Functional anatomy is dependent on brain development during childhood and adolescence. One account of functional brain development is the interactive specialization account (Johnson 2001, 2011). According to this hypothesis, brain regions start with a broad range of functionality and gradually become more specialized for specific functions. This functional specialization is driven by interaction with the environment and activity-dependent interactions between different brain regions. Therefore, the pattern of structural connectivity between brain regions plays an important role in defining the final pattern of functional specificity of specific brain regions (Johnson 2001, 2011). The interactive specialization account is consistent with the proposal that evolutionary old brain circuits are re-used, or refined, in order to support culturally dependent activities such as reading and mathematics (Dehaene and Cohen 2007; Knops et al. 2009).

Taken together, many studies point to the value of using an individualized region of interest approach, and considering the developmental aspect, when studying the functional specificity of the IPS. Since previous studies have suggested that IPS subregions differ in their connectivity to the rest of the brain (Uddin et al. 2010; Bray et al. 2013, 2015), we used connectivity-based segmentation of the IPS to examine the functional specificity of the IPS. In a sample of 66 participants, aged 6–25 (at time of the first scan), who were scanned 1–3 times at a 2-year interval, we identified 3 IPS subregions in left and right hemispheres based on patterns of structural connectivity with frontal cortex, inferior parietal lobe (IPL), and occipital cortex on an individual basis. Next, we extracted cortical thickness from these individually defined IPS regions and related cortical thickness in the IPS subregions to performance in mathematics, nonverbal reasoning, and visuospatial working memory. Next, we aimed to replicate the connectivity-based IPS segmentation in an independent sample of 56 6-year-old children who were scanned once, and examine the specificity of IPS subregions for mathematics, nonverbal reasoning, and visuospatial working memory in this sample.

Methods

Developmental Sample

Participants

Sixty-six participants (33 female, 4 left-handed), aged 6–25, who were scanned 1–3 times at a 2-year interval as part of the Brainchild project (Soderqvist et al. 2010) were included in this sample. From these participants, for 9 participants (3 who were only scanned once), there were problems in estimating their cortical thickness data (e.g., unreliable estimation of the boundary model) at one time point, resulting in 63 participants being included in cortical thickness analyzes. Gender and handedness were always included as covariates in the analyzes.

Behavioral Assessment

Mathematical Abilities. The assessment of mathematical abilities was based on the Trends in Mathematics and Science Study (Martin et al. 2004) and the Basic Number Screening Test (Gillham and Hesse 2001). There were 4 school-grade-dependent versions (Grades 2, 4, 6, and 8, suitable for 14 years and older) each taking 30 min. Versions for Grades 2 and 4 assessed magnitude judgments, number sequence, and elementary arithmetic (i.e., addition, subtraction, division, multiplication, and fractions). Versions for Grades 6 and 8 assessed elementary arithmetic and elementary algebra (i.e., simple equations with variables). The youngest participants (6-year old) did not perform the mathematics tests.

Nonverbal Reasoning. Nonverbal reasoning was assessed with Raven's Progressive Matrices (Raven 1998). The youngest participants (6-year old) only performed Subtests A–D, while all other participants performed all Subtests (A–E). There was no time limit. However, when participants did not answer an item in 1 min, they were prompted for a response.

Visuospatial Working Memory. To assess visuospatial working memory, participants performed a computerized Dot Matrix task from the Automated Working Memory Assessment battery (AWMA) (Alloway 2007). In this task, a number of dots are sequentially presented in a 4×4 matrix for 1000 ms, with a 500 ms interval. Participants are instructed to remember the location and order in which the dots appeared. The total number of correct trials was taken as the visuospatial working memory score.

Behavioral Data Analysis

The raw mathematical and nonverbal reasoning test scores were transformed to ability scores, using item response theory analyzes (see Bergman Nutley et al. 2010 for details). The ability scores take into account the difficulty of the item and the ability of the participant, allowing the combined analyzes of different age groups, even though age groups did not perform the exact same tests, since these were age dependent. Ability scores were transformed to Z-scores.

Imaging Data Acquisition

All scans were acquired on a 1.5T Siemens scanner.

DTI. At the third round of data collection, a diffusion weighted scan with the following parameters was collected: field of view (FOV) = 230×230 mm, matrix size = 128×128, 40 slices, slice thickness = 2.5 mm, b-value = 1000 s/mm^2 in 64 gradient directions.

T1. At all time points, structural T1-weighted spin echo scans were collected using a 3D magnetization prepared rapid gradient-echo (MPRAGE) sequence, with repetition time (TR) = 2300 ms, echo time (TE) = 2.92 ms, FOV = 256×256 mm, matrix size = 256×256, 176 sagittal slices, 1 mm^3 voxel size.

Imaging Data Analysis

IPS Segmentation. Diffusion weighted images were preprocessed using the FMRIB Software Library (FSL). First, the data were corrected for eddy currents and simple head movements with affine registration to a reference volume. Next, a diffusion tensor model was fitted at each voxel, from which the fractional anisotropy (FA) map was constructed. The mean FA map of each participant was normalized to the FMRIB58 template in the Montreal Neurological Institute (MNI) space using nonlinear registration (Rueckert et al. 1999). For the IPS segmentation, an IPS mask in MNI space was created by combining probabilistic regions of interest of hIP1, hIP2, and hIP3 (Eickhoff et al. 2005). As target masks, an IPL mask was taken from the Automated

Anatomical Labeling atlas (Tzourio-Mazoyer et al. 2002) and masks from frontal and occipital cortex were taken from the MNI structural atlas (Collins et al. 1995). For the tractography analyzes, these MNI space masks were normalized to each participant's native space, using the inverse of the normalization parameters created during the nonlinear registration procedure. Probabilistic tractography analyzes and IPS segmentation were performed in the participant's native space following the procedures from Behrens et al. (2003) and Johansen-Berg et al. (2005) and the results were saved in MNI space by using the normalization parameters from the nonlinear registration procedure. The FMRIB Diffusion Toolbox (FDT) toolbox was used to run probabilistic tractography, allowing for crossing fibers (Behrens et al. 2007). From each voxel in the IPS seed mask, 5000 tracts were generated. The distance correction option was used to correct for the fact that the connectivity distribution drops with increasing distance from the seed mask. Probabilistic tractography and IPS segmentation were done separately for left and right hemispheres, by using an exclusion mask of the contralateral hemisphere. For each IPS voxel, the probability of connection to each of the 3 target masks was calculated. Segmentation of the IPS was performed by classifying each IPS voxel to the target region to which it has the highest probability of connection. Results were thresholded such that only IPS voxels with a connection probability of 50% or higher were assigned to a target region. Finally, using the cluster function in FSL, continuous IPS segments for each target region were extracted for each participant.

Cortical Thickness. Reconstruction of the cortical surface was performed with Freesurfer. The software builds model boundaries between gray and white matter and between gray matter and cerebrospinal fluid (Dale et al. 1999). The T1-weighted images were processed using Freesurfers longitudinal processing stream (Reuter et al. 2012). Within the longitudinal processing stream, a subject template is built for each subject using robust registration (Reuter et al. 2010), to reduce within-subject variability and to increase reliability and power. Subject templates were visually inspected and inaccurate surface reconstructions were excluded. The boundary model was used to estimate cortical thickness at each location of the cortex. Cortical thickness in the individually defined IPS segments and the probabilistic regions of interest of hIP1, hIP2, and hIP3 was extracted for all time points using the workflow described in https://surfer.nmr.mgh.harvard.edu/fswiki/VolumeRoiCorticalThickness. The specificity of the relations between cortical thickness in the IPS segments and mathematics, nonverbal reasoning, and working memory was tested with marginal models using the mixed procedure in SPSS, using the compound symmetry type for repeated covariance.

Six-Year-Old Sample

Participants

Fifty-six 6-year-old children (24 female, $M = 80.91$ months, standard deviation = 3.47) were included in this sample. Part of the sample ($N = 12$) was selected for low working memory. Therefore, we have corrected for group membership (typically developing vs. low working memory) in the analyzes.

Behavioral Assessment

Mathematical Abilities. Mathematical abilities were measured by 3 tests, 2 that were completed on an iPad, and the third test, the verbal arithmetic task from the Wechsler Intelligence Scale for Children (WISC) (Wechsler 2004) was administered manually. The first iPad test was an addition test in which subjects were presented with arithmetical (addition) problems and responded by choosing numbers from a number line from 0 to 9. The sum never exceeds 20. The test was based on time and the subjects had 180 s to solve as many problems as possible. The second iPad test was a subtraction test that followed the same format as the addition test. In this test, the difference between the numbers never exceeded 16. Scores on each of the 3 tests were transformed into a z-score. The average z-score was then used as a compound measure of mathematics.

Nonverbal Reasoning. Nonverbal reasoning was measured by the matrices test from the WISC (Wechsler 2004). The score was transformed into a z-score.

Visuospatial Working Memory. Visuospatial working memory was measured by 3 tests: an in-house developed grid task based on the Dot Matrix task from the AWMA (Alloway 2007), block repetitions forward, and block repetitions backward (Kessels et al. 2000). Scores on each of the 3 tests were transformed into a z-score. The average z-score was then used as a compound measure of working memory.

Imaging Data Acquisition

All scans were acquired on a 3T GE scanner.

DTI. A diffusion weighted scan with the following parameters was collected: FOV = 22 cm, 63 axial slices, slice thickness = 2.3 mm, *b*-value = 1000 s/mm^2 in 32 gradient directions.

T1. At all time points, structural T1-weighted spin echo scans were collected using a 3D MPRAGE sequence, with TR = 7.9 ms, TE = 3.06 ms, FOV = 24 cm 176 axial slices, 1 mm^3 voxel size.

Imaging Data Analysis

IPS Segmentation. Diffusion weighted images were preprocessed in the same way as the data from the developmental sample. Additionally, an in house developed correction to correct for shimming effects was applied. Hereafter, IPS was segmented following the same procedures as for the developmental sample.

Cortical Thickness. Reconstruction of the cortical surface was performed with Freesurfer. However, for this data set, the cross-sectional pipeline was used. Hereafter, cortical thickness in the individually defined IPS segments and the probabilistic regions of interest of hIP1, hIP2, and hIP3 was extracted following the same procedures as for the developmental sample. For 12 participants, there were less than 10 voxels in the gray matter for the right IPS segment connected to frontal cortex. Therefore, the specificity of the relations between cortical thickness in the IPS segments and mathematics, nonverbal reasoning, and working memory was tested with marginal models using the mixed procedure in SPSS in only the 44 subjects who had a reliable cortical thickness estimation in all included IPS segments.

Results

Mathematics, Nonverbal Reasoning, and Visuospatial Working Memory are All Correlated

Consistent with the literature, mathematics, nonverbal reasoning, and visuospatial working memory were all correlated with each other, both in the developmental sample (all P's < 0.001, these association remain significant when covaried for age, all P's < 0.005) and in the 6-year-old sample (all P's < 0.002).

Individual Differences in IPS Segmentation in the Developmental Sample

The IPS region of interest was defined by combining probabilistic regions of interest of hIP1, hIP2, and hIP3 (Eickhoff et al. 2005). In order to segment the IPS, we examined the probability of connectivity of each voxel within the IPS with frontal cortex, IPL, and occipital cortex using probabilistic tract tracing on the diffusion weighted images from each individual. Next we extracted continuous clusters of voxels connected to each target region. We will refer to these IPS subregions as the IPS subregion connected to frontal cortex (F-IPS), the IPS subregion connected to IPL (P-IPS), and the IPS subregion connected to occipital cortex (O-IPS). The IPS segmentation was successful in identifying 3 different IPS segments in each hemisphere for all subjects. Generally, anterior IPS voxels were most likely to be connected to frontal cortex, lateral IPS voxels are most likely to be connected to IPL, and posterior IPS voxels were most likely to be connected to occipital cortex (Fig. 1). However, there was considerable individual variation in the location of the IPS subregions. For some participants, posterior IPS voxels were most strongly connected to frontal cortex, and for some, anterior IPS voxels show the strongest connectivity to occipital cortex (Fig. 1). The size of the IPS segments did not differ with age (all correlations between size and age were non-significant, all P's > 0.09), and also the location of the center of gravity of the IPS segments did not differ with age (all multiple regression analyzes between age and xyz-coordinates of the IPS segments were non-significant, all P's > 0.10, see Table 1 for the MNI coordinates of the center of gravity for the average IPS segments), allowing us to use the segmentation from time point 3 for all time points. Growth curve modeling showed that the development of cortical thickness for all the different IPS segments showed a linear trajectory (Supplementary Fig. 1).

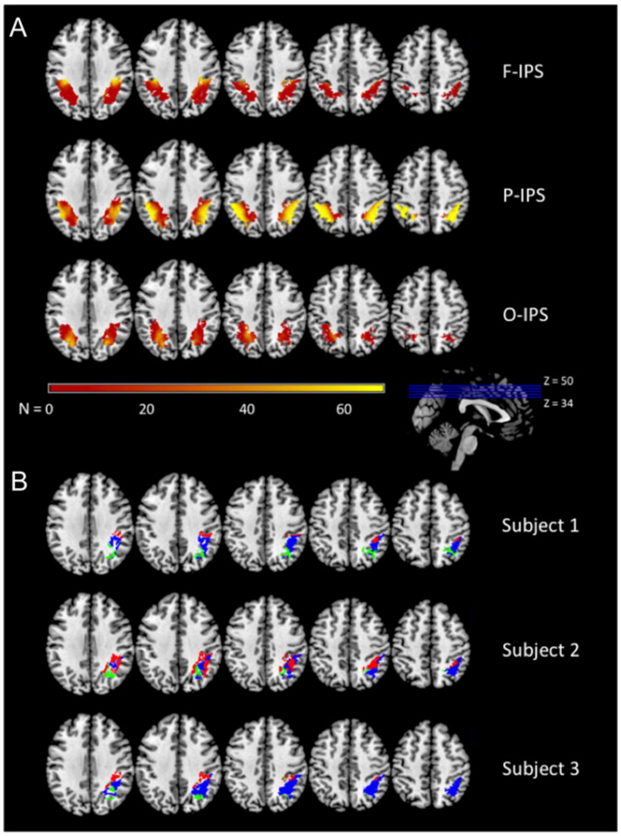

Figure 1. IPS segmentation results for the developmental sample. (*A*) Group probability maps showing for each voxel the number of subjects for whom this voxel is connected to frontal cortex, IPL, and occipital cortex. (*B*) IPS segmentation for 3 representative subjects showing right IPS segments connected to frontal cortex (in red), to IPL (in blue), and to occipital cortex (in green).

Specificity in the Relations Between IPS Segments and Cognitive Abilities

In order to examine the relations between cognitive performance and cortical thickness in each IPS segment, we first analyzed the relations between each cognitive ability and each IPS segment separately. This was done using marginal models using the mixed procedure in SPSS with cognitive score as the dependent variable and age, cortical thickness in the IPS segment, and the interaction between age and cortical thickness as predictors. These analyzes showed that cortical thickness in all IPS segments was related to mathematics (all P's < 0.05), cortical thickness in all IPS segments (all P's < 0.05) except for right O-IPS (P = 0.28) was related to visuospatial working memory, and that only cortical thickness in left P-IPS (P < 0.05) was related to nonverbal reasoning (all other P's > 0.1). The observation that almost all IPS segments are related to both mathematics and visuospatial working memory could indicate that the whole IPS is important for these abilities, but could also be observed because the variability in cortical thickness in these IPS segments goes together. Indeed, it has been shown that cortical thickness within the parietal regions is highly heritable in both children and adolescents (Lenroot et al. 2009) and in adults (Eyler et al. 2011), and that there is a strong genetic correlation in cortical thickness between parietal regions (Schmitt et al. 2008).

Therefore, we next analyzed the specificity of the association between cognitive performance and cortical thickness in each IPS segment. This was done in 3 marginal models using the mixed procedure in SPSS with cognitive score as the dependent variable and including all IPS segments in both hemispheres as independent variables. By using all cortical regions as independent variables, the model controlled for the average cortical thickness of the IPS, including age-related changes in thickness common to all parietal regions, in order to find a specific subregion related to each cognitive function.

Cortical thickness in left P-IPS was related to both nonverbal reasoning and visuospatial working memory, cortical thickness in left O-IPS was related to both mathematics and nonverbal reasoning, and cortical thickness in right F-IPS was specifically related to mathematics (see Table 2 for parameter estimates

Table 1 MNI coordinates for the centers of gravity of the average IPS segments

IPS segment	MNI coordinates		
	X	Y	Z
Left F-IPS	−34.8	−41.6	36.3
Left P-IPS	−36.4	−49.8	41.1
Left O-IPS	−27.9	−56.4	35.9
Right F-IPS	35.7	−41.5	36.9
Right P-IPS	36.8	−50.1	41.9
Right O-IPS	29.6	−57.3	35.9

and P-values). For all significant effects, lower cortical thickness within the IPS segment was related to better cognitive performance (Fig. 2).

Table 2 Parameter estimates and P-values for the relations between cortical thickness in each IPS segment and cognitive abilities in the developmental sample

IPS segment	Mathematics		Nonverbal reasoning		Visuospatial working memory	
	B	P-value	*B*	P-value	*B*	P-value
Left F-IPS	−0.30	0.403	0.30	0.423	−1.97	0.522
Left P-IPS	0.53	0.474	**−2.00**	**0.006**	**−11.56**	**0.049**
Left O-IPS	**−1.53**	**0.006**	0.22	0.711	**−10.41**	**0.035**
Right F-IPS	**−0.83**	**0.020**	0.17	0.637	−1.93	0.509
Right P-IPS	0.28	0.703	−0.62	0.390	7.26	0.217
Right O-IPS	−0.44	0.232	0.10	0.800	−0.92	0.773

Note: Significant associations are printed in bold.

No Specificity in the Relations Between Probabilistic Cytoarchitectonic IPS Segments and Cognitive Abilities

In order to integrate the results from our connectivity-based IPS segmentation, we here compare these with cytoarchitectonically defined IPS subregions (Choi et al. 2006; Scheperjans et al. 2008b). The cytoarchitectonically defined IPS subregions also show a posterior-to-anterior organization with hIP3 being close to the O-IPS, but also showing overlap with P-IPS, whereas hIP2, the most anterior cytoarchitectonic IPS subregion is close to the F-IPS, and hIP1 is most close to P-IPS (Fig. 3).

To examine whether there is also specificity in the relation between cortical thickness in the probabilistic cytoarchitectonically defined IPS subregions and cognitive performance, we extracted cortical thickness from the regions hIP1 to hIP3, and related this to the cognitive performance scores. This was done in 3 marginal models using the mixed procedure in SPSS with cognitive score as the dependent variable and including cortical thickness in all cytoarchitectonically defined IPS subregions in both hemispheres as independent variables. These analyzes showed that hIP1–hIP3 are not specifically associated with any cognitive ability (all associations were non-significant, all P's > 0.06).

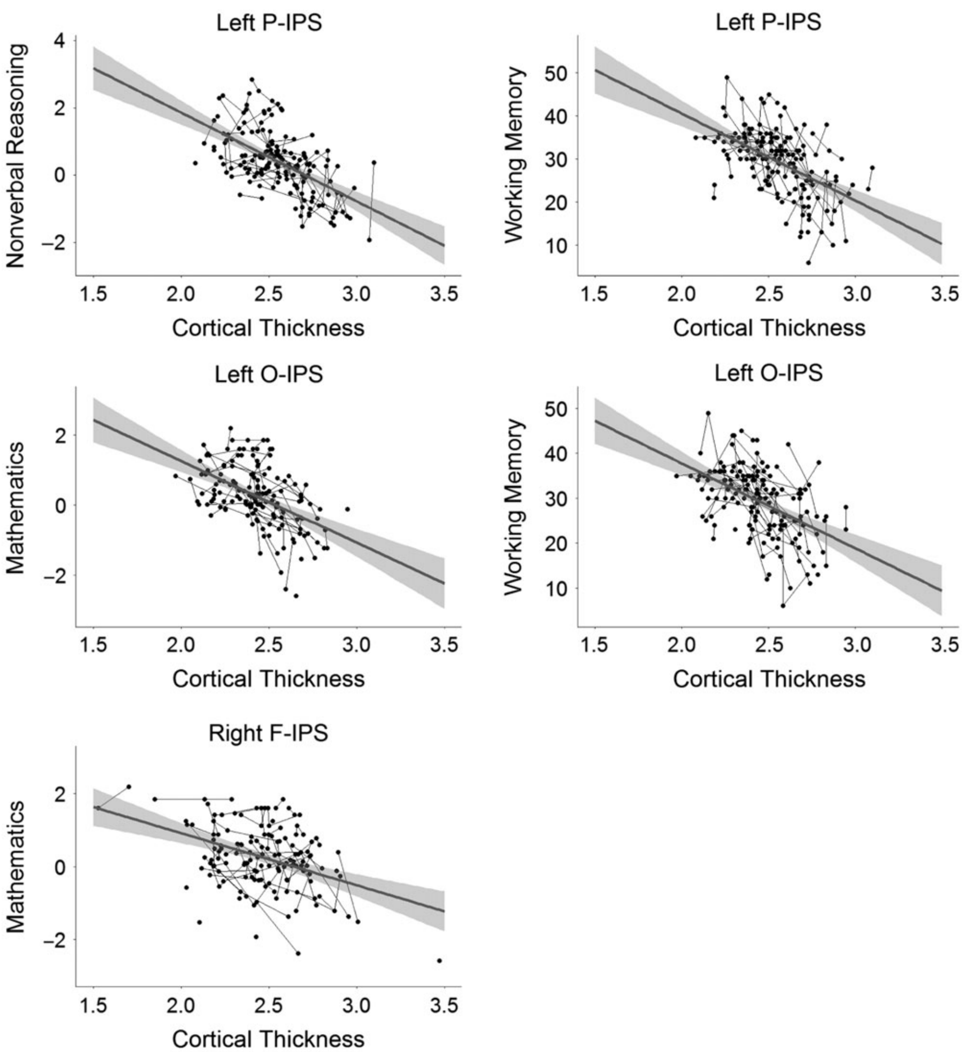

Figure 2. Associations between cortical thickness in the IPS segments and cognitive abilities in the whole developmental sample. In all segments, thinner cortex is associated with better performance.

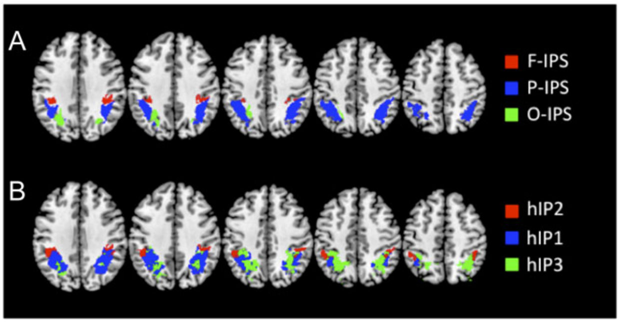

Figure 3. Comparison of different IPS subregions. (A) Segmentation solution thresholded at 50% for the developmental sample. (B) Probabilistic cytoarchitectonic IPS subregions.

Individual Differences in IPS Segmentation in 6-Year Old

Next, we aimed to replicate the IPS segmentation in an independent sample of 56 six-year old. As in the developmental sample, the segmentation of IPS in segments strongest connected to frontal cortex, IPL, and occipital cortex was successful in all 6-year old in identifying 3 different IPS segments in each hemisphere. Similar to the developmental sample, anterior IPS voxels were generally more likely to be connected to frontal cortex, lateral IPS voxels to IPL, and posterior IPS voxels were most likely to be connected to occipital cortex . However, again there was considerable individual variation in the IPS segmentation (Fig. 4).

Right Frontal IPS is Commonly Associated with Mathematics and Working Memory in 6-Year Old

To follow-up on the results from the developmental sample, we here examined how the relationships between the IPS segments and mathematics, nonverbal reasoning, and visuospatial working memory replicated in the 6-year-old sample. Marginal models using the mixed procedure in SPSS with cognitive score as the dependent variable and including all IPS segments in both hemispheres as independent variables showed that cortical thickness in right F-IPS was associated with both mathematics and visuospatial working memory in the 6-year old (see Table 3 for parameter estimates and P-values). When analyzing the relationships between cortical thickness and cognitive scores for each IPS segment separately the same pattern was observed, with R-IPS being significantly associated with mathematics and visuospatial working memory (both P's < 0.05), and no other significant relationships between cortical thickness and cognitive scores (all P's > 0.08). The associations between left P-IPS and nonverbal reasoning and visuospatial working memory and left O-IPS and mathematics and visuospatial working memory, which were observed in the developmental sample, were not replicated in the 6-year-old sample.

For the 6-year old, thicker cortex within right F-IPS was associated with better performance in mathematics and visuospatial working memory (Fig. 5), while in the developmental sample the association was negative. This reversal in the sign of the correlation has been observed before and is presumably related to the inverted-u-shape of cortical thickness over development (Shaw et al. 2006).

As in the developmental sample, cortical thickness in the probabilistic cytoarchitectonically defined IPS subregions

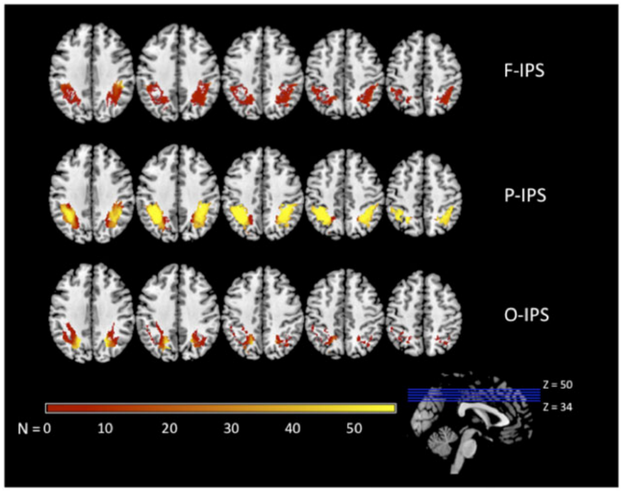

Figure 4. Group probability maps showing for each voxel the number of subjects for whom this voxel is connected to frontal cortex, IPL, and occipital cortex for the 6-year-old sample.

Table 3 Parameter estimates and P-values for the relations between cortical thickness in each IPS segment and cognitive abilities in the 6-year-old sample

IPS segment	Mathematics		Nonverbal reasoning		Visuospatial working memory	
	B	P-value	*B*	P-value	*B*	P-value
Left F-IPS	0.81	0.096	3.32	0.200	−0.15	0.716
Left P-IPS	−1.40	0.251	−8.17	0.216	−0.06	0.958
Left O-IPS	−0.73	0.349	−1.59	0.705	−0.43	0.524
Right F-IPS	**1.64**	**0.006**	5.80	0.058	**1.33**	**0.010**
Right P-IPS	−0.88	0.445	−3.14	0.612	0.49	0.627
Right O-IPS	−0.20	0.744	−1.08	0.738	−1.03	0.061

Note: Significant associations are printed in bold.

was not specifically associated with cognitive performance (all P's > 0.06).

Interactive Specialization in IPS Development

The findings that right F-IPS was associated with both mathematics and visuospatial working memory in the 6-year-old sample and specifically associated with mathematics in the complete developmental sample, led to the hypothesis that this region would become more specialized with age. In order to test this hypothesis we tested whether in the developmental sample there was in interaction effect between cortical thickness in right F-IPS and age on visuospatial working memory. Indeed, there was a significant interaction effect (F (132.06) = 6.34, $P < 0.05$) indicating that the relation between cortical thickness and visuospatial working memory changes during development.

To illustrate how right IPS is related to mathematics and visuospatial working memory during development, we divided the developmental sample in 2 groups: one group of participants aged 6–12 (the mathematics test was only available for children aged 8 and older, but the working memory test was available for children aged 6 and older) and one group of participants older than 12 years of age. Both in the younger and in

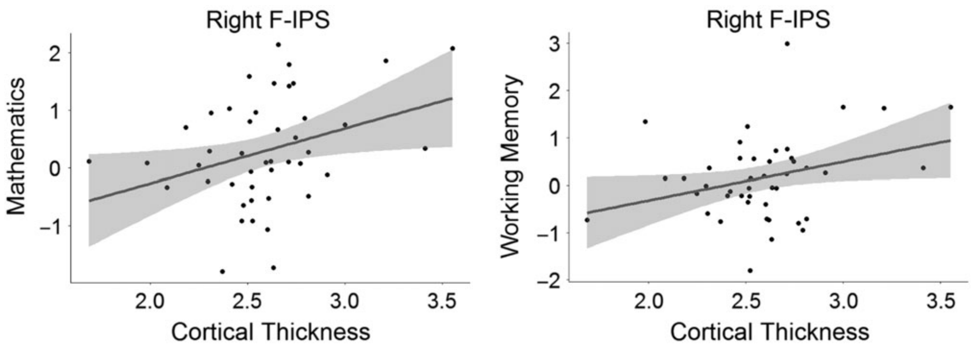

Figure 5. Associations between cortical thickness in right F-IPS and mathematics and visuospatial working memory in the 6-year-old sample. Thicker cortex in this region is associated with better mathematics and visuospatial memory in this sample.

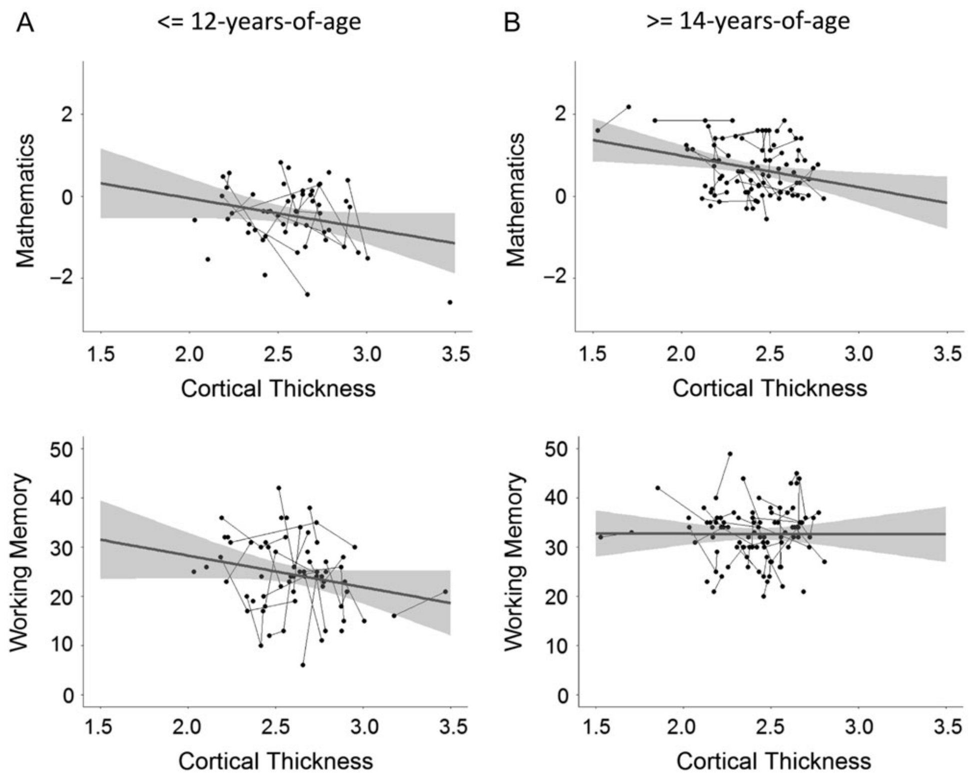

Figure 6. Associations between cortical thickness in right F-IPS and mathematics and working memory for participants until the age of 12 and for participants of 14 years and older. (*A*) Thinner cortex in IPS connected to frontal cortex is associated with better mathematics and working memory performance in children until the age of 12. (*B*) Thinner cortex in IPS connected to frontal cortex is associated with better mathematics, but not with working memory in participants of 14 years and older.

the older groups mathematics and visuospatial working memory were associated with each other (all P's < 0.005, when covaried for age all P's < 0.05). In the younger group, cortical thickness in right F-IPS was significantly associated with both mathematics (F (33.41) = 4.69, P < 0.05) and working memory (F (51.56) = 4.14, P < 0.05) (Fig. 6A), consistent with the finding in the 6-year old. However, when controlling for working memory in the mathematics analysis and vice versa, these analysis were no longer significant (all P's > 0.14), indicating that right F-IPS is not specifically associated with either mathematics or visuospatial working memory in the younger group. In contrast, in the older group, cortical thickness in right F-IPS was significantly associated only with mathematics (F (83.83) = 6.52, P < 0.02), but not with visuospatial working memory (F (80.40) = 2.05, P = 0.16) (Fig. 6B). When controlling for visuospatial working memory, which was significantly associated with mathematics as shown above, this analysis remained significant (F (77.56) = 4.47, P < 0.05), indicating that in the older group right F-IPS is specifically associated with mathematics.

Discussion

Here we identified subregions of the IPS based on its connectivity in order to examine the specificity of IPS subregions for mathematics, nonverbal reasoning, and working memory across development. Right F-IPS was associated with both mathematics and working memory in 6-year old and in older children. However, during development, this region became specifically associated with mathematics, not visuospatial working memory. Spatial attention and visuospatial working memory have repeatedly shown to activate the same parts of the IPS (Ikkai and Curtis 2011; Jerde et al. 2012). We therefore interpret the results as evidence that the right F-IPS starts out as a region devoted more generally to both spatial cognition and attention, and then acquires its specificity. This could be evidence for interactive specialization in the development of a mathematics specific region within the right IPS.

Analysis of the entire developmental sample also showed that left O-IPS was associated with both mathematics and visuospatial working memory, and that left P-IPS was associated with both nonverbal reasoning and visuospatial working memory. These left IPS associations, however, were not observed in the 6-year old sample.

Right IPS

The right F-IPS was specifically associated with mathematics in adolescents and adults. This IPS subregion shows a distinct overlap with a region identified in a meta-analysis of number tasks (Arsalidou and Taylor 2011) including among others passive number viewing, number comparison, and random number generation. Interestingly, the right IPS has been suggested to already be important for number representation in 3- and 6-months-old (Izard et al. 2008; Hyde et al. 2010) and shows longitudinal continuity in its response to a digit-to-dot array matching task between the ages of 4 and 9 (Emerson and Cantlon 2015). This early stable association between the right IPS and number skills is also in line with a study showing that the relative magnitude of right IPS activation during calculation is heritable (Pinel and Dehaene 2013). Furthermore, a recent study has suggested that the frontal part of the right IPS might be a candidate region linking the approximate number system to calculation abilities (Knops and Willmes 2014). None of these studies, however, analyzed the association between IPS and visuospatial working memory or nonverbal reasoning, and could thus not rule out a more general association to spatial processing or nonverbal cognitive tasks, as suggested by the present study of 6-year old.

Our results are generally in agreement with the idea of interactive specialization (Johnson 2001, 2011) as well as the 'recycling hypothesis' (Dehaene and Cohen 2007; Knops et al. 2009). This hypothesis proposes that neuronal networks underlying evolutionary older functions such as eye movement and spatial processing can be remodeled to learn culturally newer activities, such as learning mathematics (Dehaene and Cohen 2007). Our results show that in children the right IPS segment connected to frontal cortex is associated with both mathematics and visuospatial working memory. However, in adolescents and adults, this region becomes more strongly associated with mathematics and loses its association with working memory.

Specialization can be defined more or less strict. A strict definition of specialization would be that a brain region changes from being involved in many different functions to being specifically involved in only one function. However, this kind of specialization is unlikely. For instance, subregions of the fusiform gyrus respond more strongly to its preferred visual category, such as faces, but still show some response to the nonpreferred visual categories (Grill-Spector and Weiner 2014). Also, this specialization is not stable across the life span, but decreases with aging (Park et al. 2004). A more lenient definition of specialization is that a brain region changes from being involved in many different, but related, functions to being involved in fewer functions. This is applicable here, where the association between structure and function of the right F-IPS becomes less general during development.

An important question for future research would be to examine when in development this region specializes for mathematics and whether this specialization might be triggered by certain environmental effects, such as mathematics schooling. We expect that the exact moment when this region specializes for mathematics will vary between individuals and that part of this variability might be explained by environmental factors, such as when children start with formal mathematics schooling.

Left IPS

Left P-IPS was found to be associated with both nonverbal reasoning and visuospatial working memory in the developmental sample. This finding is in line with the general literature on nonverbal reasoning and working memory; the group probability map of this IPS subregion overlaps with the regions identified in meta-analyses of nonverbal reasoning (Wendelken 2015) and working memory (Rottschy et al. 2012). The observation that the left O-IPS was associated with both visuospatial working memory and mathematics is also in line with the literature. The group probability map of this IPS subregion overlaps with regions identified in meta-analyses of working memory (Rottschy et al. 2012) and of calculation tasks (Arsalidou and Taylor 2011). However, these associations were not replicated in the 6-year-old sample. The reason that we did not replicate these associations in the 6-year-old sample could be that these left IPS regions become important for these function later in development. For instance, the left IPS seems to become more important for mathematics with development (Ansari and Dhital 2006; Emerson and Cantlon 2015), which would explain why we did not replicate the association between left IPS and mathematics in the 6-year old.

IPS Segmentation

The IPS can be segmented in many different ways. In the current study, we decided to segment the IPS on an individual basis, based on its pattern of structural connectivity to frontal cortex, occipital cortex, and IPL, all regions important for higher cognitive processing. These results were compared with the probabilistic cytoarctictonically defined IPS subregions hIP1–hIP3. In line with the connectivity-based IPS segments, cytoarchitectonically defined IPS subregions do show differential functional and structural connectivity to the rest of the brain, with the more anterior probabilistic regions of interest of hIP1 and hIP2 showing stronger connectivity with frontal regions and the more posterior hIP3 regions showing stronger connectivity with occipital regions (Uddin et al. 2010). However, these regions did not show any specific relations with cognitive performance. These results indicate that it is important to take individual differences in brain anatomy into account, when examining brain–behavior relations.

The IPS can also be divided on an individual basis, based on functional characteristics. Using visuotopic mapping, several IPS subregions can be defined that each contain a topographic representation of the visual field (Silver and Kastner 2009), similar to retinotopic maps in the visual cortex (Wandell et al. 2007). Apart from their visual-spatial specificity, these visuotopic regions are also suggested to be differentially recruited in higher order cognitive functions (Bray et al. 2015). However, this method is limited in its coverage of the IPS. That is visuotopic maps of the IPS only cover the posterior part of the medial bank of the IPS (Silver and Kastner 2009). The correspondence of the visuotopically defined subregions to subregions defined by cytoarchitecture or structural connectivity is thus unclear.

In the current study, we used a relatively course individual segmentation of the IPS. An important line for future research would be to examine brain–behavior relations using a more fine-grained IPS segmentation. Using a more fine-grained segmentation could possibly elucidate even more specific brain–behavior relations, such as where in the IPS different mathematical operations are based. This would require very high-quality diffusion imaging, such as in the Human Connectome Project (Van Essen et al. 2013).

Conclusion

The current results show that the functional anatomy of the IPS changes over development. Using an individualized region of interest approach in a developmental population, we showed that right anterior IPS region was originally more generally associated with both visuospatial working memory and mathematics, possibly related to a more general role of the parietal lobe in spatial processing (Knops et al. 2009). During development, this region became more specifically related to mathematics. This increased specialization could be consistent with the interactive specialization account of brain development (Johnson 2001, 2011) and the idea of cortical remodeling of evolutionary older brain circuits for culturally dependent activities, such as learning mathematics (Dehaene and Cohen 2007). Our results call for more attention for individual differences in neural architecture when examining the association between brain structure and function and cognition. This approach might be a promising venue to elucidate the functional anatomy of other higher association areas.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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