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Reconfiguration of parietal circuits with cognitive tutoring in elementary school children

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Abstract

Cognitive development is shaped by brain plasticity during childhood, yet little is known about changes in large-scale functional circuits associated with learning in academically relevant cognitive domains such as mathematics. Here, we investigate plasticity of intrinsic brain circuits associated with one-on-one math tutoring and its relation to individual differences in children's learning. We focused on functional circuits associated with the intraparietal sulcus (IPS) and angular gyrus (AG), cytoarchitecturally distinct subdivisions of the human parietal cortex with different roles in numerical cognition. Tutoring improved performance and strengthened IPS connectivity with the lateral prefrontal cortex, ventral temporal-occipital cortex, and hippocampus. Crucially, increased IPS connectivity was associated with individual performance gains, highlighting the behavioral significance of plasticity in IPS circuits. Tutoring-related changes in IPS connectivity were distinct from those of the adjacent AG, which did not predict performance gains. Our findings provide new insights into plasticity of functional brain circuits associated with the development of specialized cognitive skills in children.

Keywords

Arithmetic; Functional Connectivity; Learning; Plasticity; Training

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1. Introduction

In contrast to the traditional view of brain maturation as the unfolding of a genetically preprogrammed trajectory, most current theories of brain development emphasize the role of learning, experience, and education in shaping brain function and structure (Posner & Rothbart, 2007). While previous studies of cognitive development have primarily focused on activation of individual brain areas, there is growing evidence to suggest that the emergence of regional functional specialization and fine-tuning of neuronal response properties is influenced by activity-dependent interactions and competition with other brain regions (Menon, 2013; Passingham, Stephan, & Kotter, 2002). This process of interactive specialization and reorganization of functional circuits is thought to play a prominent role in children's cognitive development (Johnson, 2001, 2011; Menon, 2013). Along the same lines, it has been proposed that repeated co-activation strengthens intrinsic functional connections between brain regions, resulting in increased differentiation between functional brain networks that subserve distinct cognitive processes (Fair et al., 2007; Fox & Raichle, 2007; Jolles, van Buchem, Crone, & Rombouts, 2013; Kelly et al., 2009; Mackey, Singley, & Bunge, 2013; Supekar, Menon, Rubin, Musen, & Greicius, 2008). These processes are particularly relevant for complex cognitive skills that rely on coordinated interactions between distributed brain structures. For example, numerical problem solving, an important component of children's cognitive development, depends on interactions between the posterior parietal cortex, lateral prefrontal cortex (PFC), and ventral temporal-occipital cortex (VTOC), regions associated with the representation and manipulation of quantity and symbolic information (Arsalidou & Taylor, 2011; Cho et al., 2012; Rosenberg-Lee, Barth, & Menon, 2011; Supekar & Menon, 2012). Despite its broad theoretical importance and practical relevance for understanding cognitive development, little is known about plasticity of intrinsic functional brain circuits related to learning in academically relevant cognitive domains in children.

Here, we use one-on-one cognitive tutoring to investigate plasticity of multi-component functional brain circuits associated with mathematical learning in elementary school children. The tutoring emphasized both procedural and conceptual knowledge as well as practicing fluent retrieval of number combinations from memory. Physical manipulatives were used to strengthen visuospatial representation of number combinations, while timed flash cards were used to encourage memory retrieval (Iuculano et al., 2015; Supekar et al., 2013). The multifaceted nature of the tutoring facilitated engagement of distributed brain regions involved in numerical, visuospatial, strategic, and mnemonic processes (Iuculano et al., 2015). Furthermore, previous findings suggest that the brain's intrinsic functional and structural network architecture provides a scaffold for the development of specialized cognitive skills (Supekar et al., 2013). More specifically, Supekar and colleagues reported that pre-tutoring brain structure and intrinsic functional connectivity were predictive of tutoring outcome, while behavioral measures, including IQ, working memory, and mathematical abilities were not. It is also likely that learning and experience *alter* functional brain circuits in ways that facilitate cognitive processing. In the present study, we, therefore, investigated how a well-designed cognitive tutoring protocol changes intrinsic functional

brain circuits in children and whether these changes are associated with individual differences in learning.

We focused on functional circuits associated with cytoarchitectonically distinct subdivisions of the posterior parietal cortex (Caspers et al., 2008; Caspers et al., 2006) that are known to play important but different roles in mathematical cognition (Ansari, 2015; Dehaene, Piazza, Pinel, & Cohen, 2003; Menon, 2015b): the intraparietal sulcus (IPS) and angular gyrus (AG). Despite their close proximity, the IPS and AG display markedly different profiles of brain response during numerical cognition (Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999; Grabner et al., 2009; Rosenberg-Lee, Chang, Young, Wu, & Menon, 2011; Wu et al., 2009) and exhibit functional connectivity with distinct brain circuits (Fox et al., 2005; Nelson et al., 2010; Uddin et al., 2010). The IPS is thought to play a particularly important role in quantity representation, numerical magnitude judgment, and arithmetic problem solving (Arsalidou & Taylor, 2011; Bugden, Price, McLean, & Ansari, 2012; Cantlon, Brannon, Carter, & Pelphey, 2006; Dehaene et al., 2003; Menon, Rivera, White, Glover, & Reiss, 2000; Piazza, Izard, Pinel, Le Bihan, & Dehaene, 2004; Rosenberg-Lee, Chang, et al., 2011; Wu et al., 2009) and has strong intrinsic connections with lateral PFC and VTOC regions (Uddin et al., 2010), associated with executive control and symbolic processing, respectively. In contrast, the AG is a key node of the default mode network, a brain system that is typically deactivated during arithmetic problem solving (Rosenberg-Lee, Lovett, & Anderson, 2009; Wu et al., 2009) and intrinsically anti-correlated with the IPS (Fox et al., 2005; Uddin et al., 2010). While the AG has been linked to verbal retrieval of math facts (Dehaene et al., 2003; Dehaene et al., 1999; Grabner et al., 2009), recent studies suggest that AG plays a more general attentional role that is not specific to math fact retrieval (Bloechle et al., 2016; Rosenberg-Lee, Chang, et al., 2011; Wu et al., 2009).

Given the central role of the IPS in numerical cognition and its co-activation with multiple subregions of the PFC and VTOC (Arsalidou & Taylor, 2011; Menon, 2015a), we hypothesized that intensive tutoring would strengthen intrinsic functional connectivity of the IPS with the PFC and VTOC. Based on an interactive specialization model, which postulates that development and learning result in increased differentiation between functional brain circuits (Johnson, 2011), we predicted that tutoring-related changes in IPS connectivity would differ from changes in AG connectivity. We reasoned that AG connectivity with the PFC and VTOC would not be strengthened due to the AG's involvement in the default mode network and its deactivation during mathematical problem solving. Instead, we predicted that learning would alter AG connectivity with other nodes of the default mode network, such as the medial temporal lobe (MTL) memory system including the hippocampus. We demonstrate that tutoring results in dissociable changes in functional circuits associated with the IPS and AG and determine the relation of these changes to individual differences in learning.

2. Materials & Methods

2.1 Overall study design

The study consisted of four phases (Jolles et al., 2015; Supekar et al., 2013): (i) initial neuropsychological assessments, (ii) Time 1 assessment of arithmetic performance and brain

imaging, (iii) 8-week one-on-one math tutoring (Fuchs et al., 2013; Fuchs et al., 2009), and (iv) Time 2 assessment of arithmetic performance and brain imaging (Figure 1A). Both brain imaging sessions started with a resting-state fMRI scan, which allowed us to examine intrinsic connectivity independent of task performance and strategy changes. The present study builds on our previous structural (Jolles et al., 2015; Supekar et al., 2013) and task-activation studies (Iuculano et al., 2015) and for the first time, examines plasticity of intrinsic functional circuits, using resting-state fMRI data from each child at both Time 1 and Time 2.

To rule out test-retest effects we recruited a separate cohort of third-grade children, a comparison group that underwent the identical scanning and testing procedures in phase i, ii, and iv of the main experiment. However, children in the comparison group did not receive math tutoring and were not enrolled in outside school math tutoring activities. Because children were enrolled in different schools and recruited all year around, it is unlikely that these children had a common experience with math instruction that contributed to consistent changes of IPS or AG connectivity.

2.2 Participants

Forty-six children in grade 3, recruited from multiple school districts in the San Francisco Bay Area, took part in the math tutoring study. Eighteen children were excluded due to excessive head movement or bad data quality during either of the scan sessions, four were excluded due to equipment failure, and two because they did not complete both resting-state scans. One child with a diagnosis of attention deficit hyperactivity disorder (ADHD) was also excluded. The final sample of the tutoring group included twenty-one children (mean age = 8.61; $SD = 0.42$; 13 females, 8 males; full-scale IQ = 103.90; $SD = 12.58$). Neuropsychological test results of the participants, including academic and cognitive achievement, are presented in Table S1. None of the children in the final sample were left-handed (as assessed using the Edinburgh handedness test), or had a history of neurological or psychiatric disorders.

Thirty-two children in grade 3 were recruited in the comparison group. Three children dropped out after the first scanning session and eight children were excluded due to excessive head movement or bad data quality during either of the scan sessions. The final sample included twenty-one children (mean age = 9.02; $SD = 0.43$; 14 females, 7 males; full-scale IQ = 118.62, $SD = 14.34$). Neuropsychological test results are presented in Table S2. None of the children in the final sample were left-handed or had a history of neurological or psychiatric disorders.

Informed consent was obtained from the legal guardian of the child, and study protocols were approved by the Stanford University Institutional Review Board.

2.3 Tutoring

Children in the tutoring group completed an intervention program adapted from Math Wise (Fuchs et al., 2009) and Galaxy Math (Fuchs et al., 2013), which combined conceptual instruction with speeded practice of simple addition and subtraction problems (Supekar et al., 2013). This tutoring program has previously been shown effective in school-based

studies of children with low math skills (Fuchs et al., 2013; Fuchs et al., 2009). Similar to MathWise and Galaxy Math, the tutoring involved a total of 15–20 hours of training, but it was condensed to 8/9 weeks with longer lessons (i.e., 3 times per week, for 40–50 minutes). The tutoring consisted of 22 lessons of increasing difficulty. Details of the lessons are described in Supplementary Materials and Methods.

2.4 Tutoring Outcome Measures

Math problem solving was assessed before and after tutoring using addition and subtraction verification tasks during fMRI scanning. There were at least two addition and two subtraction runs per session, which included 12 arithmetic problems each. For the analyses presented here, we focused on behavioral data from the first two addition and two subtraction runs that were available for analyses. Arithmetic problems were presented horizontally in green lettering on a black background. Half the math problems were correct (e.g., $3 + 4 = 7$), and the other half deviated from the correct answer by ± 1 or ± 2 (e.g., $3 + 5 = 7$). Only single-digit operand addition problems were included, and problems with 1 or 0 were excluded. The corresponding subtraction problems (e.g., $7 - 5 = 3$ and $14 - 5 = 9$) were presented in the subtraction task. In the addition task, the larger operand was equally likely to appear in the first or second position. Each trial started with a fixation asterisk for 0.5 seconds. The arithmetic problem was presented for up to 9.5 seconds, during which the child had to make a response. Participants used a response box held in their right hand, to indicate “1” if the problem was correct and “2” if the problem was incorrect. After the child made a response, the problem disappeared from the screen, and a black screen appeared for the remainder of the 9.5 seconds. Non-arithmetic control problems were randomly interspersed with arithmetic trials but were not analyzed here. In this task two numbers were presented in the format of “ $n = m$ ” where n and m were numbers between 0 and 25. Half of the control problems were presented as correctly matched pairs (e.g., $3 = 3$) and the other half deviated from the true answer by ± 1 or ± 2 (e.g., $3 = 5$). Children were asked to indicate “1” if the two numbers were the same or “2” if the two numbers were different.

To derive an aggregate measure that captures global performance changes across the addition and subtraction verification tasks, we computed an “efficiency score”, based on the definition of efficiency by Salthouse and Hedden (2002). Efficiency change was calculated as follows: (1) for each of the four behavioral measures separately (i.e., accuracy and response time (RT) for addition and subtraction problems), we calculated z-scores based on the group mean and standard deviation *across* Time 1 and Time 2; (2) we averaged the z-scores for accuracy and the inverted z-scores for RT for each participant within each time-point; (3) efficiency change was calculated by subtracting Time 1 efficiency from Time 2 efficiency (Supekar et al., 2013). Analyses of performance improvement were conducted using repeated measures ANOVAs. Outliers with performance changes > 3 *SDs* on any of the behavioral measures (accuracy and RT for addition and subtraction) were excluded from the analyses. Invalid trials (during which button presses other than 1 or 2 were recorded) were treated as missing values in the analysis. If there were more than two invalid trials in a run, we used the subsequent run for that participant. If there were signs of button box failure (i.e., lack of responses on more than 1/3 of the trials in children with otherwise high performance), we also used the subsequent run for that participant.

2.5 Brain imaging

2.5.1 Data acquisition—Brain imaging data were acquired on a 3T GE Signa scanner (General Electric, Milwaukee, WI) using the GE 8 channel head coil at the Stanford University Lucas Center. Participants were instructed to lay still with their eyes closed for the duration of the entire scan. Twenty nine axial slices (4.0 mm thickness, 0.5 mm skip) were collected parallel to the AC-PC line, using a T2* weighted gradient echo spiral in-out pulse sequence (Glover & Lai, 1998) (180 volumes; TR = 2000ms; TE=30ms, flip angle =80°, 1 interleave). Scans were acquired with a field of view of 20 × 20 cm and a matrix size of 64 × 64, providing an in-plane spatial resolution of 3.125 mm. To reduce blurring and signal loss from field in-homogeneity, an automated high-order shimming method based on spiral acquisitions was used before acquiring the functional MRI scan (Kim, Adalsteinsson, Glover, & Spielman, 2002). A high-resolution T1-weighted spoiled grass gradient recalled (SPGR) inversion recovery 3D MRI sequence was acquired to facilitate anatomical localization of resting-state fMRI connectivity maps. The following parameters were used: TI = 300 ms, TR = 8.4 ms; TE = 1.8 ms; flip angle = 15°; 22 cm field of view; 132 slices in coronal plane; 256 × 192 matrix; 2 NEX, acquired resolution = 1.5 × 0.9 × 1.1 mm. Brain imaging data of the comparison group were acquired on a 3T GE Discovery scanner (General Electric, Milwaukee, WI), using the same imaging parameters as were used in the tutoring group.

2.5.2 Movement—Head movement was minimized during scanning by a comfortable, custom-built restraint. We first excluded any children with movement larger than 5 mm in either the x, y, or z directions at either time point. In the tutoring group, the movement range was on average 0.43 (*SD* 0.46), 0.76 (*SD* 0.64), and 1.68 (*SD* 1.09) mm in the x, y, and z direction respectively at Time 1, with 0.91 (*SD* 0.91), 1.98 (*SD* 1.36), 0.70 (*SD* 0.57) degrees roll, pitch, and yaw. At Time 2, the movement range was on average 0.37 (*SD* 0.29), 0.62 (*SD* 0.55), and 1.28 (*SD* 0.91) mm in the x, y, and z direction, with 0.71 (*SD* 0.46), 1.94 (*SD* 1.10), 0.53 (*SD* 0.31) degrees roll, pitch, and yaw. Mean scan-to-scan displacement of movement (which considers both translational and rotational motion) did not exceed 0.5 mm for all participants. There were no significant differences in movement between Time 1 and Time 2 (Multivariate ANOVA: $F(6,15) = 0.77$, $p = .609$, $\eta_p^2 = .234$; Univariate ANOVAs: $p > .05$ for all six movement parameters). Therefore, it is unlikely that changes of connectivity will be driven by changes in motion. To further study the relation between movement changes and connectivity changes, and to possibly control for such differences, we performed ROI analyses, which are presented in the supplementary material.

In the comparison group, the movement range was on average 0.56 (*SD* 0.56), 1.13 (*SD* 1.16), and 1.15 (*SD* 0.89) mm in the x, y, and z direction respectively at Time 1, with 0.67 (*SD* 0.47), 2.55 (*SD* 2.17), 0.67 (*SD* 0.67) degrees roll, pitch, and yaw. At Time 2, the movement range was on average 0.34 (*SD* 0.22), 0.68 (*SD* 0.58), and 0.96 (*SD* 0.69) mm in the x, y, and z direction, with 0.44 (*SD* 0.20), 1.58 (*SD* 1.61), 0.40 (*SD* 0.20) degrees roll, pitch, and yaw. Mean scan-to-scan displacement of movement did not exceed 0.5 mm for all participants. Overall, there were no significant differences in movement between Time 1 and Time 2 (Multivariate ANOVA: $F(6,15) = 1.08$, $p = .419$, $\eta_p^2 = .301$, Univariate ANOVAs $p > .05$ for all movement parameters except roll). There were no differences between the

tutoring and comparison groups in movement changes between Time 1 and Time 2 (Multivariate ANOVA: $F(6,35) = 1.25$, $p = .306$, $\eta_p^2 = .176$; Univariate ANOVAs: $p > .05$ for all six movement parameters).

2.5.3 fMRI data preprocessing—The first 6 volumes were not analyzed to allow for signal equilibration effects. A linear shim correction was applied separately for each slice during reconstruction using a magnetic field map acquired automatically by the pulse sequence at the beginning of the scan (Glover & Lai, 1998). FMRI data were preprocessed and analyzed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). Preprocessing procedures included slice time correction, coregistration to the individual's structural data, normalization to the standard Montreal Neurological Institute (MNI) T1 template, and spatial smoothing using a Gaussian kernel (6 mm full-width at half-maximum). A bandpass filter (0.008 to 0.1 Hz) was applied to the smoothed data to remove high frequency artifacts. For coregistration, we used the individual's structural MRI scan from Time 1 or Time 2 with the highest quality rating. Data from two participants (one from the tutoring group and one from the comparison group) were normalized to the MNI template directly, omitting the coregistration step because of the poor quality of their structural data.

2.5.4 IPS and AG regions of interest (ROIs)—Our analysis specifically focused on the left IPS and AG, which are thought to be involved in distinct and often anti-correlated functional networks: the fronto-parietal network and the default mode network, respectively (Fox et al., 2005; Nelson et al., 2010; Uddin et al., 2010). Moreover, IPS and AG are believed to have different contributions to math cognition. The IPS plays a domain-specific role in approximation and complex mathematical problem solving. In contrast, some studies have implicated the AG in verbal retrieval of math facts from long-term memory (Dehaene et al., 2003; Dehaene et al., 1999), while others have argued that the AG has a domain general role in attention allocation during retrieval (Bloechle et al., 2016). Our analyses focused on IPS and AG in the left hemisphere, given their hypothesized roles in mediating symbolic number processing and arithmetic competence (Bugden et al., 2012), as well as prior findings of left-lateralized changes with learning and development (Ansari & Dhital, 2006; Cantlon et al., 2006; Jolles et al., 2015; Rivera, Reiss, Eckert, & Menon, 2005).

Observer-independent cytoarchitecturally-defined IPS and AG seed regions of interest (seed-ROIs) were created using the Anatomy Toolbox in SPM8. For the IPS, we combined the maximum probability maps of subdivisions hIP1, hIP2, and hIP3 into a single seed region (Figure 2). For the AG, we used the PGp subdivision because of its distinct pattern of brain response and connectivity from the IPS (Rosenberg-Lee, Chang, et al., 2011; Uddin et al., 2010). There was no overlap between the IPS and AG seed-ROIs. Detailed information about the anatomical boundaries of these maps has been published elsewhere (Caspers et al., 2008; Caspers et al., 2006; Choi et al., 2006). The MarsBar toolbox (<http://marsbar.sourceforge.net/>) was used to create binary seed-ROIs from these maps.

Finally, to examine whether tutoring induced connectivity changes in regions that are not related to mathematical processing, we also included a control seed-ROI encompassing the right Heschl's gyrus, which was defined using the Harvard-Oxford atlas in FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases>).

2.5.5 Individual subject analysis—For the functional connectivity analysis, we used a seed-correlation approach similar to that described in Uddin et al. (2010). First level analyses were performed on a subject-by-subject and session-by-session basis. For each seed-ROI separately, we extracted the first eigenvector time course, and we calculated how strongly that time course fitted the data at each voxel using a General Linear Model (GLM). The global time course (computed across all voxels of the brain) as well as 6 motion parameters were included as additional covariates in the model to take into account the effects of physiological noise and participant movement.

2.5.6 Functional connectivity changes in response to math tutoring—Individual contrast images were submitted to group level analyses, which were conducted across the 21 participants in the tutoring group. We conducted the following analyses: (1) paired t-tests to compare IPS and AG connectivity before and after tutoring; (2) time $\times$ region analyses using the Flexible Factorial Model to examine differences and similarities between IPS and AG in changes of functional connectivity; (3) paired t-tests to examine tutoring-related changes of functional connectivity of the IPS and AG, separately.

All functional connectivity maps were masked using a grey matter image and thresholded at $p < 0.01$ height, with FWE corrections for multiple spatial comparisons at the cluster level ($p < 0.01$, spatial extent 128 voxels). The cluster size was determined using Monte Carlo simulations implemented in Matlab (cf. Rosenberg-Lee, Barth, et al., 2011).

2.5.7 Brain-behavior correlations—ROI analyses were performed to examine whether changes in functional connectivity were associated with changes in performance efficiency (composite of accuracy and RT on the verification tasks). ROIs were defined based on the clusters that showed changes in functional connectivity with IPS and AG. We created 10 mm diameter spheres centered at the peak voxels of each cluster, from which we extracted each individual's beta values from Time 1 and Time 2. Differences in beta values were computed for each ROI in each individual and correlated with changes in individual performance efficiency.

In addition, we conducted exploratory analyses to examine whether tutoring-related performance changes were correlated with connectivity changes with right hippocampus, a region whose volume predicted individual performance gains in a prior study (Supekar et al., 2013). We used the same right hippocampal ROI that was used in the prior study, which was centered at the peak identified by the voxel-based morphometry analysis (MNI coordinates 38 -19 -18) (Supekar et al., 2013).

2.5.8 Test-retest effects in the comparison group—Finally, test-retest effects were examined using a no-contact comparison group. Differences in scanner and cognitive measures at Time 1 precluded a direct comparison with the tutoring group. Instead, we first performed an ROI analysis focusing on the peaks of the cortical and subcortical clusters that showed functional connectivity changes in the tutoring group. We examined whether IPS or AG showed connectivity changes with any of these regions, and whether connectivity changes were correlated with performance changes. Next, we performed whole-brain paired

t -tests of the IPS and AG separately, similar to the analyses that were performed in the tutoring group.

3. Results

3.1 Behavior

Performance improvement after math tutoring—To examine performance improvements associated with the tutoring, we used data from the addition and subtraction verification tasks. Two outliers (with change scores > 3 SD s) were excluded from the analyses. We found that math tutoring was associated with significant improvements in performance efficiency ($F(1,18) = 37.54$, $p < .001$, $\eta_p^2 = .676$; Figure 1B). Follow-up analyses indicated performance gains on both tasks for accuracy (addition: $F(1,18) = 9.89$, $p = .006$, $\eta_p^2 = .355$; subtraction: $F(1,18) = 21.81$, $p < .001$, $\eta_p^2 = .548$), as well as RT (addition: $F(1,18) = 32.18$, $p < .001$, $\eta_p^2 = .641$; subtraction: $F(1,18) = 5.95$, $p = .025$, $\eta_p^2 = .249$).

Test-retest effects in the comparison group—Next, we examined performance changes in the comparison group. Two participants were excluded due to data loss from technical issues during data acquisition. Overall, we did not find significant gains in performance efficiency on the verification tasks ($F(1,18) = 0.97$, $p = .337$, $\eta_p^2 = .051$). Follow-up analyses showed reduced RT on the subtraction task ($F(1,18) = 7.71$, $p = .012$, $\eta_p^2 = .300$), but there were no changes on any of the other measures (addition accuracy: $F(1,18) < .001$, $p = 1.00$, $\eta_p^2 < .001$; subtraction accuracy: $F(1,18) = 0.18$, $p = .679$, $\eta_p^2 = .010$; addition RT: $F(1,18) = 0.77$, $p = .392$, $\eta_p^2 = .041$).

3.2 Functional connectivity differences between IPS and AG seed ROIs

IPS and AG are associated with different functional brain networks—We first examined IPS and AG connectivity at Time 1. As previously described in adults (Uddin et al., 2010), IPS and AG were associated with different functional brain networks, the dorsolateral fronto-parietal network and the default mode network respectively. When IPS and AG connectivity were compared directly, we found that the left IPS showed stronger functional connectivity with supramarginal gyrus and superior parietal lobule in the posterior parietal cortex, as well as inferior and middle frontal gyrus (IFG, MFG) in the lateral PFC. Furthermore, IPS showed stronger functional connectivity with VTOC. In contrast, the AG showed stronger functional connectivity with posterior cingulate cortex, precuneus, right AG, lateral occipital cortex, and medial PFC (Table S3; Figure 3A). IPS and AG connectivity after tutoring (Time 2) was generally observed in the same brain areas as before tutoring, but to a greater extent (Figure 3B).

3.3 Changes in functional connectivity with tutoring

Changes in IPS and AG connectivity—We next examined tutoring-related changes in intrinsic functional connectivity of the IPS and AG. A flexible factorial model with Time (Time 1, Time 2) and Region (IPS, AG) as factors revealed a main effect of IPS and AG connectivity changes with the left posterior MTL (hippocampus and parahippocampal gyrus), lingual gyrus, thalamus, putamen, and IFG (Figure 4A; Table S4). To directly

contrast tutoring effects on IPS and AG connectivity, we examined the interaction between the factors Time (Time 1, Time 2) and Region (IPS, AG). This analysis indicated that, relative to the AG, the IPS showed larger increases of functional connectivity with bilateral lateral PFC (MFG and frontal pole) and left VTOC (temporal-occipital part of the inferior and middle temporal gyrus) (Figure 4B; Table S5). Right pre/postcentral gyrus and right occipital cortex showed the opposite pattern—these regions showed greater connectivity increases for the AG than the IPS. Taken together, these results suggest that changes in IPS connectivity are largely distinct from changes in the adjacent AG, although there was unexpected convergence in the MTL.

To better assess the direction of effects, we then used paired *t*-tests examining tutoring-related changes in IPS and AG connectivity separately. This analysis revealed increased left IPS connectivity with VTOC (right fusiform and left lingual gyri), lateral PFC (right IFG and frontal pole), ventromedial PFC, MTL (left hippocampus and parahippocampal gyrus), left superior temporal gyrus, and the cerebellum (Figure 5A; Table S6). In contrast, the AG showed increased functional connectivity with only the right pre/postcentral gyrus, confirming that IPS and AG related circuits are differently reconfigured by math tutoring (Figure 5B; Table S6).

No changes in Heschl's gyrus connectivity—Finally, we conducted control analyses using a seed-ROI in the right Heschl's gyrus. Heschl's gyrus is a primary sensory area, not specifically involved in any aspect of our math tutoring protocol, and therefore not expected to show changes of functional connectivity. In agreement with this hypothesis, the right Heschl's gyrus did not show any changes of functional connectivity to anywhere in the brain.

3.4 Relation between changes in functional connectivity and tutoring gains

Changes in IPS, but not AG, connectivity are associated with arithmetic performance gains—To investigate whether math tutoring-related changes in IPS and AG functional connectivity were associated with performance improvements, we examined the relation between changes in performance efficiency and changes in functional connectivity. Functional connectivity values were extracted from peaks of the cortical and subcortical clusters that showed math tutoring-related changes in IPS and AG functional connectivity (see Table S6). For the IPS, connectivity with most of the ROIs was correlated with performance gain (Figure 6A; Table 1). In contrast, changes in AG connectivity were not correlated with performance improvements (Figure 7, Table 1).

In a previous study, we found that pre-tutoring volume within a region in right hippocampus predicted individual performance gains associated with tutoring (Supekar et al., 2013). We conducted additional exploratory analyses to examine whether tutoring-related changes in IPS and AG connectivity with this right hippocampus region were also correlated with performance gains. We found a significant correlation with IPS-right hippocampus connectivity changes, but not with AG-right hippocampus connectivity changes (Figure 6B; Table 1). Taken together, these results suggest that alterations in IPS circuits underlie math

tutoring-related performance gains, highlighting the behavioral significance of the connectivity changes.

3.5 Test-retest effects on functional connectivity

No changes in IPS and AG connectivity with target regions in comparison group—To rule out test-retest effects, we examined functional connectivity changes in a comparison group with children who did not take part in math tutoring. We first performed an ROI analysis focusing on the peaks of the cortical and subcortical clusters that showed functional connectivity changes in the tutoring group (see Table S6). In contrast to the tutoring group, the comparison group did not show increased IPS or AG connectivity with any of the target regions (Table 2). Crucially, changes in IPS and AG connectivity between Time 1 and Time 2 were not correlated with changes in performance (all p s $> .07$). Next, we performed whole-brain paired t -tests of the IPS and AG separately, similar to the analyses that were performed in the tutoring group. These analyses did not reveal any significant increases of functional connectivity for IPS or AG. The only connectivity change present in the comparison group was reduced IPS connectivity with the posterior cingulate cortex (Table S7).

4. Discussion

A key goal of our study was to investigate plasticity of intrinsic brain circuits in relation to intensive cognitive tutoring in elementary school children during an important developmental stage in math skill acquisition. The cognitive tutoring program was designed to improve number knowledge and speeded retrieval of arithmetic number combinations (Fuchs et al., 2013; Fuchs et al., 2009) and engage brain systems associated with representing and manipulating numerical symbolic information. We used a network approach to examine plasticity of intrinsic functional brain circuits, incorporating the emerging view that complex cognitive tasks require the orchestrated activity of multiple brain areas (Bressler & Menon, 2010). Because of the central role of the IPS in numerical cognition, we hypothesized that tutoring would strengthen its connectivity with a distributed network of brain regions (Arsalidou & Taylor, 2011; Menon, 2015a) and that these changes would be qualitatively different from those of the anatomically adjacent AG. Our study revealed four key findings: (i) math tutoring with a specific focus on mental arithmetic improved performance and strengthened IPS connectivity with VTOC regions involved in higher order visual “object” processing, PFC regions involved in attention and cognitive control, and MTL regions involved in declarative memory; (ii) consistent with the interactive specialization hypothesis, tutoring-related changes in IPS connectivity were largely distinct from those of the adjacent AG; (iii) changes in IPS, but not AG, connectivity were correlated with individual differences in performance gains associated with tutoring; and (iv) in a comparison group of children who did not go through tutoring, IPS and AG connectivity changes were largely absent and unrelated to changes in performance. Taken together, our findings provide new insights into experience-dependent brain connectivity changes and differentiation of parietal networks underlying math learning.

Math tutoring strengthens intrinsic connectivity of the IPS

Children showed significantly stronger functional connectivity of the IPS with multiple brain regions after tutoring, compared to before tutoring. The IPS showed stronger functional connectivity with lingual and fusiform gyri in the VTOC. The IPS and VTOC form part of the dorsal and ventral association areas that process representations of numerical problems. Whereas the IPS supports representations and manipulation of quantity, the VTOC supports perceptual representations for visual number form (Arsalidou & Taylor, 2011; Dehaene & Cohen, 1995; Holloway, Battista, Vogel, & Ansari, 2013; Lyons & Ansari, 2009). Furthermore, we found increased functional connectivity between IPS and PFC regions, including IFG and frontal pole, which are involved in domain-general cognitive control processes that guide retrieval, inhibition of irrelevant facts, and maintenance of information in working memory during the initial stages of skill acquisition (Cho et al., 2012; Rosenberg-Lee, Barth, et al., 2011; Rosenberg-Lee et al., 2009). The increased and regionally specific functional interactions among the IPS, VTOC, and PFC likely support stronger integration of magnitude processing, symbol manipulation, and cognitive control, three core components of mathematical cognition.

We also found increased functional connectivity between the IPS and the hippocampus and parahippocampal gyrus in the posterior and medial aspects of the MTL. While the MTL has generally not been included in models of math cognition in adults, MTL involvement has now been consistently demonstrated in recent studies of children's arithmetic development (De Smedt, Holloway, & Ansari, 2011; Rivera et al., 2005; Rosenberg-Lee, Barth, et al., 2011). In particular, longitudinal increases in the use of retrieval strategies have been linked to MTL engagement (Cho et al., 2012; Cho, Ryali, Geary, & Menon, 2011; Qin et al., 2014). Furthermore, hippocampal volume and functional connectivity are strong predictors of performance improvements with math tutoring in children (Supekar et al., 2013). These findings are consistent with classical memory models proposing that the hippocampus plays a crucial role in integrating information across distributed cortical modules during learning, eventually leading to neocortical consolidation of facts (Frankland & Bontempi, 2005; Qin et al., 2014; Smith & Squire, 2009; Squire, Stark, & Clark, 2004; Takashima et al., 2009; Wang & Morris, 2010).

Differentiation and integration of IPS and AG systems with tutoring

The IPS and AG are adjacent subdivisions of the inferior parietal cortex, but they have different patterns of intrinsic brain connectivity (Uddin et al., 2010) and are thought to have distinct roles in mathematical cognition (Dehaene et al., 2003; Dehaene et al., 1999; Menon, 2015a). Here we demonstrate that functional segregation of IPS and AG circuits is already present in elementary school children. Before tutoring, compared to the AG, the IPS was more strongly connected to the lateral fronto-parietal network, including the posterior parietal cortex and lateral PFC. In contrast, the AG was more strongly connected to regions encompassing the default mode network, including the posterior cingulate cortex, precuneus, and medial PFC. We hypothesized that math tutoring would result in differential changes in IPS- and AG-related functional circuits. Specifically, we predicted that the IPS would show larger connectivity changes with the fronto-parietal network, while the AG would show larger connectivity changes with the MTL and other nodes of the default mode network.

This hypothesis was confirmed with respect to changes in the fronto-parietal network. Specifically, the IPS showed stronger changes in functional connectivity with the lateral PFC and VTOC.

Surprisingly, the IPS and AG showed similar levels of tutoring-related connectivity changes in connectivity with the MTL (as indicated by similar changes of beta values within the MTL; Figure 4A). Thus, the MTL appears to be a common locus of learning-related changes in IPS and AG functional circuits, such that during learning this region may aid in integration of signals from different subdivisions of the posterior parietal cortex (Menon, 2015a). In general, the commonalities between IPS- and AG-related connectivity changes are in agreement with the proposal that IPS and AG circuits operate in an integrated fashion during math cognition due to an interplay between magnitude-related processing and verbally-mediated fact retrieval that occurs automatically irrespective of task demands (Klein, Moeller, Glauche, Weiller, & Willmes, 2013; Klein et al., 2014). Further research using appropriate task paradigms is required to test this hypothesis and to examine the role of IPS, AG, and MTL circuits in this process.

Taken together, our findings suggest that, with the exception of the MTL, tutoring-related changes in IPS and AG functional connectivity are largely distinct. These findings are consistent with the interactive specialization hypothesis, which posits that learning contributes to the differentiation of functional brain circuits (Johnson, 2011). The anatomical specificity of learning-related circuit changes was further illustrated by the absence of tutoring-related connectivity changes with the right Heschl's gyrus, a control seed-ROI that was not expected to be affected by the tutoring protocol.

Tutoring-related changes in functional connectivity are behaviorally relevant

Tutoring increased performance efficiency during arithmetic problem solving. Importantly, improvements in performance were associated with functional connectivity changes of the IPS. These findings are consistent with our previous work showing a positive relation between tutoring-related performance improvement and changes of white matter integrity in a subsection of the left superior longitudinal fasciculus (Jolles et al., 2015). Crucially, changes in AG functional connectivity were not correlated with performance improvement, further demonstrating differentiation between the functional roles of IPS and AG circuits. Our findings may at first glance seem at odds with studies of math learning in adults, which have reported specific engagement of the AG for trained math problems, whereas activation of the IPS was stronger for untrained math problems (Delazer et al., 2005; Ischebeck, Zamarian, Egger, Schocke, & Delazer, 2007). However, recent studies have suggested that although the AG shows higher levels of activation for trained versus untrained problems post-training, when activation for trained problems was compared to activation for the same problems in the pre-training session, no signal changes were observed in the AG (Bloechle et al., 2016), suggesting that the AG is not involved in fact retrieval per se. The observation that the AG is typically deactivated on simple arithmetic tasks where retrieval fluency is high (Rosenberg-Lee, Chang, et al., 2011; Wu et al., 2009) provides further support for the idea that the AG is not directly involved in the retrieval of arithmetic facts. Our findings of brain-

behavior correlations associated with the IPS but not the AG are also consistent with this view.

The anatomical specificity of brain-behavior relations indicates that changes in IPS connectivity with tutoring were not related to familiarity with the scanning environment or developmental changes. To further investigate test-retest effects, we examined a different cohort of third-grade children who underwent the same scanning and testing procedures but did not take part in the tutoring sessions. We did not find significant changes in functional connectivity between the IPS (or AG) and the target regions in these children, suggesting that the observed connectivity changes in the tutoring group were specific to tutoring. Furthermore, individual differences in IPS and AG connectivity were not correlated with performance changes in the comparison group. These results further clarify the specificity of our findings relating the IPS to behavioral changes associated with tutoring.

Future Directions

The present study is the first to investigate plasticity of parietal brain circuits associated with the development of math skills in children. Further studies using randomized controlled designs are needed to investigate the generalizability of our findings in a larger group of well-matched experimental and control participants, and to better disentangle the effects of tutoring versus schooling and general development. Further studies are also needed to quantify the relative efficacy of different tutoring designs and the distinct functional circuits by which they enhance learning. Specifically, these studies should characterize the behavioral effects and underlying neural mechanisms of learning paradigms that focus on conceptual understanding and magnitude representations (i.e. number sense) training versus rote-learning and memorization of math facts. Such studies may help to further disentangle the contribution of IPS and AG systems to math learning.

Conclusion

Our study demonstrates how intrinsic connectivity of specific large-scale parietal circuits is reconfigured after 8 weeks of intensive math tutoring in children and how these changes are related to individual differences in children's performance improvements. Tutoring-related increases in IPS connectivity showed largely distinct patterns of change from those of the adjacent AG, with an unexpected convergence in the MTL. Importantly, changes in IPS, but not AG, connectivity were correlated with performance gains after math tutoring. Our findings point to distinct but interactive roles of the IPS, AG, and MTL in math cognition and learning. More generally, a better understanding of brain circuit plasticity associated with learning may facilitate the development of targeted intervention programs for children with learning disabilities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AG	Angular Gyrus
IFG	Inferior Frontal Gyrus
IPS	Intraparietal Sulcus
MTL	Medial Temporal Lobe
PFC	Prefrontal Cortex
RT	Response Time
VTOT	Ventral Temporal-Occipital Cortex

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Figure 1. Overall study design and performance improvement

(A) After the initial screening and standardized neuropsychological testing, children came in for Time 1 math assessments and brain imaging, including a resting-state fMRI scan. They then underwent an 8-week one-on-one math tutoring program, which focused on conceptual as well as procedural knowledge important to math skill development. After 8 weeks of tutoring, children came back for the Time 2 math assessment and brain imaging session. (B) Increased performance efficiency after math tutoring. Performance efficiency was measured using a composite of standardized accuracy and response time (RT) scores on addition and subtraction tasks for each child ($N = 19$). Error bars represent standard error of mean. * $p < .05$.

Figure 2. Parietal cortex IPS and AG seed ROIs

Regions of interest (ROIs) were defined based on unbiased observer-independent cytoarchitectonic regions (Caspers et al., 2006, 2008; Choi et al., 2006). AG = angular gyrus; IPS = intraparietal sulcus. Coordinates are in MNI space.

Figure 3. Differences in IPS and AG functional connectivity before (A) and after (B) tutoring Compared to the AG, the IPS showed stronger functional connectivity with supramarginal gyrus and superior parietal lobule, lateral prefrontal cortex, and ventral temporal occipital cortex. Compared to the IPS, the AG showed stronger functional connectivity with posterior cingulate cortex, precuneus, right AG, lateral occipital cortex, and medial prefrontal cortex. AG = angular gyrus; IPS = intraparietal sulcus. Coordinates are in MNI space.

Figure 4. Math tutoring-related changes in IPS versus AG connectivity

(A) An ANOVA with Time (Time 1, Time 2) and Region (IPS, AG) as factors revealed a main effect of Time in the left thalamus, posterior hippocampus, and right lateral IFG. (B) Significant interaction effects indicated that the IPS showed larger increases of functional connectivity with bilateral PFC (frontal pole and MFG) and left VTOC (temporo-occipital part of the inferior and middle temporal gyrus) compared to the AG. AG showed greater connectivity increases with right pre/postcentral gyrus and right occipital cortex relative to the IPS. Graphs show mean connectivity levels (beta) in the peaks of each cluster. In panel

A, mean connectivity levels were also plotted for a subpeak in posterior hippocampus (-22 -42 -2). Error bars represent standard error of mean. AG = angular gyrus; MFG = middle frontal gyrus; MTG = middle temporal gyrus; PFC = prefrontal cortex; IFG = inferior frontal gyrus; IPS = intraparietal sulcus; STG = superior temporal gyrus; VTOC = ventral temporal occipital cortex. Coordinates are in MNI space.

Figure 5. Tutoring-related changes in IPS and AG functional connectivity separately

(A) Paired t-tests showed increased functional connectivity between the IPS and the VTOC (right fusiform and left lingual gyri), lateral PFC (right IFG and frontal pole), ventromedial PFC, MTL (left hippocampus and parahippocampal gyrus), and left superior temporal gyrus with tutoring. (B) Paired t-tests showed increased functional connectivity between the AG and right pre/postcentral gyrus with tutoring. Graphs show mean connectivity levels (beta) in the peaks of each cluster. Error bars represent standard error of mean. AG = angular gyrus; IFG = inferior frontal gyrus; IPS = intraparietal sulcus; MTL = medial temporal lobe; PFC = prefrontal cortex; STG = superior temporal gyrus; VTOC = ventral temporal occipital cortex. Coordinates are in MNI space.

Figure 6. Tutoring-related performance gains were associated with changes in IPS connectivity (A) Increased performance efficiency was associated with tutoring-related changes between IPS and fusiform gyrus, posterior hippocampus, ventromedial PFC, and STG. (B) Performance gain was also associated with increased connectivity between IPS and a region in right hippocampus that has been shown to predict individual performance gains associated with tutoring. FC = functional connectivity; IFG = inferior frontal gyrus; IPS = intraparietal sulcus; PFC = prefrontal cortex; STG = superior temporal gyrus; * $p < .05$; ** $p < .01$.

Figure 7. Tutoring-related performance gains were not associated with changes in AG connectivity

Increased performance efficiency was not associated with tutoring-related changes between AG and right postcentral gyrus (**A**) or right hippocampus (**B**). Note that changes of AG connectivity with the peaks derived from the IPS contrast (see Table S6) were not significant either (all p 's $\geq .288$). FC = functional connectivity.

Table 1

Tutoring-related performance gains were correlated with changes in IPS, but not AG, connectivity.

	IPS FC	AG FC
<i>IPS peaks</i>		
Right Fusiform Gyrus (34 -68 -6)	0.652 **	–
Left Hippocampus (-22 -42 -2)	0.468 *	–
Right IFG (54 14 6)	0.175	–
Ventromedial PFC (0 18 -18)	0.487 *	–
Left STG (-56 -18 -6)	0.552 *	–
<i>AG peak</i>		
Right Postcentral gyrus (40 -24 50)	–	0.151
<i>ROI from Supekar et al., 2013</i>		
Right Hippocampus (38 -19 -18)	0.512 *	-0.065

Note: N = 19; MNI coordinates in brackets; AG = Angular gyrus; FC = functional connectivity; IFG = inferior frontal gyrus; IPS = Intraparietal sulcus; PFC = prefrontal cortex; STG = superior temporal gyrus.

**
 $p < .01$,

*
 $p < .05$

Table 2

Time 2 vs. Time 1 changes in IPS and AG connectivity in the comparison group were not significant.

	<i>F</i>	<i>p</i>	η_p^2
<i>IPS peaks</i>			
Right Fusiform Gyrus (34 -68 -6)	0.46	.507	.022
Left Hippocampus (-22 -42 -2)	0.57	.458	.028
Right IFG (54 14 6)	0.07	.798	.003
Ventromedial PFC (0 18 -18)	0.01	.910	.001
Left STG (-56 -18 -6)	1.04	.320	.049
<i>AG peak</i>			
Right Postcentral gyrus (40 -24 50)	0.73	.402	.035

Note: N = 21; MNI coordinates in brackets; AG = Angular gyrus; IFG = inferior frontal gyrus; IPS = Intraparietal sulcus; PFC = prefrontal cortex; STG = superior temporal gyrus.