Heterogeneous and nonlinear development of human posterior parietal cortex function

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A B S T R A C T

Human cognitive problem solving skills undergo complex experience-dependent changes from childhood to adulthood, yet most neurodevelopmental research has focused on linear changes with age. Here we challenge this limited view, and investigate spatially heterogeneous and nonlinear neurodevelopmental profiles between childhood, adolescence, and young adulthood, focusing on three cytoarchitectonically distinct posterior parietal cortex (PPC) regions implicated in numerical problem solving: intraparietal sulcus (IPS), angular gyrus (AG), and supramarginal gyrus (SMG). Adolescents demonstrated better behavioral performance relative to children, but their performance was equivalent to that of adults. However, all three groups differed significantly in their profile of activation and connectivity across the PPC subdivisions. Activation in bilateral ventral IPS subdivision IPS-hIP1, along with adjoining anterior AG subdivision, AG-PGa, and the posterior SMG subdivision, SMG-PFm, increased linearly with age, whereas the posterior AG subdivision, AG-PGp, was equally deactivated in all three groups. In contrast, the left anterior SMG subdivision, SMG-PF, showed an inverted U-shaped profile across age groups such that adolescents exhibited greater activation than both children and young adults. Critically, greater SMG-PF activation was correlated with task performance only in adolescents. Furthermore, adolescents showed greater task-related functional connectivity of the SMG-PF with ventro-temporal, anterior temporal and prefrontal cortices, relative to both children and adults. These results suggest that nonlinear up-regulation of SMG-PF and its interconnected functional circuits facilitate adult-level performance in adolescents. Our study provides novel insights into heterogeneous age-related maturation of the PPC underlying cognitive skill acquisition, and further demonstrates how anatomically precise analysis of both linear and nonlinear neurofunctional changes with age is necessary for more fully characterizing cognitive development.

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Introduction

Human problem solving skills undergo complex and experience-dependent changes from childhood to adulthood, resulting in more efficient proficiencies over time (Casey et al., 2005; Durston and Casey, 2006). The development of these skills is supported by increasingly specialized functional brain systems (Durston et al., 2006; Kwon et al., 2002; Rivera et al., 2005; Tamm et al., 2002; Uddin et al., 2010b). Much of our understanding of neurocognitive development is based on linear models of age-related changes in which brain activation increases or decreases linearly from childhood to adulthood (Adleman et al., 2002; Kwon et al., 2002; Menon et al., 2005; Ofen et al., 2007;

Rivera et al., 2005). While this approach has provided insights into key neurodevelopmental processes, it can also lead to a misleading view of the nature of cognitive skill development (Galvan et al., 2006; Geier et al., 2009; McRae et al., 2012; Van Leijenhorst et al., 2010). Linear models are limited in that they cannot capture unique effects that may occur at specific stages of development (Brenhouse and Andersen, 2011; Geier et al., 2009). Here we investigate fundamental and unaddressed questions regarding linear and nonlinear age-related changes in proficient arithmetic problem solving.

Although the majority of functional brain imaging studies of cognitive skill development have focused on linear models of age-related change (Adleman et al., 2002; Kwon et al., 2002; Menon et al., 2005; Ofen et al., 2007; Rivera et al., 2005), functional imaging studies of emotion and reward processing have provided evidence for an inverted U-shaped pattern of brain activation, characterized by increased activation from childhood to adolescence followed by decreases from adolescence to adulthood (Brenhouse and Andersen, 2011; Galvan et al., 2006; Geier

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et al., 2010; Somerville et al., 2010; Van Leijenhorst et al., 2010). In addition, studies of brain structure reveal that there are nonlinear changes in the brain from childhood to adulthood (Giedd et al., 1999; Gogtay et al., 2004; Lebel and Beaulieu, 2011; Lenroot and Giedd, 2006), suggesting that many aspects of brain development are not linear, and, importantly, highlighting unique periods of change occurring during the transitional period of adolescence. Adolescence is thought to be a paradoxical stage of development when fundamental building blocks of problem solving are established, but functional and structural maturation of the brain is not yet complete (Blakemore, 2012; Luna, 2004). Thus, the overarching goal of the current study is to contrast brain systems underlying cognitive problem solving in children, adolescents, and adults, with a specific focus on linear and non-linear profiles of age-related change and their relation to behavior.

We focus on numerical problem solving, a cognitive domain crucial for academic and professional success as well as quantitative reasoning in everyday life (Butterworth et al., 2011; Geary, 2013; Geary et al., 2013; Richland et al., 2007). Neurocognitive models of numerical problem solving have highlighted a central role of the posterior parietal cortex (PPC) in numerical task performance (Ansari, 2008; Ansari and Dhital, 2006; Arsalidou and Taylor, 2011; Cantlon and Brannon, 2006; Cohen Kadosh et al., 2008; Dehaene et al., 2003; Houde et al., 2010; Menon et al., 2000; Wu et al., 2009). The PPC is a highly heterogeneous structure, encompassing cytoarchitectonic subdivisions (Fig. 1; Caspers et al., 2008; Choi et al., 2006; Scheperjans et al., 2008a,b) that appear to play differential functional roles in numerical problem solving as evidenced by functional magnetic resonance imaging (fMRI) studies (Rosenberg-Lee et al., 2011b; Wu et al., 2009). In the intraparietal sulcus (IPS), brain activity in the more ventral and anterior subdivisions, IPS-hIP2 and IPS-hIP1 (Choi et al., 2006), is associated with representing abstract quantity information (Arsalidou and Taylor, 2011; Cohen Kadosh et al., 2011; Cohen Kadosh et al., 2008; Dehaene et al., 2003). Ventral to the IPS regions are the angular gyrus (AG) and supramarginal gyrus (SMG). Brain activity in the largest subdivision of the dorsal SMG, the SMG-PF (Caspers et al., 2006), has been linked to supporting working memory processes important for manipulating numerical information (Kaufmann et al., 2011; Metcalfe et al., 2013; Silk et al., 2010). Finally, in adults, functional dissociations during arithmetic problem solving have also been demonstrated in the AG. Activity in the anterior AG subdivision, AG-PGa, and the adjoining SMG subdivision, SMG-PFm, is associated with automatized arithmetic problem solving (Dehaene et al., 2003; Grabner et al., 2007; Rosenberg-Lee et al., 2011b), and the posterior AG subdivision, AG-PGp (Caspers et al., 2006), is inversely associated with task difficulty, showing significant deactivation (activation

below the resting baseline) as task difficulty increases (Rosenberg-Lee et al., 2011b; Wu et al., 2009). Brain function in the AG-PGp also shows prominent overlap with the PPC node of default mode network (Greicius et al., 2003; Raichle et al., 2001), a system important for internal mental processes including episodic (Cabeza et al., 2012; Cabeza et al., 2008) and semantic memory (Binder and Desai, 2011).

It is currently not known how the function of these heterogeneous subdivisions within the PPC develops and influences task performance. This is an important area to explore, as it has implications for our understanding of cognitive problem solving during critical periods of development. To this end, we used fMRI to investigate brain responses underlying arithmetic problem solving in a large cross-sectional sample of 25 children (ages 7–10), 19 adolescents (ages 13–17), and 26 young adults (ages 19–22). An arithmetic verification task involving subtraction operations allowed us to assess dynamic changes in the functional engagement of individual PPC subdivisions including the IPS, AG, and SMG. We used subtraction problems as they require more effortful use of calculation procedures, manipulation of abstract quantity, and stronger engagement of multiple subdivisions of the PPC than other operations such as addition and multiplication in adults (Chochon et al., 1999; Prado et al., 2011; Rosenberg-Lee et al., 2011b) and children (De Smedt et al., 2011). In order to better characterize the nature of age-related differences in the PPC, we used both linear and quadratic contrasts to highlight areas that demonstrated consistent developmental change across our three age groups, as well as regions that showed unique responses during adolescence.

An important question we address is how functional brain circuits underlying arithmetic problem solving change with age. Previous research has suggested that numerical cognition relies on a distributed set of inter-connected functional circuits within and outside the PPC, including prefrontal cortex (PFC), ventral-occipital temporal cortex (VTOC), anterior temporal cortex (ATC), and insula (Arsalidou and Taylor, 2011; Menon et al., 2014; Rosenberg-Lee et al., 2015; Rosenberg-Lee et al., 2011a; Supekar and Menon, 2012; Uddin et al., 2010a), and that the functional coupling between the PPC and these regions play a critical role during arithmetic tasks (Rosenberg-Lee et al., 2011a; Supekar and Menon, 2012). For example, using fMRI and an arithmetic problem-solving task, one study found that compared to children (7–9 years), young adults (19–22 years) showed stronger functional connectivity and causal interactions between the PPC and the anterior insula (Supekar and Menon, 2012). Another study demonstrated that functional coupling of fronto-parietal circuits in 2nd graders increased after one year of schooling (Rosenberg-Lee et al., 2011a). Finally, there is evidence to suggest that compared to typically developing
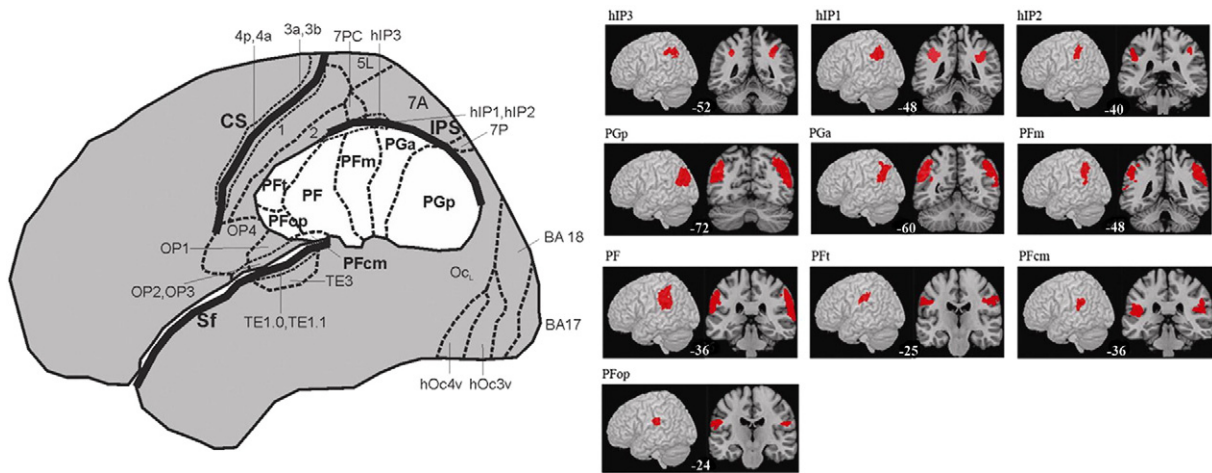
Fig. 1. Cytoarchitectonic maps of posterior parietal cortex (PPC) and its subdivisions. (*Left*) Sagittal view of the PPC regions that are typically activated during arithmetic problem solving tasks, including three intraparietal sulcus (IPS) — hIP3, hIP1, hIP2, two angular gyrus (AG) — PGp and PGa, and five supramarginal gyrus (SMG), PFm, PF, PFt, PFcm, PFop subdivisions. (*Right*) Surface renderings and coronal sections are shown, with the numbers at the bottom of each panel representing the y-axis in MNI coordinates to indicate location of the slices (Adapted from Wu et al., 2009).

children, children with developmental dyscalculia exhibited hyper-connectivity between PPC and PFC during addition and subtraction problem solving (Rosenberg-Lee et al., 2015). Little is known, however, about the development of PPC, PFC, and other functional circuits underlying problem solving over an extended period spanning childhood, adolescence and adulthood.

Here we take advantage of cytoarchitectonic maps to more accurately characterize heterogeneous patterns of age-related differences in brain activation and connectivity of distinct subregions of the PPC that may support the transition to adult-level proficiencies in problem solving. We tested the hypothesis that individual PPC subdivisions would demonstrate differential profiles of age-related differences and that these neurofunctional signatures are related to variability in behavioral performance. Specifically, we predicted that recruitment of the IPS-hIP1 and IPS-hIP2, PPC subdivisions specialized for numerical problem solving (Ansari, 2008; Cohen Kadosh et al., 2008; Dehaene et al., 2003), and the AG-PGa and the adjoining SMG-PFm (regions that have been linked to arithmetic fact retrieval; Dehaene et al., 2003; Grabner et al., 2007; Rosenberg-Lee et al., 2011b) would exhibit a linear profile of increased activation across the three age groups. We also predicted differential engagement of SMG subdivisions such as the SMG-PF between age groups, on the basis of their involvement in more mature adult-like use of working memory resources (Geier et al., 2009; Kwon et al., 2002). Specifically, we hypothesized that increased recruitment of working memory resources supported by the SMG-PF would allow adolescents to perform at adult levels, despite immature IPS recruitment (Rivera et al., 2005). For the AG-PGp, the PPC subdivision whose functional role in numerical cognition is less clear, we predicted that default mode network-related deactivation (Greicius et al., 2003; Wu et al., 2009) would be apparent in all age groups, demonstrating that even young adults do not easily retrieve subtraction problems from memory (Campbell and Xue, 2001). Finally, we investigated whether non-linear age-related differences are also apparent in brain structure, considering prior evidence of nonlinear change in the development of gray matter volume between childhood and adulthood (Giedd et al., 1999; Gogtay et al., 2004; Lebel and Beaulieu, 2011; Lenroot and Giedd, 2006).

Methods

Participants

Child and adolescent participants were recruited from a wide range of schools in the San Francisco Bay area using mailings to schools and postings at libraries and community groups. Young adults were recruited from local educational institutions in the San Francisco Bay Area through campus flyers and postings. All participants were right-handed with no reported history of psychiatric or neurological disorders. Participants' intelligence was assessed using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), with the inclusion criteria of full scale IQ above 90. Participant's mathematical and reading abilities were further assessed using the Wechsler Individual Achievement Test Second Edition (WIAT-II; Wechsler, 2001). The sample consisted of 25 children (11 males), 19 adolescents (10 males), and 26 young adults (13 males). Participant's ages ranged from 7.7 to 10.7 years ($M = 8.8$, $SD = 0.7$) for children, 13.1 to 17.5 years ($M = 15.7$, $SD = 1.4$) for adolescents, and 19.0 to 22.6 years ($M = 20.6$, $SD = 1.0$) for young adults. The three age groups did not differ in IQ, mathematical or reading abilities (Table 1).

Standard cognitive ability assessment

Mathematical abilities were assessed using the WIAT-II (Wechsler, 2001). This achievement battery includes nationally standardized measures of academic skills and problem-solving abilities for Grades 1 to 16, which are normed by grade and time of the academic year (separate Fall, Spring, or Summer for Grades 1 to 8 and yearly-based after

Table 1
Standardized IQ, mathematical, and reading ability scores for children, adolescents and adults.

Measurement	Group						
	Children (N = 25)		Adolescents (N = 19)		Adults (N = 26)		p
	M	SD	M	SD	M	SD	
Males/females	11/14		10/9		13/13		
WASI							
Verbal	112.68	14.38	116.47	9.85	116.92	13.45	.456
Performance	109.16	13.16	112.05	6.93	112.85	11.45	.473
Full Scale	112.64	10.79	116.26	6.22	116.77	12.05	.316
WIAT-II							
Numerical Operation	112.40	10.94	117.47	9.03	113.15	7.29	.166
Mathematical Reasoning	112.72	11.39	112.89	11.34	111.85	9.77	.938
Word Reading	113.88	11.18	111.79	4.73	106.92	13.95	.080
Reading Comprehension	110.68	10.16	117.79	11.66	111.04	16.17	.151

WASI = Wechsler Abbreviated Scales of Intelligence; WIAT-II = Wechsler Individual Achievement Test − Second Edition. *P*-values represent results of one-way ANOVA tests of difference among age categories.

Grade 8). The Numerical Operations subtest is a paper-and-pencil test that measures number writing and identification, rote counting, number production, and simple addition, subtraction, multiplication, and division calculations. For example, $37 + 54$ is presented vertically on the answer sheet and the participant is required to write down the solution. The Mathematical Reasoning subtest is a verbal problem-solving test that measures counting, geometric shape identification, and single- and multi-step word problem-solving involving time, money, and measurement with both verbal and visual prompts. The participant is required to solve problems with whole numbers, fractions or decimals, interpret graphs, identify mathematical patterns, and solve problems of statistics and probability. For example, a dime is presented and the participant is asked: "How many pennies does it take to equal the value of one dime?" A probability problem asks: "If you flipped a coin ten times, how many times would the coin be most likely to land on heads?"

Brain imaging

Experimental procedures

The fMRI experiment consisted of four task conditions: (1) Complex Subtraction, (2) Simple Subtraction, (3) Number Identification and (4) Passive Fixation. In the Complex Subtraction task, participants were presented with a subtraction equation involving two operands and asked to indicate, via a button box, whether the answer shown was correct or incorrect (e.g. "8−2 = 5"). The first operand ranged from 3 to 14 and the second operand from 2 to 5. Tie problems, such as "5−5 = 0", were excluded. In the Simple subtraction task, the first operand ranged from 2 to 14 and the second operand was always '1'. The answers were correct in 50% of the trials for both the Complex and Simple conditions. Incorrect answers deviated by ± 1 or ± 2 from the correct answer (Ashcraft and Battaglia, 1978). The actual and presented differences were always greater than zero. In order to control for basic visual number processing and motor response, the Number Identification task was used as a control task. In this task, arithmetic symbols were replaced by alternative keyboard symbols (e.g. "4 o 5 @ 7") and participants were asked to assess if "5" was among the presented digits. A verification, rather than verbal production, task format was used in the scanner because overt verbal responses can result in significant head movement and unusable fMRI data. Finally, in the Passive Fixation task, the symbol "*" appeared at the center of the screen and participants were asked to focus their attention on it.

Stimuli were presented in a block fMRI design in order to optimize signal detection (Friston et al., 1999). In each task, stimuli were

displayed for 5 s with an inter-trial interval of 500 ms. There were 18 trials of each task condition, which were broken up into 4 blocks of 4 or 5 trials; thus, each block lasted either 22 or 27.5 s. The order of the blocks was randomized across participants with the following constraints: in every set of 4 blocks, all of the conditions were presented and the Complex and Simple Subtraction task blocks were always separated by either a Number Identification block or a Passive Fixation block. All orders of arithmetic and non-arithmetic task conditions were equally likely. The total length of each experimental run was 6 min and 36 s.

Data acquisition

Images were acquired on a 3 T GE Signa scanner (General Electric, Milwaukee, WI) using a custom-built head coil at the Stanford University Lucas Center. Head movement was minimized during the scan by cushions placed around the participant's head. A total of 29 axial slices (4.0 mm thickness, 0.5 mm skip) parallel to the AC-PC line and covering the whole brain were imaged using a T2* weighted gradient echo spiral in-out pulse sequence (Glover and Lai, 1998) with the following parameters: TR = 2 s, TE = 30 msec, flip angle = 80°, 1 interleave. The field of view was 20 cm, and the matrix size was 64×64, providing an in-plane spatial resolution of 3.125 mm. To reduce blurring and signal loss from field inhomogeneity, an automated high-order shimming method based on spiral acquisitions was used before acquiring functional MRI scans (Kim et al., 2002). In the same scan session, high-resolution T1-weighted spoiled grass gradient recalled (SPGR) 3D MRI sequence was acquired for each participant for conducting structural analyses and to aid localization of functional data. 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; number of excitation, 2; acquired resolution = $1.5 \times 0.9 \times 1.1$ mm.

fMRI data preprocessing

Functional MRI data were pre-processed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The first 5 volumes were not analyzed to allow for signal equilibration effects. Images were reconstructed, by inverse Fourier transform, for each of the time points into $64 \times 64 \times 28$ image matrices (voxel size $3.125 \times 3.125 \times 4.5$ mm). 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 and Lai, 1998). All participants had movement less than 4 mm in all of the x, y, and z directions. A procedure similar to AFNI 3dDespike (Cox, 1996) was used to correct for transient excesses in participant movement. Deviant volumes were identified as having either scan-to-scan displacement greater than half of a voxel size (1.67 mm in this study) or change in global signal greater than 5%. The scan-to-scan displacement was computed as the square root of the sum of both translational and rotational displacement difference between two consecutive scans. Rotational displacements were converted from degrees to millimeters by assuming a brain radius of 65 mm. No participant had more than 6% deviant volumes. Deviant volumes were then interpolated using the two adjacent scans. Importantly, there were no significant group differences between the percentage of deviant volumes between children ($M = 1.03\%, SD = 1.09$), adolescents ($M = 0.56\%, SD = 0.16$) and young adults ($M = 0.64\%, SD = 0.42; p = .061$). Images were realigned to correct for head motion, corrected for errors in slice-timing, spatially transformed to standard stereotaxic space (based on the Montreal Neurologic Institute coordinate system), resampled every 2 mm using sinc interpolation and smoothed with a 6 mm full-width half-maximum Gaussian kernel to decrease spatial noise prior to statistical analysis.

Individual and group-level analysis

Statistical analysis was performed on both individual and group-level data using the general linear model (GLM) implemented in SPM8. Individual subject analyses were first performed by modeling task-related regressors as boxcar functions corresponding to the epochs during which each condition was presented, and convolved with a canonical hemodynamic response function. Task-unrelated regressors were also included using the 6 motion parameters generated in SPM8's realignment procedure.

We focused on brain responses to the Complex Subtraction (hereafter, 'Subtraction') task, contrasted with responses to the Number Identification (hereafter, 'Control') task, which provides a high-level baseline for sensory and basic number processing, as well as response selection. Crucially, the Subtraction problems used here require greater access to magnitude representations supported by the PPC (Ansari, 2008; Arsalidou and Taylor, 2011; Cohen Kadosh et al., 2008; De Smedt et al., 2011; Dehaene et al., 2003). This view has been supported by behavioral studies in which the percentage of direct retrieval used for solving subtraction problems is significantly low for both adults (58%) and children (19%; Barrouillet et al., 2008; Campbell and Xue, 2001). Therefore, we focused on Subtraction task problems as they provide an ideal problem set for investigating age-related differences in behavior and brain function.

For the first-level analysis, voxel-wise t-statistics maps of the contrasts between Subtraction and Control were generated for each participant. These contrast images were then analyzed in group-level one-sample *t*-tests to identify brain areas with significant activation (Subtraction–Control) and deactivation (Control–Subtraction) for each age group.

To assess the heterogeneous changes in brain activations across the three different age groups, we conducted group-level voxel-wise F-tests to identify brain regions that manifested linear and nonlinear age-related differences from childhood to young adulthood. Specifically, we first examined the linear age-related trend for brain activations defined by "Subtraction–Control" using the contrast codes [− 1 0 1] for the three age groups. Similarly, we then examined nonlinear age-related effects by specifically testing the quadratic trend using the contrast codes [− 0.5 1 − 0.5] for activations in the three age groups.

All significant clusters of activation from the above analyses were determined based on Monte Carlo simulations to determine the minimum cluster size that controls for false positive rate at a voxel-wise height threshold of $p < .01$ and a spatial extent threshold of $p < .05$. Monte Carlo simulations were implemented in Matlab using methods similar to the AlphaSim procedure in AFNI (Forman et al., 1995; Nichols and Hayasaka, 2003; Ward, 2000). Ten thousand iterations of random 3-D images, with the same resolution and dimensions as the fMRI data, were generated. The resulting images were masked for gray matter and then smoothed with the same 6 mm full-width half-maximum Gaussian kernel used to smooth the fMRI data. The maximum cluster size was then computed for each iteration and the probability distribution was estimated across the 10,000 iterations. The cluster threshold corresponding to a family-wise error significance level of $p < 0.05$ was determined to be 100 voxels.

Cytoarchitectonic probabilistic maps of the posterior parietal cortex

To localize the age effect in PPC, we used cytoarchitectonic probabilistic maps to characterize and label functional activations in the PPC. These maps are based on observer-independent analyses of cytoarchitechtonic organization to provide an anatomically precise and consistent basis for examining the differential profile of fMRI responses as demonstrated in several prior studies (Ashkenazi et al., 2012; Rosenberg-Lee et al., 2011b; Wu et al., 2009). These maps provide cytoarchitectonically distinct subdivisions of the three IPS (hIP3, hIP1, and hIP2, named in the order from caudal to rostral axis of the IPS), two AG (PGp and PGa), and five SMG (PFm, PF, PFt, PFcm, and PFop) regions, as described above (Fig. 1). Probability maps of each of these ROIs were evaluated using the SPM Anatomy Toolbox (Eickhoff et al., 2005). The spatial distribution of regional activations was characterized by 3 metrics— the probability that a peak in the cluster was assigned to a specific region, the percentage of an activation cluster that was in a specific region, and the percentage of a specific region that belonged to an

activated cluster. To avoid spatial overlap in these probabilistic ROIs, each voxel was assigned to the region within which it demonstrated the highest probability. This approach yields continuous non-overlapping parcellation of the PPC that can be used to uniquely localize regional responses.

Voxel-based morphometry (VBM) analysis

We examined age-related structural differences within the PPC. Structural images were processed using VBM8 toolbox (http://dbm. neuro.uni-jena.de/vbm/). Structural images were first checked for potential artifacts and then aligned to conventional anterior commissure (AC)-posterior commissure (PC) space using manually identified landmarks, including AC, PC, and the mid-sagittal plane. The realigned images were resliced, normalized to Montreal Neurological Institute (MNI) stereotactic space and segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid compartments with the following parameters: bias regularization = 0.0001, bias FWHM cutoff = 60 mm, sampling distance = 3, Hidden Markov Random Field (HMRF) weighting = 0.15. Voxel values were modulated by the Jacobian determinants derived from the spatial normalization: areas that were expanding during warping were proportionally reduced in intensity. When using modulated images for performing subsequent group comparisons, the inference is made on measures of volume rather than tissue concentration (density). Finally, the segmented modulated images for WM and GM were smoothed with an isotropic Gaussian Kernel (10 mm full width at half maximum).

gPPI analysis

We performed a generalized psychophysiological (gPPI) analysis (McLaren et al., 2012) to examine task-modulated connectivity of the PPC with the whole brain. gPPI evaluates the strength of functional interactions between a given seed and other brain regions after accounting for the activation differences between two tasks. The time series from the seed ROI was de-convolved to uncover neuronal activity and multiplied with the task design waveforms to form an interaction term. This interaction term was convolved with the hemodynamic response function (HRF) to form the PPI regressor (Friston et al., 1997). The gPPI further extends the conventional PPI to explicitly model the interaction term for each task condition in the experiment. Contrast images corresponding to differences in connectivity between Subtraction and Control conditions were generated for each subject and entered into subsequent within-group and between-group two-sample *t*-tests. The significance of the results was assessed in the same way as described in the standard GLM analysis: using a voxel-wise height threshold of $p < .01$ and a spatial extent threshold of $p < .05$, based on Monte Carlo simulations.

Results

Behavior

Fig. 2 summarizes the accuracy and reaction times of children, adolescents and young adults solving Subtraction and Control problems. Mean accuracy of each participant was entered into a two-way ANOVA with Task (Subtraction, Control) as a within-subject factor and Group (Children, Adolescents, Adults) as a between-subject factor. A significant Task effect was observed, with participants responding less accurately to subtraction than control problems (89% vs. 97%, $F (1, 67) = 45.578$, $p < .001$). There was also a significant group effect ($F (2, 67) = 21.837$, $p < .001$). Post-hoc analysis with Bonferroni correction for multiple comparisons showed that group differences resulted from children responding less accurately than adolescents (84% vs. 98%, $p < .001$) and young adults (84% vs. 97%, $p < .001$). No difference was found between adolescents and young adults (98% vs. 97%, $p = 1.000$). There was also a Task by Group interaction ($F (2, 67) = 24.413$, $p < .001$), wherein children were significantly less accurate on Subtraction compared to Control than adolescents (18% vs. 2%, $p < .001$, Bonferroni corrected) and young adults (18% vs. 2%, $p < .001$, Bonferroni corrected). There was no difference between Task effects for adolescents and young adults (2% vs. 2%, $p = 1.000$, Bonferroni corrected).

A parallel analysis was conducted on median reaction time of each participant. Participants responded more slowly to Subtraction than Control problems (2019 ms vs. 1093 ms, $F (1, 67) = 356.951$, $p < .001$). Response latencies differed among children, adolescents, and young adults ($F (2, 67) = 71.802$, $p < .001$). Post-hoc analyses using Bonferroni correction confirmed that children were slower than adolescents (2237 ms vs. 1287 ms, $p < .001$) and young adults (2237 ms vs. 1144 ms, $p < .001$). No difference was found between adolescents and young adults (1287 ms vs. 1144 ms, $p = .529$). There was also a Task by Group interaction ($F (2, 67) = 33.261$, $p < .001$), wherein children were considerably slower on Subtraction, compared to Control trials, than adolescents (1475 ms vs. 663 ms, $p < .001$, Bonferroni corrected) or young adults (1475 ms vs. 639 ms, $F (1, 49) = 50.077$, $p < .001$, Bonferroni corrected). No difference between Task effect in adolescents and young adults was found (663 ms vs. 639 ms, $p = 1.000$, Bonferroni corrected).
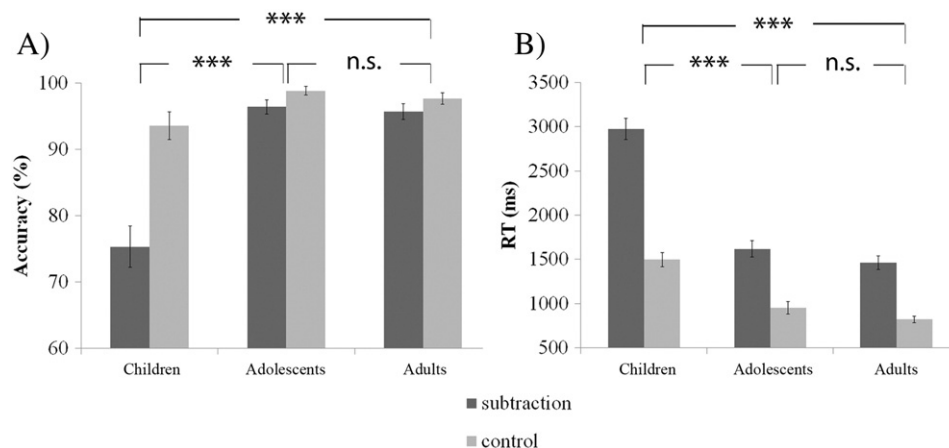

Fig. 2. Behavioral performance during Subtraction and Control problems in children, adolescents, and adults. Across all three groups, responses were less accurate and slower to Subtraction compared to Control problems ($p < .001$). This pattern was more pronounced in children than adolescents and adults ($p < .001$). Children were less accurate and slower than adolescents ($p < .001$, Bonferroni corrected), and no differences were found between adolescents and adults.

Collectively, these results provide strong evidence that the behavioral performance of foundational subtraction problem solving skills is mature by adolescence, not only in terms of accuracy but also in terms of reaction time.
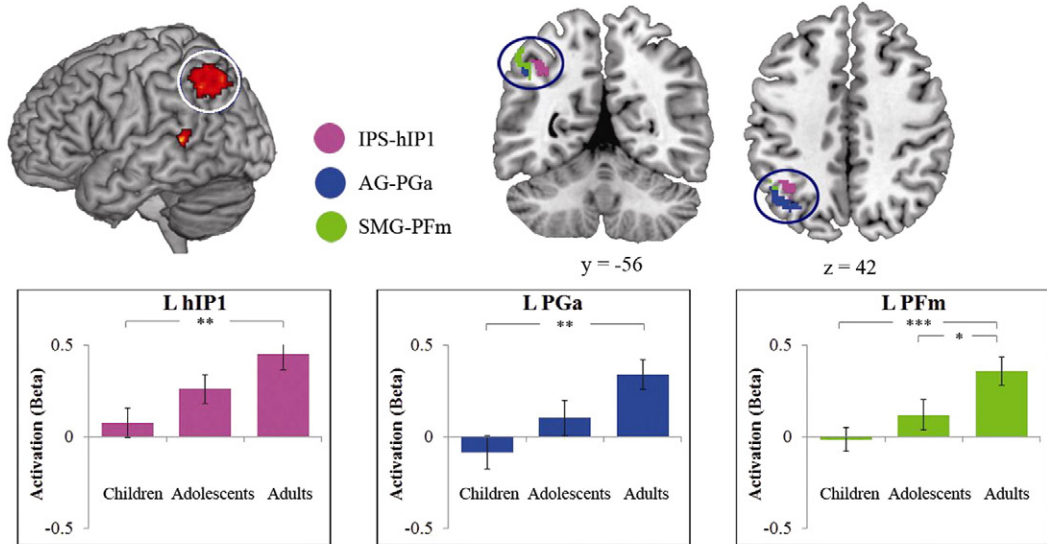
Age-related differences in brain activation

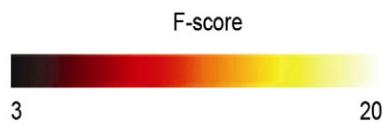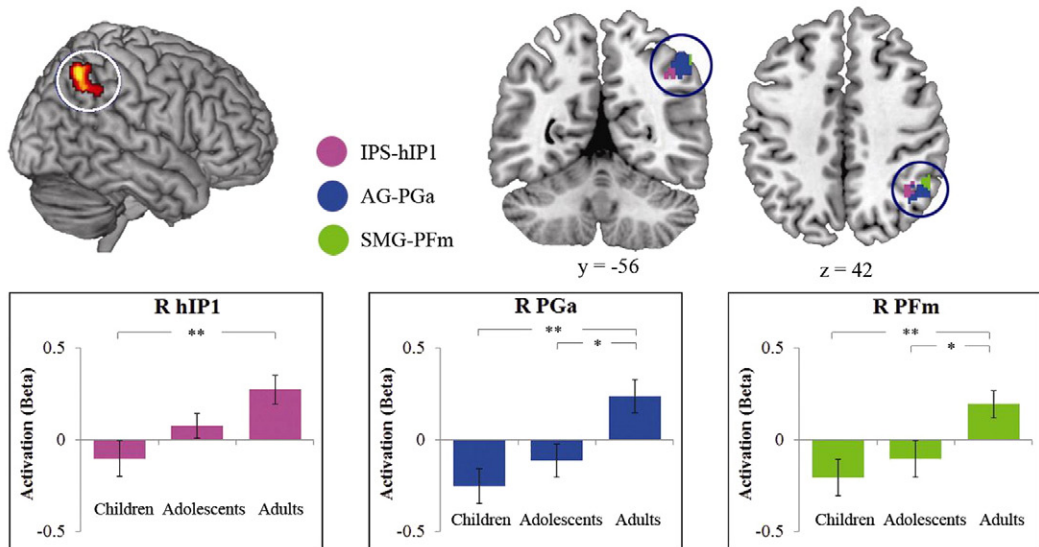#### Linear age-related differences in activation

Brain responses elicited during subtraction problem solving in children, adolescents, and young adults are illustrated in Supplementary Results 1, Figure S1, and Table S1. We first examined linear age-related differences across children, adolescents, and young adults by conducting a voxel-wise linear ANOVA using the F-contrast of [− 1 0 1] at the group level. This analysis revealed significant linear age-related differences in bilateral PPC as well as several regions outside the PPC including left MTG, right insula, and left caudate (Fig. 3, Table 2). Cluster labeling using cytoarchitectonic probabilistic maps demonstrated that both the left and right PPC clusters that showed linear age-related differences were primarily localized to the IPS-hIP1 and adjoining AG-PGa and SMG-PFm (Fig. 3, Table S2). For descriptive purposes, we use the term

Fig. 3. Brain regions that showed linear age-related increases in activation. Cytoarchitectonic probabilistic labeling indicates that activations in both (A) left and (B) right IPS-hIP1 and adjoining AG-PGa and SMG-PFm showed linear increases from childhood to adulthood. The three subdivisions together accounted for 77% of activation in the left and 85% in the right posterior parietal cortex. *p < .05. **p < .01. ***p ≤ .001.

Table 2
Brain regions that showed significant linear age-related differences during subtraction problem solving.

Region	BA	# of voxels	Peak Z-score	Peak MNI coordinates (mm)		
				X	Y	Z
L MTG	21	108	3.66	−50	−42	4
R IPS/AG/SMG	7	284	3.60	42	−56	40
R insula	48	100	3.43	28	18	−18
L caudate	11	115	3.41	−16	24	−6
	25	157	3.11	−4	0	−6
L IPS/AG/SMG	7	456	3.07	−40	−56	42

Note: Each cluster was determined using the voxel-wise height threshold of p < .01, multiple comparison correction at p < .05 using a Monte Carlo determined cluster extent of 100 voxels after gray matter masking. BA, Brodmann area. MTG, middle temporal gyrus. IPS, intraparietal sulcus. AG, angular gyrus. SMG, supramarginal gyrus.

Table 3
Brain regions that showed greater activation in adolescents during subtraction problem solving.

| Region	BA	# of voxels	Peak Z-score	Peak MNI Coordinates (mm)		
				X	Y	Z
L/R thalamus		703	5.11	−14	−18	18
L SMG	40	113	3.25	−60	−30	46

Note: Each cluster was determined using the voxel-wise height threshold of p < .01, multiple comparison correction at p < .05 using a Monte Carlo determined cluster extent of 100 voxels after gray matter masking. BA, Brodmann area. SMG, supramarginal gyrus.

IPS-hIP1 + to denote the IPS cluster and its extensions into adjoining AG-PGa and SMG-PFm.

To further validate our findings, we then conducted additional analyses on activation levels in the IPS-hIP1 + using age as a continuous variable. Regression analysis confirmed a linear model of age-related changes in the left and right IPS-hIP1 + (left: $\beta_{linear} = .033$, $p < .001$; right: $\beta_{linear} = .035$, $p = .001$). These results suggest a good correspondence between the linear profile found in the categorical analysis of children, adolescents, and young adults and linear changes determined using age as a continuous variable.

Nonlinear profile of age-related differences in activation

To investigate potential nonlinear profiles of age-related effects across children, adolescents, and young adults, we probed differences in brain activation across age groups using a quadratic F-contrast [−0.5 1 −0.5]. This contrast identified two clusters: one that spanned bilateral thalamus and a second in left SMG (Fig. 4A, Table 3). Labeling the clusters using cytoarchitectonic probabilistic maps revealed that the SMG cluster was localized to the SMG subdivision SMG-PF (Fig. 4A, Table S3). To further validate our findings, we then conducted additional analyses on activation levels in the left SMG-PF using age as a continuous variable (Fig. 4C). Regression analysis confirmed that a quadratic model of age-related changes had a significantly better fit than a linear model (quadratic model: $\beta_{quadratic} = −.009$, $p = .012$; linear model: $\beta_{linear} = .011$, $p = .345$; quadratic versus linear model:
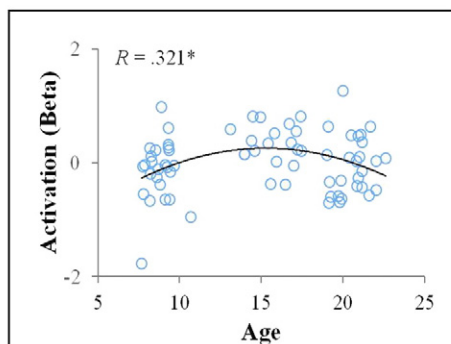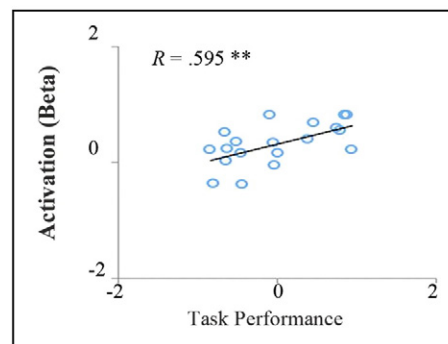

A) Nonlinear increases in left SMG-PF
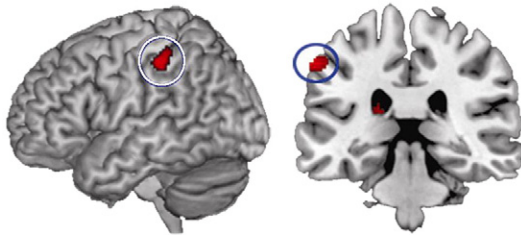
B) Age as a categorical variable
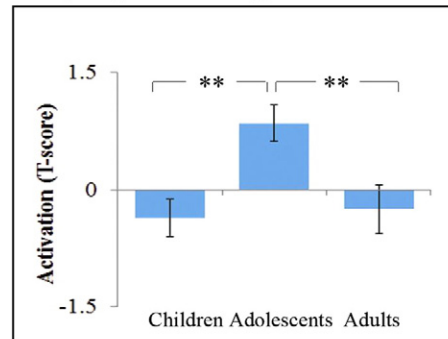
C) Age as a continuous variable

D) Brain-behavior relations in Adolescents

Fig. 4. Nonlinear age-related increases in supramarginal gyrus activation. (A) Adolescents showed greater engagement of the left supramarginal gyrus (SMG) than children and adults during subtraction problem solving. Probabilistic labeling localized the activation to SMG-PF in the more anterior aspects of the SMG and this subdivision accounted for 60% of the activations of the cluster. (B) Nonlinear profiles obtained using categorical analysis of child, adolescent and adult groups at the whole brain level. (C) Confirmatory analysis using a quadratic model of changes with age as a continuous variable. (D) Significant correlation between SMG and task performance was observed exclusively in the adolescent group, and higher SMG activation was associated with better performance. **p < .01.

$F(1, 68) = 6.7, p = .011$; see Fig. 4B–C). These results suggest a good correspondence between the inverted U-shaped profile found in the categorical analysis of children, adolescents, and young adults and quadratic effects determined using age as a continuous variable.

Age-related differences in brain deactivation

In order to investigate age-related differences in AG-PGp response, we conducted additional analyses on bilateral AG-PGp regions that showed task-induced deactivation. To avoid circularity, these regions were first identified in data pooled together from children, adolescents, and young adults. No differences in deactivation were found between children, adolescents, and adults ($p > .331$).

### Relation between SMG-PF activation and task performance in adolescents

To investigate the behavioral relevance of enhanced left SMG-PF activation in adolescents, we next examined if engagement of this region was associated with better behavioral performance on the Subtraction task. Behavioral performance was computed as a composite efficiency score by first standardizing accuracy and reaction time and then averaging the z-scores for accuracy and negative z-scores for reaction time. We found a significant positive correlation between task performance and activation levels of SMG-PF in adolescents ($r = .595, p = .007$; Fig. 4D).

Age-related differences in underlying PPC anatomy

We examined whether age-related differences in functional brain activation are also associated with changes in underlying neuroanatomy (Rivera et al., 2005). We focused on gray matter volume in the three PPC clusters identified in the analysis above — bilateral IPS-hIP1 + and left SMG-PF clusters – that showed linear and quadratic profiles of age-related differences across the three developmental groups. We examined the structural profile of gray matter volume across the three age groups. Quadratic ($p \leq .012$) but not linear effects ($p \geq .74$) were observed in both the left and right IPS-hIP1 + (Figure S3), with a slight dip in gray matter volume during adolescence. In contrast, neither linear nor quadratic age-related differences in gray matter were observed in the left SMG-PF cluster ($p \geq .491$). These results indicate that increases in left SMG-PF activation in adolescents are not associated with changes in their underlying neuroanatomy.
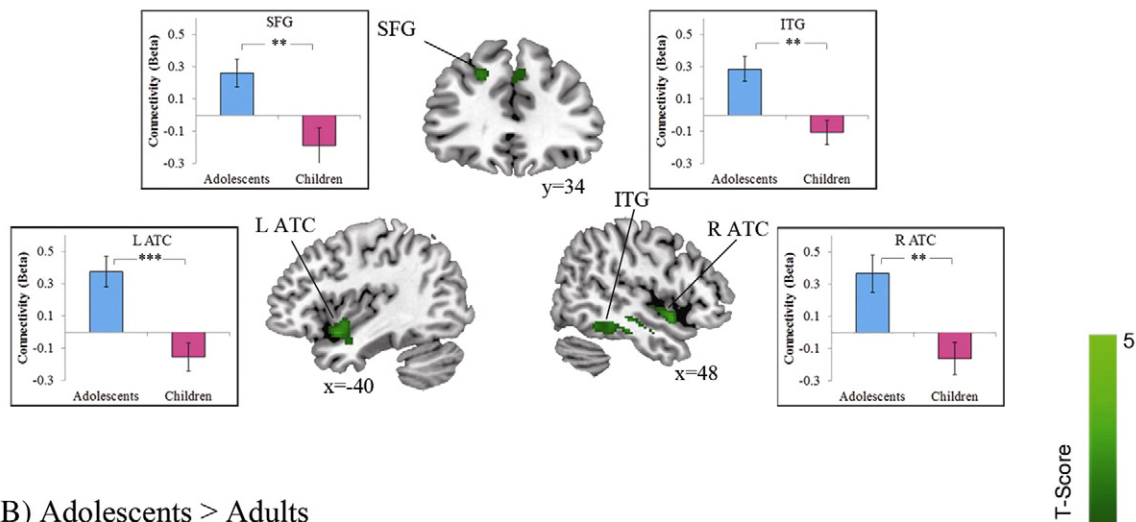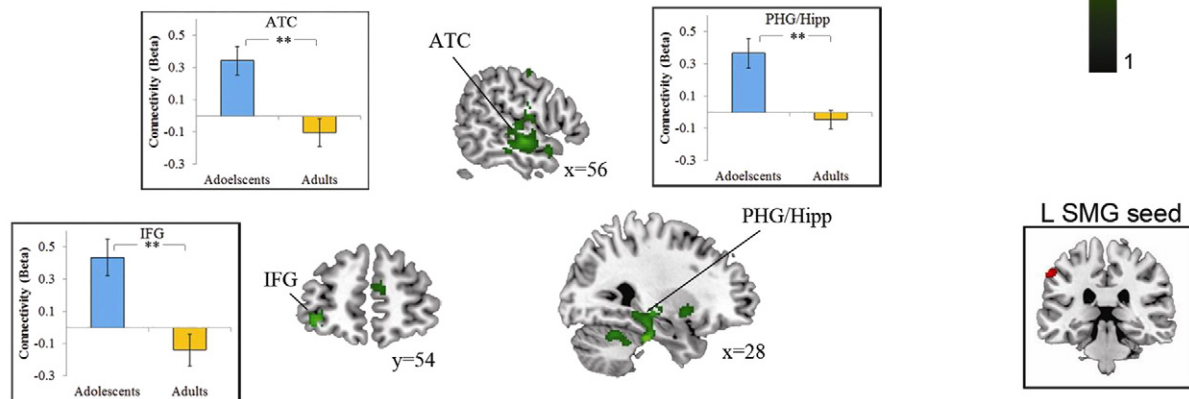
Fig. 5. Brain regions that showed differences in left supramarginal gyrus (SMG) connectivity between children, adolescents and adults. gPPI analyses were conducted using the left SMG peak that showed significantly greater activation in adolescents. (A) Adolescents exhibited greater subtraction-related SMG connectivity than children in bilateral anterior temporal cortices (ATC), right inferior temporal gyrus (ITG) and left superior frontal gyrus (SFG). (B) Adolescents also showed greater SMG connectivity than adults in medial temporal lobe including parahippocampal gyrus (PHG) and hippocampus (Hipp), ATC as well as left SFG. **$p < .01$. ***$p < .001$.

Age-related differences in left SMG connectivity

To further investigate age-related differences in functional circuits associated with unique increases in activation levels of the left SMG-PF in adolescents, we conducted a gPPI analysis of context-dependent functional connectivity. The functional cluster that showed increases in adolescents (Fig. 4A) was used as the seed region for this analysis. Pair-wise group differences in SMG-PF connectivity for the contrast of Subtraction over Control problems were assessed across the entire brain. Compared to children, adolescents showed greater left SMG-PF connectivity with the left superior frontal gyrus and bilateral anterior temporal cortices (Fig. 5A, Table 4). Compared to young adults, adolescents showed greater left SMG-PF connectivity with multiple brain regions, including right middle temporal gyrus, parahippocampal gyrus, left inferior frontal gyrus, bilateral premotor cortex, left putamen and anterior cingulate cortex (Fig. 5B, Table 4). Neither children nor young adults exhibited greater SMG-PF connectivity than adolescents in any brain region. These results indicated that engagement of the left SMG-PF in adolescents is also accompanied by increases in connectivity with distributed brain areas.

Discussion

We investigated linear and nonlinear age-related differences underlying problem solving skills between children, adolescents, and adults. Specifically, we examined whether key PPC regions involved in arithmetic problem solving would show both linear and non-linear age-related effects, against the more conventional, but influential, models of linear effects of age (Rivera et al., 2005). We demonstrate that although adolescents show adult-levels of behavioral performance, PPC activation and connectivity are different between the two age groups, reflecting continued development of the neurobiological mechanisms underlying cognition from adolescence to adulthood. Critically, we found evidence for both linear and nonlinear age-related function of the PPC characterized by a unique profile of activation and connectivity in adolescents compared to both children and adults. Notably, we found distinct age-related patterns of activation and connectivity in the three major ventral PPC cytoarchitectonic subdivisions – bilateral IPS, SMG and AG – highlighting their unique contributions to the development of cognitive skills. Finally, our results provide new insights into the neurobiological basis of the development of cognitive skills, suggesting that differential recruitment of specific brain systems in adolescence underlie adult levels of problem-solving skills.

Heterogeneous age-related differences in posterior parietal cortex

Individual subdivisions of the PPC demonstrated different patterns of age-related changes, with the IPS-hIP1 showing linear increases with age and sub-regions of the SMG and AG showing heterogenous profiles. Within the SMG, the anterior subdivision (SMG-PFm) showed a linear profile similar to that of the adjoining IPS. In contrast, the left SMG-PF showed a quadratic effect, with the adolescent group exhibiting higher activation than the child and young adult groups. Within the AG, the anterior dorsal subdivision (PGa) also showed a linear profile similar to the IPS. On the other hand, the posterior ventral AG subdivision (PGp) was strongly deactivated across all age groups. These results highlight, for the first time, heterogeneity in PPC function during arithmetic problem solving and point to unique developmental trajectories in the PPC subdivisions. It is likely that prior studies did not uncover heterogeneous and nonlinear profiles of change because of small sample sizes and the exclusive use of linear models of age-related change (Rivera et al., 2005).

Linear age-related profile of IPS and adjoining anterior SMG and AG

Converging evidence from research on infants, children, and young adults has suggested that representation of quantity is a foundational ability for numerical problem solving (Ansari, 2008; Cohen Kadosh et al., 2008; Dehaene et al., 2003; Feigenson et al., 2004; Halberda et al., 2008). The ventral–anterior IPS (IPS-hIP1), in particular, is known to play a critical role in representing quantity information in both basic numerical processing and arithmetic problem solving (Ansari, 2008; Arsalidou and Taylor, 2011; Cohen Kadosh et al., 2008; Dehaene et al., 2003; Houde et al., 2010; Wu et al., 2009), and quantity representation abilities are progressively improved with learning and experience from early infancy into young adulthood (Halberda and Feigenson, 2008; Halberda et al., 2012; Izard et al., 2009; Lipton and Spelke, 2003; Xu and Spelke, 2000). Thus, it is to be expected that neural systems supporting quantity representations within the IPS-hIP1 are increasingly engaged over time due to repeated experience with solving arithmetic problems that require manipulation of quantity. Consistent with this view, our results demonstrate that during subtraction, which involves deriving answers through quantity manipulation more than direct retrieval (Barrouillet et al., 2008; Campbell and Xue, 2001; De Smedt et al., 2011; Rosenberg-Lee et al., 2011b), IPS activation increases across the three age groups.

Linear increases with age groups were also detected in adjoining ventral PPC regions (SMG-PFm and AG-PGa), which are not generally

Table 4
Brain regions that showed significant age-related difference in gPPI connectivity.

Comparison	Region	BA	# of voxels	Peak Z-score	Peak MNI coordinates (mm)		
					X	Y	Z
Adolescents–children							
	L ATC	48	265	3.07	−44	8	−14
	R ATC	48	160	3.33	48	6	−10
	R ITG	20	274	3.22	50	−26	−20
	L SFG		124	3.08	−20	34	38
	L caudate		201	3.06	−14	12	14
	L mid cingulum	32	204	2.77	−8	26	34
Adolescents–adults							
	R MTG/PHG/hippocampus	22	6032	3.72	28	−26	−28
	L IFG	47/10	157	3.59	−36	54	−6
	L PMC	3	106	3.45	−60	−10	40
	L putamen		285	2.92	−22	12	8
	Ant cingulum	11	236	3.02	10	36	8

Note: Each cluster was determined using the voxel-wise height threshold of p < .01, multiple comparison correction at p < .05 using a Monte Carlo determined cluster extent of 100 voxels after gray matter masking. BA, Brodmann area. PHG, parahippocampal gyrus. PMC, premotor cortex. MTG, middle temporal gyrus. SFG, superior frontal gyrus. ATC, anterior temporal cortex. ITG, inferior temporal gyrus.

associated with manipulation of quantity, but may show similar activation profiles as the IPS because of their strong functional interconnections (Uddin et al., 2010a). An alternate view is that increases in SMG-PFm and AG-PGa recruitment supports the increased use of verbal retrieval strategies (Dehaene et al., 2003; Grabner et al., 2007; Rosenberg-Lee et al., 2011b), a process that undergoes protracted developmental changes in the case of subtraction problem solving skills (Barrouillet et al., 2008; Campbell and Xue, 2001; Ostad, 1999; Siegler and Shrager, 1984). Further research is needed to clarify the differential contributions of these SMG and AG regions to the changes in strategy use over development.

Nonlinear development of SMG-PF in adolescents

A major finding of our study is that the SMG-PF was more strongly activated in adolescents compared to children and young adults. Furthermore, the adolescent group showed a significant brain-behavior relationship in this region, with greater SMG-PF engagement linked to better behavioral performance. These results suggest that the SMG-PF plays a stronger role in adolescence relative to childhood or adulthood and is linked to individual differences in problem solving such that it may be utilized as a compensatory mechanism by some individuals to allow them to perform at adult-levels when other brain regions such as the IPS-hIP1 are still immature. Our findings point to an important neurobiological signature of individual differences in arithmetic problem solving, whereby adolescents who performed more similarly to children recruited the SMG-PF to a lesser degree than adolescents who demonstrated similar performance levels to those of young adults. Consistent with this result, a recent study reported that mathematical achievement of high school students was correlated with SMG-PF activation during problem solving (Price et al., 2013). Future research should seek to better understand the specific role of the SMG-PF in driving individual differences in problem-solving during adolescence.

The SMG-PF's up-regulation and links with adult-like performance in adolescence is noteworthy because this ventral subdivision of the PPC is typically engaged by cognitive tasks that require manipulation of information in working memory (Geier et al., 2009; Kwon et al., 2002). The increases in SMG-PF activation in adolescents were not associated with structural changes in the underlying neuroanatomy, suggesting that the age-related differences are primarily related to neurofunctional processes supported by the SMG-PF and, as described below, its associated functional circuits. Thus, adolescents may take advantage of a relatively mature SMG-PF to improve task performance as core number processing and verbal fact retrieval regions in the IPS and AG continue to mature. These activation differences between adolescents and adults imply the use of two different but successful neurocognitive mechanisms for similar task performance. We suggest that adolescents reach adult-like performance by relying on a combination of working memory processes supported by the SMG-PF and quantity manipulation supported by the still maturing IPS.

To better understand how the SMG-PF plays a unique role in adolescence, we investigated functional circuits associated with SMG-PF at the whole-brain level using gPPI analysis. We found that adolescents had stronger functional connectivity between the SMG-PF and multiple prefrontal and temporal cortical regions when compared to both children and young adults. Connectivity with the PFC was consistent with working memory processes (Klingberg, 2006; Klingberg et al., 2002; Rottschy et al., 2012), and connectivity with medial and anterior temporal cortex is consistent with episodic and semantic memory processes involved in learning arithmetic facts (Cho et al., 2011). Our findings therefore provide novel evidence to suggest that the SMG-PF, together with PFC and medial and anterior-lateral temporal cortices, form a memory-related functional circuit to facilitate the development of arithmetic knowledge in adolescence (Cho et al., 2012; Kaufmann et al., 2011).

Our findings extend and clarify age-related changes identified in a previous study (Rivera et al., 2005), which reported monotonic increases from age 8 to 19 years in SMG-PF activation when solving mixed addition and subtraction problems. With 15 out of 16 subjects being under the age of 18, it is likely that that Rivera et al. did not capture the quadratic effect of age in the SMG-PF we report here, sampled from broader age range (9–22 years). Taken together, these results highlight the importance of increasing the age range sampled to include late adolescence and early adulthood and considering both linear and nonlinear models for a more comprehensive understanding of the development of foundational problem solving skills into adulthood.

Age-related differences in activation and deactivation of the AG

Another noteworthy aspect of our finding relates to heterogeneous age-related differences in the AG. As noted above, the anterior subdivision, AG-PGa, and the adjoining IPS-hIP1 showed linear increases with age group. In sharp contrast, the posterior AG-PGp exhibited similar levels of deactivation (i.e. greater activation in the control, compared to the arithmetic task) in the three groups. Thus, we posit that the two AG subdivisions play differential roles in the development of problem solving skills. The AG has been linked to verbally mediated retrieval of arithmetic facts (Dehaene et al., 2003), but its precise role is not understood as most recent studies have shown consistent deactivation relative to a resting baseline condition during arithmetic problem solving (Grabner et al., 2007; Rickard et al., 2000; Rosenberg-Lee et al., 2011b; Wu et al., 2009).

In addition, Wu and colleagues previously reported that the AG-PGp shows task-related deactivation, with greater deactivation relative to a number identification control task and that greater AG deactivation is associated with poorer performance on the arithmetic task (Wu et al., 2009) as well as lower overall math abilities (Grabner et al., 2007). Interestingly, the AG-PGp deactivation regions reported by Wu et al. overlapped with the lateral parietal nodes of the default mode network (DMN) - a set of brain regions consistently linked to decreases in activation during goal-oriented effortful cognitive tasks (Greicius et al., 2003; Raichle et al., 2001; Shulman et al., 1997). In our present study, we found no differences in AG-PGp deactivation between the three groups, indicating that the disengagement of AG-PGp during difficult arithmetic tasks may be mature by mid-to-late childhood. We also found no differences in task-related deactivations in other regions overlapping with DMN nodes, including the precuneus and VMPFC across our three age groups. Together these findings suggest that the DMN nodes were equally down-regulated during effortful problem solving across development. Given these observations, it is noteworthy that the anterior AG subdivision PGa showed linear increases with age. Whether this pattern of change specifically reflects progressively greater use of retrieval strategies for subtraction problems in adolescents and adults remains to be investigated. Importantly, we suggest that future investigations should take into account heterogeneity in the development of AG sub-region function as well as in their associated functional circuits.

Implications for a deeper understanding of brain and cognitive maturation

For over two decades neuroimaging studies of problem solving have been used to probe the effects of development and maturation on brain function. This work has resulted in advances in our understanding of the biological underpinnings of learning and skill acquisition over age. However, the vast majority of this work has highlighted linear neurodevelopmental processes, typically with small sample sizes and relatively sparse age distributions. The current study, in contrast, stresses the importance of adequately sampling across distinct developmental stages in order to better characterize unique neurodevelopmental shifts that may occur during different stages of complex cognitive skill acquisition. Here we found evidence for both linear and nonlinear changes with age using a cognitively demanding subtraction problem solving task (Campbell and Xue, 2001). Our findings show, for the first time, that increased engagement of additional neural resources allows

some adolescents to reach adult-like performance as core task-relevant brain areas continue to mature with learning and exposure. Such transient brain processes may provide a scaffold for the maturation of cognitive skills. Similar profiles might apply to other cognitive domains involving problem solving and reasoning. Further studies with longitudinal designs are needed to more precisely capture growth patterns and individual differences in skill acquisition and their brain bases (Kraemer et al., 2000; Lindenberger et al., 2011; Pfefferbaum and Sullivan, 2015; Robinson et al., 2008).

Conclusions

Developmental neuroimaging studies in the past decades have provided remarkable insights into the maturation of functional brain systems in children. Here, we show that focusing on linear changes alone across the broad age range of childhood to young adulthood can lead to the oversight of important features of the developing brain. We connected a rich body of developmental cognitive neuroscience literature to characterize the emergence of dedicated brain systems in relation to ongoing behavioral changes. We provide novel evidence for linear and non-linear age-related changes in functionally heterogeneous divisions of the parietal association cortex. Our results suggest a dynamic interplay between domain general and task-specific systems in arithmetic skill development. Weaker skills and brain responses in childhood give way to adult-like performance in adolescence, supported by behaviorally relevant increases in recruitment of the SMG-PF circuits even as core quantity processing systems in the IPS-hIP1 continue to mature. Using evidence from novel systems neuroscience and analysis techniques, we suggest that successful mathematical performance is marked by a shift from neurofunctional processes that are robustly engaged only during adolescence to regions critical for mature problem solving. More broadly, our study demonstrates that analysis of both linear and nonlinear changes in dynamic relation to one another is necessary for fully characterizing human cognitive development. Further studies using longitudinal designs are needed to more precisely characterize individual differences and variability in neurocognitive trajectories.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.11.053.

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