**Early cortical surface plasticity relates to basic mathematical learning**

Running title: Early cortical plasticity relates to math learning

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**Abstract**

Children lay the foundation for later academic achievement by acquiring core mathematical abilities in the first school years. Neural reorganization processes associated with individual differences in early mathematical learning, however, are still poorly understood. To fill this research gap, we followed a sample of 5-6-year-old children longitudinally to the end of second grade in school (age 7-8 years) combining magnetic resonance imaging (MRI) with comprehensive behavioral assessments. We report significant links between the rate of neuroplastic change of cortical surface anatomy, and children's early mathematical skills. In particular, most of the behavioral variance (about 73%) of children's visuospatial abilities was explained by the change in cortical thickness in the right superior parietal cortex. Moreover, half of the behavioral variance (about 55%) of children's arithmetic abilities was explained by the change in cortical folding in the right intraparietal sulcus. Additional associations for arithmetic abilities were found for cortical thickness change of the right temporal lobe, and the left middle occipital gyrus. Visuospatial abilities were related to right precentral and supramarginal thickness, as well as right medial frontal gyrus folding plasticity. These effects were independent of other individual differences in IQ, literacy and maternal education. Our findings highlight the critical role of cortical plasticity during the acquisition of fundamental mathematical abilities.

**Keywords:** mathematical learning; visuospatial quantity processing; arithmetic; parietal cortex; brain development; gray matter

**Highlights:**

- MRI study of cortical plasticity during first years of formal math instruction
- Right superior parietal thickness change was related to visuospatial processing
- Right intraparietal sulcus folding plasticity was related to early arithmetic
- Left occipital, and right fronto-temporal regions showed further associations
- Results link cortical plasticity to basic math learning

## 1. Introduction

Mathematical abilities are crucial for everyday life, enabling us to find the right page in a book, schedule appointments or do financial transactions. Moreover, early mathematical skills are among the strongest predictors of academic achievement (Duncan et al., 2007).

Infants as young as 6 months already show an intuitive sense for magnitude (Dehaene, 2011; Xu and Spelke, 2000). This visceral understanding of numerosity increases in precision over development (Lipton and Spelke, 2003), eventually enabling preschoolers to perform approximate addition (Barth et al., 2006, 2005) and subtraction (Slaughter et al., 2006) based on visuospatial representation of magnitude. However, children acquire the skills needed for exact symbolic arithmetic not until it is formally taught in school (Barth et al., 2005). During these developmental trajectories individuals show marked variability in growth of knowledge (Brown et al., 2003; Cockcroft, 1982).

**Mature m**athematical problem-solving involves working memory, cognitive control, attention, memory, visual processing, and numerical cognition (Menon, 2015). **Importantly, developmental studies highlight a specific association between visuo-spatial processing, including visuo-spatial working memory, and emerging mathematical performance (Bull et al., 2008). This relationship, however, decreases quickly already during the first two years of school (De Smedt et al., 2009). A possible explanation for this change might be a shift from initially relying on visuo-spatial representations of magnitude and problem-solving strategies like finger counting (Rasmussen and Bisanz, 2005) to verbal retrieval strategies (De Smedt et al., 2009).**

**Considering this the heterogenous nature of mathematical problem-solving, it is not surprising that** a diverse range of brain regions has been associated with its development, including prefrontal cortex (PFC; Rivera et al., 2005; Cho et al., 2011; Evans et al., 2015) and the medial temporal lobe (MTL; Rivera et al., 2005; Cho et al., 2011; Supekar et al., 2013; Qin et al., 2014), ventral temporal-occipital cortex (VTOC; Evans et al., 2015; Rivera et al., 2005), encompassing a putative number-form area (Nemmi et al., 2018), temporo-parietal regions including the angular and supramarginal gyri (AG, SMG; Peters et al., 2016; Peters and De Smedt, 2018; Price et al., 2013) and posterior parietal cortex (PPC; Rivera et al., 2005; Cantlon et al., 2006; Menon, 2010; Qin et al., 2014), including the intraparietal sulcus (IPS; Cantlon et al., 2006; Emerson and Cantlon, 2015; Jolles et al., 2016a; Schel and Klingberg, 2017).

Importantly, previous studies demonstrate characteristic structural and functional changes within these regions while mathematical competence refines, both in terms of visuospatial magnitude processing and arithmetic abilities. In line with accounts of a ventro-temporal region specialized for the processing of numerals in adults (Hannagan et al., 2015; Yeo et al., 2017), differential functional connectivity between the VTOC and the IPS emerges already at three years of age, before children encounter formal mathematical education (Nemmi et al., 2018). Further, gradual increases in mathematical ability are associated with increasing functional connectivity of numeral-selective areas to parietal and prefrontal regions during early adolescence (Nemmi et al., 2018). Moreover, activation of prefrontal regions decreases during development, reflecting reduced reliance on working memory and attentional resources. At the same time, involvement of the IPS, SMG and anterior AG increases (Rivera et al., 2005), follows a regionally specific pattern: activation during numerical problem solving increases linearly in ventral IPS, anterior AG and the posterior SMG from child- to adulthood, reflecting the specialization of these areas for mathematical processing with time and experience (Chang et al., 2016; Rivera et al., 2005). Activation in anterior segments of the SMG, in contrast, peaks in adolescence before declining again towards adulthood (Chang et al., 2016).

In adults, the IPS and also the PPC are associated with representing and manipulating symbolic as well as non-symbolic magnitude (Piazza et al., 2007, 2006, 2004) and mental arithmetic (Knops et al., 2009; Menon et al., 2000; Venkatraman et al., 2005). Due to their specific involvement in symbolic numerical processing as compared to processing of non-symbolic visual magnitude (Peters et al., 2016), AG and SMG have been linked to the retrieval of arithmetic and numerical fact knowledge from long-term memory (Peters and De Smedt, 2018). In line with this notion, activity in AG and SMG has been shown to correlate with arithmetic expertise in adults (Grabner et al., 2007), a pattern that has also been found in adolescents (Price et al., 2013).

In six year old children, both first mathematical abilities and visuospatial working memory are associated with cortical thickness of the anterior portion of the right IPS (Schel and Klingberg, 2017). In line with this, the longitudinal change in parietal gray matter volume, alongside ventro-temporal and prefrontal regions, predicts longitudinal gain in mathematical competence in children between 7 and 14 years of age (Evans et al., 2015).

Specific brain areas have been linked to visuo-spatial magnitude processing at a preschool age (Cantlon et al., 2006) and mathematical development at a school age (Evans et al., 2015; Qin et al., 2014; Rivera et al., 2005). However, little is known about the neural correlates of emerging mathematical abilities during the first years of formal instruction in school. This is a substantial research gap, since, during this time, children move from approximate to exact calculation (Cho et al., 2011). Therefore, we investigated changes of cortical surface anatomy in children at the transition from kindergarten to second grade and related them to their mathematical performance. Recent evidence supports the notion that arithmetic and visuospatial magnitude processing, two important components of mathematical competence, are indeed supported by distinct cognitive processes. Specifically, Georges et al. (2017) found that arithmetic problem-solving abilities - but not visuospatial magnitude processing abilities - relate strongly to spatially-organized representations of number. In line with this, we expect different components of numerical cognition to be supported by different brain structures, reflected by relationships between structural change and early mathematical ability.

Links between distinct developmental trajectories of cortical anatomical measures and variable performance with respect to higher cognitive functioning have been revealed in previous work

(Raznahan et al., 2011; Schnack et al., 2015). For instance, Schnack et al. (2015) related faster rates of left-sided cortical thinning from child- to early adulthood with higher intelligence. Changes in cortical surface morphometry may be traced back to cellular processes affecting the cortical cytoarchitecture, like neuro-, glio- and synaptogenesis, synaptic pruning or progressive growth of deep cortical white matter (Natu et al., 2018; Zatorre et al., 2012). Therefore, systematic associations between behavior and the brain's surface-based trajectories might indicate changes in terms of efficiency of brain networks relevant for higher cognitive functioning (Bullmore and Sporns, 2012).

It is noteworthy that classical voxel-based morphometry analyses capture information of grey matter volume only, thus conflating information from distinct morphometric properties. Specifically, cortical volume is a composite of the thickness of the cortical ribbon and the area of its surface. This areal expansion, in turn, is reflected by degree and shape of cortical convolutions (Raznahan et al., 2011). Specifically, sustained growth of the outer cortical surface driven by continued maturation of neurons and their connectivity (Budday et al., 2015a; Richman et al., 1975) gives rise to a greater number of cortical folds and deeper sulci. Thus, while previous work focusing either on gray matter volume or cortical thickness cannot disentangle differences driven by cortical thickness and folding (Mechelli et al., 2005), our goal was to go beyond these traditional indices and further explore gyrification, cortical folding regularity and sulcus depth.

All analyses were controlled for prominent behavioral correlates in order to be able to draw specific conclusions about cortical development and mathematical ability. To this end, measures assessing reading and spelling ability, sociodemographic status, non-verbal IQ, handedness, sex and age served as covariates in the statistical models. Given that deficits in literacy and mathematical development are reported to frequently co-occur (Dirks et al., 2008; Moll et al., 2014), familial risk of developing dyslexia was also taken into account in the current work.

**The aim of the current work was to identify distinct** anatomical correlates of individual differences **in two important subcomponents of** early mathematical **skill, i.e., visuo-spatial magnitude processing and arithmetic abilities. We expected to find associations between early visuo-spatial magnitude processing abilities and structural reorganization processes within the IPS and the PPC, given their involvement in visuo-spatial imagery, and within prefrontal regions supporting visuospatial working memory (Formisano et al., 2002; Klingberg, Forssberg, & Westerberg, 2002; Kwon, Reiss, & Menon, 2002)". Further, we expected to find associations between arithmetic processing and regions known to represent numerical information, i.e. the IPS and the PPC, and the hippocampus as a region involved in arithmetic fact retrieval.**

## 2. Materials and Methods

### *2.1.Participants*

Children were recruited from the Leipzig metropolitan area between 2012 and 2013. Initial data acquisition and screening for neurological, psychiatric, hearing or vision disorders took place between 2012 and 2013. Follow-up sessions were conducted between 2015 and 2016. Twenty-eight native German, monolingual children completed the study (15 female; age range at kindergarten: 5 years, 0 months – 6 years, 0 months; mean ± SD: 5 years, 6 months ± 6 months; age range at second grade in school: 7 years, 11 months – 8 years, 11 months; mean ± SD: 8 years, 5 months ± 5 months). Fifty-four other children participated but were excluded from further analysis because they received a diagnosis of attention deficit hyperactivity disorder (n=4) or developmental dyslexia (n=9, both determined based on parental questionnaire), did not have complete datasets (i.e., did not comply with the experimental procedures in a training session, were unable to attend follow-up sessions, or exhibited imaging data corrupted by artifacts, n=22), did not complete all psychometric tests (n=3), scored below the 20th percentile rank of the population performance in standardized and age-normed reading or spelling tests (n=12) or performed below the 20th percentile in a standardized math test (clinical cases of developmental dyscalculia, n=3). One additional child had to be excluded due to an experimental error during psychometric testing. None of the remaining children scored below 85 on average in two non-verbal IQ tests. The study was approved by the Ethics Committee of the University of Leipzig, Germany. Written informed consent was obtained from parents and children gave verbal informed assent.

*2.2. Psychometric assessment*

Children's mathematical ability at the end of second grade in school was quantified using the Heidelberg computation test (HRT; Haffner et al., 2005). The HRT includes two subscales. The first subscale quantifies children's early arithmetic abilities with subtests requiring simple addition and subtraction, solving simple equations and performing greater-or-smaller-than comparisons. The second subscale assesses children's visuospatial skills, providing a composite score of tasks that require children to estimate the length of line-drawings and the number of cubes needed for cube structures, to count shapes in a visual array, to connect spatially scrambled numerals in ascending order and to extract the rule determining the sequence of a given row of numbers.

All children underwent additional psychometric assessment at both kindergarten and school age. At kindergarten age, we assessed children's non-verbal intelligence using the Wechsler preschool and primary scale of intelligence (Wechsler et al., 2009) and their handedness (Oldfield, 1971). At the end of second grade, we assessed children's spelling accuracy focusing on writing after dictation of words in the German spelling test (Stock and Schneider, 2008). We also examined reading fluency based on number of words correctly read within 1 minute as part of the German Salzburg test of reading and spelling (Moll and Landerl, 2010). Non-verbal intelligence was assessed using the Wechsler Intelligence Scale for children (WISC-IV; Petermann and Petermann, 2011).

*2.3. Sociodemographic measures*

The highest level of education (4-point scale ranging from 0 = no degree to 3= German 'Abitur' [high school diploma / A level]) and vocational qualification (5-point scale ranging from 0 = no qualification to 4 = German 'Habilitation' [postdoctoral academic qualification]) was obtained from each parent and/or primary caregiver using a questionnaire. In the final sample, maternal education ranged from 2 to 7 (mean ± SD = 4.43 ± 0.51).

*2.4. MRI data acquisition*

At kindergarten age, a training session using a mock scanner was conducted to familiarize children with the MRI procedure and to maximize compliance. In a subsequent session, scanning was performed on a 3 T Siemens TIM Trio magnetic resonance scanner (Siemens AG, Erlangen, Germany) with a 12 channel radio-frequency head coil. T1 maps were acquired using the magnetization-prepared 2 rapid acquisition gradient echo (MP2RAGE, Marques et al., 2010) method with the following parameters: TR = 5000ms; TI1/TI2 = 700/2500ms; TE = 2.82ms; FOV = 250 x 219 x 188mm; voxel size = 1.3mm$^3$; GRAPPA factor = 3.

A second MRI session was performed at the end of second grade on the same scanner upgraded to a 3T Prisma system, using a 64 channel head coil and an MP2RAGE sequence with parameters TR = 5000ms; TI1/TI2 = 700/2500ms; TE = 2.01ms; FOV = 256x240x176mm; voxel size = 1.0mm$^3$; GRAPPA factor = 2.

**Please note that we also acquired diffusion-weighted MRI as well as resting-state fMRI for both timepoints, but after quality control these data were only available for a subset of our final sample (diffusion-weighted MRI: n=24; resting-state fMRI: n=16).**

*2.5.MRI preprocessing and analysis*

Initially, T1-weighted (T1) brain images of both time points were visually inspected to exclude corrupted data caused by imaging artifacts such as ghosting, Gibbs artifact or diffuse image noise along the phase-encoding direction induced by excessive motion in the scanner. All participants that were retained for further analysis had an overall image quality of at least 86% (weighted image quality rating provided by CAT12) at both timepoints. Subsequently, brain images were extracted using Freesurfer (Version 5.3.0, http://surfer.nmr.mgh.harvard.edu/). After spatially normalizing the images to a pediatric template derived from 82 children aged 4.5–8.5 years (Fonov et al., 2009) in Montreal Neurological Institute (MNI) stereotactic space, a common group template based on all individual T1 images in MNI space from both timepoints was created with the Advanced Normalization Tools (ANTs; Avants et al., 2010, 2011).

Using the Computational Anatomy Toolbox (CAT12, http://www.neuro.uni-jena.de/cat/) for SPM12 (www.fil.ac.uk/spm/) in Matlab R2017b (The Mathworks, Inc., Natick, MA, USA), T1 data in template space were segmented into gray and white matter. For segmentation, SPM relies on anatomical priors provided as tissue probability maps. Since the tissue priors provided as a standard are derived from adult data, we replaced them with custom tissue probability maps. These maps were derived from the common group template of both timepoints to account for the anatomical details of our developmental sample, following the methodology described in Cafiero et al. (2018). Probabilistic maps of the individual tissue types were created using FSL's fast (Zhang et al., 2001). Tissue probabilities were normalized to sum to one. Finally, all maps were resampled to a resolution of 1.5mm isotropic and smoothed using a 35mm FWHM kernel, to approximate the resolution and smoothness of SPM's default anatomical priors. Additionally, gray and white matter maps created this way were also used to replace the default DARTEL template. During segmentation, surface-based maps of cortical thickness (CT), gyrification index (GI; Lüders et al., 2006), cortical folding regularity (CF; Yotter et al., 2011) and sulcus depth (SD) were extracted for each participant. Thickness data were smoothed with a 15mm FWHM kernel, and folding, gyrification and sulcus depth data were smoothed with a 20mm FWHM kernel, in accordance with the matched-filter theorem.

We performed a region of interest (ROI) based analysis focused on areas previously linked to mathematical processing in adults and children to examine the relation between developmental changes in measures of cortical surface morphometry and early mathematical ability. ROIs included the bilateral IPS **(Chang et al., 2016; He et al., 2014; Masataka et al., 2007)**, AG, SMG, hippocampus (HIP), dorso-lateral prefrontal cortex (DLPFC), ventral temporal-occipital cortex (VTOC), and bilateral visual word form area (VWFA). ROIs were derived from a multi-modal parcellation (MMP) of brain areas (Glasser et al., 2016) comprising 180 cortical regions per hemisphere (Supplementary Table S1, Figure 1a). In order to obtain participant-specific surface-based masks, the MMP (Glasser et al., 2016) was first spatially aligned with each child's MNI-T1 volumetric image and then mapped to the individual surface using the 'Map volume (Native Space) to individual surface' function in CAT12. The resulting ROIs in individual surface space were then used to mask the individual, smoothed CT, GI, SD and CF maps and extract participant-specific ROI means of all measures for both timepoints. To quantify the raw cortical change from kindergarten to second grade in school, the extracted mean values of timepoint 1 (kindergarten) were subtracted from the respective means derived from timepoint 2 (school), creating measures of $\Delta_{CT}$, $\Delta_{GI}$, $\Delta_{CF}$ and $\Delta_{SD}$ for each participant and each ROI. Based on these difference measures, the relative change rate $R_Q$ (Schnack et al., 2015) for each quantity $Q$ was computed as

$$R_Q = \left( \frac{\Delta_Q}{(Age_{time\ 2} - Age_{time\ 1}) \times \frac{Q_{time\ 1} + Q_{time\ 2}}{2}} \right) \times 100$$

These relative change rates include not only the raw anatomical change but also control for the individual variance of measures at time point 1 and 2.

Additionally, we performed whole-brain analyses in order to make sure not to overlook effects outside of our pre-defined ROIs. To this end, we created an additional set of individual templates for each child (Cafiero et al., 2018), based on the respective individual T1 MNI images using ANTs. The purpose of using individual templates was to ensure optimal alignment of data for both timepoints. The individual T1-images were spatially aligned to the respective child's template before segmentation and the surface-based measures were extracted as explained above. For each child, whole-brain maps of relative change rates ($R_{CT}$, $R_{GI}$, $R_{CF}$ and $R_{SD}$) as basis for whole-brain statistical analyses were computed following the formula above (Schnack et al., 2015).

### *2.6. Experimental design and statistical analysis*

MRI measurements and psychometric assessment were obtained from children once at kindergarten, before they underwent formal mathematics instruction, and again approximately 2 years and 11 months later at the end of second grade.

Correlations between sociodemographic and psychometric measures within each time point as well as across time, when suitable, were computed using R-3.3.1 (R Core Team, 2016).

ROI-wise partial correlations of the z-transformed relative change rates $R_{CT}$, $R_{GI}$, $R_{CF}$ and $R_{SD}$ and HRT subscales were computed using R-3.3.1 (R Core Team, 2016). Confounding variables included in the models were age at time 1, sex, handedness, non-verbal IQ at time 2, maternal education, spelling accuracy, reading speed, and familial risk of developing dyslexia. Additionally, to investigate the relation between brain maturation and the subscales of the test in a specific fashion, we added the respective other subscale score as a covariate. Further, as anatomical change measures correlate highly with size of measures at time 1, mean CT, GI, CF and SD of the respective hemisphere were used as covariates when analyzing $R_{CT}$, $R_{GI}$, $R_{CF}$ and $R_{SD}$ respectively. To control for multiple comparisons in the ROI-based analysis, we **used the Holm-Bonferroni method (Holm, 1979) at an unadjusted level of 0.05, accounting** for number of ROIs (14) and number of HRT subscales (2). **Consequently, the initial critical $\alpha$ level was set to 0.0018.**

Whole-brain correlations of individual relative change and math test (HRT) subscales were computed in SPM12. These correlations were corrected for the same confounding variables stated above. Clusters were considered significant and reported when exceeding a voxel-level threshold of $p < 0.001$ (uncorrected), with family-wise-error (FWE) correction for multiple spatial comparisons at the cluster level ($p < 0.05$).

**Table 1. Demographic information and psychometric test scores.**

| **Demographics** | *kindergarten* | *end of second grade* |
|---|---|---|
| N | 28 | ..[d] |
| Age[a] | 5;6±6 | 8;5±5 |
| Sex[b] | 13/15 | ..[d] |
| Maternal education[c] | 4.43±0.51 | ..[d] |
| Handedness[e] | 58.11±44.63 | ..[d] |
| | | |
| **Psychometrics** | | |
| Non-verbal IQ[f] | 104.61±11.54 | 113.64±11.83 |
| Arithmetic abilities[g] | -[h] | 69.64±23.17 |
| Visuospatial abilities[i] | -[h] | 77.00±20.00 |
| Spelling accuracy[j] | -[h] | 52.39±24.33 |
| Reading speed[k] | -[h] | 63.71±24.96 |

[a] mean age: years; months ± standard deviation
[b] male/female
[c] questionnaire-derived, combined score of mother's school education (4-point scale: no degree – 0 points; German 'Abitur' [high school diploma / A level] – 3 points) and vocational qualification (5-point scale: no qualification – 0 points; German 'Habilitation' [postdoctoral academic qualification] – 4 points); mean ± standard deviation
[d] data were identical for both timepoints
[e] laterality quotient (LQ): mean ± standard deviation; scores range from -100 (left handed) to 100 (right handed), left-handedness: LQ < –28, i.e. the first decile value; right-handedness: LQ > 48, i.e. the first decile value; ambidexterity: –28 < LQ < 48
[f] mean ± standard deviation; average normed IQ score is 100 with a standard deviation of ± 15
[g] percentile ranks: mean ± standard deviation; subscale of standardized math test (HRT) comprising addition, subtraction, solving simple equation and greater-or-smaller-than-comparison tasks
[h] data were only available at second timepoint
[i] percentile ranks: mean ± standard deviation; subscale of standardized math test (HRT) comprising tasks assessing length and magnitude estimation, counting, and numerical rule extraction abilities
[j] percentile ranks: mean ± standard deviation; writing after dictation
[k] percentile ranks: mean ± standard deviation; number of words correctly read within 1 minute

## 3. Results

Information on participants and their performance in psychometric testing is provided in Table 1. There were no significant correlations between any of the sociodemographic and psychometric measures for each time point, as well as across time (Supplementary Tables S2, S3 and S4).

In the ROI-based analysis, we found a significant negative correlation of change rate in cortical folding regularity and the arithmetic ability subscale within the right IPS ($R^2(16) = 0.55$, $p = 0.0004$, Figure 1b). No significant correlations were observed between any other ROI and measure (Supplementary Table S5).

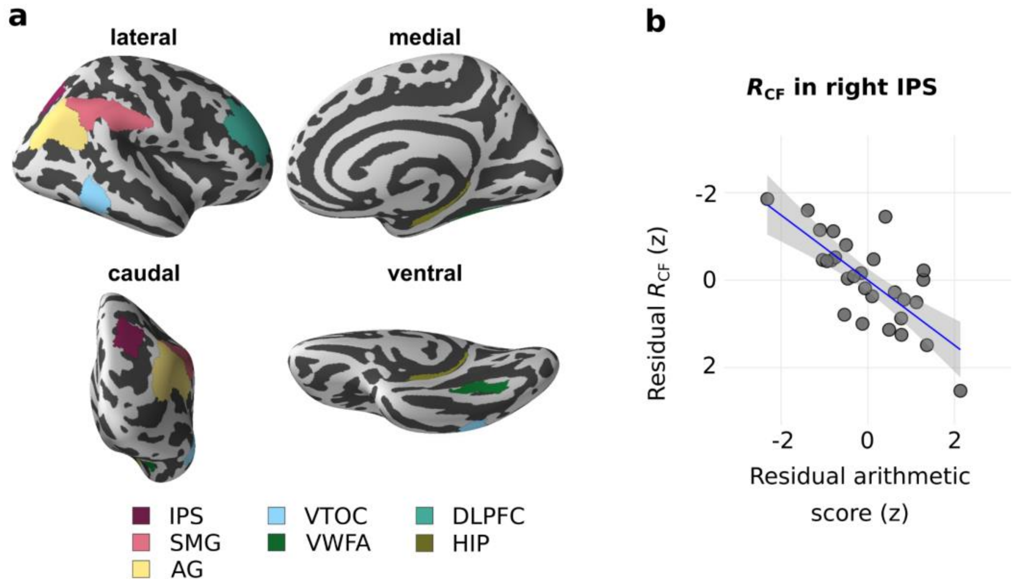


**Figure 1. Region-of-interest (ROI) analysis.** (a) Only right-hemispheric ROIs are depicted, but bilateral ROIs were used in the analysis. IPS = intraparietal sulcus; SMG = supramarginal gyrus; AG = angular gyrus; VTOC = ventral temporal-occipital cortex; VWFA = visual word form area; DLPFC = dorso-lateral prefrontal cortex; HIP = hippocampus. (b) A significant negative correlation (blue) was found between the residual mean $R_{CF}$ within the right IPS and the residual arithmetic ability score ($p < 0.05$, family-wise-error corrected for the number of behavioral measures and ROIs). (b) The scatterplot denotes the association of residualized change in cortical folding regularity and z-scored arithmetic test score after accounting for age at kindergarten, sex, handedness, non-verbal IQ at the end of second grade, maternal education, spelling accuracy, reading speed, familial risk of developing dyslexia, visuospatial performance score, and mean CF at kindergarten age. The shaded area surrounding the regression line shows the 95% confidence interval. $R_{CF}$ = change rate of cortical folding regularity.

The whole-brain analysis revealed significant relations between cortical change rates and mathematical test subscales (Table 2, Figure 2). Specifically, change in cortical thickness was negatively correlated with arithmetic abilities in the right temporal pole (TP; $R^2(16) = 0.52$, $p = 0.0330$) as well as left middle occipital gyrus (MOG; $R^2(16) = 0.52$, $p = 0.0300$) and positively correlated with visuospatial abilities in clusters in the right superior parietal cortex (SPL; $R^2(16) = 0.73$, $p < 0.0010$), two clusters within the right supramarginal gyrus (SMG; $R^2(16) = 0.40$, p

= 0.0440; $R^2(16) = 0.45$, p = 0.0480), and right postcentral gyrus ($R^2(16) = 0.51$, p = 0.0060). Additionally, change in cortical folding regularity was negatively correlated with visuospatial skills in the right middle frontal gyrus (MFG; $R^2(16) = 0.47$, p = 0.0340).

**Table 2. Cluster results of the whole brain vertex wise analysis.**

| **Location** | **Coordinates** | | | **Size[a]** | $\mathbf{R^2}$ | **P** |
|---|---|---|---|---|---|---|
| | **X** | **Y** | **Z** | | | |
| **Arithmetic abilities** | | | | | | |
| $R_{CT}$ | | | | | | |
| R temporal pole | 50 | 14 | -24 | 321 | 0.52 | 0.0330 |
| L middle occipital gyrus | -40 | -84 | 4 | 318 | 0.52 | 0.0300 |
| **Visuospatial abilities** | | | | | | |
| $R_{CF}$ | | | | | | |
| R middle frontal gyrus | 29 | 20 | 45 | 376 | 0.47 | 0.0340 |
| $R_{CT}$ | | | | | | |
| R superior parietal cortex | 17 | -66 | 54 | 576 | 0.73 | 0.0010 |
| R postcentral gyrus | 58 | -14 | 41 | 452 | 0.51 | 0.0060 |
| R supramarginal gyrus | 56 | -46 | 23 | 297 | 0.40 | 0.0440 |
| | 57 | -41 | 39 | 291 | 0.45 | 0.0480 |

[a] size in vertices; $R_{CT}$ = change in cortical thickness; $R_{CF}$ = change in cortical folding regularity.

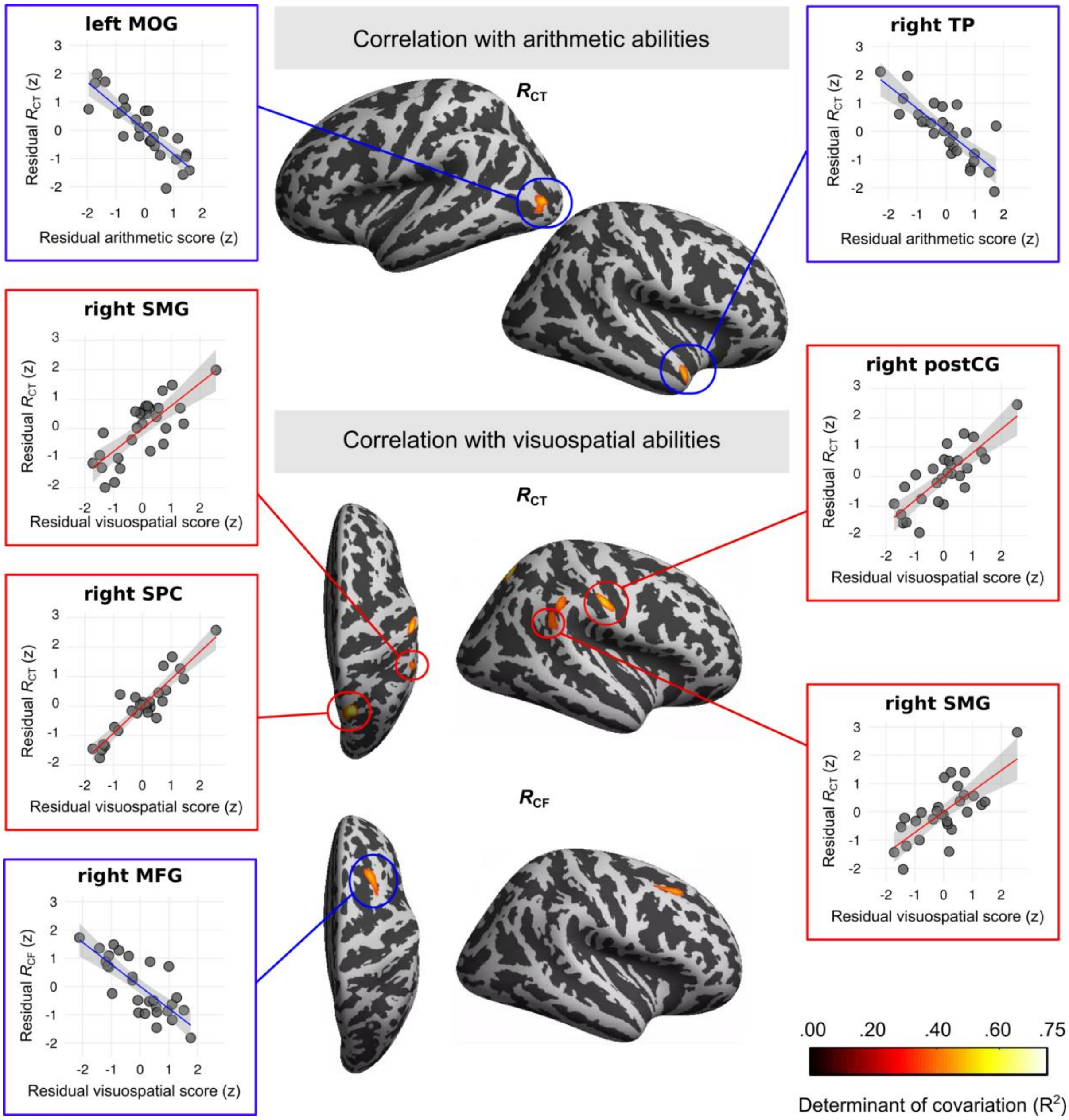


**Figure 2. Whole-brain analysis results.** Overview of clusters denoting significant partial correlations. Residual arithmetic score was significantly and negatively correlated (blue) with residual $R_{CT}$ within a cluster in the right temporal pole and middle occipital gyrus (top row). Residual visuospatial abilities were significantly and positively associated (red) with residual $R_{CT}$ in clusters within the right superior parietal cortex, postcentral gyrus, and superior marginal gyrus (mid row). Residual visuospatial abilities were also negatively correlated with residual $R_{CF}$ within a cluster in the right middle frontal gyrus (bottom row). The color bar depicts the proportion of explained variance within each cluster in terms of the determinant of covariation ($R^2$), overlaid on the inflated cortical surfaces. Scatterplots show associations of the z-scored, maximal $R^2$ value of each residual cluster and the respective residual behavioral test score after removing the effects of age at kindergarten, sex, handedness, non-verbal IQ at the end of second grade, maternal education, spelling accuracy, reading speed, familial risk of developing dyslexia, the respective other subscale of the standardized math test, and hemispheric mean value of investigated morphometric measure at kindergarten age. Shaded areas surrounding regression lines depict the respective 95% confidence level intervals. All reported results are significant at a level of $p < 0.05$ (family-wise-error corrected). $R_{CT}$ = relative change rate of cortical thickness; $R_{CF}$ = relative change rate of cortical folding regularity; MOG = middle occipital gyrus; TP = temporal pole; SMG = supramarginal gyrus; postCG = postcentral gyrus; SPC = superior parietal cortex; MFG = middle frontal gyrus.

## 4. Discussion

In this study, we examined changes in cortical anatomy associated with emerging individual differences in mathematical ability of typically developing children. In contrast to previous studies, we focused on the trajectory from kindergarten to school when children start undergoing formal mathematical education. We correlated the change in various measures of cortical surface morphometry occurring between 5 and 8 years of age with performance on a standardized, age-normed math test. Our analyses revealed a significant negative correlation between change rate of cortical folding regularity and symbolic arithmetic processing in the right IPS. Further, cortical thickness change was negatively correlated with arithmetic performance in the right temporal pole and the left middle occipital gyrus. Moreover, we detected significant positive associations between visuospatial magnitude processing and rate of cortical thickness change of the right superior parietal lobe, right supramarginal gyrus and right postentral gyrus. Additionally, we found a significant negative correlation between visuospatial magnitude processing score and change of cortical folding regularity of the right MFG.

Classical analyses of gray matter volume via voxel-based morphometry cannot disentangle differences driven by cortical thickness and folding regularity (Mechelli et al., 2005). Hence, going beyond volumetric measures, an examination of cortical surface development as provided in our study may give more detailed and specific insights into the intricate relationship between brain maturation and emerging mathematical cognition.

Cortical thickness changes may be related to processes affecting the cortical cytoarchitecture, like neuro-, glio- and synaptogenesis as well as synaptic pruning (Zatorre et al., 2012). More recent evidence also suggests that decreases in cortical thickness during development are a marker of progressive growth of deep cortical white matter (Natu et al., 2018). The spatial and temporal progression of these maturational processes follows highly heterogenous patterns throughout the cortex (Huttenlocher and Dabholkar, 1997). Cortical folding during development is driven by physical forces induced by continued growth of outer cortical layers, as neurons form new synaptic connections (Budday et al., 2015b, 2015a). Consequently, the cortical surface expands more quickly than the underlying tissue, creating compression forces that ultimately lead to surface buckling (Richman et al., 1975). Thus, a likely explanation may be that cortical folding changes reflect myelination and synaptic remodeling (Blanton et al., 2001). Nevertheless, future investigations are necessary to validate the neurobiological underpinnings of differential development of cortical surface regularity.

Our ROI analysis highlights the link between right IPS folding and mathematical ability. Comparable to our observation for the right MFG, we found a negative association between the change in folding regularity of the right IPS and arithmetic performance. This is in line with the known key role of this region for typical and atypical numerical cognition. Specifically, Cantlon et al. (2006) demonstrate right-lateralized parietal activation related to processing of magnitude in 4-year-old children. **Further, Emerson & Cantlon (2015) identify the right IPS as the sole region to continuously exhibit number-selective responses in four- to nine-year-old children, emphasizing its developmentally stable involvement in numerical processing. This finding is in agreement with reports of age-invariant adaptation effects to numerical magnitude across development (Vogel et al., 2015).** Moreover, children and adolescents with low mathematical competence show higher involvement of the right IPS than individuals with high competence when performing simple arithmetic tasks, indicating greater reliance on magnitude processing strategies that rest on basic quantity representations in the parietal cortex (De Smedt et al., 2011; Price et al., 2013). In contrast **to the continuous pattern of number-selective responses within the right IPS, number-related neural activity in left parietal regions increases from childhood until adolescence (Vogel et al., 2015).**

**Longitudinal evidence suggests an association between these left-lateralized age-related changes and the refinement of numerical skills in terms of discrimination acuity (Emerson and Cantlon, 2015). Further during typical development, the** involvement of left parietal regions **for** symbolic mathematical operations increases **over time** (Rivera et al., 2005), reflecting its functional specialization for memory-based arithmetic processing (Piazza et al., 2007). In the light of these findings, our results suggest that **initial stages of** mathematical learning **are** related to more mature intracortical synaptic connectivity of the right, but not the left, IPS. This process might refine basic magnitude processing strategies, thus strengthening the elementary representations of quantity.

Beyond our ROI results, the whole-brain analyses suggest that the rate of neuroplastic change in a region associated with semantic knowledge (Amalric and Dehaene, 2016; Menon, 2015), the right temporal pole, plays an important role for early mathematical development. In particular, cortical thickness change was negatively associated with math performance. The right anterior temporal pole is a multimodal association area known to integrate conceptual information that is distributed across different brain regions (Patterson et al., 2007). In line with this, the children in our study learned first basic mathematical concepts in the period under investigation. Mastering these concepts requires integrating knowledge of number facts, relations between magnitudes and arithmetic principles (Dowker, 2013). Given that, over development, the temporal pole steadily declines in cortical thickness (Ducharme et al., 2016; Fjell et al., 2015), the association between reduced change and high arithmetic performance suggested by our results may indicate a slower trajectory of cortical thinning. This might point to a more sustained build-up of new connections in the right temporal memory system during mathematical learning.

The only effect in the left hemisphere obtained from our analyses was a significant negative correlation of cortical thickness change rate and arithmetic abilities within the middle occipital gyrus. Located within the visual association cortex (Brodmann area 18), this region is commonly associated with early stages of visual processing like stereotactic vision (Fortin et al., 2002) and simple pattern recognition (Marcar et al., 2004). Given that mathematical education in school is primarily based on visually presented mathematical problems, this effect might reflect a result of increased visual training specifically related to the visual numerical form. The typical developmental trajectory of such low-level sensory regions follows a linear decrease in thickness (Ducharme et al., 2016), such that the current result may potentially indicate a slower rate of cortical thinning due to this increased visual training in better performing children.

The right superior parietal lobe contributes to approximate calculation already in preschool children (Cantlon et al., 2006) and supports exact symbolic calculation in adults (Knops et al., 2009). Our findings complement these data by suggesting a fundamental contribution of superior parietal lobe plasticity for the transition from approximate to exact calculation by refining visuospatial magnitude processing skills. Within the age range under investigation here, cortical thickness increases in parietal regions before subsequently declining later in life (Ducharme et al., 2016; Shaw et al., 2008). The positive association between thickness change and mathematical ability might therefore suggest that increased synaptogenesis supports mathematical learning in the first school years.

Cytoarchitectonic subdivisions of the right supramarginal gyrus have been shown to exhibit heterogenous patterns of activation across development of arithmetic problem solving skills from primary school-age until adulthood (Chang et al., 2016). Our findings add to these results, pointing towards a positive association between cortical thickness change and visuo-spatial magnitude processing already at the transition between kindergarten and second grade in school. Supramarginal cortical thickness typically decreases following a linear trajectory from childhood until adulthood (Ducharme et al., 2016). Thus, the clusters detected in the current analysis likely point towards accelerated cortical thickness change potentially driven by increases in cortical white matter, supporting the development of visuo-spatial magnitude processing abilities. It is noteworthy, however, that these associations were not revealed in our ROI analyses but only in the whole brain contrast. A reason for this discrepancy may be that we choose a rather large ROI combining SMG subregions PFop, PF, and PFm, while the whole brain analysis revealed two confined clusters partly located in PF. Thus, computing the mean cortical folding regularity across this combined region possibly concealed the relationship between behavior and cortical change indeed present in its subcomponents.

Somewhat unexpected, our analyses additionally revealed a positive association between visuospatial processing skills and cortical thickness change of the right lateral postcentral gyrus. This region is associated with cortical thinning over development (Ducharme et al., 2016). While the exact role of this region for numerical cognition is still elusive, there is evidence that functional connectivity between the right postcentral gyrus and the left angular gyrus, a key region associated with verbal mathematical fact retrieval, significantly increases after intensive math tutoring in children (Jolles et al., 2016b). Further, it is the locus of somatosensory regions that have been suggested to impact the allocation of attention in visual space (Balslev et al., 2013). In line with this, our findings suggest a link between visuospatial processing ability and more rapid growth of cortical white matter indicated by increased rates of cortical thinning.

Further, our results show that better visuospatial performance was negatively associated with change in the regularity of cortical folding within the right MFG, a region consistently activated in calculation tasks with higher working memory demands (Menon, 2000). Changes in the regularity of cortical folding are assumed to be linked to the persistent growth of superficial cortical layers driven by the formation of new intracortical synaptic connections (Budday et al., 2015b, 2015a). Children with higher mathematical ability might thus exhibit more mature intracortical synaptic connectivity in the right MFG.

In a recent study, Nemmi et al. (2018) demonstrated that the right number-form area shows specific functional connectivity to the right IPS already at three years of age. Differential connectivity to parietal and prefrontal regions associated with gains in mathematical ability, however, emerged only later around 12–14 years of age. In line with this tentative developmental trajectory, our analyses did not reveal associations between mathematical abilities and surface plasticity of the VTOC from kindergarten to second grade in school. Future studies are needed to examine the relationship between structural changes of this region and mathematical ability in older children who encounter more challenging mathematical concepts in higher grades.

Despite providing insights into associations between cortical surface plasticity and individual behavioural performance, it is impossible to derive definite conclusions about the exact role of localized cortical changes for cognitive functioning from the current data. For instance, the parietal cortex including the IPS is known to be involved in a multitude of different cognitive mechanisms beyond core mathematical processing, including non-spatial working memory and executive functioning (see Culham and Kanwisher, 2001 for a review). Even within the domain of magnitude processing, animal work suggests distinct neural processing stages within this region (Nieder et al., 2006). Thus, it is not clear which aspects involved in the complex cognitive functions investigated here the observed changes support. Still, our results guide the formation of hypotheses for future longitudinal work disentangling these specific contributions of individual areas to mathematical cognition.

A number of methodological limitations have to be considered. First, it is important to stress that the results presented here are correlational. Consequently, the current analysis cannot disentangle the extent to which brain maturational processes induce changes in individual abilities from the extent to which mathematical and visuo-spatial training re-shapes the cortical structure. Second, considering the known importance of the ROIs under investigation for mathematical processing, the null results reported here need to be interpreted with caution. Third, the scanner upgrade between time point 1 and time point 2 might bias findings if there is an interaction between upgrade and an individual factor which correlated with math skill development. **Fourth, our selection of atlas ROIs was based on insights from single studies and thus might be prone to individual variance, given the lack of an appropriate meta-analysis quantifying functional development of arithmetic and visuospatial magnitude processing in children from kindergarten to second grade in school.** Last, given the limited sample size, spatial detection of relatively small significant clusters as reported here might be sensitive to subtle methodological variations. Hence, the results from this work await confirmation in larger follow-up studies.

In conclusion, the present study provides evidence that cortical surface morphometry changes are linked to mathematical learning during the first years of formal instruction. A series of whole brain analyses highlights the importance of regions associated with working memory and semantic memory processes, such as the right middle frontal gyrus, the right precentral gyrus, and the right temporal pole. Furthermore, our results emphasize the role of surface reorganization within the right superior parietal lobe, supporting visuospatial processing, and within the right intraparietal sulcus as a crucial area for numerical magnitude processing. Thus, we identify early cortical surface plasticity as an important structural correlate of emerging arithmetic abilities during the first years of school.

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## References


Amalric, M., Dehaene, S., 2016. Origins of the brain networks for advanced mathematics in expert mathematicians. Proc. Natl. Acad. Sci. U. S. A. 113, 4909–4917. https://doi.org/10.1073/pnas.1603205113

Avants, B.B., Tustison, N.J., Song, G., Cook, P.A., Klein, A., Gee, J.C., 2011. A reproducible evaluation of ANTs similarity metric performance in brain image registration. NeuroImage 54, 2033–2044. https://doi.org/10.1016/j.neuroimage.2010.09.025

Avants, B.B., Yushkevich, P., Pluta, J., Minkoff, D., Korczykowski, M., Detre, J., Gee, J.C., 2010. The optimal template effect in hippocampus studies of diseased populations. NeuroImage 49, 2457–2466. https://doi.org/10.1016/j.neuroimage.2009.09.062

Balslev, D., Odoj, B., Karnath, H.-O., 2013. Role of Somatosensory Cortex in Visuospatial Attention. J. Neurosci. 33, 18311–18318. https://doi.org/10.1523/JNEUROSCI.1112-13.2013

Barth, H., La Mont, K., Lipton, J., Spelke, E.S., 2005. Abstract number and arithmetic in preschool children. Proc. Natl. Acad. Sci. U. S. A. 102, 14116–14121. https://doi.org/10.1073/pnas.0505512102

Barth, H., La Mont, K., Lipton, J.S., Dehaene, S., Kanwisher, N., Spelke, E.S., 2006. Non-symbolic arithmetic in adults and young children. Cognition 98, 199–222.

Blanton, R.E., Levitt, J.G., Thompson, P.M., Narr, K.L., Capetillo-Cunliffe, L., Nobel, A., Singerman, J.D., McCracken, J.T., Toga, A.W., 2001. Mapping cortical asymmetry and complexity patterns in normal children. Psychiatry Res. Neuroimaging 107, 29–43. https://doi.org/10.1016/S0925-4927(01)00091-9

Brown, M., Askew, M., Rhodes, V., Denvir, H., Ranson, E., Wiliam, D., 2003. Characterising individual and cohort progression in learning numeracy: results from the Leverhulme 5-year longitudinal study. Presented at the American Educational Research Association Annual Conference, Chicago, pp. 21–25.

Budday, S., Steinmann, P., Kuhl, E., 2015a. Physical biology of human brain development. Front. Cell. Neurosci. 9, 257. https://doi.org/10.3389/fncel.2015.00257

Budday, S., Steinmann, P., Kuhl, E., 2015b. Secondary instabilities modulate cortical complexity in the mammalian brain. Philos. Mag. 95, 3244–3256. https://doi.org/10.1080/14786435.2015.1024184

Bull, R., Espy, K.A., Wiebe, S.A., 2008. Short-Term Memory, Working Memory, and Executive Functioning in Preschoolers: Longitudinal Predictors of Mathematical Achievement at Age 7 Years. Dev. Neuropsychol. 33, 205–228. https://doi.org/10.1080/87565640801982312

Bullmore, E., Sporns, O., 2012. The economy of brain network organization. Nat. Rev. Neurosci. 13, 336–349. https://doi.org/10.1038/nrn3214

Cafiero, R., Brauer, J., Anwander, A., Friederici, A.D., 2018. The concurrence of cortical surface area expansion and white matter myelination in human brain development. Cereb. Cortex 29, 827–837. https://doi.org/10.1093/cercor/bhy277

Cantlon, J.F., Brannon, E.M., Carter, E.J., Pelphrey, K.A., 2006. Functional imaging of numerical processing in adults and 4-y-old children. PLOS Biol. 4, e125. https://doi.org/10.1371/journal.pbio.0040125

Chang, T.-T., Metcalfe, A.W.S., Padmanabhan, A., Chen, T., Menon, V., 2016. Heterogeneous and nonlinear development of human posterior parietal cortex function. NeuroImage 126, 184–195. https://doi.org/10.1016/j.neuroimage.2015.11.053

Cho, S., Ryali, S., Geary, D.C., Menon, V., 2011. How does a child solve 7 + 8? Decoding brain activity patterns associated with counting and retrieval strategies. Dev. Sci. 14, 989–1001. https://doi.org/10.1111/j.1467-7687.2011.01055.x

Cockcroft, W.H., 1982. Mathematics counts. HM Stationery Office, London.

Culham, J.C., Kanwisher, N.G., 2001. Neuroimaging of cognitive functions in human parietal cortex. Curr. Opin. Neurobiol. 11, 157–163. https://doi.org/10.1016/S0959-4388(00)00191-4

De Smedt, B., Holloway, I.D., Ansari, D., 2011. Effects of problem size and arithmetic operation on brain activation during calculation in children with varying levels of arithmetical fluency. NeuroImage, Special Issue: Educational Neuroscience 57, 771–781. https://doi.org/10.1016/j.neuroimage.2010.12.037

De Smedt, B., Janssen, R., Bouwens, K., Verschaffel, L., Boets, B., Ghesquière, P., 2009. Working memory and individual differences in mathematics achievement: A longitudinal study from first grade to second grade. J. Exp. Child Psychol. 103, 186–201. https://doi.org/10.1016/j.jecp.2009.01.004

Dehaene, S., 2011. The number sense: How the mind creates mathematics, revised and updated edition. Oxford University Press, USA.

Dirks, E., Spyer, G., van Lieshout, E.C.D.M., de Sonneville, L., 2008. Prevalence of combined reading and arithmetic disabilities. J. Learn. Disabil. 41, 460–473. https://doi.org/10.1177/0022219408321128

Dowker, A., 2013. Individual differences in arithmetical abilities. Psychology Press, New York, NY, US.

Ducharme, S., Albaugh, M.D., Nguyen, T.-V., Hudziak, J.J., Mateos-Pérez, J.M., Labbe, A., Evans, A.C., Karama, S., 2016. Trajectories of cortical thickness maturation in normal brain development — The importance of quality control procedures. NeuroImage 125, 267–279. https://doi.org/10.1016/j.neuroimage.2015.10.010

Duncan, G.J., Dowsett, C.J., Claessens, A., Magnuson, K., Huston, A.C., Klebanov, P., Pagani, L.S., Feinstein, L., Engel, M., Brooks-Gunn, J., Sexton, H., Duckworth, K., Japel, C., 2007. School readiness and later achievement. Dev. Psychol. 43, 1428–1446. https://doi.org/10.1037/0012-1649.43.6.1428

Emerson, R.W., Cantlon, J.F., 2015. Continuity and change in children's longitudinal neural responses to numbers. Dev. Sci. 18, 314–326. https://doi.org/10.1111/desc.12215

Evans, T.M., Kochalka, J., Ngoon, T.J., Wu, S.S., Qin, S., Battista, C., Menon, V., 2015. Brain structural integrity and intrinsic functional connectivity forecast 6 year longitudinal growth in children's numerical abilities. J. Neurosci. 35, 11743–11750. https://doi.org/10.1523/JNEUROSCI.0216-15.2015

Fjell, A.M., Grydeland, H., Krogsrud, S.K., Amlien, I., Rohani, D.A., Ferschmann, L., Storsve, A.B., Tamnes, C.K., Sala-Llonch, R., Due-Tønnessen, P., Bjørnerud, A., Sølsnes, A.E., Håberg, A.K., Skranes, J., Bartsch, H., Chen, C.-H., Thompson, W.K., Panizzon, M.S., Kremen, W.S., Dale, A.M., Walhovd, K.B., 2015. Development and aging of cortical thickness correspond to genetic organization patterns. Proc. Natl. Acad. Sci. U. S. A. 112, 15462–15467. https://doi.org/10.1073/pnas.1508831112

Fonov, V.S., Evans, A.C., McKinstry, R.C., Almli, C.R., Collins, D.L., 2009. Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. NeuroImage Supplement 1, S102. https://doi.org/10.1016/S1053-8119(09)70884-5

Formisano, E., Linden, D.E.J., Di Salle, F., Trojano, L., Esposito, F., Sack, A.T., Grossi, D., Zanella, F.E., Goebel, R., 2002. Tracking the Mind's Image in the Brain I: Time-Resolved fMRI during Visuospatial Mental Imagery. Neuron 35, 185–194. https://doi.org/10.1016/S0896-6273(02)00747-X

Fortin, A., Ptito, A., Faubert, J., Ptito, M., 2002. Cortical areas mediating stereopsis in the human brain: a PET study. Neuroreport 13, 895–898.

Georges, C., Hoffmann, D., Schiltz, C., 2017. Mathematical abilities in elementary school: Do they relate to number–space associations? J. Exp. Child Psychol. 161, 126–147. https://doi.org/10.1016/j.jecp.2017.04.011

Glasser, M.F., Coalson, T.S., Robinson, E.C., Hacker, C.D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J.L.R., Beckmann, C.F., Jenkinson, M., Smith, S.M., Van Essen, D.C., 2016. A multi-modal parcellation of human cerebral cortex. Nature 536, 171–178. https://doi.org/10.1038/nature18933

Grabner, R.H., Ansari, D., Reishofer, G., Stern, E., Ebner, F., Neuper, C., 2007. Individual differences in mathematical competence predict parietal brain activation during mental calculation. NeuroImage 38, 346–356. https://doi.org/10.1016/j.neuroimage.2007.07.041

Haffner, J., Baro, K., Parzer, P., Resch, F., 2005. Heidelberger Rechentest (HRT 1-4). Hogrefe, Göttingen.

Hannagan, T., Amedi, A., Cohen, L., Dehaene-Lambertz, G., Dehaene, S., 2015. Origins of the specialization for letters and numbers in ventral occipitotemporal cortex. Trends Cogn. Sci. 19, 374–382. https://doi.org/10.1016/j.tics.2015.05.006

He, L., Zuo, Z., Chen, L., Humphreys, G., 2014. Effects of Number Magnitude and Notation at 7T: Separating the Neural Response to Small and Large, Symbolic and Nonsymbolic Number. Cereb. Cortex 24, 2199–2209. https://doi.org/10.1093/cercor/bht074

Holm, S., 1979. A Simple Sequentially Rejective Multiple Test Procedure. Scand. J. Stat. 6, 65–70.

Huttenlocher, P.R., Dabholkar, A.S., 1997. Regional differences in synaptogenesis in human cerebral cortex. J. Comp. Neurol. 387, 167–178. https://doi.org/10.1002/(SICI)1096-9861(19971020)387:2<167::AID-CNE1>3.0.CO;2-Z

Jolles, D., Ashkenazi, S., Kochalka, J., Evans, T.M., Richardson, J., Rosenberg-Lee, M., Zhao, H., Supekar, K., Chen, T., Menon, V., 2016a. Parietal hyper-connectivity, aberrant brain organization, and circuit- based biomarkers in children with mathematical disabilities. Dev. Sci. 19, 613–631. https://doi.org/10.1111/desc.12399

Jolles, D., Supekar, K., Richardson, J., Tenison, C., Ashkenazi, S., Rosenberg-Lee, M., Fuchs, L., Menon, V., 2016b. Reconfiguration of parietal circuits with cognitive tutoring in elementary school children. Cortex 83, 231–245. https://doi.org/10.1016/j.cortex.2016.08.004

Klingberg, T., Forssberg, H., Westerberg, H., 2002. Increased Brain Activity in Frontal and Parietal Cortex Underlies the Development of Visuospatial Working Memory Capacity during Childhood. J. Cogn. Neurosci. 14, 1–10. https://doi.org/10.1162/089892902317205276

Knops, A., Thirion, B., Hubbard, E.M., Michel, V., Dehaene, S., 2009. Recruitment of an area involved in eye movements during mental arithmetic. Science 324, 1583–1585. https://doi.org/10.1126/science.1171599

Kwon, H., Reiss, A.L., Menon, V., 2002. Neural basis of protracted developmental changes in visuo-spatial working memory. Proc. Natl. Acad. Sci. 99, 13336–13341. https://doi.org/10.1073/pnas.162486399

Lipton, J.S., Spelke, E.S., 2003. Origins of number sense: Large-number discrimination in human infants. Cognition 14, 396–401.

Lüders, E., Thompson, P.M., Narr, K.L., Toga, A.W., Jäncke, L., Gaser, C., 2006. A curvature-based approach to estimate local gyrification on the cortical surface. NeuroImage 29, 1224–1230. https://doi.org/10.1016/j.neuroimage.2005.08.049

Marcar, V.L., Loenneker, T., Straessle, A., Jaggy, S., Kucian, K., Martin, E., 2004. An fMRI study of the cerebral macro network involved in “cue invariant” form perception and how it is influenced by stimulus complexity. NeuroImage 23, 947–955. https://doi.org/10.1016/j.neuroimage.2004.05.028

Masataka, N., Ohnishi, T., Imabayashi, E., Hirakata, M., Matsuda, H., 2007. Neural correlates for learning to read Roman numerals. Brain Lang. 100, 276–282. https://doi.org/10.1016/j.bandl.2006.11.011

Mechelli, A., Price, C.J., Friston, K.J., Ashburner, J.T., 2005. Voxel-based morphometry of the human brain: Methods and applications. Curr. Med. Imaging Rev. 1, 105–113. https://doi.org/10.2174/1573405054038726

Menon, V., 2015. Arithmetic in the child and adult brain, in: Kadosh, R.C., Dowker, A. (Eds.), The Oxford Handbook of Numerical Cognition, Oxford Library of Psychology. Oxford University Press, New York, NY, US, pp. 502–530.

Menon, V., 2010. Developmental cognitive neuroscience of arithmetic: Implications for learning and education. ZDM Int. J. Math. Educ. 42, 515–525. https://doi.org/10.1007/s11858-010-0242-0

Menon, V., Rivera, S.M., White, C.D., Glover, G.H., Reiss, A.L., 2000. Dissociating prefrontal and parietal cortex activation during arithmetic processing. NeuroImage 12, 357–365. https://doi.org/10.1006/nimg.2000.0613

Moll, K., Kunze, S., Neuhoff, N., Bruder, J., Schulte-Körne, G., 2014. Specific learning disorder: Prevalence and gender differences. PLOS ONE 9, e103537. https://doi.org/10.1371/journal.pone.0103537

Moll, K., Landerl, K., 2010. SLRT-II: Lese- und Rechtschreibtest; Weiterentwicklung des Salzburger Lese-und Rechtschreibtests (SLRT). Hans Huber, Bern.

Natu, V.S., Gomez, J., Barnett, M., Jeska, B., Kirilina, E., Jaeger, C., Zhen, Z., Cox, S., Weiner, K.S., Weiskopf, N., Grill-Spector, K., 2018. Apparent thinning of visual cortex during childhood is associated with myelination, not pruning. bioRxiv 368274. https://doi.org/10.1101/368274

Nemmi, F., Schel, M.A., Klingberg, T., 2018. Connectivity of the human number form area reveals development of a cortical network for mathematics. Front. Hum. Neurosci. 12. https://doi.org/10.3389/fnhum.2018.00465

Nieder, A., Diester, I., Tudusciuc, O., 2006. Temporal and spatial enumeration processes in the primate parietal cortex 313, 6.

Oldfield, R.C., 1971. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 9, 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Patterson, K., Nestor, P.J., Rogers, T.T., 2007. Where do you know what you know? The representation of semantic knowledge in the human brain. Nat. Rev. Neurosci. 8, 976–987. https://doi.org/10.1038/nrn2277

Petermann, F., Petermann, U., 2011. Wechsler Intelligence Scale for Children: Fourth Edition (WISC-IV). German Version. Pearson Assessment, Frankfurt am Main.

Peters, L., De Smedt, B., 2018. Arithmetic in the developing brain: A review of brain imaging studies. Dev. Cogn. Neurosci. 30, 265–279. https://doi.org/10.1016/j.dcn.2017.05.002

Peters, L., Polspoel, B., Op de Beeck, H., De Smedt, B., 2016. Brain activity during arithmetic in symbolic and non-symbolic formats in 9–12 year old children. Neuropsychologia 86, 19–28. https://doi.org/10.1016/j.neuropsychologia.2016.04.001

Piazza, M., Izard, V., Pinel, P., Le Bihan, D., Dehaene, S., 2004. Tuning curves for approximate numerosity in the human intraparietal sulcus. Neuron 44, 547–555. https://doi.org/10.1016/j.neuron.2004.10.014

Piazza, M., Mechelli, A., Price, C.J., Butterworth, B., 2006. Exact and approximate judgements of visual and auditory numerosity: An fMRI study. Brain Res. 1106, 177–188.

Piazza, M., Pinel, P., Le Bihan, D., Dehaene, S., 2007. A magnitude code common to numerosities and number symbols in human intraparietal cortex. Neuron 53, 293–305. https://doi.org/10.1016/j.neuron.2006.11.022

Price, G.R., Mazzocco, M.M.M., Ansari, D., 2013. Why Mental Arithmetic Counts: Brain Activation during Single Digit Arithmetic Predicts High School Math Scores. J. Neurosci. 33, 156–163. https://doi.org/10.1523/JNEUROSCI.2936-12.2013

Qin, S., Cho, S., Chen, T., Rosenberg-Lee, M., Geary, D.C., Menon, V., 2014. Hippocampal-neocortical functional reorganization underlies children's cognitive development. Nat. Neurosci. 17, 1263–1269. https://doi.org/10.1038/nn.3788

R Core Team, 2016. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Rasmussen, C., Bisanz, J., 2005. Representation and working memory in early arithmetic. J. Exp. Child Psychol. 91, 137–157. https://doi.org/10.1016/j.jecp.2005.01.004

Raznahan, A., Shaw, P., Lalonde, F., Stockman, M., Wallace, G.L., Greenstein, D., Clasen, L., Gogtay, N., Giedd, J.N., 2011. How Does Your Cortex Grow? J. Neurosci. Off. J. Soc. Neurosci. 31, 7174–7177. https://doi.org/10.1523/JNEUROSCI.0054-11.2011

Richman, D.P., Stewart, R.M., Hutchinson, J.W., Caviness, V.S., Jr, 1975. Mechanical model of brain convolutional development. Science 189, 18–21.

Rivera, S.M., Reiss, A.L., Eckert, M.A., Menon, V., 2005. Developmental changes in mental arithmetic: Evidence for increased functional specialization in the left inferior parietal cortex. Cereb. Cortex 15, 1779–1790. https://doi.org/10.1093/cercor/bhi055

Schel, M.A., Klingberg, T., 2017. Specialization of the right intraparietal sulcus for processing mathematics during development. Cereb. Cortex 27, 4436–4446. https://doi.org/10.1093/cercor/bhw246

Schnack, H.G., van Haren, N.E.M., Brouwer, R.M., Evans, A., Durston, S., Boomsma, D.I., Kahn, R.S., Hulshoff Pol, H.E., 2015. Changes in Thickness and Surface Area of the Human Cortex and Their Relationship with Intelligence. Cereb. Cortex 25, 1608–1617. https://doi.org/10.1093/cercor/bht357

Shaw, P., Kabani, N.J., Lerch, J.P., Eckstrand, K., Lenroot, R.K., Gogtay, N., Greenstein, D., Clasen, L., Evans, A.C., Rapoport, J.L., Giedd, J.N., Wise, S.P., 2008. Neurodevelopmental trajectories of the human cerebral cortex. J. Neurosci. 28, 3586–3594. https://doi.org/10.1523/JNEUROSCI.5309-07.2008

Slaughter, V., Kamppi, D., Paynter, J., 2006. Toddler subtraction with large sets: further evidence for an analog-magnitude representation of number. Dev. Sci. 9, 33–39. https://doi.org/10.1111/j.1467-7687.2005.00460.x

Stock, C., Schneider, W., 2008. DERET 1–2+: Deutscher Rechtschreibtest für das erste und zweite Schuljahr. Hogrefe, Göttingen.

Supekar, K., Swigart, A.G., Tenison, C., Jolles, D.D., Rosenberg-Lee, M., Fuchs, L., Menon, V., 2013. Neural predictors of individual differences in response to math tutoring in primary-grade school children. Proc. Natl. Acad. Sci. U. S. A. 110, 8230–8235. https://doi.org/10.1073/pnas.1222154110

Venkatraman, V., Ansari, D., Chee, M.W.L., 2005. Neural correlates of symbolic and non-symbolic arithmetic. Neuropsychologia 43, 744–753. https://doi.org/10.1016/j.neuropsychologia.2004.08.005

Vogel, S.E., Goffin, C., Ansari, D., 2015. Developmental specialization of the left parietal cortex for the semantic representation of Arabic numerals: An fMR-adaptation study. Dev. Cogn. Neurosci. 12, 61–73. https://doi.org/10.1016/j.dcn.2014.12.001

Wechsler, D., Petermann, F., Lipsius, M., 2009. WPPSI-III: Wechsler preschool and primary scale of intelligence. German Version. Pearson Assessment, Frankfurt am Main.

Xu, F., Spelke, E.S., 2000. Large number discrimination in 6-month-old infants. Cognition 74, B1–B11.

Yeo, D.J., Wilkey, E.D., Price, G.R., 2017. The search for the number form area: A functional neuroimaging meta-analysis. Neurosci. Biobehav. Rev. 78, 145–160. https://doi.org/10.1016/j.neubiorev.2017.04.027

Yotter, R.A., Nenadic, I., Ziegler, G., Thompson, P.M., Gaser, C., 2011. Local cortical surface complexity maps from spherical harmonic reconstructions. NeuroImage 56, 961–973. https://doi.org/10.1016/j.neuroimage.2011.02.007

Zatorre, R.J., Fields, R.D., Johansen-Berg, H., 2012. Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nat. Neurosci. 15, 528–536. https://doi.org/10.1038/nn.3045

Zhang, Y., Brady, M., Smith, S.M., 2001. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans. Med. Imaging 20, 45–57. https://doi.org/10.1109/42.906424

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**Data and code availability:** The data and/or code used in the current study are available from the corresponding author upon reasonable request.

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## Supplementary materials

**Supplementary Table S1. Definition of cortical regions of interest.**

| Regions of interest | Atlas labels[a] |
|---|---|
| left / right intraparietal sulcus (IPS) | L_IPS1_ROI, L_MIP_ROI /, R_IPS1_ROI, R_MIP_ROI |
| left / right supramarginal gyrus (SMG) | L_PFop_ROI, L_PF_ROI, L_PFm_ROI / R_PFop_ROI, R_PF_ROI, R_PFm_ROI / |
| Left / right angular gyrus (AG) | L_PGp_ROI, L_PGi_ROI, L_PGs_ROI / R_PGp_ROI, R_PGi_ROI, R_PGs_ROI / |
| left / right hippocampus | L_H_ROI / R_H_ROI |
| left / right dorso-lateral prefrontal cortex (DLPFC) | L_9p_ROI, L_p9-46v_ROI, L_46_ROI, L_a9-46v_ROI, L_9-46d_ROI, L_9a_ROI / R_9p_ROI, R_p9-46v_ROI, R_46_ROI, R_a9-46v_ROI, R_9-46d_ROI, R_9a_ROI |
| left / right ventral temporal-occipital cortex (VTOC) | L_TE1p_ROI / R_TE1p_ROI |
| left / right visual word form area (VWFA) | L_VVC_ROI / R_VVC_ROI |

BA=Brodmann area; [a] Glasser et al. (2016), *retrieved 09/01/2016 from https://balsa.wustl.edu/study/show/RVVG*; if several areas are given, they were combined to form the final region of interest.

**Supplementary Table S2. Correlations between covariates for time point 1**. Note that none of the correlations reaches significance after adjusting for multiple comparisons with alpha = 0.05.

| | **Sex** | **Handedness** | **Maternal education** | **Familial risk of developmental dyslexia** | **IQ at time point 1** |
|---|---|---|---|---|---|
| **Age at time point 1** | r= -0.36; p= 0.0555 | r= 0.13; p=0.5050 | r= 0.06; p=0.7755 | R= -0.16; p=0.4274 | r= -0.05; p=0.7985 |
| **Sex** | | r= -0.05; p=0.8133 | r= -0.02; p=0.9066 | r= 0.13; p=0.5200 | r= -0.13; p=0.4988 |
| **Handedness** | | | r= -0.14; p=0.4906 | r= -0.02; p=0.9190 | r= 0.00; p=0.9986 |
| **Maternal education** | | | | r= 0.29; p=0.1310 | r= 0.36; p=0.0622 |
| **Familial risk of developmental dyslexia** | | | | | r= 0.32; p=0.0957 |

**Supplementary Table S3. Correlations between covariates for time point 2.** Note that none of the correlations reaches significance after adjusting for multiple comparisons with alpha = 0.05.

| | Sex | Handed-ness | Maternal education | Familial risk of dyslexia | IQ at time point 2 | Spelling accuracy | Reading speed | Arithme-tic abilities | Visuo-spatial abilities |
|---|---|---|---|---|---|---|---|---|---|
| **Age at time point 2** | r=-0.13 p= 0.5246 | r=0.14; p= 0.4624 | r=0.14; p= 0.4806 | r=-0.38; p= 0.0476 | r= 0.10; p= 0.6097 | r=-0.24; p= 0.2279 | r=0.16 p= 0.4089 | r=-0.27; p= 0.1581 | r=0.05 p= 0.8159 |
| **Sex** | | r= -0.05; p=0.8133 | r= -0.02; p=0.9066 | r= 0.13; p=0.5200 | r= 0.18; p=0.3566 | r= 0.02; p=0.9263 | r= -0.43; p=0.0208 | r= -0.18; p=0.3555 | r= -0.02; p=0.9348 |
| **Handed-ness** | | | r= -0.14; p=0.4906 | r= -0.02; p=0.9190 | r= 0.17; p=0.3984 | r= -0.15; p=0.4333 | r= 0.06; p=0.7797 | r= 0.30; p=0.1224 | r= 0.07; p=0.7287 |
| **Maternal education** | | | | r= 0.29; p=0.1310 | r= 0.27; p=0.1673 | r= 0.16; p=0.4164 | r= 0.26; p=0.1878 | r= 0.23; p=0.2448 | r= 0.51; p=0.0057 |
| **Familial risk of dyslexia** | | | | | r= 0.23; p=0.2463 | r= 0.01; p=0.9691 | r= -0.28; p=0.1470 | r= 0.39; p=0.0424 | r= 0.55; p=0.0023 |
| **IQ at time point 2** | | | | | | r= -0.14; p=0.4892 | r= -0.11; p=0.5911 | r= 0.17; p=0.3930 | r= 0.24; p=0.2254 |
| **Spelling accuracy** | | | | | | | r= 0.31; p=0.1114 | r= 0.47; p=0.0114 | r= 0.19; p=0.3264 |
| **Reading speed** | | | | | | | | r= 0.25; p=0.1926 | r= 0.23; p=0.2422 |
| **Arithme-tic abilities** | | | | | | | | | r= 0.55; p=0.0023 |

**Supplementary Table S4. Correlations across time.** Significant correlations (alpha $< 0.05$) are marked in bold font and with *.

| | **Age at time point 2** | | **IQ at time point2** |
|---|---|---|---|
| **Age at time point 1** | r= 0.51; p= 0.0054* | IQ at time point1 | r= 0.33; p= 0.0827 |

**Supplementary Table S5. Results of the ROI analyses.** Significant effects are marked in italic and bold. To control for multiple comparisons, only results with a p < 0.0018 (corrected for 14 ROIs and 2 math test subscales) are considered significant. TE1p = VTOC

| | **Arithmetic abilities** | | **Visuo-spatial abilities** | | | **Arithmetic abilities** | | **Visuo-spatial abilities** | |
|---|---|---|---|---|---|---|---|---|---|
| | **$R^2$** | **P** | **$R^2$** | **P** | | **$R^2$** | **P** | **$R^2$** | **P** |
| ***$R_{CT}$*** | | | | | | | | | |
| L IPS | 0.06 | 0.3273 | 0.01 | 0.6751 | R IPS | 0.00 | 0.9574 | 0.05 | 0.3703 |
| L HIPP | 0.00 | 0.9674 | 0.09 | 0.2165 | R HIPP | 0.00 | 0.9937 | 0.01 | 0.6859 |
| L DLPFC | 0.00 | 0.9390 | 0.00 | 0.8517 | R DLPFC | 0.00 | 0.9516 | 0.02 | 0.5986 |
| L VTOC | 0.05 | 0.3639 | 0.00 | 0.8709 | R VTOC | 0.02 | 0.5922 | 0.06 | 0.3405 |
| L VWFA | 0.00 | 0.8960 | 0.06 | 0.3168 | R VWFA | 0.02 | 0.5826 | 0.11 | 0.1870 |
| L SMG | 0.00 | 0.8414 | 0.05 | 0.3880 | R SMG | 0.03 | 0.5263 | 0.08 | 0.2477 |
| L AG | 0.00 | 0.9302 | 0.03 | 0.4867 | R AG | 0.01 | 0.7384 | 0.06 | 0.3217 |
| ***$R_{CF}$*** | | | | | | | | | |
| L IPS | 0.08 | 0.2598 | 0.08 | 0.2659 | ***R IPS*** | ***0.55*** | ***0.0004*** | 0.00 | 0.9913 |
| L HIPP | 0.07 | 0.2964 | 0.00 | 0.7900 | R HIPP | 0.37 | 0.0070 | 0.04 | 0.4290 |
| L DLPFC | 0.09 | 0.2247 | 0.01 | 0.6798 | R DLPFC | 0.05 | 0.3659 | 0.00 | 0.9862 |
| L VTOC | 0.09 | 0.2138 | 0.01 | 0.6345 | R VTOC | 0.07 | 0.2917 | 0.00 | 0.9913 |
| L VWFA | 0.05 | 0.3594 | 0.08 | 0.2461 | R VWFA | 0.03 | 0.4802 | 0.07 | 0.2844 |
| L SMG | 0.01 | 0.7741 | 0.01 | 0.7311 | R SMG | 0.02 | 0.6273 | 0.02 | 0.5849 |
| L AG | 0.03 | 0.4983 | 0.00 | 0.9903 | R AG | 0.15 | 0.1152 | 0.07 | 0.2968 |
| ***$R_{GI}$*** | | | | | | | | | |
| L IPS | 0.11 | 0.1863 | 0.00 | 0.8486 | R IPS | 0.03 | 0.5195 | 0.03 | 0.4820 |
| L HIPP | 0.07 | 0.2866 | 0.02 | 0.5509 | R HIPP | 0.01 | 0.7183 | 0.01 | 0.7698 |
| L DLPFC | 0.07 | 0.3042 | 0.00 | 0.9460 | R DLPFC | 0.11 | 0.1752 | 0.03 | 0.4769 |
| L VTOC | 0.26 | 0.0307 | 0.03 | 0.5010 | R VTOC | 0.00 | 0.8141 | 0.10 | 0.2132 |
| L VWFA | 0.04 | 0.4444 | 0.00 | 0.8855 | R VWFA | 0.10 | 0.2008 | 0.01 | 0.7156 |
| L SMG | 0.13 | 0.1396 | 0.01 | 0.7301 | R SMG | 0.03 | 0.4974 | 0.00 | 0.8224 |
| L AG | 0.05 | 0.3563 | 0.07 | 0.2810 | R AG | 0.04 | 0.4414 | 0.00 | 0.8115 |
| ***$R_{SD}$*** | | | | | | | | | |
| L IPS | 0.06 | 0.3369 | 0.01 | 0.6912 | R IPS | 0.15 | 0.1090 | 0.05 | 0.3709 |
| L HIPP | 0.15 | 0.1165 | 0.01 | 0.6868 | R HIPP | 0.08 | 0.2451 | 0.04 | 0.4159 |
| L DLPFC | 0.01 | 0.7443 | 0.00 | 0.9886 | R DLPFC | 0.15 | 0.1105 | 0.13 | 0.1474 |
| L VTOC | 0.00 | 0.8179 | 0.02 | 0.5908 | R VTOC | 0.07 | 0.2919 | 0.00 | 0.9768 |
| L VWFA | 0.11 | 0.1867 | 0.01 | 0.7767 | R VWFA | 0.01 | 0.6585 | 0.01 | 0.7106 |
| L SMG | 0.04 | 0.4560 | 0.05 | 0.3763 | R SMG | 0.01 | 0.7248 | 0.07 | 0.3068 |
| L AG | 0.00 | 0.9240 | 0.06 | 0.3408 | R AG | 0.01 | 0.7139 | 0.01 | 0.7195 |

$R_{CT}$ = change in cortical thickness; $R_{CF}$ = change in cortical folding regularity; $R_{GI}$ = change in gyrification; $R_{SD}$ = change in sulcus depth; L = left hemisphere; R = right hemisphere; IPS = intraparietal sulcus; HIPP = hippocampus; DLPFC = dorso-lateral prefrontal cortex; VTOC = ventral temporal-occipital cortex; VWFA = visual word form area; SGM = supramarginal gyrus; AG = angular gyrus; $R^2$ = determinant of covariation.