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Genetic and environmental contributions to brain activation during calculation

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ABSTRACT

Twin studies have long suggested a genetic influence on inter-individual variations in mathematical abilities, and candidate genes have been identified by genome-wide association studies. However, the localization of the brain regions under genetic influence during number manipulation is still unexplored. Here we investigated fMRI data from a group of 19 MZ (monozygotic) and 13 DZ (dizygotic) adult twin pairs, scanned during a mental calculation task. We examined both the activation and the degree of functional lateralization in regions of interest (ROIs) centered on the main activated peaks. Heritability was first investigated by comparing the respective MZ and DZ correlations. Then, genetic and environmental contributions were jointly estimated by fitting a ACE model classically used in twin studies. We found that a subset of the activated network was under genetic influence, encompassing the bilateral posterior superior parietal lobules (PSPL), the right intraparietal sulcus (IPS) and a left superior frontal region. An additional region of the left inferior parietal cortex (IPC), whose deactivation correlated with a behavioral calculation score, also presented higher similarity between MZ than between DZ twins, thus offering a plausible physiological basis for the observable inheritance of math scores. Finally, the main impact of the shared environment was found in the lateralization of activation within the intraparietal sulcus. These maps of genetic and environmental contributions provide precise candidate phenotypes for further genetic association analyses, and illuminate how genetics and education shape the development of number processing networks.

Introduction

Mastering the ability to solve mathematical problems, even as simple as addition or subtraction, requires a long period of teaching and training and is reached only through several developmental stages (Butterworth, 2005; Von Aster and Shalev, 2007). Behavioral studies of young infants emphasized the importance of early numerical competences such as approximation, comparison or matching of numerical magnitude that exist prior to education (McCrink and Wynn, 2004; Xu and Spelke, 2000). This initial preverbal system is later refined by education and serves as a starting point for the subsequent acquisition of numerical symbols and emergence of exact calculation (Ansari and Dhital, 2006; Verguts and Fias, 2004). Neuroimaging studies of adults and infants converge to localize this preverbal numerical system within the parietal lobe (Cantlon et al., 2009; Castelli et al., 2006; Dehaene et al., 2003; Piazza et al., 2004; Pinel et al., 2001; Temple and Posner, 1998; Venkatraman et al., 2005). An event-related potential study showed that this parietal representation is present even in newborns (Izard et al., 2009) noticeably in the right hemisphere. These results are coherent with the existence of a core system for numerosities that maybe inherited and shared with other animal species (Cantlon and Brannon, 2007; Nieder and Miller, 2004), and forms a promising context for the search of genetic determinant of numerical skills.

Indeed, several experimental approaches consistently demonstrated the importance of genetic factors in explaining individual variability in arithmetic, both in normal and in pathological ranges. Familial studies of developmental dyscalculia, an impairment in the acquisition of arithmetical skills, showed a high prevalence of this developmental disease among siblings (Alarcón et al., 1997; Shalev et al., 2001). Quantitative genetic studies suggested a heritability estimate ranging from 0.2 to 0.9 (Oliver et al., 2004). These results were recently comforted by a genome-wide association analysis, performed on two distinct samples, which isolated ten genetic polymorphisms that may partially explain variation of individual performance in mathematics (Docherty et al., 2010). However, it is unclear whether this genetic contribution is directly related to the core numerical system or whether it reflects variations in parts of the arithmetical network related to language. Indeed, the same authors reported, based on a large twin study, that two-thirds of the genetic factors that contribute to variation in mathematic also affect reading performance (Plomin and Kovas, 2005).

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No study to date directly explored the localization of the cerebral regions underlying this genetic contribution. The only available data come from clinical populations characterized by genetic anomalies and which also present impairments in numerical abilities. The most documented pathologies are the VeloCardioFacial Syndrome (VCF) caused by a micro-deletion in the chromosome 22q11, the Turner syndrome caused by the deletion of one X chromosome, and the fragile X syndrome, caused by a mutation of the *FMR1* gene. Extensive investigation of VCF patients showed both functional (Eliez et al., 2001) and anatomical (Barnea-Goraly et al., 2005; Eliez et al., 2000) abnormalities in the left parietal region, nearby the supramarginal gyrus. A functional magnetic resonance imaging (fMRI) study of female subjects with fragile X syndrome also demonstrated a correlation between *FMR1* protein expression and activation of the left fronto-parietal network during a mental calculation task, in particular around the supramarginal/angular gyrus region (Rivera et al., 2002). Finally, a neuroimaging study of Turner syndrome showed that patients presented an abnormal recruitment of the bilateral intraparietal sulci (IPS) during exact and approximate calculation task, as well as an abnormal anatomical organization of the right intraparietal sulcus (Molko et al., 2003). All of these studies point to an atypical development of the parietal lobe. However, the severity of these diseases, usually accompanied by other cognitive impairments, does not allow evaluating the specificity of the genetic impact onto numerical cognition. It remains unclear how genetic determinants interact with education at the cerebral level in a typically developed brain.

To shed light on this question we collected behavioral and fMRI data on monozygotic (MZ) and dizygotic (DZ) twin adults performing mental calculation tasks. Because MZ twins share 100% of their genetic polymorphism while DZ twins share only 50%, any greater similarity in MZ compared to DZ should reflect a genetic contribution, given that both MZ and DZ pairs are supposed to share equally similar environments. We then aimed here to separate, within the calculation network, activations under genetic contribution from those under environmental contribution. This mapping should help us to understand if the numerical core system is effectively influenced by genetic factors. We also examined the correlations between individual fMRI activations and behavioral scores in arithmetic, an approach which may help isolate the components of the arithmetical network that contribute to the large heritability reported for mathematical skills. Finally, because it has been hypothesized that learning arithmetical rules is accompanied by the recycling of evolutionary older parietal functions, including the nearby parietal regions involved in eye movements (Knops et al., 2009; Simon et al., 2002), we also collected activations related to saccade to test whether they share any genetic contribution with the arithmetical network.

Material and methods

Subjects

19 pairs of monozygotic (MZ) twins (mean age = 23.2 years old) and 13 pairs of dizygotic (DZ) twins (mean age = 22.3 years old) participated to our study. They were all healthy right handed male adults. Zygosity was determined by genetic analysis of single nucleotide polymorphisms (SNPs) extracted from subjects' saliva (DNA collection kit from DNA Genotek/OG-250, DNA Genotek). DNA was collected in a small volume of 200 μL of TE10:1 and transferred to the French Centre National de Génotypage for genotyping. Samples were genotyped with Illumina Human 1M duo BeadChips. A genetic distance was then evaluated between siblings, allowing a precise identification of MZ and DZ twin pairs.

Behavioral data

Individual performance in arithmetic was assessed using a short timed test. Subject had to perform a series of mental calculations as fast as possible: ten additions, ten subtractions and ten two-digit multiplications with paper and pencil in 5 min. The score ranges from 0 to 1 (rate of calculations correctly performed). We additionally assessed individual reading performance by measuring the time (s) to read aloud as fast as possible a list of 20 pseudowords.

fMRI experimental design

Subjects performed two block-designed sessions of 6 min, each of them comprising two mini-blocks of a subtraction task, two mini-blocks of a control task and two mini-blocks of eye movements. Each mini-block consisted of 3 s of short visual instruction, followed by 9 trials of 2.2 s each. During the subtraction and control tasks, subjects saw a random number [1–9] projected on a video screen for 200 ms. During the subtraction task, they had to subtract this number from a fixed memorized number specified during the instruction period (11, 12, 13 or 14), and to silently name the result. During the control task, they had to silently name the number following the target one in the count sequence (i.e. mentally pronouncing “7” if they saw “6”). This task constitutes a good control in as much as it does not require complex calculation, but uses the same input (digit) and output (covert number naming) as the calculation task, as well as the same need to inhibit naming the target. During the eye movement task, participants saw a target flashed for 400 msec in the visual periphery and had to make a short saccade to it. Eight different positions, equally distributed on a circle, were randomly chosen as targets. To match the control task, a random letter [A–K] was also displayed in the middle of the screen for 200 ms.

Acquisition, preprocessing and analysis of MRI images

Images were acquired on a 1.5 T MRI scanner (General Electric Signa System) in ascending interleaved order (TR = 2400 ms, TE = 30 ms, matrix size = 64 × 64, FOV = 24 cm × 24 cm). Each volume consisted of 36 slices of 3 mm thickness. Anatomical T1 images were acquired with a spatial resolution of 1 × 1 × 1.2 mm. Data were preprocessed using SPM (statistical parametric mapping) software in the Matlab environment according to the following procedure: slice timing, subject motion estimation and correction by realignment, coregistration of the anatomical image to the MNI template, spatial normalization of functional images (resampled voxel size = 3 × 3 × 3 mm) and smoothing (5 mm FWHM). Each voxel time series was fitted with a linear combination of the canonical hemodynamic response function and its temporal derivative. A temporal high pass filter was applied (cutoff 128 s).

Individual images of functional contrasts were generated to determine the brain activation evoked by mental calculation and eye movements relative to the control task. Individual conjunction maps common to the calculation and saccade activations were also created by taking, for each voxel, the minimum value among the considered contrasts (Nichols et al., 2005). Group analysis for activation and conjunction were assessed with random effect analyses (RFX) ($p < 0.05$ after family-wise error correction for multiple comparisons) to isolate the twenty-two peaks of activation considered in this study. In this analysis, the functional images of MZ and DZ subjects were pooled together. The RFX results are thus orthogonal to the genetic analyses (described below) that aimed to detect brain regions with a higher similarity in brain activity between MZ siblings and DZ siblings.

Extraction of peak activation and laterality index

For each peak isolated in the group analysis, individual activation and laterality indices (LI) were computed in regions of interest (ROI). This approach allows extracting individual fMRI data while avoiding confounds due the known influence of genetics on brain anatomy, which is crucial when we want to compare MZ and DZ twin similarities. Our calculation method took into account the inter-individual

variability in response location and also allowed for non-strictly homotopic voxels in the left and right hemispheres. To this end, we searched for active voxels in two spheres (radius = 12 mm) centered on the peak coordinate and its contralateral homolog position, respectively (Pinel and Dehaene, 2009). We eliminated voxels with t-value inferior to 1 or that did not belong to clusters with a minimal extent of 10 voxels, ensuring that LIs were derived from genuine activation sites. We then selected the top 5% of the most activated remaining voxels and averaged their activation, resulting in left (L) and right (R) activation values. We also derived individual peak coordinates as the median of the coordinates of the selected voxels. LI was then computed using the classical formula: $LI = (R - L) / (R + L)$, ranging from −1 (total left lateralization) to +1 (total right lateralization). When no activation was found in both left and right hemispheres, the subject was rejected, as well as his sibling.

We also took advantage of the two-session design to estimate the reliability of these measures, which is crucial when testing for inheritance of a phenotype. For a given peak × task combination, we calculated the intra-subject correlation between the values extracted from runs 1 and 2 across all the subjects. This reliability was reported for the peaks common to the numerical and the eye movement tasks.

Replication using another database

To replicate the observed correlation between the fMRI activation evoked by the calculation task and the behavioral score, we used fMRI data previously collected in our laboratory from hundreds of non-twin subjects {for a complete description, see Pinel et al. (2007)}. Behavioral tests were the same as those used in the present study, and the fMRI contrast refers to the activation evoked by twenty mental subtraction trials compared to silent sentence reading or listening (Pinel et al., 2007). Data from 218 subjects, collected in two 3 T scanners, were considered here.

Genetic analysis

The logic underlying twin studies consists in isolating phenotypes that present a higher level of similarity between MZ siblings than between DZ siblings. Because MZ twins share 100% of their genetic polymorphisms while DZ twins share an average of 50% only, a significant difference in sibling similarity between the MZ and DZ groups points to a genetic effect. Here, we used two methods to evaluate this difference.

For a given phenotype (activation or lateralization index) we first estimated heritability, which represents the proportion of phenotypic variation attributable to genetic variation. We used two classical definitions: $h^2_F = 2\ (ICC_{MZ} - ICC_{DZ})$ (Falconer, 1960) and $h^2_H = (ICC_{MZ} - ICC_{DZ}) / (1 - R_{DZ})$ (Holzinger, 1929), where ICC is the intraclass correlation coefficient within the MZ or in the DZ cohorts. We estimated the probability of achieving this level of heritability by chance through a permutation analysis exchanging zygosity (MZ or DZ) among pairs of twins (1000 permutations).

Heritability could also be estimated more precisely by modeling the relative contributions of genetic and non-genetic factors in a structural equation model. We fitted a univariate ACE model to MZ and DZ covariance matrices. This model decomposes twin-pair similarities into three main latent factors: additive genetic effects (A), shared environmental effects (C), and attributes the remaining variance to both unique environmental effects (E) and measurement errors. Correlation between environmental latent factors equals 1 for MZ and DZ (similar environment). Correlation between genetic latent factors equals 1 for MZ (same genome for MZ twins) and 0.5 for DZ (half of the genes are shared on average). The OpenMx software (http://openmx.psyc.virginia.edu/) was used to estimate variances and covariance of the traits within MZ and DZ pairs, and path estimates with 95% confidence intervals estimated by bootstrap. In what follows, variance components (a^2, c^2 and e^2) computed as the square of path estimates are presented. They represent the proportion of variance accounted for each latent factor. The significance of a, c and e path coefficients was estimated from the fit of ACE models resulting from 500 permutations of zygosity (MZ or DZ) among pairs. It should be noted that, because of our small sample size, our study had a low statistical power to reject the hypotheses $a = 0$ or $c = 0$ in the ACE model. Significance of the contribution of the a and c paths in the model was also estimated using a permutation approach comparing the fits of ACE and CE model (no genetic path), and of ACE and AE models (no common environment path), respectively. After fitting ACE, AE and CE models to 500 permuted data sets, we estimated significance by computing the rank of the real p-values within the corresponding distribution of permuted data. For instance, $p(ACE\ vs\ CE) = 0.01$ means here that for only 1% of permutations a p-value lower than those of the real data was found in the ACE vs CE model comparison. The ACE model fitting was first applied on ROIs' activation and LI, which avoid confounds with MZ anatomical similarity. In a more exploratory approach, we then performed a whole brain analysis considering each voxels of functional images as a phenotype.

In the case of two inheritable traits (X and Y) that are correlated (phenotypic correlation = r_p), fitting a bivariate ACE model allows to estimate the contributions of genetic covariance to the phenotypic correlation (Plomin and DeFries, 1979). In this case, not only the cross-twin within-trait covariance is considered, but also the cross-twin covariance between the two traits. This implies additional path coefficients for the genetic and environmental latent variables between the two traits (i.e. the genetic correlation r_g, defined as the path coefficient from the genetic latent variable of the first trait to the variation of the second trait). A Cholesky decomposition was used for the bivariate ACE model (using scripts available on the OpenMx website (http://openmx.psyc.virginia.edu/)). The amount of phenotypic correlation mediated by genetic factors, referred to as the bivariate heritability (h_B), is then computed as follows: $h_B = r_g \times \sqrt{(h_x \times h_y)} / r_p$, where h_x and h_y are the heritability of trait X and Y, respectively.

Results

Scores from the behavioral calculation task show that MZ and DZ performed equally well on average (mean MZ score = 0.73, standard deviation (sd) = 0.21; mean DZ score = 0.73, sd = 0.21). In agreement with previous behavioral studies using larger numbers of subjects (Kovas et al., 2007b; Loehlin and Nichols, 1976; Oliver et al., 2004; Wadsworth et al., 1995), calculation scores were highly correlated within MZ siblings ($ICC_{MZ} = 0.53$, $p = 0.007$; $ICC_{DZ} = 0.12$, $p > 0.1$), and both estimates of heritability ($h^2_F = 0.83$, $p = 0.15$; $h^2_H = 0.47$, $p = 0.142$) and fits of the ACE model ($a^2 = 0.50$ confidence interval [0, 0.78], $c^2 = 0$ [0, 0.55], $e^2 = 0.5$ [0.21, 0.94]) suggested a preponderant genetic influence, although the comparison model analysis did not reach significance in the permutation analysis ($p(a) = 0.120$). The small size of our twin cohort likely explains this level of significance, but estimates are in the same range as measures of heritability reported in larger groups (Oliver et al., 2004).

To fully explore the respective contributions of genetic and environmental factors over the calculation network, we estimated a, c and e components of the ACE model on twenty two regions of interest centered on the most activated peaks (Table 1). These regions cover a bilateral frontoparietal network classically observed during number processing (Dehaene et al., 2003; Simon et al., 2004). Additional sites were isolated in the thalami, the cerebellum and the inferior temporal gyri. In Table 2 we reported estimates of heritability and ACE model fitting for phenotypes associated with a significant MZ correlation ($p(ICC_{MZ}) < 0.05$) only, which is the minimal requirement for detecting any significant genetic or environmental influence (Table 2.a). Significant genetic contributions were found in the activation of the left and right superior parietal cortex ($p(a) < 0.05$) and of the right intraparietal and left superior parietal cortex ($p(h^2_F)$) and

Table 1
Anatomical localization and MNI coordinates of the main peaks from the calculation network. L.H = left hemisphere R.H = left hemisphere.

Brain area	L.H coordinates			R.H coordinates		
	x	y	z	x	y	z
Intraparietal sulcus	−36	−51	42	42	−42	42
Sup. occipital gyrus	−30	−79	39	33	−60	45
Sup. parietal gyrus	−15	−69	51	12	−69	51
Sup. frontal gyrus	−30	9	60	30	9	57
Precentral gyrus	−51	12	30	48	12	27
Mid. frontal gyrus	−48	33	27	42	36	24
Inf. temporal gyrus	−51	−57	−12	54	−57	−15
Insula	−33	24	3	33	24	0
SMA	−6	21	51	6	21	54
Thalamus	−15	−21	15	15	−12	12
Cerebellum	−33	−72	−30	30	−69	−33

$p(h^2_H) < 0.05$). ICC_{MZ} was not significant for the left middle frontal peak ($p(ICC_{MZ}) = 0.14$) and also above the threshold for the left precentral peak ($p(ICC_{MZ}) = 0.082$).

For the lateralization of activation (Table 2.b), a highly significant contribution of shared environment was found for the intraparietal cortex LI ($p(c) < 0.05$) as well as a significant contribution of genetics for the middle frontal cortex LI ($p(h^2_F)$ and $p(h^2_H) < 0.05$).

In a more exploratory approach, we estimated the a, c and e components of the ACE model over each voxel of the entire brain. Fig. 1 shows the voxels associated with a significant A or C component (i.e. 95% confidence interval with a lower bound >0). In broad agreement with the above ROI analysis, large areas with a significant genetic component were found posteriorly in the left superior parietal cortex and angular gyrus, right superior parietal cortex, right precuneus and right thalamus. Other small clusters can be seen. Among them, two small regions were also isolated bilaterally in the superior frontal lobe. For the shared environment a restricted number of small regions were found bilaterally in the middle occipital gyri and in the left inferior temporal and inferior frontal gyri (pars triangularis). When comparing with the activation map of the calculation task (Fig. 1), it can be seen that all of these clusters correspond to the activated areas except in the left angular gyrus and precuneus.

The frontoparietal number processing network showing a significant genetic contribution in this voxel-based ACE model includes regions that resemble those sustaining eye movements, in particular the frontal eye fields (FEF) and lateral intraparietal area (LIP). We therefore wondered whether the genetic contribution to the activation evoked by an arithmetical task also affected the activation evoked by the non-numerical saccade task. First, to test whether the same frontoparietal voxels involved in the numerical task were also involved in the saccade task, we performed a RFX analysis on individual conjunction maps between saccade and calculation contrasts. We found a small network of five areas common to both tasks ($p < 0.05$ corrected for multiple comparisons) (Fig. 2). We further investigated the similarity between these two functional networks using a multi-voxel correlation analysis (Peelen et al., 2006). For each subject, we correlated activations for the number and the saccade tasks across voxels belonging to a small sphere centered on a given peak (radius = 3 voxels, ROI = 93 voxels) and we report the averaged correlation across participants. This method should assess whether any overlap across these two conditions is due to smoothing and anatomical proximity of their correlates or if it really reflects similar patterns of activation at the voxel level (averaged correlation significantly different from zero). Pattern of activation was highly correlated in the left (coefficient of correlation $r = 0.21$, $p = 10^{-5}$) and right ($r = 0.33$, $p = 10^{-10}$) superior frontal cortex, the right intraparietal region ($r = 0.24$, $p = 3.10^{-7}$) and left superior parietal cortex ($r = 0.24$, $p = 6.10^{-8}$). Only in the right superior parietal cortex did the correlation fail to reach significance ($r = 3.10^{-3}$, $p = 0.32$), suggesting that different voxels are recruited by the numerical and saccade task in this area.

Then, for the five peaks of this sub-network, we performed a ROI analysis of the genetic and environmental contribution to the activation evoked by the calculation and the saccade tasks, respectively. A significant genetic contribution was found during the calculation task in the left and right superior occipital, the left superior frontal

Table 2
Genetic and environmental contribution to the peaks of the calculation network. (a) Analysis of activation during the arithmetic task relative to control. For each ROI, we report the intraclass coefficient of correlation for MZ (ICC_{MZ}) and DZ (ICC_{MZ}), Falconer (h^2_F) and Holzinger (h^2_H) heritability, a^2, c^2 and e^2 estimates of the ACE model (A = additive genetic influence; C = shared environmental influence; E = nonshared environmental influence) and p-value of model comparisons (ACE versus CE model, ACE versus AE model) (b) Same analysis for the lateralization index. Bold values highlight p-values that passed the 0.05 threshold.

	ICC_{MZ}	ICC_{DZ}	h^2_F	h^2_H	a^2	c^2	e^2	ACE vs CE	ACE vs AE
Activation									
L sup. occipital	0.45	0.16	0.57	0.34	20%	18%	62%	p = 0.406	p = 0.688
			p = 0.138	p = 0.14	p = 0.382	p = 0.648	p = 0.558		
L sup. parietal	0.45	0.08	0.72	0.40	**64%**	0%	36%	**p = 0.008**	p = 0.654
			p = 0.252	p = 0.256	**p = 0.002**	p = 0.656	p = 0.998		
L sup. frontal	0.37	−0.312	**1.36**	**0.52**	27%	0%	73%	p = 0.212	p = 0.626
			p = 0.004	**p = 0.01**	p = 0.352	p = 0.628	p = 0.616		
R intraparietal	0.50	−0.08	**1.15**	**0.53**	43%	0%	57%	p = 0.106	p = 0.796
			p = 0.036	**p = 0.042**	p = 0.162	p = 0.800	p = 0.824		
R sup. occipital	0.69	0.45	0.50	0.45	9%	53%	38%	p = 0.378	p = 0.766
			p = 0.144	p = 0.140	p = 0.374	p = 0.634	p = 0.602		
R sup. parietal	0.70	0.13	**1.14**	**0.66**	**76%**	0%	24%	**p = 0.010**	p = 0.742
			p = 0.060	**p = 0.052**	**p = 0.024**	p = 0.742	p = 0.976		
R insula	0.44	0.14	0.61	0.36	16%	14%	70%	0.448	0.588
			p = 0.238	p = 0.244	p = 0.440	p = 0.572	p = 0.542		
R SMA	0.40	−0.12	1.03	0.46	25%	0%	75%	0.260	0.260
			p = 0.096	p = 0.114	p = 0.348	p = 0.624	p = 0.624		
R thalamus	0.42	−0.15	1.12	0.49	33%	0%	67%	0.186	0.644
			p = 0.132	p = 0.176	p = 0.258	p = 0.648	p = 0.716		
Lateralisation index									
Intraparietal	0.50	0.54	−0.08	−0.09	0%	**51%**	**49%**	0.474	0.346
			p > 0.1	p > 0.1	p = 0.478	**p < 0.0001**	**p < 0.0001**		
Sup. parietal	0.48	0.24	0.48	0.32	11%	31%	31%	0.396	0.670
			p > 0.1	p > 0.1	p = 0.392	p = 0.616	p = 0.616		
Mid. frontal	0.39	−0.32	**1.41**	**0.53**	25%	0%	75%	**0.044**	0.624
			p = 0.026	**p = 0.036**	p = 0.136	p = 0.624	p = 0.858		

and the right intraparietal cortex (see Fig. 2). On the other hand, we only found a trend toward a significant genetic component restricted to the activation in left superior frontal area ($p(a) = 0.068$) for the saccade task. One possibility is that the design of our eye task made it less demanding than the numerical task and was not reliable enough to allow us to capture any familial effect. However, activations during the two task were similar in three of the five ROIs ($p > 0.05$) and were higher for saccades in the left ($p = 0.001$) and the right ($p = 4.10^{-6}$) superior occipital cortex. Similarly, reliabilities of the activation measurements were comparable between the two tasks, even slightly higher for the eye movement task. They ranged from 0.47 to 0.65 for the eye movement task (average reliability = 0.54 across the five ROIs), and from 0.34 to 0.51 for the calculation task (average reliability = 0.43).

Because the multi-voxel correlation analysis showed that the same voxels were activated by the two tasks in this region, we tested to what extent they shared genetic determinants. Phenotypic correlation between averaged activation for the calculation and the eye movement tasks in the superior frontal cortex ($r_p = 0.41$) and fit of the bivariate ACE model suggests a modest genetic correlation $r_g = 0.11$. Considering the heritability of this frontal site in the numerical ($a^2 = 0.40$ see Fig. 2) and in the eye movement tasks ($a^2 = 0.31$), we could compute the bivariate heritability $h_B = 0.11 \times \sqrt{(0.40 \times 0.31)} / 0.41 = 0.09$. In other words, only 9% of the genetic contribution is shared between activation evoked by the two conditions.

To understand how genetic contributions to the calculation network may contribute to the behavioral mathematical score, we first isolated voxels whose activation correlates with behavioral calculation scores.

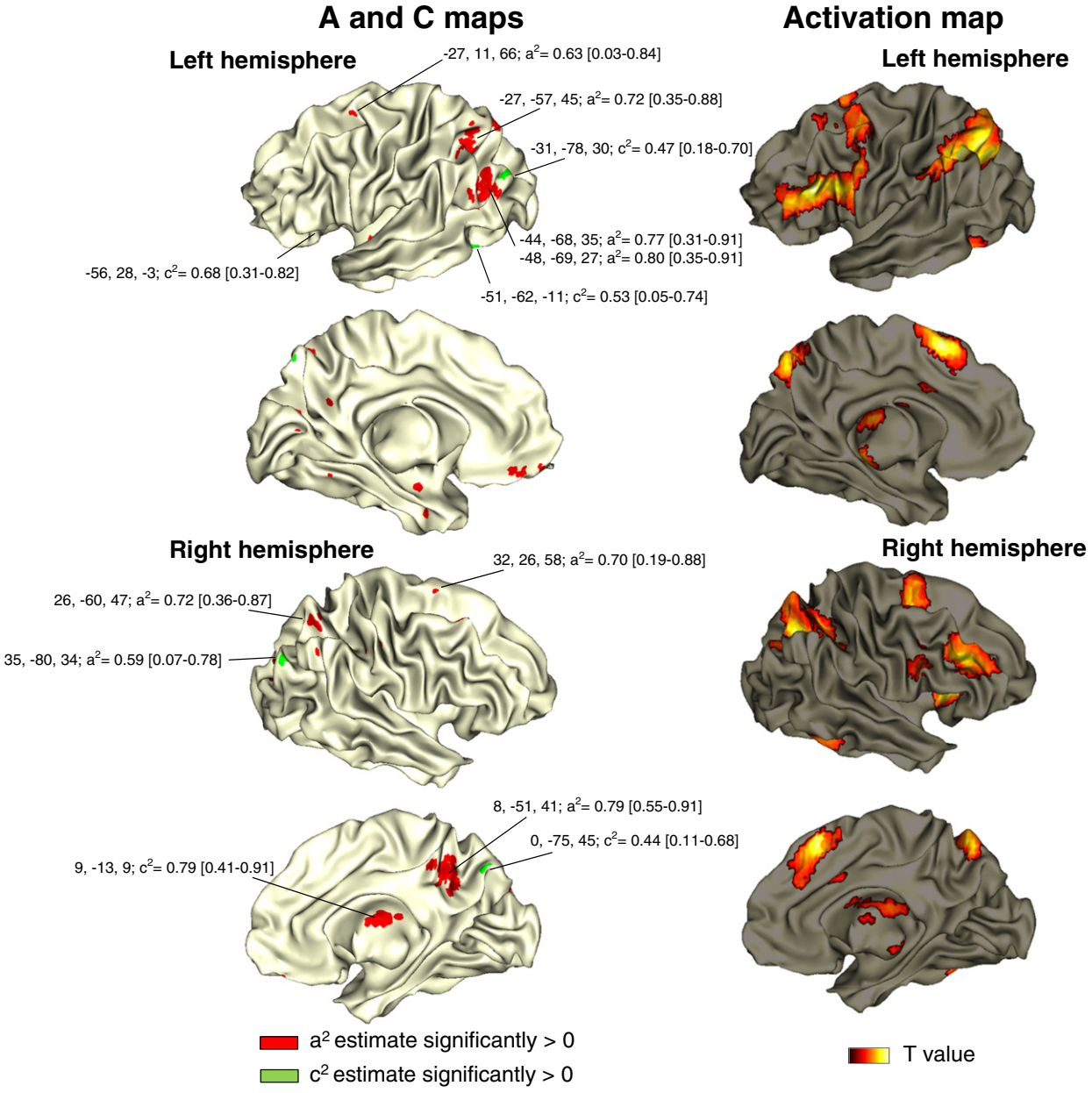
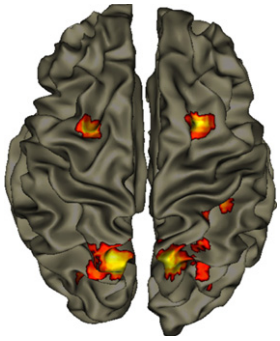


Fig. 1. Genetic (A) and environment (C) dependent aspects of brain activation during arithmetic. The left column shows brain areas associated with a significant positive A (in red) or C estimate (in green) after fitting an ACE model to brain activation data during simple arithmetic (A = additive genetic influence; C = shared environmental influence). The significant regions are shown on an inflated surface of the gray-white matter boundary. For reference, the right column shows the set of areas activated during the calculation task versus the control task (voxelwise $p < 0.05$, FWE corrected).

Saccade / Calculation Conjunction map



	Calculation > Control task							Saccade > Control task						
	h^2_F	h^2_H	a^2	c^2	e^2	ACE vs CE	ACE vs AE	h^2_F	h^2_H	a^2	c^2	e^2	ACE vs CE	ACE vs AE
L sup. occipital	0.73 p=0.25	0.40 p=0.256	**64% p=0.002**	0% p=0.656	36% p=0.998	**0.008**	0.654	-	-	-	-	-	-	-
L sup. frontal	**1.77 p<10-4**	**0.65 p=0.002**	40% p=0.168	0% p=0.760	60% p=0.778	**0.058**	0.752	1.152 p=0.120	0.50 p=0.114	**31% p=0.068**	0% p=0.594	69% p=0.93	**0.068**	0.592
R sup. occipital	**1.36 p=0.026**	**0.71 p=0.024**	**74% p=0.030**	0 % p=0.786	26% p=0.970	**0.026**	0.786	-	-	-	-	-	-	-
R sup. frontal	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R intraparietal	**1.625 p=0.002**	**0.67 p=0.004**	**54% p=0.048**	0% p=0.858	0.46 p=0.950	**0.024**	0.856	-	-	-	-	-	-	-

Fig. 2. Evaluation of genetic effects within the set of areas shared by calculation and eye movement tasks. The brain image at left shows a group analysis of the intra-individual conjunction of activations during calculation and eye movement tasks (voxelwise $p < 0.05$, FWE corrected). For each peak with a significant MZ correlation ($p < 0.05$), the table shows Falconer (h^2_F) and Holzinger (h^2_H) heritability, a, c and e estimates of the ACE model (A = additive genetic influence; C = shared environmental influence; E = nonshared environmental influence) and the p-value of model comparisons (ACE versus CE model, ACE versus AE model).

We applied a SPM regression analysis to individual calculation maps, using each individual's behavioral calculation score as regressors, but also age and reading score in order to control for other non-numerical effects. A positive correlation with the calculation score was significant in a single cluster of the left angular gyrus (MNI peak coordinates $x = -66, y = -54, z = 24$; $t_{60} = 3.78$) (Fig. 3a), a region essentially deactivated during the calculation task (no negative correlation was found at this threshold). In other words, subjects with a better arithmetic score show less deactivation of their left angular gyrus during the calculation task. The strength of the correlation was moderate, surviving only a correction for cluster size (cluster size 232 voxels, corrected p-value = 0.011 at the voxelwise threshold of $p < 0.01$). However it was replicated in a similar region in the analysis of an independent database of non-twin subjects (peak −57, 48, 39; $t_{213} = 3.64$) (Fig. 3b). Interestingly, this cluster partially overlaps with the site previously found in the left angular gyrus which exhibited a significant genetic contribution. Because the behavioral calculation score was also partially inherited, we predicted that the activation of a given MZ subject in this area should partially explain the mathematical performance of his brother. When we thus crossed the phenotypes of MZ siblings, i.e. correlating each subjects' individual score with the activation map of their sibling, we actually found a significant correlation in the left angular region (cluster size 120 voxels, voxel $p < 0.05$; peak −48, −63, 27; $t_{34} = 3.39$). No correlation was found when we applied this analysis to DZ siblings. These correlations are detailed at the group peak of correlation (coordinates −66, 54, 24) in Fig. 3b ($r_{MZ} = 0.42$, $p = 0.009$; $r_{DZ} = -0.21$, $p = 0.29$). These results suggest that the link between the angular gyrus and the calculation score is genetically mediated.

Discussion

Comparing the functional correlation in the brain activation of MZ and DZ twins during a subtraction task, we decomposed the cerebral network activated during mental arithmetic into regions showing either a genetic or an environmental contribution. Although the activity evoked by the subtraction task covers a large set of cortical and subcortical areas, functional similarity in brain activation between twins was essentially restricted to the posterior part of the parietal lobe, while no correlation was found within the inferior and middle frontal cortex.

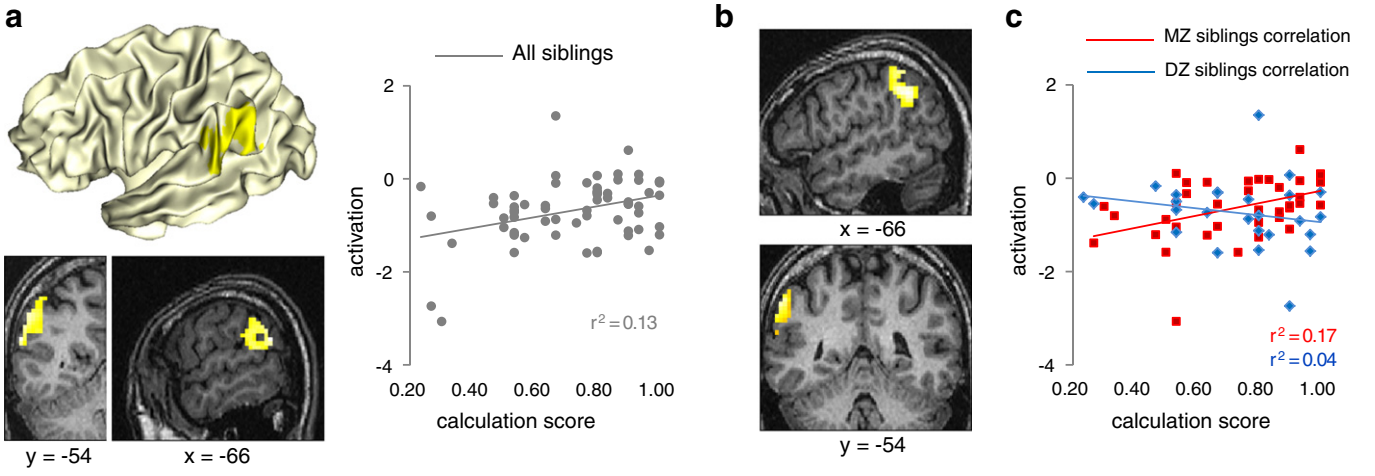


Fig. 3. Correlation between activation maps and calculation scores. (a) The yellow cluster shows voxels whose activation level in the calculation contrast correlates with the arithmetic score in the whole group of subjects ($p < 0.01$ uncorrected, corrected for cluster extent at $p < 0.05$). The significant voxels are projected on an inflated surface of the gray-white matter boundary (up) and on coronal and sagittal slices (down). Right, scatter plot of activation at the peak of correlation (−66, 54, 24) and the behavioral arithmetic score. (b) Replication of this correlation analysis on another independent database of 218 non-twin subjects. (c) Scatter plot of activation level and arithmetic score within MZ twin pairs (in red) and within DZ twin pairs (in bleu) at the peak of correlation (−66, 54, 24). In this plot, each individual twin activation value is correlated with the behavioral score of the corresponding sibling.

Three distinct subsystems could be isolated in the parietal cortex, as summarized in Fig. 4. First, a subpart of the parietal network, restricted to the bilateral PSPL and to the right IPS, exhibited a significant genetic contribution. Second, the functional asymmetry of the IPS was characterized by a strong contribution of the shared environment. Finally, the level of deactivation within the left IPC showed a significant genetic contribution and correlated with individual performance in arithmetic. Interestingly, this genetic/environmental dissection of the parietal circuit sustaining a calculation task tightly mirrors a functional decomposition proposed ten years ago (Dehaene et al., 2003). Using a meta-analysis of numerical tasks, Dehaene et al. (2003) isolated three distinct parietal circuits: the bilateral horizontal segment of the IPS, likely supporting core number processing in any format, the bilateral PSPL, shared with manipulations of other spatial dimensions, and the left IPC (in the angular gyrus) supporting the manipulation of number in a verbal form (phonological memory, arithmetical facts). Our results illustrate how each of these regions is constrained by a distinct set of genetic or environmental factors, thus shedding light on the development of the brain mechanisms of numerical cognition.

Distinct genetic and environmental influences on the IPS

The left and right IPS have been reported to host an amodal representation of number (Castelli et al., 2006; Dehaene et al., 2003; Feigenson et al., 2004; Piazza et al., 2004; Pinel et al., 2001). They are typically recruited bilaterally in various types of symbolic and non-symbolic numerical tasks in adults and children (Ansari et al., 2005; Cantlon et al., 2009). However, fMRI studies of children during arithmetic suggest that the right IPS may be particularly recruited early on (Cantlon et al., 2006). Furthermore, an event-related potential study of 3 months-old infants (Izard et al., 2008) and a functional near-infrared spectroscopy study of 6 months-old infants (Hyde et al., 2010) showed that only the right IPS reacts to a change in numerosity. Altogether, these results suggest that the right IPS may correspond to the innate numerical core system already functional in newborns (Izard et al., 2009) or young children (Xu and Spelke, 2000). Our results reinforce this view, showing that the right IPS is not fundamentally altered by education, and that its activation level essentially depends on genetic determinants. The presence of an asymmetric genetic impact in this region mirrors the existence of an atypical structure precisely located in the right intraparietal sulcus in people suffering of a genetic disease such as Turner syndrome patients (Molko et al., 2003), who often present impairments in their non-verbal processing of quantities, for instance during numerical estimation tasks (Bruandet et al., 2004). All these results point to a structural and functional development of a quantity representation in the right IPS, occurring early in life and under genetic control, prior to any formal education or experience with symbolic numbers.

Conversely, no familial factor was found to alter the activation level of the left IPS. However, after normalization by the computation of a lateralization index, we found that the environment shared by twins significantly impacted on the hemispheric asymmetry of IPS activation during the calculation task. While the importance of the left/right balance for cognitive function is still not well understood, several asymmetric properties of the numerical IPS have been previously reported and may be related to our result. For instance, the coding of numerosity exhibits asymmetrical characteristics. Using an adaptation paradigm with both sets of dots and Arabic numerals, Piazza and collaborator reported an asymmetrical cross-notation priming in the left IPS (Piazza et al., 2007). They interpreted this result as indicating a more pronounced refinement of the neuronal coding of quantities in the left IPS after exposition to numerical symbols. Such a partial specialization of the left IPS for the coding of symbolic number has been recently replicated in another adaptation study (Notebaert et al., 2012). The left and right IPS also seem to follow different developmental trajectories. The comparison of fMRI activation in children and adults performing a comparison task showed a developmental change at a restricted site of the left IPS (Ansari and Dhital, 2006). Moreover, this degree of maturation of symbolic processing in the left IPS has been reported to be directly correlated with children's arithmetic competence at school (Bugden et al., 2012). On the opposite, the right IPS seems to be less affected by learning and education. A recent decoding study of a numerical task (Damarla and Just, 2012) found that the patterns of activation evoked by non-symbolic numbers in bilateral IPS successfully allowed for generalization across subjects, while the patterns evoked by Arabic numbers, mostly supported by the left IPS, did not afford such a generalization across subjects, but were subject-dependent. We may thus hypothesize, in agreement with the present data, that this right IPS representation of number is more stable across life and is predominantly shaped by genetic factors even in adult subjects.

Changes in the left IPS during calculation seem to occur in coordination with the nearby posterior temporal region. An fMRI study of young subjects whose age ranged from 8 to 20 years showed a continuous increase in activation of the left IPS and superior temporal regions during a calculation task, while activation in frontal areas simultaneously decreased (Rivera et al., 2005). In adults, a correlation

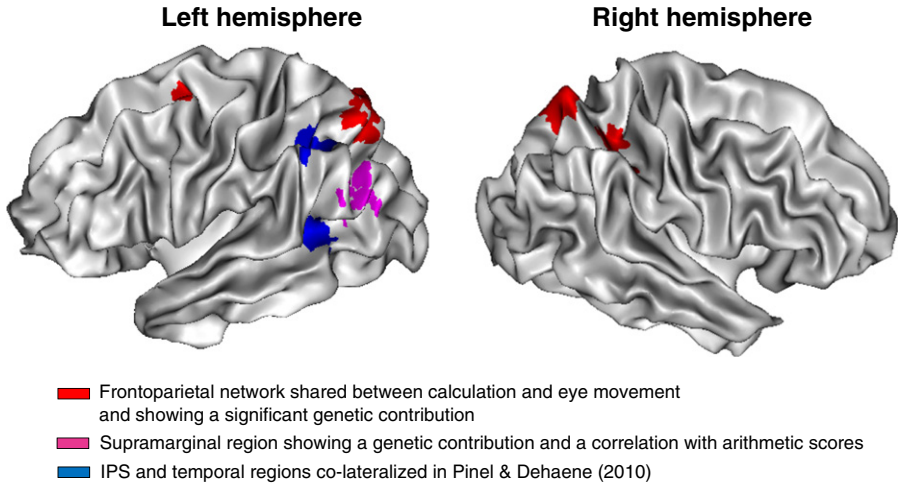


Fig. 4. Summary of genetic, environmental and functional influences in parietal areas for calculation. Red voxels: frontoparietal network for calculation showing a genetic contribution in the present study and shared with the eye movement task. Purple: the angular gyrus, deactivated during the calculation task but showing both a genetic contribution and a correlation with the behavioral arithmetic score in the present study. Blue: the left IPS region which was previously found to co-lateralize with a STS site (also in blue) activated during a reading task (Pinel and Dehaene, 2009), and whose lateralization appeared to be mostly determined by shared environmental factors in the present study.

was also found between the hemispheric asymmetry in IPS activation during a calculation task and the asymmetry in temporal activation during sentence reading in adult subjects (Pinel and Dehaene, 2009). These two co-lateralized areas are depicted in blue in Fig. 4. Such a co-lateralization may reflect the trace of a distant influence of the superior temporal organization onto the development of the numerical IPS: number words encoded within the language areas of the left superior posterior temporal cortex would interact with quantities encoded within the left intraparietal areas, leading to pronounced developmental change within this number-related region. Our present results suggest that this change occurs during the long period where both MZ and DZ twins typically share a similar environment, including schooling and familial exposure to number and symbols as main determinants.

Cortical correlates of eye movements and calculation

In addition to the right IPS, a large frontoparietal network active during calculation was found to be under strong genetic control (Fig. 4, in red). This set of brain regions comprised a left superior frontal area and two bilateral parietal regions in the PSPL, at locations overlapping with the putative human homologs of areas FEF and LIP, respectively (Colby et al., 1996; Hubbard et al., 2005; Simon et al., 2004). The coexistence of spatial and numerical functions in posterior parietal areas has been recently demonstrated in an fMRI study (Knops et al., 2009). This study showed that the knowledge of the activation pattern of these regions in response to left and right eye movements enabled to classify the activation during, subtraction and addition. This finding indicates that eye movements and arithmetic mechanisms are deeply intermixed, thus providing a hypothetical mechanism for the numerous associations that exist between number and space (Hubbard et al., 2005).

Surprisingly, we observed a low heritability of activation during eye movements, at the very same sites that showed high heritability during arithmetic. As detailed in the results, eye movement and numerical tasks activated overlapping frontoparietal areas, with similar levels of activation and similar intra-individual reliability — yet only the numerical task exhibited a strong genetic contribution. How can this surprising result be interpreted? In the context of the neuronal recycling hypothesis, it has been proposed that the development of mental calculation makes uses of a prior and phylogenetically older parietal function for coordinate transformations (Dehaene and Cohen, 2007). This model may thus explain why arithmetic with Arabic digits, a learned function which depends on education, may still show a high heritability. Furthermore, school-based calculation skills are founded upon a more basic competence for approximation (Gilmore et al., 2007, 2010) which appears much earlier in life, possibly based on innate mechanisms. Young infants, within the first year of life, already possess the ability to add and subtract small (Wynn, 1992) and large numbers (McCrink and Wynn, 2004). Future neuroimaging studies should investigate whether such cerebral mechanisms are already supported by PSPL and superior frontal regions in the first months of life. Interestingly, number knowledge and arithmetic may develop without any visual input, as is the case in congenitally blind people (Castronovo and Seron, 2007), and this capacity again relies on the usual parietal areas (Szűcs and Csépe, 2005), further strengthening the possibility that arithmetic systematically recruits a heritable and evolutionarily determined cerebral system.

However, the lack of heritability of the eye movement network remains surprising. While this is only a null result, and should be replicated with in a large group of twins, the importance of individual experience in reshaping activation related to eye movement fits with the slow maturation of saccadic eye movement mechanisms (Johnson, 1990; Munoz et al., 1998), as well as their prolonged plasticity. Indeed, recent research shows, for instance, that the left-right reversal of visual inputs by a prism, in adult subjects, induces a shift of contralateral visuomotor regions of the posterior parietal cortex toward ipsilateral locations (Brewer et al., 2012).

All in all, our data suggest that calculation skills are founded upon computational mechanisms and brain structures also used by eye movements in adult subjects, but that eye movement and calculation develop under the influence of quite different determinants. The absence of any shared genetic influence in the parietal cortex raises the question of whether these mechanisms are initially intermixed or, alternatively, converge only under the specific constraints imposed by culture and education. At this point, the present research cannot resolve this issue.

Genetic and cortical origins of inter-individual variability in calculation performance

In our data, variability in arithmetic scores was correlated with the level of deactivation in the left angular cortex: in two separate cohorts, a better score in arithmetic was associated with a lesser deactivation in this site. Furthermore, we found that both behavioral measures and the amount of brain activation during arithmetic at this cortical site (in purple, Fig. 4) exhibited a genetic contribution in the twin study. Involvement of this area in individual arithmetic skills was previously reported in an fMRI comparison of high and low performers during the verification of arithmetical problems, where higher levels of activations in the angular gyrus were associated to a better score, while the lower math group was characterized by deactivation of this area (Grabner et al., 2007). A deactivation of the angular gyrus in arithmetical task has been repeatedly reported in the literature (Dehaene et al., 1996; Grabner et al., 2007; Ischebeck et al., 2006; Rickard et al., 2000; Venkatraman et al., 2006; Zago et al., 2001), although this pattern remains ill understood. Deactivation in the angular gyrus has been first interpreted as a suppression of the default mode network during more demanding tasks (Zago et al., 2001), although a recent fMRI study challenged this view (Grabner et al., 2011). Considering the tripartite model of the parietal cortex in numerical cognition (Dehaene et al., 2003), involvement of the left inferior parietal cortex is assumed to be related to a verbal representation, and was recently associated to the learned mapping between arithmetic problems and their solution (Grabner et al., 2011). Indeed, extensive training on complex calculation problems progressively shifts the pattern of activation during arithmetic from the superior parietal cortex to the left angular gyrus (Delazer et al., 2003), at a location very close to the site we found associated with the arithmetic score. Recruitment of this area could be then interpreted as reflecting an increasing reliance on the retrieval and use of verbal facts (Grabner et al., 2009; Ischebeck et al., 2009), a strategy that progressively tends to replace the effective manipulation of quantities typically associated with intraparietal activation. On the contrary, people with a low calculation score rely more on parietal resources, thus disengaging the left angular gyrus.

It remains to be explained, however, why we observed a direct correlation between arithmetic performance and activation in the angular gyrus, but not the intraparietal sulcus. Indeed, the subtraction task also requires decomposition and manipulation of numerical quantities. Compared to multiplication, which essentially involves access to rote memory, subtraction strongly activates the intraparietal sulci (Chochon et al., 1999). Moreover, the intraparietal sulci have been reported to support number acuity, as measured by the Weber fraction in discrimination or comparison tasks with non-symbolic numerosities (Piazza et al., 2004; Piazza et al., 2007), a variable which correlates with math achievement in children (Halberda et al., 2008; Piazza et al., 2010) and adults (Gilmore et al., 2007, 2010; Piazza et al., in press). We suggest that the lack of IPS-behavior correlation in our sample may reflect the particularly behavioral score collected in our sample, which provides only a partial measure of arithmetical skills. The score we used mostly reflects the efficiency

to compute two digit additions, subtractions and complex multiplications, and is likely to rely on subjects' ability to decompose problems into easier ones and to automatically retrieve the associated results in verbal memory. Note also that we could not control for IQ or working memory skills, which were not measured. These measures may also partially explain our correlation, although this seems unlikely given that the neuroimaging literature essentially reports associations of these measures with the prefrontal cortex (Cole et al., 2012; Thompson et al., 2001).

In brief, the limited time that we had to characterize our subjects' numerical, intelligence and working memory skills, as well as the particular subtraction task that we used in our fMRI paradigm, may have prevented us from testing directly the existence of a link between genetic variability and non-verbal numerical performance within superior parietal cortex. This problem is not unique to the present study: basic numerical competences that rely solely on pure non-verbal "number sense" have not been typically investigated in previous twin studies in which the authors used composite scores based on symbolic calculation, problem solving, counting, teachers' reports, etc. (Loehlin and Nichols, 1976; Oliver et al., 2004; Wadsworth et al., 1995). To address this issue, further twins studies will be needed, specifically using numerical comparison or priming to characterize the cortical representation of quantity more directly (Piazza et al., 2007).

However, the observation of a genetic contribution to the activation in the angular gyrus is compatible with the previous reports of a high degree of inheritance of anatomical structures in this area. First, Thompson and collaborators found that gray matter density was more similar in MZ than in DZ twins in perisylvian and associative cortices, noticeably in the left-hemispheric region spreading from Wernicke's area up to the temporo-parietal junction (Thompson et al., 2001). More recently, an ACE analysis of cortical thickness collected in a large cohort of twins showed that the left supramarginal gyrus region was one of the most inheritable structure of the brain (Schmitt et al., 2008), while its right-hemispheric homolog only presents weak familial effects. Interestingly, a principal component analysis applied to the genetic correlation between all the considered regions revealed that the left supramarginal and angular regions share common genetic factors, which were not shared with superior parietal lobe. The involvement of this cortical region in the acquisition of arithmetical knowledge is thus likely to contribute to the presence of a strong genetic influence on individual arithmetic scores, especially when these scores evaluate, at least in part, verbal strategies or retrieval. Importantly, the existence of a shared region linking mathematical and verbal skills may explain why mathematical and reading abilities may share as much as two-thirds of their genetic determinants (Kovas et al., 2005; Kovas et al., 2007b).

Heterogeneity in developmental mathematical disabilities

The observation of genetic contributions at two different cortical sites plausibly associated with distinct formats of representation (a verbal format in the left angular gyrus, and a quantity or spatial format in posterior parietal cortex) may be relevant to the quest for genetic determinants of developmental dyscalculia. Dyscalculia is known to run in families, and to be associated with specific genetic diseases such as VeloCardioFacial Syndrome, Turner's syndrome and fragile X (Bruandet et al., 2004; De Smedt et al., 2007; Mazzocco and McCloskey, 2005), suggesting that it can be partially genetically determined. Furthermore, it presents a significant amount of comorbidity with both reading disabilities (dyslexia) (Barbaresi et al., 2005; Dirks et al., 2008) and with attention deficit hyperactivity disorder (ADHD) (Capano et al., 2008; Kaufmann and Nuerk, 2008). One may hypothesize that these two distinct comorbidities reflect distinct genetic disruptions, possibly related to the two cortical regions found heritable in the present study, thus raising the possibility of heterogeneity in the population of dyscalculic children.

Indeed, more detailed analyses suggest that pure dyscalculic children (without any associated impairments) may differ from other dyscalculics in the nature of their underlying cortical impairment. Dyscalculic children with an associated dyslexia perform worse in an exact calculation task (Hanich et al., 2001) and present a lower arithmetic performance compared to children suffering from a pure arithmetic impairment only (Jordon et al., 2002). Additive effects for cognitive deficits were also reported in children suffering from both dyslexia and mathematical disabilities (Landerl et al., 2009). Considering our results, mathematical disabilities associated to dyslexia may be tentatively explained by a dysfunction restricted to the left angular region and due to a particular genetic polymorphism. On the other hand, several brain imaging studies have suggested that dyscalculia in its pure form or in relation to ADHD (Vance et al., 2007) may originate from a parietal dysfunction affecting more specifically the non-verbal representation of numbers (Isaacs et al., 2001; Molko et al., 2003; Mussolin et al., 2010; Price et al., 2007). Whether distinct sets of genetic factors may cause developmental dyscalculia is still an unsolved issue (Plomin et al., 2007). However, the activation of two functional areas reported here to be under genetic control, associated with visuospatial processing in the superior parietal lobe on the one hand and to the calculation score in the left posterior perisylvian area on the other hand, provides interesting candidate phenotypes to test this hypothesis in future fMRI/genetic association studies.

According to our results, it appears that the intense middle frontal and precentral activations during calculation are free of any genetic effects and only depend on the individual environment (see Fig. 1). While this result is plausible, given that these regions are likely to be associated with late-developing, individually variable executive strategies, we note that a possible limitation of our study is that we only explored activation in mature adult brains. Indeed frontal activations have been reported as important during arithmetic learning (Ansari et al., 2005; Rivera et al., 2005) or when adults face new, untrained problems (Ischebeck et al., 2009). The prefrontal lobe is known to support a variety of generic cognitive functions required in executive control, conflict monitoring, working memory or problem solving (Duncan and Owen, 2000) that are also influenced by genetics (Egan et al., 2001; Meyer-Lindenberg et al., 2005; Thompson et al., 2001; Winterer and Goldman, 2003). We cannot therefore exclude that genetic factors would modulate the deployment of frontal mechanisms during the early stages of arithmetic learning, or using a less familiar task. For instance, in a demanding task, the N-back memory task, a twins cohort study of similar size than ours identified no genetic effect in the left angular gyrus, but observed one in the left middle frontal gyrus (Blokland et al., 2008). Additionally, a longitudinal study including thousands of twin pairs reports that about half of the genetic determinants for mathematical performance at 7 years of age are shared at 9 and 10 years of age, leaving the other half under the influence of non-shared genes (Kovas et al., 2007a). While estimates of heritability were comparable across these three ages (from 57 up to 66%), the genetic origin of this effect partially changed with age. An fMRI study similar to ours, but performed in children, would therefore be needed to determine how the genetic maps may change during arithmetic learning.

Conclusion

In conclusion, our results show that genetic determinants and shared environment have distinct and complementary impacts on the cerebral circuits for arithmetic. Both a superior frontoparietal set of areas, which also support eye movements, and the left angular gyrus, are subject to a genetic contribution. Meanwhile, the shared environment (most likely including education practices) primarily affects the functional lateralization of activation in the intraparietal sulcus. Future experiments, capitalizing on the possibility of using fMRI in young children (Ansari et al., 2005) should further specify how initial organization

and effects of education interact to generate the specialized parietal areas that we observed here in adults.

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Conflict of interest

There is no conflict of interest.

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