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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