

Beyond Hemispheric Dominance: Brain Regions Underlying the Joint Lateralization of Language and Arithmetic to the Left Hemisphere

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Abstract

Language and arithmetic are both lateralized to the left hemisphere in the majority of right-handed adults. Yet, does this similar lateralization reflect a single overall constraint of brain organization, such as an overall “dominance” of the left hemisphere for all linguistic and symbolic operations? Is it related to the lateralization of specific cerebral subregions? Or is it merely coincidental? To shed light on this issue, we performed a “colateralization analysis” over 209 healthy subjects: We investigated whether normal variations in the degree of left hemispheric asymmetry in areas involved in sentence listening and reading are mirrored in the asymmetry of areas involved in mental arithmetic. Within the language network, a region-of-interest analysis disclosed partially dissociated patterns of lateralization, inconsistent with an overall “domi-

nance” model. Only two of these areas presented a lateralization during sentence listening and reading which correlated strongly with the lateralization of two regions active during calculation. Specifically, the profile of asymmetry in the posterior superior temporal sulcus during sentence processing covaried with the asymmetry of calculation-induced activation in the intraparietal sulcus, and a similar colateralization linked the middle frontal gyrus with the superior posterior parietal lobule. Given recent neuroimaging results suggesting a late emergence of hemispheric asymmetries for symbolic arithmetic during childhood, we speculate that these colateralizations might constitute developmental traces of how the acquisition of linguistic symbols affects the cerebral organization of the arithmetic network. ■

INTRODUCTION

Strong left hemispheric asymmetry is a striking characteristic of the cerebral regions involved in language processing, both at the functional and at the anatomical level, noticeably around the peri-sylvian and temporal structures (Toga & Thompson, 2003; Geschwind & Levitsky, 1968). The left hemisphere also plays a key role in mental arithmetic, as revealed by both lesion patterns (acalculia being strongly linked to left parietal lesions, as shown by Jackson & Warrington, 1986) and by more recent fMRI (Chochon, Cohen, van de Moortele, & Dehaene, 1999). Based on the observation of joint deficits in language and calculation following unilateral brain lesions, the classical neurological wisdom stipulates that the left hemisphere is “dominant” for both language and calculation. In this vein, Semenza et al. (2006) reported, in the special case of right hemisphere aphasia, a co-occurrence of language and arithmetic impairments.

The neuropsychological concept of “dominance,” however, seems very coarse in the face of our recent ability to finely dissect, with neuroimaging methods, the specific areas involved in language and arithmetic tasks.

Are all of these areas equally lateralized to the left hemisphere, as would be predicted by a single overarching “dominance” factor? Or are there much more specific patterns of colateralization between language and arithmetic, restricted to a small subset of brain areas linking the two domains? Finally, a third possibility is that although both language and arithmetic relate to the left hemisphere, these are two independent patterns that just happen to coincide. For instance, the left hemispheric lateralization for language could result from an early asymmetry in structure and functions of the temporal lobe (Tervaniemi & Hugdahl, 2003; Chi, Dooling, & Gilles, 1977), whereas the parietal hemispheric specialization for quantities processing (the left parietal lobe being more involved in exact calculation and the right one more involved in judgment on analogical quantities; Piazza, Mechelli, Price, & Butterworth, 2006; Stanescu-Cosson et al., 2000) may mirror an initial left hemispheric advantage for processing stimuli as categories, whereas the right hemisphere shows a preference for processing analogical dimensions (Kosslyn et al., 1989; see also Vauclair, Yamazaki, & Güntürkün, 2006 for an extension to animals studies).

In the present work, we aimed to further specify the anatomical bases of the joint lateralization of language and arithmetic to the left hemisphere, using as a source

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of data the normal interindividual variability in functional lateralization. Using a very large database of fMRI activation from 209 healthy subjects, we could study the inter-correlations between the lateralization indices of many brain regions active during either sentence listening, sentence reading, or mental arithmetic tasks. As we shall see, this “colateralization analysis” suggests that functional lateralization is not a simple issue of one hemisphere “dominating” over the other, but a more subtle phenomenon linking specific cortical areas.

Our interest in the lateralization of arithmetic stemmed from a much broader debate, which concerns whether mental arithmetic is shaped by the organization of the language system (Gordon, 2004; Pica, Lemer, Izard, & Dehaene, 2004). Although arithmetical procedures are mainly based on a language-like system with a dedicated set of symbols and syntax, several published results underline the relative independence of linguistic and arithmetical abilities. Mastery of arithmetical procedures, for instance, has been reported to be dissociable from language impairment in many different neurological cases, including aphasic patients (Cohen, Dehaene, Chochon, Lehéricy, & Naccache, 2000), patients affected by semantic dementia (Cappelletti, Butterworth, & Kopelman, 2001), or agrammatic patients (Varley, Klessinger, Romanowski, & Siegal, 2005). This suggests that, at least for adult subjects, the core system for number manipulation is largely independent from the language network (Butterworth, 2005).

According to some theories, the extent to which calculation relies on a linguistic coding of numbers may depend on the arithmetic task. It is assumed in the triple-code model (Dehaene & Cohen, 1995), based on neurological dissociation reports, that quantity manipulations rely on a nonverbal analogical representation of numbers, used for instance to compare numbers or to approximate simple operations, whereas the memorization of exact arithmetical facts relies on a verbal memory store (Lefevre, 1996). To support this model, Dehaene, Piazza, Pinel, and Cohen (2003) published a meta-analysis of numerical paradigms and reported two distinct sites located in the fundus of the horizontal part of the intraparietal sulcus (hIPS) and in the angular gyrus (AG), which may be the correlates of quantity manipulation and of arithmetical fact storage, respectively. In agreement with the model, activation during a mental calculation task shifts from the hIPS to the AG after arithmetic training, as subjects rely less on active number manipulation and more on fact retrieval (Venkatraman, Siong, Chee, & Ansari, 2006; Delazer et al., 2003). The core system of “number sense,” located in the hIPS, would thus be anatomically and functionally distinct from the language areas, usually described as belonging to the inferior frontal, peri-sylvian, and superior temporal regions (Binder et al., 2000; Hickok & Poeppel, 2000).

Recently, however, it has become apparent that even within the domain of simple nonsymbolic calculations

accessible to preverbal infants (Barth, La Mont, Lipton, & Spelke, 2005; McCrink & Wynn, 2004), the acquisition of number symbols and of a verbal counting routine extends arithmetic performance and leads to a radical development of human arithmetical abilities. Compared to uneducated adults who live in remote areas of the Amazon and whose language has few number words, Western children and adults represent numerical quantities in a more precise manner (Gordon, 2004; Pica et al., 2004) and understand that numbers map onto space in a linear rather than in logarithmic manner (Dehaene, Izard, Spelke, & Pica, 2008; Siegler & Booth, 2004). During development, the integration of different codes for number (verbal and Arabic symbols, preverbal quantities, and ordinal concepts) leads to massive changes in children’s performance of simple numerical tasks such as the “give a number” task, where one simply asks a child “give me five objects” (Wynn, 1992). In summary, current theories of numerical cognition propose that the preverbal coding of numbers is profoundly changed and refined by education with numerical symbols (Dehaene, 2007; Pica et al., 2004; Carey, 1998). Although the mature systems for language and numbers appear largely dissociated in the adult brain, these views predict that they should be interdependent in the course of development. Here, we investigated whether consistent functional intercorrelations of these two systems across intersubject variability, in adulthood, may shed light on that issue as traces of a linked development.

As a first and simple marker of cerebral organization, we used an asymmetry index which evaluates, within a given cortical area, the extent to which functional activation is stronger in one hemisphere relative to the other. Reasoning that developmental constraints would be reflected in long-lasting correlations at the brain level (Andresen & Marsolek, 2005), we examined, across very different language comprehension and calculation tasks, whether language-related areas colateralize with the main areas related to mental arithmetic. Of course, the activation levels of the left and right hemispheres may also be affected by a variety of other factors such as subjects’ performance, strategies, or attention that may partially mask the predicted correlation. To mitigate this problem, we used an unusually large-scale database of 209 subjects which contains individual functional magnetic resonance images and behavioral scores (Pinel et al., 2007). Reliable networks for sentence comprehension and for simple calculation, both across the visual and auditory modalities, were available for each subject. Considering the large number of fMRI data, we hoped that our analysis would be sensitive to subtle anatomo-functional links between the two sets of language and calculation circuits.

We computed profiles of asymmetry (i.e., variations in the degree of hemispheric lateralization over the group of subjects) for each of the main areas activated during the language comprehension and calculation tasks. This

region-of-interest (ROI) approach allowed us to establish a detailed region-based description of the lateralization of the two networks. Using an intratask correlation analysis, we first examined whether a single “dominance” factor accounted for the data, or whether regional patterns of asymmetry could be isolated within the activations evoked by our paradigms. In a second step, we analyzed the correlations of the lateralization profiles across the language and arithmetic tasks, in order to isolate the areas that presented a significant joint colateralization. These pairs of areas were then specifically explored in a voxel-based whole-brain analysis to determine more precisely which voxels exhibited, in one task, an asymmetry that was well predicted by the asymmetry profile of another region in the other task. Finally, to test whether these joint colateralization patterns could be related to a structural basis, we extracted, on an independent sample of diffusion tensor images (DTI), the white matter fiber tracks linking these areas.

METHODS

Subjects and Protocol

We used fMRI data collected from 209 French healthy adult volunteers (all were right-handed, 60% women/40% men, mean age = 23.8 ± 4.4 years). The databasing procedure and the experimental protocol are detailed in Pinel et al., 2007; basically, we used a 5-minute-long functional localizer to isolate in a reliable way individual correlates of sentence reading, speech listening, and mental calculation. Twenty short sentences and 20 subtraction problems were presented via visual or auditory stimulation (half of the trials each) in a random-like order (a symbolic subtraction task was selected to ensure a strong activation of the various components of the number processing system; see Chochon et al., 1999). Twenty flashing checkerboards were also displayed and served as control for the reading task.

Imaging Data Processing

Anatomical and fMRI data were acquired on a 3-Tesla scanner (Brucker; TR = 2400 msec, 34 slices of 4-mm thickness covering the whole brain). Images were pre-processed (realignment, normalization to the Montreal Neurological Institute [MNI] template, resampled voxel size to 3 mm, 5 mm smoothing) with SPM2 (www.fil.ion.ucl.ac.uk) and analyzed according to the SPM general linear model (hemodynamic response function plus its derivative), resulting in five functional contrasts: visual sentence-checkerboard for the reading task, sentence listening-rest for speech listening task, visual calculation-visual sentence for visual mental calculation, auditory calculation-auditory sentence for auditory mental calculation, and overall calculation-sentence for calculation task. Individual conjunction image were computed to isolate a modal

components of language comprehension (Boolean intersection of the visual and the auditory language contrasts) and mental calculation (Boolean intersection of the visual and the auditory calculation contrasts).

We also computed individual whole-brain images of the degree of left/right asymmetry of activation for each of these contrasts. To this aim, the standard SPM normalization procedure was used to align each individual flipped normalized anatomy (along the *y* axis) onto the corresponding normalized anatomy image. This should maximize alignment of homolog anatomical structures in the two hemispheres despite macroscopic anatomical asymmetry (petalia and torque effects). Then, the functional contrast activation images were also realigned using the same matrix, and activation from the right hemisphere was subtracted voxel by voxel from the corresponding left hemisphere activation.

Group Analysis

Random effect analyses (RFX) were performed with SPM2 on the whole brain for group-level analyses ($p < .05$ after family-wise error correction for multiple comparisons, 20 voxels cluster extent). An RFX was performed onto the 209 individual contrasts images to show task-related activation, and a left hemisphere RFX was performed onto the 209 left-right asymmetry images to test for any significant group-level asymmetry of the functional circuits. In order to report asymmetry of activation only, displays of asymmetry RFX maps were masked by the corresponding RFX activation map. A two-sample *t*-test analysis was performed on asymmetry images to test for different pattern of lateralization between men and women.

SPM-based regression analyses were also performed on the individual asymmetry images to assess at the whole-brain hemisphere level which voxels presented an asymmetry of activation during the calculation task that correlated with the laterality index (LI) of a given ROI in reading task. To ensure that these regression analyses were unaffected by subjects' performance, which may affect level of activation especially in left parietal cortex (Menon et al., 2000), individual calculation score (available on a subset of 174 subjects) was added as a covariate (defined as the number of correct two-digit additions and subtractions solved in a limited time outside of the scanner). To benefit from the entire set of fMRI data and to maintain comparability with the ROI's LI analysis (described in the next paragraph), simple regressions with LI are also reported. Finally, to ensure that the reported colateralization were not due to a main effect of sex, we performed a third regression analysis on asymmetry images using both reading ROI's LI and subjects' sex as regressor.

Similar analyses were performed on the reading task asymmetry images, using a predictor the LI from the calculation task. We limited this SPM exploration to areas

that presented a significant correlation across tasks in the LI correlation analysis (see below).

Calculation of Laterality Index

The choice of an LI was constrained by the following aims. First, the index must be robust in the face of inter-individual variability in activation topography. In particular, it must take into account the fact that homologous areas of the left and right hemispheres do not necessarily occupy perfect mirror-image locations. Second, the LI should be a normalized index, not influenced by overall changes in amount of activation. Third, it must be unaffected by the presence of deactivation in some subjects and/or hemispheres which can create misinterpretation in term of activation asymmetry (Seghier, 2008).

These issues were addressed as follows. For each functional peak of interest, we selected two symmetrical spheres (radius = 4 voxels, i.e., 12 mm, based on the anatomical variability of individual peak reported for this paradigm in Pinel et al., 2007) respectively in the left and right hemispheres, centered on the peak coordinates of the group-level analysis. For a given subject, within each of these spheres, we then eliminated inactive or deactivated voxels with a loose criterion that their t value should be superior to 1. This procedure ensured that the activation values entered in the LI formula were always positive, thus alleviating potential problems arising from the presence of deactivation in some subjects and/or areas. Within those active voxels, we then selected the most activated voxels by keeping only up to 5% of the original sphere volume. Finally, the LI was computed by the classical formula $LI = (R - L)/(L + R)$ where L and R are, respectively, the left and right average activations of the selected voxels. The index ranged from -1 (total left lateralization) to $+1$ (total right lateralization), with 0 reflecting perfect symmetry of activation.

In this formula, activation for one hemisphere was set to zero if no voxels passed the criterion of having a t value > 1 . In this case, the LI always reached its maximum (plus or minus 1), regardless of the amount of activation in the other hemisphere. This can add noise to the analysis because even very small activations, when passing threshold in one hemisphere and not the other, are considered maximally asymmetrical. To mitigate this problem, an LI defined from a total of less than 15 activated voxels was excluded from analysis. Note that this procedure rejected about 5% of subjects for most ROI, and up to 15–30% for areas found active in only a subgroup of subjects, such as the putamen, inferior parietal, or cingulate. Critically, the main reading–calculation correlations reported here were calculated from 98% of the subjects for pSTS–hIPS and 85% for mFG–precuneus pair.

To characterize the leftward lateralization of the language comprehension cerebral network, we computed the LI from seven local peaks of the RFX analysis for

reading lateralization, which were also part of the most activated sites (6 maxima were present in both language modalities). To explore the lateralization of the calculation network, we computed the LI from all nine local peaks of the RFX analysis for areas active during calculation. For each of these peaks, we performed a two-sample t test on LI values with sex as independent variable to test for a putative difference of lateralization between male and female subjects.

We first investigated the colateralization patterns within the seven language-related ROIs, both within and across modalities of sentence presentation (visual and auditory stimulation). We then calculated the matrix of correlation corresponding to the 7×9 combinations of LI from reading and calculation tasks respectively. We report matrices of p values testing the null hypothesis of no correlation.

Fiber Tracking

To explore whether colateralization of brain areas may be sustained by direct connections via anatomical fiber bundles, we performed fiber tracking with the Brainvisa software (Cointepas et al., 2003; <http://brainvisa.info/>) on six subjects' DTIs acquired in another protocol (Siemens Trio 3-T whole-body scanner): TE/TR = 81 msec/14 sec, 0/700 s mm^{-2} $b1/b2$ factor, 41 directions, FOV = 240, $1.9 \times 1.9 \times 2$ mm voxel size, 60 slices.

Tracking was performed starting from five functionally defined seed regions: middle frontal and posterior superior temporal spheres (4 mm), centered on the peak defined by the previously described reading task RFX, and intraparietal, superior parietal and precuneus spheres defined by the calculation task. Spheres were defined in MNI space and then unnormalized to match the individual diffusion-weighted images. To estimate how these areas were linked, fiber trees were labeled according to the pair of seed regions they crossed. Resulting tracks were then converted into 3-D images, normalized to MNI coordinates and added up for a group-level description.

RESULTS

Language Lateralization

The overall networks activated during reading, speech listening, and calculation reported in Figure 1 resembled those classically reported in the literature (see Pinel et al., 2007, for a detailed description of these networks). Nearly all activated areas were strongly leftward lateralized in these three cognitive tasks (Figure 1, bottom row). Two interesting and heretofore unreported exceptions were right postcentral cortex for reading and a right middle temporal area for speech listening.

Based on those asymmetry images, the seven bilateral ROIs which reflected both strong lateralization and

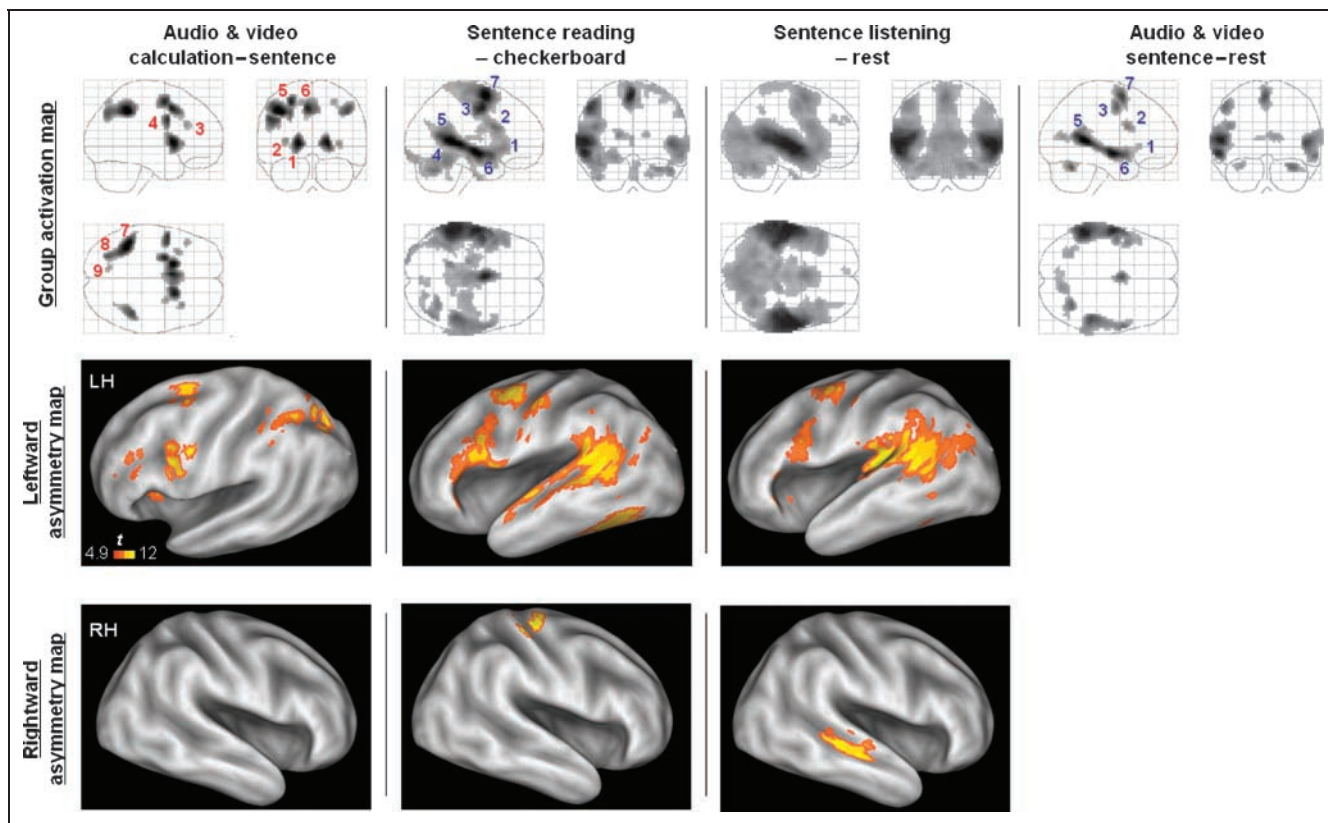


Figure 1. Hemispheric asymmetries during language and calculation. The first row (glass brains) shows sagittal, axial, and coronal views of the brain networks active during calculation, reading, speech listening, and core language comprehension, respectively ($p_{\text{corr.}} < .05$). Red numbers indicate regions of interest of the calculation circuit for which a laterality index was computed: putamen (1), insula (2), middle frontal (3), precentral (4), superior frontal (5), cingulate (6), hIPS (7), superior parietal lobule (8), and precuneus (9). Blue numbers indicate ROI of the reading circuit: inferior frontal area (1), precentral area (2), middle frontal area (3), fusiform gyrus (4), pSTS (5), aSTS (6), and cingulate (7). Note that all but one of these regions was also present in the core system of language comprehension. On the next two rows are displayed series of left (LH) and right (RH) inflated hemisphere with projections of cortical sites of significant asymmetry, respectively, in favor of the left or of the right hemisphere ($p_{\text{corr.}} < .05$).

activation of the language cerebral organization were centered on the following peaks: inferior frontal area (close to Broca's area; see Lindenberg, Fangerau, & Seitz, 2007, for a recent meta-analysis; MNI: $x = -43, y = 22, z = -2$), precentral area ($x = -47, y = 6, z = 25$), middle frontal gyrus (mFG, $x = -48, y = -3, z = 53$), fusiform gyrus (about 3 mm from the visual word form area; Cohen & Dehaene, 2004; $x = -45, y = -56, z = -10$), posterior STS (pSTS; $x = -58, y = -44, z = 8$), anterior STS (aSTS; $x = -57, y = -3, z = -9$), and cingulate ($x = -6, y = 3, z = 63$). Only the fusiform gyrus activation was specific to the visual modality.

No significant difference was observed between male and female subjects in the voxel-based analysis (voxel $p_{\text{uncorr.}} < .001, p_{\text{corr.}} < .05$ for cluster extent). The only area associated with a sex effect with a p value $< .1$ in the ROI analysis was the inferior frontal area ($p = .09$ in reading and $p = .01$ in speech listening condition, 206 degrees of freedom) with a trend toward a larger left lateralization for men (median LI = -0.24 and -0.11 for reading and speech listening, respectively) than for women (median LI = -0.16 and -0.06).

Table 1 gives the correlation of the LIs across areas, both within and across the language tasks. Looking first at the diagonal values (bottom of Table 1), we see that for all areas, the LIs were highly correlated across the two modalities of linguistic input (visual or auditory), suggesting that left lateralization in most areas arises from amodal levels of language processing. Even the fusiform peak, which did not survive corrected threshold for activation during the auditory trials, presented a trend toward leftward asymmetry during speech listening that correlated with reading activation asymmetry in this region (perhaps corresponding to a top-down activation of orthographic processing in the visual word form area during speech listening; Cohen, Jobert, Le Bihan, & Dehaene, 2004). This analysis also demonstrated that, for each subject, the LI of each selected ROI was reliably measured by our paradigm over two independent language-related conditions.

In view of this high reproducibility of the LI *within* each area, it is surprising that the LI *across* areas are sometimes weakly correlated, suggesting that many regions present relative independent pattern of hemispheric

Table 1. Reproducibility and Colateralization of Asymmetries during Language Processing

		Reading						
		Inferior Frontal	Precentral	Mid-frontal	Fusiform	Posterior STS	Anterior STS	Cingulate
Reading	Inferior Frontal	–	.008	.077	.185	<10⁻³	.001	<10⁻³
	Precentral	–	–	.001	.061	.005	.167	<10⁻³
	Mid-frontal	–	–	–	<10⁻³	<10⁻³	.033	.007
	Fusiform	–	–	–	–	<10⁻³	.013	.783
	Posterior STS	–	–	–	–	–	.002	<10⁻³
	Anterior STS	–	–	–	–	–	–	.213
	Cingulate	–	–	–	–	–	–	–
		Speech Listening						
		Inferior Frontal	Precentral	Mid-frontal	Fusiform	Posterior STS	Anterior STS	Cingulate
Speech listening	Inferior Frontal	–	<10⁻³	.004	.393	.012	.002	.047
	Precentral	–	–	<10⁻³	.429	<10⁻³	.140	.003
	Mid-frontal	–	–	–	.951	.006	.021	<10⁻³
	Fusiform	–	–	–	–	.001	.506	.579
	Posterior STS	–	–	–	–	–	.628	.046
	Anterior STS	–	–	–	–	–	–	.352
	Cingulate	–	–	–	–	–	–	–
		Reading						
		Inferior Frontal	Precentral	Mid-frontal	Fusiform	Posterior STS	Anterior STS	Cingulate
Speech listening	Inferior Frontal	<10⁻³	.019	.472	.041	.092	.372	.380
	Precentral	.027	<10⁻³	.132	.622	.307	.101	.012
	Mid-frontal	.082	.429	<10⁻³	.352	.563	.177	.903
	Fusiform	.381	.585	.178	.023	.050	.695	.666
	Posterior STS	.005	.246	.289	.031	<10⁻³	.025	.080
	Anterior STS	.016	.103	.503	.710	.410	<10⁻³	.737
	Cingulate	.120	.637	.031	.796	.476	.664	<10⁻³

LI Correlation across the Two Language Tasks

The table shows the *p* values of the correlation between the lateralization indices (LI) of the seven main language-related ROIs during language comprehension tasks. The upper part of the table reports the correlations within the same modality of language input (visual sentence reading and auditory speech listening). Bold values indicate correlation values that are similarly significant (*p* < .05) for the same pairs across modalities. The bottom part reports the correlations across two independent trial types with visual and auditory language inputs. Bold values on the diagonal highlight the level of LI reliability across modalities.

asymmetries, perhaps reflecting multiple determinants of left hemispheric bias for language in the course of development. For instance, although all of these regions are highly asymmetrically activated, always in favor of the left hemisphere, correlations between the LI of the

fusiform gyrus and of frontal areas are weak, as well as those between aSTS and precentral gyrus, cingulate and fusiform gyrus, cingulate and aSTS. It is remarkable that this pattern of weak correlation was largely similar across the two modalities of sentence presentation. Similarly,

there were notable patterns of extremely high correlation across areas, both for the reading and the speech listening tasks. Such consistently high correlations were found between the pSTS and both fusiform and frontal areas; within the frontal lobe, between precentral and both the mFG and the inferior frontal area; and finally, between the aSTS and both the mFG and the inferior frontal area. Only a few pairs of areas presented inconsistent level of LI correlation across modalities, noticeably the fusiform and mFG as well as the aSTS and pSTS, probably due to the partially modality-specific involvement of these areas, respectively, in orthographic and phonological processing.

Arithmetic Lateralization

The nine ROIs from activation for the calculation task were centered on the following maxima (Figure 1): putamen ($x = -18, y = 11, z = 4$), insula ($x = -32, y = 20, z = 6$), mFG ($x = -44, y = 39, z = 15$), precentral ($x = -48, y = 8, z = 33$), superior frontal gyrus (sFG close to frontal eye fields; Simon et al., 2004; $x = -25, y = 2, z = 59$), cingulate ($x = 0, y = 14, z = 47$; left and right parts of the sphere were here considered), hIPS (virtually identical to the location reported from in the meta-analysis of Dehaene et al., 2003; $x = -40, y = -47, z = 47$), superior parietal lobule (sPL, close to the posterior sPL from Dehaene et al., 2003; $x = -27, y = -69, z = 44$), and precuneus ($x = -14, y = -72, z = 54$).

Because lateralization of calculation is less well characterized than language lateralization, Figure 2 details the RFX lateralization map of the calculation task with a series of axial slices. All activated areas showed at least a trend toward left lateralization, often reaching very high degrees of significance: $t(208) = 17.23$ in cingular cortex slightly posterior to the activation peak, $t = 16.00$ in precentral, $t = 12.98$ in the posterior parietal lobule close to the sPL, $t = 12.34$ posterior to putamen peak, $t = 11.90$ about 3 voxels under the insula peak, $t = 10.40$ in the sFG, $t = 8.75$ in the hIPS, and $t = 8.19$ in the middle frontal area. Examination of the distributions of the LI across subjects allowed for a more detailed and anatomy-free analysis of the lateralization of these sites. A gradient emerged in the extent of lateralization for arithmetic, with the highest value for the precentral area (median LI = -0.218); medium lateralization for sPL (-0.148), hIPS (-0.125), cingulate (-0.125), sFG (-0.119), and middle frontal (-0.110); and low LI for the subcortical system: putamen (-0.028) and insula (-0.012). The partial discrepancy of the latter finding with the RFX asymmetry map may be due to the fact that subcortical peaks had approximately equal levels of BOLD activations in both hemispheres, but with a more extended activation in the left hemisphere.

No significant differences were observed between male and female subjects in the voxel-based analysis (voxel $p_{\text{uncorr.}} < .001$, $p_{\text{corr.}} < .05$ for cluster extent). The only

areas associated to a sex effect with a p value $< .1$ in the ROI analysis was the putamen area ($p = .04$, 206 degrees of freedom), with a trend toward a larger, although weak, left lateralization for men (median LI = -0.04) than for women (median LI = 0.01).

Colateralization of Language and Arithmetic: ROI Analysis

To examine how arithmetic and language colateralized, we first examined the full correlation matrix between the asymmetry of activation in the above-selected ROI, known to be asymmetrically activated during one or both of these activities. As a proxy for language asymmetry, we used the LI obtained during reading because (1) the diagonal of Table 2 indicates a very highly correlation with the LI obtained during language listening in all regions; (2) in one region (left fusiform), reading yielded stronger and more asymmetrical activation than language listening (corresponding to the putative orthographic role of this region as the visual word form area).

Surprisingly, the correlation matrix between reading and calculation LIs indicated that most of the language- and calculation-related areas varied independently in their degree of lateralization (Table 2). However, a few pairs of areas presented a significant positive correlation across tasks: The mFG LI during reading correlated with the precuneus LI during calculation ($r = .25$); the pSTS LI during reading correlated with the precentral area ($r = .28$), sFG ($r = .23$), hIPS ($r = .21$), and precuneus ($r = .23$) LI during calculation; and finally, the cingulate LI during reading correlated with the sFG LI during calculation ($r = .22$). When considering separately the auditory and visual modalities for calculation trials, only a subset of correlations survived across these two independent sets of data. On the one hand, lateralization in the pSTS during reading was reliably correlated with lateralization in the hIPS during calculation. On the other hand, mFG lateralization during reading correlated with precuneus lateralization during calculation.

Colateralization of Language and Arithmetic: Voxel-based Analyses

We first confirmed our results by a voxel-based regression approach, which consisted in examining how the LI of a selected region predicted, at the whole-brain level, the asymmetry in activation in another task.

Link 1: sFG and hIPS

Even when exploring the entire left hemisphere, only the sFG and the hIPS exhibited profiles of asymmetry during the calculation task that were significantly predicted by the lateralization index of the pSTS during

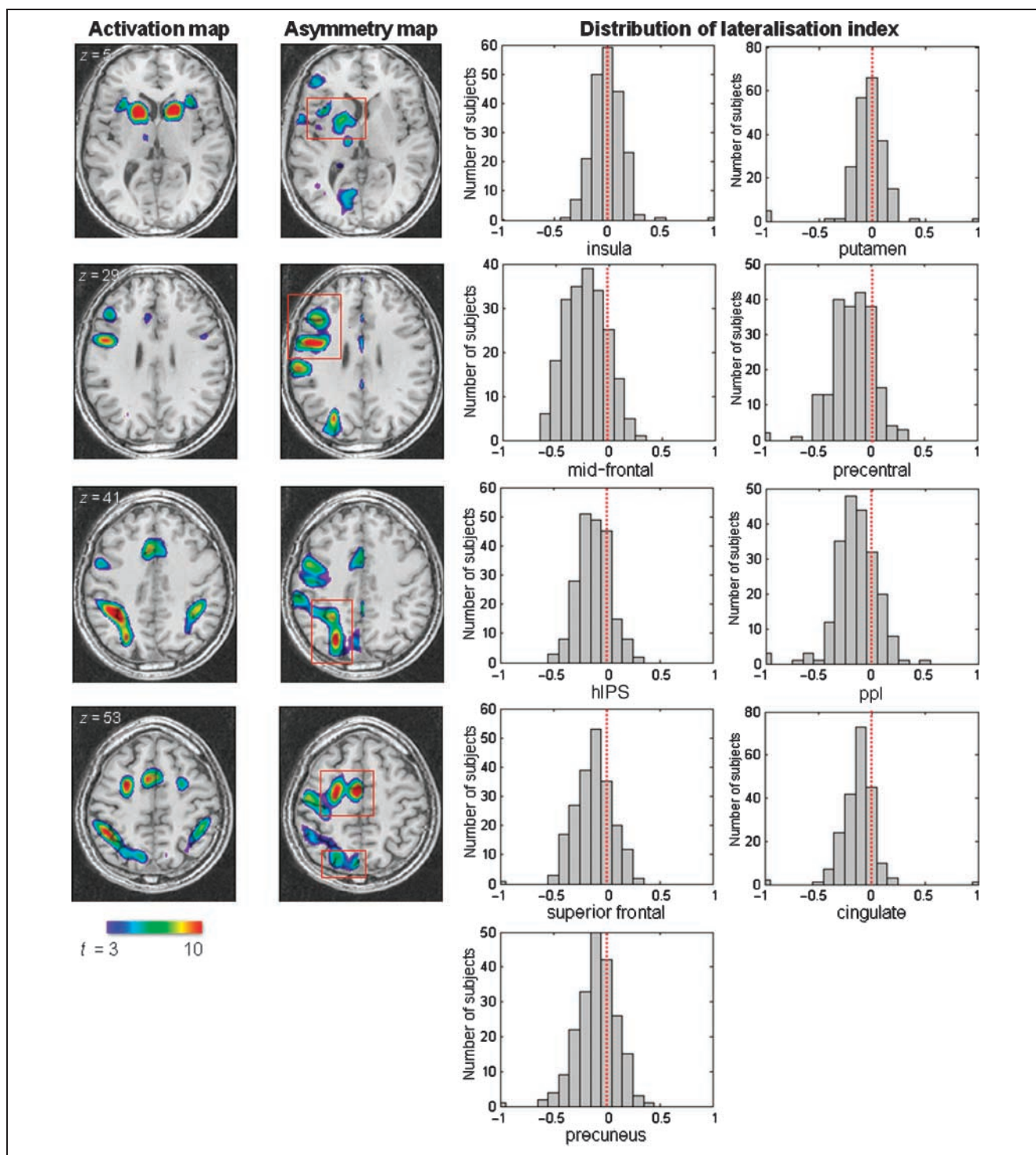


Figure 2. Quantifying functional asymmetries in the calculation network. Axial slices describe the entire pattern of activation and asymmetry for the calculation task (neurological convention) from bottom to the top of the brain (RFX group analysis, $p_{\text{corr.}} < .05$). The histograms at right show the distribution of LI across subjects for each of the nine selected ROIs. Red rectangles help locate these ROIs on the corresponding slices. ppl = posterior parietal lobe; superior frontal = superior frontal cortex.

reading ($p < .05$, corrected for multiple comparisons; see Figure 3A, Table 3). Note that, in this analysis, the subjects' arithmetical performance was regressed out as a covariate of noninterest, and thus, performance variability did not contribute to this significant colateralization.

At a lower voxelwise threshold ($p < .01$, uncorrected), additional voxels were found in the precentral gyrus and in the caudate nucleus (Table 3).

A number of control analyses were run to assess the significance of these findings. First, a simple regression

Table 2. Colateralization of Asymmetries during Calculation and Reading

	Reading							
	Inferior Frontal	Precentral	Mid-frontal	Fusiform	Posterior STS	Anterior STS	Cingulate	
Calculation	Putamen	.010*	.384	.653	.083	.394	.678	.015
	Insula	.307	.203	.137	.456	.633	.012	.184
	Mid-frontal	.077	.137	.838	.698	.050	.993	.922
	Precentral	.077	.464	.155	.736	.010*	.506	.053
	Superior Frontal	.101	.138	.080	.390	.001**	.166	.004*
	Cingulate	.235	.830	.030	.069	.060	.191	.018
	hIPS	.288	.602	.026	.174	.002*	.248	.226
	Superior Parietal	.465	.222	.510	.784	.035	.373	.486
	Precuneus	.146	.703	<10^{-3**}	.710	.002*	.100	.293
Video calculation	Putamen	.685	.391	.117	.151	.278	.920	.016
	Insula	.226	.578	.445	.713	.725	.002*	.311
	Mid-frontal	.143	.170	.778	.763	.013	.480	.311
	Precentral	.566	.175	.064	.746	.133	.892	.034
	Superior Frontal	.540	.943	.671	.913	.284	.766	.231
	Cingulate	.860	.616	.025	.388	.007*	.407	.013
	hIPS	.319	.644	.040	.510	<10^{-3**}	.783	.146
	Superior Parietal	.953	.013	.756	.981	.564	.988	.982
	Precuneus	.053	.433	.001**	.930	<10^{-3**}	.038	.069
Audio calculation	Putamen	.551	.160	.763	.721	.073	.756	.106
	Insula	.449	.443	.332	.407	.896	.297	.463
	Mid-frontal	.349	.523	.250	.846	.094	.189	.786
	Precentral	.086	.942	.198	.466	.020	.283	.158
	Superior Frontal	.100	.028	.009*	.150	.002*	.113	.009*
	Cingulate	.077	.167	.304	.053	.364	.040	.308
	hIPS	.184	.303	.107	.073	.005*	.106	.284
	Superior parietal	.186	.899	.251	.971	.067	.433	.340
	Precuneus	.265	.433	<10^{-3**}	.283	.018	.285	.815

The table shows the p values of the correlation between the lateralization indices (LI) of the reading and calculation ROIs. In each case, we report the correlation of activation asymmetry on two independent sets of trials, the reading trials (horizontally) versus the calculation trial (vertically). Significance is reported both for overall calculation trials (first part of the table), visually presented calculations only (second part) and auditory presented calculations only (third part). Bold values highlight the two correlation patterns that were deemed reliable enough.

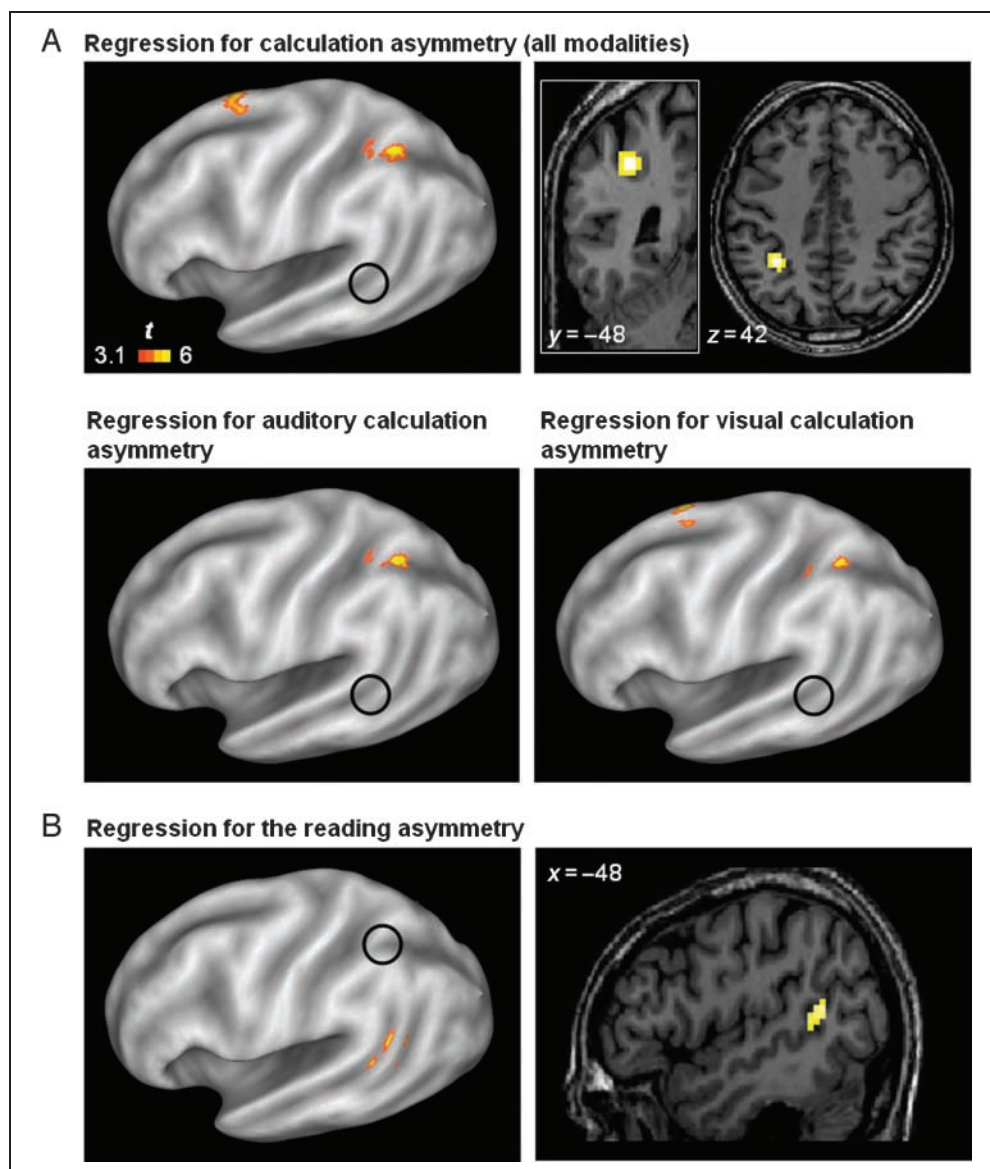
* p value < .01.

** p value < .001.

with the LI of the pSTS during reading, computed without any behavioral regressor but applied to the whole population images, gave comparable results. Three peaks survived a corrected p value of .05 for cluster extent: hIPS [-36, -48, 42; $t(207) = 4.70$, voxel $p_{\text{corr.}} < .05$], sFG [-18, 3, 66; $t(207) = 5.10$, voxel $p_{\text{uncorr.}} < .001$], and precentral peak [-51, 3, 27; $t(207) = 4.30$, voxel

$p_{\text{uncorr.}} < .001$]. Second, we checked whether the positive correlation found for calculation minus sentence processing was, in fact, due to a negative correlation with lateralization in the control task of visual sentence processing. When analyzing the contrast of sentence reading minus rest, no voxel of the superior frontal or parietal sites presented any significant asymmetry predicted by

Figure 3. Colateralized regions for reading and calculation: pSTS and hIPS. Whole-brain regression analysis of the colateralization between the reading temporal area (pSTS) and the calculation intraparietal area (hIPS; $p < .001$, uncorrected at the voxel level, $p < .05$, corrected for the cluster extent). (A) The first row shows a 3-D rendering of which voxels from the global calculation–sentence contrast showed an asymmetry that was significantly predicted by the LI of the pSTS region during reading (this “source” region is enclosed with a black circle). The SPM statistical map was projected onto an inflated left hemisphere of the template brain of the Caret software. The observed intraparietal cluster is detailed on coronal and axial slices. On the second row, similar analyses are shown separately for the auditory and visual calculation, respectively. (B) 3-D rendering of the converse analysis: reading–checkerboard contrast asymmetry predicted by the LI of the hIPS during calculation (black circle). The observed temporal cluster is detailed on the sagittal view of one subject’s anatomy.



the pSTS LI, even at a low threshold at the voxel level ($p > .01$, uncorrected). Furthermore, when we directly regressed the asymmetry of calculation versus rest to the LI of the pSTS during reading, with calculation score as a covariate (voxel $p_{\text{uncorr.}} < .001$, $p_{\text{corr.}} < .05$ for cluster extent), we still isolated the hIPS [$-36, -48, 42$; $t(173) = 4.63$], in addition to a broad sentence comprehension circuit that encompassed the pSTS [$-54, -48, 15$; $t(173) = 5.63$], the fusiform gyrus [$-42, -63, -12$; $t(173) = 5.16$], and an occipito-parietal area [$-36, -48, 42$; $t(173) = 4.63$]. Third, and most crucially, the hIPS was the only area whose asymmetry during calculation was significantly predicted by the LI of the pSTS during reading when we did separate analyses on auditory and on visual calculation trials (Figure 3A, Table 3). Finally, the multiregression analysis with sex as a second regressor gave strictly similar results with no sex effect at the selected threshold.

The converse regression analysis, starting with the LI of the hIPS region during calculation and using it as a

regressor of the images of asymmetry during reading, revealed a small set of voxels in the pSTS, close to the maxima of asymmetry during the reading task (Figure 3B, Table 3). Another significant cluster was found in the anterior cingulum, but in a region not reported here as a part of the reading network.

Link 2: mFG and Superior Parietal/Precuneus

Similar multiple regression analyses used the LI of the mFG during reading as a predictor of calculation asymmetry images, with behavioral calculation performance as a covariate of noninterest. This SPM analysis isolated two superior parietal/precuneus clusters (Figure 4A). The regression was weaker and did not survive a corrected p value at the voxel level, but approached significance at the cluster level (Table 4). Here again, a simple regression to the reading mFG LI, computed without any behavioral regressor but applied to the whole population images,

Table 3. Whole-brain Analysis of Colateralization with pSTS

Brain Area	Coordinates			Voxel			Cluster
	<i>x</i>	<i>y</i>	<i>z</i>	<i>p</i> _{uncorr.}	<i>p</i> _{FWE-corr.}	<i>t</i> (173)	<i>p</i> _{corr.}
<i>Calculation Asymmetry Regressed by the Reading pSTS LI</i>							
<i>p</i> _{uncorr.} < .001							
Intraparietal sulcus	-36	-48	42	<.001	.004*	5.26	.001
Superior frontal gyrus	-18	3	66	<.001	.010*	4.73	.011
<i>p</i> _{uncorr.} < .01							
Precentral gyrus	-48	0	30	<.001	.117	4.61	.019
Caudate nucleus	-18	-9	24	<.001	.974	3.70	.030
<i>Video Calculation Asymmetry Regressed by the Reading pSTS LI</i>							
<i>p</i> _{uncorr.} < .001							
Superior frontal gyrus	-15	3	66	<.001	.012*	5.11	.020
Intraparietal sulcus	-36	-48	42	<.001	.054*	4.48	.040
<i>p</i> _{uncorr.} < .01							
Precentral gyrus	-48	0	30	<.001	.638	4.12	.049
<i>Audio Calculation Asymmetry Regressed by the Reading pSTS LI</i>							
<i>p</i> _{uncorr.} < .001							
Intraparietal sulcus	-33	-48	42	<.001	.070	4.98	.007
<i>p</i> _{uncorr.} < .01							
Precentral gyrus	-36	-6	63	<.001	.093	4.66	.002
	<i>x</i>	<i>y</i>	<i>z</i>	<i>p</i> _{uncorr.}	<i>p</i> _{FWE-corr.}	<i>t</i> (208)	<i>p</i> _{corr.}
<i>Reading Asymmetry Regressed by the Calculation hIPS LI</i>							
<i>p</i> _{uncorr.} < .001							
Anterior cingulum	-15	33	6	<.001	.075	4.68	.006
<i>p</i> _{uncorr.} < .01							
Mid-temporal gyrus	-48	-54	15	<.001	.666	4.05	.017

Brain areas where the leftward asymmetry during calculation was significantly predicted by the lateralization index of the pSTS during reading (whole left hemisphere analysis). Regression was performed separately for the overall images of asymmetry during calculation (pooling over visual and auditory trials), for visual calculation trials only, and for auditory calculation trials only. For an exhaustive description of the regression, we reported for each case statistical mapping results with a voxel threshold of .001 and with a more liberal threshold of .01, keeping .05 as a corrected threshold for cluster extent. The bottom part of the table reports the converse analysis, that is, areas with a leftward asymmetry during reading that was significantly predicted by the lateralization index of the hIPS during calculation.

gave comparable results: sPL [-24, -66, 54; $t(207) = 3.44$, voxel $p_{\text{uncorr.}} < .001$], precuneus [-9, -69, 54; $t(207) = 3.42$, voxel $p_{\text{uncorr.}} < .001$], and postcentral gyrus [-27, -45, 51; $t(207) = 3.67$, voxel $p_{\text{uncorr.}} < .001$]. Finally, the multiregression analysis with sex as a second regressor gave strictly similar results with no sex effect at the selected threshold in active areas.

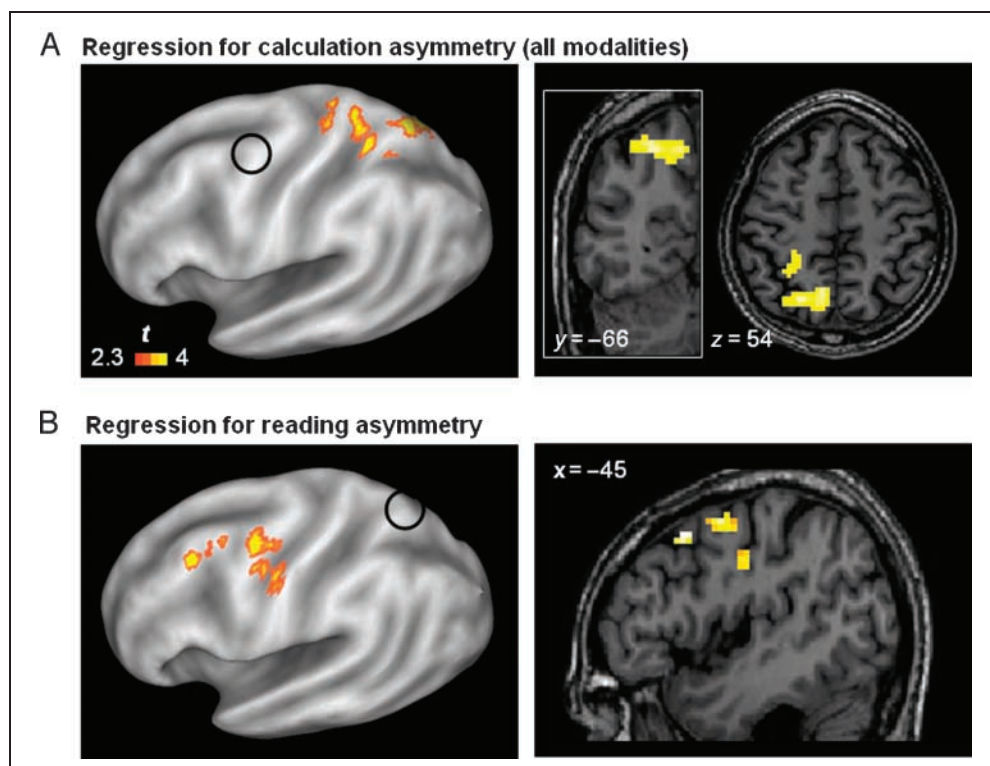
The converse regression analysis, considering the LI from the sPL during calculation as the regressor of the reading asymmetry images, showed that only a cluster of

voxels in the mFG exhibited an asymmetry during the reading task that was significantly predicted by this LI. The region clearly encompassed the ROI selected for its asymmetry during the reading task (Figure 3B, Table 3).

Relation between Colateralization and Anatomical Connectivity

In this final analysis, we wondered whether the observed patterns of colateralization between two areas related to

Figure 4. Colateralized regions for reading and calculation: mFG and posterior parietal/precuneus. Whole-brain regression analysis of the colateralization between the reading middle frontal area (mFG) and the calculation posterior parietal lobe/precuneus ($p < .01$, uncorrected at the voxel level; $p < .05$ correct for the cluster extent). (A) 3-D rendering of which voxels from the calculation–sentence contrast showed an asymmetry that was significantly predicted by the LI of the mFG during reading (black circle). The most posterior cluster is detailed on coronal and axial slices. (B) 3-D rendering of the converse analysis: reading–checkerboard contrast asymmetry predicted by the LI of the precuneus during calculation (black circle). The observed frontal clusters are detailed on the sagittal view of one subject’s anatomy.



the existence of actual anatomical connections between them, such that if one area grew more asymmetrical in the course of development, the other would also tend to develop a growing asymmetry.

Fiber tracking from DTIs provided clear structural support for our first finding of a strong pSTS–hIPS colateralization: In all of the six subjects, projections were found from the pSTS to inferior parietal cortex. As for

Table 4. Whole-brain Analysis of Colateralization with the mFG

Brain Area	Coordinates			Voxel			Cluster
	<i>x</i>	<i>y</i>	<i>z</i>	<i>p</i> _{uncorr.}	<i>p</i> _{FWE-corr.}	<i>t</i> (173)	<i>p</i> _{corr.}
<i>Calculation Asymmetry Regressed by the Reading mFG LI</i>							
<i>p</i> _{uncorr.} < .01							
Postcentral gyrus	–21	–39	66	<.001	.864	3.90	.050
Superior parietal gyrus	–24	–66	54	<.001	.999	3.46	.080
Precuneus	–9	–63	54	<.001	1.0	3.46	
	<i>x</i>	<i>y</i>	<i>z</i>	<i>p</i> _{uncorr.}	<i>p</i> _{FWE-corr.}	<i>t</i> (208)	<i>p</i> _{corr.}
<i>Reading Asymmetry Regressed by the Calculation Precuneus LI</i>							
<i>p</i> _{uncorr.} < .01							
Mid-frontal gyrus	–45	15	51	<.001	.275	4.38	.030
Mid-frontal gyrus	–48	–3	57	<.001	.596	4.11	

Brain areas where the leftward asymmetry during calculation was significantly predicted by the lateralization index of the mFG during reading (whole left hemisphere analysis). Regression was performed on the images of asymmetry during calculation, pooled over visual and auditory trials. For an exhaustive description of the regression, we reported for each case statistical mapping results with a voxel threshold of .01 and .05 as a corrected threshold for cluster extent (except for the superior parietal gyrus reported in ROI analysis). The bottom part of the table reports the converse analysis, that is, areas with a reading leftward asymmetry during reading that was significantly predicted by the lateralization index of the precuneus during calculation. Secondary peaks are reported in italic.

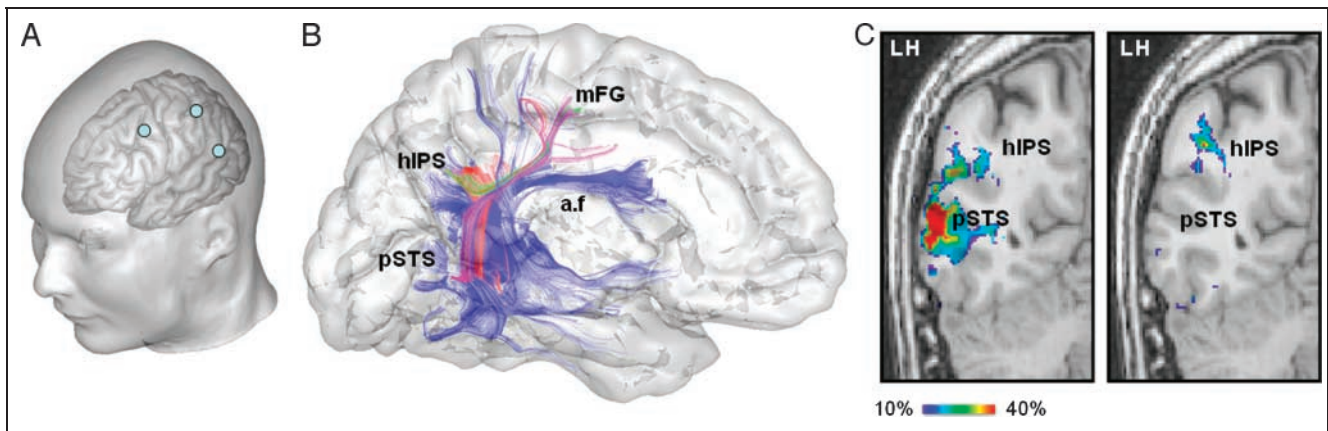


Figure 5. Anatomical connections putatively supporting the observed colateralization patterns. (A) Location on a 3-D left hemisphere of the three frontal, parietal, and temporal seed regions used for tracking. (B) Left hemisphere fibers of interest (from an internal view): long segment of the arcuate fasciculus (a.f., in blue), posterior segment linking the pSTS and hIPS (red), superior segment linking the hIPS and mFG (green), and projections connecting the mFG and pSTS (purple). (C) Coronal view of the projections to the left parietal region, respectively, from seed regions in the pSTS (left) and the mFG (right). Color scale corresponds to the amount of overlap from five different individuals. The pSTS clearly connects to the banks of the intraparietal sulcus, whereas the mFG projects more dorsally toward superior parietal cortex. hIPS = horizontal segment of the intraparietal sulcus; mFG = middle frontal gyrus; pSTS = posterior superior temporal sulcus.

the second finding, as detailed in Figure 5A, white matter tracks also connected the mFG to the dorsal parietal region (as well as, in some subjects, the mFG to the pSTS). Although no direct connections were found from the mFG to the sPL and the precuneus, dense local U-shaped fibers were found linking the three parietal seed regions (intraparietal, superior parietal, and precuneus). Furthermore, crucially, a close look at the organization of projections to parietal cortex showed an anatomical segregation of fibers originating from the pSTS and from the mFG, mirroring the parietal parcellation found by correlation with the LI (Figure 5B). Projections from the pSTS were located laterally in the inferior parietal lobule, often extending to the banks of the intraparietal sulcus, whereas those from the mFG region projected more dorsally into the sPL.

DISCUSSION

We studied the profile of functional brain asymmetries for language and calculation over a large population of 200 subjects. Our goal was to study the colateralization of these two functions across subjects, possibly reflecting an influence of language organization onto the cerebral architecture for calculation.

Purposely, our starting point was the definition of two distinct and distributed networks; a vast language network, defined by its activation to simple spoken or written sentences and supported by frontal and peri-sylvian areas, and a calculation network, defined by areas showing more activity to verbally presented subtraction problems (e.g., “compute 11 minus 3”) than to other nonnumerical sentences and supported by frontal, parietal, and subcortical regions. Although both circuits showed significant

left hemispheric asymmetry, our results indicate that the concept of a single hemispheric “dominance,” determining the lateralization of all regions of the language and calculation networks, does not suffice to explain the patterns of hemispheric asymmetries across individuals. In our data, lateralization appears as a local regional phenomenon, even within a given task. LIs are often uncorrelated across distant areas, and therefore, probably have multiple determinants. Indeed, interestingly, only two anatomically restricted sets of areas showed a correlated asymmetry across the language comprehension and the arithmetic tasks: The lateralization profile of the pSTS during reading correlated with the lateralization of the fundus of the hIPS during calculation, and the lateralization of the mFG during reading correlated with that of the sPL and the precuneus during calculation. Although the asymmetry of language areas only explained a relatively small proportion of the variance in left/right parietal organization for arithmetic, this amount was comparable to the correlation observed within some areas of the language network. Importantly, both findings were reproducible over two separate sets of data (spoken and written arithmetic problems), and both ROI-based and voxel-based analysis.

These patterns of colateralization were further supported by the presence of anatomical connections, respectively linking the pSTS with the hIPS, and the mFG with the sPL. Notably, the pattern of white matter projections from the pSTS and mFG areas toward the parietal lobe matched the pattern of colateralization between parietal voxels and those two temporal and frontal sites. Overall, these results underline an interesting subdivision of superior parietal cortex into two distinct regions that could be subject to different influences in their development and maturation.

Colateralization of the Language-related pSTS and the Core Numerical System

The global tasks used in the present study did not allow us to precisely delineate the processing stages subtended by the various brain areas reported here. However, a striking aspect of our results is that language lateralization in the pSTS is significantly related to those of the frontal and parietal regions known to be crucial for the representation and processing of numerical quantities.

The intraparietal site of colateralization reported here, especially the fundus of the intraparietal sulcus, has been systematically reported in various numerical tasks (Venkatraman, Ansari, & Chee, 2005; Dehaene et al., 2003; Delazer et al., 2003) and its neuronal coding properties have been recently investigated in humans and non-humans primates (Nieder, Diester, & Tudusciuc, 2006; Piazza, Izard, Pinel, Le Bihan, & Dehaene, 2004). Contrary to posterior parietal areas, which are shared with visuospatial tasks, and to the AG, which is thought to relate to the verbal coding of arithmetical facts, the intraparietal location reported here is thought to house an amodal representation of quantities (Piazza et al., 2006; Venkatraman et al., 2005; Eger, Sterzer, Russ, Giraud, & Kleinschmidt, 2003; Pinel, Dehaene, Riviere, & Le Bihan, 2001). We found the hIPS to be linked to the pSTS by a white matter track that could correspond to the posterior segment of the arcuate fasciculus, first described by Catani, Jones, and Ffytche (2005) in their dissection of the human perisylvian language network.

The second site of colateralization with the pSTS, located in the precentral gyrus, although found at a lower level of significance, has been repeatedly reported as being coactivated with the hIPS in nearly all arithmetic tasks requiring an active manipulation of numbers, by opposition to mere priming or adaptation paradigms (Pinel, Piazza, Le Bihan, & Dehaene, 2004; Delazer et al., 2003; Stanescu et al., 2000). It is noteworthy that the pSTS is quite remote from the precentral site (although probably connected to it via the arcuate fasciculus; see Schmahmann et al., 2007). Conversely, the precentral site shows an asymmetry entirely independent of the nearby sFG. Thus, covariations of asymmetry profiles, as identified by the present “colateralization analysis,” may reflect functionally significant connectivity rather than spatial proximity.

It is interesting that the superior temporal language area that colateralizes with the hIPS has been identified as important for mapping linguistic inputs onto the amodal representation of their meaning in adults. The pSTS can be activated by either written and spoken words or sentences (Beauchamp, Argall, Bodurka, Duy, & Martin, 2004), it appears essential for semantic-level processing of words and pictures (Vandenbulcke, Peeters, Dupont, Van Hecke, & Vandenberghe, 2007; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996), and it may form a high-level “convergence zone” linking symbolic and

nonsymbolic information (Damasio & Damasio, 1994). If so, the correlation between pSTS and hIPS asymmetry may reflect the mapping of abstract representations of number symbols (perhaps shared by Arabic numerals and by spoken and written number words), putatively coded in the left pSTS, to the corresponding numerical quantities, putatively coded in the hIPS. According to this scenario, although both left and right parietal lobes appear to encode numerosity, the left parietal region may be more susceptible to changes induced by the acquisition of number symbols because of more direct links with left hemispheric parietal and temporal areas involved in word processing. Piazza, Pinel, Le Bihan, and Dehaene (2007) first probed the convergence of symbolic and nonsymbolic representations of numbers using a cross-notation paradigm of fMRI adaptation (Arabic digits and sets of dots). They observed that the numerical information was transferred across those two notations in both the left and right hIPS, at a site only 6 mm from the present parietal area whose asymmetry correlates with the pSTS lateralization. Critically, Piazza et al. (2007) found a hemispheric asymmetry, suggesting that the coding of Arabic numerals was more precise in the left hIPS than in the right hIPS. They suggested that although both the left and right hIPS are involved in the coding of numerical quantities, the quantity code in the left hIPS is progressively refined through a direct interaction with number symbols coded in the left hemisphere, such as words or Arabic numerals. Verguts and Fias (2004) indeed showed in a neural network simulation how the interaction of symbolic and nonsymbolic codes for number could yield to such a refinement of the precision of number coding. A developmental study by Ansari and Dhital (2006) also observed that the left, but not the right, IPS exhibited an increase in the size of the numerical distance effect during a number comparison task—again compatible with the hypothesis that the left IPS is the target of a particular development, possibly including an increase in the precision of numerical coding induced by the concomitant acquisition of number symbols. Our study is compatible with this assumption and tentatively suggests that the primary source of this developmental change in the hIPS may be its direct connection with a high-level representation of numerical symbols in the pSTS.

Colateralization of the Language-related mFG and the SPL

We now turn to our second finding, the colateralization of the mFG during reading with a large extent of activation in the SPL and the precuneus during calculation. Although the SPL had been tentatively associated to visuospatial mechanisms in the context of fronto-parietal circuits (Astafiev et al., 2003; Simon et al., 2002), the mFG implicated here is much more inferiorly positioned, making this correlation of asymmetry more difficult to

interpret. The mFG site that we observed, located dorsally to Broca's region, has repeatedly been reported for both speech listening and word reading tasks (Mechelli et al., 2005; Binder et al., 2000), yet those studies did not isolate which specific linguistic process is involved. This site is also frequently activated during calculation tasks (see details in Pinel et al., 2007). It may tentatively reflect general working memory processes for storage and integration of information contained in a complex and extended verbal stimulus. Interestingly, it is known that although the frontal lobe supports working memory processes independently of the nature of inputs (Owen et al., 1998), additional posterior areas may be involved according to the nature of the content. For instance, Klingberg (2006) reported a developmental increase of the white matter connections linking frontal and superior parietal areas involved in a visuospatial memory task. Considering current theories that postulate shared mechanisms for numerical and visuospatial processing (Hubbard, Piazza, Pinel, & Dehaene, 2005), it may be proposed that, in the case of our arithmetical operations (displayed in a sentence-like presentation), which consisted of a simple canonical structure (first operand one, sign, second operand), the relation between these quantities would be jointly encoded syntactically in the mFG and spatially in the sPL. This recruitment of spatial networks would explain why numerical operations often elicit spatial attentional and motor biases (for a review, see Hubbard et al., 2005). Although speculative, this account fits with reports of impaired arithmetic procedural skills with preservation of number knowledge in the case of a frontal lesion (Lucchelli & De Renzi, 1993), and may also partially explain the spatial deficits reported in children with mathematical disabilities (Geary, Hoard, Byrd-Craven, & DeSoto, 2004; Noël, Seron, & Trovarelli, 2004).

DTI analysis showed that the colateralized mFG and sPL areas are connected by the anterior segment of the arcuate fasciculus (Catani et al., 2005). Note that although they showed similar profile of lateralization, no fibers were found to link the mFG and the precuneus. Because long-distance association fibers such as the superior longitudinal fasciculus are known to connect the frontal and posterior parietal lobes (Jellison et al., 2004), it is likely that dense local parietal connections may have artifactually limited the tracking algorithm to the anterior hIPS portion. It is also plausible that a cascade of local connections inside the parietal lobe propagates from the superior parietal lobe toward the precuneus via U-shaped association fibers.

Implications for the Development of Symbolic Arithmetic

It is tempting, although obviously speculative, to interpret the present across tasks colateralizations within a causal developmental framework. Although a detailed lateralization analysis similar to the present one remains

to be done with fMRI data from children, studies of early brain lesions and time windows for recovering linguistic abilities suggest that the hemispheric organization for language is already established within the first 5 years of life (Bates & Roe, 2001). Indeed, recent neuroimaging data indicate that a leftward lateralization of the temporal lobe can be observed during speech listening in infancy as early as 2 to 3 months after birth (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2004; Peña et al., 2003). A shift toward left hemispheric processing has been reported during a lexical task around 14 to 20 months old (Mills, Coffey-Corina, & Neville, 1997), and a strictly left-lateralized set of fronto-inferotemporal activations has been seen during an auditory semantic task in 5-year-olds (Balsamo, Xu, & Gaillard, 2006).

Contrariwise, in 5-year-old children, the number processing networks of the parietal lobe are equally activated in both hemispheres, for both digits and dots manipulation (Temple & Posner, 1998). With nonsymbolic presentations of numbers as sets of objects, activation during number processing may even show a rightward lateralization in 4-year-olds and even in infants (Izard, Dehaene-Lambertz, & Dehaene, 2008; Cantlon et al., 2007).

One possible interpretation of these lateralization patterns is that the pSTS lateralization for language precedes and progressively biases the lateralization of the hIPS for number. This implies that, although the pSTS is not part of the mature arithmetic circuit in the adult brain, proper functioning of the temporo-parietal language system may be crucial for the normal development and acquisition of mathematics. Such a developmental model would seem to fit well with the scarce developmental data available, to date, on how the number system evolves with age. Rivera, Reiss, Eckert, and Menon (2005) observed that the fMRI correlates of performance in a simple arithmetical task shifted from the frontal lobe toward a more focused temporo-parietal network as the age of the subjects varied from 8 to 19 years of age. The only two areas that increased in activity with age were a left inferior/middle temporal region and a left supramarginal/IPS region that both fall close to those observed in the present study. This fMRI result concurs with behavioral studies that indicate a progressive automatization and strengthening of the link between digit shapes and the corresponding quantities from first- to fifth-grade children (Rubinsten, Henik, Berger, & Shahar-Shalev, 2002). Indeed, in adults, this interference effect of an irrelevant Arabic digit onto a physical size comparison task has been related to intraparietal cortex (Pinel et al., 2004).

Based on this developmental scenario, it is then possible that the pivotal role of the left STS for symbol processing decreases later in life in the special case of number symbols, as number processing becomes highly automatized. Such a decrease would fit with the clinical dissociation between numerical and nonnumerical meaning reported at the adult age: Zamarian, Karner, Benke,

Donnemiller, and Delazer (2006) described a single-case study of a patient with of severe atrophy of the temporal lobe, who presented great difficulties in understanding or finding some words but performed at ceiling in number tasks, notably with all numerical formats in transcoding tasks.

Under the speculative hypothesis presented here, lateralization of the left STS would serve as a seed that constrains a subsequent cascade of secondary lateralization in the associative parietal cortices to which it is tightly interconnected (Andresen & Marsolek, 2005). It should be remembered, however, that the present correlational method is unable to assess the causality of these events. Genuinely testing this developmental model will therefore require an adaptation of the present methods to future longitudinal developmental fMRI data.

A Mosaic of Lateralizations

All in all, our study questions the very concept of hemispheric “dominance.” This concept, indeed, has been already challenged by occasional case studies that reported interhemispheric dissociations between language production and comprehension tasks (Dongwook et al., 2008; Jansen et al., 2006). Here we showed that, even within a given experimental situation such as sentence comprehension, the strongly left-lateralized speech processing network may be dissected into a complex combination of distinct patterns of asymmetry. Surprisingly, these patterns allow dissociating even closely located areas. For instance, the profile of asymmetry of the mFG is similar, during the reading task, to that of the fusiform area, but is uncorrelated with that of inferior frontal cortex. On the contrary, the latter region colateralizes strongly with remote sites in superior temporal and cingulate cortex. Thus, our results suggest that functional lateralization relates to a mosaic of partially independent left/right shifts, and results from a complex sum of regional events rather than a single overall “dominance” factor. The observed networks of long-range colateralizations may also reflect structural connections. For instance, the independent patterns of colateralization respectively associated with the pSTS and the aSTS appear to reflect fiber pathways that link the middle and posterior part of the superior temporal region to different areas of the frontal lobe in the monkey brain (Petrides & Pandya, 1988).

Our results refine the recent claim of Cai, Lavidor, Brysbaert, Paulignan, and Nazir (2008) and Hunter, Brysbaert, and Knecht (2007), who suggested that hemispheric dominance for spoken language production in the frontal lobe plays a causal role in the lateralization of the posterior reading system. Cai et al. (2008) based their claim on the observation of a colateralization of event-related potentials associated with orthographic processing (occipito-temporal N170) with those associ-

ated with verb generation (late frontal negativity), in a population of right-handed or left-handed subjects selected for their strong lateralization either to the left or to the right hemisphere in the latter task. Likewise, in a similar population, Hunter et al. (2007) found a shift in the optimal viewing position for reading to the hemifield contralateral the hemisphere that was found dominant (in frontal areas) for a verbal fluency task. In our population of normal right-handers, during reading we also found a strong colateralization of the fusiform activation with the mFG. However, there was no such colateralization with nearby inferior frontal or precentral sites, therefore indicating that lateralization must be considered at a finer scale than at the lobe level. Furthermore, the fronto-fusiform correlation vanished during the auditory speech listening task, whereas the pSTS–fusiform correlation remained very high (indeed it was the only one shared by the reading and speech listening tasks; see Table 1). These data suggest that the lateralization of orthographic processes in the fusiform may be driven much more strongly by the temporal lobe than by the frontal lobe.

The tight degree of colateralization of the pSTS with essentially all other language-related areas, especially during reading (Table 1), suggests that it represents a central node in the asymmetry of these subnetworks. This central role could be a direct consequence of the structural asymmetry which is already detectable prenatally in the planum temporale (Chi et al., 1977) and superior temporal sulcus (Dubois et al., 2008). An early asymmetry in the processing of speech sounds may create a subtle initial bias that contributes, during the development, to the establishment of a leftward asymmetry at other levels of the language system (Tervaniemi & Hugdahl, 2003; Bates & Roe, 2001).

Among the other possible determinants of the mosaic of asymmetry, our data suggest that sex is not a crucial one. We only observed a weak trend to a greater leftward asymmetry in the inferior frontal area for men (especially during speech listening) in an ROI approach, yet this was not replicated in the voxel-based analysis. This result is in accordance with a series of large-scale and meta-analysis studies (Sommer, Aleman, Bouma, & Kahn, 2004; Pujol, Deus, Losilla, & Capdevila, 1999), that found no significant sex differences for language lateralization at the population level across tasks, challenging widespread beliefs on men/women functional brain differences (Kimura, 1999; Shaywitz et al., 1995). This absence of sex effect was extended here to the left/right cortical organization of mental arithmetic. However, the lateralization of other numerical skills, such as arithmetical fact retrieval or approximate nonsymbolic calculation, should be explored further before concluding that men and women use strictly similar networks during arithmetic.

Recent results showed that many genes are expressed asymmetrically early on in fetal development (Sun,

Collura, Ruvolo, & Walsh, 2006), and that different cortical areas, noticeably peri-sylvian regions, may be characterized by different patterns of genetic expression (Abrahams et al., 2007) which, for some genes, seem specific to humans. These data indicate that the lateralization of the widespread human language networks is probably under various local genetic influences, perhaps through a cascade of successive influences on sulcal shape and connectivity patterns (Leonard, Eckert, & Kuldau, 2006). Indeed, the present fMRI analysis is part of a larger databasing effort for which fMRI, but also behavioral, connectivity and genetic data are also collected from hundreds of subjects (see Pinel et al., 2007). A next step will therefore be to clarify to what extent the patterns of collateralization reported here result from structural constraints, and at which level (fiber tracks, sulci, neural microstructures, or functional biases) do genetic factors induce local hemispheric preferences in regional brain organization.

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