Cerebral Cortex Advance Access published May 13, 2014

Cerebral Cortex
doi:10.1093/cercor/bhu048

Genetic and Environmental Influences on the Visual Word Form and Fusiform Face Areas

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Two areas of the occipitotemporal cortex show a remarkable hemispheric lateralization: written words activate the visual word form area (VWFA) in the left fusiform gyrus and faces activate a symmetrical site in the right hemisphere, the fusiform face area (FFA). While the lateralization of the VWFA fits with the leftward asymmetry of the speech processing network, origin of the rightward asymmetry for faces is still unclear. Using fMRI data from 64 subjects (including 16 monozygotic (MZ) and 13 dizygotic (DZ) twin pairs), we investigated how activations evoked by written words, faces, and spoken language are co-lateralized in the temporal lobe, and whether this organization reflects genetic factors or individual reading expertise. We found that the lateralization of the left superior temporal activation for spoken language correlates with the lateralization of occipitotemporal activations for both written words and faces. Behavioral reading scores also modulate the responses to words and faces. Estimation of genetic and environmental contributions shows that activations of the VWFA, the occipital face area, and the temporal speech areas are partially under genetic control whereas activation of the FFA is primarily influenced by individual experience. Our results stress the importance of both genetic factors and acquired expertise in the occipitotemporal organization.

Keywords: FFA, genetic, reading, temporal, VWFA

Introduction

The occipitotemporal cortex has been described as a mosaic of functional preferences (Haxby et al. 2001) comprising distinct and partially specialized cortical sectors for the encoding and recognition of various categories of visual stimuli such as faces, objects, houses, or words. The topological organization of this mosaic is remarkably consistent across the population (Ishai et al. 1999; Hasson et al. 2003).

Two of its prominent peaks present a high degree of hemispheric specialization. First, the activation evoked during the visual presentation of orthographic stimuli is strongly left-lateralized at an invariant position in the left fusiform cortex in most right-handers (Puce et al. 1996; Cohen et al. 2000), regardless of the writing system used (Bolger et al. 2005; Nakamura et al. 2005; Baker et al. 2007). Recent fMRI studies revealed functional specialization for word reading in this region, such as mirror invariance or orthographic sensitivity (Dehaene and Cohen 2011; Pegado et al. 2011; Hamamé et al. 2013; Liu et al. 2013). Cohen and his collaborators proposed to label this region the visual word form area (VWFA) (Cohen et al. 2000) and suggested that it houses a neural code for written words and pseudowords, although reports of activation of this region by non-word stimuli (Xue et al. 2006; Mei et al. 2010; Kherif et al. 2011) raised a debate concerning this proposal (Dehaene and Cohen 2011; Price and Devlin 2011). Second, the fusiform face area (FFA), a region preferentially activated by faces (Puce et al. 1996; Kanwisher et al. 1997; Yovel et al. 2008), is generally described as showing a preferential lateralization to the right hemisphere (McCarthy et al. 1997; Haxby et al. 1999; Dien 2009), which may however vary with the task (Rossion et al. 2000) and experimental procedure (Mercure et al. 2008). The FFA is a part of a larger ventral network responding to faces (O'toole et al. 2005), which includes a left-hemispheric homolog (lFFA) and bilateral posterior sites in the occipitotemporal cortex, usually referred as the occipital face areas (OFA) (Gauthier et al. 2000; Gobbini and Haxby 2007), which may be crucial for face identification (Schiltz et al. 2006).

The lateralization of visual recognition processes to opposite hemispheres for written words and for faces is supported by several brain lesion studies. While a restricted left-hemispheric lesion of the VWFA may produce pure alexia (Epelbaum et al. 2008), brain-damage restricted to the right fusiform cortex may be sufficient to produce prosopagnosia (Bouvier and Engel 2006; Schiltz et al. 2006).

Intriguingly, the VWFA and right FFA are located at nearly symmetrical positions (Kanwisher et al. 1997; Cohen and Dehaene 2004). The left-hemispheric location of the VWFA is thought to be constrained by its functional links with the spoken language network (Cai et al. 2008; Pinel and Dehaene 2009; Yoncheva et al. 2010), which is known to present a leftward asymmetry early in life, both functionally (Dehaene-Lambertz et al. 2002, 2010) and anatomically (Dubois et al. 2008; Kasprian et al. 2011; Habas et al. 2012), possibly under the influence of genetic factors (Sun et al. 2005; Pinel et al. 2012). For faces, however, the origins of the right-hemispheric lateralization of the FFA remain unknown. It might reflect a generic, early and genetically determined asymmetric organization of the visual brain, for instance for processing low visual frequencies (Woodhead et al. 2011). Alternatively, it might arise as a late consequence of developmental constraints appearing during the specialization of the occipitotemporal cortex, particularly during reading acquisition.

In support of the first view, recent studies showed that the strength of the lateralization of the FFA varies with the subjects' handedness (Willems et al. 2010). This suggests that a generic

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trait of asymmetry such as handedness, which also correlates with the lateralization of language (Knecht, Deppe, et al. 2000; Szaflarski et al. 2002), may have a broad impact on several aspects of functional hemispheric specialization, all the way down to visual areas. It is not implausible that the genetic factors that contribute to human handedness (McManus 1991; Francks et al. 2007) have broad influences on the cortex and may therefore impact on both language and FFA lateralization. While it did not directly address the issue of hemispheric asymmetry, an fMRI study of twins showed that the distribution of activity within the occipitotemporal cortex was partially inherited for faces and places, but not for pseudoword recognition (Polk et al. 2007).

According to the second view, the opposite lateralization of the VWFA and the FFA might result from a cortical competition process that would appear late in life, during the acquisition of a new expertise for reading (Dehaene et al. 2010; Cantlon et al. 2011; Scherf et al. 2011). Face and letter string identification share a requirement for detailed foveal processing. In the framework of the neuronal recycling hypothesis (Dehaene and Cohen 2007), it is assumed that learning to read reshapes the specialization profile of ventral visual areas, "recycling" part of the circuitry for invariant object and face recognition and reorienting it to process letters and their combinations (Dehaene 2005; Dehaene and Cohen 2007). Given that spoken language processing is lateralized to the left hemisphere in most right-handers, this recycling process would occur primarily in the left occipitotemporal cortex, thus displacing the fusiform face-sensitive areas toward the right hemisphere. In support of this view, a recent fMRI study comparing literate versus illiterate adults showed that acquisition of reading expertise induces both an increase in activation in response to visual words, and a reduction in activation to faces within the same left occipitotemporal area (Dehaene et al. 2010). A similar result was observed when comparing normal and impaired 9-year-old readers: not only responses to words were less left-lateralized but responses to faces were less right-lateralized in impaired readers (Monzalvo et al. 2012). These results, as well as the proximity of fusiform activations for faces and words in the left hemisphere (Puce et al. 1996; Hasson et al. 2002), comfort a model where words and faces compete for the same restricted neural territory (Dehaene 2005; Dehaene and Cohen 2007; Plaut and Behrmann 2011). The VWFA localization would therefore be ultimately determined by bottom-up visual constraints (sensitivity to high-spatial frequencies, foveal inputs, and combinations of contours) (Hasson et al. 2002) and by top-down linguistic inputs (Cai et al. 2008; Pinel and Dehaene 2009), both of which are partially genetically determined. According to this view, we would predict an influence of spoken language lateralization on the occipitotemporal responses to both written words and to faces. We would also predict that the VWFA activation and lateralization might be under as tight genetic control as the FFA (contra Polk et al. 2007).

To explore the links that may exist between the functional organization of face-, word-, and speech related regions of the ventral temporal lobe and to revisit the issue of their genetic determinants, we examined the inter-subject variability in a large cohort of typically developed adult subjects. We used fMRI to map the FFA, the OFA, the VWFA and the left temporal language-related network. We investigated how they co-lateralize and whether the hemispheric asymmetry of face areas is negatively correlated to the asymmetry of the VWFA and of language areas. Because our population included monozygotic (MZ) and dizygotic (DZ) twin pairs, we could estimate the relative contribution of environmental and genetic factors in the fMRI response of these regions. Finally, we tested whether the functional organization of these face-, word-, and speech-related regions were under the influence of shared genetic components and/or altered by the individual variations of an un-inheritable reading ability.

Materials and Methods

Subjects

Sixty-seven healthy male adults participated in our study, and 64 were kept in the final analysis (3 subjects were rejected for high movement in the scanner). This group was composed of 13 pairs of DZ twins (average age: 21.7 years old ± 3.6), 16 pairs of MZ twins (average age: 24.7 years old ± 5.6) and 6 additional unrelated subjects of similar age. For most of our subjects, pediatric data were available. No significant difference at birth was noted between MZ and DZ pairs (mean birth weight difference is 10.1% for DZ (SD 7.8), 9.4% for MZ (SD 8.3). Mean duration of gestation was also comparable (37.1 weeks [SD 2.8] for DZ, 38.6 weeks (SD 2.3) for MZ). All participants were right-handed (Edinburgh inventory) and did not present any neurological pathology or dyslexia.

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 was 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.

fMRI Experimental Design

Subjects performed 2 runs of a 1-back task on 6 categories of visual items, designed to map occipitotemporal regions responsive to words, digits, faces, houses, tools, and hand actions. An additional category (scrambled images of the previous items) served as control condition. For each category, 96 images were presented in short blocks of 8 images (1 per second, 6 blocks per session). Subjects had to press a button with their left thumb for each stimulus repetition (50% of blocks had 1 repetitions, 33% had 2 and 17% had 3). Categories were presented in a randomized order and separated by 8 s of white screen.

Subjects also performed 2 runs of an auditory task, during which they heard via earphones 3 randomly mixed type of stimuli: 10 French sentences, 10 Korean sentences (not considered here) and 10 series of 5 pure tones (predetermined random combination composed among 8 different tones ranging from 561 Hz up to 2233 Hz, avoiding the peak frequency of magnetic resonance acoustic noise, ~798 Hz). Each stimulus (2.5 s) was followed after 800 ms of silence by a short fragment of 500 ms. Subjects had to press a button with their left thumb if they considered this fragment to be a part of the prior stimulus (50% of trials). Total stimulus length was 3.8 s, presented with an ITI of 7 s, and comprising 25% of blank trials (speech stimuli and the task are derived from the study of Pallier and collaborators (Pallier et al. 2003).

Additional runs, designed to map the fronto-parietal networks supporting numerical and non-numerical processing, were acquired but will not be reported here. Before scanning, all subjects were trained with another set of stimuli to ensure they correctly understood the instructions and performed well.

Acquisition, Preprocessing and Analysis of MRI Images

Images were acquired on a 1.5T MRI scanner (General Electric Signa System) in ascending interleaved order (TRo = 2400 ms, TE = 30 ms, matrix size = 64 × 64, FOV = 24 × 24 cm). 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 statistical parametric mapping (SPM) software in Matlab environment according to the following procedure:

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slice timing, subject motion estimation and correction by realignment, co-registration of the anatomical image to the Montreal Neurological Institute (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). Visual and auditory trials were modeled as block function, with a length of 15 and 7 s. respectively.

Individual contrast images were generated using SPM to map the brain responses to auditory and visual stimuli: written words versus scrambled images, faces versus scrambled images, and spoken French sentences versus tones. Because each block was repeated twice, we could define, for each category, an overall contrast, based on all stimuli of that category pooled over the 2 runs, as well as 2 single-session contrasts. We also computed from these contrast images individual maps of hemispheric functional asymmetry: activation from the left hemisphere was subtracted voxel by voxel from the homologous right hemisphere activation. To correct for macroscopic anatomical asymmetries between homolog regions (e.g., the right sylvian scissure is steeper and shorter than the left (Toga and Thompson 2003), we first normalized the individual flipped anatomy onto the original anatomical image, using the standard SPM normalization. This should maximize alignment between the left and the flipped right anatomical structures. We then applied this correction onto the flipped functional maps and performed the subtraction of the original and flipped contrast images.

Random effect analyses (RFX) were performed with SPM ($P < 0.05$ after family-wise error correction for multiple comparisons). RFX on activation were confined to a bilateral mask of gray matter, and RFX on asymmetry were restricted to 1 hemisphere only (positive values corresponding to larger activations in the left hemisphere and negative values in the right).

Extraction of Hemispheric Activation and Laterality Index

For each peak isolated in the group analysis, individual activation and laterality indices (LIs) were computed. 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 2 spheres (radius = 12 mm) centered on the group 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, in order to ensure 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. While the number of selected voxels could vary from 0 (no activated voxel surviving the threshold) to 13 (representing 5% of the sphere), we observed that a similar amount of voxels was considered across subjects, peaks, and hemisphere. Average number ranged from 12.5 to 13 for the left hemisphere peaks and from 9.8 to 13 for the right hemisphere peaks.

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 or her twin brother. LI analysis was therefore performed on 16 MZ pairs and 13 DZ pairs.

Before testing for between-subjects correlation, an essential requirement is to guaranty the robustness of individual measures. Individual LIs were therefore computed, not only from the overall contrast pooled overall all fMRI runs, but also from images separately computed from the first and second runs. We could then estimate the intrasubject reliability of the proposed fMRI measures (i.e., measurable L.I, left and right activation). Because each session comprised only half of the total trials, we reduced the stringency of the clustering criteria, considering voxels belonging to clusters with a minimal size of 2 voxels.

Additional fMRI Analysis in an Independent Cohort

To replicate our co-lateralization analysis in an independent cohort, we examined contrast from 2 short functional localizers collected in the same session on 78 additional healthy adults (whole brain acquisition with a Siemens 3T scanner, TR = 2400 ms, voxel size = 3 × 3 × 3 mm). A functional contrast of speech processing was computed by comparing passive listening of 10 short French sentences to rest. Similarly, a functional contrast of word processing was computed by comparing silent reading of 10 short sentences to passive exposure to twenty flashing checkerboards [see full description in Pinel et al. (2007)]. Two functional contrasts were computed for face processing (adapted from Winston et al. 2002). Subjects saw 64 black and white images of faces projected during 500 ms on a video screen. In half of them, they saw an instruction (1 s) asking them to judge the trustworthiness of the face (silently pronouncing "yes" or "no"). In the other half, they were asked to determine the gender of the face and silently pronounce it ("male" or "female"). These activations were compared with a judgment task on the verticality of 32 images of checkerboards that were slightly inclined or not ("yes" or "no"). These 3 tasks were presented in a fixed random order. We used the corresponding coordinates found in the twin cohort to calculate LIs of the VWFA (word task), of the FFA and OFA (face task) and of the mSTS and pSTS (speech listening task).

Correlation Between fMRI and Behavior

We performed a series of analyses aimed at determining the correlations between activation patterns and subjects' reading performance. Two measures were available from a battery of tests routinely used in our fMRI protocols: the time needed to read a list of 20 words (10 short irregular words with a 3–4 letters length plus 10 long irregular words with a 7–9 letters length) and the time to read a list of 20 pseudowords equated to words for length and number of phonemes. Subjects had to read aloud each list as fast as they could while minimizing errors. These tests were designed to provide in a short time a rough sketch of individual reading performance. We acknowledge that the word reading test alone was not sensitive enough to exhibit relevant variation among normal adult readers, as a significant proportion of its variance-reflected nonlinguistic effects (articulation or executive speed). To sidestep this problem, we used here a normalized pseudoword reading time (RT), which reflects the increase of time when reading pseudowords compared with words (lexicality effect) and defined as follows: (pseudoword RT − word RT)/(pseudoword RT + word RT). While pseudoword reading requires an active grapheme-to-phoneme conversion, it also reflects an individual's ability to efficiently use orthographic knowledge, given the presence of pronounceable word-like sublexical components inside pseudowords (for instance, the pseudoword "evaloupe" is composed of the letters strings "eva" + "loupe" which exist in French) (Coltheart et al. 2001; Marinus and de Jong 2008).

For each peak of interest, ROI-based correlations were computed between individual normalized pseudoword RT and LI or activation level (see above). Additional voxel-based regression analyses were also performed between reading score and the individual images of functional asymmetry of face- and word-related activation within a priori defined FFA and VWFA regions. We computed the intersection of a gray matter mask with 3 spheres of 10 mm radius centered on coordinates reported in a meta-analysis of the left VWFA (−43, −54, −12, Cohen and Dehaene 2004), and the left and right FFA peaks of the seminal paper of Kanwisher and collaborators (Kanwisher et al. 1997) (−35, −63, −10 and 40, −55, −10, respectively).

Genetic Analysis

Overall Analysis

We first determined which brain measure (activation levels and lateralization indices) presented at least a significant ($P < 0.05$) correlation between MZ twins. For these selected measurements, we report an estimated heritability, which represents the proportion of phenotypic variation attributable to genetic variation. We used 2 classical definitions: $h^2_F = 2(R_{MZ} - R_{DZ})$ (Falconer 1960) and $h^2_H = (R_{MZ} - R_{DZ})/(1 - R_{DZ})$ (Holzinger 1929), where R is the intraclass correlation in 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).

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Elimination of Unreliable Subjects

We took advantage of the 2-run design to calculate the intrasubject reliability in the MZ and the DZ cohort for each measure (see Supplementary Fig. 1*a*). Subjects who presented the largest discordance between their 2 runs were rejected, until we obtained a significant between-runs correlation ($P < 0.05$) within both the MZ and DZ groups for a given measure. Depending on the measure, this procedure reduced the number of DZ pairs by 1 to 3 pairs. The intrasubject correlation analysis was extended to twins pairs (Supplementary Fig. 1*b*). While each of these estimations is based on half the total number of trials and may be then less precise than the overall analysis, this ensures similar error of measurement for MZ and DZ groups. Additionally, we could even compare the MZ and DZ twin cross-sessions correlations with intrasubject cross-sessions correlation, which reflect reliability of our measure.

ACE Model

To estimate more precisely the relative contribution of genetic and non-genetic factors, we fitted a univariate ACE model to MZ and DZ covariance matrices (Supplementary Fig. 2). This model decomposes twin- pair similarities into 3 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.

Voxel-Bases Analysis of Twin Correlation

We performed an additional voxel-based analysis comparable to the work of Polk et al. (2007). For each pair of twins, we computed, for a given contrast map (e.g., written words > scrambled), the correlation between the activation levels observed in twin 1 and twin 2, where the correlation is calculated across all voxels included in an occipitotemporal functional mask (isolated from group activation for all categories versus rest). We reported the average correlation for MZ, DZ, and pairs of unrelated individuals (random association of 2 subjects within the entire twin cohort) for the word and face contrast. Similarly, we computed the correlation between siblings' gray matter density maps to estimate the resemblance of twins' anatomical structures.

Results

Activations and Functional Asymmetries in the Temporal Lobe

The 3 networks recruited by written word perception, face perception, and native speech processing covered several frontal and temporal areas (thereafter, ROIs are referred to as $\text{Area}_{\text{task}}$, using both the name of the area and the experimental task used to activate it). We focused our study on the inferior temporal peaks evoked by written words in the left-hemispheric $\text{VWFA}_{\text{word}}$ (x, y, z MNI coordinates = −42, −48, −15, $t = 5.10$), by faces in the right-hemispheric (FFA_{face}: 42, −60, −24, $t = 12.07$; OFA_{face}: 39, −84, −12, $t = 10.89$) and by spoken sentences in the native language in the basal temporal area ($\text{BTA}_{\text{speech}}$: −42, −51, −21, $t = 8.78$) (Fig. 1). We also investigated anterior, middle, and superior temporal peaks recruited

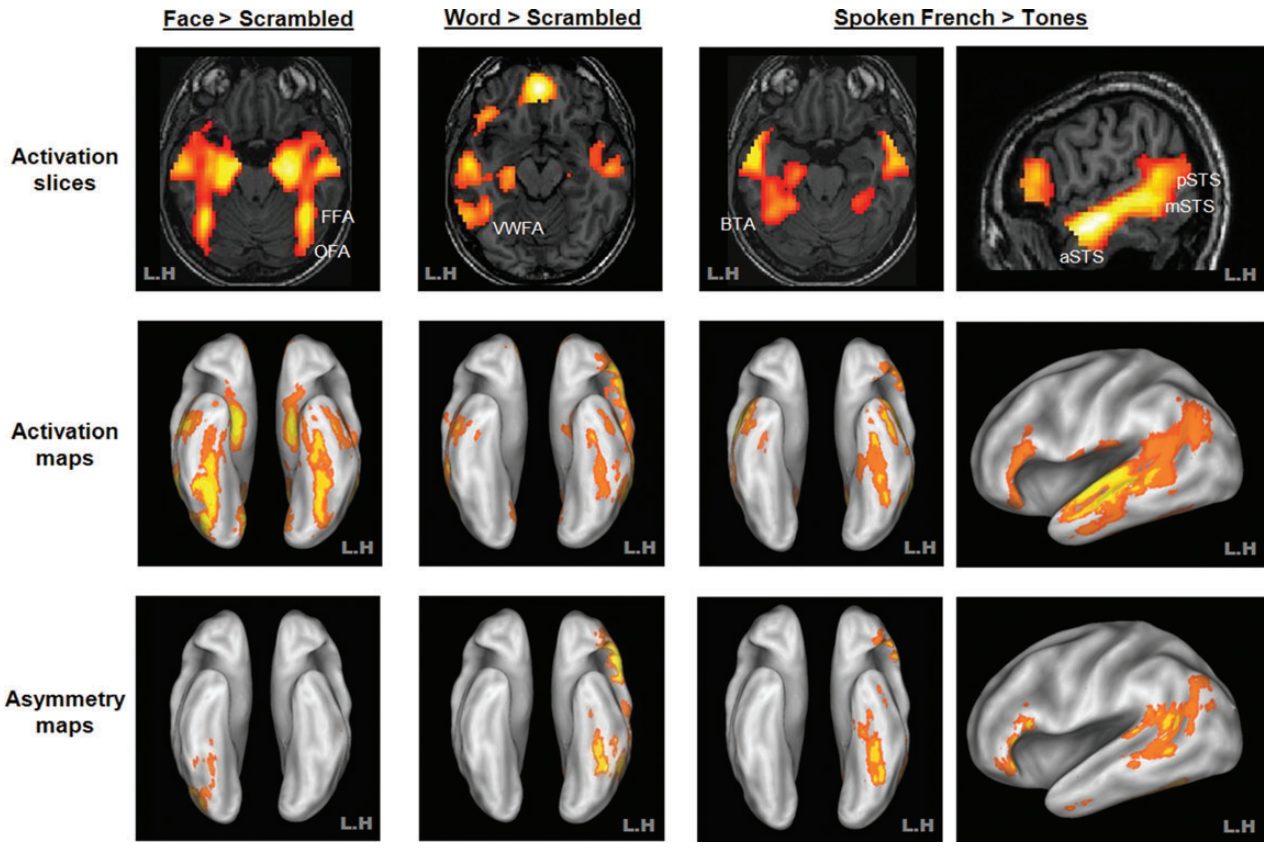

Figure 1. Activation and hemispheric asymmetries during written words, faces, and spoken language processing. The figure shows the results of a group analysis of activation and asymmetry maps for written words, faces, and speech processing relative their respective control tasks (displayed at $P < 0.05$ corrected for cluster extent, with a voxel-wise threshold of $P < 0.001$). In the first row, activations and peaks of interest are displayed on representative axial and sagittal views (L.H = left hemisphere). The 2 other rows show ventral and left lateral 3-dimensional views of the group activation and asymmetry maps projected on an inflated brain (Caret software).

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Table 1
Co-lateralization analysis

	$VWFA_{readier}$	FFA_{face}	OFA_{face}	BTA_{speech}	$aSTS_{speech}$	$mSTS_{speech}$	$pSTS_{speech}$
$VWFA_{reading}$	$r = 1$						
FFA_{face}	$r = 0.047$ $P = 0.725$	$r = 1$					
OFA_{face}	$r = -0.207$ $P = 0.120$	$r = 0.258$ $P = 0.050$	$r = 1$				
BTA_{speech}	$r = 0.278$ $P = 0.035$	$r = 0.094$ $P = 0.485$	$r = -0.039$ $P = 0.774$	$r = 1$			
$aSTS_{speech}$	$r = 0.285$ $P = 0.030$	$r = -0.116$ $P = 0.385$	$r = -0.312$ $P = 0.017$	$r = 0.290$ $P = 0.027$	$r = 1$		
$mSTS_{speech}$	$r = 0.326$ $P = 0.012$	$r = -0.314$ $P = 0.017$	$\mathbf{r = -0.475}$ $\mathbf{P = 2.10^{-4}}$	$r = 0.295$ $P = 0.025$	$\mathbf{r = 0.663}$ $\mathbf{P = 10^{-8}}$	$r = 1$	
$pSTS_{speech}$	$r = 0.119$ $P = 0.372$	$\mathbf{r = -0.403}$ $\mathbf{P = 2.10^{-4}}$	$r = -0.360$ $P = 0.006$	$r = 0.198$ $P = 0.137$	$\mathbf{r = 0.407}$ $\mathbf{P = 0.002}$	$\mathbf{r = 0.601}$ $\mathbf{P = 6.10^{-7}}$	$r = 1$

Note: Correlations between the lateralization indices of the temporal-lobe peaks responsive to written words, faces, and spoken language in the twin cohort. Gray shadings indicate uncorrected $P < 0.05$. Effects that reach significance at corrected $P < 0.05$ appear in bold (corresponding to uncorrected $P < 0.0024$, after correction for 21 tests).

by native speech listening ($aSTS_{speech}$: −66–27, 0, $T = 16.11$; $mSTS_{speech}$: −63, −42, 0, $t = 11.07$; $pSTS_{speech}$: −60, −54, 12, $t = 7.26$). Group analysis of functional asymmetry confirmed that all these regions were lateralized (Fig. 1). Performing a Student *t*-test analysis on the LIs of the 6 peaks of interest, we confirmed the significant leftward lateralization for the $VWFA_{word}$ ($P = 6 \times 10^{-11}$, mean LI = −0.36), the BTA_{speech} ($P = 1.5 \times 10^{-6}$, mean LI = −0.24), the $mSTS_{speech}$ ($P = 6 \times 10^{-5}$, mean LI = −0.17) and the $pSTS_{speech}$ ($P = 10^{-11}$, mean LI = −0.31), and the significant rightward lateralization for FFA_{face} ($P = 10^{-8}$, mean LI = +0.18) and the OFA_{face} (2.4×10^{-6}, mean LI = +0.19).

Correlations between Functional Lateralization Indices

Lateralization indices of the temporal speech areas were strongly intercorrelated (Table 1). Interestingly, both FFA_{face} and OFA_{face} LIs presented a strong negative correlation with the $pSTS_{speech}$ LI ($r = -0.403$, corrected $P = 0.048$) and with the $mSTS_{speech}$ LI ($r = -0.475$, corrected $P = 0.005$), respectively. We replicated these negative correlations in an independent cohort (Table 2). The $VWFA_{word}$ lateralization did not show any correlation with face areas LIs (in any of the 2 cohorts). However, in a direct replication of our earlier results (Pinel and Dehaene 2009), the $VWFA_{word}$ lateralization correlated positively with the lateralization of speech areas though at an uncorrected threshold ($P = 0.012$). An additional exploratory analysis of the correlations of the $VWFA_{word}$, FFA_{face} and OFA_{face} with the inferior frontal activation during speech processing (−51, 27, −3) did not show any significant result, except a trend toward an anticorrelation between the frontal site and the FFA_{face} ($P = 0.054$).

We then investigated in more details how the lateralization of temporal speech areas related to the $VWFA_{word}$ and the FFA_{face} in terms of left-/right-hemispheric activation. Splitting the group into the lower and upper 25th percentile for leftward lateralization in $mSTS_{speech}$ revealed that subjects with a strong left lateralization for spoken language have a significantly stronger left-hemispheric lateralization in $VWFA_{word}$ and a non-significant trend toward a larger right-hemispheric lateralization in FFA_{face} (Fig. 2*A*). These effects were driven by a significant lower activation in the right $VWFA_{word}$, without any significant change in the left $VWFA_{word}$ (generating a significant group × hemisphere interaction $F_{1,54} = 3.95$, $P = 0.051$) and similarly a significant lower activation in the left FFA_{face} and no significant change in the right FFA_{face} (without, however, a significant group × hemisphere interaction). In summary, for both written words and faces, changes in lateralization were primarily driven by a modulation in the strength of the activation evoked in the hemisphere opposite to the predominantly active one.

Table 2
Co-lateralization analysis in an independent cohort

	Sex task vs. control		Trustworthiness task vs. control	
	FFA_{face}	OFA_{face}	FFA_{face}	OFA_{face}
$mSTS_{speech}$	$\mathbf{r = -0.31}$ $\mathbf{P = 0.006}$	$r = -0.23$ $P = 0.044$	$\mathbf{r = -0.31}$ $\mathbf{P = 0.006}$	$\mathbf{r = -0.33}$ $\mathbf{P = 0.003}$
$pSTS_{speech}$	$r = -0.27$ $P = 0.016$	$r = -0.23$ $P = 0.042$	$r = -0.18$ $P = 0.105$	$\mathbf{r = -0.32}$ $\mathbf{P = 0.004}$
$VWFA_{reading}$	$r = -0.018$ $P = 0.872$	$r = -0.003$ $P = 0.979$	$r = 0.019$ $P = 0.867$	$\mathbf{r = -0.041}$ $\mathbf{P = 0.725}$

Note: Correlations were computed using either a sex recognition task or a trustworthiness judgment task performed on faces. Gray shadings indicate uncorrected $P < 0.05$. Effects that reach significance at corrected $P < 0.05$ appear in bold (corresponding to uncorrected $P < 0.0083$, after correction for 6 tests applied on these 2 independent sets).

A similar analysis, now splitting subjects according to their $pSTS_{speech}$ LI, showed that stronger leftward lateralization in this area was associated with a stronger rightward lateralization of the FFA_{face} (Fig. 2*B*), characterized by a significant lower activation in the left FFA_{face} (group × hemisphere interaction $F_{1,54} = 4.13$, $P = 0.047$). However, in this case, no significant effect was found on the pattern of activation of the $VWFA_{word}$.

Association with Reading

Correlation analyses between normalized pseudoword RT and ROI-based functional data revealed that normalized pseudoword RT correlated negatively with the rightward lateralization of the FFA_{face} ($r = -0.32$, $P = 0.014$) and with the leftward lateralization of the $pSTS_{speech}$ ($r = -0.26$, $P = 0.047$). No significant effect on the $VWFA_{word}$ asymmetry or activation was found ($P > 0.1$). This result was comforted when we directly compared the fMRI data of 2 groups of subjects defined by the highest and lowest normalized pseudoword RTs (25th percentiles). A faster pseudoword RT correspond to higher rightward FFA_{face} LIs (Fig. 3), corresponding to a trend toward a lower left FFA activation and a higher right FFA_{face} activation (although the group × hemisphere interaction was above

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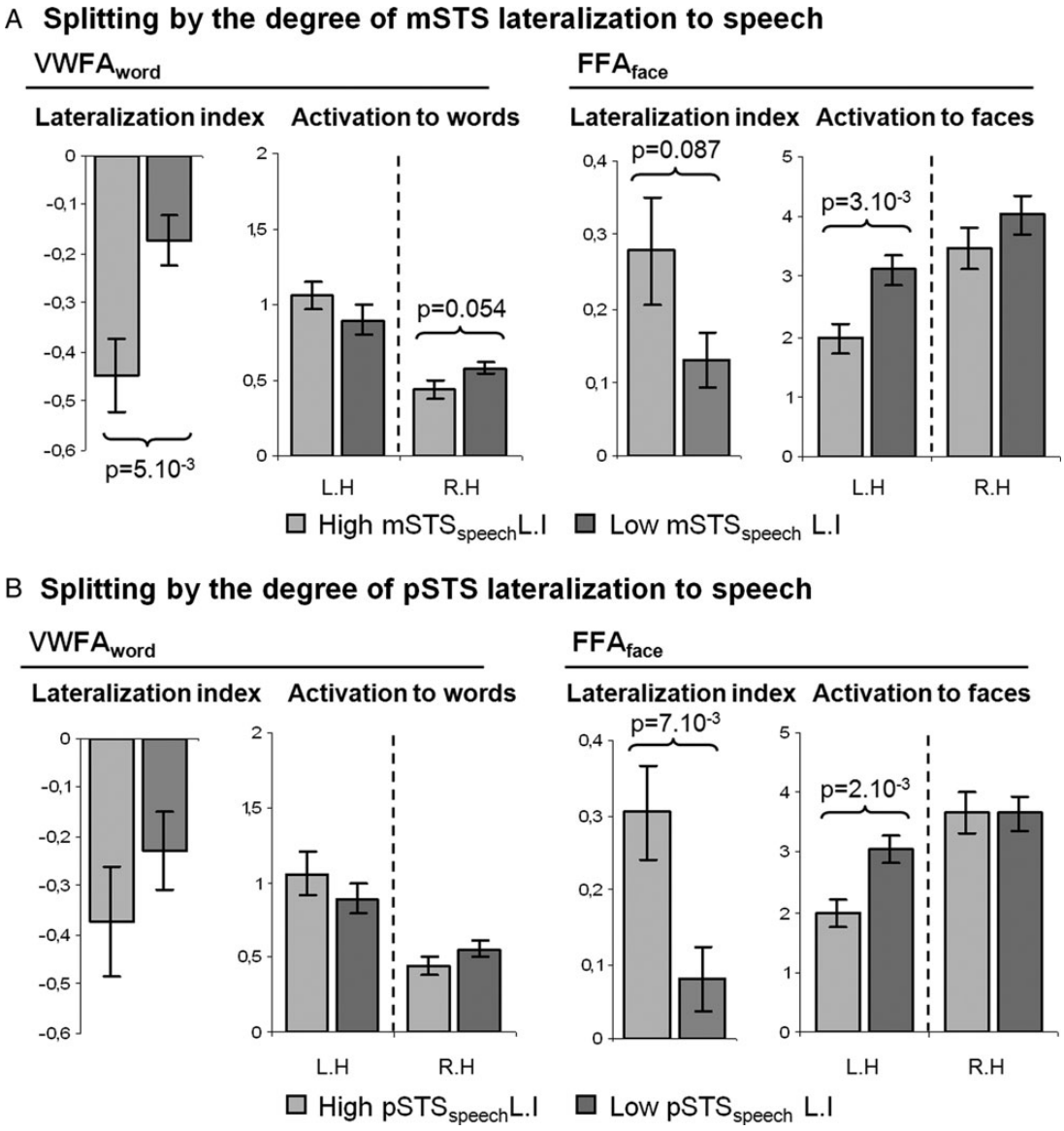

Figure 2. Spoken language lateralization correlates with the organization of the ventral visual responses to written words and faces. The figure shows the LIs and left- and right-hemispheric activations at the coordinates of the $VWFA_{word}$ and FFA_{face}, as a function of STS_{speech} lateralization. Subjects were split into 4 quartiles according to their degree of lateralization for the mSTS (*A*) or for the pSTS (*B*) during the speech task. Significant *t*-tests between the lower and upper 25th percentile for LI, for left-hemispheric activation level (L.H) and for right-hemispheric activation level (R.H), are reported. Analyses of group × hemisphere interactions are reported in the text.

the significance level; $F_{1,62} = 3.01$, $P = 0.088$). A voxel-based regression with normalized pseudoword RT confirmed a significant change of asymmetry for the face task within the a priori defined left FFA_{face} (Fig. 4*A*), but also inside the a priori defined $VWFA_{word}$ (Fig. 4*B*). Regressions in experimentally defined ROIs failed to reach significance at the corrected threshold.

The fact that we detected an association of reading behavior with the $VWFA_{word}$ lateralization in the voxel-based but not in the ROI-based approach suggests that reading performance may correlate better with the anatomical location than with the amount of activity of the $VWFA_{word}$. Indeed, a comparison of the coordinates of the left $VWFA_{word}$ between subjects with highest and lowest normalized pseudoword RTs (25th percentiles) revealed a significant group effect on the *y*-axis ($P = 0.034$) but not on the *x*-axis ($P = 0.375$) nor on the *z*-axis ($P = 0.394$). This effect, illustrated in Figure 4*C*, reflects a progressively more anterior position for the $VWFA_{word}$ as reading fluency increases, and a shorter distance to the peak of the BTA_{speech}.

Model Fitting of the FFA Lateralization with Language-Related Regressors

Because the FFA_{face} asymmetry was found to be significantly associated with both $pSTS_{speech}$ lateralization and normalized pseudoword RT, we fitted the LI of the FFA_{face} using a linear model with these 2 predictors. We obtained the following multiple regression ($F_{2,53} = 7.273$, $P = 0.0016$): LI $FFA_{face} = 0.286 - 0.255 \times [\text{LI } pSTS_{speech}] - 0.610 \times [\text{normalized pseudoword RT}]$. This model explains 19% of the variance of the FFA_{face} lateralization (the 2 variables LI $pSTS_{speech}$ and normalized pseudoword

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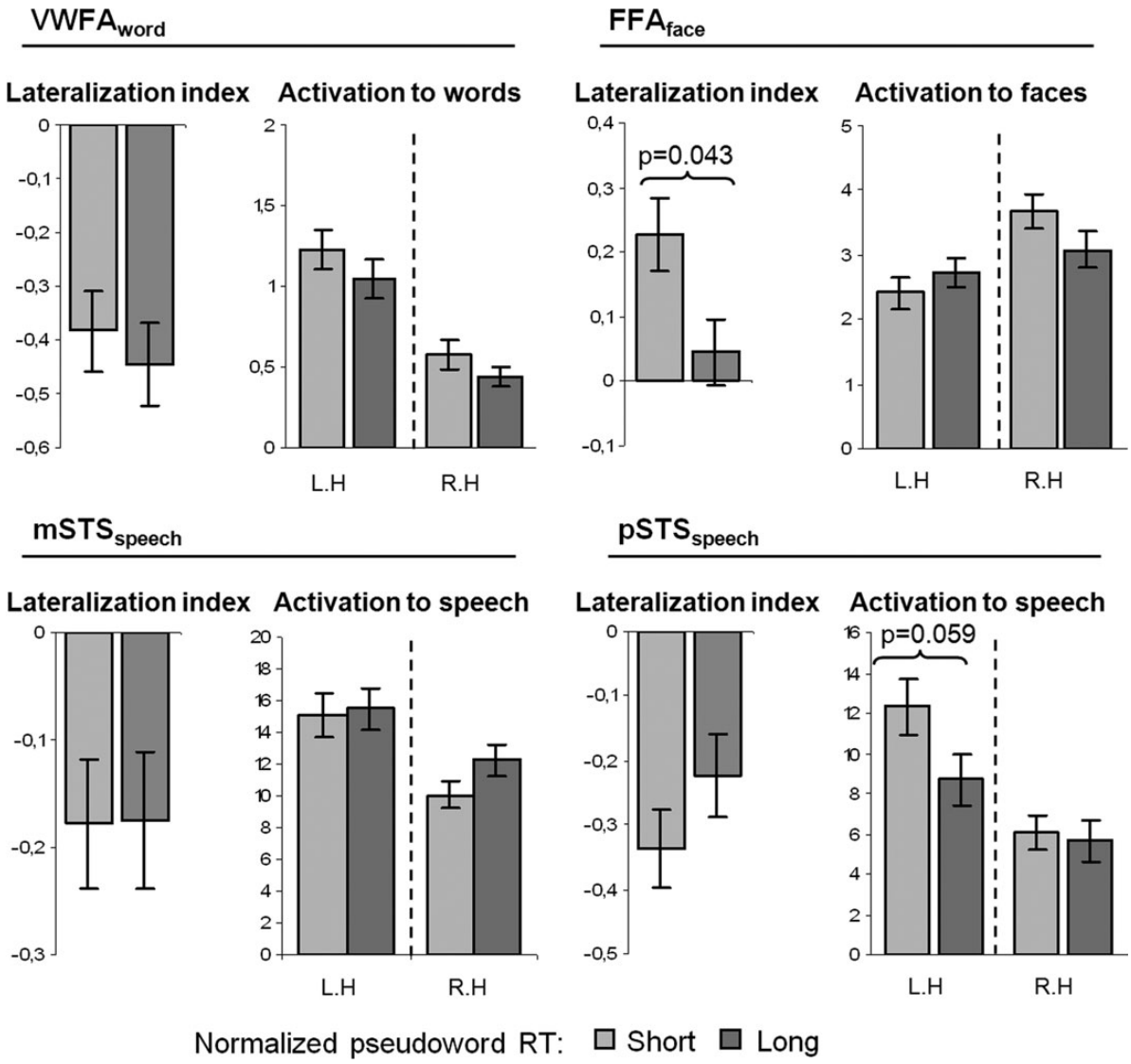

Figure 3. Influence of pseudoword reading speed on asymmetry and hemispheric activations in the temporal cortex. Subjects were split in quartiles according to their normalized pseudoword reading speed. Significant *t*-tests between the lower and upper 25th percentile for LI, for left activation level (L.H), and for right activation level (R.H) are reported. It can be seen that a short pseudoword RTs correlates with a strong right-hemispheric FFA lateralization, and with a higher activation of the left pSTS to speech. Analyses of group × hemisphere interaction are reported in the text.

RT, respectively, explain 14 and 7% of the variance). Model comparison shows that this multiple-regression model is significantly better than a regression with LI $pSTS_{speech}$ alone ($P = 0.045$) or with the behavioral reading score alone ($P = 0.005$).

Genetic and Environmental Contributions to Reading Performance and to Brain Responses

Reading Performance

Fitting the univariate ACE model on normalized pseudoword RT suggests that the normalized pseudoword RT score predominantly reflects environmental influences (mostly from non-shared environment) ($R_{MZ} = 0.24$, $R_{DZ} = 0.62$; $a = 0$, $c = 0.242$, $e = 0.758$).

MZ and DZ Correlation for Brain Measures

To evaluate the genetic contribution to brain activation patterns, for each ROI we calculated intrapair correlations within MZ (R_{MZ}) and DZ (R_{DZ}) groups for left activation, right activation and L.I (Table 3). Ten brain measures presented a significant correlation between MZ twins ($P < 0.05$), which was the minimal requirement to further study the effect of genetic or environmental influences. Remarkably, a significant R_{MZ} was found for the $VWFA_{word}$ and for the OFA_{face} measures, but not for the FFA_{face}. We wondered whether this result was due to a lower robustness of brain activation data in the FFA. We therefore performed correlation analyses after eliminating a few subject pairs who lacked sufficient intrasubject reliability (see Materials and Methods) Again significant MZ correlations were found for the left $VWFA_{word}$ activation and OFA_{face} lateralization (Fig. 5). In fact, in the case of the $VWFA_{word}$, the value of the MZ correlation even attained the level of the intrasubject correlation (measuring measurement replicability). Thus, the left $VWFA_{word}$ activation appears highly heritable. On the contrary, the MZ correlation was still low and non-significant for the 3 FFA_{face}-related measures.

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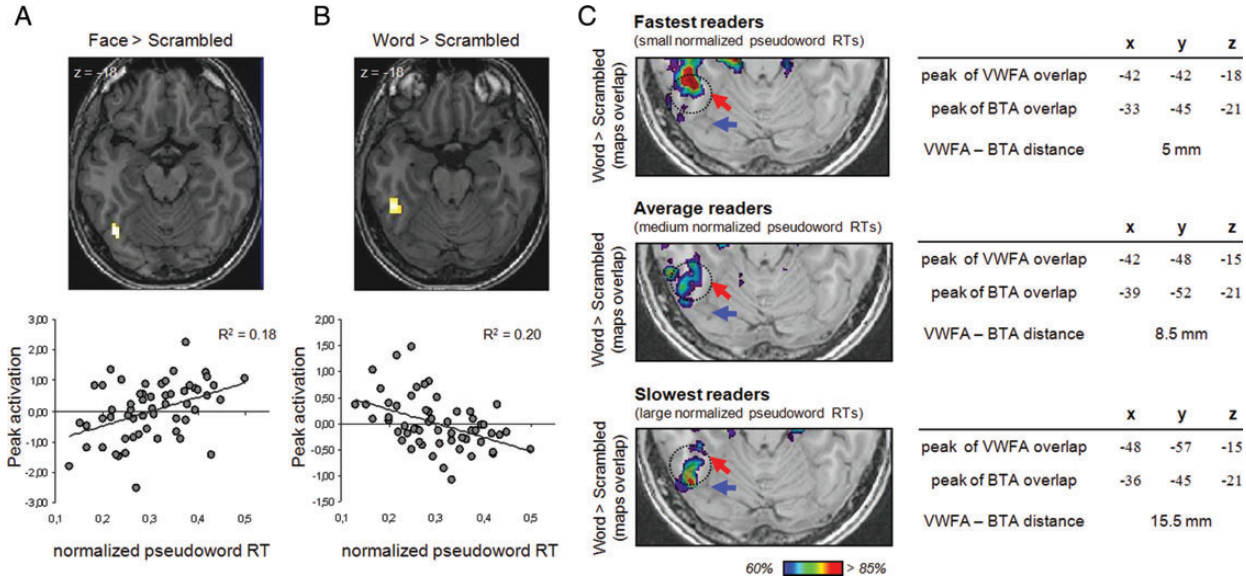

Figure 4. Reading speed predicts the asymmetry and location of the ventral visual activations to written words and faces. (*A*) Within the a priori defined left FFA_{face}, voxels exhibiting a significant positive correlation between leftward asymmetry of face-related activation and normalized pseudoword RT (peak coordinates −39, −66, −18; $T = 3.29$, voxel $P = 0.039$ corrected for the volume explored). Note that this correlation could also be interpreted as higher rightward asymmetry of face-related activation for lower normalized pseudoword RT. The graph below shows how activation evoked by faces in those left-hemispheric voxels increases with normalized pseudoword RT ($r = 0.42$, $P = 0.001$). (*B*) Fusiform voxels inside the a priori defined $VWFA_{word}$ showing a significant negative correlation between leftward asymmetry for written word-related activation and normalized pseudoword RT (peak coordinates −45, −58, −18; $T = 3.42$, voxel $P = 0.034$ corrected for the volume explored). The graph below shows how BOLD activation evoked by written words in those left-hemispheric voxels decreases when normalized pseudoword RT increases ($r = 0.45$, $P = 4 \times 10^{-4}$). (*C*) Activations evoked by written words is slightly displaced in the anterior–posterior direction in 3 groups of subjects split according to their normalized pseudoword reading speed (1/3th percentiles). The red and blue arrows point to the anterior and the posterior inferotemporal peaks. The dotted circle represents the sphere where LI and activation of the $VWFA_{word}$ were calculated. The color bar indicates for each group the fraction of subjects who presented activation in a given voxel (range here from 60% up to 85%). On the right are reported the coordinates (mm) of peaks of maximal overlap for the $VWFA_{word}$ (as seen of axial views) and BTA_{speech} (not seen here) for each group, as well as the distance between these 2 peaks.

Table 3
Twin-pair correlations of brain activation measures

ROI	Brain measure	R_{MZ}	$p(R_{MZ})$	R_{DZ}	$p(R_{DZ})$
$VWFA_{reading}$	L.I	0.225	0.166	−0.483	0.960
	Left BOLD	0.815	3.10^{-5}	0.413	0.071
	Right BOLD	0.299	0.122	−0.230	0.785
FFA_{face}	L.I	0.166	0.262	−0.297	0.849
	Left BOLD	0.279	0.139	−0.447	0.946
	Right BOLD	0.224	0.194	−0.285	0.839
OFA_{face}	L.I	0.489	0.023	0.202	0.244
	Left BOLD	0.424	0.045	0.231	0.214
	Right BOLD	−0.0124	0.519	0.198	0.249
BTA_{speech}	L.I	0.117	0.327	0.165	0.287
	Left BOLD	0.476	0.027	0.320	0.133
	Right BOLD	0.432	0.042	0.064	0.414
$aSTS_{speech}$	L.I	−0.131	0.768	−0.347	0.888
	Left BOLD	0.161	0.268	−0.171	0.721
	Right BOLD	0.387	0.062	0.178	0.271
$mSTS_{speech}$	L.I	0.368	0.270	0.175	
	Left BOLD	0.456	0.033	−0.030	0.541
	Right BOLD	0.581	0.007	0.600	0.012
$pSTS_{speech}$	L.I	0.625	0.004	0.240	0.204
	Left BOLD	0.678	0.001	0.589	0.013
	Right BOLD	0.661	0.002	0.487	0.039

Note: Columns show the MZ intraclass correlation (R_{MZ}) and DZ intraclass correlation (R_{DZ}) for each region of interest and each measure (lateralization index [LI], left and right activation values). Gray shadings indicate a significant correlation ($P < 0.05$). Estimation of heritability based on these correlations is reported in Table 4.

Estimation of the Genetic Contribution to Brain Measures

For the left $VWFA_{word}$ activation only, h^2 was significantly different from zero and both genetic and environment influences contributed to the ACE model (Table 4). An additional analysis revealed that not only activation but also number of activated voxels at a given threshold ($t > 1$) was more similar in MZ twins than in DZ twins in the left $VWFA_{word}$ [$R_{MZ} = 0.70$, $P = 8.10^{-4}$; $R_{DZ} = -0.25$, $P = 0.807$; $h^2_F = 1.90$, $p(h^2_F) = 4.10^{-4}$; $a = 58\%$, $p(a = 0) = 0.056$ in the ACE model]. No similarity in the number of activated voxels was found for MZ or DZ twins in the left or right FFA_{face}.

For the other fMRI measurements, in most cases, the 95% confidence interval crossed zero, probably due to our small sample size. Post-hoc power analysis (using the method described in Visscher 2004) suggested that a minimum of 88 subjects would have been required to achieve 80% power with a fixed 5% type I error rate for measures of the STS. For a smaller h^2, the required number of subject increased up to ~450. For the heritability of the $VWFA_{word}$ only, the estimated number of subject was enough to achieve 80% power. With these limitations in mind, an examination of the trends in Table 4, based upon both the estimates of h^2 and the coefficients of the ACE model, suggests a genetic impact on the OFA_{face} LI and on left OFA_{face} activation, as well as on right BTA_{speech} activation, left $mSTS_{speech}$ activation and $pSTS_{speech}$ LI. Conversely, a preponderant environmental influence was found for the left BTA_{speech} activation, right $mSTS_{speech}$ activation, and left and right $pSTS_{speech}$ activation.

Although exploratory, these preliminary results raise the hypothesis that the co-lateralization found between STS_{speech} and $VWFA_{word}$ on the one hand, and between STS_{speech} and OFA_{face} on the other hand (Tables 1 and 2 and Fig. 2), could be due, at least partially, to common genetic factors. We used the 2-run design to calculate across-task and across-runs MZ and DZ correlations. These measures evaluate to which extent a phenotypic correlation survives when we correlate 2 different

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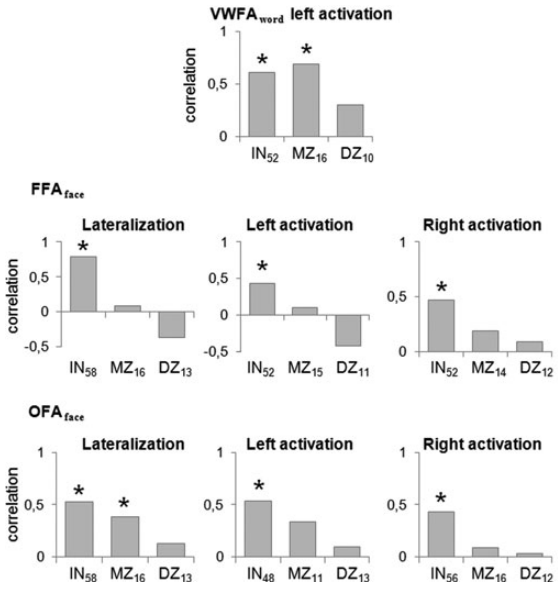

ROI	Brain phenotype	R_{MZ}	$p(R_{MZ})$	R_{DZ}	$p(R_{DZ})$
VWFA word	Left activation	0.692	5.10^{-5}	0.299	0.199
FFA face	Lateralization index	0.080	0.663	-0.372	0.062
	Left activation	0.099	0.560	-0.425	0.048
	Right activation	0.185	0.346	0.085	0.691
OFA face	Lateralization index	0.385	0.029	0.131	0.524
	Left activation	0.333	0.130	0.097	0.636
	Right activation	0.091	0.619	0.037	0.865

Figure 5. Comparison of intrasubject reliability (IN) and twin-pair correlations of activations evoked by written words and by faces. Sibling pairs with the least reliable data were excluded until a significant intrasubject correlation ($P < 0.05$) was observed within both the MZ and the DZ group (see Materials and Methods). We then examined, across the whole group of remaining subjects, how the MZ and DZ intrapair correlations compared with this reliability level. For each measure, bars show, from left to right, the intrasubject (IN), MZ, and DZ correlations. In each case, the number of remaining subjects or sibling pairs used in the estimation of the correlation is indicated as indices (for instance, MZ_{16} indicates that 16 pairs of MZ twin pairs were considered. Note that for the intrasubject correlation, all subjects were compared with themselves by separating the data into 2 fMRI runs. Thus, IN_{52} indicates that 52 subjects were considered). Stars indicate a significant correlation ($P < 0.05$). On the right are reported the values of the MZ (R_{MZ}) and DZ (R_{DZ}) intrapair correlations, as well as their *P*-value. Gray shading indicates a significant correlation ($P < 0.05$).

Table 4

Heritably and ACE model estimations for each measure presenting a significant MZ intraclass correlation in Table 3

Brain measure	Heritability estimate			ACE model			
	h_F^2	h_H^2	a^2	c^2	e^2	$p(a = 0)$	$p(c = 0)$
$VWFA_{reading}$							
Left BOLD	0.80 $P = 0.036$	0.68 $P = 0.044$	23% (0–0.85]	52% (0–84]	25% (0.10–0.48]	0.32	0.50
OFA_{face}							
L.I	0.57 $P = 0.214$	0.36 $P = 0.176$	55% (0–0.82]	0% (0–0.47]	45% (0.18–1]	1	0.16
Left BOLD	0.38 $P = 0.316$	0.25 $P = 0.314$	50% (0–0.79]	0% (0–0.48]	50% (0.20–0.84]	1	0.26
BTA_{speech}							
Left BOLD	0.23 $P = 0.308$	0.23 $P = 0.308$	0% (0–0.54]	43% (0–0.67]	57% (0.31–0.90]	0.33	1
Right BOLD	0.73 $P = 0.138$	0.340 $P = 0.172$	40% (0–0.65]	2% (0–0.57]	58% (0.30–1]	0.97	0.58
$mSTS_{speech}$							
Left BOLD	0.97 $P = 0.114$	0.47 $P = 0.102$	38% (0–0.66]	0% (0–0.43]	62% (0.32–1]	1	0.26
Right BOLD	−0.04 $P = 0.514$	−0.05 $P = 0.512$	0% (0–0.04]	62% (0.13–0.79]	38% (0.21–0.86]	0.06	1
$pSTS_{speech}$							
L.I	0.77 $P = 0.164$	0.51 $P = 0.162$	61% (0–0.84]	0% (0–0.04]	39% (0.15–0.76]	1	0.15
Left BOLD	0.18 $P = 0.376$	0.22 $P = 0.378$	3% (0–0.69]	60% (0–0.80]	37% (0–0.64]	0.17	0.93
Right BOLD	0.35 $P = 0.208$	0.40 $P = 0.236$	0% (0–0.45]	64% (0.14–0.78]	36% (0.21–0.54]	0.09	1

Note: For each measure, we report the Falconer heritability (h_F^2) and the Holzinger heritability (h_H^2). Their significance (p) was assessed from the distribution of heritability estimations computed for 1000 random permutations of MZ and DZ zygotic status. On the right columns are reported, for each measure, the value of the path coefficients fitting a univariate ACE model estimated by bootstrap, as well as an interval of confidence (A, C, and E = proportion of the variance imputable to additive genetic factors, shared environmental factors, and non-shared environmental factors, respectively). The columns $p(a = 0)$ (i.e., no genetic influence) and $p(c = 0)$ (i.e., no common environmental influence) correspond to a comparison of fit between ACE and CE models, and between ACE and AE models, respectively.

measures from 2 different siblings. In such an analysis, the run 1 of a given task is correlated with the run 2 of the other task within a twin pair (see Supplementary Fig. 1*c* for details). Table 5 shows that MZ correlations are significant for both interactions. However, comparison with 1000 permutation of zygosity showed that only the correlation between the left $VWFA_{word}$ and the left $mSTS_{speech}$ activation levels was significantly higher for MZ pairs than for DZ pairs, suggesting a genetic contribution.

Voxel-Based Analysis of MZ and DZ Correlations

The above heritability analyses probed the existence of correlations between members of a twin pair in the amount of brain activation within a region of interest. A distinct question is whether the *patterns* of brain activity resemble each other more in MZ twins than in DZ twins. When we compared the inter-siblings similarity in activation within a large occipitotemporal ROI, as Polk et al. (2007) did (Fig. 6*A*), we observed a significant difference in correlation between MZ and DZ for the face contrast ($P = 0.003$), and a similar though non-significant trend for the word contrast ($P = 0.074$). Furthermore, we found a highly significant difference for the similarity in gray matter density within the occipitotemporal ROI ($P = 6.10^{-5}$), indicating that the anatomical folding pattern was highly heritable in this region.

When the analysis of pattern similarities was restricted to a small region surrounding the peak activation to faces and to

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Table 5
Heritability of the correlations between brain measures

Brain measure	phenotype × sibling correlation			heritability estimate		
	R_{MZ}	$P(R_{MZ})$	R_{DZ}	$P(R_{DZ})$	h^2_F	h^2_H
pSTS L.I × OFA L.I	−0.26	$P = 0.037$	−0.03	$P = 0.823$	−0.46 $P = 0.177$	−0.22 $P = 0.175$
VWFA left bold × mSTS left bold	0.52	$P = 10^{-5}$	0	$P = 0.999$	1.04 $P = 0.014$	0.52 $P = 0.007$

Note: We first computed the cross-task × cross-runs MZ (R_{MZ}) and DZ (R_{DZ}) correlations. We derived from these correlation coefficients estimates of heritability using the Falconer (h^2_F) and Holzinger (h^2_H) formulas (see Materials and Methods). The significance (p) was assessed from the distribution of heritability estimates computed for 1000 random permutations of MZ and DZ zygotic status.

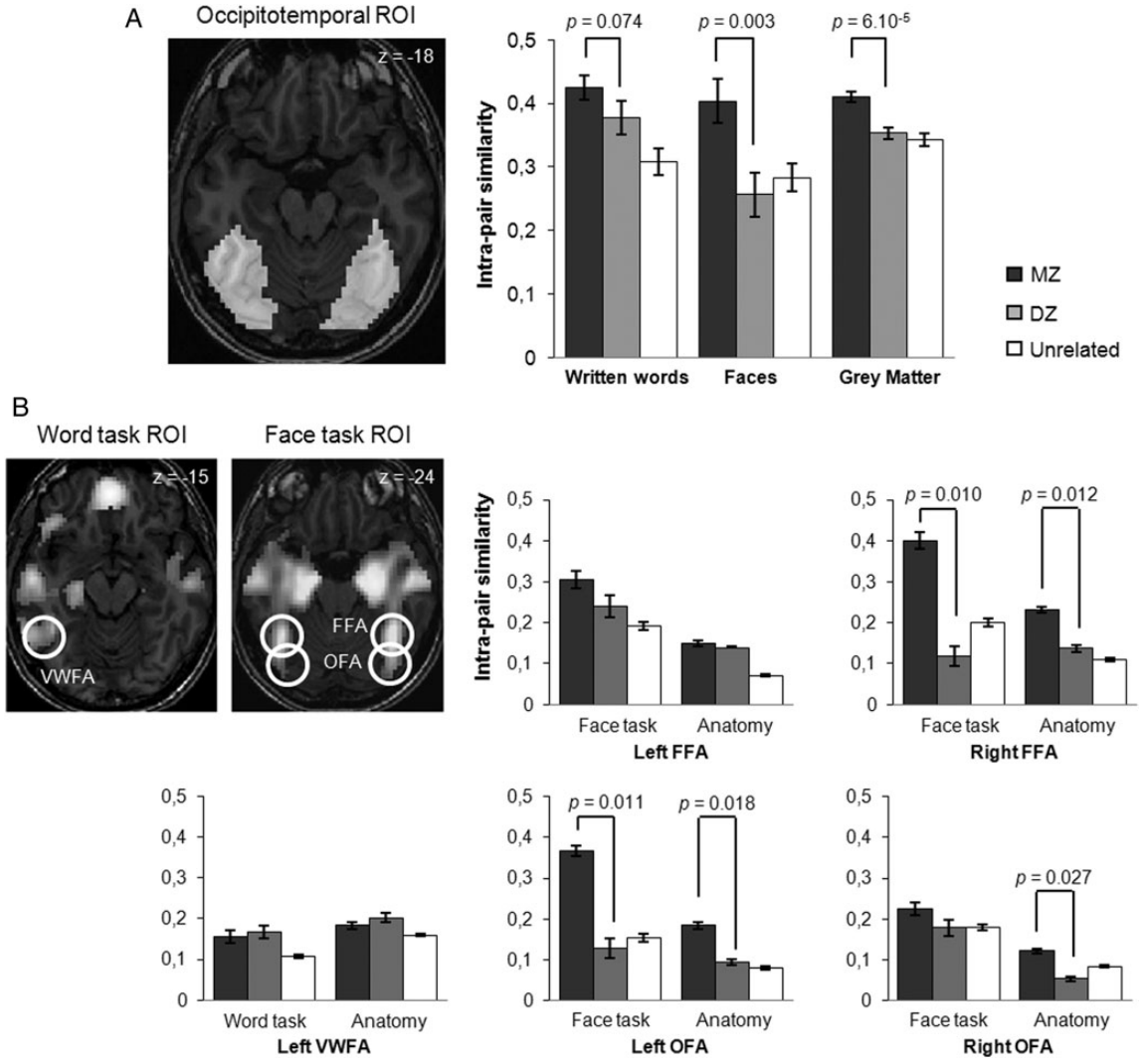

Figure 6. Voxel-based analysis of the MZ and DZ similarity in anatomical and functional activity patterns evoked by words and faces, similar to the twin study of Polk et al. (2007). (*A*) Left, representative view of the inferotemporal mask used in this analysis (axial slice, $z = -18$ mm). Right, similarity of word-related activation, face-related activation, and gray matter density for MZ, DZ, and unrelated pairs. Similarity refers here to the averaged correlation of the chosen parameter (activation or gray matter density) across the voxels in the mask. *P*-values are reported only for significant differences between MZ and DZ. (*B*) Same analysis restricted to spheres (radius = 12 mm) centered of VWFA, FFA, and OFA coordinates. Similarity was computed for anatomy and word or face activation, depending on the peak.

words (Fig. 6*B*), we could observe that gray matter patterns were more similar for MZ than for DZ twins essentially in face regions, and much less around the VWFA. This finding could explain while pattern similarity analysis fails to detect the heritability of the VWFA activation. In Supplementary Figure 3, we show some examples or MZ similarity for FFA and VWFA. In line with our analysis, it appears that siblings' FFAs are more focused and located at more similar positions, but with dissimilar activation sizes, whereas siblings' VWFAs lie at slightly different locations, but with more similar activation sizes.

Discussion

We investigated the inter-relations of the cortical responses to words, faces, and spoken language in the temporal lobe. Our

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main goal was to evaluate to what extent the VWFA and FFA activations correlate with the activations to spoken language and whether their organization depends on genetic or environmental factors. Our results showed that the VWFA activation and lateralization correlate with spoken language activation and lateralization in the posterior and middle STS, as well as with reading expertise. More surprisingly perhaps, we found that the FFA was submitted to similar influences. Analysis of correlations within MZ and DZ twin pairs suggested that while the left VWFA activation was found to be under the influence of both genetic and shared environmental factors, the FFA activation did not present any twin correlation, leading us to the tentative conclusion that FFA activation mostly depends on unique environmental experience. These new findings may shed some light on the constraints that shape the development of these 2 inferotemporal areas.

Impact of Language Lateralization on VWFA and FFA

The first important finding of this study is that up to 20% of the variance in the right FFA activation is explained by language-related factors. Furthermore, we show for the first time that the rightward lateralization of the FFA is positively correlated (in 2 independent cohorts) with the leftward lateralization of the temporal activation during speech listening, as well as with reading skills (indexed by shorter pseudoword RT). Interestingly, these results converge with recent investigations of FFA lateralization. Willems and collaborators (Willems et al. 2010) reported that the lateralization of the FFA varies with handedness, thus pointing to the possibility of a relation between FFA lateralization and other cerebral asymmetries, such as those characterizing language processing (Steinmetz et al. 1991; Binder et al. 2000; Knecht, Dräger, et al. 2000). In the same vein, in a study comparing brain activation in literate and illiterate adults, Dehaene et al. (2010) reported that the acquisition of literacy correlates with a reduced activation to faces in the left occipitotemporal sulcus, presumably due to competition with written words in this region, and a concomitant increase in the right-hemispheric lateralization of fusiform face responses. A similar finding was also reported when comparing normally developing versus dyslexic 9-year-old children (Monzalvo et al. 2012). Altogether, these data suggest that the acquisition of a visual expertise for reading reshapes the inferotemporal cortical pathway, leading to a change in face responses proportional to reading expertise.

While the study of Dehaene and collaborators (Dehaene et al. 2010) suggested that the decrease in the left occipitotemporal response to faces results from a direct competition with the nearby emergence of an area sensitive to written words, we did not find any negative correlation between the VWFA and FFA hemispheric lateralization. Rather, the present findings suggest that this reshaping might be mediated, at least in part, via the STS. First, we found that the index of left-hemispheric lateralization of the STS during spoken language processing correlated with both right-hemispheric lateralization of the FFA and with left-hemispheric lateralization of the VWFA. The latter finding replicates a co-lateralization analysis performed in a large independent cohort, where VWFA lateralization correlated significantly with the pSTS lateralization, both during reading and during speech listening (Pinel and Dehaene 2009). These cross-modal lateralizations show that the core temporal network sustaining language comprehension influences the organization of occipitotemporal word processing, possibly via the semantic content of the visual stimuli (Seghier and Price 2011) or the need to achieve an audiovisual integration of speech sounds and letters in the pSTS (Blomert 2011).

It was also previously shown that the pSTS activation to spoken language co-lateralizes with distant functional sites such as the activation of the horizontal intraparietal sulcus (hIPS) during mental arithmetic (Pinel and Dehaene 2009). This finding suggests that the pSTS lateralization for language may play an important organizing role for multiple functions. Indeed, it is only in the pSTS that a left-hemispheric lateralization is observable early on during the first few months of infancy, both in terms of functional activation to spoken language (Dehaene-Lambertz et al. 2002, 2010) and of anatomical structure (Dubois et al. 2009; Dubois et al. 2010). At this age, the VWFA and FFA are not yet in place (Golarai et al. 2007) and the intraparietal activation, which exists for nonsymbolic displays of numbers, tends to be right-lateralized (Cantlon et al. 2006; Izard et al. 2008). Thus, the influence of the pSTS on lateralization at other sites in the VWFA, FFA, and hIPS may develop later in life. In support of this notion, Dehaene and collaborators (Dehaene et al. 2010) also found that activation and lateralization of the planum temporale during spoken language was modulated by the degree of literacy even in subjects who became literate as adults. We therefore formulate the hypothesis that the emergence of the VWFA in the left occipitotemporal cortex, as well as the rightward bias for faces in the right occipitotemporal cortex, may arise as 2 joint consequences of changes in the left temporal cortex mediated by the slow development of reading expertise. This hypothesis would explain the correlation of these 2 variables with STS lateralization and with individual variations in pseudoword reading speed.

Because we also found a shared genetic influence for left VWFA and STS activation levels, it should be noted that the VWFA/STS correlation may have been inflated by the presence of MZ twins in the cohort. However, as mentioned earlier, this finding replicates a co-lateralization analysis performed in a large independent cohort of >200 non-twin subjects (Pinel and Dehaene 2009). While the present evidence is only correlational, the exact biological nature of the causal relationship between the pSTS and ventral visual areas remains to be determined. Hypothetically, one or several genes could jointly influence both the pSTS and VWFA activation. The existence of a genetic correlation for both measures supports such an assumption, which is discussed in the next section. However, developmental causes may also be considered. Using functional connectivity in normal readers during resting state (Zhao et al. 2011) or an active audiovisual task (Nath and Beauchamp 2011), some recent studies reported a significant functional connectivity between the left fusiform gyrus and the pSTS, whereas other suggest that the VWFA is more preferentially connected to the dorsal parietal attentional network (Vogel et al. 2012). These perspectives could be eventually reconciled considering that pSTS, VWFA, and parietal cortex are linked by the left arcuate fasciculus. In particular, using diffusion tensor imaging of literate and illiterate subjects (De Schotten et al. 2014) showed that literacy acquisition is accompanied by an increase of both left VWFA activation and fractional anisotropy of the posterior segment of the arcuate fasciculus linking these different regions.

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As for the FFA, no genetic correlation was found with the pSTS. The observed functional correlation must therefore originate from developmental factors. We know of no evidence of a direct functional link between language areas of the left temporal lobe and ventral visual areas responsive to faces. However, a direct structural link has been observed between the right FFA and a region of the right STS area sensitive to voices (Blank et al. 2011). Furthermore, a core system formed by the right ventral face area and bilateral temporal regions was identified using fluctuations in activation during resting state (Zhang et al. 2009). The full mechanism linking the lateralization of language-related regions of the STS and lateralization of the FFA remains to be determined. Additionally, it should be noticed that the anticorrelation of the OFA and pSTS lateralizations did not appear to be under significant genetic control. Because the ACE model suggests a predominant effect of genetic factor for both of them, it is plausible that different sets of genes explain these 2 different measures.

In the future, the causality of the impact of spoken language processing and reading development onto the organization of the face system could be addressed via the examination of FFA activation in congenitally deaf people. Early deafness impacts on both the normal development of the STS (MacSweeney et al. 2001) and the acquisition of reading skills (Conrad 1979; Goldin-Meadow and Mayberry 2001). Based on the present hypothesis, we might therefore predict that deaf people may not present the typical rightward FFA asymmetry that hearing people do. Some findings are compatible with this prediction. A preliminary study on error rate during a recognition task with lateralized visual presentation suggested a left-hemifield superiority for faces and a right hemifield superiority for words in hearing children, whereas deaf children presented similar scores for both visual fields and even a left-hemifield superiority for words (Szelag et al. 1992). In the same direction, an fMRI study reported an atypical leftward lateralization of the FFA during the recognition of facial expression in deaf subjects (McCullough et al. 2005) whereas activation was bilateral for hearing subjects. At the very least, all these data converge to suggest the necessity of a typically developing temporal language cortex for the emergence of a right-lateralized FFA.

Our data also shed some light on the development of an asymmetric specialization within the ventral pathway. We found that the leftward hemispheric asymmetry of the VWFA and the rightward asymmetry of the FFA did not arise from an increased activation in the left occipitotemporal cortex for written words and in the right fusiform cortex for faces. Rather, they related to a *decrease* in the activation of the homolog areas of the contralateral hemisphere. A similar observation was previously reported by Seghier and Price (2011) in an fMRI study where they showed that the left lateralization of the occipitotemporal activation to words resulted from a reduced activation for words relative to other nonverbal stimuli in the right hemisphere. More generally, our results fit with the scenario proposed by Cantlon et al. (2011) who interpreted the decrease for non-preferred stimuli in VWFA and FFA during child development as a "pruning" process (Cantlon et al. 2011).

Heritability of VWFA and FFA

Our second important finding concerns the heritability of the VWFA and of the FFA, respectively. Because face recognition is an ancient cognitive skill with potential survival advantage, it has been argued that face recognition may be under high genetic control. Studies of family with hereditary prosopagnosia (Duchaine et al. 2007; Grüter et al. 2008; Schmalzl et al. 2008) and of twin performance in a face memory task (Wilmer et al. 2010) support this view. On the contrary, reading is a recent cultural invention, and its brain correlates might therefore be mostly shaped by learning rather than by innate mechanisms. This was the logic behind Polk et al.'s (2007) study, which indeed observed of a higher degree of similarity in the brain activation of MZ twins compared with DZ twins during a face-matching task, but not during a written pseudoword-matching task. Polk et al. (2007) claimed that genetics plays a role only on the neural response evoked by pre-cultural stimuli (faces and places) but not by symbols learned via education.

Our results, however, disagree with this simple dichotomy between faces and written words. For the VWFA activation, we found that the MZ correlation was twice the DZ correlation, indicating a high heritability suggestive of a genetic contribution to VWFA development. Conversely, we failed to detect any significant effect of genetic or shared environment on FFA activation, which seemed to be essentially driven by individual experience.

Although our conclusion differs radically from Polk et al. (2007), we showed in the results section that this divergence is essentially due to different methodological approaches. A key difference is that we first computed indices of activation and lateralization while tolerating a spatial displacement in the exact location of activation. Only then did we estimate the heritability of these measures. This method presents the advantage of being insensitive to correlations in brain anatomy. The method adopted by Polk et al. (2007), on the other hand, consists in assessing the similarity in activation patterns within a large occipitotemporal region, separately for MZ and DZ twin pairs. Using their method, we replicated their observation of a significantly higher similarity of activation patterns for MZ than for DZ twins in the face task whereas this difference was not significant in the written word task. However, we think that this voxel-based methodology of looking for similarity in activation patterns with twin pairs is problematic because it mixes anatomical and functional heritability. Indeed, Polk and collaborators (Polk et al. 2007) also found that anatomical images of gray matter density were significantly more similar for MZ than for DZ twins, and we replicated this observation in our data. Another factor is that in the study of Polk et al. (2007), the ventral occipitotemporal word-related activations were much less extended than their face-induced activation (see their Fig. 1). Given the large size of the ROI they explored, this high proportion of non-activated voxels may have lowered the MZ similarity in activation to written words. Thus, the higher MZ similarity they observed for faces may simply reflect, in part at least, a greater anatomical similarity in MZ than DZ twins.

Relative to this prior study, our goal was to extract functional activation measures while avoiding artifacts caused by the greater anatomical resemblance between MZ twins compared with DZ twins. To this end, we relied on a location-tolerant search for any activation peaks within a sphere of interest, before computing our activation and lateralization indices (see Materials and Methods). With this method, we found that the left mSTS and VWFA activation to written words were significantly more correlated for MZ than for DZ pairs. The results suggested that a partially shared genetic contribution plays a role in the organization of these areas.

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Although it may seem paradoxical that a cultural acquisition such as reading depends on a heritable brain area, many recent studies have, in fact, found that reading acquisition is supported by a tightly constrained preexisting architecture for spoken language processing and visual recognition (Dehaene and Cohen 2007; Dehaene 2009). In particular, the location of the VWFA is highly reproducible across individuals, cultures, and reading schemes (Dehaene et al. 2002; Jobard et al. 2003; Bolger et al. 2005; Pinel et al. 2007). This is presumably because the process of identifying visual words for reading is under several functional constraints, which together specify a unique cortical site as the most efficient (Dehaene and Cohen 2007). These constraints probably include efficient processing of small foveal stimuli (Hasson et al. 2002), detection of basic geometrical shapes as found in letters (Szwed et al. 2009), and a fast connection to left-hemispheric areas involved in speech processing located in the left lateral and basal temporal cortex (Epelbaum et al. 2008; Pinel and Dehaene 2009). The latter connectivity constraint may be particularly essential, because even blind subjects show an activation precisely at the VWFA site when reading in Braille or using auditory sensory substitution (Reich et al. 2011; Striem-Amit et al. 2012). Any of these constraints may be under partial genetic control and may therefore contribute to the observed heritability of VWFA activation and lateralization. Our data stress particularly the possibility that the organization of the ventral visual cortex is primarily affected by the presence of genetically determined connections between the VWFA site and the left STS. In particular, we found that the phenotypic correlation between left $VWFA_{word}$ and the left $mSTS_{speech}$ activation levels was partially due to a genetic correlation, meaning shared gene influence. Considering that functional and anatomical STS asymmetries are present early in life (Chi et al. 1977; Dubois et al. 2010) and that functional STS asymmetry during reading is associated with a genetic polymorphism on the 6p22 chromosome (Pinel et al. 2012), the superior temporal region for language may constitute a candidate to investigate in more detail the nature of the factors that constrain the VWFA site during early brain development. In particular, future work should investigate whether the precise localization of the VWFA can be predicted based on its connectivity pattern, as was recently demonstrated for the FFA (Saygin et al. 2012).

Surprisingly, with our location-tolerant measures, FFA activation and lateralization were no longer found to be genetically heritable. This observation should be interpreted with caution for several reasons. First, this negative result may reflect a lack of power or a limitation of the twin-study method. Second, it is possible that other biological measurements of the FFA, not investigated in our fMRI study, may reveal the impact of familial factors. Nevertheless, our results fit with recent evidence that FFA development is characterized by a very slow stabilization, which leaves space for an environmental influence. In group analyses of fMRI data from young children, relatively little specificity is present for faces relative to other visual categories, and the FFA is not mature until 12 years of age in terms of its localization and specificity (Scherf et al. 2007; Cantlon et al. 2011). 9-year-old dyslexic children show a much weaker activation and right-lateralization of activations to faces than age-matched normal readers (Monzalvo et al. 2012). Although systematic analyses of fMRI data from individual children may refine this conclusion in the future, it seems that the development of the FFA is very protracted and unfolds over several years, thus submitting it to a variety of environmental influences, including a strong influence of reading and language development (Dehaene et al. 2010).

Our results should not be taken to mean that face processing is free of any genetic determinants. First, heritability only measures the portion of the variance among individuals who can be attributed to genetic differences. Our data therefore leave open the possibility that universal human genes specify several invariable aspects of the face system, to such an extent that the only residual inter-individual variability that we are able to measure is of environmental origin. Second, while Polk et al. (2007) pooled all face-related activation within a large occipitotemporal region, we separated FFA from OFA and found a trend toward a genetic component in the lateralization of the OFA activation to faces. This region has been reported to be more sensitive to parts (Yovel et al. 2005) and physical aspects of faces (Rotshtein et al. 2004). This processing stage is crucial to face recognition considering that lesions in the OFA impair it even if the FFA is preserved (Rossion et al. 2003; Steeves et al. 2006). Our results tentatively suggest an anterior–posterior dissociation in the genetics of the face network. Interestingly, such topography matches the chronology of the development of face-selective areas along the occipitotemporal cortex. Two independent fMRI studies comparing children before and after 9–10 years of age showed a posterior-to-anterior progression in face selectivity during childhood (Gathers et al. 2004; Aylward et al. 2005). Posterior occipital areas may be engaged earlier in life to process basic features of faces, whereas fusiform areas would acquire their face selectivity during a much longer period (Golarai et al. 2007; Cantlon et al. 2011), most likely driven by individual experience (Pascalis et al. 2002).

Environmental Influences on the VWFA

Besides a genetic influence on VWFA activation, our data also contain indications of significant environmental effects.

First we found that, when fitting an ACE model, half of the variance in VWFA activation was explained by the shared environment. This finding could be tentatively explained by a correlation in the education to literacy experienced by twins, whether they are mono- or di-zygotic. Educational methods (Maurer et al. 2010), school environment, access to literature, and other familial factors are likely to be parts of this shared environment.

Second, while we assessed individual reading performance with a very limited number of tests, we found one non-heritable behavioral measure that was linked to the VWFA organization. The normalized pseudoword reading speed, reported here to be essentially dependent of the environment, did not correlate directly with VWFA activation level but was found to correlate with the location of the peak activation in the VWFA along a posterior–anterior axis. The VWFA activation was significantly more anterior in the faster pseudoword readers. This effect of literacy skills may reflect a shift of activation evoked by word processing along a hierarchically organized ventral pathway (Nobre et al. 1994; Dehaene et al. 2005). Indeed, a posterior-to-anterior gradient of sensitivity for letters, bigrams, quadrigrams, and words has been reported in the left inferotemporal cortex (Vinckier et al. 2007), suggesting that the more anterior cortical sites are tuned to larger visual units of the orthographic system. Readers of English, a language with a nontransparent orthography, show more

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anterior ventral occipitotemporal activations than readers of Italian (Paulesu et al. 2000)—a finding consistent with the finding that English requires about 2 more years of reading acquisition than Italian (Seymour et al. 2003; Goswami 2008) and calls for the visual encoding of multi-letter units of a larger "grain size" (Ziegler and Goswami 2005). By analogy, in the present study, fast pseudoword readers may have learned to decode pseudowords using larger groups of letters, thus increasing their reading speed (Marinus and de Jong 2008). This would explain that, in the fMRI protocol, they exhibited a more anterior VWFA activation, indicating a parallel extraction of the multi-letter groups composing our stimuli. This observed shift was restricted to the VWFA, as other ventral language-related areas such as the BTA were found at similar positions in faster and slower readers.

The absence, in our data, of a robust score that directly measures individual reading performance is a limitation of the present study. For instance, it should have been interesting to replicate an association of reading score with the amount of activation in the left fusiform cortex during the word task, as in our previous study with illiterates (Dehaene et al. 2010), and to determine the respective roles of genetic and environmental influences in that correlation.

Conclusion

Our present findings should encourage more detailed studies aimed at elucidating the origins of the occipitotemporal mechanisms of visual word processing and face recognition.

The observed interactions between ventral face areas and perisylvian language-related regions, while far from being fully understood, suggest that language lateralization, surprisingly, may be one of the primary determinants of the organization, not only of the reading system, but also of the face recognition system.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Funding

This work was supported by Institut National de la Santé et de la Recherche Médicale (INSERM), Commissariat à l'Energie Atomique (CEA) and the James S. McDonnell Foundation.

Notes

Conflict of Interest: None declared.

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