Brain, language, and handedness: a family affair

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The left *planum temporale* is a marker of left hemisphere language specialization. We investigated the effect of individual handedness and familial sinistrality on left *planum temporale* surface area and found the size is reduced in proportion with the number of left-handed immediate family members and is lowest when one's mother is left-handed. This reduction is independent of an individual's handedness or sex and has no counterpart in the right hemisphere.

Left hemisphere dominance in language is unique to mankind. Some have proposed it must be genetically encoded and its disturbance may be related to diseases such as schizophrenia[1]. This salient feature of the human brain was discovered in 1861 by a French neurosurgeon, Paul Broca, after observing "loss of articulation" in a patient with a lesion of his left hemisphere. One hundred years later, Geschwind and Levitsky discovered, on post-mortem human brain pictures, a portion of the superior temporal cortex, named the *planum temporale* (PT), was larger in the left hemisphere compared to the right[2]. As this piece of cortex was known to be involved in the processing of language sounds[3], this asymmetry was thought to be a marker of left hemisphere dominance in language, which was later confirmed by modern neuroimaging techniques[4,5]. At the population level, PT remains the only brain area which is consistently larger on the left side.

Since most human beings are right-handed, they also use the left part of their brain to move their right (preferred) hand. This co-occurrence of left hemisphere dominance for hand and language led to hypothesize these two characteristics are inherited jointly. However, studies of aphasic patients and measures of PT in left-handers have shown variable relationships between hand preference and language area asymmetry[6]. As first postulated by Hécaen, factors other than one's handedness may thus shape brain lateralization for language, including familial sinistrality (FS), the existence (FS+) or absence (FS-) of left-handers among close relatives. More than 30% of human subjects[7] are FS+, which has been associated with less severe language deficits after left hemisphere brain lesions[8] and, therefore, lower strength of hemispheric specialization for language.

We investigated the effect of FS on PT surfaces to examine possible factors involved in left hemisphere dominance for speech (see Supplemental Methods and Results online). To test the hypothesis that a subject's left PT surface area is dependent on the presence of left-handed relatives, we measured the surface of the left and right PT[9] with brain magnetic resonance images obtained from 274 subjects. In the left hemisphere, the PT surface area was reduced by 10% (P=0.03) in FS+ subjects (n=104) compared to FS- subjects (n=170). This effect was independent of subjects' handedness, with both right and left-handed FS+ subjects having lower left PT areas (Table 1). Moreover, the left PT size appears to decrease with the number of left-handed first degree relatives (P=0.04, adjusted for family size[10]) and to be lowest when one's mother is left-handed (P=0.014, Fig. 1). Notably, the left PT surface area was independent of the subject's handedness and sex (Table 1). In addition, FS had no effect on the right hemisphere PT size.

To test the influence of FS on a quantitative measure of hand lateralization, subjects' manual asymmetry was quantified with the finger tapping test (FTT). Interestingly, FS had no significant effect (P=0.34), or interaction with sex (P=0.84) or handedness (P=0.23), on FTT asymmetry (see Supplementary Table 1 online). As expected, the difference in manual skills between the preferred hand and non-preferred hand was larger in right-handers than in left-handers, due to poor left hand performances by right-handers (P< 0.0001, ANOVA).

The present results reveal familial sinistrality is a key factor in the anatomical development of the left temporal cortex phonological areas, affecting left hemisphere dominance for speech sound processing. The presence of left-handed, immediate family members correlates with decreased leftward specialization for speech, independent of the individual's handedness and without any effect on manual lateralization[11]. This suggests different heritability mechanisms exist for handedness and hemisphere language dominance. This finding is in agreement with a report of familial aggregation, where the strength of the asymmetry of language functional networks was found to be independent of subject's handedness[12]. Recent genome-wide analyses, of human cortical patterning during development, have uncovered genes that shape the posterior temporal cortex and its asymmetries[13]. Such genes are clear candidates for language hemispheric dominance heritability, but a link to the FS trait has not been demonstrated yet. Other genes, including some linked to the X chromosome, are likely to be involved in hemisphere dominance as the offspring of left-handed mothers have the lowest PT surfaces areas.

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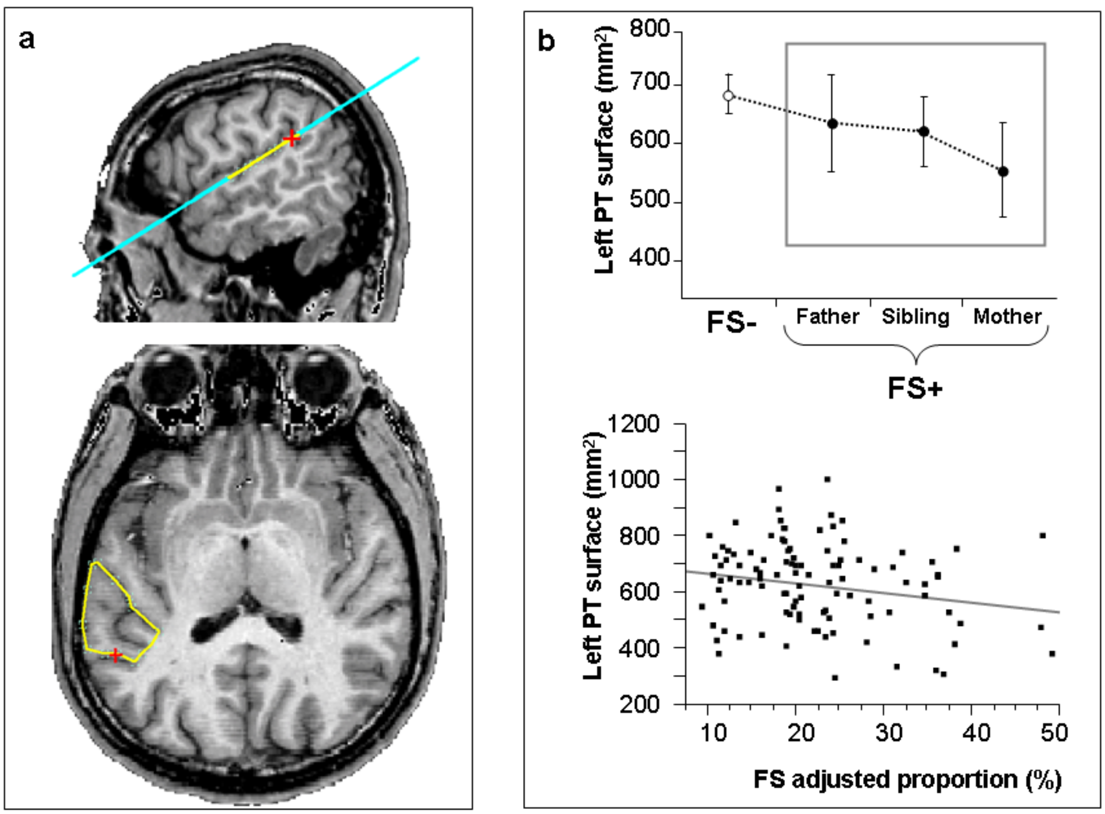
Table 1. *Planum temporale* (PT) surface area according to sex (F: female, M: male), self-reported handedness (RH: right-hander, LH: left-hander), and familial sinistrality (FS). FS is defined as the presence (FS+) or absence (FS-) of left-handed close relative(s). Values are mean ± s.d.

Sex	Handednes	Familial sinsitrality	PT surface area (mm^2)	
			Left	Right
F	RH	FS-	631 ± 150	468 ± 153
		FS+	552 ± 158	420 ± 132
	LH	FS-	691 ± 134	411 ± 178
		FS+	563 ± 128	478 ± 186
M	RH	FS-	682 ± 208	478 ± 185
		FS+	673 ± 164	503 ± 208
	LH	FS-	718 ± 209	502 ± 201
		FS+	619 ± 168	482 ± 196

Figure 1 Impact of familial sinistrality on the left *planum temporale* (PT) surface area. (**a**) Outline of a left PT (in yellow) on the oblique slice tangential to the temporal lobe upper surface. (**b**) Top: Left *PT* surface (mean ± s.d.) in subjects either without left-handed close relatives (FS-) or with a left-handed father, sibling, or mother (FS+). Bottom: linear regression analysis of the left PT surface as a function of the number of left-handed relatives, adjusted for family size.



Supplementary Methods and Results

Subjects

All subjects gave their written informed consent and the study was approved by our local Ethics Committee. The sample consisted of 274 subjects (199 males and 75 females), including 194 right-handers (134 men, 60 women) and 80 left-handers (65 men and 15 women). Handedness was self reported by the subjects. The occurrence of left-handedness in our sample was higher in men (33%) than women (20%). Familial sinistrality (FS), also self-reported by the subjects, was defined as the presence of at least one left-hander among the subject's parents and siblings; 170 subjects had no left-handed relatives (FS-) whereas 104 had at least one (FS-). FS was independent of sex (P=0.41), handedness (P=0.38), and sex by handedness (P=0.19).

The mean age was 24.3 years (s.d. = 6.1 years, range = 18-53). Left-handers were significantly younger than right-handers (2.3 years difference, P = 0.024, ANOVA) with no other significant effect due to sex or FS. The average education level of subjects was 14.7 years (s.d. = 2.2 years, range = 9-20), with no significant effect of sex or FS, but a small significant difference in favor of right-handers (0.8 year, P=0.030, ANOVA).

In the sub-sample of FS+ subjects, the average adjusted FS proportion (aFS)[10] was 0.22 (s.d. = 0.088) and independent of sex or handedness. Occurrences of a single first degree relative were 28% for a brother, 23% for a mother, 13% for a father, and 12% for a sister. No effect of sex or handedness was found on the distribution of the various possible left-handed relatives. An effect of the parents' gender was observed; 58 (55%) of the FS+ subjects had a left-handed parent, more often their mother (65%) than their father (35%), and the proportion of men having a left-handed mother was higher (73%) than for women (43%, P = 0.044).

Evaluation of manual skill

For each subject, the finger tapping test (FTT) was used to evaluate manual skill. For each hand, tappings were recorded in five sessions of 10 seconds each. The mean value is reported (Supplementary Table 1).

Image acquisition and analysis

Brain anatomical images were acquired on a 1.5 Tesla scanner (General Electric Signa) using a 3-dimensional T1-weighted sequence (0.9357 x0.9357x1.0 mm^3 voxel size). The PT surfaces were measured in the left and right-hemispheres after manual delineation, thanks to the knife cut method[9]. All images were processed by the same highly-trained operator whose reproducibility was assessed in a subset of 174 subjects. The average difference between the 2 measures was 10 ± 60 mm^2 and -2 ± 66 mm^2 and the correlation coefficient was 0.945 and 0.936, for the right and left PT, respectively.

Statistical methods

Analysis of covariance (ANCOVA) was used to assess the main effects of sex, handedness, and FS and their first order interactions on *PT* surface and FTT values. A repeated measure design was used with "hemisphere" (left or right) as the within-subject factor. Age, cultural level, and brain volume were included as covariates. To study the relationship between intensity of familial sinistrality and PT surface, a second ANCOVA was performed in the subgroup of FS+ subjects using the adjusted familial sinistrality proportion (aFS) as a covariate.

Supplementary Table 1. Manual skill according to sex, self-reported handedness, and FS. Manual preference was assessed with the Edinburgh Inventory, manual skill with the Finger Tapping Test. Values are mean ± s.d. (F, female; M, male; RH, right-hander; LH, left-hander; FS, familial sinistrality; FS+, presence of a close left-handed relative; FS-, absence of a close left-handed relative). The number of subjects (*n*) is shown in parentheses.

	Sex	Handedness	Familial sinistrality	Manual skill	
				Right hand	Left hand
ALL (274)	F (75)	RH (60)	FS- (38)	50 ± 4	43 ± 5
			FS+ (22)	50 ± 7	43 ± 6
		LH (15)	FS- (10)	48± 6	50 ± 5
			FS+ (5)	48 ± 3	49 ± 2
	M (199)	RH (134)	FS- (90)	57 ± 6	50 ± 6
			FS+ (44)	56 ± 5	50 ± 5
		LH (65)	FS- (32)	51 ± 6	54 ± 6
			FS+ (33)	54 ± 6	55 ± 7