Association between scalp hair-whorl direction and hemispheric language dominance

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Asymmetry is a common phenomenon in higher organisms. In humans, the cortical representation of language exhibits a high degree of asymmetry with a prevalence of about 90% of left hemispheric dominance, the underlying mechanisms of which are largely unknown. Another sign that exhibits a form of lateralization is the scalp hair-whorl direction, which is either clockwise or anti-clockwise. The scalp hair-whorl develops from the same germ layer as the nervous system, the ectoderm, between the 10th and 16th week in utero and has been shown to be associated with various neurodevelopmental disorders. Here, we use an established fMRI paradigm to examine the association of a solely biological marker of asymmetry, hair-whorl direction and language lateralization. We show that the mechanism that influences hair-whorl direction and handedness [Klar, A.J.S., 2003. Human handedness and scalp hair-whorl direction develop from a common genetic mechanism. Genetics 1651, 269–276.] also affects cerebral language dominance.

Introduction

Asymmetries on a population-level are a distinct feature of higher organisms, especially vertebrates. Although this phenomenon has fascinated scientists for a long time, only during the last years we are beginning to understand the underlying mechanisms which are responsible for the different forms of lateralization (Mercola and Levin, 2001). In particular, the evolution of the left–right body axis and the development of functional cortical asymmetries, e.g. handedness or language-dominance are questions under intense debate (Shaywitz et al., 1995; Berlim et al., 2003; Vallortigara et al., 1999; Klar, 1999; Provins, 1997; Geschwind and Galaburda, 1985; Corballis, 2003). The scalp hair-whorl develops from the same germ layer as the nervous system, the ectoderm, between the 10th and 16th week in utero (Bally-Cuif and Hammerschmidt, 2003). Hence, the brain and scalp hair-whorl show a pathological correlation with hair-whorl irregularities and gross cerebral malformation (Smith and Gong, 1974). Direction and placement of the whorl are markers of several medical syndromes that involve cerebral malformations (Nowaczyk and Sutcliffe, 1999; Wilson et al., 1992).

The rate of non-right-handers in the general population is about 9–11% and the occurrence of an anti-clockwise hair-whorl has been shown to be 8.4% with an about five-fold increase in non-right-handers (Klar, 2003). The association of the hair-whorl, a solely structural sign of laterality, a feature that cannot be influenced by culture or nurture, and cerebral asymmetry in a higher cognitive function, namely language representation, may enable us to detect the underlying cause of laterality per se. To investigate the connection of hair-whorl direction and language dominance, 43 male right-handed subjects (Edinburgh Handedness Index > 66) (Oldfield, 1971), 22 with clockwise and 21 with anti-clockwise hair-whorl direction, were investigated. Only right-handed male subjects were enrolled, because they show almost invariably a clear-cut left-hemispheric dominance for language function (Knecht et al., 2000). Hence, this group of subjects is most sensitive for the detection of deviant distributions of language laterality as hypothesized for subjects with anti-clockwise hair-whorl direction. Given the distribution of male right-handers with clockwise and anti-clockwise hair-whorl directions, our study sample represents two groups of highly different frequencies in the male population of about 0.90 for right-handers with clockwise and 0.05 for right-handers with anti-clockwise hair-whorls.

To assess cerebral language representation, we used functional magnetic resonance imaging (fMRI), currently the most sensitive and valid non-invasive method for language mapping (Binder et

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  Available online on ScienceDirect (www.sciencedirect.com).

Table 1
Laterality indices (LI) ranging from −1 (complete right) to +1 (complete left) of subjects with clockwise (CW) and anti-clockwise (ACW) hair-whorl direction

	Broca's area		Temporoparietal		Remaining prefrontal	
	CW	ACW	CW	ACW	CW	ACW
LI (mean ± SD)	0.95 ± 0.07	0.54 ± 0.67	0.86 ± 0.19	0.47 ± 0.60	0.90 ± 0.14	0.58 ± 0.65
Mann−Whitney U	$P < 0.05$		$P < 0.05$		$P = 0.098$	

al., 2001). We applied an established behavioral procedure with a semantic-perceptual contrast with continuous performance control. This procedure was originally developed for individual language mapping prior to neurosurgical interventions, where it has shown its validity and test−retest reliability in individual subjects (Fernández et al., 2003). It uses a blocked design with two conditions: in the active condition – the semantic task – subjects were required to identify visually presented word pairs with identical or highly similar meanings (synonyms) intermixed within a series of pairs of semantically unrelated words. In the perceptual control condition, subjects were required to identify pairs of identical consonant strings intermixed in a series of non-identical consonant strings (one letter exchanged). The cortical representation of language is predominantly restricted to a number of frontal and temporoparietal brain regions (Josse and Tzourio-Mazoyer, 2004; Price, 2000). Thus, we focused our analysis of lateralization on three regions of interest (ROI) and their homologous counterparts in the right hemisphere including all so-called eloquent language areas. ROIs were functionally defined as described in a previous study using the same procedure (Fernández et al., 2001): Broca's area ROI, a remaining prefrontal ROI combining prefrontal activations outside Broca's area, and a temporoparietal ROI including Wernicke's area. Based on data from these ROIs, we established lateralization indices, enabling us to obtain an objective and regionally specific measure of cerebral language lateralization with high validity and test−retest reliability (Fernández et al., 2003). Initially, we compared the distribution of lateralization indices between both groups of subjects. For descriptive and confirmatory purposes only, data obtained from Broca's area were thereafter used for the separation into typical and atypical language representation, since data from this ROI have shown the highest level of reliability in a previous study (Fernández et al., 2003).

Our hypotheses were: if the mechanism, underlying the lateralization of the hair-whorl direction, also causes the cerebral asymmetry underlying language lateralization, the distribution of language dominance should be significantly different in a group of subjects with clockwise than with anti-clockwise hair-whorls, with less left hemispheric dominance in the latter group.

Methods

Subjects

Forty-three right-handed healthy young males (Edinburgh-Index > 66) with normal or corrected-to-normal vision participated in the study (age: anti-clockwise group: 32.19 ± 1.52 years; clockwise group: 29.18 ± 1.21 years). The subjects had no history of neurological or psychiatric diseases. Because of the small number of people with anti-clockwise hair-whorls, the recruitment was based on local newspaper, television and radio-stations. In this recruitment, subjects with clockwise as well as anti-clockwise hair-whorls were included. Subjects were divided in two groups

according to the scalp hair-whorl direction of the main hair-whorl. Only subjects with a hair-whorl that could be clearly classified as clockwise or anti-clockwise were included. The direction of the hair-whorl was classified by two independent examiners which were otherwise blinded, based on high-resolution digital photographs. Nine out of initially 52 subjects had to be excluded, because of discordant classifications on the hair-whorl direction (five subjects), more than one hair-whorl (two subjects) or motion artifacts in the fMRI data extending the voxel size during the scanning-procedure (two subjects). Two additional subjects presented themselves with two opposing hair-whorls and were therefore excluded straightaway.

Behavioral procedure

In the scanner, a series of item pairs, either word- or consonant string pairs, were presented back-projected onto a translucent screen, which subjects viewed by way of a mirror. Both constituents of each pair were simultaneously presented for 4 s, above and below a central fixation cross. A semantic condition (synonym-judgment task) alternated with a perceptual condition (letter-matching task) every 25 s, so that six item pairs were presented for each of 30 half-cycles. Hence, the behavioral experiment took 12.5 min in total.
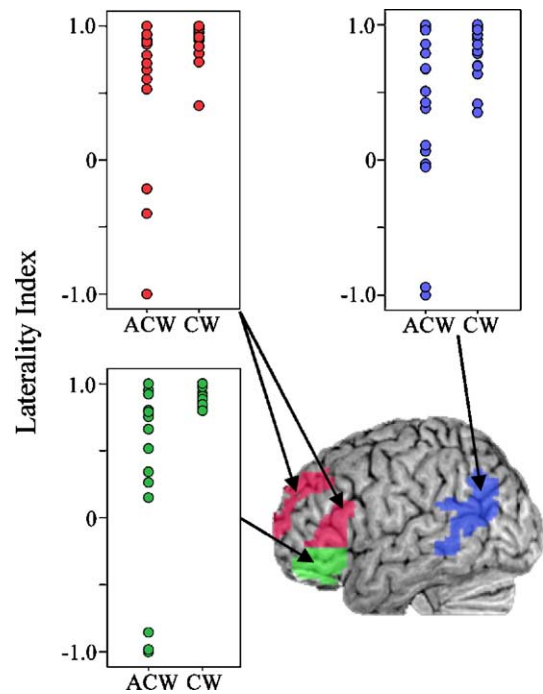

Fig. 1. Distribution of the Laterality Index. (LI: ranging from −1 (complete right) to +1 (complete left) lateralization in subjects with clockwise (CW) and anti-clockwise hair-whorl (ACW) direction in Broca's ROI (green), temporoparietal ROI (blue) and remaining prefrontal ROI (red).

The verbal stimuli were 180 common German nouns (5–11 letters), forming 45 pairs of words with identical or highly similar meanings (synonyms) and 45 pairs of semantically unrelated words. The consonant strings were developed pseudorandomly to represent 45 pairs of two identical strings and 45 pairs in which one letter was different between the two constituents. Strings were matched with words with regard to the number of letters. Subjects were required to push a button with the index finger of their right hand whenever they identified a pair of two synonyms or identical letter strings.

MRI data acquisition

16 axial slices were collected at 1.5 T (Symphony, Siemens, Erlangen, Germany): 248 T2*-weighted, gradient echo EPI-scans including eight initial scans that were discarded to achieve steady-state magnetization (slice thickness: 6 mm; interslice gap: 0.6 mm; matrix size: 64 × 64; field of view: 220 mm; echo time: 50 ms; repetition time: 3.125 s). Thereafter, we acquired a sagittal T1-weighted 3D-FLASH sequence for each subject for anatomical localization (number of slices: 120; slice thickness: 1.5 mm (no interslice gap); matrix size: 256 × 256; field of view: 230 mm; echo time: 4 ms; repetition time: 11 ms).

MRI data analysis

MR images were processed using SPM99 (www.fil.ion.ucl.ac.uk/spm/) and the following steps were performed: (1) Realignment with three-dimensional motion correction. (2) Normalization onto the MNI-atlas (Montreal Neurological Institute). (3) Spatial smoothing with a 7 mm Gaussian kernel (full width at half maximum). (4) Modelling of the expected hemodynamic responses (box-car regressor in a general linear model, GLM). This regressor was convolved with a canonical hemodynamic response function (*hrf*) to represent brain physiology. (5) Temporal filtering of the acquired time-series to reduce high- and low-frequency noise attributable to scanner drifts and physiological noise. (6) Calculation of parameter

Table 2
Distribution of typical and atypical language dominance for subjects with clockwise and anti-clockwise hair-whorl direction according to the laterality index in Broca's ROI

	Clockwise	Anti-clockwise
Typical (*n*)	22	15
Atypical (*n*)	0	6

estimates for each condition covariate from the least mean squares fit of the model to the data. (7) Definition of the preexperimentally planned effects of interest (synonym-judgment > letter-matching and letter-matching > synonym-judgment) and generation of contrast images for each subject and each effect of interest.

The Lateralization Index (LI) was derived from individual *t* maps after masking the supratentorial brain and excluding three sagittal midline planes to minimize errors due to normalization. To estimate these measures, we had objectively to adjust individual statistical thresholds as described previously (Fernández et al., 2001), because of intersubject variability in general activation levels. This was achieved by firstly calculating a mean maximum *t* value defined as the mean of those 5% of voxels showing the highest level of activation. Those voxels with a *t* value exceeding 50% of this mean maximum *t* value were included into the calculation of the Lateralization Index. The Lateralization Index was calculated by the formula:

$$LI = \frac{\sum_V X_L - \sum_V X_R}{\sum_V X_L + \sum_V X_R}$$

where V is the set of activated voxels, X_L is the *t* value of left hemispheric voxels and X_R is the *t* value of right hemispheric voxels.

Statistical analysis

To analyze differences between the two groups of subjects, a Mann–Whitney *U* test was applied, since the dependent variable
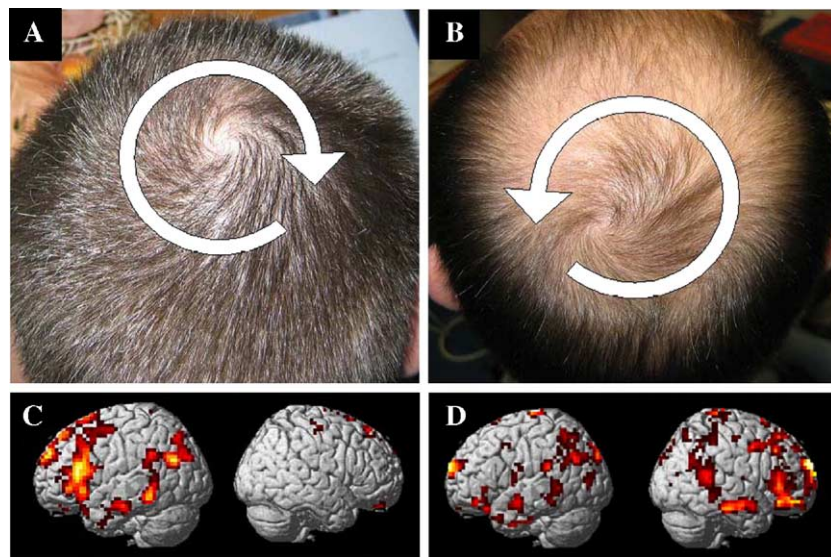

Fig. 2. Example of two subjects with clockwise (CW) and anti-clockwise (ACW) hair-whorl direction. Pictures of the scalp hair-whorl with CW (A) and ACW (B) orientation and cerebral activation maps of the synonym-judgment vs. letter-matching contrast with strong left lateralization in the CW (C) subject and right-lateralized activation in the ACW (D) subject. *P* < 0.001 uncorrected.

(the laterality index) is not normally distributed. For the comparison of the dichotomized groups according to typical or atypical language dominance, a Fisher's exact probability test was used because of less than 5 subjects in one of the categories.

Results

Lateralization of activation

Subjects with a clockwise hair-whorl showed a stronger left lateralization in all three regions of interest (ROI) than subjects with an anti-clockwise hair-whorl direction (Table 1). A statistical analysis using the Mann–Whitney U test showed a distribution of laterality indices for anti-clockwise subjects that significantly differed from the distribution of clockwise subjects in two ROIs: Broca's area and temporoparietal area. The laterality index in the remaining prefrontal area exhibited only a tendency for a differing distribution that was not statistically significant. While all clockwise subjects showed a strong left hemispheric dominance, anti-clockwise subjects exhibited a wider distribution of language lateralization ranging from strong right to strong left hemispheric dominance (Fig. 1). An example of two subjects, one with a clockwise and one with an anti-clockwise hair-whorl direction, is shown in Fig. 2.

Classification of language dominance

The subjects were classified according to their LI in Broca's area into typically, i.e. left, or atypically, i.e. bilaterally or right language dominant. We applied a rather strict threshold of 0.7 for the laterality index for the classification as left language dominant; below this threshold, subjects were classified as atypically dominant. The distribution of language dominance for clockwise and anti-clockwise subjects was significantly different, with no subject having a clockwise hair-whorl and showing atypical language dominance whereas six out of 21 subjects with anti-clockwise hair-whorl direction were classified as atypically dominant (Fisher's exact test, $P < 0.01$; Table 2).

Performance measures

Accuracy in both tasks was high (mean percentage of correct semantic judgments: 98% and string-judgments: 97%). Reaction times were significantly slower for the perceptual than for the semantic task (1593 ± 371 vs. 2420 ± 363 ms; $t = -19.5$; $P < 0.001$). Groups of subjects with anti-clockwise and clockwise hair-whorls did not differ in either reaction times nor in accuracy in both tasks (min $P = 0.121$).

Discussion

Our findings demonstrate that hair-whorl direction and cortical language representation are associated. Subjects with a clockwise hair-whorl orientation display a strong left-language dominance, whereas subjects with an anti-clockwise hair-whorl have a greater variability in cerebral language activation. This finding was previously known only for left-handed subjects.

The results of this study suggest an association between the lateralization of cerebral language representation and the direction of the scalp hair-whorl in addition to the known link of handedness and language dominance. The underlying mechanisms of cortical asymmetries are largely debated and by far not fully understood. Mechanisms ranging from genetic, developmental to cultural factors and especially their interaction have been discussed (Shaywitz et al., 1995; Berlim et al., 2003; Vallortigara et al., 1999; Klar, 1999; Provins, 1997; Geschwind and Galaburda, 1985; Sun et al., 2005). The correlation of a solely biological item that is not influenced by cultural factors, the hair-whorl, underlines the importance of genetic factors influencing cerebral asymmetries. A genetic model based on a single recessive gene underlying the association of handedness and hair-whorl direction based on the empirical distribution of each token has been proposed (Klar, 2003). Additionally, implications of this model for the development of brain laterality have been discussed (Klar, 2004, 2005). In this model, dominant R (R/R and R/r) allele-carriers are predicted to be right handed, process language in the left hemisphere and develop clockwise hair-whorls. Those homozygous for the non-functional random-recessive allele (r/r) were predicted to develop those traits, but their association will be random with respect to each trait. Our results would fit into this proposed model by showing that right-handers with an anti-clockwise hair-whorl display the same phenotype in regard to language dominance as non-right-handers. This model would also explain the finding of discordant cerebral language lateralization in monozygotic twins (Sommer et al., 2002; Klar, 2003) since twins homozygous for the random-recessive allele (r/r) could develop different lateralizations of handedness, hair-whorl direction and language representation.

The rapidly evolving field of molecular biology is presenting us with a tremendous amount of possible genes which might be responsible for the development of a left–right asymmetry in vertebrates (Schneider and Brueckner, 2000; Altmann and Brivanlou, 2001; Sun et al., 2005). Several attempts have been made to discover the genetic basis of language dominance and handedness in humans (Van Agtmael et al., 2003), but no gene has been identified so far that is responsible for the presented cortical asymmetries (Van Agtmael et al., 2001). One flaw of these attempts might have been that only handedness was considered as a phenotypical sign of laterality. Hence, subjects with potentially different genotypes were combined. The consideration of further phenotypical signs as, e.g. hair-whorl direction or cerebral language lateralization, could make it more likely to discover the genetic factor of these laterality phenomena.

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