

Short Communication

On the relationship between degree of hand-preference and degree of language lateralization



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ABSTRACT

Language lateralization and hand-preference show inter-individual variation in the degree of lateralization to the left- or right, but their relation is not fully understood. Disentangling this relation could aid elucidating the mechanisms underlying these traits. The relation between degree of language lateralization and degree of hand-preference was investigated in extended pedigrees with multi-generational left-handedness ($n = 310$). Language lateralization was measured with functional Transcranial Doppler, hand-preference with the Edinburgh Handedness Inventory. Degree of hand-preference did not mirror degree of language lateralization. Instead, the prevalence of right-hemispheric and bilateral language lateralization rises with increasing strength of left-handedness. Degree of hand-preference does not predict degree of language lateralization, thus refuting genetic models in which one mechanism defines both hand-preference and language lateralization. Instead, our findings suggest a model in which increasing strength of left-handedness is associated with increased variation in directionality of cerebral dominance.

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1. Introduction

Language lateralization and hand-preference can be described in terms of direction (right or left) as well as degree (strongly lateralized or more bilaterally represented (Isaacs, Barr, Nelson, & Devinsky, 2006)). It has been hypothesized that degree of hand-preference mirrors degree of language lateralization, e.g. that mixed-handers have the highest prevalence of bilateral lateralization and that strong left/right-handers have the highest prevalence of strong language lateralization (Annett, 1999; Crow, Crow, Done, & Leask, 1998; McManus, 1985). However, due to the low prevalence of mixed-handedness and atypical (bilateral and right-hemispheric) lateralization in unselected samples, limited data is available to test this hypothesis (Knecht et al., 2000; Pujol, Deus, Losilla, & Capdevila, 1999; Szaflarski et al., 2002). Improved understanding of the relationship between these two traits could help to investigate the development of cerebral organization, but also

inspires our understanding of the genetic underpinnings of both traits.

In this study, we investigated the relation between degree of language lateralization and degree of hand-preference and tested whether hand-preference can be used as a predictor for atypical language lateralization. We enriched the data for atypically lateralized subjects, by including large families with multiple left-handers. Hand-preference was measured with the Edinburgh Handedness Inventory, language lateralization with functional Transcranial Doppler (fTCD) in a fairly large sample.

2. Results

2.1. Direction of language lateralization and hand-preference

In the whole sample, there were 232 (74.8%) subjects with left-hemispheric lateralization and 78 (25.32%) with atypical lateralization (right-hemispheric or bilateral lateralization). In the subgroup of right-handers, there were 144 (84.2%) left-lateralized subjects and 27 (15.8%) atypical subjects. In the left-handed subgroup, there were 88 (63.3%) left-lateralized and 51 (36.7%) atypical subjects. In the male subgroup ($n = 122$), there were 64 right-handers, of which

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52 (81.32%) were left-lateralized and 12 (18.8%) atypical. Of the 58 male left-handers, there were 37 (63.8%) left-lateralized and 21 (36.2%) atypical subjects. The female subsample ($n = 188$) showed comparable figures, with 92 (86.0%) right-handers showing left-lateralization and 15 (14.0%) showing atypical lateralization. In the female left-handers there were 51 (63.0%) left-lateralized and 30 (37.0%) atypical subjects. There was no difference in prevalence of atypical lateralization between the male and female right-handers (Chi-square = 0.67, $P = 0.41$) or male and female left-handers (Chi-square = 0.01, $P = 0.92$).

2.2. Degree of language lateralization vs. degree of hand-preference

Curve estimation of continuous hand-preference (EHI lateralization indices, LI-EHI) and language lateralization (fTCD lateralization indices, LI-FTCD) data using non-linear regression as implemented in SPSS 22 showed the best fit for a cubic regression analysis with LI-EHI as the independent and LI-FTCD as the dependent variable, in comparison with linear and quadratic regression analysis ($y = 2.63 + 0.14 * x + -0.56 * x^2 + 0.95 * x^3$, $R^2 = 0.081$, $F = 9.033$, $df1 = 3$, $df2 = 306$, $p < 0.001$, Constant = 2.626, $b1 = 0.140$, $b2 = -0.561$, $b3 = 0.949$).

In the categorical analysis of degree of language lateralization, frequencies of bilateral, moderate right-hemispheric and strong right-hemispheric lateralization increased when moving from strong right-handedness to strong left-handedness, but not in all groups: mixed handedness had a lower prevalence of moderate right-lateralization (4.3%) than moderate right and left handers (6.0% and 6.9% respectively). Moderate left-handers had a lower prevalence of bilateral lateralization (17.2%) than mixed and strong left-handers (26.1% and 29.8% respectively). See Fig. 1 and Table 2 for an overview of the frequency distribution. Frequencies peaked in the strong-left-handedness subgroup for all three measures. The overall frequency distribution of atypical lateralization (bilateral, moderate right- and strong right-hemispheric lateralization collapsed) also peaked in the strong left-handedness subgroup

Table 1

Cut-off values for different categories of hand-preference and language lateralization.

Hand-preference categories	LI-EHI	Language lateralization categories	LI-FTCD
Strong right-handedness	≥ 0.75	Strong left hemispheric lateralization	$4.8 \leq LI < 8$
Moderate right-handedness	$0.25 < LI \leq 0.75$	Moderate left hemispheric lateralization	$1.6 \leq LI-FTCD < 4.8$
Mixed handedness	$-0.25 < LI < 0.25$	Bilateral lateralization	$-1.6 < LI-FTCD < 1.6$
Moderate left-handedness	$-0.75 < LI \leq -0.25$	Moderate right hemispheric lateralization	$-4.8 < LI-FTCD \leq -1.6$
Strong left-handedness	≤ -0.75	Strong right hemispheric lateralization	$-8 < LI-FTCD \leq -4.8$

(47.4%) see Fig. 2 for a depiction of language lateralization indices plotted against hand-preference indices.

2.3. Degree of hand-preference as a predictor for atypical lateralization

The mixed model analysis showed an association of all five categories of hand-preference with language lateralization ($p < 0.001$ for all cutoffs). Sensitivity was 0.78 and specificity 0.44 when using moderate left-handedness as a predictor for atypical lateralization. This changed to a sensitivity of 0.35 and a specificity of 0.78 when using strong right-handedness as a cut-off. Prediction was poor with an AUC for all models under 0.63.

3. Discussion

In this study, we investigated the relationship between degree of language lateralization and degree of hand-preference in a large sample of multigenerational pedigrees with multiple left-handers, in order to test whether degree of hand-preference can predict degree of language lateralization. 'Degree' indicates the extent to which the function is lateralized. Language lateralization could be successfully measured with functional Transcranial Doppler (fTCD) in 310 subjects, who were categorized as having strong, moderate or mixed hand-preference, as well as having strong, moderate or bilateral language lateralization (see Tables 1 and 2). We found that degree of hand-preference does not mirror degree of language lateralization. Instead, strong left-handedness showed the highest prevalence of bilaterality as well as the highest prevalence of moderate and strong right-hemispheric lateralization. Apparently, stronger left-hand preference results in a higher chance for atypical language lateralization. Thus, degree of hand-preference cannot serve to predict degree of language lateralization. The relation between degree of hand-preference and degree of language lateralization fits a cubic regression model.

In line with these results, the mixed model analysis showed that degree of hand-preference on a five point ordinal scale cannot predict atypical lateralization (i.e. bilateral and right-hemispheric lateralization, collapsed into one group). Our finding that degree of hand-preference does not mirror degree of language lateralization is in line with previous studies (Knecht et al., 2000; Pujol et al., 1999; Szaflarski et al., 2002) that did not show a direct coupling between degree of hand-preference and degree of language lateralization. Instead, the data from our study corroborates previous studies (Knecht et al., 2000; Pujol et al., 1999; Szaflarski et al., 2002) showing that the prevalence of both right- and bilateral lateralization becomes higher with increasing left-hand

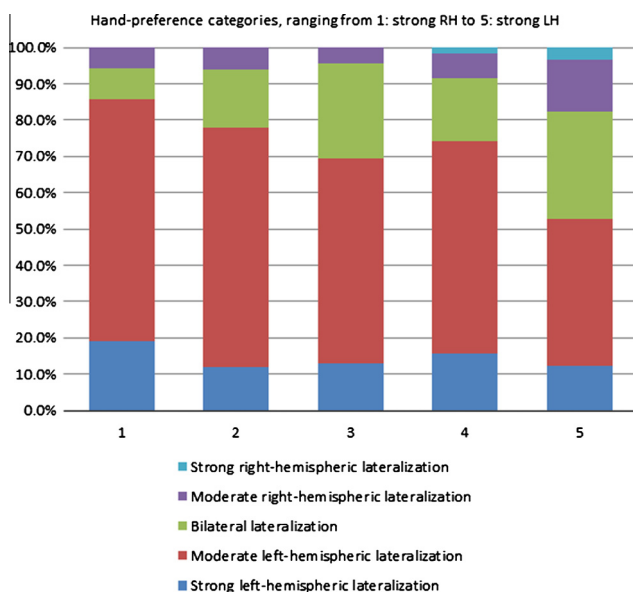


Fig. 1. Degree of language lateralization vs. degree of hand-preference. The proportion of each of 5-language lateralization categories (strong left-hemispheric, moderate left-hemispheric, bilateral, moderate right-hemispheric and strong right-hemispheric) is plotted against 5 categories of hand-preference (strong right-handedness, moderate right-handedness, mixed-handedness, moderate left-handedness, strong left-handedness).

Table 2
Crosstabulation of 5 categories of hand-preference (X-axis) and language lateralization (Y-axis), showing counts and percentages per hand-preference category.

		5-Category distribution of hand-preference					Total
		Strong RH	Moderate RH	Mixed hand	Moderate LH	Strong LH	
5-Category distribution of language lateralization	Strong <i>L</i> lateralization count	23	6	3	9	7	48
	%	19.2	12.0	13.0	15.5	12.3	15.6
	Moderate <i>L</i> lateralization count	80	33	13	34	23	183
	%	66.7	66.0	56.5	58.6	40.4	59.4
	Bilateral lateralization count	10	8	6	10	17	51
	%	8.3	16.0	26.1	17.2	29.8	16.6
	Moderate <i>R</i> lateralization count	7	3	1	4	8	23
	%	5.8	6.0	4.3	6.9	14.0	7.5
Total	Strong <i>R</i> lateralization count	0	0	0	1	2	3
	%	0.0	0.0	0.0	1.7	3.5	1.0
Total	Count	120	50	23	58	57	308
	% Of total	39.0	16.2	7.5	18.8	18.5	100.0

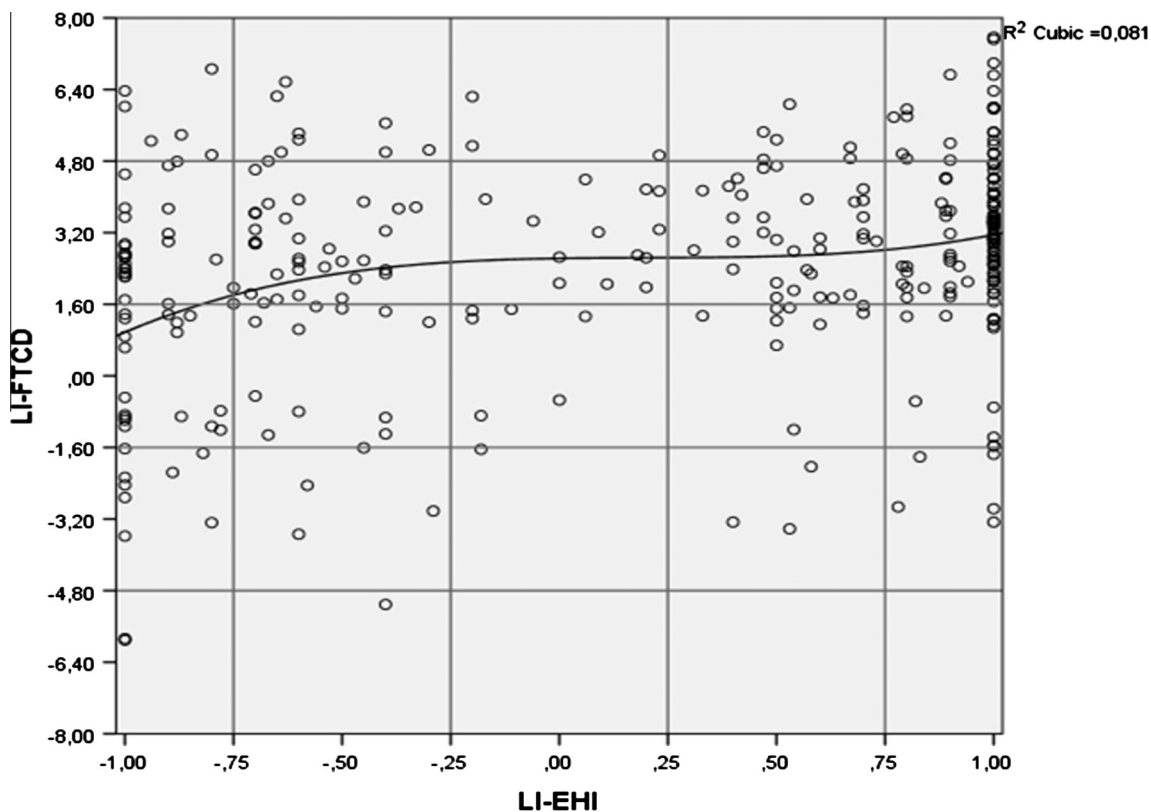


Fig. 2. Scatterplot of lateralization indices derived from the Edinburgh Handedness Inventory (LI-EHI, X-axis) plotted against lateralization indices derived from functional Transcranial Doppler (LI-FTCD, Y-axis). The cubic regression line is shown as well as grid lines showing the boundaries of the 5-categories of hand-preference and language lateralization.

preference. However, the samples in two of these studies comprised only a few subjects with atypically lateralization [Pujol et al. \(1999\)](#): 100 subjects, of which 14 had atypical dominance, [Szaflarski et al. \(2002\)](#): 50 subjects, of which 11 had atypical dominance). The landmark study of [Knecht et al. \(2000\)](#) (326 subjects, of which 62 had atypical dominance) comprised a large sample, but did not specifically address the relation between degree of hand-preference and degree of language lateralization. However, the graphical representation of their data also suggested the increase of both bilateral and right-hemispheric lateralization with increasing strength of left-handedness that was confirmed in our study.

Despite the significance of the cubic regression model, the R^2 of this model is relatively low, indicating an imperfect description of the data. This is in line with our observation that increasing strength of left-handedness is associated with increased variation

in the distribution of language lateralization indices, and, for example, not with a decrease in strength of left-hemispheric lateralization, which would have yielded a more linear distribution of data. This indicates that handedness cannot be used as a proxy of language lateralization and that the latter trait should be studied separately to inform us on cerebral organization, using techniques such as the transcranial Doppler applied in this study.

It has been hypothesized that a major gene model could underlie a chance distribution in the direction of lateralized functions. In this model, the presence of a dominant 'right-shift' ([Annett, 2004](#)) or 'dextrality' factor ([McManus, 1985](#)) drives development of right-handedness, while an increased loading of the minor allele increases the chance of random lateralization. Both the McManus and the Annett model were originally derived from epidemiological findings on the distribution of hand-preference and were

supposed to serve as a model to explain not only handedness but also cerebral lateralization. Both assumed an increased loss of directionality for language lateralization. Our findings show a different pattern, since loss of directionality in language lateralization (which can be interpreted as increased randomness) was found to be associated with increased leftward directionality for hand-preference. It is questionable whether a major gene could exert such different effects: increase the strength of left-handedness while at the same time decreasing directionality of cerebral lateralization. Alternatively, the observed relation between hand-preference and language lateralization is likely to result from several, possibly interacting genes. Indeed, recent findings suggest that hand-preference and language lateralization are complex genetic traits, that might only partially share ontogenetic factors (McManus, Davison, & Armour, 2013; Ocklenburg, Beste, Arning, Peterburs, & Güntürkün, 2014). One mechanism of interaction could be that the action of genes driving development of leftward language lateralization is inhibited once the genes that underlie development of strong left-handedness come into effect. Such a mechanism, involving different genes, might better explain the weak association between handedness and language lateralization than the major gene models.

Apart from genetic factors, other, environmental factors have been shown to influence hand-preference and language lateralization. Auer et al. showed that forced use of the left-hand due to brachial plexus lesions in original right-handers also induces a shift of lateralization (Auer et al., 2009). Further, pre-natal testosterone levels (Geschwind & Galaburda, 1985a, 1985b, 1985c; Medland et al., 2005; Witelson & Nowakowski, 1991), high maternal age (Coren & Porac, 1980) and cultural influences (Medland, Perelle, De Monte, & Ehrman, 2004) have also been suggested to influence hand-preference. Whether these factors also influence language lateralization to a similar degree is less well understood.

Our results also show that there is no difference in the prevalence of atypical lateralization in left-handed men and women. This confirms earlier findings that showed no gender differences in lateralization patterns (Knecht et al., 2000; Sommer, Aleman, Bouma, & Kahn, 2004; Sommer, Aleman, Somers, Boks, & Kahn, 2008; Szaflarski et al., 2002). Since language lateralization indices measured with fTCD are highly correlated with those measured by the intra-carotid amobarbital procedure or fMRI (Deppe et al., 2000; Knake et al., 2003; Knecht et al., 1998; Somers et al., 2011), it is not likely that our findings would have differed should we have employed any of these measurement techniques.

As with most studies on lateralization, this study is limited by the unavoidable use of arbitrary cut-off values for the different categories of degree of lateralization. In order to minimize the threshold for participation, only one language task was included in the experiment. This task allowed checking for cooperation of subjects, but not for performance. However, the task has been previously used in several functional transcranial Doppler studies of language lateralization (Deppe et al., 2000; Knecht et al., 2000) and has been shown to adequately activate language areas (Somers et al., 2011). Since no medical information was collected from participants it cannot be ruled out that language lateralization might have been influenced by medical conditions, such as stroke. Given the low mean age of our sample we argue that it is not likely that the prevalence of such subjects would be high enough to influence our results. Since it has been shown that language lateralization is determined in puberty (Helmstaedter, Kurthen, Linke, & Elger, 1997; Pataraia et al., 2004), it is neither likely that the presence of adolescents in the sample has affected our findings. As shown in the categorical analysis, the prevalence of mixed-handers and right-lateralized subjects is still relatively low, despite having enriched our sample for left-handedness. This precludes a formal statistical test of our categorical analysis.

Including only multigenerational families in this study may restrict extrapolation of our results to the general population.

Overall, this study shows that the prevalences of bilateral, moderate and strong right-hemispheric language lateralization are highest in strong left-handers and not in mixed-handers or moderate left-handed subgroups. This indicates an increased variation in degree as well as direction of language lateralization with increasing left-hand preference. As a consequence, degree of hand-preference does not predict degree of language lateralization and can as such not replace functional imaging techniques. Possibly, interacting genetic or other factors underlie the association between language lateralization and hand-preference, but it is unlikely that a single, shared genetic mechanism is involved in both handedness and language lateralization. Studying the genetics of language lateralization and hand-preference together could provide further insight into the mechanisms underlying these traits.

4. Methods

4.1. Subjects

The current study was part of a larger study on the genetics of hand-preference and language lateralization. To enrich the proportion of atypically lateralized subjects, participants were recruited from large multigenerational families with left-handedness. The rationale for this recruitment strategy is that both left-handedness and atypical language lateralization have been shown to be heritable (Anneken et al., 2004; Medland, Duffy, Wright, Geffen, & Martin, 2006) and might originate from the same genetic underpinnings (McManus, 1985). If this is true, any association between language lateralization and hand-preference should be most pronounced in subjects with familial left-handedness. Pedigrees were included if left-handed subjects were present in two generations, with at least two left-handers in one generation. From all recruited families as many members as possible were enrolled. Participants had to be at least 14 years of age. They were invited for the study by an advertisement in the local newspaper. The invitation included a screening list for hand-preference as well as familial hand-preference. A total of 368 subjects (147 males and 221 females) from 37 families participated. All were native Dutch speakers. Age ranged from 14 to 80 years. The mean age of the participants was 39 (SD = 15.74). There were 202 right-handers and 166 left-handers, classified by writing hand as indicated in a screening questionnaire. Subjects that indicated having been forced to switch from left- to right-hand writing were considered left-handed. EHI and fTCD was measured in 357 subjects (The missing 11 subjects were initially included but withdrew from actual participation). The distribution of EHI lateralization indices (LI-EHI) showed the expected J-shape. The fTCD language lateralization index (LI-fTCD) could be successfully measured in 310 subjects (122 males and 188 females). In the remaining 47 subjects the fTCD measurement failed or was inadequate, mainly because of low temporal bone translucency. The study was approved by the Human Ethics Committee of the UMC Utrecht, Utrecht, The Netherlands. After a complete description of the study, written informed consent was obtained according to the Declaration of Helsinki.

4.2. Hand-preference

Participants filled out the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971), a validated questionnaire with high reproducibility. In the EHI, subjects rate the strength of their hand-preference for 10 activities (XX = use this hand all the time, X = use this hand most of the time, 0 for both hands = no preference for this activity). A lateralization index (LI), ranging from 1 to –1 indicating

the direction and degree of hand-preference can be calculated by taking the difference between right and left ratings relative to the overall score (right-left/total).

4.3. Categorization of hand-preference

Primarily, subjects were classified as left- or right-handers (direction of preference), based on original hand-preference for writing as indicated in the EHI. To investigate the association between the degree of language lateralization and the degree of hand-preference, subjects were divided into five-categories, where hand-preference was defined as follows: strong hand-preference ($\text{LI-EHI} \geq 0.75$ or $\text{LI-EHI} \leq -0.75$), moderately strong hand-preference ($0.75 < \text{LI-EHI} \leq 0.25$ or $-0.75 < \text{LI-EHI} \leq -0.25$), or mixed-handedness ($0.25 < \text{LI-EHI} < -0.25$) (see Table 1 for an overview).

4.4. fTCD experiment: Word Generation Task

For the fTCD experiment the procedures described by Deppe et al. were followed (Deppe, Ringelstein, & Knecht (2004)). In this experiment, hemispheric activation during performance of a letter fluency task was contrasted with a control condition (Somers et al., 2011). After fixation of the headset and insonation of the middle cerebral arteries (MCAs), subjects were seated in front of a laptop computer. A word production paradigm used in several fTCD studies and validated by the Intra-carotid Amobarbital Procedure (IAP) was displayed on a screen (Knecht et al., 1996). Trials started with a 32.5 s baseline period during which the screen remained blank and subjects were instructed to think of non-verbal items (i.e. “a starry night”). At $t = 32.5$ s, a cuing tone sounded, followed by a randomly picked letter at $t = 37.5$ s that was shown for 2.5 s. Subjects were instructed to silently generate as many words as possible for 17.5 s starting with the displayed letter until the next cuing tone was presented ($t = 55$ s). Letters were shown only once. The letters Q, X and Y were excluded, since these are infrequently used in Dutch language. Subjects were instructed to overtly repeat the last silently generated words after the second tone, to control performance. A third tone ($t = 59$ s) indicated the end of a trial of which a total of 20 were performed.

4.5. fTCD experiment: data acquisition

A commercially available transcranial Doppler ultrasonography device (Multi-Dop T2, DWL, Sipplingen, Germany) was used for continuous measurements of changes in cerebral bloodflow velocity (CBFV). MCAs were insonated at a depth of 40–55 mm with two 2-MHz transducer probes attached to a screw-top headset, after placing the probes bilaterally at the temporal skull windows (Deppe et al., 2004). fTCD spectral envelope curves were recorded and stored at a rate of 28 sample-points per second.

4.6. fTCD experiment: data analysis and calculation of lateralization indices

The AVERAGE software package was used for calculation of LI-fTCD by comparing changes in CBFV during covert word generation relative to the control condition in both MCAs (Deppe, Knecht, Henningsen, & Ringelstein, 1997). AVERAGE is designed to integrate fTCD data over the corresponding cardiac cycles. Data is consequently segmented into epochs time-locked to the cuing tone. These epochs can be averaged and analyzed to calculate LIs. A measure of the mean inter-hemispheric difference in CBFV is provided by subtracting averaged changes in CBFV of the right and the left MCA during activity relative to rest (ΔCBFV). AVERAGE allows for calculation of the laterality index (LI-fTCD) by integrating the

ΔCBFV over a two second period of maximal difference between the left and right MCA during silent word generation. For an elaborate description of this methodology we refer to the paper by Deppe et al. (1997). A positive LI-fTCD reflects predominant left-hemispheric language processing. A negative sign reflects predominant right-hemispheric language processing. The magnitude of LI-fTCD reflects the degree of lateralization. Theoretically, the use of an integrating formula can result in lateralization indices ranging from ∞ to $-\infty$. However, in practice indices range from 12 (extreme left-dominance) to -12 (extreme right-dominance). In addition, AVERAGE calculates the accuracy of LI-fTCD, expressed by a confidence interval.

4.7. Language lateralization

To determine the degree of language lateralization, subjects were subdivided into five ordinal categories: strong left-hemispheric lateralization (SLL), moderate left-hemispheric lateralization (MLL), bilateral language lateralization (BLL), moderate right-hemispheric lateralization (MRL) and strong right-hemispheric language lateralization (SRL). For the 310 subjects, 99.4% of subjects had a LI-fTCD between -8 and 8 . Excluding the two outliers resulted in 308 remaining subjects for the categorical analysis, in which each category spanned 3.2 fTCD units. The five categories were defined as follows: Strong left-lateralization: $4.8 \leq \text{LI-fTCD} < 8$, moderate left-lateralization: $1.6 \leq \text{LI-fTCD} < 4.8$, bilateral language lateralization: $-1.6 < \text{LI-fTCD} < 1.6$, moderate right-lateralization $-4.8 < \text{LI-fTCD} \leq -1.6$, strong right-lateralization: $-8 < \text{LI-fTCD} \leq -4.8$. Bilateral, moderate right- and strong right-lateralization together are considered atypically lateralized.

4.8. Analysis

The continuous language lateralization (LI-fTCD) and hand-preference (LI-EHI) data were analyzed using the curve estimation module in SPSS 22. This module allows determining the best fitting regression model for non-linear distributed data. Linear, quadratic and cubic models were fitted to the data. The distribution of left-hemispheric and atypical lateralization in left- and right-handed participants was analyzed for the complete sample as well as by gender. We defined five ordinal categories ranging from strong left to strong right lateralization for both language lateralization and hand-preference. Subjects were categorized according to degree of lateralization. The prevalences within these five categories were cross-compared for the two traits. In addition, a mixed model analysis was used to investigate the association independent from family dependencies. Analyses were performed in R (R Development Core Team., 2013). The 5-hand-preference categories and gender were used as indicators and pedigree-membership as random factor. The dichotomous measure of language lateralization was used as outcome. Sensitivity and specificity were calculated for the 4 cutoffs to investigate whether any of the categories could be used as a reliable predictor for atypical language lateralization.

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