Handedness and hemispheric language dominance in healthy humans

S. Knecht, B. Dräger, M. Deppe, L. Bobe, H. Lohmann, A. Flöel, E.-B. Ringelstein and H. Henningsen

Department of Neurology, University of Münster, Germany

Correspondence to: Stefan Knecht, MD, Department of Neurology, University of Münster, Albert-Schweitzer-Strasse 33, D-48129 Münster, Germany
E-mail: knecht@uni-muenster.de

Summary

In most people the left hemisphere of the brain is dominant for language. Because of the increased incidence of atypical right-hemispheric language in left-handed neurological patients, a systematic association between handedness and dominance has long been suspected. To clarify the relationship between handedness and language dominance in healthy subjects, we measured lateralization directly by functional transcranial Doppler sonography in 326 healthy individuals using a word-generation task. The incidence of right-hemisphere language dominance was found to increase linearly with the degree of left-handedness, from 4% in strong right-handers (handedness = 100) to 15% in ambidextrous individuals and 27% in strong left-handers (handedness = –100). The relationship could be approximated by the formula: likelihood of right-hemisphere language dominance (%) = 15% – handedness (%)/10. These results clearly demonstrate that the relationship between handedness and language dominance is not an artefact of cerebral pathology but a natural phenomenon.

Keywords: language lateralization; hemispheric dominance; handedness; functional Doppler ultrasonography

Abbreviations: ANOVA = analysis of variance; fMRI = functional MRI ; fTCD = functional transcranial Doppler ultrasonography

Introduction

Language is lateralized to the left hemisphere of the brain but can occasionally also be found in the right hemisphere (Knecht *et al.*, 2000). This variability indicates the high degree of freedom with which the brain can instantiate language. Factors associated with lateralization inform us about limitation to this freedom and may also be important limitations in the recovery from aphasia after stroke by recruitment of the intact hemisphere. One factor which has been associated with language dominance is handedness.

Since the description of left-hemisphere language regions in right-handed patients by Paul Broca in the 19th century, it has been speculated that the reverse, i.e. right-hemisphere language dominance, should be true of left-handers. This claim has been widely accepted as the 'Broca rule', although Broca never explicitly postulated such a rule (Harris, 1993). Luria was among the first to point out that such an association could not be universally true because even in left-handers aphasia usually occurs after a lesion to the left hemisphere (Luria, 1976). Even now, our knowledge about the suspected association between handedness and language dominance

rests almost exclusively on studies of neurological patients. In this population, however, there is an increased incidence of pathological left-handedness and right language dominance, as the control of both dexterity and language can shift to the right hemisphere after long-standing left-hemisphere lesions (Rasmussen and Milner, 1977; Vargha-Khadem *et al.*, 1985; Woods *et al.*, 1988; Loring *et al.*, 1990). Evidence from patients with brain lesions of sudden onset, such as stroke, provide some indirect evidence about the status of right-hemisphere language dominance in healthy subjects. These studies are based on relatively small numbers of atypical aphasias, as in left-handers with right-hemisphere stroke. Furthermore, patients who present with language disturbances after right-sided cerebral infarction have not infrequently had strokes in the other hemisphere, rendering conjectures on the original hemisphere of language dominance unreliable (Pedersen *et al.*, 1995). As a consequence, studies of the incidence of aphasia after stroke in relation to handedness have provided widely diverging results. Two groups reported an increased incidence of language deficits

Table 1 *Rate of right-hemisphere dominance in relation to parental left-handedness*

	Handedness of subject					
	−75 or lower (strong left-handers)		Between −76 and 75		75 or higher (strong right-handers)	
	+	−	+	−	+	−
Parental left-handedness *n*	14	43	13	88	10	145
Degree of handedness, median (quartiles)	−100 (−100, −90)	−100 (−100, −90)	−60 (−60, 50)	−10 (−52, 42)	100 (100, 100)	100 (89, 100)
Right-hemisphere language dominance (%)	29	23	15	17	10	4

in left- or non-right-handers after right-hemisphere stroke (Gloning, 1977; Basso *et al.*, 1990). Another group found no such increase and suggested a negligible role of the right hemisphere in speech function in most left-handers who do not have early left-hemisphere damage (Kimura, 1983).

A new, very efficient perfusion-sensitive technique has made it possible to clarify the association between handedness and language dominance in healthy subjects in a representative and quantitative way. This technique is functional transcranial Doppler ultrasonography (fTCD), and is based on the same physiological principles as functional MRI (fMRI) (Deppe *et al.*, 2000). It has allowed us to measure the lateralization of language in a validated and highly reproducible way in a total of 188 healthy subjects and to control adequate cooperation in every case (Knecht *et al.*, 1998*a*, *b*). We have also employed this technique to assess the variability of language lateralization with respect to gender in healthy subjects (Knecht *et al.*, 2000). Like other researchers in the field, we had to confine our study to moderate and strong right-handers because we lacked sufficient left handers for a representative analysis (Frost *et al.*, 1999; Springer *et al.*, 1999). Thus, we had not been able to evaluate the role of handedness in language lateralization (as had been suggested by an anonymous reviewer). For the present study, we recruited more than 100 left-handed healthy subjects in addition to those reported in the previous study in order to answer the following questions: (i) can we confirm an association of language lateralization and handedness in healthy subjects? (ii) Can we quantify this relationship? (iii) Can we make predictions about the basis of language lateralization?

Methods

The work was part of the Münster functional imaging study on the variability of hemispheric specialization in health and disease (Deppe *et al.*, 1997, 2000; Knecht *et al.*, 1998*a*, *b*, 2000). Healthy volunteers were recruited by newspaper advertisement. The advertisement was intended to address especially subjects with non-right-handedness. They were not offered any financial reimbursement. Subjects were interviewed about the handedness of their parents. Possible answers were 'right', 'left' and 'unknown'. Subjects were excluded if information from a standardized questionnaire suggested the possibility of any neurological disorder, particularly perinatal asphyxia or kernicterus, head trauma, loss of consciousness, epileptic seizures, meningitis or encephalitis, or delayed or disturbed language development. Subjects were also excluded if they had failed to complete the equivalent of high school (*Realschule* or *Gymnasium*). Additionally, ~3% of subjects had to be excluded because fTCD could not be performed, due to inadequate sonographic penetration of the skull. A total of 326 subjects were thus included in the study: 198 females (age range 15–49 years, mean 26, SD 5.1) and 128 males (age range 19–46 years, mean 26, SD 4.6). All subjects gave informed consent to participation in the study, which was approved by the ethics committee of the University of Münster. Handedness was assessed by the Edinburgh Inventory (Oldfield, 1971), which ranges from −100 for strong left-handedness to +100 for strong right-handedness. Individuals were assigned to one of seven categories of handedness, which are shown in Fig. 3. Hemispheric language dominance was determined, as in previous studies, by fTCD using a word generation task validated by direct comparison with intracarotid amobarbital injection and fMRI and tested for reproducibility (Knecht *et al.*, 1996, 1997, 1998*a*, *b*; Deppe *et al.*, 1997, 1998). Details of the procedure are shown in Fig. 1.

Results

The distribution of hemispheric language dominance varied with the degree of handedness [$P < 0.0001$ by analysis of variance (ANOVA)] (Fig. 2).The more right-handed the subjects were, the lower was the relative incidence of right-hemisphere language dominance, and vice versa (Fig. 3). Overall, strong left-handers demonstrated a nearly sevenfold higher incidence of right-hemisphere language dominance than strong right-handers. In extreme left-handers the incidence of right-hemisphere language dominance was 27%,
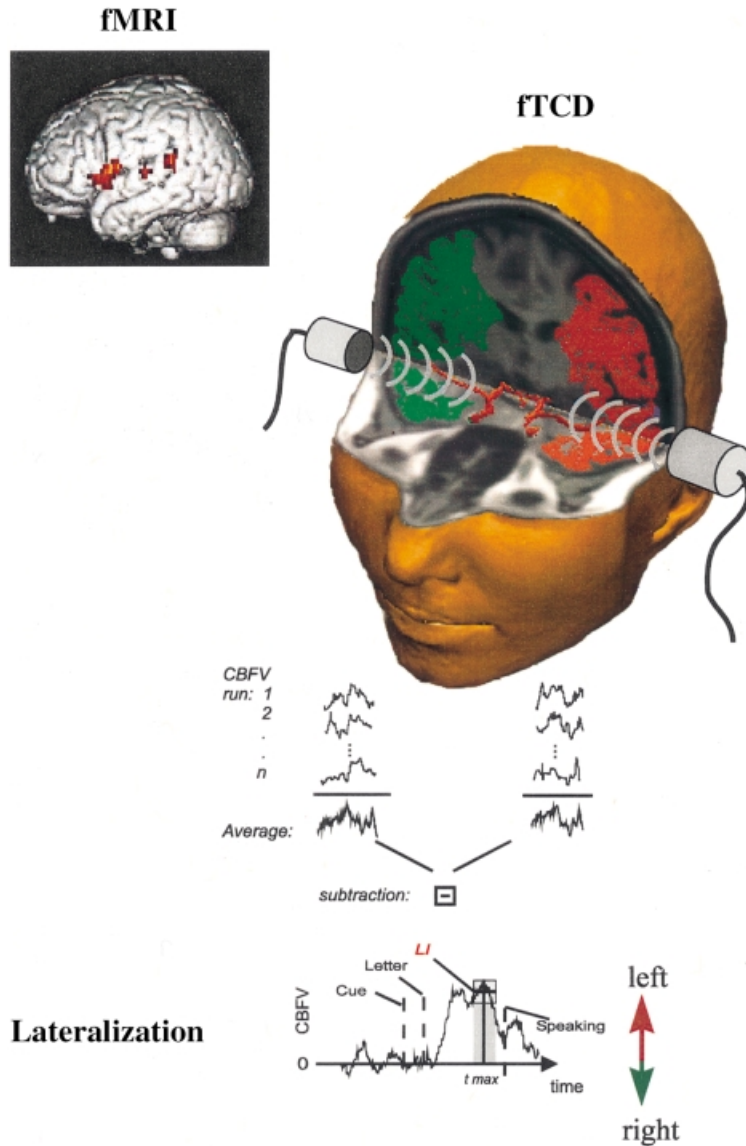
Fig. 1 Schematic illustration of the fTCD procedure in a single subject. For comparison, an fMRI of the same subject during an identical language task is shown (upper left). The fMRI analysis was performed by statistical parametric mapping, using software from the Wellcome Department of Cognitive Neurology, London, UK. fTCD measures the modulation of the cerebral blood flow velocity (CBFV) in the middle cerebral arteries (MCAs) at a depth of 50 mm during word generation. This allows the assessment of activity-related perfusion changes in the vascular territories of the left (red) and right (green) MCAs. These territories comprise potential language areas (van der Zwan *et al.*, 1993). After a cueing tone (Cue), a letter (Letter) is presented on a computer screen and the subject has to find silently as many words as possible that start with the displayed letter. Task performance is controlled by having the subject report the words (Speaking) after a second auditory signal, presented 15 s after presentation of the letter. The averaging procedure used for fTCD is depicted schematically below. CBFV changes in both MCAs during single runs (1 to *n*) of the language task are collected and averaged (usually a total of 20 runs). Subtraction of averaged CBFV changes in the right and the left MCA provides a measure of the mean interhemispheric difference in CBFV. The mean interhemispheric CBFV difference curve is time-locked to fixed events during the task. Calculation of the laterality index during word generation (LI) is based on the maximal left–right difference during word generation. The LI is highly reproducible and is proportional to lateralization, as assessed by fMRI and the Wada test (Deppe *et al.*, 1997, 1998, 2000; Knecht *et al.*, 1998*a, b*). Positive indices represent left-hemisphere language dominance; negative indices represent right-hemisphere language dominance. In this subject, a positive value indicates left-hemisphere lateralization for word generation.

whereas in extreme right-handers it was 4%. The incidences in the five intermediate groups were 27, 22, 11, 10 and 6%, respectively (Fig. 3). The rate of right-hemisphere language dominance can be approximated on the lowest order by the formula: likelihood of right-hemisphere language dominance (%) = 15% – handedness by the Edinburgh Inventory (%)/10.

Gender analysis
ANOVA on the single and combined influences of gender and handedness on language dominance showed no significant effect of gender ($P = 0.42$ and $P = 0.29$, respectively).

Analysis of familial handedness
As Table 1 shows, there was a trend for subjects with a family history of left-handedness to have a higher incidence of right-hemisphere language dominance. ANOVA on the single and combined influences of familial handedness and handedness on language dominance was limited by the small subgroups and the skewed distribution of handedness (U-shaped) and language dominance (bimodal). The single influence of familial handedness and the combined influence of familial handedness and handedness on language dominance did not reach significance ($P = 0.7$ and $P = 0.9$, respectively). Familial handedness only showed a significant effect on handedness ($P = 0.006$).
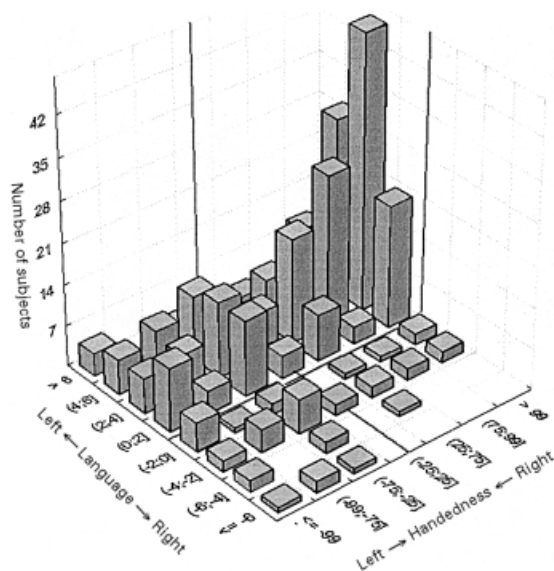
Fig. 2 Three-dimensional frequency histogram demonstrating the number of subjects (*z*-axis) with a given degree of handedness (*y*-axis) and language lateralization, as determined by fTCD (*x*-axis), in a total of 326 healthy subjects, comprising 198 females (age range 15–49 years, mean 26, SD 5.5) and 128 males (age range 19–46 years, mean 26, SD 4.6). These subjects include those reported in a preceding paper (Knecht *et al.*, 2000). Handedness was assessed by the Edinburgh Inventory (Oldfield, 1971) (positive values indicate relative right-handedness and negative values indicate relative left-handedness).

Degree of language lateralization
In addition to the correlation between language lateralization and handedness, a two-way interaction between the absolute degree of language lateralization and the direction of handedness was found, i.e. subjects in whom the side of language dominance was the same as the side of dominance in the control of dexterity had stronger lateralization than those in whom these factors were dissociated: right-handers with left language dominance and non-right-handers with right language dominance displayed stronger overall lateralization than right-handers with right language dominance and non-right-handers with left language dominance (ANOVA, $P = 0.04$) (Fig. 4). Use of the Kolmogorov–Smirnov test did not detect significant differences in the absolute degree of language lateralization between right-handers with right language dominance and non-right-handers (handedness <30) with left language dominance ($P > 0.1$). Also, no significant difference was detected between right-handers with left language dominance and non-right-handers (handedness <30) with right language dominance ($P > 0.1$).

Discussion
This is the first study to show that in healthy subjects there is a consistent and almost linear relationship between the degree of handedness and the direction of language dominance.

The relationship between handedness and language dominance has been addressed by Pujol and colleagues (Pujol *et al.*, 1999). Using a word generation task similar to ours, they performed a two-slice fMRI examination focusing on Broca's speech area in 100 healthy volunteers. They found frequent participation of the right Broca's homologue in left-handers. Our results confirm this finding. Additionally, they show that the incidence of right language dominance depends not only on the direction but also on the degree of handedness. This relationship is consistent and linear. The present findings also extend our own previous results on the variability of language lateralization in moderate and strong right-handers (Knecht *et al.*, 2000). In this group, we had found a 7% incidence of right-hemisphere language dominance. From the present sample, almost twice the size of the earlier sample, it is apparent that in strong right handers, i.e. those with a handedness index of 100 according to the Edinburgh Inventory, the incidence of right-hemisphere language dominance drops to ~4%. In their series of patients with medically intractable seizures, Rasmussen and Milner categorized handedness as either (i) right or (ii) left or mixed. Among patients without clinical evidence of early damage to the left hemisphere, they reported right speech lateralization by the amobarbital procedure in 4% of right-handers and in 15% of left- or mixed-handers (Rasmussen and Milner, 1977). Because these data were drawn from a pathological cohort, it remained unclear from this series whether the relationship
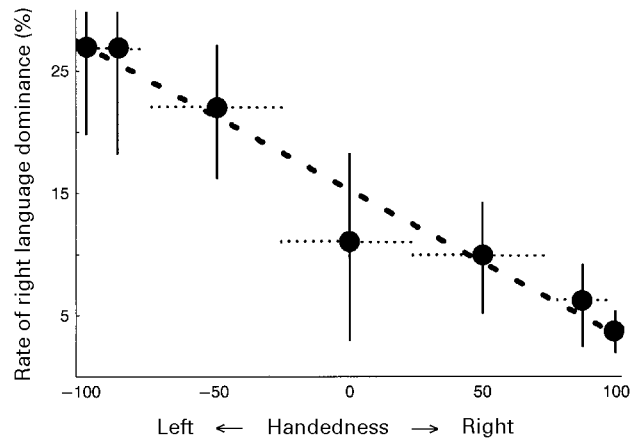
Handedness	–99 or less	more than –99; –75 or less	more than –75; –25 or less	more than –25; 25 or less	more than 25; 75 or less	more than 75; 99 or less	more than 99
n	37	26	50	18	40	48	107
Right dominance (%)	27	27	22	11	10	6	4

Fig. 3 Relationship between the degree of handedness by the Edinburgh Inventory (*x*-axis) and the incidence of right-hemisphere language dominance (*y*-axis). Bin width for each subgroup is represented by dotted horizontal lines. Error bars, represented by vertical lines, are based on the formula:

$$\sigma = \sqrt{\frac{(100 - P)\,P}{n}}$$

The relationship between the rate of right-hemisphere dominance and handedness can be approximated by the formula: likelihood of right language dominance (%) = 15% – handedness (%)/10. Specific information on the subgroups [width of handedness categories by the Edinburgh Inventory; number of subjects per category (*n*) and percent right dominance] is given in the table below the graph.

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	+	–	+	–	+	–
Parental left-handedness *n*	14	43	13	88	10	145
Degree of handedness, median (quartiles)	–100 (–100, –90)	–100 (–100, –90)	–60 (–60, 50)	–10 (–52, 42)	100 (100, 100)	100 (89, 100)
Right-hemisphere language dominance (%)	29	23	15	17	10	4

between handedness and dominance was a natural phenomenon. Furthermore, because handedness had been collapsed into only two categories, the data do not indicate whether the observed relationship between handedness and language dominance was categorical or linear. Overall, the tendency reported by Rasmussen and Milner is in accord with our data. However, the incidence of right-hemisphere dominance for language was considerably higher in our strongly left-handed healthy subjects (27%) than in the group of left- or mixed-handed epilepsy patients from the Rasmussen and Milner series (15%). This agrees well with

a linear relationship between the degree of handedness and the incidence of right-hemisphere dominance for language.

Although fTCD has a low spatial resolution, it constitutes a very practical tool to determine functional lateralization in a large number of subjects. We used a strictly mathematical distinction between right- and left-hemisphere language dominance. This approach constitutes a gross simplification of the neural basis of language, but allowed us to focus on the relationship of handedness with language lateralization. A left-hemisphere fTCD lateralization index does not exclude involvement of the right hemisphere; it only demonstrates a
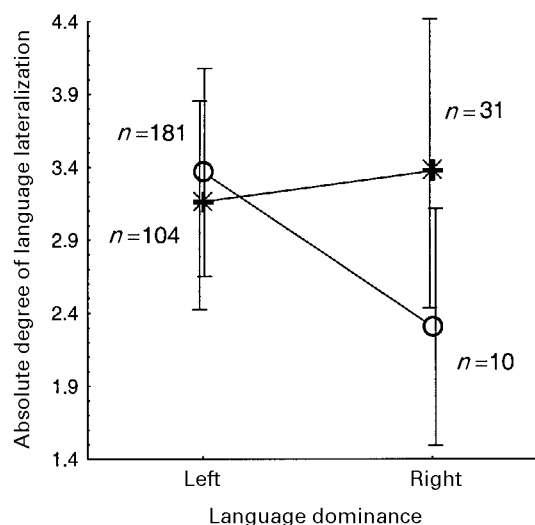
Fig. 4 Two-way interaction between the absolute degree of language lateralization for left and right language dominance (and standard deviations) in right-handers (handedness >30 by the Edinburgh Inventory, circles) and non-right-handers (handedness ≤30 by the Edinburgh handedness inventory, asterisks).

relatively large increase in perfusion during word generation by the left hemisphere. This mathematical distinction was chosen to exclude the bias which is always involved when defining 'bilateral' language lateralization (Risse *et al.*, 1997). A more 'bilateral' lateralization, i.e. a lower degree of lateralization, was found in subjects in whom dominance of manual control (handedness) and dominance of language did not fall into the same hemisphere (Fig. 4). This finding may explain why in a large series of patients those with atypical lateralization for handedness seemed to have slightly less severe aphasia than patients with typical handedness (Basso *et al.*, 1990).

Although word generation is a frequently used activation task and constitutes an essential feature in the production of language, it is only one of the multiple dimensions of language (Cuenod *et al.*, 1995; Hertz-Pannier *et al.*, 1997; Benson *et al.*, 1999). Other aspects of language, such as prosody, were not tested in our study, and could therefore show a different relationship with handedness.

For handedness, a genetic basis is established but does not fit a simple Mendelian model (Carter-Saltzman, 1980). This suggests a role for complex genetic or non-genetic factors in the formation of the phenotype (McManus, 1991; Annett, 1996). We assessed handedness with the Edinburgh Inventory. This is a preference-based measure and shows a J-shaped distribution of handedness in the general population. It differs from the more bell-shaped distribution found by skill-based measures, and it is susceptible to a cultural bias (Corballis, 1997). Because of its good test–retest reliability, the Edinburgh Inventory has been used in many studies and, unlike other measures, allows good comparison between studies (Ransil and Schachter, 1994). Handedness can safely be regarded as a two-directional phenomenon because different measures of handedness usually show a close

relationship to each other, such that individuals classified as left- or right-handers by one method are classified in the same way by other methods (Corballis, 1997). Differences in the grading system for handedness may bear on the shape of the correlation with language dominance, but there is little to suggest that this relationship would change in a fundamental way if a different measure of handedness were used.

The present study demonstrates that left-handedness is neither a precondition nor a necessary consequence of right-hemisphere language dominance. However, left-handedness increases the likelihood of right-hemisphere language dominance. Furthermore, left-handedness in either parent may have an additional effect on the likelihood of right-hemisphere language dominance (Table 2). The degree of handedness is linearly and highly significantly related to the side of language dominance. Mathematically, this relationship involves two variables and can be approximated by the following formula: likelihood of right language dominance (%) = 15% – handedness (%)/10. In biological terms, such a relationship is difficult to explain by a single causative factor. A more plausible explanation would be that handedness and language dominance are each determined by multiple factors, some of which have a role in both phenomena. Such multiple and partly overlapping factors could produce (i) a threshold effect accounting for the 4% incidence of right-hemisphere language dominance in extreme right-handers, and (ii) a modifier effect accounting for the increase in incidence of right dominance along with the increase in left-handedness. The present study provides a framework for the investigation of these factors. For example, assessment of the inheritance of language dominance by functional imaging may shed more light on the genetic underpinnings of functional asymmetry in the human brain.

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