Handedness and lateralization

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Cortical Organisation and Lateralization Of The Brain In Handedness And Dominance

According to Annett most people in our society define handedness as the hand that you use for writing (1970). Researchers define handedness as the hand that performs faster or specifically on physical tests. Paul Broca (1979), suggested that a person's handedness was opposite from that specialised hemisphere (so a right-handed person probably has a left-hemispheric language specialization). However, a majority of left-hemispheric brain specialise for language abilities. Many researchers have try to this correlation between handedness and brain lateralisation. The key reason that hand-brain link is important and is an accepted methodology is that clinicians use handedness as a marker for brain lateralization.

Language is a distributed cerebral network with differences in area involvement that relate to specific language functions (Frith et al., 1991). Vital regions in network lateralize to one hemisphere and determine lesion (Ojemann, 1991). In most people this lateralization is to the left. The only consistent information on the variability of hemispheric control between individuals are aphasias following a stroke or hemispheric inactivation by procedure in patients with brain lesions (Wada and Rasmussen, 1960). Pertaining to the unevenness of language control there is a chance of functional hemispheric reform (Rasmussen and Milner, 1977). It assumes that variation from left hemisphere language power is related to a difference like left-handedness. In right-handed subjects there is puzzling correlation of verbal language and hand dominance, both confines to a small area to the left hemisphere (Mayeux and Kandel, 1991). The actual variability of language lateralization in the general population is practically unknown. Evaluations in a representative number of healthy subjects do not exist because, in the past, no technique was available to determine language lateralization effectively and non-invasively.

This lack of information has hampered the assessment of language disturbances. There is an ongoing debate on the role of the right hemisphere in recovery from aphasia after left hemispheric strokes (Weiller et al., 1993Go; Heiss et al., 1997Go; Mimura et al., 1998Go). Particularly, in retrospective evaluations it would be important to know how many patients with left hemispheric strokes and transient disturbance of language can be expected to have been right hemisphere language dominant and to have suffered speech impairment due to other, more unspecific causes like decreased vigilance.

Moreover, knowledge concerning the exact incidence of right hemisphere language dominance in healthy righthanders would be important for functional neuroimaging studies. Here, due to lack of information, researchers often need to rely on the assumption that restricting examinations to healthy right-handers will control for a possible variability in hemispheric dominance.

Recently, a simplified functional imaging technique, functional transcranial Doppler-ultrasonography (fTCD) has become available (Aaslid, 1987Go; Hartje et al., 1994Go; Silvestrini et al., 1994Go; Rihs et al., 1995Go). It allows determination of hemispheric dominance in individual subjects in an effective, reliable and non-invasive way (Deppe et al., 1997Go; Knecht et al., 1998). This technique has now made it possible to establish the variability in the side and degree of language dominance in a representative number of healthy subjects. fTCD measures cerebral perfusion changes related to neuronal activation in a way comparable to functional MRI (fMRI) and 15O-PET (Kuschinsky, 1991Go; Jueptner and Weiller, 1995Go; Deppe et al., 1997Go, 1998Go). fTCD makes it possible to compare perfusion changes (by measuring blood flow velocities) within the territories of the two middle cerebral arteries (MCAs), which comprise the potential language areas (van der Zwan and Hillen, 1991Go). It thus provides an operational index of laterality which, in many respects, resembles the one obtained by the intracarotid amobarbital procedure (Wada test) (Wada and Rasmussen, 1960Go). Determination of language lateralization by fTCD matches precisely both the results of fMRI and the Wada test with concordance in every single case (Deppe et al., 1998Go; Knecht et al., 1998aGo).

As in many previous studies of this kind, word generation was chosen as an activation paradigm because it is one of the most effective measures of language production (Neils-Strunjas, 1998Go). On this basis language dominance was determined in a total of 188 healthy subjects. Left-handers were excluded from the study because of possible confounding effects of handedness on hemispheric dominance (Kimura, 1983Go). A careful history for brain damage in the prenatal period or in infancy was taken in order to exclude subjects with possible plastic reorganization of hemispheric dominance after brain lesions (Rasmussen and Milner, 1977Go).

The work was part of the Munster functional imaging study on the variability of hemispheric specialization in health and disease (Deppe et al., 1997Go;

Knecht et al., 1998aGo, bGo). Hemispheric language dominance was assessed in 188 healthy volunteers with 111 females (mean age 26 ± 5. 5 years, range 17-50 years) and 77 males (mean age 27 ± 3. 7 years, range 21-40 years). Subjects were excluded if, on a standardized questionnaire, they reported delayed or disturbed language development or a history of other neurological disorders, particularly perinatal asphyxia or kernicterus, head trauma, loss of consciousness, epileptic seizures, meningitis or encephalitis. They were further required to have successfully completed the equivalent of high school (`Realschule' or `Gymnasium'). Right-handedness was assessed by a handedness index in the Edinburgh Inventory of greater than 30% (Oldfield, 1971Go). Left-handers were excluded from the study, as were right-handers with a score for right-handedness lower than 30%, because, due to the small number of these subjects, an adequate evaluation of the effect of handedness on language lateralization would not have been possible. Approximately 75% of the subjects recruited had an index of more than 80% right-handedness. All subjects gave informed consent to participate in this study, which was approved by the Ethics Committee of the University of Münster.

Assessment of hemispheric language dominance was performed by a standardized fTCD technique (used in a number of previous studies) and a word generation task, validated by direct comparison with the intracarotid amobarbital injection and fMRI (Knecht et al., 1996Go, 1997Go, 1998aGo, bGo; Deppe et al., 1997Go, 1998Go). Briefly, subjects were presented with a letter on a computer screen 2. 5 s after a cueing tone. Silently they had to find as many words as possible starting with the displayed letter. For fTCD an activation paradigm strongly based on verbal fluency was used, corresponding to the fields of reported female superiority (Basso et al., 1982Go; Pizzamiglio et al., 1985Go). Task performance was controlled by instructing the subjects to report the words after a second auditory signal following 15 s after presentation of the letter. All words had to be reported within a 5-s time period. The next letter was presented in the same way after a relaxation period of 60 s. Letters were presented in random order and no letter was displayed more than once. `Q', `X' and `Y' were excluded because very few words have these as initial letters.

Changes in the cerebral blood flow velocity (CBFV) in the basal arteries were measured as an indicator of the downstream increase of the regional metabolic activity during the language task. Dual fTCD of the MCAs was performed with two 2 MHz transducer probes attached to a headband and placed bilaterally at the temporal skull windows (1Go). Details of the insonation technique, particularly the correct identification of the MCA, have been published elsewhere (Ringelstein et al., 1990Go). The spectral envelope curves of the Doppler signal were analysed off-line with the fTCD software AVERAGE developed by one of the authors (M. D.) (Deppe et al., 1997Go).

1 Schematic diagram of the way language lateralization was determined. Perfusion increases and therefore neuronal activation during word generation were assessed in the vascular territories of the left (marked in red) and right (marked in green) MCAs, which comprise the language areas. This was achieved by fTCD measurements of the CBFV changes in these arteries. Systemic effects were eliminated by calculating the differences in perfusion changes between sides. Averaging the responses over 20

repetitions (on average) in each individual made the results highly reliable. (For details, see Deppe et al., 1997.)

After automated artefact rejection, data were integrated over the corresponding cardiac cycles, segmented into epochs which related to the cueing tone and then averaged. The epochs were set to begin 15 s before and to end 35 s after the cueing tone. The mean velocity in the 15-s pre-cueing interval (Vpre. mean) was taken as the base-line value. The relative CBFV changes (dV) during cerebral activation were calculated using the formula: dV = [V(t) – Vpre. mean] x 100 / Vpre. mean where V(t) is the CBFV over time. Relative CBFV changes from repeated presentations of letters (on average 20 runs) were averaged time-locked to the cueing tone. The number of repetitions was less than 22, because no letter was presented more than once during the word generation task.

A functional TCD laterality index LIfTCDwas calculated using the formula:

Statistics

The Kolmogorov-Smirnov test was used to assess the hypothesis that laterality indices in males and females were drawn from different populations. Unlike the parametric t-test for independent samples or the Mann-Whitney U test, which tests for differences in the location of two samples (differences in means, differences in average ranks, respectively), the Kolmogorov-Smirnov test is sensitive to differences in the general shapes of the distributions in the two samples, i. e. to differences in dispersion and skewness (Spence et al., 1990Go). The Mann-Whitney test for equivalence (Wellek, 1996Go) was employed to confirm equivalence of laterality indices in men and women. A significant result in this test provides a strong positive measure for a lack of gender differences in laterality indices. We tested the null hypothesis H0: | P[LImale > LIfemale] – 1/2| >={varepsilon}versus the alternative hypothesis of equivalence H1: | P[LImale > LIfemale] – 1/2| < {varepsilon}on an error level of {alpha}= 0. 01. LImale and LIfemale represent an independent pair of laterality indices, each corresponding to the LI distributions for men and women, respectively. The equivalence interval {varepsilon}was chosen conservatively ({varepsilon} = 0. 1), compared with the specifications described by Wellek (Wellek, 1996Go). The test has been carried out by the SAS® macro Mann-Whitney test for equivalence (Institute, 1989). Because of the small number of right dominant subjects, the test could only be applied to the subgroup of left hemisphere language dominant subjects.

In six of the 194 right-handed subjects determination of language lateralization was not possible due to lack of a temporal bone window, i. e. inadequate ultrasonographic penetration of the skull by the ultrasound beam. In the remaining 188 subjects (59% females, 41% males) the overall distribution of language lateralization was bimodal with 7. 5% being right hemisphere and 92. 5% left hemisphere language dominant (2Go).

The distribution of language lateralization was equivalent in men and women (3Go). The Kolmogorov-Smirnov test did not detect any significant differences between females and males in the overall distribution (P > 0. 05). In the subgroup of left hemisphere language dominant subjects, the Mann-Whitney test for equivalence showed equivalence with P < 0. 01. The mean index of left language dominance was 3. 45 (±1. 44 SD) in females and 3. 39 (±1. 37 SD) in males. Indices in the subgroup of right hemisphere language dominant subjects were not amenable to further statistical analysis because of the limited number (n = 14). The mean index of right language dominance was -2. 09 (±1. 39 SD) in females and -2. 14 (±1. 36 SD) in males.

The average number of words found during the activation task per letter presented was not statistically different between men and women (Mann-Whitney U test, P = 0. 81) or subjects with left or right hemisphere language dominance (Mann-Whitney U test, P = 0. 26). It was also independent of the index of lateralization (correlation coefficient r = 0. 027).

These are the first data on the natural distribution of language dominance in a large series of healthy right-handed subjects. They demonstrate equivalence of language lateralization for word generation in males and females, and they suggest that 1 in 13 healthy right-handed subjects is right hemisphere dominant for language.

Methodology

There is debate whether language can be treated as a separate mental faculty or should be approached as part of a more general cognitive system (Fodor, 1983Go). Moreover, language comprises receptive and expressive aspects and is intertwined with prosody, memory and attention (Knecht et al., 1996Go; Binder et al., 1997Go). Therefore, the assessment of language lateralization based on a single activation task provides just one index of the interindividual variability in language processing. This approach can nevertheless serve as a first step in elucidating the factors underlying the diversity of large scale neural language organization.

fTCD lends itself to determination of hemispheric language dominance. The index of lateralization obtained by fTCD based on word generation is very reliable and closely corresponds to (i) the outcome of the intracarotid amobarbital procedure and (ii) the index of lateralization obtained by fMRI (Deppe et al., 1998Go; Knecht et al., 1998aGo). Other techniques like head turning, event-related potentials, transcranial high frequency magnetic stimulation or the dichotic listening test used for the evaluation of language dominance have so far failed to provide results that are reproducible and in sufficient concordance with the intracarotid amobarbital procedure (Bryden and Allard, 1981Go; Jancke et al., 1992Go; Jennum et al., 1994Go; Segalowitz and Berge, 1995Go; O'Leary et al., 1996Go; Hugdahl et al., 1997Go).

Unlike the intracarotid amobarbital procedure and as opposed to brain lesions, functional imaging techniques including fTCD assess brain activation and not inactivation. They are set to determine the location and relative amount of the maximal activation while diffuse or bilateral activations are cancelled out. Thus, fTCD is insensitive to a lesser activation in the contralateral hemisphere. Moreover, fTCD cannot determine whether an activated region during a task is a critical region that, when damaged, will result in a loss of that particular function. This shortcoming holds for all functional imaging techniques. However, the fact that determination of language lateralization by fMRI and fTCD correspond closely to that determined by the intracarotid amobarbital inactivation suggests that activated regions match critical regions and therefore provide essential information on the risk for language loss (Desmond et al., 1995Go; Binder et al., 1996Go; Knecht et al., 1998aGo).

Sex

Fuelled by the general interest in `la petite différence', the lack of information about the natural distribution of language dominance has led to far-reaching speculations about possible differences in language lateralizations between the sexes. This discussion has been characterized by a high acceptance for positive results. Thus, despite considerable data to the contrary, there is a strong belief that language in women, on average, is less lateralized than in men (Bakan and Putnam, 1974Go; Levy and Reid, 1976Go; McGlone, 1980Go; McKeever et al., 1983Go; Hough et al., 1994Go; Rugg, 1995Go). The idea of an increased bilaterality in women has received support by a recent fMRI study in 19 males and 19 females (Shaywitz et al., 1995Go) in which activation related to a rhyming task was found to be more bilateral in women than in men. It has been conjectured that an increased bilaterality of language in women would lead to a decreased susceptibility to unilateral infarctions explaining a greater male than female proportion of aphasics (McGlone, 1980Go).

Kertesz and Sheppard then showed that aphasias were as frequent in males as in females, as long as sex differences in the incidence of infarcts were taken into account (Kertesz and Sheppard, 1981Go). Similar results were obtained in a more recent epidemiological study (Pedersen et al., 1995Go). Recently, using fMRI, Frost and colleagues found no differences between sexes during a language comprehension task when group averages were compared (Frost et al., 1999Go). Our data provide the first direct evidence that language lateralization during word generation in men and women is also equivalent in variablity. In fact, they not only show a lack of significant differences but they positively demonstrate significance of equivalence in healthy subjects even though this finding is based on a word generation task, i. e. a field of reported female superiority (Kimura and Harshman, 1984Go). Equivalence of hemispheric lateralization between sexes during word generation does not exclude gender differences in subfunctions of language like rhyming, which we did not investigate. As was pointed out before, such a difference has been reported by Shaywitz and colleagues in a small series of subjects examined by fMRI (Shaywitz et al., 1995Go). However, in line with our results, these researchers did not find gender differences in other language tasks.

Right hemisphere language dominance

The predominance of right-handedness and left hemisphere language lateralization has led some theorists to suggest that a gestural system of communication with dominance of the right hand provided the neural architecture for vocal articulation in human evolution (Hewes, 1973Go; Kimura, 1987Go). If indeed handedness and language were coupled because they share the same neural resources, then any deviation from this pattern would have to be pathological. Right hemisphere language dominance in right-handers or left hemisphere language dominance in left-handers reported from the intracarotid amobarbital procedure does not challenge this view, because this procedure is only performed in patients with brain pathology. However, the present findings in healthy subjects indicate that even under natural conditions the association between handedness and language dominance is not an absolute one. Because 75% of subjects were strongly right-handed (> 80%) and the remaining had handedness indices of

> 30%, the effect of the degree of handedness on language lateralization could not be evaluated in the present study. Comparison of left- and right-handers will be necessary to test whether a relative association between handedness and language dominance exists in healthy subjects.

The extreme argument could be put forward that all of our presumed healthy subjects with right hemisphere dominance must have suffered covert brain damage resulting in a shift of language into the right hemisphere. A similar argument has been made to explain left-handedness in healthy subjects (Coren, 1990Go). We believe that covert brain damage was unlikely. The medical history in all subjects was unrevealing and the scholastic achievement was similar. The average number of words produced during the task did not differ between subjects with left or right hemisphere language dominance and the pattern of language lateralization variability was bimodal with maxima for left- and right-hemisphere dominance (2Go). If there had been subclinical damage to language relevant areas in the left hemisphere resulting in a shift to the right, one would have expected impaired word fluency and more cases with little lateralization because of a bilateral representation of language functions. This was not the case. We therefore suggest that right hemisphere language dominance is not a pathological but a natural phenomenon.

Previous estimates of `atypical’ right hemisphere language dominance were either based on the results from the intracarotid amobarbital test in patients evaluated for resective neurosurgery or on the occurrence of `crossed aphasia’, i. e. aphasias after right hemispheric lesions. In patients with epilepsy submitted to the intracarotid amobarbital test the number of right-handers with right hemisphere language dominance was 4% in a large series and rose to 12% when a left hemisphere lesion was defined (Rasmussen and Milner, 1977Go). Because the Wada test is only performed in patients with brain lesions, which are often associated with a secondary transfer of cortical functions from the damaged to the intact hemisphere, these numbers cannot be extrapolated to healthy subjects (Helmstaedter et al., 1994Go). By evaluation of stroke-patients with crossed aphasia, the incidence of right hemisphere language dominance in right-handers has been inferred to be between 1 and 2% in the majority of series (Gloning, 1977Go; Borod et al., 1985Go; Kertesz, 1985Go).

On the one hand, this low estimate of right hemisphere language dominance in previously healthy subjects made aphasias in right-handers after right-sided lesions seem an exceptional event and has resulted in almost 100 reports on `crossed aphasia' in the last 30 years. On the other hand, difficulties in the assessment of language performance due to physical exhaustion and deficits in sustained attention in the early stages after stroke and reorganizational restitution in the later stages may have facilitated an underdiagnosis of aphasia in right hemispheric stroke patients in many studies. Not every patient with a cerebral infarction in the respective language dominant hemisphere will suffer damage of the language areas and become aphasic. The overall rate of aphasia due to stroke has been found to be 38% in the acute state and 18% at discharge from the hospital (Pedersen et al., 1995Go). Reasoning from the effects of brain activation to the effects of brain lesions is problematic but results from activation studies may be conceptually useful to the understanding of lesion-deficit variability in the clinical context (Willmes and Poeck, 1993Go). In a single recent study on 880 stroke patients it was reported, in passing, that of right-handed aphasics 9% had right hemispheric lesions (Pedersen et al., 1995Go). In a study on language deficits in servicemen who had suffered penetrating brain wounds, 18% of the aphasics had suffered right hemispheric lesions (Mohr et al., 1980Go). However, here the possible effects of diffuse brain damage by the impact of a bullet and the effect of variable handedness pose methodological limitations. Our cohort was similar in age to these soldiers. We found an incidence of 7. 5% of right hemisphere dominance in our activation study of healthy subjects. This combined evidence suggests that about 1 in 13 previously healthy right-handed patients with a right hemispheric infarction could be at risk of suffering language impairments because this is the hemisphere dominant for word generation. Conversely, after left hemispheric infarctions right-handed patients, who in retrospective evaluations seem to have recovered well from language disturbances, and on fMRI or PET may even show language related activation in the right hemisphere, may do so because they had been right hemisphere language dominant to begin with.

Presently, we do not know the relevance of the extent of language lateralization by fTCD. Low indices of lateralization indicate that there is a bihemispheric activation during word generation. Although reported in studies based on the Wada test, bilateral language representation in stroke patients has probably been neglected because persistent aphasia in these subjects may only occur after bilateral damage (Benbadis et al., 1995Go). This is very rare and patients rarely survive. However, subjects with low indices of lateralization may be the ones who, after unilateral damage of traditional language regions, do not show marked aphasia and recover well by further recruitment of the intact hemisphere.

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