

Handedness and functional MRI-activation patterns in sentence processing

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We investigate differences of cerebral activation in 12 right-handed and left-handed participants, respectively, using a sentence-processing task. Functional MRI shows activation of left-frontal and inferior-parietal speech areas (BA 44, BA9, BA 40) in both groups, but a stronger bilateral activation in left-handers. Direct group comparison reveals a stronger activation in right-frontal cortex

(BA 47, BA 6) and left cerebellum in left-handers. Laterality indices for the inferior-frontal cortex are less asymmetric in left-handers and are not related to the degree of handedness. Thus, our results show that sentence-processing induced enhanced activation involving a bilateral network in left-handed participants. *NeuroReport* 18:1339–1343 © 2007 Lippincott Williams & Wilkins.

Keywords: functional imaging, handedness, language lateralization, sentence processing

Introduction

In right-handed participants (RHs) a left-hemispheric dominance for language processing has been established by a variety of techniques. Noninvasive imaging studies in healthy participants demonstrated that approximately 95% of RHs have a left-hemispheric dominance in word generation and semantic decision tasks [1,2]. In 22–47% of left-handed participants (LHs), such studies showed a stronger right or bilateral language representation [3–5], one study showed a correlation with the degree of handedness [6]. To date, only one study [7] investigated differences at sentence level between LHs and RHs in a speech comprehension task and reported also bilateral activation in LHs.

Given that both sentence-level comprehension and production recruit additional brain areas compared with word level processing [8–10], lateralization data obtained in LHs with word-level tasks may not be generalizing to language processing at the sentence level. We therefore investigated possible activation differences in RHs and LHs during a sentence completion tasks.

Methods

Participants

Using the Edinburgh Handedness Inventory (EHI) [11], we included 12 RHs (six women, six men; mean age 27 ± 3 years, EHI 95 ± 7) and 12 LHs (six women, six men; mean age 28 ± 4 years, EHI 79 ± 10) in our study. The native language of all participants was German. All participants were free of neurological or psychiatric disorders and had normal or corrected to normal vision. After full explanations of risks and purposes of this study, all participants gave

written informed consent. The study was approved by the local Ethics committee of the Heinrich-Heine-University Düsseldorf.

Experimental setting

For investigating language processing at the sentence level, we used a sentence completion paradigm described in detail elsewhere [13,14]. German semantically low-constraining sentence frames (e.g. *Gestern ... er etwas* – Yesterday he ... something) were presented visually for 1000 ms followed by a fixation cross (500 ms) and German infinitive verb forms (e.g. *sagen-say*), which were presented for 1250 ms. Participants were instructed to produce covertly a complete sentence with the correctly inflected verb form (e.g. '*Gestern sagte er etwas.*' – Yesterday he said something.) within the next 1000 ms. The total trial duration was 3750 ms. Stimuli were projected onto a screen-mirror-system attached at the head coil. In a control condition (fixation), participants were instructed to fixate a cross that appeared on the computer screen for 3750 ms. Sixteen blocks (eight blocks/conditions) with a total of 128 trials were presented with an alternating order of experimental and control condition.

Before the functional MRI (fMRI) experiment participants were trained on the task and performed the task overtly on 16 sentences. Performance was high in both groups. RHs produced 99.5% and LHs produced 99.3% correct sentences.

Functional MRI recording

Functional imaging was performed on a Siemens Vision 1.5T MRI scanner (Erlangen, Germany) using standard echo-planar imaging (EPI: TR, 4 s; TE, 66 ms; flip angle, 90° ; voxel size, $3 \times 3 \times 4.4 \text{ mm}^3$) with a standard radio frequency

head coil for signal transmission and reception. Thirty consecutive slices oriented parallel to the AC-PC plane were acquired in a contiguous order, covering the whole brain. Slice thickness was 4 mm with a gap between slices of 0.4 mm. Image analysis was performed using the fMRI analysis software package Brain Voyager 4.9 (Brain Innovation, Maastricht, The Netherlands, 2000). Using MRI, slice position parameters of the T2*-weighted measurements, the 2D slice time-course data were coregistered with anatomical 3D Gradient Echo data sets. Functional images were realigned to correct for head movements between scans. A trilinear interpolation with a maximum of 1000 iterations and 12.5% data reduction was used for correction. Pre-processing of the volume time courses involved slice scan-time correction and temporal high-pass filtering with a 3-minute cut-off to remove slow periodic drifts. For spatial data smoothing a Gaussian filter (FWHM=8 mm) was used. The volumes were normalized into Talairach space. A random effects analysis was performed to transfer the results to the main population. We report activations exceeding a voxel-wise significance threshold of $P < 0.0005$ (uncorrected for multiple comparisons) and a cluster size of > 50 voxels conducted separately for LHs and RHs. For between-groups comparisons a voxel-wise significance threshold of $P < 0.001$ (uncorrected) is reported. Stereotaxic coordinates of the center of gravity of the functional clusters were determined.

Lateralization indices

To ensure comparability with previous studies, we determined lateralization indices (LIs) in the posterior inferior frontal gyrus [3–5]. The statistical parametric maps for the contrast 'Sentence completion' versus 'Fixation' were thresholded at $P < 0.0001$ (uncorrected for multiple comparisons) for each participant and we determined the number of activated voxels for all clusters that were located with the majority of voxels in the posterior inferior frontal gyri (pars opercularis and pars triangularis, BA 44/45) determined on anatomical borders [15]. Two participants (one in each group) were excluded from the LI-analysis, as there was no activation at this threshold. LIs were calculated as the ratio of $(L-R)/(L+R) \times 100$, where L and R are the numbers of activated voxels in the left and right hemisphere, respectively. A LI=100 indicates a strong left, a LI=-100 a strong right hemispheric lateralization [4,16]. A possible disadvantage of this voxel-count-based method is its sensitivity to the choice of the threshold of the statistical probability map on which the voxel-count is based. We also calculated threshold-independent LIs from the maximal β -values of posterior inferior frontal activation clusters for each participant. Following Pujol *et al.* [3], we classified participants with $LI > 25$ as left dominant and $LI > 50$ as strongly left dominant for language, with $LI < -25$ as right dominant and $LI < -50$ as strongly right dominant and with $25 \geq LI \geq -25$ as bilateral or symmetrical. As LIs were not normally distributed, the Mann-Whitney- U -test was used for statistical analysis of between-group differences. Finally, we performed a correlation analysis (Spearman's ρ) of LIs with handedness scores.

Results

In the right-handed group 'Sentence completion' in comparison with 'Fixation' induced a widespread predominantly

left-lateralized activation pattern (Table 1). The activation included the middle (BA6, BA 9) and inferior frontal gyrus (BA 44, BA 47), middle temporal gyrus (BA 22) and inferior parietal cortex (BA 40, BA 7). Additionally, a large bilateral occipital activation was found.

In the left-handed group the 'Sentence completion' task yielded a more bilateral activation pattern (Table 1). Both parietal (BA 40) and frontal (BA 9/10) activation areas were present in both the hemispheres. Additionally, there was activation in the right precentral gyrus and the right-sided putamen. The inferior frontal cortex (BA 47) showed also bilateral activation. The direct comparison of the sentence-completion conditions between LHs versus RHs showed significantly stronger right-sided activations for the left-handed group in two frontal areas, BA 47 and BA 6 (Fig. 1), and the left cerebellum. In contrast, the reverse comparison (RH > LH) yielded no activated areas.

The LIs calculated from the number of activated voxels revealed a strong left hemispheric lateralization in the inferior frontal gyrus in most RHs: 10/11 (91%) of the RHs showed a strong left-dominant lateralization (LI: 56–100), whereas 1/11 (9%) had a weak left-hemispheric dominance (one participant, LI: 45). The percent values are indicated for reasons of the comparability with other studies, although normally the group is too small for this.

No participant showed a dominance of the right hemisphere or a bilateral activation pattern. In contrast, only 5/11 (45%) of the LHs showed a strong left-sided dominance (LI: 75–100) and 2/11 (18%) showed a weak left-sided dominance (LI: 22; 38). In 2/11 (18%) of LHs activation was bilateral (LI: 1; 22) and in 2/11 (18%) language lateralization was right-dominant (LI: -42; -92) (Fig. 2b). On the basis of the LIs calculated from the β values 84% of the RHs had a strong left lateralization (LI: 100) and 2/12 (16%) of the RHs a bilateral lateralization (LI: 6; 13). In LHs, 7/12 (58%) showed a left-hemispheric dominance (LI: 27–100), whereas 5/12 (42%) showed a bilateral lateralization (LI: -4–17). Group comparison of the LIs showed significantly weaker left lateralization in LHs for both, voxel-count based and β -value-based approaches (Fig. 2a).

Figure 2b shows individual LIs plotted against handedness scores. Within groups the two measures were not significantly correlated (Spearman's ρ : LHs: $r=0.26$, $P=0.44$; RHs: $r=0.427$, $P=0.166$).

Discussion

In this study, we investigated the cerebral activation of RHs and LHs during a covert sentence-completion task. We found a strongly left lateralized activation in RHs and a more bilateral organization in LHs. The activation pattern observed for sentence completion in RHs is in accordance with previous studies that compared sentence processing with control conditions below the sentence level [17] (for an overview see Ref. [18]). A direct comparison between the two groups showed significantly stronger activation of the right inferior frontal cortex (BA 47, BA 6) and the left cerebellum in LHs. The analyses of single-participant laterality indices based on the number of activated voxels showed a clear left-hemispheric dominance for language in 91% of RHs, which is in accordance with previous studies [1–3,5]. This finding suggests that additional sentence processing components involved in our task did not alter the dominance pattern observed in RHs using

Table 1 Activated areas for inflection versus fixation in right-handers and left-handers

BA	Hemisphere	Structure	Gyrus	x	y	z	Voxels
RH							
6	L	Frontal	Medial	-5	-6	54	229
6	L	Frontal	Precentral	-33	-10	59	562
46	L	Frontal	Middle	-47	35	14	684
44/45/9	L	Frontal	Inferior	-48	8	33	9540
22	L	Temporal	Middle	-56	-33	1	797
7	L	Parietal	Precuneus	-28	-66	30	1008
40	L	Parietal	Inferior	-40	-48	37	3292
40	L	Parietal	Postcentral	-48	-31	48	363
40	L	Parietal	Supramarginal	-61	-46	30	208
17/18/ 19/37	L/R	Occipital		-7	-72	-14	33154
	L	Basal ganglia	Caudate	-21	17	17	223
	R	Basal ganglia	Caudate	9	20	11	54
	L/R	Cerebellum					
LH							
6	R	Frontal	Medial	2	1	53	1001
32	L	Frontal	Medial	-6	12	45	474
6	R	Frontal	Precentral	44	2	35	6308
47	R	Frontal	Inferior	45	17	-7	68
44/45/9	L	Frontal	Inferior	-44	7	29	24758
9	L	Frontal	Middle	-28	33	24	82
10	R	Frontal	Middle	37	48	6	158
22	L	Temporal	Middle	-58	-40	21	52
40	L	Parietal	Supramarginal	-61	-50	33	60
40	R	Parietal	Inferior	37	-35	37	184
41	R	Temporal	Superior	41	-35	4	637
18	L	Occipital	Middle	-9	-93	13	79
17/18/ 19/37	L	Occipital		-4	-67	-1	146624
	L	Basal ganglia	Caudate	-13	22	0	504
	R	Basal ganglia	Caudate	22	-5	25	177
	R	Basal ganglia	Putamen	18	-4	12	242
	L	Thalamus	Pulvinar	-23	-22	6	444
	L	Midbrain	Red nucleus	-9	-21	-3	220
		Brainstem	Pons	19	-33	-31	550
	L/R	Cerebellum		-30	-55	-42	28

Random effects analysis at $P < 0.0005$ uncorrected for multiple comparisons was performed. Areas about 50 voxels are reported. BA, Brodmann area.

word-level tasks. In LHs previous studies investigating word-level processing reported variable dominance patterns. Although Hund-Georgiadis *et al.* [5] found a right-hemispheric dominance in 41% of LH and Knecht *et al.* [6] in 23–29%, Pujol *et al.* [3] observed only 10% right-hemispheric dominance in his cohort of 50 LHs. With a right-dominance for 18% of LHs, our result does not support the relatively high proportion of right-hemispheric dominance reported by Hund-Georgiadis *et al.* [5], but agrees with results of the other studies. One reason for the variability in proportions of right-dominant LHs may have been the thresholds of the statistical maps on the basis of which LIs were determined, because more liberal thresholds typically result in more bilateral activation patterns. We, therefore, also calculated LIs using maximal β -weights, which are not affected by the choice of statistical thresholds. This measure reduced both the number of RHs classified as left-dominant and the number of LHs classified as right-dominant. It is therefore unlikely that the procedure based on voxel-counts underestimated the proportion of right-dominant LHs. Furthermore, an influence of sex on language lateralization could be a reason for differences as was suggested by other findings [19,20]. A recent meta-analysis, however, failed to confirm that sex plays a role in language lateralization [21].

Most probably, diverging reports on the proportions of right-hemispheric dominance in LHs are due to different classification criteria. Hund-Georgiadis *et al.* [5] assumed a hemispheric dominance for language when the LI was above or below ± 10 from zero. In contrast, Pujol *et al.* [3] and, nearly in the same way, Szaflarski *et al.* [4] classified indices above or below ± 25 as left-dominant or right-dominant. Thus, it seems that differences in the reported language dominance in LHs are mainly due to different classification criteria. Nevertheless, it is important to acknowledge that in all studies LHs were found to be more likely to exhibit a bihemispheric or right-sided functional activation pattern irrespective of the language task used.

Another point we investigated was the relationship between language lateralization and the degree of handedness. It would be useful from a clinical point of view if the degree of handedness were informative with respect to language lateralization. Whereas some studies failed to demonstrate such a correlation [1,5], a strong correlation between degree of handedness and lateralization of speech has been reported for a mixed group of LHs and RHs [6]. Yet another study [4] reported for a group of LHs and ambidextrous participants that the correlation between hand preference and language lateralization varied across brain regions and language tasks with a stronger correlation

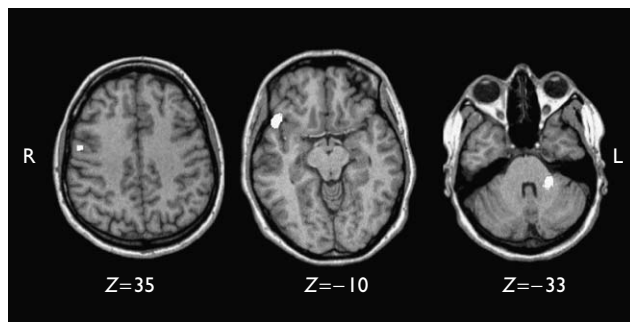


Fig. 1 Group comparison between right-handers and left-handers (LHs > RHs) in the 'Sentence completion' condition (random effects analysis, $P < 0.001$, uncorrected). Activations were shown in right inferior frontal gyrus ($x=47$, $y=17$, $z=-8$, 386 voxel), right precentral gyrus ($x=54$, $y=-5$, $z=35$, 55 voxels) and left cerebellum ($x=-20$, $y=-36$, $z=-31$; 232 voxels). LHs, left-handed participants; RHs, right-handed participants.

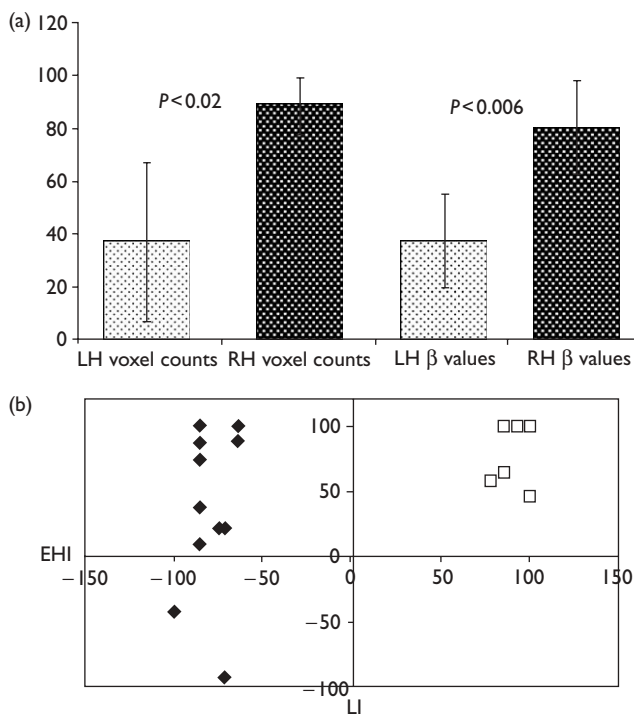


Fig. 2 LIs for LHs and RHs. (a) Means and standard errors of LIs in inferior frontal cortex (BA44/45) in LHs and RHs. LIs based on β -weights and voxel-counts are shown. (b) Voxel-count-based LIs (y -axis) plotted against Edinburgh handedness-scores (x -axis) for RHs (white squares) and LHs (black squares). LIs, lateralization indices. LHs, left-handed participants; RHs, right-handed participants.

for frontal speech areas. Also Josse *et al.* [22] found no relationship between hand preference and brain activation during story listening but a correlation of hand preference with brain activation during verb generation. Thus, the above mentioned studies suggest that a functional asymmetry of frontal regions may be reflected in manual preference and language production, as both probably rely on higher order motor control systems responsible for action [23]. In our study, there was no correlation between the degree of handedness measured with the EHI and the

language lateralization in inferior frontal cortex (BA 44/47) in either group. With respect to RHs, our data are in accordance with a previous study on a right-handed population [1]. LHs in our study showed considerable variability of handedness, and strong left-handedness was not a predictor for right hemispheric language representation. The discordant lateralization of language and bimanual motor control in a left-handed piano player accords with our observation [24]. Despite the absence of individual predictability of language lateralization in LHs the probability of bilateral language lateralization in this group was greater than in RHs. This is in accordance with the Right-Shift-Theory of Annett [25] who hypothesized a probabilistic lateralization of handedness and language functions if an assumed genetic bias for left lateralization is absent. Further studies with larger populations will be needed to settle this issue.

Conclusion

Our results showed a more bilateral activation in the inferior frontal cortex in LHs. This was not related to the handedness score, so that degree of handedness and lateralization of language functions may not be coupled in LHs.

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