

Colateralization of Broca's area and the visual word form area in left-handers: fMRI evidence

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Abstract

Language production has been found to be lateralized in the left hemisphere (LH) for 95% of right-handed people and about 75% of left-handers. The prevalence of atypical right hemispheric (RH) or bilateral lateralization for reading and colateralization of production with word reading laterality has never been tested in a large sample. In this study, we scanned fifty-seven left-handers who had previously been identified as being clearly left ($N = 30$), bilateral ($N = 7$) or clearly right ($N = 20$) dominant for speech on the basis of fMRI activity in the inferior frontal gyrus (pars opercularis/pars triangularis) during a silent word generation task. They were asked to perform a lexical decision task, in which words were contrasted against checkerboards, to test the lateralization of reading in the ventral occipitotemporal region. Lateralization indices for both tasks correlated significantly ($r = 0.59$). The majority of subjects showed most activity during lexical decision in the hemisphere that was identified as their word production dominant hemisphere. However, more than half of the sample ($N = 31$) had bilateral activity for the lexical decision task without a clear dominant role for either the LH or RH, and three showed a crossed frontotemporal lateralization pattern. These findings have consequences for neurobiological models relating phonological and orthographic processes, and for lateralization measurements for clinical purposes.

Keywords: Broca's area, Cerebral lateralization, fMRI, Reading, Speech, vOT (ventral occipito-temporal) activity, VWFA (Visual Word Form Area)

Language processing is considered as one of the most lateralized cerebral functions in humans. At the anatomical level, the hemispheric asymmetry has been attributed to a larger size of the left planum temporale (a posterior region of the Sylvian fissure), and to different slopes of the Sylvian fissures in the two hemispheres (Geschwind & Levitsky, 1968; Josse, Mazoyer, Crivello & Tzourio-Mazoyer, 2003). At a functional level, a left hemispheric specialization was reported for a variety of language-related regions, among which the inferior frontal gyrus (IFG) crucial for speech production and more posterior brain regions such as the ventral occipitotemporal (vOT) region involved in reading.

Despite the well-established role of IFG for speech production and the vOT for reading, it is still not clear how these frontal and occipitotemporal regions interact with each other. If they are closely interrelated, one would expect the anterior and posterior regions to lateralize to the same hemisphere in order to decrease the time costs of information exchange¹. Psychological models of visual word recognition nearly all incorporate a contribution of phonological information to visual word recognition based on a large variety of behavioral evidence (e.g., Dimitropoulou, Duñabeitia & Carreiras, 2011; Ferrand & Grainger, 1992; Rastle & Brysbaert, 2006), but fast interactions between IFG and vOT are not yet widely integrated in neurological models of reading (e.g., Cohen et al., 2000; Dehaene et al., 2004; Dehaene, Cohen, Sigman & Vinckier, 2005). Dehaene and colleagues believe that the vOT is specifically specialized for the binding of letters into words. They called it the visual word form area (VWFA; Cohen et al., 2000) as it responded to orthographic letter strings, invariantly of retinal location, case, font or horizontal/vertical format (see also Cai, Paulignan, Brysbaert, Ibarrola & Nazir, 2010; Dehaene et al., 2004; McCandliss, Cohen & Dehaene, 2003). Others believe that the vOT is not dedicated to visual word form processing because it also responds to picture naming, repeating auditory words etc. (e.g., Devlin, Jamison, Gonnerman & Matthews, 2006; Duncan, Pattamadilok & Devlin, 2010; Price & Devlin, 2003, 2011; Twomey, Duncan, Price & Devlin, 2011). The latter view considers the

¹ Note that the direction of laterality within an activated region can be influenced by both excitatory and inhibitory connections from the LH/RH homologue areas. For example, Seghier, Josse, Leff and Price (2011) and Seghier, Kherif, Josse and Price (2011) found lateralities to vary according to the amount of right hemispheric activity in a word matching task. This could also indirectly influence the colateralization patterns between two or more regions.

vOT as an interface in the reading process: The neurons in vOT that are sensitive to visual bigrams (and to whole words more anteriorly) are in constant interaction with neurons coding for the nonvisual characteristics of the stimuli such as their phonology or meaning. Such fast interactions would predict that the vOT is lateralized to the same side as the IFG, assuming that the cross-talk between these areas would be slowed down if their activity were dominantly situated in different hemispheres.

Indeed, studies reported left hemispheric lateralizations in language-related tasks for both IFG and vOT (e.g., Xue et al., 2005; Seghier, Kherif, et al., 2011). Seghier, Kherif, et al. (2011) for example, compared the degree of lateralization during a semantic vs. perceptual word matching task in 50 brain regions. Their voxel-based laterality maps showed consistent LH lateralization in frontal regions and the vOT at group level.

However, a number of studies have reported individual cases of crossed frontal and temporal language dominance (e.g., Baciú et al., 2003; Jansen et al., 2006; Kamada et al., 2006; Lee et al., 2008), with for example speech being controlled by the left hemisphere (LH) and reading by the right hemisphere (RH). Similarly, in a large-scale fMRI study Pinel and Dehaene (2010) argued against an overall dominance view of brain regions because very few regions related to sentence processing (situated in the posterior superior temporal sulcus and the middle frontal gyrus) colateralized with brain areas involved in mental arithmetic (in particular a horizontal segment of the intraparietal sulcus and the superior parietal lobule). Even the correlations between the laterality indices (LIs) in vOT and frontal areas (inferior, pre-central, mid-frontal) in sentence processing often were not significant (Pinel & Dehaene: Table 1), making the authors conclude that "... although all of these regions are highly asymmetrically activated, always in favor of the left hemisphere, correlations between the LI of the fusiform gyrus and of frontal areas are weak." (Pinel & Dehaene, 2010, p.53). Pinel and Dehaene claimed that the brain should be seen as a mosaic of independently lateralized regions, although one has to keep in mind that their findings point to an absence of a correlation in the *degree* of lateralization in right-handed LH-dominant participants rather than colateralization across hemispheres itself.

So far, only two small-scale studies directly investigated the colateralization of the IFG during speech (measured as activity in the so-called Broca's area, i.e. pars opercularis (Brodmann Area [BA] 44) and the pars triangularis (BA 45)) and vOT during reading at an individual level. Cai, Lavidor, Brysbaert, Paulignan and Nazir (2008) assessed the lateralization of speech by comparing event-related potentials (ERPs) in the left and right IFG during a verb generation task. The lateralization of word reading was tested in a lexical decision task (LDT). Eight right-handed subjects showing a typical frontal lateralization for speech in the left hemisphere (LH) also showed the strongest negative mean ERP in the LH for the visual word form area during word reading in the LDT. Four RH speech dominant participants consistently showed stronger reading ERPs in the RH compared to the LH. Cai et al. (2008) attributed the perfect colateralization of the frontal and occipito-temporal language areas to the need for fast interactions between these regions during word reading. In a second study run by Cai et al. (2010), 11 participants were identified as LH lateralized in the word generation task and five participants were atypically RH lateralized. The LIs of the vOT during reading in a LDT again correlated significantly with the LIs calculated from the IFG ($r = 0.59$), but one right-handed person with LH dominance in IFG and one left-handed participant with RH dominance in IFG showed crossed laterality. Cai et al. (2010) pointed to the possibility that weak activity during the word reading task could have caused the exceptions. In particular, the pattern of the right-handed participant was not clear, as she showed the expected LH dominance of vOT when the words were presented vertically (when there was more activity in vOT).

All in all, the evidence about the colateralization of frontal and occipito-temporal language processing brain areas is far from clear. As we have argued a number of times (Ellis & Brysbaert, 2010a, 2010b; Hunter & Brysbaert, 2008; Van der Haegen, Cai, Seurinck & Brysbaert, 2011), the best way to examine laterality patterns is to compare a group of participants with typical LH language dominance (found in about 95% of right-handers and 75% of left-handers; Knecht et al., 2000) with a group of participants with atypical RH or bilateral language dominance. Cai et al. (2008, 2010) followed this approach, but only tested small samples of four and five participants with atypical dominance so that only coarse conclusions about the variability of

frontotemporal laterality patterns could be drawn. Other studies did report large-scale results, but their correlations between LIs were based on a homogeneous sample of participants with typical language dominance, mostly right-handers (e.g., Pinel & Dehaene, 2010). Still other studies did not analyze lateralization data at the individual level, but only reported colateralizations at group level (e.g., Seghier, Kherif, et al., 2011). It is important however to investigate the degree of inter-subject variability in language lateralization across different functions both for theoretical and clinical purposes. As for the latter, large variability would indicate that an overall lateralization index of language is misleading for preoperative assessments when surgeons want to minimize the damage in the dominant hemisphere (Seghier, Kherif et al., 2011). Rather, separate LIs for different language functions should be obtained.

In the present study, we explored the relationship between the occipitotemporal word reading region vOT and the frontal phonology-related speech region IFG in a sample of 57 participants who reported to write and draw with their left hand. If these regions are lateralized independently for most of the participants, we should see many cases of crossed laterality. On the other hand, if the lateralization of vOT is influenced by the laterality of the speech areas, we would expect that if the asymmetry of IFG changes, the lateralization of vOT will shift as well for the majority of participants.

We could test a large number of participants with atypical brain dominance in IFG because we first screened 265 left-handed participants with a behavioral picture and word visual half field task (see Method section). Participants showing an indication of atypical speech laterality in these tasks were invited for a fMRI study that contained a silent word generation task and the currently discussed LDT. In addition, participants that presumably had LH speech dominance were selected as control participants.

Method

Participants

In a previous study (Van der Haegen et al., 2011), 50 participants were selected from a large group of 250 left-handers to take part in a fMRI silent word generation task. The selection was based on their performance in a behavioral picture and word visual half field task. Pictures or words were shown in the parafovea. Stimuli were presented in bilateral pairs to avoid attentional biases. The target that had to be named was indicated by an arrow in the middle of the screen. Hunter and Brysbaert (2008) demonstrated that these tasks can serve as a screening method to find people with atypical speech dominance. The partial crossing of optic fibers makes stimuli presented in LVF/RVF initially fall into the RH/LH respectively, so that shorter naming latencies for stimuli in LVF can point to a RH dominance for speech (see also Barca et al., 2011). In Van der Haegen et al. (2011), we invited participants who were faster in naming pictures and/or words in LVF than in RVF to the fMRI study with a silent word generation task as they were potential atypical subjects. A control group of left-handed participants with RVF advantages were also scanned to compare the data of the atypical participants with those who had typical LH dominance.

For the present study, 7 extra participants were scanned bringing the total sample to 57 left-handers (41 females, 16 males; age ranging between 18 and 29 years with mean age = 20.8 years). All were students of Belgian universities or higher education schools with Dutch as their native language and with normal or corrected-to-normal vision. Table 1 shows their mean handedness scores obtained via a Dutch translation of the Edinburgh Inventory Questionnaire (Oldfield, 1971). The scale ranged from -3 (extreme left preference) to +3 (extreme right preference). All participants reported to write and draw with their left hand. Three out of 57 participants had a positive handedness value, because they did not use their left hand for the eight actions other than writing and drawing in the handedness questionnaire (e.g. using scissors). We did not consider them as an exclusion criterium to increase variability of the sample and thus increase the chances of finding a broad range of LI scores. Participants fulfilled the

conditions to be scanned and signed an informed consent form according to the guidelines of the Ethics Committee of the Ghent University Hospital.

Tasks and Stimuli

Word generation task

The lateralization of speech was measured by activity in the inferior frontal region (Broca's area: pars opercularis + pars triangularis) during a silent word generation task. The same task was previously used by Cai et al. (2010) among others (Abbott, Waites, Lillywhite & Jackson, 2010; Badzakova-Trajkov, Häberling, Roberts & Corballis, 2010; Hunter & Brysbaert, 2008; Knecht et al., 1996). Participants were asked to silently generate as many words as possible starting with a letter presented in the middle of the screen (b, d, k, l, m, n, p, r, s or t) during ten blocks of 15s. Ten other blocks of 15s contained the control task: The letter string *baba* appeared on the screen and participants were asked to silently repeat this nonword as long as it was presented. Finally, activation and control blocks were alternated with rest blocks of 15s indicated by a horizontal line on the screen, in which participants were asked to relax. A practice phase outside the scanner ensured that everyone understood the task correctly.

Lexical Decision Task

The LDT task aimed to assess the lateralization of word reading by looking at activity in the vOT. Stimuli consisted of 24 high frequent words (mean log₁₀ Frequency/million = 2.16, range 1.89-2.44), 24 low frequent words (mean log₁₀ Frequency/million = 0.61, range 0-1), 24 consonant strings and 24 scrambled words. Words were 4-7 letters long, with six words of each word length. The length of the consonant strings was equal to the word lengths. Scrambled words were created by scrambling images of word stimuli at the pixel level; they matched the words in length/size. Stimuli were displayed in Courier New, in black on a white background.

An event-related design was used for this task. Each trial began with a centrally presented fixation cross. After a variable duration of 500-2000 ms, a stimulus was displayed for 800 ms followed by a short horizontal line for 2s until the end of the trial. Participants were required to press the *yes* button with the left index finger if the stimulus was a word and to press the *no* button with the right index finger if the stimulus was no existing word. They were told to perform the task as fast as possible from the moment the stimulus appeared. All stimuli were displayed once in random order.

Stimulus presentation and fMRI Data Acquisition

Stimuli were presented using Presentation software (NeuroBehavioral Systems, CA, United States) and projected onto a translucent screen. Participants watched the screen via a mirror installed in front of their eyes in the scanner.

Whole-brain images were acquired using a 3-Tesla Siemens Trio MRI scanner (Siemens Medical Systems, Erlangen, Germany) at the Ghent University Hospital with an 8-channel radiofrequency head coil.

Functional images were obtained using a T2*-weighted gradient-echo EPI sequence [TR = 2630, TE = 35 ms, image matrix = 64 * 64, FOV = 224 mm, flip angle = 80°, slice thickness = 3.0 cm, distance factor = 17%, voxel size = 3.5 * 3.5 * 3 mm³]. These settings gave 40 axial slices parallel to the anterior-posterior commissure. A high-resolution anatomical image was obtained using a T1-weighted 3D MPRAGE sequence [TR = 1550 ms, TE = 2.39 ms, image matrix = 256 * 256, FOV = 220 mm, flip angle = 9°, voxel size = 0.9 × 0.9 × 0.9 mm³].

fMRI Data Analysis

fMRI data analysis was performed with SPM5 (Wellcome Trust Centre for Neuroimaging, London, UK). The first four images were discarded in each session in order to obtain a magnetization equilibrium. Functional images were preprocessed by (1) a correction for slice time delays caused by the interleaved acquisition of images; (2) spatial realignment using rigid body transformation to correct for head movements; (3)

coregistration of individual anatomical images to a mean functional image; (4) normalization to the Montreal Neurological Institute (MNI) T1 template; and (5) spatial smoothing with a 3 mm full width at half maximum (FWHM) Gaussian Kernel to optimize the images for individual analyses. The pre-processed data from each participant were then entered into first-level statistical analysis. For the word generation task, experimental conditions were modeled using a canonical hemodynamic response function (HRF; Friston, Jezzard & Turner, 1994) convolved with a boxcar function in a General Linear Model (GLM). Error trials and six estimated head movement parameters were added into the models as regressors-of-no-interests.

Individual contrast images in the word generation task were obtained by contrasting the word generation condition (target letter display) with the control condition (*baba* repetition). For the LDT task, modeling consisted of convolving the onset time series of the different stimulus types with canonical HRF with time derivatives. The contrast of interest was the horizontal word condition against the scrambled word condition.

Individual LIs for production in the word generation task were calculated for the region formed by the pars opercularis (approximately BA44) and pars triangularis (approximately BA45) in the AAL template (Tzourio-Mazoyer et al., 2002). For the LDT, we adopted the predefined vOT mask used in Twomey et al. (2011). This box ranged from $X = -30$ to -54 , $Y = -45$ to -70 and $Z = -30$ to -4 and a mirror-reversed box in RH, excluding cerebellar regions. We further restricted this mask to the fusiform and inferior temporal gyri. Participants showing no activation at an uncorrected $p < 0.01$ level in this mask were excluded because their vOT activity would be too weak to calculate reliable LIs.

LI values were computed with the LI Toolbox 1.02 of Wilke and Lidzba (2007). We decided to use this toolbox as it has been shown that traditional LI calculations based on a normalized difference of number of activated voxels in LH and RH surviving an arbitrarily chosen threshold produce fluctuating estimations (e.g., Abbott et al., 2010; see Seghier, 2008 for a review). In contrast, the LI toolbox produces a weighted mean LI. For each ROI, 20 thresholds levels were defined by equal steps from 0 to the

maximum t-value. Hundred bootstrap resamples (sample ratio $k = .25$) were taken in all ROIs in LH and RH. Only the central 50% of those 10 000 possible were preserved to avoid statistical outliers. A weighted overall mean LI was calculated on the basis of the remaining data by assigning a higher weight to the higher thresholds. More details can be found in Wilke and Schmithorst (2006). Final LI values ranged from -1 (only active voxels in RH) to +1 (only active voxels in LH). Participants with $LI > 0.5$ were considered as left dominant, those with $LI < -0.5$ were defined as right dominant.

Results

Behavioral Results

No participant reported any difficulty in completing the word generation task. In the LDT, participants made on average 2.9% errors, proving that everyone found the task easy to perform. Overall mean RT was 601 ms, with no significant difference in latencies between the word and nonword stimuli [$F < 1$]. The fMRI analysis was based on all correct trials. Behavioral LDT data of five LH speech dominants (participants 32, 33, 35, 40 and 50 in Table 1) failed to be recorded. We decided to leave these participants in the sample, given the high overall performance.

fMRI Results

Figure 1 shows the lateralization patterns of all subjects for IFG activity (Broca's area: pars opercularis + pars triangularis) during silent word generation and vOT activity during LDT. Individual LI values, calculated by the LI toolbox of Wilke and Lidzba (2007), can be seen in Table 1. Finally, Table 2 gives an overview of percentages of LH/RH or bilateral dominance based on the LIs for IFG/word generation and vOT/LDT word reading.

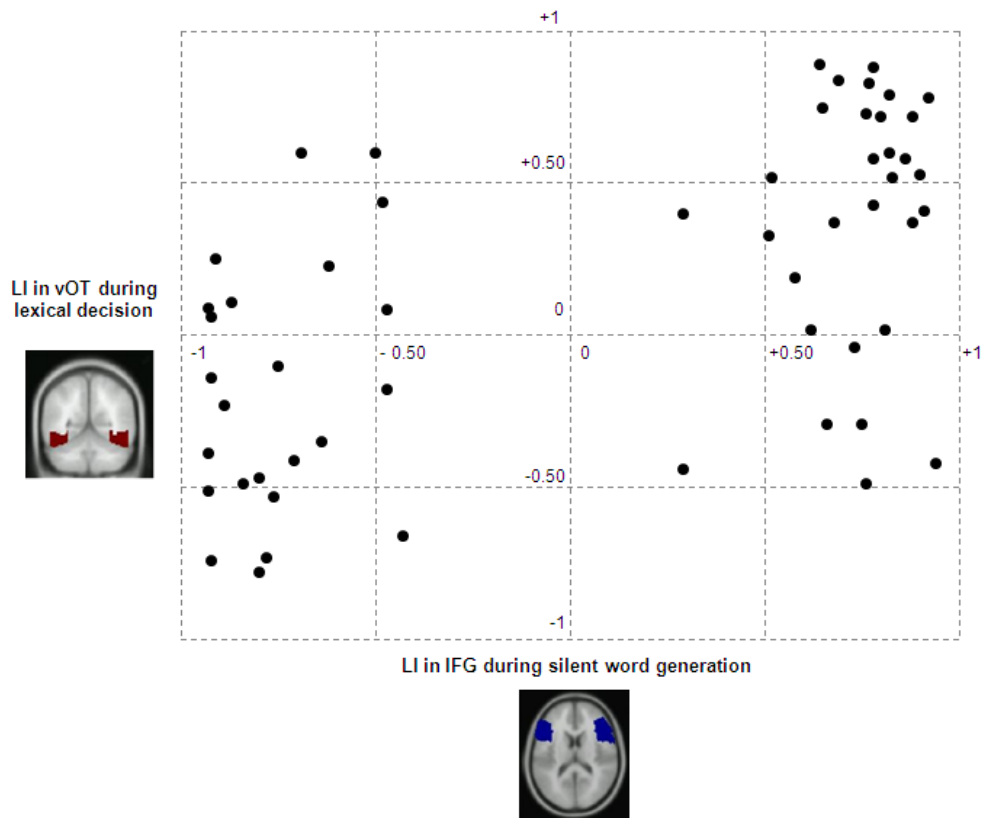


Figure 1. Lateralization patterns for 55 participants. Two participants without significant vOT activation at an uncorrected $p < .01$ level are not shown. The x-axis displays the LIs based on activity in the IFG during silent word generation; The y-axis shows the LIs in vOT during lexical decision making.

Subject	Handedness	Word generation		Lexical decision			
		IFG LI	vOT LI	LH vOT peak (x,y,z)	Z-score	RH vOT peak (x,y,z)	Z-score
1	-3,0	-0,94	No sig. activation				
2	-2,0	-0,93	0,09				
3	-1,7	-0,93	-0,51				
4	-2,2	-0,93	-0,39				
5	-3,0	-0,92	-0,14			(46,-52,-24)	4,64
6	-1,4	-0,92	0,06	(-46,-56,-24)	3,21		
7	-2,6	-0,92	-0,74			(35,-52,-21)	4,29
8	-2,8	-0,91	0,25	(-35,-70,-14)	4,38	(46,-63,-18)	4,1
9	-3,0	-0,89	-0,23				
10	-3,0	-0,87	0,11	(-35,-46,-21);(-42,-63,-10)	5.12;3.86	(49,-63,-10)	3,65
11	-2,9	-0,84	-0,49				
12	-3,0	-0,80	-0,78			(52,-63,-10)	4,09
13	-2,1	-0,80	-0,47			(42,-52,-14)	3,33
14	-3,0	-0,78	-0,73			(49,-70,-10)	3,75
15	-0,5	-0,76	-0,53			(38,-70,-18)	3,78
16	-1,9	-0,75	-0,10	(-32,-56,-21)	4,08	(52,60,-10)	3,63
17	-2,5	-0,71	-0,41	(-35,-49,-18)	4,61	(42,-70,-18)	4,61
18	-2,9	-0,69	0,60	(-42,-49,-21)	5,11		
19	-0,5	-0,64	-0,35				
20	-2,8	-0,62	0,23				
21	-1,9	-0,50	0,60	(-49,-70,-14)	3,69		
22	-2,4	-0,48	0,44	(-49,-66,-10)	5,68	(52,-66,-10);(46,-52,-10)	4.15; 3.68
23	-1,5	-0,47	-0,18				
24	-2,5	-0,47	0,08	(-35,-49,-21)	3,46	(52,-60,-14)	3,36
25	-2,6	-0,43	-0,66			(38,-46,-21)	3,69

26	-1,8	0,29	-0,44			(52,-52,-14)	3,14
27	1,6	0,29	0,40				
28	-3,0	0,51	0,33	(-38,-49,-16)	3,82	(38,-52,-10)	3,65
29	-2,7	0,52	0,52	(-42,-63,-18)	4,01		
30	-2,6	0,58	0,19				
31	-2,9	0,62	0,02	(-38,-49,-18)	3,56	(38,-52,-14)	3,69
32	-1,1	0,64	0,89	(-49,-52,-10)	3,82		
33	-3,0	0,65	0,75	(-52,-60,-14)	4,09		
34	-2,7	0,66	-0,29			(38,-49,-18)	3,83
35	-3,0	0,68	0,37	(-42,-66,-21)	3,66		
36	-3,0	0,69	0,84	(-38,-66,-18)	3,57		
37	-2,4	0,73	-0,04	(-46,-52,-24)	4,43	(46,-70,-10)	3,69
38	-2,8	0,75	-0,29				
39	-1,8	0,76	-0,49				
40	-2,6	0,76	0,73	(-32,-52,-21)	3		
41	-2,3	0,77	No sig. activation				
42	-2,1	0,77	0,83				
43	0,5	0,78	0,43	(-38,-49,-21)	4,01		
44	0,6	0,78	0,58	(-38,-49,-18)	3,53		
45	-2,6	0,78	0,88	(-42,-66,-10)	3,68		
46	-2,2	0,80	0,72	(-46,-63,-18)	4,13		
47	-2,0	0,81	0,02				
48	-2,8	0,82	0,79	(-46,-52,-21)	3,14		
49	-2,9	0,82	0,60				
50	-2,2	0,83	0,52	(-38,-52,-24)	3,76		
51	-2,4	0,86	0,58	(-38,-52,-24)	5,24		
52	-2,9	0,88	0,72				
53	-0,9	0,88	0,37	(-42,-66,-14)	3,06		

54	-2,9	0,90	0,53	(-38,-70,-14)	3,1	
55	-1,5	0,91	0,41			
56	-3,0	0,92	0,78	(-38,-66,-14)	4,33	
57	-2,8	0,94	-0,42			(49,-66,-18) 4,6

TABLE 1.

Individual handedness scores (mean preference score between -3 and +3), LIs in inferior frontal gyrus during silent word generation (target letter vs. *baba* repetition) and LIs, left and right hemispheric peak coordinates and Z-scores in vOT during LDT (horizontal words vs. checkerboards). Note that subjects are sorted with ascending LI values in inferior frontal gyrus in the interest of readability of the table (i.e., from most RH dominant to most LH dominant). vOT peaks of subjects showing strong activity in vOT ($Z > 3.7$) after small volume correction are highlighted in bold, those with Z scores between 3.0 and 3.7 are written in normal font. Subjects without reported vOT peaks had Z-scores below 3.0.

	IFG (word generation)	vOT (LDT)
RH dominant	35,1	10,9
LH dominant	52,6	32,7
Bilateral	12,3	56,4

TABLE 2.

Percentages of participants showing right hemispheric (RH), left hemispheric (LH) or bilateral dominance for the word generation task (i.e., activation in the inferior frontal gyrus, IFG) and lexical decision task (LDT; i.e. activation in the ventral occipito-temporal region, vOT). Percentages of IFG are based on all 57 participants; percentages of vOT are based on 55 participants, because 2 participants showed unreliably low activity in this task.

For the word generation task, group analyses for the participants with LH dominance showed strong activity in the left inferior/middle frontal gyrus (with a peak in the pars opercularis) extending to the cingulate gyrus, the precentral gyrus and the SMA, the left angular gyrus, bilateral putamen and thalamus, bilateral precuneus, and the right cerebellum. A reversed pattern was observed for the RH dominant participants. No regions other than the IFG ROI showed robust activity for all individuals (at $p < .05$, FWE corrected). At the individual analysis level, 30 participants showed a clear left lateralized activation pattern in IFG (i.e. with LIs score above + 0.50 in the combined activity of pars opercularis and triangularis; 21 females and 9 males) with values ranging from 0.51 to 0.94, 20 participants showed a clear right lateralized pattern ($LI < -0.50$; 16 females and 4 males) with values ranging from -0.62 to -0.94, and 7 participants can be considered as more or less bilateral for speech (LIs between -0.50 and +0.50; 4 females and 3 males) with LIs between -0.50 and 0.29.

For the LDT, both RH and LH speech dominant groups showed right lateralized activity in the postcentral and precentral gyri, and in the left cerebellum, which corresponds to the left finger tapping for words. The activation further extended to the right thalamus and the putamen. For the group of participants with typical LH speech dominance, we also observed left-lateralized vOT activity at the same threshold ($p < 0.001$ uncorrected, $k=10$). No vOT activity was observed for the group of atypical RH

participants at the same threshold ($p < 0.001$) but a right vOT activity was observed at a slightly lower threshold ($p < 0.005$; peak at 46, -60, -21, $t=3.81$). At an individual level, two participants (one RH and one LH dominant) were excluded from further analyses because they showed no significant activation at an uncorrected $p < .01$ level in the predefined vOT box. Among the remaining participants, 18 showed clear LH reading laterality with vOT LI values higher than +0.50, ranging from 0.52 to 0.89. Sixteen of them were also clearly left lateralized for speech. Subject 18 had a clear crossed lateralization pattern as her IFG LI was -0.69 and her vOT LI +0.60. Subject 21 had an IFG LI of -0.50 combined with a vOT LI of +0.60. Only six participants were clearly RH lateralized in vOT with LIs ranging from -0.78 to -0.51. Among them, five were also clearly RH lateralized in IFG and one showed bilateral speech activity with an IFG LI of -0.43.

Next, a correlational analysis based on the individually calculated LIs was performed. The overall correlation between IFG LIs in word generation and vOT LIs in LDT ($N = 55$) was strongly significant in the positive direction ($r = .59$; $p < .001$), indicating that both regions colateralized.

At the same time, Figure 1 illustrates that the laterality pattern was much less clear for vOT than for IFG. The majority of the participants ($N = 31$) had bilateral vOT activity with LIs between -0.49 and +0.44. For the participants with a positive LI values for both tasks, the mean IFG LI was 0.73 ($N = 31$) and mean vOT LI was +0.48 ($N = 34$). For participants with negative values, the means were -0.75 for IFG ($N = 24$) and -0.41 for vOT ($N = 21$). About half of these participants were LH dominant for speech, the other half was RH dominant. In particular the participants with RH dominant IFG seemed to be less lateralized in vOT. Here we also saw the two clearest cases of crossed lateralization (the abovementioned Subjects 18 and 21). Subject 39 can be considered as a third participant with crossed laterality, with an IFG LI of +0.76 and a vOT LI of -0.49. This means that 3/55 or only 6% of all participants showed a clearly crossed lateralization pattern.

To further investigate the individual vOT activity pattern, we checked the strength of the vOT activity during the LDT for each participant within the pre-defined bilateral region of interest. A small volume correction was applied (Worsley et al., 1996). The threshold $p < 0.05$ after correction for number of independent comparisons within the pre-defined region corresponded to a voxel threshold of $Z > 3.7$. All peaks of vOT activation surviving this threshold are reported in Table 1. We also report peaks of $Z > 3.0$ as trends. It can be noticed that for 17/55 or 29.8% of the participants, no significant vOT activity could be reported.

Discussion

In this study, we further explored the colateralization between 1) speech production as assessed by the activity in IFG (Broca's area: pars opercularis and pars triangularis) measured in a silent word generation task and 2) word reading as defined by the activity in the vOT region during a LDT with horizontally presented words. Previous small-scale studies such as Cai et al. (2008, 2010) located both functions in the same hemisphere for 26 out of 28 participants in total. This seems to be in line with the scarcity of single case studies reporting crossed lateralities in both healthy participants and patients (Baciu et al., 2003; Jansen et al., 2006; Kamada et al., 2006; Lee et al., 2008). The use of a global language LI was also criticized by Seghier, Kherif et al. (2011), because they found large inter-subject variabilities of lateralization across language-related brain regions.

By testing a large sample of left-handers we explored the degree of frontal-temporal lateralization variability in healthy participants. Similar to Cai et al. (2008, 2010), the vast majority of participants showed most vOT activation in the same hemisphere as the one with the most activity in IFG, leading to a positive correlation of 0.59 between both LIs. As a matter of fact, only 3/55 participants (6%) showed clear evidence for a cross-lateralization if laterality was defined as a LI index of +0.50 or -0.50. With a slightly lower criterion, two more participants would qualify.

We can assume that the number of crossed lateralizations would be even smaller among right-handers. Genetic models of left-handedness attribute hand preference in

these individuals to a chance factor. For instance, the model of McManus (1985) focuses on the relationship between handedness and cerebral dominance. In particular, it tries to explain why the correlation between hand preference and language dominance is much higher among right-handers (less than 5% crossed laterality: right-hand preference and RH language dominance) than among left-handers (more than 70% crossed laterality: left-hand preference and LH language dominance). McManus's (1985) theory claims that handedness is determined by a gene with two alleles. A homozygous gene with two D (Dextral) alleles always leads to right-handedness and left hemisphere dominance, a homozygous gene with two C (Chance) alleles produces random preferences (both for handedness and language laterality), and a heterozygous DC type leads to a pattern in-between. Because left-handers always possess at least one C-allele, they are expected to show much more variability in language dominance and, arguably, in the lateralization of other brain areas as well. Only the right-handers with one or two C-alleles are expected to show crossed lateralities. The frequency of the C-allele is estimated to be around .15, so that only a small percentage of right-handers is expected to have crossed laterality. As a result, left-handers may be more prone to crossed laterality of speech production and visual word recognition, although this explanation is still speculative at present and only one of several potentially genetic influences. In line with these predictions, Cai et al. (2010) reported more variability in their atypical (left-handed) participants than in their typical (predominantly right-handed) participants.

The high correlation between IFG and vOT lateralizations in our study was accompanied by a higher percentage of bilateral language representation in vOT than in IFG. The evidence for stronger asymmetry in IFG than vOT agrees with the hypothesis that speech production is the most lateralized function (Kosslyn, 1987), because the rapid coordination of movements involved in speech require a single control center. There may be more scope for bilateral representation in the word reading system. This by itself could be the reason for the low incidence of crossed laterality, as persons with inverse lateralities of vOT and IFG might be more liable to involve the contralateral vOT tissue in order to optimize the interactions with IFG.

Another interesting finding of the current study is that there was a tendency towards more LH vOT involvement in participants with RH dominant IFG than there was RH vOT activation in participants with a LH-asymmetry for IFG. The higher incidence of finding opposite LI values for vOT and IFG in RH speech dominants was also observed by Cai et al. (2010), who mentioned a possible explanation for this. Reversed functional asymmetries are not always associated with deviations at the anatomical level (Sun & Walsh, 2006). In addition, given that the anatomic frontotemporal connections seem to be stronger in LH than in RH (Glasser & Rilling, 2008; Powell et al., 2006), this could imply that some right IFG dominant participants have less developed connections between their RH IFG and RH vOT cortex, even though their speech production is atypical at the functional level. This suggestion of course is a general observation and needs future research by for example Diffusion Tensor Imaging techniques in the same group of participants.

Reading direction could be a second factor in the shift towards a stronger LH vOT involvement in RH dominant participants. As all participants were native Dutch speakers, they all read from left to right. It is well known that readers have an asymmetric perceptual span in line with their reading direction. For left to right readers the span is estimated to go from about three to four letters at the left side to about 14-15 letters at the right side (Rayner, 1998). This means that more information is extracted from the right visual field than the left visual field, putting the left vOT in the lead. Interestingly, the reading direction did not result in a massive shift of vOT asymmetry to LH dominance, suggesting that the impact of the reading direction on vOT asymmetry is rather limited.

The observed data agree with Pinel and Dehaene (2010) in showing that the interhemispheric interactions do not seem to preclude a rather large variety of LI indices in different brain regions. It is not the case that strong laterality in one region is indicative of similar strong laterality in another region, even not when both regions are assumed to interact intensely. In other words, the degree of lateralization of two language functions is not as consistent as the direction of these lateralities. This has implications for preoperative examinations in patients. Seghier, Kherif et al. (2011)

already argued for measuring regional instead of global LIs when they found a combination of strongly left lateralized activity in angular gyrus with relatively low lateralized activity in the ventral precentral gyrus in their 82 subjects (44 right-handers, 38 left-handers) performing a semantic word matching task. Similarly, Tzourio-Mazoyer, Josse, Crivello and Mazoyer (2004) found LH/LH, LH/RH and RH/RH patterns during a PET study of a word generation (IFG) and story listening (middle and inferior temporal regions) task. The independence of LIs in various regions is likely to be clearer the more different the functions are.

At present, our conclusions are limited to the colateralization of speech production in IFG with LDT word reading in vOT. The language network obviously goes far beyond these two regions and the many-to-many mapping of brain structures and functions makes the colateralization analysis incomplete. For example, the superior temporal sulcus (STS) is another important node in the lateralized language network. Richardson, Seghier, Leff, Thomas and Price (2011) investigated different possible pathways including the posterior inferior occipital region, vOT and anterior/posterior STS by means of dynamic causal modeling. They concluded that different routes can be followed between these regions to link orthographic, phonological and semantic processing, which illustrates that linking two language areas is only part of the complex language network. Similarly, Pinel and Dehaene found weak correlations between the LIs of the fusiform gyrus and frontal regions, but observed strong colateralizations between the posterior STS and fusiform/frontal areas. They discussed that the STS may be a keystone in the language network, because previous studies demonstrated an early leftward temporal lateralization for speech listening that can already develop after two or three months (Dehaene-Lambertz, Dehaene & Hertz-Pannier, 2002). Only nine participants showed superior temporal activity in our sample (at an uncorrected $p < 0.01$ level with $Z > 3$, defined as a sphere ROI of 15 voxels around $x = -53$, $y = -13$, $z = 0$; see Jobard, Crivello & Tzourio-Mazoyer, 2003), but this could be attributed to an overall high activity level around the STS, so that no conclusions about STS can be made in our sample with this LDT. Jobard et al. (2003) argued that superior temporal activity is part of a network converting graphemes into phonemes when reading words or

pseudowords. The decision between words and nonwords in our LDT presumably did not require phonological computations.

Future research is needed to complete the currently presented colateralization results between vOT and IFG with LIs of for example the STS. It would then be possible to see how different subareas of the language network are linked to each other in terms of lateralization. Moreover, additional LI values of other regions are needed because the vOT is not purely dedicated to LDT word reading (Dehaene et al., 2004; Price & Devlin, 2003, 2011), and the IFG is activated in more tasks than word generation as well (Hagoort, 2009; Lindenberg, Fangerau & Seitz, 2007). Other tasks will also create the possibility to perform other analyses than correlational analyses. For example, a dynamic causal modeling analysis allows to test which connections between different regions fit best with the acquired activation maps (Friston, Harrison & Penny, 2003). This could not be applied to the current data, because the IFG and vOT ROIs were defined in two different tasks (word generation vs. LDT respectively) and because there was too much variability in ROI activation at the individual level. In addition, functional and anatomical connectivity analyses could explore whether the different patterns of asymmetry can be associated with differences in connection strength.

Finally, future research can investigate whether opposite asymmetries have processing consequences. Would participants with deviating LIs in IFG and vOT rely less on phonology in visual word processing than participants with similar LIs? There is a large range of tasks that can be used to address these questions (e.g., Rastle & Brysbaert, 2006).

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