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The Left Ventral Occipito-Temporal Response to Words Depends on Language Lateralization but Not on Visual Familiarity

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The sensitivity of the left ventral occipito-temporal (vOT) cortex to visual word processing has triggered a considerable debate about the role of this region in reading. One popular view is that the left vOT underlies the perceptual expertise needed for rapid skilled reading. Because skilled reading breaks down when words are presented in a visually unfamiliar format, we tested this hypothesis by analyzing vOT responses to horizontally presented words (familiar format) and vertically presented words (unfamiliar format). In addition, we compared the activity in participants with left and right cerebral dominance for language generation. Our results revealed 1) that the vOT activity during reading is lateralized to the same side as the inferior frontal activity during word generation, 2) that vertically and horizontally presented words triggered the same amount of activity in the vOT of the dominant hemisphere, but 3) that there was significantly more activity for vertically presented words in the vOT of the nondominant hemisphere. We suggest that the reading-related activity in vOT reflects the integration of general perceptual processes with language processing in the anterior brain regions and is not limited to skilled reading in the familiar horizontal format.

Keywords: cerebral lateralization, perceptual expertise in reading, visual familiarity, visual word reading, vOT (ventral occipito-temporal) activity

Introduction

Neuroimaging studies have established that in most individuals the brain areas involved in visual word reading rapidly become lateralized to the left cerebral hemisphere (Nobre et al. 1994; Cohen et al. 2000). These studies typically highlight the critical role of a ventral occipito-temporal (vOT) region around the left occipito-temporal sulcus at the junction between the inferior temporal gyrus and the fusiform gyrus (Price 2000; Jobard et al. 2003; Dehaene et al. 2005), which is activated about 150–200 ms after word onset (Tarkiainen et al. 1999; Cohen et al. 2000). Although some researchers believe that this area is specifically dedicated to the extraction of invariant visuo-orthographic information via a posterior-to-anterior hierarchy of local combination detectors (Cohen et al. 2000; McCandliss et al. 2003; Dehaene et al. 2004, 2005), others suggest that the functional role of the region is wider and depends on the task given. In the case of reading, it serves as the interface between the visual processes involved in word reading and the higher level phonological and semantic processes needed for language understanding (Price and Devlin 2003; Nazir et al. 2004; Devlin et al. 2006; Reinke et al. 2008). According to the latter view, the left bias of activity in the vOT is not due to some specialization of this region for language processing but is a consequence of top-down connections from the anterior language areas, which are generally lateralized to the left hemisphere (LH, Hillis et al. 2005; Powell et al. 2006; Ben-Shachar et al. 2007; Cai et al. 2008; Reinke et al. 2008).

Anatomical support for the latter assumption comes from tractography studies revealing more extensive fronto-temporal connectivity via the arcuate fasciculus in the LH than in the right hemisphere (RH) (Powell et al. 2006). This asymmetry is not present in nonhuman primates (Rilling et al. 2008), even though their brains show similar anatomical differences between the left and the right brain halves in the homologue of Broca's area, suggesting that the asymmetrical frontal brain structures associated with language ability may have existed before humans evolved (Cantalupo and Hopkins 2001).

More direct evidence for the relationship between anterior language structures and vOT activity during reading comes from a study by Cai et al. (2008) who compared the laterality of reading-related vOT activity in healthy individuals with reversed hemispheric dominance for language generation. Although the structures supporting speech production are generally lateralized to the LH, atypical language lateralization (i.e., bilateral or RH dominance) can be observed in 25–30% of strong left handers (Knecht et al. 2000). By analyzing event-related potentials (ERPs) of native French readers with typical and atypical language generation lateralization, Cai et al. (2008) showed that independently of where the words were displayed in the visual field, reading-related vOT activity lateralized to the hemisphere that was dominant for speech. Despite its location within the ventral visual stream, vOT activity in word reading seemed thus to lateralize to the same hemisphere as the one involved in spoken language production.

Given the suggested link between the anterior language regions and the vOT stream of the same hemisphere, a follow-up question is whether reading-related d-vOT activity (d- and nd- will be used to indicate vOT regions of the hemisphere that is dominant or nondominant for language generation) is affected by a manipulation that disrupts fast parallel letter processing in reading. Rapid word recognition in skilled readers relies on familiarity with the visual aspects of the words (Nazir 2000; Huckauf and Nazir 2007; Nazir and Huckauf 2008). Displaying words in an unusual format (e.g., vertically) disrupts this skill and reading switches from a fast parallel mode to a more laborious serial letter-processing mode that is characteristic of beginning readers (Bub and Lewine 1988; Ellis et al. 1988; Aghababian and Nazir 2000; Lavidor et al. 2001). The role of the d-vOT region in this serial letter-processing mode is unclear. According to the local combination detector hypothesis proposed by Dehaene et al. (2005), d-vOT activity is the end product of a chain of bottom-up transformations applied to horizontally presented word stimuli: Learning to read tunes a posterior-to-anterior hierarchy of neurons with increasing receptor fields to increasingly complex word fragments, and the capacity of these detectors to rapidly identify words depends on the visual format used during learning. The rapid parallel encoding of letters and complex word fragments through the hierarchy of converging detectors is thus contingent on familiar local feature combinations within and between neighboring letters (with limited tolerance to perceptual variations including letter spacing and slight rotation) and should break down when words depart from the standard format (Cohen et al. 2008). In other words, displaying words in unusual visual formats (which disrupt familiar local feature combinations) should alter the pattern of d-vOT activity. Alternatively, however, if the d-vOT region serves as the interface by which information extracted from visual stimuli makes contact with linguistic processes (Posner and Carr 1992), this region should be active whatever the visual word format is.

To verify this hypothesis, we used functional magnetic resonance imaging (fMRI) 1) to replicate the ERP findings reported by Cai et al. (2008) and 2) to determine whether the d-vOT region is similarly engaged during reading of horizontally and vertically displayed words. We tested individuals with LH and RH dominance for language generation identified during silent word generation (Petersen et al. 1988; Binder 1997; Hunter and Brysbaert 2008). Subsequently, participants of each group performed a lexical decision task using horizontally and vertically displayed stimuli. In the vertical-display condition, component letters were presented in upright orientation, which minimized familiar local feature combinations between the letters and which also excluded interpretation in terms of mental rotation. The correlation between the 2 lateralization indices (LIs) was determined, and cerebral activity during horizontal and vertical displays in the lexical decision task was analyzed and compared.

Materials and Methods

Participants

Seven right-handed participants and 9 left-handed participants as assessed by the Edinburgh handedness inventory (Oldfield 1971) took part in the study (mean age 24.2 years; range 20–35 years). Three participants had been tested in a previous ERP study in which they were identified as RH dominant for language production (Cai et al. 2008). All participants were native speakers of French and had at least 13 years of education. All had normal or corrected-to-normal vision. No neurological or psychiatric history was reported. Participants gave written informed consent prior to participation and were free to withdraw from the experiment at any time. They were paid for their participation. The protocol was approved by the ethics committee Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale.

Experimental Design and Procedure

Visual stimuli were generated with Presentation software (Neurobehavioral Systems, http://www.neurobs.com) and projected onto a translucent screen with a Canon Xeed SX50 projector. The screen was viewed through a mirror in the scanner, which was installed in front of the participant's eyes. Participants were trained outside the scanner prior to the actual experiment to ensure that they understood the tasks.

Word Generation Task

Stimuli. Ten letters served as stimuli (b, c, d, g, l, m, n, p, r, and t). Target letter selection was based on a pretest with native French speakers. This allowed us to exclude letters for which only a few words could be generated. Stimuli were displayed in white on a black background.

Task. The task contained 10 cycles. Each cycle consisted of one activation task (duration 15 s), one control task (15 s), and 2 15-s rest periods between the tasks (Fig. 1*A*). A cycle started with an activation task during which a letter was displayed at the center of the screen for 15 s and participants were requested to silently generate as many words as possible that started with the letter. The activation task was followed by a rest period during which a short line was displayed on the screen and participants were requested to relax. In the subsequent control task, the letter sequence "roro" was displayed on the screen for 15 s and participants were instructed to mentally repeat roro, which is pronounceable but meaningless in French. The control task was followed by another rest period. This cycle was repeated 10 times with 10 different letters displayed in random order. The task took 10 min to complete.

Lexical Decision Task

Stimuli. Two lists (A and B), each containing 24 lowercase words, 24 lowercase pseudowords, and 24 checkerboards, served as stimuli. Words in the lists were 4–7 letters long (in equal proportions) and were matched for frequency (range 11.4–149.8 per million; mean 44.7 and 44.2 per million; $P = 0.97$), syllable number (range 1–3; mean 1.71 and 1.75; $P = 0.82$), and orthographic neighborhood size (mean 3.88 and 3.79; $P = 0.94$) (http://www.lexique.org; New et al. 2004). Words consisted of nouns (50%), verbs (25%), and adjectives (25%). Pseudowords, generated from the same words by replacing 1 or 2 letters while preserving the C-C/V-V rule, were matched on length and bi-/tri-gram frequency to word stimuli. Pseudowords of list A were created from words of list B and vice versa. Checkerboards (alternating black and white cells) of the same length and width as the orthographic stimuli were used as baseline condition. Stimuli were displayed in Courier New, white on a black background. Maximum stimulus eccentricity (from the center to the outer letter) was ±2.0° on the horizontal axis (letter height 0.75°) and ±3.0° on the vertical axis (letter width 0.6°).

Task. The task was conducted in an event-related fMRI design. Participants performed 2 experimental runs (Fig. 1*B*). In the first run, one of the lists served as the stimulus list and was presented in the

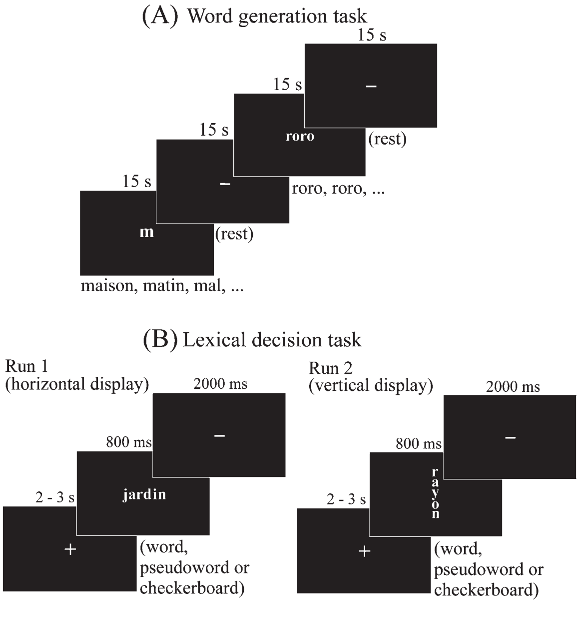


Figure 1. Experimental design of (*A*) Word generation task and (*B*) Lexical decision task. In the lexical decision task, all the stimuli (words, pseudowords, and checkerboards) used in Run 1 were presented horizontally, and those used in Run 2 were presented vertically.

horizontal format; in the second run, the other list was presented in the vertical format. In both runs, a trial began with the presentation of a central cross-hair that served as fixation. Participants were instructed to maintain their gaze on the cross. After a variable interval of 2–3 s, a word, pseudoword, or checkerboard was displayed for 800 ms at the center of the screen. At the offset of the stimulus, a short line appeared on the screen prompting participants to respond. If the stimulus was a word, they were required to press the "yes" button with the index finger of the right hand and if it was a pseudoword or checkerboard, the "no" button with the middle finger. The next trial was triggered automatically 2 s after the offset of the stimulus. All stimuli were displayed twice in a randomized order. Overall, the duration per block was approximately 12 min.

FMRI Data Acquisition

Images were acquired using a 1.5-T MRI scanner (Siemens Sonata Maestro Class; Siemens, Erlangen, Germany) at the CERMEP "Imagerie du vivant" in Lyon. Functional images were obtained using a $T2^*$-weighted gradient-echo echo planar imaging sequence (repetition time [TR] = 2500 ms; echo time [TE] = 60 ms; and flip angle 90°). Twenty-six axial slices oriented parallel to the anterior commissure–posterior commissure line covering the whole brain were taken (slice thickness 4.40 mm; matrix 64 × 64; and field of view [FOV] = 230 mm). Following functional image acquisition, a high-resolution T1-weighted anatomical image was acquired (TR = 1880 ms; TE = 3.93 ms; flip angle 15°; matrix 256 × 256; FOV = 256 mm; and slice thickness 1 mm).

FMRI Data Analysis

The FMRI data processing was done with SPM5. The first 4 images of each session were discarded to eliminate nonequilibrium effects of magnetization. Functional images were corrected for slice acquisition delays and spatially realigned. Individual anatomical images were coregistered to mean functional images. Functional images and anatomical images were normalized to Montreal Neurological Institute (MNI) T1 template and smoothed with an isotropic Gaussian kernel (full width at half maximum 8 mm).

For the word generation task, experimental conditions were modeled for each participant using a boxcar function convolved with a hemodynamic response function (HRF) (Friston et al. 1994) in the context of the general linear model (GLM). Individual LIs were calculated for the inferior frontal gyrus (IFG) pars triangularis and pars opercularis in the MNI stereotactic space (Tzourio-Mazoyer et al. 2002) for the contrast "word generation against roro repetition." To take into account interindividual variability, calculations of LIs were based on the magnitude of signal change defined by the *t*-values, at a series of variable thresholds of significance (Deblaere et al. 2004; Jansen et al. 2006). Following Wilke and Schmithorst (2006), we used a default of 20 thresholding intervals (equally sized steps from 0 to the maximum *t*-value in the investigated region). At each threshold, the Bootstrap method (100 bootstrap resamples with a resample ratio of $k = 0.25$ were generated for each side from all the voxels in the investigated frontal region. From these resamples, all 10 000 possible LI combinations were calculated) combined with a trimmed mean_{25} ("trimming" the upper and lower 25% to only use the central 50% of data points) was applied to enhance stability by detecting and restricting the influence of statistical or artifactual outliers. A weighted mean LI for each individual was then calculated on the series of LIs weighted by the respective thresholds (for more details, see Wilke and Schmithorst 2006). This calculation was realized by the help of the LI Toolbox 1.02 (Wilke and Lidzba 2007). Participants with an LI > 0.5 were defined as "typical," that is, left lateralized for word generation, and those with an LI < −0.5 were defined as "atypical." Participants with an LI between −0.5 and 0.5 were considered "bilateral."

For the lexical decision task, the blood oxygenation level–dependent (BOLD) impulse response to different event types were modeled in the context of the GLM, using canonical HRF convolved with a delta (event-related) function. For each participant (typical and atypical), individual activation peaks for the contrast "horizontally displayed words against checkerboards" as well as for the contrast "vertically displayed words against checkerboards" were identified in a region corresponding to the vOT, which was defined as the bilateral fusiform and inferior temporal gyri within a box of ($X = -34$ to -55, $Y = -34$ to -68, and $Z = -4$ to -26) and its mirror-reversed box in the RH (these coordinates were chosen with reference to the activation peaks reported by Jobard et al. 2003 for 35 neuroimaging studies on word reading). Weighted mean LIs for this region (words against checkerboards) were also calculated for the 2 contrasts using the same approach as described for the word generation task. Correlation analyses were then performed on the LIs of IFG activity during word generation and LIs of the vOT activity during word reading in the 2 display formats.

Finally, random-effects group analysis was performed to examine whole-brain activity for words contrasting checkerboards in different display formats. Given the limited number of atypical participants, this analysis was performed for the group of typical participants only. Brain regions activated independently of stimulus format and those specific to either horizontal or vertical formats were also identified. To investigate the effects of visual familiarity as well as lexical effects on the left vOT region, percent BOLD signal change for each condition (i.e., words, pseudowords and checkerboards in horizontal and in vertical formats) was calculated for a region of interest (ROI) surrounding the activation peak in the left vOT and its homologue in the RH. Repeated-measures analysis of variance (ANOVA) was performed on these data. ROI analyses were also performed in occipital regions that showed activity for words contrasting checkerboards independently of display conditions and inferior frontal region that showed activity specific to vertically displayed words.

Results

Behavioral Results

All participants performed the word generation task without difficulty. Behavioral data for the lexical decision task from one participant could not be analyzed because she replied prior to the offset of the stimulus and the program failed to record the responses. The remaining 15 participants made on average 2.9% lexical decision errors for the horizontally displayed stimuli and 8.1% for the vertically displayed stimuli. The overall effect of display format was significant ($P < 0.001$). Response time was not analyzed because participants were instructed not to respond before the offset of the stimulus, which causes a temporal "leveling effect."

fMRI Results

Lateralization of Frontal Activity during Word Generation and vOT Activity during Word Reading

Frontal activity during word generation. Individual weighted mean LIs for the IFG during word generation are given in Table 1. Eleven participants were identified as typical (left lateralized), and 5 participants were identified as atypical (right lateralized).

Figure 2 plots the LI curves as a function of the threshold *t* values for one typical and one atypical participant. Random-effects group analysis performed on the typical participants showed widespread activity in the left IFG extending to dorsolateral prefrontal region and premotor cortex (BA 6, 9, 44, 45, 46, and 47 in the LH, and bilateral insula and anterior cingulated cortex), supplementary motor area (SMA), bilateral thalamus and basal ganglia, midbrain, and right cerebellum (voxelwise $P < 0.001$ and cluster extent $P < 0.05$ corrected). These results are in line with previous studies with right-handed participants (Binder et al. 1996; Yetkin et al. 1998). The same analysis performed on the 5 atypical participants showed

Table 1

Individual data (activation peak and LIs) in the word generation task and the lexical decision task[a]

Subject	Word generation	Lexical decision (horizontal words > checkerboards)										Lexical decision (vertical words > checkerboards)								
	Inferior frontal LI	vOT LI	Left vOT				Right vOT				Inferior occipital LI	vOT LI	Left vOT				Right vOT			
			x	*y*	*z*	*Z*	*x*	*y*	*z*	*Z*			*x*	*y*	*z*	*Z*	*x*	*y*	*z*	*Z*
a1	−0.94	−0.69	—				36	−50	−20	2.13[b]	−0.46	−0.18	—				34	−48	−16	2.16[b]
a2	−0.89	−0.58					44	−64	−10	4.4	−0.39	0.02					38	−36	−20	2.92
a3	−0.86	0.59	−48	−52	−14	3.85	54	−56	−14	2.67	−0.58	−0.31	−44	−66	−10	4.74	48	−58	−8	4.60
a4	−0.8	−0.40					40	−38	−24	3.92	0.19	−0.56					36	−38	−18	3.74
a5	−0.75	−0.80					44	−62	−18	3.12	0.05	−0.56					44	−62	−18	4.15
t0	*0.66*	*−0.97*					*44*	*−62*	*−22*	*3.07*	0.56	*0.94*	*−48*	*−68*	*−10*	*3.58*				
t1	0.72	0.16	−40	−54	−14	5.57	34	−44	−22	3.72	−0.28	0.75	−38	−54	−12	7.05				
t2	0.75	*0.81*	No significant activation[b]								0.31	0.43	−46	−48	−10	3.49				
t3	0.81	0.51	−46	−54	−6	4.40					−0.39	0.59	−46	−68	−10	5.22	54	−60	−6	4.51
t4	0.83	0.11	−46	−48	−14	2.61					−0.04	−0.08	−42	−54	−16	4.18	42	−56	−14	4.66
t5	0.88	0.57	−46	−50	−12	3.01					−0.53	0.45	−42	−58	−14	6.06	40	−62	−10	5.51
t6	0.89	0.36	−36	−48	−24	3.29					0.08	*0.36*	No significant activation[b]							
t7	0.92	0.88	−42	−44	−16	2.71					−0.24	0.75	−42	−62	−14	3.58				
t8	0.95	0.65	−40	−46	−16	3.54					0.79	0.89	−44	−52	−10	3.02				
t9	0.97	0.66	−48	−40	−16	2.55					−0.74	0.62	−38	−68	−14	5.61				
t10	0.97	0.71	−36	−48	−12	2.62					0.57	0.76	−46	−58	−14	5.44				
Typical group			*−46*	*−46*	*−16*	*4.70*							*−44*	*−50*	*−14*	*4.00*				

[a] From left to right: Individual LIs for inferior frontal activity during word generation (word generation > roro repetition); LIs (and activation peaks) for vOT activity and inferior occipital activity during lexical decision (words > checkerboards) in horizontal format; and LIs (and activation peaks) for vOT activity in vertical format. Individual vOT activation peaks were identified at $P < 10^{-2}$.

[b] Indicates that no significant activity was found at $P < 10^{-2}$. For these cases, $P < 0.05$ was applied.

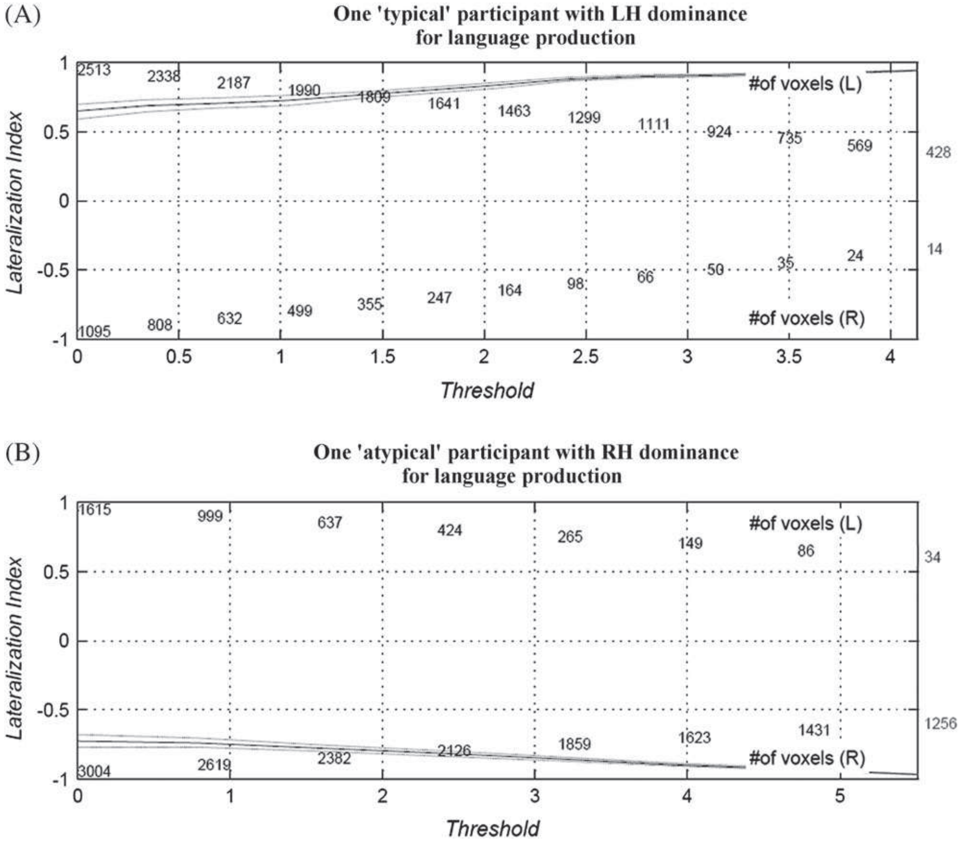


Figure 2. Individual lateralization index curves for inferior frontal regions during word generation (word generation > roro repetition). (*A*) One typical participant with LH dominance for language (weighted mean LI = 0.88); (*B*) One atypical RH dominant participant (weighted mean LI = −0.89). A series of *t* values was taken as thresholds. Bootstrap method (100 resamples with a resample ratio of 0.25 are generated for each side, from which all 10 000 possible LI combinations are calculated based on voxel values) combined with a trimmed mean$_{25}$ ("trimming" the upper and lower 25% to only use the central 50% of data points) was applied at each threshold, until no activated voxel was found in the inferior frontal region in one hemisphere. A weighted mean LI was then calculated based on LIs at different thresholds weighted by the respective threshold. Positive LI indicates left lateralization and negative LI indicates right lateralization of frontal activity.

significant activity in the right IFG extending to dorsolateral prefrontal cortex and premotor cortex (BA 6, 9, 44, insula in the RH, and bilateral BA47 and anterior cingulated cortex), SMA, bilateral basal ganglia, and midbrain. Widespread clusters of frontal activity are thus clearly lateralized to opposite hemispheres in typical and atypical participants.

Individual vOT activity during word reading. For each participant, the individual peak of vOT activity was identified within the predefined ROI ($P < 0.01$ uncorrected), and individual weighted mean LIs for this ROI were calculated separately for horizontal and vertical-display formats (contrast "words against checkerboards").

Horizontal display: As indicated in Figure 3 and Table 1, 10 of the 11 typical participants showed left-lateralized vOT activity, and one showed right-lateralized vOT activity. Note that for one participant, vOT activity was weak and did not pass the level of significance. The LI of this participant nevertheless indicated LH dominance. Four of the 5 atypical participants showed right-lateralized activity and one showed left-lateralized activity. Note though that the intragroup variation of *y*-values is larger in the atypical than in the typical population, which will be further discussed in the Discussion section.

Vertical display: Figure 3 and Table 1 also show that, 15 of the 16 participants had significant vOT activity in the vertical-display condition. Occipito-temporal activity was generally stronger and more extended for vertically than for the horizontal-displayed stimuli (Fig. 5), which sometimes presented some difficulty in identifying isolated vOT peaks at the individual level (i.e., because this peak was masked by a more posterior peak in an extended occipito-temporal activation cluster).

Correlation between IFG activity during word generation and vOT activity during word reading. Figure 4 plots the individual LIs for IFG activity during word generation and the corresponding LIs for vOT activity during word reading (in the horizontal- and vertical-display conditions, respectively). Given the lack of intermediate IFG LIs (i.e., all LIs approach the 2 extreme values), a point-biserial correlation analysis was performed instead of a Pearson correlation, and the results reflected strong intergroup difference by showing a significant positive correlation between the IFG LIs and vOT LIs (for horizontal-display condition: $r = 0.59$; $P = 0.016$; for vertical-display condition: $r = 0.85$; $P < 0.01$).

Note that there were 2 outliers in the data for the horizontal-display format (one typical and one atypical participant). However, in the vertical-display format, these 2 participants showed a laterality index in line with their word generation. The 2 outliers in the horizontal-display condition are likely caused by a low level of activity in this condition. To keep the group homogeneous, in the further group analyses performed on the typical participants, the outlier was excluded.

Analyses of the Brain Activity during the Lexical Decision Task (Typical Participants Only)

Whole-brain analysis as a function of display format. Horizontal display: Random-effects analysis on the contrast horizontally displayed words against checkerboards of the 10 remaining typical participants revealed clusters of significant activity in the left vOT region (peaked at −46, −46, −16; $Z = 4.70$; see Fig. 5), left occipital cortex, left IFG (BA45/47), left precentral and postcentral gyri, and right putamen and thalamus (voxel-level threshold $P < 0.001$, cluster-level threshold $P < 0.05$). At a lower threshold ($P < 0.01$, cluster extent 200 voxels), additional significant activity was observed bilaterally in the putamen, the thalamus, the precentral gyrus, and the occipital cortex but there was still no significant right-vOT activity.

Vertical display: The same analysis for the vertical-display condition showed significant activation in the left vOT region (peaked at −44, −50, −14; $Z = 4.00$; see Fig. 5), bilateral occipital cortex, and left IFG/insula (peaked at −58, 10, 22; $Z = 4.35$ in pars opercularis; extending to pars triangularis). At a lower threshold ($P < 0.01$, cluster extent 200 voxels), additional

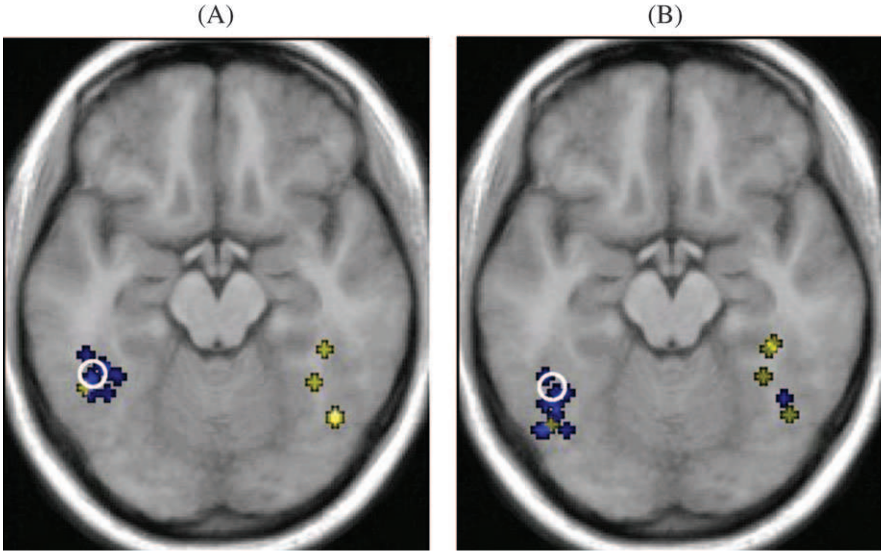


Figure 3. The peaks of vOT responses to words (against checkerboards) identified in individual subjects (typical participants: blue crosses; atypical participants: yellow crosses). The white circles indicate the peak response in the group analysis of the typical participants. (*A*) Horizontal-display format; (*B*) vertical-display format. The data have been projected onto an axial slice ($z = -16$) of an averaged anatomical image.

significant activity was observed in the left posterior occipito-parietal regions (peaked at –30, –74, 26; $Z = 3.34$ and –26, –66, 40; $Z = 3.15$), the right IFG pars opercularis (peaked at 48, 12, 26; $Z = 3.19$) and the SMA.

Comparison of the 2 display formats. Figure 5 plots group activation peaks for the horizontal (in violet) and the vertical (in cyan) display formats (words against checkerboards). As can be seen from this comparison, the left-lateralized vOT activity in the horizontal and vertical-display formats largely overlapped (indicated by the white color).

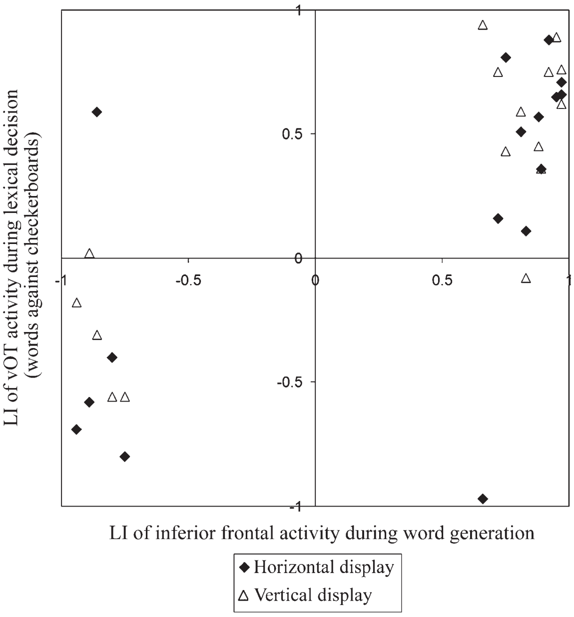


Figure 4. The significant correlation between the LIs for the inferior frontal activity during word generation (against roro repetition) and the LIs for the vOT activity during lexical decision (words against checkerboards) in horizontal (black diamond) or vertical (hollow triangle) format. Point-biserial correlation coefficient was tested given that the inferior frontal LIs values all approach the extreme values −1 or 1. Notice that the 2 outliers in the horizontal-display condition did not show a deviating pattern in the vertical-display condition.

Activation common to both formats: Regions activated independently of word format were identified by masking the contrast horizontally displayed words against checkerboards inclusively with the contrast vertically displayed words against checkerboards and vice versa (both at voxelwise threshold $P < 0.001$ and cluster-level threshold $P < 0.05$). The results revealed 2 regions: a left vOT cluster (peaked at –46, –48, –14; $Z = 4.50$ for horizontally displayed words; and at –44, –50, –14; $Z = 4.00$ for vertically displayed words) and a left inferior occipital cluster (peaked at –40, –82, –6; $Z = 3.83$ for horizontally displayed words and at –40, –84, –8; $Z = 3.60$ for vertically displayed words). Activity in the 2 regions will be further examined in the next two sections.

Format-specific activation: Regions activated specifically for horizontally displayed words were identified by the contrast "horizontally against vertically displayed words" inclusively masked by the contrast horizontally displayed words against checkerboards (both at $P < 0.001$ and cluster-level $P < 0.05$). This comparison revealed no significant activity specific to horizontally displayed words. Regions that were specifically activated for the vertically displayed words were identified by the contrast "vertically against horizontally displayed words" inclusively masked by the contrast "vertically displayed words against checkerboards." Activity specific to vertically displayed words was observed in left posterior superior IFG (peaked at –54, 10, 28; $Z = 3.94$; pars opercularis) and will also be further analyzed in "ROI Analysis for IFG Pars Opercularis."

ROI analysis for vOT regions (words, pseudowords, and checkerboards). To further investigate the vOT activity common to the 2 formats, a left vOT ROI was defined as a sphere of all the voxels within a 6-mm radius surrounding the average of the 2 peaks identified in the previous subsection (which gives the coordinates [–45, –49, –14]). The percentage BOLD signal change was calculated for this ROI. To better investigate lexicality effects, pseudowords were included in

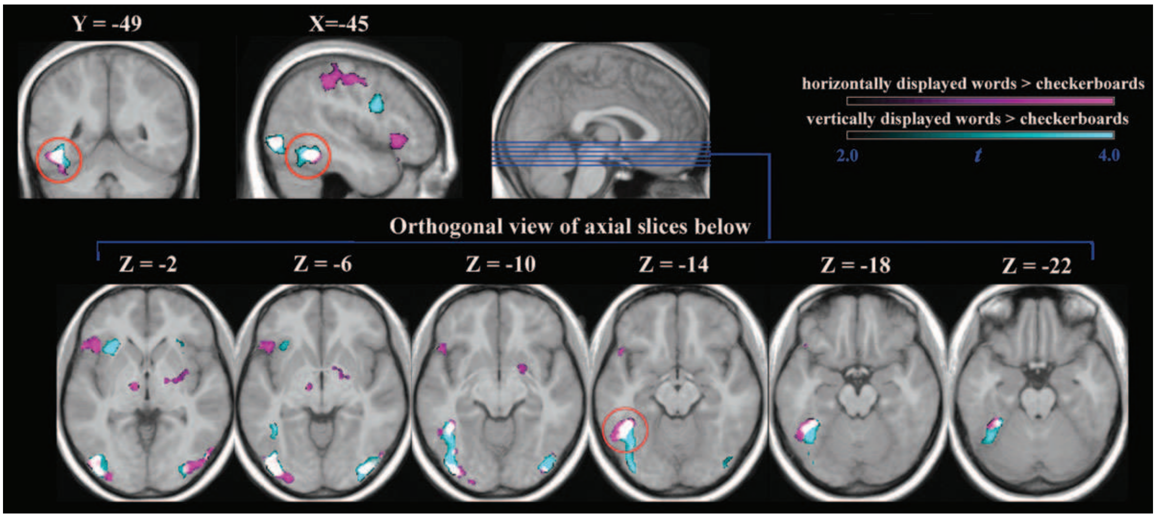
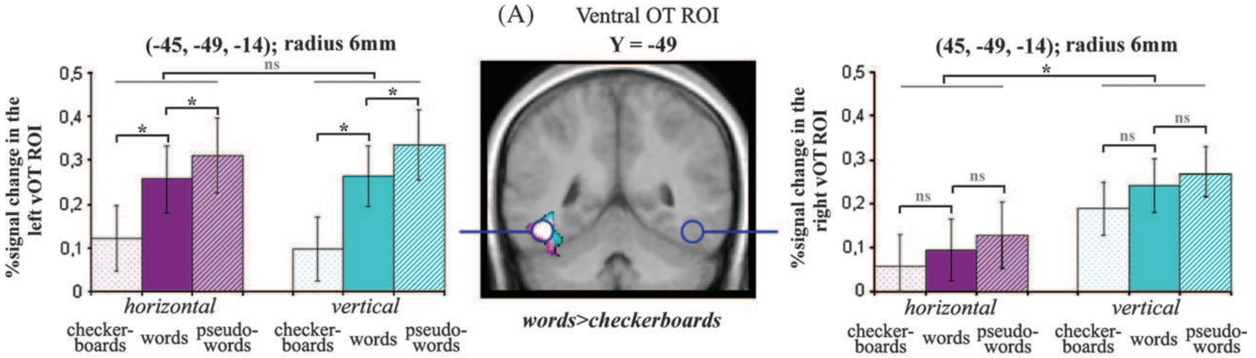


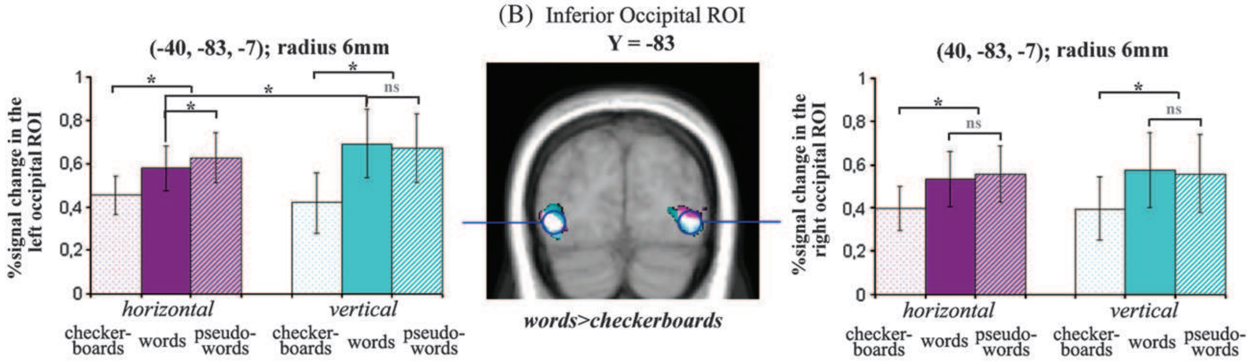
Figure 5. VOT responses to words (against checkerboards) during lexical decision task for the group of 10 typical participants with LH dominance for word generation. Activity in the horizontal-display format is indicated in violet, and activity in the vertical-display format in cyan. VOT responses peaked at (−46, −46, −16) ($Z = 4.70$) in the horizontal format and at (−44, −50, −14) ($Z = 4.00$) in the vertical format (indicated by the red circle). The white color specifies regions that were responsive in both display conditions. Activation was overlaid on the averaged anatomical image of the same participants, coregistered, and normalized at the individual level.

this analysis. Two-way repeated measure ANOVAs (display format × stimulus type) were performed. Results (Fig. 6*A*) showed no effects of visual format ($F(1,9) = 0.00$, $P = 0.98$) but a significant effect of stimulus type ($F(2,18) = 55.8$, $P < 0.001$). Post-hoc Neuman–Keuls tests showed that activity was strongest for pseudowords, followed by words, and was weakest for checkerboards. The difference in activity between each comparison was statistically significant (words vs. checkerboards: $P < 0.001$; pseudowords vs. checkerboards: $P < 0.001$; and pseudowords vs. words: $P = 0.047$).

The same analysis was performed on the mirror ROI in the RH. In contrast to activity in the LH, this analysis revealed a significant main effect of visual format with a stronger activity for the vertical format ($F(1,9) = 6.8$, $P = 0.028$) and a main effect of stimulus type ($F(2,18) = 4.4$, $P = 0.029$). Post-hoc Neuman–Keuls tests, however, showed no significant difference in right-vOT activity between any 2 stimulus types (checkerboards vs. words: $P = 0.22$; checkerboards vs. pseudowords $P = 0.43$ and words vs. pseudowords: $P = 0.12$). Because the right-vOT responses to vertical checkerboards were also high, contrasting words with checkerboards (as was done for the previous whole-brain analysis and for the calculation of the LIs) concealed the right-vOT activity for words in the vertical condition.

A 3-way repeated measure ANOVA (hemisphere × display format × stimulus type) confirmed the main effect of stimulus type ($F(2,18) = 28.1$, $P < 0.001$) and showed a significant





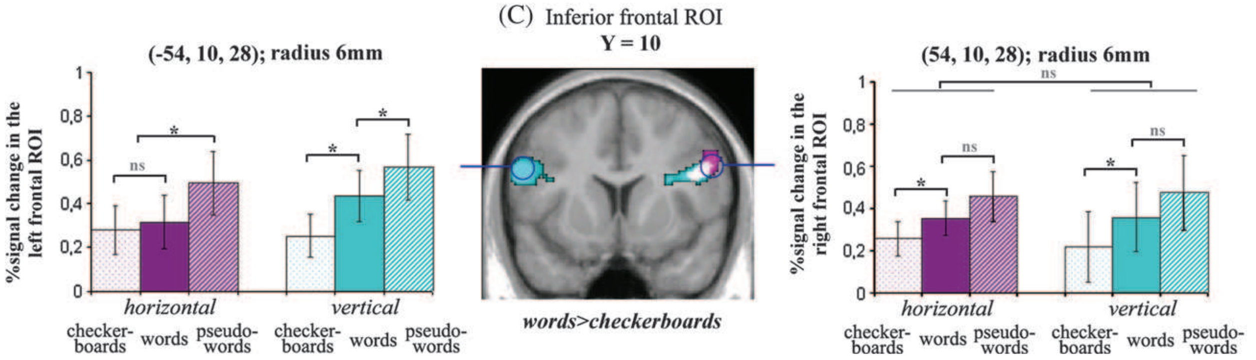


Figure 6. Profiles of left and right (*A*) vOT activity, (*B*) inferior occipital activity, and (*C*) frontal activity for different stimulus types (checkerboards, words, and pseudowords) in participants with typical lateralization for word generation. The central slides plot the activity in the 2 display formats for words against checkerboards (horizontal format in violet and vertical format in cyan). For illustration purposes, we used a voxelwise threshold of $P < 10^{-2}$ and a threshold of 200 voxels for cluster extent. (*A*) Left vOT responses showed no effect of display format but a significant lexicality effect. In contrast, right-vOT responses showed a significant effect of display format and no significant lexicality effect. For horizontally displayed stimuli, right-vOT activity was weaker than in the remaining conditions. (*) Indicates significant differences at $P < 0.05$. (*B*) Inferior occipital activity for words and pseudowords did not differ but was stronger than activity for checkerboards. In the LH, inferior occipital activity was less strong for horizontally displayed words than for vertically displayed words. (*C*) In the LH, inferior frontal activity for horizontally displayed words and checkerboards did not differ and was weaker than activity for pseudowords and vertically displayed words. There is no effect of format in the RH.

hemisphere × stimulus type interaction ($F(2,18)=15.9$, $P < 0.001$) as well as a hemisphere × format interaction ($F(1, 9)=13.5$, $P = 0.005$). Post-hoc Neuman–Keuls test showed no effect of format for the LH ($P = 0.971$) but a significant effect of format for the RH ($P = 0.015$). vOT activity for horizontally displayed stimuli was generally less strong in the RH than in the LH ($P = 0.036$), whereas for vertically displayed stimuli, no such difference was observed ($P = 0.999$).

ROI analysis for inferior occipital regions (words, pseudowords, and checkerboards). To further investigate inferior occipital activity common to the 2 formats, ROIs were defined as a sphere of all the voxels within a 6-mm radius surrounding the average of the 2 peaks identified in "Activation common to both formats" (which gives the coordinate [−40, −83, −7]) and the homologous region in the RH. Percentage BOLD signal change for this ROI was calculated for checkerboards, words, and pseudowords in the 2 display conditions (Fig. 6*B*). Three-way repeated-measures ANOVAs (hemisphere × display format × stimulus type) showed no effects of hemisphere ($P = 0.34$) or display format ($P = 0.70$) but a significant main effect of stimulus type ($F(2,18) = 21.9$, $P < 0.001$). The interactions between format × stimulus type ($F(2,18)=3.78$, $P = 0.042$) and between hemisphere × format × stimulus type ($F(2,18)=3.56$, $P = 0.0497$) were also significant. Post-hoc Neuman–Keuls tests revealed that, independently of display format, activity for words and pseudowords was significantly stronger than activity for checkerboards in both hemispheres (all $P < 0.001$). Activity for words and pseudowords only differed in the horizontal format in the LH (pseudowords > words, $P = 0.030$; in all the other conditions P = ns). In the LH, activity for vertically displayed words was also significantly stronger than activity for horizontally displayed words ($P < 0.001$); this was not so in the RH ($P = 0.21$).

To identify potential relations between the laterality of vOT activity and inferior occipital activity during word reading, individual LIs were calculated for the latter region (contrast horizontally displayed words against checkerboards). For this, an ROI was defined as bilateral occipital gyri within a box of ($X = −30$ to $−50$, $Y = −72$ to $−92$, and $Z = 2$ to $−18$) and its mirror-reversed box in the RH. Results showed bilateral activity for typical participants (−0.05 ± 0.49) as well as for atypical participants (−0.24 ± 0.34). No correlation was found between LIs for activity in the inferior occipital regions and in the vOT regions ($P = 0.78$ ns) (see Table 1).

ROI analysis for IFG pars opercularis (words, pseudowords, and checkerboards). To further investigate IFG activity specific to vertically displayed words, an ROI was defined as a sphere of all the voxels within 6 mm of the activation peak (−54, 10, 28) identified in "Comparison of the 2 Display Formats". Percentage signal change in each condition was calculated for the ROI and a 2-way repeated measure ANOVA (format × stimulus type) was performed (Fig. 6*C*). Results showed a main effect of stimulus type ($P < 0.001$) and a significant format × stimulus type interaction ($P = 0.04$). Post-hoc Neuman–Keuls tests showed that for horizontal-display format, activity for words was not different from checkerboards ($P = 0.17$ ns), whereas activity for pseudowords was significantly stronger than for words and checkerboards ($P = 0.018$ and $P = 0.002$). In the vertically display format, activity for words and for pseudowords was both significantly stronger than for checkerboards ($P = 0.013$ and $P < 0.001$), and activity for pseudowords was also stronger than activity for words ($P = 0.040$).

The same analysis was also performed on a mirror ROI in the right frontal region. Results showed only a main effect of stimulus type ($P < 0.001$) and no effect of format ($P = 0.96$). Post-hoc Neuman–Keuls tests showed that activity was stronger for pseudowords and words (pseudowords vs. words: $P = 0.060$) than for checkerboards (words vs. checkerboards: $P = 0.046$; pseudowords vs. checkerboards: $P = 0.002$).

Discussion

The present study was designed 1) to investigate the correlation between the laterality of the anterior cortical structures that are involved in language generation and the laterality of reading-related vOT activity and 2) to determine whether reading-related vOT activity is affected by a manipulation that disrupts the fast parallel letter-processing of normal reading. Our results provide clear answers to both questions.

Laterality of vOT Activity

By testing participants with typical LH and atypical RH dominance for word generation, the present study validated the ERP results reported by Cai et al. (2008). In all but one participant with typical frontal LH dominance for language generation, vOT responses during word reading (contrasted with checkerboards) were observed in the LH, whereas in 4 of the 5 participants with atypical RH dominance, vOT responses were observed in the RH. By contrast, no correlation was found between the laterality of vOT activity and the laterality of inferior occipital activity. This result is thus suggestive of the assumption set forth by several investigators that top-down connections from anterior language areas adjust visual word processing at the level of the d-vOT region (Hillis et al. 2005; Ben-Shachar et al. 2007; Cai et al. 2008; Reinke et al. 2008). Although the 2 deviating participants (one typical and one atypical) suggest that the correlation may not be 100% (see also Janssen et al. 2006), it should be kept in mind that some deviating pattern could result from weak word-specific activity.

A further interesting observation is that there seems to be more anterior–posterior variability in the vOT activation peaks of the RH dominant participants than the LH dominant participants (Fig. 3 and Table 1), in particular for the familiar, horizontal-display condition. One reason might be that the atypical functional lateralization of language is not accompanied by a reversion of the anatomical asymmetries observed in the typical brain (Kennedy et al. 1999; see Sun and Walsh 2006 for a review). Therefore, compared with the LH dominant participants, the fronto-temporal anatomical connectivity (cf. Powell et al. 2006) in the dominant hemisphere for the RH dominant participants could be less extensive, which may explain the bigger variances in the atypical participants. Further work is underway to clarify this point by investigating the difference in anatomical and functional connectivity in the populations with different language lateralization.

The Effect of the Visual Format on the vOT Activity

Further analyses of the BOLD signal changes in the typical participants also revealed that d-vOT responses, which were strongest for pseudowords, intermediate for words, and smallest for checkerboards, were virtually the same for the 2 display formats. Given that reading vertically displayed words involves slow, serial letter processing (Bub and Lewine 1988; Ellis et al. 1988; Aghababian and Nazir 2000; Nazir 2000; Lavidor et al. 2001; Nazir and Huckauf 2008), this means that the reading-related activity in the d-vOT cannot be taken as an indicator of the rapid parallel letter-processing characteristic of skilled reading.

Some previous studies have reported different patterns of d-vOT responses to familiar and unfamiliar display formats (e.g., format familiarity was manipulated by increasing the interletter spaces or by rotating words in Cohen et al. 2008). It should be noted, however, that the protocol we used in the present study is different from the one used by Cohen et al. (2008): Although in our protocol the letters were presented normally, Cohen et al. rotated complete words, which may have involved different below-letter-level processing to mentally rotate the stimulus before word-level processing started. Furthermore, although the occipito-temporal activity peak (which was more posterior) observed in their study could reflect an (extra) activity for rotated letters/words, it does not exclude the possibility of a more anterior vOT activity that was masked as a result of the posterior peak in an extended cluster.

Vertical word presentation resulted in some extra activation posterior to d-vOT (Fig. 3), but the effect of presentation format was much more pronounced in the nd-vOT region, with significantly higher activity for vertical than for horizontal words (Fig. 6*A*). In fact, for vertically displayed stimuli, nd-vOT responses were nearly as strong as d-vOT responses. In addition, the nd-vOT responses did not differentiate between stimulus types. Nondominant vOT activity in reading has been reported before by Turkeltaub et al. (2003) in a study on the development of neural reading mechanisms in children (6–22 years). The authors observed a decrease of activity in the (nondominant) right ventral visual stream associated with improved reading skills and interpreted this as decreasing reliance on general form-recognition mechanisms in the RH (see also Shaywitz et al. 2002).

The finding of stronger nd-vOT activity for vertically presented words in our study could be interpreted as an extra involvement of RH (or bilateral) form-recognition procedures in the processing of visually unfamiliar stimuli, analogous to what has been hypothesized for beginning readers. The nd-vOT becomes progressively less involved in normal word reading as the reader becomes more skilled (see Xue and Poldrack 2007 for a similar suggestion). This interpretation is in line with the finding that that the nd-vOT response did not differ for words, pseudowords, and other stimuli (suggesting that the activity is not specific to words, which would explain why the nd-vOT activity is often not observed in studies using a relative high-level baseline). Again, the precise mechanisms of the interactions between nd-vOT and d-vOT need to be further clarified.

Independent of the interpretation of the nd-vOT activity, the fact that vertically and horizontally presented words elicit the same amount of d-vOT activation does not fit well with the idea that d-vOT activation underlies the perceptual expertise needed for rapid skilled reading (McCandliss et al. 2003; Dehaene et al. 2005). Instead, our results point more in the direction of the hypothesis that reading-related vOT activity arises from the integration of (general) form recognition with lateralized anterior language processes: vOT activity is the result of interactive (top-down) processes and not simply from bottom-up perceptual learning.

Activity in the Bilateral Inferior Occipital Regions and the Left IFG Pars Opercularis

The data of our typical participants also revealed significant responses to orthographic stimuli in the inferior occipital regions (bilaterally) and in the left IFG pars opercularis. The bilateral inferior occipital cortices showed similar activity to vertically and horizontally displayed words and more to words and pseudowords than to checkerboards, although it should be noted that there was a trend toward less activity for horizontally presented words than in the other conditions. This activity might be related to the extraction of visual features from letters (which were the same in the vertically and the horizontally presented words). Activation of inferior occipital regions in visual word processing has been observed before but has not received much attention. Notice that this region roughly corresponds to the so-called “occipital face area” (Haxby et al. 1999; Gauthier et al. 2000), which together with the “fusiform face area” plays a critical role in face recognition (Rossion et al. 2003). It is also interesting to note that a previous study showed decreased activity in this region after visual word form training (Xue and Poldrack, 2007). Further studies are expected to clarify the specific function of this region for visual word processing.

The left but not the right posterior IFG (pars opercularis) showed activity specific to vertically displayed words. Further analyses revealed that this left frontal region was also responsive to pseudowords in both formats. Note that all these stimuli elicit a serial letter-processing mode, which involves grapheme–phoneme conversion (Fiebach et al. 2002; Jobard et al. 2003). Activity in the IFG pars opercularis is therefore likely to reflect phonological processes involved in reading (see also Fiez et al. 1999; Bookheimer 2002; Tan et al. 2005). The requirement to link phonological and orthographical information in reading is probably the main reason why the vOT lateralizes to the same side as the language areas in the frontal lobes.

Conclusion

The entire pattern of results reported here is very suggestive of the assumption that reading-related d-vOT responses result from the integration of general visual form recognition within the network devoted to language processing (e.g., Booth et al. 2003; Devlin et al. 2006; Ben-Shachar et al. 2007; Kronbichler et al. 2007, 2009; Bolger et al. 2008). Note that this proposal is coherent with the fact that the vOT region is also involved in the processing of visual forms such as pictures (e.g., Price and Devlin 2004; Hillis et al. 2005; Wright et al. 2008). What clearly differentiates the processing of visual words and the processing of other visual forms is the linguistic nature of the stimuli. Reading-specific perceptual expertise results in a lasting reliance on the vOT region in the language dominant hemisphere and decreasing reliance on the vOT region in the nondominant hemisphere.

Notes

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