Article

Hierarchical Coding of Letter Strings in the Ventral Stream: Dissecting the Inner Organization of the Visual Word-Form System

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SUMMARY

Visual word recognition has been proposed to rely on a hierarchy of increasingly complex neuronal detectors, from individual letters to bigrams and morphemes. We used fMRI to test whether such a hierarchy is present in the left occipitotemporal cortex, at the site of the visual word-form area, and with an anterior-to-posterior progression. We exposed adult readers to (1) false-font strings; (2) strings of infrequent letters; (3) strings of frequent letters but rare bigrams; (4) strings with frequent bigrams but rare quadrigrams; (5) strings with frequent quadrigrams; (6) real words. A gradient of selectivity was observed through the entire span of the occipitotemporal cortex, with activation becoming more selective for higher-level stimuli toward the anterior fusiform region. A similar gradient was also seen in left inferior frontoinsular cortex. Those gradients were asymmetrical in favor of the left hemisphere. We conclude that the left occipitotemporal visual word-form area, far from being a homogeneous structure, presents a high degree of functional and spatial hierarchical organization which must result from a tuning process during reading acquisition.

INTRODUCTION

In literate adults, the first stages of word reading involve extracting from the retinal stimulus a representation of letter strings invariant for changes in size, position, font, or case. This abstract representation of letter strings, which has been termed the visual word form (VWF; Warrington and Shallice, 1980), is computed by a set of visual processes (the VWF system) that have been acquired by expert readers over years of training (Aghababian and Nazir, 2000). Brain-imaging experiments (for a review, see Jobard et al. [2003]) and neuropsychological observations of patients with pure alexia (Cohen et al., 2003) have evidenced the crucial role of part of the left ventral occipitotemporal cortex in such expert visual word processing. This led to the labeling of a patch of cortex lateral to the midportion of the fusiform gyrus as the VWF area (VWFA) (Cohen et al., 2000). The VWFA responds to words more than to other control shapes such as checkerboards (e.g., Cohen et al. [2002]) and shows adaptations to idiosyncratic features of the reader's writing system such as orthographic constraints (Cohen et al., 2002; Binder et al., 2006) and invariance for case change (Dehaene et al., 2001, 2004). In children, it shows a growing responsivity and specialization for a specific writing system as a function of increasing expertise for reading (Maurer et al., 2006; Shaywitz et al., 2002).

Although this region is routinely seen as globally activated in single subjects during reading tasks, its internal organization and how it supports invariant recognition of visual words remain unknown. As a guide to this research, we recently proposed a schematic neural model of the computations that might be performed in the ventral cortex during reading (the local combination detector or LCD model; Dehaene et al., 2005). Although the LCD embraces lower levels of coding in V1/V2, it is mostly relevant to the VWF system proper, i.e., the levels of coding that have been tuned to the detection of familiar letters and groups of letters. The model starts with the hypothesis that word recognition obeys the same principles that govern the organization of the primate ventral visual system. Neurophysiological observations in the macaque monkey have led to construe it as a hierarchy of converging neural detectors with progressively larger receptor fields, tuned to increasingly complex objects (Booth and Rolls, 1998; Rolls, 2000). The LCD model thus proposes that words are encoded through a posterior to anterior hierarchy of neurons tuned to increasingly larger and more complex
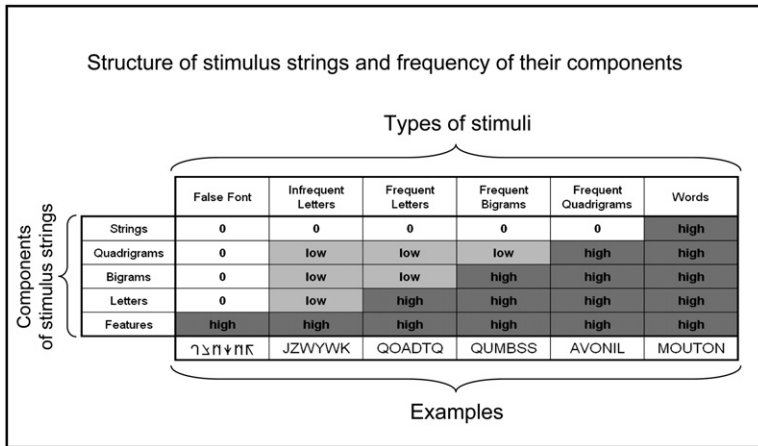
Figure 1. Design and Examples of the Scale of Stimuli with an Increasing Structural Similarity to Real Words

(i) False-font strings made up of the same visual features as real letters; (ii) strings of infrequent letters forming rare bigrams; (iii) strings of frequent letters forming rare bigrams; (iv) strings of frequent letters forming frequent bigrams but rare quadrigrams; (v) strings of frequent letters forming frequent bigrams and frequent quadrigrams; (vi) real words. Cell color represents the frequency of the string components (features, letters, bigrams, quadrigrams, whole strings). Dark gray cells correspond to high-frequency components, light gray cells to low-frequency components, white cells to null-frequency components. Assuming that the visual cortex hosts detectors for high-frequency components, any given stimulus level is expected to activate the same detectors as the preceding one, plus additional detectors tuned to components of the next level.

word fragments, such as visual features, single letters, bigrams, quadrigrams, and possibly whole words. At each of these levels, the model supposes that, as a result of exposure to print and of adaptative learning processes, neural detectors have become dedicated to the recognition of frequent fragments that are useful to encode existing words. Thus, at each level, more neurons should respond to frequent fragments of words (e.g., the letter bigrams "WH" or "QU" in English) than to fragments that have been encountered with low frequency (e.g., the bigrams "QH" or "WU"). Finally, the LCD model supposes that this hierarchy also solves the spatial invariance problem because neurons that are sensitive to higher level of this hierarchy also have broader receptive fields and invariance for size, until at the highest level, neurons become capable of responding with spatial invariance across most if not all the visual field.

From an anatomical point of view, the LCD model speculates that most of these neurons are located within the VWFA, with a posterior to anterior gradient. The peak of this region lies at about Talairach coordinates −42 −57 −12, but it extends in the anteroposterior direction across at least 2 cm. According to the LCD model, this large anterior-to-posterior extension reflects the heterogeneous and hierarchically organized processes which together form the visual word-form system. Here, we used fMRI to test specifically whether a hierachy of detectors of increasingly larger word fragments is present in the left occipitotemporal cortex. To evaluate this prediction, we scanned adult readers with fMRI while they were exposed to six types of stimuli with an increasing structural similarity to real words: (1) false-font strings; (2) strings of infrequent letters forming rare bigrams; (3) strings of frequent letters forming rare bigrams; (4) strings of frequent letters forming frequent bigrams but rare quadrigrams; (5) strings of frequent letters forming frequent bigrams and frequent quadrigrams; (6) real words (Figure 1).

This material allowed us to assess three increasingly specific predictions of the LCD model. The first prediction is that those hierarchically organized stimuli should contact an increasingly larger fraction of the neural hierarchy of detectors mentioned before, thus leading to increasing activation of the VWF system. Second, the LCD model predicts that in keeping with the general anatomical organization of the ventral stream, the neuronal hierarchy is deployed from posterior to anterior sectors of the occipitotemporal cortex. Thus, more anterior regions should be selective for closer approximations to real words. The more we move forward in the ventral stream, the larger the expected difference between high- versus low-frequency bigrams, high- versus low-frequency quadrigrams, etc. Finally, the LCD model puts forward a third and more speculative prediction: the different types of detectors might be segregated in discrete successive strips of cortex, with quadrigram detectors anterior to bigram detectors, themselves anterior to letter detectors. This would yield stepwise topographical differences between consecutive conditions. The effects of letter, bigram, and quadrigram frequency might therefore be confined to narrow and increasingly anterior strips of cortex, although our ability to see such spatial boundaries might be blurred by spatial smoothing, partial volume effects, and intersubject averaging.

In summary, we used fMRI to probe the internal structure of the VWF system, assessing the hypotheses of (1) hierarchical functional organization, (2) posterior-to-anterior gradient, and (3) discrete anatomical territories. As our aim was to study the stages of word coding during the bottom-up progression of visual information, it was essential to restrict as much as possible top-down effects which can modulate or even reverse activation patterns in the visual cortex (e.g., consonant-strings may cause more activation than real words in a one-back task [Tagamets et al., 2000]). To this end, we presented our stimuli at

a very fast rate, within short blocks, with a low-level task that only required subjects to detect an occasional string of "####." We expected this task to impose a constant strategic processing load across the different types of stimuli, therefore allowing us to reveal the differences in their cortical coding unconfounded by task-related changes.

RESULTS

Behavior
Neither accuracy (98.9% hit responses) nor response latency (mean 498 ms) was significantly affected by the type of block during which targets were presented. This was true when comparing the six main categories of stimuli and when comparing stimuli with or without vowels (all $p > 0.1$).

fMRI Results
The Word-Reading Network
In order to delineate the overall word-reading network, and particularly its occipitotemporal component, we contrasted words minus rest (voxelwise threshold $p < 0.001$; cluster size threshold $p < 0.05$ corrected, i.e., minimum cluster size 38 voxels) (Table 1). Cortical activations included bilateral occipitotemporal cortex (extending from Montreal Neurological Institute coordinates $y = -100$ to $y = -30$), anterior insula/Broca's area, intraparietal cortex, left-predominant prerolandic cortex, and the left SMA. Occipitotemporal activations followed the anterior-posterior axis of the fusiform gyri, with a mesial extension to the lingual gyri. In order not to miss meaningful activations, we studied the same contrast at a lower voxelwise threshold while keeping the same stringent threshold for cluster extent ($p < 0.01$; cluster size threshold $p < 0.05$ corrected, i.e., minimum cluster size 159 voxels). This analysis showed the same regions, although somewhat larger, plus an additional cluster in the left superior temporal sulcus (Table 1 and Figure 2).

Overall Influence of Stimulus Type
Next, we studied the overall influence of stimulus type on brain activations, again with a special focus on occipitotemporal cortex. We computed the overall F test comparing the six hierarchical conditions, averaging over the vowel/no-vowel distinction (voxelwise threshold $p < 0.01$; cluster size threshold 125 voxels). For this type of analysis, the theory of Gaussian fields as implemented in SPM2 does not provide statistics relative to cluster extent. The threshold for cluster extent was therefore selected empirically, in order for occipitotemporal activation to encompass a large extent of the word-reading network. Statistical validity was checked by using false detection rate thresholding ($p < 0.05$), which showed the same network as the initial method (see Figure S1 in the Supplemental Data available with this article online). This test showed a bilateral network mostly overlapping with the word-reading network (Figure 2). Ventral activations were anterior to about $y = -80$, indicating that the poste-

Table 1. Main Activation Peaks of the Word-Reading Network as Identified by Contrasting Real Words Minus Rest

Side	Region	Z Score	Coordinates
Left	Occipitotemporal	5.52	−28 −90 −10
	Intraparietal	4.92	−28 −80 28
	Insula/Broca's area	4.85	−26 28 −2
	Prerolandic	4.16	−46 6 32
	SMA	4.90	−6 2 56
	Superior temporal sulcus	3.11	−64 −34 2
Right	Occipitotemporal	5.41	44 −74 −12
	Intraparietal	4.21	32 −70 28
	Insula/Broca's area	3.98	28 28 −2
	Prerolandic	3.56	46 4 34

rior occipital cortex was activated by words but did not significantly discriminate the various types of stimuli. Moreover, ventral activations tended to be slightly more mesial and with a lesser anterior extension in the right than in the left hemisphere. Outside of the visual system, we noted (1) that frontal activations were strongly left predominant, indicative of a specialization for language processing, and (2) that the parietal regions activated by words did not discriminate the different types of stimuli.

Presence of Vowels
For three levels of the scale of stimuli (infrequent letters, frequent letters, frequent bigrams), half the stimuli comprised vowels while the other half did not. To determine whether this parameter had any influence on activations, we computed the contrast of stimuli with vowels minus the stimuli with no vowels, restricted to the three relevant levels. This showed no significant effect at the usual thresholds ($p < 0.001$ or $p < 0.01$, cluster size threshold $p < 0.05$ corrected). Therefore, in the following analyses, activations were pooled across the vowel/no-vowel distinction.

Hierarchical Functional Organization of the Occipitotemporal Cortex
Our first prediction was that the average activation profiles over the left occipitotemporal cortex should show a monotonous increase with the level of approximation to real words. This profile was studied for the left occipitotemporal cluster, as identified before with the F test assessing the overall effect of stimulus type (Figure 2). We computed the average activation relative to rest for each type of stimulus and each subject within this cluster and entered those values in an ANOVA. Activations differed across conditions ($F(5,55) = 22.4$; $p < 10^{-11}$), with an ordering which followed exactly the scale of proximity to real words, except that false fonts induced activations comparable to the letters condition. All five conditions involving real-letter strings differed strongly ($F(4,44) = 26.3$; $p < 10^{-10}$), and pairwise comparisons between successive real-letters
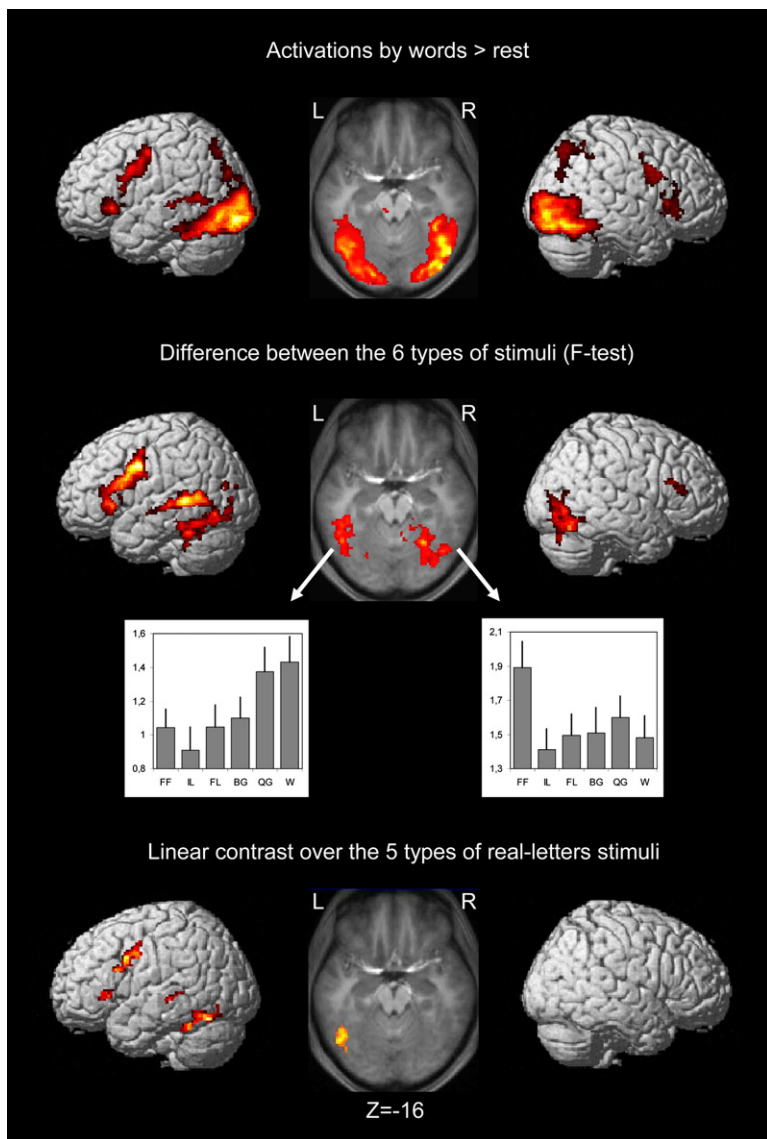
Figure 2. Activations Induced in the Left and Right Occipitotemporal Cortex and in the Whole Brain by Real Words and by Letter Strings with an Increasing Similarity to Real Words

Top row: Brain activations induced by real words minus rest (voxelwise p < 0.01, cluster-wise p < 0.05 corrected), including roughly symmetrical activations of the ventral occipitotemporal cortex. Middle row: Brain regions showing a significant effect of stimulus type (F test, voxelwise p < 0.01, cluster size ≥ 125 voxels), mostly a subset of the word-reading network, including the anterior segment of the ventral occipitotemporal cortex. Histograms show the average activation relative to rest for the six types of stimuli in the left and right ventral regions. Left-sided activations follow the scale of proximity to real words, while right-sided activations are larger for false fonts than for real-letters stimuli, which do not differ among them. Error bars represent 1 SEM across subjects after subtraction of each subject's individual mean. Bottom row: Linear contrast defined over the five types of real-letters stimuli, detecting regions whose activation increased with the proximity of stimuli to real words. The visual word forma area showed such a functional profile, while there was no activation in the symmetrical right-hemispheric region.

conditions showed a significant difference between infrequent letters and frequent letters (F(1,11) = 31.1; p < 10^{-3}) and between frequent bigrams and frequent quadrigrams (F(1,11) = 10.3; p < 0.01).

We performed the same analyses with the contralateral right occipitotemporal cluster (Figure 2). Experimental conditions differed (F(5,55) = 13.4; p < 10^{-7}), although with a profile quite different from the left hemisphere (condition × side interaction, F(5,55) = 40.9; p < 10^{-15}). False fonts induced larger activations than all real-letter conditions, which did not differ (p > 0.05). This pattern was roughly opposite to the left-hemispheric one, thus resulting in a significant difference between hemispheres (false/real letters × side interaction F(1,11) = 56.5; p < 10^{-4}).

As a more specific test of our first hypothesis (hierarchical functional organization), we computed a linear contrast modeling the proximity to real words, excluding the false font condition. As expected, this contrast was significant in the left hemisphere (t(11) = 8.2; p < 10^{-5}), nonsignificant in the right hemisphere (t(11) = 1.7; p = 0.11), and there was a strong interaction between the linear contrast and hemisphere (t(11) = 6.7; p < 10^{-4}). In order to identify formally the regions responsible for this overall pattern, we defined the same linear contrast with SPM2, looking for voxels whose activation increased with the proximity of stimuli to real words (voxelwise threshold p < 0.001, cluster size threshold p < 0.05 corrected). As shown in Figure 2 (bottom line), activations were now strictly left unilateral, only the left visual word-form region showing this functional profile (MNI coordinates −40 −48 −22, z = 5.18). Left frontal regions (prerolandic and Broca's area), the left superior temporal sulcus and the SMA were also significant in this contrast (see Table S2).

In summary, while both the left and the right occipitotemporal regions were activated by alphabetic stimuli, there was a clear-cut functional asymmetry, only the
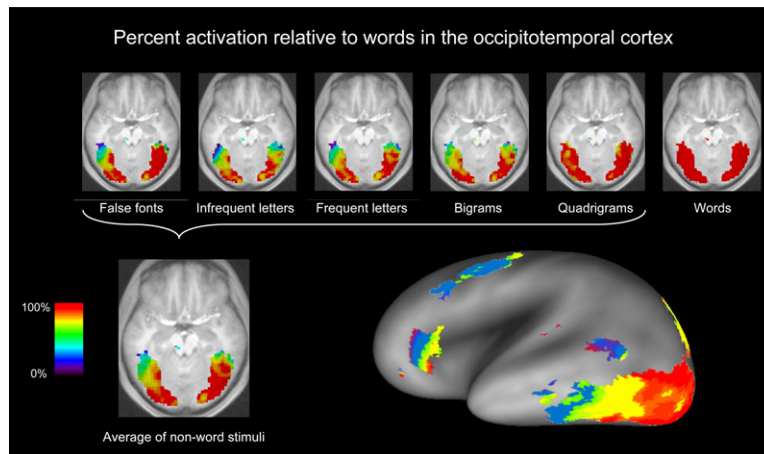
Figure 3. Gradient Images Illustrating the Spatial Layout of Sensitivity of the Occipitotemporal Cortex to Stimulus Manipulation

Top row: Percent activation by the six types of stimuli relative to real words in the ventral occipitotemporal cortex. More anterior sectors are activated by increasingly closer approximations to real words. Bottom left: The gradient image averaged over nonword stimuli shows a drop of signal in more anterior ventral regions, indexing an increasing sensitivity to stimulus structure, most clearly visible in the left hemisphere. Bottom right: Inferolateral view of the same averaged gradient image, overlaid on an inflated left hemisphere. In addition to the ventral gradient, a smaller gradient is also visible in Broca's area.

left-hemispheric VWFA following the scale of proximity of stimuli to real words.

Internal Organization of the Ventral Occipitotemporal Cortex

In order to assess our second prediction of a spatial gradient with increasing selectivity for higher-level stimuli in more anterior regions, we then studied the spatial distribution of voxels with different profiles of sensitivity to stimulus type.

Gradient Images

To normalize for differences in overall activation level in different regions within the word-reading network, we divided the contrast image of each type of stimulus relative to rest by the contrast image of real words relative to rest. Those ratio images were masked by the word-reading network defined before at a voxelwise threshold p < 0.01 (Figure 3). We observed that (1) for all categories of stimuli except frequent quadrigrams, activations appear to decrease progressively as one moves toward more anterior sectors of ventral cortex; (2) this decrease is faster for stimuli more remote from real words, such as false fonts or infrequent letters, than for the higher-level frequent-bigram stimuli, while there is little visible difference between frequent quadrigrams and real words.

In order to have a synthetic view of the sensitivity of the ventral cortex to stimulus manipulation, we applied the same normalization and masking procedure to the average of the contrast images for all types of stimuli except words (Figure 3). The resulting ratio image indexes the extent to which the nonword conditions caused activation comparable to the word condition. Regions activated by nonword categories as much as by real words are characterized by a ratio of 1, while regions activated to a lesser degree by some nonword categories than by words show lower ratios. At the extreme, a region responsive only to words should exhibit a ratio of 0. This summary ratio image showed a large-scale gradient running through the entire posterior-to-anterior extent of the ventral occipitotemporal cortex, with a smooth decrease in activation in more anterior regions, indicating a progressively increasing sensitivity to stimulus structure.

In principle, this decrease of ratio images along the ventral cortex could be due to an increase in the absolute activations induced by real words, rather than to a progressive loss of responsivity to stimuli that differ from words. We verified that such was not the case by showing that absolute activations induced by words relative to rest actually decreased from posterior to anterior regions of the ventral cortex.

Finally, there was a hint of interhemispheric asymmetry in the gradient images, with a more clear-cut drop of relative activations in the left than in right hemisphere when moving forward in the occipitotemporal cortex (Figure 3).

Analyses of ROIs

In order to submit this informal observation of a gradient to a formal statistical test, we defined six nonoverlapping spherical regions of interest (ROIs) (4 mm radius, 33 voxels) sampling the left occipitotemporal cortex. ROIs were located along the main axis of the fusiform word-activation cluster, at fixed locations across subjects (Figure 4; very similar results were obtained when the x and z coordinates were allowed to vary across subjects to match individual activations, see Figure S3). We chose anteroposterior coordinates ranging from y = −96 to y = −40. Three ROIs were centered at the y coordinates proposed by the LCD model as representative of successive stages of word encoding, putatively corresponding respectively to letter, bigram, and quadrigram coding (y = −64, −56, and −48) (Dehaene et al., 2005). Along the x and z coordinates, each ROI was centered on the maximum voxel of the overall F test comparing the six hierarchical conditions. Six further ROIs were defined in the right ventral stream following the same method. We also placed two ROIs on the bilateral lingual peaks of the overall F test. For each subject, the average activation relative to rest was computed within each ROI for each type of stimulus and divided by the activation for words minus rest. Those values were entered in ANOVAs using ROIs, stimulus type, and side as within-subject factors and subjects as random factor.
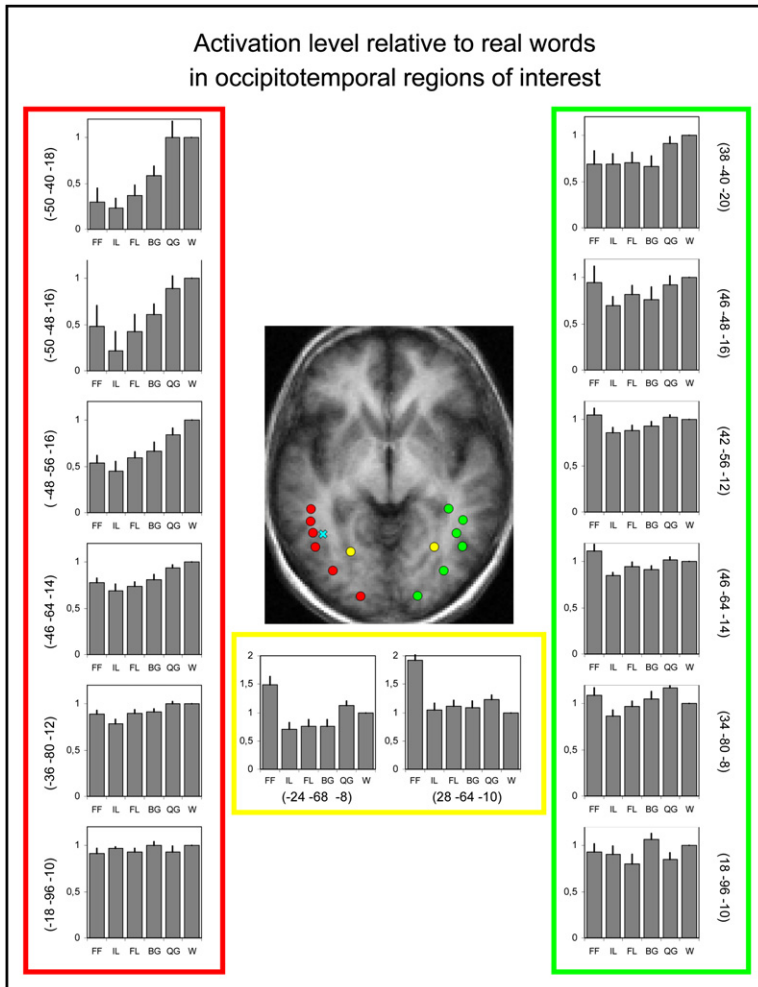
Figure 4. Percent Activation Relative to Real Words in Regions of Interest Sampling the Ventral Occipitotemporal Cortex

In the left fusiform region (red), activations followed strictly the scale of stimulus proximity to real words, and the amplitude of this effect increased steadily when moving to more anterior regions. The right fusiform region (green) did not show the same pattern of specialization. The bilateral lingual cortex (yellow) showed larger activations for false-fonts than for real-letters stimuli, which did not differ. The blue cross indicates the peak of the visual word-form area as identified by Cohen et al. (2002) at coordinates −42 −57 −15. Error bars represent 1 SEM across subjects.

Left Fusiform ROIs. An ANOVA on left fusiform ROIs revealed two main features, apparent on inspection of the histograms (Figure 4). First, there was a strong overall effect of stimulus type $(F(5,55) = 21.3; p < 10^{-11})$, which was present in all ROIs (all $p < 10^{-3}$) except in the most posterior occipital ROI $(p = 0.42)$. Like in a previous analysis, false fonts yielded activations comparable to infrequent-letters or frequent-letters stimuli, i.e., somewhat stronger than expected. Putting false fonts aside, in all ROIs except for the most posterior one, activations followed strictly the scale of stimulus proximity to real words. Second, the amplitude of this effect increased steadily when moving to more anterior ROIs, as reflected in a strong interaction of ROI and stimulus type $(F(25,275) = 4.78; p < 10^{-10})$.

In order to assess more specifically our hypotheses, we computed statistical contrasts, excluding the false font condition. To test the first hypothesis (hierarchical functional organization), we computed a "functional" linear contrast, modeling the proximity to real words. This contrast was significant when averaging over ROIs $(t(11) = 7.27, p < 10^{-4})$, confirming the overall correlation of left fusiform activation with the degree of word approximation,

as shown before in the analysis of average ventral activations. In order to test the second hypothesis (posterior to anterior increase in selectivity), we computed an "anatomical" linear contrast testing for a linear decrease of activation to nonword stimuli relative to words, when moving from posterior to anterior ROIs $(t(11) = 3.46; p = 0.0053)$. Most importantly, the interaction of the "functional" and the "anatomical" contrasts was significant $(t(11) = 6.5; p < 10^{-4})$. This interaction is the crucial test for our second hypothesis, as it selectively tests for a posterior-to-anterior increase in functional selectivity to the ordered hierarchy of stimuli as they become increasingly closer to real words. Indeed, as visible on the histograms (Figure 4), the posterior-to-anterior activation decrease was smaller for stimuli closer to words, with a significant decrease for all stimuli (all $p < 0.01$) except for frequent quadrigrams $(p = 0.96)$.

Finally, we tested the third prediction, according to which the effect of letter, bigram, and quadrigram frequency might appear at discrete levels along the ventral pathway, rather than affect activations in a continuous manner. In order to assess this hypothesis, we tested

polynomial contrasts modeling deviations from a purely linear profile when moving forward in the ventral cortex. If there were a sharp anatomical boundary with successive regions containing only letter, bigram, or quadrigram-sensitive neurons, one would expect that the response to a given stimulus condition (e.g., high-frequency letters with low-frequency bigrams), as one moves anteriorily, would show a sudden sharp drop in activation (in this instance, at the spatial location where bigrams are coded). Thus, one would predict a nonlinear profile of activation across ROIs, with the sudden drop creating a significant quadratic or cubic contrast as a function of spatial location. Symmetrically, at a given location, one would expect activation as a function of the six hierarchical stimulation conditions to exhibit a nonlinear profile, because stimuli below the hierarchical level coded at this location should fail to activate it. However, quadratic and third-degree contrasts testing for such nonlinear effects were not significant, either globally, separately for each type of stimuli, or separately for each location (all $p > 0.05$). As visible in Figure 3, the evolution of activation as a function of space or conditions was always smooth and essentially linear. These results thus provide no support for discrete boundaries and are compatible with a progressive increase in selectivity to increasingly word-like stimuli.

Right Fusiform ROIs. In the right fusiform, there was a main effect of stimulus type ($F(5,55) = 5.59$; $p < 10^{-3}$), with an interaction with ROI (interaction ROI × stimulus type, $F(25,275) = 2.23$; $p < 10^{-3}$). However, the effect of stimulus type was smaller in the right than in the left hemisphere (interaction of side × stimulus type, $F(5,55) = 8.65$; $p < 10^{-5}$). Most importantly, and contrary to the left hemisphere, the order of activation amplitude did not obey the scale of proximity to real words in any of the right fusiform ROIs.

The "functional" linear contrast comparing types of stimuli was significant overall ($t(11) = 4.9$, $p < 10^{-3}$), although it was smaller than in the left fusiform (side × stimulus type interaction, $t(11) = 4.2$, $p = 0.0014$). The "anatomical" contrast was nonsignificant ($p = 0.11$), showing that there was no overall decrease in activation along the right fusiform, at variance with the left-hemispheric pattern (interaction side × ROI, $t(11) = 2.4$, $p < 0.05$). There was no significant interaction of the "functional" and "anatomical" linear contrasts ($p = 0.15$), contrary to what prevailed in the left hemisphere (side × stimulus type × ROI $t(11) = 6.97$; $p < 10^{-4}$).

Because hemispheric asymmetries in ventral occipito-temporal cortex were of special interest, we systematically tested, region by region, whether the functional profile of selectivity, as tested by the linear contrast across the five categories of letter strings, differed between the two hemispheres. No significant difference was found in the two most posterior regions (respectively $p = 0.4$ and 0.6), which indeed showed little functional selectivity in either hemisphere. The asymmetry was significant in all more anterior regions (resp. $p = 0.009$, $p = 0.0012$, $p = 0.011$, and $p < 10^{-4}$), thus starting at around $y = -64$ in MNI coordinates.

Lingual ROIs. The lingual ROIs showed a pattern of activation in both hemispheres, which was quite distinct from those observed along the fusiform cluster. The effect of stimulus type ($F(5,55) = 13.3$; $p < 10^{-7}$), which did not interact with side, resulted from a much stronger activation to false fonts than to all other stimulus types (all $p < 0.0015$), which did not differ ($p > 0.05$).

Activations in Other Language-Related Regions

Since we collected fMRI data from the entire cortex, our study afforded an opportunity to also examine if other brain regions were selectively or hierarchically responsive to word-like stimuli (Figure 5). Inspection of the overall activation ratio images revealed, within Broca's area and its right-hemispheric equivalent, a gradient pattern reminiscent of the fusiform pattern (Figure 6): in the left hemisphere, the most mesial sector of Broca's area did not show a difference between conditions, while activations were increasingly selective when moving laterally. The right-hemispheric cluster did not exhibit the same orderly pattern. To submit this observation to statistical analysis, we sampled Broca's area along a transversal axis. A ROI was centered at the maximum of the overall F-test comparing stimulus types (-46 22 0), and two other ROIs were placed manually so as to sample optimally the gradient pattern within the small Broca cluster. Three ROIs were placed symmetrically in the right hemisphere. Additional ROIs were placed at the main left parietal peak of the word-reading network, as well as at selected peaks of the overall F-test reported before: superior temporal sulcus (STS), supplementary motor area (SMA), prerolandic cortex.

ROIs in Broca's Area

In the left hemisphere, the effect of stimulus type differed across ROIs (interaction $F(10,110) = 2.0$; $p < 0.05$). The mesial ROI was activated by all types of stimuli (all $p < 0.03$), which did not differ ($p > 0.1$). In contrast, the effect of stimulus type was highly significant in the lateral and intermediate ROIs (both $p < 10^{-4}$), which were activated by frequent-quadrigrams (both $p < 0.003$) and, for the intermediate ROI only, by frequent-bigrams stimuli ($p < 0.01$). In the right hemisphere, there was no interaction and no main effect of stimulus type or ROI. Indeed, side interacted significantly with the factors ROI, stimulus type, and their interaction (all $p < 0.03$).

Other Areas

As visible on Figure 5, stimulus manipulation induced various activation profiles in nonvisual regions of the left-hemispheric convexity (interaction stimulus type × ROI, $F(20, 220) = 2.8$; $p = 10^{-4}$). Intraparietal activations were significant relative to rest for all types of stimuli (all $p < 10^{-4}$), although not quite to the same degree (stimulus type, $p < 0.01$). In contrast, the STS, like the lateral part of Broca's area, was activated exclusively by frequent quadrigrams ($p < 10^{-5}$) and words. Finally, the prerolandic region and the SMA, which also did not differ (interaction $p = 0.2$), showed a roughly continuous increase across conditions (stimulus type, $p < 10^{-5}$).
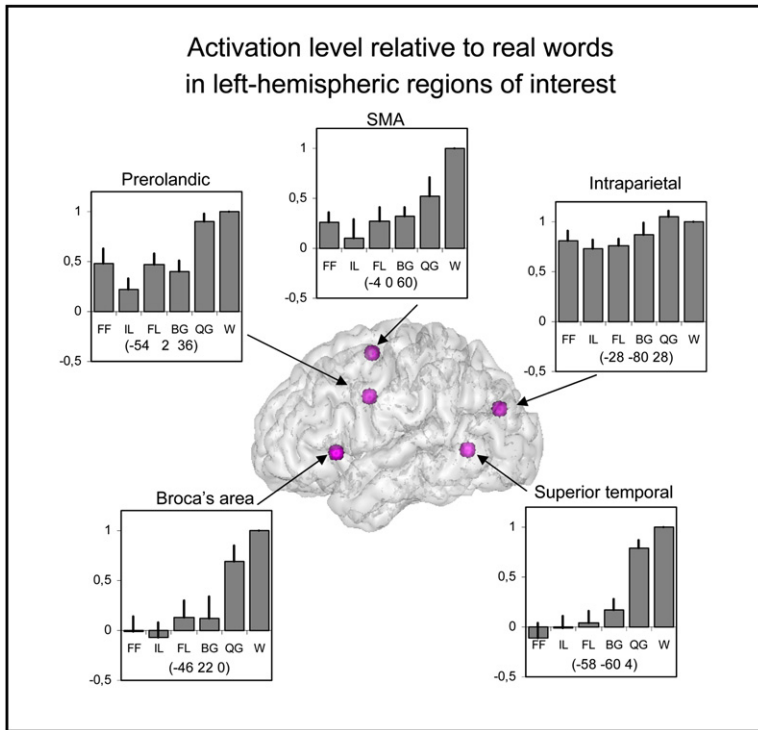
Figure 5. Various Activation Profiles in Nonvisual Regions of the Left Hemisphere (Percent Activation Relative to Real Words)

Intraparietal cortex was activated by all types of stimuli. Broca's area and the STS were activated only by readable pseudowords and words. The prerolandic and SMA cortex showed a more continuous increase across conditions. Error bars represent 1 SEM across subjects.

DISCUSSION

Our aim was to test three core predictions of the LCD model on the internal structure of the system for visual word perception. We will first discuss those predictions, concentrating on the left-hemispheric ventral visual cortex. Next, we will discuss the differences between left- and right-hemispheric activation patterns and how they clarify the nature of hemispheric specialization for reading.
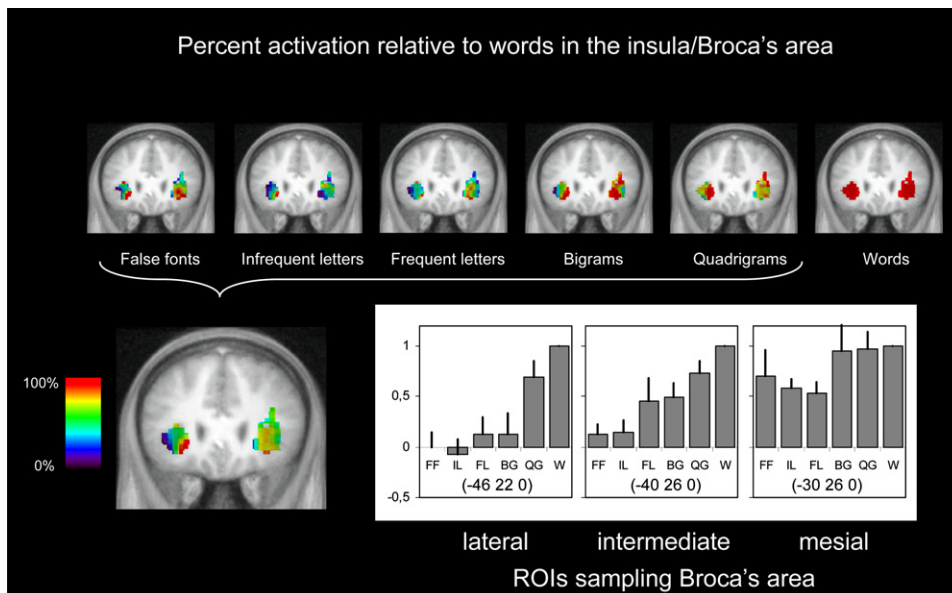

Figure 6. Gradient Images Illustrating the Sensitivity of Broca's Area to Stimulus Manipulation

Mesial-to-lateral gradient of increasing sensitivity to stimulus structure in the left inferior frontal region (Broca's area; same conventions as in Figure 3). Histograms show the activation profile in three ROIs sampling Broca's area. The contralateral right-hemispheric region did not show the same internal organization. Error bars represent 1 SEM across subjects.

Tuning to Orthographic Regularity

Our results replicated and extended previous work showing that the left occipitotemporal region, at the site of the postulated visual word-form area (VWFA), preferentially responds to words or orthographically regular pseudowords than to orthographically illegal stimuli (infrequent letters, frequent letters, and frequent bigrams; Ben-Shachar et al., 2007; Cohen et al., 2002; Pammer et al., 2004; Price et al., 1996). In our experiment, stimuli in all conditions were strings of equal length and therefore quite similar from a purely visual point of view. Hence, the fact that they induced variable activations as a function of their similarity to real words implies that the VWFA has become attuned to orthographic regularities of the reader's language in the course of learning to read.

We observed that the frequent-quadrigrams stimuli, which consisted mostly in readable pseudowords conforming to French orthographic rules, did not differ significantly from real words. This result is consistent with previous observations of an absence of differences between words and pseudowords in this area (Dehaene et al., 2002; Wydell et al., 2003) or even of a greater activation to pseudowords than words (Fiez et al., 1999; Xu et al., 2001). It is compatible with the conclusion that the orthographic regularity of letter strings, rather than their lexical status, is the relevant variable for this region (Binder et al., 2006; Cohen et al., 2002; Dehaene et al., 2005).

In apparent contradiction with the present results, some previous studies have observed stronger activations to consonant strings than to words (e.g., Cohen et al. [2003], Tagamets et al. [2000]). However, such occasional reversals only occurred when the experimental tasks were more difficult to perform with consonant strings than with words, such as for instance working memory manipulations (Tagamets et al., 2000). In the present study, we used a low-level task which did not depend on the identity of the stimuli (detection of an occasional string of ######). This aspect of our design, combined with a fast presentation rate (one stimulus every 300 ms) was intended to emphasize bottom-up processing and thus provided a more direct image of the visual coding properties of the VWFA.

Hierarchical Functional Organization

We presented participants with a hierarchy of stimuli, designed according to our recent proposal that a neural hierarchy of letter, bigram, and quadrigram detectors underlies invariant word recognition in the VWFA (Dehaene et al., 2005; Grainger and Whitney, 2004; Whitney, 2001). In agreement with the hypothesis that stimuli higher on this scale recruit additional neurons, we found that activations pooled over the whole VWF system increased for stimuli forming closer statistical approximations to real words. Part of our results overlap with those of a recent study by Binder et al. (2006), who collected fMRI data while subjects were presented with letter strings at four levels of positional bigram frequency, ranging from very low to high. Binder et al. (2006) observed that activation in-

creased monotonically with bigram frequency in the left occipitotemporal region (but not the right), at the usual main peak of the VWFA (coordinates −43 −57 −12). Binder et al.'s (2006) study is complementary to ours in several ways. They manipulated bigram frequency as a continuous variable, whereas we only tested a contrast of low- versus high-frequency bigrams. They also took into account the position at which bigrams are encountered in a word. However, our study distinguished the frequency of various subcomponents (letters, bigrams, quadrigrams) postulated to intervene at different stages of invariant word recognition, whereas these parameters were highly correlated in Binder et al.'s (2006) study. Our results demonstrate effects of letter and quadrigram frequency above and beyond those of bigram frequency, suggesting that all of these levels (Dehaene et al., 2005), not just bigrams (Grainger and Whitney, 2004; Whitney, 2001), may be useful subcomponents of visual word recognition. Binder et al.'s (2006) study also did not reveal any topographical subspecialization within the VWF system, contrary to the present one.

One aspect of our results was not strictly compatible with our postulated hierarchical organization. We expected that false fonts would induce weaker activations than actual strings of letters. Actually, false fonts yielded an activation level comparable to infrequent-letters and frequent-letters stimuli, i.e., the real-letters stimuli most remote from real words. This slight deviation from our expectations should not be overemphasized, however, because the physical matching of false fonts with other stimuli is necessarily less perfect than between all other conditions, which are based on the set of real letters. Moreover, although not explicitly involved in the experimental task, the false-font stimuli might induce stronger attentional engagement than perceptually highly familiar real letters. It is also possible that subjects had to pay more attention in the false font blocks in order to reach the same level of behavioral performance in detecting the ###### target in the false-font and letter string conditions. Thus Starrfelt and Gerlach (2007) showed that a difficult visual task with object pictures can yield larger activations of the VWFA than word reading. As a further instance of attentional modulation in the ventral cortex during reading, Nobre et al. (1998) showed that paying attention to one of two interleaved word streams results in an amplification of ventral temporal potentials evoked by the attended words.

Finally, we note that the false-font condition yielded intense activation of the neighboring lingual gyrus. Partial spillover of this activation into the more lateral fusiform gyrus, due to partial volume effects and/or smoothing, may thus have contributed to the slightly elevated fusiform activation in the false-font condition. The reason for the intense lingual activation by false fonts is unknown. According to Lerner et al. (2001), this region is not sensitive to image scrambling, suggesting a local coding of visual information. One may speculate that such a local code may be the preferentially attended level of coding for

unfamiliar shapes that cannot be easily recoded at a higher level.

Posterior-to-Anterior Gradient

Dissecting the ventral pathway into a series of ROIs allowed us to assess the second prediction derived from the LCD model, namely, that the more anterior an area is within the visual word form region, the more selective it is to letters strings comprising complex and frequent components, i.e., stimuli higher in our stimulus scale. This hypothesis was clearly supported by our observations. The most posterior fusiform ROI ($y = -96$) was activated equally by all types of stimuli. The next more-anterior ROI ($y = -80$) showed the first indication of a hierarchical preference for stimuli according to their proximity to real words. This functional hierarchy then increased steadily to the most anterior ROI ($y = -40$). Equivalently, for a fixed-stimulation condition, there was a posterior-to-anterior activation decrease significant for all stimuli except for frequent quadrigrams, and this decrease was smaller for stimuli closer to words.

Our results are the first to reveal a gradient-like spatial organization *within* the VWFA, which was up to now largely considered as a homogeneous region. Only one previous study (Dehaene et al., 2004), using a subliminal priming design, showed that the type of prime-target similarity which causes fMRI priming varies according to the anterior-posterior location in left occipitotemporal cortex. In the most posterior region ($y = -64$), priming depended on the repetition of the same letters at the same location (consistent with a dominance of location-specific but case-independent letter detectors). At an intermediate location ($y = -56$), priming resisted to a shift of one letter location, suggesting increased spatial invariance. Finally, at a more anterior location ($y = -48$), priming became dependent on the similarity of the entire prime and target strings (and thus reduced for anagram pairs such as range/anger), suggesting greater reliance on larger size, order-dependent units such as bigrams or quadrigrams.

The present data are in good agreement with findings from MEG studies. MEG activations in bilateral occipital cortex do not distinguish words and strings of geometrical symbols, while a more anterior left-lateralized region overlapping with the VWFA shows higher amplitudes for real-letter stimuli than for symbols (Tarkiainen et al., 1999, 2002). As for the contrast between words and pseudowords, it does not show significant effects in the ventral visual cortex (Wydell et al., 2003). This pattern is congruent with the present results: In posterior ROIs, we found no difference between words and false-font stimuli, while a large advantage for words appeared in more anterior left-hemispheric ROIs, with no significant difference between real words and pseudowords (i.e., strings with frequent quadrigrams; Figure 4). In a recent fMRI study, James et al. (2005) found larger activations for pseudowords than for consonant strings at coordinates TC -46 -54 -7, while the two types of stimuli did not differ at the more posterior coordinates TC -31 -64 -5. This in-

creasing difference between legible pseudowords and consonant strings when moving forward in the ventral cortex, with a significant difference around TC $y = -56$, is also in agreement with the present data.

Our most anterior ROI (TC -48 -40 -16) was within millimeters of the average location of activation peaks gathered in a recent meta-analysis of reading activations, and mostly related to contrasts between words and lower-level stimuli (Jobard et al., 2003). Anterior to this point, the left temporal lobe shows supramodal rather than visual activations (reviewed in Cohen et al. [2002]), with modulations by semantic parameters which we did not manipulate here (reviewed in Giraud and Price [2001]). The functional dissociation between the two ends of the fusiform cortex was clearly illustrated by intracerebral recordings (McCarthy et al., 1995; Nobre et al., 1994; Nobre and McCarthy, 1995). In posterior fusiform regions, ERPs elicited by strings of letters do not differ among content words, function words, pseudowords, or illegible nonwords. In contrast, electrodes in the antero-mesial sector of the ventral temporal cortex are sensitive to lexicosemantic effects, such as the distinction between nouns and function words, semantic priming, or semantic congruity of sentence termination. Note that the difference between pseudowords and consonant strings observed in the VWFA vanishes in anterior regions achieving lexicosemantic coding, which may not be sensitive to structural differences between varieties of nonlexical strings (TC -42 -37 -3; James et al., 2005).

Our finding of a large-scale gradient is consistent with studies of visual responses outside the reading domain, both in humans and in nonhuman primates. Neurophysiological studies point to a progression in receptive field size, spatial invariance, and preferred feature complexity of inferotemporal neurons as one moves anteriorily in the primate IT cortex (for review see Rolls [2000], Sawamura et al. [2005]). Human fMRI studies indicate that more anterior areas of ventral occipitotemporal cortex are increasingly sensitive to scrambling of the image into a variable number of blocks, suggesting that they care about increasingly large fragments of objects and faces (Grill-Spector et al., 1998; Lerner et al., 2001). Our experiment can be considered as an analog of these object-scrambling manipulations in the reading domain, since our frequent-letter, frequent-bigram, and frequent-quadrigram stimuli consist in scrambled and reassembled word fragments of varying size. This parallel between words and images supports our proposal that the cerebral architecture for reading relies on coding principles similar to those involved in object and face recognition and only partially "recycled" during reading acquisition to become tuned to a specific alphabet and orthography (Dehaene et al., 2005).

We note that other spatial gradients have been identified in human ventral temporal cortex, including (1) a posterior-anterior gradient of progressively reduced sensitivity to presentation rate (Mukamel et al., 2004) and (2) an orthogonal, lateral-to-mesial gradient of preference for

foveal versus lateral presentation (Hasson et al., 2002). Together, these intersecting gradients may constrain the development of categorical preferences in occipitotemporal cortex and thus begin to provide an explanation for their remarkable reproducibility across subjects.

Continuous Gradient Rather Than Discrete Anatomical Territories

The LCD model led to a third prediction, that the successive types of neural detectors for letters, bigrams, etc. might be segregated in discrete strips of cortex, arranged in a posterior-to-anterior manner. Our results, however, provided no support for such a discrete organization with sharp boundaries in occipitotemporal cortex. Instead, we found a continuous posterior-to-anterior progression of slowly increasing selectivity to higher levels of the stimulus hierarchy. There are several possible interpretations of this finding, whose separation will require further research. First, the proposed LCD architecture remains speculative, and although the present results are compatible with it, they cannot be considered as providing an unambiguous demonstration. It remains possible that, with our manipulations of letter, bigram, and quadrigram frequency, we incidentally hit upon an orthographic manipulation of similarity to real words which is the real determinant of VWFA activation. The existence of bigram-detecting neurons should therefore be submitted to further tests, either by direct intracranial recordings (Gaillard et al., 2006) or by the fMRI priming method, which was previously used to suggest the existence of location-specific but case-independent letter detectors (Dehaene et al., 2004).

Alternatively, even if the hierarchical LCD architecture was approximately correct, the postulated neural detectors might be mixed within the same voxel, with only the proportion of letter, bigram, and quadrigram detectors changing progressively from posterior to anterior. This may seem plausible given that, in the monkey inferotemporal cortex, single-cell electrophysiology has failed, until now, to reveal a strict segregation of part-face versus whole-face neurons or of view-selective versus view-independent neurons (Tanaka, 1996). Even if such an organization exists, it could have been blurred by low fMRI resolution, smoothing, and intersubject averaging. Single-subject high-resolution fMRI of ventral cortex, which now potentially opens the possibility of detecting a mosaic structure of intermingled categorical preference in ventral temporal cortex will be useful to address this issue (see Grill-Spector et al. [2006] and the ensuing comments and erratum).

Hemispheric Specialization

We observed a clear-cut asymmetry in the functional properties of the ventral occipitotemporal cortex. While the left hemisphere showed an orderly preference for stimuli as a function of their similarity to real words, only a small similar trend was observed in the most anterior right temporal ROI. In other, more posterior ROIs, the right

ventral cortex did not discriminate between the different types of real-letters stimuli, thus creating a highly significant stimulus × hemisphere interaction. This asymmetry is clearly captured by Figure 2, bottom line. Another asymmetry in our data is that the activation by false fonts tended to be larger than by words in the right ventral cortex (again with the exception of the most anterior ROI), while the converse held for the left hemisphere.

These asymmetries are in agreement with previous evidence that while both left and right occipitotemporal cortices are activated by alphabetic strings, this activation is stronger than for checkerboards only in the left hemisphere (Cohen et al., 2003). Binder et al. (2006) also observed a bigram frequency effect solely in the left hemisphere. While Ben-Shachar et al. (2007) did not find a significant asymmetry in the functional profile of resistance to noise of the left and right occipitotemporal cortices, they worked on images normalized for peak activation level and noted that, prior to normalization, a superior response to words than to line drawings was observed in left but not right ventral cortex.

According to our framework (Cohen et al., 2003; Dehaene et al., 2005), the earlier stages of the LCD architecture, which involve units with small receptive fields, are distributed across both hemispheres, each hemisphere representing letters displayed in the opposite hemifield. At later stages, information converges to the left hemisphere, extending spatial invariance across both hemifields. We propose that such convergence is achieved in the midfusiform, where activation common to words presented in either hemifield begins to be observed (Ben-Shachar et al., 2007; Cohen et al., 2000, 2002), in agreement with other evidence of activation by ipsilateral visual stimuli (Tootell et al., 1998). The present data accord with this interpretation, since they show a functional asymmetry only in the ROIs anterior to y = −64, with no significant functional asymmetry for letters posterior to this point.

Other Regions

Although our study was designed to study ventral cortex, it also yielded interesting data on other regions. The left posterior middle temporal region showed a strong preference for words and frequent-quadrigram stimuli and essentially no response to other strings (Figure 5). This region has been associated with lexicosemantic processing based on its sensitivity to crossnotation and synonym priming (Devlin et al., 2004; Nakamura et al., 2005). If validated, this interpretation would imply that the frequent-quadrigram stimuli received at least an attempt at semantic interpretation, consistent with their internal composition comprising many lexical roots and morphemes.

More novel was the discovery of a hierarchical anatomical gradient within the left inferior frontal region. The lateral inferior frontal responded to words and frequent quadrigrams, consistent with its postulated role in semantic selection processes (Thompson-Schill et al., 1997). Surprisingly, however, the mesial inferior frontal cortex, abutting the anterior insula, was responsive to all stimuli

including the unpronounceable false-font and infrequent-letter stimuli. This is inconsistent with the supposed role of this region in speech articulation (Hillis et al., 2004) and remains unexplained. Given the parallel between the large-scale posterior gradient seen in occipitotemporal cortex and the smaller-scale gradient seen in inferior frontal cortex, it is tempting to postulate that topographically organized connections link these two regions. Indeed, direct neuronal connections have been traced from the fusiform gyrus to Broca and Wernicke's area (Di Virgilio and Clarke, 1997), and the presence of a topographical mapping, perhaps subtended by the occipitofrontal fasciculus, could be studied with diffusion tensor imaging (Catani et al., 2003).

Conclusion

The main finding of the present article is that a gradient of increased sensitivity to larger and higher-level components of words is present within the visual word-form system. In agreement with the proposed LCD model, this region of cortex can no longer be considered as functionally homogeneous. This discovery opens many new questions for future research. Is this region solely sensitive to the distributional statistics of letter groupings, or do reading-relevant units such as graphemes (Goswami and Ziegler, 2006), syllables, or morphemes (Prinzmetal, 1990) also play a distinctive role? Can we use fMRI to probe the postulated bigram code more directly? Can we explicitly test the hypothesis, merely stipulated here, that the brain uses an open bigram code (pairs of letters possibly including an intermediate letter) rather than merely representing consecutive letters? Higher-resolution fMRI, possibly combined with priming techniques, should render these questions more tractable.

EXPERIMENTAL PROCEDURES

Subjects

Twelve right-handed native French speakers with normal or corrected-to-normal vision participated in this experiment (four men and eight women, mean age 24 years). All subjects gave written informed consent and were naive about the aims of the experiment.

Stimuli

Full details concerning the construction of stimuli are provided as Supplemental Data. We devised six categories of stimuli, each consisting of 320 strings of six uppercase characters, with an increasing structural similarity to real words: (1) false-font strings; (2–5) nonword letter strings; and (6) real French words. Nonwords (categories 2 to 5) were constructed by an automated program which randomly selected letter strings according to rules regarding the frequency of their components: (2) strings with infrequent letters, bigrams, and quadrigrams; (3) strings with frequent letters but infrequent bigrams and quadrigrams; (4) strings with frequent letters and bigrams but infrequent quadrigrams; (5) strings with frequent letters, bigrams, and quadrigrams. For brevity, those stimuli will be referred to as "infrequent letters," "frequent letters," "frequent bigrams," and "frequent quadrigrams," respectively. In summary, as illustrated in Figure 1, each category differed from the preceding one by having one additional level of high-frequency components. Infrequent-letters, frequent-letters, and frequent-bigrams conditions were further divided into

two equal subsets: in one subset, letter strings comprised only consonants; in the other subset, letter strings included at least a vowel. The real French words (category 6) were selected in order to be as close as possible to the strings in the frequent-quadrigrams category in the frequency of their components. Finally, false-font strings (category 1) were generated using a custom-designed pseudofont with fixed character spacing, where each uppercase letter was replaced by an unfamiliar shape with an almost equal number of strokes and angles, and an overall similar visual appearance.

Experimental Design

The experiment consisted of four fMRI runs. Each run consisted of 24 short homogeneous activation blocks, i.e., four blocks for each of the six categories of stimuli (two blocks per category whenever the vowel/no vowel distinction was relevant), in random order. Each block consisted in the fast presentation of 20 stimuli from a given category. Each stimulus was displayed for 100 ms, followed by a 200 ms fixation. The order of stimuli within blocks was quasirandomized, in order to minimize letters repetition in consecutive strings: the mean number of repeated letters was <1, and no letter was ever repeated at the same position in consecutive strings. Activation blocks were separated by rest periods of 4, 6, or 8 s (mean 6 s), during which the fixation dot remained visible. In half of the blocks of each type, a stimulus randomly selected from the sixth to the twentieth ranks was replaced by the ###### string.

Stimuli were presented in the center of the field of view, printed in light gray on a black background, subtending an average horizontal angle of 4.1 degrees. Subjects were instructed to fix the central dot at all times and to press a button with their right thumb whenever a target (i.e., the ###### string) was presented.

For the analysis of behavioral responses, the first button press between 300 ms and 1300 ms was considered as a hit. An absence of response during this period was considered as a miss. All other responses were considered as false alarms. Accuracy was compared between conditions using χ^2 tests. Response latencies to hit responses were compared using an ANOVA with subjects as random factor.

fMRI Acquisition and Analysis

We used a 3-Tesla body system (Bruker, Germany) and a gradient-echo planar imaging sequence sensitive to brain oxygen-level-dependent (BOLD) contrast (40 contiguous axial slices, 3 mm thickness; TR = 2400 ms; angle = 82°, TE = 30 ms, in-plane resolution = 3 × 3 mm, matrix = 64 × 64). In each run, 125 functional volumes were acquired. The first four volumes were discarded to reach equilibrium. T1-weighted images were also acquired for anatomical localization.

Data processing, performed with SPM2 software, included corrections for EPI distortion, slice acquisition time, and motion; normalization; Gaussian smoothing (3 mm FWHM); fitting with a linear combination of functions derived by convolving a standard hemodynamic response function with the known time series of the stimulus types. Blocks were modeled as 6 s events and targets as punctual events. This approach was valid due to the completely orthogonal distribution of targets and of types of block, with an equal probability of occurrence of a target in all types of experimental blocks. Results were assessed using a random-effect group analysis. Statistical thresholds are presented in the Results section. All corrections for multiple comparisons were performed across the whole brain using the standard procedure implemented in SPM2. Activations related to the types of experimental blocks are reported in the Results section; activations related to the sporadic target words are reported as Supplemental Data (Figure S2).

Supplemental Data

The Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/55/1/143/DC1/.

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Supplemental Data

Hierarchical Coding of Letter Strings in the Ventral

Stream: Dissecting the Inner Organization

of the Visual Word-Form System

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1. Construction of Stimuli

We devised 6 categories of stimuli, each consisting of 320 strings of 6 uppercase characters, with an increasing structural similarity to real words: (1) false font strings; (2-5) non-word letter strings; and (6) real French words.

The non-words (categories 2 to 5) were constructed by an automatized program which randomly selected letter strings according to rules regarding the frequency of their components. We first computed an index of the frequency of three types of components in the French lexicon: single letters, bigrams (i.e. ordered pairs of letters, contiguous or separated by a single letter), and quadrigrams (i.e. ordered sets of 4 contiguous letters). This frequency index was computed using the "Lexique 2" database (New et al., 2004) and discarding words with a frequency lower than 2 per million. For each component C, we first computed a weighted sum of its occurrences in French words, $\sum_{Wi \in L} o(C, W_i) \times f(W_i)$, where W_i are words in corpus L; $o(C, W_i)$ is the number of occurrences of component C in word W_i; and $f(W_i)$ is the frequency of word W_i. This value was converted to a frequency by dividing it by the sum over all components of the same type as C. For any given string of letters, components were considered as "frequent" on average if their mean log frequency was above the 55th percentile of the frequency distribution. They were considered as "infrequent" below the 45th percentile. The computer then automatically generated a large number of stimuli falling in four categories of non-words: (2) strings with infrequent letters, bigrams and quadrigrams; (3) strings with frequent letters but infrequent bigrams and quadrigrams; (4) strings with frequent letters and bigrams but infrequent quadrigrams; (5) strings with frequent letters, bigrams, quadrigrams (we verified that none of these lists contained real French words). For brevity, those stimuli will be referred to as "infrequent-letters", "frequent-letters", "frequent-bigrams", and "frequent-quadrigrams", respectively.

We verified the properties of these stimuli by computing the mean log frequency of their component letters, bigrams, and quadrigrams, and submitted them to statistical analysis (t-tests). As desired, letter frequency was significantly lower in infrequent-letters stimuli than in each of the other three categories of non-words (all p<0.001), which did not differ among them (p>0.1). Bigram frequency was significantly lower in both infrequent-letters and frequent-letters stimuli, which did not differ among them (p>0.1), than in each of the other two categories (all p<0.001), which did not differ among them either (p>0.1). Quadrigram frequency was significantly higher in frequent-quadrigram stimuli than in each of the other three categories (all p<0.001), which did not differ among them (p>0.1). In summary, as

illustrated in Figure 1, each category differed from the preceding one by having one additional level of high-frequency components.
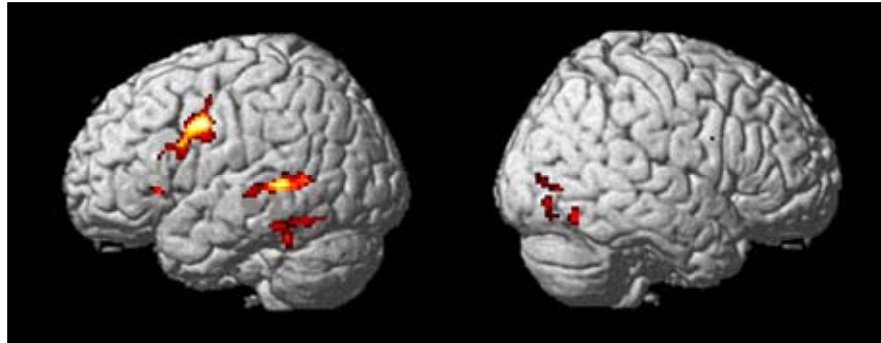
Infrequent-letters, frequent-letters, and frequent-bigrams conditions were further divided into two equal subsets: in one subset, letter strings comprised only consonants; in the other subset, letter strings included at least a vowel. Both subsets obeyed the same constraints as described before, and they did not differ in the frequency of letters, bigrams, and quadrigrams (all $p > 0.1$).

The real French words (category 6) were selected in order to be as close as possible to the strings in the frequent-quadrigrams category in the frequency of their components. In spite of those efforts, we found it unavoidable that the mean log frequencies of letters, bigrams and quadrigrams were somewhat higher in words than in frequent-quadrigrams stimuli ($p < 0.05$).

Finally, false-font strings (category 1) were generated using a custom-designed pseudo-font with fixed character spacing, where each uppercase letter was replaced by an unfamiliar shape with an almost equal number of strokes and angles and an overall similar visual appearance. False font strings were transcriptions of the strings in the infrequent-letters condition, using this novel false font.

2. Figure S1: Difference between the 6 Types of Stimuli (F-test)

Brain regions showing a significant effect of stimulus type (F-test; False Detection Rate p<0.05). The only difference with the middle row of the main article's Figure 2 is the method which was for statistical assessment. Both methods show essentially the same network.

3. Table S1: Coordinates of the Regions of Interest

Regions of interest consisted of spheres (4 mm radius, 33 voxels) centered on the indicated MNI coordinates.

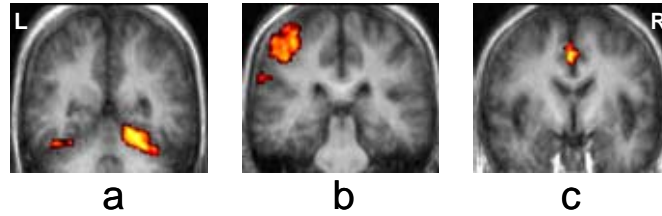| Left hemisphere	Coordinates	Right hemisphere	Coordinates
Fusiform gyrus	-50 -40 -18	Fusiform gyrus	38 -40 -20
	-50 -48 -16		46 -48 -16
	-48 -56 -16		42 -56 -12
	-46 -64 -14		46 -64 -14
	-36 -80 -12		34 -80 -8
	-18 -96 -10		18 -96 -10
Lingual gyrus	-24 -68 -8	Lingual gyrus	28 -64 -10
Prerolandic	-54 2 36		
SMA	-4 0 60		
Intraparietal cortex	-28 -80 28		
Broca's area lateral	-46 22 0	« Broca's area » lateral	46 22 4
Broca's area intermediate	-40 26 0	« Broca's area » intermediate	40 26 0
Broca's area mesial	-30 26 0	« Broca's area » mesial	30 26 0
Superior temporal sulcus	-58 -60 4		

4. Table S2: Linear Contrast over the 5 Types of Real-Letters Stimuli

Peak activations for the linear contrast defined over the 5 types of real-letters stimuli, detecting regions whose activation increased with the proximity of stimuli to real words (voxelwise threshold p<0.001, cluster size threshold p<0.05 corrected). As shown in Figure 2 (bottom line), only left-hemispheric regions (including the VWFA) showed such a functional profile, while there was no activation in symmetrical right-hemispheric regions.

Area	Coordinates	Z value
Visual word forma area	-40 -48 -22	5.18
Left prerolandic	-52 6 34	4.47
Broca's area	-34 28 0	4.00
Left superior temporal sulcus	-60 -28 -2	3.62
SMA	-6 0 60	3.58

5. Figure S2: Response-Related Activations

Activations related to the occurrence of target words, showing regions plausibly related to the generation of the motor response, including (a) the cerebellum ipsilateral to the response hand (right hemisphere), (b) the contralateral motor cortex (left hemisphere), and (c) premotor mesial frontal cortex. There were only minimal activations in visual regions, confirming that there was essentially no contamination between target-related and stimuli-related activations (voxelwise threshold p<0.001, cluster size threshold p<0.05 corrected).

a   b   c

6. Figure S3: Common vs. Individually Defined ROIs

As described in the main body of the article, ROIs were located at the same coordinates in all subjects. In order to determine whether the spatial pattern of activations could be captured more accurately by taking into account anatomical variability, we also applied a different procedure, consisting of adjusting the position of ROIs to individual activations. Keeping the same Y coordinates as in the standard method, we selected the X and Z coordinates of each ROI to match the *individual* maximum of the activation induced by words at the given Y. The figure represents activations for the 6 types of stimuli relative to words in the 6 left fusiform regions, labeled from posterior (1) to anterior (6). The pattern was the same whether ROIs were common to all subjects (same data as in the main paper's Figure 4), or adjusted for each individual subject.