

Functional specificity of the visual word form area: General activation for words and symbols but specific network activation for words

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Accepted 24 April 2007

Available online 24 May 2007

Abstract

The functional specificity of the brain region known as the Visual Word Form Area (VWFA) was examined using fMRI. We explored whether this area serves a general role in processing symbolic stimuli, rather than being selective for the processing of words. Brain activity was measured during a visual 1-back task to English words, meaningful symbols (e.g., \$, %), digits, words in an unfamiliar language (Hebrew), and geometric control stimuli. Mean activity in the functionally defined VWFA, as well as a pattern of whole-brain activity identified using a multivariate technique, did not differ for words and symbols, but was distinguished from that seen with other stimuli. However, functional connectivity analysis of this region identified a network of regions that was specific to words, including the left hippocampus, left lateral temporal, and left prefrontal cortex. Results support the hypothesis that activity in the VWFA plays a general role in processing abstract stimuli; however, the left VWFA is part of a unique network of brain regions active only during the word condition. These findings suggest that it is the neural “context” of the VWFA, i.e., the broader activity distributed in the brain that is correlated with VWFA, that is specific for visual word representation, not activity in this brain region per se.

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Keywords: Visual word form area; fMRI; Network; Language; Partial least squares; Neural context

1. Introduction

Studies of human visual processing suggest that particular attributes and categories of visual stimuli are represented and processed in specialized regions of extrastriate cortex. Processing occurs mainly in two separate pathways; a ventral stream that deals with object recognition, and a dorsal stream that mediates processing of motion, spatial relationships, and visually guided movement (Desimone & Ungerleider, 1989; Goodale & Milner, 1992; Ungerleider

& Mishkin, 1982). Previous work suggests there is modularity during initial visual processing of certain classes of stimuli, and distinct regions have been identified that respond preferentially to letter strings (Allison, McCarthy, Nobre, Puce, & Belger, 1994; Nobre, Allison, & McCarthy, 1994; Polk & Farah, 1998), faces (Allison, Puce, Spencer, & McCarthy, 1999; Haxby et al., 1994; Kanwisher, McDermott, & Chun, 1997; Sergent, Ohta, & MacDonald, 1992), and colors (Allison et al., 1994; Zeki et al., 1991), among other categories. Other evidence exists to show that activity in these regions represents an early, automatic stage of category processing (Puce, Allison, Asgari, Gore, & McCarthy, 1996).

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Recent neuroimaging and electrophysiological studies designed to characterize the early stages of visual word processing have led some authors (Cohen et al., 2000; Cohen et al., 2002; Dehaene et al., 2001; Dehaene, Le Clec, Poline, Le Bihan, & Cohen, 2002) to suggest the existence of a specialized region in the left fusiform gyrus, termed the visual word form area (VWFA). This region is postulated to be involved in processing the prelexical representation of visual word forms. Specifically, it has been suggested that this region computes an invariant structural representation of visual words, and is therefore active whenever literate viewers are presented with strings of letters (Cohen et al., 2000). In support of this hypothesis, neuropsychological studies show that lesions to this region result in deficits in word reading, with a sparing of auditory word comprehension and production (Beversdorf, Ratcliffe, Rhodes, & Reeves, 1997; Binder & Mohr, 1992; Damasio & Damasio, 1983; Leff et al., 2001). Although some have shown that VWFA activity can be modulated by attending to isolated letters (Flowers et al., 2004), studies comparing meaningless letter strings to words agree that the area is (1) more responsive to written words or pseudowords than consonant letter strings (Cohen et al., 2000, 2002), (2) is activated irrespective of typographical case (Dehaene et al., 2001; Polk & Farah, 2002), and (3) does not activate (or does so to a lesser degree) when the same words are presented in the auditory modality (Dehaene et al., 2002). In fact, McCandliss, Cohen, and Dehaene (2003) suggest this area of cortex has developed to be specifically tuned, through experience, to the properties of a writing system.

In contrast, Price and Devlin (2003) suggest a broader role for the VWFA. In their view, the VWFA participates in several functions, as defined by its interactions with other cortical areas, and is engaged when participants name, view, or generate verbs to pictures of objects (Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 1995; Etard et al., 2000; Murtha, Chertkow, Beauregard, & Evans, 1999). They suggest that the VWFA is not specific to orthography, but is involved in processing object structure generally. Additionally, there is a debate as to whether this area responds to auditory as well as visual stimuli. Specifically, Price, Winterburn, Giraud, Moore, and Noppeney (2003) suggest that it is a poly-modal structure driven by visual input, but also activated by other modalities, depending on the task. Perhaps most important for the current study, Price and Devlin suggest the possibility that the function of the area of left occipitotemporal cortex termed the “VWFA” depends critically on its interactions with other areas. Delineating the neural correlates of the visual word form system would thus require identification of the *group* of interacting regions that is unique to visual word form processing. The present study provides evidence that such a unique network does in fact exist.

Further evidence against the notion of the VWFA as specific for prelexical word processing comes from researchers emphasizing the role of expertise in the perception of various types of stimuli (Gauthier, Tarr, Anderson,

Skudlarski, & Gore, 1999, 2000; Polk & Farah, 1998). They argue that regions within the cortex devoted to object recognition become specialized for categories of objects through experience. This hypothesis has also been proposed for the VWFA, and tested by Kronbichler et al. (2004), who suggested that this region extracts and stores abstract patterns during initial presentation of visual objects, and that these patterns serve as recognition units when the same objects are subsequently encountered. In support of this idea, they showed that the VWFA is sensitive to the frequency with which letter strings are encountered, decreasing in activity in response to increasing word frequency. Their finding is at odds with the assumed prelexical function of the VWFA (Cohen et al., 2000, 2002; Dehaene et al., 2002, 2001). However, as their study was limited to letter stimuli, the possible role of this region in extraction and storage of other abstract patterns was never examined.

In the current study we hypothesized that activity in the VWFA would increase during presentation of words and symbols, both of which contain abstract visual information. As Kronbichler and colleagues (2004) showed a relative decrease in activity in VWFA with increasing word frequency, it may be that the VWFA is engaged, to varying degrees, during initial extraction and storage of any potentially symbolic visual information, even if it is novel to the participant. This last claim was never explicitly tested in Kronbichler et al.’s study, although the implication of their work is that processing of unfamiliar “letter-like” stimuli would lead to a relative increase in VWFA activation. To test this idea, we examined the responsiveness of the VWFA to words written in a language with an orthographic system unknown to the participants (Hebrew), and to known symbolic stimuli (e.g., \$, ♀). This allowed us to examine how unfamiliarity with a novel, but potentially symbolic, visual stimulus changes the degree of VWFA activation. We also included digits as visual stimuli in this experiment; although digits are abstract meaningful symbols, there is some evidence they are processed by a unique region of cortex (Allison et al., 1994; Halpern et al., 2004; James, James, Jobard, Wong, & Gauthier, 2005), and it was uncertain whether Arabic numerals would activate the VWFA.

Thus, our experiment used functional MRI to better describe two aspects of the role of this region in the left fusiform gyrus. First, we examined whether the VWFA plays a role in the representation of non-word abstract stimuli, as suggested by the results of Kronbichler et al. (2004). Next we examined the larger question of whether the VWFA recruits a network of brain regions unique to word processing, as suggested by Price and Devlin (2003). To this end we used traditional univariate fMRI analyses, as well as multivariate analysis of the fMRI data to examine whole-brain patterns of activity and functional interactions of the VWFA with the rest of the brain. In this experiment participants performed a 1-back task with either meaningful symbols (e.g., \$), English words, digits, Hebrew words, or geometric control stimuli.

2. Materials and methods

2.1. Participants

Eight right-handed, native English-speaking, non-Hebrew reading or speaking participants (6 men, 2 women) between the ages of 20 and 35 (mean age 24.1 years) participated in the experiment. All participants were free of neurological or psychiatric history, determined by a screening interview prior to participation. All participants had anatomical MRIs free of any visible abnormalities. All gave written informed consent.

2.2. Task procedure

During the experimental task, stimuli were centrally presented through binocular fiber optic goggles (Avotec Inc., Jensen Beach, FL). Stimuli were displayed in black on a white background for 1500 ms, separated by a 500 ms blank screen. Blocks of stimuli were presented, consisting of five categories: English words; meaningful symbols; digits; Hebrew words; and control stimuli (see Fig. 1). There were 16 different exemplars in each category. Words, both English and Hebrew, were common, four-letter nouns and verbs. Participants were not told that they would be seeing Hebrew. During participant screening, however, they were asked if they could read Hebrew, and this question may have given participants reason to presume that the unknown stimuli were in fact Hebrew. Digit stimuli consisted of a set of four different numbers per display. Symbols were common characters that contained meaningful information, displayed as a repeating set of four items to match the physical size of the four-letter words. On a given “symbol” trial the stimulus consisted of a character repeated four times, such that the display communicated only one idea, as is the case for the word stimuli. That is, “\$\$\$\$” represents the concept of “money”, just as the word “play” represents a type of activity. Presenting different symbol characters in a display (e.g., “&,\$#%”) would have introduced multiple ideas and/or meanings (such as “and”, “money”, “number”, and “percent” in our example), making such stimuli different from words in terms of the number of meanings that could be extracted. Because our intention in this study was to examine how

<u>Words</u>	PLAY	HALF	KEEP	DOOR
<u>Symbols</u>	????	⊗⊗⊗⊗	♀♀♀♀	♣♣♣♣
<u>Digits</u>	2814	6812	5907	2401
<u>Hebrew</u>	אפשר	תקרה	עכבר	בריא
<u>Control</u>	■ ■	■ ■ ■	■ ■ ■	■ ■ ■ ■

Fig. 1. Sample stimuli from each of the conditions.

the VWFA is engaged, to varying degrees, during initial extraction and storage of any potentially symbolic visual information, we did not wish to introduce multiple meanings within our symbols, which might have occurred had we presented different symbol characters in our symbol displays. Control stimuli consisted of four solid black squares, with one square in each location corresponding to the location of a letter/symbol. Within the letter/symbol location, the square was randomly placed in a 3×2 array.

To ensure participants were attending to the presented stimuli, they were asked to perform a 1-back working memory task during the functional scans. Participants were asked to press a button using the middle finger of the right-hand each time a presented stimulus was identical to the stimulus just preceding it, and to press a separate button using the index finger when the stimuli were non-identical. During each functional run, two blocks of each stimulus category were presented, and 10 stimuli were presented per block. Within each block, stimuli were presented in a pseudorandom order such that there were two immediate repetitions (targets) per block. There was a 2 s rest between blocks. In addition, three 20 s blocks of a blank screen were presented at the beginning, midpoint, and end of each functional run (i.e., the Rest condition), for use as baseline in subsequent analyses. Five functional runs were completed for each participant, with block order counterbalanced across participants in a pseudorandomized order. In total, each participant was scanned for 200 trials (=400 s) per condition.

2.3. Image acquisition and analysis

Functional volumes were acquired in an axial orientation, and consisted of 26 slices encompassing the whole brain. Images were acquired using a 1.5 T Signa MRI system (GE Medical Systems, Waukesha, WI), with a single-shot T2*-weighted gradient echo pulse sequence with spiral readout (TR = 2000 ms, TE = 40 ms, FOV = 20 cm, flip angle = 80°, 3.1 mm \times 3.1 mm \times 5.0 mm voxel size). Each of the five functional runs lasted 296 s, yielding 148 functional images per run. The first ten images of a run, in which transient signal changes occurred as the scanner reached a steady state, were excluded from all analyses. A standard 3D T1-weighted anatomical image was also acquired for each participant.

Anatomical and functional images were reconstructed offline and Analysis of Functional Neuroimages (AFNI) (Cox, 1996) was used to pre-process the images and define the VWFA (see below). Functional images were realigned for each participant to a single image in each run to correct for movement, followed by between-run realignment to a single image of the first functional run. Individual participants' datasets were spatially normalized to the standard brain atlas of Talairach and Tournoux (1988) to allow for group analysis.

For identification of the VWFA, contrast images were calculated using the multiple regression module of AFNI

(3dDeconvolve) for each participant, contrasting the Word condition to Rest. First, to determine activation for the group, a mixed effects ANOVA (with participants as a random factor and condition as the fixed factor) was performed on the individually calculated contrast images. This identified the average VWFA across subjects. However, since brain structure can vary from subject to subject, we also identified a functional region of interest for each subject individually. To do this we used a cluster analysis on each subject's Word vs. Rest contrast image to delineate the functional region of interest (ROI) for the left VWFA and a homologous region in the right fusiform gyrus. Regions located in the left and right fusiform areas with at least 150 μ l volume (approximately 3 original sized, contiguous voxels) where the threshold was over $t = 7.5$ ($p < .001$) were identified and used as the ROIs. A corrected threshold was estimated using the AFNI plugin *alphasim*. For both the VWFA and the right fusiform ROI, the average percent-change relative to Rest was calculated for each condition by averaging all blocks of a condition. This resulted in an average one-block time course for each condition. Due to the delay in the hemodynamic response and the time it takes for the additive effects to occur across a block, statistical analyses ignored the first three time points for each averaged time course. For the ROIs, repeated measures ANOVAs were performed to compare level of activity among the five conditions. Post hoc comparisons were made using paired t -tests with Bonferroni corrections for multiple comparisons. Additional analyses were performed contrasting the Word condition to the Control condition for a more narrowly defined functional ROI (i.e., after removing any influence of low level sensory and motor activity). Identical procedures were followed in this set of analyses.

For determining activity in brain regions outside the VWFA, i.e., whole-brain patterns of activity, we used a multivariate analyses, partial least squares (PLS) (McIntosh, Bookstein, Haxby, & Grady, 1996), as multivariate approaches are more appropriate and sensitive for this purpose. We also used PLS to assess functional connectivity of the VWFA, or how activity in the VWFA was correlated with activity in the rest of the brain. PLS identifies a group of brain regions that together covary with some aspect of the experimental design, and is based on the assumption that cognitive processes are the result of integrated activity of dynamic brain networks, rather than the action of any single region acting independently. The analysis first computes the cross-covariance between the experimental design (i.e., tasks), and activity in all brain voxels during each cognitive task, averaged over all task blocks and runs for each subject. This cross-covariance matrix is then decomposed using singular value decomposition, in order to identify latent variables (LV), or orthogonal patterns of brain activity. In this analysis we did not specify the design matrix (contrasts) in advance, but rather let the algorithm identify the contrasts that accounted for significant amounts of covariance. Within each LV, each voxel is given a positive

or negative value (or salience), which represents how that voxel is related to the LV. These values are then multiplied by the individual images of each condition for each participant and summed across the voxels in order to derive an estimate of how robustly each participant displays that spatial pattern (termed 'brain score'). The different tasks or behaviors are also given a 'task score', which can also be positive or negative, which identifies how strongly that particular task (or behavior) is related to the positively or negatively weighted voxels of that LV.

PLS uses two different methods to test for statistical significance. First, each LV is statistically assessed using a permutation test (McIntosh et al., 1996). Secondly, the reliability of each brain voxel's contribution to the pattern seen on each LV was determined through bootstrap resampling (Efron & Tibshirani, 1986; Sampson, Streissguth, Barr, & Bookstein, 1989). This technique produces a bootstrap ratio (BSR: the ratio of the salience of the voxel to the standard error of that salience), and an associated approximate p -value. A reliable contribution for a given voxel was defined as a ratio of its salience, to the standard error of the salience, greater than or equal to 3.0, which approximates a p value of .01.

PLS first was used to determine how brain activity was modulated across all of the conditions, including rest, an analysis that was analogous to the AFNI analysis contrasting VWFA activity in all conditions to rest. In order to examine the subtler differences between the five task conditions, a second analysis was conducted excluding the rest condition, which contributed a disproportionate share of the variance. Finally, we used PLS to assess functional connectivity of the VWFA, i.e., the correlations between activity in this region and the rest of the brain. To do this, we extracted the mean of the normalized values for the "seed" region from each condition in each participant. We then calculated the correlations between seed activity and activity in all other brain voxels across participants within each condition, and then compared these correlation values across tasks (as in Grady et al., 2003). In choosing a seed voxel for this analysis, we used the VWFA area in the left fusiform gyrus ($X = -44$, $Y = -58$, $Z = -11$) identified by the PLS analysis that contrasted all of the task conditions and Rest (see Section 3). We did this for two reasons: (1) since the univariate and multivariate analyses use different algorithms, we could not assume that the VWFA would be in exactly the same location in both analyses; (2) also as AFNI uses Talairach space and PLS uses MNI space, this would alter the coordinates of the VWFA slightly.¹

¹ When comparing reported Talairach coordinates, it is important to keep in mind that some studies used SPM and report coordinates in MNI space, whereas others report Talairach coordinates. With an affine transformation from MNI to Talairach, MNI of $x = 44$ becomes Talairach $x = 37.92$. For lateral regions such as the VWFA, the difference between MNI and Talairach may account for some inconsistencies between previously published studies in localizing the VWFA. Whether one uses an affine or linear transformation from one coordinate system to another will also effect the localization.

Because of these differences, we wanted to use a seed coordinate, for our connectivity analysis, which was derived in PLS rather than using coordinates derived from the AFNI analysis. It should be noted, however, that both our AFNI and PLS coordinates for the VWFA region fall close to previously published coordinates for the VWFA (Cohen et al., 2000; Flowers et al., 2004). In the connectivity analysis, the bootstrap also provided confidence intervals for each correlation between the external measure (activity in the VWFA) and the brain scores (summary measures of brain activity calculated for each participant) for each condition on each LV. These correlations provide a measure of whether the pattern of activity seen for each condition is correlated reliably with the external variable. The 95% confidence interval was used as the threshold for reliability for these correlations. All coordinates resulting from the PLS analyses were converted to Talairach coordinates using the algorithm developed by Brett and colleagues (imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach), and these are the coordinates reported in Table 2.

3. Results

3.1. Behavioral data

Performance on the 1-back task in all conditions was at ceiling (see Table 1) with no accuracy differences between

Table 1
Accuracy and response time in each condition (standard deviations in brackets)

Task and measure	Control	Word	Digit	Symbol	Hebrew
Accuracy (%)	97 (2.6)	97 (2.0)	98 (1.6)	98 (1.6)	97 (2.8)
Response time (ms)	674 (116)	582 (63)	599 (84)	640 (97)	685 (129)

Table 2
Brain regions identified using partial least squares analyses

Gyrus or region	Hem	BA	X	Y	Z	Ratio
(a) Regions with more activation for 1-back tasks compared to Rest						
Fusiform (VWFA)	L	37	-44	-58	-11	3.8
Fusiform	R	19	36	-66	-20	5.1
Cuneus	R	18	24	-89	-2	4.1
Middle frontal	L	46	-48	31	24	5.8
Anterior cingulate	R	32	8	31	24	5.5
(b) Regions with more activity during Word and Symbol conditions compared to Control, Digit, and Hebrew						
Fusiform	L	19	-28	-66	-13	4.1
Inferior frontal	L	45	-44	35	6	4.3
Inferior frontal	R	47	48	47	-2	4.6
Anterior cingulate	R	32	0	50	-3	6.3
(c) Regions showing functional connectivity with left VWFA in Word condition only						
Orbitofrontal	R	11	12	39	-15	6.1
Middle frontal	L	9	-48	27	35	3.4
Lingual	L	18	-16	-81	-9	4.9
Hippocampus	L		-40	-23	-12	6.3

X (right/left), negative values are in the Left Hemisphere; Y (anterior/posterior), negative values are posterior to the zero point (located at the anterior commissure); Z (superior/inferior), negative values are inferior to the plane defined by the anterior and posterior commissures. Abbreviations: Hem, hemisphere; R, right; L, left; BA, Brodmann area; Ratio, reliability ratio from the PLS bootstrap analysis, which is a measure of how strongly each region covaries with the pattern of activity seen on the LV. Coordinates are in Talairach space.

stimulus conditions. In a repeated measures ANOVA, there was a significant effect of condition on response times ($F(4, 28) = 6.9, p < .01$), but post hoc *t*-tests, using the Bonferroni correction for multiple comparisons, indicated that the only significant pairwise difference was between Symbol and Digit ($p < .05$). However, there were trends for a difference between Word and Symbol ($p = .053$) and between Digit and Control ($p = .07$).

3.2. VWFA signal change across conditions

The group-level VWFA was defined in two different contrasts: one liberal contrast, Word vs. Rest, and also in a more narrowly defined Word vs. Control contrast. In both contrasts, we found a cluster of activity in the left fusiform gyrus with more activity to words (Figs. 2a and b, respectively). Peak activity in the VWFA identified in the Word vs. Rest contrast, in Talairach coordinates, was $X = -34, Y = -68, Z = -12$ (extent $x: -40$ to $-27, y: -78$ to $-63, z: -15$ to -2). Peak activity in the VWFA identified in the Word vs. Control contrast, in Talairach coordinates, was $X = -35, Y = -71, Z = -14$. Thus, the regions from each of the two contrasts were centered in approximately the same location, with the cluster from the Word vs. Control contrast being a subset of the cluster from the Word vs. Rest contrast.

We also functionally identified the VWFA and a homologous region in the right fusiform ($X = 32, Y = -56, Z = -12$; extent $x: 27$ to $37, y: -60$ to $-50, z: -17$ to -9 ; see also Fig. 2a), in each participant and extracted the mean percent signal change in these regions for each of the five tasks, compared to Rest (Fig. 3). In the VWFA cluster (Fig. 3a), the mean percent signal change was significantly different from Rest in each of the tasks ($p < .01$). To

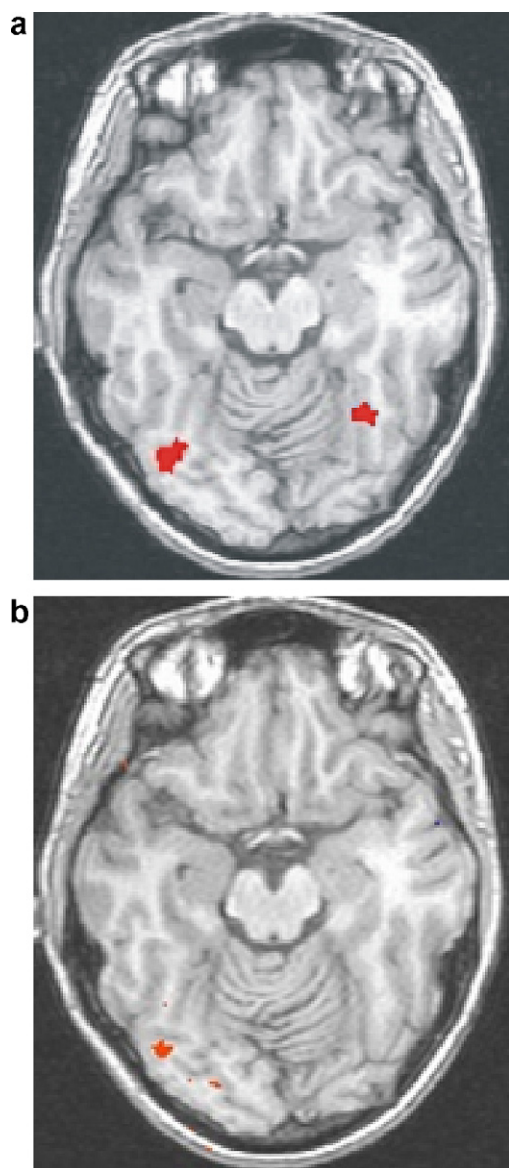


Fig. 2. (a) Brain regions from the group analysis, overlaid onto a single participant's axial image at $Z = -12$ (relative to the anterior–posterior commissure plane), which were more active (at $p < .001$ uncorrected) during the Word relative to Rest condition. The red cluster of activity in the left fusiform gyrus is the VWFA. Peak activity in the VWFA in Talairach coordinates was $X = -34$, $Y = -68$, $Z = -12$ (extent $x: -40$ to -27 , $y: -78$ to -63 , $z: -15$ to -2). The red cluster in the right fusiform also showed increased activity to Words ($X = 32$, $Y = -56$, $Z = -12$; extent $x: 27$ to 37 , $y: -60$ to -50 , $z: -17$ to -9). (b) Brain regions from the group analysis, overlaid onto a single participant's axial image at $Z = -14$ (relative to the anterior–posterior commissure plane), which were more active (at $p < .001$, uncorrected) for the Word relative to Control condition. The red cluster of activity in the left fusiform gyrus is in the VWFA. Peak activity in the VWFA in Talairach coordinates was $X = -35$, $Y = -71$, $Z = -14$.

compare activity across conditions, the time frame in which the response peaked and stabilized across the block was used, and analyzed using a repeated measures ANOVA. In the VWFA, there was a significant effect of condition ($F(4, 28) = 23.9$, $p < .001$). Critically, there was no differ-

ence between activity in the Word compared to Symbol condition. Activity in the Word condition did differ significantly from all other remaining conditions (corrected $ps < .05$). Activity during the Symbol condition differed significantly from that in the Control condition ($p < .05$), and the difference between activity in the Symbol and Digit ($p < .07$) and Symbol and Hebrew conditions approached significance ($p < .07$). To strengthen our confidence in this result, we repeated these analyses using the VWFA cluster identified in the Word vs. Control contrast, and found similar results.

To show that the pattern of effects described above was selective to the left fusiform region, we examined activation patterns in a similar region in the right fusiform ($X = 32$, $Y = -56$, $Z = -12$; see also Fig. 2a) that also was significantly active for Words compared to Rest. There was a significant effect of condition on these measures ($F(4, 28) = 5.5$, $p < .05$), but activity in the Word, Control, Digits, and Symbol conditions did not differ from one another (Fig. 3b). Only activity in the Hebrew condition differed from the other conditions, with higher activation than in all other conditions ($p < .05$), except Symbol. Thus, the pattern of activity that differentiated the Word condition from other visual conditions, but that was common to both Words and Symbols, was specific to the left fusiform gyrus (the VWFA).

3.3. Whole brain and network analyses

We first performed a task PLS intended to identify patterns of brain activity across all conditions, including rest. The analysis revealed one significant LV ($p < .001$), which identified a group of regions where activity in all the task conditions was differentiated from activity at rest. These included a region in the left fusiform gyrus ($X = -44$, $Y = -58$, $Z = -11$), within the same general location as the left VWFA identified in the previous analysis (with AFNI; $X = -34$, $Y = -68$, $Z = -12$), in which the experimental conditions were contrasted with the rest condition. Other areas active across all tasks were right fusiform and left dorsolateral prefrontal cortex (see Table 2a).

We then conducted a second task PLS analysis, to identify patterns of brain activity that could differentiate our five experimental conditions (Word, Symbol, Digit, Hebrew, and Control), removing the variance in the model associated with the rest condition. This analysis revealed two significant LVs. One of these LVs ($p < .05$) identified a group of regions with increased activity in the Word and Symbol conditions compared to the Digit, Hebrew, and Control conditions (see Fig. 4, areas in red, and Table 2b). The Word and Symbol conditions were associated with activity in the left fusiform gyrus ($X = -28$, $Y = -66$, $Z = -13$). This region was within the bounds of the VWFA cluster seen in Fig. 2a, which had an extent of $x: -40$ to -27 , $y: -78$ to -63 , $z: -15$ to -2 . The Word and Symbol conditions were also associated with more activity in bilateral inferior frontal gyri and the right ante-

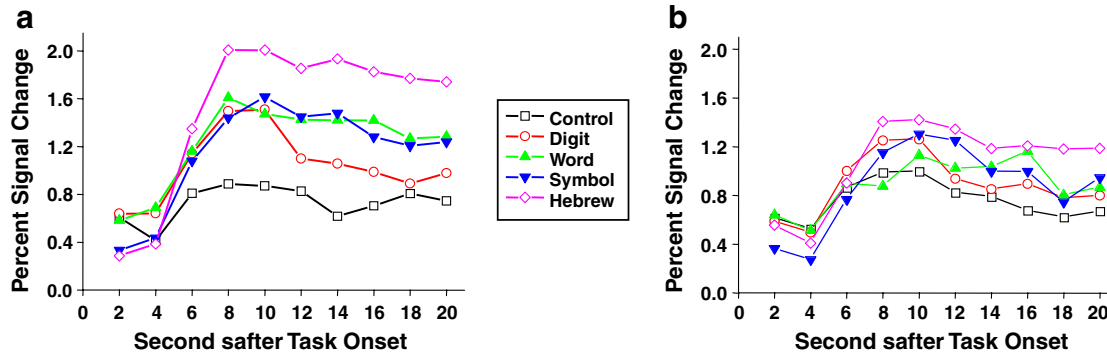


Fig. 3. (a) Mean percent signal change, averaged across all participants, for each condition, compared to Rest, in the VWFA. The magnitude of activation was similar in the Word and Symbol condition. Activity in the Word condition differed significantly from all other remaining conditions. Activity during the Symbol condition differed significantly from that in the Control condition, and the difference between activity in the Symbol and Digit, and Symbol and Hebrew conditions approached significance. (b) Mean percent signal change, averaged across all participants, for each condition compared to Rest, is shown in the right fusiform gyrus for comparison. Activation increased in all conditions compared to Rest, though here there was no significant difference in activation between Word, Digit, Symbol, and Control tasks.

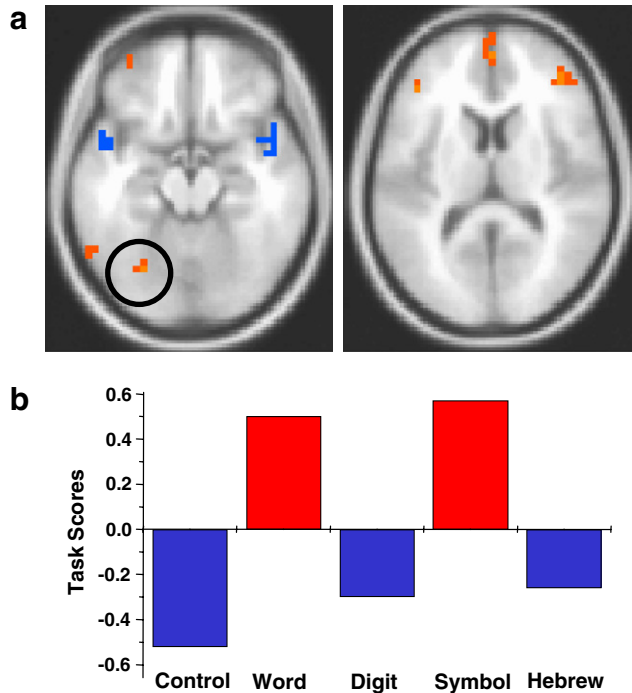


Fig. 4. Results of the PLS analysis contrasting the five conditions are shown on a standard axial MRI (at $Z = -12$ and $Z = +8$ in the Talairach system). (a) Regions in red showed an increase in activity in the Word and Symbol conditions (bootstrap ratio > 3) and (b) were associated with positive task scores on this LV (red bars). These areas included the VWFA (circled), anterior cingulate, and bilateral inferior frontal regions (see also Table 2b).

rior cingulate (see Table 2b). In contrast, the Digit, Hebrew, and Control conditions were associated with increased activity in the right parietal cortex ($X = 24$, $Y = -66$, $Z = 44$, BA 7, ratio = 5.9), and bilateral anterior temporal regions ($X = 44$, $Y = -15$, $Z = -9$, BA 21, ratio = 6.6; $X = -51$, $Y = 12$, $Z = -17$, BA 38, ratio = 3.3; shown in Fig. 4a in blue). The other significant LV

($p < .002$) showed increased activity during the Symbol and Hebrew conditions in the posterior fusiform gyrus bilaterally ($X = 36$, $Y = -70$, $Z = -17$, BA 19, ratio = 5.5; $X = -40$, $Y = -66$, $Z = -17$, BA 19, ratio = 4.3), and the left lingual gyrus ($X = -12$, $Y = -58$, $Z = -4$, BA 19, ratio = 4.6). Increased activity for the Word, Digit, and Control conditions was seen in the left inferior frontal gyrus ($X = -63$, $Y = 20$, $Z = 6$, BA 44/45, ratio = -5.9), and the left superior temporal gyrus ($X = -48$, $Y = -31$, $Z = 16$, BA 19, ratio = -4.7).

Although the Word and Symbol conditions were associated with modulations of activity in a similar group of brain regions, to determine the engagement of neural networks, it is necessary to examine directly the *functional connectivity* of this region, i.e., how activity in the VWFA is correlated with activity in other brain areas. To address whether the VWFA recruits a network of regions specific to words, we examined the functional connectivity of this region using the area of left fusiform active in all conditions compared to rest, from the first PLS analysis (-44 , -58 , -11). A set of regions (shown in Fig. 5 in red) emerged from this analysis where activity was significantly and positively correlated with activity in the VWFA only during the Word condition, and not any of the others ($p < .001$). Areas positively correlated with the VWFA during the Word condition were left hippocampus, left lateral temporal cortex, and a left prefrontal region (see Table 2c). The pattern of activity seen on this LV indicates that the VWFA is positively correlated with these areas during the word condition, and negatively correlated with the areas shown in blue in Fig. 5. Conversely, during the other conditions the VWFA is positively correlated with the areas shown in blue, and negatively with areas shown in red in Fig. 5. These blue regions included the middle frontal gyrus ($X = 20$, $Y = 27$, $Z = 32$, BA 9, ratio = 4.7), the cingulate gyrus ($X = 8$, $Y = -4$, $Z = 33$, BA 24, ratio = 3.8), and the superior temporal gyrus ($X = -63$, $Y = -23$, $Z = 12$, BA 22, ratio = 4.3).

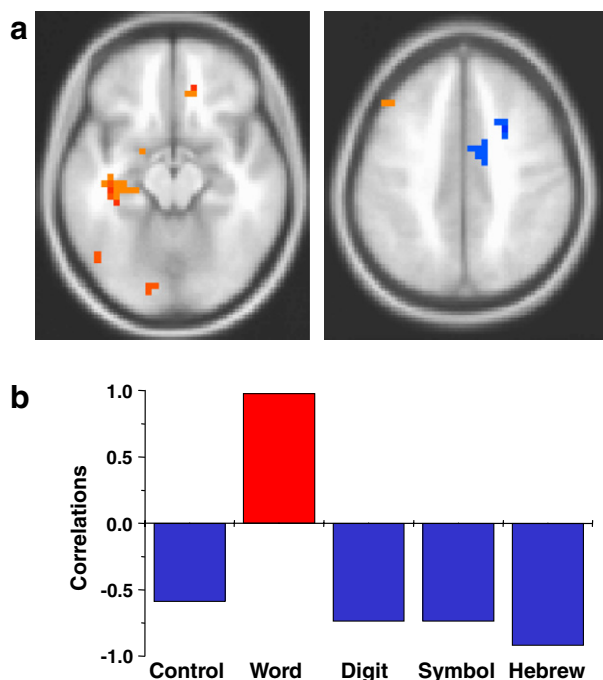


Fig. 5. Results of the functional connectivity analysis are shown on a standard axial MRI. (a) Areas where activity was positively correlated with activity in the VWFA only during the Word condition are shown in red (at $Z = -12$ and $Z = +36$ in the Talairach system). In all other conditions the VWFA was correlated with the areas shown in blue. (b) Correlations of brain scores and activation signal in the VWFA across the conditions. All were reliable at the 95% confidence interval. The positive correlation in the Word condition (red bar) indicates that as activity in areas shown in red increases (i.e., the brain scores become more positive), activity in the VWFA increases. Negative correlations in the other conditions (blue bars) indicate that as activity in the areas shown in blue increases (brain scores become more negative) activity in the VWFA increases in these conditions.

4. Discussion

Our study was designed to examine the functional specificity of the brain region known as the Visual Word Form Area (VWFA), using fMRI. We explored whether this area serves a general role in extracting and storing information from abstract symbolic visual stimuli, and/or unfamiliar but potentially symbolic stimuli, rather than being selective for the processing of words. We also examined whether the VWFA is connected functionally with a unique network of brain regions only during the processing of words, as suggested by Price and Devlin (2003). Our results provide support for both of these ideas, namely that the region called the VWFA is more responsive to words, known symbols, and unfamiliar orthographic stimuli, than other visual stimuli, but also participates in a network of brain areas that is unique to words. This suggests both a general role in processing symbolic representation of both familiar and novel stimuli, and a specific role in word processing.

Previous work has shown that the VWFA is engaged, to varying degrees, depending on how often a particular stimulus is encountered (less activation with increased frequency). This has led researchers (Kronbichler et al.,

2004) to suggest that the VWFA plays a specific role during initial extraction, and storage of information from novel visual stimuli, that goes beyond the processing of words alone. Our finding that activity in the left fusiform region was not significantly different for English words and meaningful visual symbols, but was distinct from that seen when other types of stimuli are used, supports this hypothesis. These results were found regardless of whether the VWFA was defined in the Word vs. Rest contrast or in the Word vs. Control contrast. Furthermore, we identified (using a multivariate approach), a pattern of brain regions commonly activated during both the Word and Symbol conditions, which was distinct from that seen for the other conditions. Thus, regardless of how we examined activity in the VWFA, the results suggest considerable similarity in this region's involvement in the processing of words and known symbols.

Most importantly for the present study, our analysis of the functional connectivity of the VWFA showed, for the first time, that its activity is correlated with a unique set of brain regions, during the processing of actual words, but not other types of materials. Thus, although the magnitude of activity in the left VWFA is similar when viewing words and symbols, the left fusiform does participate in a *network* that is specific to words, consistent with the suggestion of Price and Devlin (2003). This network mostly included other left hemisphere regions involved in verbal memory (the hippocampus) or language function (middle frontal; Fiez, Tranel, Seager-Frerichs, & Damasio, 2006; Yokoyama et al., 2006), indicating that this VWFA-linked network may participate in more than one type of linguistic processing. In addition, this word-related network was distinct from the set of regions that characterized both the Word and Symbol conditions. This suggests that the processing common to words and symbols may involve more general aspects of meaning extraction, whereas that limited to words may be more phonological or linguistically based.

The differences in brain activity seen for the left fusiform region across conditions cannot be explained on the basis of task difficulty. Accuracy was similarly high in all conditions. In addition, the response time during the Word condition did not differ significantly from the others. Thus, differences in response speed cannot account for the pattern of brain activation found. Similarly, it is unlikely that the increased level of activity seen in the Hebrew condition reflects a higher level of difficulty for that condition. If that were true, we should have observed differences in accuracy or response time for this condition, but we did not.

Of note, our data showed that the digit condition did not activate the VWFA to the same extent as did the Word and Symbol conditions. One may have expected the Digit condition to activate the VWFA in the same way as these latter two conditions, since they are also familiar, meaningful, visual stimuli. As suggested in other work, however, different brain regions may be devoted to processing visually presented digits (Allison et al., 1994; Halpern et al., 2004; James et al., 2005; Szucs & Csepe, 2004). Indeed there

are neurological cases of acalculia in which representation of numbers is affected, but not representation of words, or other meaningful stimuli (Basso, Burgio, & Caporali, 2000). Our data suggest that the left fusiform region processes digits, but as this activity was not sustained across the entire block, other areas may take over processing of this material.

Based on the present data we suggest, in line with Kronbichler et al. (2004), that the left VWFA is engaged during the processing of familiar, abstract, visual stimuli. We suggest that this region functions to extract and store information from abstract stimuli, whether presented using letters or symbolic characters. Such a suggestion runs counter to the assumed prelexical function of the VWFA, suggested by proponents of the VWFA theory (Cohen et al., 2000, 2002; Dehaene et al., 2001, 2002). In addition, based on the current data, we also suggest that the VWFA plays a role in initial extraction, and storage, of information from novel visual stimuli. In support of this claim, our data show strong activity in the VWFA for abstract visual stimuli unknown to the participants (i.e., Hebrew). Our results also are consistent with those of Kronbichler et al. (2004) who showed that activity in the left VWFA was higher for pseudowords and low-frequency words compared to high-frequency words. Both their study and ours suggest that this area is sensitive to familiarity of words or “word-like” stimuli. An increase in activation of the VWFA, during presentation of Hebrew, may occur for the same reasons as during presentation of pseudowords and low-frequency words: extraction and storage of *new*, or unfamiliar, “word-like” or “letter-like” patterns. Consistent with this idea was the pattern of activity that distinguished the Symbol and Hebrew conditions from the other conditions. This pattern was characterized mainly by increased activity in posterior extrastriate regions, suggesting that increased visual analysis is involved in processing these stimuli, perhaps due to their complexity or novelty. Thus, although our explanation of the increased VWFA activity in the Hebrew condition is somewhat speculative, our finding of increased activity in this condition, as well during the Symbol condition, clearly shows that the role of the VWFA cannot be limited to the processing of visually presented words.

If the VWFA is not dedicated to lexical processing, or prelexical processing of letters, but also involved in processing abstract stimuli, then an important question is why a left hemisphere region should be used for this process. The answer may lie in the close relationship between extraction of meaning (or semantics) from abstract symbols, to language. Words are a common example of meaningful stimuli in which the meaning is purely symbolic and not related to the physical characteristics of the words themselves. The ability to use abstract symbols, and to read, are thus closely intertwined, although reading can be thought of as just one example of the ability to use abstract symbols. Piaget (1962) suggested that the development of symbolic representation precedes reading in child

development, but his work does not distinguish between abstract symbolic meaning and representational symbols. Other evidence suggests that the understanding of abstract symbolic representation develops after 4 years of age. This is near the point in maturation at which reading skills are developed, suggesting the two may be interdependent (Apperly, Williams, & Williams, 2004; Bialystok & Martin, 2003). The acquisition of both reading skills and abstract symbol use at the same developmental stage is in line with our finding that the left fusiform responds equivalently to written words and symbols, as well as to novel orthographic stimuli.

In conclusion, these results support the hypothesis that the VWFA plays a general role in processing abstract stimuli, and is in line with recent work suggesting that a network of brain regions, that includes the left fusiform, can be engaged to varying degrees depending on the nature of the stimuli (James & Gauthier, 2006). Importantly, however, we show that the left VWFA interacts with a unique network of other brain regions during the processing of visually presented words. Our data suggest that it would be more fruitful in the future if researchers in this field began to think more in terms of a visual word form *network*, rather than focusing on activity in any single brain region, whether in the left fusiform gyrus or elsewhere, as representing our ability to extract meaning from visually presented words.

Acknowledgments

The academic contributions of the first (K.R.) and second author (M.F.) to the study were equivalent. This work was supported by grants from the Canadian Institutes of Health Research (C.G. and K.O.), the Natural Science and Engineering Research Council of Canada (M.F.), Baycrest Foundation and the Jack and Rita Catherall Fund (M.F.), and the Rotman Research Institute (K.R.). We thank the staff of the MRI Centre at Sunnybrook and Women’s College Health Science Centre for their assistance in carrying out this experiment. We also thank Asaf Gilboa for providing us with Hebrew words and Donaya Hongwanishkul for assisting with stimulus preparation.

References

- Allison, T., McCarthy, G., Nobre, A., Puce, A., & Belger, A. (1994). Human extrastriate visual cortex and the perception of faces, words, numbers and colors. *Cerebral Cortex*, *5*, 544–554.
- Allison, T., Puce, A., Spencer, D. D., & McCarthy, G. (1999). Electrophysiological studies of human face perception. I: Potentials generated in occipitotemporal cortex by face and non-face stimuli. *Cerebral Cortex*, *9*, 415–430.
- Apperly, I., Williams, E., & Williams, J. (2004). Three- to four-year-olds’ recognition that symbols have a stable meaning: Pictures are understood before written words. *Journal of Child Development*, *75*, 1510–1522.
- Basso, A., Burgio, F., & Caporali, A. (2000). Acalculia, aphasia, and spatial disorders in left and right brain-damaged patients. *Cortex*, *36*, 265–280.

- Beversdorf, D. Q., Ratcliffe, N. R., Rhodes, C. H., & Reeves, A. G. (1997). Pure alexia: Clinical-pathologic evidence for a lateralized visual language association cortex. *Clinical Neuropathology*, 16, 328–331.
- Bialystok, E., & Martin, M. M. (2003). Notation to symbol: Development in children's understanding of print. *Journal of Experimental Child Psychology*, 86, 223–243.
- Binder, J. R., & Mohr, J. P. (1992). The topography of callosal reading pathways. A case-control analysis. *Brain*, 115, 1807–1826.
- Bookheimer, S. Y., Zeffiro, T. A., Blaxton, T., Gaillard, W., & Theodore, W. (1995). Regional cerebral blood flow during object naming and word reading. *Human Brain Mapping*, 3, 93–106.
- Cohen, L., Dehaene, S., Naccache, L., Lehericy, S., Dehaene-Lambertz, G., Henaff, M. A., et al. (2000). The visual word form area: Spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. *Brain*, 123, 291–307.
- Cohen, L., Lehericy, S., Chochon, F., Lemer, C., Rivaud, S., & Dehaene, S. (2002). Language-specific tuning of visual cortex? Functional properties of the Visual Word Form Area. *Brain*, 125, 1054–1069.
- Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computational Biomedical Research*, 29, 162–173.
- Damasio, A. R., & Damasio, H. (1983). The anatomic basis of pure alexia. *Neurology*, 33, 1573–1583.
- Dehaene, S., Le Clec, H. G., Poline, J. B., Le Bihan, D., & Cohen, L. (2002). The visual word form area: A prelexical representation of visual words in the fusiform gyrus. *Neuroreport*, 13, 321–325.
- Dehaene, S., Naccache, L., Cohen, L., Bihan, D. L., Mangin, J. F., Poline, J. B., et al. (2001). Cerebral mechanisms of word masking and unconscious repetition priming. *Nature Neuroscience*, 4, 752–758.
- Desimone, R., & Ungerleider, L. G. (1989). Neural mechanisms of visual processing in monkeys. In H. Goodglass & A. R. Damasio (Eds.). *Handbook of neuropsychology* (Vol. 2, pp. 267–300). Amsterdam: Elsevier.
- Efron, B., & Tibshirani, R. (1986). Bootstrap methods for standard errors, confidence intervals and other measures of statistical accuracy. *Statistical Science*, 1, 54–77.
- Etard, O., Mellet, E., Papathanassiou, D., Benali, K., Houde, O., Mazoyer, B., et al. (2000). Picture naming without Broca's and Wernicke's area. *Neuroreport*, 11, 617–622.
- Fiez, J. A., Tranel, D., Seager-Frerichs, D., & Damasio, H. (2006). Specific reading and phonological processing deficits are associated with damage to the left frontal operculum. *Cortex*, 42, 624–643.
- Flowers, D. L., Jones, K., Noble, K., VanMeter, J., Zeffiro, T. A., Wood, F. B., et al. (2004). Attention to single letters activates left extrastriate cortex. *Neuroimage*, 21, 829–839.
- Gauthier, I., Skudlarski, P., Gore, J. C., & Anderson, A. W. (2000). Expertise for cars and birds recruits brain areas involved in face recognition. *Nature Neuroscience*, 3, 191–197.
- Gauthier, I., Tarr, M. J., Anderson, A. W., Skudlarski, P., & Gore, J. C. (1999). Activation of the middle fusiform 'face area' increases with expertise in recognizing novel objects. *Nature Neuroscience*, 2, 568–573.
- Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neuroscience*, 15, 20–25.
- Grady, C. L., McIntosh, A. R., Beig, S., Keightley, M. L., Burian, H., & Black, S. E. (2003). Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer disease. *Journal of Neuroscience*, 23, 986–993.
- Halpern, C. H., Glosser, G., Clark, R., Gee, J., Moore, P., Dennis, K., et al. (2004). Dissociation of numbers and objects in corticobasal degeneration and semantic dementia. *Neurology*, 62, 1163–1169.
- Haxby, J. V., Horwitz, B., Ungerleider, L. G., Maisog, J. M., Pietrini, P., & Grady, C. L. (1994). The functional organization of human extrastriate cortex: A PET-rCBF study of selective attention to faces and locations. *Journal of Neuroscience*, 14, 6336–6353.
- James, K. H., & Gauthier, I. (2006). Letter processing automatically recruits a sensory-motor brain network. *Neuropsychologia*, 44, 2937–2949.
- James, K. H., James, Y., Jobard, G., Wong, A. C.-N., & Gauthier, I. (2005). Letter processing in the visual system: Different activation patterns for single letters and strings. *Cognitive, Affective, & Behavioural Neuroscience*, 5, 452–466.
- Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: A module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience*, 17, 4302–4311.
- Kronbichler, M., Hutzler, F., Wimmer, H., Mair, A., Staffen, W., & Ladurner, G. (2004). The visual word form area and the frequency with which words are encountered: Evidence from a parametric fMRI study. *Neuroimage*, 21, 946–953.
- Leff, A. P., Crewes, H., Plant, G. T., Scott, S. K., Kennard, C., & Wise, R. J. (2001). The functional anatomy of single-word reading in patients with hemianopic and pure alexia. *Brain*, 124, 510–521.
- McCandliss, B. D., Cohen, L., & Dehaene, S. (2003). The visual word form area: Expertise for reading in the fusiform gyrus. *Trends in Cognitive Science*, 7, 293–299.
- McIntosh, A. R., Bookstein, F. L., Haxby, J. V., & Grady, C. L. (1996). Spatial pattern analysis of functional brain images using partial least squares. *NeuroImage*, 3, 143–157.
- Murtha, S., Chertkow, H., Beauregard, M., & Evans, A. (1999). The neural substrate of picture naming. *Journal of Cognitive Neuroscience*, 11, 399–423.
- Nobre, A. C., Allison, T., & McCarthy, G. (1994). Word recognition in the human inferior temporal lobe. *Nature*, 372, 260–263.
- Piaget, J. (1962). *Play, dreams, and imitation in childhood*. New York: Wiley.
- Polk, T. A., & Farah, M. J. (1998). The neural development and organization of letter recognition: Evidence from functional neuroimaging, computational modeling, and behavioral studies. *Proceedings of the National Academy of Science of the United States of America*, 95, 847–852.
- Polk, T. A., & Farah, M. J. (2002). Functional MRI evidence for an abstract, not perceptual, word-form area. *Journal of Experimental Psychology-General*, 131, 65–72.
- Price, C. J., & Devlin, J. T. (2003). The myth of the visual word form area. *Neuroimage*, 19, 473–481.
- Price, C. J., Winterburn, D., Giraud, A. L., Moore, C. J., & Noppeney, U. (2003). Cortical localisation of the visual and auditory word form areas: A reconsideration of the evidence. *Brain & Language*, 86, 272–286.
- Puce, A., Allison, T., Asgari, M., Gore, J. C., & McCarthy, G. (1996). Differential sensitivity of human visual cortex to faces, letterstrings, and textures: A functional magnetic resonance imaging study. *Journal of Neuroscience*, 16, 5205–5215.
- Sampson, P. D., Streissguth, A. P., Barr, H. M., & Bookstein, F. L. (1989). Neurobehavioral effects of prenatal alcohol: Part II. Partial least squares analysis. *Neurotoxicology and Teratology*, 11, 477–491.
- Sergent, J., Ohta, S., & MacDonald, B. (1992). Functional neuroanatomy of face and object processing. A positron emission tomography study. *Brain*, 115, 15–36.
- Szucs, D., & Csepe, V. (2004). Access to numerical information is dependent on the modality of stimulus presentation in mental addition: A combined ERP and behavioural study. *Cognitive Brain Research*, 19, 10–27.
- Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. New York: Thieme Medical Publishers, Inc..
- Ungerleider, L. G., & Mishkin, M. (1982). Two cortical visual systems. In D. J. Ingle, M. A. Goodale, & R. J. W. Mansfield (Eds.), *Analysis of visual behavior* (pp. 549–586). Cambridge: MIT Press.
- Yokoyama, S., Miyamoto, T., Riera, J., Kin, J., Akitsuki, Y., Iwata, K., et al. (2006). Cortical mechanisms involved in the processing of verbs: An fMRI study. *Journal of Cognitive Neuroscience*, 18, 1304–1313.
- Zeki, S., Watson, J. D. G., Lueck, C. J., Friston, K. J., Kennard, C., & Frackowiak, R. S. J. (1991). A direct demonstration of functional specialization in human visual cortex. *Journal of Neuroscience*, 11, 641–649.