RESEARCH ARTICLE

Priming for letters and pseudoletters in mid-fusiform cortex: examining letter selectivity and case invariance

E. Darcy Burgund · Yi Guo · Elyse L. Aurbach

Abstract A large body of research indicates a critical role for the left mid-fusiform cortex in reading, however, the extent to which this area is dedicated exclusively to the processing of words and letters has been debated. Two questions regarding left mid-fusiform function are critical to this debate: (1) Are letters stored preferentially compared to visually equivalent non-letters (letter selectivity)? (2) Are letter representations abstract with respect to changes in letter case (e.g., A/a; case invariance)? The present study addressed these questions by comparing priming for letters and pseudoletters in left and right mid-fusiform regions using functional magnetic resonance imaging while subjects performed a same/different matching task. Results revealed priming for letters but not pseudoletters in the left mid-fusiform region, suggesting that representations are letter selective. However, no priming for different-case-primed letters was observed in this region, indicating that representations are not case invariant. In addition, priming for pseudoletters but not letters was observed in the homologous right mid-fusiform region. Overall, findings contradict strongly modular theories of letter/word processing and suggest that left and right mid-fusiform regions support generic object processes that are differentially effective for representing disparate types of visual stimuli.

Keywords fMRI · Fusiform · Reading · Letters · Priming · Hemisphere

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Introduction

Neuroimaging studies of occipital-temporal cortex have revealed an area within the left mid-fusiform gyrus (approximate Brodmann Area 37) that exhibits greater neural activity for words and pseudowords than for random letter strings of the same length (Beauregard et al. 1997; Büchel et al. 1998; Cohen et al. 2002; James et al. 2005; McCandliss et al. 2003; Price et al. 1996; Rees et al. 1999; Xu et al. 2001). While there is general agreement regarding this area's involvement in reading, its precise function has been debated (Cohen and Dehaene 2004; Price and Devlin 2003, 2004). In particular, Cohen, Dehaene, and colleagues have proposed that this area is specifically dedicated to the processing of visual word and pseudoword forms, compared to other stimuli [visual word form area (VWFA) hypothesis; Cohen and Dehaene, 2004; Cohen et al. 2000, 2002]. In contrast to this modular perspective, others have argued that the putative VWFA is a generic object processor that responds differentially according to task and stimulus demands, and is not dedicated to the processing of words per se (Binder et al. 2006; Joseph et al. 2003, 2006; Kronbichler et al. 2004; Mechelli et al. 2003; Price and Devlin 2003, 2004; Rogers et al. 2005; Starrfelt and Gerlach 2007; Xue et al. 2006).

Critical to this debate is the question of whether the left mid-fusiform area is tuned preferentially to the shapes of letters in the known language, compared to similar non-letter forms (James et al. 2005). Indeed, Cohen and Dehaene (2004) describe preferential tuning to letters versus non-letters as the first of their criteria for functional specialization within the VWFA. In line with this argument, greater responses in the VWFA have been observed for letter strings than for visually equivalent strings of pseudoletters (Price et al. 1996; Vinckier et al. 2007).

Likewise, letter-selective responses have been observed in this area for letter strings compared to faces (Puce et al. 1996). Nonetheless, more recent comparisons of letters to visually equivalent stimuli have produced less definitive results. For example, Pernet et al. (2005) observed selective responses in the VWFA for (familiar) Roman letters compared to (unfamiliar) Korean characters and geometric shapes, but only during a categorization task and not during a discrimination task, suggesting that letter selectivity in the VWFA is task dependent and not a mandatory function of this area (Joseph et al. 2006). In a related study, James et al. (2005) observed greater activity in the VWFA for Roman letters compared to Chinese characters, but not compared to digits and not during a voxel-based analysis, suggesting that preferential tuning to letters in the VWFA is weak and includes tuning to some non-letter forms. Finally, other studies have observed equivalent activity for letters and pseudoletters (Tagamets et al. 2000) and for letters and common objects (Joseph et al. 2006), seriously challenging the letter selectivity criterion of the VWFA hypothesis.

The present study re-examined the question of letter selectivity in the VWFA by comparing priming for letters and visually equivalent pseudoletters. Priming in neural signals manifests as a decrease in the amount of signal associated with processing a primed (repeated) compared to an unprimed (unrepeated) stimulus (Buckner et al. 1995, 1998; Maccotta and Buckner 2004; Schacter and Buckner 1998; but see Henson et al. 2000; Turk-Browne et al. 2007), and may be more sensitive to differences between stimulus types than estimates of overall activity (Grill-Spector and Malach 2001). Indeed, priming has been used to assess representations in the VWFA and is one of the main methods with which support for the hypothesis has been garnered. For example, greater priming within the VWFA for same-primed words (e.g., RAGE–RAGE) compared to anagram-primed words (e.g., GEAR–RAGE) suggests that representations in this area are sensitive to whole word forms (Dehaene et al. 2004). As such, comparisons of priming magnitude may provide a clearer picture of letter selectivity in the VWFA. In particular, if representations are tuned preferentially to the shapes of real letters, as posited by the VWFA hypothesis (Cohen and Dehaene 2004), priming in this area should be greater for letter than pseudoletter forms. In contrast, if representations support a more generic object recognition process, priming for letters and pseudoletters may not differ.

The examination of priming in the present experiment also permitted the investigation of another criterion for functional specialization within the VWFA—namely, that visual representations within this area are abstract with respect to letter case (Cohen and Dehaene 2004; Dehaene et al. 2001, 2004). Like letter selectivity, case invariance is an essential feature of the VWFA hypothesis because it is a functional property that distinguishes this area from a generic object-processing area. In particular, Cohen and Dehaene (2004) argue that the VWFA develops to perform arbitrary mappings between letters, such as matching 'A' and 'a' and distinguishing 'O' and 'Q', which are unique to reading and which cannot be accomplished by a generic object recognition system. Support for case invariance has been garnered by studies observing equivalent priming for same- and different letter-case-primed words (e.g., RAGE–RAGE vs. rage–RAGE; Dehaene et al. 2001, 2004). However, since stimuli in these studies were real words, priming may have been based on shared orthographic and/or semantic information, as suggested by some (e.g., Devlin et al. 2006), rather than on abstract visual representations. Indeed, when single letters are examined, priming in the VWFA is font specific (Gauthier et al. 2000), indicating a high level of visual sensitivity in this area for linguistic stimuli that do not have orthography or semantics, and contrasting directly with the invariance criterion of the VWFA hypothesis. Nonetheless, evidence addressing the question of case invariance in the VWFA is scarce. Thus, we examined the question directly by including a different letter-case-primed condition in our current design. If representations in the VWFA are letter-case invariant, as argued by Cohen and Dehaene (2004), equivalent priming should be observed for same- and different-case-primed letters. If representations support a more generic object recognition process, priming for same-case letters should be greater than priming for different-case letters.

Methods

Subjects

Nineteen volunteers (9 males; mean age 20.25 ± 1.34 years) from Rice University participated for payment. Subjects were screened using a detailed questionnaire to ensure that they had no history of neurological or psychiatric problems. In addition, all subjects were right-handed, had normal or corrected-to-normal vision, and were native speakers/readers of English. Informed consent was obtained from each subject in accordance with the guidelines and approval of the Rice University Institutional Review Board.

Materials

Stimuli were pairs of letters and pairs of unfamiliar pseudoletters (see Figs. 1, 2). Twelve letters with dissimilar forms across upper- and lowercase versions (A, B, D, E, G, H, M, N, Q, R, T, and Y; Boles and Clifford 1989) were selected from the Roman alphabet. Dissimilar letters were used in
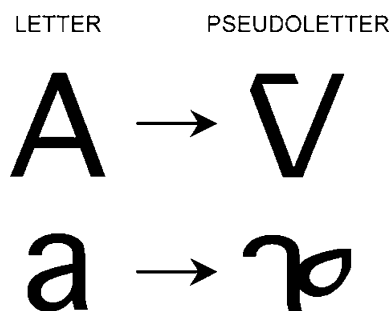
Fig. 1 Examples of letters and their pseudoletter counterparts. Pseudoletters were created from letters by moving one or two lines to a different location (see text for details). The pseudoletter for uppercase 'A' was created by moving two lines; the pseudoletter for lowercase 'a' was created by moving one line

the present experiment because they provide a stronger test of case invariance than similar letters (e.g., C/c; Dehaene et al. 2004). Letters were presented in Geneva font, and both upper- and lowercase versions were used. Pseudoletters were created from letters by moving one or two lines to a different location. For example, as illustrated in Fig. 1, the pseudoletter for uppercase 'A' was created by moving two lines to different locations, and the pseudoletter for lowercase 'a' was created by moving one line to a different location. Thus, stimuli were 24-letter forms (upper- and lowercase versions of 12 letters) and their 24 pseudoletter counterparts. Overall, letters and pseudoletters had the same number of lines, and similar numbers of line junctions and enclosed spaces (both $Ps > 0.425$ by paired t test). All pairs were presented centrally, in white against a black background, and subtended approximately $1.5° \times 3.5°$ of visual angle in the vertical and horizontal dimensions, respectively. Presentations and response-time measurement were controlled by the PsyScope software package (Cohen et al. 1993).

Procedure

Letter and pseudoletter pairs were presented for 500 ms each at intervals of 2.5, 5, and 7.5 s (average rate of 1 pair per 5 s). A fixation cross (+) preceded each presentation and remained on the screen between stimulus trials. For each stimulus pair, subjects were instructed to decide whether items were exactly the same (e.g., A A) or different (e.g., A B), and to indicate their response as quickly as possible by pushing a button on the button wand. Subjects pushed one button with their right (or left) hand to indicate a "same" response, and another button with their left (or right) hand to indicate a "different" response. The hand (left vs. right) used to indicate a "same" response was counterbalanced across subjects. Before the task began, subjects engaged in seven practice trials to ensure that they understood the instructions.
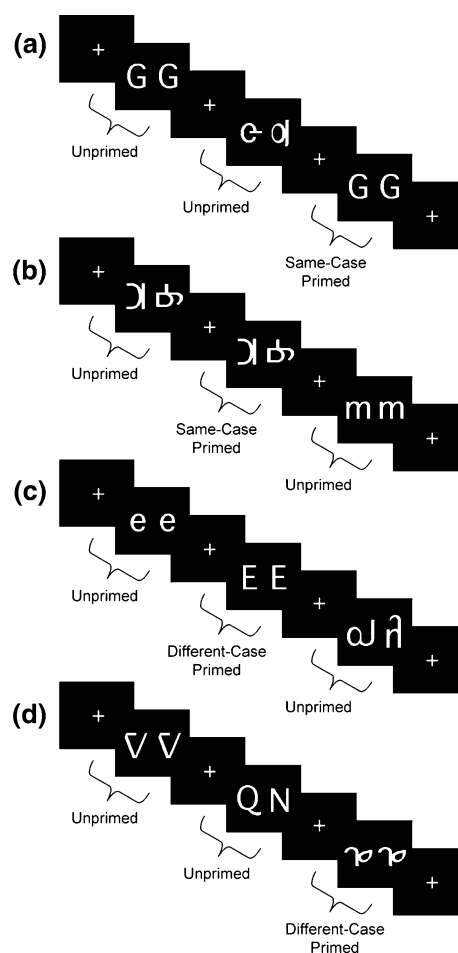

Fig. 2 Examples of different trial types in the visual-matching task. For both letter and pseudoletter pairs, same-case-primed pairs were preceded by the same pair in the same letter case (**a**, **b**), and different-case-primed pairs were preceded by the same pair in the different letter case (**c**, **d**). For half of the trials, primed and unprimed pairs were separated by one trial (**a**, **d**). This intervening trial was always the other stimulus type compared to the primed pair (e.g., pseudoletters if the primed pair was letters; letters if the primed pair was pseudoletters). For the other half of the trials, primed and unprimed trials followed consecutively (**b**, **c**)

Subjects engaged in six runs of the matching task. Within each run, half (24) of the stimulus pairs were composed of letters, and half were composed on pseudoletters. In addition, for both types of pair, half were presented in uppercase (other half in lowercase), and half were "same"-response pairs (other half were "different"-response). Most important, within each run, one-sixth of the pairs (8) were "same-case primed," meaning that they had been preceded by the same pair in the same letter case, one-sixth of the pairs were "different-case primed," meaning that they had been preceded by the same pair in the different letter case, and two-thirds of the pairs (32) were "unprimed," meaning that they had not been preceded by the same pair (see Fig. 2). Thus, across all runs, 24 letter pairs were same-case primed, 24 were different-case primed, and 96 were

unprimed. Similarly for pseudoletter pairs, 24 were same-case primed, 24 were different-case primed, and 96 were unprimed. Note, however, that in the case of pseudoletters, different-case primed pairs are essentially unprimed pairs, since there is no learned relationship between these forms. Each run lasted approximately 4.5 min.

Image acquisition and analysis

Magnetic resonance imaging data were acquired on a Siemens 3T Allegra scanner (Erlangen, Germany). Anatomical images were acquired first, using a transverse MP-RAGE T1-weighted sequence (Siemens) with a voxel size of $0.5 \times 0.5 \times 1$ mm (TR = 1,200 ms; TE = 2.93 ms; flip angle = 12°). Functional images were acquired using an echo-planar sequence (TR = 2,500 ms; TE = 40 ms; flip angle = 90°; voxel size = 3.5×3.5 in-plane resolution). During each functional run, 108 sets of 26 contiguous 4-mm thick axial images were acquired parallel to the anterior–posterior commissure plane.

Data from each subject were preprocessed to remove noise and artifacts, including correction for movement within and across runs using a rigid-body rotation and translation algorithm (Friston et al. 1994; Snyder 1996). Image slices were temporally realigned (using sinc interpolation) to the midpoint of the first slice, accounting for differences in the acquisition time for each individual slice. Data were then resampled into 2-mm isotropic voxels and warped into a standardized atlas space (Talairach and Tournoux 1988).

Preprocessed data were analyzed based on the General Linear Model (GLM; Friston et al. 1994; Josephs et al. 1997; Miezin et al. 2000; Worsley and Friston 1995; Zarahn et al. 1997), using the FIDL analysis package (http://www.nil.wustl.edu/~fidl). Neural signals during the six conditions of interest [Stimulus Type (2) × Prime Type (3)] were modeled in the GLM at the seven time points (i.e., image acquisitions) immediately following each stimulus onset. In addition, a factor was coded to account for the within-run linear trend (linear drift and a constant term). All effects were modeled simultaneously in the GLM for each subject.

Regions of interest were defined both a priori and based on exploratory analyses. A region of interest in the left mid-fusiform cortex (centered at $x = -44$, $y = -52$, $z = -20$; Talairach and Tournoux 1988) was defined based on coordinates provided by Dehaene et al. (2001; see Fig. 3a). Although several left mid-fusiform regions were examined in the Dehaene et al. study, this particular region was selected for the current analysis because it was the one that exhibited case-invariant priming. Moreover, this region is within the area defined by a meta-analysis of 35 word-reading studies (Jobard et al. 2003) and is close to regions

examined in previous investigations of letter selectivity (James et al. 2005; Joseph et al. 2006; Pernet et al. 2005; Tagamets et al. 2000). In addition, the homologous region in the right hemisphere ($x = 44$, $y = -52$, $z = -20$; Talairach and Tournoux 1988) was defined as a control (see Fig. 3b). If letter selectivity and case invariance are properties of the left mid-fusiform region exclusively, as argued by the VWFA hypothesis (Cohen and Dehaene 2004), this right hemisphere region should not exhibit either effect. Both regions were 15-mm diameter spheres centered on the coordinates in each hemisphere. Each included 251 $2 \times 2 \times 2$ mm voxels.

Neural signals during the critical conditions were averaged across all voxels in each region, and the average of the estimated signal at time points 2–4 (5–10 s post-stimulus onset; i.e., the peak of a typical hemodynamic response function) was subjected to analysis (described below). This technique assumes (a) that signals conform to the typical hemodynamic response function and (b) that meaningful differences between tasks are observed in the response function's peak.

Exploratory regions were defined based on results from two separate voxel-wise, repeated-measures analyses of variance (ANOVAs). In one analysis, referred to as "same case", the three-way interaction of Prime Type (same-case primed vs. unprimed) × Stimulus Type (letter vs. pseudoletter) × Time (across the seven estimated time points) was assessed. In the other analysis, referred to as "different case", the three-way interaction of Prime Type (different-case primed vs. unprimed) × Stimulus Type (letter vs. pseudoletter) × Time (across the seven estimated time points) was assessed. The Z statistical images produced by these analyses were smoothed by a 4-mm radius hard sphere kernel, sphericity adjusted, to account for weak correlations between time points, and Monte Carlo corrected, using a threshold of $Z = 4.0$ (24 contiguous voxels; Forman et al. 1995; McAvoy et al. 2001). A peak (local extremum) search algorithm was used to identify the coordinates (Talairach and Tournoux 1988) of activation peaks in the corrected images. Peaks separated by less than 10 mm in each image were consolidated by coordinate averaging, and spheres (20-mm diameter) were centered on each peak.

Results

Performance

Response times for correct trials were analyzed in a repeated-measures ANOVA with Stimulus Type (letters vs. pseudoletters) and Prime Type (same-case primed vs. different-case primed vs. unprimed) as within-subjects

Fig. 3 BOLD signal change (%) as a function of Stimulus Type (letters vs. pseudoletters), Prime Type (same-case primed vs. different-case primed vs. unprimed), and Time (at the seven estimated time points) in a priori left (**a**) and right (**b**) mid-fusiform regions
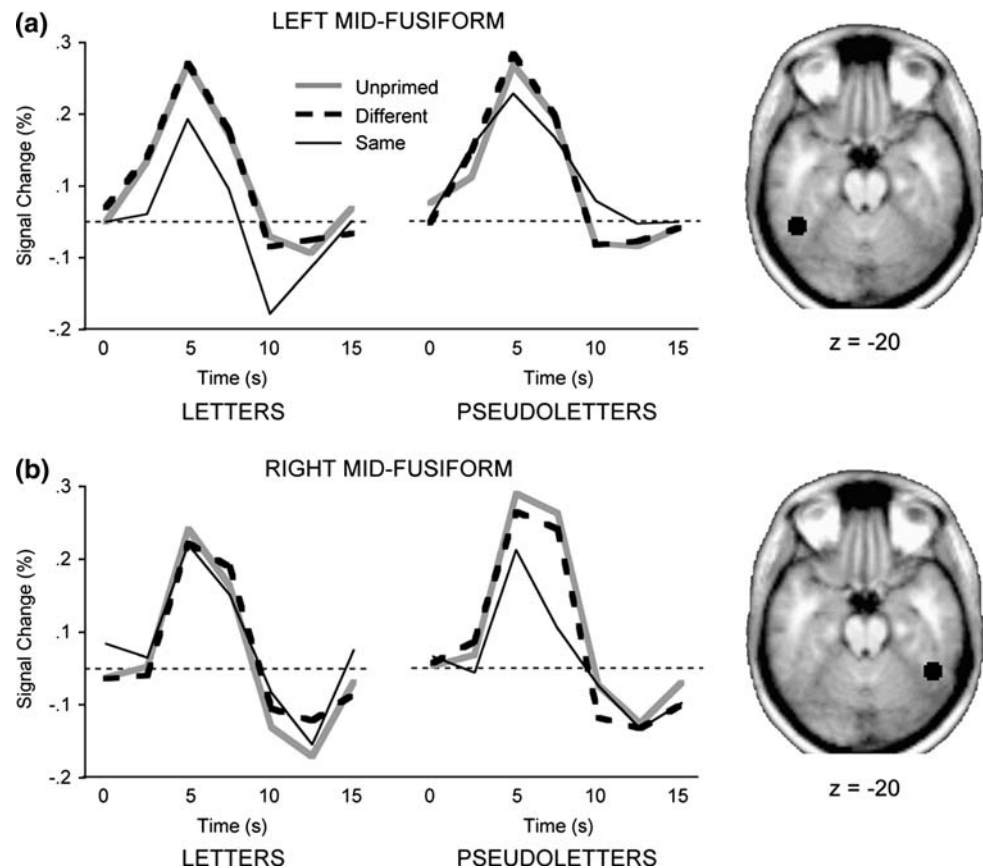

Table 1 Mean response times (ms) and error rates (%) as a function of Stimulus and Prime Type

Stimulus Type	Prime Type		
	Unprimed	Different-case primed	Same-case primed
Letters	828 ± 149 (1.3 ± 1.4)	823 ± 154 (1.5 ± 3.5)	774 ± 154 (1.1 ± 1.9)
Pseudoletters	873 ± 161 (2.4 ± 1.7)	851 ± 165 (2.2 ± 2.9)	821 ± 168 (0.9 ± 1.7)

Error rates are in parentheses. ± indicates standard deviation from the mean

independent variables (see Table 1). Response times were longer for pseudoletter pairs (849 ms) than for letter pairs (808 ms), $F(1, 18) = 21.01$, $P = 0.0002$, for a main effect of Stimulus Type. In addition, a main effect of Prime Type was observed, $F(2, 36) = 23.22$, $P < 0.0001$, in which response times were faster for same-case-primed pairs (797 ms) than different-case-primed pairs (837 ms), $t(18) = 4.58$, $P = 0.0002$, and unprimed pairs (851 ms), $t(18) = 6.23$, $P < 0.0001$, which did not differ significantly, $t(18) = 1.93$, $P = 0.069$. This priming effect was similar for letter and pseudoletter pairs, as indicated by no interaction of Stimulus Type × Prime Type, $F < 1$. Finally, error rates were extremely low (<2.5%) and did not exhibit any main or interacting effects, all Ps > 0.149.

Neuroimaging

A priori mid-fusiform regions

Neural signals in a priori mid-fusiform regions were analyzed in a three-way, repeated-measures ANOVA with Stimulus Type (letters vs. pseudoletters), Prime Type (same-case primed vs. different-case primed vs. unprimed), and Hemisphere (left vs. right) as within-subjects independent variables. None of the main effects or two-way interactions were significant, all Ps > 0.417; the three-way interaction approached significance, $F(2, 36) = 3.08$, $P = 0.058$ (see Fig. 3).

Critically however, as noted in "Methods", the "different-case-primed" label was not entirely appropriate for the

pseudoletter pairs, since no relationship between these forms had been previously learned. Thus, the three-way analysis was re-computed excluding the different-case-primed condition. This analysis produced a significant interaction of Stimulus Type × Prime Type × Hemisphere, $F(1, 18) = 6.24$, $P = 0.022$. Tests of the simple effects revealed a reduction in signal for same-case-primed pairs (0.066%) compared to unprimed letter pairs (0.142%), $t(18) = 2.27$, $P = 0.036$, but no difference in signal between same-case-primed (0.131%) and unprimed pseudoletter pairs (0.138%), $t(18) = 0.175$, $P = 0.863$, in the left fusiform region (see Fig. 3a). In the right fusiform region, signals were reduced for same-case-primed (0.070%) compared to unprimed pseudoletter pairs (0.156%), $t(18) = 2.15$, $P = 0.046$, but did not differ between same-case-primed (0.095%) and unprimed letter pairs (0.102%), $t(18) = 0.151$, $P = 0.882$ (see Fig. 3b).

The same analysis performed with different-case-primed items instead of same-case-primed items did not produce any significant effects, all Ps > 0.217. Furthermore, none of the paired t tests comparing different-case-primed to unprimed items in each of the Hemisphere × Stimulus Type conditions produced significant effects, all Ps > 0.594.

It should be noted, however, that the time between prime and test presentations was quite long on some trials (up to 17.5 s), and that different-case priming across shorter intervals might have been diluted by a lack of priming across these long gaps. To address this possibility, data were reanalyzed excluding all trials except those in which the test item followed the prime immediately (inter-trial interval of 2.5 s). Similar to the analysis of all trials, no significant effects were observed in the short-interval trials, all Ps > 0.329. Thus, no priming was observed for the different-case letters or different-case pseudoletters, even when the interval between prime and test was short.

Exploratory regions

Three regions emerged from the "same case" analysis assessing the interaction of Stimulus Type × Prime Type (same-case primed vs. unprimed) × Time (see Table 2; Fig. 4). Most important, two of these were in the mid-fusiform cortex, replicating results from the analysis of a priori regions. A region in the left mid-fusiform exhibited greater priming for letters than for pseudoletters, $F(1, 18) = 7.08$, $P = 0.016$, for the Stimulus Type × Prime Type interaction at time points 2–4 (see Fig. 4a), while a region in the right fusiform exhibited greater priming for pseudoletters than for letters, $F(1, 18) = 6.13$, $P = 0.024$ (see Fig. 4b). In addition, a region within the cuneus also exhibited greater priming for pseudoletters than for letters, $F(1, 18) = 6.59$, $P = 0.019$ (see Fig. 4c). No regions emerged from the analogous "different case" analysis computed with all trials or with short-interval trials only.

Table 2 Exploratory regions exhibiting interaction of Stimulus Type, Prime Type (same-case primed vs. unprimed), and Time

Region	x	y	z	Peak Z	Vox
L mid-fusiform	−41	−51	−18	4.01	183
R mid-fusiform	33	−55	−18	4.32	113
R cuneus	8	−82	19	4.14	98

Peak locations (x, y, z in mm) in the Talairach and Tournoux (1988) atlas with associated significance (Peak Z) and number of voxels (Vox)

Discussion

A large body of neuropsychological and neuroimaging research indicates a critical role for the left mid-fusiform cortex in reading, however, the precise function of this area remains a topic of much debate (e.g., Cohen and Dehaene 2004; Price and Devlin 2003, 2004). On the one hand, it has been argued that this area is dedicated specifically to the processing of visual word forms (VWFA hypothesis; Cohen and Dehaene 2004; Cohen et al. 2000, 2002). In contrast, others have argued that this area is a generic object processor, not dedicated to the processing of words per se (Binder et al. 2006; Joseph et al. 2006, 2003; Kronbichler et al. 2004; Mechelli et al. 2003; Price and Devlin 2003, 2004; Rogers et al. 2005; Starrfelt and Gerlach 2007; Xue et al. 2006).

We addressed this controversy in the present study by examining two critical features of the VWFA hypothesis—(1) that representations in left mid-fusiform cortex are tuned preferentially to the shapes of letters, compared to visually similar non-letters (letter selectivity) and (2) that these representations are insensitive to changes across letter case, even when different-case letters are dissimilar looking (e.g., A/a) (case invariance; Cohen and Dehaene 2004). Letter selectivity was assessed by comparing the magnitude of priming for letters and pseudoletters in the putative VWFA, and in a homologous right hemisphere region; case invariance was assessed by comparing the magnitude of priming for same- and different-case-primed letters in these areas. Results provide mixed support for these criteria. Supporting the letter selectivity criterion, priming was observed for letter but not pseudoletter pairs in the left mid-fusiform region, but not in the right hemisphere region. Opposing the case invariance criterion, priming for letters in the left mid-fusiform region was case dependent. These findings are discussed in turn below.

Letter selectivity

Examinations of letter selectivity are essential to the question of whether the left mid-fusiform supports word-specific or generic object processing. In the present study, we

Fig. 4 BOLD signal change (%) as a function of Stimulus Type (letters vs. pseudoletters), Prime Type (same-case primed vs. unprimed), and Time (at the seven estimated time points) in exploratory regions. Regions were defined based on voxel-wise analysis of the Stimulus Type × Prime Type × Time interaction (see text for details)
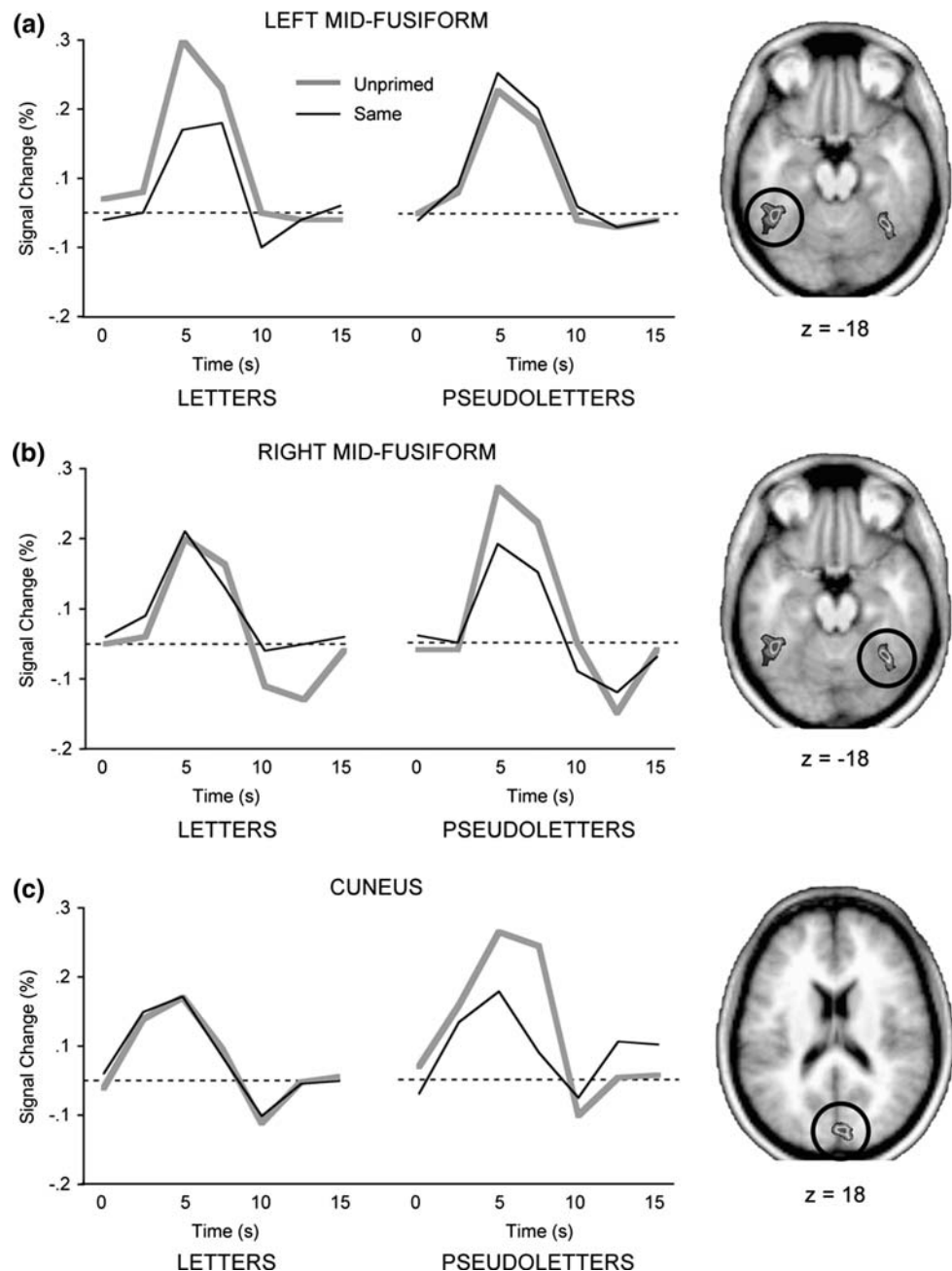
observed priming for letters but not for visually equivalent pseudoletters in the putative VWFA, suggesting that representations in this area store letters preferentially over other stimuli, as argued by Cohen and Dehaene (2004). This finding converges with results from previous studies exhibiting differential activity for letters and non-letters in this area (James et al. 2005; Pernet et al. 2005; Price et al. 1996; Puce et al. 1996; Vinckier et al. 2007); however, it contrasts with findings of equivalent activity for letters and non-letters (James et al. 2005; Joseph et al. 2006; Pernet et al. 2005; Tagamets et al. 2000). Critically, previous studies have compared overall activity for letters and non-letters, which may not be as sensitive to differences between stimu-

lus types as estimates of repetition priming (Grill-Spector and Malach 2001). Indeed, estimates of overall activity in the left mid-fusiform did not differ for letters and pseudoletters in the present study. Thus, results indicate that priming estimates can reveal properties of visual processing systems that are not revealed by overall activity estimates.

Importantly, the finding of letter selectivity in the VWFA in the present study challenges previous claims regarding the role of task demands in this region. In particular, based on the observation of differential overall activity for letters and non-letters [geometric shapes and (unfamiliar) Korean characters] during a categorization task but not during a discrimination task, Pernet et al. (2005) argue that

letter selectivity in the VWFA is task dependent, and not a required characteristic of the region's function. Although the present study did not examine task demands specifically, the task employed (decide if items within pair are identical or different) was very similar to Pernet et al.'s discrimination task (detect pairs in which items differ by a single feature). Thus, results from the present study indicate that letter selectivity may be observed in the VWFA, even during tasks requiring fine-grained discrimination, when priming is examined.

It should be noted that, although the comparison of letter and pseudoletter priming in the present study revealed evidence for letter selectivity in the VWFA, comparisons of letter priming and priming for other types of non-letter stimuli, such as digits, could reveal a more graded pattern of selectivity. For example, James et al. (2005) observed greater overall activity for Roman letters compared to Chinese characters, but not compared to digits, suggesting that selectivity in the left mid-fusiform is not restricted to letters. Nonetheless, as noted above, comparisons of overall activity may not be as sensitive to stimulus differences as comparisons of priming, and therefore, priming for letters could be greater than priming for digits, even though overall activity for each stimulus type is the same. As such, future comparisons of letter priming to priming for multiple types of non-letter stimuli are necessary to delineate the full extent of selectivity in the left mid-fusiform.

According to the VWFA hypothesis (Cohen and Dehaene 2004), the letter selectivity observed in the present study indicates perceptual representations for letters stored in the left fusiform cortex. It may be important to note, however, that letter selectivity in this region could have emerged due to factors not associated with perceptual representations. For one, letters were less perceptually demanding than pseudoletters, as indicated by their faster response times, and as such may have been primed more readily. In addition, subjects may have approached the matching task differently for letters and pseudoletters, using names for letters and visual memory for pseudoletters. Although these possibilities cannot be ruled out entirely, they seem unlikely in light of the priming for pseudoletters in the homologous right hemisphere region. Indeed, perceptual demand and task implementation are both factors that could affect priming throughout the brain. Thus, the opposite pattern of priming in homologous left and right hemisphere regions suggests that letter-selective priming emerges from letter-selective representations in the left fusiform cortex.

Case dependence

While results from the present study are generally in line with the letter selectivity criterion of the VWFA hypothesis

(Cohen and Dehaene 2004), they contrast directly with the case invariance criterion of the hypothesis (Cohen and Dehaene 2004; Dehaene et al. 2001, 2004). Indeed, no priming was observed for different-case letters in the left mid-fusiform region, indicating that representations in this area are sensitive to changes in letter case. As noted in the Introduction, previous studies observing case-invariant priming have used whole words as stimuli (Dehaene et al. 2001, 2004), which, unlike single letters, share orthographic and semantic information across different-case formats (e.g., Devlin et al. 2006). In contrast, priming was case dependent when pairs of single letters were tested in the present experiment. Similarly, others have observed font-dependent priming for single letters in the VWFA (Gauthier et al. 2000), which, although different from the case-dependent priming examined in the present study, also indicates a high degree of visual specificity for single letters in this region. Of course, a study comparing different-case priming for single letters, non-pronounceable letter strings, pronounceable letter strings (pseudowords), and words would help to identify the level (orthographic, phonological, or semantic) at which case invariance is achieved. Indeed, previous work has identified distinct neuronal mechanisms for semantic and phonological contributions to reading (Mechelli et al. 2005). Moreover, it is possible that the VWFA supports two forms of priming—a case-dependent form for single letters, and a case-invariant form for words. Nonetheless, results from the present study contrast with the strong version of the VWFA hypothesis, suggesting that case-invariant priming in previous studies emerged from non-visual properties of words, rather than from case-abstract letter representations.

This conclusion poses a serious challenge to Cohen and Dehaene's (2004) proposal that the VWFA develops to perform arbitrary mappings across letter case, and as such, undermines their claim that this region accomplishes goals that cannot be accomplished by a generic object-processing system. In other words, if the goals that distinguish reading from other object recognition tasks are not accomplished by the VWFA, it is unlikely that this area developed to accomplish these goals. Of course, the finding of letter selectivity in the present study cannot be ignored. Nonetheless, without evidence for case invariance, this selectivity is less readily interpreted. On the one hand, it is possible that letter selectivity supports a weaker version of the VWFA hypothesis in which the left mid-fusiform responds selectively to letters compared to other stimuli, but does so in a case-dependent manner. On the other hand, letter selectivity in the present study may have reflected a preference for familiar over unfamiliar stimuli in a generic object-processing region (e.g., Binder et al. 2006; Kronbichler et al. 2004). Regardless, results from the present study do not support the strong version of the VWFA hypothesis, which predicts both letter selectivity *and* case invariance.

Hemisphere asymmetry

Although results from the present study do not clearly support the VWFA hypothesis, they do suggest that this area functions differently from other areas—namely, the homologous right mid-fusiform region. The right hemisphere region was examined in the present study as a control for questions regarding the left mid-fusiform, and our only prediction regarding its function was that it should differ from that of the left hemisphere region, according to the VWFA hypothesis (Cohen and Dehaene 2004; Cohen et al. 2000, 2002). Interestingly, the right mid-fusiform region exhibited the *opposite* pattern of selectivity in priming from the left hemisphere region—priming for pseudoletters but not letters. Thus, the right mid-fusiform, not only differs from the left, but also may support its own unique form of stimulus selectivity.

In line with this idea, Marsolek and colleagues have proposed a dual subsystems model of visual-form recognition in which novel visual information is processed and stored more effectively in the right hemisphere than the left (Burgund and Marsolek 2000; Deason and Marsolek 2005; Marsolek 1995; Marsolek and Burgund 1997; Marsolek et al. 1996). In particular, it is argued that a subsystem operating more effectively in the right hemisphere than the left relies on holistic, form-specific representations that may be particularly useful for storing novel information, whereas a subsystem operating more effectively in the left hemisphere than the right stores feature-based, form-abstract representations that may be particularly useful for storing familiar information. Although Marsolek and colleagues have relied on divided-visual-field presentations to assess hemisphere asymmetries behaviorally, similar neuroimaging studies suggest that these subsystems are located in mid-fusiform cortex, close to the regions examined in the present study (Koutstaal et al. 2001; Simons et al. 2003; Vuilleumier et al. 2002). Critically however, the dual subsystems theory differs from the VWFA theory (e.g., Cohen and Dehaene 2004; Cohen et al. 2000, 2002) in that the left mid-fusiform is not claimed to be selective for the processing of letters/words per se, but rather, is engaged when stimulus and task demands require abstract, feature-based processing (Burgund and Marsolek 2000; Deason and Marsolek 2005; Marsolek 1995; Marsolek and Burgund 1997). Thus, differential selectivity for letters and pseudoletters across hemispheres in the present study may reflect the operations of dissociable abstract and specific subsystems.

It may be important to note that while the present study observed decreased activity for primed compared to unprimed pseudoletters in the right mid-fusiform, a previous study observed increased activity for primed compared to unprimed pseudoletters in this region (Henson et al. 2000). We suspect that these different patterns may be due to differences in the significance granted pseudoletters by the different tasks employed in the two studies. In particular, pseudoletters in the present study were granted the same importance as letters, in that subjects were asked to respond similarly on letter and pseudoletter trials. This may have biased the system to begin to form stable representations for the pseudoletter stimuli. By contrast, pseudoletters in the Henson et al. study had little task significance, in that subjects did not respond to them and responded only to a target symbol (e.g., '!') in a stream of pseudoletter and symbol stimuli. This de-emphasis of the importance of pseudoletters may have biased the system against forming stable representations for these stimuli. Thus, the direction of the difference between primed and unprimed pseudoletters may depend on the significance of these stimuli to the task being performed. Of course, future studies comparing priming for pseudoletters under different task conditions are needed to resolve this issue.

Conclusion

Results from the present study contradict the strong version of the VWFA hypothesis, which predicts both letter selectivity and case invariance in the left mid-fusiform cortex (e.g., Cohen and Dehaene 2004). Rather, results are in line with the perspective that left and right mid-fusiform regions support generic object processes that may be differentially effective for representing disparate types of visual stimuli. Moreover, results highlight the value of comparing priming estimates in studies of mid-fusiform function, and suggest that it may be more sensitive than estimates of overall activity to differences between stimulus types.

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