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Attention to single letters activates left extrastriate cortex

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Brain imaging studies examining the component processes of reading using words, non-words, and letter strings frequently report task-related activity in the left extrastriate cortex. Processing of these linguistic materials involves varying degrees of semantic, phonological, and orthographic analysis that are sensitive to individual differences in reading skill and history. In contrast, single letter processing becomes automatized early in life and is not modulated by later linguistic experience to the same degree as are words. In this study, skilled readers attended to different aspects (single letters, symbols, and colors) of an identical stimulus set during separate sessions of functional magnetic resonance imaging (fMRI). Whereas activation in some portions of ventral extrastriate cortex was shared by attention to both alphabetic and non-alphabetic features, a letter-specific area was identified in a portion of left extrastriate cortex (Brodmann's Area 37), lateral to the visual word form area. Our results demonstrate that while minimizing activity related to word-level lexical properties, cortical responses to letter recognition can be isolated from figural and color characteristics of simple stimuli. The practical utility of this finding is discussed in terms of early identification of reading disability.

Keywords: Reading; Cortex; Linduistic experience

Introduction

The neural representation of reading processes has been the focus of a large number of studies over the last 15 years, dating back to the first observation made by Petersen et al. (1988) using Positron Emission Tomography (PET). Converging evidence points to several areas in the left hemisphere that are typically involved in reading: posterior superior temporal, inferior parietal, inferior prefrontal, and extrastriate cortices (Fiez and Petersen, 1998; Joseph et al., 2001; Price et al., 1996; Pugh et al., 2000; Turkeltaub et al., 2002). The latter area, particularly that part of the ventral visual processing pathway at the lateral and ventral temporal occipital junction (Brodmann's Areas 19 and 37), has attracted interest recently because of its role in successful reading acquisition (Pugh et al., 2001; Shaywitz et al., 2002). There is also mounting evidence that left extrastriate cortex and its associated projections have a role in developmental dyslexia, a disorder of reading acquisition. In a magnetoencephalography study, Salmelin et al. (1996) detected a reduced early processing component localized in the left inferior temporal–occipital cortex in dyslexics viewing words. Using PET, Rumsey et al. (1997) and Horwitz et al. (1998) found less activity in the same region in subjects with dyslexia who read non-words. Brunswick et al. (1999) also reported less activation of BA 21/37 within a dyslexic sample reading either real words or non-words. Simos et al. (2002) have reported enhancement of neural activity in this and other left hemisphere regions in dyslexic children following a program of remedial instruction. These findings converge on the importance of the left extrastriate cortex in reading-related activities (see Eden and Zeffiro, 1998, for a review); however, its explicit role in the reading process is still under active investigation (Cohen et al., 2000, 2002; Price and Devlin, 2003; Pugh et al., 2001).

Distinct processing streams have been identified within extrastriate cortex that respond variably to different stimulus types: letter strings (Allison et al., 1994; Nobre et al., 1994; Polk and Farah, 1998; Tarkiainen et al., 1999), words and non-words (Bookheimer et al., 1995; Buchel et al., 1998; Dietz et al., under review; Kuriki et al., 1998; Mechelli et al., 2000; Moore and Price, 1999; Price and Friston, 1999), objects and visual patterns (Kawashima et al., 1998; Kourtzi and Kanwisher, 2000), faces (Allison et al., 1999, Clark et al., 1996; Haxby et al., 1994; Kanwisher et al., 1998). Using PET, Garrett et al. (2000) reported that accuracy in distinguishing single letters from non-letter stimuli is correlated with activity in left BA 37 in good readers. Letter identification, as a special case of object recognition, is particularly relevant since it has long been known that, in non-human primates, recognition of familiar objects activates the posterior inferior temporal–occipital region, part of the ventral visual processing stream (Ungerleider and Mishkin, 1982). Furthermore, Cohen et al. (2002) have proposed that activation of visual object perception processes is an essential step to reading print.

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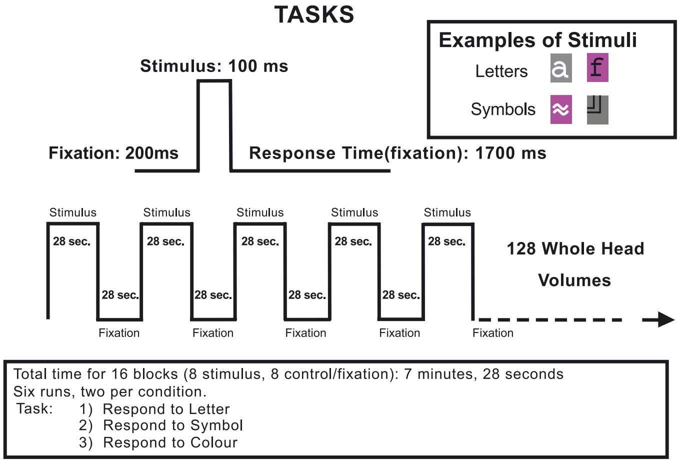

Total time for 16 blocks (8 stimulus, 8 control/fixation): 7 minutes, 28 seconds
Six runs, two per condition.
Task: 1) Respond to Letter
2) Respond to Symbol
3) Respond to Colour

Fig. 1. Schematic of the design for fMRI data acquisition and examples of Letter and Symbol stimuli. (The full stimulus set in available in the online appendix.) Data were acquired for each condition during separate acquisitions and conditions were counterbalanced.

Although most brain imaging studies have focused on the processing of whole words (contrasted to non-words, letter strings, or false fonts), the behavioral literature has shown that accomplished readers can be distinguished from impoverished readers by tasks that simply require individuals to name letters (Wolf, 1986; Wolf and Bowers, 1999). Letter knowledge and speed of letter naming are particularly sensitive predictors of advanced reading acquisition in children. Dyslexic children and adolescents are compromised in their accuracy (Semrud-Clikeman et al., 2000) and speed (Wolf, 1986) in naming letters and numbers. However, poorer naming speed cannot be accounted for by less reading experience, or the inability to actually articulate the names of the letters (Wolf, 1986). Faster letter naming speed was found to be positively correlated with reading compensation in adult dyslexics, emphasizing the importance of letter naming skills in reading outcome (Felton et al., 1990; Flowers, 1995). As identification of letters is an early predictor of later reading success and distinguishes adult dyslexics, this pre-lexical skill would be expected to exhibit regional functional specialization in extrastriate visual cortex. Coupling a task that can be accomplished by children or low-literate adults with brain imaging methods may prove useful in predicting reading acquisition at an early stage, possibly leading to identification of effective remedial instruction.

Corbetta et al. (1990, 1991) illustrated modulation in regional cerebral blood flow in extrastriate visual areas based on attending to different aspects of the same visual stimuli. While other studies have demonstrated task-specific areas of activation within the ventral extrastriate cortex when task demands were focused on different aspects of a stimulus within the same modality (Kawashima et al., 1998; Martin et al., 1995; Price and Friston, 1997; Shulman et al., 1997), none of these studies included simple alphabetic material. Tarkiainen et al. (1999) studied single letters compared to symbols, but subjects passively viewed stimuli that may not have been matched for visual complexity. Jessen et al. (1999) and Pugh et al. (1997) each employed strings of letters but did not draw attention to the letter versus non-letter features.

In this study, subjects were instructed to direct attention to letters or non-letter symbols or to their color, while viewing the same set of letters and symbols in black or white. This extends previous reports of category-specific activation by investigating whether, within extrastriate visual cortex, simple letter detection could be isolated from objects with similar features (non-letter symbols with angularity and contour not unlike that of letters) and from an orthogonal attribute (color). To our knowledge, this is the first study to systematically examine the language-specific functions of the posterior temporal–occipital region by varying attention to linguistic and non-linguistic aspects of a set of simple visual stimuli below the letter string or word levels. In separate acquisition runs (see Fig. 1), 11 subjects were instructed to respond by button press if the stimulus presented was either (1) a letter, (2) a non-letter symbol, or (3) of a black color, making it possible to examine which regions in the posterior temporal–occipital pathway mediate the alphabetic (letter) versus non-alphabetic (shape and color) properties of the stimuli. Functional magnetic resonance imaging (fMRI) was chosen for its excellent spatial resolution, sensitivity, and ease of use in subjects of all ages. Our results demonstrate clear task-related brain activation in extrastriate visual cortex during letter recognition that is not shared by other stimulus features (such as form or color), suggesting this as a potentially important neural substrate associated with accomplished reading.

Methods

Subjects

Eleven adult subjects (eight female, four non-white), mean age 27.1 (range 18–35 years), and mean education 16.6 years (range 14 to 21) were recruited by advertisement from the community. All subjects were right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). Subjects were first screened by telephone and then by a battery of cognitive tests and questionnaires to rule in normal IQ and to rule out persisting or compensated reading disability, Attention Deficit/Hyperactivity Disorder, and current psychiatric condition. Exclusion criteria were first language other than English, nicotine dependence, psychoactive substance use disorder, history or presence of Axis I psychiatric disorder (American Psychiatric Association, 1994), significant medical or neurological illness (including migraine in the subject or in a first degree relative), history of closed head injury or concussion, current use of medications other than birth control pills, known history of birth complications, history of learning disability, or hearing problems. Subjects reported being free of metal and females were not pregnant.

All subjects had normal or corrected vision (Sloan Letters, Good-Lite Co., Forest Park, IL) and normal local and global stereopsis (using the Randot and the TNO, respectively). Color blindness was ruled out using the Tests of Color-Deficiency (Ishihara, 1996). Subjects completed a modified version of the Wender Utah Rating Scale to identify symptoms of Attention Deficit Hyperactivity Disorder based on self-report (Ward et al., 1993). The SCL-90 determined current psychiatric status (Derogatis, 1994). Written informed consent was obtained and subjects were paid for their participation. The protocol was approved by the Georgetown University Medical Center Institutional Review Board. The research participants were studied at the Georgetown University Medical Center's General Clinical research Center.

The test battery carefully screened subjects for normal single-word reading skills as well as for indications of residual deficits in underlying skills associated with reading acquisition (decoding, phonemic awareness, naming fluency, and auditory sequential memory). The reading skills test battery included the following tests: Woodcock Reading Mastery Test—Revised Normative Update (WRMT-R, NU) subtests for Letter-Word Identification and Word Attack to evaluate word recognition and non-word decoding skills (Woodcock, 1998); Decoding Skills Test to measure levels of single-word reading and decoding skill using mono- and polysyllabic real and analogous non-words (Richardson and DiBenedetto, 1985); Test of Auditory Analysis Skill to assess of the ability to segment spoken words into syllables or sounds (Rosner, 1975); and Lindamood Auditory Conceptualization test to test phoneme sequences presented in isolation and within word-like strings in the auditory modality (Lindamood and Lindamood, 1979). Naming fluency was assessed by the Rapid Automatized Naming Test (Denckla and Rudel, 1976a,b). Subjects were excluded if their score on any reading skill test was less than the 25th percentile. Published norms were used where available; otherwise, cut-offs were based on the distribution of scores from a large sample of adult subjects in whom developmental reading disability had been ruled out by childhood testing (Felton et al., 1990; Flowers, 1995). Additional tests included the Digit Span subtest from the Wechsler Adult Intelligence Test, 3rd Edition (WAIS-III), which served as a measure of auditory working memory (Wechsler, 1997); and the Test of Written Spelling-2 (TWS-2), which gave a measure of orthographic skill with predictable (phonetically regular) and unpredictable (irregular) words (Larsen and Hammill, 1986). Table 1 summarizes the group's performance on all tests.

Table 1
Mean test scores and standard deviations for eleven subjects[a]

	Mean	SD
Real and non-word reading tests:		
WRMT-R (NU) Single Word ID (mean = 100; SD = 15)	123.5	14.4
WRMT-R (NU) Word Attack (mean = 100; SD = 15)	121.2	16.3
Decoding skills test-real words (max. 60)	59.8	0.6
Decoding skills test-non words (max. 60)	57.7	3.3
Spelling test (mean = 100; SD = 15):		
Test of written spelling-2	123.4	14.1
Phonological awareness tests:		
Test of auditory analysis skills (13)	12.7	0.9
Lindamood auditory conceptualization test (100)	97.9	3.9
Rapid automatized naming test:		
Colors and objects (mean seconds)	28.2	2.2
Letters and numbers (mean seconds)	16.9	3.1
Auditory sequential memory test:		
WAIS-III Digit Span (mean = 10; SD = 3)	13.3	2.9

[a] Maximum scores for tests without standard scores are given in parentheses (see text for test descriptions).

Data acquisition

Multi-slice echo-planar images (EPIs) were transversely acquired on a 1.5 Tesla Siemens Vision scanner with a 40 ms echo time (TE), 3.5 s repetition (TR), 64 × 64 acquisition matrix, 230 mm field of view (FOV) with 40 non-interleaved 3.0 mm slices and 0.6 mm gap, yielding a 3.6 mm^3 voxel size. A high resolution structural scan was acquired in the sagittal plane during the same session using a 3D MPRAGE sequence: TR = 15 ms, TE = 7 ms, 12° flip angle, NEX=1, 1 mm slices thickness, 256 × 256 matrix, 256 mm field of view, yielding a 1 mm^3 voxel size.

Stimuli and experimental design

The same stimuli were used for each of the three tasks, only the instructions changed: pressing a button in response to the presentation of (1) LETTERS, (2) SYMBOLS, or (3) COLOR (i.e., when the stimulus was black). Directing attention to different features of the stimuli during identical runs allowed processing of letters to be isolated from the processing of a similar form (symbols) and from the processing of an orthogonal feature (color). Task order was counterbalanced across subjects and each condition run was repeated twice. Before scanning, subjects practiced the tasks to a criterion of at least 75% hits and no more than 25% false alarms. Stimuli were selected from 12 letters (six upper and six lower case) and 12 non-letter symbols, matching the letters with respect to angularity and contour, and each was foveally presented in either black or white on a uniform magenta background (see insert in Fig. 1; a display of the full stimulus set is provided in Appendix A). Thus, the task conditions called for a more subtle distinction of features than those reported in previous studies. During each of the six functional imaging runs, subjects viewed 28-s blocks of the stimulus condition alternating with 28-s blocks of a control condition. During the control condition, only a fixation cross was present. The task condition consisted of letters randomized for case type and color, interspersed with non-letter symbols, 14 stimuli per block presented 2 s apart for 100 ms using a Sharp LCD projector (Sharp Electronics Corp., Osaka, Japan) and Superlab Pro (Cedrus Corp., San Pedro, CA). There was a 50% probability of a letter versus a symbol and a 50% probability that the stimuli were black versus white in any block. Subjects were instructed to fixate on the cross during both stimulus and control blocks. As diagramed in Fig. 1, each functional run consisted of a total of 16 blocks (eight stimulus and eight control, beginning with a stimulus block), lasted 7 min and 28 s for a total of 128 total whole-head volumes.

Data analysis

Functional MRI data

Pre-processing of the MRI data was carried out in MEDx 3.2 (Sensor Systems, Inc., Sterling, VA). The EPI data for each subject were motion corrected by realigning all images to the mean of all the images in the first run using AIR 3.08 (Woods et al., 1998a,b). A spatial Gaussian filter with a FWHM of 7.2 mm^3 was then applied. To remove global differences from scan-to-scan, ratio normalization was applied by dividing each scan by its global whole-brain mean and multiplying by 1000. A high-pass Butterworth temporal filter with a cut-off twice the cycle length (112 s) and a Hamming window with a 90% inclusion width was applied to remove physiologic noise. For each task condition, a mean difference image was computed by collapsing across the two runs of the same task and subtracting the mean of the control (FIXATION) blocks from the mean of the corresponding stimulus blocks (LETTER, SYMBOL, or COLOR). The resulting mean difference images for each subject for each task were transformed into the MNI305 atlas space based on the transformation parameters derived from a second-order polynomial warp (Woods et al., 1998a,b) of the mean of all the motion-corrected images for the task to the EPI template provided with SPM99 (http://www.fil.ion.ucl.ac.uk/spm). This resulted in a set of spatially normalized mean difference images at a resolution of 2-mm cubic voxels. Since the EPI template is based on the MNI305 atlas space, to facilitate labeling, all coordinates derived from the statistical analyses were corrected to the atlas of Talairach and Tournoux (1988) for comparison with other published results (Duncan et al., 2000).

To identify areas common to all three tasks as well as those specific only to attending letters, we performed the following three statistical analyses.

Activity observed in LETTER, SYMBOL or COLOR processing. In the first analysis, a single group t test for each contrast (LETTER, SYMBOL, OR COLOR minus FIXATION) was computed. Each task was compared to its own fixation baseline. These three t-maps were converted to Z-maps and thresholded at $Z > 3.1$ ($P < 0.001$, uncorrected). A cluster analysis identified foci of activations consisting of more than 60 contiguous voxels.

Activity common to LETTER, SYMBOL, and COLOR processing. Using the same critical threshold, the three Z-maps, computed as described above, were then conjoined to identify areas activated for all three conditions. The probability that a voxel would exceed the $Z > 3.1$, $P < 0.001$ threshold in all three contrasts by chance alone is $(0.001)^3$ or 10^{-9}. A cluster analysis identified foci of activations consisting of more than 60 contiguous voxels.

Activity observed for LETTER-specific processing. To identify the areas specific to letter processing, a conjunction analysis (as implemented in SPM96) was performed combining the [Letter-Fixation > Symbol-Fixation] contrast with the [Letter-Fixation > Color-Fixation] contrast (Price and Friston, 1996). The power of this version of conjunction analysis is that it eliminates any interaction between letter processing and symbol or color processing. The conjunction was corrected for multiple comparisons using a mask of all voxels derived from the LETTER minus FIXATION contrast above a threshold of $Z > 3.1$, $P < 0.001$ uncorrected. This resulted in a corrected critical threshold of $P < 0.05$. Clusters in the conjunction were identified by identifying adjacent voxels above the critical threshold.

Similar conjunction analyses were performed to identify regions specific to symbol and color processing using the corresponding SYMBOL minus FIXATION and COLOR minus FIXATION contrasts to generate the multiple comparison masks.

Behavioral data

1. To evaluate subjects' task performance across the three conditions, paired two-tailed t tests were carried out between accuracy measures (d-prime) and mean response times for each condition.
2. To establish if functional brain activation was confounded by any differences in performance identified in step 1, we carried out a Pearson correlation between response time and MRI signal change in each voxel.

Results

Functional MRI results

Task specific activity

The locations of the maximally activated voxels within clusters specific to LETTER, SYMBOL, and COLOR processing are summarized in Table 2. Consistent with previous results, these included loci in the fusiform gyrus, parietal, and inferior frontal, non-primary motor cortex, putamen, and thalamus.

Activity common to LETTER, SYMBOL, and COLOR processing

Using the maps generated in the first step of the analysis, task-related signal changes common to all three tasks (LETTER, SYMBOL, and COLOR) were identified (see Table 2). Activity across all three tasks was observed in bilateral fusiform gyrus (ventral BA 37/19), with greater extent for the LETTER recognition condition. Although there was activity in right frontal cortex in response to all three tasks, these areas did not overlap spatially. Both COLOR and SYMBOL conditions activated left motor cortex (BA 4) and thalamus, but these regions failed to reach significance in LETTER processing. Hence, there were no other areas common to all three conditions except for bilateral BA 37/19.

Activity observed for LETTER-specific processing

Conjunction analysis of [LETTER-FIXATION > SYMBOL-FIXATION] and [LETTER-FIXATION > COLOR-FIXATION] yielded regions of greater activity in the left middle occipital gyrus (in the lateral portion of BA 37) and in bilateral portions of the inferior frontal gyri (see Table 3 and Fig. 2). These three regions emerged as the only areas significantly more involved in LETTER processing when compared to SYMBOL and COLOR processing (see Fig. 2).

To demonstrate that SYMBOL and COLOR processing do not make similar demands on BA 37, we repeated this analysis to identify regions uniquely related to either SYMBOL processing or COLOR processing. The SYMBOL contrast [(SYMBOL-FIXATION > LETTER-FIXATION) AND (SYMBOL-FIXATION > COLOR-FIXATION)] yielded only two non-primary motor regions of activation in the Pre-Supplementary Motor Area and dorsolateral prefrontal cortex (indicated in Table 3). There were no regions of isolated COLOR processing. Thus, neither non-letter conjunction analysis yielded activation in extrastriate cortex.

In summary, we have identified (1) activity underlying each condition separately (LETTER, SYMBOL, and COLOR processing) when contrasted to a resting baseline and (2) a focus in ventral left extrastriate cortex that was common to LETTER, SYMBOL, and COLOR processing. This region was posterior and medial in location to the focus identified in the conjunction analysis that revealed a significant preference for LETTER processing. These last two observations are visually displayed in Fig. 3, which illustrates the spatial distinction between the posterior region of shared processing (BA 37/19) and the anterior area reserved uniquely for letter processing (BA 37). The region of shared processing lies within the VWFA of Cohen et al. (2000); its center coordinate is x: −41; y: −68; z: −9 and its bounding box is x: −33 to −48; y: −53 to −82; z: +2 to −19. This can be compared to the bounding box for the VWFA of Cohen et al. (2000) including x: −30 to −50; y: −30 to −80; z: < 0.

Behavioral data

Task accuracy and response times

Mean accuracy, in order of d-prime values, was: LETTER = 4.15, COLOR = 4.11, SYMBOL = 3.95. Paired two-tailed t tests of accuracy between task conditions yielded no significant differences (all P values > 0.20). Mean response times, in ascending order, were: COLOR = 378 ms, LETTER = 417 m, and SYMBOL = 445 ms. Responses were significantly faster in the COLOR condition compared to either SYMBOL (P = 0.0001) or LETTER (P = 0.0005) conditions. SYMBOL and LETTER also differed from each other (P = 0.002). In summary, response time for the COLOR task was faster than for the LETTER task which in turn was faster than for the SYMBOL task.

Correlations between performance and brain activation

Although accuracy was matched, response time measures obtained during the scans differed significantly across all three tasks. Therefore, response time data were correlated with the fMRI signal to ensure that the performance did not account for the BA 37 finding. This analysis revealed no correlations between brain activity in the SYMBOL or COLOR tasks. A small correlation was found in the region of the right superior central sulcus for the LETTER condition (Z = 3.9, voxel size = 16). Therefore, response time differences cannot account for our findings in extrastriate cortex.

Discussion

The aim of this study was to determine if regions of the extrastriate visual cortex, previously found to be engaged in lexical processing, could be preferentially activated in response to simpler alphabetic stimuli, without the inherent complexities and learning history associated with reading words and pseudowords. In particular, we wished to establish if the recognition of letters, a skill highly predictive of reading deve-lopment, would result in unique task-related activity in skilled readers.

The first finding from this study of letter, symbol, and color processing confirms prior observations of significant bilateral signal increase in a large portion of ventral extrastriate cortex during the discrimination of either alphabetic or non-alphabetic forms. Thus, consistent with previous reports, a large portion of the ventral and lateral posterior temporal occipital cortex was found to be involved in processing two-dimensional forms, of which letters and symbols are examples. However, the most important finding is that under the same stimulus presentation conditions, when subjects attended to letters rather than other visual features, areas significantly enhanced by alphabetic processing were identified in the left lateral portion of the middle occipital gyrus (BA 37). This finding is consistent with expectations from previous studies that words and word-like stimuli are processed in this region. However, here, we elicited activation using a rather elemental stimulus set, minimally loaded with semantic, phonological, and orthographic associations when compared to the word, pseudoword, and letter-string stimuli often employed. Of equal importance is that neither attending to non-letter symbols nor to the color of the stimuli resulted in preferential activation in the left ventral extrastriate cortex. Although previous studies have reported color-specific activation in V4 to monochromatic stimuli (McKeefry and Zeki, 1997), this was not found in the present study.

Not surprisingly, signal enhancement in the ventral extrastriate (fusiform gyrus, bilaterally) is elicited by all three task demands, possibly reflecting covert processing of the "ignored" aspects of the stimuli. For example, Frith et al. (1995) and Price et al. (1996) have demonstrated that subjects process stimuli beyond the "functional demands" of the task. Accordingly, angle and edge features of the stimuli used in the present study may elicit common responses even if the task requirement is to attend only to their chromatic features. In like manner, letters and symbols may both be processed as objects. However, a region that is responsive to the alphabetic features of the stimuli may be unable to ignore them despite instructions to attend to other features. Consistent with the proposition that lingual/fusiform gyrus activity is related to visual complexity rather than lexicality (Indefrey et al., 1997), large ventral portions of BA 37 were activated during all three task conditions and not to letters selectively.

The emergence of an independent region for letter processing in BA 37 (as revealed in the conjunction analysis) is consistent with the previously proposed idea that object form recognition is an orderly, distributed process in the ventral extrastriate region within which unique patterns of activity are evoked by different object types. Logically, the identification of objects in general would have species-specific survival value worth the allocation of neural resources and specialization by categories and their attributes has been demonstrated (Ishai et al., 1999, 2000; Martin et al., 1996; McCandliss et al., 2003, 1995; Puce et al., 1996). The process is not haphazard but remarkably consistent across subjects in the location of these specialized regions as demonstrated by the fact that cortical insults result in predictable deficits. For example, interrupting connections to the left inferior occipital–temporal region can selectively affect reading (Binder and Mohr, 1992; Dejerine, 1892; Henderson, 1986; Henderson et al., 1985; Rapcsak et al., 1987) and injury to the lingual/fusiform region may affect face recognition (Tranel et al., 1988).

Polk and Farah (1998) and Polk et al. (2002) suggest a mechanism whereby exposure to a visual environment that frequently includes groups of stimulus types, such as letters or digits,

Table 2
Location of significant local maxima for significant clusters by task

Name	LETTER-FIXATION							SYMBOL-FIXATION							COLOR-FIXATION						
	Volume (cm^3)	*X*	*Y*	*Z*	Peak *Z*-score	*P* value	%-Change	Volume (cm^3)	*X*	*Y*	*Z*	Peak *Z*-score	*P* value	%-Change	Volume (cm^3)	*X*	*Y*	*Z*	Peak *Z*-score	*P* value	%-Change
L Fusiform Gyrus (19/37)	45.1	−42	−71	−9	4.58	0.0008	2.28	5.9	−44	−69	−14	4.63	0.0013	2.52	11.3	−42	−59	−17	5.04	0.0005	2.73
R Fusiform Gyrus (19/37)	38.3	54	−71	−20	4.41	0.0011	2.31	4.5	46	−65	−22	4.76	0.0002	2.83	1.7	40	−70	−6	3.96	0.0073	2.49
L Inferior Frontal Gyrus (47)	1.6	−42	30	−12	3.69	0.0205	1.93														
R Inferior Frontal Gyrus (47)	1.7	48	23	−5	3.43	0.0499	2.1														
Supplemental Motor Area (6)	12.6	−11	15	48	3.97	0.0065	2.31														
L Superior Parietal Gyrus (40/7)								2.2	−56	−41	45	4.45	0.0008	2.32							
R Superior Parietal Gyrus (40/7)								6.2	43	−53	46	4.43	0.0031	2.55							
L Premotor (6)								13.2	−51	12	43	4.5	0.0006	2.82							
L PreSMA (6)								5.9	−8	16	49	3.94	0.0073	2.12							
Thalamus								10.6	−14	−4	13	4.57	0.0009	2.62	2.9	−12	−6	17	4.8	0.0017	2.45
R Middle Frontal Gyrus (46)															3.8	40	32	20	5.45	<0.0001	2.92
L Motor (M1) (4)															4.0	−46	−20	47	3.87	0.0097	2.22
Putamen															5.9	−29	−6	−11	4.84	0.0001	2.33

Note. BA = Brodmann's Area; SMA = Supplemental Motor Area; *X* = sagittal, *Y* = coronal, *Z* = axial coordinates in Talairach and Tournoux (1988) stereotaxic atlas (minus signs indicate left hemisphere, posterior to AC and inferior to the AC-PC line, respectively).

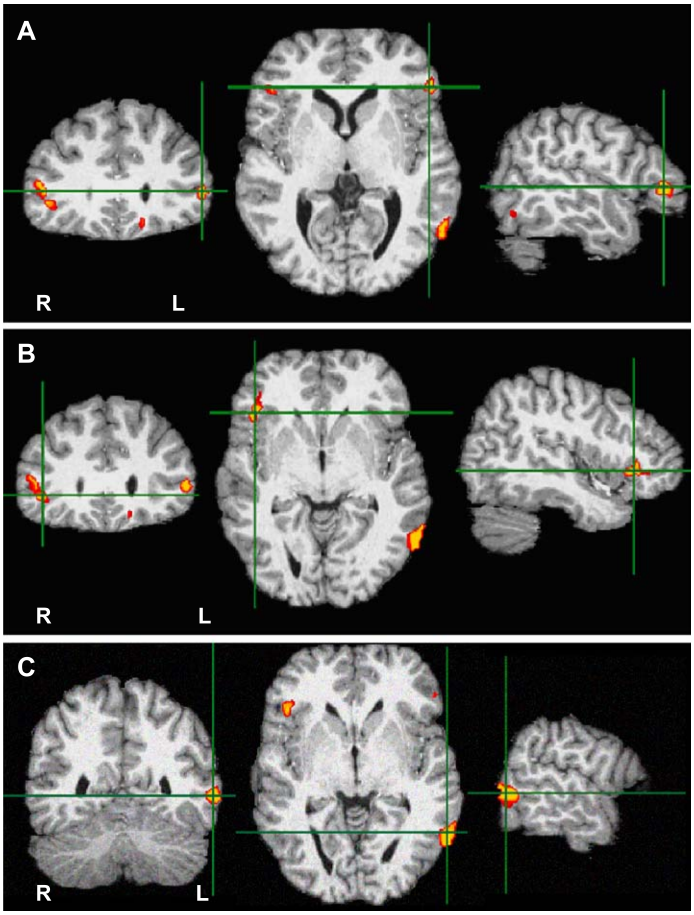

Fig. 2. The three panels show the three areas identified in a group analysis ($n = 11$) by the contrast [(LETTER-FIXATION) > (SYMBOL-FIXATION)] and [(LETTER-FIXATION) > (COLOR-FIXATION)] with a critical threshold of $Z > 3.1$, $P < 0.05$ corrected for multiple comparisons. The coronal, axial, and sagittal planes through the peak of each area are shown in radiological convention from left to right. These clusters, with Talairach coordinates for the local maxima listed in parentheses, are: (A) left inferior frontal gyrus (−55, 36, 4); (B) right inferior frontal gyrus (46, 31, −3); and (C) left lateral occipital gyrus (−62, −57, −6).

leads to correlation-based learning. According to their model of self-organizing networks, regions within cortex devoted to object recognition become specialized for categories of objects. Such effects of expertise on ventral extrastriate activity have been demonstrated by Gauthier et al. (1999) They found bilateral changes in the fusiform face area that were associated with gaining experience. Also, subjects who were experts in cars and birds activated the right fusiform face area more than did non-experts (Gauthier et al., 2000). Our results suggest that a region specifically sensitive to letters, adjacent to other "object" areas, can be recruited through experience with salient features in the environment that have adaptive value (Desimone, 1996), even though the

Table 3
Location of significant local maxima for activation specific to task

LETTER-FIXATION > COLOR-FIXATION and LETTER-FIXATION > SYMBOL-FIXATION

Name	BA	Volume (cm^3)	*X*	*Y*	*Z*	Peak *Z*-score	Peak corrected *P*	%-Change
L Middle Occipital Gyrus	37	1.7	−62	−57	−6	3.58	0.0018	N/A
L Inferior Frontal Gyrus	47	1.0	−55	36	4	3.32	0.004	N/A
R Inferior Frontal Gyrus	47	1.1	46	31	−3	4.08	0.0095	N/A

SYMBOL-FIXATION > COLOR-FIXATION and SYMBOL-FIXATION > LETTER-FIXATION

Name	BA	Volume (cm^3)	*X*	Y	Z	Peak *Z*-score	Peak corrected *P*	%-Change
L PreSMA	6	1.0	−2	17	50	3.53	0.0023	N/A
R Dorsolateral Premotor	6	1.4	31	7	49	3.68	0.0015	N/A

Note. BA = Brodmann's Area; SMA = Supplemental Motor Area; *X* = sagittal, *Y* = coronal, *Z* = axial coordinates in Talairach and Tournoux (1988) stereotaxic atlas (minus signs indicate left hemisphere, posterior to AC and inferior to the AC-PC line, respectively). Percent change calculations cannot be computed for a conjunction. There were no significant activations for the COLOR conjunction (COLOR-Fix >LETTER-Fix and COLOR-Fix>SYMBOL-Fix).

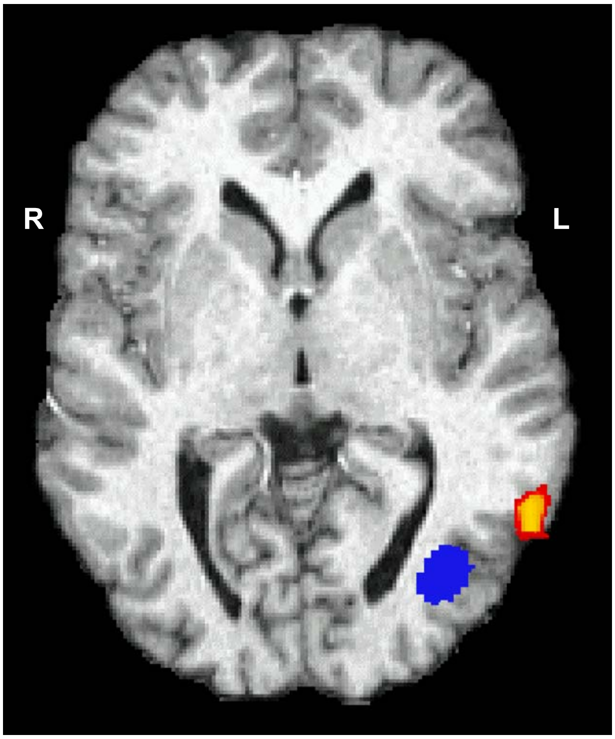

Fig. 3. An axial slice showing the relative spatial locations between the area of activation common to all three tasks (shown in blue using an uncorrected critical threshold of $P < 0.001$ for each contrast) and the area of activation specific to letter processing identified in the conjunction analysis (shown in flame scale using a multiple comparisons corrected threshold of $P < 0.05$). The bounding box around the region of shared activity is: x: −33 to −48; y: −53 to −82; z: 2 to −19. This can be compared to the VWFA of Cohen et al. (2000): x: −30 to −50; y: −30 to −80; z: < 0. Notably, the letter-specific area lies anterior and lateral to this region.

"adaptive" value of letters is used here in the cultural rather than in the evolutionary sense. The fact that some letter-induced activity is not shared with symbol processing, despite their visual similarity, suggests that letters acquire a special object category with respect to BA 37. Future studies examining the mechanism of expertise acquisition for letters and symbols could yield valuable information for reading instructions.

Letter expertise would be expected to play an important role in the strength of activation of ventral extrastriate cortex given its role in reading. Fluent retrieval of practiced labels is an important predictor of reading acquisition in children and is correlated with reading compensation in dyslexic adults (Felton et al., 1990; Flowers, 1995). Several investigators have found that letter naming in kindergarten and first grade children contributes significant, independent variance to early reading acquisition (Badian, 1995, 1998; Catts, 2001; Elbro et al., 1998; Scanlon and Vellutino, 1996). It is further known that many poor readers require substantially more exposures to letters and words to become fluent (Ehri and Wilce, 1983; Reitsma, 1983). It follows that the left lateral extrastriate cortex, selectively activated during single letter identification in good readers, would be only weakly recruited by poor readers either because of inadequate neural responsiveness (in the region or its afferent connections) or inadequate experience. Further investigation will be required to determine if functional studies in conjunction with behavioral characteristics can improve early detection of poor readers and identify an effective mode of instruction.

Portions of BA 37 identified in the current study as contributing jointly to the processing of letter, symbol and color processing, lie within the bounding box of the visual word form area (VWFA) reported by Cohen et al. (2000) (see Fig. 3). This confirms expectations that the VWFA also responds to symbols (McCandliss et al., 2003). However, a different region identified in our second analysis as specific to letter processing was more than a centimeter lateral to the edge of the VWFA. These results suggest that letters enjoy a special status that elicits processing beyond the VWFA.

Our letter-specific findings have focused on extrastriate visual cortex. We now turn to the role of the ventral prefrontal activity (bilateral BA 47) in attending to letters. It has been argued that ventral and dorsal visual processing streams preferentially interact with ventral (BA 47/10/11) and dorsal prefrontal (BA6) regions, respectively, when attention is directed to different aspects of the same stimulus (Courtney et al., 1996; Haxby et al., 1994). Alternatively, it has been proposed that the inferior frontal cortex is part of a network including pre-motor and parietal regions that is employed in strategic management of material held in working memory (Mecklinger et al., 2000). Other studies have reported specific memory functions to be associated with BA 47. For example, Bokde et al. (2001) reported functional connectivity between left BA 47/11 and left BA 37 during a one-back word memory task and Poldrack et al. (1999) made a case for bilateral BA 47 semantic processes even when phonological components of the task were controlled. The report of bilateral BA 47 activity in association with a semantic decision task (Pugh et al., 1996) is consistent with the latter proposition, even though Haxby et al. (1996) found left BA 47/11 activation during encoding (of faces). Fiez and colleagues have hypothesized that left BA 47 is involved with "effortful retrieval, maintenance, and/or control of semantic information" and their meta-analysis supports such task and code specific parcellation of inferior frontal regions (Chein et al., 2002; Fiez, 1997). Thus, greater inferior frontal enhancement during letter recognition may be explained by the activation of working memory circuits or semantic processes that are tapped by attention to alphabetic than non-alphabetic stimuli.

The interactivity of frontal and posterior ventral visual stream activity is further delineated by Ishai et al. (2000) who demonstrated the top-down nature of a frontal–parietal–ventral visual network. Similar to our finding of a preferential "letter" area, Ishai et al. found general (shared) activation to different stimulus types (faces, houses, and chairs) as well as smaller content-specific regions of neural enhancement. Importantly, they showed that imagining these different objects activated the same portions of BA 37 as the actual percepts, evidence that—independent of retinal input—stored visual representations can be reactivated because of instructions to imagine a previously experienced object. Similarly, O'Craven and Kanwisher (2000) have shown selective activation in both ventral and dorsal visual streams when subjects imagined either faces or places. They concluded that perceptually driven neural responsiveness of these regions does not account for all ventral stream activity; rather, top-down processes also selectively activate category-specific regions. Therefore, the letter-specific activation of both left extrastriate and inferior frontal cortices may in part represent the interrelatedness of these regions in retrieving previously experienced visual representations.

Right BA 47 enhancement has been associated with an invalid cue during a directed attention task (Arrington et al., 2000) as well as with withholding a response (Garrett et al., 2000). In the latter study, which used stimuli identical to those used here, right BA47/11 activity was inversely correlated with subjects' false-positive rates and reciprocally related to left BA 37 activation. Although this study was not designed to clarify these different interpretations, a future direction would be to correlate in a larger sample the activity in regions of interest with task performance as well as to carry out functional connectivity analyses among the three areas of isolated activation.

Modulation of neural responsiveness within the ventral visual pathway has been demonstrated both at very early (Shulman et al., 1997) and also at later processing stages (Wojciulik et al., 1998). For example, attention to faces increases the neural response of the fusiform face area as distinct from the color- or motion-specific regions (Haxby et al., 1994). Similar dissociations have been reported in response to attention directed to widely disparate characteristics of identical visual stimuli, such as the color, shape, or speed of objects (Corbetta et al., 1991). However, the present study used a unique design to focus attention on linguistic versus non-linguistic aspects of identical stimulus sets, thereby extending previous findings to include letter recognition as a special case of object recognition. Therefore, a letter-specific response was obtained under demands of attending selectively to different items within the same stimulus set, demonstrating the strength of the letter representation.

Conclusions

Using a unique experimental approach in which activation of left extrastriate cortex was modulated by task demand, this study demonstrates, for the first time, that single-letter identification can be functionally isolated from other visual attributes of a pre-lexical stimulus. Attending to single letters resulted in activation of the lateral portion of left extrastriate cortex, placing it lateral and anterior to a location previously termed the visual word form area. In general, BA 37 has been noted for its hypoactivity in dyslexic readers and may be inversely related to left inferior frontal cortex in that population (Pugh et al., 2000). As this task is relatively effortless for pre-literate children and poor readers alike, it is suitable for studies of impaired reading populations where it is important to equate performance (Price and Friston, 1999). Further, the task is ecologically valid insofar as it is associated with a skill shown to be essential to efficient reading acquisition. Thus, we propose that this task has important utility in (1) understanding pre-lexical processes, (2) studying the differential cortical function of normal and dyslexic readers, and (3) investigating the predictive potential of functional imaging in identifying children at risk for poor reading.

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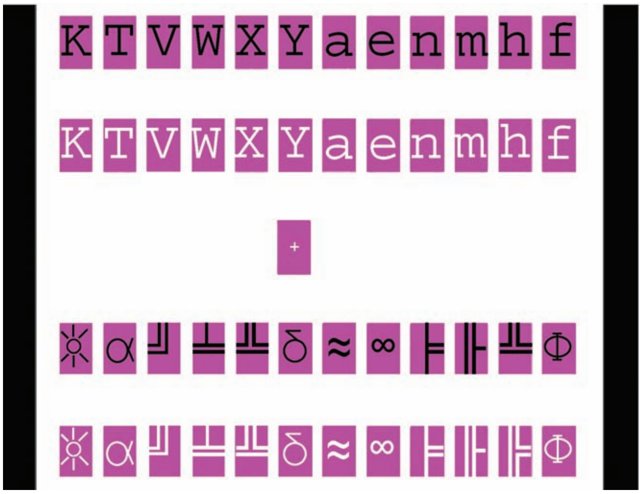
Appendix A

Letter (12) and non-letter (12) stimuli in black and white on magenta background.



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