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# Neural Specialization for Letter Recognition

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## Abstract

■ Functional magnetic resonance imaging (fMRI) was used to estimate neural activity while subjects viewed strings of consonants, digits, and shapes. An area on or near the left fusiform gyrus was found that responded significantly more to letters than digits. Similar results were obtained when consonants were used whose visual features were matched

with the digits and when an active matching task was used, suggesting that the results cannot be easily attributed to artifacts of the stimuli or task. These results demonstrate that neural specialization in the human brain can extend to a category of stimuli that is culturally defined and that is acquired many years postnatally. ■

## INTRODUCTION

Localization of function is a ubiquitous feature of brain organization that extends to numerous high-level cognitive and perceptual functions such as semantics (Martin, Wiggs, Ungerleider, & Haxby, 1996; McCarthy & Warrington, 1988), phonology (Fiez, Raichle, Miezin, & Petersen, 1995), syntax (Stromswold, Caplan, Alpert, & Rauch, 1996), and the perception of faces (Kanwisher, McDermott, & Chun, 1997). The localization of these high-level functions is surprising to some, as it implies that gross brain organization respects such complex and subtle distinctions as those between linguistic categories or between faces and nonfaces. Nevertheless, it is conceivable that these distinctions exist at the level of the human genome, and thus govern the large-scale organization of the brain by genetic mechanisms, as both language and face recognition have considerable evolutionary histories.

The localization of some cognitive functions, however, cannot be easily reconciled with a genetic account. For example, it is now well established that the ability to recognize visual words can be selectively impaired by brain damage even while the ability to write, to recognize other visual objects, and to comprehend spoken language is relatively preserved, a pattern of impairments known as "pure alexia" (Shallice & Saffran, 1986; Kremin, 1982; Patterson & Kay, 1982; Warrington & Shallice, 1980; Hecaen & Kremin, 1976; Benson & Geschwind, 1969; Dejerine, 1892). This syndrome is typically associated with damage to the posterior portion of the left hemisphere (Binder & Mohr, 1992; Damasio & Damasio, 1983).

Given that pure alexia dissociates from other visual recognition deficits and from other language deficits, it is natural to assume that it reflects damage to a neural system that includes modules specialized for orthography. Many theories of pure alexia do indeed make that assumption. For example, the traditional account of pure alexia is that it is due to a "disconnection" between visual information in the right hemisphere and an orthography-specific module in the left hemisphere that represents the "optical image for words" (Geschwind, 1965; Dejerine, 1892). Warrington and Shallice (1980) proposed that pure alexia reflects damage to a word-form system that is used to represent all word-like stimuli (but not other visual stimuli). Patterson and Kay (1982) also assumed a reading-specific module like the word-form system although they attributed pure alexia to an impairment in the transmission of letter information to that module. Arguin and Bub (1993, 1994) suggested that the processing of letters themselves (specifically, the computation of abstract orthographic codes) was impaired, but again this theory assumes a neural module that is specialized for reading.

Neuroimaging experiments have also found evidence for left posterior brain areas that are specifically activated during reading tasks. In two early positron emission tomography (PET) studies, Petersen, Fox, Posner, Mintun, and Raichle (1988) and Petersen, Fox, Snyder, and Raichle (1990) found that visually presented orthographic stimuli led to activation in the left inferior extrastriate cortex. A number of subsequent imaging studies have also found that words and word-like visual stimuli lead to activation in the left ventral visual stream and have refined this activation's localization to be on or near the left fusiform gyrus in Brodmann's area (BA) 37 (and perhaps BA 19) (Cohen et al., 2000; Buchel, Price,

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& Friston, 1998; Beauregard et al., 1997; Herbster, Mintun, Nebes, & Becker, 1997; see Rumsey et al., 1997; Menard, Kosslyn, Thompson, Alpert, & Rauch, 1996; Puce, Allison, Asgari, Gore, & McCarthy, 1996; Pugh et al., 1996; Small et al., 1996; Price et al., 1994; Howard et al., 1992 for evidence of more superior activation).

The evidence from patients and neuroimaging does not conclusively demonstrate the existence of a neural module that is specialized for reading, however. For example, some theories have explained pure alexia in terms of a more general perceptual problem without appealing to a neural module that is specialized for orthography. Farah and Wallace (1991), Levine and Calvanio (1978), and Kinsbourne and Warrington (1962) have all presented evidence consistent with the hypothesis that pure alexia arises from a difficulty in encoding many separate visual forms simultaneously or in very rapid succession. According to this view, the fact that the impairment manifests itself most clearly in reading simply reflects the fact that reading, perhaps more than any other visual recognition task, requires the simultaneous recognition of multiple forms (i.e., the letters in words). In particular, such theories need not assume the existence of a neural module that is specialized for reading.

In short, the issue of whether pure alexia implies reading-specific neural modules (and therefore experience-dependent neural specialization) is unresolved. And, of course, the same arguments can be applied to the neuroimaging evidence. Given that words differ from other visual stimuli along a variety of dimensions, neuroimaging results demonstrating localized neural activity associated with reading need not imply that the activated areas are specialized specifically for reading.

There have also been reports of neuropsychological dissociations within the domain of reading. In rare cases, patients who have a profound deficit in recognizing letters nevertheless have significantly less difficulty in recognizing digits and numbers (Gardner, 1974; Greenblatt, 1973) and there is some electrophysiological work consistent with this dissociation (Allison, McCarthy, Nobre, Puce, & Belger, 1994). These results provide stronger evidence for reading-specific neural modules than do selective impairments in visual word recognition, because letters and digits are so closely matched along most stimulus dimensions. Furthermore, the neurological impairment seems to extend to individual letters and digits and is thus not vulnerable to an alternative interpretation based on simultaneous form perception. There is much less evidence suggesting that the visual recognition of digits depends on specialized neural tissue. Although many patients have been reported who have problems processing numerical information (so-called acalculia), we know of no patients whose impairment is restricted to the “visual” processing of numbers relative to letters.

The possibility of specialized letter representations has also been suggested in behavioral studies of normal subjects performing visual search. Subjects are faster, more accurate, and less sensitive to the number of distractors when searching for a letter among digits, compared with a letter among letters (Jonides & Gleitman, 1972). A neural architecture in which letter recognition is partially segregated from digit recognition would predict such an “alphanumeric category effect,” assuming that different letters are represented in the same cortical area and therefore interact and interfere with each other.

There are, however, some differences between letters and digits that could potentially explain these dissociations. For example, there may be subtle visual differences between many letters and digits (e.g., straight vs. curved lines, visual complexity) that could potentially influence the results. Furthermore, there are more letters than digits. If forced to guess on the basis of partial or uncertain information, the smaller number of possibilities among digits (10 as opposed to 26) will result in better performance. This disparity could also potentially explain selective impairments in letter recognition compared with digit recognition in neurological patients: Perhaps these patients are simply more impaired on the harder task (letter recognition) compared with the easier task (digit recognition).

In this article, we report the results of two functional magnetic resonance imaging (fMRI) studies designed to investigate whether the brains of skilled readers include a module that is specialized for letter recognition relative to digit recognition. Such a finding would have important implications for our understanding of functional localization, both quantitatively and qualitatively. Quantitatively, to the extent that psychological capacities can be compared using some common metric of “breadth,” the existence of a specialized “letter area” would constitute one of the narrowest functions known to have a distinct localization. Qualitatively, specialized letter recognition would be a clear demonstration of the localization of a function that is acquired many years postnatally.

## **EXPERIMENT 1: PASSIVE VIEWING OF CONSONANTS AND DIGITS**

In a recent review article, Polk and Farah (1998) presented a brief summary of some neuroimaging evidence consistent with the hypothesis that an area on or near the left fusiform gyrus is specialized for letter recognition relative to digit recognition. We begin with a complete description of that experiment along with a new analysis of the data.

The experiment was designed to look for more direct and unambiguous evidence for specialized letter representations in the visual system, by using fMRI to estimate neural activity while participants passively viewed strings

of consonants, strings of digits, strings of shapes, and fixation points. We analyzed three planned comparisons: letter/digit versus shape (LD vs. S), letter versus digit (L vs. D), and digit versus letters (D vs. L). The LD vs. S comparison was designed to identify brain areas that responded to writing more than other visual stimuli. The other two comparisons were designed to identify brain areas that responded to one category of written stimuli more than another.

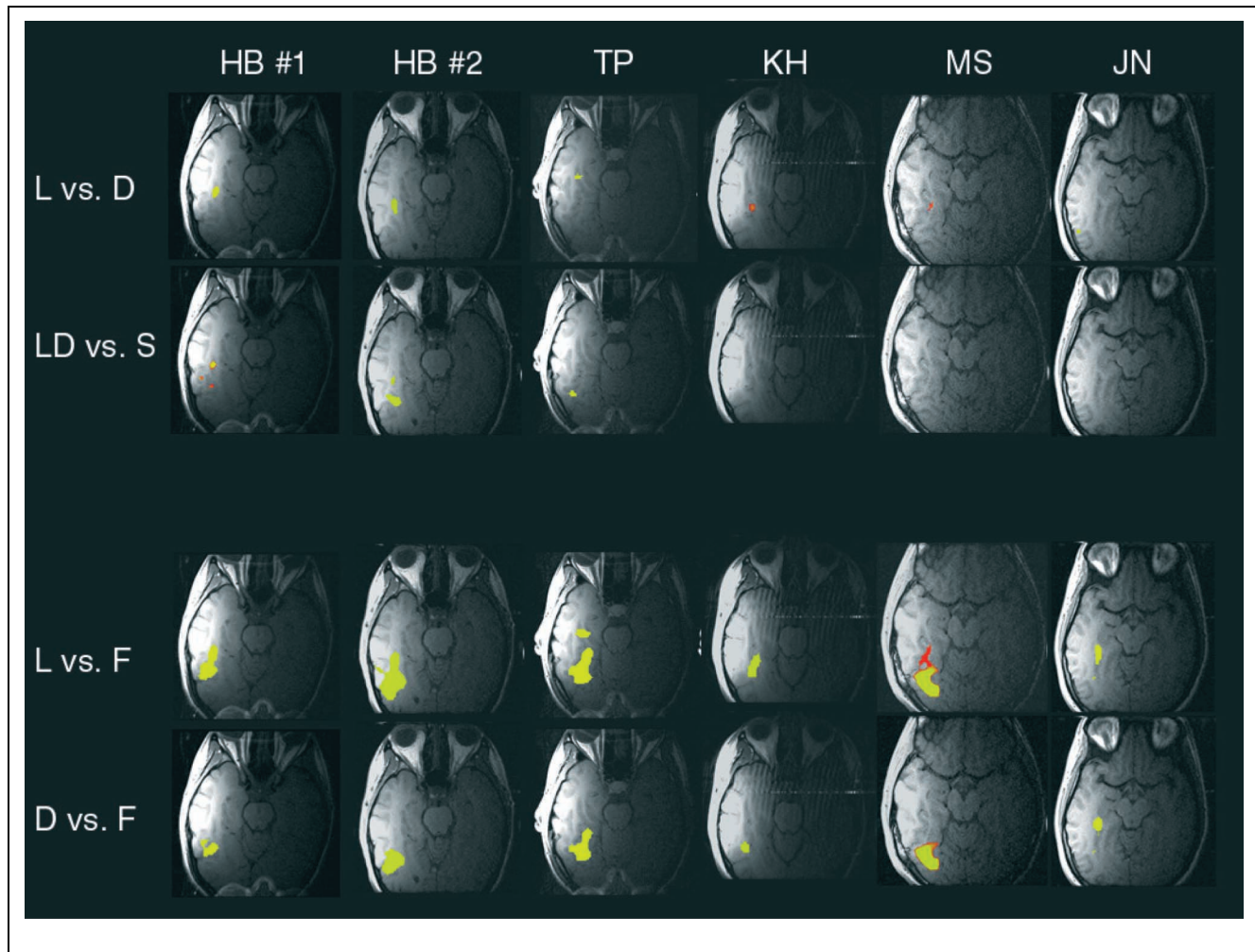
## Results

The L vs. D comparison revealed significant activation in individual subjects (top row of Figure 1; see Table 1 for Talairach coordinates). In all six sessions, an area in the left ventral visual cortex responded more to letters than digits, although in two of the sessions this activation did not reach statistical significance after correcting for the multiple comparisons [Subject K.H. had 17 contiguous

voxels above  $t = 2.5$  around Talairach coordinates  $(-37, -42, -7)$ ; Subject M.S. had 19 contiguous voxels above  $t = 2.5$  around Talairach coordinates  $(-35, -38, -6)$ ; these subthreshold activations are shown in red<sup>1</sup>]. Two sessions were run in the same subject (H.B. #1 and H.B. #2) 6 weeks apart, and showed significant L vs. D activation in the same area both times. Five of these six activations were in approximately the same area on or near the left fusiform gyrus [within 5 mm of Talairach coordinates  $(-37, -38, -7)$ , except for T.P. whose activation was more anterior], while one of these activations (subject J.N.) was significantly more lateral and posterior.

The D vs. L comparison did not show any significant activations at the  $p < .0167$  level (.05 after correcting for three planned comparisons) in any subject and has therefore not been included in the figure.

The LD vs. S comparison revealed significant activation in three of the six sessions (second row of Figure 1;



**Figure 1.** Significant differences in the blood-oxygenation level dependent (BOLD) MRI signal during passive viewing of L vs. D, LD vs. S, L vs. F, and D vs. F in Experiment 1. Each column represents a single scanning session and each row represents a different comparison. Activations that were significant after correcting for multiple comparisons are shown in yellow; those that were subthreshold are shown in red. The figure shows the single horizontal brain slice with the largest number of voxels above the corrected significance threshold for the L vs. D comparison. The left hemisphere appears on the left and the right hemisphere on the right.

**Table 1.** The Talairach Coordinates and Spatial Extent of Activations to Planned Comparisons in Experiment 1

<i>Comparison and participant</i>	<i>Center of mass</i>	<i>Extent X</i>	<i>Extent Y</i>	<i>Extent Z</i>
<i>L vs. D</i>				
H.B. #1	-38, -34, -6	-40, -37	-38, -31	-10, -3
H.B. #2	-38, -36, -7	-39, -37	-42, -30	-10, -5
T.P.	-37, -19, -8	-39, -36	-20, -18	-14, -2
K.H.	-37, -42, -7	-39, -35	-44, -40	-10, -5
M.S.	-35, -38, -6	-36, -34	-39, -38	-8, -4
J.N.	-50, -70, -4	-51, -48	-70, -69	-5, -2
<i>LD vs. S</i>				
H.B. #1	-38, -34, -6	-40, -37	-37, -32	-9, -4
	-40, -59, -7	-41, -39	-60, -58	-8, -6
	-51, -49, -9	-51, -50	-50, -49	-10, -8
H.B. #2	-40, -60, -5	-49, -31	-64, -56	-14, +4
	-39, -36, -5	-42, -37	-39, -34	-12, +4
T.P.	-41, -68, -8	-43, -40	-70, -66	-10, -5

see Table 1 for Talairach coordinates). In H.B. #1, this activation included the area activated by the L vs. D comparison, but in H.B. #2 and T.P. this comparison activated a more posterior site. (A more posterior site was also activated in H.B. #1 but at a subthreshold level; this activation is shown in red.)

We also performed a post hoc analysis comparing letters vs. fixation (L vs. F in Figure 1) and digits vs. fixation (D vs. F in Figure 1) using the same thresholds we adopted for our other comparisons. In all five sessions in which we observed fusiform activation in the L vs. D comparison (all but J.N.), that same area was also activated by the L vs. F comparison (although in subject M.S. this activation, like his L vs. D activation, was subthreshold and is shown in red). In contrast, the more lateral and posterior site activated by the L vs. D comparison in subject J.N. was not significantly activated by the L vs. F comparison.

The D vs. F comparison did not show activation at this threshold in this area in any of the sessions. Although this comparison did not reach significance, most voxels in this area did respond more to digits than fixation on average in all the sessions except for subject J.N. (in subject M.S., some voxels responded more to digits than fixation while others responded more to fixation than digits). Indeed, a post hoc region-of-interest (ROI) analysis that only analyzed voxels from the L vs. D activation sites (and therefore corrected for far fewer multiple comparisons) did reveal significant D vs. F activation in this area in three of the other five sessions (H.B. #1, H.B. #2, and K.H.; T.P. and M.S. still failed to show D vs.

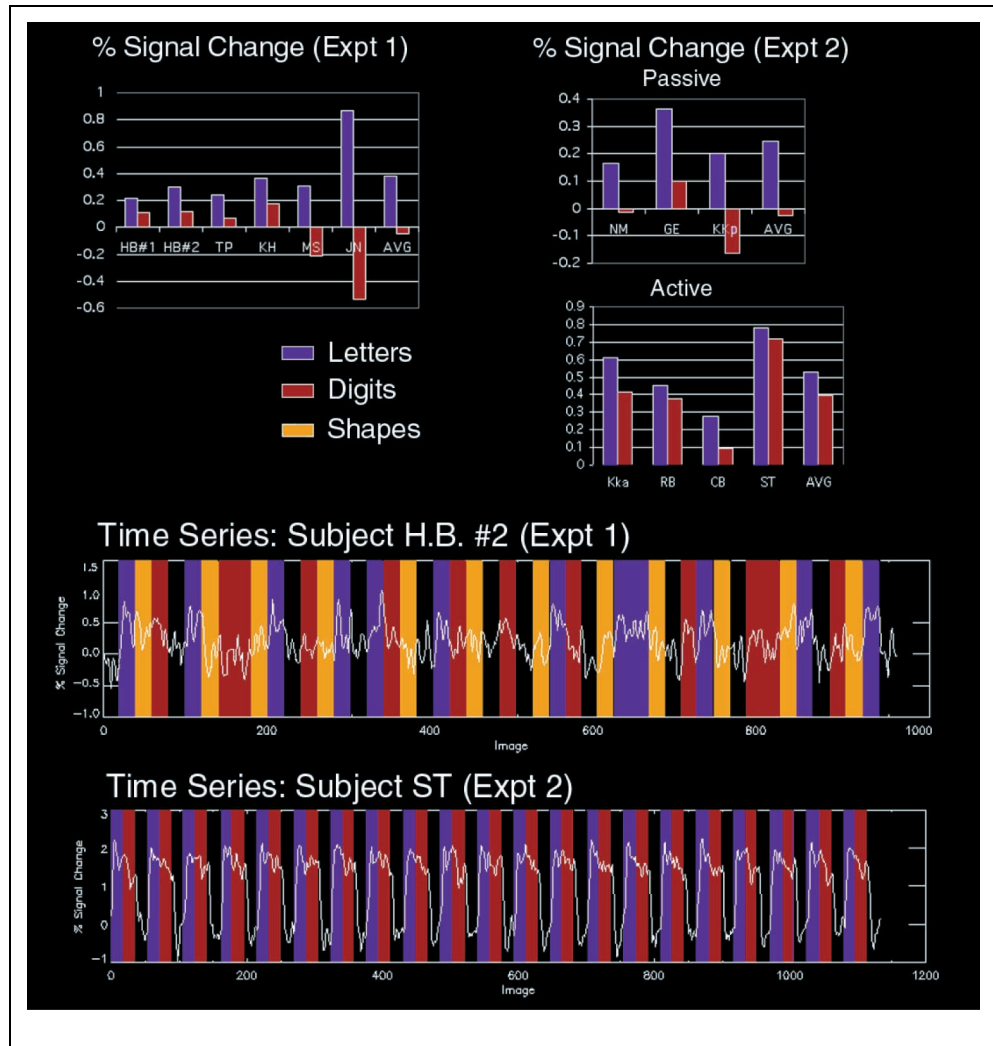
F activation). Subject J.N. actually showed significant deactivation in the D vs. F comparison in the site activated by the L vs. D comparison (not shown), suggesting that the L vs. D activation was actually due to deactivation by digits rather than activation by letters.

Finally, we analyzed the average signal strength in the letter and digit conditions relative to fixation in the voxels that were activated in the L vs. D comparison (Figure 2). In four of the subjects, the signal increased in the digit condition relative to fixation and in the other two subjects the signal decreased. Subject J.N. again appeared somewhat anomalous, exhibiting much larger signal changes relative to fixation than the other subjects and also showing a much larger decrease in signal during the digit condition. On average, these voxels exhibited a 0.39% increase in signal during the letter condition relative to fixation, a 0.05% decrease in signal during the digit condition (excluding subject J.N., the average signal in the digit condition was 0.05% larger than during fixation), and a 0.12% increase in signal during the shape condition relative to fixation.<sup>2</sup> Figure 2 also shows a time series plot from the activated area in an individual subject from the experiment (H.B. #2).

## Discussion

These results demonstrate that, at least in some literate subjects, certain ventral visual areas respond significantly more to letters than digits. In five of the six sessions, an area on or near the left fusiform gyrus was more responsive to letters than digits. Furthermore, this acti-

**Figure 2.** Percent change in the BOLD fMRI signal in brain areas that were activated by the L vs. D comparison. Results from Experiment 1 are shown in the top left and results from Experiment 2 are shown in the top right (with results from the passive condition in the top graph and results from the active condition in the graph below). Purple bars indicate percent signal change in the letter condition relative to the fixation condition. Red bars indicate percent signal change in the digit condition relative to the fixation condition. The bottom half of the figure shows time series from voxels that were significantly activated by the L vs. D comparison in one subject from each experiment. The first time series is from a subject who exhibited a typical signal change between the letter and digit conditions (Subject H.B. #2 from Experiment 1). The second time series is from the subject who showed the smallest signal change between these two conditions in either experiment (Subject S.T. from Experiment 2). The graphs plot the percent signal change relative to the average signal during the fixation condition. Purple bars indicate letter blocks, red bars indicate digit blocks, orange bars indicate shape blocks, and black bars indicate fixation blocks.



vation was due to activation by letters rather than deactivation by digits (compared to fixation): The L vs. F comparison also significantly activated this area, but there was no significant difference between digits and fixation (and certainly not a deactivation by digits).

Subject J.N. also showed a significant L vs. D activation, but we suspect that this activation was artifactual: It was substantially more lateral and posterior than that activation in the other subjects, this area was not significantly activated in the L vs. F comparison, and it was significantly deactivated by the D vs. F comparison. Given that it occurred near the edge of the brain, this activation may have been a motion artifact.

In contrast to the L vs. D results, none of the sessions produced significant D vs. L activations. Because we used a surface coil in this experiment, it is possible that such activations did occur, but that they were too far from the surface coil to be detected (e.g., in the right hemisphere). In the second experiment, we used a head coil with which we could record from the entire brain.

The LD vs. S comparison (Figure 1) revealed significant activation in three of the sessions (H.B. #1, H.B. #2, and T.P.), but not in the other three (even at lower thresholds). Some of these activations were in the same area that was activated in the L vs. D comparison (the anterior site in H.B. #1 and H.B. #2), but in all three sessions a more posterior site was activated that was less sensitive to the distinction between letters and digits than was the L vs. D site (in H.B. #1 this activation did not reach threshold after correcting for all the multiple comparisons and is shown in red). These posterior sites were also significantly active in both the L vs. F and D vs. F comparisons in all three subjects (bottom two rows of Figure 1), consistent with an interpretation in which this area responds to both letters and digits without a significant distinction. The failure to find such activation in the other sessions, however, makes it difficult to draw solid inferences about it.

Overall, the results from Experiment 1 are consistent with the hypothesis that an area in the left fusiform



gyrus of at least some literate adults is specialized for processing letters relative to digits. In some, but not all, of the subjects, this area also responded more to digits than fixation (although this effect was not significant), an interesting issue to which we will return. In contrast to the letter activations, we failed to find any evidence of specialization for number processing relative to letter processing in this area of the brain. Finally, in some, but not all, of the sessions, we found a more posterior site that responded significantly more to letters and digits than to shapes, but that did not distinguish letters and digits to the same extent that the more anterior site did.

There are other possible interpretations of the results that do not assume that this fusiform area is specialized for letters relative to digits. Perhaps the most obvious is that the letters were chosen from a set of 20 candidate letters while the digits were chosen from a set of 8 candidate digits. As a result, each individual digit was presented more often than each individual letter. It is therefore conceivable that the digits required less processing because of a repetition priming effect and therefore produced less activation relative to the letters.

Another possibility is that there are subtle visual features that distinguish most letters and digits that could account for the results. For example, 12 of the 20 uppercase consonants that we used were composed entirely of straight line segments (AFHKLMNTVWXZ), whereas 6 of the 8 digits involved curves (235689). Perhaps this difference could have accounted for the previous results. Or perhaps uppercase letters are more visually complex than digits on average (e.g., involving more line segments or vertices). Experiment 2 was designed to address some of these issues.

## **EXPERIMENT 2: ACTIVE AND PASSIVE PROCESSING OF MATCHED LETTERS AND DIGITS**

We ran a variant of the first experiment in order to extend the results and rule out some alternative interpretations. In this experiment, we constructed sets of consonants and digits that contained the same number of elements and that were better matched for visual features and complexity. We recorded from the entire brain and we had some subjects perform the passive viewing task and had others perform an active string-matching task in order to test whether the results would generalize to a different task. The critical comparisons for our purposes involved the letters and digits (the shapes were much less similar to the letters than were the digits), so we decided to increase the number of observations and power for these comparisons by focusing exclusively on the letter and digit stimuli and excluding the shapes. We thus analyzed two planned comparisons: L vs. D and D vs. L. In order to further increase our power, we restricted our analysis to two ROIs defined a priori, a left inferior ROI for the L vs. D

comparison and a right inferior ROI for the D vs. L comparison (see Methods for details).

## **Results**

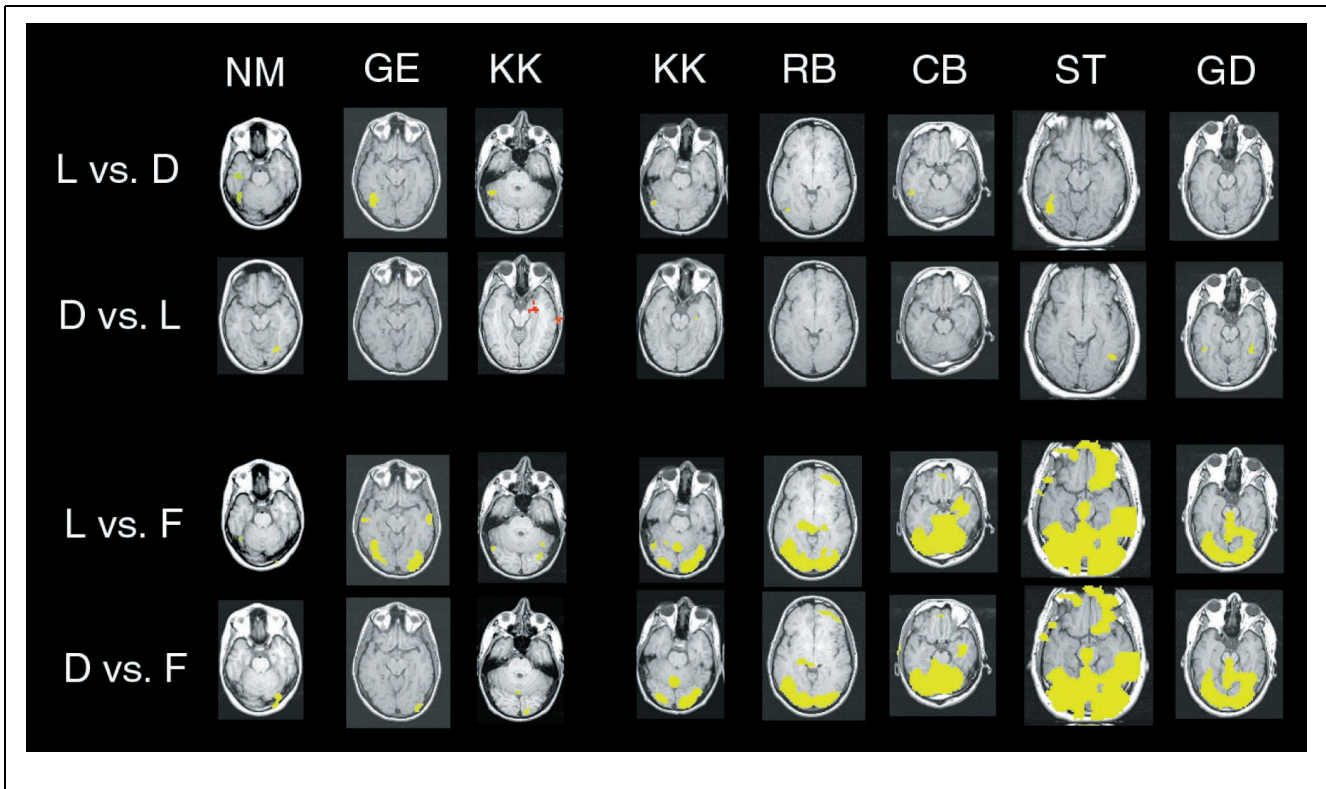
Figure 3 shows the results (see Table 2 for Talairach coordinates). Each row in the figure reflects a different comparison. The top two rows show the planned comparisons: L vs. D (top row) and D vs. L (second row). The bottom two rows show two post hoc comparisons that are helpful in interpreting the results from the planned comparisons: L vs. F (third row) and D vs. F (bottom row).

Each column shows the results from one particular subject. The first three columns present data from subjects performing the passive viewing task and the other five columns present data from subjects performing the active string-matching task.

The L vs. D comparison revealed significant activation in seven out of eight subjects (all three passive subjects and four out of five active subjects; shown in yellow in the top row of Figure 3). Consistent with the results from Experiment 1, these activations were in approximately the same area in the left inferior occipitotemporal cortex, on or near the fusiform gyrus [within 9 mm of Talairach coordinates ( $-44, -49, -9$ ) except for subject R.B. whose activation appeared to be in a sulcus and was more superior]. Subject K.K., who was scanned once performing a passive viewing task (third column in Figure 3) and once performing an active string-matching task (fourth column in Figure 3), exhibited L vs. D activation in approximately the same area for both scans.

The D vs. L comparison revealed significant activation in the right inferior ROI in three out of the eight subjects [N.M. (passive) and subjects S.T. and G.D. (active); shown in yellow in the second row of Figure 3]. These activation sites were roughly homologous to the L vs. D sites in the left hemisphere although they tended to be about 5–10 mm superior and, in N.M.'s case, a bit more medial.

Because the evidence for significant D vs. L activation within our a priori ROIs was mixed, we also performed a post hoc, exploratory analysis of the D vs. L comparison across the whole brain. In subjects G.E., R.B., and C.B., there was no significant activation. In subjects N.M. and S.T., the right inferior activation within the ROI was the most activated site and no other sites approached significance. In subject G.D., a homologous left inferior site was significantly active, even after correcting for all the voxels in the brain and the two planned comparisons, and is shown in yellow (last column, second row, Figure 3). In both scans of subject K.K. (both the passive viewing and active matching scans), an area in the right hippocampal formation was substantially activated by the D vs. L comparison. In the active matching condition, this right hippocampal activation was sufficiently robust to be significant after correcting for all the voxels



**Figure 3.** Significant differences in the BOLD MRI signal when processing L vs. D, D vs. L, L vs. F, and D vs. F in Experiment 2. Each column shows the results in one particular brain slice from one particular subject. The first three columns show data from subjects in the passive viewing condition. The other five columns show data from subjects in the active string-matching condition. Activations that were significant after correcting for multiple comparisons are shown in yellow; those that were subthreshold are shown in red. The left hemisphere appears on the left and the right hemisphere on the right.

**Table 2.** The Talairach Coordinates and Spatial Extent of Activations to Planned Comparisons in Experiment 2

<i>Comparison and subject</i>	<i>Center of mass</i>	<i>Extent X</i>	<i>Extent Y</i>	<i>Extent Z</i>
<i>L vs. D</i>				
N.M. passive	-39, -52, -9	-45, -34	-58, -47	-16, -3
	-41, -21, -12	-44, -38	-23, -19	-16, -9
G.E. passive	-42, -52, -7	-50, -34	-60, -44	-12, -2
K.K. passive	-44, -45, -12	-51, -38	-47, -43	-15, -9
K.K. active	-46, -53, -11	-48, -43	-56, -50	-16, -6
R.B. active	-43, -65, +1	-44, -42	-66, -64	-2, +3
C.B. active	-49, -42, -10	-51, -46	-45, -40	-14, -5
S.T. active	-45, -52, -7	-51, -39	-67, -37	-16, +2
<i>D vs. L</i>				
N.M. passive	23, -68, -3	21, 25	-70, -67	-8, +1
K.K. passive	27, -17, -10	20, 34	-19, -15	-12, -8
K.K. active	33, -19, -11	32, 34	-21, -17	-13, -9
S.T. active	45, -52, -1	40, 49	-55, -49	-3, +1
G.D. active	40, -48, -3	30, 50	-55, -40	-7, +1



in the brain as well as the two planned comparisons and is shown in yellow (rightmost column, second row, Figure 3). When this same subject performed the passive viewing task, the D vs. L comparison revealed 13 contiguous voxels with a  $t$  value greater than or equal to 2.8 in the same area. This level of activation was not sufficient to reach significance after correcting for multiple comparisons and is shown in red (fourth column, second row, Figure 3). Of course, it should be kept in mind that these analyses were post hoc; these effects were not predicted a priori.

We also performed a post hoc analysis comparing L vs. F (Figure 3) and D vs. F (Figure 3) in the whole brain. As we observed in Experiment 1, the left inferior sites that were activated by the L vs. D comparison were also activated by the L vs. F comparison. The D vs. F comparison revealed significant activation in this area in three of the seven sessions that exhibited significant L vs. D activation (subjects R.B., C.B., and S.T.), but not in the other four. Notably, all three of these sessions involved active string matching, which produced much more robust activations relative to fixation than did the passive viewing task. Even in the one active subject who did not exhibit significant D vs. F activation in the L vs. D area (subject K.K., active), most voxels in this area did respond more to digits than fixation. Furthermore, a post hoc ROI analysis that only analyzed voxels from the L vs. D activation site (and therefore corrected for far fewer multiple comparisons) did reveal significant D vs. F activation in this area in this subject.

We also analyzed the average signal strength in voxels that were activated by the L vs. D comparison (Figure 2). The results from the passive condition were comparable to those from Experiment 1: An average signal increase of 0.25% was observed during the letter condition relative to fixation and an average decrease of 0.03% was observed during the digit condition. In keeping with the statistical results just described, the active condition exhibited larger signal changes relative to fixation than did the passive condition and digit matching did lead to increases in the signal compared with fixation (though these changes were smaller than during letter matching). The average increase in signal during letter matching relative to fixation was 0.53% and the average increase in signal during digit matching was 0.40%. Figure 2 also shows a time series plot from the activated L–D area from one of the subjects in the active condition (S.T.); this subject exhibited the largest digit response in this area of any subject in either experiment.

Both of the subjects from the active condition who exhibited significant D vs. L activation (S.T. and G.D.) also exhibited significant D vs. F activation in this area. Subject G.D. also exhibited significant L vs. F activation in this area whereas subject S.T. did not. In contrast, the one subject from the passive condition who showed significant D vs. L activity (N.M.) did not exhibit signifi-

cant D vs. F or L vs. F activation in this area. This site was more active for digits than fixation in this subject (15 contiguous voxels were above  $t = 2.5$ , not significant) and was slightly less active for letters than fixation (also not significant). The right hippocampal sites observed in subject K.K. were also not significantly activated by the D vs. F comparison and, for the L vs. F comparison, these sites showed substantial deactivation (significant in K.K., active). These results suggest that the right hippocampal D vs. L activations observed in K.K. were due to deactivation by letters rather than to activation by digits.

## Discussion

These results replicate and extend the finding of a visual area that responds significantly more to letters than digits. In seven out of eight sessions, a left ventral occipitotemporal area was more responsive to letters than digits. This result was observed in both the passive viewing task as well as the active string-matching task. One of the subjects (K.K.) was scanned in both conditions and showed significant L vs. D activation in the same area both times. As in the first experiment, all of the L vs. D activations were due to activation by letters rather than deactivation by digits: The L vs. F comparison also significantly activated the same area and this area was not significantly deactivated by D vs. F.

The response of this putative letter area to digits depended on the task. In the passive viewing task, the area did not exhibit a reliable response to digits relative to fixation. In the active string-matching task, however, the letter area did tend to exhibit a greater response to digits than to fixation. We will return to the implications of these results in the General Discussion.

The evidence for specialized processing of digits relative to letters was mixed. Three of the eight sessions (N.M., S.T., and G.D.) revealed significant D vs. L activation in the predicted right inferior visual ROI, but the other five did not. This area was also activated by the D vs. F comparison in the two subjects performing the active matching task and there was subthreshold D vs. F activation in this area in the other (passive) subject. There was some evidence of D vs. L activation in the right hippocampal formation in the two sessions with Subject K.K., but these activations appear to have been due to deactivation by letters rather than activation by digits.

In short, the main result from this experiment was consistent with that from Experiment 1: We found evidence consistent with the hypothesis that an area in the left inferior visual cortex is specialized for visually processing letters relative to digits (at least in some literate adults). Furthermore, the results from this experiment cannot be easily reconciled with some of the alternative interpretations of Experiment 1. For example, the same number of letters and digits were used and no string included any repeated symbols. The frequency of

presentation of the letters and digits was exactly matched. An interpretation based on a repetition priming effect is therefore no longer tenable. Similarly, because letters were chosen whose visual features were matched with the digits, it is difficult to attribute the observed letter specialization to differences in the visual features of the two categories. In particular, whereas the letters in Experiment 1, as a whole, involved more straight lines and were more complex than the digits, there were no such obvious gross differences between the visual features of the stimuli in Experiment 2. Finally, the observed letter specialization was also observed when the task itself was changed from a passive viewing task to an active string-matching task. The results therefore cannot be attributed to some artifact of the passive viewing task. This experiment also revealed some evidence for specialized processing of digits relative to letters although the results were not as consistent.

## GENERAL DISCUSSION

These experiments found evidence for an area on or near the left fusiform gyrus that responds significantly more to letters than digits. As will be discussed, this finding has potentially important implications, but there are also caveats that must be kept in mind when interpreting the results of this, and most other, functional neuroimaging experiments. First, and perhaps most important, activation in a functional neuroimaging study does not imply that the activated site is functionally necessary for the behavior being performed. For example, the activation may reflect some supplemental activity that is not functionally required for the task. It is therefore important to interpret the results of neuroimaging studies in the context of patient studies. In the case of the present studies, our neuroimaging results converge with patient work in emphasizing the importance of left inferior visual regions in the visual processing of letters.

Another important issue involves whether the so-called letter area also plays some role in processing digits, or whether it is involved “exclusively” in the processing of letters. The present data do not unambiguously distinguish these alternatives. As was previously discussed, in some cases (typically involving active string matching rather than passive viewing), the letter area responds more to digits than it does to fixation. This result raises the possibility that this area is also involved in processing digits, but that it responds preferentially to letters relative to digits. In keeping with this interpretation, Ishai, Ungerleider, Martin, Schouten, and Haxby (1999) presented evidence that ventral visual areas that respond preferentially to one category of visual stimulus (faces, houses, or chairs), also exhibit significant, if smaller, responses to stimuli from other categories. They argued that the representation of a visual stimulus is not localized to a single, category-specific module, but

is distributed across multiple ventral visual areas. Another possibility is that the area is involved exclusively in the processing of letters and that its occasional response to digits relative to fixation reflects the fact that digit strings are more similar to letter strings than is a fixation point. After all, even if a cortical area were specialized for the processing of one category of visual stimuli, one might expect that area to partially respond to other stimuli that are visually similar to members of that category.

Neither of these interpretations explain the lack of any digit response (and even a deactivation by digits relative to fixation) in some of the passive subjects (and in the average digit response across passive subjects in both experiments). Nor do they explain why the active string-matching task would lead to greater digit responses in this area compared with the passive viewing task. These findings raise the possibility that activation in the letter area by digits reflects a kind of spillover effect. For example, perhaps the letter area gets co-opted to help out with digit processing in the more demanding active matching task. Or perhaps the activation of this area by digits simply reflects a vascular, rather than functional, spillover. In any case, the major claim that is warranted based on the present results is that the letter area responds significantly more to letters than digits; it is in this sense that we mean the area is specialized for letters relative to digits.

A number of previous neuroimaging studies have found evidence that areas near our activation site are activated when subjects read words and word-like stimuli (e.g., Cohen et al., 2000; Paulesu et al., 2000; Buchel et al., 1998; Wagner et al., 1998; Beauregard et al., 1997; Rumsey et al., 1997). Beauregard et al. (1997) found activation near this site when subjects read letter strings as well as abstract, concrete, and emotional words. They argued that it might reflect the neural substrate of the orthographic lexicon. Similarly, Cohen et al. (2000) found that a left fusiform area was the common site of activation for words presented to either hemifield and argued that it corresponds to a visual word-form area.

Research with neurological patients is also consistent with a critical role for the left inferior occipitotemporal cortex in reading. In an analysis of lesion topography across a set of brain-damaged patients suffering from pure alexia, Binder and Mohr (1992) found the ventral temporal lobe including the fusiform gyrus to be the common lesion site. Similarly, Beversdorf, Ratcliffe, Rhodes, and Reeves (1997) described a pure alexic reader whose brain was studied intensively postmortem. A lesion was found that primarily affected the left fusiform gyrus and the associated white matter and they discussed the case in terms of a word-form impairment.

It is unclear whether the inferior occipitotemporal area associated with word reading in these neuroimaging and neuropsychological studies is the same area that was differentially responsive to letters and digits in the current experiments. After all, many pure alexic patients

are still able to read individual letters despite not being able to read whole words. This pattern of impairments raises the possibility that letter recognition and word recognition depend on partially segregated neural substrates. On the other hand, assuming that word recognition is more demanding than letter recognition, partial damage to a word system could potentially leave letter recognition relatively preserved. Existing data therefore do not unambiguously indicate whether letter and word recognition are subserved by the same or different neural substrates.

Fewer studies have examined neural activity when subjects process consonant strings like those used in the present experiments. Puce et al. (1996) used fMRI to record neural activity while subjects processed letter strings, faces, and textures. They found that letter strings preferentially activated the left occipitotemporal and inferior occipital sulcus relative to the other stimuli. Similarly, Tagamets, Novick, Chalmers, and Friedman (2000) found that matching orthographic stimuli, including consonant strings, produced robust activation in the left ventral pathway (including fusiform and inferior occipital cortex) relative to matching geometric shapes. Nobre, Allison, and McCarthy (1994), recording field potentials from electrodes in the inferior temporal lobe, found that a part of the posterior fusiform gyrus responded preferentially to letter strings and words compared with other visual stimuli, including faces. Consistent with the present results, Allison, McCarthy, Nobre, Puce, and Belger (1994), also recording from chronically implanted electrodes, found that some fusiform sites distinguished between letters and digits.

The specialization of a region of visual cortex for letters, relative to digits, is not the first finding that a complex and subtle stimulus distinction is respected by the human brain. As already noted, there are regions in the human visual cortex that appear to be specialized for faces relative to other objects (Kanwisher et al., 1997; McCarthy, Puce, Gore, & Allison, 1997; Puce, Allison, Gore, & McCarthy, 1995). There is also evidence that some ventral cortical areas respond preferentially to "building" stimuli (Aguirre, Zarahn, & D'Esposito, 1998a; Epstein & Kanwisher, 1998) relative to other stimulus categories. Experience-driven changes in brain organization have also been reported in previous work. Experience can enlarge or shrink preexisting brain areas (Ungerleider, 1995; Merzenich & Kaas, 1982) and, if one considers the input from each eye to be a separate category of stimulus, it can also drive localization of function (Hubel & Wiesel, 1977).

The present findings go beyond previous findings in three ways. First, the category of letters is one of the narrowest categories of visual stimulus to be processed by a specialized neural substrate. That is, the minimal specifications required to judge something a letter as opposed to a number would appear to be far more exacting than the minimal specifications required to

judge something to be a face as opposed to a nonface or a building as opposed to a nonbuilding. (And certainly more exacting than the relatively simple distinction between eye of origin that leads to the development of ocular dominance columns.) Second, in the present case, experience has done more than change the size or efficiency of a functional area already known to exist; any description of the acquired function of this area must include the distinction between letters and nonletter forms as similar as digits, and in this sense, it is an area specialized for letters. Third, and most important, the category of letters, relative to the category of digits, is an entirely arbitrary category distinction with no evolutionary history. Unlike the known segregation of faces and nonfaces, or left eye versus right, the present finding implies that school-age learning can lead to the creation of new functionally defined brain areas. How might that happen?

In previous computational work, we proposed a cooccurrence hypothesis to explain how a letter area might be created (Polk & Farah, 1995a). The account is based on three simple and widely accepted premises, one about the environment and two about the computational properties of cortex: First, letters tend to occur in the presence of other letters rather than in the presence of digits. Second, cortical learning is correlation-driven. Third, distinct representations within a local area of cortex interact or compete with each other. Over a wide range of other processing assumptions, we obtained segregation of letter representations in a self-organizing neural network.

Letters occur more frequently than digits, and the spatial and temporal correlations among letters are stronger (e.g., digits are often used to enumerate text or other nonnumerical items). In a later study, we found that training the network on a set of inputs that satisfied these assumptions led to a segregated representation for letters, but not for digits, consistent with our empirical finding that letter specialization is more robust than digit specialization.

We also tested this co-occurrence hypothesis in a behavioral study by studying the alphanumeric category effect in visual search (the finding that a letter is detected more quickly and accurately in the context of digits than in the context of letters, Jonides & Gleitman, 1972). If this category effect is indeed a behavioral manifestation of a neural architecture in which the processes underlying letter and digit recognition are partially distinct, then the co-occurrence hypothesis would predict that the effect would be reduced in subjects whose visual environment violates the assumed co-occurrence of letters with letters. Consistent with this prediction, postal workers who sort Canadian postal codes (which are composed of alternating letters and digits, rather than pure letter or digit strings) showed a smaller category effect than control subjects (Polk & Farah, 1995b).

## METHODS

### Experiment 1

#### *Participants*

Two male and three female, right-handed adults between the ages of 18 and 30 participated. One of the females (Subject H.B.) participated twice to allow us to assess the extent to which the results would replicate within a subject. Subjects reported having normal vision, no history of visual problems, no history of reading problems or learning disabilities, and no history of neurological disease or head injury. All were fluent speakers and readers of English, and no other languages. Subjects were paid US\$20 for their participation.

#### *Apparatus and Materials*

Data were collected using a 1.5-T GE signa system equipped with fast gradients for echo-planar imaging. A 5-in. surface coil was placed over the left ear of the participants to increase sensitivity in the left inferior temporal cortex and anterior parts of the left inferior occipital cortex (however, note that using a surface coil undermined our ability to detect signal in other parts of the brain). The stimuli were presented using a Macintosh 5400c laptop computer using SuperLab 1.68 (Cedrus). This computer was connected to an LCD projector mounted on an overhead projector which back-projected stimuli onto a screen that stood at the foot of the MRI table that the subjects lay on.

Each stimulus consisted of either a fixation point (a "+" in 36-point Geneva font) or a string of eight symbols, either uppercase consonants, digits, or shapes. The letters and digits were presented in 36-point Geneva font and the shapes were matched in size to the letters and digits. All stimuli were centered in the middle of the screen. Letters were randomly chosen except that vowels and the letter "Y" were excluded so that the strings would not be pronounceable. Digits were randomly chosen except that "0" and "1" were excluded to avoid the possibility of confusion with the letters "O" and "I." Shapes were randomly chosen from the following set: equilateral triangle, square, diamond, circle, half circle, asterisk, rectangle, check mark, donut, and cross.

#### *Procedure*

Following the acquisition of sagittal (TR = 500, TE = 11, 128 × 256, 1NEX) and axial (TR = 600, TE = 15, 192 × 256, 2NEX) T1-weighted localizer images, gradient echo, echo-planar fMRI was performed in 12 contiguous 3-mm axial slices (TR = 2000 msec, TE = 50 msec, 64 × 64 pixels in a 16-cm field of view for a resolution of 2.5 × 2.5 × 3 mm) centered over the left inferior temporal cortex and anterior parts of the left inferior occipital cortex. Subjects participated in 6–8 fMRI runs (5 min 40 sec each) in which they passively viewed blocks of letter

strings, blocks of digit strings, blocks of shape strings, and blocks of fixation points (baseline). Each run began with a 20-sec fixation block, which was not analyzed (used to permit tissue to reach steady-state magnetization). The remaining 5 min 20 sec consisted of two blocks of each of the four stimulus types in counter-balanced order. The blocks lasted 40 sec each and contained 40 trials in which stimuli were displayed for 150 msec, one per second. Subjects were instructed to try to encode all the symbols in each briefly presented stimulus before it disappeared.

#### *Statistical Analysis*

A slice-wise motion compensation method removed spatially coherent signal changes via the application of a partial correlation method to each slice in time (Zarahn, Aguirre, & D'Esposito, 1997). The raw data for each subject were smoothed in space with a 3-voxel FWHM Gaussian kernel and in time with an empirically derived hemodynamic response function (Zarahn et al., 1997). The data were analyzed using a modified general linear model for serially correlated error terms (Worsley & Friston, 1995), which included an estimate of intrinsic temporal autocorrelation under the null hypothesis (Aguirre, Zarahn, & D'Esposito, 1997) and sine and cosine terms for frequencies below that of the task. This analysis has been empirically demonstrated to hold the map-wise false-positive rate at or below tabular values (Aguirre et al., 1997). A critical *t* value was calculated for each map using the result of Worsley (1994). In order to correct for the three planned comparisons, we set the desired map-wise alpha level to be .05/3, thus correcting for both the multiple comparisons across voxels and the three planned comparisons. A cluster requirement (3 voxels) was also employed (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994). Each subject was analyzed individually rather than being pooled together into a group analysis. We adopted this approach under the assumption that letter recognition is not innate and that the locations of letter-specific activation sites might be too variable to be accurately coregistered in a group analysis. The results from each session should therefore be viewed as a separate experiment or case study.

### Experiment 2

#### *Participants*

Seven normal, right-handed subjects (six men, one woman), age 18–35, participated. There were two conditions (passive viewing vs. active matching) which were manipulated between subjects. One participant (subject K.K.) participated in both the passive and active conditions to allow us to assess the extent to which the results would replicate within a subject across tasks. Subjects reported having normal vision, no history of

visual problems, no history of reading problems or learning disabilities, and no history of neurological disease or head injury. All were fluent speakers and readers of English, and no other languages. Subjects were paid US\$20 for their participation.

### Apparatus and Materials

The same equipment that was used in the first experiment was used in the second, except that we used a standard clinical quadrature radiofrequency head coil rather than a surface coil (so that we could record from the entire brain).

We again used consonants, digits, and fixation points, but we excluded shapes in Experiment 2. We used a restricted set of eight consonants so that we used the same number of consonants as digits and matched the consonants and digits in terms of their underlying visual features. We used a sans serif font with a very simple style (in order to make it easier to match) and chose eight consonants (among the 20 candidates) whose visual features most closely matched those of the digits we were using (Figure 4). Rather than constructing completely random letter and digit strings, we first constructed a set of digit strings that were random except that no digits were repeated in any individual string. We then constructed the letter strings from the digit strings by replacing each digit with its matched letter.

### Procedure

Following the acquisition of sagittal (TR = 500, TE = 11, 128 × 256, 1NEX) and axial (TR = 600, TE = 15, 192 × 256, 2NEX) T1-weighted localizer images, gradient echo, echo-planar fMRI was performed in 21 contiguous 5 mm axial slices (TR = 2000 msec, TE = 50 msec, 64 × 64 pixels in a 24-cm field of view for a resolution of 3.75 × 3.75 × 5 mm). For the passive condition, three subjects participated in 6–8 fMRI runs (5 min 44 sec each) in which they passively viewed blocks of letter strings, blocks of digit strings, and blocks of fixation points (baseline). Each run began with a 20-sec fixation block, which was not analyzed (allowing the signal to reach a steady state and allowing the subject to become acclimated). The remaining 5 min 24 sec consisted of three blocks of each of the three stimulus types. The blocks

Digit	2	3	4	5	6	7	8	9
Letter	Q	C	H	R	G	L	S	P

**Figure 4.** Consonants and digits used in Experiment 2. Of the 20 candidate consonants, eight were chosen based on their visual similarity to the digits being used.

lasted 36 sec each and contained 36 trials in which stimuli were displayed for 150 msec, one per second. Subjects were instructed to try to encode all the symbols in each briefly presented stimulus before it disappeared.

Five subjects participated in the active condition and the same consonants, digits, and fixation points were used, but rather than being presented with a single string of symbols in the letter and digit conditions, the subjects were asked to distinguish pairs of strings as “same” or “different” by pressing one of two buttons. The strings were presented on the same horizontal line separated by three blank spaces and were centered in the middle of the screen. Each of the two strings in each string pair consisted of six symbols without any repeated symbols. Half of the pairs were identical and half differed in a single symbol. The order of same and different trials was random. Again, the digit trials were constructed first and then the letter trials were built by replacing each digit with its matched letter. The fixation condition was identical to the fixation condition in Experiment 1. As in the passive viewing scan, each run consisted of nine blocks lasting 36 sec each: three blocks of digit strings, three blocks of consonant strings, and three blocks of fixation stimuli.<sup>3</sup> For this scan, however, stimuli were displayed until the subject made a response at which point the next trial was immediately presented. Our intent was to try to equate the amount of processing in the letter and digit conditions by having the subject spend the entire time working on the task in both conditions.

### Statistical Analysis

After image reconstruction and prior to motion correction, the data were sinc interpolated (by shifting the phase of the Fourier components) in time to correct for the differential timing of fMRI slice acquisition in space (Aguirre, Zarahn, & D’Esposito, 1998b). The data were then motion corrected using a six-parameter, rigid-body, least-squares realignment routine (Friston et al., 1995). Finally, three-dimensional spatial smoothing with a 3-mm Gaussian kernel was applied. Voxel-wise analysis of the functional imaging data was conducted to identify voxels with a significant response. Appropriate statistical models were created for the concatenated blood-oxygenation level dependent (BOLD) data for each subject. This analysis employed the modified general linear model of Worsley and Friston (1995). Regressors of interest were generated from boxcar models of neural activity, convolved with an empirically derived hemodynamic response function to obtain predicted fMRI signal changes. To account for intrinsic temporal autocorrelation in the data, a 1/frequency function was fit to the (square root of the) average BOLD power spectrum from each subject, ignoring those frequencies at which power attributable to task might be expected. The time-domain representation of the 1/f curve was placed with-

in the K matrix (Zarahn et al., 1997; Worsley & Friston, 1995) along with a filter designed to remove low-frequency confounds (below 0.014 Hz) and high-frequency noise at the Nyquist frequency (0.0125 Hz), and a high-pass kernel (a standard HRF, Aguirre et al., 1998b). The removal of low frequencies and application of exogenous smoothing are necessary, even in the presence of the  $1/f$  model, because there is substantial variability in the actual magnitude of the low-frequency power from voxel to voxel (Friston et al., 2000).

We analyzed two planned comparisons: L vs. D and D vs. L (shapes were excluded in Experiment 2). In order to correct for these two comparisons, we set the desired map-wise alpha level to be  $.05/2$ , thus correcting for both the multiple comparisons across voxels and the two planned comparisons. Also, we adopted an ROI analysis when possible. Because we used a head coil rather than a surface coil in this experiment, our signal-to-noise ratio was reduced and we also had data for far more voxels. A power analysis indicated that we might not be able to observe significant activations if we corrected for every voxel in the brain. We therefore restricted our analysis to certain ROIs that were defined a priori.

Based on the first experiment, we expected the L vs. D comparison to produce activations in the left inferior visual cortex from which the surface coil had recorded. We therefore specified ROIs for each subject that covered the left fusiform gyrus, left lingual gyrus, and left inferior temporal gyrus. We then restricted analysis of the L vs. D comparison to voxels within this ROI and set the desired map-wise alpha level to correct for the multiple comparisons involved in analyzing those voxels.

For the D vs. L comparison, our a priori hypotheses about activation sites were less clear. The first experiment suggested that we could safely exclude the voxels in the ROI we chose for the L vs. D comparison, but because that experiment did not record from the entire brain, it did not provide clear guidelines about which other regions, if any, might be involved. One obvious possibility is the ventral visual stream in the right hemisphere. Research with split-brain patients (Seymour, Reuter-Lorenz, & Gazzaniga, 1994; Gazzaniga & Hillyard, 1971; Gazzaniga & Smylie, 1984) and with patients who have substantial left hemisphere damage (Dehaene & Cohen, 1991; Grafman, Kampen, Rosenberg, Salazar, & Boller, 1989) suggests that the right hemisphere is capable of identifying and comparing numbers. And given that this experiment involved visual tasks, it is natural to hypothesize that the ventral visual stream would be critically involved. Accordingly, we defined ROIs in the right ventral visual cortex for each subject that were homologous to the ROIs in the left hemisphere that we used for the L vs. D comparison (i.e., covering the fusiform, lingual, and inferior temporal gyri). We then restricted analysis of the D vs. L comparison to voxels within this ROI and set the desired map-

wise alpha level to correct for the multiple comparisons involved in analyzing those voxels.

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The data reported in this experiment have been deposited in the fMRI Data Center (<http://www.fmridc.org>). The accession number is 2-2001-11287.

## Notes

1. Note that we have slightly revised our estimates of these Talairach coordinates compared with those reported in Polk and Farah (1998).
2. In more recent studies conducted at the University of Michigan, we have observed larger percent signal changes ( $\sim 2\text{--}3\%$ ) for passive viewing of consonants relative to fixation. We have not been able to identify the reason for this discrepancy because there were many differences in the data acquisition (different machine, pulse sequence, magnetic field, etc.). In any case, the reliability of the activations as measured by statistical results ( $t$  values) seems to be consistent.
3. We recently adopted an analysis package (VoxBo, [www.voxbo.org](http://www.voxbo.org)) in which the temporal autocorrelation in the data can be empirically fit from the subject's own data while ignoring frequencies at which task power was present. Doing so provides a more accurate model of the so-called  $1/f$  noise and reduces the probability of spurious false-positive results (see Zarahn et al., 1997, for details). We therefore adopted a fixed block order within subject for the last five subjects that we ran (G.E., R.B., C.T., S.T., G.D.) so that the task power would be isolated to specific, known frequencies that could be ignored when fitting the temporal autocorrelation function. The first three subjects (N.M., K.K. passive, and K.K. active) were run with the block order counterbalanced.

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