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The roles of the "visual word form area" in reading

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Activation of the left midfusiform gyrus in response to reading words and pseudowords is such a reliable finding in functional imaging that this region has been called "the visual word form area" (VWFA). However, this label has recently been challenged, because activation in VWFA is also observed in other lexical tasks. We evaluated whether VWFA is necessary, sufficient, or specialized for reading by examining how frequently acute lesions in VWFA disrupt tasks that require access to written word forms versus other lexical tasks. We administered lexical tasks with spoken and written input and output, and identified damage or dysfunction of VWFA and other regions of interest (ROI) on diffusion- and perfusion-weighted imaging (DWI and PWI) in 80 patients within 24 h of onset of acute left ischemic stroke. Associations between abnormalities in each region of interest and impairment on lexical tasks were evaluated with chi-squared tests. Damage or dysfunction of VWFA was not significantly associated with impairment of written word comprehension or lexical decision, but was significantly associated with impairment on all tasks requiring lexical output: oral reading and oral naming (visual or tactile input), and written naming. We account for these results and results from functional imaging by proposing that the left midfusiform gyrus normally has two roles in reading: (1) computation of location- and modality-independent grapheme sequences from written word stimuli, and (2) a modality-independent stage of lexical processing that links modality-specific input and output representations. VWFA is not necessary for the former because the right homologue of VWFA can immediately assume this role.

Keywords: Magnetic resonance diffusion-weighted imaging; Perfusion-weighted imaging; Reading; Dyslexia; Fusiform gyrus

What criteria must be met for an area of the brain to be labeled with a specific function such as "primary visual cortex," "visual word form area" (VWFA), or "fusiform face area"? Such a label might imply a one-to-one relationship between structure and function. In this case, the identified area of the brain would presumably be both necessary and sufficient for the function. However, it is not clear that any area of the brain is entirely necessary in the sense that no other area could assume its function. For example, even though damage to the primary visual cortex reliably causes contralateral homonymous hemianopia (Holmes and Lister, 1916; Horton and Hoyt, 1991; McFadzean et al., 2002; Wong and Sharpe, 1999), adjacent areas can assume the visual functions and allow recovery from hemianopia (Slotnick et al., 2002). However, in this paper, we will consider an area to be essential for a function if damage to the area consistently causes impairment of that function, at least immediately after the onset of damage. It is also true that no area of the brain is truly sufficient for a function because no behavioral or cognitive function can be carried out in isolation. To illustrate, the primary visual cortex has a crucial role in early visual processing, but that processing cannot take place without input from the retina and transfer of input from the retina to visual cortex via optic tracts and optic radiations. However, in this paper, we will consider a region sufficient for a process if some component of processing can be carried out exclusively by that region. An alternative interpretation of a functionally labeled region of the brain is that the area is specific for a particular component of processing, even if it is not necessary or sufficient. For instance, the primary auditory cortex (Heschl's gyrus) appears to be specifically tuned to processing auditory rather than visual or tactile input (Iversen and Mishkin, 1973; Merzenich and Brugge, 1973). However, neither left nor right Heschl's gyrus is necessary for auditory perception; damage to one or the other does not result in acute deafness because the contralateral Heschl's gyrus also processes auditory input from both ears (although unilateral damage can result in more subtle auditory perceptual deficits; Boatman, 2002). Heschl's gyrus is also not sufficient for auditory perception because other components of the auditory pathway are also crucial in this function. Nevertheless, Heschl's gyrus is aptly named primary auditory cortex because it is specialized for a particular component of auditory processing (and may be considered sufficient for that

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component). Such specialization of function might be seen only in cortical regions known as "primary", "unimodal", or "idiotypic", such as primary visual and primary auditory cortex, rather than in "association" or "heteromodal" cortex (Mesulam, 2000). However, even specialization of the primary cortex is not absolute; for example, the primary visual cortex shows activation during reading Braille in blind subjects (Büchel et al., 1998a; Sadato et al., 1996, 1998, 2002), and lesions in the primary visual cortex can disrupt Braille reading in blind subjects (Cohen et al., 1997; Hamilton et al., 2000).

One heteromodal region of the cortex that has been functionally labeled is the left midfusiform gyrus, which has been called "the visual word form area" (VWFA) (Cohen et al., 2000, 2002). The assignment of this label was based on the robust finding in functional imaging studies of activation in the left midfusiform gyrus (part of Brodmann's Area, or BA, 37) in response to written words and orthographically legal pseudowords, relative to non-alphabetic visual stimuli (Price et al., 1996; Puce et al., 1996; but see Howard et al., 1992) and relative to consonant strings that violate orthographic constraints (see Cohen and Dehaene, 2004 for review). Reliable activation across subjects in this area has been observed regardless of the spatial location of the stimuli (right or left visual field) or typographic case or font (e.g., Cohen et al., 2000, 2002; Dehaene et al., 2001, 2002). Furthermore, activation of the left midfusiform gyrus is greater in response to letters than digits (Polk et al., 2002) and greater for letters versus geometric shapes (Gros et al., 2001). Activation in this area is also stronger to visual presentation of kanji characters versus scrambled kanji (Uchida et al., 1999). Cohen and Dehaene (2004) therefore defend the christening of the left midfusiform gyrus as the "VWFA" on the basis that there is evidence for functional specialization within the visual system (e.g., that visual neurons have become attuned to computational requirements of a certain script) and that there is reproducible localization of these neurons, such that reading consistently results in activation of this region.

However, Price et al. (2003) and Price and Devlin (2003,2004) have argued that this region is not only specific to reading, but also shows activation in functional imaging studies during a variety of lexical tasks, including naming, repetition, and Braille reading. Consistent with their alternative conclusion that the VWFA is essential for modality-independent lexical processing, several studies have reported that damage or dysfunction of the left midfusiform gyrus is associated with impairments in oral naming as well as oral reading (Foundas et al., 1998; Raymer et al., 1997). One possible explanation of these findings is that different parts of the midfusiform gyrus are necessary for accessing visual word forms, spoken word forms, and other aspects of lexical processing (Büchel et al., 1998b). An alternative explanation is that this region is not crucial for accessing visual word forms for reading, but is consistently activated during reading either because the stimuli elicit "automatic" access to modality-independent lexical representations for output (e.g., silent reading) or because both left and right midfusiform gyri are specialized for computing word forms from visual input, but either one is sufficient (with input from each striate cortex).

Another objection raised by Price and Devlin (2003) to the left midfusiform gyrus being labeled the VWFA is that patients with impaired reading attributed to disrupted access to orthographic word forms (patients with pure alexia) do not typically have lesions involving left midfusiform gyrus. However, many of these patients do have lesions in the left occipital cortex and splenium of the corpus collosum, which together might disrupt visual input to the left midfusiform gyrus (Chialant and Caramazza, 1998; Cohen et al., 2003; Damasio and Damasio, 1986; Dejerine, 1892; Geschwind, 1965). Nevertheless, lesion studies have more frequently identified the left angular gyrus as the area most important for accessing visual word forms for reading in studies of chronic stroke (Benson, 1979; Black and Behrmann, 1994; Dejerine, 1891; Vanier and Caplan, 1985) and acute stroke (Hillis et al., 2001a). The left angular gyrus does not, however, commonly show activation in reading tasks (Jobard et al., 2003; but see Binder et al., 2003; Joubert et al., 2004 for exceptions). The discrepant results from functional imaging and lesion studies might be explained by weaknesses of one method or the other in identifying structure–function relationships or by proposing that left midfusiform and angular gyri have two separate roles in computing or accessing visual word forms.

In this paper, we examine the extent to which the VWFA is necessary, sufficient, or specialized for processing of visual word forms by identifying deficits associated with acute damage or dysfunction of this region. It is assumed that if the VWFA is necessary for computing or accessing visual word forms, damage or dysfunction to this region should reliably result in acutely impaired written word comprehension and visual lexical decision—two tasks that require access to visual word forms but not access to lexical representations for output. It is also assumed that if VWFA is sufficient for visual word form processing that damage or dysfunction of other brain regions (e.g., left angular gyrus) should not reliably be associated with disruption of this component of reading. Finally, it is assumed that if VWFA is specialized for processing visual word forms, damage or dysfunction of this area should not reliably result in impairment of tasks that do not require processing of visual word forms (e.g., oral naming from tactile input). Thus, to determine the role(s) of VWFA in reading and other lexical tasks, we evaluated the associations between acute damage or dysfunction involving VWFA (and other cortical regions) and impairment in written word comprehension, lexical decision, and naming from visual and tactile input in 80 patients within 24 h of onset of stroke.

Methods

Subjects

We studied a consecutive series of 80 adult patients with acute left hemisphere ischemic stroke who met the following inclusion criteria: (1) presentation within 24 h of stroke onset; (2) premorbid proficiency in English; (3) at least a 10th grade education; (4) premorbidly right handed; and (5) provision of informed consent by the patient or closest relative. Exclusion criteria included (1) premorbid reading difficulty (by self-report); (2) known history of hearing loss or uncorrected visual loss; (3) contraindication for MRI (e.g., implanted ferrous metal, claustrophobia); (4) altered level of consciousness; or (5) need for ongoing sedation. Age ranged from 29 to 87 years, with a mean of 60.2 (±16). Education ranged from 10 to 18 years with a mean of 13.5 (±2.1). Patients with strokes in all supratentorial left hemisphere regions, in the territories of the left anterior cerebral, middle cerebral, or posterior cerebral arteries (and "watershed" areas between these territories), were included.

Behavioral measures

Within 24 h from onset, subjects were administered a battery of lexical tasks that included oral and written naming of pictures (17 items each), oral naming of objects to tactile exploration (17 items), oral reading of words (34 items) and pronounceable pseudowords (25 items), written lexical decision (59 items), written word or picture verification (17 items, each presented with two foils and one target), and spoken word or picture verification (17 items, each presented with two foils and one target). In the word or picture verification tasks, each item was presented three times, once with the target (e.g., the word boot with a picture of a boot), once with a semantic foil (e.g., the word boot with a picture of a glove), and once with a visually and phonologically related foil (e.g., the word boot with a picture of a boat) in random order within a sequence. The same item was not presented consecutively with the target and foils, but separated by 16 items. Credit for an item was given only if the patient correctly accepted the target and rejected both foils. Word or name stimuli were matched in frequency, length (in phonemes and letters), and grammatical word class across tasks; the same items were not presented in more than one task.

Imaging

MRI scans, including diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI), T2, FLAIR, and Gradient Echo were obtained within 24 h of stroke onset on a GE Signa 1.5 T, echo planar imaging capable system. DWI trace images were obtained with a multislice, isotropic, single-shot EPI sequence, with $b_{\max}$ = 1000 s/mm^2 and TR/TE of 10,000/120 ms. PWI sequences were obtained with single-shot gradient echo EPI PWI, with TR/TE of 2000/60 ms, after 20 cc GdDTPA bolus was power injected at a rate of 5 cc/s; whole brain coverage was obtained with 17 slices.

A subset of 15 patients also had a high-resolution T1-weighted anatomical scan, using a three-dimensional spoiled gradient recalled echo (SPGR) pulse sequence, with the following scan parameters: TR/TE 6.4/1.5 ms, TI 300 ms, 20° flip angle, slice thickness 1.5 mm, 124 sections. This scan, carried out 1 or 3 days post onset of stroke, allowed registration to the Montreal Neurologic Institute (MNI) atlas of all the sequences obtained at Day 1.

Two technicians, blinded to language testing, examined five brain regions in the left hemisphere for the presence or absence of hypoperfusion or infarct. The following regions of interest (ROI) were identified using published templates (Damasio and Damasio, 1989): left angular gyrus (BA 39), supramarginal gyrus (BA 40), posterior superior temporal gyrus (BA 22), and BA 37. Additionally, VWFA was defined as part of BA 37 in the midfusiform gyrus, corresponding to the area of activation described as VWFA in Cohen et al. (2000, 2003). For the main analysis, VWFA was transferred by hand onto Damasio and Damasio templates. For the subset of patients whose scans were co-registered to the MNI atlas, scans were overlaid on a figure from Cohen et al. (2003) showing the areas of activation corresponding to the VWFA on the MNI atlas, centered on $x = -44$, $y = -52$, and $z = -20$. The five ROIs were selected for examination because they have been associated with written word recognition or comprehension in previous functional imaging or lesion studies. Although the main methodology used for identifying a region as abnormal is somewhat subjective, there was very high interjudge reliability in identifying the presence or absence of infarct or hypoperfusion in each region across the two technicians (96% point-to-point percent agreement). Furthermore, the division of the brain by Brodmann's areas is somewhat arbitrary; but the intersubject variability in cytoarchitectural fields defies precise and rational division of the brain based on structural imaging. That is, although vowel-based approaches are less subjective and more precise in some ways, a given voxel in a normalized brain of one subject may not correspond to the same cytoarchitectural field (or even the same gyrus) as the same voxel in a different individual. Nevertheless, so that our results could be directly compared to results of functional imaging, for the subset of patients for whom we obtained SPGR sequences, we registered scans to the MNI atlas using the National Library of Medicine Insight Segmentation and Registration Toolkit (ITK; http://www.itk.org) and then inserted these scans into a brain-image database (Braid; (Herskovits, 2000)) to examine the VWFA as defined by Cohen et al. (2003). For both the template analysis and the analysis using Braid, a region was defined as "infarcted" (densely ischemic) if it was bright on DWI and dark on apparent diffusion coefficient maps. If a ROI showed dense ischemia or infarct in part of a ROI, but less than half of that ROI, that case was excluded from that analysis because it was unclear whether such a region should be considered dysfunctional. A region was considered hypoperfused if the mean delay in time to peak (TTP) arrival of contrast (Gadolinium) across voxels in that ROI was >2.5 s delayed relative to the TTP in the homologous region in the right hemisphere (a threshold based on previously published evidence that regions with this degree of delay correspond to dysfunctional tissue, even if they are not necessarily at risk for progression to infarction without reperfusion; see Hillis et al., 2000, 2001b, 2004 for discussion). A region was considered to be dysfunctional if it was either infarcted (with or without reperfusion), hypoperfused, or both.

Associations between damage or dysfunction of each ROI and impairment of written word comprehension and written lexical decision were evaluated using chi-squared tests. An alpha level of $P < 0.005$ was used based on the Bonferroni correction for multiple comparisons. Additional analyses included association between damage or dysfunction of VWFA and each of the following lexical tasks: oral reading, oral naming of pictures, oral naming of objects from tactile exploration ("tactile naming"), and written naming of pictures. For this analysis we used an alpha level of $P < 0.0125$. Impairment on a given lexical task was defined as >10% errors based on norms from hospitalized control subjects (Hillis et al., 2002c).

Results

Impairments associated with dysfunction in VWFA

Using data from all 80 patients, there was no association between hypoperfusion and/or infarct in VWFA and impaired written word comprehension measured with written word or picture verification (χ^2 = 2.1; *df*1; ns; see Table 1). There was also no significant association between written word comprehension and imaging abnormality in VWFA when DWI and PWI abnormalities were examined separately (for DWI: χ^2 = 0.07; *df*1; ns; for PWI: χ^2 = 1.1; *df*1; ns). Similarly, there was no association between hypoperfusion/infarct in VWFA and written lexical decision (χ^2 = 0.16; *df*1; ns; see Table 2); lexical decision data

Table 1
Relationship between damage or dysfunction of VWFA and impaired written word comprehension

	Infarct/hypoperfusion including *VWFA*		Total
	Present	Absent	
Deficit in written word comprehension	31	11	42
No deficit in written word comprehension	22	16	38
Total	53	27	80

were only available for 61 patients, because 19 patients either failed to understand the task or declined to complete it. There was also no significant association between impaired written lexical decision and abnormality in VWFA when DWI and PWI abnormalities were considered separately (DWI: χ^2 = 0.03; *df*1; ns; PWI: χ^2 = 0.86; *df*1; ns). Of 53 patients with hypoperfusion/infarct including VWFA, 22 subjects had intact written word comprehension and 15 had intact written lexical decision (see examples of patients with intact written word comprehension and lexical decision in Fig. 1). Of the 31 patients who had hypoperfusion/infarct of VWFA and did show impaired written word comprehension, all 31 also had infarct or hypoperfusion of Wernicke's area and/or the left angular gyrus (see examples of patients with impaired written word comprehension; Fig. 2).

Damage or dysfunction of VWFA was significantly associated with impaired oral reading (χ^2 = 10.8; *df*1; P = 0.001), oral naming of pictures (χ^2 = 18.9; *df*1; P < 0.0001), oral naming to tactile exploration (χ^2 = 8.2; *df*1; P < 0.004), and written naming of pictures (χ^2 = 13.5; *df*1; P < 0.0002). Scans of patients with hypoperfusion of VWFA with impaired oral and written naming, but intact written word comprehension and lexical decision, are shown in Fig. 3. Furthermore, a patient with relatively focal hypoperfusion of BA 37, including VWFA, at Day 1 showed impaired oral picture and tactile naming and written picture naming but intact written word comprehension and lexical decision at Day 1. When this region was reperfused at Day 3, he showed recovery of oral and written naming as illustrated in Fig. 4.

For the subset of 15 patients whose scans were co-registered with the MNI atlas, infarct/hypoperfusion of VWFA was significantly associated with impaired oral naming (Fisher's Exact: P = 0.01), but not impaired oral reading (P = 0.17), written word comprehension, (P = 1.0), or written lexical decision (P = 1.0). There was no dissociation between impairments of written word comprehension and lexical decision among these cases. Written naming and tactile naming were not examined in this analysis, because some patients had no data for these tasks (e.g., due to hemiplegia of the dominant hand). Fig. 5 provides an example of the PWI scan of a patient with impaired oral naming but intact written word comprehension and lexical decision, overlaid on the MNI atlas cut, showing that the area of hypoperfusion included VWFA as defined by Cohen et al. (2003).

Areas of dysfunction associated with impairment of written word comprehension and lexical decision

Impaired written word comprehension was strongly associated with hypoperfusion or infarct of left posterior superior temporal gyrus (χ^2 = 18.8; *df*1; P < 0.0001) and left angular gyrus (χ^2 = 32.7; *df*1; P < 0.0001). All patients with deficits in written word comprehension had hypoperfusion/infarct of left posterior superior temporal gyrus or left angular gyrus. Impaired lexical decision was significantly associated with hypoperfusion/infarct only of left angular gyrus (χ^2 = 29.2; *df*1; P < 0.0001) after Bonferroni correction. All of the patients with impaired lexical decision associated with hypoperfusion/infarct of left angular gyrus were also impaired in oral reading of both words and pseudowords. Scans from patients with impaired written word comprehension, lexical decision, and oral reading of words and pseudowords, with dysfunction of left angular gyrus but not VWFA are shown in Fig. 6. Fig. 7 provides data on the deficits among patients with various combinations of lesions involving left VWFA, posterior superior temporal gyrus, and angular gyrus. Naming deficits included impaired oral naming of pictures and objects to tactile exploration, because there were no cases with impairment in one but not the other (although a few patients did not have tactile naming data); cases of pure motor speech impairment that interfered with oral reading or naming were not considered to have naming or oral reading deficits. Lexical decision is not included in this graph, because not all patients were able to complete the lexical decision tasks. Regions of hypoperfusion or infarct associated with impaired spoken word comprehension, written naming, and spelling to dictation have been reported previously (Hillis et al., 2001b, 2002a, 2003).

Discussion

The most important and clearest results of this study are that (1) patients with hypoperfusion or infarct of the left midfusiform gyrus consistently showed impaired oral and written naming, frequently associated with impaired oral reading; and (2) impaired written word comprehension was most strongly associated with hypoperfusion or infarct of the left posterior, superior temporal, and angular gyri. While these results are consistent with traditional concepts of neural regions crucial for reading and naming, they seem surprising in light of more recent data from functional neuroimaging studies that have emphasized the role of the left midfusiform gyrus in reading. However, below we provide a neuroanatomical model of reading that can account for data from both lesions studies and functional imaging, which illustrates how evidence from these sources may be complementary in evaluating hypotheses about the structure–function relationships in the brain.

Damage or dysfunction of VWFA in acute stroke was not associated with deficits in written word comprehension or lexical decision, indicating that this region is not necessary for accessing or computing visual word forms for reading. Why then is activation of this region such a reliable finding in functional imaging studies of word and pseudoword reading? One account

Table 2
Relationship between damage or dysfunction of VWFA and impaired written lexical decision

	Infarct or hypoperfusion including *VWFA*		Total
	Present	Absent	
Deficit in written lexical decision	24	12	36
No deficit in written lexical decision	15	10	25
Total	39	22	61

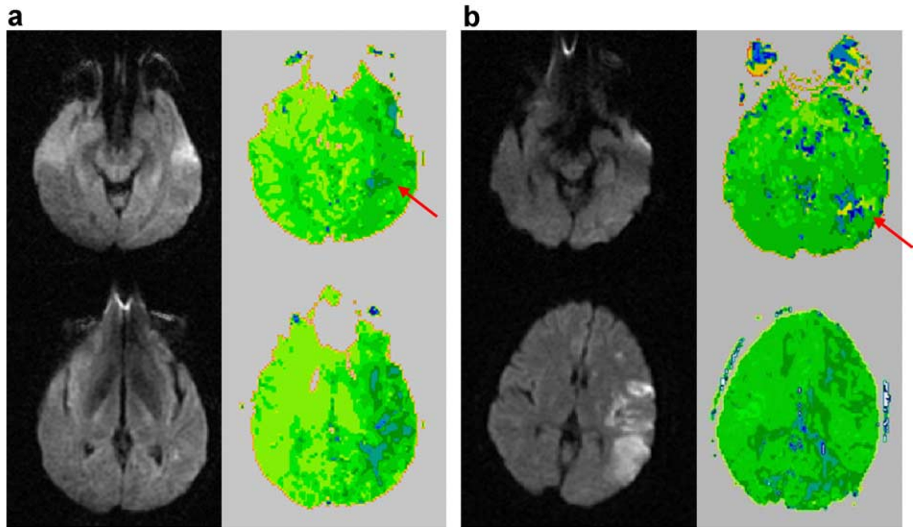

Fig. 1. DWI (left) and PWI (right) scans of two patients (panels a and b) with hypoperfusion or infarct including VWFA, with normal written word comprehension and lexical decision but impaired naming. Hypoperfused areas appear blue. The red arrow points to VWFA. All figures in this paper show the left half of the brain on the right (neuroradiological convention).

that appears to be consistent with both functional imaging and lesion studies is that one role of the left midfusiform gyrus (VWFA) is the computation of a word-centered representation of the string of graphemes from the visual stimulus (a component of processing that is essential to reading), but that this role can be equally carried out by the homologous region of the right hemisphere (r-VWFA). Then, if there is damage or dysfunction of left VWFA, r-VWFA can immediately assume this function. This role may typically be carried out primarily on the left because computation of a word-centered representation of the string of graphemes is required to access stored orthographic information—stored linguistic knowledge of how words are spelled or how they relate to phonology—in the left hemisphere.

This role of the VWFA (and r-VWFA) in computing a prelexical representation of the sequence of graphemes is not inconsistent with the role of the VWFA postulated by Cohen et al. (2000, 2002, 2003). That is, Cohen et al. (2003) propose that early visual processing of words and letter strings requires computation of a series of increasingly abstract representations of the visual stimulus, beginning with a retinotopic representation of the variations in light intensities, and culminating in a representation of the abstract letter identities (graphemes) that no longer specifies location, size, font, or case of the stimulus. It is this location- and font-independent representation of the alphabetic stimulus that Cohen et al. (2003) hypothesize to be computed in VWFA. They cite a very similar proposal by Hillis and Caramazza (1995) and Hillis and Caramazza (1990) based on theories of visual processing and word recognition from Marr and Nishihara (1978) (see also Marr, 1982) and Monk (1985), along with evidence from patients with neglect dyslexia. Although Cohen et al. label this prelexical

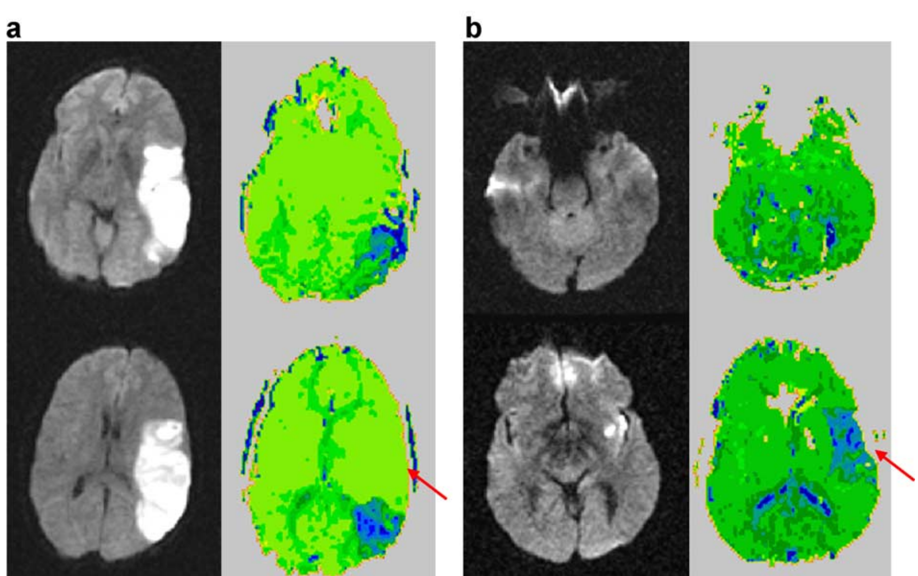

Fig. 2. DWI and PWI scans of two patients with impaired written word comprehension and lexical decision with hypoperfusion or infarct of left posterior superior temporal lobe (BA 22). The purple arrows point to BA 22.

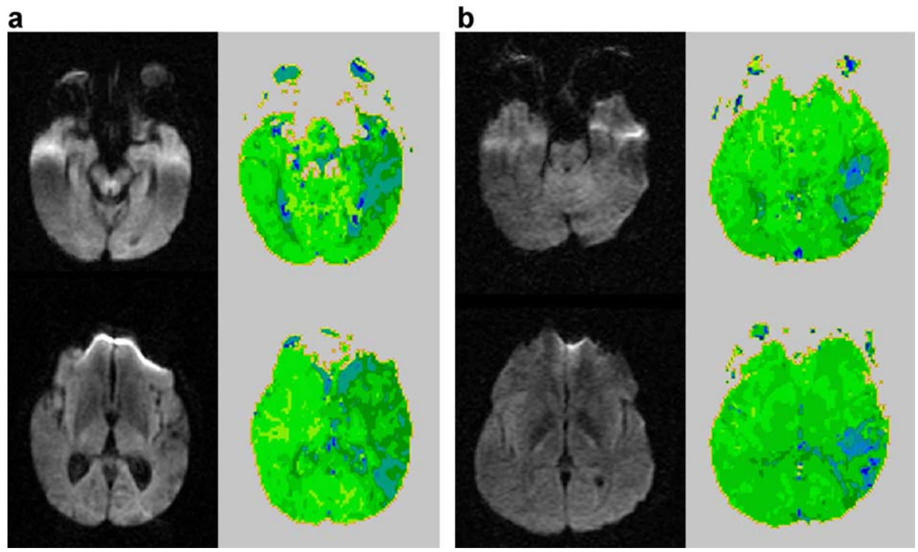

Fig. 3. DWI and PWI scans from patients with impaired oral and written naming of objects and pictures and impaired oral reading but intact written word comprehension and lexical decision, with hypoperfusion of VWFA.

representation that is computed during the reading task "the visual word form", it is likely that the same level of representation is computed from verbal input when recognizing words spelled aloud and is computed for pseudowords (see Hillis and Caramazza, 1990, 1995 for evidence). Because it requires no stored knowledge of spelling or spelling-sound correspondences, it is clearly different from the sort of "visual word form" (or lexical-orthographic representation) proposed in models of reading described in some of the prevailing models of reading (e.g., Coltheart et al., 1993; Morton and Patterson, 1980; Warrington and Shallice, 1980).

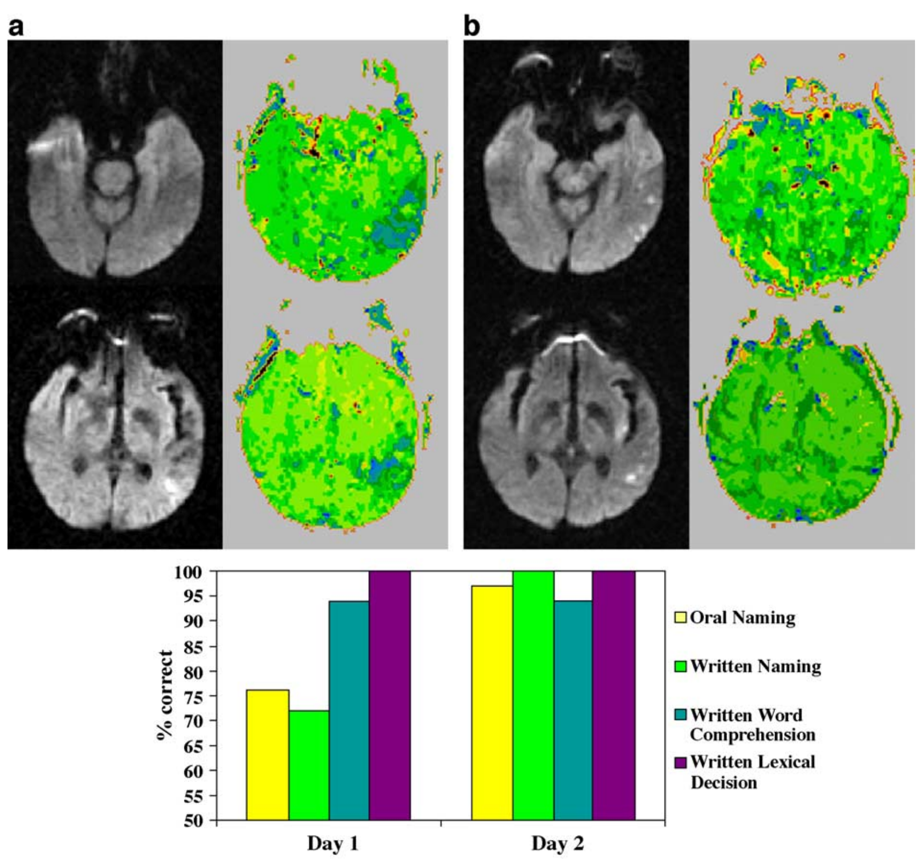

Fig. 4. DWI and PWI scans before and after reperfusion of BA 37 (including VWFA). At Day 1, BA 37 was hypoperfused, and oral naming of both pictures and objects to tactile exploration (combined for this graph) and written naming of pictures were impaired. At Day 2, BA 37 was normally perfused, and oral and written naming performance returned to normal.

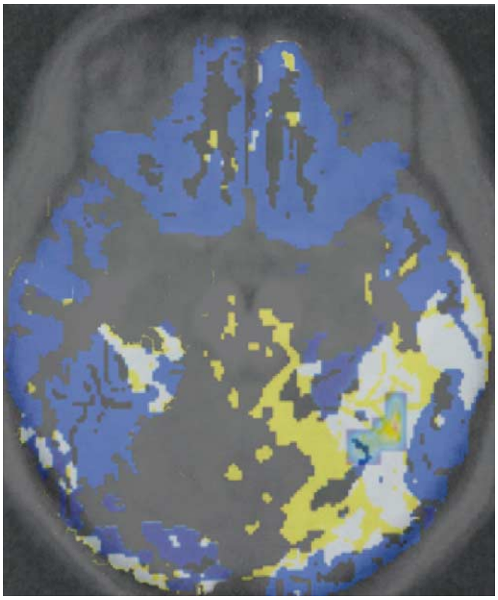

Fig. 5. PWI scan of a patient with hypoperfusion of BA 37, including VWFA, co-registered with the MNI atlas, superimposed on a figure from Cohen et al., 2003 (but flipped to the neuroradiological convention of left on right). The squares correspond to areas of activation on fMRI indicating VWFA. Blue areas in this figure correspond to normal cortex. White areas correspond to hypoperfused cortical tissue on PWI; the yellow areas are areas corresponding to hypoperfused noncortical tissue.

Therefore, we have called this computed representation of the string of graphemes the "graphemic description". In the model by Cohen et al. (2003), this prelexical, computed graphemic description directly projects to structures involved in phonological and lexical–semantic processing. However, it seems likely that stored knowledge about orthography (how words are spelled or how grapheme sequences correspond to phonology) is another essential component of reading that follows computation of a graphemic description and precedes lexical semantic processing.

We therefore propose a modification of the Cohen et al. (2003) (see also McCandliss et al., 2003) model that postulates an additional component of reading—orthography–phonology conversion (at both word and subword levels), as shown in Fig. 8. Although there has been intense debate as to whether there are separate mechanisms for sublexical and lexical reading, computational models of reading provide some evidence that storage of the spelling of familiar words (an orthographic lexicon) may not be distinct from learned correspondences between orthography and phonology (Plaut and Shallice, 1993; Seidenberg and McClelland, 1989). In our model, learned representations of word spellings and orthography-to-phonology correspondences at least depend on the same general area of the brain (and may depend on the same mechanisms). We propose that these essential components of reading are carried out in the left angular gyrus based on our finding that impairments of written lexical decision, written word comprehension, and oral reading of both words and pseudowords (tasks that all depend on learned aspects of orthography) were all associated with damage or dysfunction of the left angular gyrus.

The proposal that left or right midfusiform gyrus (VWFA) is essential for computing a grapheme description and the left angular gyrus is essential for accessing stored orthographic knowledge is consistent with results from a variety of functional imaging and lesion studies. First, the proposed role of VWFA in computing graphemic descriptions would account for the many functional imaging studies that have reported activation in left VWFA in response to visually presented words and pronounceable pseudowords, relative to nonalphabetic visual stimuli (Price et al., 1996; Puce et al., 1996), irrespective of the spatial location of the stimuli (right or left visual field) or typographic case (e.g., Cohen et al., 2000, 2002, 2003, Dehaene et al., 2001, 2002; Polk and Farah, 2002). Some studies have also reported activation of bilateral midfusiform gyrus in reading tasks, such as lexical decision (Fiebach et al., 2002), consistent with our proposal that both left and right midfusiform gyri are engaged in computing graphemic descriptions (but only one or the other is essential for this component of reading or lexical decision). Finally, electrophysiological studies indicating that activity in this region occurs early in processing written words (Salmelin et al., 1996, Tarkiainen et al., 1999) also support a role of VWFA in prelexical processing.

The proposed role of left angular gyrus in accessing stored orthographic information for words is also consistent with a recent

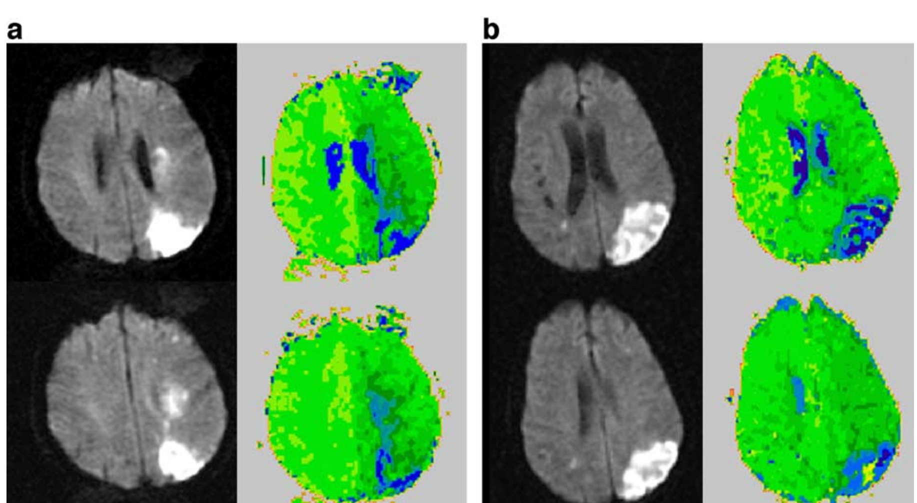

Fig. 6. DWI and PWI scans of patients with impaired written word comprehension and lexical decision, and impaired oral reading of words and pseudowords, associated with hypoperfusion of the left angular gyrus.

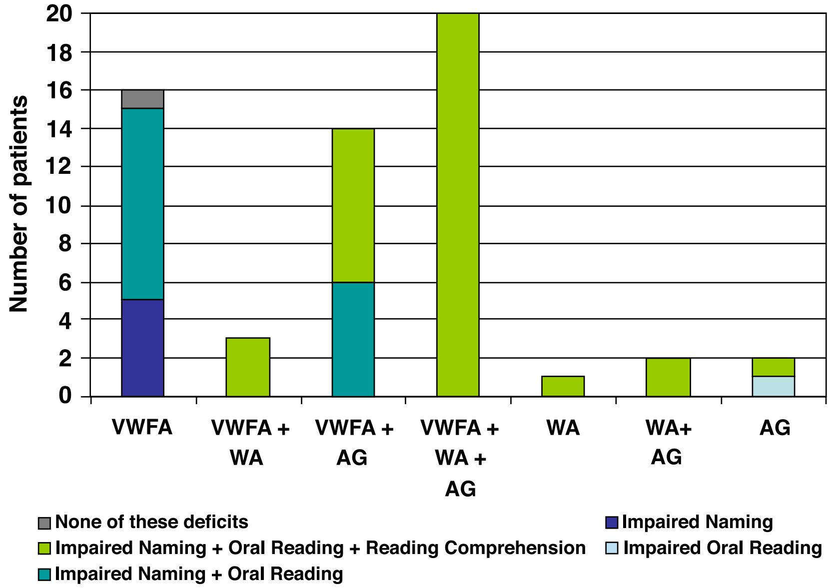

Fig. 7. Number of patients with impairments of oral reading, oral naming, or written word comprehension (written word or picture verification) associated with lesions including the VWFA, Wernike's area (WA), or left angular gyrus (AG).

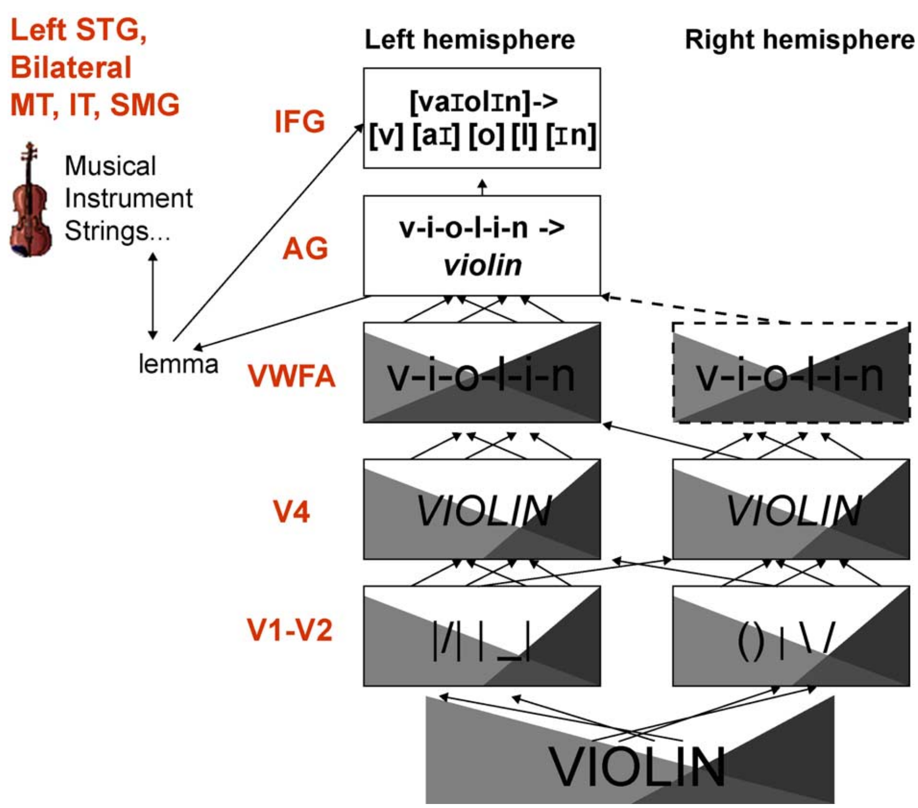

Fig. 8. A schematic representation of the proposed processes underlying reading and their neuroanatomical substrates (modified from Cohen et al., 2003). We propose that early visual processing and computation of viewer-centered and stimulus-centered representations of the written word depend on bilateral V1–V4; computation of a word-centered graphemic description depends on the left or right VWFA; access to mechanisms for orthography–phonology conversion (word and subword levels) depends on the left angular gyrus (AG); access to a lexical or lemma representation for output depends on left BA 37 (including VWFA); and phonological–articulatory mechanisms depend on the left posterior inferior frontal gyrus (IFG). Semantic representations are distributed throughout the left temporal lobe and supramarginal gyrus, and linked to lemma representations or phonological or orthographic representations through left posterior superior temporal gyrus (STG). Pale grey represents right hemisphere spatial attention and dark grey represents left hemisphere spatial attention (see Hillis and Caramazza, 1995 for discussion of spatial attention processes in reading).

fMRI study of reading that reported activation in the left angular gyrus in response to high-frequency words relative to consonant strings and pseudowords relative to consonant strings (Joubert et al., 2004). These data can be accounted for by our hypothesis that the left angular gyrus is involved in orthography-to-phonology conversion at both the word and subword level. Similarly, Binder et al. (2003) reported activation in the left angular gyrus during lexical decision. This model is also consistent with a large number of lesion studies indicating that the left angular gyrus is critical to reading and spelling (Benson, 1979; Black and Behrmann, 1994; Dejerine, 1892; Vanier and Caplan, 1985), and studies of Japanese patients with alexia and agraphia particularly for Kana (sublexical characters with phonetic value but no meaning) caused by left angular gyrus lesions (Sakurai, 2004).

However, the proposed role of left midfusiform gyrus in computing graphemic descriptions cannot account for results of studies showing activation of this region in other lexical tasks, such as repetition and naming (Price and Devlin, 2003; Price et al., 2003), or studies reporting impaired oral naming associated with lesions to this region (e.g., Hillis et al., 2002b; Raymer et al., 1997). Furthermore, this role of left midfusiform gyrus would not account for our result that damage or dysfunction of this region was strongly associated with deficits in all lexical output tasks (oral naming from visual or tactile input, oral reading, and written naming). These results together provide the basis for hypothesizing that left midfusiform gyrus (VWFA) is also essential for accessing lexical representations for output, irrespective of input or output modality. Such a modality-independent level of processing shared by oral and written naming has been specified in many recent models of naming and sentence production (Butterworth, 1989; Levelt et al., 1991). Whether there are separate parts of VWFA or separate subsets of neurons responsible for this role versus the role of computing graphemic descriptions is unclear. One possibility is that prelexical graphemic descriptions may be processed in the posterior left midfusiform and occipital gyri, whereas access to modality-independent word forms is dependent on more anterior portions of left midfusiform gyrus. This proposal would account for reports of alexia with agraphia with worse performance with Kanji (Japanese ideograms or lexical forms) than Kana (sublexical “syllograms”) due to lesions involving left BA 37, alongside cases of pure alexia with worse performance with Kana due to more posterior lesions (see Sakurai, 2004 for review). Another possibility is that columns of neurons in the same general region are selective to particular types of stimuli (e.g., Puce et al., 1999) or functions (Cohen and Dehaene, 2004). However, it seems equally plausible that the same neurons may be recruited in (1) computing a location-independent and a modality-independent representation of a grapheme string from input, and (2) computing or accessing a modality-independent representation that links modality-specific lexical input and output. This second role of VWFA may account for the left hemisphere predominance in activating left VWFA during silent reading, because this task might result in “automatic” activation of modality-independent lexical representations. The proposal that VWFA has an essential role in modality-independent lexical processing (for output) is also consistent with a wealth of data from both functional imaging studies and lesion studies, as reviewed by Büchel et al. (1998b), Price and Devlin (2003), and Price et al. (2003).

This proposal also fits well with data from functional imaging studies of reading development in normal and disabled readers, as reviewed by Pugh et al. (2001). These authors review evidence for proposing that reading depends on the integrity of two left hemisphere circuits: (1) a dorsal, temporoparietal circuit associated with analytic processing that is essential for integrating orthographic with phonological and lexical–semantic features of printed words, and (2) a ventral, occipitotemporal circuit that involves rapid access to lexical representations. They propose that children learn to read by initially relying on the slower, dorsal, rule-based system involving the left angular gyrus, supramarginal gyrus, and posterior aspect of the superior temporal gyrus. However, as internal representations (lexical or word form representations) are developed, children can read by the faster, ventral system for activating these word forms involving left extrastriate regions and fusiform gyrus. In support of this proposal, Pugh et al. (2001) cite evidence from functional imaging that the dorsal region (including angular gyrus) shows greater activation during pseudoword relative to word reading, increased activation during phonological analysis, and decreased activation with faster presentation rates, as would be predicted by the proposed role of left angular gyrus in word and subword orthography to phonology conversion. The authors also propose that this dorsal system engages the left inferior frontal gyrus during pseudoword and word reading for fine-grained articulatory or phonologic recoding (Fiez and Petersen, 1998; see also Bokde et al., 2001; Jobard et al., 2003; Fiebach et al., 2002). In contrast, the ventral system (including left midfusiform gyrus) shows greater activation during familiar word reading relative to pseudoword reading (Tagamets et al., 2000), which would be predicted by the role of the VWFA in lexical output. Furthermore, activation in the ventral system increases with age and reading skill (Pugh et al., 2001), as would be predicted by the role of this region in lexical processing. Reading-disabled subjects can show reduced activation in any of these regions (Pugh et al., 2001; Paulesu et al., 2001; Temple et al., 2001), just as dysfunction of either the left angular gyrus or left BA 37 was associated with impaired oral reading after acute stroke in this study. Furthermore, there is evidence from PET studies that reading-disabled subjects show less connectivity between left BA 37 and left angular gyrus during oral reading than do normal readers (Horwitz et al., 1998). These data are all consistent with our proposal that reading involves early computation of a graphemic description in the left or right midfusiform gyrus (in BA 37), orthography-to-phonology conversion at the word and pseudoword level in left angular gyrus, and access to learned, modality-independent lexical representations for output in BA 37 (including VWFA).

Additional evidence for the role of the temporo-occipital system, which includes VWFA, in pre-lexical computation of a graphemic description comes from electrophysiological studies involving MEG. These studies show differential evoked responses to words and pseudowords (which require computation of a graphemic description) versus nonlinguistic visual stimuli in the occipitotemporal region 150–180 ms after presentation, and later evoked responses in the temporoparietal region at about 250 ms (Salmelin et al., 1996). The early activation in the occipitotemporal region may reflect computation of a graphemic description, and later activation in the temporoparietal region may reflect orthography to phonology conversion in the left angular gyrus.

One prediction that follows from the above proposals is that either right or left midfusiform gyrus (along with connections from the primary visual cortex to the intact midfusiform gyrus and from the intact midfusiform gyrus to left angular gyrus and posterior superior temporal gyrus) is critical for written word comprehension. The combination of lesions that “disconnect” left VWFA from visual input (e.g., left striate cortex and splenium) and disconnect r-VWFA from left superior temporal and angular gyri (white matter tracks between right and left temporal gyri, which are restricted to the splenium; Huang et al., submitted for publication) should cause severe alexia, as first described by Dejerine (1892). Although many cases of pure alexia have been reported to have this combination of lesions (e.g., Binder and Mohr, 1992; Chialant and Caramazza, 1998; Cohen et al., in press; Miozzo and Caramazza, 1998; Saffran and Coslett, 1998), some patients with pure alexia do not have splenial lesions but have only left fusiform lesions (Binder and Mohr, 1992; Saffran and Coslett, 1998). However, because the splenium is in the same vascular territory as the fusiform gyrus, these cases may have had hypoperfusion of the splenium that functionally disconnected r-VWFA from left temporal regions, because patients splenial callosal lesions have less severe and more transient reading impairment (Binder and Mohr, 1992). To illustrate, one patient we have recently studied had letter-by-letter reading with severely impaired written word comprehension and lexical decision but relatively spared recognition of orally spelled words, along with optic aphasia (impaired naming of pictures, with relatively spared naming to tactile exploration). DWI showed an acute infarct involving left occipital and fusiform gyri; and PWI showed severe hypoperfusion of the entire posterior cerebral artery territory, including the splenium. His reading and picture naming improved when the splenium was reperfused (allowing contributions from the r-VWFA to left temporal regions); although he had a mild, persistent modality-independent anomia due to the lesion involving left VWFA (Marsh and Hillis, submitted for publication). This patient and all other patients with letter-by-letter reading we have studied were excluded from the present study because they presented more than 24 h post onset of symptoms.

In summary, data from functional imaging studies, electrophysiological studies, chronic lesion/deficit association studies, and our own studies of DWI, PWI, and concurrent language testing in acute stroke converge in support of the hypothesis that the left midfusiform gyrus (“VWFA”) is engaged in, and perhaps specialized for, two components of lexical processing: (1) computation of a font-, case-, and location-independent representation of the string of graphemes (the graphemic description) early in the reading task; and (2) modality-independent stage of lexical processing required for linking learned, modality-specific lexical input and output representations. Our data indicate that the left midfusiform gyrus is not necessary for the former processing component, probably because this component can be carried out equally by the right midfusiform gyrus (r-VWFA). However, the left midfusiform gyrus is probably necessary for the latter component, in the sense that lesions reliably cause impairment in modality-independent lexical processing for output, at least early after damage. This modality-independent stage of lexical processing involving BA 37, or orthographic–phonological representations computed in the left angular gyrus, may serve to access semantic information in other areas of temporal and parietal cortex. The strong association between left posterior superior temporal gyrus and written word comprehension identified in this study indicates that this region (BA 22) may also be involved in linking written words to their meanings, although it is unlikely that semantic representations *per se* are computed in the left posterior superior temporal gyrus (see Hillis et al., 2001a,b for a similar proposal about the role of BA 22 in linking spoken words to their meanings, supported by evidence from chronic and temporary lesions and functional imaging). Modality-independent lexical representations computed in the left BA 37 and orthography–phonology correspondence computed in the left angular gyrus may also serve to access modality-specific representations for output and phonologic–articulatory mechanisms in the left inferior frontal gyrus. Although lesion data of the sort we have reported can demonstrate that a region is not sufficient for a particular function (e.g., left VWFA is not sufficient for access to orthographic lexical representations, because damage to other regions can disrupt this function), lesion data cannot be used to demonstrate that an area is sufficient for a given function. Functional imaging studies are more suited for identifying all of the regions that are engaged in a particular process. It is clear that none of our regions of interest is alone sufficient for reading, which is a complex task that clearly engages a network of regions in occipital, temporal, parietal, and frontal cortices that are variably activated depending on the familiarity and orthographic regularity of the stimulus, presentation rate, and age and skill of the reader. However, discrete regions may be necessary, sufficient, or specialized for their respective component functions within this complex task.

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