Published in final edited form as:

Cogn Neuropsychol. 2014 July ; 31(0): 511–528. doi:10.1080/02643294.2014.884060.

The Roles of Occipitotemporal Cortex in Reading, Spelling, and Naming

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Abstract

We evaluated the hypothesis that Brodmann's area 37 within left occipitotemporal cortex has at least two important functions in lexical processing. One role is the computation of case-, font-, location-, and orientation-independent grapheme descriptions for written word recognition and production (reading and spelling). This role may depend on the medial part of BA 37, in left midfusiform gyrus. The second role is in accessing modality-independent lexical representations for output, for naming and for reading and spelling of irregular or exception words. This role may depend on the lateral part of BA 37 in inferior temporal cortex. We tested these hypotheses in 234 participants with acute left hemisphere ischemic stroke who underwent MRI and language testing within 48 hours of onset of stroke symptoms.

Keywords

reading; spelling; naming; lesion studies; acute ischemic stroke; aphasia

Introduction

Brodmann's area (BA) 37, within occipitotemporal cortex, is located primarily in caudal fusiform gyrus and inferior temporal gyrus on the medial-basal and lateral surfaces of the caudal temporal lobe. It shares a boundary on the caudal end with occipital cortex (BA 19); and shares a boundary on the dorsal side with parietal cortex (angular gyrus, BA 39). It is bounded rostrally by inferior temporal BA 20 and middle temporal BA 21 (Brodmann, 1909). A specific part of this area on the left, in the midfusiform gyrus and temporoccipital sulcus, has been proposed to be essential for reading. Functional imaging studies have found that this area is activated relatively specifically by orthographic stimuli, often more so for

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Disclosures: None

words and letters than letter-like symbols or unreadable letter strings and exhibits invariance to a number of visual characteristics such as case, language specific script and types of visual stimulation (Bolger et al., 2005; Baker et al., 2007; Cohen et al., 2000, 2002; Cohen & Dehaene, 2004; Dehaene et al., 2001, 2002; Dehaene & Cohen, 2011; Polk & Farah, 2002; Rauschecker et al., 2011).

In fact, some authors believe the left midfusiform gyrus is sufficiently specific and specialized enough to reading that they have dubbed it the “visual word form area” (VWFA) (Cohen et al., 2000, 2002, 2004; Dehaene et al., 2001, 2004, 2005; Dehaene & Cohen, 2011). There have been further recent specifications of the VWFA proposal, as delineated in this issue (see also Cohen et al., 2008; Dehaene et al., 2005; Vinckier et al., 2007). However, others (e.g. Price & Devlin, 2003, 2011) have proposed that midfusiform gyrus is critical for modality independent lexical processing, on the basis that this area shows activation in response to a variety of non-reading lexical tasks, and the fact that lesions in this area are associated with other lexical deficits such as naming (Büchel, Price, Frackowiak & Friston, 1998; Devlin et al., 2006; Mycroft et al., 2009; Price & Devlin, 2003, 2004, 2011; Wright et al., 2008).

In an effort to reconcile these conflicting findings, we hypothesized that left BA 37 is consistently engaged in written word recognition, but not necessary or specific to written word recognition (because right BA 37 could also perform this function), but left BA 37 is necessary for modality-independent lexical output (Hillis et al., 2005). To test this hypothesis, we studied 80 participants, 40 with acute lesions (infarct/hypoperfusion) in left BA 37 (including midfusiform or “VWFA”), and found that ischemia in left BA 37 was not associated with impaired written lexical decision or written word/picture verification, but was associated with impaired oral naming of pictures or objects (tactile input) and oral reading. We concluded that left BA 37 is not essential for written word comprehension or lexical decision (even though it is consistently activated during these tasks), because right BA 37 can immediately assume its function. However, most of the lesions in that study included much more of left BA 37 than just midfusiform gyrus. Furthermore, our tasks of untimed written word-picture verification and lexical decision might not have been sensitive to reading functions of the midfusiform gyrus.

Cohen et al. (2003) also proposed the right homologue of VWFA (“R-VWFA”) in right BA 37 is responsible for residual (but impaired) reading in participants with left VWFA lesions who read letter-by-letter. Likewise, Bartolomeo et al. (1998) reported a participant with letter-by-letter reading after a lesion in left BA 37. After a right BA 37 stroke, most of the residual reading in this individual was impaired, indicating that R-VWFA had assumed the functions of the damaged L-VWFA.

More and Price (1999) identified three distinct ventral occipitotemporal regions for reading and object naming based on functional imaging data. Similarly, Cohen and colleagues (Cohen, Jobert, Le Bihan, & Dehaene, 2004) proposed that there are two separate areas in left occipitotemporal cortex: the VWFA, which is essential for computing a location-, font-independent graphemic description (McCandliss et al., 2003) and the lateral inferiotemporal multimodality area (LIMA). The VWFA consists of the left occipitotemporal sulcus and the

fusiform cortex just medial to it. The LIMA is lateral to the occipitotemporal sulcus, in the inferior temporal cortex, and is important for a variety of lexical tasks including naming and recognition of Braille. This LIMA may be critical for modality-independent lexical processing, rather than an orthographic-specific processes.

Here we build on the hypothesis proposed by Cohen et al. (2004). We propose that there are two roles of left BA 37 in lexical processing, perhaps two populations of cells with somewhat different spatial distributions within occipitotemporal cortex or BA 37. The hypothesized roles are:

1. Computation of a word-centered grapheme description, independent of size, font, location, or *orientation*, critical for reading *and spelling*, which might depend on either left *or right* BA 37, in midfusiform gyrus or occipitotemporal sulcus (so-called “VWFA”). Computation of a word-centered grapheme description is necessary for spelling while the word (or pseudoword) is being spelled aloud or written (the level of the “graphemic buffer”) and is necessary for reading words (or pseudowords) in various formats, orientations, and locations (Caramazza & Hillis, 1990).
2. Modality-independent lexical access (linking semantics to lexical representations *for output*); i.e. oral and written naming regardless of input, oral reading and spelling of irregular words, which might depend on inferior temporal cortex, lateral to left VWFA.

On this hypothesis, lesions to medial left BA 37 or midfusiform cortex (“VWFA”) alone are not responsible for “pure alexia” or “alexia without agraphia” (an isolated deficit in reading) for two reasons. First, alexia without agraphia would require deafferentation of left medial BA 37 from visual input (e.g. by lesions to both the left occipital cortex and the splenium or other white matter tracts to midfusiform from right occipital cortex, such as the inferior longitudinal fasciculus (ILF; Epelbaum et al., 2008). Secondly, on this account, lesions of left medial BA 37 would cause spelling as well as reading deficits, and length effects in both. There is some independent evidence from functional imaging and previous lesion studies that left VWFA is an important node in the network underlying both reading and spelling (Beeson et al., 2003; McCandliss et al., 2003; Purcell et al., 2011; Rapp & Lipka, 2011). Figure 1 shows that areas of activation associated with spelling are very similar to areas of activation associated with reading in healthy controls, and that this area (in left midfusiform cortex) is an area where acute ischemia is associated with acute impairment in written spelling to dictation of words and pseudowords as well as oral reading of words and pseudowords (Philipose et al., 2007).

There is also some evidence that left medial BA 37 or midfusiform cortex and left inferior temporal cortex lateral to midfusiform cortex may have distinct roles in language. For example, longitudinal imaging and language assessment of participants with primary progressive aphasia indicates that atrophy of left fusiform is associated with decline in spelling, while atrophy of left lateral inferior temporal cortex is associated with decline in oral naming (Race et al., in press).

It is somewhat surprising that these areas have not been examined more commonly in stroke studies, as they are relatively frequently affected by stroke, and they are dissociable areas in stroke, because they have distinct vascular supplies. Medial BA 37 (midfusiform), occipital cortex, and splenium are supplied by the posterior cerebral artery. The occipitotemporal sulcus is in the watershed territory between the middle cerebral artery and the posterior cerebral artery; “watershed” strokes that result in infarcts in this area unilaterally or even bilaterally are not uncommon after cardiac bypass surgery, carotid endarterectomy, or other surgeries in participants with cerebrovascular disease, particularly surgeries in which the aorta or carotid must be temporarily clamped during the surgery). In contrast, lateral BA 37 in the inferior temporal cortex is supplied by the inferior branch of the MCA in most people. It is among the areas that has the highest vulnerability to ischemia due to hypoperfusion in stroke patients (Payabvash et al., 2011).

There are a number of hypotheses that would follow from our expanded proposal about the occipitotemporal cortex or BA 37. First, most strokes that affect left BA 37 will affect both reading and spelling, because both areas/roles of left BA 37 are important in reading and spelling (although the roles are somewhat different). Second, if the two areas of left BA 37 that have distinct roles are not entirely overlapping in terms of spatial extent, some (small) strokes will impair naming but not reading/spelling pseudowords and regular words. In such cases we would expect that those that selectively impair naming or modality-independent lexical output would be more lateral, involving the LIMA in inferior temporal cortex. Third, some (small) strokes should selectively impair reading and spelling of words and pseudowords, but not naming or other non-orthographic lexical processing (e.g. sign language). We would expect strokes that selectively impair computation of a location-independent, font-independent, orientation-independent orthographic representation (graphemic description) would involve medial BA 37 (VWFA) *AND* white matter connections to right VWFA.

Finally, we would not expect ‘alexia without agraphia’ (“pure alexia”) from lesions restricted to left BA 37. Rather, only lesions that disrupt visual input to left BA 37 (e.g. occipital cortex and splenium; or ILF) *but not left BA 37* itself will impair reading (and naming), but not impair spelling. That is, deafferentation of left BA 37 could account for impaired ability to compute a graphemic description (in midfusiform cortex) or to access a lexical representation for output (in the LIMA). This account is essentially the account given for optic aphasia – impaired ability to name from vision with retained ability to name from other modalities given by Freund (1889), who proposed that the deficit resulted from impaired access to language from vision due to (1) left occipital lesion and (2) disconnection between right occipital lobe and left hemisphere language areas (due to splenial lesion). Dejerine’s case (1892 (1895) of alexia without agraphia as a disconnection syndrome also likely spared midfusiform cortex, but affected white matter tracts connecting it to the two common “visual centers” and to the angular gyrus. Similarly, Epelbaum et al. (2008) demonstrated that deafferentation of midfusiform cortex (caused by a lesion to the ILF) without damage to midfusiform cortex itself could cause alexia without agraphia.

We tested our hypotheses about the associations and dissociations between reading, spelling, and naming after acute lesions to left BA 37 in a series of 234 participants with acute left

hemisphere ischemic stroke. This was a retrospective analysis of prospectively collected data. That is, the data were collected with the goal of testing hypotheses about the relationship between lexical processing and areas of infarct and/or hypoperfusion. However, the specific hypotheses tested in this paper were developed after data had been acquired.

Methods

Participants

All participants had acute left hemisphere ischemic stroke, admitted within 24 hours symptom onset and tested with MRI and language testing within 24 hours of admission to the hospital. Exclusion criteria included: decreased level of consciousness, sedation, inability to provide informed consent or indicate a family member to provide an informed consent, hemorrhage on initial imaging, left handedness, lack of premorbid proficiency in English, previous neurological or psychiatry disease. Participants' age ranged from 18 to 80 (mean 55.6 years). Mean education was 13.3 years ($SD=3.2$). Of the 234 participants, 122 (52.1%) were women. Informed consent was obtained according to the consent process approved by the IRB at Johns Hopkins University School of Medicine.

Language Tests

Participants were administered a set of lexical tasks with stimuli matched for length (all stimuli), as well as for frequency and word class (for words). The tasks included (a) oral naming of black and white pictures (from Snodgrass & Vanderwart, 1980; $n=17$), (b) oral naming of objects with tactile input ($n=17$), (c) oral reading of words ($n=34$) and pseudowords ($n=25$), (d) spelling to dictation of words ($n=34$) and pseudowords ($n=25$). Norms were obtained for the language tests from 46 control participants who were awaiting surgical repair of unruptured intracerebral aneurysm or awaiting cardiac bypass surgery (Hillis et al., 2002). The control participants were not significantly different in age or education from our stroke participants, and were also hospitalized, and from the same socioeconomic backgrounds as our stroke participants. The mean age of the control participants was 60.2 years ($SD=13.4$) and mean education was 13.3 years ($SD=3.2$). Mean scores for the normal controls for each subtest ranged from 98.0% ($SD=3.1$) correct in oral reading to 100% ($SD=0$) correct in tactile naming. Abnormal performance was defined as 89% correct or lower; normal performance was defined as 90% correct or higher. This cut of was selected because 89% was 3 SD below the mean. No control participant scored below 90% correct on any subtest of the lexical battery. Participants were considered to have abnormal performance if they scored below 90% correct on any one or more of the subtests. Participants with $<10^{\text{th}}$ grade education or self-identified premorbid reading or spelling deficits are not included in tests of reading or spelling.

Imaging

MRI and language testing were obtained within 24 hours from admission to the hospital. Participants had T2, FLAIR (Fluid Attenuation Inversion Recovery to evaluate for old lesions), Susceptibility Weighted Images (to evaluate for hemorrhage), Perfusion Weighted Imaging (PWI to evaluate for areas of hypoperfusion), Diffusion Weighted Imaging (DWI; to evaluate for acute ischemia). Time to peak (ttp) maps and DWI were co-registered with

T2 which have better spatial resolution, and analyzed in ImageJ. A technician, blinded to the performance on the Lexical Battery, scored images for infarct in BA 37 (bright on DWI, dark on Apparent Diffusion Coefficient maps) and/or hypoperfusion (>4 sec delay in TTP in left BA 37 compared to right BA 37) using a published templates to identify the most likely area of BA 37 (Damasio & Damasio, 1989). A threshold of >4 delay in TTP was selected because this area corresponds to dysfunctional tissue based on previous studies (Hillis, 2007; Sobesky et al., 2004). Then, a neurologist (AH), blinded to language performance, identified whether the ischemia was in medial or lateral BA 37 or both. Medial BA 37 was defined as medial to, and including, the occipitotemporal sulcus; lateral was defined as lateral to the occipitotemporal sulcus. Inter-rater reliability in determining presence/absence of infarct/hypoperfusion in medial and lateral BA37 was assessed by a second neurologist (RL) on 10% of the scans, including all scans in which the participants showed a dissociation between reading and spelling. The independent assessment of two stroke neurologists (AH and RL) showed 95.8% point-to-point agreement in determining presence/absence of infarct/hypoperfusion in medial and lateral BA 37. The only disagreement was in determining if hypoperfusion involved medial vs. both medial and lateral BA 37, resolved by consensus. There were originally 336 participants in the dataset; 102 were excluded because they had no PWI or uninterpretable PWI and also had no infarct in left BA 37 (n=102), because in these participants it was impossible to determine whether or not they had ischemia in BA 37. However, participants who did have infarct in BA 37 were included even if they did not have a PWI, because there was no question about whether or not there was dysfunction in left BA 37 in these cases. Therefore, the population includes an over-representation of participants with BA 37 lesions (n=103, from 234 total cases), compared to a random sample of left hemisphere stroke participants. However, as we were mostly interested in participants with dysfunctional tissue in left BA 37, and a comparable number of participants without dysfunctional tissue in left BA 37 to serve as controls, the resulting study population served our needs well.

Statistical Analyses

Error rates in reading, spelling and naming for participants with and without damage to left BA 37 were compared using unpaired t-tests. Associations between hypoperfusion/infarct in left BA 37 and specific lexical deficits were evaluated using chi-squared tests. Further, we also tested the associations between more focal lesion sites (medial/lateral BA 37) and selective lexical deficits.

Results

Out of the 234 participants with left hemisphere stroke, 103 had infarct/hypoperfusion involving BA 37. Ischemia in left BA 37 was significantly associated with deficits in oral reading: X^2 (df1)=80.1; $p=0.00001$; oral picture naming: X^2 (df1)= 100.2; $p=0.00001$; tactile naming X^2 (df1)= 26.6; $p=0.00001$; and spelling to dictation: X^2 (df1)=41.9; $p=0.00001$. See Table 1 for the relationship between infarct/hypoperfusion in left BA 37 and lexical tasks. Mean error rates in reading, spelling and naming were significantly different between participants with lesion (tissue dysfunction) in left BA 37 and participants without lesion in BA 37 ($p<0.0001$ for each task). See Figure 2 for mean error rates for the three tasks.

Although fewer participants completed the task of tactile naming compared to picture naming, results were similar. Those with tissue dysfunction in left BA 37 were significantly more impaired in tactile naming compared to participants without tissue dysfunction in left BA 37 (mean $44.2 \pm SE 5.9$ vs. mean 10.2 ± 2.5 ; $df127$; $p<0.0001$). The mean difference in percent correct for those with minus without tissue dysfunction in left BA 37 (and 95% confidence interval) for each task was as follows: picture naming -38.34 (-46.5 to -30.2); reading -44.2 (-52.3 to -36.2); spelling -42.2 (-55.9 to -28.5).

Below are the results for each hypothesis.

Hypothesis 1: Most strokes that affect left BA 37 will affect both reading and spelling, because both areas/roles of left BA 37 are important in reading and spelling

A total of 103 participants had infarct/hypoperfusion involving BA 37. Of the 103 participants with left BA 37 ischemia, only one had intact spelling. However, in 18 participants spelling could not be tested due to right hand dysfunction or premorbid spelling difficulty. The one participant with left BA 37 ischemia who had intact spelling also had intact reading and naming, and only tiny infarcts (and normal perfusion) in left BA 37. Of these 103 participants with ischemia in left BA 37, 84.5% (87) had impaired oral reading, spelling, and oral naming; 7.8% (8) had impaired naming and spelling, but intact reading; 3.9% (4) had impaired reading and spelling, but intact naming; 2.9% (3) had neither impaired reading nor naming (but 1 had impaired spelling).

Most (87) of the 103 participants with ischemia in BA 37 had impaired reading, spelling, and naming. Many were due to infarct/hypoperfusion of both lateral and medial BA 37 due to left carotid stenosis or occlusion or embolic strokes. For example, the participant whose scans are shown in Figure 3 was only 9% correct in oral reading, and made both visual and phonologically plausible errors and mixed errors (e.g. mutiny-> mutton). In oral picture naming he was 56% correct, and made mostly semantic errors, such as: ostrich-> "swan." He was 0% correct in spelling to dictation. Errors were "don't know" partial responses (single letters), or phonologically plausible errors (pencil-> pincel; violin-> violyn).

Only 1 participant with ischemia in BA 37 (of 103) had naming and oral reading that was markedly anomie in conversation; however, she had hypoperfusion of both left medial BA 37 ("VWFA", including midfusiform and occipitotemporal sulcus) and lateral (inferior temporal cortex) BA 37 due to critical stenosis of the left ICA. Her errors in oral naming were semantic errors of which she was aware (e.g. sun-> star, no). Errors in spelling were insertions, deletions, substitutions, and transpositions that increased with word length. She underwent stenting of the left ICA. Immediately after reperfusion of left BA 37 following stenting (Figure 4), her spelling errors and naming errors resolved.

Hypothesis 2: Strokes that selectively impair naming or modality-independent lexical output should involve lateral left BA 37, involving the LIMA in inferior temporal cortex.

A total of 8 participants with ischemia in BA 37 (of 103) had impaired naming (>10% errors) but intact oral reading. Of these 8 participants, 7 had infarcts/hypoperfusion of lateral BA 37 in inferior temporal cortex. All of these participants could read sublexically; all had

intact pseudoword reading, consistent with impaired modality-independent lexical access. For example, the participant whose scans are shown in figure 5a had severely impaired naming with picture or tactile stimuli at day 1, making mostly semantic errors (e.g. ostrich->goose), but had intact written and spoken word comprehension when lateral inferior temporal cortex was hypoperfused. At the same time, he made no errors in oral reading, and made only phonologically plausible errors in spelling to dictation (e.g., fault->falt; door->dorr). When this area was reperfused his semantic errors in naming and his spelling errors resolved (although he failed to identify one object to tactile exploration); see figure 5b. Likewise, the participant whose scans are shown in Figure 5c made semantic errors in picture and tactile naming at Day 1 (e.g. tactile: knife-> fork; apple-> orange; picture: bee-> fly), when lateral left BA 37, inferior temporal cortex, was hypoperfused, but no errors at Day 3, when it was reperfused. He made no errors in oral reading either day. He was not tested on spelling, as he said he was premorbidly a poor speller.

There was only one participant with ischemia in BA 37 and impaired naming (>10% errors) but “intact” oral reading whose ischemia was in medial left BA 37 (VWFA), rather than lateral left BA 37. Although this participant’s oral reading was within normal limits based on the 10% error cut off (91.4% correct), she made errors that were consistently on the right sides of words (e.g. import-> important; fish-> firm). In spelling to dictation, she was only 89.7% correct, and made errors on regular and irregular words. Errors were phonologically implausible and included insertions, deletions, substitutions, and transpositions of letters (e.g. bribe-> brib; apple-> aple) consistent with a “graphemic buffer” type of deficit, although there were not enough errors to confirm a word length effect. In oral naming she also made circumlocutions and semantic errors (e.g. frog-> “kanga thing”; cup-> “glass”) and accuracy was much lower: 35.3% for naming pictures, 58.8% for naming to tactile exploration. We hypothesized that her spelling errors and occasional reading errors were due to ischemia in the left midfusiform cortex; and her naming deficits may have been due to ischemia in the left thalamus. All of her errors resolved when the PCA territory (including left midfusiform and thalamus) was reperfused (Figure 5d).

Hypothesis 3: Strokes that selectively impair computation of a location-independent, font-independent, orientation-independent lexical representation (graphemic description) - i.e., affecting reading and spelling but not naming - should involve medial left BA 37 (“VWFA”) in left midfusiform cortex and perhaps white matter connections to right midfusiform cortex.

There were 4 participants with ischemia in BA 37 with impaired reading and spelling, but intact naming. Of these 4, 3 had infarct/hypoperfusion in medial left BA 37 (VWFA). For example, the participant whose scans are shown in Figure 5e made 19% errors in oral reading, with visual errors all at the ends of words and pseudowords (e.g. import-> important; lart-> lark). This participant made 40% errors in spelling to dictation, with insertions, deletions, substitutions, and transpositions, equally affecting words and pseudowords (e.g. envelope-> evope; chain-> chans; bottle-> bottee; drown-> drown; heef-> hefp). There was one exception to the localization: one participant with reading impairment without naming impairment had dorsal-lateral infarct within left BA 37. None of the participants with reading impairment and ischemia in BA 37 had intact spelling.

The dissociations between reading and naming in participants with infarct and/or hypoperfusion of medial or lateral left BA 37 are summarized in Table 2. The association between lesion site (medial/lateral) and type of deficit was significant (X^2 (df1)= 4.7; $p = .03$). Additionally, when we divided all of the participants into those whose lesions affected left medial BA 37, lateral BA 37, neither, or both, there were significant differences between groups in the mean performance across groups for oral naming, oral reading, and spelling to dictation ($p < 0.0001$). That is, there was a significant effect of lesion location on accuracy of naming [$F(3, 230) = 35.1$, $p < 0.0001$], oral reading [$F(3, 230) = 46.8$, $p < 0.0001$], and spelling [$F(3, 88) = 18.0$, $p < 0.0001$]. Table 3 summarizes error rates across tasks for each group.

Hypothesis 4: Lesions of left BA 37 *alone* will not cause alexia without agraphia, but lesions that *disrupt visual input* to left BA 37 (e.g. occipital cortex and splenium; or ILF) will impair reading (and naming) significantly more than spelling.

There were only a few cases of ‘alexia without agraphia’ (impaired oral reading, with relatively spared spelling) in this study of acute ischemic stroke. All of these participants had lesions disrupting visual input to BA 37, in left occipital cortex, as well as the splenium of the corpus callosum, “deafferenting” medial BA 37. They all also had impaired naming of pictures, with relatively spared naming with tactile input (“optic aphasia”). For example, the participant whose DWI scans are shown in Figure 6 had 0% correct oral reading of words and pseudowords. She made errors of the type: “nose-> n-o-n-e... [nonIn]” and “sum-> s-a...safe”. Oral naming of pictures was 12% correct. Errors were a mixture of semantic and perseveration on a theme (e.g. lamp-> “a weight of some kind”; accordion-> “a scale of some kind”). Oral naming from tactile input was much better: 41% correct. Errors were similar to errors in picture naming, but closer and more often correct (e.g. dice: “piece of a puzzle”). Written spelling to dictation was within normal limits for her age (94.7% correct). Her errors were perseverative letters and strokes, often observed in homonymous hemianopia, with poor monitoring of written output (e.g. celery-> celerry; carrot-> carrott). Oral spelling to dictation was slightly more accurate at 96.5% correct. She had infarcts in left occipital cortex and splenium of corpus callosum. Arterial spin labeling perfusion imaging done at the same time (done instead of PWI, because her kidney function precluded use of contrast for PWI) showed normal, symmetric perfusion of the hemispheres.

In cases in which medial BA 37 was also infarcted, then the participants also had some agraphia. For example, the scans of another participant who clinically had “alexia without agraphia” including letter-by-letter reading and disproportionately poor reading compared to spelling are shown in Figure 7. This participant had infarct in the entire left PCA territory, including left occipital lobe, fusiform, occipitotemporal sulcus, splenium, and thalamus. Oral reading was 0% correct; errors were of the type: thanks-> “t-h-e-r... there.” Oral naming of pictures was also 0% correct; errors were semantic substitutions, such as eraser-> “pencil”. In contrast, oral naming from tactile input was 95% correct. Errors were semantically related: cup-> “a holder for a cup.” Written spelling to dictation was much more accurate than reading at 33% correct, but included insertions, deletions, substitutions, mostly at the ends of words (e.g. feather-> featherer; chair-> chaim).

Discussion

The goal of the present study was to evaluate the hypothesis that there are at least two roles of the left Brodmann's area 37 in lexical processing: one that is critical for reading and spelling and another critical for naming. To explore these questions, we tested 234 participants with dysfunctional tissue in left BA 37 on a battery of lexical tasks including reading, naming and spelling.

Results of this study are consistent with our hypothesis that there are two roles of left BA 37 in lexical processing that may have somewhat distinct locations within the occipitotemporal cortex. One role is important for computing a location-, font-, and orientation-independent grapheme description (a sequence of abstract letter identities) from a written word or pseudoword (for reading) or to produce a written word or pseudoword (for spelling). The area medial to, and including, left occipitotemporal sulcus within the fusiform cortex appears to be at least one important site underlying this function. Left medial BA 37 may not be *critical* to computing a graphemic description, as it is possible that *right* BA 37 might accomplish this role when left BA 37 is damaged. This proposal would explain why some individuals are impaired in reading only when there is concomitant damage or hypoperfusion of the white matter tracts between right and left fusiform (splenium) (e.g. Marsh & Hillis, 2005). When this area is deafferented - cannot be acutely accessed from vision - because of concurrent lesions in left occipital cortex and splenium or ILF, the individual will have alexia without agraphia (also referred to as pure alexia), as demonstrated by several cases in the literature as well as a few cases in this study. Computation of a word-centered grapheme description, independent of location, font, and orientation (which seems depend on at least medial BA 37), is one component of the "graphemic buffer" - required in all spelling tasks -- to maintain the sequence of graphemes while the word or pseudoword is written or spelled aloud (Caramazza et al., 1987; Posteraro et al., 1988). The graphemic buffer seems to depend on this area, but also other areas (Cloutman et al., 2009). The graphemic buffer may require a number of cognitive components, including not only computation of the graphemic description, but also maintenance of this representation (and refresher mechanisms?) while the word is being pronounced or spelled, which might depend on frontal and/or parietal areas. In this discussion of the first role of left BA 37, note that we do not claim that computation of a location-, font-, and orientation-independent graphemic description is the *only* role of left medial BA 37 (or that it is the only area necessary for this role).

A second role of left BA 37 is access to lexical representations for output, such as naming picture or objects from tactile exploration. Because of its role in modality-independent lexical access, this area may be activated by "automatic" naming of word in silent reading and lexical decision tasks in functional imaging studies of orthographic processing. This role seems to often rely on inferior temporal cortex, lateral to midfusiform cortex. Lesion studies, including the present study, indicate that this lateral area is essential for accessing modality-independent lexical representations from meaning (for naming) irrespective of input (DeLeon et al., 2007; Hillis et al., 2006; Reineck et al., 2005; Raymer et al., 1997). Disconnection of this area from visual input would cause impaired naming from vision, with relatively spared tactile naming.

Although previous studies have provided some evidence for these two roles of left BA 37 in lexical processing (e.g. Cohen et al., 2004), we have presented some unique data. First, we have shown in a relatively large number of participants that acute lesions in these areas are significantly associated with the hypothesized deficits. Secondly, in some individuals, we were able to show that restoring tissue function in the critical area restored the hypothesized function. That is, restoring blood flow to medial left BA 37 resulted in recovery of reading and spelling in the participant whose scans are shown in Figure 5d, and restoring blood flow to lateral left BA 37 resulted in recovery of picture and tactile naming as well as spelling in the participants whose scans are shown in Figure 5a and c.

It is not the case that the participants in this study with BA 37 lesions had large MCA strokes, affecting all language tasks. The participants with lesions in left BA 37 had relatively small strokes. The mean infarct size for participants with lesions involving BA37 was 37.7 cc (SD=46.4); a total MCA stroke is about 311 cc. The majority of participants in this study did not have testing of comprehension. However, our previous studies have shown that ischemia in left BA 37 is associated with impaired naming, but not impaired auditory comprehension or reading comprehension in the same participants (Hillis et al., 2005, 2006).

There are a number of competing accounts of the roles of occipitotemporal cortex in lexical processing that have been put forth to explain different kinds of data. We can examine the extent to which they might also account for our data.

Roberts et al. (2013) explored the hypothesis that ventral occipitotemporal cortex is retinotopically organized, with high acuity foveal input projecting primarily to the posterior fusiform gyrus (pFG), making this region crucial for coding high spatial frequency information. Because high spatial frequencies are critical for fine-grained visual discrimination, the authors hypothesized that damage to the left pFG should have an adverse effect not only on efficient reading, as observed in pure alexia, but also on the processing of complex non-orthographic visual stimuli such as object naming. Consistent with the hypothesis, they found prolonged response latencies both in reading (pure alexia) and object naming. Although our study did not address the question whether the occipitotemporal area is retinotopically organized, the fact that orthographic tasks and naming were concurrently impaired in most participants in the current study fits with the proposal that BA37 is important in processing orthographic and non-orthographic stimuli. We emphasized a role of lateral BA 37 in lexical output (associated with impairments in both tactile and picture naming). However, we did not address the plausible hypothesis put forth by Roberts and colleagues (and others as noted below) that at least part of medial BA 37 (posterior fusiform) is critical for object and/or face recognition as well as a computing a graphemic description for reading and spelling.

Behrmann and Plaut (2012) investigated whether faces and words are subserved by independent neural mechanisms located in occipitotemporal cortex in opposite hemispheres by studying participants with pure alexia following a lesion restricted to the left hemisphere and participants with prosopagnosia following a lesion restricted to the right hemisphere. They found that both patient groups were impaired at both reading and face processing, relative to their controls, but each was impaired to a greater extent in the stimulus class

usually associated with their hemispheric side of lesion (left lesioned more impaired at word reading, right lesioned more impaired at face processing). This result implies that the right occipitotemporal cortex (VWFA-equivalent) might, under normal circumstances, contribute to the parallel letter processing thought to be a function of the left VWFA, and reflects the similarity in the mechanism supporting word recognition in both hemispheres, albeit with greater weight on the left side. This is in line with our hypothesis that midfusiform cortex (part of left BA 37) is consistently engaged in written word recognition, but not necessary or specific to written word recognition (because right midfusiform cortex could also perform this function), but left BA 37 is necessary for modality-independent lexical output.

Malach and colleagues (Levy et al., 2001; Hasson et al., 2002; Malach et al., 2002) put forth a proposal regarding the organization of the occipitotemporal cortex based on functional imaging studies in normal subjects. They have proposed the notion of a retinotopically organized occipitotemporal area (Malach et al., 2002), which runs from the posterior fusiform gyrus to the collateral sulcus. Within this region, specific areas respond maximally to different object categories (animals, objects, houses, faces, and words). Hasson et al. (2002) proposed that this graded functional separation reflects the visual demands of each type of stimuli and, in turn, the acuity variation across retinal eccentricity. These results are interesting and plausible, but somewhat orthogonal to our data. We did not evaluate object recognition, as impaired object recognition generally requires bilateral damage to (or atrophy in) the anterior fusiform cortex, as in semantic variant primary progressive aphasia or bilateral stroke. The role we have proposed of the midfusiform cortex in computing a grapheme description does not preclude its proposed role in object recognition.

For example, Price and Devlin (2011) proposed that ventral occipitotemporal (vOT) cortex integrates visuospatial features abstracted from sensory inputs with higher level associations such as speech sounds, actions and meanings. In this context, specialization for orthography emerges from regional interactions without assuming that vOT is selectively tuned to orthographic features. Reading impairment is the most notable effect of selective damage to the ventral occipitotemporal cortex (vOT). Most participants with vOT damage also have difficulty naming objects, consistent with a generic difficulty linking visual inputs to the language system. According to the Interactive Account, damage to vOT will disconnect forward and backward connections at all levels of the hierarchy, leading to imprecise perceptual inference. This will have a disproportionate effect on reading because written words comprise the same component parts occurring repeatedly in different, but sometimes highly similar, combinations (e.g. attitude, altitude, aptitude). Object recognition will also be impaired when vOT is disconnected from occipital and higher order language areas, but it will be less impaired than reading when it can proceed on the basis of holistic shape information and a limited number of defining features. As they predicted, most participants in our study were impaired on both reading and naming. In most cases, the rate of errors was greater for naming than for reading. This proposal provides a complementary account of the role of the medial portion of left BA 37, midfusiform gyrus, which we have proposed is engaged in computing a location and orientation-independent grapheme description for reading and spelling. Indeed, this area may be responsible for the function we have proposed in reading and spelling, but not selectively, as it may have a similar role in object recognition on the Price and Devlin account.

Limitations of this study include the limited language testing we were able to complete at the acute stage, and the fact that not all participants completed all testing (spelling and tactile naming). Further, the lexical tasks used in this study cannot provide a good measure of severity of impairment. It should be noted the study was not designed to test our hypotheses; this was a retrospective analysis of prospectively collected data. If we had designed the study to test our hypotheses, we might have included more carefully selected stimuli or additional tests for reading, spelling, and naming. There are also limitations in precise localization of the lesions that are inherent in all lesion-deficit mapping studies, because of the individual differences in gyri, sulci, brain shapes, and cytoarchitecture across individuals (see Crinion et al., 2012 for discussion). We used a broad region of interest approach, because we were interested in a functional region (BA 37). There is no way to be precise about where BA 37 is in a particular individual, but there is broad regularity (it always includes fusiform gyrus and inferior temporal gyrus, not frontal cortex or parietal cortex), so anatomical landmarks can be used to approximate its location with a high degree of inter-rater reliability. The strengths of the study are that we included a large number of participants at the acute stage, before reorganization or recovery, so that the relationship between the area of dysfunctional tissue and the deficit is relatively straightforward.

Acknowledgments

This research was supported by NIH grants R01 DC05375 and R01 DC 03681 from the National Institute on Deafness and Other Communication Disorders. We gratefully acknowledge this support and the participation of the participants.

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Figure 1. Overlap in areas engaged in or critical for reading and spelling across studies

- a. Voxels where acute ischemia is associated with impaired spelling of words in acute stroke (Philipose et al., 2007)
- b. Voxels where activation is associated with reading of words in healthy controls (McCandliss et al., 2003)
- c. Voxels where activation is associated with spelling of words healthy controls (Beeson, et al. 2003)
- d. Voxels where activation is associated with spelling in meta-analysis of fMRI studies (Purcell, et al., 2011)
- e. Voxels where activation is associated with reading (blue) and spelling (green) (Rapp & Lipka, 2011)

Figure 2.

Mean error rates for naming (N=234 participants), reading (N=234), spelling (N=92), and tactile naming (N=129) for participants with lesion in BA 37 and without lesion in BA 37. The error bars represent standard errors.

Figure 3. DWI (top panel) and PWI (lower panel) showing small area of hypoperfusion (blue area) of both lateral and medial BA 37 in participant with impaired reading, spelling, and naming at Day 1.

Figure 4.

DWI (top panel) and PWI (lower panel) scans of a participant at Day 1 (left) and Day 2 (right, after stenting of left carotid artery). At Day 1 she had anomia in conversation, occasional reading errors, and marked difficulty with spelling. After treatment to restore perfusion of left medial and lateral BA 37, reading, spelling, and naming errors resolved.

Figure 5.

- (a) DWI (left) and PWI (right) of participant with frequent semantic errors in naming and phonologically plausible errors in spelling to dictation, and no errors in oral reading, associated with lateral left BA 37 (inferior temporal cortex) hypoperfusion at Day 1 (left top panel) and resolution of naming and spelling errors with reperfusion of lateral left BA 37 at Day 3 (lower panel)
- (b) Percent correct responses on naming and comprehension tasks, by the participant whose scans are shown Panel (a) in before and after reperfusion of lateral BA 37
- (c) DWI (left) and PWI (right) of participant who made semantic errors in picture and tactile naming at Day 1 associated with lateral left BA 37 (inferior temporal cortex) hypoperfusion (top panel), and resolution of naming errors with reperfusion of lateral left BA 37 at Day 3 (lower panel)
- (d) DWI (left) and PWI (right) of participant who made errors at the ends of words in oral reading and "graphemic buffer" type errors in spelling and made semantic errors in naming at Day 1 (top panel) when the medial left BA 37 and left thalamus were hypoperfused, and showed resolution of all errors when these areas were reperfused (lower panel)
- (e) DWI (top panel) and PWI (lower panel) of participant with ischemia in left BA 37 with impaired reading and spelling, but intact naming associated with infarct/hypoperfusion in medial left BA 37.

Figure 6.

DWI scans of a participant with alexia without agraphia. She had acute lesion in left occipital cortex (left) and left splenium and thalamus (right), all in the PCA territory.

Figure 7. DWI scans of a participant with alexia, letter-by-letter reading and optic aphasia, much milder dysgraphia than alexia, associated with infarct in left medial BA 37, as well as occipital cortex, splenium, and thalamus.

Table 1

Relationship between Infarct/hypoperfusion in BA 37 and (a) Oral Reading, (b) Oral Picture Naming, (c) Naming Objects: Tactile Input, (d) Spelling to Dictation

	Oral Reading X ² (df1)= 80.1; p=0.00001		Oral Picture Naming X ² (df1)= 100.2; p=0.00001		Naming Objects with Tactile Input X ² (df1)= 26.6 p=0.00001		Spelling to Dictation X ² (df1)= 41.9; p=0.00001	
	Deficit	No Deficit	Deficit	No Deficit	Deficit	No Deficit	Deficit	No Deficit
Participants with infarct &/or Hypoperfusion in BA 37	91	12	95	8	37	17	84	1
Participants with no infarct or Hypoperfusion in BA 37	39	92	35	96	17	57	30	24

Table 2

Summary of Results of Dissociation between Reading and Naming in Participants with Ischemia in Left BA 37

	Infarct/Hypoperfusion In Medial BA 37 (VWFA)	Infarct/Hypoperfusion In Lateral BA 37 (Inferior Temporal Cortex)
Impaired Naming Spared Reading (n=8)	1	7
Spared Naming Impaired Reading (n=4)	3	1

Mean error rates in oral picture naming, oral reading, and written spelling to dictation in participants with ischemia involving left BA medial BA 37, left lateral BA 37, both, or neither.

Table 3

Group	N	Mean (SD) Naming	Mean (SD) Reading	Mean (SD) Spelling	Volume of Infarct (cc)
No ischemia in Left BA 37	131	11.3 (21.1)	12.8 (21.7)	23.7 (28.9)	8.4 (23.4)
Ischemia in Medial BA 37 Only	4	10.5 (15.2)	53.5 (34.3)	34.0 (8.5)	11.9 (16.5)
Ischemia in Lateral BA 37 Only	11	28.0 (36.4)	25.8 (35.4)	26.2 (41.9)	56.2 (65.8)
Ischemia in Medial & Lateral BA 37	88	54.3 (40.6)	61.2 (38.9)	73.8 (33.4)	35.5 (41.4)