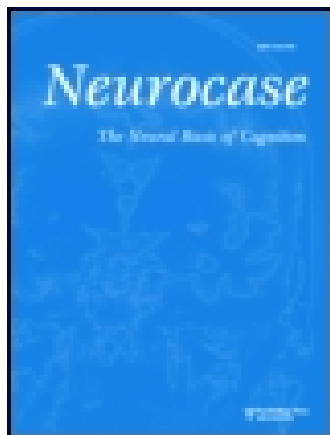


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# The Crucial Role of Posterior Frontal Regions in Modality Specific Components of the Spelling Process

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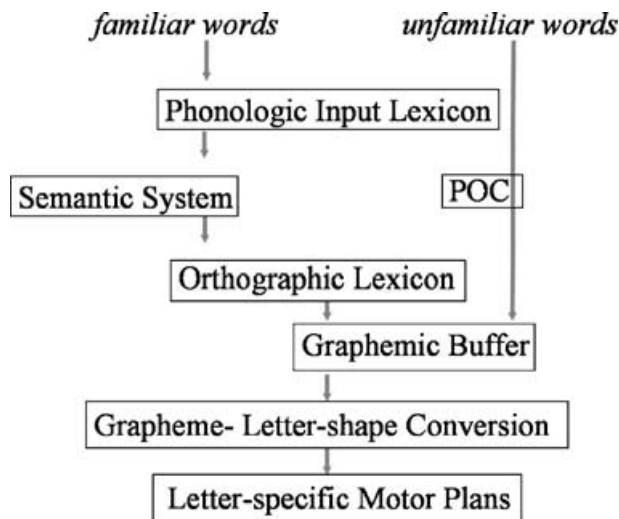
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## Abstract

Although it is commonly assumed that posterior temporo-parietal regions are the regions of the brain essential for accessing orthographic representations for written output, patients with lesions in these areas also have reading and/or naming impairments at least early after stroke onset. This observation raises the possibility that these regions are important for components of spelling that are not specific to written output. The goal of the present study was to identify any regions of the brain that, when damaged, result in selective impairment in accessing orthographic representations for written output. We studied 54 consecutive right-handed patients with acute, left hemisphere ischemic stroke, who were able to perform the motor aspects of writing with the right hand and had at least a 10th grade education, on a battery of lexical tasks designed to identify impaired and spared cognitive processes underlying spelling and with advanced magnetic resonance imaging. Only five patients had pure agraphia, and had evidence of impaired access to lexical-orthographic representations for output; and all five had infarct or ischemia in Brodmann's area 44 and 45. Analysis of performance across tasks of three of these patients, whose performance has not been previously reported, provides evidence for additional impairment in converting graphemes to letter shapes or letter-specific motor programs. These three patients, unlike previously reported patients with lexical-orthographic impairment and compromised function in Brodmann's area 44 and 45, also had infarcts in Brodmann's area 6. On the basis of these cases, and those in the literature, we propose a network of brain regions involved in writing words, each with a separate function. This proposal emphasizes the role of left posterior frontal regions in modality-specific output processes.

Written language has become increasingly important in today's society, in which many of us communicate more frequently by e-mail than by telephone, and conduct a variety of transactions from shopping to banking on the internet. But writing is one of the most complex language functions, and is thus highly sensitive to damage or disease in the left hemisphere. Writing prose is a skill that is often mastered rather late in one's education (if at all), but even writing of single words entails a large number of cognitive functions. To illustrate, to write to dictation the word "fair" in the phrase, "fair weather", it is necessary to: (1) analyze the auditory stimulus and recognize it as a familiar (known) word by accessing the corresponding lexical representation in the phonological lexicon, (2) grasp its meaning, by accessing the corresponding semantic representation (to differentiate it from the word "fare"); (3) retrieve its learned spelling by accessing the lexical-orthographic representation in the orthographic lex-

icon; (4) hold the series of graphemes that constitute the orthographic representation in a short-term memory system, the graphic buffer; (5) convert each grapheme to a particular letter shape or letter-specific motor plan; and (6) execute the complex movements of the fingers, wrist, and arm to write the letters (as schematically depicted in Fig. 1; see Ellis and Young, 1988; Shallice, 1988; Rapp, 2002 for reviews). When we encounter a new spoken word, for which we have not learned the spelling, there is no stored orthographic representation to access in order to spell it. In this case, we spell by converting the phonological sequence to a sequence of graphemes, which must then be held in the graphemic buffer while individual graphemes are converted to allographs or motor programs and written output. These phonology-to-orthography conversion (POC) mechanisms are likely to interact with lexical mechanisms for word spelling, as well (Hillis *et al.*, 1999a; Rapp, 2002; Houghton and Zory, 2003).



**Fig. 1.** A schematic representation of the cognitive processes underlying spelling.

Focal brain damage can disrupt any one or more of these cognitive processes or representations, affecting spelling in different ways. Selectively impaired access to orthographic representations for written production is manifested by impaired spelling of irregular words, with relatively spared spelling of regular words and pseudowords (which can be spelled via sublexical POC mechanisms), phonologically plausible spelling errors (e.g., fair spelled “fare” or “phair,” indicating reliance on POC mechanisms when the orthographic representation is not accessed), and significantly better spelling of high frequency compared to low frequency words (since high frequency words are thought to have a lower threshold of activation, and thus less vulnerable to impaired access).

Most studies of the neuroanatomical correlates of impaired access to the orthographic lexicon for spelling implicate lesions in the temporo-parietal-occipital junction, in particular damage to Brodmann’s areas (BA) 39 and 37 (see Rapsack and Beeson, 2002, for review). However, damage to left BA 39 (angular gyrus) typically also affects reading (particularly sublexical reading), and damage to BA 37 (posterior inferior temporal gyrus) typically also affects access to lexical-phonological representations of words for naming and lexical-orthographic representation of words for reading (see Hillis and Rapp, in press, for review). Consistent with this hypothesis, most reported patients with impaired access to the orthographic lexicon for spelling have had impaired reading and/or oral naming at least early after stroke onset (Beauvois and Derouesne, 1981; Hatfield and Patterson, 1983; Roeltgen and Heilman, 1984; Baxter and Warrington, 1987). Pure agraphia from the onset of stroke is rare (or missed, because writing is not often evaluated early after stroke), but such cases provide the strongest evidence that there are regions of the brain specifically devoted to particular cognitive processes underlying spelling. Cases of impaired access to orthographic representations for written output, without impaired access to orthographic representa-

tions for input (reading) would also provide evidence for separate orthographic representations or separate access procedures for reading and spelling, and would provide the opportunity to identify the neural correlates of these writing-specific cognitive mechanisms. We have previously described three patients with pure agraphia at the onset of stroke, with evidence of impaired access to orthographic representations for output (RCM in Hillis *et al.*, 1999a; and two cases in Hillis *et al.*, 2003). All three patients made semantic errors in written naming and spelling to dictation (in the face of intact semantics tested by comprehension), made more errors on verbs than nouns, and were very poor in spelling pseudowords. All three had infarcts or low blood flow (hypoperfusion corresponding to dysfunctional tissue) in BA 44 and 45. In the two patients with low blood flow, but no infarct, in BA 44 and 45, restored blood flow to that area resulted in improved spelling of verbs (and nouns) but not pseudowords, indicating that poor pseudoword spelling may have been a premorbid weakness in each case. The fact that MRI abnormalities were limited to left frontal regions in all three cases indicated that access to orthographic representations for written output may depend at least as much on BA 44 and 45 as it does on BA 39 and 37.

In this study, we evaluated the hypothesis that small strokes in the posterior left frontal regions (Brodmann’s areas 44 and 45) can disrupt access to orthographic representations for writing while sparing access to orthographic representations for reading. We studied a consecutive series of 156 right-handed patients within 24 hours of onset of left hemisphere ischemic stroke on a battery of lexical tasks. Of these, the 54 patients who had completed the 10th grade and were able to use their right hand for writing were included in the study. The profile of performance across tasks, including error types and parameters that affected accuracy, was used to identify impaired and spared components of the spelling system. Patients all had magnetic resonance imaging, including diffusion-weighted imaging (DWI, which is highly sensitive to infarct or dense ischemia at onset of stroke) and perfusion-weighted imaging (PWI, which shows areas of low blood flow corresponding to functionally inactive tissue) within one day of stroke onset as well, to identify the regions of the brain responsible for their deficits. From this series, we identified five patients with pure agraphia, with evidence of impaired access to orthographic representations for written output, but spared access to orthographic representations in reading, and spared access to phonological representations for oral naming and oral reading. Two of these cases have been previously described (Hillis *et al.*, 2003); description of their cases will not be repeated here. In each case the MRI abnormality was limited to the left posterior frontal lobe. None of the cases could be attributed to premorbid spelling deficits, since in each case the agraphia recovered or improved substantially within a month. Furthermore, on the basis of these cases and complementary cases in the literature, we propose that access to orthographic representations requires the function of at least three brain regions: (1) posterior, inferior/middle

temporal gyrus (BA 37), which is essential for accessing both orthographic and phonological representations from semantics (and possibly for accessing orthographic representations from visual input); (2) angular gyrus (BA 39), which is essential for POC and orthography-to-phonology conversion (OPC), and accessing orthographic representations from these sublexical mechanisms; and (3) posterior, inferior frontal gyrus (BA 44 and 45), which is essential for converting abstract lexical representations to modality-specific motor output (and for selection of specific morphological forms). In addition, nearby BA 6, which was affected in three of the patients with pure agraphia, appears to be essential for converting graphemes to specific letter shapes or letter-specific motor plans for writing both words and pseudowords.

## Subjects

A consecutive series of 54 right-handed patients, age 21 to 87 (mean = 68.2) years, 53% female, who presented within 24 hours from the onset or worsening of symptoms of left, supratentorial ischemic stroke, and had no exclusion criteria were studied. Exclusion criteria were: (1) right hemiplegia, or hemiparesis severe enough to interfere with motor aspects of writing; (2) contraindication for MRI (e.g., claustrophobia; pacemaker or other implanted ferrous metal); (3) allergy to gadolinium; (4) hemorrhage on initial CT or MRI; (4) impaired level of consciousness or agitation requiring ongoing sedation; (5) <10th grade education; (6) self-report or family-report of premorbid reading or writing problems; (7) pre-existing dementia; (8) pre-existing known hearing loss; or (9) premorbid lack of proficiency in spoken and written English. Informed consent was obtained by a process approved by the Institutional Review Board at Johns Hopkins University School of Medicine. Informed consent was provided by identified decision makers (closest living relative of each patient) for patients with impaired language comprehension, but these patients also assented to the research, to the degree they understood its goals and procedures.

### Language tests

**Lexical Battery.** Tests included: oral naming of 17 pictures and 17 objects, oral reading of 34 words and 25 pseudowords matched in length in letters and phonemes, spelling to dictation of 34 words and 25 pseudowords matched in length in letters and phonemes; repetition of 34 words and 25 pseudowords matched in length in letters and phonemes; and spoken and written word/picture verification (51 items each; with 17 targets, 17 semantic foils, and 17 visually and phonologically similar foils). For an item to be scored as accurate on the word/picture verification tests, the patients had to correctly reject both foils and accept the correct name, which avoids giving credit for pseudocorrect responses due to saying “yes” to all items or “no” to all items. Oral naming and oral reading responses were scored as accurate if they were phonemically correct productions of the target word (but phonemes could be slightly distorted or stiff in dysarthric patients, as long as they

were recognized as the target phonemes). If the patient produced a name that was a synonym or a superordinate of the target in naming, the individual was asked to provide another name for the picture, or a more specific name. Word stimuli on all of these subtests were matched in word frequency, grammatical word class, and length in letters and phonemes to words in other subtests of the battery. Two additional forms of this battery, with word stimuli matched in word length, grammatical word class, and frequency and pseudoword stimuli matched in length, were administered in follow-up testing (once at 3–5 days, and once at 1 month).

Normative data on this lexical battery were obtained from 46 hospitalized control subjects, comparable in age, education, and gender ratio to the stroke patients, and who had similar health problems (except acute stroke) and distractions and stressors of the hospital environment. Control subjects scored 94.9% correct or better on each subtest of our battery. Mean scores for each subtest ranged from 98.0% (s.d. = 2.5) correct in oral reading to 100% (s.d. = 0) correct in tactile naming. Control subjects with education level below 10th grade, or who reported premorbid problems reading or writing, were excluded from scoring of reading and writing subtests.

In addition, on Day 1, patients were presented with 30 pictures of objects (representing nouns) and 30 pictures of actions (representing verbs) for oral and written naming in an ABBA design (see Berndt *et al.*, 1997 or Hillis *et al.*, 2002a for details of the stimuli and normative data). The pictures were black and white line drawings (and were the same stimuli used by Berndt *et al.*, 1997). Each picture was presented with the question, “What is the name of this?” (for objects) or, “What is this person doing?” (for actions).

Patients who made >10% errors in written naming and spelling-to-dictation (i.e., >2 standard deviations below normal, and <8.2% errors (<2 standard deviations below normal) in other lexical tasks were considered to have pure agraphia. These patients were administered portions of the Johns Hopkins Dysgraphia Battery (see Beeson and Hillis, 2002 for details) to further examine spared and impaired components of the spelling system. The Johns Hopkins Dysgraphia Battery includes written spelling to dictation of 134 words and 68 pseudowords, oral spelling of 42 words and 20 pseudowords, direct and delayed copy transcoding from upper to lower case (and vice versa) on 42 words and 20 pseudowords. Subtests are designed to evaluate the effects of grammatical word class, word length, concreteness, regularity, and lexicality. Unfortunately, due to time constraints, not all subtests of this battery were administered to each patient, as reported below.

Performance on these batteries was then analyzed to identify which of the pure agraphic patients had impairment in accessing orthographic representations for output. These cases met the following criteria: (1) impaired performance (>10% errors) in written naming (nouns and verbs combined); >10 errors in spelling to dictation of irregular words and regular words combined; (2) production of phonologically plausible spelling errors (indicating reliance on

sublexical POC mechanisms when a word is not accessed in the lexicon); (3) pseudowords spelled more accurately than words; and (4) high frequency words spelled significantly more accurately than low frequency words.

### Imaging

DWI and PWI scans were obtained on Day 1 and short-term follow-up at Day 2 to 6 (mean Day 3.0) on a GE Signa 1.5 Tesla scanner. DWI trace images (TR/TE of 10,000 ms/120 ms) were obtained using  $b_{\max} = 1000 \text{ s/mm}^2$ . Also,  $b_{\min} = 0$  images were used to generate ADC maps to confirm the acuity of the DWI lesion. Single shot gradient echo EPI perfusion images (TR/TE of 2000/60 ms) were obtained with power injection of 20 cc GdDTPA (Gadolinium) at a rate of 5 cc/s. This PWI sequence allows 17 slices to be recorded for whole brain coverage.

The presence or absence of infarct/dense ischemia (on DWI) and of hypoperfusion (on PWI) in each of 12 regions of interest was determined by a trained technician, who was blinded to the results of the language testing. The technician used published templates (Damasio and Damasio, 1989) to identify the BAs on each cut and a separate atlas to identify the thalamus and insula on each cut (Mai *et al.*, 1997). PWI abnormalities were identified on post-processed time-to-peak (TTP) maps, displayed on a 20-color scale in which each color change corresponds to 2 s difference in delay in time to peak arrival of Gadolinium to each voxel (i.e., one color difference = 0.5–2.5 s delay; two color differences = 2.51–4.5 s, etc.). An area was considered hypoperfused if the delay in TTP was >2.5 s delayed (at least two color differences), compared to the homologous region in the opposite hemisphere. Each TTP map was analyzed together with its corresponding T2 image of the same cut, since T2 has better spatial resolution. Regions of interest (ROI) were: BA 6, BA10, BA 18/19, BA 20, BA 21, BA 22, BA 37, BA 39, BA 40,

BA 44/45, thalamus, and insula. Subcortical regions other than the thalamus were not analyzed because an earlier study indicated that infarcts restricted to nonthalamic subcortical regions were not associated with language deficits in acute stroke, unless there was also cortical hypoperfusion. These results indicate that cortical hypoperfusion, rather than the subcortical lesion, was responsible for the deficits in these cases (Hillis, Wityk, Barker, Beauchamp, Gailloud, Murphy, Cooper and Metter, 2002).

### Results

Of the 54 patients who met the criteria for the study, only five patients had pure agraphia, with evidence of impaired access to orthographic representations for written output. Performance of two of these patients has been previously reported (Hillis *et al.*, 2003). Details of performance across lexical tasks by each of the three patients not previously reported are described below. The key features of dysgraphia in each case are summarized in Table 1.

#### Case 1

Case 1 is a 66 year old, right-handed woman with a 12th grade education who developed sudden onset difficulty spelling while she was trying to send an e-mail message. She called for an ambulance, but had some trouble with motor aspects of speaking. On examination in the hospital she had impaired motor speech production and impaired spelling, but no weakness. She had some right arm heaviness. She spoke in short phrases or complete, grammatical sentences, but she was nonfluent with numerous self-corrections of articulatory errors. Her problem with speech production met our criteria for apraxia of speech, or impaired motor planning and programming of speech articulation: (1) halting, effortful

**Table 1.** Summary of spelling characteristics in the three cases

	Case 1	Case 2	Case 3
<i>Evidence for impaired access to orthographic output lexicon</i>			
Intact oral naming, auditory comprehension & reading	Yes	Yes	Yes
Impaired written naming and spelling to dictation	Yes	Yes	Yes
Significantly poorer written naming of verbs than nouns	Yes	Yes	Yes
Significantly poorer written naming of low frequency words compared to high frequency words	Yes	Yes	Yes
Significantly poorer spelling of words than pseudowords	Trend ( $p = .06$ )	Yes	Yes
Predominance of phonologically plausible errors in spelling	Yes	Yes	Yes
Recovery of spelling within one month (not premorbid deficit)	Yes	Partial	Partial
<i>Evidence for superimposed impairment in converting graphemes to allographs</i>			
Impaired transcoding from upper to lower case and vice versa	Yes	Yes	DNT
Deletions, substitutions, insertions, and mixed errors in writing and transcoding words and pseudowords	Yes	Yes	Yes
Oral spelling better than written spelling	Yes	Yes	DNT
Well formed letters (not apraxia dysgraphia)	Yes	Yes	Yes
Intact direct copy in the same case (not apraxia dysgraphia)	Yes	Yes	DNT
Absence of length effect in spelling (not graphemic buffer deficit)	Yes	Yes	Yes
Equivalent direct and delayed copy transcoding (not graphemic buffer deficit)	Yes	Yes	DNT

articulation; (2) numerous and varied off-target attempts to articulate words in all oral tasks (e.g., moon → “noon, moom, moon”; and (3) impaired prosody, not attributable to reduced rate, range, or strength of movements of the lips, tongue, jaw, palate, or vocal cords (i.e., not dysarthria). She had more trouble articulating polysyllabic words than mono- or bisyllabic words.

### *Language testing*

Because most items on the lexical battery and noun and verb battery are monosyllabic or bisyllabic words, she made only 3% errors in oral naming of 30 verbs; 7% errors in oral naming of 30 nouns matched in surface frequency to the verbs; 6% errors on oral naming of objects to tactile exploration, and 6% errors on oral naming of pictures matched in frequency and word length to the object names. She made 8% errors on both oral reading and repetition of words. She also made no errors on either spoken or written word/picture verification. Auditory lexical decision was incorrect for 4% of 59 items; written lexical decision was flawless. In short, performance on verbal lexical tasks and reading was within normal limits, although she had a motor speech impairment affecting production of polysyllabic words. In contrast, written production was severely impaired: with written naming stimuli matched in frequency and word length to the oral naming tasks, she made significantly more errors on written naming (53% in written naming vs. 6% in oral naming;  $p < .007$ ). On the noun and verb stimuli, she made significantly more errors on written than oral naming of verbs (80% for written vs. 3% for oral naming;  $p < .0001$ ) and nouns (50% vs. 7%;  $p < .03$ ). Of note, she was also significantly more impaired in written naming of verbs than nouns (80% vs. 50%;  $p < .03$ ). In spelling to dictation, she made errors on 41% of the words versus 19% of pseudowords ( $p < .06$ ). On the Johns Hopkins University Dysgraphia Battery (JHU Dysgraphia Battery), she made significantly more errors on spelling low frequency words relative to high frequency words (59% vs. 22%;  $p < .04$ ). The significant effects of lexicality, word class, and frequency, in the face of intact lexical-semantics (word comprehension) indicate that Case 1 was impaired in accessing orthographic representations (especially verbs) from the orthographic lexicon for written output.

Across tasks, 70% of her spelling errors were phonologically plausible (e.g., chair → chear, skirt → skertt), consistent with the hypothesis that she often used POC mechanisms to spell words when she was unable to access orthographic representations from the lexicon. However, she also made some letter substitution, deletion, and transposition errors on both words (e.g., mountain → mountaim; train → tirin) and pseudowords (plove → poove; kreb → kred). These errors are comparable to errors produced by patients with damage at the level of the graphemic buffer. However, against the possibility that Case 1 had damage at the level of the graphemic buffer, on the JHU Dysgraphia Battery, she showed no effect of word length on spelling accuracy. On a list of 14 words of each length, counterbalanced for word class and

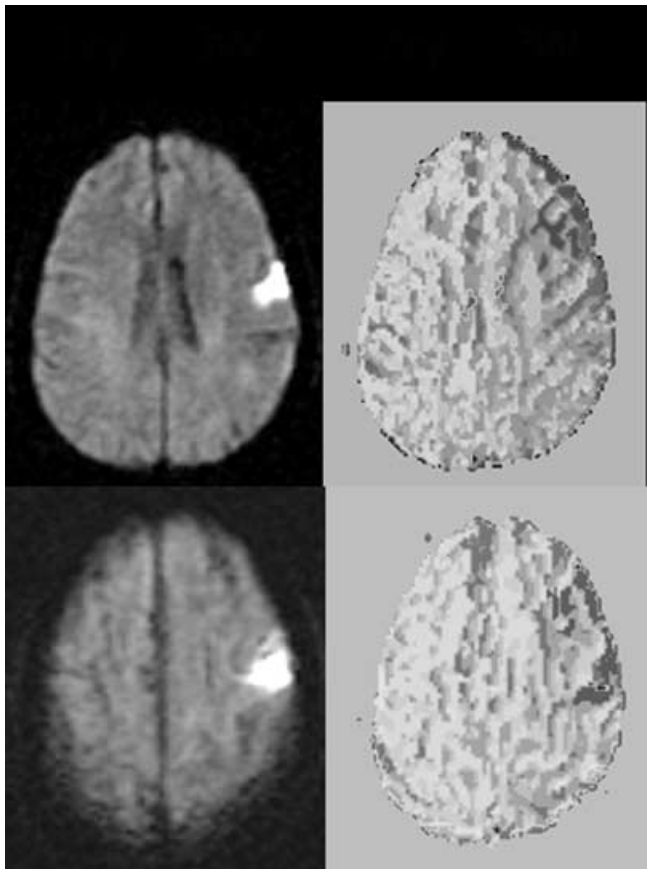
frequency, her error rates were: 29% for 5 letter words; 83% for 6 letter words; 43% for 7-letter words, and 57% for 8-letter words. Furthermore, it was noted that she also often mixed cases in writing (e.g., shirt → shiRT), and she spontaneously commented that she did not know how to write the lower case of several letters. These observations indicated that her superimposed letter errors in spelling words and pseudowords may have been due to impaired conversion of graphemes to letter shapes or letter-specific motor programs. Additional evidence for this conclusion is her performance on direct copy transcoding from upper to lower case and lower to upper case: she made errors transcoding 77% of words and 70% of pseudowords (Fig. 1). Performance on delayed copy transcoding was very similar (actually slightly better): errors on 38% of words and 50% of pseudowords, providing further evidence against impairment at the level of the graphemic buffer. Performance on direct copy, without the requirement of changing case, was flawless, indicating that her errors were not due to problems with motor execution (additional evidence came from her errors in transcoding, which were generally either well formed but incorrect letters or well formed letters in the wrong case). However, a large percentage (33%) of her letter substitutions shared a predominance of motor strokes, compared to the percentage of letter stroke-related substitutions made by patients with damage at the level of the graphemic buffer (2–11%, as reported by Rapp and Caramazza, 1997, using their stroke-feature metric for our patients as well). These results suggest that the substitution errors by Case 1 may have arisen in converting graphemes to letter-specific motor plans. Many of her case substitution errors (e.g., T-t) may have represented another type of stroke-related substitution error. However, at other times, the case substitutions were conscious efforts to painstakingly copy the stimulus, when she was unable to transcode it in the alternate case.

### *Imaging*

Case 1's MRI scans showed a very small acute infarct in BA 6, with a larger area of hypoperfusion (dysfunctional tissue) involving BA 6, 44 and 45 (Fig. 2). There were no other regions of hypoperfusion or infarct.

### *Recovery*

Case 1 was retested five days later, after increasing her blood pressure in an attempt to restore blood flow to the hypoperfused tissue that was not yet infarcted. By Day 5, her apraxia of speech recovered. She had fluent, well-articulated speech, and no errors in oral naming, oral reading, or repetition. On form 2 of the lexical battery, her spelling had also improved to within normal limits (although, she reported, not normal for her). She improved from 53% to 6% errors ( $p < .007$ ) on written naming of 17 pictures; from 41% to 6% errors ( $p = .001$ ) in spelling to dictation of 34 words; and from 19% to 4% errors on spelling to dictation of pseudowords. Her transcoding also recovered to 100% correct, and she no longer mixed cases in spelling. These data provide strong evidence that her spelling impairment at onset of stroke was not due to a



**Fig. 2.** MRI scans of Case 1 at Day 1 of stroke. Left panel: DWI sequences; right panel: PWI sequences. Darker areas are hypoperfused tissue.

premorbid spelling deficit. Her rapid recovery provides evidence of restored blood flow to BA 44, 45, and 6. However, since she also had infarct (or, less likely, dense ischemia without infarct) in BA 6, she may have also shown reorganization of structure/function relationships, such that other regions of the brain “took over” the impaired spelling. Unfortunately, she declined repeat imaging.

### Case 2

Case 2 is a 59 year-old, right-handed woman with a master’s degree in education, who worked as a high school English teacher until her stroke. She developed sudden onset difficulty writing on the blackboard while teaching. She was admitted to the hospital, where a neurological examination (which did not include spelling) was entirely normal. She was initially thought to have had a transient ischemic attack (TIA), but an MRI on Day 1 demonstrated a small stroke. Further testing revealed persistent spelling impairment.

#### Language testing

On the lexical battery, Case 2 made no errors in oral naming of pictures or objects or in spoken or word/picture verification. Performance was within normal limits on oral reading of words and pseudowords (8% errors) and written lexical

decision (4% errors). In contrast, spelling was markedly impaired. She made errors on written naming of 76% of 17 pictures. In spelling to dictation she made errors on 38% of words vs. 4% of pseudowords ( $p < .002$ ), matched in length to the words, indicating that her spelling impairment was due to impaired access to lexical orthographic representations of words in the orthographic lexicon for output, with relatively spared access to POC mechanisms. Consistent with this hypothesis, she made more errors in spelling 30 verbs than in spelling 30 nouns (43% vs. 13% errors;  $p = .02$ ). In spelling to dictation on the JHU Dysgraphia Battery, she again made more errors on words than pseudowords (37% vs. 10%;  $p < .01$ ), and more errors on low frequency than high frequency words (63% vs. 36% errors;  $p < .05$ ). She again showed a word class effect, with more errors on verbs than nouns. Error rates for each word class, matched in frequency and word length, were as follows: nouns 38%; verbs 56%; adjectives 45%; functors 50%. The majority (90%) of her errors were phonologically plausible both in written spelling (scheme → skeeme; joke → joak; chair → chear; carrot → caret; 67% of errors) and oral spelling (luscious → lutious, act → acked; bowl → boule; wheel-weele), indicating that she relied on POC mechanisms when she failed to access the orthographic representation in the orthographic lexicon.

However, Case 2 also made more errors in written than oral spelling (on lists matched for word frequency and length for words and length in phonemes and letters for pseudowords): 54% vs. 22% errors ( $p < .0006$ ), respectively, for written and oral spelling of 59 items on the lexical battery. In written but not oral spelling she occasionally made errors on pseudowords and made phonologically implausible errors on words (e.g., triumph → trumph) and pseudowords (plin → pleh). Even when she was asked to spell aloud what she had written, immediately after she had written a response, she made fewer errors in oral than written spelling (eg., asked to write “hall”, she responded, *hatt* ... “h-a-l-l”; and when asked to write “tupp” /t<sup>h</sup> p/, she responded, *tuff* ... “t-u-p-p”). Thus, in written spelling she made an additional type of common error, not seen in her oral spelling: letter substitution, insertion or deletion in both words and pseudoword spelling (e.g., decay → decar; buke → buarke). As in Case 1, these errors were not attributable to impairment at the level of the graphemic buffer, because there was no effect of word length on the JHU Dysgraphia Battery: 57% errors for 4-letter words, 86% errors for 5 letter words, 64% errors for 6 letter words, 71% errors for 7-letter words, and 86% errors for 8-letter words, on 14 words of each length, matched for word frequency and word class. Also, she made the identical number and types of errors on delayed copy transcoding (18% errors on 50 items) as in direct copy transcoding (18% errors on 50 items); there was no difference in transcoding for words vs pseudowords. Her errors in transcoding included case errors (FAITH → faITH, in which the target response is faith) and letter substitutions, deletions, and insertions (under → unber; poem → poen; provide → proide). Direct copy without changing case was intact, but very slow. As in Case 1, a

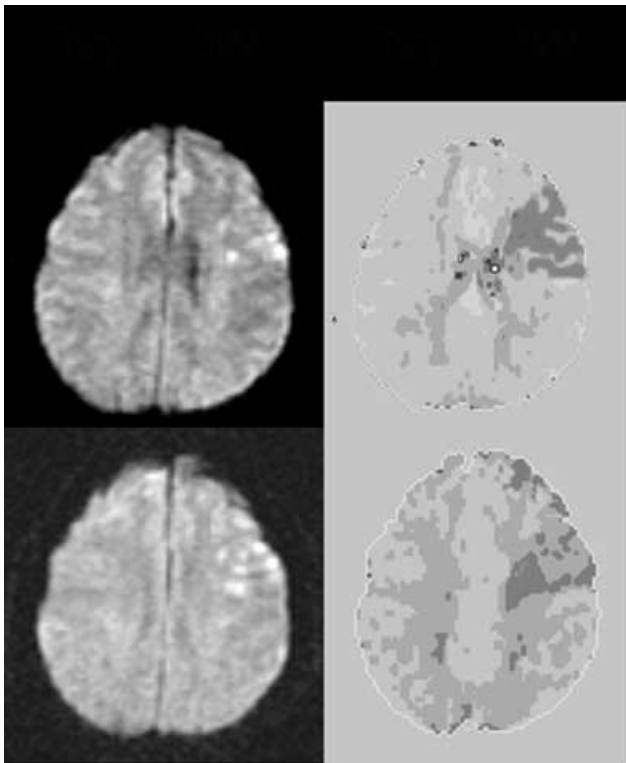
large percentage of her errors (33%) fulfilled the Rapp and Caramazza criteria for sharing predominance of stroke features. As in Case 1, some of her case errors in transcoding may have also been stroke-related errors, although others were simply copies of the stimulus when she was unable to accurately transcode the letter.

#### Imaging

The MRI scans of Case 2 on Day 1 showed patchy ischemic infarct in BA 44, 45, and 6 on DWI, and hypoperfusion of the same regions on PWI (Fig. 3).

#### Recovery

Case 2 was retested 5 days after stroke, on form 2 of the lexical battery, and showed no significant improvement. However, when she was tested again, on form 3 of the lexical battery one month later, she showed substantial recovery. On the lexical battery, performance on auditory and verbal tasks was still normal: she made no errors in word/picture verification, 6% errors in oral naming, 2% errors in repetition. She improved from 76% errors to 0% ( $p < .001$ ) errors in written naming. Spelling to dictation improved from 54% to 36% ( $p < .05$ ) on the same list of 59 items; all of her remaining errors were on verbs or adjectives. These data provide evidence that Case 2's impaired access to orthographic representations at stroke onset was not due to a premorbid spelling deficit (as we expected, based on her profession).



**Fig. 3.** MRI scans of Case 2 at Day 1 of stroke. Left panel: DWI sequences; right panel: PWI sequences. Darker areas are hypoperfused tissue.

### Case 3

Case 3 is a 35 year old, right-handed woman with a 10th grade education and a history of smoking who worked at the hospital as a physical therapy aide. She experienced intermittent right hand and leg numbness for several months, followed by acute impairment of motor speech and spelling. She had some transient right-sided weakness as well. She was admitted for evaluation and treatment.

#### Language testing

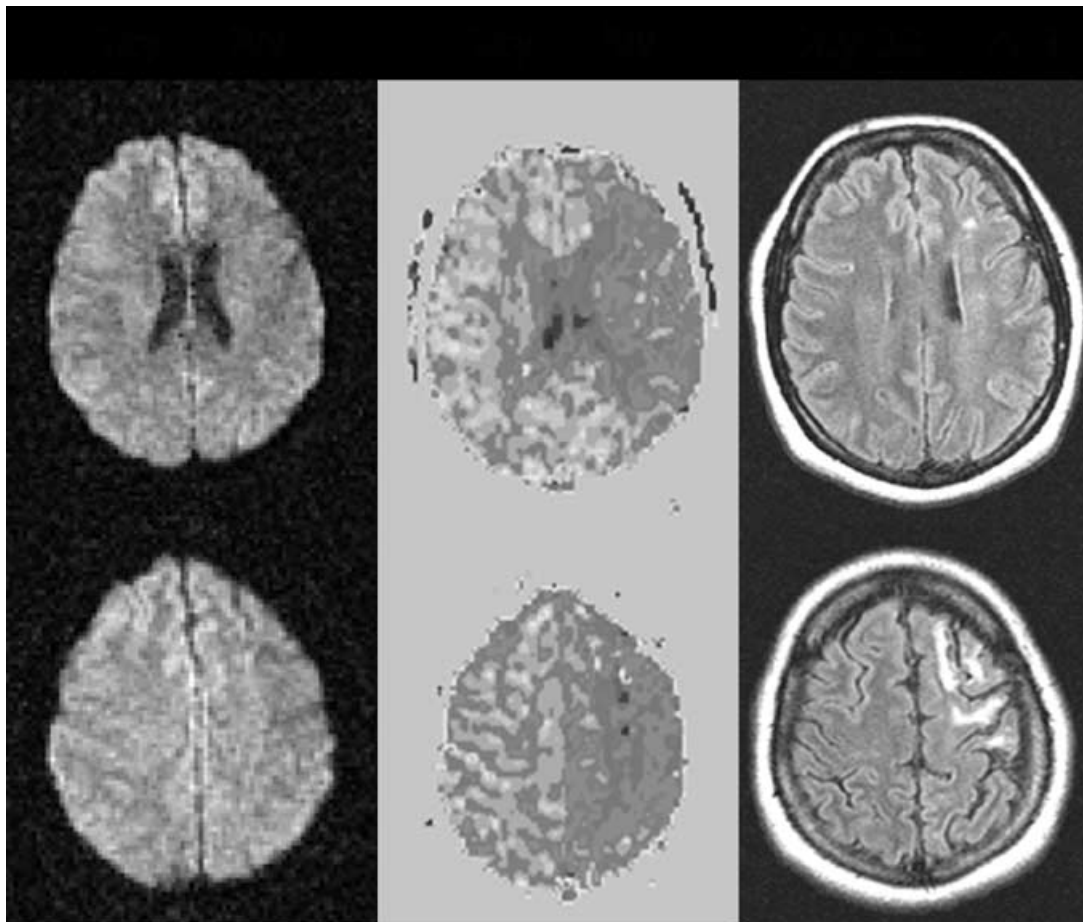
On the lexical battery, performance was error-free on spoken word/picture verification; she made one error (sheet/sheep) (6% error rate) on written word/picture verification. Oral reading was mildly affected by her motor speech impairment, although performance was within normal limits: she made 7% errors in reading words and pseudowords. However, she made no errors in oral naming or repetition on the lexical battery. Performance was also within normal limits in auditory lexical decision (8% errors) and written lexical decision (6% errors). Performance was below the normal range only on spelling tasks. Written naming was incorrect on 53% of 17 pictures. She misspelled 53% of words, and 12% of pseudowords ( $p < .002$ ) to dictation on the lexical battery, indicating that she relied on POC mechanisms when she failed to access orthographic representations of words in the lexicon. Consistent with this hypothesis, the majority (62%) of her errors were phonologically plausible (e.g., snail → snale; carrot → carret). Also consistent with a lexical deficit in writing, on the test of noun and verb naming, she showed a significant effect of word class in written naming. She made 23% errors on nouns compared to 60% errors on verbs ( $p < .01$ ), but no errors in oral naming of nouns or verbs.

However, like Cases 1 and 2, Case 3 made some deletion, insertion, substitution, and mixed errors in spelling both words and pseudowords (e.g., thumb → thump, church → chuih). These errors were unlikely to be due to impairment at the level of the graphemic buffer, since there was no consistent effect of word length on spelling accuracy. Error rates were as follows: 25% for 4-letter words, 53% for 5-letter words, 60% for 6-letter words, 36% for 7-letter words, and 100% for 8-letter words. A trend toward more errors on longer words was likely due to greater opportunity for deletion and substitution errors on longer words. Furthermore, as in the other two cases, many (24%) of her letter substitutions shared a predominance of letter strokes, using the stroke-feature matrix of Rapp and Caramazza (1997), a percentage that is higher than in patients with damage at the level of the graphemic buffer. Unfortunately, the copy transcoding tasks were not administered in her case.

#### Imaging

The MRI scans of Case 3 showed no stroke on DWI, but dense hypoperfusion in BA 6, 44 and 45. A month later, a follow-up FLAIR scan showed that the hypoperfusion region did progress to patchy infarct in BA 6, 44, and 45 (Fig. 4).





**Fig. 4.** MRI scans of Case 3. Left panel: DWI sequences at onset; center panel: PWI sequences at onset (darker areas correspond to hypoperfused tissue); right panel: FLAIR sequences one month after onset.

### Recovery

When Form 2 of the lexical battery was administered 5 days after the initial testing, there was little improvement in spelling. In spelling to dictation, she improved from 53% to 46% misspelled words, but still misspelled 13% of pseudowords. Written naming remained incorrect for 53% of pictures. MR imaging also showed no change in the hypoperfusion and no new infarct. At that point, as in Case 2, the blood pressure in Case 3 was increased in an attempt to restore blood flow to the region of hypoperfusion that had not yet infarcted. When Form 3 was administered one month later, she showed improvement to 44% errors in spelling words and 3% in spelling pseudowords to dictation. Written naming of pictured objects improved to 24% errors. By one month post onset of stroke virtually all of her errors were phonologically plausible (e.g., paradox → paradocks; grief → greaf; melt → mealt). Performance on other lexical tests remained within normal limits. Repeat imaging showed partially improved perfusion of BA 44, 45, and 6.

In summary, all three cases showed pure agraphia, with phonologically plausible errors in spelling and better spelling of pseudowords than words (indicating impaired access to the

orthographic representations, with reliance on phonology-orthography conversion for spelling). However, each patient also made some errors in spelling regular words and pseudowords and transcoding from upper to lower case in writing, attributable to concurrent impairment in converting graphemes to letter shapes or letter-specific motor plans. Since a large percentage of letter substitution errors by each patient shared a predominance of letter strokes with the target, we favor the hypothesis that their impairment was in converting abstract graphemes to letter-specific motor programs in these cases, although other cases may be impaired in accessing abstract letter shapes or “allographs” (see Friedman and Alexander, 1989; Rapp and Caramazza, 1997; Rapcsak and Beeson, 2002 for discussion of this distinction). The patients also made errors in case (upper vs. lower), that were not included among the substitution errors, but that also shared many stroke-features. None of the patients showed a significant effect of word length, ruling out damage to the graphemic buffer (which can also cause a pure agraphia, with impaired oral and written spelling of words and pseudowords). A summary of the results of testing in each case is provided in Table 1.

## Group results

If left posterior frontal regions (BA 44, 45, and 6) are crucial for a particular component or components of the spelling system (such as accessing lexical orthographic representations for output or converting abstract letter shapes to letter-specific motor programs), nearly all patients with damage to those regions should have impaired spelling, at least at the onset of stroke. Of the total 54 patients studied, 29 patients had infarct and/or hypoperfusion of BA 44 and 45. All of these patients had impaired spelling. However, all of the other patients (not reported above) had more extensive areas of abnormality and additional language deficits. Similarly, of the 54 patients, 26 patients had infarct and/or hypoperfusion of BA 6. Only 2 of these patients had intact writing. All of these additional patients with functional inactivation of left posterior frontal regions (and other regions) were impaired in spelling both words and pseudowords. These data provide additional evidence for the crucial role of these posterior frontal areas for writing.

## Discussion

Detailed analysis of performance across lexical tasks in three cases of pure agraphia at the onset of stroke has provided evidence for two levels of impairment in the spelling process in each case: (1) access to lexical orthographic representations, particularly for verbs; and (2) conversion of abstract letter identities (graphemes) to particular letter shapes for

written output. The striking similarity in pattern of performance, along with a striking similarity in the site of lesion, across these cases, allows us to address some issues about the regions of the brain that are essential for these spelling processes and about the nature of the processing mechanisms.

The first issue concerns the regions of the brain essential for accessing lexical orthographic representations for output. A recent review of previous single case studies of subjects with impairment at the level of the orthographic output lexicon (that is, cases of “lexical agraphia” or “surface agraphia”) indicated that the most common lesioned area in these cases is the left temporoparietal junction, particularly BA 37 (posterior middle/inferior temporal gyrus) and BA 39 (angular gyrus) (Rapcsak and Beeson, 2002). A few of the cases had lesions in left ventral BA 37, extending to the occipital lobe (Patterson and Kay, 1982; Rapcsak *et al.*, 1990). However, all of these reviewed cases who had posterior temporo-parietal damage had impaired reading with or without oral naming, at least early after stroke (Table 2). Thus, in each of these cases, there was impaired access to lexical orthographic representations for input (reading) as well as output (writing). In contrast, the three previously reported cases of “lexical agraphia” who had damage restricted to the left posterior frontal cortex had normal naming and word reading, although some had impaired nonword reading (and spelling). This evidence suggests that left posterior inferior temporal (BA 37), temporo-occipital cortex, and angular gyrus (BA 39) are crucial for accessing the orthographic lexicon for either reading or writing (see Hillis and Rapp for review), while left posterior

**Table 2.** Summary of cases in the literature

Author and year	Impaired naming	Impaired word reading	Site of lesion
<i>Cases with impaired picture naming and/or word reading</i>			
Beauvois and Derouesne, 1981	Not mentioned	Yes	Left angular gyrus, posterior temporal, inferior longitudinal fasciculus, geniculostriate fibres
Harasty <i>et al.</i> , 1996	Yes	Not mentioned	Atrophy in bilateral angular gyri and BA 37
Goodman and Caramazza, 1986a, b	Yes	Not mentioned	Left posterior temporo-parietal region
Behrmann and Bub, 1992	Yes	Yes	Left temporal lobe
Roeltgen and Heilman, 1983	Yes	Yes	Right parietal lobe
Roeltgen and Heilman, 1984	Case 1. No	Yes	Left parieto-occipital hemorrhage
	Case 2. Yes	Yes	Left parieto-occipital, small left frontal, right occipital
	Case 3. Yes	Yes	Left medial occipital, lateral superior parietal
	Case 4. No	Yes	Left posterior temporal, angular gyrus, parieto-occipital lobule and lateral occipital gyrus
Goodman-Schulman and Caramazza, 1987	Yes	Not mentioned	Left hemisphere damage
Baxter and Warrington, 1987	No	Yes	Widening of the frontal and vertex sulci and mild cortical atrophy
Soma <i>et al.</i> , 1989	Case 1: Yes	Yes	Left posterior temporal lobe
	Case 2: Yes	Yes	Posterior left middle and inferior temporal gyri
	Case 3: Yes	Yes	Left temporal region
Hatfield and Patterson, 1983	Yes	Yes	Left posterior cerebral hemorrhage; left temporo-parietal, occipito-temporal resection
Rothi, Roeltgen, and Kooistra, 1987	No	Yes	Right posterior parietal-occipital
<i>Cases without impaired picture naming and/or word reading</i>			
Rapcsak <i>et al.</i> , 1988	Not mentioned	No	Left precentral gyrus
Hillis, Wityk, Barker, and Caramazza, 2002	Case 1: No	No	Left posterior inferior frontal and precentral gyri
	Case 2: No	No	Left posterior inferior frontal and precentral gyri
Hillis <i>et al.</i> , 1999a	No	No	Left posterior inferior frontal and precentral gyri

frontal cortex (BA 44, 45, and 6) may be crucial for modality-specific spelling processes.

Studies dating back to 1891 have implicated the role of BA 39 in both reading and writing (Dejerine, 1891; Benson and Geschwind, 1969). Numerous recent lesion studies have also reported cases of alexia and agraphia following damage to BA 39 (Benson, 1979; Beauvois and Derouesne, 1981; Roeltgen and Heilman, 1985; Black and Behrmann, 1994). More recent studies have also reported patients with lesions or functional inactivation of BA 39 who show impaired access to lexical orthographic representations for reading (Hillis *et al.*, 2001a; Love *et al.*, 2002).

In a study of reading in 40 acute patients, we found that hypoperfusion and/or infarct of BA 39 was associated with impaired access to lexical orthographic representations and orthography to phonology conversion (OPC) mechanisms. Hypoperfusion and/or infarct of BA 40 (supramarginal gyrus) was also associated with impaired use of OPC mechanisms (Hillis *et al.*, 2001b). Functional imaging studies have also revealed activation in BA 39 in reading (Horowitz *et al.*, 1998), perhaps specifically involved in sublexical reading via OPC mechanisms (Turkeltaub *et al.*, 2002). Similarly, in a study of spelling in 80 acute stroke patients, BA 39 was associated with impaired use of sublexical POC mechanisms (Hillis *et al.*, 2002b). Two fMRI studies of spelling have shown activation in BA 39 in most (but not all) individual subjects (Rapp and Hsieh, 2001; Beeson *et al.*, 2003). Together, these studies indicate that BA 39 may be crucial for using sublexical OPC and POC mechanisms either to access a lexical representation (see Hillis and Caramazza, 1991) or to “assemble” a response in reading or spelling. Nevertheless, damage to other regions, such as BA 40 and BA 44/45 may also disrupt sublexical POC and OPC mechanisms (see Rapcsak and Beeson, 2002 for review). For example, damage to BA 44/45 may interfere with phonological segmentation necessary for POC and phonological assembly for OPC.

All of the cases of lexical agraphia reviewed by Rapczak and Beeson (2002) who had lesions in BA 37 also had impaired access to phonological representations for output (e.g., in oral naming; see Table 2). A large number of previous lesion studies have implicated lesions in BA 37 in impaired spoken word retrieval (Nielson, 1948; Alexander and Benson, 1991; Benson, 1994; Hillis *et al.*, 2002c; Whatmough and Chertkow, 2002) as well as in impaired written word retrieval (Rapcsak and Beeson, 2002; Hillis and Rapp, in press, for review), and impaired written word recognition in reading (Samuelsson, 2000). In a study of forty acute stroke patients, we found that impaired access to orthographic representations for reading, and impaired access to phonological representations for oral reading and oral naming (with intact comprehension), were both strongly associated with hypoperfusion and/or infarct of BA 37 (Hillis *et al.*, 2001b). Furthermore, we reported that a patient with hypoperfusion in BA 37 had impaired oral naming and oral reading, but intact comprehension; and when blood flow was restored to BA 37, his oral reading and oral naming recovered. These data provide

additional evidence that BA 37 is crucial for accessing phonological as well as orthographic lexical representations for output.

Functional imaging studies of reading or writing have also shown activation of BA 37 and 39 in accessing orthographic representations for reading and spelling. For example, Howard *et al.* (1992) reported PET studies showing activation of BA 37 in tasks used to isolate the orthographic input lexicon. Since that time, a large number of fMRI studies have found activation in the ventral part of BA 37 (which has come to be known as the “visual word form area” or VWFA) in accessing orthographic representations or graphemes for reading (Cohen *et al.*, 2000, 2002; Dehaene *et al.*, 2001, 2002; Gros *et al.*, 2001; Polk *et al.*, 2002; Turkeltaub *et al.*, 2002). However, the same region also shows activation during spelling (Petrides *et al.*, 1995; Nakamura *et al.*, 2000; Rapp and Hsieh, 2001; Beeson *et al.*, 2003) and in response to auditorily presented words (Demonet *et al.*, 1992, 1994; Chee *et al.*, 1999; Buckner *et al.*, 2001; Giraud and Price, 2001; Wise *et al.*, 2001; Price *et al.*, 2003). Furthermore, studies have revealed activation of BA 37 in reading Braille in blind subjects (Buchel *et al.*, 1998), and in sign language in deaf subjects (Corina *et al.*, 2003).

Thus, lesion studies and functional imaging studies provide converging evidence that BA 37 is a region crucial for accessing multimodality or amodal lexical representations from visual, tactile, or semantic input (Buchel *et al.*, 1998; Price *et al.*, 2003). This region may be important in the first stage of word retrieval, as proposed by two-stage models of lexical processing that include a “lemma” level of representation, that is modality-independent (e.g., Dell, 1986; Levelt *et al.*, 1999).

In contrast to the multimodal lexical impairments associated with lesions in BA 37, we identified modality-specific lexical output impairments associated with functional inactivation of BA 44, 45, and 6. The fact that our patients had pure agraphia from the onset of stroke (with or without a motor speech impairment, but without other language deficits) indicates that these posterior frontal regions are important for modality-specific components of written output. However, the effects of word frequency, word class, and lexicality (words more impaired than pseudowords) indicate that the modality-specific impairment is not just a “peripheral” writing impairment, but one that involves accessing lexical representations. We propose that BA 44 and 45 are crucial for accessing a modality-specific orthographic representation (with a specific morphological form) from a modality-independent lexical representation (or “lemma”) or from a graphemic string assembled by POC mechanisms. The fact that the morphology (e.g., prefixes or suffixes) must be specified at this level of processing may explain why damage to this area affects verbs more than nouns (see Shapiro *et al.*, 2001, for a similar argument). That is, to write “running” in response to a picture or video of someone running requires selecting a specific morphological form (run, running, or runs, all of which would be correct). It is possible that this selection of a morphological

form is a modality-specific process that depends on either BA 44/45 or a nearby region (e.g., BA 9) that is concomitantly affected by infarct and/or hypoperfusion in our cases. In contrast, there is only one correct morphological form for a picture of an object (e.g., boot, assuming there is only one boot shown). The extra morphological processing for producing verbs may account for the greater impairment in modality-specific verb naming associated with posterior frontal regions.

We have previously described three other patients who presented with pure agraphia at the onset of stroke, all of whom have had lesions and/or hypoperfusion in BA 44 and 45 (RCM in Hillis *et al.*, 1999a; and two cases in Hillis *et al.*, 2003). In each of these cases, there was evidence for proposing impaired access to orthographic representations for written output. Furthermore, in the two cases where blood flow was restored to BA 44 and 45 prior to infarction, there was immediate recovery of access to orthographic representations, particularly of verbs (Hillis *et al.*, 2003), providing additional evidence that this region was crucial for accessing the orthographic representations of verbs. However, unlike the current cases, there was little evidence for impaired conversion of graphemes to letter shapes or letter-specific motor plans, indicating that the latter process may depend on BA 6 (which was normal in these two cases). This hypothesis is consistent with previous reports of impaired production of specific letters shapes following lesions in BA 6 (Anderson *et al.*, 1990). Furthermore, the patient described by Friedman and Alexander (1989) as having “a problem passing information from the activated letter image to the graphic motor pattern” (GV) had damage to the medial frontal lobe, sparing temporal and parietal regions. Likewise, one of the patients (HL) reported by Rapp and Caramazza (1997) to have disruption at the level of “effector independent representations dedicated to stroke feature specification” (a characterization that seems comparable to impairment in converting graphemes to letter-specific motor plans), and also impaired access to lexical orthographic representations resulting in phonologically plausible spelling errors, had a left posterior frontal lesion, as well as a left temporo-occipital infarct (the latter of which may account for his reading impairment shortly after stroke onset, which resolved before the spelling deficit). Consistent evidence for a role of this region in letter-specific motor plans comes from functional imaging studies showing activation in BA 6 during writing minus tapping and writing minus oral naming (Katanoda *et al.*, 2001). Another patient described by Rapp and Caramazza (1997), JGE, made similar letter substitution errors at HL, but JGE’s errors were associated with a letter recognition impairment. Her deficit, which affected both written input and output, was associated with a posterior temporal lesion, including BA 37 (along with damage to bilateral occipital and left thalamic lesions), consistent with the hypothesis that more posterior lesions affect modality-independent components of orthographic processing.

The previous three patients we reported with pure agraphia at onset of stroke also differed from the cases in this study in

that the majority of errors in written naming and dictation were omissions or semantically related word substitutions (e.g., rose → tulip), despite intact lexical semantic processing, and they were poor in spelling pseudowords. When RCM gradually recovered POC mechanisms, she made fewer semantic errors in spelling to dictation, consistent with the hypothesis that partial orthographic information assembled by POC mechanisms and intact semantic input together accessed orthographic representations (see Hillis *et al.*, 1999b for discussion). The impaired POC mechanisms in these cases indicate that, as suggested earlier, parts of BA 44 and 45 may also be important for phonological analysis needed for POC. Consistent with this hypothesis, Marien *et al.* (2001) reported a case of impaired use of POC mechanisms for spelling following a lesion involving the left operculum (BA 44), precentral gyrus, and insula. The fact that the cases in the present report were unimpaired, or less impaired, in POC is consistent with the observation that none of the present patients had complete damage to BA 44 and 45. That is, the part of BA 44 and 45 that is essential for POC mechanisms may have been spared in these cases. These results are consistent with functional neuroimaging studies indicating that different parts of left inferior frontal gyrus may have different roles in phonological, lexical/semantic, and syntactic processing (see Bookheimer, 2002 for review).

Two other patients in the literature have been reported to have isolated “lexical agraphia” (impaired access to the orthographic output lexicon) from the onset of stroke. One patient, described by Rapcsak *et al.* (1988) had a motor speech impairment and lexical agraphia from a lesion in the left post-central gyrus, very close to the region identified as infarcted or hypoperfused in our patients. Since this patient did not have perfusion imaging, it is possible that he had hypoperfused tissue surrounding the acute infarct (which may have included nearby BA 44/45). Alternatively, the cytoarchitectural BA 44 and 45 may have extended to the region infarcted in this patient. He had no temporal or parietal lesion. Another patient, described by Rothi, Roeltgen, and Kooistra (1987) had a lesion in the right posterior parietal-occipital lesion. This patient had more trouble spelling words than pseudowords and more trouble spelling irregular than regular words, but also had a mild impairment of reading. His deficit might be accounted for by impaired access to orthographic representations for both reading and writing, or may be due to his relatively low education level (8th grade), rather than due to his right hemisphere stroke. Finally, several historical cases provide evidence for pure agraphia due to left frontal regions, although the limited testing makes it difficult to discern the precise components of writing that were impaired (see Exner, 1881; see also Barriere *et al.*, this issue).

In summary, we have reported three cases of pure agraphia from the onset of stroke who showed impaired access to orthographic representations for output, and impaired conversion of graphemes to letter-specific motor plans, following damage or dysfunction of BA 44, 45 and 6. These cases, along with a review of lesions in cases of agraphia in the literature

provided the basis for proposing that written naming depends on a network of brain regions. More specifically, it is proposed that writing a word requires function of at least the following regions: (1) BA 39, which is essential for functions common to written language input and output (e.g., accessing lexical representations via sublexical OPC or POC assembly); (2) BA 37, which is important for functions common to spoken and written lexical output and perhaps lexical input (e.g., accessing modality-independent lexical representations from semantics, vision, or tactile input); (3) parts of BA 44 and 45 (and perhaps precentral gyrus), which are crucial for modality-specific output functions (e.g., accessing modality-specific orthographic representations with specific morphological forms from modality-independent lexical representations in BA 37); and (4) BA 6, which may be crucial for converting graphemes to specific letter shapes or letter-specific motor programs.

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