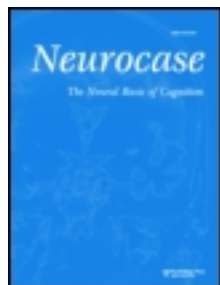


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## Neurocase: The Neural Basis of Cognition

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### Alexia due to ischemic stroke of the visual word form area

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## Alexia due to ischemic stroke of the visual word form area

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The visual word form area (VWFA) is a region in the posterior left occipitotemporal cortex adjacent to the fusiform gyrus hypothesized to mediate word recognition. Evidence supporting the role of this area in reading comes from neuroimaging studies of normal subjects, case-controlled lesion studies, and studies of patients with surgical resection of the VWFA for tumors or epilepsy. Based on these prior reports, a small discrete lesion to the VWFA would be expected to cause alexia in a literate person without prior brain process, but such a case has not previously been reported to our knowledge. Here, we report the case of a previously-healthy 63-year-old man with the acute onset of alexia without other significant impairments. Magnetic resonance imaging (MRI) of the brain revealed a small ischemic stroke localized to the inferior left occipitotemporal cortex, corresponding to the approximate location of the putative VWFA. Characteristic of pure alexia, testing in the weeks following the stroke revealed a letter-by-letter reading strategy and a word length effect on single word reading. Formal visual field testing was normal. There was no color anomia, or object or face recognition deficits, although a mild agraphia may have been present. This case of acute-onset alexia in a previously normal individual due to a small stroke restricted to the VWFA and sparing occipital cortex and white matter pathways supports the conclusion that the VWFA is crucial for reading.

**Keywords:** Alexia; Pure alexia; Alexia without agraphia; Visual word form area; Agraphia; Dyslexia; Dysgraphia; Reading.

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Dejerine (1892) provided the first description of alexia without agraphia. Patients with alexia without agraphia retain the ability to write, but lose the ability to read, including the ability to read words that they themselves have just written. Dejerine postulated that the disorder was caused by a disconnection between occipital cortex and the left angular gyrus, the latter structure thought to represent the visual image of the word. Based largely on functional neuroimaging work, this specific function is now thought to be subserved by a brain area termed the visual word form area (VWFA), located in the posterior left occipitotemporal gyrus (Cohen, 2000). However, the role of the putative VWFA remains highly controversial, in part because there exist no reports of discrete lesions restricted to this area in previously normal individuals (Price & Devlin, 2003). An alternative possibility is that, rather than being caused by damage to a specific brain region required for reading, pure alexia is due to a more general visual impairment of which alexia is perhaps the most salient aspect (Starrfelt, Habekost, & Leff, 2009). Here, we present a case in which a discrete ischemic stroke located at the anterior edge of the putative VWFA caused alexia without clear evidence of other visual or language deficits.

### CASE REPORT

A 63-year-old male with medication-controlled hypertension and a history of cigarette smoking noted a sudden onset inability to read while at work. He recognized words as such, but stated that “the words wouldn’t click.” He denied other symptoms.

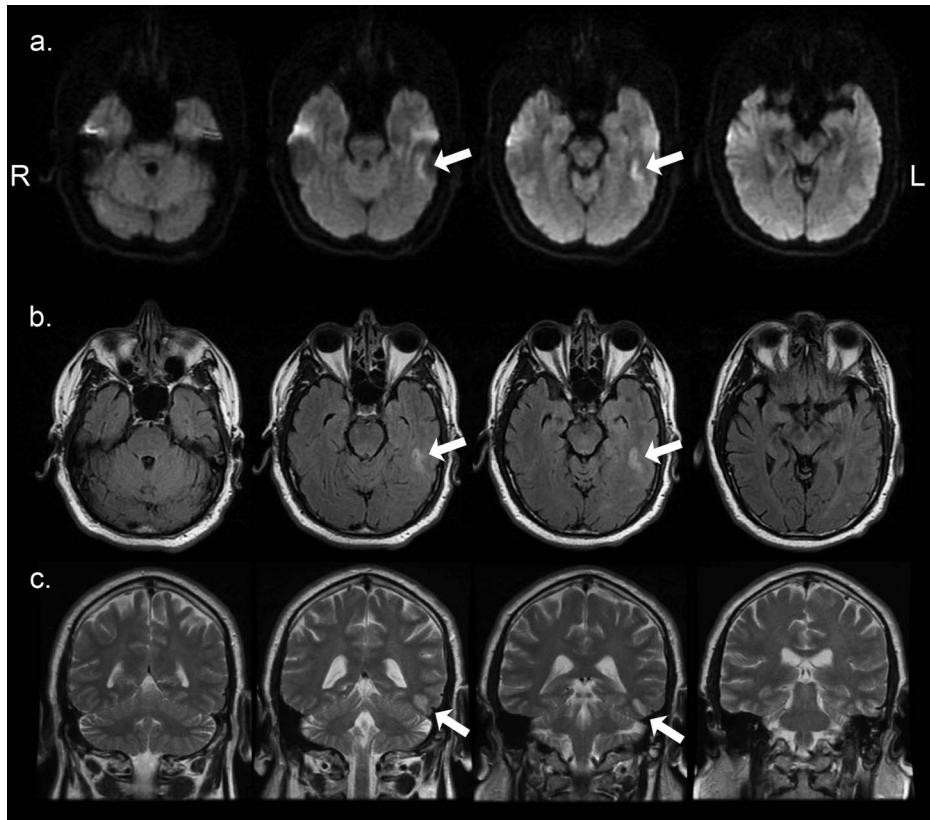
On clinical examination, the subject could not name or point to written words or pseudowords; even with unlimited time, he read “desk” as “dish,” “flame” as “thame,” and “blape” as “flap.” Naming of pictures and objects was normal. Auditory comprehension and spontaneous writing and writing to dictation were normal. Performance of serial 7’s, forward and reverse digit span, and recall of 3 words at 5 minutes, were all normal. More detailed language and cognitive testing from the acute phase of the stroke is unfortunately not available. Visual fields were full. Ophthalmologic evaluation, including Goldman kinetic perimetry, confirmed that visual fields were full. Pseudoisochromatic plate testing revealed

a congenital deficiency of red/green discrimination, but no new color processing deficits were present.

MRI of the brain on the day of clinical presentation revealed a small ischemic stroke located in the occipitotemporal sulcus at the anterior edge of the putative VWFA (see Figure 1). The area of restricted diffusion centered on MNI coordinates: X,  $-38$  to  $-50$ ; Y,  $-30$  to  $-50$ ; Z,  $-10$  to  $-22$ . Coronal T2 images demonstrate that the area of restricted diffusion is primarily cortical, without substantial involvement of longitudinal white matter fibers. A follow up MRI was performed 12 days later, which showed faintly persistent restricted diffusion in the same location, and contrast enhancement within the occipitotemporal sulcus at the location of the stroke (Figure 2).

Clinical speech-language pathology evaluation one month later with the Boston Diagnostic Aphasia Examination revealed an Aphasia Severity Rating scale score of 4 (indicating mild impairment), with intact auditory comprehension and oral expression as well as intact performance on tests of word reading, but impairment on oral reading of sentences with comprehension (11/15 items correct) and on reading comprehension (6/10). Mechanics of writing were intact, but spelling was mildly impaired, particularly with irregularly spelled words and function words (written picture naming, 9/12 items correct; cognitive/grammatical influences on written word retrieval, 21/24). The patient could not provide a baseline writing sample for comparison of spelling to premorbid ability.

Subsequent evaluation six weeks after the stroke revealed accurate but effortful reading, with a self-described letter-by-letter reading strategy and a significant length effect (see Figure 3). There were no effects of imageability (PALPA scores: 18/20 correct on items with high imageability, 17/20 correct on items with low imageability), frequency (high frequency words, 19/20; low frequency words, 16/20), or regularity (regular words, 29/30; exception words, 29/30), on reading accuracy. Two weeks later (eight weeks after the stroke), reading was faster, and the length effect was diminished (Figure 2). Performance on the Philadelphia Naming Test and the face similarity subtest of the Philadelphia Face Perception Battery were normal.



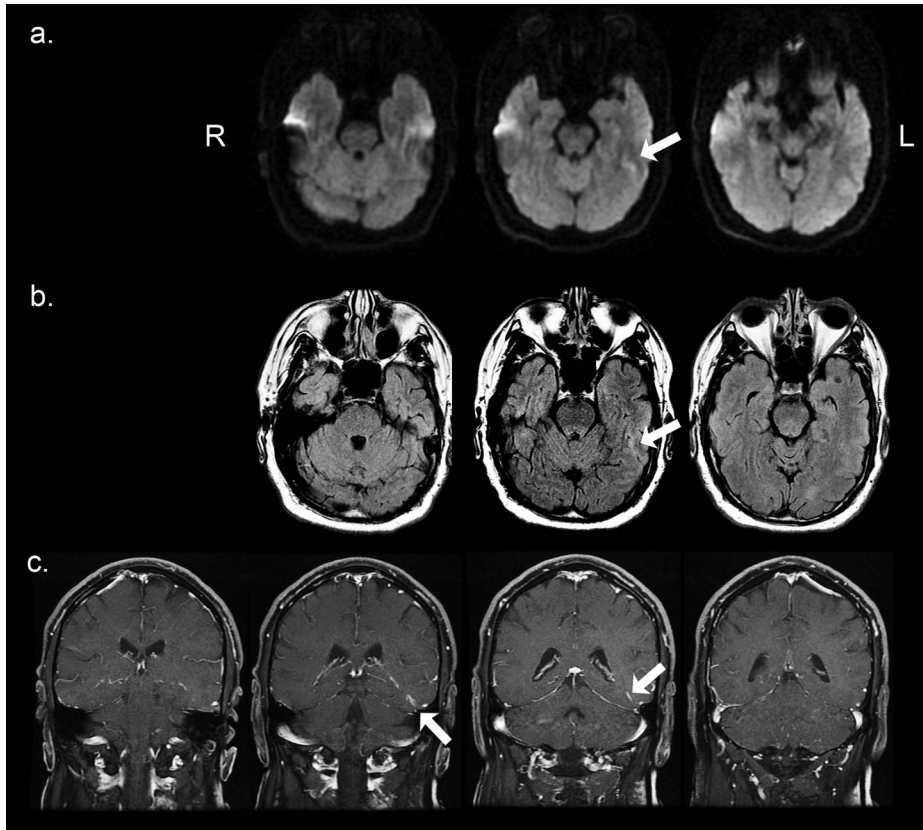
**Figure 1.** Neuroimaging data on the day of the stroke. (a) Axial DWI showing restricted diffusion involving the left occipitotemporal sulcus. (b) Corresponding Axial T2 fluid attenuated inversion recovery (FLAIR) images. (c) Coronal T2 images demonstrating the infarct involves mainly the gray matter in the occipitotemporal sulcus. Slices are shown encompassing the entire lesions, with one normal slice on either side for reference.

## DISCUSSION

The VWFA, a region in the ventral occipitotemporal cortex, has been regarded by some as crucial for visual identification of words (Cohen, 2000; Cohen, 2002; Dehaene, Cohen, Sigman, & Vinckier, 2005). This concept remains highly controversial, in part because the corresponding brain region is activated by a variety of visual stimuli (Price & Devlin, 2003). Some authors argue that pure alexia results instead from a more general visual impairment causing reduced visual speed which simply has a disproportionate impact on reading of words (Starrfelt, 2009). In addition to numerous prior neuroimaging studies in normal subjects (Cohen & Dehaene, 2004), prior lesion studies have linked the VWFA to reading (and sometimes writing) in surgical cases of VWFA resection (Gaillard, 2006; Tsapkini & Rapp, 2010; Tsapkini, Vindiola, & Rapp, 2011), case-controlled comparisons of patients with different lesion locations (Binder & Mohr, 1992), or

acute lesion symptom mapping (Hillis, 2005). Here, we have presented additional complementary evidence of the important role of the VWFA in reading from a novel case of a previously normal individual who became dyslexic after circumscribed, isolated damage to the region of the VWFA.

The coordinates of the lesion presented here are somewhat anterior to many previously reported values for the location of the VWFA. The center of the VWFA is thought to reside at MNI coordinates of  $x = -43$ ,  $y = -54$ , and  $z = -12$  (with a standard deviation of  $\sim 5$  mm for each measurement) based on the peak of blood oxygen level dependent (BOLD) signal activation on functional MRI. These estimates are formulated via averaging across subjects, typically by examining the peak activity within each subject, a method that may discount the extent of activity in individuals beyond the location of their peak activity. The lesion reported here does overlap with the anterior extent of the range of previously reported locations for the VWFA. For

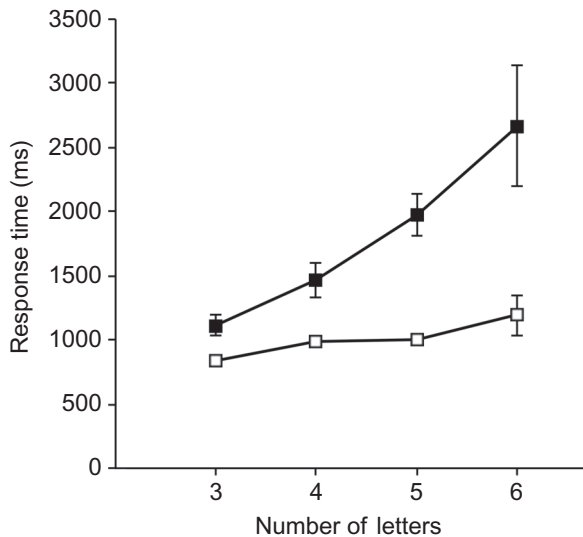


**Figure 2.** Neuroimaging data 12 days after the stroke. (a) Axial DWI showing restricted diffusion involving the left occipitotemporal sulcus. (b) Corresponding Axial T2 fluid attenuated inversion recovery (FLAIR) images demonstrating resolution of edema at the location of the infarct, with only a possible mild hyperintensity persisting. (c) Coronal post-contrast T1 images demonstrating enhancement within only the occipitotemporal sulcus, again suggesting that the infarct was mainly restricted to the gray matter. Slices are shown encompassing the entire lesions, with one normal slice on either side for reference.

example, Cohen et al. (2002) report values for the VWFA with coordinates centered on  $y = -45$  and  $-48$  and  $z = -21$ .

The syndrome of alexia without agraphia is frequently attributed to damage to or disconnection from the VWFA. These subjects often exhibit various forms of anomia and/or visual processing deficits (Behrmann, Nelson, & Sekuler, 1998). The typical lesion associated with alexia without agraphia includes posterior cerebral cortical lesions along with damage to white matter tracts that mediate interhemispheric transfer of visual information, such as the forceps major and/or splenium of the corpus callosum (Damasio & Damasio, 1983). Leff et al. (2001) reviewed published cases of pure alexia (>120) over an approximately 40-year period and found that 92% of all subjects had some sort of homonymous visual field defect. A few cases of alexia without agraphia and without

visual field deficit or color anomia were reported in the pre-MRI era. For example, Vincent, Sadowsky, Saunders, and Reeves (1977) reported the case of a subject with apparently mild alexia without agraphia, hemianopsia or color-naming deficit, who had a cerebellar meningioma compressing the left temporal-occipital cortex. Other reported cases of alexia without agraphia without visual field defect or color-naming deficit in the literature were caused by widespread brain damage and each case presented with other cognitive deficits, including aphasia and other forms of visual agnosia. Ajax (1967) reported a subject with alexia without agraphia due to a left occipital arteriovenous malformation who was without field defect on confrontational testing and was without color-naming deficit; however, perimetry was not performed, although the subject did have a clear field cut after surgical excision of the lesion. The subject reported



**Figure 3.** Length effect. The subject's reading latency increased with longer letter strings, consistent with a letter-by-letter reading strategy as seen in alexia without agraphia (solid squares; six weeks post-stroke). The effect was diminished two weeks later (open squares; eight weeks post-stroke). Error bars are S.E.M.

by Greenblatt (1973) was unable to cooperate with formal visual field testing, but did not have a field cut on bedside screening. Both the cases of Ajax and Greenblatt involved lesions encompassing the ventromedial left occipital cortex and the splenium of the corpus callosum. In more recently reported cases of pure alexia with lesions that include areas corresponding to the VWFA, damage extends well beyond the VWFA to more extensive regions of medial occipital cortex and underlying white matter pathways (Leff, Spitsyna, Plant, and Wise, 2006; Marsh & Hillis, 2005, Starrfelt, 2009).

Perhaps most relevant to this case, Gaillard and colleagues (2006) reported a subject with an epileptic focus at the location of the putative VWFA who underwent surgical resection of this site. The subject developed alexia without agraphia, without other visual perceptual deficits or aphasia. As in the present case, the authors observed a length effect, which improved over a period of weeks to months, and functional MRI demonstrated a shift of activity posteriorly in the left ventral occipital cortex. In a similar case, resection of a left fusiform oligodendroglioma resulted in compromise of lexical orthographic processes in both reading and writing (Tsapkini & Rapp, 2010), and fMRI demonstrated reorganization of bilateral posterior fusiform gyrus activity (Tsapkini, 2011). Although of clear interest, the interpretation of these cases is complicated by the fact that the presence of an epileptic focus or

tumor at the site of the VWFA may have induced longer term changes in brain organization for reading.

While the subject here exhibited a letter-by-letter reading strategy with prominent word length effect in response times at six weeks post-stroke, he made relatively few errors in reading at this time. The improvement from the acute presentation to the clinical speech-language assessment four weeks later may have been due to resolution of swelling (as indicated by the reduced FLAIR signal abnormality on the second MRI) or resolution of an ischemic penumbra. Marsh and Hillis (2005) reported a case of pure alexia and optic aphasia with a lesion involving the posterior portion of the occipital lobe and fusiform gyrus in which the acutely hypoperfused area included the splenium of the corpus callosum and other white matter fibers. Reperfusion of the splenium corresponded with improvement in reading and naming. It is possible that the ischemic penumbra in the current case included white matter connections to the VWFA also, but this is not possible to confirm because no perfusion scans were obtained. Regardless, any residual perfusion abnormality likely resolved prior to the more detailed assessments (performed 4–8 weeks later), so the observed reading deficits at these assessments, including the reported letter-by-letter reading strategy and prominent length effect observed six weeks after the stroke are likely explained solely based on the small infarct to the area of the VWFA. Notably, the acute clinical evaluation did not reveal any dysgraphia, but the patient made a few spelling errors four weeks after the stroke which make it difficult to rule out a co-occurring mild dysgraphia here. As such, we do not feel this case can inform the debate regarding whether the VWFA is involved in spelling as well as reading (Purcell, Turkeltaub, Eden, & Rapp, 2011; Tsapkini & Rapp, 2010).

In summary, we report an instance of new-onset dyslexia attributable to a small discrete lesion restricted to the approximate location of the VWFA in a previously normal individual. Although this case was somewhat limited because only clinical data were available for the first month after presentation and no additional research-based neuroimaging could be obtained, the available data strongly support the claim that the VWFA is essential for reading, and that even a small isolated lesion to the area of the VWFA in a previously normal individual can cause alexia. The subject employed a compensatory "letter-by-letter" reading strategy as manifested by significant effects

of word length, a finding that is characteristic of alexia without agraphia (Coslett, 2000). This case demonstrates that the clinical syndrome of alexia without agraphia can occur due to a lesion of the VWFA, although the involvement of the VWFA may induce a greater degree of spelling impairment than in the classically described syndrome (Hillis, 2005; Tsapkini & Rapp, 2010). We note the previous reports of alexia without agraphia in the context of discrete lesions that do not involve the VWFA (e.g. Greenblatt, 1973), and suggest that these may be attributable to other causes, such as a disconnection of the VWFA from visual input.

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