The functional anatomy of single-word reading in patients with hemianopic and pure alexia

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Summary
We investigated single-word reading in normal subjects and patients with alexia following a left occipital infarct, using PET. The most posterior brain region to show a lateralized response was at the left occipitotemporal junction, in the inferior temporal gyrus. This region was activated when normal subjects, patients with hemianopic alexia and patients with an incomplete right homonymous hemianopia, but no reading deficit, viewed single words presented at increasing rates. This same area was damaged in a patient with pure alexia (‘alexia without agraphia’) and no hemianopia, who read words slowly using a letter-by-letter strategy. Although the exact level of the functional deficit is controversial, pure alexia is the result of an inability to map a percept of all the letters in a familiar letter string on to the mental representation of the whole word form. However, the commonest deficit associated with ‘pure’ alexia is a right homonymous field defect; an impairment that may, by itself, interfere with single-word reading because of inability to see the letters towards the end of a word. The relative contributions of pure and hemianopic alexia in individual patients needs to be assessed, as the latter has been shown to respond well to specific rehabilitation programmes.

Keywords: alexia, hemianopia, functional imaging, review

Abbreviations: HA = hemianopic alexia; HC = hemianopic controls; msPL = milliseconds per additional letter over and above three letters; rCBF = regional cerebral blood flow; RT = reaction time; SPM = statistical parametric mapping; WLE = word length effect; w.p.m. = words per minute

Introduction
Most models of reading include a word form recognition system (McCarthy and Warrington, 1990). Literate adults recognize and read aloud familiar words of differing letter lengths at a uniform speed: the letters of the whole word are processed in parallel, and not letter-by-letter. Foveal and parafoveal vision (having radii of 1° and 5° around fixation, respectively) afford the acuity to discern words of up to nine letters without the reader having to make an eye movement within the word (Just and Carpenter, 1987). Unfamiliar words may cause a reader to make extra forward or regressive saccades to complete word identification.

Alexia denotes the presence of a reading disorder that prevents comprehension of written language (Damasio, 1977). Although dyslexia is an equivalent term, it is most often used to refer to a range of disorders seen in people who fail to develop normal reading skills in childhood. Therefore, the term alexia implies that the reading disorder has come on after the ability to read has been acquired, and is usually secondary to dominant cerebral hemisphere pathology.

The classification of alexia has gone through several changes, both in the neurological (Benson and Geschwind, 1969) and the neuropsychological literature (Shallice, 1988). Alexia is often found in association with a generalized language disorder, such as in patients with pathology involving the left temporal or parietal regions. Classically, involvement of the left angular gyrus is associated with the syndrome of ‘alexia with agraphia’ (Dejerine, 1892). Many aspects of reading may be affected, writing errors tending to mirror errors made during spoken word output. Alexia associated with aphasia after lesions involving the anterior part of middle cerebral artery territory has also been recognized: originally described in the late 19th century, it was more fully characterized by Benson, who termed it ‘the third alexia’ (Benson, 1977).
This paper is concerned with alexic syndromes not associated with a more general aphasic disorder, the most well known being Dejerine’s syndrome of ‘alexia without agraphia’. These types of alexia are classified as peripheral by psychologists, as they are associated with a misperception of words rather than a disturbance of language (Shallice, 1988). The deficit results in impaired mapping of the visual structure of the word onto its neurally encoded representation in the long term memory store (lexicon) of familiar words. When stroke has resulted in a peripheral alexia, the lesion is invariably in posterior cerebral artery territory.

The earliest description of an acquired reading disorder dates back to AD 30 (Benton, 1964) but it was in 1877 that the term ‘word blindness’ or ‘Wortblindheit’ was first used by Kussmaul. He also observed the association with a right homonymous hemianopia (Kussmaul, 1877). Jules Dejerine, in two single case studies, described his two-way classification of acquired alexia, alexia with agraphia and alexia without agraphia (‘écécite verbale pure avec intégrité de l’écriture spontanée et sous dicte’) (Dejerine, 1892). Alexia without agraphia and ‘pure alexia’ are synonymous terms: the term ‘letter-by-letter reading’ invokes the strategy often used by patients to overcome their deficit. Pure alexia may initially present as global alexia, when patients have difficulty with, or are unable to recognize and name letters (Binder and Mohr, 1992). Dejerine’s original case, Monsieur C., who lived for 5 years after his initial stroke, never recovered letter form recognition, and today would be regarded as having persistent global alexia. Interestingly, Monsieur C. consulted an ophthalmologist (Landolt) when he first noticed a problem with his reading. Landolt is reported to have documented a right homonymous hemianopia and hemiachromatopsia (Bub et al., 1993); the extent and duration of these latter two signs are not recorded in the original case report by Dejerine.

Hemianopic alexia (HA), a third form of peripheral alexia separate from pure and global alexia, was probably first recognized in 1907 by Wilbrand (Wilbrand, 1907). Beringer and Stein (Beringer and Stein, 1930) reported a similar patient, and observed that his eye-movements when reading were abnormal, a clinical observation subsequently confirmed by electro-oculography (Mackensen, 1962; Gassel and Williams, 1963). In HA, word recognition is considered to be intact (Zihl, 1995), but the presence of a right homonymous hemianopia leads to a disruption of the visuomotor coordination of eye movements during text reading (Leff et al., 2000). The subject’s reading speed is dependent on the amount of parafoveal vision to the right of fixation, with 5° of sparing compatible with normal reading speeds (Zihl, 1995). Finally, there is neglect alexia, where the patient consistently makes errors with either the initial or last letters of a word; paradoxically, in a few patients with right homonymous hemianopia, the errors may be on the initial letter.

Most patients do not fall neatly into these categories. It is rare to find someone with pure alexia who does not also have a right visual field defect, with the possibility of a co-existent hemianopic or neglect alexia. It is, however, possible to find individual patients with a left occipital lesion and right visual field defect without reading problems. Binder and Mohr used this latter group as controls when correlating lesion site with type of alexia (Binder and Mohr, 1992). Their patients with pure alexia had damage involving the left occipitotemporal junction, or the connections to and from this region.

Using PET, we investigated reading in: normal subjects; patients with HA; patients with normal reading and a right macular sparing homonymous hemianopia; and a single patient with pure alexia and no hemianopia. The results for text reading in these subjects have been published recently (Leff et al., 2000). This paper describes the results on single-word reading, with two aims: (i) to confirm that a left-lateralized neural system at the occipitotemporal junction is responsible for access to visual lexical (whole word) representations; (ii) to critically review the behavioural definition of pure alexia as a reading disorder characterized by a monotonic increase in reading reaction time with words of varying length, irrespective of the slope.

The results are discussed in relation to a review of both the functional imaging data on single-word reading and the behavioural data on 107 cases of pure alexia published over the past 40 years.

Methods

Subjects

Each participant gave informed consent to participate in the study. The ICSM Research Ethics Committee approved the project and permission to administer radioisotopes was given by the Department of Health. Five normal subjects (three female), aged 40–61 years, were studied. The eight patients (three female), aged 40–76 years, had completed left occipital strokes, and those with alexia had stable reading impairments. They were scanned 1–4 years after their stroke. All had English as their first language and were right-handed.

Four of the patients had HA; i.e. they were disproportionately slower at reading text compared with single words. Their single-word reading speeds, along with those of the other patients and normal subjects, are shown in Fig. 1. Their text reading speeds were measured using the last three passages from Form 2 of the Neale battery (Neale, 1989) which is designed for use with children and adolescents. Raw reading speeds in words per minute (w.p.m.) were converted into adjusted reading ages, the ceiling score being 13+. The HA patients’ average reading speed was 68 w.p.m. (range 57–86, equivalent to a reading age of 8–10 years). The three hemianopic controls (HC) averaged 120 w.p.m. (range 106–138, equivalent to a reading age of 13+). Subject A.R. with pure alexia, could not manage text reading.

A.R. had pure alexia without agraphia or hemianopia. He had left school, aged 14 years, with no qualifications and reported that he was never very good at spelling. He read...
Robert was a newspaper editor but not a bookseller. He had Type II diabetes and hypertension. In 1994, he had a left occipital haemorrhage. His visual fields, eye movements, and sensorimotor function were normal. Initially, he could not recognize letters, but this resolved incompletely, and he was able to read some words using an explicit letter-by-letter strategy. There was a monotonic increase in his reaction times to words of increasing length. He was slow but mostly accurate at letter identification (both naming and cross-case letter matching). There was no evidence of attentional alexia as he could identify flanking letters as quickly and accurately as single letters. He could write to command, but could not read easily what he had written, and he was slow at copying text. In contrast, his number reading was relatively preserved. He could name numbers comprising up to seven digits. His verbal and performance IQ were 89 and 88 on the shortened version of the Wechsler Adult Intelligence Scale—Revised. His memory was impaired for words and faces on a standard recognition memory test (Warrington, 1984). He was in the normal range for picture naming (Coughlan and Warrington, 1978), and he had no evidence of other aphasic disorder. He could name colours correctly, and he did not have hemiachromatopsia. He was tested using the Visual Object and Space Processing Battery (Warrington and James, 1991) and there was no evidence of a visuo-perceptual or visuospatial deficit. An MRI scan 3 years after the haemorrhage showed a lesion in the left occipital lobe involving medial and lateral structures, but sparing primary visual cortex, its geniculostriate afferents and the splenium of the corpus callosum (Figs 2 and 3).

Visual and reading assessments
The visual fields of the patients were assessed with an automated Humphrey (static) perimeter, using the manufacturer’s 30–2 and 10–2 protocols, except for the patient with pure alexia, A.R., whose fields were assessed using Goldmann (dynamic) perimetry because he was unable to complete automated testing. Single-word reading speeds for all subjects were measured using a voice-key activated program on an Apple Mac computer. The words were three, five, seven and nine letters in length, with 25 examples of each, all taken from the same battery as those used in the PET scan (see below) (Coltheart, 1981). As A.R. often read words explicitly letter-by-letter, triggering the next stimulus too early, he was timed manually using the words printed on the card. As his reading speeds were so slow, this will have resulted in only small inaccuracies. Single-word reading speeds were obtained in six normal volunteers, aged 48–64 years, three of whom also underwent PET scanning.

Stimuli during scanning
All stimuli used were single syllable, English words (nouns and verbs) obtained from the MRC psycholinguistics database. The words were either four or five letters long, as

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**Fig. 1** Voice-key recorded reaction times for three, five, seven and nine-letter words ($n = 25$ for each data point). Mean reaction times are shown in ms with standard error bars. The data for the six normal subjects has been compressed into one plot as they were all so similar. Normal subjects (N) are shown in filled squares; hemianopic controls (HC) in filled circles; hemianopic alexics (HA) in open circles; and the single patient with pure alexia (A.R.) in open squares on a separate graph, as the scale on the ordinate is thousands of milliseconds. Below the graphs are the values of the slopes for each subject in msPL. The normal subjects have been grouped and the slope of their reaction times is expressed in 95% confidence intervals (CI).

<table>
<thead>
<tr>
<th>Word length (number of letters)</th>
<th>N1–N6 95% CI</th>
<th>HC1</th>
<th>HC2</th>
<th>HC3</th>
<th>HA1</th>
<th>HA2</th>
<th>HA3</th>
<th>HA4</th>
<th>A.R.</th>
</tr>
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<tr>
<td>Slope</td>
<td>–6 to 10</td>
<td>4</td>
<td>13</td>
<td>16</td>
<td>51</td>
<td>87</td>
<td>117</td>
<td>162</td>
<td>2402</td>
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Fig. 2 Foveal and pre-striate activations for the four subject groups are shown. The normal subjects’ data (N) are coregistered onto a standard $T_1$ MRI template, while the hemianopic controls (HC) and hemianopic alexics (HA) are coregistered onto a mean template made from the individual patient’s $T_1$ MRI scans. The transaxial level for these three images is $z = -10$. Because the data for the subject with pure alexia (A.R.) was not spatially normalized, no $z$ coordinate can be used to describe the level of the transaxial slice showing his individual PET data coregistered to his MRI scan; it is slightly higher than the other subjects but still within striate cortex. Below these images are representational visual field analyses for the first three groups using Humphrey perimetry. The Goldmann charts for A.R. are shown as well; these were recorded using a very small and faint target (Il1a).
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Fig. 3 Functional imaging data from the conjunction analysis across all three groups (N/HC/HA) showing the left occipitotemporal activation. The peak voxel was at \(-42, -72, -16\) with a Z-score of 6.96. The same data set is shown co-registered onto three templates, from left to right. (N) The standard 99 MRI template for normal subjects. (HH) A mean template made from all seven hemianopic subjects (HC + HA); medial but not lateral left occipital structures have been damaged. (A.R.) A.R., the subject with pure alexia, shows preservation of a small portion of the medial occipital cortex but damage to lateral and ventral occipital cortex including the occipitotemporal junction. The group activation is well within the boundaries of his defect. A.R.’s MRI (unlike in Fig. 2) has been normalized into MNI space to allow this spatial comparison to be made.

We wished the HA subjects to be able to read most of the single-word presentations without having to make a rightward saccade. The mean imageability of the stimuli was 511 (range 353–647, with a total possible range of 100–700) (Coltheart, 1981), and mean log frequency 1.5 (range 10–99 words per million) on the Kucera and Francis scale (Kucera and Francis, 1967). The stimuli were presented in the centre of an Apple Mac Powerbook 540c screen viewed from 50 cm. They were presented in 42-point Helvetica script, in lower case. The stimuli were selected randomly by the PsyScope software (Cohen et al., 1993). When presenting the words at faster rates, intervals between the words were shortened appropriately; all single-word stimuli were presented for 500 ms each, with a crosshair presented during the preceding 500 ms. The rates varied from 0 to 80 w.p.m. (5, 20, 40, 60, and 80 w.p.m.). The zero rate was an ‘anticipation’ condition, when subjects were shown a single word before regional cerebral blood flow (rCBF) was measured, a crosshair appeared for the next minute, but the subjects expected to see more words during this minute. As part of a separate study into HA, subjects were also shown horizontal word arrays, but these scans are not used in the statistical analyses presented here. Other than patient A.R., who was only scanned during exposure to single words and not text arrays, none of the subjects reported problems perceiving the stimuli, even at the fastest rate of 80 w.p.m. Subjects had 12–16 scans each, 8–10 of which were single-word trials at the rates mentioned above. The order of scans was randomized across subjects and conditions. Subjects viewed the words but made no response and were not instructed to respond specifically to the stimuli, but to ‘read and understand the words’. The assumption was that the normal subjects and
patients attended to the stimuli, and that implicit processing of the word forms in the individual patients proceeded up to a level dictated by the presence of their particular lesion.

**PET data acquisition**

Subjects were studied using a CTI-Siemens (Knoxville, Tenn., USA) ECAT EXACT HR++/966 PET scanner operated in high-sensitivity 3D mode. H$_2^{15}$O was administered intravenously. After a delay of ~30 s, a rise in head counts was detected which peaked ~30 s later. The data were acquired in one 90 s frame, beginning with the rising phase of the head curve. The relative distribution of rCBF in the brain is indexed by the accumulated counts over the scanning period, which reliably reflect flow in the physiological range. The part of the head curve most sensitive to changes in regional perfusion is during the steepest part of its rise. The interval between successive H$_2^{15}$O administrations was 6 min. Correction for attenuation was made at the beginning of each study by performing a transmission scan with external sources of $^{125}$Cs. Images were reconstructed by 3D filtered back projection (Hanning filter, cut off frequency 0.5 cycles per pixel) and displayed in a 128 × 128 pixel format with 95 planes, creating ~2 mm cubic voxels.

**Image and statistical analysis**

SPM99 software (Wellcome Department of Cognitive Neurology, Queen Square, London: http://www.filion.ucl.ac.uk/spm) was used to realign the individual PET scans, forming a mean image in the process; this was then spatially transformed (normalized) into standard MNI (Montreal Neurological Institute) space (Evans et al., 1993). This transformation allowed comparisons across individuals to be made. All the patients were normalized into the same space using a program developed in-house, which utilizes a hand-drawn mask of the portion of the brain affected by the stroke (derived from a high resolution MRI scan). This mask guides the normalization procedure, so that the algorithm for finding the edge of the brain does not treat the edge of the infarct as a normal contour of the brain surface. Individual activation scans were then smoothed using an isotropic 16 mm full-width, half-maximum Gaussian kernel to account for variation in gyral anatomy and to improve the signal-to-noise ratio. The subjects were entered into the design matrix in three groups: N (normals), HC (hemianopic controls) and HA. A.R. was analysed in a separate, single-subject, analysis. We created, on a voxel-by-voxel basis, statistical parametric maps (SPMs) of the $t$ statistics of the correlation of activity with the rate of presented words. The analysis included a blocked ANCOVA (analysis of covariance) with global counts as confound to remove the effect of global changes in perfusion across scans. The threshold for significance for a change of activity in the peak voxel of an activated region was set at $P < 0.05$, corrected for analyses across the whole volume of the brain (Z-score > 4.75), for the grouped data. The significance of A.R.’s single subject data was set at, $P < 0.001$, uncorrected (Z-score > 3.1), provided that the activated region was located in the same region observed during reading in normal subjects: the threshold was set at $P < 0.05$, corrected for other regions.

We analysed our subjects as five groups: (i) five normal subjects (N); (ii) four patients with left occipital stroke, right homonymous hemianopia involving right foveal or parafoveal vision and HA; (iii) three patients with left occipital stroke, right homonymous hemianopia sparing right foveal and parafoveal vision and normal single-word and text reading speeds (HC); (iv) the seven hemianopic subjects grouped together (HH); (v) A.R. with pure alexia and no right visual field defect.

**Results**

**Behavioural data**

Individual subject’s single-word reading speeds for three, five, seven and nine-letter words are shown in Fig. 1, with reaction times (RT) in milliseconds. Some normal subjects had a very mild word length effect (WLE), due to the inclusion of nine letter words. The 95% confidence intervals for the grouped average slope was −6 to 10 ms per additional letter over and above three letters (msPL). The three hemianopic control patients also had a slight WLE but no more than 16 msPL. The four patients with hemianopic alexia had a greater WLE than either the normal or hemianopic controls; 50–160 msPL. A.R. also showed a classical monotonic increase in reaction times, although the effect was an order of magnitude greater than the patients with hemianopic alexia. His data for nine-letter words is not shown, as he only identified four out of 25 stimuli correctly.

**PET data**

When viewing single words, the normal subjects activated left and right striate cortex, representing foveal vision, and left and right ventral prestriate cortex, with an approximately linear increase of activity in response to the increasing rates of seeing words. The HC group, with at least partial sparing of right parafoveal vision, had a very similar pattern of activation. The HA group, with impaired vision up to fixation in at least one right visual quadrant, did not activate left foveal striate cortex, the consequence of either infarction of this region or its geniculostriate connections. However, there were both left and right ventral prestriate activations. The activation on the left, without information from left striate cortex, must have resulted from callosal transfer of information from the right prestriate cortex. A.R. was analysed as a single subject because normalizing patients using the method outlined above results in loss of data from the immediate peri-infarct region. As his scan data does not occupy the same stereotactic space as the data from the other three groups, direct comparisons cannot be made.
Nevertheless, reference to A.R.’s individual MRI scan shows that when he viewed words there was activation of both left and right foveal striate cortex, which is consistent with the perimetry showing that he had preserved foveal and parafoveal vision in his right visual hemifield (Fig. 2).

More rostral (anterior) activity, at the left and right occipitotemporal junctions, was determined using data from all subjects except A.R., as they all had intact cortex in these regions. A conjunction analysis was performed to demonstrate regions of activity common to groups N and HH. There was a common and asymmetrical activation on the left, which we superimposed on both the normal MRI template available in SPM99 and a mean MRI image made from the individual scans of all seven subjects in group HH, transformed into the stereotactic space employed by SPM99 (Fig. 3). The activation at the left occipitotemporal junction, rendered onto the spatially transformed MRI image of A.R., clearly lay within his lesion, which extended more laterally and ventrally than any of the lesions of the patients in group HH.

The only other areas activated in this conjunction analysis of groups N and HH were located in the left lateral and medial premotor cortex (stereotactic coordinates, –62 +04 +38 and –02 –02 +68, respectively). Previous studies have shown that silent reading is associated with activation of pre-articulatory speech systems (Price, 1997).

Individual analyses of groups N, HA and HC were undertaken. The only additional result from these analyses was that group HA activated the right occipitotemporal junction (Z-score = .504; stereotactic coordinates, +54 –66 –08). This region was not observed in the conjunction analysis, where groups N and HC showed no trend of activation (P > 0.05, uncorrected).

**Discussion**

This study has demonstrated the central role of the left occipitotemporal junction in single-word recognition. This region was activated in normal subjects and in patients with right visual field defects sparing right foveal and parafoveal vision. The patients with hemianopic alexia also activated the left occipitotemporal junction despite an absence of input from the ipsilateral primary and prestriate visual cortex. The single patient with pure alexia without right hemianopia had destruction of the left occipitotemporal cortex but preservation of the left primary visual cortex (V1); his profound impairment of single-word reading was strikingly different from the mild slowing of single-word reading with few errors, in the patients with hemianopic alexia. The following conclusions can be drawn from this study: (i) destruction of the left occipitotemporal junction is responsible for a severe impairment in single-word recognition (pure alexia); (ii) the afferent connections from right occipital cortex to the left occipitotemporal junction, via the splenium of the corpus callosum and the left forceps major, are sufficient to support single-word recognition in patients with right visual field defects encroaching up to the mid-line.

The conclusions from our observations can be put into the perspective of the abundant lesion-deficit literature on pure alexia. In the last 40 years there have been over 120 cases of pure alexia reported in the literature. Most have been published as individual case histories, but a few authors have collected 10 or more cases (De Renzi et al., 1982; Damasio and Damasio, 1983; Binder and Mohr, 1992), or have reported their patients within a general review encompassing other reported cases (Cohen and Dehaene, 1995; Behrmann et al., 1998). Within the details of these cases there is heterogeneity, which is, at least in part, due to the way some authors have stretched the definition of pure alexia. It has been proposed by Benson and Geschwind that to fulfill the diagnostic criteria for pure alexia, patients must have: a severe disturbance of reading comprehension, with linguistically correct writing (either spontaneously or to dictation); normal oral spelling; and an absence of aphasia and dementia (Benson and Geschwind, 1969). Adhering closely to this definition means excluding some of the reported cases. Thus, a few patients had degenerative dementia, although it was asserted that the pathology was predominantly localized to the occipitoparietotemporal junction, so-called ‘posterior dementia’ (Staller et al., 1978; Price and Humphreys, 1995). Excluding cases where the patient had an associated aphasia is more problematic. As mentioned earlier, alexia following a middle cerebral artery territory stroke is commonly associated with a more generalized language disorder, but posterior cerebral artery territory infarction may be associated with a number of aphasic deficits, such as colour anomia or anomia for photographs of objects (De Renzi et al., 1987). Therefore, it would seem reasonable that a mild impairment of naming should not prohibit a diagnosis of pure alexia, as it may be an associated deficit depending on the extent of the left posterior cerebral artery territory infarction. Several cases have been reported as examples of pure alexia without hemianopia (a rare condition), when the lesion was outside the occipital lobe and the subject had evidence of a more generalized language disorder (Levine and Calviano, 1978; Pirozzolo et al., 1981; Doctor et al., 1990; Iragui and Kritchovsky, 1991; Friedman et al., 1993; Sinn and Blanken, 1999). Finally, it is difficult to interpret cases with multiple lesions, if the lesions that were dismissed as making a contribution to the alexia occurred either in known language areas or in both occipital hemispheres (Buxbaum et al., 1999). However, after taking account of all these reservations, there were 107 out of 120 cases for which there were published data.

**Studies of cases categorized as pure alexia with an associated hemianopia**

Ninety-eight out of 107 patients categorized as pure alexia had a right homonymous field defect of some sort, including one case where the title and abstract indicated that the patient did not have a visual field defect, only for mention of a right
upper quadrantanopia to be made in the case history (Leegaard et al., 1988). A homonymous field defect was the most common deficit associated with ‘pure’ alexia. Seventy-six cases had either a homonymous field defect that was described as ‘dense’ or macular splitting; the other 22 had either a right upper homonymous quadrantanopia or a macular sparing hemianopia. As normal readers fixate to the left of centre of a word (Nazir et al., 1992) and masking right parafoveal or foveal vision interferes with whole word recognition in normal subjects (Bouma, 1973), it is surprising that none of the authors felt that the coexisting hemianopia had any significant effect on the WLE observed in any of their cases. This may be due to the an emerging consensus that pure alexia describes anybody who shows a WLE, regardless of absolute RTs. These vary by so much as to call into question whether the patients are suffering from the same perceptual disorder. Of the 48 cases where WLE was reported, the average time to read three-letter words was 4.7 s, but the range was 0.8–90.0 s. For seven-letter words the average was 13.1 s, with a range of 1.2–83.0 s. Thus, the perceptual disorder across all these cases is very variable, even when making allowance for differences in the speed at which individual patients can make use of a reversed spelling strategy to read aloud words that have been assembled letter-by-letter. As we have shown in the four hemianopic patients included in this study, a macular splitting hemianopia can add a WLE of 51–162 ms per letter (Fig. 1). Therefore, a significant proportion of the WLE in patients with quicker reading speeds may be due to an isolated hemianopic impairment rather than pure alexia. In our view, nine cases may need re-evaluating (Levine and Calvanio, 1978; Coslett and Saffran, 1989; Farah and Wallace, 1991; Arguin and Bub, 1994), especially those in whom seven-letter word reading speeds were <2.5 s: cases D.S. (Behrmann and Shallice, 1995), I.S. and M.W. (Behrmann et al., 1998) and I.H. (Bowers et al., 1996).

**Pure alexia without hemianopia**

Nine out of 107 were reported as having full visual fields. However, many patients with hemianopia have reduced acuity rather than complete visual loss in the affected field segment. This can be missed on clinical confrontation testing. Thus, Lühdorf and Paulson reported a patient with pure alexia but normal visual fields on ‘bedside’ examination, who had a macular-splitting, partial, homonymous hemianopia on testing with Goldmann perimetry (Lühdorf and Paulson, 1977). This attention to the methodological assessment of perimetry may appear pedantic, but as reading is critically dependent on the acuity offered by foveal and parafoveal vision (Rayner and Bertera, 1979), even a partial reduction in acuity to the right of fixation can be expected to increase reading times. Of the nine pure alexic patients without hemianopia, only four had quantitative assessments of their visual fields. Not all had neuroimaging or post-mortem examinations to localize precisely their lesions, but of those who did, one had a lesion of the left occipitoparietal cortex (Price and Humphreys, 1992), four had damage to the left occipitotemporal cortex, or to the subcortical white matter beneath (Uitti et al., 1984; Caffarra, 1987; Warrington and Langdon, 1994; Benito-Leon et al., 1997) and in a further three, specific mention was made of involvement of the occipitotemporal junction (Greenblatt, 1973; Henderson et al., 1985; Beversdorf et al., 1997).

The reason why pure alexia without hemianopia is rare is that occipital lobe ischaemic infarction following posterior cerebral artery occlusion very commonly affects the ipsilateral optic radiation and primary visual cortex, as well as intrahemispheric prestriate connections. When the aetiology was known, ischaemic stroke was the most common pathology associated with pure alexia with hemianopia (65 out of 79 = 82%). Only one out of eight cases of alexia without hemianopia in whom the aetiology was reported had an infarct; the rest had a primary intracerebral haemorrhage (three), tumour (three) or pyogenic abscess (one). Our case, A.R., had a cerebral haemorrhage.

**Global alexia and the contribution of general visual impairment**

At the more disabling end of the spectrum, pure alexia merges with global alexia, a failure to recognize individual letters. Letter recognition impairment is not all-or-none, and many patients labelled as pure alexics make a few errors when naming letters. Even in the absence of errors, letter naming may be slow (Patterson and Kay, 1982). Furthermore, patients who present acutely with global alexia may recover over days or weeks to a condition of pure alexia (Leegaard et al., 1988; Coslett et al., 1993). Although the majority of patients with pure alexia are slow and sometimes inaccurate when naming isolated letters, when reading letter-by-letter they are usually slower to recognize a word than would be suggested by multiplying their mean RT to identify individual letters by the number of letters in a word. Some patients exhibit simultanagnosia for letter strings (Warrington et al., 1993), while some do not, leading to speculation that some patients may have a problem with holding the individual letters in short-term memory (Verstichel and Cambier, 1997). Others have argued that pure alexia is not letter specific, and that patients have subtle deficits in distinguishing small symbols that differ from each other only slightly (Behrmann et al., 1998; Chmielowska et al., 1999). In these tests, rows of small abstract images, one to be matched to a probe, are presented, but no allowance is made for the contribution that a co-existing hemianopia might have on the RTs to identify the target within the row of distractors. A further confounding factor is lesion site and size. Subjects with extensive or progressive lesions that involve the inferior parietal lobe can have multiple associated visual impairments, including a general simultanagnosia (Kinsbourne and Warrington, 1962). The fact that some pure alexic subjects have normal RTs when reading numbers, as was the case with A.R., argues
strongly against all patients with pure alexia having a low level visual impairment (Hinshelwood, 1900; Albert et al., 1973; Henderson, 1987).

Functional imaging studies of reading in normal subjects

Other functional imaging studies have identified a role for the left occipitotemporal junction in single-word reading. As we only varied word rate and not word or symbol form, we cannot conclude from our study that this area is specific for word forms. Other studies have attempted to identify the locus of the long-term representations of visual word forms by contrasting real words with pseudowords (Price et al., 1996c), consonantal strings or false fonts (Petersen et al., 1990) and rotated or mirror-reversed words (Goebel et al., 1998). Several factors complicate a comparison of results across seemingly similar functional neuroimaging studies. Foremost is the difference in task demands, which may result in different patterns of observed activations. In our study, subjects were asked to ‘passively’ read words, with the disadvantage that there is no measure of whether the subjects were attending to the words, or what cognitive processes they were performing on them when they had read them. The major advantage is that silent reading is a natural act. Top-down (Miller, 2000) modulation by cortex engaged in forced-choice, two-way decision tasks on word and word-like stimuli may modulate the signal recorded in input processors of words and word-like stimuli, and affect the distribution of signal when other processes have to be engaged specifically to perform the unusual task. For example, activations associated with eye movements may become apparent when subjects have explicitly to scan within a single word to detect a particular feature, a process not engaged by normal subjects when reading a word for meaning (Goebel et al., 1998). Other studies, which have required subjects to articulate a response to words and word-like stimuli, activate both output (articulatory) processes and input (auditory) processes in response to the sound of the subject’s own articulations (Howard et al., 1992). The assumption is usually made that these processes are engaged in both the activation and control tasks, and ‘subtract out’ the contrast. The second issue involves changes in the standard reference space used by SPM software. Early versions of this software, up to and including SPM95, used templates which would spatially transform, or normalize, individual subject’s data sets into Talairach and Tournoux space, based on their standard atlas from a single post-mortem brain (Talairach and Tournoux, 1988). Later versions (including SPM99) use a different template, occupying a stereotactic space defined by the Montreal Neurological Institute (Evans et al., 1993). Unfortunately, as these two templates differ from each other in non-linear ways, there is no simple correction factor to apply to convert coordinates from one system to the other. The coordinates for the peak voxel in the occipitotemporal junction from this study (–42 –72 –16), correspond approximately to –41 –70 –10 in Talairach and Tournoux space.

There has been a long debate in the psychological literature about which property of a word is most responsible for its recognition (Cattel, 1886; Henderson and Chard, 1980; Besner, 1989; Healy and Cunningham, 1992). In practice, it seems likely that readers use many cues to identify words including word shape, letter composition and syntactic and semantic features of the surrounding prose. Comparisons between viewing real words and pseudowords have failed to identify the left occipitotemporal cortex (Price et al., 1996b). It has been argued that this is because a pseudoword (a pronounceable, legal, non-word such as ‘ultimate’) activates the system responsible for long term lexical memories as it attempts to map the input onto a real word representation (e.g. ‘ultimate’ or ‘estimate’). Tarkiainen and colleagues used magnetoencephalography to investigate the early visual processing of words and letters (Tarkiainen et al., 1999). They embedded their stimuli in increasing amounts of visual noise, such that at the highest level, the stimuli became illegible. They found a signal, ~200 ms after stimulus presentation, at the left occipitotemporal junction, in response to letters, syllables and words, but not geometric symbols. They also found that the level of noise affected the time course and strength of activity in this region and that the level of noise also correlated to the subjects’ RTs. They concluded that this area is not a word-form area per se, but a ‘module’ or complex filter acting as a critical interface between visual and language domains.

Reviews of the functional imaging of early visual processing have noted the discrepancies between studies to date (Price, 1997; Fiez and Peterson, 1998). However, at least six have found a left lateralized response to words at or near the occipitotemporal junction (Petersen et al., 1989; Bookheimer et al., 1995; Nobre et al., 1997; Beauregard et al., 1997; Tarkiainen et al., 1999; Cohen et al., 2000), with little or no activity in the mirror region, with the exception of one study, which demonstrated bilateral signal (Price et al., 1996a). Some studies in which subjects passively viewed words did not demonstrate activation in the left occipitotemporal junction, but implicated another region as the site for ‘word-form processing’. Petersen and colleagues identified the left medial occipital lobe (Petersen et al., 1988; Petersen et al., 1990) and Menard and colleagues, the left angular gyrus (Menard et al., 1996). Notwithstanding these observed, asymmetrical activations, the absence of a more ventral, occipitotemporal activation may have been simply because the scanning field of view in these two experiments was restricted, as neither study reported an activated locus lower than –4 mm in the Z plane. One study observed activations in both the left occipitotemporal and left middle temporal gyrus and concluded that the latter was the site of the visual word form system (Beauregard et al., 1997).

In conclusion, a lesion affecting either primary visual cortex on the left, or its geniculostriate afferents, but sparing
both the left occipitotemporal junction and its connections to the right occipital lobe, will cause hemianopic alexia if right foveal vision is compromised. This latter condition can be confused with pure alexia as the latter may also be associated with a macular-splitting homonymous field defect and both cause a monotonic increase in RTs. Patients with predominantly hemianopic alexia will have only moderate increases in RTs compared with those found in normal subjects, especially for three-letter words that can still be read without having to make one or more saccades within the word. If the lesion either destroys the temporo-occipital junction or its afferents from both left and right visual cortex, pure alexia, associated with greater impairment in single-word reading, will result. The distinction between the pure and hemianopic contributions to the alexic deficit experienced by patients is clinically important as specific rehabilitation programmes now exist which have been shown to speed up reading in patients with hemianopic alexia (Kerkhoff et al., 1992; Leff et al., 2000).

References


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