

The visual word form area

Spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients

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Summary

A standard model of word reading postulates that visual information is initially processed by occipitotemporal areas contralateral to the stimulated hemifield, from whence it is subsequently transferred to the visual word form (VWF) system, a left inferior temporal region specifically devoted to the processing of letter strings. For stimuli displayed in the left visual field, this transfer proceeds from the right to the left hemisphere through the posterior portion of the corpus callosum. In order to characterize the spatial and temporal organization of these processes, reading tasks with split-field presentation were performed by five control subjects and by two patients suffering from left hemialexia following posterior callosal lesions. The subjects' responses were studied using behavioural measures and functional brain imaging techniques, providing both high spatial resolution (functional MRI, fMRI) and high temporal resolution (high-density event-related potentials, ERPs). Early visual processing was revealed as activations contralateral to stimulation, located by fMRI in the inferior occipitotemporal region and presumably coincident with

area V4. A negative wave occurring 150–160 ms post-stimulus, also strictly contralateral to stimulation, was recorded over posterior electrodes. In contrast with these hemifield-dependent effects, the VWF system was revealed as a strictly left-hemispheric activation which, in control subjects, was identical for stimuli presented in the left or in the right hemifield and was located in the middle portion of the left fusiform gyrus. The electrical signature of the VWF system consisted of a unilateral sharp negativity, recorded 180–200 ms post-stimulus over left inferior temporal electrodes. In callosal patients, due to the inability of visual information to pass across the posterior part of the corpus callosum, the VWF system was activated only by stimuli presented in the right visual field. Similarly, a significant influence of the word/non-word status on ERPs recorded over the left hemisphere was discernible for either hemifield in controls, while it affected only right-hemifield stimuli in callosal patients. These findings provide direct support for the main components of the classical model of reading and help specify their timing and cerebral substrates.

Keywords: functional MRI; event-related potentials; reading; corpus callosum; language; area V4; split-brain

Abbreviations: BOLD = blood oxygenation level-dependent; ERPs = event-related potentials; fMRI = functional MRI; LVF = left visual field; RVF = right visual field; SPM = statistical parametric mapping; VWF = visual word form

Introduction

In 1892, Dejerine reported the case of a patient who, following a left inferior occipitotemporal lesion, selectively lost his ability to read letters and words, although his visual field was intact (Dejerine, 1892; Geschwind, 1965). This observation showed that, while each hemisphere is able to process stimuli from the opposite half of the visual world, the reading process requires that visual information reaches language structures uniquely located within the left hemisphere. For right visual

field (RVF) stimuli, which are primarily perceived by the left visual cortex, this process relies exclusively on pathways confined to the left hemisphere. In contrast, left visual field (LVF) stimuli, which are perceived by the right visual cortex, must first transit from the right to the left hemisphere through the splenium of the corpus callosum. Dejerine proposed that a lesion which is sufficient to give rise to pure alexia should affect the left occipitotemporal white matter, interrupting

fibres leading to language areas (particularly to the left angular gyrus) both directly from the left visual cortex and from the right visual cortex via the corpus callosum. As a consequence, pure alexia would affect words irrespective of their location in space (Dejerine, 1892).

This framework was later found to account naturally for the reading deficit associated with posterior callosal lesions. As predicted by the model proposed by Dejerine (Dejerine, 1892), such patients can read normally words presented in their RVF, while words presented in their LVF cannot gain access to the left-hemispheric language systems and cannot be read (Trescher and Ford, 1937; Maspes, 1948; Sugishita *et al.*, 1978; Damasio *et al.*, 1980; Levine and Calvanio, 1980; Sidtis *et al.*, 1981; Abe *et al.*, 1986; Degos *et al.*, 1987; Habib *et al.*, 1990; Cohen and Dehaene, 1996; Suzuki *et al.*, 1998). Along these lines, callosal alexia may be considered as a form of pure alexia limited to the left half of the visual field.

More recent observations and theories have led to a partial revision of the ideas put forward by Dejerine (Dejerine, 1892; Bub *et al.*, 1993). It is now established that the left inferior temporal structures, whose lesion causes pure alexia, do not passively carry information from primary visual areas to the left parietal lobe but play an active role in visual form processing as part of the visual 'what' pathway (Ungerleider and Mishkin, 1982; Binder and Mohr, 1992). The representation of visual words that is ultimately computed by left temporal visual structures may correspond to the so-called visual word form (VWF) and can be conceived of as an ordered string of identified letters or graphemes invariant across changes in spatial location, case, font, type of script, etc. (Warrington and Shallice, 1980; Hillis and Caramazza, 1995). The VWF can then trigger the retrieval of the word's meaning, grammatical features, pronunciation, etc. In this somewhat modernized framework, pure alexia is thought to result from the destruction of the VWF system or from its deprivation of visual input. Similarly, in left callosal alexia, patients are able to build a normal VWF only for words presented in their RVF.

The aim of this study is to explore the main postulates of this now classical view concerning the contribution of the left and right hemispheres to the early phases of reading, with special emphasis on the role of the corpus callosum. We therefore presented word reading and non-word detection tasks to a group of normal controls and to two patients with lesions of the posterior part of their corpus callosum. In order to ascertain the respective contribution of the two hemispheres, we used a tachistoscopic split-field display. The subjects' responses were studied using behavioural measures (error rates and vocal reaction times) and functional brain imaging techniques, providing both high spatial resolution [functional MRI (fMRI)] and high temporal resolution [high-density event-related potentials (ERPs)].

The following set of predictions were made concerning normal subjects. (i) Normal subjects should be able to read both LVF and RVF words with roughly equal accuracy,

possibly with a moderate advantage for RVF stimuli (Grüsser and Landis, 1991). (ii) Initial visual processing should be confined to the hemisphere contralateral to the stimulated hemifield. (iii) Left temporal activations corresponding to the VWF system should be identical for both LVF and RVF stimulation, possibly with an additional short time-lag for LVF stimulation due to callosal transfer. (iv) All subsequent processing should be common to LVF and RVF stimulation; in particular, lexical effects (word/non-word differences) should isolate the same left-hemispheric areas, whether the LVF or RVF is stimulated.

In patients with posterior callosal lesions the predictions differed from those of normal subjects on several points. (i) Patients should show alexia only for words presented in their LVF. (ii) Initial visual processing should normally be lateralized to the hemisphere contralateral to the stimulated hemifield. (iii) Left temporal activations corresponding to the VWF system should be normal for RVF stimuli but absent for LVF stimuli. (iv) All subsequent processing should be normal with RVF stimulation. For LVF stimulation, late activations may eventually involve both left and right hemispheres, depending on (a) the ability of the right hemisphere to identify and understand words; (b) the preservation of anterior callosal connections; and (c) the engagement of appropriate bihemispheric cognitive strategies.

Methods

Subjects

Control subjects

Five right-handed subjects (four women and one man) participated in the study. They were matched to the patients in age (20–30 years), educational level (university) and laterality (all subjects were fully right-handed according to the Edinburgh Inventory). All were drug free, had no neurological or psychiatric history, and had normal anatomical MRIs (Fig. 1). All gave their written informed consent. The experiment was approved by the Ethical Committee of the Hôpital de Bicêtre.

Patients

Patient R.A.V. was a 30-year-old right-handed woman who, following an infarct in the posterior half of her corpus callosum, presented signs of inter-hemispheric disconnection affecting the visual, haptic and auditory modalities (Fig. 1). She was totally unable to read aloud any word presented in her LVF, producing many perseverative responses. No evidence was found for any implicit word identification abilities in her right hemisphere. She responded at chance level in a semantic classification task with LVF words (for a detailed description, see Cohen and Dehaene, 1996, 1998).

Patient A.C. was a 25-year-old right-handed man who, following surgery for a haemorrhage in his left mesial parietal lobe due to a small arteriovenous malformation, presented a

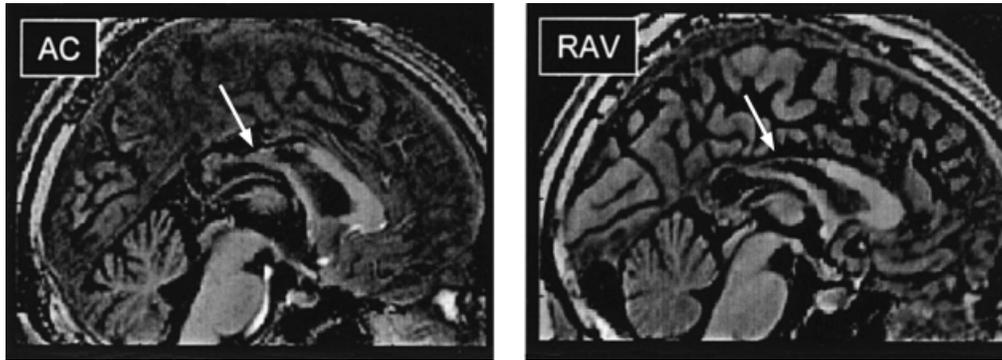


Fig. 1 Sagittal MRI brain sections in two patients (A.C. and R.A.V.) with posterior callosal lesions (white arrows).

split of the posterior half of his corpus callosum (Fig. 1) (for a detailed description, see Michel *et al.*, 1996). Initially, he made 30–80% errors when reading aloud words presented in his LVF. His performance subsequently improved through the use of compensation strategies, although his reading latencies remained very long with LVF stimuli (see Discussion).

Stimuli

Word lists

Stimuli were based on 80 common nouns, four to six letters and one or two syllables in length. All were frequent and highly imageable words (mean \log_{10} frequency/million = 2.04, range 1.55–3.30; mean imageability rating = 4.77, range 4–5) (Content *et al.*, 1990). Words were divided into two lists of 40 words, matched one-to-one in terms of number of letters and syllables. The two lists were also matched in overall frequency and approximately matched in semantic content. Each list was further divided into four sets of 10 words. These sets were matched pairwise. Words belonging to the two sets in a pair were matched one-to-one in number of letters, number of syllables and imageability, and were matched in overall frequency. In summary, we eventually obtained four pairs of matched 10-word sets (sets a and a', b and b', c and c', d and d').

MRI stimuli

For the MRI experiment, each sequence consisted of an alternation of activation periods and rest periods. During activation periods, participants were presented with words flashed either to their RVF or LVF. Four acquisition sequences were derived from the word lists described before.

- (i) rest RVF(a) LVF(a') rest LVF(b) RVF(b') rest
- (ii) rest LVF(c) RVF(c') rest RVF(d) LVF(d') rest
- (iii) rest LVF(a) RVF(a') rest RVF(b) LVF(b') rest
- (iv) rest RVF(c) LVF(c') rest LVF(d) RVF(d') rest

Thus, each word appeared once in the RVF and once in the LVF. Words were shuffled randomly within each set of 10

trials. The same random order was applied to the two sets of 10 words in a pair (a and a', b and b', etc). The four sequences were run with each participant.

ERPs and behavioural stimuli

For the behavioural and ERP experiments, each of the 80 real words was associated with a non-word consisting of a random string of consonants matched in number of letters. We opposed words to consonant strings rather than to pronounceable pseudo-words in order to maximize the ERP differences between these two types of stimuli and therefore to obtain a reliable marker of the onset of lexicality effects. Stimuli were organized in four blocks of 40 items. Each block comprised two paired sets of 10 words, as described before, and their corresponding non-words. Each block was run twice, once with the words from a set in the RVF and the words from the other set in the LVF, and once in the opposite presentation. Stimuli were shuffled randomly within each block of 40 trials.

Procedure

Task parameters

With all testing methods, subjects were asked to fixate a permanent central cross-hair while stimuli were flashed in their right or left visual hemifield. Due to the variable sites at which behavioural and ERP tests were carried out, some unwanted variability was introduced in the display parameters. The mean eccentricity and maximum size of stimuli were, respectively, 4.9° and 6.5° for fMRI, 4.4° and 2.9° for ERPs and 2.6° and 2.5° for behavioural testing.

During behavioural testing, each trial consisted of a 2500 ms blank screen, followed by a 200 ms presentation of the target; the next trial was triggered by the subject's vocal response, with a maximum waiting time of 4000 ms. Subjects were instructed to name real words and to say mentally the word 'RIEN' (nothing) upon seeing non-words. Each fMRI or ERP trial consisted of a 3800 ms blank screen, followed by a 200 ms presentation of the target. Instructions were the

same as for the behavioural task, except that responses were to be uttered mentally.

fMRI

For each task, a series of trials consisted of 20 s of initial fixation, followed by six blocks of 40 s each (two blocks for each of the three conditions of fixation, LVF words or RVF words). Four such series were acquired for each subject. In each, 36 functional volumes sensitive to blood oxygenation level-dependent (BOLD) contrast were acquired with a T₂-weighted gradient-echo, an echo planar imaging sequence on a 1.5 Tesla Signa Imager (General Electric; Milwaukee, Wisc., USA) [TR (repetition time) = 6666 ms, α = 90°, TE (echo time) = 60 ms, field of view = 240 × 240 mm, in-plane resolution = 3.75 × 3.75 mm]. Each volume comprised 13 axial slices of 6 mm thickness covering most of the brain (the cerebellum and the top of the cortex were missed). The first three volumes were discarded to reach signal equilibrium. High-resolution images [3D fast gradient-echo inversion-recovery sequence, TI (inversion time) = 600 ms, TR = 1100 ms, TE = 2 ms, α (flip angle) = 20°, field of view = 240 × 180 mm, slice thickness = 1.2 mm, in-plane resolution = 0.94 × 0.94 mm] were also acquired for anatomical localization.

Functional images were analysed with the Statistical Parametric Mapping software (SPM96). To correct for motion, functional scans were realigned using the last image as a reference. The anatomical image was transformed stereotactically to Talairach coordinates using the standard template of the Montreal Neurological Institute. The functional scans were then normalized using the same transformation. Functional images were smoothed with a Gaussian spatial filter of 5 mm. The resulting images had cubic voxels of 3 × 3 × 3 mm³. Each of the three types of block was modelled by two activation functions corresponding to the early and late components of the BOLD response within a given block. Covariates of non-interest implemented a high-pass filter set at a period of 300 s.

Separate analyses were used for each subject. In addition, we also performed a group analysis pooling the data from the five normal subjects. To identify active areas, the conjunction analysis implemented in SPM96 was first used to identify voxels that were significantly more active during word reading as opposed to fixation, and that did not show a significant difference between RVF and LVF stimulation. We then examined separately the contrasts for activations during either condition relative to fixation. Finally, we searched for activation differences between LVF and RVF stimulation by using direct contrasts between those two conditions. To ensure that those differences reflected activation relative to fixation, those contrasts were masked by the appropriate contrast relative to rest (e.g. the LVF > RVF contrast was masked by the LVF > fixation contrast, $P < 0.05$). Unless otherwise stated, a voxel-wise threshold of 0.001, corrected for multiple comparisons to $P < 0.05$, was used.

ERPs

In a separate session, ERPs were sampled at 125 Hz with a 128-electrode geodesic sensor net reference to the vertex (Tucker, 1993). We rejected trials with voltages exceeding ± 100 μ V, transients exceeding ± 50 μ V or EOG activity exceeding ± 70 μ V. The remaining trials were averaged in synchrony with stimulus onset, digitally transformed to an average reference, band-pass filtered (0.5–20 Hz) and corrected for baseline over a 200-ms window prior to stimulus onset. 2D maps of scalp voltage were constructed by spherical spline interpolation (Perrin *et al.*, 1989). Experimental conditions were compared using sample-by-sample *t*-tests, with a criterion of $P < 0.05$ for five consecutive samples on at least eight electrodes simultaneously. On specific electrodes and windows of interest, ANOVAs (analyses of variance) were also conducted on mean voltage with hemifield (LVF or RVF) and lexicality (word or non-words) as factors, and subjects (in the group analysis of the five controls) or single trials (in analyses of individual patients) as random variables. Electrodes and time-windows were selected as those showing the peak effect for the relevant comparison (e.g. lexicality effect). Due to inter-individual variability, electrodes and peak times could differ slightly across subjects. We therefore verified that the effect of interest was found on several neighbouring electrodes and time samples.

Results

Normal subjects

Behavioural results

Control subjects made an average of 21.3% errors when reading aloud real words and 1.0% errors when detecting consonant strings. There was an overall RVF advantage for word reading [16.7% versus 25.8% errors, $\chi^2(1) = 6.03$, $P = 0.014$]. Trials with failures of the voice key or with reaction times longer than 4 s were excluded from the reaction time analysis (10.4%). A moderate RVF advantage was observed (Fig. 2). Controls were 89 ms faster reading RVF than LVF words [712 ms versus 800 ms, respectively; $F(1,4) = 4.5$, $P = 0.10$] and 17 ms faster detecting RVF than LVF non-words [739 ms versus 722 ms, respectively; $F(1,4) = 3.7$, $P = 0.13$].

fMRI

Activations independent of hemifield. We first consider the fMRI activations which were common to LVF and RVF words. As shown in Fig. 3, a large network comprising left inferior temporal, bilateral parietal, bilateral prefrontal and mesial frontal regions was seen (Table 1). In particular, a highly significant activation was observed in the left fusiform gyrus (Talairach coordinates: $x = -42$, $y = -57$, $z = -6$, $Z = 8.49$). This activation was strictly unilateral. Even at a lower threshold of $P < 0.01$, uncorrected, no similar activation appeared in the right inferior occipitotemporal cortex.

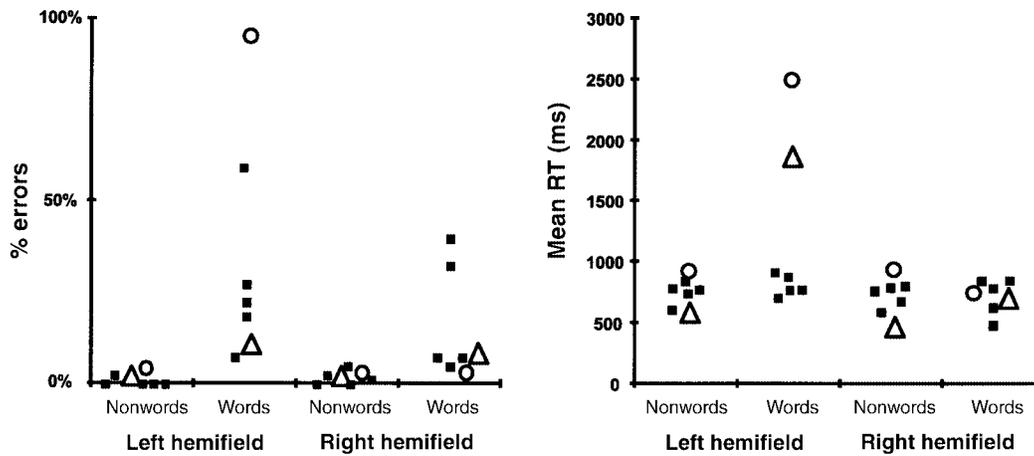


Fig. 2 Rate of errors and mean vocal reaction times for control subjects (solid squares), patient A.C. (triangles) and patient R.A.V. (circles). Both patients were slower or more error-prone than controls when attempting to name words presented in their LVF.

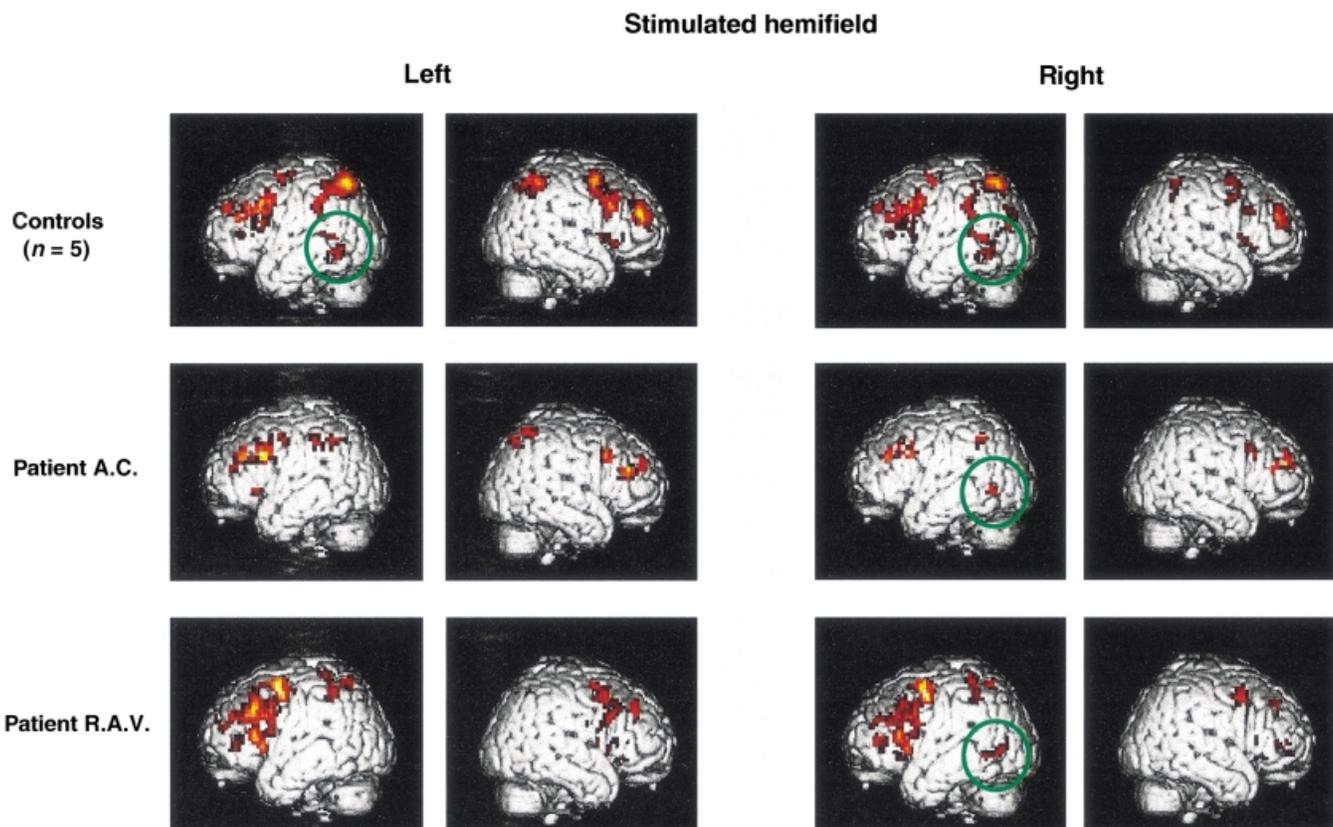


Fig. 3 Global view of the cerebral network activated during LVF or RVF word reading relative to rest. In control subjects, a left fusiform region was activated irrespective of the stimulated hemifield, while it was activated only by RVF stimulation in callosal patients (green circles).

We then attempted to identify this hemifield-independent left fusiform activation in each subject. Because this area is relatively small, we used a stringent voxel-wise threshold of 0.0001 so that even a relatively small cluster of active voxels might achieve a corrected level of significance of $P < 0.05$. In four subjects, the conjunction of activations in LVF and

RVF conditions isolated a highly significant activation close to the peak activation in the group analysis (Fig. 4 and Table 2). The fifth subject showed no detectable activation in this area either in the conjunction of RVF and LVF, or in separate tests for RVF versus rest and LVF versus rest. However, at an uncorrected level of significance of $P < 0.001$, a cluster

of four voxels was observed in the conjunction analysis (Table 2). Higher variance may have prevented the emergence of a more significant cluster in this subject.

Activations dependent on hemifield. Finally, we examined which areas showed differential activation depending on the stimulated hemifield. In single-subject analyses few differences were found, probably due to lack of statistical power given the low rate of stimulation (one stimulus lasting 200 ms every 4 s). As expected in the group analysis, however, based on the known cross-over of visual pathways, two left extrastriate occipital areas were significantly more activated by RVF than by LVF words (Talairach coordinates: $x = -21, y = -72, z = -6, Z = 6.79$; $x = -24, y = -81, z = 24, Z = 7.49$) (Fig. 5). Conversely, one right extrastriate occipital area was significantly more activated by LVF than by RVF words (Talairach coordinates: $x = 30, y = -69, z = -12, Z = 7.99$). Comparison with published coordinates of extrastriate retinotopic areas in normal subjects suggests that these activations probably correspond to area V4 (see Discussion). Smaller activation differences were also seen in favour of the RVF in the posterior right caudate, bilateral cingulate and right postcentral gyri, and in favour of the LVF in the right posterior parietal cortex, right cingulate and right inferior frontal gyri. Some of these activations may correspond to an attentional network involved in orienting attention to the contralateral hemifield.

ERPs

The first detectable electrical event was the P1, which peaked at 136 ms for LVF stimuli and at 120 ms for RVF stimuli. The P1 topography clearly differed for LVF and RVF stimulation, though in both cases the peak voltage was observed over left electrodes, as described previously ('paradoxical lateralization' of P1; Brigell *et al.*, 1993). By 150–160 ms post-stimulus, the N1 waveform was clearly visible as a sharp posterior negativity strictly contralateral to the stimulated hemifield (Fig. 6, upper row). An ANOVA was performed on voltages averaged over a 24 ms time-window covering the onset of the N1 (144–168 ms). On the left inferior temporal electrode where the N1 peaked, voltages were significantly more negative for RVF than for LVF stimuli [$F(1,4) = 9.67, P = 0.02$, one-tailed]. On the symmetrical right inferior temporal electrode, a symmetrical pattern was observed [$F(1,4) = 7.79, P = 0.025$, one-tailed]. At this time, there was no difference between words and non-words on either electrode ($P > 0.6$, for both) nor any interaction of this lexicality factor with hemifield ($P > 0.6$, for both).

By 180–200 ms the waveforms became highly similar for LVF and RVF stimulation. Both types of stimuli evoked a left temporal negativity accompanied by a diffuse anterior positivity (Fig. 6, second row). An ANOVA on the same left temporal electrode as above, with voltages averaged over a 24 ms time-window surrounding the N1 peak (200–224 ms), showed a main negativity with no effect of hemifield

Table 1 Significant activations in control subjects in the conjunction of LVF and RVF words relative to rest

Anatomical region	Talairach coordinates			Z-score
	x	y	z	
Left dorsolateral prefrontal	-39	15	30	8.19
	-36	48	33	8.10
Right dorsolateral prefrontal	42	45	27	7.63
	45	6	57	6.93
Superior frontal gyrus (mesial part)	0	9	54	8.80
Right inferior frontal gyrus/anterior insula	30	33	6	5.27
Right inferior frontal gyrus	51	21	0	5.84
Left precentral sulcus	-33	-3	57	5.95
Left superior parietal lobule	-30	-63	57	9.05
Right inferior parietal lobule	39	-51	42	7.88
Left inferior parietal lobule	-51	-39	57	6.99
Left middle temporal gyrus	-57	-54	6	5.34
Left fusiform gyrus	-42	-57	-6	8.49
Left precuneus	-27	-57	21	5.56

Voxel-wise threshold of $P < 0.001$, corrected for multiple comparisons to $P < 0.05$; only main peaks are listed.

Fig. 4 Individual mapping on coronal MRI sections of left inferior temporal activations during LVF or RVF word reading relative to rest. Curves represent the variations of the BOLD signal of this cluster in a conjunction analysis (LVF and RVF versus rest). In controls there was a signal increase during both LVF (L) and RVF (R) stimulation relative to rest (-). In patients an increase was observed only during RVF stimulation.

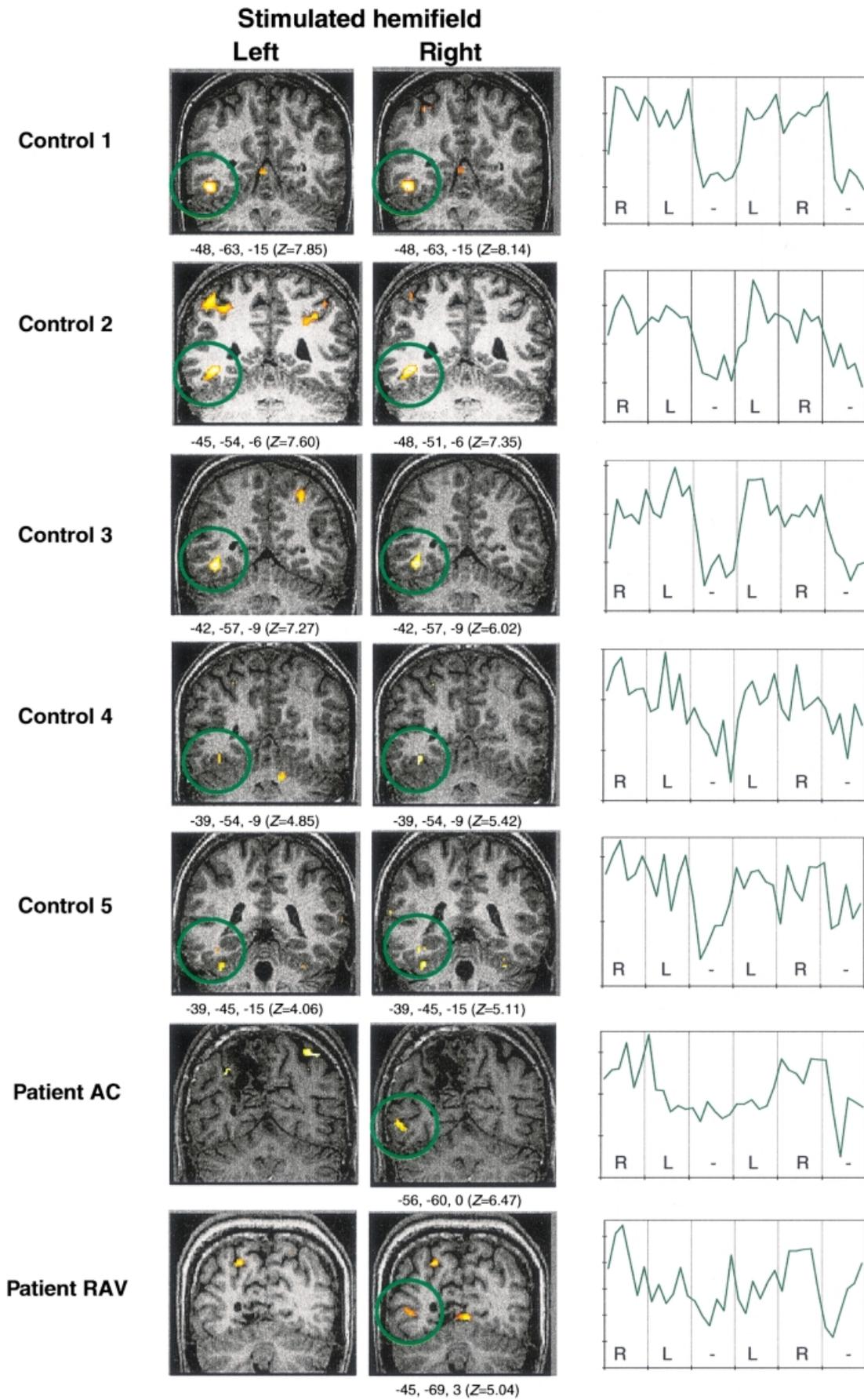


Table 2 Individual left fusiform activations observed in control subjects in the conjunction of LVF and RVF words relative to rest, and in the two patients in the comparison of RVF words versus rest and versus LVF words

	Talairach coordinates			Z-score	No. of voxels
	x	y	z		
Controls					
1	-48	-63	-15	9.12	57
2	-45	-51	-6	8.40	38
3	-42	-57	-9	7.58	44
4	-39	-54	-15	7.70	11
5	-39	-45	-15	5.23	4
Average of five controls	-43	-54	-12		
SD	3.9	6.7	4.2		
Patient A.C.					
RVF versus rest	-56	-60	0	5.35	5
RVF versus LVF	-44	-64	-4	6.93	16
Patient R.A.V.					
RVF versus rest	-48	-60	-3	5.49	31
RVF versus LVF	-48	-54	0	5.86	13
	-39	-66	3	4.17	12

Voxel-wise threshold of $P < 0.0001$, corrected for multiple comparisons to $P < 0.05$; for control 5, $P < 0.001$, uncorrected.

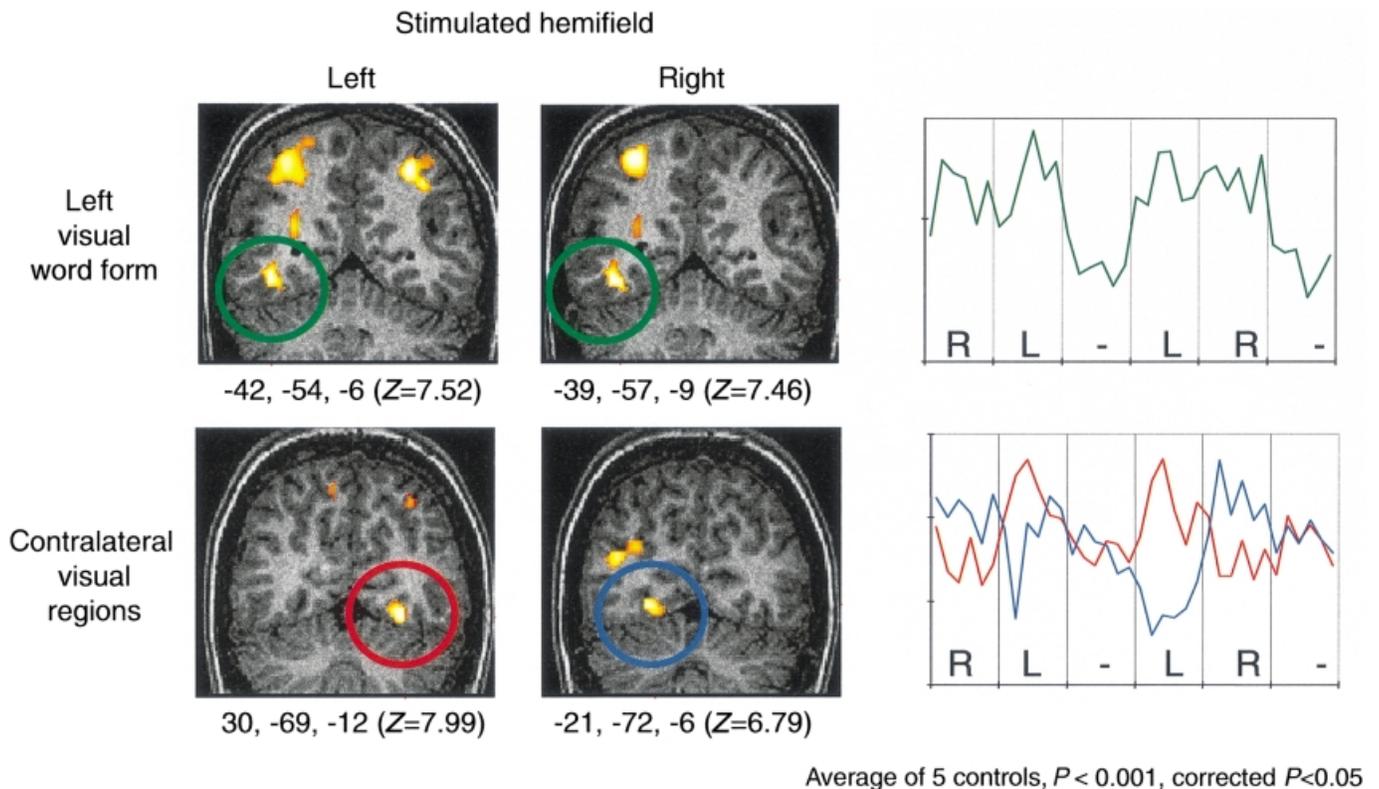


Fig. 5 Occipitotemporal activations during word reading in control subjects, mapped on coronal MRI sections, with the corresponding BOLD curves. *Upper panel:* left fusiform activation independent of the stimulated hemifield and presumably corresponding to the visual form system (green circles). BOLD curves show a similar activity level for words presented in either hemifield. *Lower panel:* mesial occipitotemporal activations contralateral to the stimulated hemifield and presumably corresponding to area V4 (blue and red circles). BOLD curves show a crossover of activity depending on the stimulated hemifield.

$[F(1,4) = 0.96, P = 0.4]$ or any difference between words and non-words $[F(1,4) = 0.85, P = 0.4]$. These two factors interacted $[F(1,4) = 9.21, P = 0.04]$, however, suggesting

that this was still a transition period during which hemifield effects waned while lexical effects began to emerge. From this point on, ERPs to LVF and RVF stimuli became virtually

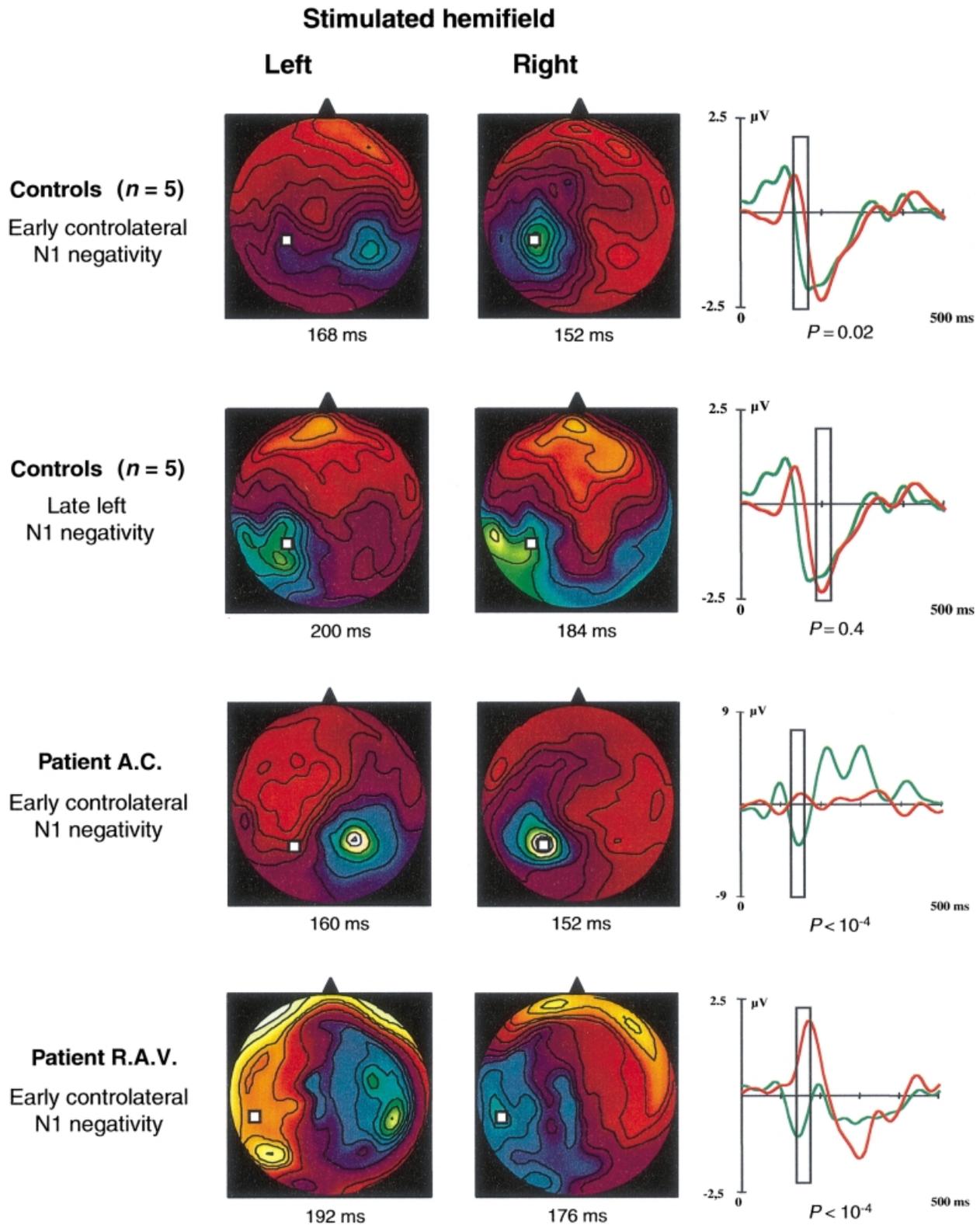


Fig. 6 Topography of the N1 wave and average potentials recorded on a left temporal electrode (white square) in control subjects and callosal patients following RVF stimulation (green curves) or LVF stimulation (red curves). ANOVAs were performed on voltages averaged over 24 ms time-windows covering the onset or the peak of the N1 (rectangles). In controls and patients the early portion of the N1 consisted of a sharp posterior negativity strictly contralateral to the stimulated hemifield. In controls LVF and RVF stimuli then evoked an identical left temporal negativity, presumably corresponding to the VWF system. Note that the initial divergence of LVF and RVF stimuli seen prior to the N1 in controls and patient A.C. is not due to noise, but reflects the differing topography of the P1 waveforms.

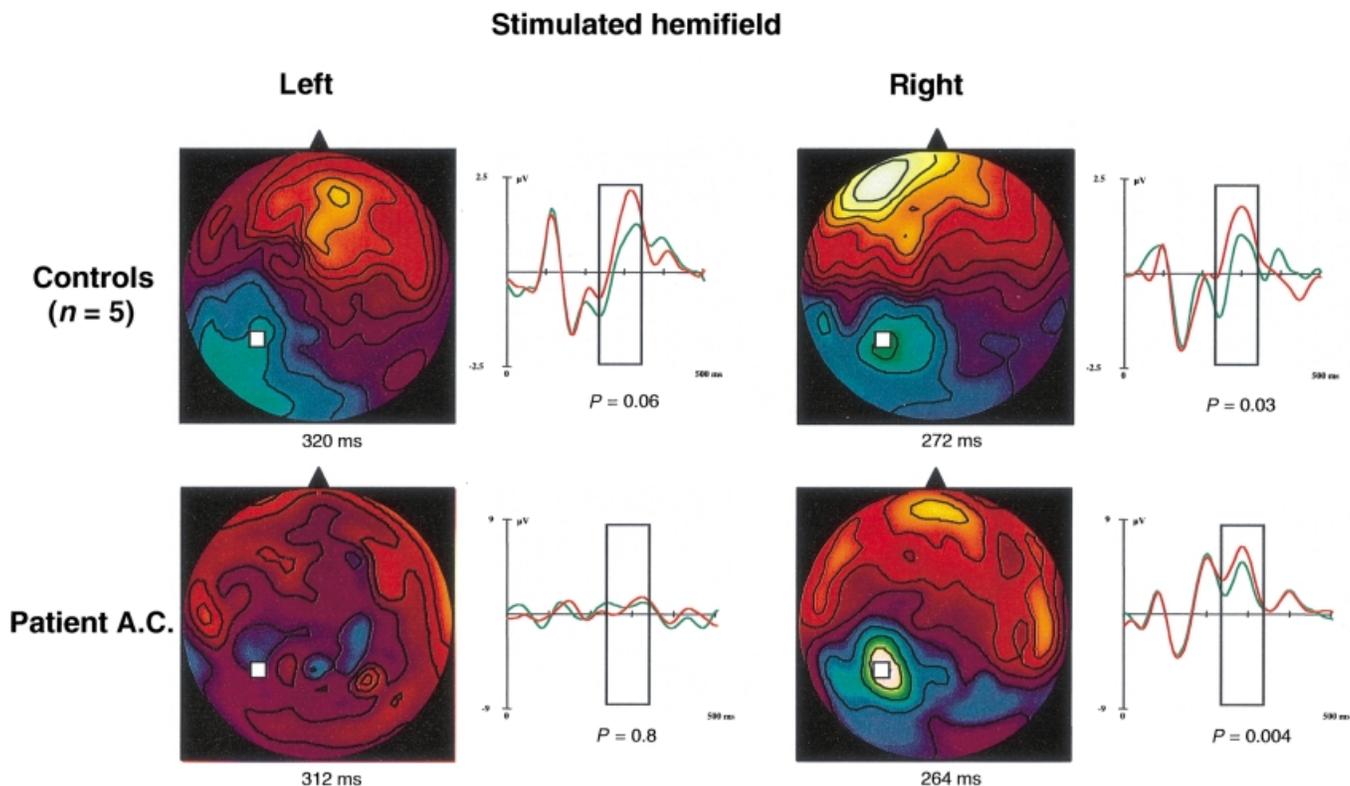


Fig. 7 Topography of the subtracted ERPs to words and non-words, and average potentials recorded on a left temporal electrode (white square) in control subjects and patient A.C. ANOVAs were performed on voltages averaged over a 240–360 ms time-window (rectangles). In controls word stimuli (green curves) elicited a prolonged left temporal negativity relative to non-words (red curves), irrespective of the stimulated hemifield, but only following RVF stimulation in patient A.C.

indistinguishable, both in their topography and in their latency, suggesting identical processing, while word/non-word status acquired a significant impact.

Examination of the topography of the subtracted ERPs to words and non-words as a function of time revealed a major difference starting at around 200 ms post-stimulus. As expected from previous publications (e.g. Dehaene, 1995, and references therein), relative to non-words, word stimuli elicited a prolonged left temporal negativity accompanied by a diffuse anterior positivity (Fig. 7, upper panel). An ANOVA on left temporal voltages averaged from 240 to 360 ms and revealed a main difference between words and non-words [$F(1,4) = 5.11$, $P = 0.04$, one-tailed], with no hemifield effect [$F(1,4) = 0.27$, $P = 0.6$] and no interaction [$F(1,4) = 1.66$, $P = 0.27$]. The word/non-word difference showed the same topography whether the stimuli were presented in the LVF or the RVF, suggesting convergent processing within the left temporal lobe.

Callosal patients

Behavioural results

Patient A.C. made few errors, with no significant difference in error rate between RVF and LVF stimuli (seven errors out of 160 stimuli, nine errors out of 160 stimuli, respectively). All errors but two affected real words and generally consisted

of the production of a visually related word. However, the patient claimed that he actually did not see the stimuli but rather mental pictures corresponding to the meaning of words, which he then named reasonably easily. Naming latencies objectively reflected this anomalous, albeit successful, naming process. Trials with failures of the voice key or with reaction times longer than 4 s were excluded from reaction time analysis (10.9%). With RVF stimuli, the mean reaction time for A.C. was 714 ms for words and 502 ms for non-words. With LVF stimuli, the mean reaction time was 1800 ms for words and 512 ms for non-words. Thus, while there was no significant latency difference between hemifields for detecting non-words [$F(1,147) < 1$], there was a 1086 ms difference for reading aloud real words [$F(1,134) = 114.6$, $P < 0.001$] (see Fig. 2).

Like patient A.C., patient R.A.V. made few errors with RVF stimuli (four errors out of 160 stimuli) and could accurately detect non-words presented in her LVF (3 errors out of 180 stimuli). However, she was unable to read real words presented in her LVF (76 errors out of 80 stimuli). As reported previously, her errors generally consisted of words unrelated to the stimuli, with numerous perseverations (Cohen and Dehaene, 1996, 1998). Fifteen per cent of trials were excluded from reaction time analysis. With RVF stimuli the mean reaction time for R.A.V. was 786 ms for words and 897 ms for non-words. With LVF stimuli, the mean reaction

time was 2160 ms for words and 943 ms for non-words. Thus, while there was no significant latency difference between hemifields for detecting non-words [$F(1,139) < 1$], there was a 1374 ms difference for reading aloud real words [$F(1,129) = 122.3, P < 0.0001$] (Fig. 2).

In summary, both patients behaved as reported in previous studies in which they had participated: (i) A.C. and R.A.V. could process normally words and non-words presented in their RVF; (ii) A.C. and R.A.V. could accurately discriminate words from consonant strings in their LVF; (iii) A.C. managed to read accurately frequent and concrete words presented in his LVF, but apparently resorted to slow semantic strategies; (iv) R.A.V. showed no evidence of recognizing words presented in her LVF; (v) for both patients, response latencies were much slower than normal only for real words presented in their LVF (Fig. 2).

fMRI

In patient A.C., the conjunction of LVF and RVF conditions identified bilateral dorsolateral, prefrontal and left parietal activations. In patient R.A.V., the same conjunction yielded a large network of active areas including bilateral caudate, bilateral precentral and inferior frontal, left dorsolateral prefrontal, anterior cingulate and left parietal cortices. These activations were essentially identical to those observed in normal subjects. The only striking difference was the absence of the left fusiform activation which was seen in the controls. Even using the threshold of 0.0001, corrected for multiple comparisons to $P < 0.05$, which was applied in the individual analysis of control subjects, no significant left fusiform activity common to RVF and LVF was found.

We then analysed separately the LVF and RVF conditions. The analysis of the RVF condition relative to rest, with the same thresholds, yielded a clear activation of the left fusiform area, with peak coordinates comparable to those found in normal subjects (Table 1). Patients differed from controls in that this activation was absent in the LVF condition relative to rest (Figs 3 and 4). This resulted in a significantly greater activation for RVF than for LVF stimulation in this region in both patients (Table 1). We interpret this pattern of activation as a failure of LVF words to activate the left VWF area, which was still normally activated by RVF words. Note that it seems highly unlikely that this region could be considered as a normal retinotopic area, because no significant hemifield effect was found in such a lateral and anterior position in any of the controls (Fig. 5).

Finally, we examined the differences between LVF and RVF conditions in other brain areas. Aside from the above left fusiform region, no area showed greater activation for RVF than for LVF stimulation in either patient. Conversely, however, in both patients, LVF stimulation yielded greater activation in bilateral precentral, dorsolateral prefrontal and cingulate areas as well as in the right posterior parietal region (with an additional symmetrical left parietal focus in patient R.A.V.). Part of this network was also observed in the controls

and may be associated with attention to contralateral stimuli. However, the significant increase in left precentral and prefrontal activation associated with LVF words was unique to patients (Fig. 3) and may have reflected the slow and effortful search for a verbal response that was observed behaviourally in this condition.

ERPs

The first detectable electrical event, the P1, peaked for LVF stimuli at 128 ms and for RVF stimuli at 104 ms in patient A.C. In patient R.A.V., ERP recordings were more noisy and the P1 could not be unequivocally detected. The N1, however, was observed in both patients as a posterior negativity strictly contralateral to the stimulated hemifield (Fig. 6, lower two rows). On the left temporal electrode where the N1 peaked, voltages were significantly more negative for RVF than for LVF stimuli [A.C., $F(1,188) = 26.9, P < 0.0001$; R.A.V., $F(1,188) = 65.4, P < 0.0001$]. On the symmetrical right inferior temporal electrode, a symmetrical pattern was observed [A.C., $F(1,189) = 17.8, P < 0.0001$; R.A.V., $F(1,188) = 138.9, P < 0.0001$]. At this time, there was no difference between words and non-words on either electrode ($P > 0.3$, for both), or any interaction of the lexicality factor with hemifield ($P > 0.6$, for both). Hence, the characteristics of the early N1 were highly comparable between the patients and the controls.

Contrary to the controls, however, both patients showed a prolonged influence of the hemifield of stimulation on ERP recordings, which persisted throughout the epoch. On the same time-window (180–200 ms) in which the controls showed a converging left temporal negativity to LVF and RVF stimuli, both patients showed highly significant hemifield differences [R.A.V., $F(1,188) = 8.09, P = 0.004$; A.C., $F(1,185) = 135.9, P < 0.0001$]. In patient R.A.V. this was essentially due to long-lasting negativities contralateral to the stimulated hemifield, following which no clear electrical events could be picked out. In patient A.C., with LVF stimuli, the left N1 was immediately followed by an intense left temporoparietal positivity which was not seen for RVF stimuli. A complex sequence of electrical events ensued, which remained highly different for LVF and RVF stimuli up until about 620 ms. At this time, a similar pattern of left dorsal frontal negativity was observed irrespective of the stimulated hemifield.

In patient A.C. the effects of lexicality on ERPs closely replicated those observed in the controls, but only when stimuli were presented in the RVF (Fig. 7, lower panel). Thus, left temporal voltages were more negative for RVF words than for RVF non-words [$F(1,96) = 8.46, P = 0.004$], but there was no such difference with LVF stimuli ($P = 0.8$). This resulted in a marginally significant interaction between hemifield and lexicality ($P = 0.06$). Due to the noise in the recordings for patient R.A.V., no significant lexicality effects were observed.

Discussion

The standard model of word reading, which dates back to Dejerine (Dejerine, 1892), postulates that a single, left-lateralized word identification process is used to read words presented either in the left or in the right hemifield. This implies that visual information, which is initially confined to the hemisphere contralateral to the stimulated hemifield, must be transferred towards the left inferior temporal region. For LVF stimuli, this transfer requires an intact callosal splenium. Our experiments assessed this model using behavioural, fMRI and ERP techniques in five normal subjects and in two patients with posterior callosal lesions. In this discussion we first examine the four main predictions derived from the model concerning normal subjects and then turn to the points on which patients differed from the normal pattern.

Anatomy of reading in normal subjects

A first, behavioural prediction was that normal subjects should be able to read words in both hemifields, though possibly with some degree of RVF advantage. Indeed, a behavioural RVF advantage was observed in both error rates and response latencies. In the literature, a similar RVF advantage for the processing of verbal material has been obtained using a variety of experimental methods (for review, see Grüsser and Landis, 1991). It is generally thought to reflect, more or less directly, the left-hemispheric dominance for language. In order to reach the left hemisphere, LVF stimuli must follow a less direct, and hence longer and more noisy pathway than RVF stimuli. It has also been suggested that an attentional bias towards the RVF, induced by the performance of verbal tasks, may contribute to the behavioural asymmetry (Kinsbourne, 1970). The current results, by revealing the direct versus transcallosal pathways to the left-hemispheric reading system, largely support the first interpretation, although additional attentional factors cannot be ruled out.

A second prediction was that initial processing should be confined to early visual areas contralateral to the stimulated hemifield. Indeed, the first 160 ms of ERPs were dominated by hemifield-dependent events, the P1 and the early portion of the N1. The topography of the early N1 was strictly contralateral to stimulation. fMRI also revealed tightly localized activations contralateral to stimulation in the posterior and mesial occipitotemporal region. These activations were too weak to appear in individual analyses, presumably because of the low rate of stimulus presentation (200 ms stimulation every 4 s). Nevertheless, they were clearly apparent in the group analysis. A comparison with published coordinates from a number of previous PET and fMRI studies of early visual processing suggests that they coincide with area V4 (see Fig. 8, left panel) (Zeki *et al.*, 1991; DeYoe *et al.*, 1996; McKeefry and Zeki, 1997; Hadjikhani *et al.*, 1998; Hasnain *et al.*, 1998; Howard *et al.*, 1998; Zeki and Marini, 1998). This area is known from

electrophysiological and lesion studies in animals to contribute to colour and form vision (DeYoe and Van Essen, 1988; Schiller and Lee, 1991). In humans, lesions of V4 have been claimed to yield concomitant impairments of colour and shape processing (Rizzo *et al.*, 1992). ERP studies of V4 activation timing in humans yield figures in a range of 120–170 ms post-stimulus (Allison *et al.*, 1993; Plendl *et al.*, 1993; Buchner *et al.*, 1994; Lange *et al.*, 1998), which agrees well with our early N1. It is likely that the lack of measurable activation in primary visual areas contralateral to stimulation resulted from the low rate and short duration of stimulation. Indeed, the timing of neuronal activity reflects more directly stimulus duration in primary visual areas than in areas involved in later stages of visual processing (e.g. Rolls and Tovee, 1994). At this stage, letter strings are still processed by two distinct systems, each devoted to one hemifield, and have not yet reached a location-invariant processing stage.

A third prediction was that such a common processing stage is achieved later on in the left inferior temporal lobe and following callosal transfer for LVF stimuli. In agreement with this expectation ERPs elicited by LVF and RVF stimuli converged to a statistically indistinguishable topography with a sharp negativity over left inferior temporal electrodes, by 180–200 ms post-stimulus. In fMRI, all normal subjects showed an activation common to RVF and LVF stimuli in the middle portion of the left fusiform gyrus. We propose that this activation corresponds to the VWF system. Anatomically, this activation was generally located within the depth of the sulcus which marks the boundary between the fusiform gyrus and the inferior temporal gyrus, clearly anterior and lateral to area V4. This region coincides with the critical lesion site causing pure alexia, a neuropsychological deficit which is thought to reflect the breakdown of the VWF system (Dejerine, 1892; Damasio and Damasio, 1983; Binder and Mohr, 1992; Cohen and Dehaene, 1995; Beversdorf *et al.*, 1997). Its Talairach coordinates fit well with several previous studies of word reading, which are summarized in Fig. 8 (right panel). For instance, Beauregard and colleagues using PET (Beauregard *et al.*, 1997) and Wagner and colleagues and Puce and colleagues using fMRI (Puce *et al.*, 1996; Wagner *et al.*, 1998) observed activation peaks in this area when subjects were presented with words or letter strings relative to fixation and/or to non-word stimuli. An even more direct study by Nobre and colleagues used intracranial electrical recordings to isolate specific electrode sites where activity was specifically elicited by word stimuli (Nobre *et al.*, 1994). Their results are in excellent agreement with ours in two respects. First, the coordinates that they report fall within the range of the individual peaks that we observed. Secondly, they report that words elicit a sharp negativity with a peak latency near 200 ms, which coincides with the latency of our scalp-recorded hemifield-independent negativity. Recently, results similar in terms of both timing and anatomical location were obtained in normal subjects using magnetoencephalography (Salmelin *et al.*, 1996).

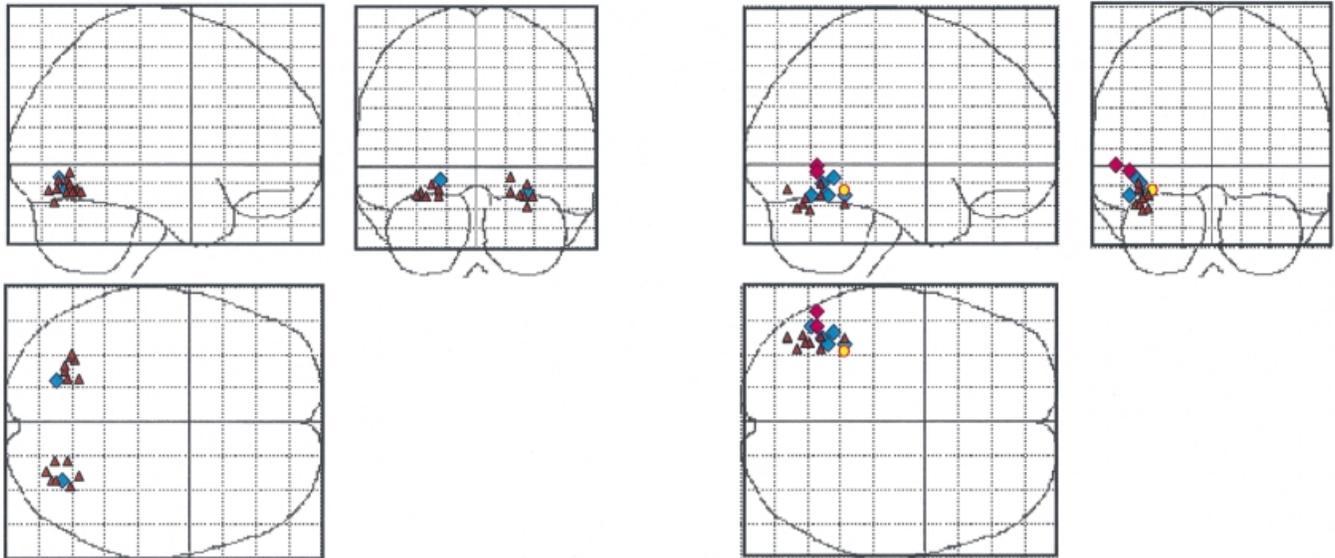


Fig. 8 Glass brain plots in Talairach space of activations observed in the present study and of comparable activations reported in the literature. *Left panel*: mesial extrastriate activations contralateral to the stimulated hemifield obtained in the present study (blue diamonds) and area V4 as localized in previous studies (red triangles) (Zeki *et al.*, 1991; McKeefry and Zeki, 1997; Hadjikhani *et al.*, 1998; Hasnain *et al.*, 1998; Howard *et al.*, 1998; Zeki and Marini, 1998). *Right panel*: left fusiform activations, presumably corresponding to the VWF system, obtained in the present study (controls: blue diamonds, patients: pink diamonds), and in previous studies using PET and fMRI (red triangles) (Puce *et al.*, 1996; Beauregard *et al.*, 1997; Wagner *et al.*, 1998) and using intracranial electrical recording (yellow circle) (Nobre *et al.*, 1994).

In spite of these converging results, the localization of the VWF has been the matter of some controversy which the present results may partially resolve. In original studies by Petersen and colleagues, contrasting words or pseudo-words with fixation or with false-font stimuli resulted in mesial extrastriate activations (Petersen *et al.*, 1988, 1990; see also Bookheimer *et al.*, 1995). Hasnain and colleagues reported similarly located activations which, following Petersen and colleagues, they also labelled as ‘visual word form’. However, they did not actually use word stimuli, but only random dot patterns (Hasnain *et al.*, 1998), and their study therefore suggests that this visual activation is not specifically related to word processing, though its exact contribution to visual processing is unknown. In Talairach space, these activations appear much more mesial and superior than ours and we found no activation peaks in the close vicinity of activations noted by Petersen and colleagues (Petersen *et al.*, 1988, 1990).

A second set of studies localized the VWF to the left lateral posterior temporal lobe (Howard *et al.*, 1992; Price *et al.*, 1994; Vandenberghe *et al.*, 1996; Gorno Tempini *et al.*, 1998). We also observed a significant activation common to LVF and RVF words in this region (see Table 1). However, two arguments make this region an unlikely candidate for the VWF system. First, it is now known to be active in a variety of linguistic tasks that do not involve word reading, including auditory processing of single words (Price *et al.*, 1996; Chee *et al.*, 1999) and story listening (Perani *et al.*, 1996; Dehaene *et al.*, 1997). Secondly, it clearly falls outside of the critical lesion site causing pure alexia (Dejerine, 1892; Damasio and Damasio, 1983; Binder and Mohr, 1992; Cohen

and Dehaene, 1995; Beversdorf *et al.*, 1997). Rather, lesions of the left posterior temporal lobe are associated with Wernicke’s aphasia and/or with alexia with agraphia. Hence, as acknowledged ever since Dejerine (Dejerine, 1892), this region is likely to play an important role in later stages of the reading process. This idea received recent support from the demonstration of a strong correlation of activity between this region and the left fusiform gyrus during reading (Horwitz *et al.*, 1998). In summary, this posterior lateral temporoparietal region may be associated with phonological and/or semantic word processing, but not with a strictly visual function (for reviews, see Price, 1997, 1998). We suggest that the term VWF system should be reserved for the actual visual area of the left ventral temporal lobe which is activated by letter strings more than by other types of visual stimuli.

A fourth prediction of the standard model of word reading was that all processing stages that follow the computation of the VWF should be identical, irrespective of the stimulated hemifield. Both fMRI and ERP results confirmed this prediction. Most of the activations observed with fMRI were common to LVF and RVF stimuli. These activations constituted a bilateral frontoparietotemporal network of cerebral areas with left-sided predominance (Fig. 3). Some of the activations, mainly in the left temporal and left precentral regions, may correspond to components of the language comprehension and production processes that are engaged during reading. Others, including the bilateral, dorsolateral and mesial prefrontal, and bilateral parietal regions, may be related to the orientation of attention to peripheral visual stimuli (Nobre *et al.*, 1997). Similarly, ERPs

to LVF and RVF stimuli were statistically indistinguishable beyond the first 200 ms. In particular, the differences between words and non-words were identical whether the stimuli were presented in the LVF or in the RVF. In both cases, ERPs to real words showed a long-lasting left temporal negativity relative to random letter strings. The onset of this effect (~200–240 ms) is compatible with previous ERP studies (e.g. Dehaene, 1995) and indicates that by that time, a left-lateralized processing system specific to real words is being accessed. Although we did not compare words with non-words in fMRI, the topography of this ERP effect is compatible with an activation of the left lateral temporoparietal region common to LVF and RVF words (discussed above) and presumably associated with phonological and/or semantic processing.

We expected that left-hemispheric activations elicited by LVF stimuli should be slightly delayed relative to those elicited by RVF stimuli, due to the additional callosal transfer. Our ERP recordings, however, did not provide clear evidence for this effect. Other ERP studies suggest that this effect should be in the order of 10–15 ms (Brown *et al.*, 1998). Our recording parameters (digitizing at 125 Hz and low-pass filtering at 20 Hz) might have been suboptimal to detect such a small delay.

Reading in callosal patients

The behavioural and brain-imaging data acquired in the two callosal patients departed from the normal pattern in two closely related respects, which were predictable from the classical model of word reading by Dejerine (Dejerine, 1892): (i) at the behavioural level, patients were impaired at reading LVF words; and (ii) brain imaging data revealed that the VWF system was activated by RVF words but not by LVF words.

Both patients showed an impaired reading of LVF words, contrasting with a perfectly normal performance with RVF words. This is a direct consequence of the inability of visual stimuli initially perceived by the right hemisphere to reach the left-hemispheric VWF system through the splenium of the corpus callosum. However, the precise pattern of reading impairment differed between the two patients. Patient R.A.V. was unable to read correctly a single LVF word, as would be expected in the standard framework, which postulates that the right hemisphere does not possess, by itself, any word identification abilities. In contrast, patient A.C. did not make more errors than control subjects. However, his reading of LVF words was exceedingly slow and his verbally reported introspection confirmed that reading did not follow a normal process. In their initial study of patient A.C., Michel and colleagues (Michel *et al.*, 1996) reported that, when attempting to read aloud words presented in his LVF, he made 30–80% errors and showed classical features of deep dyslexia. In particular, he performed better with concrete words than with abstract or grammatical words and was virtually unable to read aloud any non-words. He also often

resorted to semantic approaches and actually made frequent semantic errors. The reading accuracy of A.C. improved progressively following the initial study. However, while his error rate decreased over time, it still took him several seconds of effort to read aloud familiar LVF words. It was proposed that A.C., just like the posterior split patient reported by Sidtis and colleagues (Sidtis *et al.*, 1981), could understand some familiar LVF words with his right hemisphere and then transferred semantic information from his right to his left hemisphere through the intact anterior portion of his corpus callosum. At the time of the present study this indirect procedure allowed patient A.C. to name accurately the frequent and concrete words that were used as stimuli (see also Habib *et al.*, 1990). Thus, in spite of the idiosyncratic compensation strategy used by A.C., both patients showed left hemialexia, as is invariably observed following posterior callosal lesions (Trescher and Ford, 1937; Maspes, 1948; Sugishita *et al.*, 1978; Damasio *et al.*, 1980; Levine and Calvanio, 1980; Sidtis *et al.*, 1981; Abe *et al.*, 1986; Degos *et al.*, 1987; Habib *et al.*, 1990; Cohen and Dehaene, 1996; Suzuki *et al.*, 1998).

One should note that despite their left hemialexia, patients A.C. and R.A.V. were as proficient as control subjects at detecting non-words presented in their LVF. It should be noted that the task of detecting non-words differs in important respects from the task of reading aloud real words. The non-words that were used here consisted of consonant strings incompatible with the orthographic principles of the French writing system and which are impossible to translate into phonology. Actually, each and every non-word comprised numerous redundant violations of such orthographic principles. There is some independent evidence that detecting non-words, a task which does not require a full-blown lexical system, but may rely on visual familiarity, is in the grasp of the right hemisphere. Thus, complete split-brain patients have been shown to perform accurately in lexical decision tasks with stimuli displayed in their LVF (e.g. Sergent, 1987). The role of the right hemisphere has also been advocated to account for the observation that some pure alexic patients, despite their complete inability to read aloud words, can still accurately and rapidly detect non-words (Coslett and Saffran, 1989; Coslett *et al.*, 1993; Bub and Arguin, 1995). However, we can provide no evidence relevant to this issue; exploring the cerebral mechanisms of non-word processing per se was not in the scope of the present study and our fMRI experiment did not even include non-word stimuli.

In brief, we suggest that the patients' behavioural deficit was related to the fact that they differed from controls in the pattern of activation of their VWF system. In controls, a left inferior temporal activation was elicited identically by LVF and RVF words, both with fMRI and with ERPs. In patients, this activation was observed only with RVF stimulation, confirming that LVF words could not activate the VWF system, and hence could not enter the normal left-hemispheric reading pathway. As a consequence, the influence of the words/non-words status on ERPs was also restricted to RVF

stimuli. These abnormalities in the pattern of brain activity may thus be considered as the direct cerebral correlate of left hemialexia.

Some fMRI results that were observed in the callosal patients and that could not be directly predicted from the standard model of reading deserve further discussion. First, although the locations of the VWF system were tightly clustered in controls and in patients A.C. and R.A.V., we noticed that the activation was slightly more superior and lateral in patients than in controls. While this difference may well be due to normal inter-individual variability (see Table 2), it is also possible that the brain lesions and the ensuing atrophy induced a slight displacement of the activated brain tissue. Indeed, as visible in Fig. 4, the activation foci corresponding to the VWF system fell at the same anteroposterior level as the patients' brain lesions. Secondly, we observed a significant activation increase in left precentral and prefrontal areas associated with LVF words relative to RVF words (Fig. 3). This difference, which did not exist in control subjects, may have reflected the slow and effortful search for a verbal response that was carried out by both patients in this condition (for reviews, see Cabeza and Nyberg, 1997; Gabrieli *et al.*, 1998). Finally, we did not observe systematic differences in activation patterns between the two patients that may account for the difference in their reading accuracy.

Characterization of the VWF area

The main contribution of this study is to isolate a specific stage of the reading process, the VWF system, and to begin to characterize it in space and time. An area of the left fusiform gyrus was isolated which responds identically to word stimuli in the LVF and RVF. Much work remains to be done to establish the nature of the computations that are carried out in this area. Our experiment establishes that activity in this region is invariant across left and right retinal locations of stimulation. This implies that it lies at the convergence of retinotopically organized visual pathways and must contain visual neurons with receptive fields encompassing both hemifields. It may therefore be homologous to inferotemporal areas in the monkey where cells with wide receptive fields, selectivity to high-level visual features, and size and position invariance can be found (Ito *et al.*, 1995; Tanaka, 1996). By analogy, one may speculate that the human VWF area comprises a distributed representation of the visual shapes of letters sufficient to represent unambiguously specific alphabetic strings.

Suggested further research would be to investigate how specific this representation is to words, given that activation in a similar location can be elicited by object perception (for reviews, see Cabeza and Nyberg, 1997; Farah and Aguirre, 1999). One of the most striking features of the VWF system is its strict lateralization to the left hemisphere. The reasons for this left lateralization as well as for the right-lateralization of the fusiform face area at a symmetrical location (Kanwisher

et al., 1997) remain to be determined. Finally, given that reading is a recent cultural acquisition and emerges relatively late in life, one of the most puzzling features of this region is its reproducible localization across subjects. How the genetically determined organization of visual and verbal areas of the human brain interact with cultural factors to produce a well-defined cortical region responsive to words should be addressed in further developmental and cross-cultural brain-imaging studies.

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