Language-specific tuning of visual cortex? Functional properties of the Visual Word Form Area

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Summary

The first steps in the process of reading a printed word belong to the domain of visual object perception. They culminate in a representation of letter strings as an ordered set of abstract letter identities, a representation known as the Visual Word Form (VWF). Brain lesions in patients with pure alexia and functional imaging data suggest that the VWF is subtended by a restricted patch of left-hemispheric fusiform cortex, which is reproducibly activated during reading. In order to determine whether the operation of this Visual Word Form Area (VWFA) depends exclusively on the visual features of stimuli, or is influenced by language-dependent parameters, brain activations induced by words, consonant strings and chequerboards were compared in normal subjects using functional MRI (fMRI). Stimuli were presented in the left or right visual hemifield. The VWFA was identified in both a blocked-design experiment and an event-related experiment as a left-hemispheric inferotemporal area showing a stronger activation to alphabetic strings than to chequerboards, and invariant for the spatial location of stimuli. In both experiments, stronger activations of the VWFA to words than to strings of consonants were observed. Considering that the VWFA is equally activated by real words and by readable pseudowords, this result demonstrates that the VWFA is initially plastic and becomes attuned to the orthographic regularities that constrain letter combination during the acquisition of literacy. Additionally, the use of split-field stimulation shed some light on the cerebral bases of the classical right visual field (RVF) advantage in reading. A left occipital extrastriate area was found to be activated by RVF letter strings more than by chequerboards, while no symmetrical region was observed in the right hemisphere. Moreover, activations in the precuneus and the left thalamus were observed when subjects were reading RVF versus left visual field (LVF) words, and are likely to reflect the attentional component of the RVF advantage.

Introduction

The first steps in the process of reading a printed word belong to the domain of visual object perception. Just as in the case of common objects or faces, the ultimate goal of these initial stages is to build up a representation of the input that is invariant for various irrelevant perceptual dimensions (Riesenhuber and Poggio, 1999). Letter strings can be identified irrespective of their location in the visual field, of the colour of the ink, of the case, size, type of font, etc. According to Warrington and Shallice, the visual identification of letter strings is achieved by an abstract representation that has been termed the Visual Word Form (VWF) (Warrington and Shallice, 1980).

The left fusiform gyrus and the VWF system

While reading involves a large network of connected cortical regions (see reviews in Price, 1997; Fiez and Petersen, 1998), we formulated the hypothesis that an area located in the mid-portion of the left fusiform gyrus, which activates whenever literate subjects read printed words, contributes crucially to

the cerebral basis of the VWF, and accordingly proposed to label this left fusiform region the Visual Word Form Area (VWFA) (Cohen *et al*., 2000). We have shown recently that this area can be identified in any single individual as a region showing a response to visual words, independently of their location on the retina. Its peak is consistently found at the same location in Talairach space (approximately –43 –54 –12), with a standard deviation of only ~0.5 cm (Cohen *et al*., 2000). It is also thought to be the source of electrical and magnetic fields that are recorded over the left ventral occipito-temporal region, with a latency of ~150–200 ms, whenever subjects see words (Nobre *et al*., 1994; Salmelin *et al*., 1996; Tarkiainen *et al*., 1999; Cohen *et al*., 2000). For the sake of simplicity, we will refer to this region as the VWFA, although it should be clear that this denomination rests on functional hypotheses that are still open to debate.

The VWFA hypothesis gains support from both brain imaging and neuropsychological data suggesting that the representation subtended by the VWFA is invariant for the spatial location and the specific case or font used to present the words. The VWFA is activated by words irrespective of the visual hemifield in which words are presented, and thus represents stimuli in a location-invariant format (Cohen *et al*., 2000). Furthermore, a recent study using masked repetition priming demonstrates invariance for typographic case (Dehaene *et al*., 2001): the VWFA shows a reduced activation to conscious words whenever the target is primed by the subliminal presentation of the same word. Crucially, this repetition suppression effect is identical irrespective of the case in which the prime is printed. Observations of brain damaged patients provide a set of parallel data. The VWFA seems to be the critical lesion site for pure alexia, a unimodal deficit of word reading, with sparing of writing and of auditory word comprehension (Dejerine, 1892; Damasio and Damasio, 1983; Binder and Mohr, 1992; Beversdorf *et al*., 1997; Leff *et al*., 2001). Although the lesion affects the left inferotemporal cortex, the deficit typically extends to the entire visual field of those patients who are not hemianopic (Dejerine, 1892). Finally, patients with severe pure alexia may be unable to reach a case-invariant representation of letters, as evidenced for instance by their inability to decide whether 'a' and 'A' represent the same abstract grapheme (e.g. Miozzo and Caramazza, 1998).

Less clear at present is whether the middle portion of the left fusiform gyrus houses a strictly visual representation of words, as our VWF hypothesis predicts. Certainly, many studies report no activation of this region during spoken word processing (for reviews see Binder *et al*., 2000; Giraud and Price, 2001). In a recent study, using an identical same– different judgement task with pairs of visual or auditory stimuli, we have demonstrated that while the VWFA is strongly activated by strings of letters, it shows no activation to auditory words or pseudowords (Dehaene *et al*., 2002). It therefore appears as a unimodal area, at least as far as word perception is concerned. However, in some studies, words in the auditory or tactile modality have been shown to induce

left fusiform activations, which should not be expected if this region was purely devoted to visual processing (Démonet *et al*., 1992; Démonet *et al*., 1994; Binder *et al*., 1996; Vandenberghe *et al*., 1996; D'Esposito *et al*., 1997; Büchel *et al*., 1998; Perani *et al*., 1998; Chee *et al*., 1999; Buckner *et al*., 2000; Pihlajamäki *et al*., 2000; Wise *et al*., 2000; Giraud and Price, 2001). Such evidence has been taken as an indication that the fusiform gyrus could embody the phono- logical output lexicon (Brunswick *et al*., 1999) or support lexical access from semantics (Foundas *et al*., 1998).

This objection to the VWFA hypothesis, however, seems less than conclusive. First, the mid-fusiform gyrus may encompass several distinct areas involved in language processing. The VWFA proper would occupy the middle portion of the left fusiform gyrus, with Talairach coordinates (TC) close to $y = -60$, while increasingly more abstract and supramodal representations would occupy its more anterior sectors. This idea is compatible with an overview of 20 recent imaging studies reporting left fusiform activations that fell within the following bounding coordinates: $-50 < x < -30$; $-80 < y < -30$; $z < 0$. Fourteen fusiform activation peaks were elicited by non-visual verbal stimuli, or were common to visual and non-visual stimuli, thus suggesting an abstract representation beyond the VWF system. Those peaks had an average anteroposterior coordinate of $y = -43$ (range –54 to –32), clearly anterior to our postulated VWFA (Démonet *et al*., 1992; Démonet *et al*., 1994; Binder *et al*., 1996; Price *et al*., 1996*b*; D'Esposito *et al*., 1997; Büchel *et al*., 1998; Perani *et al*., 1998; Chee *et al*., 1999; Buckner *et al*., 2000; Wise *et al*., 2000). Interestingly, all these activations correspond to contrasts between conditions with higher versus lower semantic processing demands, which is in good agreement with the idea that this region is the siege of an abstract supramodal representation of words. Conversely, we compiled 25 activation peaks observed when contrasting alphabetic strings with non-alphabetic stimuli such as false fonts or fixation, which might correspond to the real VWFA. These had a significantly more posterior average coordinate of $y = -60$ (range –43 to –70) $[t(37) = 5.9; P = 10^{-6}]$ (Price *et al*., 1996*a*; Puce *et al*., 1996; Beauregard *et al*., 1997; Wagner *et al*., 1998; Brunswick *et al*., 1999; Fiez *et al*., 1999; Kiehl *et al*., 1999; Buckner *et al*., 2000; Paulesu *et al*., 2000; Tagamets *et al*., 2000; Xu *et al*., 2001). Thus, this analysis is suggestive of an anterior-to-posterior functional differenti- ation in the fusiform gyrus, with a supramodal sector anterior to the VWFA proper. However, such evidence should obviously be interpreted with the greatest caution given the potential pitfalls of comparisons that merge various tasks, imaging and statistical methods.

Secondly, in interpreting fusiform activations during non- visual word processing, one should consider that visual regions, including primary cortex, can be activated from the top down in the absence of any visual stimulation, depending on the cognitive strategy induced by the task (Kosslyn *et al*., 1999; Tomita *et al*., 1999). Top-down activations have been evidenced in high-level visual cortex comparable to the

VWFA, using mental imagery tasks for faces or places (Ishai *et al.*, 2000). Buckner and colleagues proposed that top-down influences from frontal regions accounted for the fusiform responses to auditory verbal stimuli in a stem completion task (Buckner *et al.*, 2000). This may also explain the activation of the VWFA when Japanese subjects were asked to write complex kanji ideograms or to imagine doing so, a task that may have an important visual component (Tokunaga *et al.*, 1999; Nakamura *et al.*, 2000).

Thirdly, as a further indication that the VWFA supports an essentially visual representation of words, lesions affecting the mid-fusiform gyrus give rise to pure alexia (Binder and Mohr, 1992; Leff *et al.*, 2001), while lesions that induce deficits of lexical retrieval seem to impinge on the polar (Grabowski *et al.*, 2001) or lateral temporal cortex (Foundas *et al.*, 1998). Therefore, as a conclusion of this brief overview, and although the issue cannot be considered as fully settled at present, the bulk of the evidence seems consistent with our hypothesis that the left mid-fusiform region activated during reading is the cerebral substrate of an abstract visual representation of letter strings akin to the VWF.

Language-specific tuning in the fusiform gyrus?

In the present paper, we examine whether these properties depend, at least in part, on a process of fine tuning of the VWFA to the process of visual word recognition in the course of learning to read. Are the properties of the VWFA influenced by the acquisition of a specific language and of a specific writing system? Or is this cortical sector merely responding spontaneously to the kind of features that compose letters and words? This issue can be broken down into three distinct questions.

First, is the VWFA tuned to specific letter shapes, as opposed to visually equivalent pseudoletters? Few studies have compared directly the activation of the VWFA induced by letters and pseudoletters. In early PET experiments, Petersen *et al.* (1990) showed stronger activations to words than to strings of pseudocharacters in mesial extrastriate cortex. This region, however, was far more mesial and superior than the VWFA as defined here. More recently, Price and colleagues have obtained stronger activations to strings of consonants than to strings of pseudoletters at coordinates close to the VWFA (Price *et al.*, 1996*a*). Secondly, is the VWFA sensitive to the lexical status of letter strings? Several studies using PET scanning reveal left fusiform activations stronger for pseudowords than for real words (Brunswick *et al.*, 1999; Fiez *et al.*, 1999; Xu *et al.*, 2001). We have recently observed a similar trend in an event-related fMRI study (Dehaene *et al.*, 2002). Thirdly, one may ask whether this area is tuned to the orthographic rules that constrain which combinations of letters are legal in a given writing system. This question can be addressed by comparing activations induced by legal versus illegal strings of real letters. Beauregard and colleagues mention stronger basal

temporal activations for words than for random letters (Beauregard *et al.*, 1997). However, they report neither a direct test of this contrast, nor the exact TCs. Price and colleagues, using a visual feature detection task, observed stronger activations for pseudowords than for consonant strings at coordinates compatible with the VWFA (TC –46 –52 –12) (Price *et al.*, 1996*a*). However, in this blocked-design PET study, the activation of the VWFA might have been contaminated by attentional fluctuations between blocks of consonant strings and blocks of pseudowords, as only the latter are likely to engage subjects in spelling-to-sound translation and in lexical access to orthographically similar real words. Similar methodological remarks apply to a recent PET study by Xu and colleagues (Xu *et al.*, 2001), as well as to block-design fMRI studies (Büchel *et al.*, 1998; Rees *et al.*, 1999).

In the present study, our goal is to determine whether the functional properties of the VWFA have been attuned to the orthographic regularities of the writing system. We do not address the general issue of the parcellation of ventral temporal cortex into multiple domain-specific areas (see, for example, Kanwisher *et al.*, 1999; Gauthier, 2000; Haxby *et al.*, 2000). We are primarily concerned with the clarification of the role that the VWFA plays in reading. Nevertheless, our results may prove relevant to some aspects of the specialization debate. If indeed the VWFA turns out to be more activated by words than by consonant strings, it would imply that the activation of inferotemporal areas does not depend exclusively on the geometric features of the incoming stimuli. More specifically, it would shed light on the role of experience in the development of the functional tuning of the VWFA, and it would imply that this area has become partially specialized for reading.

We studied the activation of the VWFA by real words, compared with consonant strings. Consonant strings are well matched to words in their visual features, yet they radically violate the language-dependent letter combination rules. If the VWFA has become attuned to the processing of words in the subjects' script, it should respond more to words than to consonant strings. If, on the contrary, the VWFA is tuned only to the visual features of letter strings, it should be activated equally for both types of stimuli. In order to distinguish the VWFA from other ventral temporal regions responsive to visual words, we recorded fMRI activations during the presentation of stimuli in either the left or the right hemifield. We reasoned that most of the reading network, starting from the VWFA, should be activated identically for words presented in the left and right halves of the visual field (Fig. 1). Note that beyond the isolation of position-invariant activations, the split-field display technique can also reveal distinct patterns of activation for stimuli presented in the left and right visual hemifields (LVF and RVF, respectively). A secondary goal of our experiments, therefore, was to use such hemifield-dependent activations to shed some light on the mechanisms that underlie the well known advantage for verbal stimuli presented in the RVF (Grüsser and Landis,
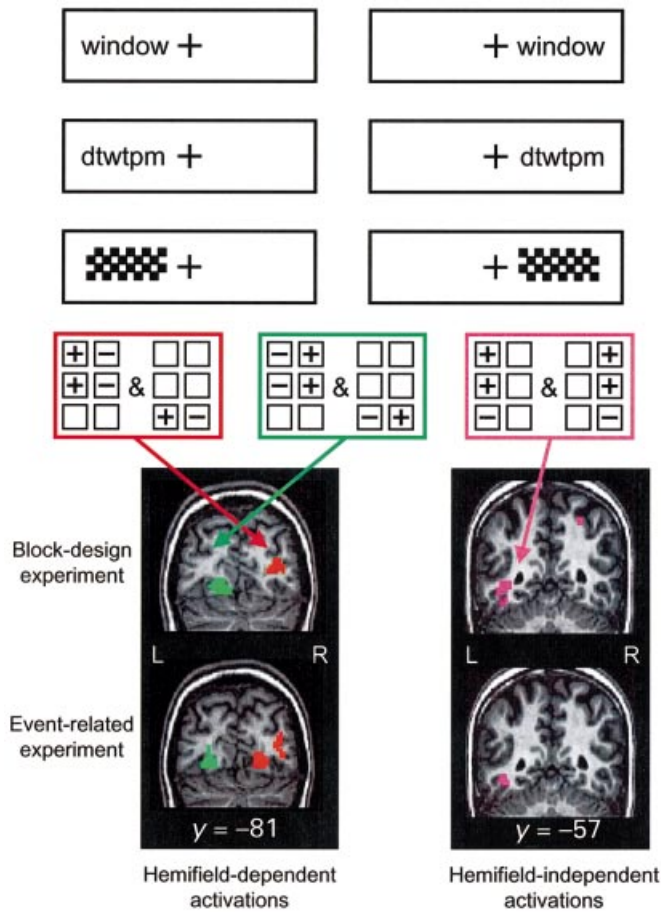
Fig. 1 Illustration of the six types of stimuli used in Experiments 1 and 2. The stimuli were words, consonant strings and chequerboards displayed in either the left or the right hemifield. The main contrasts that were used in the analysis of data are summarized in coloured rectangles, with arrows pointing to the corresponding cerebral activations in group analyses (voxelwise $P < 0.01$; corrected $P < 0.05$ for cluster extent). Red and green: posterior hemifield-dependent activations induced by alphabetic stimuli and chequerboards. Magenta: activation of the VWFA induced by alphabetic stimuli relative to chequerboards in either hemifield. Activations were highly similar in the block-design and the event-related experiments.

1991). In the first experiment, we compared words and consonant strings using a blocked-design fMRI paradigm. In the second experiment, in order to prevent any attentional fluctuation between blocks, we adapted the same paradigm to an event-related fMRI design.

Experiment 1
Methods
Subjects
Seven subjects (six females, one male), all aged 20–30 years, with a university education, and fully right-handed according to the Edinburgh Inventory, participated in the study. All were drug free, had no neurological or psychiatric history,

and had normal anatomical MRIs. All gave their written informed consent. The experiment was approved by the Ethical Committee of the Hôpital de Bicêtre.

Stimuli
Word stimuli consisted of 168 frequent and highly imageable nouns (mean $\log_{10}$ of frequency/million = 1.75, range 1.0–3.3; mean imageability rating = 4.8, range 4–6) (Content *et al.*, 1990), 3–6 letters and 1–3 syllables in length. Non-words were derived from words by creating 168 consonant strings matched one-to-one in number of letters. The frequency distribution of consonants was the same in consonant strings as in real words. All words and non-words were presented in lower case letters, once in the LVF and once in the RVF. Stimulus presentation was controlled by the Expe6 software (Pallier *et al.*, 1997).

Experimental tasks
Subjects were asked to fixate a permanent central fixation point, while stimuli were flashed in their right or left visual hemifield (Fig. 1). Words and non-words extended from 2° to a maximum of 6° away from fixation. Chequerboards consisted of 12×4 small rectangles, and extended from 2° to 6° away from fixation, with approximately the same vertical size as letter strings. Each trial consisted of a 550 ms fixation period followed by a 200 ms presentation of the target. Subjects were asked to pay attention to all stimuli, words, non-words and chequerboards.

Procedure
fMRI experiment
Subjects received three fMRI sequences, each comprising 12 experimental blocks, i.e. two blocks for each condition. Each block comprised 28 trials. Blocks were presented in pseudo-random order within sequences, so as to maximize the variety of transitions between conditions while avoiding any repetition of the same condition in successive blocks. Trials were presented in random order within blocks. The order of blocks within sequences and the order of trials within blocks differed across the three sequences, but were identical for all subjects. The order of sequences was randomized across subjects.

Behavioural control
In seven subjects, including five subjects from the fMRI experiment, eye movements and word identification were studied outside of the MRI scanner. The angular parameters of the stimuli were the same as in the fMRI experiment. Eye movements were monitored using an Iris infrared-light eyetracker (Skalar Medical, Delft, The Netherlands). First,
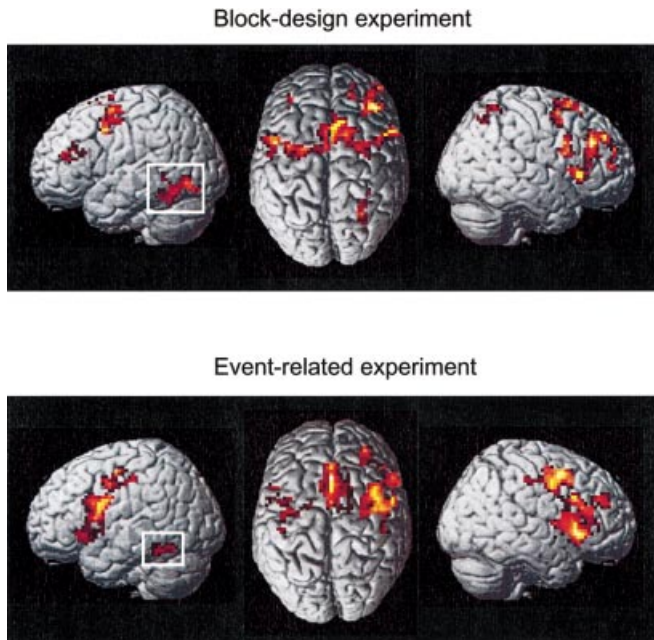
Block-design experiment

Event-related experiment

Fig. 2 Cortical network activated by alphabetic stimuli relative to checkerboards, including the left fusiform VWFA (white square) (group analyses; voxelwise $P < 0.01$, corrected $P < 0.05$ for cluster extent).

subjects were presented with a complete sequence from the fMRI experiment, with the original timing parameters. Eye movements were monitored but no overt response was required. Secondly, subjects were presented with 56 real words drawn from the fMRI material. Words were presented once in each hemifield, arranged in four blocks of 28 words each (RVF, LVF, RVF, LVF). We used a longer stimulus onset asynchrony (SOA) than in the fMRI experiment (2000 ms), in order to allow for overt naming. Naming errors and eye movements were monitored.

Imaging parameters
Each sequence consisted of 12 s of initial fixation, followed by 12 stimulation blocks of 21 s each, as described before, followed by 12 s of final fixation. In each sequence, 92 functional volumes sensitive to blood oxygen level dependent (BOLD) contrast were acquired with a T_2-weighted gradient echo, echo planar imaging sequence on a 1.5 tesla Signa Imager [General Electric, TR (relaxation time) = 3000 ms, $\propto$ = 90°, TE (echo time) = 60 ms, field of view = 240 × 240 mm, in-plane resolution = 3.75 × 3.75 mm²]. Each volume comprised 20 axial slices of 5 mm thickness covering most of the brain. The first four 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, $\propto$ = 20°, field of view = 240 × 180 mm, slice thickness = 1.5 mm, in-plane resolution = 0.94 × 0.94 mm²) were also acquired for anatomical localization.

Statistical analysis of fMRI data
Functional images were analysed with the Statistical Parametric Mapping software (SPM99b). To correct for motion, functional scans were realigned using the last image as a reference. The anatomical image was transformed stereotactically to TCs 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 to a final smoothness of ~ 8 mm. The resulting images had cubic voxels of 3 × 3 × 3 mm³. For single-subject analyses, activation on each of the six types of trial was modelled by a combination of the standard SPM haemodynamic function and its temporal derivative. Only the former function was used for statistical contrasts. Three additional variables of non-interest modelled constant differences across the four sequences. Long-term signal variations were eliminated with a high-pass filter set at 120 s. Low-pass filtering was achieved by convolution with the haemodynamic response function. We also performed a random-effect group analysis with subjects as random variable.

Results
Subjects made significantly more errors when reading aloud LVF words than RVF words (29.8% versus 14.5% errors; Wilcoxon one-tailed test $P = 0.014$). The reading performance thus displayed the classical RVF advantage for verbal material, replicating the results obtained in a previous fMRI study with split-field reading (Cohen *et al.*, 2000). The relatively high error rate in this behavioural test is imputable to the simultaneous recording of eye movements, which required subjects to inhibit eye blinks while wearing cumbersome equipment close to the eyes. The mean number of saccades was 1.7 (0.5% of trials) during a complete fMRI sequence with covert naming instructions. Thus, the stimulation paradigm used in this study allowed for a satisfactory identification of target words, while keeping lateral saccades at a minimum.

Group analyses
In group analyses, we used a voxelwise threshold of $P < 0.01$, with a corrected $P < 0.05$ for cluster extent. We tested the contrast of alphabetic stimuli (words or consonant strings) versus chequerboards. This revealed a bilateral cortical network, including bilateral mesial frontal and rolandic cortex, right intraparietal and prefrontal cortex, Broca's area, and a left inferotemporal focus (Fig. 2 and Table 1). The highly significant left fusiform focus closely matched the previously reported coordinates of the VWFA [TC –39 –57 –9; $t(6) = 10.01$]. No activation was observed at the homologous location in the right hemisphere. As the reason for using lateralized stimuli was to pick out activations invariant for spatial location, we checked that this region was

Table 1 *Experiment 1: group analysis of the reading network activated by alphabetic stimuli relative to chequerboards*

Alphabetic stimuli versus chequerboards									LVF	RVF	Interaction with hemifield	Words versus consonants
Main effect									*t*	*t*	*t*	*t*
Side	Area	TC			Cluster			Peak voxel *t*				
		x	*y*	*z*	*P* corrected	No. of voxels	*t*					
Left	Fusiform (VWFA)	–39	–57	–9	<0.001	349	10.01*	8.05*	6.17*	2.94***	3.10***
Left	Rolandic	–21	–3	60	0.005	80	11.44*	3.48**	7.64*	3.24***	5.06*
Left	Rolandic	–48	3	45	0.034	59	7.75*	2.30***	2.48***	0.68	3.69**
Left	Broca's area	–30	21	9	0.003	88	7.60*	1.54	3.36**	0.92	2.35***
Right	Prefrontal	18	45	33	<0.001	446	10.46*	1.41	1.74	0.15	4.45**
Right	Rolandic	51	9	30	0.016	67	9.39*	3.18**	3.34*	0.01	3.95**
Right	Intraparietal	33	–39	51	<0.001	135	9.24*	0.69	5.07*	3.15***	1.94
Bilateral	Mesial frontal	12	21	60	<0.001	364	8.76*	1.69	2.60***	0.84	5.70*

*$P < 0.001$; **$P < 0.01$; ***$P < 0.05$ (two-tailed P for the interaction column, one-tailed P otherwise).
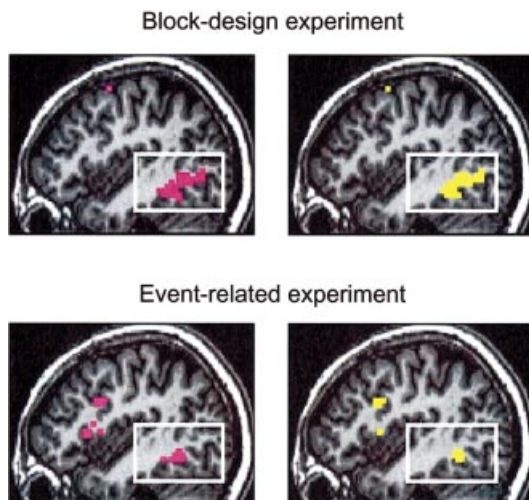

Fig. 3 Sagittal cut at coordinate $x = -40$, showing the activation of the VWFA by alphabetic stimuli relative to chequerboards (magenta; voxelwise $P < 0.01$ for both the right and the left hemifield). The major part of the VWFA shows a stronger activation for words than for consonant strings (yellow; voxelwise $P < 0.05$).

also activated in analyses restricted either to LVF stimuli [TC –39 –57 –9; $t(6) = 8.05$; 121 voxels] or to RVF stimuli [TC –39 –60 –12; $t(6) = 7.80$; 272 voxels]. The left fusiform activation, defined as the voxels responsive to alphabetic stimuli in both the LVF and the RVF (voxelwise $P < 0.01$ each), extended from $y = -75$ to $y = -35$ along the sagittal axis, stopping short of the temporal magnetic susceptibility artifact. The difference between alphabetic stimuli and chequerboards was stronger for RVF than for LVF stimuli at the peak of the VWFA [interaction with hemifield, $t(6) = 2.94$; $P < 0.05$], as well as at the left rolandic and right intraparietal peaks [$t(6) = 3.24$ and $t(6) = 3.15$; both $Ps < 0.05$] (see Table 1). This interaction might be related to the behavioural RVF advantage in reading tasks.

The VWFA activation was significantly stronger for words than for consonant strings at the peak voxel [$t(6) = 3.10$, $P = 0.011$]. Due to the intrinsic resolution of the fMRI method and to the smoothing of functional images, this statistical test performed at the peak voxel actually reflects the activity of a larger surrounding cortical volume. Nevertheless, in order to check further that the effect was not restricted to this single voxel, we looked for voxels activated more strongly by words than by consonant strings (voxelwise $P < 0.05$) within the reading network, defined as the voxels responsive to alphabetic stimuli in both the LVF and the RVF (voxelwise $P < 0.01$ each). We found a cluster of 56 voxels coextensive with the VWFA [TC –33 –69 –6; $t(6) = 5.69$; voxelwise $P = 0.002$; $P < 0.001$ for cluster extent corrected for multiple comparisons within the search volume]. As shown in Fig. 3, this lexicality effect was characteristic of a large set of left fusiform voxels in the vicinity of the peak of the VWFA. The effect was of the same size, whether the stimuli were presented in the RVF or the LVF [interaction with hemifield, $t(6) = 0.32$]. Stronger activation to words was also observed at all other peaks of the reading network, except for the right intraparietal focus (see Table 1), again without interaction with the visual hemifield (all interaction $Ps > 0.16$).

The VWFA was distinct from more posterior hemifield-dependent occipito-temporal regions that showed greater activation to contralateral than to ipsilateral stimulation [LVF: TC 33 –81 15, $t(6) = 15.97$, 518 voxels; RVF: TC –18 –84 –6, $t(6) = 10.90$, 490 voxels], whether the stimuli consisted of alphabetic strings or chequerboards (all $Ps < 0.0005$ at the peak voxel; Fig. 1). We tested whether the nature of the stimuli influenced the activation of those regions, defined as the sets of voxels activated by contralateral versus ipsilateral alphabetic strings, and by contralateral versus ipsilateral checkerboards (for each test, voxel-level $P < 0.01$, corrected $P < 0.05$ for cluster extent).
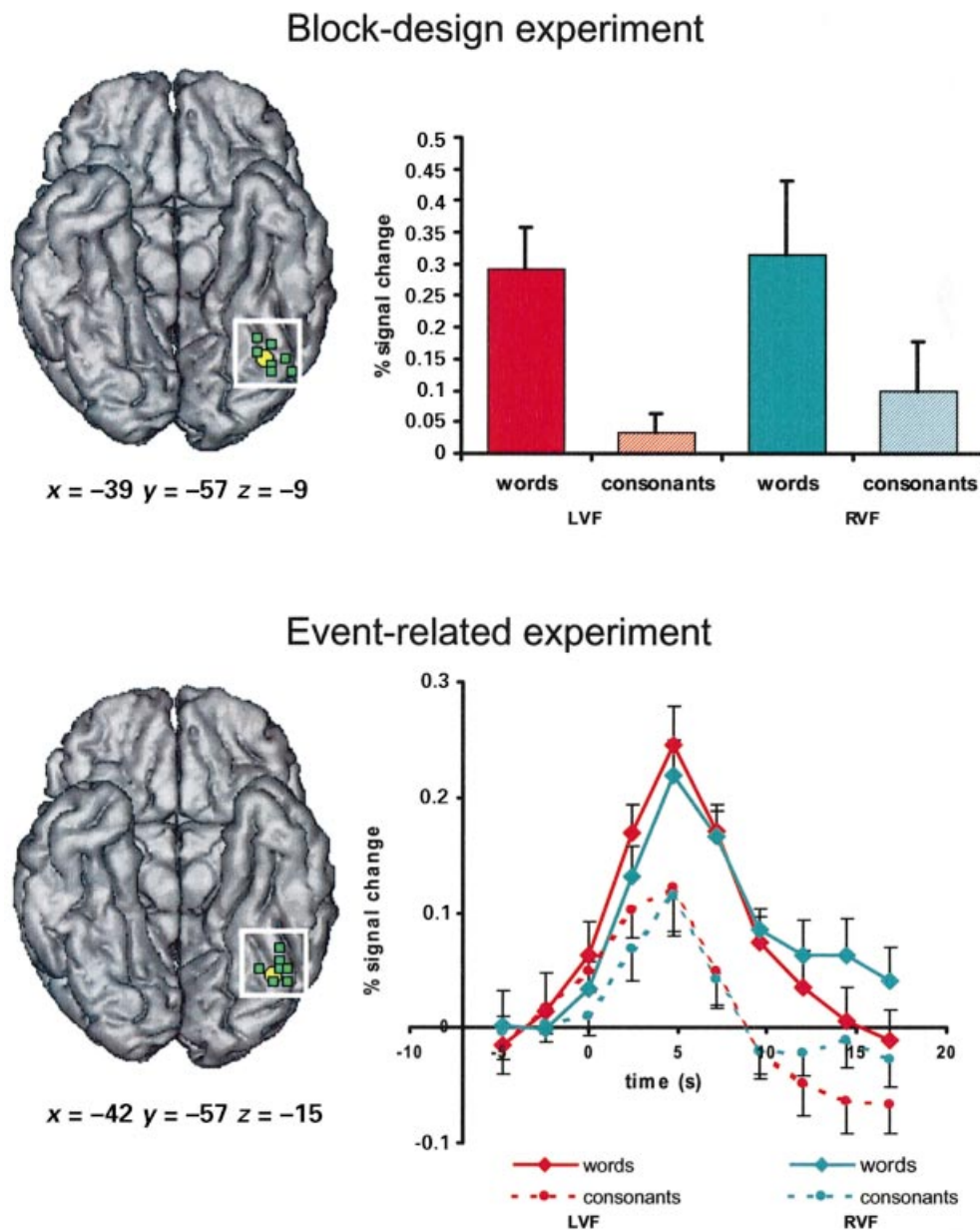
Block-design experiment

$x = -39$ $y = -57$ $z = -9$

Event-related experiment

$x = -42$ $y = -57$ $z = -15$

Fig. 4 (*Left panel*) peak of the VWFA identified in individual subjects (green squares) and in the group analyses (yellow circles) projected onto the inferior surface of a normalized brain. (*Right panel*) percentage change in BOLD signal for words and consonant strings versus chequerboards in the left and right hemifields at the peak of the group VWFA, averaged across subjects (bars represent the intersubject standard error). In both the block-design and the event-related experiments, alphabetic stimuli yielded significant activations relative to chequerboards, and real words relative to consonant strings.

To increase sensitivity, these regions were searched for voxels showing differential activation to contralateral alphabetic versus chequerboard stimuli, using a statistical test corrected for multiple comparisons within the small volume thus defined. In the right hemisphere, no difference was observed. In the left hemisphere, however, a small hemifield-dependent region posterior to the VWFA was more responsive to contralateral alphabetic stimuli than to chequerboards [TC -24 -78 -12; $t(6) = 5.60$; $P < 0.001$; corrected $P = 0.003$ for cluster extent]. No difference between words and consonant strings was observed at this peak location ($P > 0.05$).

Individual analyses

In individual analyses, we used a voxelwise threshold of $P < 0.001$, with a corrected $P < 0.05$ for cluster extent. We looked for the VWFA in each individual subject, using the contrast between alphabetic stimuli and checkerboards, masked by the same contrast restricted to LVF and to RVF stimuli (voxelwise $P < 0.01$ each). As shown in Fig. 4 and Table 2, all seven subjects showed a significant activation in the immediate vicinity of the peak isolated in the group analysis. The location of this focus was remarkably stable across subjects, with a standard deviation of 5 mm, 5 mm and 4 mm

Table 2 *Experiment 1: activations of the left fusiform VWFA in individual subjects*

Subject	Alphabetic stimuli versus chequerboards						Words versus consonants
	TC			Cluster		Peak voxel	*t*
	x	*y*	*z*	*P* corrected	No. of voxels	*t*	
1	–42	–60	–15	0.005	30	9.93*	6.46*
2	–42	–63	–21	<0.001	415	12.94*	3.15*
3	–51	–63	–12	<0.001	94	11.29*	3.6*
4	–36	–48	–18	0.002	32	7.25*	1.9***
5	–36	–54	–18	0.008	20	6.79*	5.64*
6	–48	–57	–9	0.005	13	6.11*	2.97**
7	–42	–51	–15	<0.001	59	9.03*	1.05
Mean	–42	–57	–15				
Standard deviation	5	5	4				

*$P < 0.001$; **$P < 0.05$; ***$P < 0.01$. Due to the small size of the VWFA cluster in Subjects 5 and 6, the voxelwise threshold was raised to 10^{-4} in order to reach clusterwise significance. In Subject 7 there was a significant difference between words and consonant strings 6 mm away from the peak of the VWFA ($t = 3.42$; $P = 0.024$ corrected for multiple comparisons in a 6 mm radius sphere).

Table 3 *Experiment 1: activations of the right hemispheric counterpart of the VWFA in individual subjects*

Subject No.	Alphabetic stimuli versus checkerboards						Words versus consonants
	TC			Cluster		Peak voxel	*t*
	x	*y*	*z*	*P* corrected	No. of voxels	*t*	
3	51	–60	–15	0.001	18	8.12*	3.52*
7	42	–45	–15	0.001	18	6.13*	1.34

*$P < 0.001$. Due to the relatively small size of the cluster, the voxelwise threshold was raised to 10^{-4} in order to reach clusterwise significance.

along the *x*-, *y*- and *z*-axes, respectively. In only two subjects was the peak activation significantly stronger for RVF than for LVF alphabetic stimuli.

The contrast of words versus consonant strings was significant in six out of seven subjects at the peak of the individually identified VWFA (Table 2). In the remaining subject, a significant cluster was found within a few millimetres of the expected coordinates [TC –42 –57 –15; $t(90) = 3.42$; voxelwise $P = 0.024$ corrected for multiple comparisons in a 12 mm sphere centred on the expected location]. As in the group analysis, the effect of lexical status did not interact with visual hemifield ($P > 0.05$ in all subjects).

In addition to the VWFA proper, two out of seven subjects showed a right fusiform activation cluster for alphabetic stimuli relative to checkerboards and invariant for spatial location (Table 3). In one of these two subjects (Subject 3), this peak showed a significant effect of lexicality, with no interaction with hemifield. Figure 5 shows a summary of the functional properties of the left and right fusiform foci in this individual subject.

The posterior hemifield-dependent activations could be identified in all subjects at coordinates close to the peaks of

the group analysis, using the contrast between contralateral and ipsilateral stimuli, masked by the same contrast restricted to alphabetic stimuli and to chequerboards (voxelwise $P < 0.01$ each). We looked, within those regions, for increased activations for contralateral alphabetic strings relative to chequerboards (voxelwise $P < 0.01$; $P < 0.05$ for cluster extent corrected for multiple comparisons within the small volume). In agreement with the group analysis, left-hemispheric activations were found in all subjects. A similar region was also found in the right hemisphere of four out of seven subjects, although it was always smaller and less significant than in the left hemisphere. In three out of seven subjects, the left-hemispheric peak activation was stronger for words than for consonant strings ($P < 0.05$). Such was also the case for one out of four subjects with a right-hemispheric activation ($P < 0.05$).

Correlates of the RVF advantage
We attempted further to identify the neural correlates of the behavioural RVF advantage in word reading. Behaviourally, we observed a better performance for real words displayed in the RVF than for similar words displayed in the LVF. We
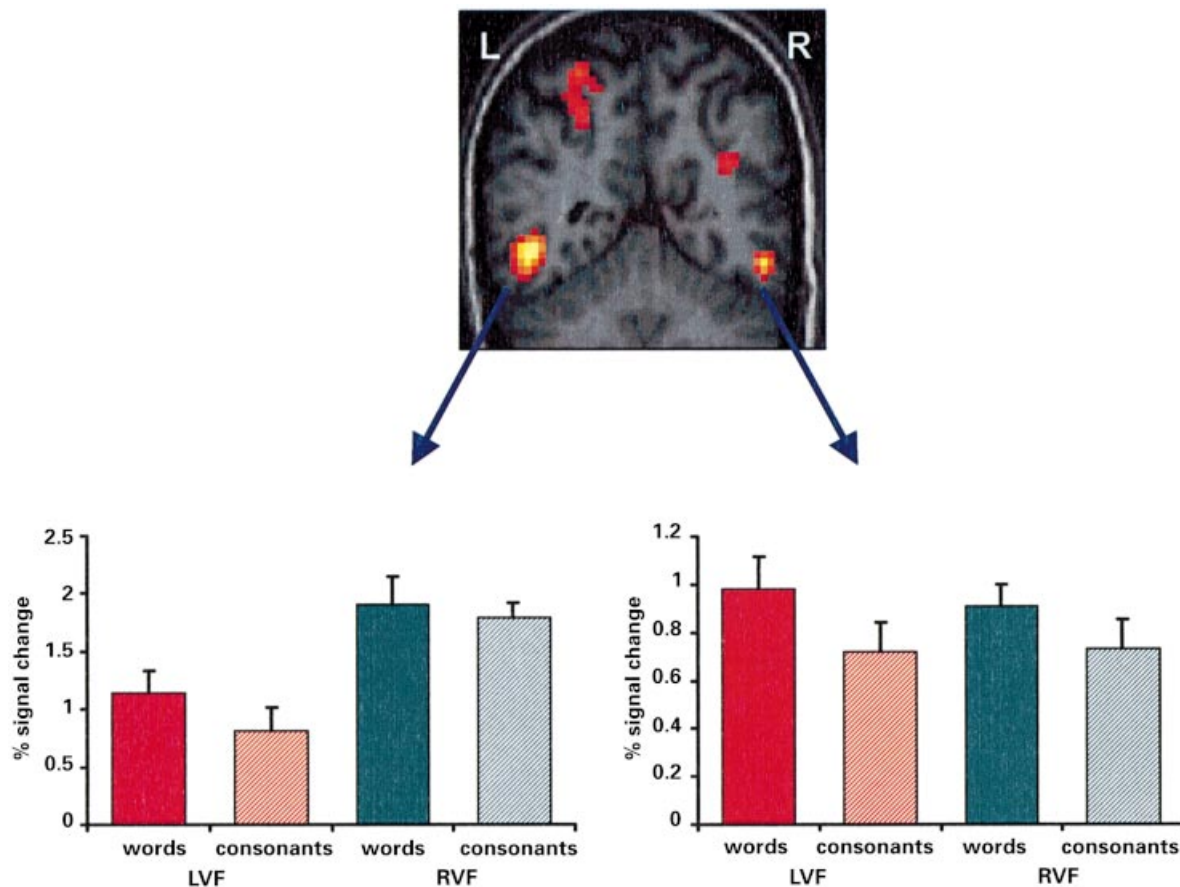
Fig. 5 Fusiform activations, with percentage change in BOLD signal, in Subject 3 (Experiment 1). In addition to the real VWFA, this subject showed a symmetrical but smaller right-hemispheric activation for alphabetic stimuli. Both foci were more strongly activated by real words than by consonant strings.

therefore analysed fMRI data using the very same contrast, with the same statistical thresholds as in previous group analyses. Several regions were more strongly activated by RVF than LVF words. They naturally included the left occipital hemifield-dependent region described earlier (TC –30 –78 –3), but also three additional regions: the left precuneus (TC –12 –51 45), the left thalamus (TC –18 –24 3) and a small right prerolandic focus (TC 48 –15 36). Note that these three regions did not show a stronger activation to RVF than to LVF chequerboards ($P > 0.30$ for all three). The opposite contrast (LVF versus RVF words) only revealed right occipital regions (TC 30 –81 18).

Experiment 2

In Experiment 1, the VWFA was reliably identified on the basis of positional invariance, and was shown to be more strongly activated by real words than by consonant strings. However, this difference does not necessarily reflect the intrinsic processing properties of the VWFA. Rather, it could be a consequence of the blocked structure of the experiment. During the blocks with consonant strings, the subjects' general level of arousal or their attention to alphabetic

processing might have decreased relative to the blocks in which real words were presented. Such a non-specific attentional influence might explain at least in part why the VWFA, among other regions, was influenced by orthographic well-formedness. In order to clarify this point, we performed a second experiment, very similar to Experiment 1 except that we resorted to using an event-related design, with the six types of trial randomly intermixed. We expected that this design would largely avoid the spurious effects of task-related attentional fluctuations.

Methods
Subjects
Nine subjects (seven female, two male), fulfilling the same criteria as in Experiment 1, participated in the study.

Stimuli, tasks and procedure
We used a subset of the verbal material of Experiment 1, comprising 100 words and the corresponding consonant strings. All words and non-words were presented in lower case letters, once in the LVF and once in the RVF. The

Table 4 *Experiment 2: group analysis of the reading network activated by alphabetic stimuli relative to checkerboards*

Side	Area	Alphabetic stimuli versus checkerboards						LVF	RVF	Interaction with hemifield	Words vs consonants
		Main effect						*t*	*t*	*t*	*t*
		TC			Cluster		Peak voxel				
		x	*y*	*z*	*P* corrected	No. of voxels	*t*				
Left	VWFA	–42	–57	–15	0.031	101	4.61*	4.70*	3.57**	1.14	2.31***
Left	Rolandic	–42	–3	42	0.001	184	8.57*	4.57*	2.44***	1.41	0.85
Left	Broca's area	–45	12	12	<0.001	426	6.38*	2.32***	3.81**	0.66	1.35
Right	Prefrontal	45	18	0			9.02*	9.33*	4.77*	0.68	4.13**
Right	Rolandic	39	6	51			7.54*	3.10**	4.33**	0.24	0.78
Right	Mesial frontal	–6	–3	48	<0.001	1663	9.46*	3.21**	1.24	0.82	0.05

*$P < 0.001$; **$P < 0.01$; ***$P < 0.05$ (two-tailed P for the interaction column, one-tailed P otherwise). Since the right hemispheric rolandic and prefrontal activations belonged to the cluster whose main peak was mesial frontal, these two peaks are reported without clusterwise significance level.

experimental task was the same as in Experiment 1, except that each trial consisted of a 2200 ms fixation period followed by a 200 ms presentation of the target. Subjects received four fMRI sequences, each comprising a total of 150 trials (25 words, 25 consonant strings and 25 checkerboards in each hemifield). Trials were presented in a random order within sequences. As a behavioural control, seven other right-handed subjects were presented with the same material (except the checkerboards) outside of the MRI device. They were asked to name real words and to utter the word 'consonants' when presented with consonant strings. Errors and naming latencies were monitored.

Imaging parameters and statistical analysis of fMRI data

Each sequence consisted of 12 s of initial fixation, followed by 150 stimulation trials. In each sequence, 155 functional volumes sensitive to blood oxygen level dependent contrast were acquired using the same parameters as in Experiment 1, except for the TR (2400 ms) and the number of functional axial slices ($n = 16$). The first five volumes were discarded to reach signal equilibrium. Anatomical images were acquired as in Experiment 1. Functional images were corrected for slice acquisition delays by Fourier interpolation, and then realigned, normalized and smoothed as in Experiment 1. For statistical modelling, we applied the same procedures and parameters as in Experiment 1.

Results

Subjects tested outside the MRI magnet again showed a significant advantage when reading aloud RVF versus LVF words, both on error rates (3.1% versus 9.4% errors; Wilcoxon one-tailed $P = 0.012$) and on latencies [mean correct latency: 707 ms versus 758 ms; $t(6) = 4.73$; one-tailed $P = 0.0016$].

Group analyses

In group analyses, we used a voxelwise threshold of $P < 0.01$, with a corrected $P < 0.05$ for cluster extent. We tested the global contrast between alphabetic stimuli and chequerboards. A bilateral cortical network was observed, similar to the pattern reported in Experiment 1 (Fig. 2 and Table 4). It included the left fusiform VWFA, located within a few millimetres of the coordinates observed in Experiment 1 (TC –42 –57 –15). The same contrast restricted to RVF or LVF stimuli was significant at the peak voxel of the VWFA (both Ps < 0.004), with no significant interaction, thus achieving invariance for spatial location. The left fusiform activation, defined as in Experiment 1, extended from $y = –60$ to $y = –41$ along the sagittal axis, stopping at ~ 6 mm from the temporal magnetic susceptibility artifact.

As in Experiment 1, the VWFA was activated more strongly by real words than by consonant strings [$t(8) = 2.31$; $P < 0.025$]. Applying the same statistical procedure as in Experiment 1, we found that the peak of the VWFA belonged to a cluster of 12 voxels coextensive with the VWFA [TC –42 –54 –12; $t(8) = 2.71$; voxelwise $P = 0.013$; $P < 0.001$ for cluster extent]. As shown in Fig. 3, this lexicality effect concerned the major part of the VWFA. Again, there was no interaction between lexicality and hemifield ($P > 0.15$).

Replicating Experiment 1, we found posterior hemifield-dependent activations to contralateral stimuli [LVF: TC 36 –72 –3, $t(8) = 20.49$, 1093 voxels; RVF: TC –24 –81 –3, $t(8) = 7.07$, 509 voxels], responding to both alphabetic strings and checkerboards (all Ps < 0.005 at the peak voxel; Fig. 1). However, contrary to Experiment 1, no difference between contralateral alphabetic stimuli versus chequerboards was found within these hemifield-dependent activations.

Individual analyses

This event-related experiment was less sensitive than its blocked-design counterpart, and individual analyses often

Table 5 *Experiment 2: activations of the left fusiform VWFA in individual subjects*

Subject	Alphabetic stimuli versus checkerboards						Words versus consonants
	TC			Cluster		Peak voxel	*t*
	x	*y*	*z*	*P* corrected	No. of voxels	*t*	
1	–45	–51	–21	<0.001	6479	5.95*	0.56
2	–42	–60	–12	<0.001	257	7.2*	1.72
3	–36	–54	–24	>0.05	9	3.08*	0.08
4	–45	–54	–18	0.001	202	6.47*	0.37
5	–45	–45	–18	<0.001	196	4.98*	4.12*
6							
7	–48	–54	–12	>0.05	14	2.99**	1.78
8	–48	–60	–15	>0.05	70	3.98*	0.59
9	–42	–60	–12	0.007	143	7.03*	0.56
Mean	–44	–55	–17				
SD	4	5	4				

*$P < 0.001$; **$P < 0.01$.

yielded marginal results. In an attempt to identify the VWFA in individual subjects, we used the global contrast of alphabetic stimuli versus chequerboards, at a lowered threshold (voxelwise $P < 0.01$). In eight out of nine subjects, an activation cluster was observed in the immediate vicinity of the peak determined in the group analysis (see Table 5 and Fig. 4). This cluster, however, reached a corrected $P < 0.05$ for cluster extent in only five out of eight subjects. Still, the location of this focus was remarkably stable across subjects, with standard deviations of 4, 5 and 4 mm along the *x*-, *y*- and *z*-axes, respectively. At the peak of the VWFA, the contrast of real words versus consonant strings was significant in only one subject. No right-hemispheric equivalent of the VWFA was found in any of the subjects.

Correlates of the RVF advantage

As in Experiment 1, we compared activations induced by real words displayed in the RVF versus in the LVF. As before, the left occipital hemifield-dependent region was activated (TC –21 –84 0), as well as the precuneus (TC –9 –54 30). Again, the precuneus did not show a stronger activation to RVF than to LVF chequerboards ($P > 0.50$). The opposite contrast (LVF versus RVF words) only revealed right occipital regions (TC 33 –69 –6 and 36 –78 12, respectively).

Discrepancies between Experiments 1 and 2

Before turning to the general discussion, we will briefly consider some apparent discrepancies between the general pictures of the reading network that emerged from the two experiments. If we consider Fig. 2 and Tables 1 and 4, in which the contrast of alphabetic stimuli versus chequerboards is reported, some discrepancies appear in the pattern of frontal and parietal activations, beyond the overall similarity of the activation patterns.

First, in Experiment 2, there was a stronger bilateral inferior rolandic activation than in Experiment 1. This region corresponds to the sensorimotor cortex devoted to the control of facial and articulatory movements. In Experiment 2, the display of each stimulus was followed by a 2200 ms fixation period, while this period lasted only 550 ms in Experiment 1. Thus, if an overt vocal response had been required, subjects would have had sufficient time to utter it only in Experiment 2. It is therefore plausible that in Experiment 2 subjects could covertly read stimuli up to a full-fledged motor plan, which might be reflected in the strong lower rolandic activations.

Secondly, the activation of the anterior portion of Broca's area which was apparent in Experiment 1 was apparently lacking in Experiment 2. Actually, this region was activated in Experiment 2 also [$t(8) = 3.06$; $P < 0.01$ at the peak voxel TC –30 21 9], but it was included in the large left inferior frontal cluster of 426 voxels with a rolandic main peak. This cluster included a secondary peak within a few millimetres of the activation observed in Experiment 1 [TC –33 27 6; $t(8) = 3.78$; $P = 0.003$].

Thirdly, the right parietal activation observed in Experiment 1 was lacking in Experiment 2. This lack of activation persisted even when lowering the statistical threshold, and should be considered meaningful. This discrepancy should be related to the major difference in task structure between the two experiments. In Experiment 1, subjects could focus their attention in advance towards the region of space where the next stimulus was expected, while in Experiment 2 the location of the next stimulus was always unpredictable. Considering its role in the orientation of spatial attention (see review in Mesulam, 1999), it is not surprising that the right parietal cortex was more strongly involved in the block-design than in the event-related experiment. As an illustration of converging data, Gitelman and colleagues elicited right parietal activations very similar to the present ones by inducing lateralized expectancy for subsequent target

appearance, irrespective of the direction of the attentional shift (Gitelman *et al*., 1999).

Discussion

In this study, normal subjects were presented with real words, consonant strings and chequerboards in their left or right visual hemifield. The first experiment followed a blocked-design paradigm, while in the second experiment the six types of stimuli were randomly mixed, following an event-related design. The analysis of activations concentrated on fusiform regions, and particularly on the putative VWFA.

Localization of the VWFA

The VWFA was identified easily in both experiments as a left-hemispheric inferotemporal area displaying two key features. First, it shows a stronger activation to alphabetic stimuli than to checkerboards. Secondly, it is invariant for spatial location, as revealed by comparable activation patterns irrespective of the stimulated hemifield. Over the two experiments, this area could be detected unambiguously in 15 out of 16 subjects. It was located in the mid-portion of the fusiform gyrus, generally within the occipitotemporal sulcus. The TCs of the VWFA were remarkably stable across subjects and across experiments, invariably falling within a radius of a few millimetres. This location is in good agreement with a number of previous activation studies (for reviews see Cohen *et al*., 2000; Dehaene *et al*., 2001; Dehaene *et al*., 2002). The VWFA was shown to be activated by meaningless visual letter strings (either pronounceable pseudowords or consonant strings) relative to non-alphabetic visual stimuli such as false fonts or faces (Price *et al*., 1996*a*; Puce *et al*., 1996), or by similar contrasts using real words (Beauregard *et al*., 1997; Wagner *et al*., 1998; Fiez *et al*., 1999; Kiehl *et al*., 1999; Buckner *et al*., 2000; Paulesu *et al*., 2000). The VWFA also appears to be strongly lateralized. A symmetrical right-hemispheric homologue could be identified in only two out of 16 subjects, and it was always much more weakly activated than its left-hemispheric counterpart.

Differences between words and consonant strings

Our main goal was to establish whether the VWFA was tuned to language-dependent parameters, and particularly to the orthographic regularities that constrain the combination of letters into pronounceable strings. In both experiments, we observed stronger activations to words than to strings of consonants, in good agreement with previous studies using PET or block-design fMRI (Price *et al*., 1996*a*; Büchel *et al*., 1998; Rees *et al*., 1999; Xu *et al*., 2001). It may be objected that in Experiment 1 this effect could reflect attentional fluctuations between blocks: with real words subjects could engage in attention-demanding phonological and semantic

operations, therefore increasing the general level of activation of the entire word processing network. This amplification would include the VWFA and be confounded with any intrinsic preference of this region for words over consonant strings. In Experiment 2, however, all types of stimuli alternated randomly at a rapid rate, making it unlikely that there would be any systematic difference in attentional engagement between words and consonant strings. One may note in retrospect that the amplitude of the lexicality effect in terms of the percentage change in BOLD signal was comparable in both experiments (Fig. 4), suggesting that attentional factors actually had little influence even on the lexicality effect observed in Experiment 1. Still, different tasks and experimental designs are likely to induce different levels of involvement and of top-down activation of the VWFA. Thus, Rees and colleagues found a difference between words and consonant strings only whenever subjects paid attention to the stream of alphabetic stimuli (as opposed to a concurrent stream of object pictures) (Rees *et al*., 1999). However, once stimuli enter the field of attention, a difference between words and consonants can be elicited using a variety of tasks [e.g. passive viewing as in the present study, visual feature detection as in Price *et al*. (1996*a*), etc.]. Task-related parameters may also explain why, in contrast with a number of previous studies, Tagamets and colleagues showed no change of activation in the VWFA across words, pseudo-words, consonant strings and even false fonts (Tagamets *et al*., 2000). At the same time, they showed progressively increasing activations in parietal and frontal regions presumably involved in attentional control, and an amplification of posterior visual regions. It is possible that the demanding repetition detection task grew more difficult with more unfamiliar stimuli, progressively amplifying the activity of visual regions, including the VWFA. This effect could have masked the intrinsic preference of this region for words over consonant strings and false fonts.

Our results clearly show that the operation of the VWFA is influenced by language-dependent parameters, and does not depend exclusively on the visual features of stimuli. However, words and consonant strings differ not only in their obedience to letter combination rules, but also in their lexical status. Only words possess stable semantic and phonological representations in memory. Therefore, critical to any detailed interpretation of the present data is the status of the VWFA relative to pseudowords, which are comparable to real words inasmuch as they obey orthographic rules, and comparable to consonant strings inasmuch as they lack a lexical representation. We capitalized on previous data showing, in comparable experimental settings, that pseudo-words induced an activation of the VWFA at least as strongly as did real words (Brunswick *et al*., 1999; Fiez *et al*., 1999; Xu *et al*., 2001; Dehaene *et al*., 2002). This result is congruent with the postulated function of the VWFA, namely the representation of any well-formed letter string at a prelexical level to serve as input to subsequent language-related processes. We may therefore conclude that the weaker

activation of the VWFA by consonant strings is indeed due to their violation of letter combination rules, and not to their lack of a lexical entry *per se*.

Note that the superiority of words over consonant strings could in principle reflect the simple presence of vowels, rather than the obedience to orthographic rules. If this hypothesis were true, one would predict identical activation levels for non-words such as BRSTEAIU and for real words or pseudowords. This possibility remains to be tested in future experiments.

Cerebral bases of the RVF advantage in reading

The primary reason for using split-field presentation of stimuli was to isolate areas invariant for spatial position. However, it also provided an opportunity to observe behavioural asymmetries, and to try to clarify some of their underlying mechanisms. In both experiments we observed the classical behavioural advantage for RVF over LVF words. Schematically, two types of theories have been proposed to account for this RVF advantage, although these two approaches are by no means mutually exclusive. According to 'structural' accounts, RVF verbal stimuli benefit from a more effective processing by virtue of a direct access to the left-hemisphere language areas, while LVF stimuli must follow a longer and 'noisier' transcallosal pathway. It is also possible that the left-hemispheric retinotopic areas that process RVF stimuli are more adequately tuned to visual word recognition than their right-sided counterparts. According to 'attentional' accounts, the RVF advantage results from an attentional bias toward the right side of space during reading. This bias could result from the intrinsically verbal nature of the task, yielding a global left-hemispheric activation (Kinsbourne, 1970), or from various strategies adopted by the reader, some of which may depend on the direction of reading. For instance, bilingual subjects tend to report arrays of Hebrew letters starting with the rightmost letter, and arrays of English letters starting with the leftmost letter (Lubow *et al.*, 1994). Similarly, the preferred point of initial eye fixation is left of word centre in English (with most of the word falling in the RVF) and right of word centre in Hebrew (Deutsch and Rayner, 1999; Aghababian and Nazir, 2000), suggesting that attentional biases contribute to the RVF advantage in left-to-right reading systems.

Our brain-imaging results suggest that both mechanisms are at work during split-field word reading. First, when examining the activations induced by RVF or LVF words relative to words presented in the opposite hemifield, we found the expected contralateral occipital activations. These activations probably reflect relatively low-level processing of contralateral stimuli, and may be thought to be essentially equivalent in the left and right hemisphere. Nevertheless, as mentioned earlier as one possible 'structural' component of the RVF advantage, these perceptual regions may be better

tuned to reading in the left hemisphere than in the right. Indeed, in Experiment 1, a left extrastriate region that was only responsive to contralateral hemifield stimulation was significantly more activated by words than by checkerboards, while no such difference was observed in the right-hemispheric extrastriate areas. Interpretation should be cautious, since this difference was not replicated in Experiment 2 with an event-related design (and, therefore, a decreased statistical power). One interesting possibility, which should be subjected to further testing, is that this region has developed greater perceptual learning for words than its right-hemispheric counterpart, due to normal readers' bias for fixating words left of their geometrical centre (Nazir, 2000). This region may be the equivalent, in the domain of word perception, of the so-called Occipital Face Area, a region of similar location responding to faces more than to common objects or letters (Kanwisher *et al.*, 1997; Gauthier *et al.*, 2000).

Secondly, when comparing RVF versus LVF words, we observed in both experiments a predominantly left-sided activation of the precuneus, while the LVF versus RVF contrast never yielded any activation beyond the hemifield-dependent occipital areas. Furthermore, the precuneus was not activated when comparing RVF versus LVF checkerboards. This confirms that the pattern of activation was not related to some non-specific visual processing asymmetry, but probably to the RVF advantage specific to word processing. In Experiment 1, a stronger activation for RVF than for LVF words was also observed in the left thalamus. Both the precuneus and the thalamus can plausibly be related to the orientation of attention towards the opposite side of space: spatial attentional shifts are correlated with activations in the thalamus and precuneus (Gitelman *et al.*, 1999), and thalamic lesions can result in contralateral spatial neglect (for reviews see Mesulam, 1999; Vallar, 2001).

The emergence of the VWFA

In conclusion, is it possible to propose a broader view of the properties of the VWFA that are relevant to its role in reading? Writing systems are a recent cultural invention, and it is clear that in children, prior to the acquisition of reading, the patch of cortex that will eventually become the VWFA obviously cannot possess any predisposition for a specific spelling system. Why then is this particular region selected, within the extent of the ventral visual cortex, to play a central role in the processing of letter strings? The fact that the location of the VWFA is highly reproducible across subjects suggests that some initial properties intrinsic to this region and to its pattern of connectivity are the cause of its subsequent specialization for reading. Recently, Levy and colleagues have shown that high-level inferotemporal visual areas are localized according to a central versus peripheral visual field bias (Levy *et al.*, 2001). They show that regions sensitive to faces such as the so-called Fusiform Face Area (FFA) (Kanwisher *et al.*, 1997) fall within an antero-posterior

strip of cortex that is biased toward representing foveal stimuli, while regions more reactive to pictures of buildings fall in a more lateral periphery-biased strip. Reading typically requires predominantly foveal processing, and it may be expected that the VWFA should be located close to the FFA in terms of excentricity bias. This appears to be the case, as the coordinates of the VWFA are essentially symmetrical to those of the FFA (Kanwisher *et al.*, 1997; Tarr and Gauthier, 2000).

Lerner and colleagues have also described another gradient of perceptual predisposition, orthogonal to the eccentricity gradient, corresponding to a shift from sensitivity to local object features to a more holistic mode of representation as one goes from posterior to more anterior occipitotemporal cortex (Lerner et al., 2001). One may speculate that, even prior to the acquisition of reading, the VWFA shows a particular combination of eccentricity tuning, local versus global processing, and other parameters such as invariance for position and size (Ito *et al.*, 1995; Grill-Spector *et al.*, 1999), which makes it particularly suitable for representing strings of letters. This approach is related to the object-form topology hypothesis proposed by Haxby and collaborators (Ishai *et al.*, 1999; Haxby *et al.*, 2000), according to which regions of the ventral visual cortex differ in their perceptual predisposition for various categories of objects such as chairs, faces or buildings. Interhemispheric differences in those basic perceptual abilities may play a role in the genesis of the clear-cut asymmetry of the VWFA. Hemispheric differences in the processing of parts versus whole objects, or in low versus high spatial frequencies, may contribute to the emergence of this lateralization (see, for example, Kitterle and Selig, 1991; Robertson and Lamb, 1991).

In addition to its intrinsic perceptual predispositions, the anatomical and functional shaping of the mature VWFA may also result from its connections to other components of the language system. Anatomical links between the visual system and left-hemispheric language areas may have a causal role in the left-lateralization of the VWFA, possibly in combination with the aforementioned perceptual asymmetries. Indeed, in developmental dyslexics, phonological impairments may lead to an abnormal development of the VWFA. Although the VWFA is probably not the primary origin of dyslexia (Habib, 2000), it is one of the brain regions that do not activate normally in dyslexic subjects during reading (Helenius *et al.*, 1999; Paulesu *et al.*, 2001). One may speculate that this defect is a consequence of a phonological impairment on the fine tuning of the VWFA for reading.

We are now in a position to summarize the impact of the acquisition of reading on the functional properties of the VWFA. Learning to read entails learning to recognize letter shapes, learning that different shapes may correspond to a single abstract letter identity (e.g. 'a' and 'A'), and learning that only some combinations of those letters are legal. All three types of knowledge are reflected in the functional properties of the VWFA. First, the VWFA is activated more strongly by real characters than by pseudofonts of equal visual complexity (Price *et al.*, 1996*a*; Tarkiainen *et al.*, 1999). Secondly, the VWFA represents words in an abstract case-invariant format, as shown by the recent finding of a case-independent word repetition priming in this region (Dehaene *et al.*, 2001). Thirdly, we have demonstrated in the present study that the orthographic regularities that distinguish legal from illegal strings are also incorporated in the functional properties of the VWFA. All of these properties imply that the VWFA is plastic and becomes progressively attuned to details of the reading process during the acquisition of literacy.

Acknowledgements

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