Direct Intracranial, fMRI, and Lesion Evidence for the Causal Role of Left Inferotemporal Cortex in Reading

Case Study

Raphaël Gaillard,[1,3] Lionel Naccache,[1,3,6]
Philippe Pinel,[1] Stéphane Clémenceau,[4]
Emmanuelle Volle,[5] Dominique Hasboun,[2,6]
Sophie Dupont,[2,6] Michel Baulac,[2,6]
Stanislas Dehaene,[1] Claude Adam,[3]
and Laurent Cohen[1,2,6,*]
[1] INSERM, U562,
CEA/DSV, IFR 49
Orsay
France
[2] Department of Neurology
[3] Department of Clinical Neurophysiology
[4] Department of Neurosurgery
[5] Department of Neuroradiology
AP-HP, Hôpital de la Salpêtrière
IFR 70, Paris
France
[6] Université Paris VI
Faculté Pitié-Salpêtrière
Paris
France

Summary

Models of the "visual word form system" postulate that a left occipitotemporal region implements the automatic visual word recognition required for efficient reading. This theory was assessed in a patient in whom reading was explored with behavioral measures, fMRI, and intracranial local field potentials. Prior to surgery, when reading was normal, fMRI revealed a normal mosaic of ventral visual selectivity for words, faces, houses, and tools. Intracranial recordings demonstrated that the left occipitotemporal cortex responded with a short latency to conscious but also to subliminal words. Surgery removed a small portion of word-responsive occipitotemporal cortex overlapping with the word-specific fMRI activation. The patient developed a marked reading deficit, while recognition of other visual categories remained intact. Furthermore, in the post-surgery fMRI map of visual cortex, only word-specific activations disappeared. Altogether, these results provide direct evidence for the causal role of the left occipitotemporal cortex in the recognition of visual words.

Introduction

The initial stage of word reading consists of the fast and parallel identification of letter strings, independently from CASE, *font*, size, or ^location in the visual field (Dehaene et al., 2005; Mayall et al., 1997). This invariant recognition process allows readers to access the body of word-associated knowledge, including meaning and phonology. The computation of this invariant visual representation, which has been termed the "visual word

*Correspondence: laurent.cohen@psl.aphp.fr

form," is thought to be subtended by the left ventral occipitotemporal cortex (Booth and Rolls, 1998; Cohen and Dehaene, 2004; Cohen et al., 2000). Nevertheless, the nature and specificity of this contribution have been the matter of a continuing debate (e.g., Price and Devlin, 2003).

The role of the left occipitotemporal cortex in reading has been studied using a variety of techniques, each contributing to the general picture, but each hindered by intrinsic shortcomings (for recent reviews see Cohen and Dehaene, 2004; Jobard et al., 2003; McCandliss et al., 2003). Thus, PET and fMRI have been decisive for delineating a reproducible focus of activation (the Visual Word Form Area or VWFA), located lateral to the mid-portion of the left fusiform gyrus. This region is activated by strings of letters relative to rest or to low-level stimuli (Cohen et al., 2000, 2002), but also relative to other categories of visual objects such as faces or houses (Gauthier et al., 2000; Hasson et al., 2002; Puce et al., 1996). Those techniques also allowed to identify some functional properties of the VWFA that are important for reading, such as invariance for position in space (Cohen et al., 2002), invariance for case changes (Dehaene et al., 2001), and encoding of letter order (Dehaene et al., 2004). Those high-level encoding properties emerge progressively along a posterior to anterior gradient, ranging from about Talairach coordinates (TC) $Y = -70$ to about TC $Y = -50$ (Dehaene et al., 2005; see also Mechelli et al., 2005).

PET and fMRI have limited temporal resolution, and the precise unfolding of activations had to be explored using electromagnetic recordings. The VWFA overlaps with the reconstructed source of electrical fields that are recorded on the scalp during word reading, with a latency of about 150–200 ms (Cohen et al., 2000; Posner et al., 1999). Converging results have been obtained with MEG, which may represent an improvement over EEG in terms of spatial resolution (Marinkovic et al., 2003; Simos et al., 2002; Tarkiainen et al., 1999). However, both methods still face the difficulty of inferring the location of sources on the basis of surface recordings. Data conciliating good resolution both in space and in time have been obtained with intracerebral recordings of local field potentials (LFPs) in epileptic patients. Those studies confirmed that printed words trigger P150 or N200 waves, as well as event-related spectral changes, in the ventral occipitotemporal cortex, with left-hemispheric predominance (Allison et al., 1994, 1999; Nobre et al., 1994; Tanji et al., 2005). Moreover, such waves are larger or occasionally exclusive for letter strings compared to a variety of control stimuli such as faces, flowers, or objects.

However, imaging methods are solely correlational and thus cannot identify which areas play a causally indispensable role, among the set of those activated during reading. Addressing this issue requires the observation of reading deficits associated with the dysfunction of well defined brain areas. The causal involvement of the VWFA in reading is implied by the overlap of the activation site observed in normal subjects with the critical

lesion site associated with pure alexia, an acquired deficit of visual word recognition (Cohen et al., 2003). As a potential alternative to permanent lesions, transient inactivations can be induced by TMS. However, the ventral occipitotemporal cortex is remote from the skull surface and inaccessible to this technique. Finally, it is possible to interfere with the functioning of those regions by stimulating the intracerebral electrodes that are used for LFP recording. However, the evidence available to date is of little relevance to reading per se, as it mostly relates to a broad language deficit induced by stimulation of a loosely defined Basal Temporal Language Area encompassing anterior sectors of the ventral temporal cortex (Lüders et al., 1991). Recently, through the stimulation of left ventral electrodes, Usui et al. (2003) elicited a deficit in naming but not in understanding kanji words and object pictures, with no deficit for kana words, a complex syndrome differing from pure alexia.

Thus, acquired lesions still appear as the clearest source of evidence for studying the causal involvement of specific brain regions in reading. However, lesions are often large and do not respect the boundaries of functional areas, thus hindering fine-grained correlation with cognitive functions. Moreover, acquired lesions such as strokes occur unexpectedly, so that the patients' performance cannot be compared directly to their premorbid abilities. Studies which try to interpret patients' behavior on the basis of functional imaging face a similar problem. In the absence of data acquired prior to the lesion, it may be difficult to interpret the functional pattern as a consequence of the lesion or of the patients' idiosyncratic organization.

Within this context, the present paper arose from a rare clinical opportunity. We were able to study the role of the ventral occipitotemporal cortex in reading in a single patient who underwent the surgical resection of a small patch of cortex close to the VWFA and developed pure alexia. Although the research was performed under tight temporal constraints, we gathered behavioral and fMRI data before and after surgery, thus allowing for a sensitive analysis of the lesion's consequences on the functional organization of the ventral visual stream. We also obtained intracranial LFP data.

From the theoretical point of view, this unique combination of data from the same person presents several opportunities. First, the intracranial LFPs recorded from an electrode close to the VWFA, as defined by both fMRI data and subsequent lesion data, allowed us to confirm the latency and profile of this region's response to written words. Using a masking paradigm, we could confirm its fast response to subliminal words and study the differences between subliminal and supraliminal processing—issues that were previously studied only with fMRI and ERPs.

Second, as the patient developed pure alexia following surgery, we had a unique opportunity to study the causal involvement of a finely characterized functional area in visual word perception. The postsurgical study was carried out shortly after occurrence of the lesion, ensuring that no reorganization of the reading system had taken place. Note also that the lesion size was much smaller than in most previous research with vascular cases.

Finally, fMRI data were used to inform the debate on specialization within the ventral visual pathway for cate-

gories such as printed words, faces, houses, etc. In a recent review (Cohen and Dehaene, 2004), we argued that, although evidence for functional specialization and reproducible localization is mounting, the regional selectivity of the VWFA for word processing remains a matter of debate. It is likely that ventral occipito-temporal cortex consists of interlocking neural populations that are only partially segregated by visual category (Haxby et al., 2001). Nevertheless, we have suggested that there is partial regional selectivity, in as much as VWFA lesions may yield isolated reading deficits, in the absence of substantial face or object recognition impairments. However, even in this weaker sense, selectivity is still a matter of debate (Price and Devlin, 2003). In the present study, the patient was tested behaviorally and with fMRI, using pictures from various categories, allowing us to study the selectivity of the behavioral and functional imaging anomalies that resulted from the lesion.

Results

Case Study
Medical History
The patient was a 46-year-old right-handed man, suffering from epilepsy since the age of 12. Seizures started with a loss of contact and leftward rotation of his eyes and head. Then he engaged in automatic behavior, followed by rare secondary generalization. Interictal status was normal. Presurgical epilepsy evaluation included video-EEG, PET-scanning, and neuropsychological assessment. Based on these examinations, left occipito-temporal lobe epilepsy was diagnosed. As the localization of the epileptogenic focus remained unclear, intracerebral stereo EEG (SEEG) was performed.

A first implantation localized a focus to the posterior left inferior temporal gyrus. As another epileptogenic focus was suspected, a second more posterior implantation was performed. After discussion of the potential risks and benefits of surgery, including the eventuality of a reading impairment, a focal corticectomy was performed. After surgery, the patient presented with letter-by-letter (LBL) reading. The patient gave his written informed consent, and the project was approved by the Ethical Committees of the Salpêtrière and the Bicêtre hospitals.

Analysis of the Cortical Resection
Along the rostrocaudal axis, the resection spanned the occipitotemporal boundary, extending approximately from TC Y = −60 to TC Y = −80 (Figure 1). It affected the inferior occipital/temporal and the fusiform gyri, reaching the collateral sulcus and sparing the lingual/parahippocampic gyrus. The lesion thus overlapped with the critical lesion site associated with pure alexia (Cohen et al., 2003).

Behavioral Study
Presurgical Assessment
The patient had a verbal IQ of 87 and a performance IQ of 113. Oral language production, comprehension, and repetition were normal. During postictal periods, he showed some word-finding difficulties, a reduced digit span (forward: 2), and a general cognitive slowing. The patient was normal in the DO80 picture-naming test (2/80 errors), which includes a variety of living and
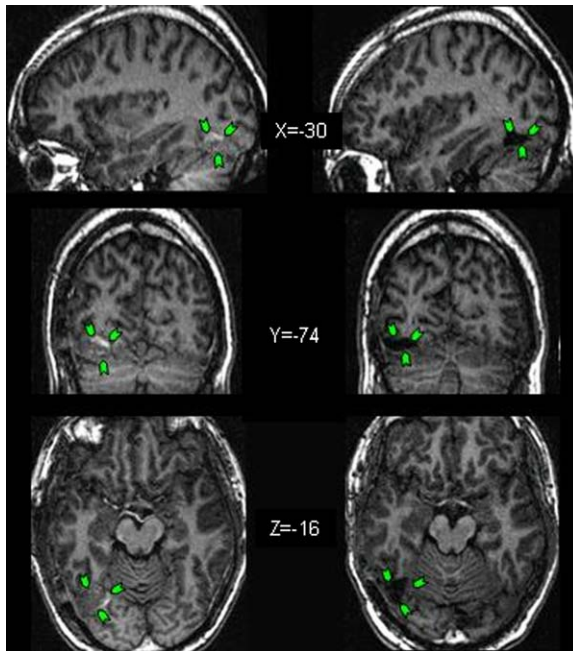
Figure 1. Left Occipitotemporal Surgical Resection

T1-weighted MRI of the patient's normalized brain, 2 weeks (left) and 6 months (right) after surgery, showing the lesion (green arrows) affecting the ventral occipitotemporal cortex between TC y = −80 and y = −60.
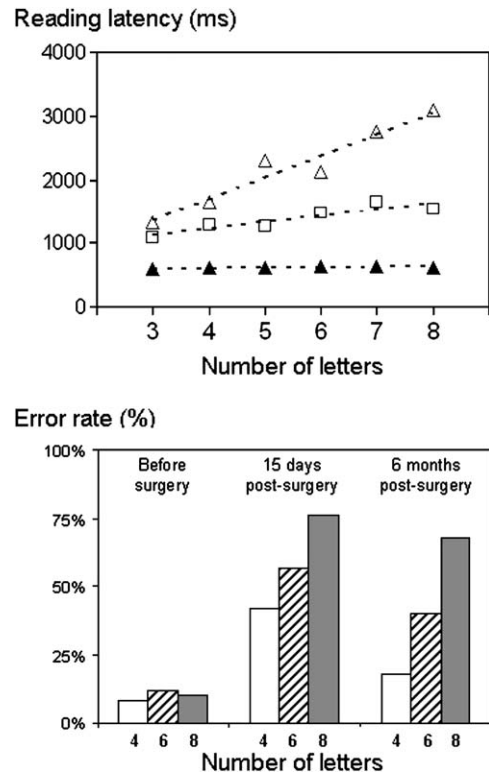

Figure 2. Reading Performance Before and After Surgery

(Top panel) Word reading latencies. Before surgery, latencies were short and showed no influence of word length (solid triangles). Two weeks after surgery, responses were slow, showing a pattern of letter-by-letter reading (open triangles). Six months later, despite some improvement, the same pattern persisted (open squares). (Bottom panel) Error rate for briefly flashed words. Before surgery, errors were few. After surgery, both early and late, the patient made numerous errors, with a clear influence of word length.

nonliving items (22 animals, 30 tools, 7 vegetables or plants, 7 pieces of furniture, 14 others). He was also flawless in Warrington's facial recognition test (0/25 errors).

The patient was flawless at writing to dictation a list of 36 frequent words (3 to 9 letters), and at converting uppercase letters to lowercase or conversely. He did not complain of any reading difficulty. In a first formal reading test, he was presented with 165 lowercase nouns, 3 to 8 letters in length. Stimuli were presented centrally (maximum angle: 8°). The patient was asked to read words aloud as rapidly as possible. Stimuli remained visible until a response was produced. Responses were fast and accurate (mean latency: 610 ms, excluding five trials with hesitation or error). Importantly, reading latencies were constant irrespective of word length (p > 0.2). In a second test, the patient was presented twice with a set of 186 familiar words, 4, 6, or 8 letters in length. Stimuli were flashed for 200 ms, randomly in the left or right hemifield. Error rates did not differ between hemifields, and data were pooled. The patient made 10% reading errors, with no influence of word length (Figure 2).

The patient was also accurate in a lexical decision task. We used the same 184 words as in the LFP experiment 4, and 184 matched readable pseudowords. Stimuli were presented centrally (maximum angle: 8°). Stimuli remained visible for 500 ms. Mean latency for words was 740 ms, excluding four trials longer than 3000 ms and 11 errors (6%). There was an effect of frequency (p < 0.02) with no effect of word length (p = 0.67).

Postsurgical Assessment

Goldman perimetry showed a normal visual field. Two weeks after surgery, the patient was seizure-free, with an improved digit span (forward 6) and better overall cognitive functioning. He had no difficulties recognizing common objects, places, or faces. His performance was still at ceiling in picture naming (2/80 errors) and in face recognition (0/25 errors). He showed no difficulty and no slowing in those tasks relative to the presurgical session.

Oral language production, comprehension, and repetition were still normal. The patient was still flawless in the dictation test and in converting letters between cases. However, he complained of reading difficulties and there was a clear-cut change in his reading pattern (Figure 2). In the first reading task, he showed increased latencies (mean latency: 2240 ms, excluding five trials; between sessions: p < 0.001). Furthermore, there was now a typical pattern of LBL reading, with longer latencies for longer words (regression p < 0.001; slope 342 ms per letter). In the flashed word reading task, the patient now made 58% errors, with a large effect of word length (42%, 56%, and 76% errors for 4, 6, and 8 letter words). In lexical decision, the mean RT for words was 1327 ms, excluding eight trials longer than 3000 ms and 30 errors (16%), significantly slower than before surgery (p < 0.0001), with an effect of word length (p < 0.05).

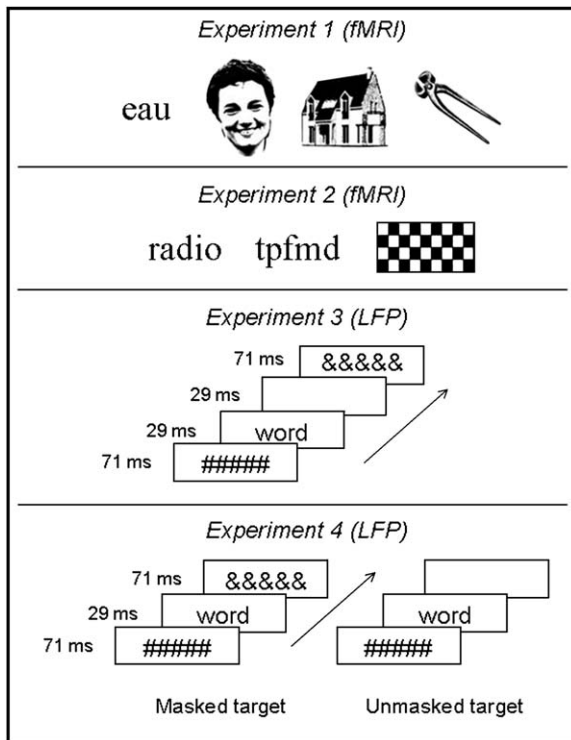Reading tasks were run again 6 months after surgery (Figure 2). Despite some improvement, the pattern was

Figure 3. Examples of Stimuli from fMRI Experiments 1 and 2, and Structure of Trials for the Intracerebral LFP Experiments 3 and 4

Figure 4. fMRI Experiment 1

Occipitotemporal activations before and after surgery, for each stimulus type relative to the others (p < 0.01). Following surgery (green arrow), the patient had pure alexia, and the activations induced by words in the VWFA disappeared. All the other clusters remained present. The bottom 3D image shows the relative position of the VWFA and of other category-dependent clusters before surgery. The VWFA activation is just anterior to the lesion (green) and contiguous to intracerebral electrodes (magenta).

comparable to the early postsurgery session. In the timed reading task, the mean latency was 1381 ms, i.e., more than twice slower than before surgery, with a significant length effect (p < 0.001; slope 102 ms per letter). In the flashed reading task, the patient still made 42% errors, with a large length effect (18%, 40%, and 68% errors for 4, 6, and 8 letter words).

In summary, the patient showed no reading deficit before surgery. After surgery, he showed typical and long-lasting pure alexia with LBL reading. In the following fMRI study, we tried to clarify the mechanisms underlying visual word perception.

Functional MRI Explorations of Reading

We performed two fMRI experiments in order to identify the functional properties of the patient's inferotemporal areas involved in visual word processing, before and after surgery. We wished to relate presurgical activations to the intracerebral recordings described later and to relate postsurgical activations to the reading deficit and to lesion topography. Apart from one final whole-brain analysis, we only report activations in the temporal and occipital cortex.

Experiment 1: Words, Faces, Houses, and Tools

Our aim was to map the occipitotemporal activations induced by written words and by other categories of visual objects known to elicit distinct topography of activation, namely pictures of faces, houses, and tools (Figure 3). We wanted (1) to identify the VWFA on the basis of its preference for words relative to other complex stimuli, (2) to identify the changes in the activation pattern following surgery, and (3) to determine to what extent the
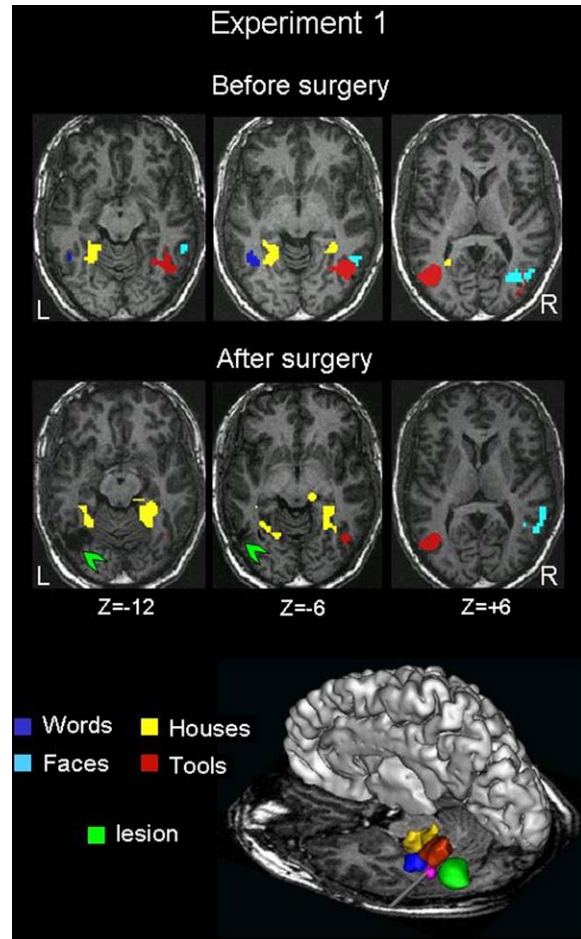
behavioral and activation changes were specific to reading, or globally affected visual object processing.

We first analyzed presurgery activations. In order to isolate regions with a relative selectivity, each category was contrasted with the mean of the other three categories. We found distinct foci of activation for the four categories (Figure 4). For words, activations peaked in the region of the VWFA, in the depth of the left occipito-temporal sulcus (TC −42 −57 −6; Z = 5.33). For faces, there was a right lateral occipito-temporal cluster (TC 48 −72 6; Z = 5.75). When lowering the voxelwise threshold to p < 0.01, this cluster extended ventrally to the Fusiform Face Area (TC 39 −63 0; Z = 2.95). The contrast for houses showed bilateral activations in the Parahippocampal Place Area (left: TC −24 −57 −6; Z = 6.95; right: TC 33 −42 −9; Z = 5.47), and in the left occipital pole (TC −27 −93 21; Z = 5.97). The right parahippocampic cluster was just below the extent threshold (0.05 < p < 0.06). As it was intense, it reached significance

when raising the voxelwise threshold to a more stringent level of p < 0.0001. For tools, there were bilateral left-predominant activations in the lateral occipitotemporal region (left: TC −45 −75 9; Z > 8; right: TC 45 −66 −3; Z = 5.48). The VWFA showed no significant activation relative to rest for categories other than words (all p values > 0.05 at the peak voxel).

The same analyses were applied to the data collected after surgery. In contrast to the initial session, words did not elicit significant activation relative to other categories. Moreover, even the contrast of words minus rest showed no ventral activation, but only bilateral posterior occipital clusters (left: TC −30 −90 21; Z > 8; TC −45 −72 9; Z = 5.20; right: TC 42 −78 9; Z = 4.78). Accordingly, comparing the contrast of words minus rest in the presurgery minus the postsurgery session showed a significant decrease of activation in the VWFA (TC −42 −57 −6; Z = 3.90).

In contrast with the disappearance of the VWFA, faces, houses, and tools yielded activations similar to the presurgery session (Figure 4). Faces activated the right lateral occipito-temporal cortex (TC 60 −42 6; Z = 4.93), extending to the FFA region at a lower threshold. Houses activated the bilateral parahippocampic gyrus (left: TC −27 −48 –12; Z = 5.45; right: TC 27 –42 −12; Z > 8), plus a right occipital cluster (TC 36 −75 18; Z = 6.40). The symmetrical left occipital cluster was still present, although below statistical threshold (TC −27 −93 18; Z = 4.39). Tools activated bilaterally the lateral occipito-temporal cortex (left: TC −45 −72 9; Z = 7.05; right: TC 21 −78 18; Z = 5.40). We made the same comparisons between sessions for faces, house, and tools as described before for words. In contrast to the decrease of the VWFA activation by words, this showed no significant decrease of the category-specific regions identified before surgery, except for a decrease in the left cluster for tools (TC −45 −78 6; Z = 4.17), which nevertheless remained strongly activated. Additional analyses of the response profiles of category-selective regions are provided as Supplemental Data available online.

In summary, before surgery we identified occipitotemporal regions with a relative preference for distinct types of visual categories. This pattern was normal despite the patient's epilepsy. Faces activated inferior occipital, lateral, and ventral temporal regions of the right hemisphere (for example see Haxby et al., 1999). Houses activated the parahippocampal gyrus bilaterally (Epstein et al., 1999; Hasson et al., 2002), and tools activated bilateral temporal regions (Chao et al., 1999). After surgery the activation of the VWFA by words disappeared, while other activations persisted. The complete and selective disappearance of the VWFA activation was thus parallel to the selective deficit for word perception that followed surgery.

Experiment 1 leaves open the question of the mechanisms of the effective LBL reading, which contrasted with the absence of ventral activation by words. However, this experiment was ill-suited to study LBL reading. Words were displayed briefly and at a fast rate, while it took the patient more than 2 s to read even 5 letter words. Moreover, the patient was only asked to perform a repetition detection task that could be performed on the basis of a low-level analysis. In experiment 2, we applied a protocol that has been used

previously to clarify the bases of LBL reading (Cohen et al., 2003). Particularly, we resorted to longer interstimulus intervals and display durations, allowing LBL reading to emerge.

Experiment 2: Words, Consonant, and Checkerboards

We contrasted alphabetic stimuli (words and consonant strings) versus checkerboards and rest (Figure 3). In normals, this procedure allows for a clear delineation of the VWFA, which is activated by alphabetic stimuli more than by checkerboards. This protocol also allowed us to delineate brain networks subtending LBL reading (Cohen et al., 2003, 2004; Henry et al., 2005).

We first analyzed presurgery activations. In order to isolate regions with a selectivity for alphabetic processing, we contrasted alphabetic stimuli (i.e., words and consonants) minus checkerboards. This showed a network of left-predominant fronto-parieto-temporal activations, including the VWFA (TC −42 −51 −3; Z > 8; TC −48 −54 −15; Z = 5.90) (Figure 5). In addition to the VWFA, the basic contrast of alphabetic stimuli minus rest showed bilateral posterior occipital activations (left: TC −33 −87 18; Z > 8; right: TC 39 −84 0; Z > 8), and a right-hemispheric cluster symmetrical to the VWFA (the R-VWFA) (TC 36 −51 −6; Z = 5.04). The contrasts of words minus consonant strings showed a cluster in the left posterior MTG (TC −57 −54 −3; Z = 4.77) but no difference in the region of the VWFA (e.g., p = 0.13 at the peak voxel).

After surgery, the contrast of alphabetic stimuli minus checkerboards showed only a left posterior occipital cluster (TC −36 −90 18; Z = 7.36), which was already present before surgery although somewhat below the extent threshold. In contrast, the left ventral temporal activation was no longer observed. Even the simple contrast of alphabetic stimuli minus rest showed no activation in the vicinity of the VWFA, while the strong bilateral occipital activations observed before surgery were still present. In the right hemisphere, however, this contrast identified the R-VWFA activation observed before surgery (TC 36 −51 −6; Z = 4.43), although the cluster extent of five voxels was too small to reach a whole-brain corrected threshold of p < 0.05. It was significant if corrected within a 12 mm sphere centered on the peak from the first session.

On closer scrutiny, the disappearance of the VWFA from those overall contrasts pooling all alphabetic stimuli was actually due to its complete lack of activation by consonant strings. Indeed, the contrast of consonants minus rest showed no brain activation except for the usual bilateral occipital clusters. The significance of this disappearance was assessed by subtracting the contrast of consonant strings minus rest in the presurgery minus the postsurgery session. This showed a significant reduction in the VWFA (TC −42 −51 −3; Z = 4.80). In contrast, real words activated a large bilateral network relative to rest, including the left ventral temporal cortex at coordinates slightly more posterior and ventral (TC −45 −60 −18; Z = 4.74) (voxelwise threshold p < 0.0005.) than the presurgical peak of the VWFA.

As in previous studies of patients with LBL reading (Cohen et al., 2003, 2004; Henry et al., 2005), the network associated with the reading of real words could be shown by directly contrasting words minus consonant
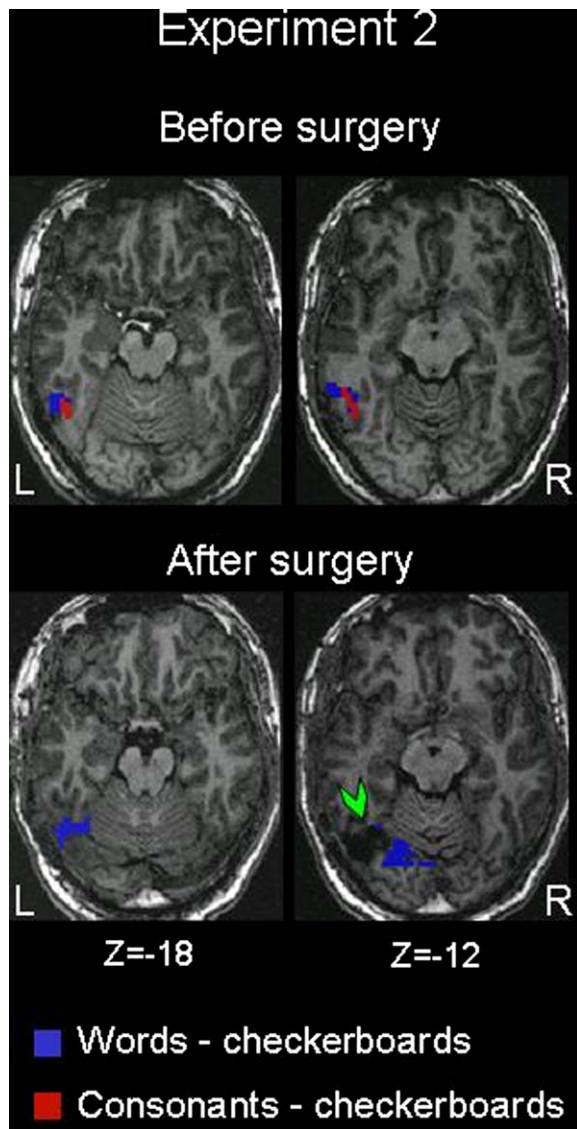
Figure 5. fMRI Experiment 2

Occipitotemporal activations before and after surgery, for words or consonant strings relative to checkerboards (p < 0.01). Following surgery (green arrow), the activations induced by consonant strings in the VWFA disappeared. However, when the patient was reading words letter-by-letter, activations were present in the residual left occipitotemporal cortex.

strings. It included the same left ventral cluster as mentioned just before (TC −45 −60 −18; Z = 5.18).

If indeed the activation of the left ventral occipitotemporal cortex by real words reflects the patient's engagement in LBL reading, perhaps by top-down means, it should be associated with a larger network of areas recruited by other components of the effortful LBL strategy, such as serial scanning of letters and working memory. To identify those newly involved components, we searched the whole brain for increased activation by words minus checkerboards in the postsurgery relative to the presurgery session (see figure in the Supplemental Data). This showed bilateral clusters in the frontal eye fields (left: TC −45 12 42; Z > 8; right: TC 45 3 48;

Z > 8) and premotor cortex, posterior parietal lobes (left: −24 −54 57; Z = 4.48 (voxelwise threshold p < 0.0005); right: TC 15 −54 42; Z = 4.09), anterior cingulate cortex (TC 9 30 30; Z = 7.27); and left-hemispheric clusters in the dorsolateral prefrontal cortex (TC −36 39 24; Z > 8), the lateral occipital lobe (TC −30 −87 30; Z = 6.02) and the ventral occipital cortex postero-mesial to the resection (TC −21 −69 −15; Z = 3.83).

In summary, this experiment corroborates experiment 1 regarding the overall activation pattern of the VWFA. Consonant strings activated the VWFA before but not after surgery. This suggests that the lesion resulted in the loss of the automatic activation normally induced in the VWFA by the passive viewing of any letter string, even as illegal as strings of consonants. With real words, however, a novel result of the present experiment is that we now observed left ventral temporal activations even after surgery. However this postsurgical cluster was abnormal in several respects. First, it was slightly more posterior and ventral than the presurgical cluster observed in both experiments 1 and 2, suggesting that it corresponded to earlier stages of the visual word form system. Second, this activation was not automatic, as it was before surgery. It was now restricted to situations in which the patient engaged in LBL reading, i.e., in experiment 2 but not in experiment 1, and with real words but not with consonant strings. Third, this cluster was part of a wider postsurgical increase of activation in left occipitotemporal regions that was associated with LBL reading. This included ventral cortex at about TC y = −70, close to activations showing location-specific priming for repeated letters (Dehaene et al., 2004). Again this is suggestive of activations at early stages of alphabetic processing.

Intracerebral Recordings of LFPs Evoked by Printed Words

The correlations between lesion anatomy, behavioral impairments, and changes in fMRI activations allowed us to dissect the causal and functional implication of the left inferotemporal cortex in reading. We now supplement our database with intracerebral recordings gathered before surgery, which should provide data with high temporal and spatial resolution.

We used the LFP information to confront two different issues. First, the availability of a direct electrophysiological record allowed us to test existing ERP and MEG models of visual word form activity (Cohen et al., 2000; Marinkovic et al., 2003; Salmelin et al., 1996; Simos et al., 2002), which postulate that this activation occurs around 170 ms following word onset and generates the scalp N1 or M1. Although previous intracranial evidence is available on this issue (Allison et al., 1994, 1999; Nobre et al., 1994), it has not been accrued in the context of a well-localized VWFA, as defined here by both fMRI and postlesional neuropsychological data. Second, we used the LFP data to test the hypothesis of a fast bottom-up activation of the VWFA even when the word stimulus is made invisible by masking. Previous experiments used ERPs and fMRI to demonstrate that a small but detectable activation of the VWFA occurs during subliminal word presentations and can prime subsequent processing of a related word (Dehaene et al., 2001; Kiefer, 2002). However, the availability of an intracranial signal arising from a small,

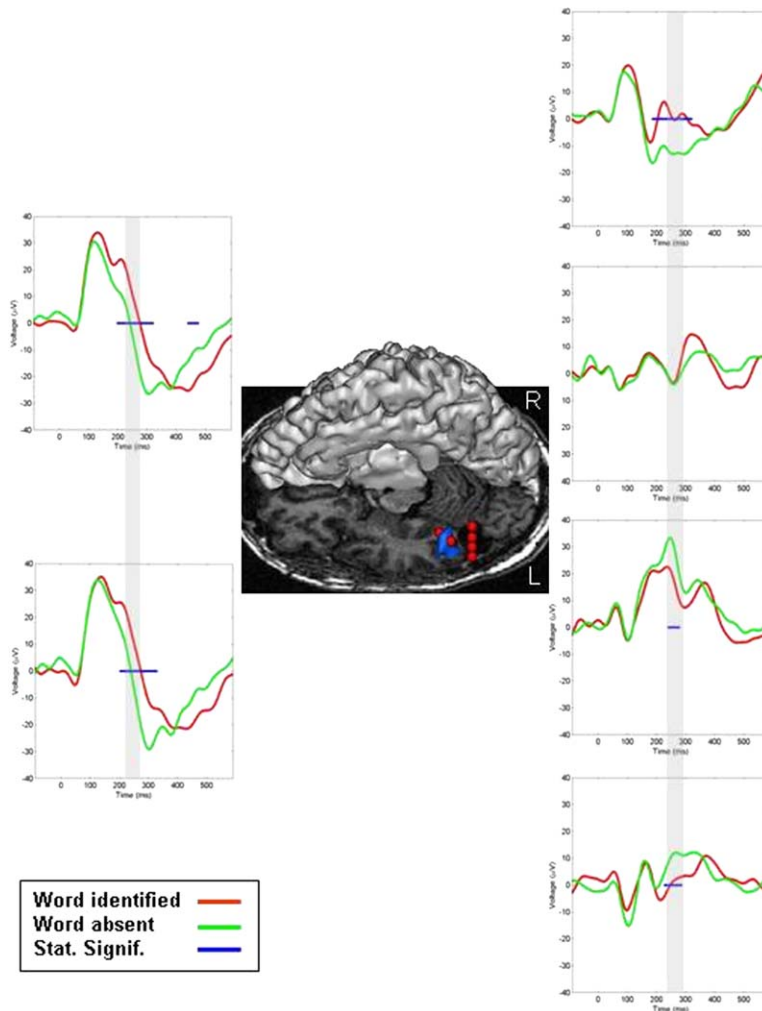## Experiment 3: LFPs evoked by words in the left fusiform gyrus

Figure 6. LFP Experiment 3

LFPs evoked by conscious words (red lines) as compared to blank trials (green lines), on left fusiform contacts overlapping with the fMRI activation of the VWFA (left column), and with the surgical resection (right column). Vertical gray bars indicate the temporal windows in which occurs a polarity inversion between the two mesial and the two lateral contacts of the posterior electrode. The central image depicts the 3D location of the contacts (red spheres) and of the VWFA activation (blue) superimposed on the postsurgery MRI.

well-delimited cortical region should provide statistically stronger and temporally more refined evidence. By contrasting masked and unmasked presentations of words, we tested directly the hypothesis that fast feedforward activation is preserved during subliminal processing and that masking acts by preventing a subsequent temporal extension of activity at the same location that normally occurs on conscious trials (Dehaene et al., 2001; Kovacs et al., 1995; Lamme et al., 2002).

The patient was stereotactically implanted on two occasions with depth electrodes (12 and 8 months before surgery).

Experiment 3: Perception of Visible Words (Pilot Study)

During the first implantation, the patient participated in a pilot experiment exploring the conscious perception of masked words presented close to perception threshold (Figure 3). The patient was asked to name words that were presented very briefly. He also received blank trials in which the word was replaced by a blank screen.

The patient correctly identified 62 out of 128 words (48.4%). We only report the LFPs evoked by correctly identified words and compare them to blank trials. Indeed, trials on which words were not correctly identified were heterogeneous, including nondetection, but also various semantic and morphological errors. The design of this pilot experiment did not allow us to record enough trials within each of those trial populations to obtain clear LFPs. Moreover, blank and correctly identified trials are equivalent to the blank and unmasked conditions that will be studied in experiment 4. On the basis of the analysis of the main LFP experiment 4, we defined two temporal windows of interest: an early window ranging from 110 to 380 ms after word onset, and a late window ranging from 380 to 500 ms.

The comparison of words minus blank trials showed an effect on 13 out of 35 contacts: 7 in the early window only, 5 in the late window only, and 1 in both windows. Four contacts were located in the region that would be removed. Three of them showed an early effect, with a mean peak latency of 250 ms (230 ms, 260 ms, 260 ms, respectively) (Figure 6). A polarity inversion occurred between the most mesial and the two lateral of those contacts, allowing for a precise localization of the

underlying generator at the second mesial contact, at approximate TC −37 −66 13.

Two slightly more anterior contacts overlapped with the fMRI activation of the VWFA (experiment 2: contrast of alphabetical stimuli minus checkerboards). One showed only an early effect (peak at 280 ms), and the other both an early (peak at 280 ms) and a late effect (peak at 460 ms).

In summary, these preliminary results show that the left ventral occipitotemporal cortex was highly responsive to words. Furthermore, the polarity inversion correlates nicely with the fMRI and lesion data to pinpoint a small region of the occipitotemporal sulcus as being the main region of activation during word reading.

Experiment 4: Perception of Visible and Subliminal Words

We presented unmasked visible and masked subliminal words. On masked trials, words were presented using the same method as in experiment 3, except that no blank screen was inserted between the target word and the post-mask (Figure 3). Masked trials were randomly intermixed with unmasked trials, in which the post-stimulus mask was removed. On blank trials, the target word was replaced with a blank screen. The patient was engaged in a forced-choice task of categorizing each word as threatening or nonthreatening.

The patient accurately categorized unmasked words according to their emotional content (d′ = 1.7; p < 10^{-4} in χ^2 test), while performance dropped to chance level for masked words (d′ = 0.012; p = 0.9 in χ^2 test). Rejection rates due to artifacts or epileptic activity were inferior to 9% for all reported electrodes.

LFPs were averaged separately for masked words, unmasked words, and blank trials. We then compared words versus blank trials. For unmasked trials, there was an effect of word presence on 24 out of 25 contacts (96%). For masked trials, however, this affected only 9 of the 25 contacts (36%) (Figure 7).

LFP Correlates of Masked Words. The vast majority of the LFPs evoked by masked words were confined to an early temporal window. We therefore distinguished an early effect ranging from 110 to 380 ms after word onset (mean peak latency 229 ± 48 ms), and late effects ranging from 380 to 500 ms (Figure 7). Only one contact located in the occipital pole (TC −15 −101 −11) showed both early (110–200 ms) and late (435–495 ms) effects for masked words.

LFP Correlates of Unmasked Words. In the unmasked condition, 18 out of 24 contacts with an effect of word presence showed two distinct phases in this effect (mean peak latency = 255 ± 34 ms for the early effect, and 430 ± 35 ms for the late effect), with a polarity inversion between the early and the late phases defined as before in 16 out of the 18 electrodes. According to this distinction, five contacts presented a late effect only (mean peak latency 428 ± 30 ms), and a single contact had only an early effect (peak latency = 255 ms). Notably, the five contacts showing only a late effect were located in the dorsal occipito-parietal cortex (TC Z > 13).

LFPs to masked words were always less intense and less significant than to unmasked words. We computed the ratio of the effect size for visible and masked words averaged over the early temporal window, across the 19

Experiment 4: LFP correlates of masked and unmasked words during the first 500 ms
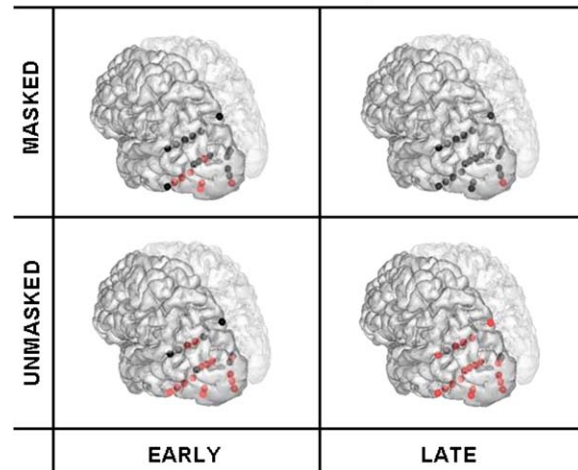
Figure 7. LFP Experiment 4

Summary of the LFP correlates of masked and unmasked words in the early (110–380 ms) and late (380–500 ms) temporal windows. Red contacts correspond to a significant difference between words and blank trials. The effect elicited by masked words was restricted to the early window. The effect of visible words spanned a larger number of contacts and was sustained over both the early and the late periods.

electrodes that showed an early correlate of visible words, and we found a ratio of 1.4.

Fusiform LFPs. We now focus on the left (n = 4) and right (n = 3) fusiform contacts. In the left hemisphere, the electrode was located at the anterior edge of the cortical patch that would be subsequently removed (Figure 8). All contacts were affected by the presence of unmasked words and showed both early and late effects, ranging from 220 to 500 ms. For masked words, three left and three right contacts showed an early effect, while none showed a late effect (see Figure 7). The (early) effect for masked word was similar for left and right fusiform contacts (ratio = 1.09). In contrast, a strong asymmetry was observed for the unmasked words, for which the effect was much larger in the left hemisphere both in the early and late temporal windows (ratio = 1.76 and 1.73, respectively).

Correlates of Lexical Parameters in the Fusiform Cortex. LFPs were averaged in separate conditions in order to explore the correlates of word frequency (below versus above median frequency), word length (3 to 5 versus 6 to 8 letters), lexical category (verbs versus nouns), and emotional valence (threatening versus nonthreatening) for the seven fusiform contacts. For unmasked words, only one left fusiform contact showed a word frequency effect between 460 and 500 ms, with a more negative voltage for high-frequency words (Figure 8). No effect was found for other fusiform contacts. For masked words, two left and one right fusiform contacts showed a similar effect. There was no effect of length for unmasked words on any of the fusiform contacts. Interestingly, such an effect was observed on eight occipital contacts posterior to the fusiform cortex. This is suggestive of a progressive extraction of a visual word representation invariant for physical parameters such as

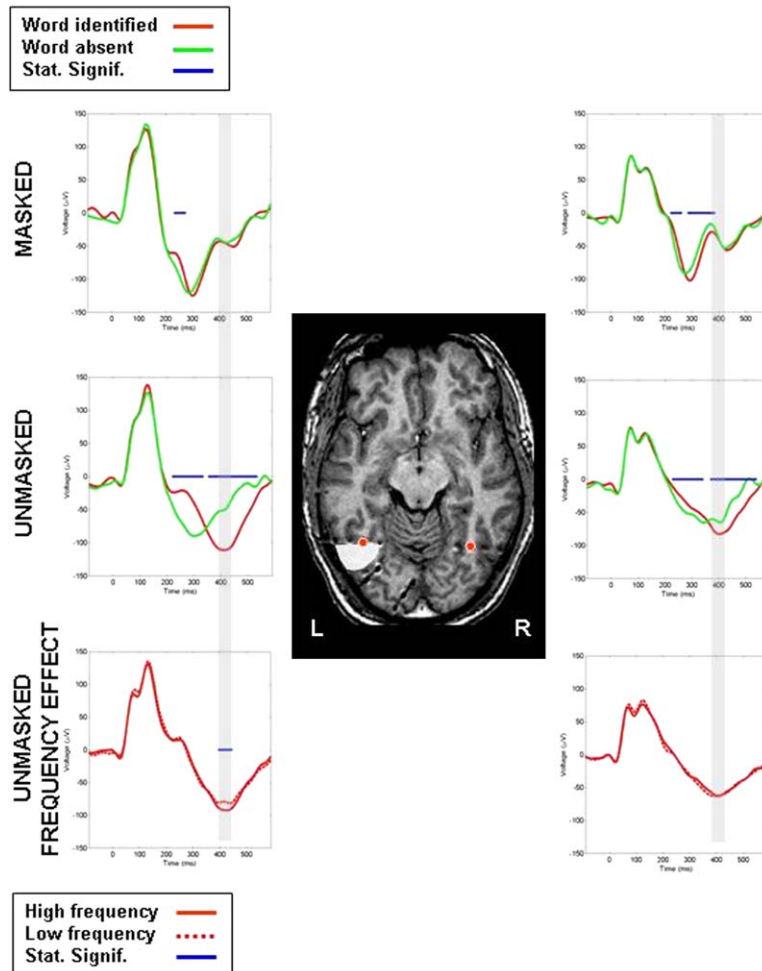**Experiment 4: LFPs evoked by words in the left and right fusiform gyri**

Figure 8. LFP Experiment 4

LFPs evoked on left and right fusiform contacts (left and right columns, respectively), by words (red lines) as compared to blank trials (green lines). Neural activity evoked bilaterally by consciously perceived unmasked words (middle panels) was more intense and longer-lasting than for masked stimuli (upper panels). Bottom panels show a left-lateralized effect of word frequency in a temporal window indicated by vertical gray bars. Blue lines indicate samples with a significant difference between conditions. The central image depicts the location of the relevant contacts (red dots) on a presurgery MRI with implanted electrodes. The to-be-resected region is shown in white.

word length. For masked words, no word length effect could be observed. Finally, lexical category and emotional valence did not affect fusiform LFPs in either masked or unmasked conditions.

In summary, our results provide important indications about the processing of subliminal words. Cortical activity evoked by the unconscious words was highly significant within the occipitotemporal region, but remained spatially confined to the ventral pathway and was temporally evanescent. This confirms previous observations using less-sensitive fMRI and ERP methods in normal subjects (see for example Dehaene et al., 2001). It suggests that a feedforward wave of activation can be elicited in the absence of consciousness. They also indicate that the occipito-temporal region is sufficiently attuned to words to respond very efficiently even under difficult masking conditions. Indeed, the finding of a frequency effect in at least some electrodes in the subliminal condition suggests that lexical access may occur for subliminal words, as supported by previous behavioral and intracranial evidence (Forster, 1998; Naccache et al., 2005).

Our data also provide evidence concerning the difference between conscious and nonconscious visual pro-

cessing. In contrast to the subliminal condition, neural activity evoked by conscious words concerned a larger array of electrodes and brain regions and was temporally more sustained. These results could not have been obtained unambiguously from scalp recordings, because the late components of ERPs or MEG signals overlap in time, thus making it difficult or impossible to attribute them to well-defined cortical sources. They fit entirely with recordings from the amygdala obtained in the same paradigm (Naccache et al., 2005), where we observed an effect of the emotional valence of words that was present in the subliminal condition but was amplified and lengthened in the conscious condition. Both observations fit with similar studies in area V1 and the frontal eye fields in macaque monkeys (Lamme et al., 2002; Thompson and Schall, 1999). They are consistent with models that postulate that the crossing of the consciousness threshold is associated with amplification, temporal maintenance, and long-distance broadcast of visual signals arising from specific posterior brain regions (Dehaene and Naccache, 2001; Lamme et al., 1998).

Activation latencies observed here are compatible with the generation of the scalp-recorded N1 component of the ERP, which typically peaks around 170 ms.

Here the latency was only slightly slower, which could be due to several factors, including epilepsy as well as the presence of masks that could have interfered with the fast perception of words. Indeed, Dehaene et al. (2001) observed that the peak of the scalp-recorded N1 to words moved to 252 ms in a partial masking paradigm.

It is of particular interest to note that while masked word LFPs were comparable for left and right fusiform gyri, a strong asymmetry could be observed for unmasked words. This suggests that the conscious visual information received a more focused and presumably more specialized treatment in the left hemisphere. Indeed, intracranial recordings also provided detailed information about the parameters that can modulate VWFA activity. Low-level visual features such as word length, which affected more posterior occipital contacts, had no impact on left fusiform LFPs, consistent with the hypothesis that this region holds an abstract visual code. Conversely, activity recorded in this region was modulated by a lexical frequency effect, while the right fusiform region did not show this functional property (Kronbichler et al., 2004). Taken together, these data support both the concept of a specialization of the left fusiform gyrus to encode abstract representation of words, and the strategic mobilization of this region during conscious reading.

Discussion

We will first summarize how the observations gathered before the patient's operation inform us on the functioning of the ventral visual pathway during reading, stressing the convergence of data from multiple methods. Those data essentially conformed to a normal pattern, both in terms of behavior and brain activity. We will then discuss the anatomical location of the lesion, the disruption it introduced in the normal processing system, and its behavioral and functional consequences. We will conclude by discussing how this case is relevant to the issue of category selectivity in the ventral visual pathway.

Reading Status before Surgery
Before surgery, the patient showed no language impairment and no reading difficulty. Reading latencies were fast and constant, irrespective of word length, a testimony of the functional integrity of his ventral visual pathway. In literate adults, letters are identified in parallel, with no influence of length on reading latency, at least within a range of about 3 to 6 letters (Lavidor and Ellis, 2002; Weekes, 1997). This ability emerges progressively, as children initially show a strong word length effect suggestive of LBL reading (Aghababian and Nazir, 2000). The left ventral visual pathway is crucial for this perceptual expertise, as demonstrated by the loss of parallel reading in patients with left occipitotemporal lesions affecting the VWFA (Cohen et al., 2003).

In agreement with this normal behavior, anatomical MRI showed no lesion in the occipitotemporal cortex before surgery. More importantly, the pattern of activation was also normal. Printed words yielded activations extending from the occipital pole to the ventral temporal cortex bilaterally. In its more anterior sector, this stream showed the distinctive features of the visual word form

system, namely functional selectivity and left-hemispheric predominance. This was evidenced by contrasting printed words versus other classes of visual objects (experiment 1), or alphabetic strings versus checkerboards (experiment 2). In both experiments, those contrasts revealed a left-lateralized cluster, at peak coordinates in the range of VWFA activations observed in normal subjects (for reviews see Cohen et al., 2002; Jobard et al., 2003).

Intracerebral LFP recordings allowed us to follow the temporal unfolding of word processing in the vicinity of the fMRI activations, from posterior occipital correlates of word presence occurring about 110 ms after word onset, to later correlates in the VWFA starting at about 220 ms. Those latencies fit with previous intracerebral recordings (Allison et al., 1999; Nobre et al., 1994), scalp ERPs (Cohen et al., 2000; Posner et al., 1999), and MEG data (Pammer et al., 2004; Tarkiainen et al., 1999). As an original contribution of this study, the coregistration of electrodes and fMRI images within a single subject demonstrates that the generator of those waves overlaps with the VWFA activations observed with fMRI.

Furthermore, the present LFP recordings provided unique information inaccessible to fMRI, namely the existence of two temporal epochs with distinct functional properties in the activation of the fusiform cortex. An early response spanning from 220 to 380 ms after word onset was elicited both by visible words and by unconsciously perceived masked words. It was temporally brief, confined to occipitotemporal electrodes, and did not show any asymmetry between the left and right fusiform cortices when the words were masked. Taken together these properties suggest that this early response mainly corresponds to automatic bottom-up word processing. A later component spanning from 380 ms to 550 ms after word onset was recorded on a larger number of electrodes, including regions located outside the ventral pathway, such as the left posterior cingulate cortex and precuneus. Moreover, this component was exclusively restricted to consciously visible words. It was lateralized to the left fusiform region, as were fMRI activations of the VWFA. Finally, this late effect was sensitive to word frequency. These properties are suggestive of a conscious top-down processing of word stimuli during reading.

Expected and Observed Consequences of the Cortical Resection
For any visual object, an increasingly abstract and invariant representation is built up through a hierarchy of neural levels (Riesenhuber and Poggio, 1999; Rolls, 2000; Tanaka, 1996). This idea was recently incorporated in a neural model of word processing in the ventral visual system (the Local Combination Detector or LCD model, Dehaene et al., 2005). The model postulates that word recognition proceeds along a cascade of areas spanning the ventral visual cortex from posterior occipital regions (TC Y < −80), possibly through areas V4 and V8 (TC Y ≈ −70), to relatively anterior fusiform regions (TC Y ≈ −40). It suggests, in particular, that the VWFA can be dissected into successive peaks with an increasing invariance for location and an increasing dependence of letter order, from letter detectors (around Y = −64) to bigram (Y = −56) and possibly morpheme detectors (Y = −48).

Is it possible to specify the location of our patient's lesion within this processing pathway? We noted that the lesion extended between TC Y = −60 and Y = −80, suggesting that a posterior sector of the VWFA and more posterior association areas were involved. The precision of conclusions based on approximate normalized coordinates should however be taken with some caution, due to interindividual variability, to subtle modifications possibly associated to the patient's epilepsy, and to the limitations of the normalization process. As functional data were gathered before surgery, the lesion may be localized relative to the patient's own functional anatomy. The lesion's anterior edge was just posterior to the main fMRI peak of the VWFA (TC Y $\approx$ −55), resulting in its deafferentation from visual input. This functional characterization of the removed tissue was supplemented by LFPs recorded in its immediate vicinity, which revealed a polarity inversion between two contacts located within the to-be-removed area. One may thus conclude that the cortical patch that was removed encompassed the posterior sector of the VWFA, a region postulated to be associated with letter and bigram detectors (Dehaene et al., 2005).

The loss of parallel reading, as revealed by the observed effect of word length on reading latencies recorded after surgery, appears as a logical consequence of this lesion. In line with the LCD framework, we speculate that this lesion prevented the convergence of letter detectors onto more anterior regions representing strings of simultaneous letters, thus interfering with normal reading. The main effect of the lesion would be to deafferent the spared fusiform cortex anterior to the lesion, which indeed failed to be activated by letter strings under conditions of fast presentation. An alternative possibility might be that the surgical lesions induced some kind of structural lesion of the anterior VWFA not visible on anatomical images. This however is unlikely, as the anterior VWFA could still be activated during the slow presentation of words, presumably through top-down input. Other variants of alexia resulting from a disconnected and hypoactive VWFA have been described, either due to callosal lesions depriving the VWFA from left-hemifield input (Cohen et al., 2000, 2003), or due to extensive left-hemispheric white matter lesions disconnecting a spared fusiform cortex (Cohen et al., 2004). Furthermore, the deficit was still present 6 months after surgery, albeit with some degree of functional compensation. This confirms that the VWFA is indeed indispensable for expert reading. Months of rehabilitation may improve the speed of LBL reading strategies (Henry et al., 2005), but cannot restore the parallel perceptual expertise developed in the VWF system over years of practice (Aghababian and Nazir, 2000).

A causal link is thus firmly established between a lesion to this sector of the ventral cortex and the genesis of alexia. Furthermore, we studied the involvement of the residual ventral cortex in LBL reading after surgery. It is difficult to determine with certainty which structures achieved letter identification after surgery. However, it is likely that ventral regions posterior to the lesion played a crucial role. They showed a strong increase of activation by words, during the postsurgery relative to the presurgery session. This increase also concerned a distributed network subtending other components of LBL

reading, such as attentional processes and spatial scanning (frontal eye fields, posterior parietal lobes), verbal short-term memory and lexical search (left dorsolateral prefrontal), and effortful cognitive processing (anterior cingulate). There are indications that left posterior ventral regions are connected with dorsolateral frontal cortex (Bokde et al., 2001) and that they collaborate in serial grapheme-to-phoneme conversion during normal pseudoword reading (Mechelli et al., 2005) and possibly during LBL reading. Note that in other patients with more extensive left-sided lesions, residual letter identification may rely on symmetrical right-hemispheric regions (Cohen et al., 2003, 2004).

Partial Regional Selectivity for Visual Word Recognition

As our patient had a small and well-defined lesion and showed a limited behavioral deficit, the case is also relevant to the issue of regional selectivity for word processing in the VWFA. Our view is that, although multiple neural populations may be intermixed in any region of the ventral visual cortex, the VWFA plays a particular and largely indispensable role in the recognition of visual words, while it may not be strictly necessary to the efficient perception of other visual categories such as faces, objects, or scenes (Cohen and Dehaene, 2004). This view differs from other proposal that attribute to this region a broad function at the interface between visual recognition and components of language processing such as lexical access or phonological encoding (Price and Devlin, 2003). Although we studied reading more extensively than the perception of other types of visual stimuli, our patient presented a clear-cut reading impairment following surgery, while his performance remained flawless in object recognition and naming, face processing, and general language abilities. Such selectivity may be difficult to observe in patients with more customary lesions resulting from strokes or tumors, which often affect a larger extent of cortex and white matter. The small size of the present lesion thus provides precious support to the idea of partial regional selectivity for word perception in the ventral cortex.

Functional MRI data are also relevant to the issue of regional selectivity in a more traditional neuroimaging sense, namely its activation by different categories of pictures. Before surgery, we identified distinct areas with a relative preference for words, buildings, faces, and tools. Moreover, the VWFA showed no activation relative to rest by categories other than words. This suggests that, although a limited sample of visual categories was studied, this area showed a fair degree of regional selectivity. Finally, the two arguments for regional selectivity (category-specificity both in the deficit and in the activation pattern) are mutually strengthened by the fact that following surgery, only the word-related activation focus disappeared, while all others remained essentially unchanged.

Experimental Procedures

fMRI Experiment 1
Procedure
The patient was presented with an alternation of blocks of pictures (8000 ms per block) and blocks of rest with a central fixation point

(7800 ms per block). Each stimulation block included eight black and white pictures from one of four categories: 3 letter words, faces, tools, or houses (Figure 3). Pictures were displayed for 600 ms and followed by a 400 ms blank screen. The experiment included two sequences, each comprising 24 blocks of pictures (six for each category) and 24 blocks of rest. Blocks were presented in pseudorandom order within sequences, so as to maximize the variety of transitions between conditions while avoiding repetition of the same condition in successive blocks. The patient was asked to press a button whenever a picture was identical to the previous one, which was the case for 20% of stimuli (one to three repetitions per block). Responses were not recorded. The whole experiment was run before and after surgery, with differently ordered stimuli.

Imaging Parameters
Each sequence consisted of 10 s of initial rest, followed by the alternation of blocks. In each sequence, 157 functional volumes sensitive to blood oxygen level-dependent (BOLD) contrast were acquired with a T2-weighted gradient echo, echo planar imaging sequence on a 1.5 tesla Signa Imager (TR = 2500 ms, α = 90°, TE = 60 ms, FOV = 240 × 240 mm, in-plane resolution = 3.75 × 3.75 mm^2). Each volume comprised 17 axial slices of 5 mm thickness covering most of the brain. The first four volumes were discarded to reach equilibrium. T1-weighted images were also acquired for anatomical localization.

Analysis of MRI Data
Images were analyzed with the SPM99 software. The anatomical image was linearly normalized using the standard T1 template. Functional scans were realigned, normalized, and smoothed with a Gaussian filter (5 mm FWHM). The resulting images had voxels of 3 × 3 × 3 mm^3. Activation on each type of trial was modeled by a combination of the standard SPM hemodynamic function and its temporal derivative. Only the former function was used for statistical contrasts. Variables of noninterest modeled constant differences across sequences. A high-pass filter (240 s) was applied. Low-pass filtering was achieved by convolution with the hemodynamic function.

Unless otherwise stated, we used a voxelwise threshold of p < 0.001, with a statistical threshold for cluster extent of p < 0.05, corrected. Correction for multiple comparisons was made within the whole volume of acquisition. When a contrast was compared between pre- and postsurgery sessions, statistics were corrected within the volume activated by that contrast pooled across both sessions (p < 0.001).

fMRI Experiment 2
We used the same imaging procedure as described in Cohen et al. (2003). The patient was presented with four types of short alternating blocks: rest with a central fixation point, real words, consonant strings, and checkerboards covering approximately the same field as letter strings. The experiment was run before and after surgery, with differently ordered stimuli. We used the same general imaging and analysis parameters as in experiment 1.

Intracerebral LFPs: General Methods
Electrodes Implantation
The patient was implanted on two occasions with depth electrodes (Ad-Tech Medical Instruments, Racine, WI). Electrodes were 2.3 mm long and 1 mm diameter cylinders, with interelectrode distance of 10 mm. The structures to be explored were defined on the basis of ictal manifestations, electroencephalography (EEG), and neuroimaging studies. In both implantations, probes were implanted roughly perpendicular to the sagittal plane.

First Implantation. Twelve months before surgery, nine intracerebral probes were inserted in the left hemisphere, corresponding to a total of 36 electrode contacts. The tips of the probes targeted the amygdala, the hippocampus, the ventral temporal cortex including the posterior fusiform gyrus. Analyzable signal was recorded from 35 of the 36 contacts.

Second Implantation. Eight months before surgery, seven intracerebral probes were inserted in the left hemisphere, and one in the right hemisphere, corresponding to a total of 32 electrode contacts. The fusiform gyrus was targeted in both hemispheres. Other target regions included striate, extrastriate, lateral occipital, cuneus, pre-

cuneus, and posterior cingulate cortices. Analyzable signal was recorded from 25 of the 32 contacts.

Signal Analysis
The local field potential (LFP) was digitized at 400 Hz from intracerebral electrodes referenced to the vertex (Nicolet-BMSI, Madison, WI). Epochs were notch-filtered (50 Hz) then extracted (from −500 ms to +1000 ms from word onset). They were submitted to automatic artifact rejection (±300 μV threshold). In order to maximize the number of epochs recorded from fusiform electrode contacts, we adopted the following procedure: the signal was automatically thresholded from 0 to 500 ms from word onset on these seven fusiform contacts (temporal window of interest), while for all other contacts it was thresholded from −500 ms to +1000 ms from word onset. In addition, all trials were visually inspected, and trials with epileptic activity were rejected. Epochs were then low-pass filtered (20 Hz) using EEGLab software (Delorme and Makeig, 2004). LFPs were then averaged. Experimental conditions were compared by sample-by-sample t tests with a criterion of p < 0.05 for a minimum of 15 consecutive samples.

Experiment 3
We presented masked words using a previously described procedure (Naccache et al., 2005). A single word or a blank screen was presented very briefly (29 ms), preceded and followed by masks consisting of strings of characters (71 ms each). A 29 ms blank screen was inserted between the target word and the post-mask, making words often visible (Figure 3). The patient was asked to name words. He received 128 word trials (four repetitions of a 32 word list). He also received 64 blank trials in which the word was replaced by a blank screen.

Experiment 4
We presented unmasked visible and masked subliminal words. On masked trials, words were presented using the same method as in experiment 3, but with no blank screen between the target word and the post-mask (see Figure 3). Masked trials were randomly intermixed with unmasked trials, in which the post-stimulus mask was removed. The patient was engaged in a forced-choice task of categorizing words as threatening or not by pressing response buttons. We used two distinct lists of 92 words each (adapted from Isenberg et al., 1999) for the masked and unmasked trials, so that the masked words were never seen consciously. In each list, half of the words were threatening (e.g., "kill") and were varied in frequency, length (3 to 8 letters), and lexical category (verbs and nouns). The other half included neutral words (e.g., "cousin"), matched for frequency, length, and category.

Over two testing sessions, the patient received a total of 1100 trials: five sets of 92 masked words, five sets of 92 unmasked words, 90 masked blank trials, and 90 unmasked blank trials. Blank trials had the same structure as trials with words, except that words were replaced by a blank screen. Masked and unmasked words were reversed between the first and second sessions.

Supplemental Data
The Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/50/2/191/DC1/.

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