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Pure alexia as a disconnection syndrome: New diffusion imaging evidence for an old concept

Stéphane Epelbaum[a,c,d,e,f], Philippe Pinel[c,d,f], Raphael Gaillard[c,d,f], Christine Delmaire[b], Muriel Perrin[d], Sophie Dupont[a,e], Stanislas Dehaene[c,d,f] and Laurent Cohen[a,c,e,f,*]

[a]AP-HP, Hôpital de la Salpêtrière, Department of Neurology, Paris, France
[b]AP-HP, Hôpital de la Salpêtr2ière, Department of Neuroradiology, Paris, France
[c]INSERM, U562, Gif sur Yvette, France
[d]CEA, DSV, UNAF, IFR 49, Gif sur Yvette, France
[e]Université Paris VI, Faculté de Médecine Pitié-Salpêtrière, IFR 70, Paris, France
[f]Collège de France, Paris, France

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ABSTRACT

Functional neuroimaging and studies of brain-damaged patients made it possible to delineate the main components of the cerebral system for word reading. However, the anatomical connections subtending the flow of information within this network are still poorly defined. Here we study the connectivity of the Visual Word Form Area (VWFA), a pivotal component of the reading network achieving the invariant identification of letter strings, and reproducibly located in the left lateral occipitotemporal sulcus. Diffusion images and functional imaging data were gathered in a patient who developed pure alexia following a small surgical lesion in the vicinity of his VWFA. We had a unique opportunity to compare images obtained before, early after, and late after surgery. Analysis of diffusion images with white matter tractography and voxel-based morphometry showed that the VWFA was mainly linked to the occipital cortex through the inferior longitudinal fasciculus (ILF), and to perisylvian language areas (supramarginal gyrus) through the arcuate fasciculus. After surgery, we observed the progressive and selective degeneration of the ILF, while the VWFA was anatomically intact. This allowed us to establish the critical causal role of this fiber tract in normal reading, and to show that its disruption is one pathophysiological mechanism of pure alexia, thus clarifying a long-standing debate on the role of disconnection in neurocognitive disorders.

1. Introduction

Ever since its clinical and anatomical description in the 19th century, pure alexia has epitomized the debate on the role of disconnections in neuropsychological deficits (Charcot, 1890; Dejerine, 1892; Kussmaul, 1877) (see also Catani and Mesulam, 2008a, this issue). Indeed, the dramatic contrast between, on the one hand, roughly preserved vision and language and,

* *Corresponding author*. Service de Neurologie 1, Hôpital de la Salpêtrière, 47/83 Bd de l'Hôpital, 75651 Paris, Cedex 13, France.
E-mail address: laurent.cohen@psl.aphp.fr (L. Cohen).
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on the other hand, the inability to name printed words is by itself suggestive of an impaired communication between vision and speech. Hence an emphasis was often put on white matter lesions in the genesis of pure alexia (Dejerine, 1892). However, other authors suggested that the visual cortex might include regions specialized for the representation of printed letters, and that lesions to such cortical structures could yield pure alexia (Binder and Mohr, 1992; Lecours et al., 1983). Traditional pathological evidence did not provide any simple answer to this debate. Cases of alexia with pure cortical lesions were reported (e.g., Beversdorf et al., 1997), while cases of combined lesions of the left primary visual cortex and of the corpus callosum supported accounts of an interhemispheric disconnection between intact right-sided visual cortex and left-sided language areas (Geschwind, 1965).

Functional imaging techniques allowed to restate more accurately the terms of the discussion by identifying the main cortical components of the reading system (for reviews, see Bolger et al., 2005; Fiebach et al., 2002; Jobard et al., 2003; Price and Mechelli, 2005), by determining their role in reading, and by studying their dynamic interplay (Salmelin and Kujala, 2006; Simos et al., 2002) (Fig. 1). Pivotal in the reading network is the computation of the abstract identity of visually perceived strings of letters. This representation, called the ''Visual Word Form'', is thought to be the end product of word analysis in the ventral ''What'' visual system (for a neural model, see Dehaene et al., 2005). It serves as input to subsequent language-related processes including access to the lexicon and letter-to-sound conversion (Fig. 1). Functional imaging evidence indicates that the computation of the Visual Word Form is subtended by a region of the left occipitotemporal cortex, reproducibly located in the mid-portion of the left lateral occipitotemporal sulcus (OTS), for which the label of Visual Word Form Area (VWFA) was proposed (Cohen et al., 2000, 2002; Devlin et al., 2004; Jobard et al., 2003). Moreover, as illustrated in Fig. 1, recent imaging data suggest that invariance is achieved within the VWFA through a posterior-to-anterior hierarchy of neurons with increasing receptor fields, tuned to increasingly complex word fragments (Vinckier et al., 2007) (Dehaene et al., 2004), as proposed in the Local Combination Detector (LCD) model of word reading (Dehaene et al., 2005). Note also that the framework presented in Fig. 1 emphasizes the ventral visual system and refers only sketchily to the dorsal system and its role in single word reading (on this issue see Cohen et al., in press; Vinckier et al., 2006).

On this background, pure alexia may be construed as a selective inability to achieve a Visual Word Form representation, in the absence of general visual impairment or speech disorders (Warrington and Shallice, 1980). In agreement with early evidence, we showed that the critical region of overlap of lesions responsible for pure alexia coincides with the normal activation focus of the VWFA (Cohen et al., 2003). Unsurprisingly, massive surgical resection of the occipitotemporal white matter with cortical sparing may induce an equivalent deficit, by way of a complete deafferentation of the VWFA (Cohen et al., 2004). However, the precise course of connections to and from this region remains to be clarified. So-called central acquired dyslexias are thought to result from lesions affecting the reading network downstream from the VWF system (Fig. 1). Thus phonological and deep dyslexia mostly results from perisylvian vascular lesions disrupting the phonological reading route. In contrast, the most dramatic cases of Surface Dyslexia appear during the course of semantic dementia, with lesions affecting the lexico-semantic reading route in the lateral and anterior temporal neocortex (Woollams et al., 2007).

Here we study the anatomical connectivity of the reading network within the left hemisphere, focusing on the pathways conveying visual input to the VWFA and those projecting from the VWFA to language-related areas. To this end, we used diffusion imaging in a patient suffering from pure alexia due to a small surgical resection in his left occipitotemporal region. This patient was expected to be particularly informative because, on the basis of functional imaging, we speculated that alexia resulted from deafferentation of the VWFA from visual input (Gaillard et al., 2006). Most importantly, we had the unique opportunity to gather diffusion images in the same patient at 3 points in time: before the occurrence of the lesion, in the early post-lesion stage, and 6 months later, allowing for a longitudinal within-subject study of the evolution of fiber tracts, in correlation with the occurrence of the reading deficit.

1.1. *Case history*

The patient's case was reported by Gaillard et al. (2006), who studied the contribution of the VWFA to reading using intracerebral electrical recordings, functional magnetic resonance imaging (fMRI) and neuropsychological evidence. In summary, 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. Epilepsy evaluation included video-electroencephalogram (EEG), positron emission tomography (PET)-scanning, and neuropsychological assessment. Based on these examinations, left occipitotemporal lobe epilepsy was suspected. As a surgical procedure was considered, intra-cerebral electrodes were implanted in order to pinpoint the epileptogenic focus. At the same time, word reading and visual object perception were studied with fMRI. Imaging revealed a normal mosaic of ventral visual selectivity for words, faces, houses, and tools. Surgery removed a small portion of cortex in the vicinity of the VWFA (Fig. 2). Following surgery, the patient developed pure alexia with letter-by-letter reading, while recognition of other visual categories remained intact. Goldman perimetry showed a normal visual field. Among other behavioral tests, the patient was asked to read aloud words flashed for 200 msec, randomly in his right or left hemifield. As reported in Gaillard et al. (2006), his normal pre-surgical performance dropped to 42% errors 6 months post-surgery. A point not mentioned in the initial report but relevant to the present study is that this deficit affected equally words presented in the left and right hemifields (44% and 40% errors, respectively; $\chi^2(1) = .45$; $p = .50$). The same fMRI experiments as before surgery were performed a second time. Activations induced by the fast presentation of words disappeared, while activations related to the fast presentation of faces, houses or tools were unchanged relative to the pre-surgery session. However, the residual VWFA was still activated when words were presented long enough for the patient to engage

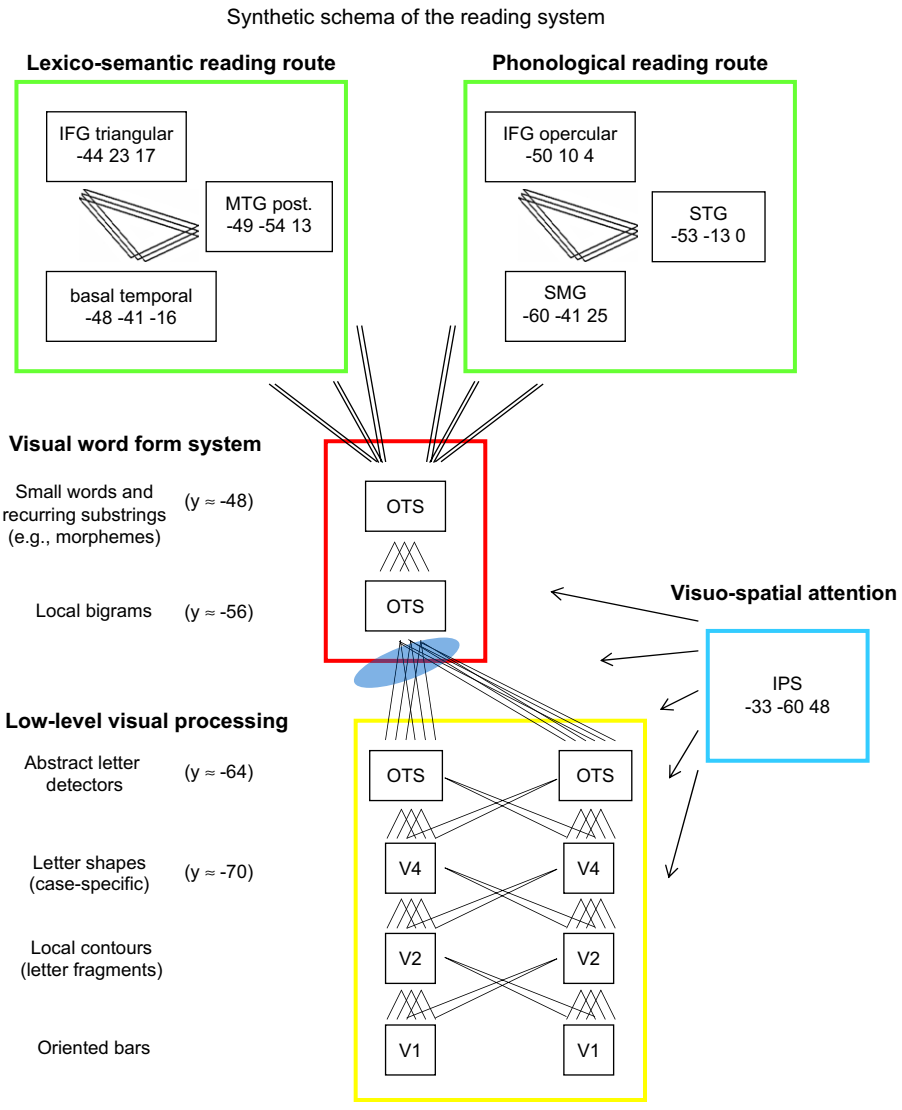

Fig. 1 – Synthetic schema of the reading system, merging propositions from Dehaene et al. (2005) and Cohen et al. (2003). Low-level processing is achieved in each hemisphere for the contralateral half of the visual field (yellow). Information converges on the VWF System where an invariant representation of letter strings is computed. The ventral visual system then feeds the lexico-semantic and phonological reading routes. The blue ellipsis indicates the proposed locus of the patient's lesion, disconnecting the VWFA from its input. The proposed normalized coordinates for the lexico-semantic and phonological reading routes are from a meta-analysis of 35 PET and fMRI studies (Jobard et al., 2003), and the coordinates of the visuo-spatial attention system are from Gitelman et al. (2005). IFG: inferior frontal gyrus; MTG: middle temporal gyrus; SMG: supramarginal gyrus; OTS: occipitotemporal sulcus; IPS: intraparietal sulcus.

in letter-by-letter reading. This suggested that alexia might result form the disconnection from its input of a partially intact VWFA. Altogether, these results provided direct evidence for the causal and specific role of the left occipitotemporal cortex in the recognition of visual words.

1.2. *Goals of the study*

Contrary to other patients (Binder and Mohr, 1992; Cohen et al., 2003; Damasio and Damasio, 1983), this patient's alexia could not be interpreted as a straightforward consequence of a disrupted VWFA. First, the resection was located slightly posterior to the main peak of the VWFA. Second, after surgery the cortex at the site of the VWFA was no longer activated by the perception of briefly flashed words, but was still activated during letter-by-letter reading of words displayed for a sufficient duration. We therefore proposed that the VWFA was largely intact but deprived of its normal input from lower-level visual cortex. Residual activation during letter-by-letter reading was interpreted as reflecting putative top–down influence of central components of the reading system.

This hypothesis was proposed on functional grounds, but it could not be anatomically substantiated, as the surgical

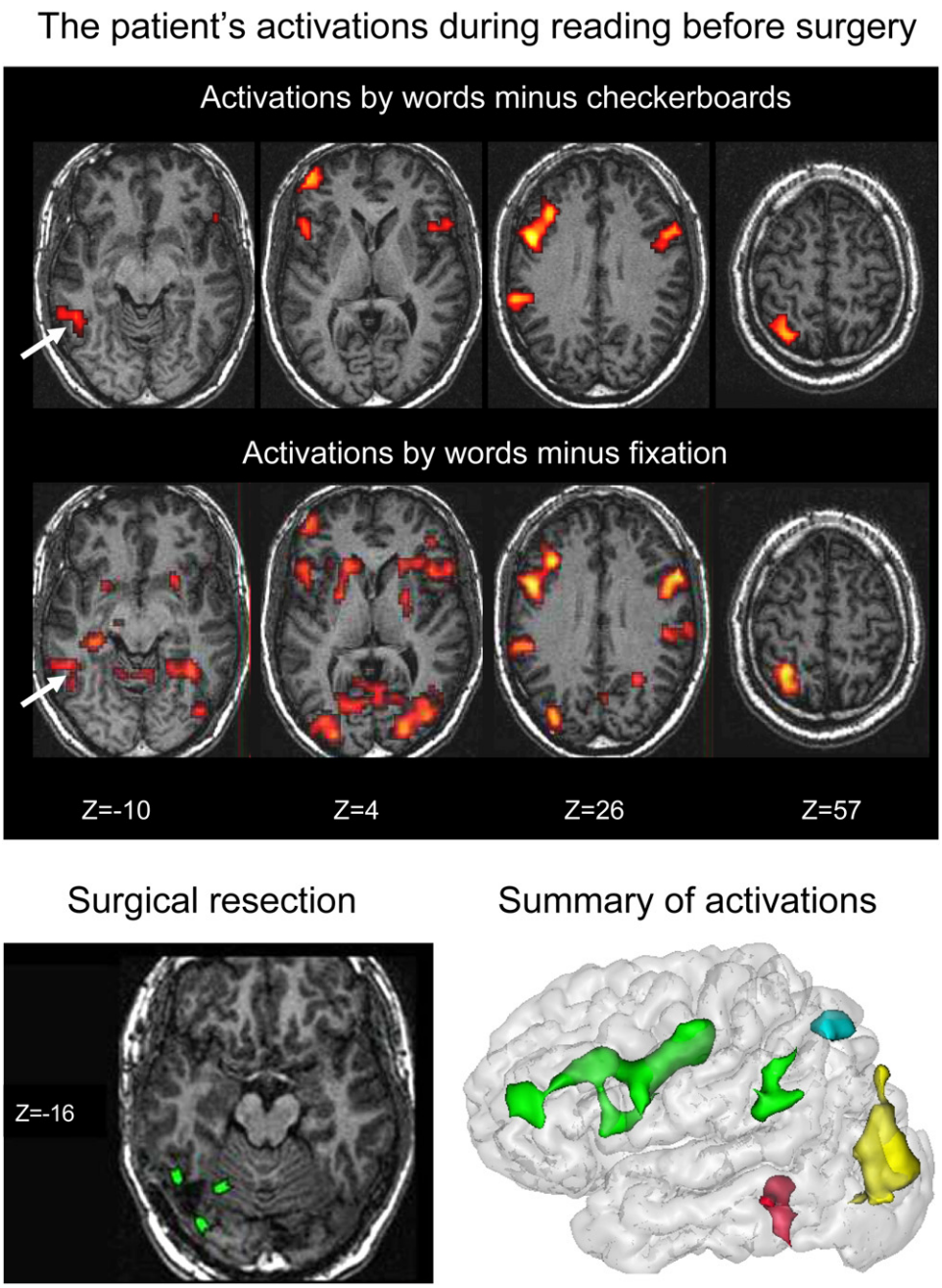

Fig. 2 – Top panel: fMRI activations observed before surgery during word reading relative to checkerboard viewing (top row) and relative to fixation (second row) (voxelwise $p < .001$; clusterwise $p < .05$), showing a left-predominant network including the VWFA (arrow). Bottom left panel: axial T1-weighted MRI image of the patient's brain 6 months after surgery showing the left occipitotemporal lesion (green arrows). Bottom right panel: translucent view of the patient's normalized left-hemisphere showing activations by words relative to checkerboards, including the VWFA (red), inferior parietal and frontal language areas (green), superior parietal attention-related structures (blue); and activations by words relative to fixation in the occipital cortex (yellow). The proposed functional interpretation of those activations is denoted by color codes, which are the same as in Fig. 1.

lesion appeared to be strictly cortical on anatomical images. Our goal here is to assess the disconnection hypothesis with diffusion MRI data, using both fiber tracking and voxel-based morphometry (VBM) methods. More generally we take this case as an opportunity to clarify the connectivity of the reading system by studying the degeneration of occipito-temporal fiber tracts.

2. Methods

2.1. *Acquisition of anatomical and diffusion images*

T1-weighted and diffusion-weighted brain images were acquired in the patient, before surgery, 15 days and 6 months

after surgery, on a 1.5 T (GE) magnet with standard head coil-for signal reception. Equivalent images were acquired in 17 control subjects. Diffusion imaging was performed using echo-planar imaging with the following parameters: time of repetition (TR)/time of echo (TE)/flip angle = 10 sec/88 msec/90°; matrix = 128 × 128; field of view = 380 × 380 mm^2; slice thickness = 3 mm with no gap (3 mm isotropic voxels); 4 excitations; acquisition time = 5:20 min. Diffusion weighting was performed along 6 independent directions, with a b-value of 900 sec/mm^2. Diffusion images covered the whole brain, excluding the cerebellum. The patient and control subjects gave written informed consent and the study was approved by the local Ethics Committee.

2.2. *Functional imaging study*

A full description of the functional activation paradigms and acquisition parameters can be found in Gaillard et al. (2006). In the present study, we refer to one of the pre-surgery reading experiments. In this experiment, the patient was presented with 4 types of short alternating blocks: rest with a central fixation point, real words, consonant strings, and checkerboards. In order to delineate the main components of the patient's reading network, we used the contrasts of words minus checkerboards and words minus rest (voxelwise threshold: $p < .001$; threshold for cluster extent: $p < .05$ corrected). We also used the contrast of words minus checkerboards at a somewhat lower threshold (voxelwise threshold: $p < .01$; threshold for cluster extent: $p < .05$ corrected) in order to isolate a VWFA cluster sufficiently large to encroach on the neighbouring white matter, so as to serve as a starting point for fiber tracking (Conturo et al., 1999).

2.3. *VBM*

In order to characterize the local differences between the patient and control subjects in white and grey matter density and in fractional anisotropy (FA), we used VBM (Ashburner and Friston, 2000). Separate analyses were performed with SPM2 for the pre-surgery, early and late post-surgery acquisitions. White and grey matter images were segmented, normalized and smoothed (Gaussian filter of 5 mm FWHM) (C. Gaser; http://dbm.neuro.uni-jena.de/vbm). Images were then compared between the patient and controls on a voxel-by-voxel basis, using one-way analysis of variances (ANOVAs) with a voxelwise threshold of $p < .001$, and a threshold for cluster extent of 200 voxels for the white and grey matter, and of 15 voxels for FA (for a methodological discussion see Salmond et al., 2002).

2.4. *Tractography*

White matter tractography was performed using the Brainvisa/Anatomist software (SHFJ-CEA, IFR49, Orsay, France). First, a region of interest (ROI) is defined, to be used as the starting point of the tracking process. Here we used the patient's individual VWFA, identified before surgery as the left occipitotemporal cluster activated by the contrast of word reading minus checkerboard viewing. This ROI was created in the normalized Talairach space, in which the patient's functional data had been analyzed, and was subsequently transformed into the subject's native space in order to match the pre-surgery and post-surgery native diffusion images. Second, fibers were tracked using the following parameters: deterministic protocol of the FACT type (Mori et al., 1999); anisotropy threshold = .2; maximum angle = 45°; tracking step = 1 mm. Each resulting tract was visually inspected to check for aberrant paths. The main tracts were then studied individually, to determine their anatomical topography, the number of constituting fibers, and the mean FA.

3. Results

In order to set the stage for the study of anatomical connectivity, we will first describe and interpret the word reading network, as identified by brain activations during word reading. We will then study the structure of the patient's white matter before surgery, with an emphasis on the connectivity of the VWFA. Finally, we will determine which changes were induced in this pattern of connectivity by the surgical resection, and discuss whether those changes support the hypothesis of a disconnection of the VWFA from visual input as an account of the patient's reading impairment.

3.1. *Activations observed during word reading before surgery*

Our first step was to delineate cortical areas contributing to word reading on the basis of the patient's individual functional activations observed before surgery (Fig. 2). The word reading network, as identified by the contrast of words minus checkerboards, included the VWFA (Talairach coordinates – TC −48 −54 −15; $Z = 5.94$), the left supra-marginal gyrus (TC −60 −36 27; $Z = 6.05$), the left intraparietal cortex (TC −30 −60 60; $Z = 6.92$), Broca's area (TC −45 12 6; $Z = 4.79$), and the bilateral precentral gyri (left: TC −42 0 36; $Z = 7.41$; right: TC 36 0 36; $Z > 8$). Furthermore, we identified bilateral occipital regions by contrasting words minus rest (left: TC −33 −87 18, $Z > 8$; right: TC 30 −81 0, $Z > 8$).

Schematically, those activations may match several important components of the reading system as outlined in Fig. 1. First, occipital activations correspond to low-level visual word processing. The activation of such areas, located between about TC $y = -90$ and $y = -65$, is modulated by physical parameters such as word length, visual contrast (Mechelli et al., 2000), stimulus degradation (Helenius et al., 1999; Jernigan et al., 1998), stimulus rate and duration (Price and Friston, 1997; Price et al., 1996). Second, activation of the VWFA corresponds to the computation of an abstract representation of letter strings. Thus, the VWFA is activated by strings of letters irrespective of their position in the visual field (Cohen et al., 2000), and in a code invariant for the upper- lower-case distinction (Dehaene et al., 2001, 2004). Third, left supramarginal and inferior frontal activations presumably correspond to central language-related components of reading. Referring to a meta-analysis of 35 fMRI and PET studies of reading (Jobard et al., 2003), those 2 regions appear to be mostly involved in the so-called ''surface'' reading route,

based on letter-to-sound conversion. However, we did not observe significant activations in regions more involved in the access to lexical-semantic information (Jobard et al., 2003). Fourth, left intraparietal activations probably subtend spatial and attentional processes (Gitelman et al., 1999; Kanwisher and Wojciulik, 2000), which also contribute to word reading (Gitelman et al., 2005). The importance of those areas for reading may be illustrated by patients with attentional dyslexia following left parietal lesions (Friedmann and Gvion, 2001; Mayall and Humphreys, 2002; Shallice and Warrington, 1977; Warrington et al., 1993). Keeping in mind this broad interpretation of the components of the patient's reading network, we now turn to the study of white matter, in search for the connections of the VWFA.

3.2. *White matter structure before surgery*

3.2.1. *Diffusion tensor imaging (DTI) tracking*

DTI-based fiber tracking starting from the VWFA showed 2 thick tracts, plus some sparser groups of fibers (Fig. 3). The first tract, which for brevity we label "VWFA-Occ", extended backwards from the VWFA, eventually reaching the left infero-medial occipital cortex. It corresponded to the horizontal part of the inferior longitudinal fasciculus (ILF), linking occipital and inferior temporal cortex (Catani et al., 2003; Schmahmann et al., 2007). It was composed of 1010 fibers and its mean FA was .54. It is important to note that the number of fibers refers to the outcome of the specific tracking algorithm which was used, and cannot be translated directly into an absolute number of axons. The main interest of such quantification is to allow for a comparative follow-up of the size of fiber tracts over time. The second tract, which we label "VWFA–SMG", ascended from the VWFA inward up to the depth of the supramarginal gyrus (SMG), precisely targeting the patient's supramarginal functional activation cluster. It then divided into smaller branches heading for the supramarginal cortex, the intraparietal cortex, with a few fibers directed towards the left frontal lobe. This tract belongs to the posterior and inferior portion of the arcuate (or superior longitudinal) fasciculus, linking parietal and temporal cortex. It was composed of 456 fibers and had a mean FA of .56.

The other tracts were composed of much fewer fibers. Although their characterization may be less reliable, we describe them briefly. A tract originated from the posterior edge of the VWFA–SMG (45 fibers; mean FA = .53), and a still thinner tract (9 fibers) stemmed from the anterior aspect of the VWFA and made its way forward to the anterior temporal and prefrontal cortices. Finally, 2 U-shape fibers were seen linking the VWFA to neighbouring gyri.

In order to better characterize the visual input pathways, we used the occipital termination of the VWFA-Occ tract as a tracking seed. This revealed 3 divergent bundles, naturally including the ILF (160 fibers; mean FA = .48), but also callosal fibers (169 fibers; mean FA = .7) and optic radiations (132 fibers; mean FA = .47) (Fig. 6, top). Those tracts are the 3 known components of the stratum sagittale, a complex layer of white matter bordering the posterior horn of the lateral ventricle (Burgel et al., 2006; Dejerine, 1895; Schmahmann and Pandya, 2006). Optic radiations and callosal fibers are critically involved in early stages of the reading process, as they presumably convey information from the right and left visual

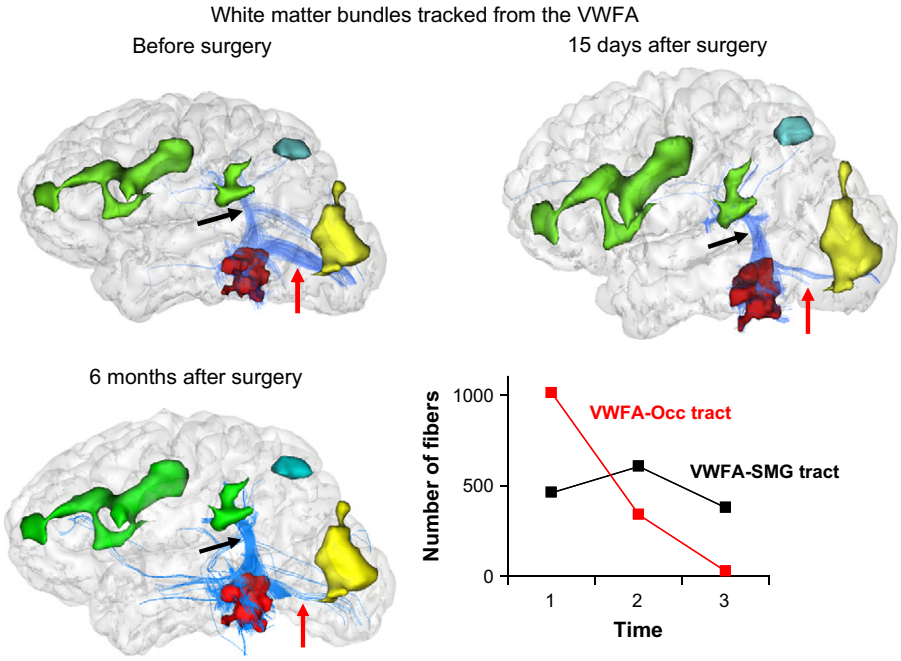

Fig. 3 – White matter tracts (blue) identified by using the patient's VWFA as the seed of the tracking algorithm. Before surgery, 2 main tracks were apparent, linking the VWFA to the occipital cortex (red arrows) and to the supramarginal gyrus (black arrows). After surgery, the VWFA-Occ tract disappeared almost entirely, while the VWFA–SMG tract was preserved, as illustrated by the evolution of the number of fibers over time.

hemifields, respectively, to the left occipitotemporal cortex and the VWFA.

3.2.2. *VBM*

Comparison of the patient's images prior to the surgical intervention with those of control subjects showed small spots of reduced white matter density and of reduced FA, identically located in the bilateral frontal cingular gyrus, in the left parietal cingular gyrus, and in the left parietal white matter (Fig. 4). There was no difference between the patient and controls in grey matter density.

3.2.3. *Summary*

Fiber tracking from the VWFA showed 2 main tracts. One tract connected the VWFA to the left occipital cortex. We propose that its role in reading is to convey visual information from low-level visual cortex to the VWFA. The second tract connected the VWFA to the supra-marginal gyrus and possibly to left prefrontal areas. This tract plausibly conveyed letter identity for further language processing such as letter-to-sound translation, which is thought to involve superior temporal and SMG cortex (Jobard et al., 2003; van Atteveldt et al., 2004). This pattern supports the general idea that the VWFA stands at the interface between visual word input and central reading process.

Fig. 3 shows that the posterior termination of the VWFA-Occ tract is somewhat ventral to the occipital activation cluster. This is likely due to the fact that functional acquisitions excluded the most posterior and inferior sector of the occipital lobes, below a plane including transversal lines defined by ($y = -99$; $z = 12$) and ($y = -71$; $z = -13$), while this volume was included in diffusion acquisitions. The cortical termination of the VWFA-Occ tract falls just in this region of truncated activation.

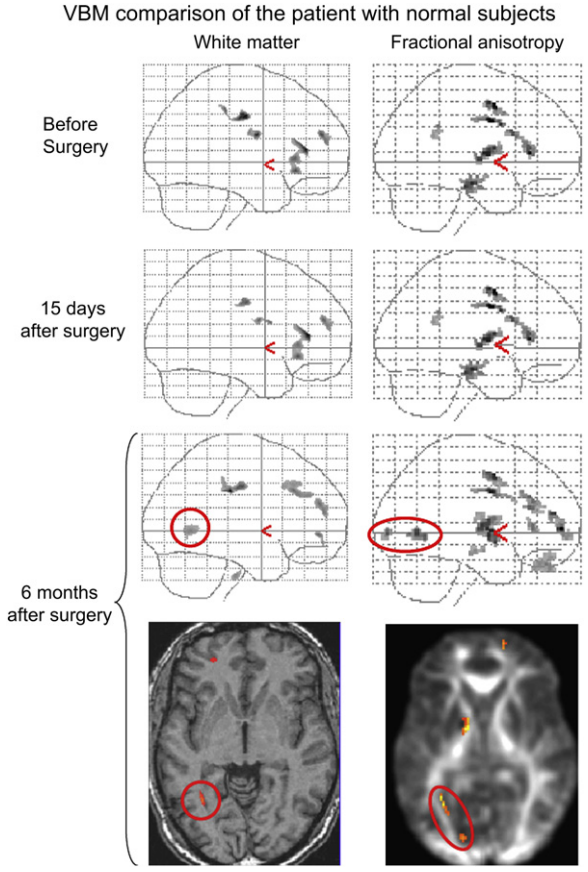

Fig. 4 – VBM comparison of the patient with normal subjects, based on white matter density (left column) and on FA of diffusion (right column), before (top row), 15 days after (second row), and 6 months after surgery (third and bottom rows). Before surgery, the patient showed a few spots of reduction for the 2 parameters. This pattern was unchanged early after surgery. Six months later, a novel left occipitotemporal region showed a decrease in both white matter density and FA as a consequence of the lesion. This region was just posterior and superior to the VWFA activation.

3.3. *White matter structure after surgery*

3.3.1. *DTI tracking*

Fifteen days after surgery, fiber bundles tracked from the VWFA showed the same pattern as before surgery, with the same 2 prominent tracts connecting the VWFA to the occipital region and to the SMG, respectively (Fig. 3). The stability of the pattern of connectivity is of great methodological significance, as it demonstrates the good within-subject reproducibility of tracking. Note, however, that the VWFA-Occ tract now comprised 334 fibers (mean FA = .52), as compared to the presurgery contingent of 1010 fibers (67% reduction). There was no decrease in the VWFA–SMG tract, which now comprised 606 fibers (mean FA = .5).

Six months later, the dissociated evolution of the 2 main bundles connecting the VWFA was confirmed. On the one hand, the VWFA–SMG tract remained essentially intact (377 fibers; mean FA = .53). On the other hand, the VWFA-Occ tract had almost vanished. It stopped within millimetres after leaving the VWFA, only 25 residual fibers (mean FA = .51) out of the initial 1010 (2.5%) making their way towards the occipital lobe (test comparing the slopes over time of the number of fibers between the 2 tracts: $F(1,2) = 8.8$; $p < .1$). Thus, starting from the VWFA, the tract could not be followed beyond the vicinity of the surgical resection.

However, losing track of fibers does not imply that the tract was actually disrupted in its entire length. In order to determine whether there would be anatomically preserved fibers beyond the obstacle opposed to tracking by the lesion, we tracked the ILF in the opposite direction. The occipital termination, as defined before surgery, was used as a tracking seed. This showed the persistence of 80 fibers (mean FA = .47) up to the vicinity of the lesion, where tracking was again interrupted. Thus, although backward tracking was lost in the vicinity of the lesion, forward tracking showed that the tract persisted in most of its length, although with a substantially reduced number of residual fibers.

3.3.2. *VBM*

Fifteen days after surgery, the significant differences between the patient and control subjects were identical to those observed before surgery, for both white matter density and FA (Fig. 4). The small number of images precluded a direct

statistical comparison between pre- and post-surgery data, but this stability points to excellent within-subject reproducibility of VBM analyses.

Six months after the intervention, VBM showed an area of decreased grey matter density corresponding to the cortical resection itself. More importantly, a new region of reduced white matter density and FA appeared in the left inferior temporal lobe (Fig. 4), slightly above and medial to the cortical resection (Fig. 5). This proximity suggests that this novel anomaly was due to an impact of the surgical procedure on the immediately adjacent white matter.[1] In order to determine whether the entire length of the VWFA-Occ tract had degenerated, even remote from the initial lesion, we lowered the voxelwise threshold to $p < .05$. This increased to 158 voxels the number of occipito-temporal voxels with an abnormally low FA, this cluster forming a perfect cast of the whole length of the tract.[2]

Finally, images combining the results of fiber tracking and of VBM analyses showed a neat overlap of the occipitotemporal area of reduced FA and of the interruption of the tracking of the VWFA-Occ bundle (Fig. 5).

3.3.3. *Summary*

Diffusion data acquired 2 weeks after surgery showed a 2/3 reduction in the number of fibers tracked from the VWFA to the occipital region, a change that was not significant using VMB. No substantial change affected the other tracts. Over the 6 months following surgery, this pattern was strengthened, as both methods converged to reveal the continuing disruption of the VWFA-Occ tract, contrasting with the preservation of the VWFA–SMG tract.

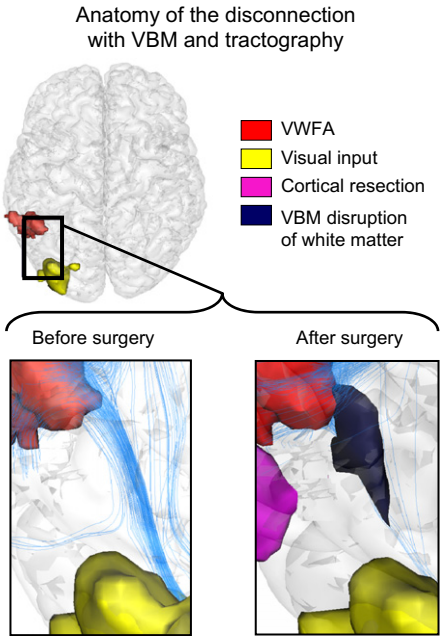

Fig. 5 – Close-up views of the connections (blue) between the occipital cortex (yellow) and the VWFA (red), combining VBM and tractography. Before surgery (left) the 2 regions were strongly connected through the ILF. Six months after surgery (right), underlying the cortical resection (purple), there was a small area of white matter disruption identified with VBM (dark blue) associated with the degeneration of the fiber tract.

4. Discussion

We used diffusion imaging in a pure alexic patient, in order to evaluate the hypothesis, based on functional imaging data, that pure alexia resulted from a deafferentation of the VWFA from visual input. Beyond this specific patient, we expected this case to clarify the anatomical connectivity within the reading network.

4.1. *Normal connectivity of the VWFA*

Before the surgical lesion, we found that the patient's VWFA was connected mainly to the occipital cortex through the ILF, and to the SMG through the arcuate fasciculus (Catani et al., 2003, 2005) (see also Catani and Mesulam, 2008b, this issue; Catani and Thiebaut de Schotten, 2008, this issue; Raudruff et al., 2008, this issue). This pattern of connection is in good agreement with studies of monkey brains. The macaque equivalent of the VWFA putatively falls within the IT complex, maybe more specifically in areas TF and TE (Cohen et al., 2000; Halgren et al., 1999; Orban et al., 2004). Using autoradiography with a radiolabeled tract-tracer, Schmahmann and Pandya (2006) showed that area TF projects both to the IPL and to the ventral occipital cortex. Those 2 bundles might correspond to the 2 main tracts identified in the patient. Other projections are directed to the anterior temporal lobe and to the anterior and hippocampal commissures. Injections in area TE show a very similar pattern, with additional callosal projections. Reciprocally, injections in the occipital cortex (areas V4v and V3v) reveal forward projections to areas TE and TF, in addition to projections to other occipital regions and to the callosal splenium.

Note that the patient's impaired white matter region probably included U-shaped fibers, due to its immediately subcortical position. Such fibers together with longer-range fibers of the ILF proper contribute to the occipito-temporal connections as described in humans by Catani et al. (2003).

It should be stressed that while the 2 main bundles identified by the present tractography method are quite reliable, considering their thickness, their fit with independent anatomical data, and their reproducibility across successive acquisitions, we cannot exclude that our study missed other existing tracts, particularly in regions of complex 3D crossing

[1] In order to check the reliability of the VBM comparison between the patient and controls (Jones et al., 2005), we run it again with different values of smoothing (0, 10, and 16 mm FWHM, in addition to the original 5 mm). The 0 and 10 mm filters yielded essentially the same result, while the occipitotemporal cluster was too small to survive smoothing with a 16 mm filter.

[2] The comparison between the patient and controls 6 months after surgery showed 2 small additional spots of reduced FA which were not present before surgery, in the right superior frontal sulcus (TC 32 30 22) and in the left orbitofrontal region (TC −14 38 −26).

of fibers. The limitations due to performing tractography on a DTI dataset with only 6 directions should also be acknowledged (see also Jones, 2008, this issue). Thus the few fibers that we observed projecting forward in the direction of anterior temporal and frontal regions, probably through the inferior fronto-occipital fasciculus, may well underestimate such anterior projections (Catani et al., 2003). Those may be of great importance for the so-called ''deep'' lexical word reading route bypassing piecemeal letter-to-sound translation (e.g., Jefferies et al., 2004; Jobard et al., 2003; Mechelli et al., 2005). The inferior fronto-occipital fasciculus might also be involved in the very fast frontal activations observed during word reading (Pammer et al., 2004). In contrast, the ''surface'' route performing rule-based letter-to-sound translation may rely more heavily on projections from the VWFA to inferior parietal cortex through the arcuate fasciculus (e.g., van Atteveldt et al., 2004). We may also have missed callosal connections of the ventral temporal cortex, including the VWFA, which are difficult to make out using diffusion imaging (Abe et al., 2004; Hofer and Frahm, 2006). We did observe a few fibers leaving the VWFA in the direction of the callosum, and a few fibers leaving the callosum in the direction of the VWFA, but none of them managed to bridge the 2 structures, suggesting that the stratum sagittale may constitute an obstacle particularly difficult to cross for conventional tracking techniques. However, such limitations to the sensitivity of diffusion imaging do not prevent the reliable study of the main tracts which were positively identified. Obviously, further studies in groups of normal subjects are required to clarify the full pattern of anatomical connectivity in the reading network. As a final point of method, as the patient suffered from long-standing epilepsy, some caution may be advisable in generalizing results to normal subjects. Indeed, we observed small areas of white matter anomaly relative to the control group even before surgery. However, this does not substantially limit the inferences which we can draw regarding the normal reading system: before surgery, the patient's reading performance was entirely normal; his activation pattern during reading and other visual tasks was also normal; and those few spots of abnormal white matter fell clearly outside of the reading network.

4.2. *Disconnection as one pathophysiological cause of pure alexia*

Following surgery, the ILF was damaged just behind the VWFA, and subsequently it degenerated back to its occipital termination. Those conclusions were supported by converging techniques of fiber tracking and VBM. Thus, the proposed pathophysiological mechanism of alexia is that the lesion of the ILF impeded the transmission of visual information from the occipital lobes to the VWFA.

It is likely that the degeneration started from the white matter underlying the cortical resection, just posterior to the VWFA, and that it extended thence to the entire length of the tract, back to its occipital end. Connections between visual areas comprise contingents of feed forward fibers projecting from lower- to higher-level visual regions, and of fibers running in the opposite direction (Felleman and Van Essen, 1991; Lamme and Roelfsema, 2000). It may be speculated that following the focal disruption of the tract close to the VWFA, fibers running backwards to the occipital lobe were interrupted close to their starting point and underwent Wallerian degeneration in their entire length, while fibers originating in the occipital lobe persisted along most of their trajectory and could still be tracked starting from the occipital lobe (Thomalla et al., 2005). This would explain the interruption of fiber tracking at the same point when starting either from the VWFA or from the occipital lobe, as well as the persistence of a measurable but reduced contingent of fibers along the whole length of the tract, as shown by both tracking and VBM.

As mentioned in the case history, the patient was alexic for words presented in either visual hemifield. Alexia in the right hemifield is easily explained by the fact that the left ILF projects from left-hemispheric retinotopic areas to the VWFA. Why then was the patient also alexic in his left hemifield, as are most alexic patients? There is neuropsychological evidence from both selective lesions (Suzuki et al., 1998) and selective sparing (Funnell et al., 2000) of the ventral splenium suggesting that this sector of the corpus callosum conveys specific information on written stimuli, as opposed to pictures or shapes. However, in the present case, there was no callosal lesion to account for interhemispheric disconnection. Therefore, one may infer that it is the left temporal lesion which prevented word information arriving from the right occipital cortex from joining the left-hemispheric reading pathway. This scenario is compatible with our tracking data (Fig. 6), which show that callosal fibers contacted the left ILF close to the patient's lesion, a lesion which might therefore prevent left-hemifield information from reaching the VWFA. Once callosal fibers from the right occipital lobe arrive in the left hemisphere, 2 possibilities should be considered. Either there is a necessary relay in left occipital cortex and a subsequent projection to the VWFA, or visual information projects directly from the right occipital cortex to the VWFA (Clarke, 2003). Because isolated left occipital lesions do not yield alexia, a left occipital relay does not seem necessary for normal reading, and the latter account seems more plausible. This hypothesis is also supported by the study of a patient with posterior callosal lesion and alexia restricted to his left hemifield (Molko et al., 2002). In this patient, DTI showed that the callosal lesion was followed by the degeneration of a tract projecting from right occipital cortex to the VWFA.

Impairments at slightly different points of the reading network can result in variants of pure alexia. Alexia restricted to the left hemifield results from lesions only affecting interhemispheric pathways (Cohen et al., 2000, 2003; Michel et al., 1996; Suzuki et al., 1998), while the much less documented alexia restricted to the right hemifield might reflect slightly more posterior lesions of the ILF allowing right-hemispheric information to reach the VWFA (Castro-Caldas and Salgado, 1984). Although anatomical evidence is scarce, the so-called subangular alexia may correspond to a further variant of disconnection-related alexia, due to disrupted projections from the VWFA to the left parietal lobe during their course in the parietal white matter (Greenblatt, 1976; Iragui and Kritchevsky, 1991). We would predict that lesions selectively affecting the posterior indirect segment of the arcuate fasciculus (see Catani and Mesulam, 2008b, this issue) downstream from the VWFA, could yield such a variant of pure alexia.

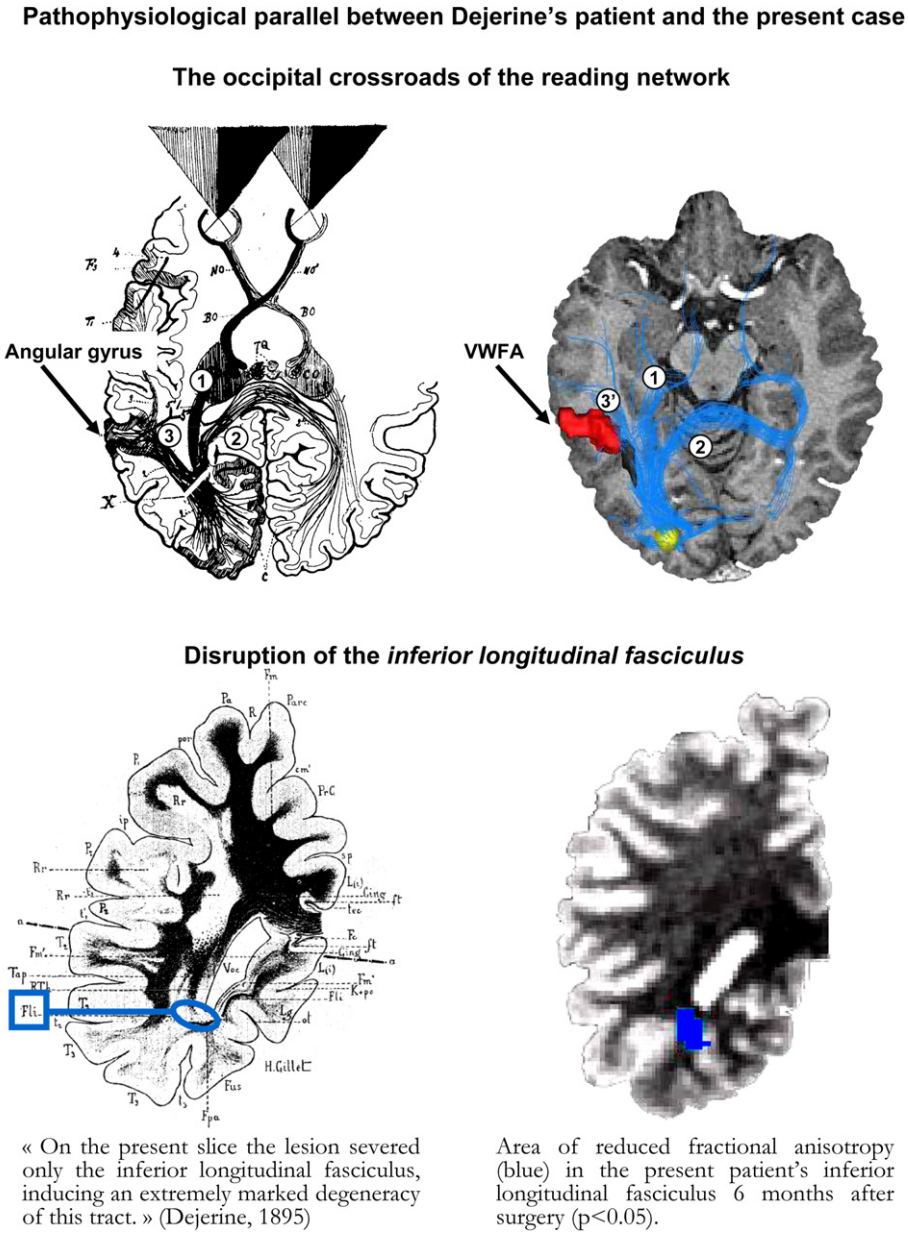

Fig. 6 – Top row: schematic depiction of the reading network according to Dejerine (1892) (left), and fibers tracked from the occipital extremity (yellow) of the ILF in the present patient (right). During reading, the left occipital cortex receives input from the left lateral geniculate through the optic radiations (1), from the opposite hemisphere through callosal fibers (2), and it projects to later stations in the reading network. Dejerine (1892) proposed that the target of such projections was the angular gyrus, although the corresponding fiber tract was purely hypothetical (3). According to the current data, the target of occipital projections is actually the VWFA (red), which is reached through the ILF (3'), which was disrupted in the present patient (dark blue). Bottom row: vertical cut of the left occipitotemporal region, passing through the posterior part of the callosal splenium, in Dejerine's (1895) patient (left) and in the current patient (right), showing in both cases the disruption of the ILF, presumably responsible for the deafferentation of the VWFA.

In summary, diffusion imaging allowed us to determine the anatomical substrate of the disconnection of the VWFA from visual input, namely the disrupted ILF. This disconnection was initially suspected by observing that after surgery the VWFA was not activated during fast word presentation, although it was anatomically intact. Functional imaging also suggested that the VWFA was activated during letter-by-letter reading. The arcuate fasciculus, which links the VWFA and the SMG, remained unaffected by surgery. It is therefore likely that it mediated top–down influences from the parietal lobe on the VWFA, explaining such residual activations. Note that the activation of visual codes in the VWFA might have contributed to the patient's relatively fast letter-by-letter reading, although this causal role in the patient's behavior

remains uncertain. Indeed, letter-by-letter reading may prevail not only in patients with a disconnection, but also in patients with cortical lesions disrupting the VWFA itself (Binder and Mohr, 1992; Cohen et al., 2003).

As a point of history, we noted that although lesions were markedly different, the pathophysiology of alexia may be the same in the present case and in the patient described by Dejerine (1892, 1895). First, the VWFA *per se* was probably spared in both cases. In Dejerine's patient, the cortical lesion affected "*the occipital tip, the basis of the cuneus, of the lingual and fusiform gyri, (…) the grey matter of the gyri bordering the posterior part of the mesial temporo-occipital sulcus.*" In agreement with Dejerine's sketches, the lesion was thus apparently too posterior and mesial to encroach on the VWFA. Second, the ILF was affected in both cases in its course from the occipital cortex to the VWFA. In Dejerine's patient, the white matter disruption affected the occipital pole and extended into the temporal lobe along the ILF. This was illustrated by Dejerine (1895) on a vertical cut of the patient's left occipitotemporal region, passing through the posterior part of the splenium (Fig. 6). This slice was anterior to the cortical lesion but showed the lesioned ILF close to the root of the fusiform gyrus (at approximately TC $Y = -60$). Dejerine explained that the ILF was actually affected in most of its length. In more posterior slices, the lesion "*destroyed completely the tapetum, thalamic radiations, and the inferior longitudinal fasciculus.*" In more anterior slices, the ILF showed "*an extremely marked degeneration which can be followed forwards beyond the amygdalar nucleus.*" In summary, Dejerine's anatomical observations suggest that the VWFA was spared but that the ILF was affected by the softening and by Wallerian degeneration.

Beyond anatomical detail, there are indications that between 1892 and 1895 Dejerine's construal of pure alexia shifted towards the recognition of a critical involvement of the ILF. It is well known that in 1892 Dejerine put forward the hypothesis that "*the connections between [the] two common visual centers and [the] visual word center (left angular gyrus) were interrupted.*" He was, however, extremely cautious in inferring the anatomical basis of this disconnection, plainly asking "*through which fibres are those connections established? Are those associations established through grey cortex or, more probably, through the white masses? We can only suspect such fibres, without being able to demonstrate their trajectory, and not even their existence.*" Accordingly, the drawing by which Dejerine summarised his interpretation (Fig. 6) was explicitly presented as a *schematic* depiction, with hypothetical fiber bundles more akin to the arrows of functional cognitive models. In his 1895 study of white matter tracts, Dejerine returned to this case. However, having identified no actual tract connecting directly the occipital cortex to the angular gyrus (and indeed no such tract has been identified yet in humans), he now emphasized the role of the ILF, in which he recognized "*first and foremost an association bundle linking the occipital lobe, and in particular the visual region, to the temporal lobe.*" Dejerine observed that "*this tract degenerates following occipital lesions and is affected in (…) pure word blindness*", suggesting that he appreciated the importance of the ILF in conveying visual information during reading, and its possible involvement in the pathophysiology of pure alexia.

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