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

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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,

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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