Intracranial dissection of word reading mechanisms

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Reading a word gives access, within a fraction of a second, to a rich variety of information stored in memory, including meaning, grammatical features, and pronunciation. In parallel to memory retrieval, we can convert any string of letters into a sequence of speech sounds, provided that the string conforms sufficiently to the regularities of orthography (1). A prerequisite to the operation of both those reading routes is that letters and their order be rapidly and accurately identified by the visual system. This critical step is achieved in the ventral occipitotemporal (VOT) cortex, a broad region devoted to visual object recognition. The orthographic encoding process is strongly lateralized to the left hemisphere, a bias correlated to and probably resulting from the usual left lateralization of language areas (2).

The causal role of the left VOT cortex in reading was revealed by 19th century neuropsychology through the study of patients with a reading impairment following left VOT lesions (3). Among other tags, this deficit has been termed pure alexia, a label that emphasizes that even in severe cases preventing the identification of single letters, all other facets of visual perception may be spared, including the recognition of faces, objects, and places. One century later, pioneering functional imaging studies elucidated this finding by showing that the VOT cortex area harbors patches of cortex selectively activated by different categories of items, including a word-selective region. Thus, Nobre et al. (4), using intracranial electroencephalography (iEEG) in epileptic patients implanted for diagnostic purposes, observed evoked potentials in the posterior fusiform region about 200 ms after stimulation by strings of letters, but not by pictures of faces, butterflies, or cars. In PNAS, Hirshorn et al. (5) report novel findings on the left VOT cortex contribution to reading, combining, in a kind of methodological tour de force, the study of reading deficit before and after surgical brain lesion, iEEG recordings, and direct cortical stimulation. The authors endeavor to address the so-called "visual word form" (VWF) hypothesis, an issue that calls for some further historical clarification.

The Visual Word Form Hypothesis

In 2000, combining functional MRI (fMRI) and scalp EEG in normal subjects and in patients with posterior callosal lesions, we confirmed that reading is associated with activations in a highly reproducible region, the midsegment of the lateral occipitotemporal sulcus, occurring 180–200 ms after stimulation (6). We proposed calling this region the visual word form area (VWFA), in reference to the cognitive concept of visual word form, a mental representation of abstract ordered letter identities (7). Over the next 15 y, there was a blossoming of imaging studies that uncovered a host of reading-related functional features of the VWFA, including: invariance for upper vs. lowercase words, printed vs. handwritten words, spatial location, and mirror reversal with objects but not with words; tuning to familiar alphabets; sensitivity to lexical status, to the frequency of words, and of sublexical components, such as letters or bigrams (ordered pairs of letters); subtle differences across languages and across scripts; and functional changes during reading acquisition in children or in adults (for recent reviews, see refs. 8–10). This body of empirical research was often discussed in relation to a theoretical divide between proponents and opponents of the VWF hypothesis, depending on their belief in the existence of specialization for reading in the left VOT cortex (9, 11). Without retracing a decade-long debate, which partly stemmed from the polysemy of the word "specialization" (12), it is fair to say that today the hard core of the VWF hypothesis is that at least some reading-specific properties of the VWFA result from local neural changes that have taken place in the visual cortex during reading acquisition (8). According to the opposing view, such properties result entirely from top-down influences from areas involved in phonology and semantics, occurring online during word reading (11).

Hirshorn et al. (5) endeavor to assess the VWF hypothesis by studying four patients implanted for intractable epilepsy. Before reaching their core experiment, Hirshorn et al. (5) go through three preliminary

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steps. First, in line with Nobre et al. (4) and others since, Hirshorn et al. (5) identify intracranial electrodes showing selectivity for words, relative to body pictures and meaningless images. Then, the authors go beyond what functional imaging can afford, by demonstrating a causal link between the VWFA and reading performance. One patient underwent the surgical removal of a brain fragment encompassing a word-selective electrode. This removal allowed Hirshorn et al. (5), similar to Gaillard et al. (13), to document the advent of pure alexia, as evidenced by a slowing down of naming, selective for words, letters, and Arabic numerals, and by the emergence of letter-by-letter reading, compensating for the loss of the normal parallel letter encoding. Two patients also underwent direct cortical stimulation through word-selective electrodes, resulting in interference with word naming, as revealed either by a slowing down of word naming or by actual alexia (14).

The Inner Workings of Word Reading

The most original contribution of the article by Hirshorn et al. (5) comes from iEEG recordings gathered during word reading, which allowed them to distinguish two phases in VWFA activity. It would be simplistic to view the VWFA as a homogeneous module mapping low-level visual features into ordered letter identities at one fell swoop. The local combination detector (LCD) model, emphasizing the bottom-up component of orthographic encoding, proposes that letter strings are processed along the VOT cortex, through a hierarchy of neurons with increasing receptive fields, increasing invariance, and increasing complexity of orthographic representations, from lines to letters and possibly up to morphemes or short words (15). According to this view, the functional features of the VWFA listed above should emerge in different places and at different time points. There is some empirical evidence on such internal complexity of the VWFA, each technique contributing within its intrinsic limitations. Thus, fMRI showed a posterior-to-anterior gradient with successive responses to abstract letter identity (16), bigrams (17), and short words (18). By virtue of their temporal resolution, scalp recordings with EEG and magnetoencephalography allow us to track reading-specific activations starting from about 150 ms after stimulus onset; to timestamp the influence of psycholinguistic variables, such as orthographic regularity, lexical status, imageability, or frequency; and to try disentangling bottom-up from top-down effects (for a review, see ref. 19).

In this context, iEEG has the valuable potential of dissecting orthographic encoding in both time and space. Using multivariate classification techniques applied to iEEG recordings, Hirshorn et al. (5) could decode different properties of word stimuli during successive phases. During an early period (around 200 ms after stimulus onset), the classifier could distinguish between words comprised of low vs. high-frequency bigrams, and between different words provided that they shared no common letter. During a later period (around 500 ms after word onset), it could distinguish between words sharing all but one letter (i.e., words with different lexical content but orthographically almost identical). Such succession of sublexical and lexical stages in the VWFA matches previous iEEG evidence. Nobre et al. (4) already found that the N200 wave recorded in the posterior fusiform region was specific to letter strings irrespective of their lexical status or orthographic regularity, whereas the amplitude of the more anterior P400 wave differed between words and consonant strings, between content words and grammatical words, and was sensitive to semantic and sentential context. More recently, Thesen et al. (20), combining fMRI, magnetoencephalography, and iEEG, distinguished within the left fusiform cortex a letter-form area posterior to the VWFA proper, and showed that those two areas activate sequentially with a 60-ms time lag.

Hirshorn et al. report novel findings on the left VOT cortex contribution to reading, combining, in a kind of methodological tour de force, the study of reading deficit before and after surgical brain lesion, iEEG recordings, and direct cortical stimulation.

From their findings, Hirshorn et al. (5) derive two main arguments in support of the VWF hypothesis. First, lesion study and in situ electrical stimulation both confirm that patches of cortex exist that are required for the recognition of alphabetic stimuli, but not of other complex visual objects. Such selective impairments are indeed difficult to account for without assuming some local specialization for orthographic processing. Their second argument, based upon the sequential sensitivity of the VWFA to sublexical and lexical parameters, may be more disputable. In the absence of recordings in remote language areas, one could argue that such effects result from top-down influences rather than from local neural properties. Particularly, top-down influences on the VWFA, whose existence is beyond doubt (21, 22), might explain lexical effects (23). Conversely, however, sensitivity to bigram frequency likely results from local tuning of the visual cortex. Indeed, using strings of letters both meaningless and impossible to sound out, Binder et al. (17) showed sensitivity to bigram frequency in the VWFA and nowhere else across the whole brain.

To conclude, the study by Hirshorn et al. (5) adds an interesting contribution to the functional dissection of visual word perception. However, it is fair to say that this topic has only been roughed out so far. Distinctions between embedded letters, bigrams, and full letter strings, such as used in most imaging studies, may not be sufficient to account for the diversity of orthographic representations required for efficient reading. Thus, it has been proposed that distinct fine-grained and coarse-grained orthographic codes would constitute optimal input to the phonological and lexical reading routes, respectively (24). iEEG may have a major role to play, particularly through single-unit recordings, to approach the neuronal implementation of such codes. The tight association of iEEG recordings with whole-brain imaging methods would be required to characterize the flow of information within the VWFA and across the whole reading network, including mutual influences between the visual and language areas.

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1 Coltheart M (2012) Modeling reading: The dual-route approach. *The Science of Reading: A Handbook, Blackwell Handbooks of Developmental Psychology*, eds Snowling MJ, Hulme C (Blackwell Publishing, Malden, MA), pp 6–23.

2 Cai Q, Paulignan Y, Brysbaert M, Ibarrola D, Nazir TA (2010) The left ventral occipito-temporal response to words depends on language lateralization but not on visual familiarity. *Cereb Cortex* 20(5):1153–1163.

3 Dejerine J (1892) Contribution à l'étude anatomo-pathologique et clinique des différentes variétés de cécité verbale. *Mem Soc Biol* 4:61–90.
4 Nobre AC, Allison T, McCarthy G (1994) Word recognition in the human inferior temporal lobe. *Nature* 372(6503):260–263.
5 Hirshorn EA, et al. (2016) Decoding and disrupting left midfusiform gyrus activity during word reading. *Proc Natl Acad Sci USA* 113:8162–8167.
6 Cohen L, et al. (2000) The visual word form area: Spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. *Brain* 123(Pt 2):291–307.
7 Warrington EK, Shallice T (1980) Word-form dyslexia. *Brain* 103(1):99–112.
8 Dehaene S, Cohen L, Morais J, Kolinsky R (2015) Illiterate to literate: Behavioural and cerebral changes induced by reading acquisition. *Nat Rev Neurosci* 16(4): 234–244.
9 Dehaene S, Cohen L (2011) The unique role of the visual word form area in reading. *Trends Cogn Sci* 15(6):254–262.
10 Price CJ (2012) A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *Neuroimage* 62(2):816–847.
11 Price CJ, Devlin JT (2011) The interactive account of ventral occipitotemporal contributions to reading. *Trends Cogn Sci* 15(6):246–253.
12 Cohen L, Dehaene S (2004) Specialization within the ventral stream: The case for the visual word form area. *Neuroimage* 22(1):466–476.
13 Gaillard R, et al. (2006) Direct intracranial, FMRI, and lesion evidence for the causal role of left inferotemporal cortex in reading. *Neuron* 50(2):191–204.
14 Mani J, et al. (2008) Evidence for a basal temporal visual language center: Cortical stimulation producing pure alexia. *Neurology* 71(20):1621–1627.
15 Dehaene S, Cohen L, Sigman M, Vinckier F (2005) The neural code for written words: A proposal. *Trends Cogn Sci* 9(7):335–341.
16 Dehaene S, et al. (2004) Letter binding and invariant recognition of masked words: Behavioral and neuroimaging evidence. *Psychol Sci* 15(5):307–313.
17 Binder JR, Medler DA, Westbury CF, Liebenthal E, Buchanan L (2006) Tuning of the human left fusiform gyrus to sublexical orthographic structure. *Neuroimage* 33(2):739–748.
18 Glezer LS, Jiang X, Riesenhuber M (2009) Evidence for highly selective neuronal tuning to whole words in the "visual word form area". *Neuron* 62(2):199–204.
19 Carreiras M, Armstrong BC, Perea M, Frost R (2014) The what, when, where, and how of visual word recognition. *Trends Cogn Sci* 18(2):90–98.
20 Thesen T, et al. (2012) Sequential then interactive processing of letters and words in the left fusiform gyrus. *Nat Commun* 3:1284.
21 Dehaene S, et al. (2010) How learning to read changes the cortical networks for vision and language. *Science* 330(6009):1359–1364.
22 Yoncheva YN, Zevin JD, Maurer U, McCandliss BD (2010) Auditory selective attention to speech modulates activity in the visual word form area. *Cereb Cortex* 20(3):622–632.
23 Mainy N, et al. (2008) Cortical dynamics of word recognition. *Hum Brain Mapp* 29(11):1215–1230.
24 Grainger J, Ziegler JC (2011) A dual-route approach to orthographic processing. *Front Psychol* 2:54.