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The neurobiological basis of seeing words

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This review summarizes recent ideas about the cortical circuits for seeing words, an important part of the brain system for reading. Historically, the link between the visual cortex and reading has been contentious. One influential position is that the visual cortex plays a minimal role, limited to identifying contours, and that information about these contours is delivered to cortical regions specialized for reading and language. An alternative position is that specializations for seeing words develop within the visual cortex itself. Modern neuroimaging measurements—including both functional magnetic resonance imaging (fMRI) and diffusion weighted imaging with tractography (DTI) data—support the position that circuitry for seeing the statistical regularities of word forms develops within the ventral occipitotemporal cortex, which also contains important circuitry for seeing faces, colors, and forms. This review explains new findings about the visual pathways, including visual field maps, as well as new findings about how we see words. The measurements from the two fields are in close cortical proximity, and there are good opportunities for coordinating theoretical ideas about function in the ventral occipitotemporal cortex.

Keywords: reading; visual word form area; DTI; fMRI; visual field maps; retinotopy

Introduction

Over the last 25 years, there have been significant advances in understanding the neural basis of reading. To appreciate how far neuroscientists have come, consider this example from Just and Carpenter's book on reading and language.[1] In this excerpt, they summarize a then-current hypothesis about the biological basis of reading dysfunction.

> Another biologically based explanation of dyslexia is a diagnosis of *minimal brain dysfunction*. This term is sometimes applied when the reader shows no obvious evidence of brain damage, although there may be a subtle pattern of symptoms that suggests neural involvement. However, this approach generally does not provide a satisfactory explanation of dyslexia (Gibson & Levin, 1975). First, the pattern of symptoms is often so subtle that the diagnosis becomes circular. Reading or learning problems are taken as evidence of the minimal brain dysfunction, and the minimal brain dysfunction is the explanation of the reading or learning problems. Second, many dyslexics do not show signs of any neurological problems. (p. 389)

The phrase *minimal brain dysfunction* makes clear how little was known about the neurobiology of reading at that time. Minimal meant, essentially, "it's in there, you just can't measure it." Brain dysfunction could mean anything. It is precisely the sort of phrase and hypothesis that any scientist would like to eliminate from the literature. Progress in neuroimaging methods, coupled with vigorous research programs from laboratories around the world, has replaced the vague hypothesis of minimal brain dysfunction with much sharper and more precise ideas.

This review summarizes recent advances in understanding one aspect of the adult reading brain: the cortical circuits that are trained to rapidly recognize the written word. Historically, the overlap between the study of visual neuroscience and reading was less than it might have been because of the wide supposition, initiated by Wernicke, that the visual cortex contributed rather little to seeing words. The

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classic hypothesis was that a primitive visual representation was sent to the language cortex, where it became the domain of other brain systems.[2,3]

In recent years, cognitive neuroscientists have emphasized the presence of a deeper relationship between visual circuitry and reading, [4–6] with much of this work focused on circuits within human ventral occipital-temporal (VOT). At the same time, vision scientists have explored the responses to objects, faces, color, and other perceptual categories in human VOT and its apparent homolog in macaque inferotemporal cortex.[7–13] Neurons in the VOT cortex transform their responses with training,[14–17] and lesions in the VOT cortex can significantly disrupt the ability to recognize new forms, faces, and colors.[18,19] The VOT is adjacent to the classic visual cortex and includes several retinotopic maps of the visual field.[20,21] The VOT is also relatively close to cortical regions critical for memory and language. Hence, the VOT circuitry is well positioned to learn to recognize specific visual signals and communicate its analyses to cortical circuits specialized for sound and language. A principal objective of this review is to continue to combine the findings from the fields of vision science and reading and especially to identify insights that advance both areas.

During the previous 25 years, neuroimaging technology has changed dramatically; consequently, the limits of our measurements and the theories we can evaluate have changed substantially. The next section on "Neuroimaging principles" includes some observations about the evolution of neuroimaging instruments and analysis methods that pertain specifically to understanding the cortical circuits for seeing words. The section "Seeing words: functional signals" describes the evolution of thinking about functional responses in the human ventral occipital cortex, including both measures of visual field maps and measures of responses to words. The section "Seeing words: connections" reviews measurements of the white matter pathways that carry reading signals along with some speculations about the pathways near VOT. The review concludes with some brief remarks on how neurobiology may offer some insights into reading development and interventions.

Neuroimaging principles

The improvement in functional neuroimaging from positron emission tomography (PET) in the early 1980s to modern magnetic resonance imaging (MRI) data is dramatic (Fig. 1). Many advances in identifying and understanding brain systems for reading can be traced directly to the improvements in data quality acquired from functional and structural MRI.

MRI advances the experimental measures of the human brain in three ways that are specifically helpful for studying cortical circuits for seeing words. First, the spatial scale of key VOT regions is on the order of one or two square centimeters on the cortical surface, and this surface area is compressed to a modest volume by the cortical folding pattern. To understand the activity on the cortical surface, it is important to obtain reliable signals at a spatial resolution that distinguish cortical signals on opposite sides of a sulcus or gyrus. Using MRI, reasonable signal-to-noise ratios (SNRs) at a spatial resolution smaller than the cortical thickness (2–4 mm) can be achieved in individual subjects. To achieve this resolution, it is important—and possible—to use analysis methods that preserve the instrumental resolution.

Second, MR technology is safe for repeated measurements on a single subject.[26] This enables investigators to measure multiple brain structures and responses in a single participant, using many replications and sophisticated behavioral paradigms. The ability to study individuals is of great scientific value for reading, because skills acquired by learning and plasticity may have different neural implementations. Measurements with lower SNR instruments require averaging neuroimaging measures from multiple participants, and this operation effectively reduces spatial resolution to a point where one might fail to correctly isolate signals on the opposite sides of a sulcus. Giving up this resolution and averaging across observers makes sense only if participant response differences are random or unimportant. The SNR in functional and structural MR, accompanied by appropriate analysis methods, enables one to measure at a few millimeters of spatial resolution in individual participants.

Third, it is possible to use MR to measure several different types of tissue properties and, in this way, expand our knowledge about living brain tissue and networks. A particularly important advance is the new class of diffusion-weighted imaging methods that estimate tissue properties of the long-range axons in the white matter.[27–29] Prior to these

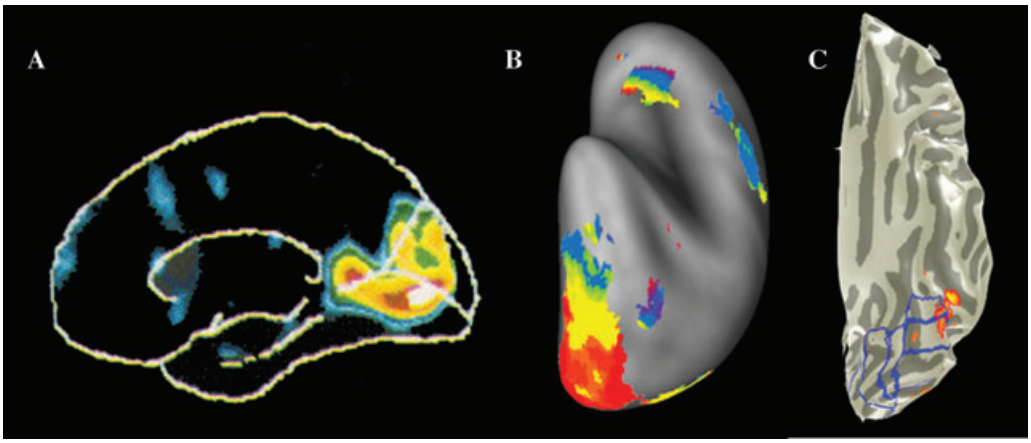

Figure 1. The spatial resolution of neuroimaging. Neuroimaging methods have steadily improved from PET measurements of group-averaged responses (left-hand side, image from Ref. 22, Fig. 1D) to group average fMRI on 3-D surfaces (middle, ventrolateral view, image from Ref. 23, Fig. 3), to fMRI data (words vs. phase-scrambled words) coordinated with visual field maps (blue outlines) in individual subjects (right-hand side, ventral view). The maps were obtained by retinotopic mapping procedures.[24] The word-related activation is near the foveal representation of ventral occipital maps (VO-1 and VO-2); V2 and V3 are also outlined. Measuring robust signals repeatedly in individual subjects and using different paradigms may clarify the relationship between different systems and help us to understand individual differences. Right panel image courtesy of M. Ben-Shachar and A. Rauschecker.

methods, the human white matter pathways and their microstructures were inaccessible to measurement in the living brain. Even pathways thought to be important for reading, such as the left arcuate fasciculus (Fig. 2), were impossible to identify in living subjects. These pathways and their microstructural properties can now be measured routinely in experiments lasting less than an hour. Cognitive measurements with the same individual provide a tool for relating white matter structure and cognitive function. Identifying the communication pathways in any network—neural or electronic—is an essential part of understanding that system. Many of the theoretical ideas about reading are speculations about dysfunction in these communication pathways, and, for the first time, these hypotheses can be tested through direct measurement of the living human brain.

These advances in technology have produced new findings about the brain in many different fields. In the VOT, vision scientists have been able to identify visual field maps; in these same regions, cognitive scientists have identified specialized circuitry for seeing words (compare Fig. 1b and c). To understand the VOT fully, it will be necessary to coordinate these observations. The possibility of powerful interactions between the development of reading and other visual skills has been raised.[17,30] The next section examines recent ideas about the visual cortex generally and seeing words specifically to explore how these fields might usefully coordinate their findings.

Seeing words: functional signals

Visual cortex specializations

Vision begins with image formation (cornea and lens) and light absorption (photoreceptors). All visual functions, including reading, are influenced by these processes. The lens and photoreceptor properties—including wavelength selectivity, spatial blurring, and sampling—are imposed on all natural vision. A person without an image formation system or a light encoding system simply cannot see.

Beginning in the retinal circuitry, visual processing is divided into a diverse array of parallel and more specialized circuits. For example, signals from the cone photoreceptors are processed by more than 15 types of retinal circuits, whose outputs are carried by the axons in the optic nerve.[31] These retinal circuits can be distinguished by their anatomical properties, their stimulus selectivity, and by their distinct brain projection zones.[32–34] Several of these retinal circuits are specialized for general vision functions, such as eye movements, pupil control, and controlling circadian cycles.[35–37] In addition, there are many

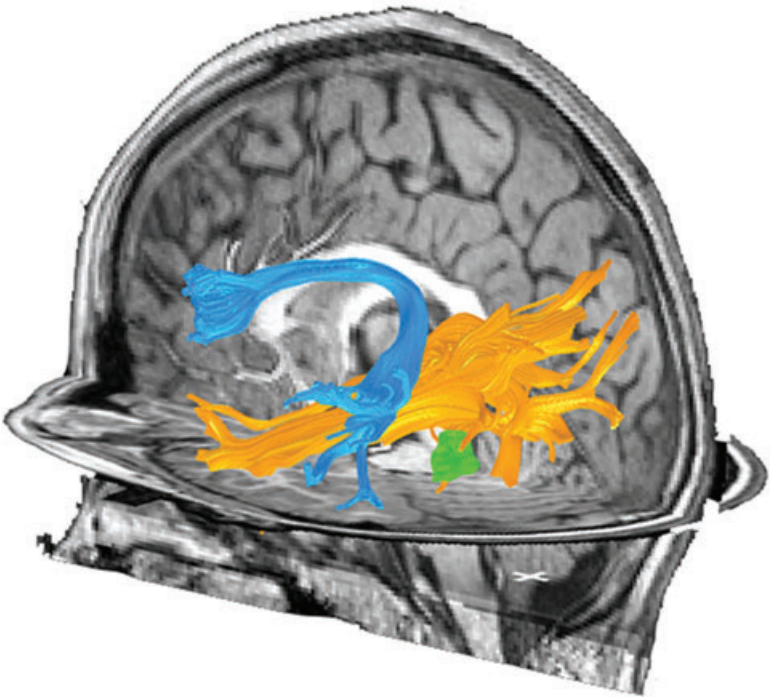

Figure 2. **Diffusion imaging and fiber tractography estimates. The arcuate fasciculus (blue) and inferior longitudinal fasciculus (orange) tracts are shown. These pathways were estimated using a streamline tracking technique. The position of the visual word form area (VWFA) on the cortical surface is shown by the small green region of interest. The VWFA was estimated by comparing responses to words with phase-scrambled versions of words. Image courtesy of Jason Yeatman.**

types of retinal circuits that carry signals specialized for different aspects of visual perception, including color, high temporal frequency information, and fine spatial details. Dysfunction in one component of the system does not always obliterate visual function: an individual who has only cone vision but no rod vision can still see. The principle I emphasize is that specialization for function is present in the retinal circuitry, the earliest stages of vision.

Retinal neurons are derived from central nervous system stem cells, and it seems plausible that the computational principles in the retina will also be present in the visual cortex. The principle of increasing cortical specialization has been advanced by many, but it was Semir Zeki who wrote most forcefully about the concept of *functional specialization.* [21,38] An example of increasing cortical specialization is the primary visual cortex (V1), which receives several types of specialized information from the retina and thalamus (LGN).[39] The circuits within V1 further transform these inputs in a functionally specific way (center-surround receptive fields are transformed to oriented receptive fields; monocular cells become binocular), and these are communicated to cortical regions that are further specialized for color, motion, depth, and so forth.[20,28,38] A further principle is that each zone in the visual cortex generates feedback signals that may influence the incoming stream. [40]

The presence of so many specializations in the visual cortex calls for some theory of their organization; a simple list of specializations is unsatisfying. There are two widely known models of cortical specialization. The first is the hierarchical analysis of visual cortex,[41] which conceives of the visual circuitry as a series of stages increasingly specialized for features while reducing response dependency on spatial position. In the reading literature, Dehaene and colleagues[6] adopt this view. Another organizational theme is the bifurcation of visual signals into a dorsal and ventral stream[42,43] that specialize in different visual tasks. In this case, the ventral stream would contain specialized regions for the rapid interpretation of the spatial pattern of words, though of course other parts of the visual pathways may provide needed circuitry for spatial attention

and phonological recoding. A third but less-known organizational principle is the idea that the visual cortex is divided into a series of distinct specialized clusters of visual field maps.[20,21,44–46] In the following, we keep these principles in mind as we consider the circuitry for seeing words.

Neurology

Both a task analysis of reading—see the word, hear the sound, understand the meaning—and the discovery of patients who see generally but do not see words efficiently—and must read them letter-by-letter—make the existence of circuitry specialized for seeing words plausible.[47,48] Until the late 1980s, however, the opportunity to identify the specific circuitry in the living human cortex was beyond reach. Scientists were left to rely on fascinating but sparse neurological reports coupled with behavioral testing and cognitive theory.[25,26]

One important early analysis was described by Kinsbourne and Warrington.[25] Using brief stimulus presentations (with a tachistoscope), they examined a series of individuals who were incapable of efficiently seeing a whole word, although these individuals could slowly make out individual letters. They studied one individual with a very large lesion in the left ventral occipital temporal cortex (Fig. 3). They characterize her reading as follows:

> She spelt out aloud all but the very shortest words, letter by letter, and then arrived at the correct word by a process of auditory recall. Reading was therefore very slow, and she was reluctant to attempt it. Any attempt to read more quickly was vitiated by numerous paralexic errors. (p. 699, Ref. 25)

At first, reading dysfunction was considered a symptom of simultagnosia, an inability to perceive or attend to multiple objects (in this case letters) at the same time.[50] Kinsbourne and Warrington accepted this interpretation because their subjects read letter-by-letter—as if they could only see one letter at a time—and these subjects also had difficulties in seeing more than one object at a time. In later papers, they suggested that letter-by-letter reading and the difficulty in perceiving multiple visual objects at the same time were caused by different neural dysfunctions.[49] Given the understanding of visual cortex at that time, it was natural to suggest that the dissociation must arise because one deficit (simultagnosia) was essentially visual and the other (alexia) had more to do with language. This was supported by the anatomy, which showed that some subjects with letter-by-letter reading had lesions in the temporoparietal junction (TPJ), not in the visual cortex.[49]

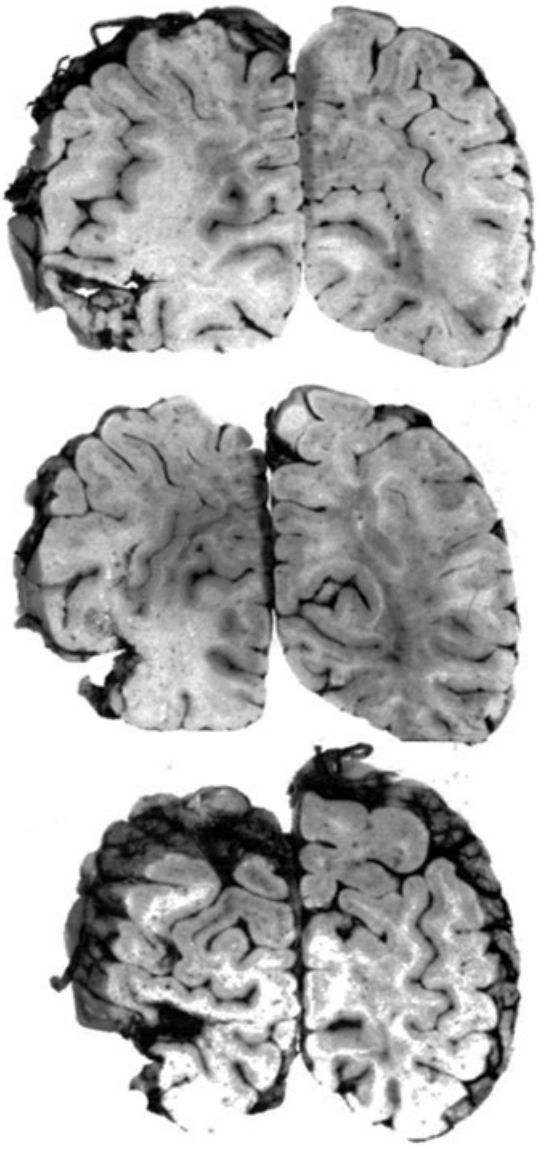

Figure 3. **Postmortem images of an alexic subject's brain. Images are from the subjects studied by Kinsbourne and Warrington.[25] Neurological cases often present with extensive damage that spans the gray matter and nearby white matter.**

The more modern understanding of the visual cortex allows that letter-by-letter reading and simultagnosia might arise from damage to distinct functional specializations that are both within

the visual cortex. Examples are the neurological conditions of prosopagnosia and cerebral achromatopsia, both arising from damage to VOT, often occur together and yet are dissociated in some patients.[18,51,52] Hence, the dissociation of simultagnosia and letter-by-letter reading may also be explained by dysfunctions within the visual cortex. Further uncertainty exists because letter-by-letter reading might arise from multiple causes, including dysfunction outside of the visual cortex. Hence, these data are not decisive concerning the specific role of VOT in seeing words. The method of studying patients with lesions is probably too coarse to be decisive about these points because naturally occurring lesions are rarely specific enough to distinguish parts of VOT or pathways.

PET and intracranial measures

PET offered the first opportunity to measure cortical activity in subjects engaged in reading. Two groups, one in St. Louis[53–56] and another in London,[57–60] measured PET responses while subjects read. The St. Louis group reported that "certain areas in the left, medial extrastriate visual cortex were activated by visually presented pseudowords that obey English spelling rules, as well as by actual words. These areas were not activated by nonsense strings of letters or letter-like forms. Thus visual word form computations are based on learned distinctions between words and nonwords."[22] The London group failed to see the activation in the left medial extrastriate cortex and reported instead "a lexicon for written word recognition in the posterior part of the left middle temporal gyrus."[57] Potential reasons for this discrepancy were considered in subsequent papers.[61] As the images in Fig. 1 make evident (see also Ref. 21), the spatial resolution and SNR of PET imaging in that era was adequate only at a coarse scale, say, for identifying regions on the cortical surface of 3–4 cm^2 or more.

At about this time, Nobre and colleagues reported measurements of intracranial potentials measured in 23 individuals about to undergo surgical resection for epilepsy.[62] Reading words evoked a large field potential in VOT near the occipital-temporal boundary with a peak-amplitude approximately 200 ms after the stimulus presentation. There was a second evoked potential in the anterior ventral-temporal cortex that peaked about 400 ms following the presentation of a word form. Nobre *et al.* summarized their findings by writing that there are "two discrete portions of the fusiform gyrus responded preferentially to letter strings. A region of the posterior fusiform gyrus responded equally to words and nonwords and was unaffected by the semantic context in which words were presented. In contrast, a region of the anterior fusiform gyrus was sensitive to these stimulus dimensions" (Abstract). Intracranial measurements have higher spatial and temporal resolution than the contemporaneous PET measurements. Nobre *et al.* made no reference to the debate between the St. Louis and London groups. The authors did not comment on the London group's view that the angular gyrus computed word forms, presumably because no measurements were made in that region. Nobre *et al.*'s measures gave some support to the St. Louis group's view that there are word-evoked signals in VOT, but the location of the field potentials are significantly more lateral than the medial extrastriate observation with PET.

Visualization of the VOT responses: a complaint

Other groups also used PET to understand brain activity while reading. For example, Rumsey *et al.*[63] reported a difference between good and poor readers in mid-to-posterior temporoparietal, left superior and middle temporal, and left fusiform. Brunswick *et al.*[64] wrote that their "most important finding was that in both studies dyslexics showed reduced activation in the left inferior temporal lobe." Paulesu *et al.*[65] summarized the principal response difference between good and poor readers as having "the maximum peak in the middle temporal gyrus and additional peaks in the inferior and superior temporal gyri and middle occipital gyrus."

The visualizations in this literature introduce some confusion, at least for me (Fig. 4). The rendering gives the impression that the principal difference is on the surface of the left temporal lobe, which is where Temple[66] places it in her review: "Neuroimaging studies of phonological processing in adult dyslexics, despite many experimental differences (i.e., imaging methodology, extent of deficit, and tasks used), have all reported a reduction or absence of activity in left hemisphere temporal-parietal cortex in dyslexic adults" (p. 178). When the reported coordinates are rendered using modern methods, it is clear that all of these papers describe

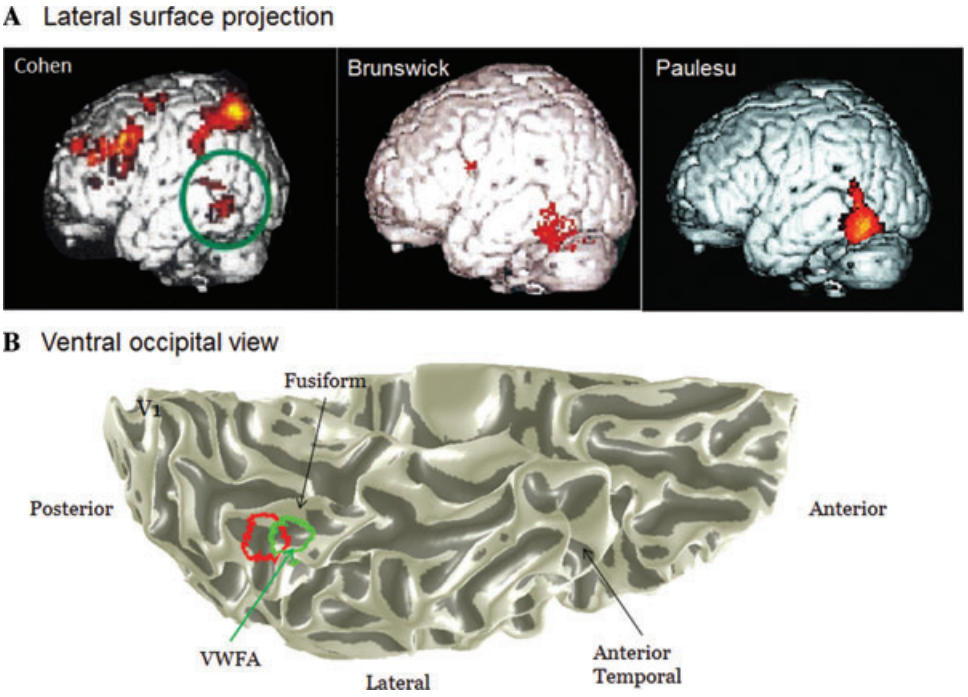

Figure 4. **Visualizations of PET and fMRI activation of seeing words. The three images at the top show a method of rendering data used in the early 2000s by many groups (images from Ref. 4, 64, and 65). The activations are projected on the lateral surface, but that is not their true location; one must consult additional figures to determine the true location on the brain. When the locations of these activations are rendered on a 3-D mesh of the cortex (red outline), it is clear that the principal locus is in VOT. Difficulties in understanding the spatial location of these activations are present in the literature (e.g., Ref. 66, Fig. 1).**

activations in the VOT (Fig. 4, bottom panel). The postprocessing tools and visualization methods play a significant role in communicating the results.

Retinotropic maps and the VWFA

By the year 2000, Cohen, Dehaene *et al.* could confidently describe "A standard model of word reading . . . [that includes] a left inferior temporal region specifically devoted to the processing of letter strings."[4] Using functional magnetic resonance imaging (fMRI), they located this region in the middle portion of the left fusiform gyrus and named it the visual word form area (VWFA). They proposed that responses in the left VWFA were "identical for stimuli presented in the left or in the right hemifield." Responsiveness to stimuli throughout the visual field distinguished the VWFA from the retinotopic cortex, such as V1 or hV4, which are mainly responsive to a hemifield. The VWFA label was met critically[67] but is now widely used. The evidence for a causal role of the VWFA in seeing words is compelling (e.g., Ref. 68).

A decade ago, little was known about the visual organization on the ventral occipital surface. fMRI measures located the human visual field maps V1/2/3, near the occipital pole and spanning calcarine cortex.[69–72] There were disputes, however, about VOT maps,[73–75] and frequently investigators either supposed that the VOT did not contain retinotopic maps or simply referred to the region diffusely as V4/V8/VO.

Retinotopic mapping methods have improved, and, at present, multiple groups agree that there is a series of visual field maps in the VOT cortex (reviewed in Refs. 20 and 45). It is possible to measure visual field maps along with responses to a VWFA localizer measured in a single participant within the VOT (see Fig. 1c and Ref. 76). The data from the participant in Figure 5 are a second example that is typical of our subjects; in this person, the VWFA is slightly anterior to hV4 and near the foveal representation of the ventral occipital maps (VO-1, VO-2). The VWFA is also close to two temporal-occipital maps (TO-1, TO-2).

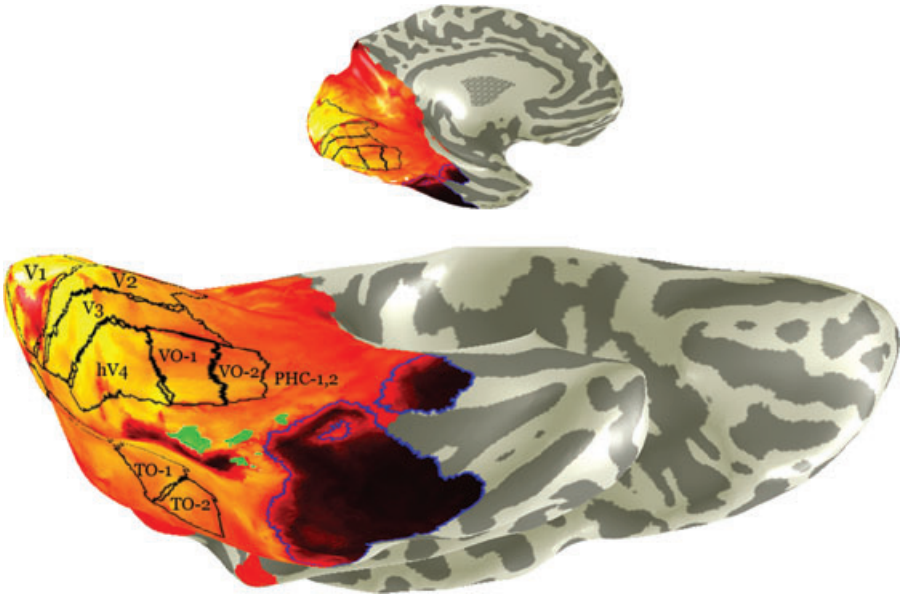

Figure 5. **Instrumental limitations of BOLD measurements in the ventral occipital temporal (VOT) cortex. The small image at the top shows a medial view of the left hemisphere. The outlined regions are several visual field maps, including V1/2/3 and hV4, VO-1, and VO-2. The main image shows the same brain from a ventral view. The visual field maps are labeled, and the green overlay shows the regions activated by a VWFA localizer (words vs. phase-scrambled words). The light-dark orange shading is a measure of the mean BOLD signal level. When the mean level is very low, the signal-to-noise of the measurements is poor.[77] This view emphasizes two difficulties in VOT measurements. The dark region in the temporal lobe is caused by susceptibility artifacts from the auditory canal. The dark line abutting the VWFA is caused by the transverse sinus, which induces a distortion in the mean magnetic field (B0). Across subjects, the artifact positions vary with respect to the cortical surface and limit the measurements of cortical responses. Image: courtesy of Jonathan Winawer.**

The TO maps fall within motion-selective cortex, hMT^{+};[72,81,82] while the TO maps are conservatively labeled by their anatomical position, TO-1 is likely to be MT, and TO-2 is one of the nearby motion-selective maps, such as medial superior temporal cortex (MST).[83,84]

Functional responses to words in VOT

Over the last decade, the reading community has used a wide range of experimental methods to characterize the responses to words in the VOT. Much of this analysis has centered on the VWFA, but frequently the measured regions are quite large and extend into the ventral occipital lobe. Little attention has been given to the challenge of coordinating the visual field map findings with responses to seeing words, and it is not uncommon to see images such as those in Figure 1(b) and (c) in which the two fields claim the same territory (e.g., Ref. 85).

One objective in many of these studies is to decide whether the VOT circuitry is essentially visual, say, representing edges and simple shapes, or alternatively does VOT circuitry include language-specific information (e.g., see Refs. 16, 67, and 86). Another comparison is to measure responses to pseudowords (nonlexical orthographically legal letter strings); there is agreement that responses to pseudowords are similar, but slightly larger, than responses to words.[87–90] The response to both is somewhat larger than the responses to other simple visual stimuli (e.g., line drawings).[91] In the VWFA, priming (fMRI adaptation) occurs between certain letter string stimuli but not others, showing some degree of invariance to font and size.[86,92–94] The VWFA also responds selectively in languages with nonalphabetic writing.[95] Finally, responses in VOT change as subjects learn to see forms.[16,88,96,97]

The range of model assumptions available to predict these results is quite large, and many of the specific assumptions underpinning the flow chart models favored by cognitive neuroscientists—such as the tuning to words of individual neurons—are not yet testable.[87] In one model aimed at summarizing the VWFA findings, Dehaene *et al.*[6]

propose that the posterior VOT includes the circuitry necessary to transform visual information into a lexical representation. Their model, the local combinations of detectors (LCD), proposes that visual (prelexical) circuitry in the posterior VOT is recombined into increasingly abstract word form representations within anterior VOT. Some authors entertain the hypothesis that the VOT represents full words (lexical)[87,88,89,98,99] and memory for words.[100] Others suggest that the VOT responses are essentially visual and that increased responses to word forms are due to feedback signals from language areas rather than circuitry within the VWFA.[67,91,101] The principle that functional lateralization is associated with feedback from language rather than feed-forward processing is supported by evoked potential data showing that the VWFA is lateralized to the same hemisphere as language processing, rather than to the left hemisphere.[102]

The reading community's interest on deciding between language and vision recapitulates the disagreement between Wernicke and Dejerine. Advances in characterizing the visual cortex appear to have reduced some of the force of the dispute. Most significantly, there is now general acceptance that responses in the visual cortex reflect the statistical properties of natural images.[103] This makes it much less surprising to propose that responses in the VOT reflect the statistical properties of a cultural artifact, word forms.

fMRI limitations

There are several important technical challenges in coordinating the fMRI work between these two fields. One important issue concerns the ability to make spatially resolved measurements in the VOT.

Figure 5 illustrates the inhomogeneity of blood oxygen level dependent (BOLD) signals in the VOT. The surface coloring represents the mean BOLD signal, and it is evident that the mean differs significantly across the surface. The large dark region in the anterior temporal lobe corresponds to the susceptibility artifact arising from the auditory canals. There will be no reliable BOLD activation in these dark regions. In the presence of additive instrumental noise, the SNR will be very inhomogeneous, and indeed this region is notoriously difficult to measure.[104] The anterior portion of the identified VWFA approaches this region and then stops, so that it is entirely possible that the true cortical response continues into this region but cannot be detected because of the artifact. I am unaware of methods that equate signal-to-noise along the entire ventral temporal cortex, and most fMRI reports are probably blinded to cortical responses in the portion of VOT near the auditory canal.

Equally important, though more subtle, is the long dark region adjacent to the VWFA. This low SNR region is present in most subjects and appears to arise from the transverse sinus, a large blood vessel close to the surface of cortex.[77] This sinus obscures measurements in hV4, is present in every subject, and has a variable position with respect to the visual field maps and presumably the VWFA. It is likely that the variable position of the sinus implies that one can measure responses from portions of the VWFA, but that some responses are masked. The VOT is a tough neighborhood for fMRI measurement.

Neither of these two artifacts, from the auditory canal or the transverse sinus, is overcome by averaging. fMRI measurements within these regions will require new techniques.[105] Understanding these measurement limitations is important as we ask increasingly refined questions about the spatial distribution and functional role of the signals in the VOT.

Beyond the instrumental limitations, the resolution of theoretical issues can be hindered by experimental design (e.g., group averaging) and postprocessing strategies (e.g., volumetric smoothing). For example, to achieve whole brain coverage, investigators often use large voxel sizes (4–5 mm). The data are commonly blurred in postprocessing by 5–10 mm in three dimensions (extending into the white matter) to satisfy statistical constraints and reduce imperfections from aligning different subjects. Experiments are designed to combine data from multiple subjects into a single coordinate frame, further blurring the measurements and making it impossible to identify the responses of individual participants with respect to their own functional organization (e.g., visual field maps). No unambiguous processing methods exist for clarifying whether VOT responses are initiated by signals from visual cortex or language areas, and it seems likely that both are involved.

In general, the fMRI community has not yet set standards for communicating the SNR of the measurements. Weak or absent signals are interpreted as

if they are properties of the brain and incorporated as part of the theory, rather than being acknowledged as instrumental limitations. Hopefully, this will change.

Motion cortex and seeing words

Over the last 30 years, a series of investigators reported correlations between reading performance and motion and depth perception[106–109] as well as fMRI responses in portions of the visual pathways that are responsive to such stimuli.[110–113] This literature is not often considered along with reports about the VWFA, and one likely reason for neglecting these reliable reports might be traced to Wernicke's notion: the visual system identifies the lines and edges of letters and this nonlinguistic information is quickly communicated to language centers (angular gyrus). In this view, it is hard to understand why the motion-selective visual cortex would have an impact on reading static, high contrast targets.

If the more modern view of the visual system is accepted—that within the visual cortex (VOT) there is a great deal of specialization for form and motion—a role in reading for the circuitry within the human TO maps becomes more plausible. The neurons in these maps influence motion perception, eye movement, and attention,[114–118] and these maps are in close proximity to VOT (Fig. 5). If the visual system is capable of learning to recognize specific forms, it may also be capable of learning the specialized eye movements and visual attention patterns needed for reading.

Moreover, the motion-selective cortex appears to have an ancient origin[119] so that the processing by TO cluster neurons is likely to contribute to seeing objects generally; it seems likely that newer cortical regions developed in the presence of TO circuitry and use its analyses advantageously. If there is such dependence, TO circuitry deficits could be another possible source of reading disability. John Stein has long promoted this view,[107] and the hypothesis that dyslexia is a visuo-spatial attention disorder remains under active consideration. For example, Sperling and colleagues have explored the specific hypothesis that noise exclusion, a form of visual attention, is important,[120,121] and these ideas have been recently reviewed.[122] Multiple investigators have shown that the motion-selective cortex responds weakly in dyslexics, and it is too soon to exclude the possibility that in some individuals TO circuitry is a cause of poor reading.

Seeing words: connections

While neuroscientists focus their measurements on signals at individual neurons or even at a single synapse on a single neuron, clinical neurology often confronts phenomena on a much larger spatial scale.[3,123,124] Patients frequently suffer damage to both gray matter and the long-range projections in the white matter (Fig. 4). Perhaps for this reason, Wernicke[2] and Geschwind[123,124] emphasized the important role of axons in understanding brain and neurological disorders. Neurological conditions caused by improper connections are often described as disconnection syndromes: alexia is a classic example.[a]

But what signals are disconnected? Dejerine proposed that the visual brain is educated by experience to see combinations of letters through perceptual training. Wernicke, who did not accept the existence of visual circuitry representing individual words, argued that the visual brain learns to see only letters (not letter combinations or words). At that time, very little was known about the visual cortex; even the location of the primary visual cortex was in dispute.[20] The modern understanding that there are multiple visual field maps well beyond primary visual cortex had not emerged, and the predominant assumption was that the zones between primary sensory and motor regions were "association cortex," a diffuse term that remains widely used but means little. Advances in understanding the visual cortex have replaced the diffuse notion of the association cortex with a much more specific view. These regions of cortex include retinotopic maps, have specific response patterns to visual stimuli, and contain circuitry that can be modified by learning.

[a] This framing in terms of connections is also summarized as a dissent from localization (see Ref. 125), but there is not much difference between localization of information within cell bodies (cortex) or their axons (white matter); damage that impedes signal integration at the neuron's cell body or communication between neurons both disturb brain function. Rather, the question of localization concerns whether information at the cell body and on the axon is specific to an attribute (e.g., color vs. form) or general (e.g., a distributed set of weights that can be decoded to represent multiple attributes).

Hence, Dejerine's hypothesis that learning to see words might be embedded within a portion of the visual circuitry is consistent with the modern understanding of the visual cortex.

If VOT circuitry learns to see words, how can the developing child's brain be sure that the trained circuitry communicates its analysis to the correct language areas? Are there conditions in which visual cortex learns to recognize word patterns, but the communication links fail? If the link fails, is it because people do not always recruit the same VOT regions for reading or because the projection from the region fails to develop? Does the brain use connection architectures designed to reduce developmental failures, say by sending all projections to another location (parahippocampal) that specializes in the appropriate distribution of learned visual inputs?

One approach to analyzing these issues is through the use of MR diffusion imaging and tractography algorithms. These methods together provide estimates of the position and cellular properties of large white matter tracts in the living human brain.[126] These methods and algorithms offer an opportunity, for the first time, to explore connectivity questions in healthy participants to complement the observations in neurology.

There has been progress in clarifying the white matter pathways involved in reading broadly as well as some progress in analyzing the specific white matter pathways that communicate to the VOT. The new work advances a century of neurological investigations. Here, I focus on the recent advances, though making some effort to place them in context. As in the case of fMRI, there are significant instrumental and algorithmic limitations for diffusion imaging and tractography. I regret that there is not enough space or time to review these issues here.

Neurology

The reader may wish to consult the excellent review by Bub *et al.*[127] for a fascinating description of Dejerine and his work; a very brief summary is presented here.

In a postmortem study of the alexic patient, Monsieur C, Dejerine documented large white matter lesions.[128] The massive damage within the ventral occipital white matter is rarely discussed because it is so massive. This region contains the inferior longitudinal fasciculus (ILF, Fig. 2) as well as portions of the optic radiation.

In addition to the ventral damage, Monsieur C had a lesion in the posterior part of the corpus callosum (splenium). Dejerine viewed the splenial disconnection as unimportant, but Wernicke suspected that disruption of this pathway was necessary for alexia to occur. He argued that the visual interpretation of letters (not words) is carried out in both the left and right occipital cortex and that information from right to left hemisphere language centers pass through the splenium. Without a splenial lesion, Wernicke argued, reading would be supported by right hemisphere letter processing.

Below, I discuss new analyses relating to both the ILF and callosal pathways. The extensive reading literature related to the arcuate fasciculus, superior longitudinal fasciculus, and corticospinal tract has been reviewed recently elsewhere.[76]

Inferior longitudinal fasciculus

Most of the VOT is within the conventional zone identified as the visual cortex, and, thus, it is easily accessible via relatively short-range white matter projections (U-fibers) to the VO cluster and to the hV4 field map. In a very thorough analysis, Epelbaum *et al.*[129] investigated the inputs to the VWFA in a patient about to undergo a surgical resection. The resection was positioned slightly posterior to the VWFA. Epelbaum *et al.* used several techniques, including functional and diffusion imaging, to measure the brain of this patient. There is a controversy over whether there is a truly long-range ILF[130] or whether the ILF as labeled by neurologists is simply a series of U-fibers;[131] however, for the purpose of the Epelbaum study, the distinction is not important. Epelbaum *et al.* suggest that the pathways carrying the VWFA output to the language cortex are within the left arcuate fasciculus. In data from our laboratory, the cortical terminations of the arcuate are not close to the VWFA (Fig. 2), but these are difficult measurements and we are continuing to explore the issue.

Callosal pathways

The role of splenial fibers in alexia has been much discussed.[48,123,124,78] Some puzzling inconsistencies remain in the literature, although a great deal has been learned over the years. In considering several of the classic papers, I draw the reader's attention to a few key points.

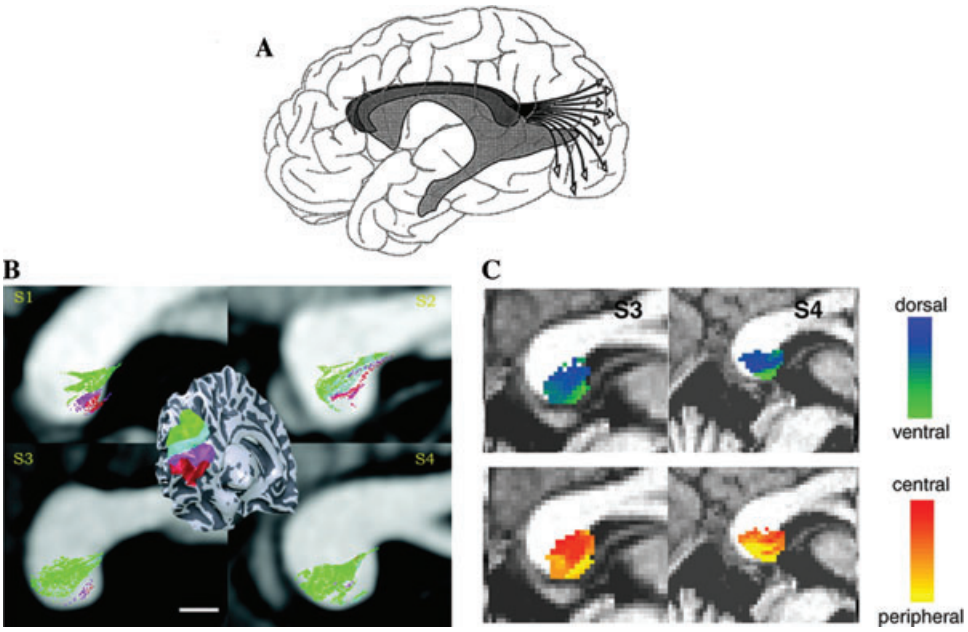

Figure 6. **Advances in measuring the posterior callosal pathways. (A) Speculations about the posterior callosal pathways were an important part of theorizing about reading, but until recently these pathways could not be measured (image from Ref. 78, Fig. 9A). (B) Using diffusion MR and tractography, certain aspects of the posterior callosal pathways can be measured, including the projection zones of these pathways in the occipital lobe (Ref. 79, Fig. 4). (C) The retinotopic organization of the splenial projections (image from Ref. 80, Fig. 3).**

Geschwind[124] remarks that "alexia invariably occurred after left occipital lobectomy but was transient in all cases, clearing in a few months. The splenium, of course, was left intact so that there was a path from the right occipital cortex to the left angular gyrus" (p. 260, Ref. 124). The existence of such a path has not been definitively established—or denied—at this point in time.

Damasio and Damasio[48] concluded that there is an important role for a group of splenial fibers. They specifically refer to fibers "that terminate in inferior visual association cortices . . . [passing through] the middle component of fibers of the splenium, considered on the dorsoventral axis." They distinguish these from dorsal fibers that were intact in many of their alexic patients.

Binder and Mohr[78] were unconvinced that VOT was important for reading ("Finally, reading is unaffected by medial and ventral occipital lesions" [p. 1820, Ref. 78]). They did conclude that alexic patients "have extensive lesions affecting the splenium, major forceps or dorsal occipital white matter" (p. 1819). Binder and Mohr summarized their view of the relationship between callosal fibers and reading in a sketch (Fig. 6A), and they used this diagram to emphasize the importance of the dorsal fibers in alexia.

Subsequently, there has been further progress in understanding the posterior callosal pathways. The patient studied by Epelbaum *et al.*[129] did not have a detectable degeneration in the splenium of the corpus callosum but the alexia was present in both the right and left visual field. It is quite likely that right hemisphere fibers projecting to the left VOT might have been interrupted by the VOT resection in their patient. An earlier study from the same group measured a patient with a pericallosal resection with alexia in only the left hemifield.[132] This supports the principle that splenial fibers send important information for reading to the left VOT.

In recent years, human diffusion measurements have offered better estimates of the position and properties of the occipital-callosal fibers. Dougherty *et al.*[79] located the position and mapped these fibers in the splenium to within a few millimeters (Fig. 6B). Saenz and Fine[80] also analyzed the representation of the visual field map within the splenium, showing an eccentricity representation and an angle map

(Fig. 6C). Both groups place the occipital-callosal fibers in the most posterior ventral position within the splenium.

Unpublished measurements in our lab suggest a pathway from the middle portion of the splenium that passes superior to the ventricle and descends to the VWFA (Alison Kevan and Michael Perry, personal communication). This pathway supports Damasio and Damasio's suggestion[48] that the key splenial pathway is dorsal to the ventricle en route to the VOT. The observation is also consistent with Binder and Mohr's observation that dorsal-occipital white matter lesions give rise to alexia.[78]

The corpus callosum is a large and important structure, and the fibers traversing the midsagittal plane are nearly parallel to each other. This makes the callosum an excellent target for diffusion imaging because axial and radial diffusivity measures within the midsagittal section of the callosum (before the fibers curve) primarily reflect the cellular structure of the axons; in certain other parts of white matter the presence of fiber curvature and crossing fibers makes diffusion measurements difficult to interpret. Consequently, there have been several recent studies examining the relationship between callosal white matter microstructure and reading.[133–135] All of these studies find correlations between reading performance and diffusion measurements in a region just anterior to the occipital-callosal fibers in the splenium. Over the next few years, it may be possible to separate out further the different pathways in the posterior callosum and to understand both their projections and the role that they play in different aspects of reading performance.

Discussion

An important application of these findings is how we might evaluate and guide the development of these reading pathways in children.[136] Around the world, children spend many hours in training that is designed, in part, to develop cortical circuits for rapidly recognizing and interpreting written word forms. This training is carried out in different languages, using different orthographies, and with different procedures. The widespread training in reading offers scientists an opportunity to investigate how young brains learn to recognize visual forms; understanding the neural basis of reading development can inform us about visual recognition and developmental plasticity. Perhaps through a deeper understanding of these mechanisms we can discover methods to improve the training used in schools.

The analysis of reading development typically begins by noting that learning to see word forms requires explicit training and practice, as opposed to seeing faces and objects. While this is true, it is also the case that there are many culturally specific patterns that must be learned by brain circuitry.[30] It seems likely that some neural circuits are genetically endowed with the ability to learn (plasticity), and for some regions this ability remains available through the life span. The retained plasticity can be contrasted with the development of other visual circuits, such as binocular vision, which appear to follow a programmed developmental process that stabilizes during childhood.[137–140] Extrapolating from primate investigations in the inferotemporal cortex,[15,141] many investigators believe that the VOT circuitry is a likely location for visual circuitry that retains its ability to learn through much of life.

The visual circuitry needed to see word forms must coordinate its development with parts of visual cortex that provide stable input. For example, it is obvious that the retina and V1 must develop sufficiently to provide necessary inputs. Basic changes in the organization in these visual circuits would be problematic for regions that aim to learn new classes of visual stimuli. For example, learning to see words in the VOT might be impeded if it is undertaken at a time when the key inputs to the VOT signals from other visual circuits have not yet stabilized. This is one reason why the motion-selective visual cortex may matter for the neural circuitry that is trained to see words.[107,110,111,113,142,143]

There is a large and growing literature measuring the development of VOT responses and the development of key white matter pathways. The reader might consult the recent series of functional MRI studies from Brem *et al.*[144–147] Earlier work by several groups, including Shaywitz, Shaywitz, and Pugh[148–151] and Booth[152–154] have been influential (see recent reviews, Refs. 155 and 156). Finally, the reader might note a parallel literature that is expanding, perhaps at a faster rate, to measure and understand the development of gray and white matter properties[157–160] and their relationships to reading.[161,162] There have already been studies of the

effect of interventions on white matter[163] and abnormal development,[164] and surely many more will be reported.

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Conflicts of interest

The author declares no conflicts of interest.

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