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White matter pathways in reading

Michal Ben-Shachar, Robert F Dougherty and Brian A Wandell

Skilled reading requires mapping of visual text to sound and meaning. Because reading relies on neural systems spread across the brain, a full understanding of this cognitive ability involves the identification of pathways that communicate information between these processing regions. In the past few years, diffusion tensor imaging has been used to identify correlations between white matter properties and reading skills in adults and children. White matter differences have been found in left temporo-parietal areas and in posterior callosal tracts. We review these findings and relate them to possible pathways that are important for various aspects of reading. We describe how the results from diffusion tensor imaging can be integrated with functional results in good and poor readers.

Addresses
Stanford Institute for Reading and Learning and Department of Psychology, Stanford University, Stanford, CA 94305, USA

Corresponding author: Ben-Shachar, Michal (michal@white.stanford.edu)

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Introduction

Performing any cognitive task relies on coordinated processing in multiple, often distant brain regions. In the specific case of reading, the brain integrates signals from cortical regions specialized for processing visual, phonological and linguistic information. These regions are separated by many centimeters [1–3,4•,5] and thus depend on the accurate formation of specific white matter connections during development. Skilled reading requires proficient processing in gray matter areas, as well as appropriate connection topology and efficient signal transmission within the white matter pathways.

The significance of white matter development and integrity for cognition is demonstrated in various neurological disorders. Perhaps the best known examples are the dramatic cases of callosal disconnection in so-called 'split-brain' patients [6]. These patients frequently fail to produce complex linguistic responses based on stimuli presented in the left visual field, because such responses rely on the transmission of information from visual areas in the right hemisphere to language regions in the left hemisphere. There are also important examples in which white matter diseases lead to specific cognitive disabilities. Geschwind particularly emphasized the idea that acquired reading disorders are manifestations of a 'disconnection syndrome' in which damage to white matter disrupts communication between key cortical reading mechanisms [7,8•]. For example, localized damage to white matter in multiple sclerosis can cause alexia without agraphia (pure alexia; see Glossary), presumably through interference with visual signal transmission by white matter pathways [9]. Such neurological cases demonstrate that interference with transmission of signals between cortical regions powerfully influences specific reading skills in adults (Box 1).

Advances in computational imaging methods over the past decade enable us to study the anatomy of healthy human white matter circuits at millimeter resolution. These computational methods use data from magnetic resonance imaging (MRI) pulse sequences that measure the apparent diffusion coefficients (ADC; see Glossary) of water within brain tissue in specific directions [10–14]. Because water diffusion is restricted by cell membranes and large molecules, these directional diffusion measurements provide information about the local orientation and microstructure of axon bundles (fascicles; see Glossary) and their associated glia. Thus, these directional diffusion measurements can be used to reconstruct the trajectory of white matter fascicles and estimate their structural properties.

In this paper, we review findings from the past five years that relate reading skills to white matter properties in healthy adult and child readers. Figure 1 shows a three-dimensional reconstruction of three major white matter pathways in the vicinity of the reading-related white matter regions: the corona radiata, the superior longitudinal fasciculus and the corpus callosum. In the following sections, we briefly review methodological principles of diffusion tensor imaging (DTI) and the findings that relate reading and white matter properties. We then propose three alternative interpretations for these findings, each highlighting a different pathway from the ones depicted in Figure 1. We conclude with an integration of the cortical areas and white matter pathways that are important for reading.

Measuring white matter properties: diffusion tensor imaging

Diffusion weighted imaging has been used in clinical applications for two decades [10,15]. It is only recently

Glossary

Apparent diffusion coefficient (ADC): In diffusion magnetic resonance imaging, the diffusion coefficient is proportional to the velocity of the diffusing water molecules in the measured tissue. The free diffusion of water at body temperature is $\sim 3\ \mu m^2$ per millisecond. However, water in tissue is impeded by large molecules and cell membranes. Therefore, the diffusion measurements are referred to as apparent diffusion coefficients, because the water is not freely diffusing. In diffusion imaging, the ADC is measured independently in each voxel of the image.

Conduction aphasia: Aphasia is a language deficit caused by brain damage. One of the first disconnection syndromes to be described by Wernicke was conduction aphasia, which is classically defined by speech repetition errors. Wernicke hypothesized that conduction aphasia is caused by a lesion involving the arcuate fasciculus, which connects Broca's and Wernicke's language areas. Recent studies describe conduction aphasia in terms of a phonological working-memory impairment [93].

Diffusion tensor: Water diffusion in a homogeneous medium is fully described by Brownian motion, with equal (isotropic) diffusion in all directions. When diffusion takes place in an inhomogeneous medium (e.g. white matter), diffusion can no longer be described by a scalar diffusion coefficient, because it is impeded to different extents in different directions. A simple model of anisotropic diffusion is a tensor — a 3 x 3 symmetric positive-definite matrix that describes the diffusion in all directions.

Fascicle (fasciculus): A bundle of axons (nerve fibers).

Fleschig's rule: Primary sensory areas are connected with adjacent association cortices through U-fibers, but they do not have long range connections within or between hemispheres. This principle was introduced by Paul Emil Flechsig (1847–1929) and adopted by Norman Geschwind, but it seems inconsistent with recent evidence (e.g. V1 projects directly to areas MT and TEO in monkeys) [94].

Fractional anisotropy (FA): A measure of the degree of anisotropy in a tensor model of diffusion at a given voxel. FA values are bounded between zero (a perfect sphere) and one (an infinitely long cigar-shape). See the main text for the formula that defines FA.

Mean diffusivity (MD): The mean of the eigenvalues of the diffusion tensor or, equivalently, the trace of the diffusion tensor divided by 3. This parameter quantifies the size of the diffusion ellipsoid. The MD measure is invariant with respect to the orientation of the diffusion tensor and tends to vary little across brain tissue.

Oblate: A mathematical term used to describe a planar (pancake-shaped) ellipsoid, where the two largest eigenvalues are equal. An oblate spheroid is created by rotating an ellipse around its minor axis.

Principal diffusion direction (PDD): The direction corresponding to the largest eigenvalue of the diffusion tensor.

Prolate: A mathematical term used to describe an elongated (cigar-shaped) ellipsoid, where the two smallest eigenvalues are equal. A prolate spheroid is created by rotating an ellipse around its major axis.

Pure alexia: Alexia without agraphia; reading difficulties without accompanying writing difficulties following a brain lesion. This condition was originally described by Dejerine (Box 1). Pure alexia is sometimes accompanied by letter-by-letter reading, in which the patient first names the letters before naming the word. For a cognitive neuropsychology perspective, see [95] and other articles in the same issue. For a recent review of functional imaging results, see [96].

Tractography (fiber tracking): An analysis method applied to DTI data to estimate fascicles. Deterministic fiber-tracking algorithms generally follow the PDD in each voxel, connecting voxels that form a smooth path. Probabilistic fiber-tracking methods generate a multiplicity of tracts and estimate a likelihood that a particular collection of voxels belongs to a common tract.

that computational methods were developed to interpret the data in terms of the properties of white matter pathways. An important contribution to this effort was made by Basser *et al.* [16], who introduced the diffusion tensor model (see Glossary) to summarize multi-directional ADC measurements within a voxel.

The model is simple. Suppose that A_μ is an ADC in the direction μ, where μ is a unit vector. The DTI model predicts that $A_\mu = \mu^T D \mu$, where D is a 3 x 3, symmetric positive-definite matrix, called the diffusion tensor. The tensor D is estimated by measuring the ADC in at least six independent directions. The tensor model is visualized as an ellipsoidal surface that represents the mean diffusion distance expected of a water molecule within the voxel. The ellipsoid is characterized by its principal directions (eigenvectors) and their lengths (eigenvalues).

Several parameters are commonly derived from the ellipsoidal model (see [17••] for a detailed and accessible review). Suppose the three terms λ_i are the eigenvalues of the diffusion tensor, sorted by their magnitude in descending order. The term 'principal diffusion direction' (PDD; see Glossary) refers to the direction of the eigenvector associated with the largest eigenvalue (λ_1). When the diffusivity is anisotropic such that diffusion is much greater along the principal axis than the others ($\lambda_1 >> \lambda_2, \lambda_3$), the PDD indicates the predominant orientation of the fascicles within the voxel. In addition, two important scalars are commonly used: mean diffusivity (MD; see Glossary) and fractional anisotropy (FA; see Glossary). MD is simply the mean of the three eigenvalues and quantifies the size of the diffusion ellipsoid. It is roughly constant across brain tissue. FA is proportional to the normalized standard deviation of the eigenvalues [18]; it is computed using the formula:

$$FA = \sqrt{\frac{3}{2}} \sqrt{\frac{\sum_{i=1,2,3} (\lambda_i - \bar{\lambda})^2}{\sum_{i=1,2,3} \lambda_i^2}}$$

FA is a scalar between zero and one: zero indicates a perfect sphere; increasing FA values indicate that the diffusion ellipsoid is increasingly anisotropic (elongated in one or two of the three dimensions). FA varies considerably across brain tissue; for example, it is much higher in white matter than in gray matter.

FA is used widely as a statistical summary of DTI measurements in the white matter, mostly because it is a scalar quantity that varies meaningfully across the white matter and can be analyzed using conventional univariate statistical methods [19–22]. Lower FA found in various neurological populations at any white matter region is typically interpreted as indicating reduced myelination

and therefore less efficient axonal signal conduction. However, this inference is over simplified because multiple factors contribute to FA [23]. Furthermore, FA is blind to important differences in the ADC data, such as differences in the principal diffusion direction or in shape: similar FA values are obtained for prolate (elongated) ellipsoids and oblate (pancake-shaped) ones (see Glossary). To compensate for the limitations of FA and to increase the value of the diffusion tensor model, some authors are developing methods to test more general, multivariate, hypotheses about the diffusion tensors [24,25] (A Schwartzman, PhD thesis, Stanford University, CA USA, 2006). These methods increase the sensitivity of group comparisons in DTI datasets, and supply a more detailed description of the difference between populations.

The tensor is a reasonable model of the expected pattern of diffusion in many, but not all, regions of the white matter. In particular, regions that contain crossing or sharply curved fascicles are not accurately modeled by a tensor. To address such limitations, several research groups are developing more complex models of diffusion [26•,27•,28]. However, these models require more measurements and thus significantly longer scan times. The efficiency, mathematical simplicity and power of the tensor model suggest that DTI will continue to be the method of choice for many researchers and clinicians.

Differences in white matter properties of good and poor readers

Klingberg *et al.* [29] were the first to use DTI to search for white matter abnormalities in developmental dyslexics. They compared FA, voxel by voxel, between the brains of six adult poor readers who had a history of developmental dyslexia and eleven normal-reading controls (the brains had all been co-registered to a template). They found a significant bilateral temporo-parietal difference in FA between the groups, and a correlation between reading and FA in a left temporo-parietal white matter region. The center of mass of the left region that they identified is shown by the yellow sphere in Figure 2a,f,g.

It is remarkable that there is a relationship between diffusion anisotropy in a localized white matter region and reading skill. It is tempting to assume that the white matter difference is the cause of the reading deficit. However, the causal direction might also run from reading experience to white matter properties: it is possible that poor readers accumulate fewer hours of exposure to print, which could alter development of white matter in reading circuits. Such a hypothesis would be consistent with the widely asserted view that many aspects of the brain are highly plastic throughout the lifespan [30–32]. To evaluate the likelihood of this causal direction, several independent research groups extended the white matter measurements from adults to children [33,34••–36••]. For example, Deutsch *et al.* [34••] showed that the FA difference is present in a group of children aged 7–13 years; they also confirmed the presence of the relationship in adults. The correlation in children between specific measures of reading and FA reduces the likelihood that white matter changes are caused by altered experience.

From voxels to white matter pathways

The identification of a microstructural difference in white matter between groups supports the general hypothesis that developmental dyslexia involves a disconnection between cortical areas involved in reading. That hypothesis was proposed initially based on studies of alexia in neurological patients (Box 1) [7,37–39]. The disconnection concept was further supported by analyses of functional connectivity using functional MRI (fMRI) and positron emission tomography (PET) data [40–42]. The

Box 1 Occipital reading pathways — a historical review

Despite the limited tools available at the end of the 19th century, Jules Dejerine managed to develop a general model of reading pathways that remains an important starting point for discussion to this day. Dejerine based his model on extensive studies of postmortem brain anatomy, and specifically on two neurological case studies: the famous Monsieur C who suffered from alexia without agraphia (pure alexia), and an earlier case study of a patient who suffered from alexia with agraphia [37,88,89]. Post mortem, Dejerine observed in the case of alexia with agraphia a large cortical lesion in inferior parietal and superior temporal cortex, around the inferior part of the angular gyrus and subjacent white matter. In the pure alexic there were several lesion sites, including occipital ventral and dorsal-medial cortical lesions, and also an occipital white matter lesion and a small inferior splenial lesion (Figure I of this box). Dejerine's interpretation designated the left angular gyrus as the cerebral center for the representation of visual images of letters.

Dejerine's model (Figures Ic and IIa of this box) proposes that visual information from the left visual hemifield, represented by the right occipital cortex, normally crosses over to the left hemisphere where it is transferred to the language system. This assumption still dominates recent theories of occipital reading pathways [82•]. Thus, even though Dejerine did not attribute much importance to Monsieur C's splenial lesion [90], his model clearly highlights the importance of occipital callosal projections in reading.

There are many different views in the literature as to which specific callosal bundle is relevant to reading. Geschwind [7] suggested that visual input is processed in parallel by the right and left hemispheres, with information flowing from Brodman's area (BA)17 to BA18/19 to the angular gyrus, bilaterally. He argued, on the basis of Fleschig's rule (see Glossary), that cross over to the left hemisphere can take place at the level of the visual association cortex and at the level of the angular gyrus, but not at the level of BA17. This model (Figure IIb) is supported by the lack of permanent alexia following a left occipital lobectomy [7,91].

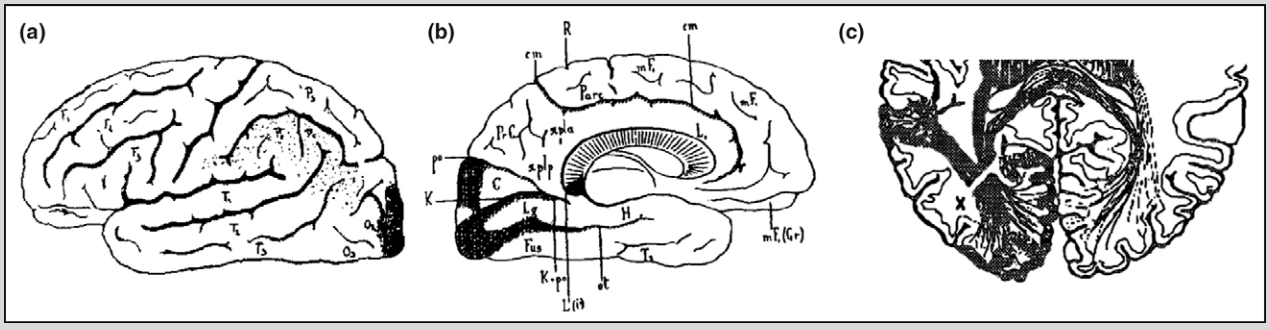
Damasio and Damasio [90] conducted an important analysis of computed tomography data from pure alexics. On the basis of analysis of lesion locations on normalized templates, they concluded that pure

Box 1 (*Continued*)

alexia is caused by a lesion in the left paraventricular occipital white matter. Only one callosal fiber group is pertinent for reading according to this study: middle splenial fibers that continue in the inferior forceps major. Data from monkeys suggest that these callosal fibers interconnect left and right area 19 [92]. These results place the callosal crossing in Damasio and Damasio's model at the level of BA19 (possibly hV4; Figure IIc). A recent model based on DTI and functional imaging is depicted in Figure IId [80]. Note the resemblance between Dejerine's model more than a hundred years ago and recent models of occipital reading pathways.

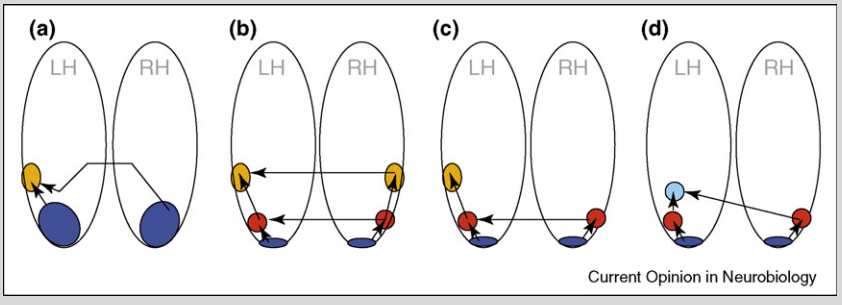
An important anatomical question concerns the trajectory of the callosal reading pathways. Early works assume that the relevant callosal pathways travel inferior to the posterior horn of the lateral ventricle. In a more recent analysis of computed tomography data, Binder and Mohr [38] identified a crucial white matter lesion dorsal to the posterior horn of the lateral ventricle in a group of five global alexics (but not in a group of five spelling dyslexics, who were capable of letter-by-letter reading). This result might indicate the involvement of callosal connections to lateral temporal areas, in agreement with recent results from our laboratory where similar callosal fiber tracts are implicated in reading [70]. Binder and Mohr [38] emphasized the behavioral variability in alexic patients; they suggested that this variability can be explained by the distributed nature of the reading connections as they emerge from the callosum. Specifically, they proposed that the reading pathways fan out towards a wide network of lateral occipito-temporal regions and that damage can occur within different portions of these pathways. This model awaits experimental verification.

Figure I



Lesion sites and hypothesized mechanism of pure alexia according to Dejerine. **(a,b)** Dejerine's depiction of the locations of the lesions in the patient with pure alexia [37]. The lesions, shown as dark areas, include occipital (mostly medial) cortical locations, occipital white matter and a small splenial lesion (b). The dotted area on the lateral surface (a) denotes a later lesion that caused alexia with agraphia shortly before the patient's death. **(c)** Dejerine's hypothesis for a disconnection between the occipital lobes and the left angular gyrus, resulting in pure alexia. Images reproduced, with permission from Elsevier, from [39,89].

Figure II

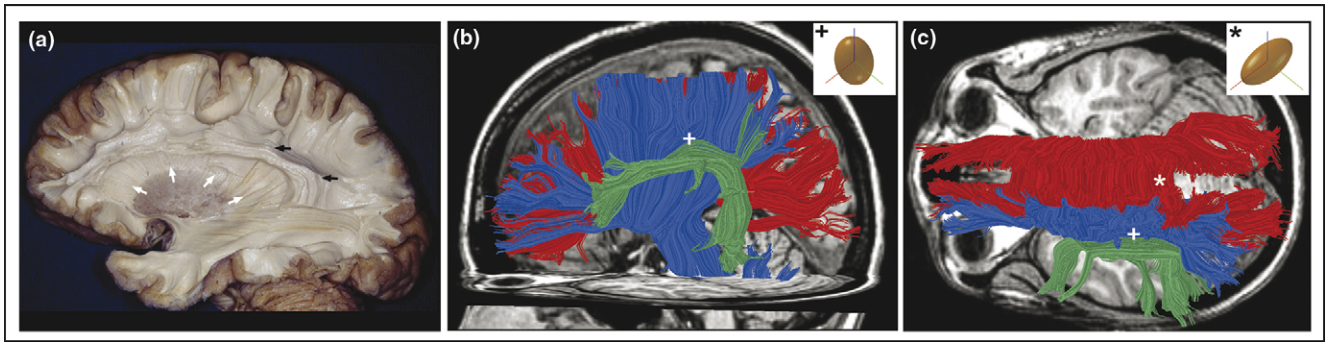


Models of occipital reading pathways. **(a)** Dejerine's model, from 1892 [37]. Information is transferred from the left and right occipital lobes (blue) to the left angular gyrus (orange), which relays visual information to the language system. **(b)** Geschwind's model, from 1965 [7]. Visual information flows from the primary visual cortex (blue) to secondary association cortices (red) to the angular gyri (orange). Information processing is bilateral, with crossing at the levels of the visual association cortex and the angular gyrus. **(c)** The model of Damasio and Damasio, from 1983 [90]. Only one callosal fiber group is crucial for reading, crossing in the middle of the splenium. This tract probably connects the bilateral BA19, based on data from monkey anatomy (see main text of this box). **(d)** The model of Molko and colleagues, from 2002 [80]. Retinotopic areas (presumably left and right hV4 or VO; shown in red) project to left fusiform gyrus (light blue), which constructs an invariant representation of the letter string. Although this model replaces the angular gyrus with the fusiform gyrus (a major change in cortical terms), the pathway scheme is very similar to earlier models of occipital reading pathways.

question one must now ask is what, precisely, is being disconnected?

The difference in FA between good and poor readers was initially interpreted as implicating connections between temporo-parietal and frontal cortical areas along the arcuate fasciculus: '. . .axons in the region of interest were predominantly oriented in the anterior–posterior direction. The present finding thus demonstrates a plausible structural basis for the functional disconnection of temporo-parietal

Figure 1



Roadmap of major white matter pathways in diffusion tensor imaging (DTI) studies of reading. **(a)** Postmortem white matter dissection showing the superior longitudinal fasciculus (SLF, black arrows) and the corona radiata (white arrows). Image courtesy of Professor Uğur Türe. **(b,c)** Fiber-tracking estimates of the corona radiata (blue), the SLF (green) and the corpus callosum (red) in a single adult female. The images show these fiber tracts from lateral (b) and top (c) views of the left hemisphere. The insets show the tensor shape for a temporo-parietal voxel in a region of the corona radiata that borders the SLF (location marked by a plus sign) and a voxel in the posterior callosum (location marked by an asterisk). There is a noticeable difference in the principal diffusion direction (PDD) and anisotropy at these two voxels.

and frontal cortices that has been previously suggested to occur in developmental dyslexia.' (page 497 of [29]). The arcuate fasciculus is commonly considered a crucial language pathway, connecting Wernicke's area in left posterior superior temporal cortex and Broca's area in the left inferior frontal gyrus [43,44]. This view dates back to the Wernicke–Lichtheim model [45,46] but has recently been criticized in light of autoradiographic tracer studies in monkey [47,48] and cases of cortical conduction aphasia (see Glossary) [49]. Here, we use the more general term SLF when we refer to the dorsal pathway that connects temporo-parietal cortex with lateral frontal cortex [50•,51,52•].

The inference from a voxel-based difference to a white matter fiber tract is crucial for a system-level understanding of reading pathways. At the time of the Klingberg study [29], the best guess was based on the PDD in the relevant voxels, but this method is very limited. For example, the SLF contains voxels that have left–right PDD (e.g. horizontal tract segments that connect between lateral cortical locations and medial regions in the core white matter); it also contains voxels that have dorsal–ventral PDD (e.g. vertical tract segments in core white matter subjacent to the temporal and parietal cortex) and voxels that have anterior–posterior PDD (running between the parietal and frontal lobe). Nearby voxels that have similar PDD might belong to different pathways (e.g. to the fronto-occipital fasciculus). Thus, PDD by itself does not provide a reliable tool for the assignment of voxels to fiber tracts.

The field has now developed new computational methods to estimate the assignment of voxels to white matter structures [27•,53–55]. Using these fiber-tracking methods (tractography; see Glossary) we can reconstruct the fiber tracts that pass through white matter regions where a difference in diffusion properties was found, or alternatively, follow the tracts that connect functionally defined cortical regions. We briefly describe this method in the next section. We then return to discuss the nature of the impaired pathway in developmental dyslexia, and relate these findings to the neuropsychological literature.

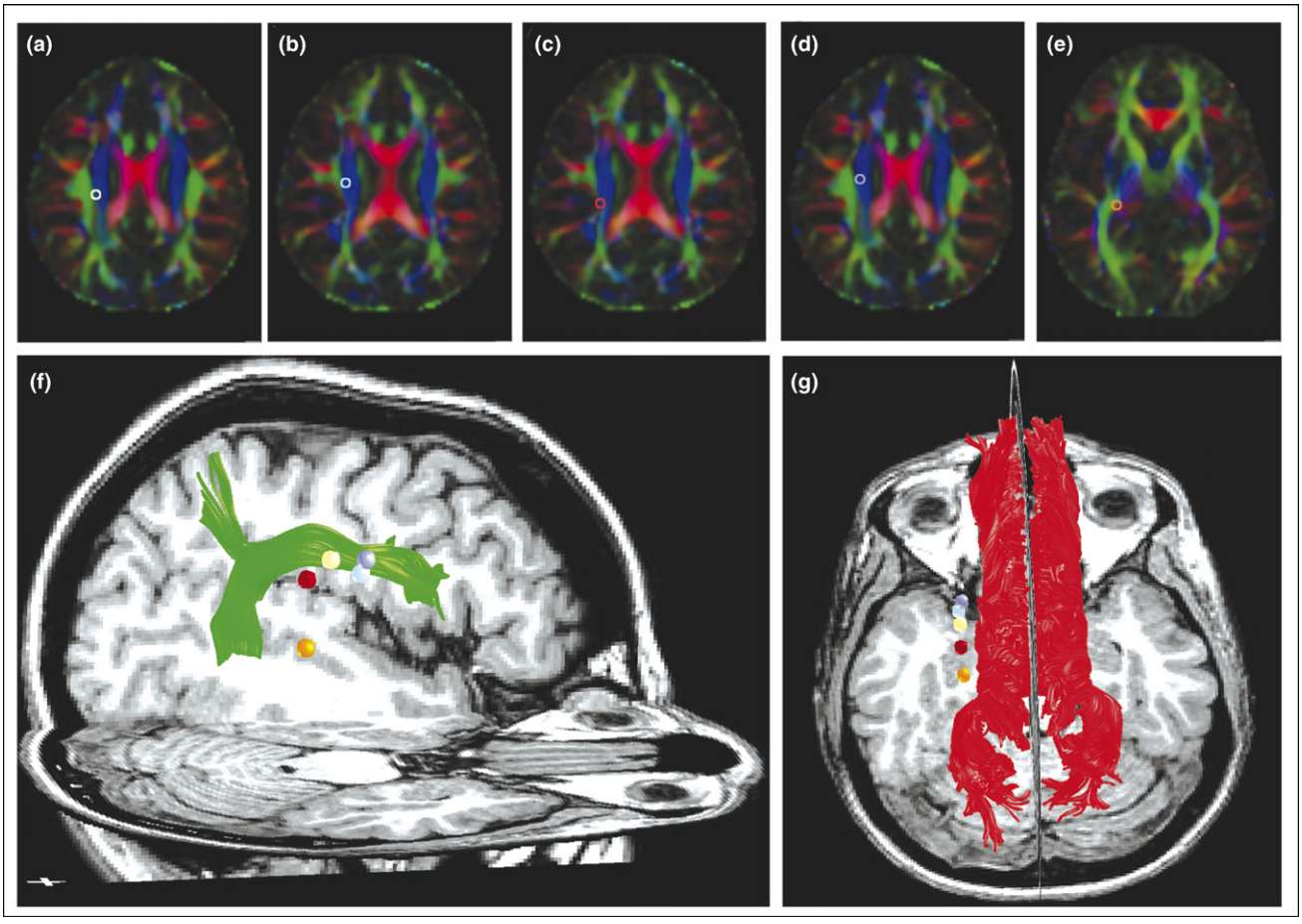
Measuring white matter properties: fiber tracking

Fiber tract reconstruction methods deduce the presence of a pathway by examining the agreement and reliability of PDDs in nearby diffusion tensors. For example, when one discovers a set of highly oriented ellipsoids that trace a smooth path through white matter, it is reasonable to believe these voxels should be grouped together as a tract estimate. There are various methods for fiber tracking; the value and limitations of these methods have been reviewed and analyzed elsewhere [17••,55,56••]. We believe that these methods successfully identify the largest (at least 5 mm cross-section diameter) fascicular tracts in the core white matter. Current methods fail to detect smaller tracts accurately, such as those that form the thin tendrils of white matter in the occipital lobe. Further, it is common to 'lose' a pathway as it interdigitates with a second, larger tract that heads in a different direction. Despite these limitations, fiber tracking provides valuable and unique information: there are no other methods for measuring the white matter pathways in the living human brain. Fiber tracking yields valid and repeatable results within certain regions of the white matter [56••,57,58].

White matter pathways important for reading

Several investigators have recently used fiber tracking to better interpret reading-related group differences with respect to the position of white matter pathways

Figure 2



Reading-related group-differences in white matter. **(a-e)** Circles (3 mm radius) indicate locations of peak group fractional anisotropy (FA) differences from five DTI studies: [29] (a, yellow, $z = 28$ [MNI standard space]); [35••] (b, light blue, $z = 24$); [34••] (c, dark red, $z = 24$); [36••] (d, purple, $z = 28$); [33] (e, orange, $z = 5$). These locations are shown on axial slices of an individual's brain warped to MNI space. In the cases where only Talairach coordinates were reported, we converted those to MNI coordinates. Left hemisphere is on the left of each image. The PDD in each voxel was computed from the tensor, and color coded as follows: left–right, red; anterior–posterior, green; inferior–superior, blue. Notice that the PDD is determined independently for each voxel and does not correspond uniquely to a pathway. For example, there are many green voxels that do not belong to the SLF. **(f,g)** Locations of FA differences from these five studies are shown by spheres (3 mm radius) in three-dimensional space. This view clarifies the position of the locations with respect to the SLF (f) and the corpus callosum (g). Scale bar at the bottom left of (f) indicates 1 cm. Sphere colors correspond to circle colors in (a-e).

[35••,36••]. These studies identified the fiber tracts that pass through the regions where FA correlated with reading skills. Both studies found that the main region that showed an FA difference consisted of fibers oriented in the superior–inferior direction. These fibers are in the posterior limb of the internal capsule, a part of the corona radiata. Neither research group found the differences to fall principally within the SLF (but note that the region of interest in [36••] captured only a small region in one axial slice through the SLF). Beaulieu *et al.* [35••] found additional smaller clusters in anterior callosal tracts, the superior fronto-occipital fasciculus and the anterior internal capsule. The location of FA group differences within the corona radiata is further supported by PDD analysis [34••]. Figure 2 illustrates the relative location of the peak FA differences within the corona radiata, medial to the SLF and lateral to the corpus callosum.

A reading-related group difference within the corona radiata is surprising and difficult to interpret. Taken at face value, this finding suggests that the left corona radiata is an important pathway in reading and that these axons are more permeable to water diffusion, or that their directional coherence is reduced in some individuals, causing worse performance on reading measures such as word identification [59]. The corona radiata connects the cerebellum, thalamus, brainstem and spinal cord with dorsal cortical motor and somatosensory regions. This pathway could be related to cerebellar deficits sometimes reported in dyslexia [60–62]. Indeed, detailed anatomical

studies reliably find reduced right anterior cerebellum volume in poor readers [63,64,65••]. Right cerebellar activations are found in language and reading tasks, but to our knowledge no correlation between reading skills and cerebellar activation has been demonstrated.

A different interpretation was suggested in [35••]. According to this account, the reduced FA in the left corona radiata reflects differences in the pathways that interdigitate with the corona radiata, specifically the SLF: 'Although fibers from the PLIC [posterior limb of the internal capsule] pass right through the cluster, it is conceivable that other relevant white matter fibers crossing at this level, such as the adjacent SLF, could be responsible for the correlation with reading ability. However, standard six-direction diffusion tensor imaging is not able to extract the complex fiber crossings that are rampant in this portion of the brain.' (page 1269 in [35••]). Together with [29], this account suggests that the main problem in developmental dyslexia lies in the SLF and is thus within the language domain and not specific to reading. Such a view predicts that developmental dyslexia should be associated with symptoms of conduction aphasia, such as impaired sentence repetition [66].

Here, we add a third possible interpretation of the relationship between reading measures and FA in the corona radiata; this interpretation focuses on the corpus callosum. Several groups have described differences in the shape of the corpus callosum, including an enlarged splenium, in developmental dyslexia [67–69]. Moreover, the importance of callosal transfer for reading has been demonstrated by lesion studies (Box 1). The connection between callosal differences and FA effects in the corona radiata might seem puzzling but, as we now explain, callosal differences can have two separate effects on FA within the corona radiata.

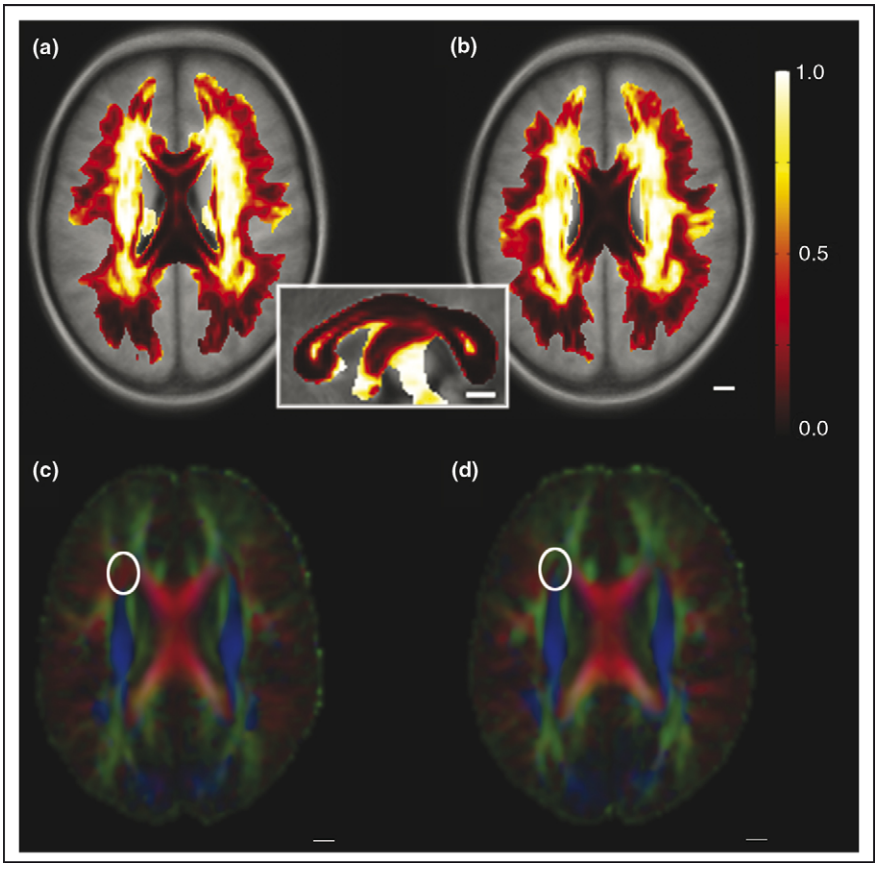
First, it might be that an enlarged splenium in poor readers represents exuberant growth of callosal fibers. Such growth could displace the corona radiata tract in an anterior direction or alter the diffusivity in the voxels that are dominated by corona radiata fibers. In support of the displacement hypothesis, a recent study found a significant difference in the PDD between good and poor readers in the anterior portion of the corona radiata [24]. The results show a shift of the corona radiata in the anterior direction in seven poor readers compared with seven controls (Figure 3c,d) [34••]. Notice that in four out of the five studies shown in Figure 2, FA differences were detected by co-registering all brains to a template and applying voxel-by-voxel statistical tests. In the presence of systematic structural differences within white matter, warping brains to a common template using a non-diffusion-weighted structural image (which is blind to these differences) can lead to apparent FA differences because the voxels represent different structures in the two groups (see [36••] for a region-of-interest analysis that avoids this problem).

Second, differences in callosal fibers that interdigitate with the corona radiata might change the diffusivity measurements within parts of the corona radiata. Ordinarily, the callosal fibers are oriented primarily in the left–right direction, roughly orthogonal to the corona radiata fibers. Differences between poor and good readers in either size or number of callosal fibers can be manifest in voxels where callosal fibers pass through the corona radiata. For example, if poor readers have denser interhemispheric connections, we expect reduced FA in the corona radiata, due to the increased proportion of crossing fibers (and thus reduced directional coherence) in corona radiata voxels. This hypothesis is supported by several findings. It explains why the difference appears consistently in a superior axial plane that corresponds roughly to the location of crossover by callosal pathways through the corona radiata (in the planes $z = 24$ to $z = 28$ in [29,34••–36••], although not in [33]). Further, given that the corpus callosum crosses both the left and the right corona radiata, right hemisphere differences are expected at a similar z level. Indeed, group differences in FA are found at about the same axial slice in the right hemisphere [29,34••,35••]. However, these differences are smaller than those in the left hemisphere and are not accompanied by a specific correlation with reading [29,34••].

If differences in the corpus callosum cause the FA effect observed in the corona radiata, why are no FA or PDD effects found in the corpus callosum in whole brain analyses? We suspect that the answer lies in methodological limitations of voxel-based FA analyses. We recently showed that co-registration of a group of brains yields FA variance that is far from uniform across white matter [57]. Consequently, the statistical power of a test for FA differences will vary greatly across white matter regions (Figure 3a,b). The corpus callosum has very low statistical power for an FA statistic because the large differences in the callosal shape across individuals are not well corrected by commonly used spatial normalization methods (Figure 3, inset). Therefore, a search for group differences in co-registered brains has very low sensitivity to FA differences in the callosum.

Callosal differences in diffusivity can be measured using more sensitive methods that begin by identifying callosal crossing regions in individual subjects. Using this method, we recently analyzed DTI data from a large group of children [70]. We used fiber tracking to segment the callosum into regions based on their likely cortical projection zones [71]. Diffusion properties in fibers that connect the temporal lobes correlated significantly with reading measures; specifically, there was a negative correlation between FA and phonological awareness in

Figure 3



Power of the FA statistic and location of reading-related PDD difference. **(a,b)** The statistical power for a hypothetical *t*-test comparing FA between two groups is shown, assuming a typical FA effect size of 0.12 and sample size of 30. The FA variance was estimated from a population of 54 children aged 7–12 years. Axial slices are shown at MNI levels $z = 24$ (a) and $z = 28$ (b). The inset shows the statistical power in the corpus callosum cropped from a midsagittal slice. Note that most of the callosum has very low power. **(c,d)** A comparison of mean PDD images from controls (c; $n = 7$) and poor readers (d; $n = 7$). Color coding is the same as in Figure 2a. The white outline shows a location that has a significant PDD difference in this slice (MNI $z = 24$; differences were also detected in corresponding voxels in other slices, not shown). The difference is found at the anterior corona radiata bordering frontal corpus callosum fibers. See [24] for more detail. Scale bars, 1 cm.

these fibers. The cause of this correlation is a positive relationship between phonological awareness and diffusivity perpendicular to the main axis of these callosal fibers. One possible interpretation of these results is that good readers have fewer but larger axons connecting the left and right temporal lobes.

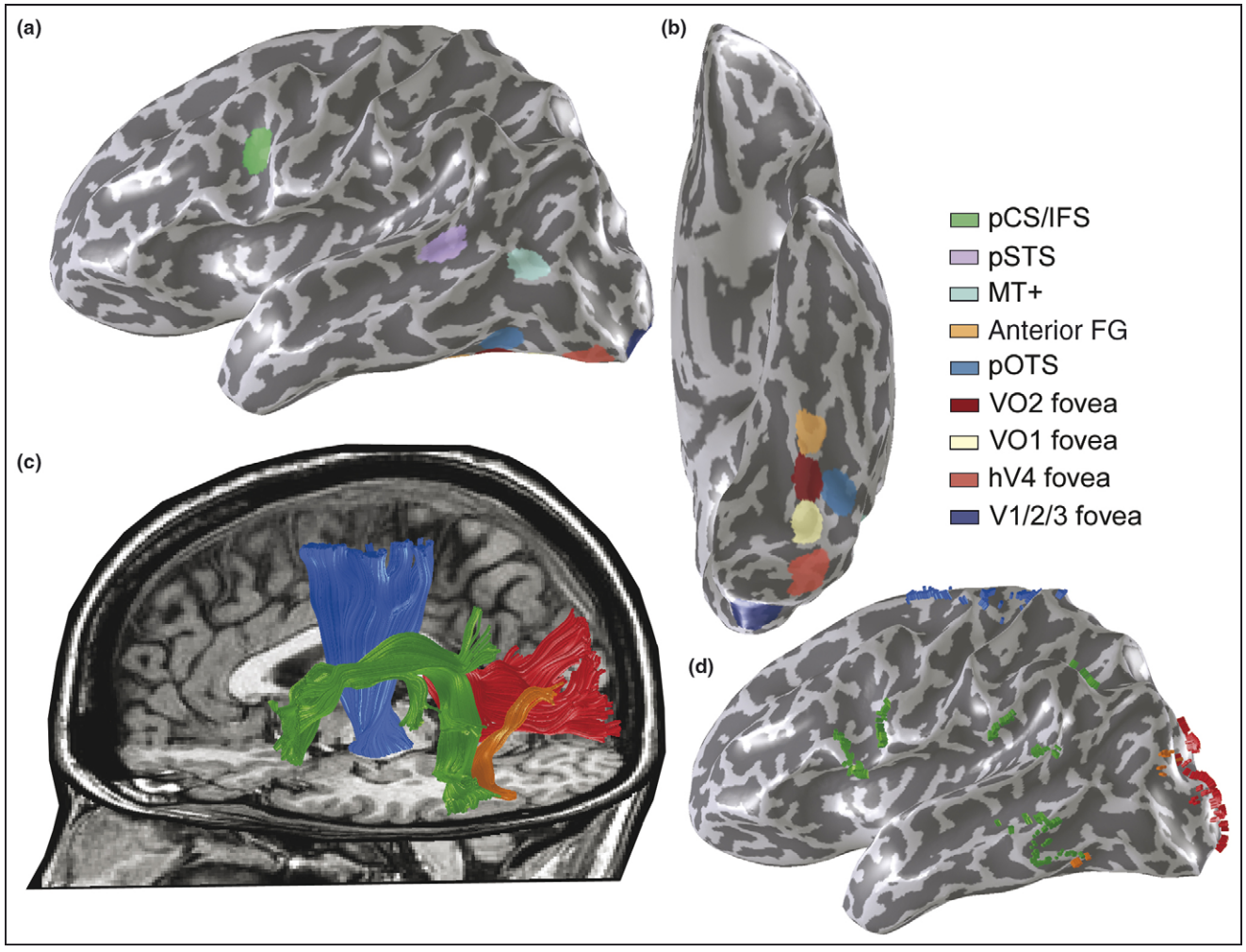
Integration

In this review, we focus on white matter pathways that underlie reading. This choice is motivated by the emergence of diffusion tensor imaging as a useful methodology for the study of reading circuits in healthy adults and children. We do not mean to imply that white matter differences are more important or in some way more basic than functional measurements in reading-related gray matter regions. Clearly, reading relies on processing in multiple regions, in addition to the intact transmission of signals between them. In this last section, we consider how white matter pathways for reading are situated with respect to the cortical regions that are important for reading.

Figure 4 summarizes cortical regions and white matter structures that are part of the reading pathways. Reading is normally a foveal task; the cortical pathways for reading start in the foveal part of V1, located in the posterior calcarine sulcus and extending around the occipital pole (Figure 4a,b). In nearly every fMRI reading experiment, there is activation within the foveal regions of retinotopic maps V1, V2, hV4 and the VO cluster [72,73].

Individual differences in the anatomy and physiology of the magnocellular processing stream have been associated with reading skills [74,75]. The magnocellular stream within the visual pathways includes the lateral geniculate nucleus of the thalamus, magnocellular

Figure 4



Summary of cortical areas and white matter pathways for reading. **(a,b)** Locations of cortical areas related to reading are shown on an inflated cortical surface of a left hemisphere from an adult individual. Sulci are shown in dark gray and gyri in light gray. (a) Lateral view, showing area MT+ (activation for moving versus stationary stimuli), the posterior superior temporal sulcus (pSTS; activation for visual rhyming judgments versus orientation judgments), and the junction of the precentral sulcus with the inferior frontal sulcus (pCS/IFS; activation for visual rhyming judgments versus orientation judgments). (b) Ventral view, showing the foveal parts of the maps in V1/2/3, hV4, VO1 and VO2, as defined by retinotopic mapping [72]. Visual words compared with checkerboards (presented parafoveally) activate the posterior occipito-temporal sulcus (pOTS) and anterior fusiform gyrus (FG) [73]. **(c,d)** White matter pathways important for reading are shown in a three-plane lateral view (c) and as fiber tract endpoints projected on to the inflated cortical surface (d). Pathways include the superior longitudinal fasciculus (SLF; green), occipital and temporal callosal fibers (red) and corona radiata fibers that pass through the posterior limb of the internal capsule (blue). Dorsal fibers that connect the pOTS with the lateral cortical surface at the border between occipital and temporal lobes are also shown (orange). We hypothesize that these fibers and branches of the SLF are important for integrating information about letter shape, letter location, lexical properties and phonology.

populations in V1, and the human motion area MT+. fMRI studies show differences between adult developmental dyslexics and controls, in the functional properties of MT+ (and V1, given stimulation paradigms that select magnocellular populations) [5,76]. Recent results from our laboratory show a correlation between contrast responsivity in MT+ and measures of phonological awareness in a large group of children [77]. Although MT+ is well established as motion-sensitive cortex, these results suggest possible interactions between MT+ and reading pathways that are yet to be explored.

Anterior to hV4 and lateral to VO1, centered in the posterior occipito-temporal sulcus (pOTS), lies a region commonly referred to as the 'visual word form area' [78,79]. This region responds to words and pseudowords in both visual fields, presumably via signals carried by callosal connections from the contralateral hV4 [80] or from the

contralateral pOTS [73]. A similar region has been recently associated with pure alexia, but not with hemianopic alexia [81]. There is a debate with respect to the specific role of the pOTS in reading: Dehaene and others propose that this region codes sublexical orthographic units [82•,83]; Price and collaborators propose that this region acts as an interface between an invariant representation of a visual stimulus (e.g. words or objects) and its phonological and semantic attributes [4•,84]. Our group found higher sensitivity for words than for line drawings and false fonts in the pOTS bilaterally [73]. These results contrast with the common view that locates this region in the left hemisphere only. We suggest that the reported left lateralization in the pOTS reflects differences in top-down connections from left-lateralized language areas [85•]. These regions are located on the lateral surface of the posterior superior temporal and inferior frontal cortex (Figure 4a). The importance of these regions for reading has been documented in numerous studies showing that poor readers have reduced activation in the junction between the temporal and inferior parietal cortex in the left hemisphere, and altered lateralization in the inferior frontal region [1,86,87].

Three of the larger white matter pathways that carry signals significant for reading are shown in Figure 4c; estimates of the cortical projection zones of these pathways are shown in Figure 4d. The posterior callosal segment (red) includes fibers that project to occipital and temporal cortex; these have been implicated in DTI studies of reading with children [70] and alexic patients [80]. These fibers probably include essential visual signals, such as homotopic callosal connections between the bilateral MT+, bilateral angular gyrus (or posterior superior temporal sulcus) and bilateral pOTS. The fibers in these tracts probably interdigitate with the inferior longitudinal fasciculus on their way to the lateral and ventral cortical surface. Current fiber-tracking technology does not reliably identify such callosal fibers.

We also identify in Figure 4 two fiber bundles that run dorsally from the vicinity of the pOTS region: the SLF (Figure 4c,d, green) and a separate dorsal fiber group that connects to the superior lateral occipital cortex (Figure 4c,d, orange). These pathways might be a relay between ventral word-shape recognition systems, perisylvian phonological and semantic systems, and dorsal visual systems. Our ability to estimate the exact cortical destination of these fibers is limited, however, because FA drops near gray matter, reducing the reliability of the diffusion direction for the purpose of fiber-tracking. Figure 4c,d further shows the corona radiata (blue). Locations within this structure are correlated with reading performance, although as we have argued these correlations might be driven by the fibers that pass through the corona radiata rather than by the fibers comprising the structure itself.

Taken together, these images of the white matter structures and activated cortical regions form an emerging picture of the pathways essential for reading. There remain white matter fascicles hidden from current DTI methods; there are many questions about the specific computational functions within the gray matter regions. Even so, the advances in the past five years have been very promising and one might hope that a combined structural, functional and computational model for the reading pathways could be reached.

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