Comment on "The Geometric Structure of the Brain Fiber Pathways"

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Wedeen *et al*. (Reports, 30 March 2012, p. 1628) proposed a geometrical grid pattern in the brain that could help the understanding of the brain's organization and connectivity. We show that whole-brain fiber crossing quantification does not support their theory. Our results suggest that the grid pattern is most likely an artifact attributable to the limitations of their method.

In the history of neuroscience, the development of new methods to investigate brain anatomy has been pivotal to our understanding of the complexity of cognition and behavior (*1*). Nevertheless, newly developed methods need to be validated and their limitations precisely identified under rigorous experimental conditions before trying to infer general principles of brain organization derived from their application. Golgi, for example, reported that the brain was organized like a "continuous net" (i.e., reticular theory) because his staining method did not reveal the presence of synapses (*2*).

Over the past 10 years, advances in diffusion magnetic resonance imaging have opened a new window into the architecture of human brain

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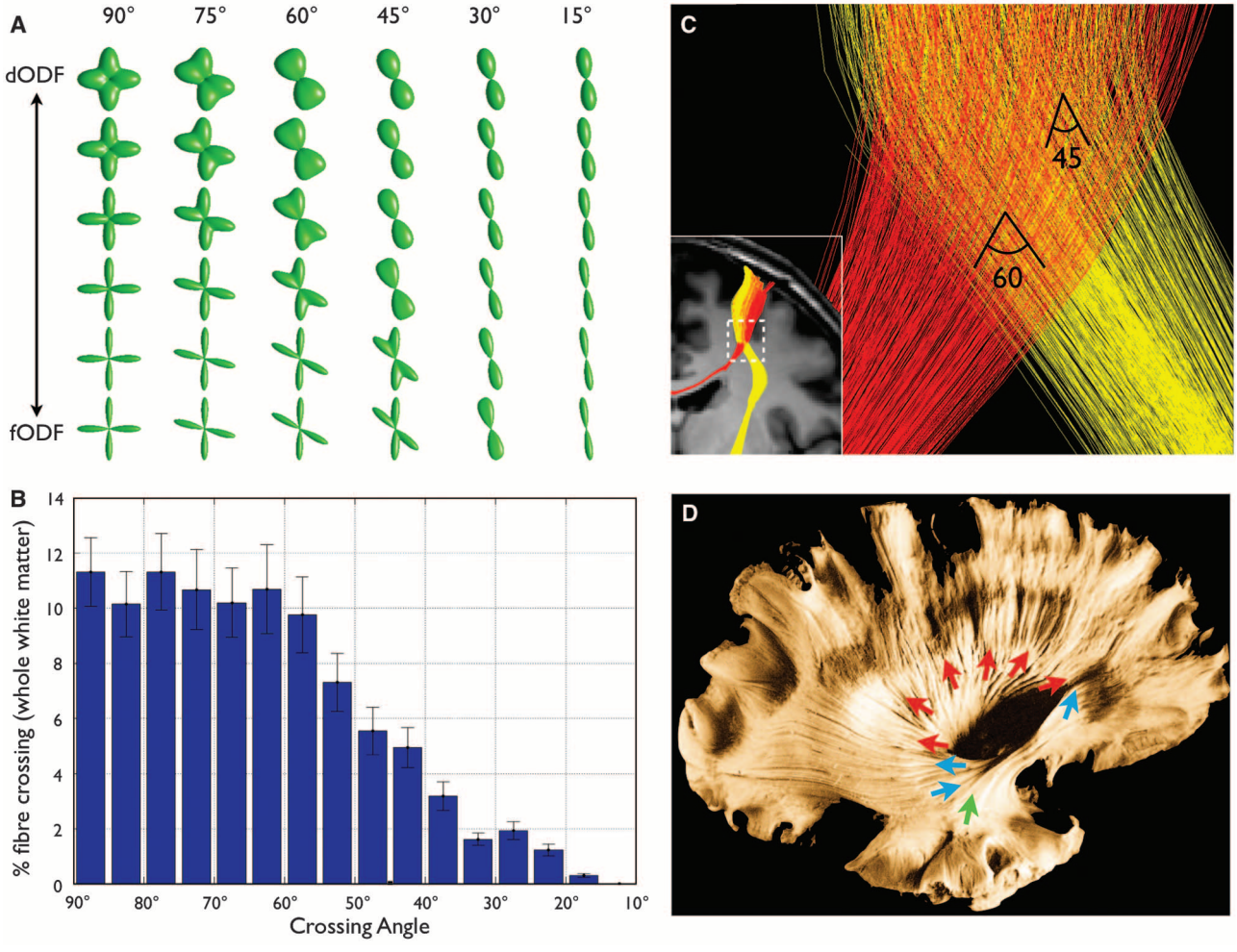

Fig. 1. (**A**) Visualization of the possible ODF profiles according to different methods and different crossing angles. Some dODF methods are limited in resolving crossing below 75°, whereas fODF methods resolve crossing at 45° or lower. (**B**) Distribution of the percentage of voxels containing fibers crossing at different angles in a sample of 10 healthy human brains. The plateau between 55° and 90° suggests that orthogonal crossing is not the most prevalent configuration in the human brain. The histogram is likely to underestimate the presence of crossing angles <45°, and therefore the 12% prevalence of 90° crossing probably represents an overestimation. (**C**) Tractography reconstruction of the crossing between the corpus callosum (red) and the corticospinal tract (yellow) connections that, according to (*3*), contains only orthogonal fibers. In this reconstruction, based on SD, the crossing is at angles of 60° or lower. (**D**) Postmortem blunt dissections of the thalamic projections (red arrows), inferior-fronto-occipital fasciculus (blue arrows), and uncinate (green arrow) show that the three tracts fan out or merge to run in parallel rather than crossing orthogonally [modified from (*15*)].

networks. Wedeen *et al*. (*3*) used diffusion spectrum imaging (DSI) to support a theory that white matter fibers form a regular grid by crossing almost orthogonally and uniformly in the entire brain. We believe that this interpretation is open to criticism due to the intrinsic limitations of DSI. DSI resolves multiple fiber orientations by estimating the average diffusion propagator within each voxel and extracting the orientation distribution function (ODF) in which each lobe corresponds to a dominant diffusion orientation. Fiber orientations are then extracted as local maxima of each lobe. Many diffusion methods are available today to resolve multiple fiber orientations. Some methods, such as DSI, qBall imaging (*4*), or diffusion orientation transform (*5*) estimate smoother ODF profiles directly from the diffusion characteristic of the fiber (i.e., diffusion-ODF or dODF) (Fig. 1A, top row). Other methods are able to obtain sharper ODF profiles by extracting directly the underlying fiber orientation (i.e., fiber-ODF or fODF) using a specific diffusion model for white matter fibers. The latter approaches are usually described as spherical deconvolution (SD) methods (*6*, *7*), and they generally show a higher angular resolution (i.e., the ability to resolve crossing fibers at smaller angles) compared with methods based on dODFs (*8*) (Fig. 1A, bottom row).

Figure 1A shows a possible range of solutions for decreasing crossing angles for both dODF and fODF methods. For orthogonal crossing, all ODF profiles are able to distinguish two orientations, whereas for lower angles, only sharper profiles are able to resolve the crossing. Wedeen *et al*. (*3*) use a method that—according to previous publications where similar acquisition protocols were used and more methodological details were available (*9*–*11*)—is likely to have an angular resolution closer to the top row of Fig. 1A. This low angular resolution has a negative impact on the tractography reconstructions shown in (*3*) because it does not allow separation of fibers that cross at nonorthogonal angles, thus making a grid structure of interwoven sheets a very likely configuration. Additionally, the low angular resolution creates artifactual trajectories, such as streamlines stopping in the deep white matter (*3*), which is not consistent with the known anatomy.

As an example of the high probability of nonorthogonal crossing in the human brain, Fig. 1B shows the distribution of the angles of fiber crossing in a sample of 10 healthy human brains based on a SD approach that has been demonstrated to consistently resolve crossing above at least 45° (*7*). These data show that orthogonal crossing is as likely as nonorthogonal crossing and represents less than 12% of the total crossings in the human white matter. These findings question the hypothesis of a brain consisting of a net made of orthogonal intertwined connections. Furthermore, the experimental results reported by Wedeen *et al*. (*3*) are mainly qualitative. In our view, the lack of a quantitative and comprehensive analysis of the entire brain across individuals limits their ability to extend their conclusions to the whole brain or infer any interspecies reproducibility. Indeed, our group-based analysis suggests that the analysis performed on selected regions of interest (*3*) led them to generate a systematic error that replicates across regions of interest and between brain samples of different animal species.

To demonstrate that their method is limited in visualizing pathways crossing at smaller angles, Fig. 1C shows a tractography reconstruction of a region from (*3*) to contain only orthogonal crossing. In our reconstruction, the crossing of the corticospinal tract with the corpus callosum is mainly at 60° in the lower region and at smaller angles in upper regions (*12*). This nonorthogonal configuration is common also for many other tracts, such as the uncinate and inferior fronto-occipital fasciculus in the extreme capsule (Fig. 1D) or the splenium and optic radiations in the occipital lobe. Furthermore, crossing is not the only configuration in complex fiber architecture. Fanning, merging, and kissing are other modalities that are frequently observed in postmortem anatomy and not visible with current diffusion methods (Fig. 1D) (*13*). Finally, the grid model does not take into account the presence of thalamic fibers, which project radially in all brain regions. This implies that most white matter voxels have multiple populations of fibers where, in the same plane, thalamic, callosal, and other projection tracts merge at progressively tangential angles to reach the same cortical areas.

Unfortunately, DSI, as well as other diffusion methods, is limited in resolving these configurations and, therefore, all current tractography reconstructions are biased toward solving only crossing. This information is well known to anatomists, and there is a serious risk in proposing the grid model as "a means to validate MRI tractography through consistency with grid structure" (*3*). Finally, current diffusion methods have a relatively low spatial resolution compared with neurohistology. Diffusion-based reconstructions of streamlines should, therefore, not be equated to axonal pathways because they clearly represent an oversimplification of the true white matter complexity inside each voxel.

Diffusion imaging is certainly a promising technique for the study of white matter architecture. Wedeen *et al*. (*3*) have reported findings suggesting that the human brain is organized like a three-dimensional New York City street grid (*14*). We conclude that this view is biased by the limits of their technique and does not correspond to the real anatomy. To us, the architecture of the brain, seen through the lens of alternative diffusion methods, bears a closer resemblance to the intricate streets of Victorian London.

References and Notes

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