The Ultimate Network

Mapping the brain's wiring with diffusional kurtosis imaging

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Neuroimaging is on the verge of revealing some of the brain's long-kept secrets and in so doing could revolutionize our understanding of neurodegenerative and other neurological diseases.

Novel imaging modalities are exposing tiny cracks in the brain's microarchitecture that could herald the onset of disease long before the first clinical symptoms appear. They are also being used to map the white matter fiber tracts or "networks" that carry messages from one part of the brain to the other, a process known as *fiber tractography*.

Mapping all those connections in the healthy brain is the goal of a nationwide initiative known as the Human Connectome Project (humanconnectomeproject.org). Once the connectome of the healthy human brain—a blueprint of its wiring—has been completed, work will begin on the connectomes of a variety of neurological disorders. Comparing the connectome of a diseased brain to that of the healthy brain should help identify areas of faulty wiring that can become the focus of therapy.

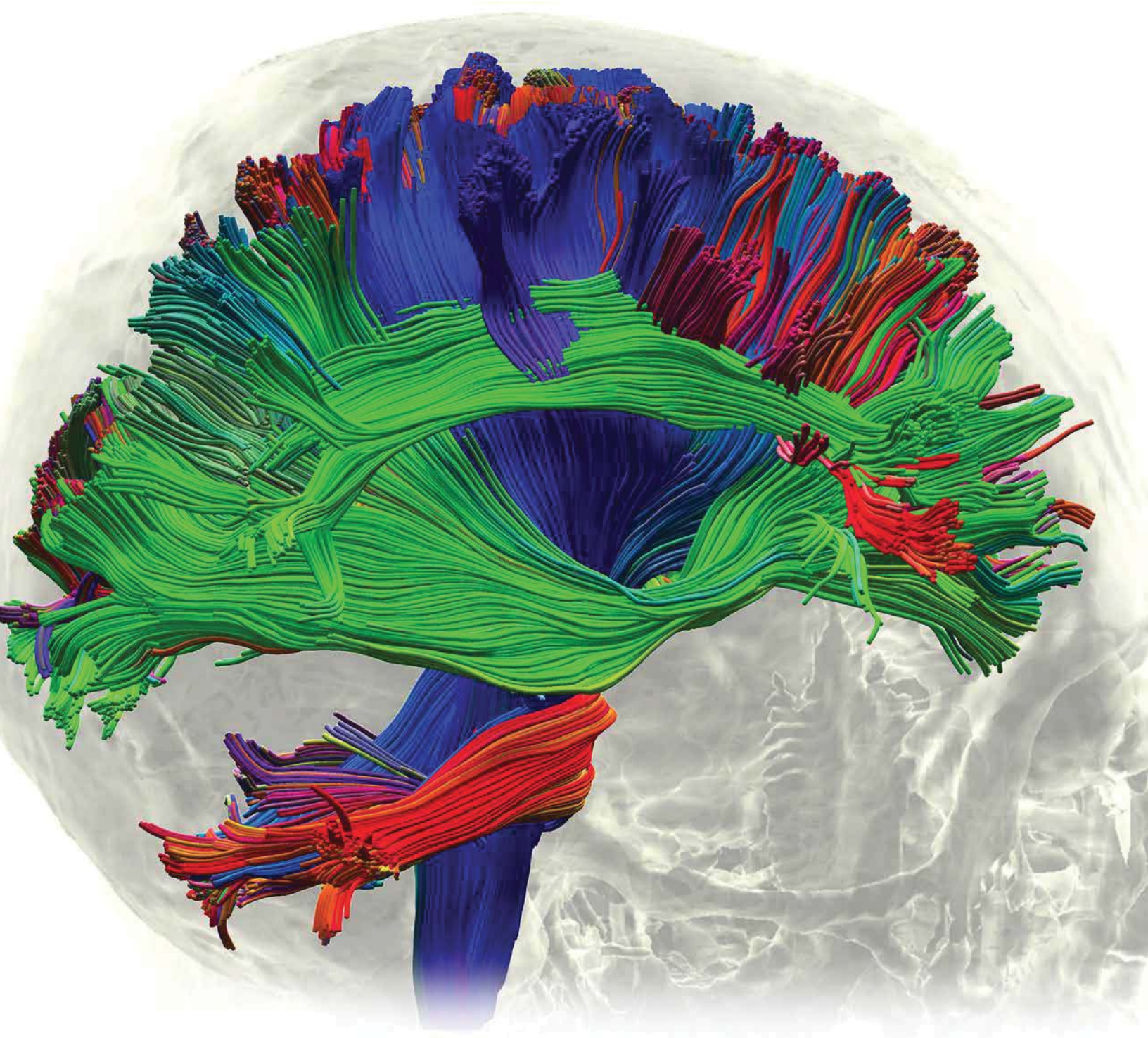
The imaging tool of choice for gaining deeper insight into both the brain's microarchitecture and its wiring has been diffusion magnetic resonance imaging (dMRI), and in particular diffusion tensor imaging (DTI). DTI, which maps the diffusion of water through brain tissue, can be used to determine both the rate and directionality of diffusion. The dMRI image is composed of thousands of voxels (a portmanteau word combining "volume" and "pixel"), each containing a shape that represents the diffusion of water in that area of tissue. These range from spheroids that represent isotropic (i.e., direction-independent) diffusion to ellipsoids that represent anistropic (i.e., direction-dependent) diffusion.

Although diffusion spectrum imaging (DSI) is by far the most sensitive dMRI imaging technique, DTI has been widely adopted in the clinic because of its simplicity and because images can be obtained in just a few minutes (vs 40 minutes with DSI) using widely available scanners and processed using standardized methodologies.

But is DTI the best tool for moving neuroimaging forward, or has it simply been the most convenient?

Diffusional Kurtosis Imaging

Joseph A. Helpern, Ph.D., SmartState™ Endowed Chair in Brain Imaging and Director of MUSC's Center for Biomedical Imaging, and long-time collaborator **Jens H. Jensen, Ph.D.,** noted a fundamental limitation of DTI—it assumes a normal or Gaussian



White matter fiber architecture of the brain. Image courtesy of G. Russell Glenn. Diffusional kurtosis imaging can be used for fiber tractography.

Dr. Joseph Helpern (above) and long-time collaborator Dr. Jens Jensen developed DKI, a new dMRI technique

distribution of water diffusion throughout the tissue. When a barrier impedes diffusion—as is common in complex physiologic milieus—the diffusion deviates from the Gaussian model; the degree to which it does so is known as the *kurtosis*. In a seminal 2005 article, Helpern and Jensen described diffusional kurtosis imaging (DKI), a dMRI technique that uses kurtosis metrics to arrive at more precise and detailed measures of tissue microstructure.[1]

Credited with building the first 3-Tesla human MRI machine, Helpern knows what it takes to create a new imaging technology and translate it effectively into the clinic. "There is a high bar for change," says Helpern. "You have to show that it is at least as good as what you are trying to change, doesn't cost more, and doesn't create longer imaging times for the patient."

Helpern believes that DKI provides much more data on microstructural changes than DTI but is more clinically translatable than DSI, the gold standard of dMRI imaging. Data for DKI can be acquired on the same scanners used for DTI and almost as quickly. "DTI takes three to four minutes, and DKI could take six to seven—a little longer, but only by a few minutes," explains Helpern. Several major medical centers, including New York University and the Medical University of South Carolina, have already incorporated DKI into their standard clinical protocols. Because DKI builds upon the DTI dataset, a DKI-based protocol provides supplemental information to physicians without sacrificing any of the DTI data.

In stroke patients, for example, supplemental DKI information continues to suggest microstructural abnormalities in the region of the stroke long after the DTI image has returned to normal. "The contrast that you see in the stroke area with DKI is not the same as the contrast in DTI images. Something is going on there," explains Helpern. "Maybe the additional information could help differentiate which tissue is salvageable and which is not. We don't know, but that's the kind of question we are exploring."

Helpern and his colleagues are busy mining the additional data provided by DKI to see whether it enhances our understanding of neurological or neurodegenerative diseases such as Alzheimer's disease (AD),[2,3] stroke,[4] Parkinson's disease, and attention deficit hyperactivity disorder[5] or enables an earlier or more definitive diagnosis. For example, it was long presumed in AD that neurons died first, leading axons to wither. Recently, however, some have wondered whether structural damage to axons could precipitate the death of neurons. With its sensitivity to microstructural changes, DKI could help answer that question, and if it does so affirmatively, could be used to detect the early changes in axonal structure that presage the onset of AD.

In the ten years since Helpern and Jensen first described DKI, more than 380 laboratories worldwide have begun to explore its usefulness in a wide variety of diseases, particularly in the early diagnosis or staging of neurodegenerative diseases, such as Parkinson's and Huntington's; traumatic brain injury; stroke; and a variety of tumors.[6]

To help speed research with DKI and the recruitment of patients for clinical trials, Helpern's laboratory has invited other laboratories conducting DKI research worldwide to work cooperatively through the Kurtosis Imaging Network (KIN), which serves as a clearinghouse for DKI data. "I wanted to provide a playground for these labs to deposit data, so that instead of having to get DKI images of 500 AD patients, 50 sites could get ten AD patients each, thereby pooling their resources." explains Helpern.

Helpern knows that critics will likely question whether data obtained with scanners at different sites can be usefully compared, but he has confidence in DKI. "A technique that will survive has to survive in the real world and not just in one medical center," says Helpern. "Using data from multiple scanners will add noise to your data, but if your technique is strong enough, it will survive that additional noise."

Fiber Tractography

Not all of the clinical applications of DKI—most notably its ability to distinguish when fiber tracts cross each other in tractography—were foreseen by Helpern and Jensen. "When we started doing kurtosis, we weren't even thinking about tractography," admits Helpern.

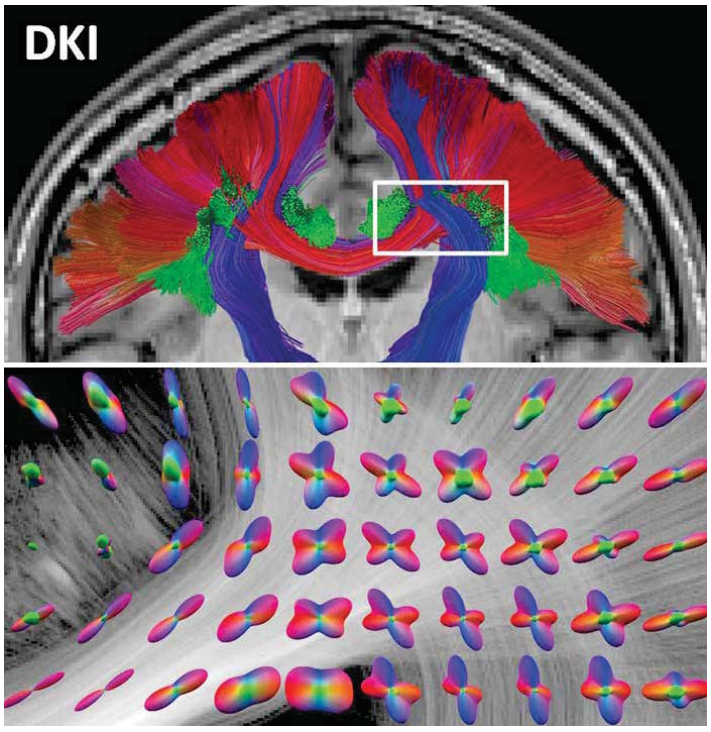
White matter fiber tracts are the insulated wires that connect the brain to the spinal cord and one area of the brain to others. White matter is named for the whitish myelin sheaths (insulation) that cover the many axons (wires) that make up these fiber tracts.

Water flows more freely in parallel with fiber tracts than perpendicular to them. "If water is diffusing inside axons, which are the wires of the brain, it can diffuse down axons more easily than through their insulation (the myelin sheath)," explains Helpern. "It goes down the pipe, if you will."

Because water has the propensity to travel "down the axon" and because DTI can be used to determine the directionality of its diffusion, DTI can be used to track the fiber as it passes from voxel to voxel. The Human Connectome Project is following the trajectories of many such fiber tracts, essentially creating a blueprint of the brain's connections.

However, in almost 30% of voxels in an MRI image, two or more fiber tracts cross, causing the typical algorithms used with DTI to fail. As a result, DTI cannot determine the direction of both fibers and can mistakenly interpret the crossing as an abnormality or lesion. Such fiber crossings can be resolved effectively with the far more sensitive DSI method but at the cost of longer imaging times and more complicated post-processing.

DKI, which collects more information than DTI but less than DSI, offers a useful compromise. Like DSI, it can resolve fiber crossings and so accurately map the trajectories of white matter fiber tracts. Like DTI, it can do so in a clinically relevant time frame. The connectomes of disease that will be developed by the Human Connectome Project could offer useful reference maps against which to compare tractography obtained from at-risk patients, leading to earlier and more definitive diagnoses of neurological diseases. However, that promise will only be realized if there is a reliable clinical tool for performing fiber tractography. Both sensitive and clinically translatable, DKI is certainly a strong contender to be that tool.



Diffusional kurtosis imaging (DKI) is well-suited to tractography because, unlike diffusion tensor imaging, it can resolve fiber crossings (bottom panel).

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