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Watching the Brain Work: Looking at the Network Connections

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tion and data processing among different institutions, validating the robustness and accuracy of the variables in everyday clinical practice, and, ultimately, improving the lives of patients with brain tumors.

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A cursory glance at the article *High-Resolution Line Scan Diffusion Tensor Imaging of White Matter Fiber Tract Anatomy* by Mamata and colleagues (page 67) may initially appear to the reader as a primarily technical investigation extolling the virtues of yet another MR technique tailored for academic rather than clinical applications. The greater importance of this investigation, however, is evident regarding the potential scope of new anatomic information disclosed by the recent efforts with this technique. In vivo depiction of the underlying neuronal infrastructure of the brain not only promotes greater understanding of the complexity of everyday motor and sensory processes and the ways that disease can affect these functions; it also will allow us to begin to visualize the underpinnings of more profound neurologic phenomena such as consciousness, attention, and awareness. Therefore, the importance of these network connections is not a trivial issue, and this brief but broad editorial introduction will try to provide a perspective for the information generated by Mamata et al as well as others who have already and will continue to publish on this topic.

In today's clinical practice, most routine MR imaging (including functional MR imaging) used to determine the functional implications of cerebral lesions largely relies on an analysis of the relationships and functional imaging correlates to deep and superficial gray matter structures. This is an understandable natural consequence of readily identifiable gray matter landmarks such as sulcal and gyral anatomy as well as many well-defined deep gray matter margins. In addition, the discrete motor and sensory functions associated with the gray matter anatomy are assessable to clinical observation when mapping or in the presence of disease-related injury. The underlying white matter tracts, on the other hand, are more opaque to routine imaging and clinical evaluation owing to less visible margins and more complex functional associations.

It is also easy to oversimplify brain activity by only considering structures that encode sensory information and command movements because of the misperception of white matter fibers as mere conduits for the appropriate gray matter centers involved in sensory and motor function. This absurd scheme can reduce most brain functions to one large reflex arc. Motor and sensory regions, however, account for only a fraction (approximately 20%) of the cerebral cortex. Most of the brain consists of the so-called association

cortices that enable diverse functions collectively referred to as "cognition." Some of these functions include awareness of physical and social circumstances (consciousness), the ability to have thoughts and emotions, sexual attraction, expressions of these thoughts with language, emotional memory, etc. It can be argued that cognitive abilities represent the most complex, important, and intriguing cerebral functions. In other words, these are the very psychological and neurologic processes that help to define our selves and our lives.

A closer look at association white matter tracts illuminates the complexity of the neuronal network and readily dispels the notion of a simple one-to-one connection from one cortical neuron to another. The signals these fibers project to other association cortices via the thalamus have already been processed in the primary motor and sensory areas and are fed back to the association regions for further processing. The information, therefore, is a relay from other cortical areas rather than of primary motor or peripheral sensory signals. This type of corticocortical connection explains the observed enrichment or multiplication of input fibers from other cortical areas to any one particular association area. The functional implications for this increasingly complex network foster the speculation about subcortical processing of complex behavior. For example, the association fibers that project to and from the inferior temporal lobe are more closely scrutinized in patients with agnosias such as prosopagnosia (inability to identify familiar individuals by their facial features). The structure of the connecting fibers may be a key component to understanding this type of neurologic dysfunction. Attention disorders may also require evaluation of the white matter fibers projecting to the parietal cortex in addition to the surface structures. Parietal cortex dysfunction may, in fact, reflect disorganization of the underlying association fibers.

Most of the evidence that supports our anatomic understanding of these white matter tracts is derived from anatomic tracing studies in nonhuman primates supplemented by limited pathway tracings done in postmortem human brain tissue. The inferred functional association of this information then depends on critical correlation with clinical observations of patients with cortical lesions. The ability to demonstrate these tracts in vivo, therefore, represents a huge advantage in direct observation and may even generate

new observations and conclusions that can challenge assumptions built upon the previous indirect data.

The ability to visualize the network of white matter tracts that connect the association cortices as well as the motor and sensory areas provides a valuable insight into cerebral function and pathologic characteristics that exceeds merely identifying at-risk areas for surgery. This is not meant to understate the importance of recognizing the proximity of important white matter tracts such as the projection fibers (ie, cortical spinal tracts, optic radiations, etc.) to surgical or irradiation fields, a clear and immediate advantageous application for the information gathered by these newer techniques. Identification of the white matter tracts would not only allow for more accurate preprocedural prediction of clinical outcome for a variety of treatment options but may also enable recognition of the clinical importance of particular brain lesions, which may have been given only cursory analysis in the past. In expressive aphasia, for example, we are aware that the affected Broca's area is in the inferior frontal gyrus of the dominant hemisphere. We can also map anterior language function by using blood-oxygenation-level–dependent (BOLD) functional MR imaging. Current routine imaging techniques are incapable of depicting the white matter tracks that are important determinants of spontaneous speech recovery. Recognition of strategically located lesions that affect these tracts, therefore, becomes problematic. One such tract relevant for speech is the medial subcallosal fasciculus, which connects the supplementary motor area and the cingulate gyrus to the corpus striatum to facilitate the initiation, preparation, and limbic aspects of spontaneous speech. Another relevant white matter pathway provides motor execution and sensory feedback between the primary sensorimotor cortex and the oral apparatus. Strategically located middle cerebral artery distribution infarctions that affect both of these pathways can then prevent any relevant spontaneous speech by hindering speech initiation, motor execution, or sensory feedback, with or without inferior frontal gyrus cortical involvement. Recovery of spontaneous speech associated with a Broca's aphasia is directly related to the degree of involvement of these white matter tracts. This common clinical scenario illustrates just one application of information from white matter tract visualization that allows neuroradiologists to routinely provide relevant interpretations about clinical dysfunction on the basis of a "simple" morphologic analysis of the neuronal network.

Another exciting area of application is the imaging of patients with movement disorders that extend beyond the basal ganglia, midbrain, and premotor or motor cortices to include characterization of the connecting white matter tracts and enable an analysis of the planning, initiation, execution, and coordination of movement. In addition, recent applications of BOLD functional MR imaging to map functionally connected regions of the brain in psychiatric and neurodegenerative diseases can be combined with diffusion tensor imaging of white matter networks to evaluate these disorders, which have otherwise been relatively excluded from routine imaging.

Mamata et al's described technique also seems to circumvent some of the genuine problems encountered with standard echo-planar diffusion tensor imaging. The indicated advantageous reduction of the $T2^*$ effects can be conceptually paraphrased as the result of producing a three-dimensional column that is effectively a single voxel in thickness that is frequency encoded without the need for phase encoding. The dramatic reduction of $T2^*$ effects is made possible by the ability to use a much shorter TE, because phase encoding is not required. The markedly decreased susceptibility effect near the skull base is one obvious visual manifestation of this technique.

This overall enthusiasm for diffusion tensor imaging, however, is for its potential and not the current reality. We must remind ourselves that the technique at its current stage of development effectively represents only an improved in vivo method of producing white matter contrast. This is a method that, so far, only allows the visualization of the gross directional orientation of fibers in the white matter, which is not the same as detecting specific white matter tracts. This technique, therefore, cannot distinguish different adjacent white matter tracts that are oriented in the same direction within the examined area. Furthermore, the actual physical connection of white matter tracts within one voxel with a similar (or dissimilar) eigenvector in an adjacent voxel is an assumption that cannot be definitively determined by the technique. Some particularly tortuous white matter tracts, for example, that temporarily merge with or lie close to various other white matter tracts at different points throughout their course would be quite problematic. The seemingly reasonable connection between directional vectors in different voxels based on existing anatomic information is an unproven assumption that may be vulnerable to specious reasoning in future developments. The eigenvector also only represents the longest axis of a diffusion ellipsoid and may not be representative of the actual path of the particular tract one wishes to map. Nonetheless, the initial information produced by diffusion tensor imaging has immediate value and applications. The technical challenge for the near future is to clearly distinguish the individual tracts that are defined by their common functionality.

The everyday implementation of this method is another substantial obstacle. The availability, complete but facile application, and required postprocessing techniques of diffusion tensor imaging are substantial practical issues. A glance at the list of Mamata's coauthors hints at the required time, effort, manpower, and skills needed to produce this type of data. Rapid commercial developments for the seamless and efficient application and integration of this technique into daily clinical practice would require an uncommon level of vendor responsiveness to the needs of neuroradiologists.

Diffusion tensor data engender profound basic science and clinical implications, with neuroradiology

occupying an immediately vital and strategic position. Our proficiency in integrating imaging techniques that illustrate both the morphologic and physiologic characteristics of the brain is paramount and is a currently evolving strategy for daily clinical practice at some academic institutions. This combination of information gained from diffusion tensor imaging and several MR imaging techniques that depict the physiologic behavior of the brain, including functional MR imaging, spectroscopy, and cerebral vascular imaging, promotes the exciting prospect of understanding functional and morphologic network aberrations in the clinical presentation of many neurologic disorders.

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Transient Ischemic Attacks: Added Specificity from Modern MR Imaging

In this issue of the *AJNR*, Rovira and colleagues (page 77) present diffusion-weighted MR findings from a series of patients after transient ischemic attacks (TIAs). Data were collected on lesions detected with diffusion-weighted MR imaging within 10 days of symptom onset in a group of 58 patients. In this study, TIA was defined as stroke symptoms that completely resolved within 24 hours. Most patients manifested lesions, either in deep parenchymal foci or involving the cortex, despite the symptom resolution. The percentage of that majority exceeds previously defined percentages in other reports.

A TIA has generally referred to a patient with clinical stroke that then resolves within the first day after onset. Colloquially this has varied greatly. For some, the time period for recovery shortens, even down to a 1-hour increment for return to a normal baseline of neurologic function. Of greater concern have been variations of definition regarding the symptoms, where for some any deficit that resolves may suffice, but for others only specific dysfunction registers. Then of course we are all faced with great variation among specialists who evaluate not only the initial set of symptoms but also the effectiveness of the recovery. Surely the neurologic examination by a neurologist will differ from that of a primary care provider or a busy emergency room doctor.

Investigation of patients with TIA with diffusion-weighted MR imaging has varied widely in the timing of image acquisition relative to the onset of symptoms. Even in Rovira et al's study, the imaging occurred any time within the first 10 days after the neurologic event. Indeed, only a small minority of patients underwent imaging examination in the first 2 days after onset. In a previous report, the imaging occurred in the first 3 days after TIA (1). Range of timing limits the study of the precise cause of infarct and does not yet answer to the sensitivity of the technique in the first hours after onset when therapeutic interventions are under consideration. Sensitivity at early onset remains a concern, as data from our series of MR imaging in hyperacute stroke patients and from others investigators show us that a substantially low number of patients imaged very acutely will have false-negative diffusion-weighted imaging findings (2).

The duration of the transient symptoms in patients with TIA seems to correlate directly with the likelihood of positive findings on diffusion-weighted images. The current study reports average symptom duration of 1 hour for those patients without any imaging evidence of ischemia compared with 7 hours for those with a lesion on diffusion-weighted images. This reinforces the intuitive conclusion that longer standing deficits, even when they resolve, do represent more substantial insults. The current investigation should also pique our interest, because many of the lesions identified had cortical involvement. Thus, we should not consider a TIA as limited to deep perforating artery territories.

The TIA remains an important and timely health issue for us all, as it represents a leading diagnosis for emergency room visits and admissions to hospitals. Of greater concern, patients evaluated for TIA often "bounce back" with either repeat transient events, delayed permanent cerebral infarcts, or even fatalities (3). Therefore, TIA represents a prevalent, high-risk diagnosis for our patient population. However, TIA remains a diagnosis based on symptoms and their resolution, and until recently, lacking in objective findings so useful for classification, characterization, and comprehension of the underlying disease processes.

The advance of diffusion-weighted MR imaging has provided exactly this objectivity, and not surprisingly we have encountered a wide range of variations beneath the catchall term of TIA. The imaging data add needed specificity to the evaluation, for now we can distinguish those who have undergone a true transient phenomena, even when lacking image-based sequelae, from those who have had infarction, although the natural redundant neurologic pathways have quickly compensated for the loss. We must continue to pursue the application of advanced imaging of patients with TIA, perhaps for example, with evaluation of the perfusion parameters in affected regions. We must strive to define those who have ischemia that may produce infarct, and further define those lesions that will produce permanent debilitation