

Current Literature

In Clinical Science



Is DTI Increasing the Connectivity Between the Magnet Suite and the Clinic?

Spatial Patterns of Water Diffusion Along White Matter Tracts in Temporal Lobe Epilepsy. Concha L, Kim H, Bernasconi A, Bernhardt BC, Bernasconi, N. *Neurology* 2012;79:455–462.

OBJECTIVES: Diffusion tensor imaging (DTI) tractography has shown tract-specific pathology in temporal lobe epilepsy (TLE). This technique normally yields a single value per diffusion parameter per tract, potentially reducing the sensitivity for the detection of focal changes. Our goal was to spatially characterize diffusion abnormalities of fasciculi carrying temporal lobe connections. **METHODS:** We studied 30 patients with drug-resistant TLE and 21 healthy control subjects. Twenty-four patients underwent DTI toward the end of video-EEG telemetry, with an average of 50–54 hours between the last seizure and DTI examination. After manual dissection of the uncinate and inferior longitudinal and arcuate bundle, they were spatially matched based on their distance to the temporal lobe, providing between-subject correspondence of tract segments. We evaluated point-wise differences in diffusion parameters along each tract at group and subject levels. **RESULTS:** Our approach localized increased mean diffusivity restricted to or more prominent within the ipsilateral temporal lobe. These abnormalities tapered off as tracts exited the temporal lobe. We observed that the shorter the interval between the last seizure and DTI, the higher the mean diffusivity (MD) of the ipsilateral tracts. Linear discriminant analysis of tract segments correctly lateralized 87% of patients. **CONCLUSIONS:** The centrifugal pattern of white matter diffusion abnormalities probably reflects astrogliosis and microstructure derangement related to seizure activity in the vicinity of the focus. The negative correlation between the interval from last seizure and MD suggests a role for postictal vasogenic edema. The ability to assess tracts segmentally may contribute to a better understanding of the extent of white matter pathology in epilepsy and assist in the presurgical evaluation of patients with TLE, particularly those with unremarkable conventional imaging results.

Microstructural White Matter Abnormality and Frontal Cognitive Dysfunctions in Juvenile Myoclonic Epilepsy. Kim JH, Suh SI, Park SY, Seo WK, Koh I, Koh SB, Seol HY.

Epilepsia 2012;538:1371–1378.

PURPOSE: Previous neuroimaging studies provide growing evidence that patients with juvenile myoclonic epilepsy (JME) have both structural and functional abnormalities of the thalamus and frontal lobe gray matter. However, limited data are available regarding the issue of white matter (WM) involvement, making the microstructural WM changes in JME largely unknown. In the present study, we investigated changes of WM integrity in patients with JME and their relationships with cognitive functions and epilepsy-specific clinical factors. **METHODS:** We performed diffusion tensor imaging (DTI) and neuropsychological assessment in 25 patients with JME and 30 control subjects matched for age, gender, and education level. Between-group comparisons of fractional anisotropy (FA) and mean diffusivity (MD) were carried out in a whole-brain voxel-wise manner by using tract-based spatial statistics (TBSS). In addition, both FA and MD were correlated with cognitive performance and epilepsy-specific clinical variables to investigate the influence of these clinical and cognitive factors on WM integrity changes. **KEY FINDINGS:** Neuropsychological evaluation revealed that patients with JME had poorer performance than control subjects on most of the frontal function tests. TBSS demonstrated that, compared to controls, patients with JME had significantly reduced FA and increased MD in bilateral anterior and superior corona radiata, genu and body of corpus callosum, and multiple frontal WM tracts. Disease severity, as assessed by the number of generalized tonic-clonic seizures in given years, was negatively correlated with FA and positively correlated with MD extracted from regions of significant differences between patients and controls in TBSS. **SIGNIFICANCE:** Our findings of widespread disturbance of microstructural WM integrity in the frontal lobe and corpus callosum that interconnects frontal cortices could further support the pathophysiologic hypothesis of thalamofrontal network abnormality in JME. These WM abnormalities may implicate frontal cognitive dysfunctions and disease progression in JME.



Commentary

Functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) provide noninvasive whole-brain physiologic and anatomic information. fMRI has a temporal resolution of a few seconds during a specific task performance and is used in the decision pathway of surgical resection for epilepsy. Can DTI provide similarly useful information based on its temporal resolution? These two papers suggest that aspects of DTI—the fractional anisotropy (FA) and the mean diffusivity (MD) of the white matter—are useful for understanding the localization and sequelae of seizure occurrence in patients with epilepsy.

By way of background, DTI approximates the white matter tracks in the brain and is derived from measures of water diffusion. The underlying physical tenet is that the tubular axonal structures comprising white matter restrict water diffusion. Water diffuses in a more perpendicular plane when limited by white matter tracks (termed “anisotropy”) compared to water diffusing randomly in all planes in less-confining structures (termed “isotropy”). This seems intuitive, but measuring it and resolving it in a neuroimage is a miracle of mathematical and physical bioengineering. By applying a probabilistic mathematical function—specifically, a Gaussian probability density function with a covariance matrix defined by the diffusion tensor at each voxel—even white matter tracks that curve and cross can be outlined by diffusion characteristics (1). It turns out the white matter track of a young, healthy person has high FA and low MD; that is, all the water molecules are dutifully oriented in the appropriate direction along the track.

The anisotropy changes as humans age; predictably, this change is in the direction of less organization rather than more. FA worsening is characterized by decreasing values, and MD worsening is characterized by increasing values. In fact, this is what has been found in a study of normal young subjects, aged 20–30 years, compared to normal mature subjects, aged 60–71 years (2). FA was significantly lower in older compared to younger adults in numerous white matter regions, specifically 1) the anterior, superior, and posterior corona radiata, 2) the white matter of the superior, middle, frontal, and straight gyri, 3) white matter of the precuneus and superior parietal lobe, 4) parts of the cingulate (mainly dorsal), 5) the body and column of the fornix, 6) the forceps minor and major, 7) external capsule, internal capsule, and 8) sagittal stratum. An increase in MD was found in many of the same structures but additionally in the genu of the corpus callosum. One might hope that there was a brain structure that improved in diffusivity over time, but none were found in this study.

The decline in diffusivity over time is likely due to age-associated white matter microstructural alterations, which include an increase in brain water content, minor fiber loss, demyelination, and disruption of axon structure (2). Gliosis and secondary Wallerian degeneration may be later characteristics of white matter aging, producing the progressive diffusivity changes (2).

Epilepsy clinicians rely on the dynamism of the ictal SPECT, the interictal PET, fMRI for language and motor cortex mapping. FA is also a dynamic imaging result that decreases in association with decreasing hippocampal volume in TLE, and with increasing duration of epilepsy (as does hippocampal

volume) in a recent cross-sectional study of temporal lobe epilepsy patients (3).

In the two recent studies, researchers extend the implications of diffusivity in epilepsy. In one study of 30 intractable epilepsy patients undergoing video-EEG monitoring as part of a presurgical evaluation, DTI was undertaken at the end of the monitoring period (4). The investigators evaluated segments of the white matter tracks connected to the temporal lobe: the uncinate fasciculus, the inferior longitudinal fasciculus, and the arcuate fasciculus. The segments of these fasciculi nearest to the ipsilateral temporal lobe showed an increase in diffusivity compared to the contralateral temporal lobe. The diffusivity increase began tapering off within the tract along its path outside temporal lobe and was equal to the contralateral diffusivity score at the portion most distal from the temporal lobe. MD increases were most marked in the intratemporal uncinate and inferior longitudinal fasciculus and less so in the arcuate fasciculus. This may be because the arcuate has little hippocampal connectivity but rather has lateral temporal connectivity. The most remarkable finding was that of an association between increased MD and a shorter time interval from the last seizure, with an average of 50–54 hr since the last seizure. The investigators also report—although the patient numbers are small—that successful surgical outcome was associated with higher MD values. These results, with the acute changes thought to be due to seizure-produced vasogenic edema, indicate that MD could be clinically useful as both structurally and physiologically localizing in an epilepsy surgery evaluation.

The second study evaluated FA and MD in 27 young patients with JME, using well-defined inclusion criteria, and a group of 31 age-matched healthy controls (5). All subjects underwent neuropsychological testing, with an emphasis on frontal lobe executive function evaluation. As expected from previous work, the neuropsychological tests showed significantly worse scores in the JME group of patients for attention, working memory, and executive functions compared to controls. Perhaps not expected was the significant FA reductions and MD increases present in the JME group compared to the control group. These alterations were highly symmetric and involved bilateral superior and anterior corona radiata, genu and body of corpus callosum, and multiple middle and superior frontal white matter tracts. There were no areas of reduced FA or increased MD in controls compared to JME patients.

The diffusivity results, however, did not correlate with the neuropsychological scores; the authors speculate that a longitudinal study may reveal an association. It is possible their findings indicate that seizure occurrence itself has profound effect in FA and MD. They report that generalized tonic-clonic seizure (GTC) frequency but not epilepsy duration, correlated with increased diffusivity. GTCs from JME, but not just the presence of the JME genetic predisposition, correlated with decreased white matter microstructural integrity.

The derivation of diffusivity is complex—but perhaps its meaning in epilepsy is not. Simplistically, acute and chronic increases in white matter diffusivity indicate dysfunctional and prematurely aging white matter due to seizure occurrence. These findings suggest a useful role for white matter diffusivity



values in epilepsy assessment, perhaps including seizure localization and eventually the neuropsychological consequences of recurrent seizures.

by Cynthia L. Harden, MD

References

1. Bick AS, Mayer A, Levin N. From research to clinical practice: Implementation of functional magnetic imaging and white matter tractography in the clinical environment. *J Neurol Sci* 2012;312:158–165.
2. Burzynska AZ, Preuschhof C, Bäckman L, Nyberg L, Li SC, Lindenberg U, Heekeren HR. Age-related differences in white matter microstructure: Region-specific patterns of diffusivity. *Neuroimage* 2010;49:2104–2112.
3. Keller SS, Schoene-Bake JC, Gerdes JS, Weber B, Deppe M. Concomitant fractional anisotropy and volumetric abnormalities in temporal lobe epilepsy: Cross-sectional evidence for progressive neurologic injury. *PLoS One* 2012;7:e46791. doi:10.1371/journal.pone.0046791.
4. Concha L, Kim H, Bernasconi A, Bernhardt BC, Bernasconi N. Spatial patterns of water diffusion along white matter tracts in temporal lobe epilepsy. *Neurology* 2012;79:455–462.
5. Kim JH, Suh SI, Park SY, Seo WK, Koh I, Koh SB, Seol HY. Microstructural white matter abnormality and frontal cognitive dysfunctions in juvenile myoclonic epilepsy. *Epilepsia* 2012;53:1371–1378.



American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today's Date: *1-18-13*
2. First Name *Cynthia* Last Name *Hanks* Degree *MD*
3. Are you the Main Assigned Author? Yes No

If no, enter your name as co-author:

4. Manuscript/Article Title: *Epilepsy Currents*
5. Journal Issue you are submitting for: *Epilepsy Currents*

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship just add rows to this table.

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Grant	<input checked="" type="checkbox"/>				
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>				
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>				
4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>				
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>				
6. Provision of writing assistance, medicines, equipment, or administrative support.	<input checked="" type="checkbox"/>				
7. Other	<input checked="" type="checkbox"/>				

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.

Section #3 Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship just add rows to this table.

Type of relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Board membership	<input type="checkbox"/>				
2. Consultancy	<input checked="" type="checkbox"/>	✓		<i>Usher Smith</i>	
3. Employment	<input type="checkbox"/>				
4. Expert testimony	<input type="checkbox"/>				
5. Grants/grants pending	<input checked="" type="checkbox"/>	<i>UAB</i>	✓	<i>NIH, Miller Family/EPDP</i>	
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	✓		<i>Blair UCB, Audbeck</i>	
7. Payment for manuscript preparation.	<input type="checkbox"/>				
8. Patents (planned, pending or issued)	<input type="checkbox"/>				
9. Royalties	<input checked="" type="checkbox"/>	✓		<i>Up-to-Date</i>	
10. Payment for development of educational presentations	<input type="checkbox"/>				
11. Stock/s tock options	<input type="checkbox"/>				
12. Travel/accom modations/meeting expenses unrelated to activities listed.**	<input type="checkbox"/>				
13. Other (err on the side of full disclosure)	<input type="checkbox"/>				

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section #4 Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest.
 Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.
Epilepsy Currents Editorial Board