



Deep White Matter Track Record of Functional Integrity in Childhood Absence Epilepsy

White Matter Impairment in the Basal Ganglia-Thalamocortical Circuit of Drug-Naïve Childhood Absence Epilepsy.

Yang T, Guo Z, Luo C, Li Q, Yan B, Liu L, Gong Q, Yao D, Zhou D. *Epilepsy Res* 2012;99:267–273.

PURPOSE: It is unknown whether white matter abnormalities exist in childhood absence epilepsy (CAE), a syndrome of idiopathic epilepsy (IGE). Diffusion tensor imaging (DTI) can noninvasively quantify white matter integrity. This study used DTI to investigate abnormal changes in white matter of untreated CAE patients. **METHODS:** Subjects included nine patients with untreated CAE and nine age- and sex-matched healthy controls. Diffusion tensor imaging parameters were voxel based and statistically compared between patients and controls. The correlations between DTI parameters in regions of interest (ROIs) and age of seizure onset or duration of epilepsy were analyzed. **RESULTS:** Untreated CAE patients had a significantly higher fractional anisotropy (FA) value in the bilateral thalamus, anterior corpus callosum and upper brainstem, while also displaying a lower FA value in prefrontal white matter, anterior cingulate, and bilateral posterior limbs of the internal capsule compared to control subjects. An increase in mean diffusivity (MD) value was observed in parietal lobe white matter, prefrontal white matter, and posterior cerebellar hemispheres, in addition to subcortical structures including bilateral putamen and posterior limb of internal capsule. There were MD significant correlations between ROI diffusion parameters and the duration of the disease or the age of onset. **CONCLUSIONS:** The results showed white matter integrity impairment in the basal ganglia thalamocortical circuit of drug-naïve CAE patients. These abnormalities in white matter may be related to increased cortical excitability and cause cognitive, linguistic, and behavioral/emotional deficits both during and between seizures.

Commentary

The ability to demonstrate the extent of a white matter connected epileptic circuit is possible by utilizing diffusion-based magnetic resonance (MR) imaging. Such MR sequences have a long history of detecting seizure-related changes in white matter associated diffusion. These MRI abnormalities have been shown to occur both interictally, and during complex partial status epilepticus (1). Diffusion weighted MR imaging (DWI) sequences measure the magnitude of water movement by applying an additional directional gradient to standard T2-weighted echo planar imaging sequences. These standard imaging sets acquire the data in the three cardinal planes (XYZ) and average the data to get an estimate of the total diffusion within a voxel. The result can be expressed as the apparent diffusion coefficient (ADC). So, the magnitude of diffusion, or mean diffusivity (MD) in DWI is the average of the ADC. Diffusion tensor imaging (DTI) is an evolution of this technique, capable of demonstrating seizure-associated changes in the directionality of water diffusion not possible with DWI and fluid attenuation inversion recovery (FLAIR) sequences (2–4).

The recent review by Yang et al. demonstrates DTI-related differences in extensive deep cerebral, bilateral thalamic, brainstem, and cerebellar white matter circuits in a small cohort of newly diagnosed drug-naïve children with childhood absence epilepsy (CAE) compared with age- and sex-matched controls. Furthermore, the article attempts to suggest a causal relationship of such DTI-related changes with cognitive and emotional deficits often seen in these children.

From an imaging technology perspective, DTI is based on the knowledge that the diffusion of water molecules within brain white matter is not equal in all directions. Diffusion is typically restricted by cell membranes of myelinated neurons, called anisotropic diffusion, or fractional anisotropy (FA). FA represents a measure of the directionality of water diffusion. Water does not diffuse across intact axonal fibers but rather along their major axis. So, intact brain white matter promotes anisotropic diffusion, where anisotropy indices tend toward 1. Conversely, isotropic diffusion, where water diffuses in no apparent direction, represents altered or disrupted white matter pathways. In this scenario, the FA index approaches zero. The MD, or trace, is a measurement of the amplitude of the diffusional motion, putatively reflective of cell hydration.

Chronic changes seen with DTI following years of focal-onset seizures have been well described in the literature. For example, the usual pattern in mesial temporal sclerosis and cortical dysplasia is a reduced FA and increased MD on the

Epilepsy Currents, Vol. 12, No. 6 (November/December) 2012 pp. 234–235
© American Epilepsy Society

OPEN ACCESS Freely available online



involved side (3, 5). In support of secondary epileptogenesis in humans, chronic DTI-related changes are not confined to the ipsilateral hippocampus alone but are often seen contralaterally (6, 7), as well as in the relay pathways of the thalamus (8). In longstanding temporal lobe epilepsy, a significantly reduced FA is often seen in the posterior corpus callosum in patients compared with controls. This finding suggests widespread changes owing to chronic influences from distant connected epileptic sources.

Conversely, transient postictal changes in FA compared with interictal DTI measures can be utilized to visualize transient subacute remnants of the directionality of an epileptic circuit recruited by partial-onset seizures (2, 9). These transient postictal measures are not typically useful in those patients in whom secondarily generalized seizures have occurred immediately prior to postictal MRI. Such widespread propagation pathways become too complex to analyze.

DTI-related alterations as demonstrated by Yang et al. in recently diagnosed drug-naïve children with typical absence epilepsy are relatively new in the literature. Yang et al. found significantly increased FA in the thalami, bilaterally and upper brainstem of untreated CAE patients. The study also demonstrated increased FA in the anterior corpus callosum. This finding is in contrast to reduced FA observed in the posterior corpus callosum, robustly implicated in temporal lobe epilepsy. This information reinforces the presence of an overactive neural circuit in the anterior corpus callosum of CAE patients compared with normal controls. These data suggest intact anterior corpus callosum integrity with increased axonal bundle diameters. The findings support the use of corpus callosotomy to potentially disrupt the bulk of interhemispheric communication of intractable epileptic circuits shared by the localization-related frontal lobe and generalized epilepsies. Yang et al. also demonstrated a reduced FA in the prefrontal white matter, anterior cingulate, and posterior limbs of the internal capsule bilaterally compared with normal controls. This finding is suggestive of disrupted axonal integrity in those regions. In addition, the authors found an increased MD in the putamen bilaterally, an indirect measure of increased subcortical neuronal hydration. These data suggest that the basal ganglia pathways are, in part, associated with the generation of epileptic activity in CAE seen as generalized spike-wave discharges on scalp EEG. Of interest, the authors reported an increased MD extending to the cerebellum. This structure has consistently been associated with both transient hyper- and hypo-perfusion-related alterations reported in the ictal single positron emission computed tomography (SPECT) literature. The electrophysiological connection of the cerebellum as a deep brain modulator of epileptiform activity is well established. However, its complete role in the epilepsies remains unknown.

Evaluating functional connectivity patterns in infants and children along with longitudinal follow-up has not been well studied until recently (10). Information gained from DTI can begin to decipher the extensive network underpinnings of

cognitive differences between unimpaired children without epilepsy and those with absence epilepsy. Yang et al., however, suggest causality of cognitive and behavioral relationships with DTI in the absence of close neuropsychological and psychiatric assessment in the patient cohort.

As diffusion tensor models evolve, improved visualization of affected neural circuits will be likely introduced in the diagnostic evaluation of widespread epileptic networks. For example, the magnitude and direction of the principal eigenvector within a DTI voxel will be better utilized to mathematically produce colorized fiber orientation maps. As a result, improved fiber tracking with an ability to resolve crossing fiber tracts will generate better modeling of deep cerebral epileptic networks extending throughout the brain.

The neuroimaging information presented by Yang et al., even though lacking robust statistical power, sets the stage for attempting to better understand structural changes in extensive epileptic circuits. Using DTI with larger patient cohorts will contribute toward understanding neurocognitive deficits in children with a common childhood epilepsy syndrome.

by Marvin A. Rossi, MD, PhD

References

1. Lansberg MG, O'Brien MW, Norbash AM, Moseley ME, Morrell A, Albers GW. MRI abnormalities associated with partial status epilepticus. *Neurology* 1999;52:1021–1027.
2. Diehl B, Symms MR, Boulby PA, Salmenpera T, Wheeler-Kingshott CAM, Barker GJ, Duncan JS. Postictal diffusion tensor imaging. *Epilepsy Res* 2005;65:137–146.
3. Salmenpera TM, Symms MR, Boulby PA, Barker GJ, Duncan JS. Postictal diffusion weighted imaging. *Epilepsy Res* 2006;70:133–143.
4. Yogarajah M, Duncan JS. Diffusion-based magnetic resonance imaging and tractography in epilepsy. *Epilepsia* 2008;49:189–200.
5. Assaf BA, Mohamed B, Abou-Khaled KJ, Williams JM, Yazeji MS, Haselgrove J, Faro SH. Diffusion tensor imaging of the hippocampal formation in temporal lobe epilepsy. *Brain* 2003;24:1857–1862.
6. Arfanakis K, Hermann BP, Rogers BP, Carew JD, Seidenberg M, Meyerand ME. Diffusion tensor MRI in temporal lobe epilepsy. *Magn Reson Imaging* 2002;20:511–519.
7. Thivard L, Lehericy S, Krainik A, Adam C, Dormont D, Chiras J, Baulac M, Dupont S. Diffusion tensor imaging in medial temporal lobe epilepsy with hippocampal sclerosis. *Neuroimage* 2005;28:682–690.
8. Kimiwada T, Juhasz C, Makki M, Muzik O, Chugani DC, Asano E, Chugani HT. Hippocampal and thalamic diffusion abnormalities in children with temporal lobe epilepsy. *Epilepsia* 2006;47:167–175.
9. Rossi MA, Stebbins G, Murphy C, Greene D, Brinker S, Sarcu D, Tenharmel A, Stoub T, Stein MA, Hoepfner TJ, Byrne RW, Moseley ME, Bammer RA, Bild S, Dennis J, Arnett N, Balabanove A, Bergen D, Kanner AM, Smith MC. Predicting white matter pathways for direct neurostimulation therapy. *Epilepsy Res* 2010;91:176–186.
10. Chu-Shore CJ, Caviness VS, Cash SS. Neural networks in the developing human brain. In: *Network Approaches to Diseases of the Brain*. (Bianchi MT, Caviness VS, Cash SS, eds.) Boston: Bentham Books, 2012:21–31.



American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.

Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships

Use this section to report 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.



American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today's Date: 8/28/2012
2. First Name Marvin Last Name Rossi Degree MD, PhD
3. Are you the Main Assigned Author? Yes No

If no, enter your name as co-author:

4. Manuscript/Article Title: Deep White Matter Integrity in Childhood Absence Epilepsy: Water Movement Tracked Through the Epileptic Circuit
5. Journal Issue you are submitting for: 12.6

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 checked="" type="checkbox"/>				
2. Consultancy	<input checked="" type="checkbox"/>				
3. Employment	<input checked="" type="checkbox"/>				
4. Expert testimony	<input checked="" type="checkbox"/>				
5. Grants/grants pending	<input checked="" type="checkbox"/>				
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>				
7. Payment for manuscript preparation.	<input checked="" type="checkbox"/>				
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>				
9. Royalties	<input checked="" type="checkbox"/>				
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>				
11. Stock/stock options	<input checked="" type="checkbox"/>				
12. Travel/accommodations/meeting expenses unrelated to activities listed.**	<input checked="" type="checkbox"/>				
13. Other (err on the side of full disclosure)	<input checked="" 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:

Marvin A Rossi MD, PhD

Thank you for your assistance.
Epilepsy Currents Editorial Board