# PEDIATRIC NEUROLOGY BRIEFS
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**J. GORDON MILLICHAP, M.D., F.R.C.P., EDITOR**

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## ELECTROENCEPHALOGRAPHY

### EEG AFTER FEBRILE SEIZURE IS PREDICTIVE OF EPILEPSY

Researchers in pediatric neurology and electroencephalography at the University of Yamanashi, Japan, studied the EEG in children referred within 7-20 days after a febrile seizure (FS), and determined the utility of localization of paroxysmal discharges as a predictor for subsequent epilepsy. Of 119 patients with FS, 26 (21.8%) had paroxysmal abnormalities in the EEG and 9 (7.6%) patients developed epilepsy. Patients with complex FS (n=20, 17%) had a significantly higher risk of development of epilepsy than those with simple FS (n=99, 83%); $p<0.05$; they also had a higher incidence of abnormal EEGs (9/20, [45%], vs 17/99, [17%]; $p<0.05$). Patients with EEG abnormality had a significantly higher risk of development of epilepsy than those without EEG abnormality ($p<0.01$). Risk of epilepsy varied with the localization of paroxysmal discharge: 10% in children with generalized paroxysmal spike and wave activity; 28.5% with rolandic discharges; 75% with frontal paroxysms; and none with occipital paroxysmal discharges. Compared with generalized EEG foci, the relative risk for development of epilepsy in children presenting with frontal foci was 27.0, and significantly higher than those with paroxysms in other regions ($p<0.035$). Serial EEG is recommended in FS patients showing frontal paroxysmal EEG abnormalities. (Kanemura H, Mizorogi S, Aoyagi K, Sugita K, Aihara M. EEG characteristics predict subsequent epilepsy in children with febrile seizure. **Brain Dev** April 2012;34:302-307). (Respond: Hideaki Kanemura MD, Department of Pediatrics, University of Yamanashi, 1110 Chuo, Yamanashi 409-3898, Japan. E-mail: ykimu@yamanashi.ac.jp).

COMMENT. The electroencephalogram is not included in the American Academy of Pediatrics guidelines for the neurodiagnostic evaluation of the child with a first simple FS (AAP. **Pediatrics** 1996;97:769-775). In contrast, several reports have documented the value of the EEG in prediction of the development of recurrent afebrile

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seizures and epilepsy following a complex FS (see **Pediatr Neurol Briefs** August 2011;25(8):59). The risk of epilepsy following a simple FS is about 2% (Nelson KB, Ellenberg JH. **N Engl J Med** 1976;295:1029-1033) whereas the risk following a complex FS in a child with developmental delay is 9.2% (Hesdorffer DC et al. **Ann Neurol** 2011;70(1):93-100). In children with normal development and simple FS, the risk is only 1.1% but significantly greater than for healthy children with no FS (0.5%; p=0.027). In a prospective study of 428 children with a first FS followed for 2 years or more, unprovoked seizures occurred in 26 (6%). Risk factors for unprovoked seizures included neurodevelopmental abnormalities, complex FS, a family history of epilepsy, recurrent FS, and brief duration of fever before initial FS. (Berg AT, Shinnar S. **Neurology** 1996;47(2):562-568).

A review of the literature from 1947 to 1964 uncovered 36 publications in which the EEG findings were reported in relation to FS and 23 included number and percent with paroxysmal discharges (mean 25%). (Millichap JG. **Febrile Convulsions**. New York, Macmillan, 1968). In our prospective 2-year follow-up study of 76 FS patients with EEGs, paroxysmal discharges were recorded in 18 (24%); they were more frequent in patients who developed non-FS (61%) than in those with FS alone (12%). The discharges were generalized in 11 patients and focal in 7 (Millichap JG et al. **Neurology** 1960;10:643-653). Age was a significant factor in relation to the incidence of abnormal EEGs; patients with abnormal records were 3-10 years (mean 7 years) old and those with normal records were 1-7 years (mean 3 years) old. In her extensive investigations of the EEG and FS, Lennox MA also reported that paroxysmal records occurred mainly in children 5 years or older (**Amer J Dis Child** 1949;78:868-882). Repeated EEGs at follow-up subsequent to a FS were recommended to determine prognosis and risk of nonfebrile seizures. The present study concludes with a similar recommendation, but more specifically in patients with EEG showing frontal paroxysmal foci.

## NONCONVULSIVE ELECTROGRAPHIC STATUS EPILEPTICUS

Researchers at the University of Cincinnati, OH, examined medical records of 75 children, aged 3 months to 21 years (mean age 7.8 years), for prevalence of nonconvulsive status epilepticus (NCSE) by searching a clinical EEG database (n=18) or consecutive inpatient EEG referrals for NCSE over an 8-month period (n=57). NCSE was identified in 26 patients (35%) and in 8 of 57 (14%) patients referred for possible NCSE (>50% from outside the ICU). An acute etiology for encephalopathy was determined in 31 of 75 (41%) patients; it was an extra CNS infection and fever in 12, CNS infection in 8, and hypoxia in 12. Less than half the patients with NCSE were critically ill; 4 NCSE patients (15%) died, and 8 (31%) had significant neurologic morbidity on discharge. Compared to patients identified with NCSE, of the 49 patients without NCSE, 4 (8%) died and 2 (4%) had neurologic morbidity. The majority of patients (15 of 26, 58%) identified with NCSE were in the neurology service. A clinical seizure was witnessed in 24 (92%) patients with NCSE. Of 57 patients with acute neuroimaging within 24 hours of EEG, 20 showed abnormalities including multifocal cortical edema and acute hydrocephalus. Clinical seizures and acute neuroimaging abnormality were associated with an 82% probability of NCSE. NCSE was accompanied by electrographic or electroclinical seizures within the first hour of monitoring; the median duration of

monitoring was 11.5 hours. Continuous EEG monitoring is recommended in children with acute encephalopathy. (Greiner HM, Holland K, Leach JL, Horn PS, Hershey AD, Rose DF. Nonconvulsive status epilepticus: the encephalopathic pediatric patient. **Pediatrics** March 2012;129(3):e748-55). (Respond: Hansel M Greiner MD, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, MLC 2015, Cincinnati, OH 45229. E-mail: hansel.greiner@cchmc.org).

COMMENT. Risk factors for NCSE in children include a prior clinical seizure and acute cortical imaging abnormality. When both of these variables were present, the probability of NCSE was high (82%). If NCSE is suspected, continuous EEG monitoring is important not only in high-risk neonates in the ICU but also in children and adolescents with disturbed consciousness and symptoms of encephalopathy. The Cincinnati investigators defined NCSE as continuous 30-minute electrographic seizure activity with non-convulsive clinical symptoms or repeated briefer electrographic seizures comprising at least 30 minutes of a 1-hour period (Greiner HM et al. 2012).

A NCSE etiological classification included metabolic disorders, coma, acute cerebral lesions, and preexisting epilepsy (Maganti R et al. **Epilepsy Behav** 2008;12(4):572-586). NCSE constitutes about 25-50% of all cases of status epilepticus. In comatose patients, NCSE diagnosis is often difficult and potentially fatal if untreated. The EEG may show a variety of rhythmic or periodic patterns, some of unclear significance. Of 19 pediatric patients with NCSE identified from the database of the Columbia University Epilepsy Center, 6 had periodic lateralized epileptiform discharges (PLEDS), and 1 had generalized PEDS. Periodic discharges were associated with worse outcome. (Tay SK et al. **Epilepsia** 2006;47(9):1504-1509). The most frequent etiology of NCSE in this study was acute hypoxic-ischemic encephalopathy (26%); other causes included metabolic (21%), infection (16%), AED change (16%), refractory epilepsy (11%), and intracranial hemorrhage (11%). Prompt recognition of NCSE by continuous EEG monitoring should lead to early treatment and improved prognosis.

## HIGH-FREQUENCY EEG OSCILLATIONS: NEW BIOMARKER IN EPILEPSY

Researchers at University Medical Center Utrecht, The Netherlands and other centers review the pathophysiology, clinical relevance, identification, and interpretation of high-frequency oscillations (HFOs, >80Hz) in the epileptic EEG. HFOs are further classified in ripples (80-250Hz), fast ripples (250-600Hz), and very-HFOs (>1,000Hz). HFOs are observed between seizures, at seizure onset, and during seizures. Interictal HFOs occur during slow-wave sleep. The intracranial EEG is sampled at =/> 2,000Hz. In patients with focal epilepsy who may benefit from surgery, removal of brain tissue generating HFOs results in better outcome than removal of the seizure onset zone. Interictal HFOs are reliable markers of the seizure onset zone, and better than epileptic spikes. HFOs occur in different types of epilepsy, mesiotemporal with hippocampal sclerosis and also in extratemporal epilepsies with tumors, focal cortical dysplasia, and nodular heterotopia. HFOs are sometimes recorded in nonlesional epilepsies. Evaluation of seizures with HFO recordings >80Hz may improve the pre-surgical workup and outcome and reduce the necessity for invasive monitoring. (Zijlmans M, Jiruska P,

Zelmann R, Leijten FSS, Jeffreys JGR, Gotman J. High-frequency oscillations as a new biomarker for epilepsy. **Ann Neurol** February 2012;71:169-178). (Respond: Dr Zijlmans, Department of Neurology and Neurosurgery, University Medical Center Utrecht, The Netherlands. E-mail: g.j.m.zijlmans@umcutrecht.nl).

COMMENT. Methods used to determine the extent of epileptic foci of brain tissue before and during cortical resection include EEG telemetry, ECoG, MRI, histological, and immunohistochemical. Tissue markers of epileptic foci include mitochondrial "hypermetabolic" neurons and a-B-crystallin (Sarnat HB et al. **Can J Neurol Sci** 2011;38(6):909-17)(Sarnat HB, Flores-Sarnat L. *ibid.* 2009;36(5):566-74) (**Pediatr Neurol Briefs** 2012;26(1):5-6)(*ibid.* 2009;23(11);81-82). The Annals review provides a comprehensive account of the utility of HSOs as a biomarker of epileptogenesis.

HSOs are studied primarily in mesiotemporal epilepsies. In a series of 30 consecutive pediatric patients at UCLA undergoing surgery for refractory epilepsy due mainly to extratemporal lesions, ECoGs were recorded at 2,000Hz and visually inspected for fast ripples (FR 250-500Hz). FR episodes were identified in ECoGs from 24 patients (80%); FR-containing cortex was removed in 19 and all became seizure-free. FR-containing cortex was found outside of abnormalities defined by MRI and FDG-PET in 6 children. The authors conclude that interictal fast ripples are an excellent surrogate marker of epileptogenesis. (Wu JY et al. **Neurology** 2010;75(19):1686-94).

## EEG PATTERNS AND GENOTYPES IN ANGELMAN SYNDROME

Researchers at the Children's Hospital, Boston, other centers in the US, and Poznan University, Poland, prospectively analyzed EEGs from participants in the NIH Angelman Syndrome Natural History Study. Of 160 enrolled patients (2006-2010), 115 had complete data (58 boys, median age 3.6 years). EEG findings included intermittent rhythmic delta waves (83.5%), interictal epileptiform discharges (74.2%), intermittent rhythmic theta waves (43.5%), and posterior rhythm slowing (43.5%). Centro-occipital and centro-temporal delta waves decreased with age (p=0.01 and 0.03), and EEG patterns are age-dependent. EEG patterns and seizure types were not correlated significantly with genotypes. Using a classification tree to predict specific genotypes based on EEG features, deletions class-2 (5.0Mb) were associated with >50% intermittent rhythmic theta activity, and deletions class-1 (5.9Mb) with <50% intermittent rhythmic theta activity and epileptiform discharges while awake. EEG patterns are important biomarkers in Angelman syndrome and may suggest the underlying genetic etiology. (Vendrame M, Loddenkemper T, Zarowski M, et al. Analysis of EEG patterns and genotypes in patients with Angelman syndrome. **Epilepsy Behav** March 2012;23:261-265).(Response: Dr Sanjeev V Kothare, Children's Hospital Boston, Fegan 9, 300 Longwood Ave, Boston, MA 02115. E-mail: Sanjeev.Kothare@childrens.harvard.edu).

COMMENT. Boyd SG and colleagues at Great Ormond Street Children's Hospital, London, UK first described EEG patterns that were considered characteristic of Angelman syndrome: 1) Persistent rhythmic 4-6/s activity (>200mcV) while awake; 2) prolonged runs of rhythmic 2-3/sec activity (200-500 mcV) anteriorly; and 3) spikes

mixed with 3-4/s waves (>200 mcV) posteriorly, mainly with eye-closure. Discharges mixed with slow components on eye-closure was the most frequent finding in patients aged 11 months to >12 years. (Boyd SG et al. **Eur J Pediatr** 1988;147:508-513). Six children had no history of seizures and the EEG features helped identify patients at an early age.

The EEG findings in the present report are comparable to those of Boyd, and a notched delta pattern, also characteristic of Angelman syndrome, is found in patients presenting <4 years of age. Researchers at the Epilepsy Center, Children's Memorial Hospital, Chicago, evaluated the notched delta pattern in diagnosis of patients with a suggestive phenotype of Angelman syndrome. A retrospective review of video-EEG recordings with notched delta pattern found 38% specificity for Angelman syndrome. (Korff CM, Kelley KR, Nordli DR. **J Clin Neurophysiol** 2005;22(4):238-243).

# INFECTIOUS DISEASES

## EPILEPTOGENESIS IN CALCIFIED NEUROCYSTICERCOSIS

Researchers at Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India, and University of Texas Medical School at Houston performed dynamic contrast-enhanced (DCE) MRI and determined serum matrix metalloproteinase-9 (MMP-9) levels and MMP-9 gene polymorphisms in 30 subjects with a single calcified lesion of neurocysticercosis without any perilesional abnormality. These measures showed significant differences between 2 groups, each containing 15 patients, one with and one without seizures. In symptomatic subjects, serum MMP-9 levels and MMP-9 gene polymorphisms, the determinants of blood brain barrier permeability, were significantly higher compared with asymptomatic subjects with calcified cysticercus lesions and controls. There may be different degrees of perilesional inflammation with similar MRI calcified neurocysticercosis lesions in patients with or without seizures. The subject's threshold of inflammation probably determines the occurrence of seizures. (Gupta RK, Awasthi R, Rathore RKS, et al. Understanding epileptogenesis in calcified neurocysticercosis with perfusion MRI. **Neurology** Feb 28, 2012;78:618-625). (Response and reprints. Prof Gupta: E-mail: rgupta@sgpgi.ac.in).

COMMENT. Albendazole and praziquantel, the two antiparasitic drugs used in treatment of neurocysticercosis, hasten radiologic resolution of cysts but may exacerbate the seizures resulting from the host inflammatory response. In patients with single inflamed brain parenchymal cysts, treatment is often withheld and is controversial. Approximately 10-20% of single cysticercal granuloma heal by calcification, and these patients are at higher risk of developing epilepsy (Rathore C et al. Editorial. **Neurology** 2012;78:612-613). Treatment is usually recommended for patients with nonenhancing or multiple cysticerci, and coadministration of corticosteroids for the first 2 or 3 days of therapy may decrease adverse effects. Arachnoiditis, vasculitis, or diffuse cerebral edema (cysticercal encephalitis) is treated with corticosteroids and albendazole or praziquantel. Anticonvulsant treatment is recommended until seizures are controlled for 1 to 2 years and there is radiological evidence of resolution. Calcified cysts usually require indefinite anticonvulsant therapy. Neurosurgery is indicated in patients with single intraventricular

cysts and hydrocephalus. An ocular cyst should be ruled out before treatment with albendazole that may exacerbate inflammation. (American Academy of Pediatrics **Red Book**, 27th ed, Elk Grove Village, IL, AAP, 2006, pp 646-7).

## LYME NEUROBORRELIOSIS AND ALICE IN WONDERLAND SYNDROME

Pediatric neurologists at the Floating Hospital, Tufts University, Boston, MA report a 7-year-old boy with Alice in Wonderland syndrome associated with Lyme disease. He initially awakened with a nightmare, scared and screaming, saying that "his mind was running fast" and he heard "baseball fans cheering." He vomited the following day but had no headache. Three nights later he awoke, went down stairs, and was pale and scared. He had repetitive swallowing and lip-smacking and said "my head is running fast." Next evening while reading, the book appeared to be a distance away, and he said the letters were becoming smaller.

During 36 hours of video EEG recording he had 3 events of distorted perception, a feeling of becoming smaller and the book print farther away, none associated with evidence of seizure. A Lyme disease test at the 6th day, performed at the insistence of the mother, was positive. CSF revealed lymphocytes 22/mm3, protein 23/mg/dl, and glucose 63 mg/dl. Lyme disease Western blot immunoglobulin M on 10th day tested positive in serum and CSF. Lyme PCR on CSF was negative and MRI was normal. He was treated with IV ceftriaxone for 21 days, and symptoms resolved after 3 days. He had no rash and no recurrence at 12-month follow-up. No personal or family history of migraine or epilepsy was elicited. Alice in Wonderland syndrome, or metamorphopsia, should be added to the clinical spectrum of Lyme neuroborreliosis, and a high index of suspicion is required in diagnosis. (Binalsheikh IM, Griesemer D, Wang S, Alvarez-Altalef R. Lyme neuroborreliosis presenting as Alice in Wonderland syndrome. **Pediatr Neurol** March 2012;46;185-186). (Response: Dr Binalsheikh. E-mail: alsheikh55@yahoo.com).

COMMENT. "Curiouser and curiouser!" said Alice, when she grew and expanded like a telescope after eating the cake. Distortions of form, size, movement, color, or sense of time are characteristic of metamorphopsia that may occur as a sensory aura during migraine or frontal lobe epilepsy. A PubMed literature search lists reports of several infectious agents associated with Alice in Wonderland syndrome, including Epstein-Barr virus, varicella, coxsackievirus B1, H1N1 influenza virus, and infectious mononucleosis. Lyme disease in the Tufts' case presents with visual and other illusions without systemic manifestations of neuroborreliosis. Alice in Wonderland syndrome is a benign disorder of childhood caused most frequently by migraine or Epstein-Barr virus infection. (Losada-Del Pozo R et al. **Rev Neurol** 2011;53(11):641-648).

# CEREBRAL MALFORMATIONS

## HEMORRHAGE RISK OF CAVERNOUS MALFORMATION

Researchers at the Mayo Clinic, Rochester, MN reviewed the records and radiograph data of 292 patients (47.3% male) seen between 1989 and 1999 with a

diagnosis of intracerebral cavernous malformation (ICM). The mean age at diagnosis was 45.8 years (range 3.5-88.9 years). Seventy-four patients presented with hemorrhage, 108 with seizure or focal deficit (symptoms not related to hemorrhage), and 110 were asymptomatic. The overall annual rate of hemorrhage at follow-up in the patients grouped according to presenting symptoms was 6.19%, 2.18%, and 0.33%, respectively. The median length of follow-up was 7.3 years (range 0-25 years); 68 patients underwent surgical excision. Patients who presented initially with symptomatic hemorrhage were at higher risk for future hemorrhage ($p<0.001$), and hemorrhage risk decreased with time; 81% were free of prospective hemorrhage at 10.6 years. Of 32 patients with prospective symptomatic hemorrhage, 19 (59%) initially presented with hemorrhage. The annual statistically significant risk factors for prospective hemorrhage included younger age ($p=0.02$) (without adjustment for gender etc.), male gender ($p=0.02$), infratentorial location ($p=0.015$), initial presentation as hemorrhage ($p<0.001$), and multiplicity of ICMs ($p=0.01$). Pregnancy was not a risk factor. The median time from first to second hemorrhage was 8 months. (Flemming KD, Link MJ, Christianson TJH, Brown RD Jr. Prospective hemorrhage risk of intracerebral cavernous malformations. **Neurology** Feb 2012;78:632-636). (Response: Dr Flemming. E-mail: flemming.kelly@mayo.edu).

COMMENT. In an editorial, Salman and Murray question whether a risk of re-bleeding of 10-20% in the first 2 years of follow-up of cavernous malformations warrants early neurosurgical excision. (Salman RA, Murray GD. **Neurology** 2012;78:614-615). This question is addressed in the following studies in Switzerland.

In a multicenter study of 79 pediatric patients with cerebral cavernous malformation (CCM) treated by surgical resection at University Hospital, Zurich, 77.3% became seizure free. Resection was the treatment of choice if lesions caused medically refractory epilepsy or other persistent symptoms. (Hugelshofer M, et al. **J Neurosurg Pediatr** 2011;8(5):522-525). Mean age at presentation was 9.7 years, and mean age at operation was 11.3 years. One-quarter of all CCMs affect children.

In a study of outcome of 20 children with CCM treated in Berne, Switzerland, average age at presentation was 8.5 years (range 7 months to 16 years). Presentation was acute hemorrhage in 17 (85%), seizures in 9 (45%), focal neurologic symptoms in 5 (25%), and headache only in 3 (15%). Location was supratentorial in 15 (75%). Treatment was conservative in 10 and surgical in 10. Neurological sequelae at follow-up (0.5-10 years) occurred in 6 (30%) patients. (Bigi S et al. **Eur J Pediatr Neurol** 2011;15(2):109-116).

A study of the natural history of CCM in 92 children and young adults at the University of Michigan, Ann Arbor, found the imaging prevalence of CCM increased with advancing age ($p=0.002$). Multiple CMs occurred in 28 (30%) patients. Thirty patients presented with hemorrhage, and the hemorrhage rate was 8% per patient-year in the symptomatic group. Symptomatic hemorrhage after long-term follow-up was associated with initial acute hemorrhage ($p=0.02$). (Al-Holou WN et al. **J Neurosurg Pediatr** 2012;9(2):198-205).

A prospective, Scotland, population-based cohort study of 139 adults with CCM, radiologically validated, found the risk of recurrent intracranial hemorrhage or focal neurological deficit from a CCM is greater than the risk of a first event, greater for women than for men ($p=0.01$), and declines over 5 years from 9.8% in year 1 to 5.0% in

year 5. (Salman R A-S et al. **Lancet Neurol** March 2012;11:217-224). The increased risk in women in this study of adults only is different from that in the Mayo Clinic study showing a preponderant risk in males.

## SECKEL SYNDROME WITH HOLOPROSENCEPHALY

A case of Seckel syndrome (SS) accompanied by semilobar holoprosencephaly and arthrogryposis is reported from Erciyes University, Kayseri, Turkey. Seckel syndrome is a rare autosomal recessive disorder characterized by prenatal and postnatal growth retardation, microcephaly, and "bird-like" face with prominent, beak-like nose and micrognathia. A 1-day-old female newborn was admitted with dysmorphic features and feeding difficulties. The parents were consanguineous. In addition to typical features of SS, the baby had arthrogryposis, and cranial MRI showed semilobar holoprosencephaly, lissencephaly/pachygyria, dilated occipital horn of the lateral ventricle, hypoplasia of the frontal horn, non-cleavage of the basal ganglia and frontal lobe, and dysgenesis of the corpus callosum. Neuronal migration disorders should be investigated in infants born with facial characteristics of SS. (Sarici DS, Akin MA, Kara A, Duganay S, Kurtoglu S. Seckel syndrome accompanied by semilobar holoprosencephaly. **Pediatr Neurol** March 2012;46:189-191). (Respond: Dr Sarici. E-mail: drdilekcoban@yahoo.com.tr).

COMMENT. Holoprosencephaly (HP) is presented as a new associated feature of SS. Based on grades of severity, this case is a semilobar form of HP. The mechanism of the facial dysmorphism in SS may be attributable to defective mesencephalic neural crest tissue formation (Sarnat HB, Flores-Sarnat L. **J Child Neurol** 2001;16;918-931).

# LEARNING DISABILITIES

## TRACTOGRAPHY NEUROANATOMICAL STUDY OF DYSLEXIA

Researchers at Catholic University of Leuven, Belgium used diffusion tensor imaging tractography, a structural MRI technique, to assess the integrity of white matter tracts involved in reading. Group comparisons of 20 adults with dyslexia and 20 typical reading adults showed a significantly reduced fractional anisotropy (i.e. an index of the amount of anisotropy) in the left arcuate fasciculus of dyslexics, reflecting reduced myelination. Performance on phoneme awareness and speech perception was specifically related to the integrity of the left arcuate fasciculus (dorsal phonological route underlying grapheme-phoneme decoding), whereas orthographic (direct word) processing was related to fractional anisotropy values in the left inferior fronto-occipital fasciculus (ventral orthographic route). Structural anomalies found in the left arcuate fasciculus of dyslexics corroborate the hypothesis of dyslexia as a disorder of network connections. (Vandermosten M et al. **Brain** 2012;135:935-948).(Response: M Vandermosten. E-mail: maaike.vandermosten@ppw.kuleuven.be).

COMMENT. Dyslexics have reduced white matter integrity in the component of the left arcuate fasciculus that links Wernicke's to Broca's area.