Networks underlying paroxysmal fast activity and slow spike and wave in Lennox-Gastaut syndrome

Neelan Pillay, MBChB,
FRCPC
John S. Archer, FRACP,
PhD
Radwa A.B. Badawy,
MBBCh, PhD
Danny F. Flanagan, PhD
Samuel F. Berkovic, MD,
FRACP
Graeme Jackson, BSc
(Hons), MD, FRACP

Correspondence to
Dr. Jackson:
gjackson@brain.org.au

ABSTRACT

Objective: To use EEG-fMRI to determine which structures are critically involved in the generation of paroxysmal fast activity (PFA) and slow spike and wave (SSW) (1.5–2.5 Hz), the characteristic interictal discharges of Lennox-Gastaut syndrome (LGS).

Methods: We studied 13 well-characterized patients with LGS using structural imaging and EEG-fMRI at 3 tesla. Ten patients had cortical structural abnormalities. PFA and SSW were considered as separate events in the fMRI analysis.

Results: Simultaneous with fMRI, PFA was recorded in 6 patients and SSW in 9 (in 2, both were recorded). PFA events showed almost uniform increases in blood oxygen level-dependent (BOLD) signal in “association” cortical areas, as well as brainstem, basal ganglia, and thalamus. SSW showed a different pattern of BOLD signal change with many areas of decreased BOLD signal, mostly in primary cortical areas. Two patients with prior callosotomy had lateralized as well as generalized PFA. The lateralized PFA was associated with a hemispheric version of the PFA pattern we report here.

Conclusion: PFA is associated with activity in a diffuse network that includes association cortices as well as an unusual pattern of simultaneous activation of subcortical structures (brainstem, thalamus, and basal ganglia). By comparison, the SSW pattern is quite different, with cortical and subcortical activations and deactivations. Regardless of etiology, it appears that 2 key, but distinct, patterns of diffuse brain network involvement contribute to the defining electrophysiologic features of LGS.

Neurology® 2013;81:665–673

GLOSSARY

BOLD = blood oxygen level-dependent; **DANA** = diffuse association network activation; **GGE** = genetic generalized epilepsy; **GSW** = generalized spike and wave; **IED** = interictal epileptiform discharge; **LGS** = Lennox-Gastaut syndrome; **MCD** = malformations of cortical development; **PFA** = paroxysmal fast activity; **SPM** = Statistical Parametric Mapping; **SSW** = slow spike and wave; **VEM** = video EEG monitoring.

Lennox-Gastaut syndrome (LGS) is a severe childhood-onset epilepsy syndrome.¹ The generalized seizures of LGS include tonic, tonic-clonic, and atypical absences, while the characteristic and defining interictal discharges are generalized paroxysmal fast activity (PFA) and slow spike and wave (SSW) (1.5–2.5 Hz). Most patients have intellectual disability.^{2–4}

The generalized nature of the electroclinical features associated with this syndrome has suggested it may be secondary to diffuse brain pathologies. However, in a proportion of patients, a structural abnormality is identified that may be causative.⁵ The underlying networks involved in the generation of these epileptiform events are poorly understood—knowledge that is essential to further the neurobiological understanding and practical classification of such cases.

The simultaneous measurement of EEG and fMRI has a demonstrated ability to advance the understanding of brain regions involved in interictal epileptiform activity.^{6,7} EEG-fMRI studies have identified changes in blood oxygen level-dependent (BOLD) contrast related to focal^{8–12} and generalized epileptiform activity.^{13–18}

Supplemental data at
www.neurology.org

From the Brain Research Institute (N.P., J.S.A., R.A.B.B., D.F.F., G.J.), Florey Institute of Neuroscience and Mental Health; Department of Neurology (J.S.A., R.A.B.B., S.F.B., G.J.), Austin Health, Heidelberg; Epilepsy Research Centre (J.S.A., R.A.B.B., S.F.B., G.J.), Department of Medicine, University of Melbourne, Australia; and Department of Clinical Neurosciences (N.P.), Foothills Medical Centre, University of Calgary, Canada.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

We studied a cohort of patients with EEG-fMRI at high field (3 tesla), seeking to characterize the patterns of BOLD signal changes associated with the 2 interictal discharges that are characteristic for LGS (SSW and PFA) in order to investigate the following: 1) the spatial extent of cortical brain activity changes (both increases and decreases) associated with each of those 2 types of discharges (PFA and SSW); and 2) the extent of involvement of thalamic and other subcortical structures, including brainstem, in each of these discharge types.

METHODS Patients. All patients for this study were recruited from the Epilepsy Clinics and Comprehensive Epilepsy Program of Austin Health (Melbourne, Australia). Thirteen patients (5 women, mean age 35 years, range 25–52 years) fulfilling the criteria of an electroclinical diagnosis of LGS were recruited.^{1,19} Criteria included a) childhood onset, b) tonic seizures, c) developmental delay, and d) routine EEGs and/or video EEG monitoring (VEM) showing PFA and/or SSW.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Austin Health Human Research Ethics Committee, and informed written consent was obtained from all patients and, when appointed, their legal guardian. All patients were able to understand and cooperate with the imaging and simultaneous EEG procedures.

EEG recording. EEG and MRI were performed as described in our previous studies.^{15,20} No sedatives were administered for the procedure. Recording was in the “10–20” format. EEG was acquired using our in-house system. Magnetic resonance gradient artifacts were removed from the EEG signal offline, and ballistocardiogram and movement artifacts were reduced using head-movement detection coils.²¹ Real-time display, filtering, and recording were performed using software developed in-house. The entire recording was conducted without activation procedures, and patients were encouraged to sleep.

MRI acquisitions. fMRI data were obtained using a 3-tesla GE Signa LX whole-body scanner (General Electric, Milwaukee, WI) with continuous acquisition of gradient-recalled echo planar image volumes (repetition time = 3,200 milliseconds, echo time = 40 milliseconds, flip angle = 80° with axial oblique slices 3.2 mm thick + 0.2-mm gap, 22-cm field of view, 64 × 64 matrix). Conventional 3-tesla structural T1 and T2 images were acquired in all cases.

Data analysis. EEG. Prior EEGs from routine and long-term VEM records were available for comparison of morphology and field distribution of interictal epileptiform discharges (IEDs). The EEG was analyzed offline independently by 2 experienced EEG reviewers (N.P., D.F.) and then together for consensus for acceptance or rejection of IEDs. The EEG was reviewed in bipolar and referential montages. The IEDs were categorized into SSW, PFA, and focal IEDs to allow separate fMRI event-related activation maps.

Electrographic and clinical seizure events identified on the EEG were also marked but treated as events of no interest for the purposes of this analysis. Events with significant motion, as measured with our highly sensitive in-house motion coils,²¹ were also excluded to avoid contamination of activation maps by motion artifact.

fMRI analysis. fMRI data were preprocessed and analyzed using Statistical Parametric Mapping (SPM)8b (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8b/>). Data preprocessing was performed,²² and motion was modeled.²³ We formed 24 regressors using a truncated Volterra expansion of the motion parameters²⁴—specifically, linear and quadratic terms of the 6 motion parameters in both the current and previous scans. Spatial smoothing was with a 6-mm isotropic Gaussian kernel for individual studies and 8 mm for group analysis. We used standard fMRI event-related analysis, with the annotations on the study EEG used to determine onset and duration of events. The SPM hemodynamic response function was used to model event-related BOLD signal changes. Regional increases and decreases in BOLD signal changes associated with epileptiform events were determined using 1-tailed *t* tests. Individual voxels were thresholded at $p < 0.01$ (uncorrected), and clusters of voxels were identified in the SPMs when their extent size was significant at a threshold of $p < 0.025$ with a correction for multiple comparisons (equivalent to $p < 0.05$, 2-tailed).

Penetration maps. These were constructed by overlaying all results from the group. The color scale represents how many of the subjects had activation above the threshold p value. For example, all subjects showing above-threshold positive values would be yellow, all subjects showing above-threshold negative values green. This approach shows areas of activation frequently seen in the group, although it is not a formal statistical approach.

RESULTS Subjects. Epilepsy onset was before 8 years of age in 10 of 13 cases (table). All 13 patients had tonic seizures on history and 11 had documented tonic seizures on routine EEG or VEM. All patients were intellectually disabled, and despite this, tolerated the study remarkably well, usually falling asleep in the scanner. Nine patients completed the 1-hour EEG-fMRI scan, and 3 more tolerated more than 30 minutes of the EEG-fMRI scan.

Structural abnormalities. In 10 patients (77%), MRI was abnormal (malformations of cortical development [MCD] in 5). The lesions in this group varied greatly considering the similar epilepsy phenotype. Focal developmental and traumatic lesions were common (figure 1, A–C). In patients 1 and 3, we found clear structural lesions that had not been previously identified, an important consideration in older patients with spoiled gradient-echo imaging who may not have been imaged in their early years, and who were subsequently institutionalized and conservatively managed.

Interictal discharges. A total of 21 datasets were obtained from the 13 patients: some had more than one type of epileptiform discharge (see table). Most patients had 1 or 2 IED categories recognized during their EEG-fMRI studies. Six patients had PFA recorded for analysis and 9 had SSWs (table). Focal or multifocal sharp waves were identified in 2 patients. For each subject, we calculated the total time in the study during which epileptiform events were seen. This was done by measuring the duration of each event marked in the EEG and adding all these times

Table Clinical, imaging, and electrophysiologic data					
Patient no.	Onset age (age studied), y	Seizure types, clinical and VEM	Etiology	MRI findings	Discharge types ^a during EEG-fMRI (s)
1	7 (42)	Tonic	MCD	R frontal dysplasia	PFA (37)
		Absence			SSW (48)
		GTC			
2	10 (37)	Tonic	Unknown	Normal	PFA (42)
		Atonic			SSW (91)
		Absence			
3	6 (40)	Tonic	MCD	L parietal transmantle dysplasia	PFA (30)
		Absence			
		GTC			
4	13 (40)	Tonic	Unknown	Normal, post-CC	PFA bilateral (59)
		Absence			PFA L (9)
		GTC			PFA R (20)
					Focal L (39)
					Focal R (15)
5	3 (40)	Tonic	MCD	Lissencephaly maximum posterior	SSW (563)
		Absence			
		GTC			
		Myoclonic			
6	0.3 (41)	Tonic	HIE	Diffuse cerebral atrophy	SSW (27)
		Absence			
		GTC			
7	6 (52)	Tonic	MCD	Lissencephaly maximum anterior	SSW (52)
		Absence			
		Myoclonic			
8	4 (43)	Tonic	MCD	Abnormal gyral pattern	SSW (46)
		Absence			
		GTC			
9	0.3 (27)	Tonic	HIE	Bilateral parietal and perirolandic encephalomalacia	SSW (6)
		Absence			
		GTC			
10	3 (42)	Tonic	TBI	L frontal gliosis posttraumatic	SSW (4)
		Absence			
		GTC			
11	3 (35)	Tonic	MCD	R frontal	PFA (28)
		Absence		Post-ATL L	PFA R (22)
		Myoclonic		Post-CC	PFA L (18)
12	12 (45)	Tonic	Unknown	Normal	PFA (6)
		Absence			
		GTC			
13	2 (25)	Tonic	MCD	Lissencephaly	SSW (4)
		Absence	Abnormal chromosome 2q37	Diffuse cortical atrophy	

Abbreviations: ATL = anterior temporal lobectomy; CC = corpus callosotomy; GTC = generalized tonic-clonic; HIE = hypoxic ischemic encephalopathy; MCD = malformations of cortical development; PFA = paroxysmal fast activity; SSW = slow spike and wave; TBI = traumatic brain injury; VEM = video EEG monitoring. ^aThe discharge types recorded simultaneous with fMRI (last column) are shown. The number given in seconds is the sum of the length of all individual epileptiform events recorded during the EEG. This reflects the power of the study and provides a guide for interpretation of the robustness of the result. Individual events are typically short discharges on the order of a few seconds and relate to this result by how frequently they occurred.

(A) Patient 1: coronal T1-weighted image showing right frontal cortical dysplasia (arrow) and a sample of PFA (left EEG panel in A) and SSW (right EEG panel in A) recorded during the fMRI acquisition. (B) Patient 3: coronal T1-weighted image showing left transmantle cortical dysplasia (arrow) and a sample of PFA. (C) Patient 5: axial T1-weighted image showing diffuse bilateral posterior cortical dysplasia and a sample of SSW recorded. (D) Patient 7: sagittal T1-weighted image showing diffuse frontal cortical dysplasia and lissencephaly and a sample of SSW recorded. Time scale can be seen in the figure; sensitivity was optimized to demonstrate the discharges for each subject. PFA = paroxysmal fast activity; SSW = slow spike and wave.

together. A study with frequent events has many seconds of events in the analysis, and a study with infrequent events may only have a few seconds of data in which epileptiform activity occurred (table; also listed in the figures).

Paroxysmal fast activity. In all 6 patients with PFA, the cortical BOLD signal change was almost exclusively positive. The penetrance map shows the distribution of this activation (figure 2A; individual cases are shown in figure e-1 on the *Neurology*[®] Web site at www.neurology.org). PFA-related BOLD increases predominately affected broad cortical “association” areas in the frontal, parietal occipital, and temporal lobes but appeared not to involve the primary cortices.

In 5 of these 6 PFA datasets, there was BOLD signal increase in the thalamus. Increased BOLD signal in the caudate and basal ganglia was also observed in 5 of 6 patients. When the pattern was unilateral or had a lateralized emphasis, the lateralization of the PFA and BOLD signal change correlated with the side of anatomical lesions, and the side of maximal thalamic involvement correlated with the side of maximal cortical changes.

The brainstem showed increased BOLD signals at subcollicular level in 4 of the 6 patients with PFA. Cerebellar activation was seen in the majority of subjects (5 of 6).

Good samples of both PFA as well as SSW were recorded in 2 subjects, and both of these individuals demonstrate the essential features of the pattern seen in the whole group (figure 3).

Slow spike and wave. SSW discharges were recorded in 9 patients. They were associated with a mixture of negative and positive cortical BOLD signal changes (figures 2, e-1, and e-2).

Unlike PFA, the cortical pattern in SSW was variable (figure e-2). Part of this is likely attributable to a limited amount of data (patients 9, 10, 13). Patients 6, 7, and 8 had weak activations that were difficult to interpret. Patients 1, 2, and 5 had strong activations that are best interpreted by reference to the penetrance map (figure 2). This shows that deactivation tended to be in primary cortical areas (motor, visual, and auditory) and midline parietal cortex. There were scattered positive activations in other areas of cortex, particularly some areas of frontal cortex.

Combined thresholded SPM “penetrance maps” for PFA (A) and SSW (B) showing the overall pattern of cortical and subcortical activation and deactivation for these epileptiform events. The color scale represents the number of subjects with significant activation in that voxel (yellow is above threshold voxels for all 6 subjects with PFA and 9 for SSW). Increases in BOLD signal are shown in warm colors and decreases in cool colors. There is no BOLD response of the primary cortical areas in PFA; primary motor, visual, and auditory cortex (arrows) show no activated or deactivated voxels, while all these areas show decreased BOLD during SSW (similarly oriented arrows in B). In association cortex (e.g., arrowhead in parietal cortex) there is strong activation during SSW and no change in BOLD during PFA. This is true of all association areas except some areas of frontal cortex that show deactivation in the SSW. Subcortical structures, such as brainstem and caudate, show activation in PFA and deactivation in SSW. Despite more variability in individual results with SSW, overlaying all cases leads to this recognizable pattern. BOLD = blood oxygen level-dependent; PFA = paroxysmal fast activity; SPM = Statistical Parametric Mapping; SSW = slow spike and wave.

BOLD signal changes in the thalamus were present in 4 patients. These were bilaterally positive in 2 (patients 1 and 5), bilaterally negative in one (patient 6), and positive changes on one side and negative changes on the other in one (patient 2).

There was reduced BOLD activity in the caudate in 4 patients and this is well seen in the penetrance map (figure 2). The brainstem showed BOLD signal change at subcollicular level in 4 patients (increased in 2 and decreased in 2).

Focal and lateralized discharges. Focal IEDs were recorded in 2 patients (patients 4 and 11 shown in figure e-2). Two independent foci were recorded in patient 4 (one right and one left). The focal discharges were associated with cortical activations that were concordant with the site of IEDs.

Two patients had prior corpus callosotomy (patients 4 and 11, figure 4). In these patients, PFA discharges variably showed a right- or left-hemisphere emphasis. These lateralized PFA discharges correspondingly produced a lateralized recruitment of the network we have described above.

DISCUSSION The chief finding in our study is that PFA and SSW (the 2 defining electrographic features

of LGS) have distinctive and markedly different patterns of cortical and subcortical BOLD signal changes. PFA shows a distinctive, diffuse, and consistent “activation” of many parts of the brain, particularly in association cortex (figure 2).

PFA shows activation across broad areas of cortex, but appears to spare the primary cortices. PFA shows increased BOLD signal in a number of subcortical structures including the thalamus, basal ganglia, and brainstem, all known to have broad connections to the “association cortices.” This observation of activation in many areas associated with association cortex and its subcortical system, but excluding primary cortex, has led us to call the network activation that we see in PFA “diffuse association network activation” (DANA). Furthermore, in most cases, differences in the left/right or anterior/posterior emphasis of the scalp discharges were reflected in the proportional left/right or anterior/posterior recruitment of this diffuse network.

For low-voltage fast activity (PFA) to be visible diffusely across the scalp EEG, there needs to be extensive “near-surface” cortical generation of this synchronous activity.^{25,26} The filtering effects of the scalp mean that faster frequencies will only be detected when their source is close to the recording electrodes. Consistent

Figure 3 Different patterns of PFA and SSW events in the same individuals

EEG-fMRI findings from the 2 patients in whom robust activation maps of both PFA and SSW were obtained. The number given in seconds in the figure is the sum of the length of all individual epileptiform events recorded during the EEG. This reflects the power of the study and provides a guide for interpretation of the robustness of the result. Individual events are typically short discharges on the order of a few seconds. This demonstrates that PFA and SSW are associated with these distinctive activation patterns (see figure 2) when seen at a group level and also within specific individual subjects, confirming that this is a fundamental difference in network behavior. PFA = paroxysmal fast activity; SSW = slow spike and wave.

with cortical generation of the EEG discharges, we found that widespread PFA correlates with intense and widespread cortical BOLD signal increase. This differs from the activation along with deactivation patterns hitherto described in genetic generalized epilepsy (GGE) and focal epilepsies.^{13–16,20,27–29} These discharges were not associated with movement as measured by our sensitive motion coils, which record even tiny in-magnet movements.

Our findings show some difference to a recent study of LGS,¹⁸ although this may be attributable to a difference in the IED classification as well as in the cohorts studied. That study reported that there was no consistent pattern associated with “polyspike” (the category they used that included PFA); however, they used a second-order group analysis on a small sample size, and this may have affected their interpretation. We did not attempt a second-order analysis because we were aware that we had insufficient data for that methodology, and instead chose the nonparametric penetrance map that leads us to identify a clear common pattern across our cohort. Using that method, we noted prominent thalamic activation associated with PFA. Siniatchkin et al.¹⁸ also found thalamic activation when they combined all IED categories (PFA and SSW), an approach that may have obscured the cortical changes we observed, which differ between the 2 discharge types. We acknowledge that we studied these patients as adults, after many years of seizures, which

may have affected the activation patterns. In PFA, we found basal ganglia (including caudate) and brainstem BOLD signal increase, and again the previous study also reported brainstem activation with combined event categories.¹⁸

It has been suggested that the combination of brainstem and thalamic activation may represent a common pathogenetic pathway from infantile spasms to LGS.¹⁸ Our results also imply that a distributed cortical network may be required for the rapid, high-frequency synchronization required to generate PFA. This DANA network differs from the network reported in generalized spike-and-wave discharges of GGE, where those discharges are typically accompanied by a decrease in BOLD signal in the caudate nuclei and brainstem.^{15,16,20,27}

SSW generated a clearly different pattern of BOLD signal change than PFA. The SSW pattern of deactivation in the posterior cingulate and precuneus also differs from the changes previously reported in the typical spike and wave of GGE.^{13–16,29–31} SSW in LGS is more irregular and asymmetrical and often less rhythmic and sustained compared with typical 3-Hz spike-wave discharges. While the overall EEG appearance of SSW may give an impression of homogeneous widespread generalized cortical activity, the inconsistent and patchy activations in our cases may reflect these well-known irregular EEG findings. SSW differed from typical generalized spike and wave (GSW)^{15,27,29} in

In this subject, there were independent focal left or right discharges, as well as diffuse PFA that had either left, right, or generalized or diffuse EEG lateralization. BOLD signal changes are impressively concordant with the accompanying EEG events. Focal EEG discharges show essentially focal activations whereas hemi-generalized discharges show lateralized diffuse association network activation, and generalized PFA shows essentially the pattern characteristic of the group result shown in figure 2. BOLD = blood oxygen level-dependent; PFA = paroxysmal fast activity.

several ways, including deactivation in the primary cortical areas, variability of the pattern, inconsistency of thalamic activation, and the occasional positive activation in caudate and basal ganglia. Further studies are needed to explore the reliability of these features.

The role of the thalamus in LGS has been less clear than in GGE, where there are several animal models of absence seizures and GSW discharges^{31,32} confirming that both the thalamus and primary cortical areas are involved in the typical 3-Hz spike-wave discharges observed on EEG.^{32,33} We found definite thalamic activation in only 4 cases with SSW, suggesting less robust thalamus involvement in the SSW of LGS. Interestingly, inconsistent thalamic involvement (only 55% of cases) in bilateral synchrony has also been reported.³⁴

Beyond the general findings associated with PFA and SSW in our cohort reported above, we also noted that in some patients, even though the EEG appeared to be generalized, the BOLD signal characteristics of discharges had lateralized features or even suggestions of focality. In all cases, these findings were concordant with the patient's EEG or structural findings. This suggests that cortical lesions can be activated along with this diffuse activation of the association networks (DANA),

possibly co-opting it as an epileptic network or at least engaging this system in the epileptic activity in LGS. EEG-fMRI maps may be showing both the DANA and an epileptogenic focus that is likely to drive the network instability. In the patients with LGS who had prior corpus callosotomy, predominately unilateral DANA changes were seen with unilateral PFA discharges. This suggests that the network in each hemisphere is capable of independently recruiting and sustaining this disturbed network activity in LGS (see figure e-2).

"Association cortex" is a relatively nonspecific term that includes much of the brain, and, indeed, PFA appears to diffusely activate most of these nonprimary cortical areas. It is characterized by cortico-cortical connections both directly and via the thalamus, as well as inputs from brainstem.³¹ Unlike the thalamic nuclei that receive peripheral sensory information and project to primary sensory cortices, projections to the association cortex from thalamus often originate in other regions of the cortex (e.g., the pulvinar to parietal association cortex and medial dorsal nucleus to frontal areas). This means that the association cortices could act as a network easily capable of engagement and activation by abnormal nonprimary cortex activity. It

should be noted here that the association cortex does not normally act as a single highly connected network as it appears in the PFA discharges—each area is defined by distinct, if overlapping and interacting, subsets of thalamic, cortico-cortical, and subcortical connections.³⁵

In conclusion, our results show distinctive patterns of BOLD signal changes with PFA and SSW. PFA shows positive activation in all parts of the association system including brainstem, thalamus, and association cortex. The presence of cortical structural pathologies in many of our patients implies an important role for cortex as the site of the primary pathology generating the LGS phenotype, particularly via input to association cortical networks. This includes involvement of the subcortical structures of the association system and this network is likely to be involved in epileptogenesis. DANA reflects pathologic engagement of brain functions that may partly explain the clinical phenotype of LGS. The defining feature of this involvement is that there is diffuse and apparently nonphysiologic simultaneous positive activation of association cortex and related subcortical structures (the “association network”) in PFA.

AUTHOR CONTRIBUTIONS

Dr. Pillay contributed to the design and conceptualization of the study, analysis and interpretation of the data, and drafting the manuscript for intellectual content. Dr. Archer, Dr. Badawy, and Dr. Flanagan contributed to analysis and interpretation of the data and revising the manuscript for intellectual content. Dr. Berkovic contributed to the design and conceptualization of the study, analysis and interpretation of the data, and revising the manuscript for intellectual content. Dr. Jackson contributed to the design and conceptualization of the study, analysis interpretation of the data, and drafting the manuscript for intellectual content.

ACKNOWLEDGMENT

The authors gratefully acknowledge Kate Stone and Shawna Farquharson for assistance in acquiring and collecting data for this study as well as the epileptologists at Austin Health for referral of patients and the patients themselves who were highly cooperative with the study.

STUDY FUNDING

Supported by the National Health and Medical Research Council of Australia Program grant (628952) and an NHMRC practitioner fellowship to G.J. (527800), NHMRC Project grants 368650, 318900, 628725, and the Operational Infrastructure Support Program of the State Government of Victoria, Australia.

DISCLOSURE

N. Pillay has served on scientific advisory boards for UCB, has received speaker honoraria from UCB, and has received unrestricted educational grants from UCB and Eisai. J. Archer, R. Badawy, and D. Flanagan report no disclosures. S. Berkovic has served on scientific advisory boards for UCB and Janssen-Cilag; may accrue future revenue on pending patent WO61/010176: therapeutic compound that relates to discovery of *PCDH19* gene as the cause of familial epilepsy with mental retardation limited to females; is one of the inventors listed on a patent held by Bionomics Inc. on diagnostic testing of using the *SCN1A* gene, international publication number WO2006/133508, filed June 16, 2006; has received speaker honoraria from UCB; has received unrestricted educational grants from UCB, Janssen-Cilag, and Sanofi-Aventis; and receives/has received research support from the National Health and Medical Research Council of Australia and National Institute of Neurological

Disorders and Stroke. G. Jackson receives royalties for publication of the book *Magnetic Resonance in Epilepsy*, Elsevier Inc. (2005), serves on the scientific advisory committee for NeuroSciences Victoria (NSV), and holds a provisional patent with the WIPO-2010 for the image processing system (WO2011106821). G. Jackson has received support from the following government entities: National Health and Medical Research Council, practitioner fellowship; National Health and Medical Research Council, program grant, ID 628952; National Health and Medical Research Council, project grant; NIH grant NS-R37-NS31146; and VNI program grant. Go to Neurology.org for full disclosures.

Received January 24, 2013. Accepted in final form April 26, 2013.

REFERENCES

1. Arzimanoglou A, French J, Blume WT, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *Lancet Neurol* 2009;8:82–93.
2. Dulac O, N'Guyen T. The Lennox-Gastaut syndrome. *Epilepsia* 1993;34:S7–S17.
3. Aicardi J. Syndromic classification in the management of childhood epilepsy. *J Child Neurol* 1994;9:14–18.
4. Blume WT. Pathogenesis of Lennox-Gastaut syndrome: considerations and hypotheses. *Epileptic Disord* 2001;3:183–196.
5. Bladin PF. Adult Lennox Gastaut syndrome: patients with large focal structural lesions. *Clin Exp Neurol* 1985;21:105–114.
6. Hamandi K, Salek-Haddadi A, Fish DR, Lemieux L. EEG/functional MRI in epilepsy: the Queen Square experience. *J Clin Neurophysiol* 2004;21:241–248.
7. Gotman J, Kobayashi E, Bagshaw AP, Benar CG, Dubeau F. Combining EEG and fMRI: a multimodal tool for epilepsy research. *J Magn Reson Imaging* 2006;23:906–920.
8. Krakow K, Woermann FG, Symms MR, et al. EEG-triggered functional MRI of interictal epileptiform activity in patients with partial seizures. *Brain* 1999;122(pt 9):1679–1688.
9. Al-Asmi A, Benar CG, Gross DW, et al. fMRI activation in continuous and spike-triggered EEG-fMRI studies of epileptic spikes. *Epilepsia* 2003;44:1328–1339.
10. Salek-Haddadi A, Diehl B, Hamandi K, et al. Hemodynamic correlates of epileptiform discharges: an EEG-fMRI study of 63 patients with focal epilepsy. *Brain Res* 2006;1088:148–166.
11. Kobayashi E, Bagshaw AP, Benar CG, et al. Temporal and extratemporal BOLD responses to temporal lobe interictal spikes. *Epilepsia* 2006;47:343–354.
12. Carney PW, Masterton RA, Flanagan D, Berkovic SF, Jackson GD. The frontal lobe in absence epilepsy: EEG-fMRI findings. *Neurology* 2012;78:1157–1165.
13. Aghakhani Y, Bagshaw AP, Benar CG, et al. fMRI activation during spike and wave discharges in idiopathic generalized epilepsy. *Brain* 2004;127:1127–1144.
14. Hamandi K, Laufs H, Noth U, Carmichael DW, Duncan JS, Lemieux L. BOLD and perfusion changes during epileptic generalised spike wave activity. *Neuroimage* 2008;39:608–618.
15. Archer JS, Abbott DF, Waites AB, Jackson GD. fMRI “deactivation” of the posterior cingulate during generalized spike and wave. *Neuroimage* 2003;20:1915–1922.
16. Gotman J, Grova C, Bagshaw A, Kobayashi E, Aghakhani Y, Dubeau F. Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. *Proc Natl Acad Sci USA* 2005;102:15236–15240.

17. Pillay N, Flanagan D, Abbott D, Jackson GD. Functional epilepsy networks: EEG-fMRI in secondary generalized epilepsy with Lennox Gastaut syndrome. *Epilepsia* 2008;49:398.
18. Siniatchkin M, Coropceanu D, Moeller F, Boor R, Stephani U. EEG-fMRI reveals activation of brainstem and thalamus in patients with Lennox-Gastaut syndrome. *Epilepsia* 2011;52:766–774.
19. Markand ON. Lennox-Gastaut syndrome (childhood epileptic encephalopathy). *J Clin Neurophysiol* 2003;20:426–441.
20. Carney PW, Masterton RA, Harvey AS, Scheffer IE, Berkovic SF, Jackson GD. The core network in absence epilepsy: differences in cortical and thalamic BOLD response. *Neurology* 2010;75:904–911.
21. Masterton RA, Abbott DF, Fleming SW, Jackson GD. Measurement and reduction of motion and ballistocardiogram artefacts from simultaneous EEG and fMRI recordings. *Neuroimage* 2007;37:202–211.
22. Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. *Magn Reson Med* 1996;35:346–355.
23. Lemieux L, Salek-Haddadi A, Lund TE, Laufs H, Carmichael D. Modelling large motion events in fMRI studies of patients with epilepsy. *Magn Reson Imaging* 2007;25:894–901.
24. Friston K, Stephan KM, Heather JD, et al. A multivariate analysis of evoked responses in EEG and MEG data. *Neuroimage* 1996;3:167–174.
25. Tao JX, Baldwin M, Hawes-Ebersole S, Ebersole JS. Cortical substrates of scalp EEG epileptiform discharges. *J Clin Neurophysiol* 2007;24:96–100.
26. Ebersole JS. Defining epileptogenic foci: past, present, future. *J Clin Neurophysiol* 1997;14:470–483.
27. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci USA* 2001;98:676–682.
28. Salek-Haddadi A, Lemieux L, Merschhemke M, Friston KJ, Duncan JS, Fish DR. Functional magnetic resonance imaging of human absence seizures. *Ann Neurol* 2003;53:663–667.
29. Laufs H, Lengler U, Hamandi K, Kleinschmidt A, Krakow K. Linking generalized spike-and-wave discharges and resting state brain activity by using EEG/fMRI in a patient with absence seizures. *Epilepsia* 2006;47:444–448.
30. Steriade M, Amzica F, Neckelmann D, Timofeev I. Spike-wave complexes and fast components of cortically generated seizures. II. Extra- and intracellular patterns. *J Neurophysiol* 1998;80:1456–1479.
31. Norden AD, Blumenfeld H. The role of subcortical structures in human epilepsy. *Epilepsy Behav* 2002;3:219–231.
32. Blumenfeld H. From molecules to networks: cortical/subcortical interactions in the pathophysiology of idiopathic generalized epilepsy. *Epilepsia* 2003;44:S7–S15.
33. McCormick DA, Contreras D. On the cellular and network bases of epileptic seizures. *Annu Rev Physiol* 2001;63:815–846.
34. Aghakhani Y, Kobayashi E, Bagshaw AP, et al. Cortical and thalamic fMRI responses in partial epilepsy with focal and bilateral synchronous spikes. *Clin Neurophysiol* 2006;117:177–191.
35. Schmahmann JD, Pandya DN, Wang R, et al. Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. *Brain* 2007;130:630–653.

17.5 CME Credits. 10% Savings.

The AAN Fall Conference—coming to the popular Encore Wynn Las Vegas October 25–27—is a unique opportunity to earn up to 17.5 *AMA PRA Category 1 credits*[™] before the end of the year.

Choose from:

- Neurology Update—save 10% when you register for the full program track!
- Practice Management—save 10% when you register for the full program track!
- Neuromuscular Disease Update
- Dystonia Workshop
- Physician-led Advocacy
- More!

Early registration deadline: October 1 / Hotel registration deadline: September 23

AAN 2013 Fall Conference: Convenient. Concise. Connected. Learn more and register now at www.AAN.com/view/2013fall