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Abstract—Using functional MRI (fMRI) with concurrent EEG monitoring the authors studied cortical activation associated with epileptiform discharges in three patients with fixation-off sensitivity. The EEG paroxysmal activity elicited by eliminating central vision correlated significantly with an increased blood oxygen level-dependent signal in the extrastriate cortex (Brodmann areas 19 and 37). fMRI provides a unique opportunity for localizing precisely the cortical areas generating paroxysmal activity in patients with fixation-off sensitivity.

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The increased blood flow related to neuronal activity can be detected with high spatial and temporal resolution by blood oxygen level-dependent functional MRI (BOLD fMRI).¹ First reported in 1994,² this technique is now used in epilepsy to study epileptiform activity during seizures and subclinical interictal discharges.^{3,4}

In patients with fixation-off sensitivity (FOS), the elimination of central vision and fixation induces EEG sustained occipital monolateral or bilateral high-amplitude spike waves that immediately subside with eye opening. FOS differs from scotosensitivity, a condition that denotes epilepsy or EEG abnormalities elicited by completely eliminating retinal stimulation by light. The cerebral mechanisms underlying FOS remain unclear.⁵ FOS provides an ideal natural model for BOLD fMRI mapping of epileptiform activity because it overcomes the common difficulties in studying epilepsy in humans, namely the unpredictability of discharges and the frequently associated clinical manifestations. Nevertheless, to our knowledge, only one patient with fMRI activation and one patient with PET activation during FOS discharges have been reported.^{6,7} In this study, we sought more precise information about the cerebral areas generating epileptiform discharges in patients with FOS.

Methods. *Patients.* We studied 3 female patients (Patients 1, 2, and 3; 25, 28, and 30 years old) with FOS. Since infancy each experienced seizures refractory to medications. Their EEG findings after eliminating central vision and fixation were characterized by sustained, high-amplitude, spike wave occipital activity. During FOS episodes, none of the patients experienced clinical symptoms; only Patient 3 sporadically perceived “weak lights” in the left visual field. Patients 1 and 2 had normal neuropsychological findings; Patient 3 achieved low scores for visual-

spatial tasks. The results of standard MRI scans, visual evoked potentials, and visual field perimetry were normal. Three healthy, age-matched subjects were studied as control subjects. All patients and control subjects gave informed consent, and research was approved by the local ethical committee.

Imaging. fMRI data were acquired with a 1.5-T magnet (Philips Gyroscan, the Netherlands). Head movements were minimized with foam padding and a restraining strap. T2*-weighted echoplanar images (64 × 64 matrix, over a 240 mm field of view) consisted of 25 consecutive axial sections (4-mm-thick, repetition time/echo time = 3000/50 milliseconds, flip angle 90°, and 1 single excitation). Each functional study consisted of multiple 15-second epochs of baseline (“off,” eyes open) and activation (“on,” eyes closed), in a boxcar configuration; a total 120 consecutive dynamics (3 seconds each) were acquired. During scanning, subjects closed and opened their eyes after verbal commands given through earphones.

For image processing and statistical analysis of the fMRI time series data, we used SPM99 (<http://www.fil.ion.ucl.ac.uk/spm>, Wellcome Department of Cognitive Neurology, London, UK). All images were realigned to the first, corrected for motion artifacts, normalized into the Montreal Neurologic Institute (MNI) stereotactic space⁸ and smoothed with an 8 mm full width at half maximum gaussian kernel. Activated voxels were identified with the general linear model approach for time series data,⁹ using a delayed boxcar model function specifically designed for each subject, and based on the epileptiform activity timing disclosed by the coregistered EEG (see below). Data for each individual then were analyzed to detect signal changes significantly related to the epileptiform phenomena elicited by eye closure. A *t*-statistic was used to determine significance on a voxel-by-voxel basis and the data were transformed into a normal distribution (Z statistic). Regions of condition-associated signal changes then were displayed with a statistical threshold based on the amplitude ($p < 0.05$, corrected for multiple comparisons) and extent ($p < 0.05$) of the regions of activation.⁹ Within them, the location of voxels with maximal signal increase was expressed in terms of x, y, and z in the MNI space.⁸

EEG coregistration. Throughout fMRI scanning, EEG signals were concurrently monitored using a 32-channel, MR-compatible cap (EBNeuro, Florence, Italy) with silver electrodes, connected to a nonmagnetic headbox. EEG digitized signals (sample rate 256 Hz) were transmitted to a digital recording system through a fiberoptic cable. During

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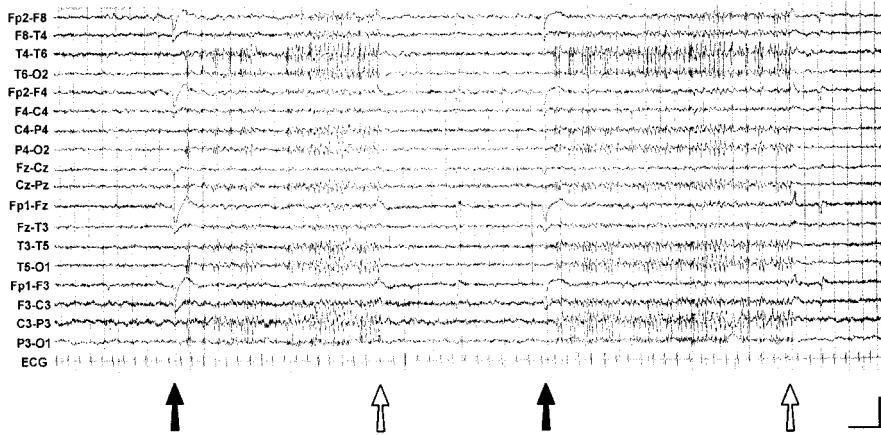


Figure 1. EEG recording of a representative subject (Patient 1). Eighteen EEG channels are displayed in longitudinal montage. The epileptiform activity, characterized by continuous spike-wave complexes (3.5 Hz), is located in the temporal-occipital regions bilaterally. Note the constant delay (approximately 1 second) between eye closure and the onset of paroxysmal activity. Black arrows indicate eye closure; white arrows indicate eye opening. Calibration = 2 seconds, 100 µV.

acquisition, the gradient-induced artifacts on EEG signal were removed by digital filtering. Eye movements were monitored by detecting the blink artifacts on the EEG recording.

Results. In all three patients, the quality of EEG monitoring during acquisition of fMRI data was sufficient to easily detect the epileptiform activity. The EEG signals typically showed sustained spike wave (2.5–3.5 Hz) occipital activity during eye closure (figure 1). In Patients 2 and 3, the epileptiform discharges involved the right hemisphere alone; in Patient 1, they were bilateral. Patients 1 and 2 had a steady delay of approximately 1 second between eye closure and the onset of paroxysmal activity (0.9 ± 0.3 second mean delay for Patient 1, 1.0 ± 0.2 seconds for Patient 2) (see figure 1). Conversely, in Patient 3, this delay varied between 1 and 6 seconds (2.3 ± 1.5 second mean delay). In all patients, the epileptiform discharges abruptly ceased immediately after eye reopening. The EEG signals recorded during the fMRI acquisition matched those of prescanning recordings and were of sufficiently good quality to easily identify the epileptiform activity (figure 2).

While in all three patients the “eyes open” condition induced the expected activation of primary visual areas, the “eyes closed” condition induced a significant occipital activation. Neither condition activated other brain areas (figure 3). The “eyes open” and “eyes closed” conditions both activated spatially separate brain areas. Eye closure activated cortical regions of the occipital lobe in and around Brodmann areas 19 and 37 (middle and inferior occipital gyri, fusiform gyrus). In Patient 1, whose EEG showed bilateral paroxysmal activity, fMRI showed a symmetric pattern of activation. In Patients 2 and 3, there was agreement between fMRI location of the activated focus in the right hemisphere and the EEG findings. The “eyes closed” condition did not induce appreciable activation in any of the control subjects.

Discussion. Our findings show that FOS is an ideal natural model for fMRI studies designed to map epileptiform activity. It discloses, with excellent spatial resolution and high reproducibility between subjects, cerebral activation temporally correlated to the EEG abnormalities. Control experiments conducted with the same fMRI paradigm and using identical data analysis showed that the “eyes closed” condition induced no significant activation; hence, the activation pattern during eye closure in patients

unquestionably arose not from eye closure but from epileptiform spiking. In all three patients, eye closure invariably activated precise cortical regions of the occipital lobe (middle and inferior occipital gyri and the fusiform gyrus, Brodmann areas 19 and 37), thus corroborating the spatial information from surface EEG recordings. Because the function of most neurons in this area is to process complex visual stimuli, such as direction or speed of visual motion (area V5),¹⁰ the paroxysmal activity detected in pa-

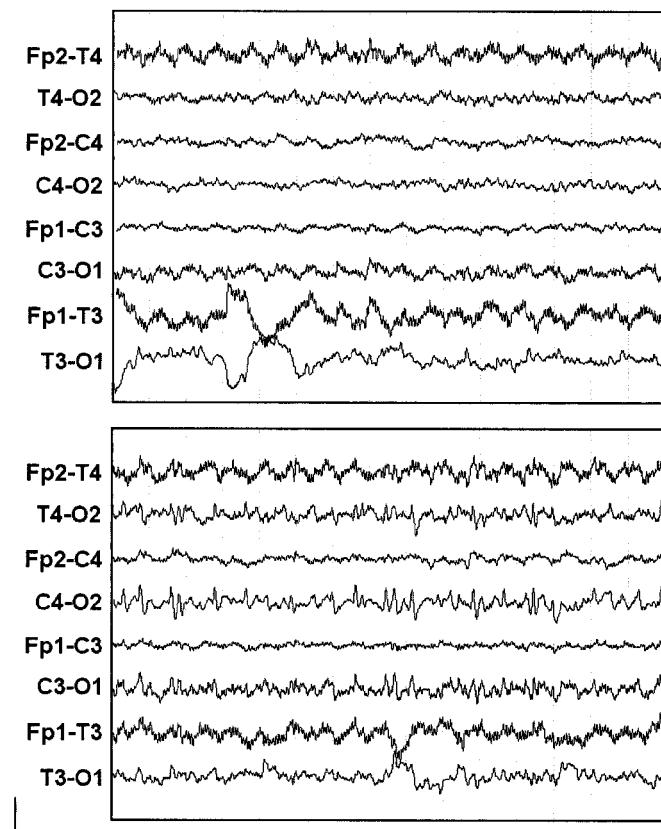


Figure 2. EEG recording during MR acquisition, after filtering of gradient-induced artifacts. Fifteen-second periods of “eyes open” (upper panel) and “eyes closed” (lower panel) conditions. The paroxysmal activity is still easily identifiable. Calibration = 1 second, 100 µV.

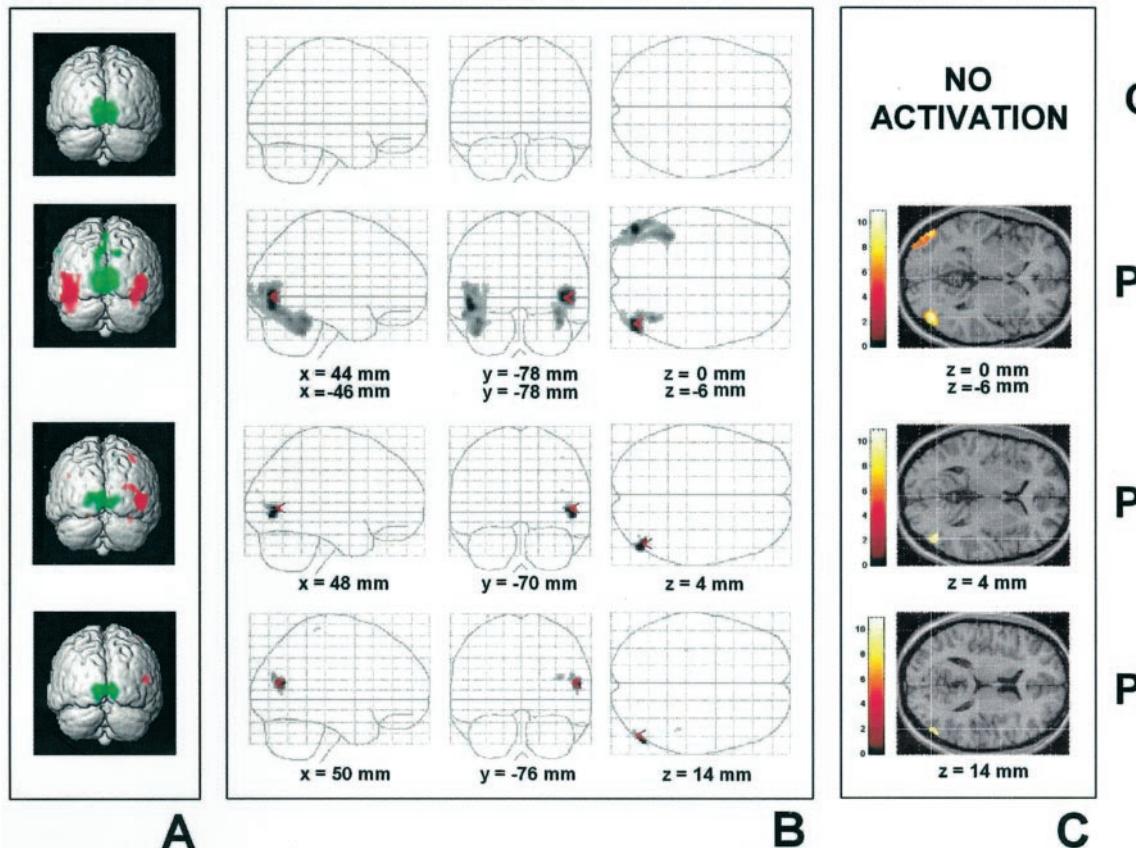


Figure 3. Statistical parametric maps illustrating cortical areas activated in a representative control subject and the three patients. (A) Display on a three-dimensional render of significantly active areas in two conditions (red, “eyes closed” condition; green, “eyes opened” condition). (B) Glass-brain projections for each subject show “eyes closed” activations thresholded at $p < 0.05$ (corrected for multiple comparisons) for amplitude and extent. (C) The “eyes closed” activated areas (same thresholding) are superimposed on a structural image; color bars show t scores. Coordinates of local maxima of signal increase (expressed as x, y, and z in the Montreal Neurologic Institute space) are displayed below each slice. As expected, eyes opening induced activation of primary visual areas in both healthy subjects and patients, and eyes closure did not induce any activation in control subjects. Conversely, in all patients, eye closure elicited activity in the extrastriate cortex in the occipital lobe (Brodmann areas 19 and 37). Note the high intersubject reproducibility of activations.

tients with FOS could reflect an intrinsic neuronal dysfunction—i.e., increased excitability of the neurons in these areas after deprivation of visual input.

We found high within-subject and between-subject variability for the time elapsing between eye closure and the onset of the related epileptiform activity (approximately 1 second in Patients 1 and 2, 1–6 seconds in Patient 3; see Results). Concurrent EEG recording overcame this problem enabling us to optimize the fMRI data analysis according to the temporal distribution of the epileptiform activity patients manifested during data acquisition. In Patients 1 and 2, when we conducted a preliminary fMRI analysis using the raw data uncorrected for the EEG findings (data not shown), the activation pattern related to the epileptiform phenomena had lower significance and lower spatial resolution than the pattern for the corrected data described here. In Patient 3, fMRI showed significant cerebral activation only when we used a model of analysis constructed ad hoc from the EEG findings. If the delay between eye closure and onset of the epileptiform activity is

unduly variable, then combined EEG recordings and fMRI seem the ideal method for studying patients with FOS. In contrast, in patients in whom EEG recordings before and after the fMRI acquisitions show a relatively stable delay, simultaneous EEG monitoring is unnecessary.

Our results essentially agree with those from the only two published studies in patients with FOS.^{6,7} Yet whereas in the patient described in the only published fMRI study,⁶ eye closure elicited weak activity also in the frontocentral regions, in our three patients, it activated extrastriate cortical areas alone. The probable reason is that during the eyes closed condition their patient manifested marked impairment of various cognitive tasks, whereas our patients had practically normal neuropsychological findings. Therefore, these combined findings strongly suggest that the observed frontocentral activation is important for the manifestation of cognitive impairment during epileptiform discharges.⁶

Furthermore, in contrast to the previous fMRI

study,⁶ reporting that eye closure and eye opening activated adjacent visual cortical areas, we found that the two conditions activated distinct visual cortical areas clearly separated by other areas that invariably remained inactive (see figure 3A). The better temporal definition of the epileptiform activity we obtained using a model of analysis corrected for coregistered EEG findings may explain why significantly condition-associated signal areas yielded higher spatial differentiation.

Future fMRI studies conducted in these patients with paradigms commonly used to activate the brain regions involved in the perception of the complex components of visual stimuli are needed to confirm current findings and to localize with greater certainty the brain areas generating paroxysmal activity in patients with FOS.

The fMRI approach used in this study may help to clarify pathophysiologic mechanisms in other kinds of epileptic activities such as photosensitive epilepsies and evoked parietal spikes characterized by a predictable temporal pattern constantly elicited by specific stimulations.

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Chronic inflammatory demyelinating polyneuropathy presenting with features of GBS

Abstract—The authors report five patients with inflammatory demyelinating polyneuropathy with a Guillain–Barré syndrome (GBS)–like onset and initial clinical features, but with persistent symptoms similar to chronic inflammatory demyelinating polyneuropathy (CIDP). Patients in the chronic phase improved with corticosteroid or IV immunoglobulin therapy. Patients with apparent GBS who show persistent symptoms may benefit from corticosteroids or other treatment that is beneficial in the management of CIDP.

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is characterized by chronic, progressive onset with or without exacerbations and recurrences.¹ Patients may benefit from corticosteroid, plasma exchange (PE), or IV immunoglobulin (IVIg) therapy.^{2–4} Guillain–Barré syndrome (GBS) is characterized by

acute onset of symptoms, and frequently a preceding infectious event such as flu-like or diarrheal symptoms; corticosteroid therapy is not considered beneficial,⁵ but PE or IVIg therapy shortens disability.⁶ CIDP and GBS are considered separate clinical entities, and specific diagnostic criteria have been established.^{7,8}

We describe five patients with acute motor paralysis with GBS-like onset in whom symptoms persisted. They then become clinicopathologically similar to CIDP in the chronic phase.

Case reports. *Patient 1.* A 13-year-old boy had fever and cough for 3 days. Ten days later, he developed distal muscle weakness and numbness in all four extremities. These symptoms worsened rapidly, and he needed support to stand and walk at 7 days from onset of neurologic illness.

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