Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain

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Our objective was to evaluate the brain regions showing increased and decreased metabolism in patients at the time of generalized bursts of epileptic discharges in order to understand their mechanism of generation and effect on brain function. By recording the electroencephalogram during the functional MRI, changes in the blood oxygenation level-dependent signal were obtained in response to epileptic discharges observed in the electroencephalogram of 15 patients with idiopathic generalized epilepsy. A group analysis was performed to determine the regions of positive (activation) and negative (deactivation) blood oxygenation level-dependent responses that were common to the patients. Activations were found bilaterally and symmetrical in the thalamus, mesial midfrontal region, insulae, and midline and bilateral cerebellum and on the borders of the lateral ventricles. Deactivations were bilateral and symmetrical in the anterior frontal and parietal regions and in the posterior cingulate gyri and were seen in the left posterior temporal region. Activations in thalamus and midfrontal regions confirm known involvement of these regions in the generation or spread of generalized epileptic discharges. Involvement of the insulae in generalized discharges had not previously been described. Cerebellar activation is not believed to reflect the generation of discharges. Deactivations in frontal and parietal regions remarkably followed the pattern of the default state of brain function. Thalamocortical activation and suspension of the default state may combine to cause the actual state of reduced responsiveness observed in patients during spike-and-wave discharges. This brief lapse of responsiveness may therefore not result only from the epileptic discharge but also from its effect on normal brain function.

absence | epilepsy | thalamus

The electroencephalogram (EEG) of patients with epilepsy presents paroxysmal discharges that depend on the type of epilepsy. In epilepsy that has been termed “idiopathic generalized” according to the Commission on Classification and Terminology of the International League Against Epilepsy (1), the most common type of discharge is the 2- to 3-Hz spike-and-wave burst, which occurs simultaneously over wide cortical regions, most often with an anterior predominance. The origin of this discharge and of the absence seizures that often accompany spike-and-wave bursts when they last several seconds has been a subject of investigation and controversy for many years (see ref. 2 for a review), particularly with respect to the involvement of subcortical structures. The recently developed method of combined EEG and functional magnetic resonance imaging (fMRI) (EEG/fMRI) allows the investigation of the brain regions, cortical and subcortical, that are involved in metabolic changes as a result of epileptic discharges seen in the scalp EEG. In our recent publication (3), we described for each individual the patterns of increases and decreases in blood oxygenation level-dependent (BOLD) signal resulting from bursts of spike-and-wave discharges recorded in the EEG of a group of 15 patients with idiopathic generalized epilepsy (IGE). Our findings included a variety of patterns of BOLD response, with the following most remarkable features:

- Responses were generally symmetrical in both hemispheres.
- Positive (activation) and negative (deactivation) BOLD changes were observed.
- Thalamic responses were present in most patients, most often as activation.
- Posterior cortical responses were frequent, most often as deactivation, and in contrast to the known predominance of the EEG discharges in frontal regions.
- Anterior cortical responses were present sometimes as activations and sometimes as deactivations.

This diversity of responses was puzzling, and we discussed how neuronal excitation and inhibition could contribute to this heterogeneity, in the context of the known thalamocortical interactions characterizing these discharges.

Subsequent to that publication, we became aware of the similarity between the pattern of deactivation seen in some of our patients and the pattern of deactivation seen in normal subjects when the resting awake state is disturbed by external stimuli or cognitive tasks, leading to the concept of a “default” state of brain function (4). This pattern includes deactivation in the parietal regions, the posterior cingulate gyrus, and in the anterior frontal regions, symmetrically. If a link between the spike-and-wave discharges and the suspension of the default state of the brain could be demonstrated, this would explain the distribution of many of the deactivations we found and shed light on the effect of spike-and-wave on brain function. In addition, it could possibly strengthen the concept of default state of brain function itself.

We therefore performed a group analysis on the data from the 15 patients of our previous study (3) to assess the activations and deactivations that were consistent across the patients. Such group analyses have rarely been performed in the study of epileptic patients with EEG/fMRI because of the heterogeneity of the clinical and EEG data, as well as of the fMRI responses, particularly in patients with focal epilepsy. The patients with IGE, who can present generalized seizures of different types, are nevertheless considered a homogeneous epilepsy group because of clinical characteristics and natural history. Furthermore, we are studying their widespread epileptic discharges, and these discharges are quite similar, justifying the group analysis approach.

Subjects

The subjects of our initial study were 25 patients with IGE who underwent an EEG/fMRI study. Of these patients, 15 had
spike-and-wave bursts during the scanning period, and only those patients could be included in the current study because the method evaluates the BOLD response to epileptic discharges. These 15 patients were aged 18–66 years (mean age; 35) and included 14 women. According to the Commission on Classification and Terminology of the International League Against Epilepsy (1), the clinical epilepsy syndromes were juvenile absence epilepsy in six patients, childhood absence epilepsy in three patients, generalized tonic–clonic seizures alone in three patients, juvenile myoclonic epilepsy in one patient, childhood absence epilepsy with facial myoclonus in one patient, and juvenile absence epilepsy with eyelid myoclonus in one patient. All but one were receiving antiepileptic medications. All patients except five had some residual seizures. The anatomical MRI was normal in all but three patients: nonspecific periventricular white matter changes were present in one patient, a pineal gland cyst in one patient, and mild ventricular dilatation in one patient. The patients had a mean rate of epileptic discharges of 44 per h of scanning (range, 10–153 per h) and a mean duration of bursts of 2.5 s (range, 1–14 s).

Methods

Patients underwent a 2-h recording session, after giving informed consent. The study was approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital. EEG was continuously recorded inside the MRI scanner (Sonata 1.5T, Siemens) by using 21 MRI-compatible electrodes (Ag/AgCl) placed on the scalp according to the 10-20 system. Subjects’ heads were immobilized by using a pillow filled with foam microspheres. Data were transmitted from an EMR32 (Schwarzer, Munich; 1 kHz sampling rate) amplifier via an optic fiber cable to the EEG monitor located outside the scanner room. An anatomical acquisition (1-mm slice thickness; 256 × 256 matrix; TE, 9.2 ms; TR, 22 ms; flip angle, 30°) was performed for superimposition with functional images and intersubject registration. BOLD fMRI data were collected in runs of 6 min with the patient in the resting state (EPI sequence; voxel dimensions 5 × 5 × 5 mm; 25 slices; 64 × 64 matrix; TE, 50 ms; TR, 3 s; flip angle, 90°), with 1–2 min between runs and a total of 6–14 runs per scanning session.

We postprocessed the EEG acquired inside the scanner, for offline MRI artifact removal and filtering by using FMR software (Schwarzer, Munich). An experienced neurophysiologist reviewed filtered EEGs and marked bursts of spike-and-wave.

The functional images were motion-corrected and smoothed [6-mm full-width at half-maximum (FWHM)] by using the software package from the Brain Imaging Center of the Montreal Neurological Institute. Models and signals were prewhitened with an autoregressive filter of order 1, and low frequency residuals of the previous analysis. Average FWHM was 13.5 mm within the brain, but FWHM maps suggested a high degree of spatial nonstationarity. We used a nonstationary random-field theory cluster size test described by Hayasaka et al. (8). All voxels with a T value <3.17 or less than −3.17 (uncorrected P < 0.001) located within a mask of the brain were considered for this cluster analysis. The method computes the corrected P-value of the spatial extent of each cluster, taking into account the fact that the spatial smoothness was not stationary. Every cluster showing a corrected P < 0.05 for its spatial extent was considered significant.

Results

The significant clusters of activation and deactivation are listed in Table 1 for each of the four HRFs. Movement was limited to <1° throughout the recordings except for three runs of three different patients. The estimation of motion parameters and movement correction was performed as indicated in Methods. Removing the three runs containing movement >1° did not alter substantially the results given in Activations and Deactivations.

Activations. The activations were generally symmetrical, involving homologous areas, and close to the midline and most apparent in the analysis with an HRF peaking at 5 s. The clusters found with the 3-s HRF are a subset of those found at 5-s HRF and are therefore not illustrated. The largest cluster includes the thalamus and insulae in both hemispheres (Fig. 1B). The highest T values were found in the thalamus in both hemispheres (T = 5.2). Other regions of significant activation included a wide band of mesial frontal cortex (Fig. 1C) and the cerebellum (Fig. 1A and C). There was also an activation that closely followed the lateral ventricles, only apparent in the analysis with an HRF peaking at 7 s (Fig. 1D).

Deactivations. The deactivations were also largely symmetrical, involving homologous areas, often more laterally than the activations, and were most significant in the 9-s HRF analysis. The deactivations seen with the 7-s HRF are a subset of those seen with the 9-s HRF and are not illustrated. A very large cluster of deactivation included the mesial and lateral aspects of anterior frontal regions (all views of Fig. 2). There was a large cluster including the posterior portion of the cingulate gyrus and Montreal Neurological Institute (7), and the resulting geometrical transformations were used to resample the results of individual fMRI analyses Ei and Si. The group analysis was performed by using a random-effects linear model with the effects, Ei (as data), and fixed-effects standard deviations, Si, taken from the previous analysis. This model was fitted by using restricted maximum likelihood and provided notably an estimate of the random-effects variance (5). This last estimate was particularly noisy because of the low degrees of freedom (14 in the present study). To increase the sensitivity of this group analysis, we used the method proposed by Worsley et al. (5), which consists in estimating the ratio of the random-effects variance to the fixed-effects variance, and then regularizing this ratio by spatial smoothing. The variance of the effect is finally estimated by the smoothed ratio multiplied by the fixed-effects variance. The amount of smoothing was chosen to achieve 100 effective degrees of freedom. Note that by using such an approach only the variance ratio is smoothed but not the effects, Ei. This group analysis, to which we will refer as a mixed-effects group analysis, provided the statistics E, S, and T.
the left parietal region and another one involving the right parietal area (Fig. 2 B–D). Finally, there was a smaller cluster in the left posterior temporal area (Fig. 2 A).

**Discussion**

The 15 patients studied had IGE and anteriorly dominant spike-or polyspike-and-wave discharges, therefore constituting a relatively homogeneous group. Despite the variability in their epilepsy syndromes, one can hypothesize a common mechanism for their epileptic discharges. A group analysis takes into account trends in the data that are common to the group but may not necessarily be significant in the majority of individuals. Moreover, the group analysis, by using mixed-effects, has the advantage of taking into account both intra- and intersubject sources of variability to extract common trends within the mean (5). It is of interest that very few of the voxels passed the single-voxel threshold. The significant regions were therefore found because of the clustering of voxels with activation or deactivation, and these regions could be uncovered by using a nonstationary random-field theory cluster-size test (8). In some respects, the group analysis confirmed our original findings. It also revealed results about which we could have barely speculated in the analysis of individuals.

Activations in the group analysis were most significant in the analysis with an HRF peaking at 5 s, whereas deactivations were most significant with the HRF peaking at 9 s. This finding is in agreement with the observation of our original publication (3) and of another study (6) in patients with focal epilepsy, that

<table>
<thead>
<tr>
<th>Cluster no.</th>
<th>HRF peaks</th>
<th>Activation/deactivation</th>
<th>Volume, mm³</th>
<th>Location</th>
<th>P value</th>
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</thead>
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<tr>
<td>1</td>
<td>3</td>
<td>Activation</td>
<td>15,200</td>
<td>R insula</td>
<td>0.000</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
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<td>10,776</td>
<td>L insula</td>
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<tr>
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<td>3</td>
<td>Activation</td>
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<td>4</td>
<td>5</td>
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<td>36,048</td>
<td>Bilateral thalami and insulae</td>
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</tr>
<tr>
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<td>5</td>
<td>Activation</td>
<td>10,096</td>
<td>Cerebellum</td>
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</tr>
<tr>
<td>6</td>
<td>5</td>
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<td>Mesial frontal</td>
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</tr>
<tr>
<td>7</td>
<td>7</td>
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<td>Lateral ventricles (bilateral)</td>
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<tr>
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<td>Deactivation</td>
<td>94,272</td>
<td>Bilateral mesial and lateral anterior frontal</td>
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<tr>
<td>13</td>
<td>9</td>
<td>Deactivation</td>
<td>4,696</td>
<td>L posterior temporal</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Within each HRF, clusters are ordered by decreasing volume and decreasing level of significance. Clusters 4–7 are illustrated in Fig. 1. Clusters 10–13 are illustrated in Fig. 2. Corrected $P < 0.05$. L, left; R, right.

**Fig. 1.** Significant positive BOLD response observed from the group analysis of 15 IGE patients obtained by using the HRF peaking at 5 s (A–C) and at 7 s (D), corrected $P < 0.05$ for spatial extent. Functional data are superimposed on the average brain template of the Montreal Neurological Institute. (A) Axial view showing activation in the cerebellum (cluster 5) and inferior part of the insula (cluster 4). (B) Axial view showing the largest cluster (cluster 4) and involving the thalamus and insulae. (C) Sagittal interhemispheric view showing an activation along a wide band of mesial frontal cortex (cluster 6) and within the cerebellum (cluster 5). (D) Sagittal view of the right hemisphere 2 cm away from the midline showing an activation within the ventricles (cluster 7). This activation was bilateral and followed the ventricles until the trigone.

**Fig. 2.** Significant negative BOLD response observed from the group analysis of 15 IGE patients obtained by using HRF peaking at 9 s, corrected $P < 0.05$ for spatial extent. (A) Axial view showing bilateral deactivations in mesial and lateral anterior frontal areas (cluster 10) and in the left posterior temporal area (cluster 13). (B) Axial view 1 cm higher than A and showing deactivations in frontal regions (cluster 10), in parietal areas (clusters 11 and 12), and in the posterior cingulate gyrus (cluster 11). (C) Axial view 2 cm above B and showing the same frontal and parietal clusters. (D) Sagittal view of the right hemisphere 1 cm away from the midline and showing a deactivation within the mesial prefrontal area (cluster 10) and the posterior cingulate gyrus (cluster 11).
deactivations tended to peak later than activations. It is also clear that, in this patient group, deactivations and activations were spatially separated, not even adjacent, and therefore the deactivations are very unlikely to be the result of an undershoot after an activation. Although we cannot formally exclude the possibility of a vascular steal phenomenon, the distance between regions of activation and deactivation, as well as their difference in timing, make this unlikely.

The most significant activation was in the thalamus, bilaterally, a structure that has long been suspected to be involved in the generation of generalized epileptic discharges, in interaction with the cortex (9). This result confirms the pattern seen in the majority of subjects, and its significance in the context of generalized epileptic discharges was discussed extensively by Aghakhani et al. (3). The group analysis also revealed, however, large midline frontal, bilateral insular, and cerebellar activations. Midline frontal regions have been implicated in the spreading and generalization of discharges of focal origin (10) but not specifically in the generation of generalized discharges. This finding is in agreement with the frequent midfrontal amplitude predominance in the EEG of these discharges. It is also in midfrontal regions that another thalamocortical phenomenon, the sleep spindle, is most prominent, and the link between the two has been established (11, 12).

More surprising was the finding of bilateral activation in the insulae. The insula is a region of convergence of multisensory inputs that has recently been implicated in focal seizures (13) but not in generalized discharges. The insula has widespread thalamic connections, however (14), which may explain its activation during generalized spike-and-wave. A clear activation was seen in the cerebellum. Cerebellar ictal hyperperfusion has been observed in patients with partial seizures, contralateral to the seizure focus (15), and it is therefore not so surprising to see bilateral involvement during bilateral discharges. Intense involvement of the cerebellum during spike-and-wave discharges has been observed in an experimental model, independently of movement, with the suggestion that cerebellar neurons may contribute to spike-and-wave rhythmicity (16). The role of the cerebellum during generalized seizures or discharges has been reviewed by Norden and Blumenfeld (17), but they do not propose a specific hypothesis regarding its function during seizures.

The positive response found in the lateral ventricles is surprising and of course cannot be explained by the usual mechanisms thought to underlie an increase in the BOLD signal. We conjecture that this is an artefactual finding, although we do not have an explanation for it. The ventricles change volume with respiration and the cardiac cycle, but our results originate in a change correlated to the spike-and-wave discharges, and such discharges are not known to be related to these physiological rhythms. Our patients did not, at the time of the study, manifest myoclonic jerks with their spike-and-wave discharges, and only three have a history of myoclonic jerks. We have verified that movement was minimal and movement correction was always performed. This response is therefore unlikely to be related to movement. Could it be that the widespread increase in blood volume resulting from the discharges results in a transitory reduction of volumes of the ventricles and hence a change in the magnetic characteristics of the border of the ventricles?

The group analysis revealed deactivations, including bilateral parietal and anterior frontal regions and the posterior cingulate gyrus. Deactivation in the posterior cingulate gyrus was also reported by Archer et al. (18), after group analysis of an EEG/fMRI study of five patients with spike-and-wave discharges. The authors interpreted this deactivation as possibly being related to the generation of the epileptic discharge itself or to unspecific attention mechanisms. This study, however, used a spike-triggered fMRI paradigm, less powerful than the continuous recording performed in our study, and this may explain why it found only a subset of the deactivated regions found in our study. A small cluster of deactivation was also found in our study in the posterior left temporal region. It is noteworthy that a symmetrical right temporal cluster appeared when we slightly lowered the statistic threshold, indicating that temporal deactivation may be bilateral but more consistent on the left.

Raichle and his colleagues (4, 19) have analyzed many fMRI and positron-emission tomography (PET) studies involving a “resting state” that is contrasted to a state during which a variety of tasks are performed. They found that, during many such experiments, the task condition is accompanied by a deactivation involving the frontoparietal cortical regions, including the posterior cingulate gyrus. They have hypothesized that this deactivation, which is not task-specific and which is relative to the resting state, corresponds in fact to the arrest of the “default state of the brain” during which the subject is not performing any specific task, but is awake and conscious. As soon as a task is presented, this state is suspended, and the subject concentrates on the task at hand. Our group analysis of spike-and-wave discharges showed deactivations that had a strikingly similar distribution to the deactivations found as a result of the interruption of this default state of the brain.

During EEG/fMRI recordings, our epileptic subjects lay with their eyes closed, as during the rest condition of the abovementioned experiments. Our data suggest that, during a generalized epileptic discharge, the default state may also be momentarily suspended, not as a result of an external requirement to perform a task, but as a result of the epileptic discharge. We can hypothesize that spike-and-wave bursts cause a partial suspension of the default state of the brain. Therefore, this suspension of the normal state of attention, combined with a dampening in the perception of sensory inputs and reduction in the ability to respond resulting from activation in the thalamus, midfrontal regions, and insulae, may explain the state of altered consciousness seen during generalized epileptic discharges. This explanation may provide a more accurate understanding of the mental state of patients during spike-and-wave discharges than the usual “loss of consciousness,” which Gloor (20) thought unspecific and not a very useful description of the manifestation of epileptic seizures. Patients with spike-and-wave do not experience a clinical absence with every burst, but responsiveness is often impaired during such bursts (21), and the level of cognitive impairment increases when discharges become longer (see ref. 22 for a review). Similarly, it has been shown that the default state of the brain can be gradually and actively attenuated in accordance with the difficulty of the task (23, 24).

Frontal and parietal regions have also been involved in various conditions related to more severe alterations of consciousness. Generalized tonic–clonic seizures result in a profound loss of consciousness, and it has been hypothesized from blood flow studies (25) that frontal and parietal regions are primarily involved in the loss of consciousness, although in this case with increases in blood flow. When consciousness is impaired during temporal lobe seizures, frontal and parietal association areas show a decrease in blood flow (26). In the vegetative state, a more sustained and severe cortical impairment, frontoparietal regions show a decrease in glucose consumption (27), although in a somewhat different spatial distribution, with important involvement of premotor areas. The authors attribute impaired awareness in the vegetative state to this decrease and to decreased connectivity between frontal regions and the posterior cingulate area. These results are consistent with the concept of the default state of the brain implicating high metabolism in frontoparietal regions when nonspecific attention is maintained and with our interpretation of their role during generalized epileptic discharges.
We noted that the hemodynamic response functions of deactivations tended to peak later (7–9 s) than those of activations (~5 s). It is possible that there is a 2- or 3-s delay between the onset of the epileptic burst, which results itself in the activations, and the suspension of the default state, which is represented by deactivations. An alternative explanation is that the mechanisms of generation of activations and deactivations are different, resulting in deactivations occurring later than activations. This hypothesis is supported by previous observations that deactivations also tend to peak later than activations in focal epilepsy (6).

We reexamined our original individual data with the hindsight of these results and found that a deactivation with the pattern of the default state of the brain was clearly present in 4 of 15 subjects, could be recognized but was more diffuse or partial in another 4 subjects, was present only in its posterior regions in 4 subjects, and was clearly absent in 3 subjects.

In conclusion, it may be that the synchronized neuronal activity represented by the spike-and-wave discharges is reflected in the thalamocortical BOLD activations, whereas the regions of deactivation reflect the suspension of the default state of brain function resulting indirectly from this discharge. It is interesting to note that for the activation there is a good correspondence between neuronal activity (EEG) and fMRI results, whereas the most prominent deactivation (parietal and posterior) probably corresponds to a neuronal change that does not result in highly synchronized EEG activity and therefore has no clear EEG parallel. The combination of EEG and fMRI is a powerful tool in the study of brain function. Here, it allowed a bridge between a vast amount of research on the mechanisms of the generation of spike-and-wave activity and the equally vast amount of research on the state of the brain at rest, providing insight into the state of the brain during a brief epileptic discharge.

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