Widespread epileptic networks in focal epilepsies: EEG-fMRI study

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Summary

Purpose—To assess the extent of brain involvement during focal epileptic activity, we studied patterns of cortical and subcortical metabolic changes coinciding with interictal epileptic discharges (IEDs) using group analysis of simultaneous electroencephalography and functional magnetic resonance imaging (EEG-fMRI) scans in patients with focal epilepsy.

Methods—We selected patients with temporal lobe epilepsy (TLE, $n = 32$), frontal lobe epilepsy (FLE, $n = 14$), and posterior quadrant epilepsy (PQE, $n = 20$) from our 3 Tesla EEG-fMRI database. We applied group analysis upon the blood oxygen–level dependent (BOLD) response associated with focal IEDs.

Key Findings—Patients with TLE and FLE showed activations and deactivations, whereas in PQE only deactivations occurred. In TLE and FLE, the largest activation was in the mid–cingulate gyri bilaterally. In FLE, activations were also found in the ipsilateral frontal operculum, thalamus, and internal capsule, and in the contralateral cerebellum, whereas in TLE, we found additional activations in the ipsilateral mesial and neocortical temporal regions, insula, and cerebellar cortex. All three groups showed deactivations in default mode network regions, the most widespread being in the TLE group, and less in PQE and FLE.

Significance—These results indicate that different epileptic syndromes result in unique and widespread networks related to focal IEDs. Default mode regions are deactivated in response to focal discharges in all three groups with syndrome specific pattern. We conclude that focal IEDs

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Disclosure

None of the authors has any conflict of interest to disclose. The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm this report is consistent with those guidelines.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Clinical, EEG, and neuroimaging findings of 66 patients enrolled in the study and the presumed lateralization and localization of the epileptic generator.

Table S2. Results of subgroup analysis of patients with unilateral mesial TLE ($n = 16$).

Table S3. Results of subgroup analysis of the 2nd and 3rd quartiles of TLE patients based on the frequency of their epileptic discharges ($n = 16$).

Table S4. Results of subgroup analysis of the 2nd and 3rd quartiles of FLE patients based on the frequency of their epileptic discharges ($n = 7$).

Table S5. Results of subgroup analysis of the 2nd and 3rd quartiles of PQE patients based on the frequency of their epileptic discharges ($n = 10$).

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are associated with specific networks of widespread metabolic changes that may cause more substantial disturbance to brain function than might be appreciated from the focal nature of the scalp EEG discharges.

Keywords

Focal epileptic discharges; Frontal lobe epilepsy; Temporal lobe epilepsy; Posterior quadrant epilepsy; Default mode network

Electroencephalography–functional magnetic resonance imaging (EEG–fMRI) is a noninvasive technique that allows visualizing the brain’s hemodynamic changes associated with epileptic activity. This method utilizes the high temporal resolution of EEG and the high spatial resolution of fMRI to study metabolic activity of the whole brain, simultaneously. EEG–fMRI has become a valuable tool in the presurgical evaluation of patients with pharmacoresistant epilepsy and to study epileptic networks (Zijlmans et al., 2007; Gotman, 2008; Thornton et al., 2010).

Group analyses of EEG–fMRI scans from selected sets of patients demonstrate metabolic changes that may not be apparent in individual patients. For instance, studies of patients with generalized epilepsies show common bilateral activation in cortical regions, thalami, and cerebellum, whereas the caudate nuclei and default mode network (DMN) regions were deactivated (Gotman et al., 2005; Carney et al., 2010; Siniatchkin et al., 2011). The extent of networks involved in focal epileptic activity is much less clear; group analysis of EEG–fMRI has been limited to studies of temporal lobe epilepsy (TLE) and heterogeneous groups of focal epilepsy patients and using 1.5 Tesla scans (Laufs et al., 2007; Kobayashi et al., 2009; Laufs et al., 2011). A group analysis of 19 patients with different focal epileptic syndromes converged to a single activation cluster in the ipsilateral anterior piriform cortex (Laufs et al., 2011).

We report the epileptic networks associated with focal interictal epileptiform discharges (IEDs) using 3T EEG–fMRI. We selected patients with TLE, frontal lobe epilepsy (FLE), and posterior quadrant epilepsy (PQE) and performed group analyses. We describe blood oxygen–level dependent (BOLD) responses of cortical, subcortical, and DMN regions differentially involved in each patient group.

Methods

Subjects

Between April 2006 and December 2010, 168 consecutive 3T EEG–fMRI scans were performed in focal epilepsy patients: 16 had no IEDs, 16 had no BOLD response, and 34 had technical problems preventing interpretation (significant movements during the scan, persistent ballistocardiogram artifact, loss of important EEG channel, or other patient-related causes). To ensure the accurate coregistration required for group analysis, we excluded patients younger than 16 ($n = 2$) or with large structural or postsurgical lesions ($n = 28$). In concordance with the aim of the study, we excluded patients that had only secondary generalized epileptic activity during the scan and included only patients with clear focal

discharges (6 did not have any). Spike frequency was not a selection criterion (2–1,451 spikes/study; median, 35 spikes/study).

For the purpose of grouping the 66 patients into the three clinical groups, three neurologists carefully reviewed the clinical, electrophysiologic, and imaging findings of the patients (Table S1). Findings from depth electrode studies were considered when available, and data from neuropsychological assessments were used as well (not reported). Based on these data, patients were grouped into TLE (32 patients), FLE (14), and PQE (20 patients: eight temporoparietooccipital, four occipital, three parietal, three temporoparietal, and two temporooccipital). A subgroup of 16 unilateral mesial TLE patients (# 1–6, 8, 11–13, 16–19, 22, and 24 in Table S1) were studied separately as well. In cases of bilateral epilepsy, lateralization was defined by the laterality of the IED recorded in the scanner.

Patients provided written informed consent for the EEG-fMRI studies, as approved by the research ethics committee of the Montreal Neurological Institute and Hospital.

EEG-fMRI acquisition

EEG was recorded while the patients were in the scanner (Trio, Siemens, Erlangen, Germany) using 25 Ag/AgCl electrodes placed according to the 10–20 and 10–10 International System, as described elsewhere (Moeller et al., 2009). An MR-compatible amplifier was used (BrainAmp; Brain Products, Munich, Germany; 5 kHz sampling). Subjects' heads were immobilized with a pillow filled with foam microspheres.

Scanning started with an anatomic acquisition (1-mm slice thickness, 256×256 matrix, echo time (TE) = 9.2 msec, repetition time (TR) = 22 msec, flip angle 30 degrees). BOLD fMRI data were collected in runs of 6 min with the patient resting (two echo planar imaging [EPI] acquisition protocols: 1. until July 2008, 31 scans – voxel dimensions $5 \times 5 \times 5$ mm, 25 slices, 64×64 matrix, TE = 30 msec, TR = 1,750 msec, flip angle 90 degrees; 2. from July 2008, 35 scans – voxel dimensions $3.7 \times 3.7 \times 3.7$ mm, 33 slices, 64×64 matrix, TE = 25 msec, TR = 1,900 msec, flip angle 70 degrees. The different TRs were used as regressors in the analyses. Scans lasted 12–90 min per patient (average, 66 min).

EEG preparation

Scanner artifacts were corrected using BRAIN VISION ANALYZER software (Allen et al., 2000). The ballistocardiogram artifact was removed with the assistance of independent component analysis (Bénar et al., 2003), or by detection of the R waves on electrocardiography (ECG), averaging, and subtraction. IEDs were marked as isolated or run of events by an electroencephalographer. Runs of events were modeled as blocks, and the percentage of runs out of the total number of IEDs was similar across the three groups (TLE: 8/32, FLE: 3/14, PQE: 4/20). IEDs were classified according to their spatial distribution (hemisphere and lobe[s]). All patients but one had a single IED type per scan. One patient with TLE had bilateral independent temporal discharges, and had two IED types analyzed.

Functional image processing

Functional images were motion corrected and spatially smoothed at 6 mm full width at half maximum (FWHM) using software from the Montreal Neurological Institute (<http://www.bic.mni.mcgill.ca/ServicesSoftware/HomePage/>). Runs showing intrarun motion larger than 2 mm or 2 degrees were excluded. Models and signals were prewhitened with an autoregressive filter of order 1. The global time course, modeling low frequency drifts, and motion parameters were used as confounds in the analysis (Lund et al., 2006). Low frequency drifts were modeled using cosine basis functions ranging from 0 to 0.02 Hz. Motion parameters were included as confounds using a first-order Volterra expansion (24 regressors).

Maps of the t statistic (t-maps) were created using the timing of each IED as an event in the fMRI analysis (Worsley et al., 2002). The regressor of interest used to model the BOLD response to the IEDs was the timing of the epileptic events convolved with a hemodynamic response function (HRF). To take into account variability in the response to IEDs, we used four HRFs consisting of gamma functions peaking at 3, 5, 7, and 9 s. Using multiple HRFs allows capturing more BOLD changes that are associated with IEDs than using a canonical HRF, as demonstrated by Bagshaw et al. (2004). For single-subject analysis, we combine the four t-maps by taking the maximum t-value at each voxel. Group analysis requires the estimation at each voxel of the effect and the standard deviation of the single patient level analysis and we therefore looked at the four HRF models independently, which allowed us to study variability in the BOLD responses at the group level.

Because some patients showed bursts of spikes, low frequency fluctuations (<0.02 Hz) may be present in the regressor of interest. To avoid degeneracy of the general linear model due to correlations between the regressor of interest and cosine basis functions used to model low frequency drifts, we applied a high-pass filter at 0.02 Hz to the regressor of interest.

The group analysis described below was repeated for each HRF. For each subject i , data for each run were first registered and resampled to the position of the first run using a rigid transformation (three rotations, three translations) to correct for possible movement. Statistical results for each run were then averaged using a fixed-effects model, leading for subject i to an estimation of the global statistics of the BOLD response E_i , its standard deviation S_i , and the resulting t-statistic $t_i = E_i/S_i$.

Group analysis

The group analysis method was described before (Gotman et al., 2005). The 66 anatomic scans were normalized in the stereotactic space of the Montreal Neurological Institute template (Collins et al., 1994). The resulting geometric transformations were used to resample individual fMRI analyses E_i and S_i in the stereotactic space. Images from studies corresponding to right hemispheric spikes were right–left flipped, such that the hemisphere ipsilateral to all IEDs became the left. The group analysis was performed using a random-effects linear model with the effects E_i as data and fixed-effects standard deviations S_i taken from the individual subjects. This model was fitted using restricted maximum likelihood and provided an estimate of the random effects variance (Worsley et al., 2002). As the estimation

of random effects variance may be noisy (24 d.f.), we increased sensitivity by estimating the ratio of the random-effects variance to the fixed-effects variance, and regularizing this ratio by spatial smoothing (Worsley et al., 2002). The variance 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. With this approach, only the variance ratio is smoothed but not the effects E_i . This mixed-effects analysis provided the statistics E , S , and t .

The resulting t images were thresholded using the minimum given by Bonferroni correction and random field theory, taking into account the nonisotropic spatial correlation of errors. Maps of the group statistics were first estimated at each voxel from the residuals of the previous analysis. The average brain FWHM was used to identify cluster sizes with significant BOLD responses. Voxels selected for cluster analysis were considered significant at uncorrected $p < 0.005$ and located within a brain mask. Clusters showing a corrected $p < 0.05$ were considered significant.

To reduce the possibility of bias toward patients with high spike frequencies, we repeated the group analyses after discarding the lower and upper quartiles of each patient group based on spiking frequency (excluding patients with rare and frequent spikes).

Results

Sixty-six patients divided in three epilepsy groups (TLE, FLE, and PQE) were studied with four HRFs peaking 3, 5, 7, and 9 s after the discharge.

In TLE patients, using HRF peaking at 3 s, the group analysis (Table 1, Fig. 1) showed the largest activation cluster in the cingulate gyri (ipsi > contralateral). The second cluster by volume included the insula, amygdala, and anterior hippocampus ipsilateral to the focus. This cluster had the highest t -value. Deactivations were found in the contralateral inferior parietal lobule and bilaterally in the posterior cingulate cortex (PCC) and precuneus (contra > ipsi). With the 5-s HRF, the same clusters were found, in addition to activation in the ipsilateral cerebellar hemisphere and deactivation in the contralateral posterior temporal cortex. Using the 7 s HRF, activations were found in the ipsilateral insula, cingulate gyri (ipsi > contra), and ipsilateral superior cerebellum, and deactivations were evident in the inferior parietal lobules, PCC, and precuneus bilaterally (contra > ipsi). Finally, with the 9-s HRF, there was only a deactivation in the contralateral inferior parietal lobule (not shown in figure).

The subgroup analysis of 16 patients with unilateral mesial TLE (Table S2) show similarly involved structures as with the whole TLE group (Table 1) with some changes: First, the t -values and cluster volumes were lower, in agreement with a smaller group size. Secondly, the involvement of the mid-cingulate gyrus was unilateral (ipsi) rather than bilateral, and the cerebellar activation was smaller in volume and not significant after correcting for cluster volume.

In patients with FLE, group analysis (Table 2, Fig. 2) resulted in similar clusters when using HRFs peaking at 3 and 5 s: activations in the cingulate gyri (ipsi > contra), the contralateral

superior cerebellum and ipsilateral frontal operculum, medial thalamus, genu and posterior limb of the internal capsule, and deactivation in the contralateral inferior parietal lobule. Using 7-s and 9-s HRFs yielded similar results: activations in the cingulate gyri (ipsi > contra), ipsilateral frontal operculum, and contralateral superior cerebellum, and deactivations in the cuneus bilaterally (ipsi > contra) and contralateral superior parietal lobule.

In patients with PQE, results (Table 3, Fig. 3) showed only deactivation clusters in the PCC and precuneus bilaterally when using the 3-s and 5-s HRFs, and no activations. No activation or deactivation was found with the 7-s and 9-s HRFs.

The same analyses were repeated including only the second and third quartiles of the patients in each group, based on IED frequency (excluding patients with rare or frequent spikes). Results are in Tables S3, S4, and S5. Because half of the patients were used, results yielded smaller volumes of significant clusters. The significant responses in the restricted analysis were a subset of those seen with all patients. In the FLE group, there was also activation in the brainstem reticular formation. We lowered the threshold of significance (Tables S3, S4, and S5) and found that all the regions that became included corresponded to those having a significant response in the full analysis. This implies that findings are unlikely to be biased by patients with high IED rates, but rather result from the commonalities in each group.

Discussion

Our study, which included relatively large groups of patients with diverse types of epileptic discharges, indicates that focal IEDs recorded from scalp EEG may represent only a fraction of broader events that involve widespread brain areas despite their focal appearance. Intracerebral EEG studies allow the investigation of epileptic networks with very high time resolution but they have several limitations: they are invasive and explore only a small fraction of the brain, often ignoring regions remote from the focus. EEG-fMRI is unique in its functional exploration of the whole brain noninvasively at the time of a discharge and its ability to perform group analyses. Whereas EEG-fMRI studies of individual patients emphasize the regions with the highest involvement in each patient, usually coinciding with the epileptic focus, group analyses deemphasize patient-specific changes and look at regions that are consistently involved in the group, even if such regions are not apparent in individual analyses because their response is subthreshold.

The method of analysis using multiple HRFs at different latencies, as opposed to using a single canonical HRF, has been shown to increase the sensitivity to capture IED-related BOLD changes (Bagshaw et al., 2004). However, the biologic significance of the results arising from different HRFs is unknown. Therefore, we avoid allocating temporal significance to our results and limit our discussion into terms of “activations” and “deactivations” regardless of which HRF is used. However, we observed that BOLD changes in specific regions occur maximally with a certain HRF, and less significantly with the “neighboring” HRFs (Tables 1–3). Furthermore, no region showed both activation and deactivation, or a bimodal appearance across the different HRFs, thus making it unlikely that

a deactivation corresponds to an undershoot of an earlier activation. These observations give further support for the use of the multiple HRF approach.

Our study revealed widespread activations and deactivations outside the epileptic focus in the three groups studied. In TLE, the findings confirmed prior observations obtained at 1.5 Tesla: activation of the temporal lobe structures and insula and deactivation of the PCC, precuneus, and inferior parietal lobules. In addition, we found significant activations in the mid-cingulate gyri and cerebellum. In FLE, a group of patient that has not been studied before in isolation, a distinct cortical-subcortical network was found composed of the mid-cingulate gyri, frontal operculum, thalamus, cerebellum, and internal capsule. We found different patterns of deactivation in DMN nodes in FLE and PQE as well, showing that deactivation of DMN is a more prevalent phenomenon in focal epilepsy and is not restricted to TLE as reported previously (Laufs et al., 2007).

Activation

We found widespread increased BOLD responses, with different patterns in the different focal epileptic syndromes. Surprisingly, in patients with FLE, significant clusters of activation were observed in cortical, subcortical, and white matter compartments, despite the relative heterogeneity of the epilepsy syndromes in this group. Review of the individual patients' scans in this group did not disclose any consistently activated cortical region, decreasing the likelihood that our findings (e.g., in the cingulate gyrus or the frontal operculum) are due to increased representation of epileptic foci in these regions, but rather suggests that IEDs from different frontal regions involve common neuronal networks. On the other hand, we could not find a similar common activation in PQE. This group included 20 patients with epileptic foci originating from distinct posterior head regions with a possibly higher variability than the FLE group.

The TLE group showed an activated cluster in the mesial temporal, insula, and superior temporal neocortex ipsilateral to the focus, most likely directly linked to temporal lobe spikes. Hippocampal and insular activations were found in a similar group of patients (Laufs et al., 2007). Our findings include what was found in an earlier study of patients with TLE (Kobayashi et al., 2009), however, in that study the cluster also included the lentiform nucleus. The involvement of this extra structure may have originated in the lower resolution caused by lower magnet strength (1.5 T) and broader smoothing (8 mm) than in the current study. Half of our patients with TLE had unilateral mesial temporal generators, whereas the other half had neocortical or bilateral foci (Table S1). The similarities in the results of the whole TLE group and a more homogeneous subgroup of unilateral mesial TLE patients, suggest that the common metabolic abnormalities observed are not restricted only to unilateral mesial TLE, but rather represent the metabolic changes associated with temporal spikes in general. It might be inferred also that the involvement of the contralateral cingulate and the cerebellum are more prevalent with a more widespread disease involving either neocortical or bilateral epileptogenicity. The small number of lateral cases prevented us from analyzing this subtype separately.

The largest activations were found in the mid-cingulate gyri bilaterally in TLE and FLE. The involvement of this region has been reported in idiopathic generalized epilepsy (Gotman

et al., 2005) and in continuous spike and wave during slow wave sleep (Siniatchkin et al., 2010), but not in functional studies of focal epilepsy. Anatomic and pathologic data explain the implication of the cingulate gyrus in TLE: mesial temporal seizures propagate preferentially to the frontal lobe, in particular to the prefrontal areas (Lieb et al., 1991) and to the cingulate gyrus (Engel, 1993). In addition, patients with TLE demonstrate reduction of gray matter volume bilaterally in the cingulate gyri (Bernasconi et al., 2004); and bilateral abnormalities of axonal integrity in the cingulum, as measured by diffusion tensor imaging (DTI), were shown in patients with unilateral mesial TLE (Concha et al., 2005, 2007). A study of cortical thickness in children with diverse FLE syndromes demonstrated significant cortical thinning in the cingulate gyrus and frontal operculum among other regions (Widjaja et al., 2011). Of interest, both regions were activated in the FLE group. The common involvement of the cingulate gyri in TLE and FLE probably results from rapid spread of epileptic activity originating from the temporal and frontal areas, and might contribute to the difficulty of clinically differentiating between epileptic activities originating from these two lobes. The involvement of this region in generalized discharges as well makes it a potential target of experimental investigation and more intense scrutiny in future functional studies.

In FLE, the BOLD increase in the ipsilateral medial thalamus provides evidence of involvement of this structure during interictal discharges, which is in agreement with studies of the ictal state or studies reflecting background state of the brain: Interictal PET showed a decrease in thalamic glucose metabolism in FLE patients ipsilateral to the focus (Benedek et al., 2004), and single photon emission computed tomography (SPECT) studies show thalamic ictal hyperperfusion and interictal hypoperfusion ipsilateral to the focus (Duncan et al., 1997; Takano et al., 2001); a DTI study of patients with FLE demonstrated reduced fractional anisotropy in the thalamus (Wang et al., 2011). On the other hand, the absence of thalamic activation in TLE is surprising, since thalamic atrophy was documented in patients with TLE (Natsume et al., 2003). This lack of thalamic response remained even after an important lowering of the statistical threshold (from 2.6 to 1.6). This could be explained by more widespread thalamocortical connections in the frontal lobe and their involvement in frontal lobe discharges (Behrens et al., 2003; Zhang et al., 2010).

The cerebellum is activated in FLE contralaterally and in TLE ipsilaterally to the focus. The known crossed cerebellar hyperperfusion in ictal SPECT studies was seen more consistently with frontal than with temporal epileptic foci (Marks et al., 1992). This is consistent with the fact that corticopontocerebellar fibers originate mainly from the frontal, parietal and occipital lobes (Brodal, 1972) whereas temporal lobe projections to the cerebellum are sparse and bilateral with ipsilateral predominance (Heath & Harper, 1974; Dietrichs, 1985). Moreover, a study of gray matter volumes in patients with TLE showed a decrease in cerebellar hemisphere volume ipsilateral to the temporal focus and an increase contralaterally (Riederer et al., 2008). Finally, a DTI study comparing subjects with TLE to healthy controls demonstrated reduced fractional anisotropy in the ipsilateral cerebellum (Riley et al., 2010).

BOLD changes in the white matter are controversial because they are thought to represent the activity of cell bodies. Recently, however, evidence demonstrated activation in the corpus callosum during tasks requiring inter-hemispheric transfer (Tettamanti et al., 2002;

Mazerolle et al., 2008) and in the posterior limb of the internal capsule during a tapping task (Gawryluk et al., 2011). We found ipsilateral activations in the genu and posterior limb of the internal capsule in the FLE group. These structures include fibers of the corticobulbar and corticospinal tracts originating from the motor cortices (Englander et al., 1975). IEDs originating from the supplementary motor area (SMA) spread preferentially to the primary motor cortex very rapidly (within 25 msec) (Baumgartner et al., 1996), but data about spread of frontal IEDs originating outside the SMA are not available. However, transcranial magnetic stimulation showed that premotor-motor cortex inhibition is decreased ipsilaterally to the frontal focus (Hamer et al., 2005), suggesting a subthreshold effect of frontal lobe discharges over the motor cortex in the interictal period. These findings could partially explain our BOLD data showing possible involvement in the descending motor pathways in FLE, but the absence of metabolic changes in the cortical motor areas (except the frontal operculum) needs further explanation. DTI and probabilistic tractography of the descending motor fibers in FLE may provide an answer to these questions.

Deactivation

In the three types of syndromes examined (TLE, FLE, and PQE) interictal epileptic activity results in deactivation in regions of the DMN. The most widespread involvement was in TLE (inferior parietal lobules, PCC, and precuneus bilaterally); involvement was more confined in PQE (PCC and pre-cuneus) and FLE (contralateral inferior parietal lobule). The PCC, precuneus, and inferior parietal lobules were already shown to be deactivated in SPECT and EEG-fMRI studies of TLE (Blumenfeld et al., 2004; Laufs et al., 2007; Kobayashi et al., 2009), but were not demonstrated in patients with extra-TLE (Laufs et al., 2007). Our data show that deactivation in DMN regions is not restricted to TLE, but rather is a more common finding in the three groups tested, with, however, a variable extent and different nodes involved among the different groups. These extended deactivations accompanying focal epileptic discharges, at times seen on the individual patient level, could contribute to decreased attention sometimes coinciding with focal IEDs (Aarts et al., 1984; Binnie, 2003), and already invoked to explain lapses of attention in generalized discharges (Gotman et al., 2005).

We also found deactivations in regions not traditionally part of the DMN: the cuneus bilaterally and contralateral superior parietal lobule in FLE and the posterior temporal cortex in TLE. This latter area has sometimes been associated with the DMN (Andrews-Hanna et al., 2010).

Conclusions

In summary, BOLD changes associated with focal interictal epileptic activity are widespread and span the superficial and deep gray and white matter. Our data show that TLE, FLE, and PQE result in unique networks related to focal IEDs. Frontal lobe spikes, despite their spatial heterogeneity, result in common regions of BOLD responses, pointing to an unexpected commonality in this group; the mid-cingulate gyri are involved in both temporal and frontal epileptic discharges, a characteristic they have in common with generalized discharges. DMN regions are deactivated in all three epileptic groups each with a specific pattern; and

subcortical structures, the cerebellum and thalamus, as well as the internal capsule also participate in these epileptic circuits. Epileptic spikes are primarily focal events but the EEG-fMRI approach has allowed demonstrating that they clearly involve widespread brain regions and may have more important consequences on brain function than usually thought. The clinical implications are of a prime interest, since these metabolic changes could provide a functional basis to understand acute and chronic alterations of brain activity such as consciousness and cognition in patients with focal epilepsy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the Canadian Institutes of Health Research (MOP-38079).

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Figure 1.

Group analysis results of TLE group ($n = 32$) for hemodynamic response functions peaking at 3, 5, and 7 s after the interictal epileptic discharges. Axial slices (6 mm) are shown. Resulting t-maps ($p < 0.005$ noncorrected) after cluster size test ($p < 0.05$ corrected for spatial extent) show significant activation clusters in the mid-cingulate gyri bilaterally, and in the ipsilateral insula, mesial and lateral temporal regions, and cerebellum. Significant deactivations are found bilaterally in the inferior parietal lobules, posterior cingulate cortex, and precuneus and in the contralateral posterior temporal cortex.

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Figure 2.

Group analysis results of FLE group ($n = 14$) for hemodynamic response functions peaking at 3, 5, and 7 s after the interictal epileptic discharges. Axial slices (6 mm) are shown. Resulting t-maps ($p < 0.005$ noncorrected) after cluster size test ($p < 0.05$ corrected for spatial extent) show significant activation clusters bilaterally in the cingulate gyri, and in the ipsilateral frontal operculum, medial thalamus, and internal capsule as well as the contralateral cerebellum. Significant deactivation clusters are found in the contralateral inferior and superior parietal lobules and in the cunei bilaterally.

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Figure 3.

Group analysis results of PQE group ($n = 20$) for hemodynamic response functions peaking at 3 and 5 s after the interictal epileptic discharges. Axial slices (6 mm) are shown. Resulting t-maps ($p < 0.005$ noncorrected) after cluster size test ($p < 0.05$ corrected for spatial extent) show significant deactivation clusters in the posterior cingulate cortex and precuneus bilaterally.

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Table 1

Group analysis results for patients with temporal lobe epilepsy

HRF peak (s)	Cluster no.	BOLD response type	Volume (mm ³)	Spatial extent corrected p-value	Max t-value	Location
3	1	Activation	12,736	0.000	4.49	Cingulate gyri (ipsi > contra)
	2		9,504	0.000	4.55	Insula, amygdala, and anterior hippocampus (ipsi)
3	1	Deactivation	5,128	0.000	-4.15	Inferior parietal lobule (contra)
	2		2,280	0.042	-3.74	PCC and precuneus (contra > ipsi)
5	1	Activation	20,944	0.000	4.98	Insula, amygdala, anterior hippocampus, and anterior superior temporal (ipsi)
	2		10,744	0.000	4.41	Cingulate gyri (ipsi > contra)
5	3		6,520	0.000	3.82	Superior cerebellum (ipsi)
	1	Deactivation	5,728	0.000	-4.04	PCC and precuneus (contra > ipsi)
	2		5,008	0.000	-3.36	Inferior parietal lobule (contra)
	3		2,504	0.047	-3.45	Posterior temporal (contra)
7	1	Activation	6,768	0.000	4.13	Insula (ipsi)
	2		5,976	0.000	4.03	Cingulate gyri (ipsi > contra)
	3		4,272	0.004	3.73	Superior cerebellum (ipsi)
7	1	Deactivation	5,352	0.000	-3.51	PCC and precuneus (contra > ipsi)
	2		4,960	0.001	-3.81	Inferior parietal lobule (contra)
	3		3,352	0.016	-3.31	Inferior parietal lobule (ipsi)
9	1	Deactivation	3,504	0.015	-3.56	Inferior parietal lobule (contra)

Patients (n = 32). Significant clusters of activation and deactivation corresponding to the four hemodynamic response functions (HRFs) (p < 0.05 corrected for spatial extent). Within each HRF, clusters are ordered by decreasing volume.

Contra, contralateral; ipsi, ipsilateral; PCC, posterior cingulate cortex, for all tables.

Table 2

Group analysis results for patients with frontal lobe epilepsy

HRF peak (s)	Cluster no.	BOLD response type	Volume (mm ³)	Spatial extent corrected p-value	Max t-value	Location
3	1	Activation	9,216	0.000	5.14	Cingulate gyri (ipsi > contra)
	2		4,560	0.000	3.38	Superior cerebellum (contra)
	3		4,336	0.000	4.00	Frontal operculum (ipsi)
	4		1,928	0.034	3.26	Medial thalamus, genu and posterior limb of internal capsule (ipsi)
3	1	Deactivation	5,728	0.000	-3.60	Inferior parietal lobule (contra)
5	1	Activation	7,696	0.000	4.99	Cingulate gyri (ipsi > contra)
	2		5,432	0.000	4.25	Superior cerebellum (contra)
	3		4,976	0.000	3.54	Frontal operculum (ipsi)
	4		2,632	0.007	3.65	Medial thalamus, genu and posterior limb of internal capsule (ipsi)
5	1	Deactivation	2,280	0.017	-3.40	Inferior parietal lobule (contra)
7	1	Activation	3,960	0.000	4.35	Cingulate gyri (ipsi > contra)
	2		3,496	0.002	3.96	Frontal operculum (ipsi)
	3		2,320	0.022	3.80	Superior cerebellum (contra)
7	1	Deactivation	11,120	0.000	-3.41	Cuneil (ipsi > contra)
	2		2,336	0.021	-3.36	Superior parietal lobule (contra)
9	1	Deactivation	34,056	0.000	-3.80	Cuneil (ipsi > contra)
	2		4,672	0.000	-3.81	Superior parietal lobule (contra)

Patients (n = 14). Significant clusters of activation and deactivation corresponding to the four hemodynamic response functions (HRFs) (corrected p < 0.05 for spatial extent). Within each HRF, clusters are ordered by decreasing volume.

Table 3

Group analysis results for patients with posterior quadrant epilepsy

HRF peak (s)	Cluster no.	BOLD response type	Volume (mm ³)	Spatial extent corrected p-value	Max t-value	Location
3	1	Deactivation	6,336	0.000	-4.30	PCC and precuneus (bilateral)
5	1	Deactivation	5,976	0.000	-3.82	PCC and precuneus (bilateral)

Patients (n = 20). Significant clusters of deactivation corresponding to hemodynamic response functions (HRFs) peaking at 3 and 5 s (corrected p < 0.05 for spatial extent). Within each HRF, clusters are ordered by decreasing volume.