Negative BOLD Responses to Epileptic Spikes

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Abstract: Simultaneous electroencephalogram/functional magnetic resonance imaging (EEG-fMRI) during interictal epileptiform discharges can result in positive (activation) and negative (deactivation) changes in the blood oxygenation level-dependent (BOLD) signal. Activation probably reflects increased neuronal activity and energy demand, but deactivation is more difficult to explain. Our objective was to evaluate the occurrence and significance of deactivations related to epileptiform discharges in epilepsy. We reviewed all EEG-fMRI studies from our database, identified those with robust responses ($P = 0.01$, with ≥ 5 contiguous voxels with a $|t| > 3.1$, including ≥ 1 voxel at $|t| > 5.0$), and divided them into three groups: activation ($A = 8$), deactivation ($D = 9$), and both responses ($AD = 43$). We correlated responses with discharge type and location and evaluated their spatial relationship with regions involved in the “default” brain state (Raichle et al. [2001]: Proc Natl Acad Sci 98:676–682). Deactivations were seen in 52/60 studies ($AD+D$): 26 related to focal discharges, 12 bilateral, and 14 generalized. Deactivations were usually distant from anatomical areas related to the discharges and more frequently related to polyspike- and spike-and-slow waves than to spikes. The “default” pattern occurred in 10/43 AD studies, often associated with bursts of generalized discharges. In conclusion, deactivations are frequent, mostly with concomitant activation, for focal and generalized discharges. Discharges followed by a slow wave are more likely to result in deactivation, suggesting neuronal inhibition as the underlying phenomenon. Involvement of the “default” areas, related to bursts of generalized discharges, provides evidence of a subclinical effect of the discharges, temporarily suspending normal brain function in the resting state. *Hum Brain Mapp* 27:488–497, 2006. © 2006 Wiley-Liss, Inc.

Key words: deactivation; EEG-fMRI; epileptiform discharges; epilepsy; MRI

INTRODUCTION

Combined recording of electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) can be used for noninvasive assessment of blood oxygenation level-dependent (BOLD) changes at the time of an epileptic discharge [Bénar et al., 2002]. The first spike-related EEG-fMRI studies reported only the occurrence of activation (positive changes in BOLD contrast), frequently seen in areas that were concordant with the distribution of the potentials on the scalp [Jäger et al., 2002; Krakow et al., 2001; Patel et al., 1999]. Later, it became clear that these responses were more complex and not always colocalized with the discharge. BOLD changes as a result of epileptic activity can be positive or negative deviations from the baseline, and these responses can be observed close to the presumed epileptic focus but also in distant brain areas [Al-Asmi et al., 2003; Aghakhani et al., 2004; Archer et al., 2003; Bagshaw et al., 2004; Kobayashi et al., 2005]. The presence of a negative

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deviation in BOLD signal, a deactivation, in EEG-fMRI studies was first highlighted in patients with generalized epilepsy and bursts of generalized discharges, but it has been also observed in patients with focal epilepsy and focal EEG abnormalities [Aghakhani et al., 2004; Kobayashi et al., 2004].

Deactivations have been observed in fMRI experiments with different stimuli and tasks [Born et al., 2002; Hamzei et al., 2002; Northoff et al., 2004], as well as studies of alpha rhythm [Goldman et al., 2002; Laufs et al., 2003]. Whereas activation probably reflects an increase in neuronal activity and energy demand, the neurophysiological basis of deactivation is more difficult to explain, but could be related to a reduction in neuronal activity, regional suppression of afferent inputs or “vascular steal” mechanisms [Shmuel et al., 2002]. Deactivations have been reported in areas directly or indirectly involved in stimulus processing or task completion, such as ipsilateral motor cortex in finger tapping [Hamzei et al., 2002], associative auditory cortex in acoustic stimuli [Czisch et al., 2004], and visual cortex in visual stimulation [Born et al., 2002].

Other functional studies have also shown deactivated areas that are task-independent, involving bilaterally the anterior frontal, dorsolateral and mesial parietal regions, and posterior cingulate gyri [Raichle et al., 2001]. These regions show a consistent decrease in the BOLD signal during various stimuli and tasks, which led Raichle et al. [2001] to introduce the concept of a “default” state of brain activity: at rest these areas are tonically activated and become deactivated during a stimulus or a task.

We investigated, in patients with focal or generalized epilepsies, the characteristics of EEG-fMRI studies that produced robust deactivation, as compared to studies that had only robust activation or both types of responses. We assessed the distribution of deactivation and its relationship with the presence of activation and the type and spatial distribution of the epileptic discharge. Our goal was to determine if there is a specific situation in which a deactivation can be expected and the meaning of this type of BOLD change at the time of epileptic discharges.

SUBJECTS AND METHODS

From our EEG-fMRI database, we retrospectively selected the studies acquired from March 2001 to August 2004, performed under the following protocol.

EEG-fMRI Acquisition

Patients underwent a 2-hour recording session after giving informed consent, 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, Erlangen, Germany) using 21 MRI compatible electrodes (Ag/AgCl) placed on the scalp according to the 10-20 system. Subjects’ heads were immobilized with a pillow filled with foam microspheres. Data were transmitted from an EMR32 (1 kHz sampling rate; Schwarzer, Munich, Germany) or a BrainAmp (Brain Prod-

ucts, Munich, Germany; 5 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. BOLD fMRI data were collected in runs of 6 min with the patient in the resting state (voxel dimensions $5 \times 5 \times 5$ mm, 25 slices, 64×64 matrix, TE = 50 ms, TR = 3 s, flip angle 90°), with a total of 6–14 runs per scanning session. The variability in the number of runs in different patients is caused by the various technical issues that must be solved prior to the beginning of the scanning session and sometimes by the patient’s desire to stop the study. This is less likely to be a factor of interindividual variability than the number of spikes, which varies over a much broader range and over which we have no control.

EEG Processing

EEGs underwent MRI artifact removal and filtering offline with the FEMR or Vision Analyzer software. Filtered EEGs were reviewed by an experienced neurophysiologist and epileptic discharges marked according to spatial distribution, morphology, and duration. Spikes and sharp-slow waves were considered under the same category and both were denominated spikes. An EEG-fMRI study was defined for each type of discharge in a given recording, so that those with different spatial distribution or duration were analyzed separately. Studies with only one event were excluded.

EEG Parameters Studied

The following parameters were correlated with the type of fMRI response: (1) isolated events vs. bursts; (2) spikes vs. polyspikes or spike-and-wave; and (3) focal vs. bilateral vs. generalized spatial distribution.

fMRI Data Processing

The fMRI images were motion corrected and smoothed (6 mm full width at half maximum) using in-house software. Temporal autocorrelations were accounted for by fitting an AR model of order 1 according to the methods of Worsley et al. [2002], and low frequency drifts in the signal were modeled with a third-order polynomial fitted to each run. Maps of the t statistic (t -maps) were created using the timing of each spike as an event in the fMRI analysis [fMRIstat, Worsley et al., 2002]. At each voxel the maximum t value was taken from four individual t maps created with four hemodynamic response functions with peaks at 3, 5, 7 and 9 seconds [Bagshaw et al., 2005]. Therefore, for each study, a t -map was created with the maximum absolute t -value at each voxel (either positive or negative) derived from one of the four individual maps. This was done because the hemodynamic response function of epileptic spikes is variable and not well known [Bénar et al., 2002].

A potential problem with this approach, particularly in the current context, concerns the negative undershoot that is often observed following the positive peak. If this had a

Figure 1.

Schematic representation of thresholds used for determining robust and minimal activation (in red) and deactivation (in blue), for each study. On the right, studies that were included (AD, A, and D) and those that were excluded due to threshold criteria.

higher t value than the initial positive peak, we would identify a deactivation that was in reality the undershoot of a previous positive response. In general this is not the case, as the observed positive and negative responses do not spatially overlap [Bagshaw et al., 2004]. In order to confirm this for the patients analyzed in this study, positive responses in the t map created with the HRF peaking at 3 s were compared with negative responses in the t map created using the 9-s HRF for all patients who showed both positive and negative responses (only the 3- and 9-s HRFs were sufficiently separated in time for the undershoot hypothesis to be considered). Of 43 studies analyzed some spatial overlap was observed in two. In one of these the peak of the positive cluster in the 3-s HRF and the negative cluster in the 9-s HRF were 12 mm apart, with some overlap of the rest of the clusters. In the other the deactivation was widespread and included some voxels that were activated with the 3-s HRF. In general, therefore, the deactivations observed in this study were not related to the undershoot of an earlier positive response.

EEG events with different morphology and topography were identified and grouped into types accordingly. If, in a given run, more than one type of event occurred, one column was added in the design matrix for each type of event, leading to a multiple regressor approach. For each type of event a separate t map was produced. The different maps represent separate analyses but they are generated using multiple regressors.

Data Analysis

We were interested in evaluating studies with “robust” responses and therefore we established a threshold for a $P = 0.01$ (minimum of five contiguous voxels with a $|t| > 3.1$ [Cao, 1999], including at least one voxel at $|t| > 5.0$, corrected for the multiple comparisons resulting from the number of

voxels in the brain and for the use of four hemodynamic response functions). Studies were divided into three groups: those showing robust activation only (A), robust deactivation only (D), and both responses (AD). If we had followed these criteria strictly (e.g., robust deactivation and no activation for group D), we would have had very few subjects because many studies that show robust deactivation also show some activation, even if less significant. We therefore took the following approach (Fig. 1): if a study had a robust deactivation but also an activation that was statistically significant but “minimal” (with $3.1 < t < 3.7$), it was kept in the D group. Studies with a robust deactivation and an activation that was more than minimal but not sufficient to be robust were excluded, as they did not have a clear enough result for the purpose of this study. Similarly, we kept in the A group studies with a robust activation and a minimal deactivation. Studies with a robust activation and a deactivation that was more than minimal but not enough to be robust were excluded. Localization of responses was determined by superimposition of the anatomical MRI acquisition and t -stat maps using Anatomist (online at <http://www.brainvisa.info>).

We first examined the frequency of deactivations in focal, bilateral, and generalized epileptic EEG discharges, and whether the spatial distribution of the deactivation corresponded to that of the discharge. A general anatomical concordance between the EEG distribution and the fMRI responses was evaluated for the studies with focal or bilateral discharges and considered present when the response involved the regions generating the discharge. For instance, if a study shows left frontotemporal deactivation and the spikes are restricted to Fp1 and F3 electrodes (which cover the anterior left frontal region), this response is classified as concordant, even though not restricted to the area “seen” by these electrodes. We considered a response focal when it

involved only one quadrant, bilateral when homologous quadrants were involved, and diffuse when three or more quadrants were involved. Second, we established the relationship between the type of response (activation or deactivation or both) and the following parameters of the discharges: morphology (spikes vs. polyspikes or spike-and-wave), spatial distribution (focal, bilateral, or generalized), and duration (single events or bursts).

We then examined how often we found a pattern of deactivation corresponding to the proposed “default” state of brain function [Raichle et al., 2001], because this is one of the most prominent observations in many different fMRI experiments, and is not related to any specific task or stimulus. Finally, in the AD group, we also established the spatial relationship between activation and deactivation by superimposition of the two maps over the anatomical images.

RESULTS

From 172 EEG-fMRI studies in our database, 28 (16%) did not show any responses. Responses were observed in 144 studies, from which 84 were excluded due to the threshold limits we imposed for inclusion of only robust responses. Therefore, 60 studies (from 43 patients) fulfilled our selection criteria: 43 were in group AD (71.5%), 9 in group D (15%), and 8 in group A (13.5%). Discharges were generalized in 14 studies, bilateral in 12, and focal in 34. Structural lesions were present in 37 studies, 6 were postoperative, and 17 had normal MRI, with no difference in the results among the AD, A, and D groups.

The number and the rate of discharges was larger in group A (median number 44, range 5–582; median rate 0.93 spikes/min, range 0.8–8.8) than in group AD (median 18, range 2–319; median rate 0.28 spikes/min, range 0.03–7.6) or group D (median 24, range 7–47; median rate 0.37 spikes/min, range 0.1–0.98), but not significantly so. A negative BOLD response was observed in 52 studies (groups AD and D). In the 43 AD studies responses were most frequently diffuse, both for deactivations (25/43, 58%) and activations (31/43, 72%). Diffuse responses were observed in 50% of group A and in 33% of group D.

Location of Deactivation vs. Distribution of Discharge

Deactivations were seen in 26/34 studies with focal discharges, 12/12 with bilateral, and in 14/14 studies with generalized discharges (Table I). In response to focal discharges, deactivation was bilateral in 19/26 (73%) and concordant (Figs. 2A, 3A, 4) in 16/26 studies (61.5%). Similarly, deactivation in bilateral discharges was usually bilateral (9/12, or 75%), and concordant in 8/12 studies (66.5%, Fig. 3B). For generalized discharges, deactivation was always bilateral, with either anterior-posterior distribution (9/14, or 64%) or restricted to the posterior regions (5/14, or 36%), and never observed solely in anterior regions.

TABLE I. Location of deactivation versus distribution of discharge

Studies with deactivation	Epileptic discharge			
	Focal	Bilateral	Generalized	Total
N	26	12	14	52
Deactivation laterality				
Unilateral	7	3	0	10
Bilateral	19	9	14	42
Concordance with IED				
Concordant	16	8	*	24
Discordant	10	4	*	14
Deactivation in “default”				
Yes	3	1	6	10
No	23	11	8	42

*Concordance between discharge and fMRI regions of deactivation is not relevant for generalized discharges.
IED, interictal epileptiform discharge.

Discharge Parameters vs. BOLD Responses

For all types of discharges, AD was the most frequent pattern of response observed (Table II), but groups A and D originated almost exclusively from spikes. Spike and wave discharges always resulted in deactivation. With respect to distribution (Table II), focal discharges resulted more frequently in AD (56% of the studies), but also in D and A, whereas bilateral and generalized discharges behaved similarly to each other and were almost always associated with AD responses (92 and 93%, with no A and rare D types of response).

Deactivations in group D were usually focal (Fig. 2A), although some deactivations seen in group D were also bilateral and involved anterior and posterior quadrants (Fig. 2B). In group AD deactivations were usually more diffuse (Fig. 3).

With respect to duration (Table II), isolated discharges resulted in AD in 54% of the studies, the other half being equally distributed between D and A. On the other hand, bursts of epileptic activity were associated with AD in 88% of studies.

Deactivation in “Default” Mode

Interestingly, we found that deactivation with the pattern of the “default” mode of brain function was only seen in group AD, occurring in 10 such studies (23%, Fig. 5, Table I). It was notable that 9/10 were related to bursts, whereas isolated discharges occurred in only one. This pattern of deactivation was observed in 43% of generalized, 8% of bilateral, and 11.5% of focal discharges. Among the remaining 42 studies with deactivation, incomplete involvement of the “default” related areas was seen in eight studies: a posterior pattern, i.e., bilateral posterior cingulum and parieto-occipital regions, in five generalized studies (four from group AD and one from group D); a unilateral parietal and bilateral frontal involvement in one study from generalized discharges in group D, and in two other studies from group AD (one generalized and one with bilateral discharges) the deactivation was quite diffuse, but maximum in the “default” regions.

Figure 2.

Patterns of deactivation in group D. **A:** Focal concordant deactivation to T5-P3-O1 spikes in a patient with temporoparietal epilepsy and a left frontal subcortical cyst. **B:** Bilateral anterior and posterior deactivation in response to Fp2-F4-F8 spikes from a patient with frontal lobe epilepsy and previous surgery (right temporal and frontal resections).

Figure 3.

Concomitant activation and deactivation (AD group) in two studies from two different patients. **A:** This EEG-fMRI study is from a patient with secondary generalized epilepsy associated with double cortex syndrome. Left frontal spikes and sharp-slow waves (maximum at electrode F3) resulted in concordant left frontal deactivation, with concomitant involvement of bilateral posterior

cingulate and mesial parieto-occipital regions. Activation was seen over the left frontotemporal and centroparietal regions. **B:** Bilateral temporo-occipital spikes and sharp-slow waves (T6-O2, T5-O1) in a patient with occipital lobe epilepsy and bilateral parieto-occipital cortical atrophy resulted in bilateral occipital deactivation and right frontal activation.

Spatial Relationship Between Deactivation and Activation

This relationship could only be examined in group AD. Activation and deactivation tended to be diffuse in this group and it was not surprising to find that both responses occurred

in the same hemisphere in 42 (97.5%); among these, 33 occurred in the same lobe (76.5%), and among this last group 21 were adjacent to each other (49%).

Among the eight studies of group AD with responses that could be considered as focal (restricted to a maximum

Figure 4.

Deactivation only, related to F8-T4 spikes, in a patient with temporal lobe epilepsy and right hippocampal developmental changes, concordant with the spikes. There is also deactivation in the left temporo-occipital region.

of two quadrants), activations and deactivations occurred in the same lobe in only four and in only one were they adjacent to each other. Therefore, focal activations and deactivations occurring close to each other were found in only 5 of 43 studies (11.5%).

DISCUSSION

Deactivations are often observed in fMRI experiments, but poorly understood. A very transient deactivation followed by a sustained activation has been attributed to an increased neuronal activity with insufficient compensatory increase in

blood flow (the initial dip phenomenon, Frostig et al. [1990]). The vascular steal theory, with reduced local blood flow independent of local changes in neuronal activity and oxygen consumption, but due to an adjacent region of high metabolic demand and increased blood flow, has also been proposed. Although it may be valid for the microvasculature environment, it does not explain deactivations that are distant from areas of activation, nor deactivations occurring by themselves [Gusnard and Raichle, 2001].

Although we had observed that patients with generalized epilepsy and bursts of epileptic discharges showed wide-

TABLE II. Discharge parameters versus BOLD responses

	AD (n = 43)	D (n = 9)	A (n = 8)	Total (n = 60)
IED morphology				
PSW	15 (88%)	2 (12%)	0	17
S	28 (65%)	7 (16%)	8 (19%)	43
IED distribution				
Focal	19 (56%)	7 (20.5%)	8 (23.5%)	34
Bilateral	11 (92%)	1 (8%)	0	12
Generalized	13 (93%)	1 (7%)	0	14
IED duration				
Isolated	15 (54%)	6 (21%)	7 (25%)	28
Bursts	28 (88%)	3 (9%)	1 (3%)	32

AD, activation + deactivation; D, deactivation only; A, activation only; IED, interictal epileptiform discharge; PSW, polyspike/spike-and-slow waves; S, spikes.

Figure 5.

The “default” pattern of deactivation, involving bilaterally the anterior frontal areas, dorsolateral and mesial parieto-occipital regions, and posterior cingulate gyri in three different studies. **A:** Related to bursts of generalized sharp-slow waves in a patient with idiopathic generalized epilepsy. **B:** In response to bursts of sharp-slow waves over Fp2-F4-Fz in a patient with post-traumatic frontal lobe epilepsy and frontal encephalomalacia. **C:** In a patient with left hemispheric epilepsy and a small cystic lesion in the right occipital region. Discharges were characterized by F3-C3-T3-T5 isolated spikes.

spread cortical deactivation [Aghakhani et al., 2004] and involvement of the posterior cingulum [Aghakhani et al., 2004; Archer et al., 2003], there have been no studies that systematically tried to clarify the pattern of negative BOLD responses to different types of epileptic discharges. Deactivations were also previously related to focal epilepsies [Al-Asmi et al., 2003; Bagshaw et al., 2004; Kobayashi et al., 2004], but they were studied from a different perspective than in the current study. Epileptic discharges are a marker of the neuronal hyperexcitability underlying epilepsy, and therefore the observation of deactivation related to them is intriguing. In this study we tried to understand in which situations we could expect to see a robust deactivation, and clarify whether there is a common pattern for its occurrence. We aimed to evaluate only robust responses in order to exclude those deactivated areas that were just above the standard threshold of statistical significance. Our first finding was that although this very stringent criterion lead to the

exclusion of more than half of the studies in our database that had shown BOLD responses, robust deactivations were just as frequent as robust activations. They were found for both focal and generalized discharges. Most of the studies relating to generalized discharges (which corresponded originally to about 10% of our database) were included due to their highly significant responses. Nevertheless, there is still a much larger number of studies derived from focal discharges, and this distribution has to be taken into account when looking at frequencies of a different pattern of responses in the present analysis. We have to acknowledge that excluding 84 studies that showed responses below the thresholds we established here may have resulted in interesting findings being discarded in all three groups of responses. However, it might be more difficult to draw conclusions in a larger series of studies with many less significant deactivations, some of which may represent random deviations above the statistical threshold.

From the 60 included studies (41.5% of our database), deactivation was found in 52 (86.5%), the great majority (71.5%) with concomitant activation, and both responses were usually diffuse. Activations only (13.5%) or deactivations only (15%) were much less frequent. In group AD activation and deactivation did not overlap, and in the few studies where responses were not diffuse, only 11.5% showed close spatial relationship between the two types of responses, which suggests that deactivations are not a result of the vascular steal mechanism. Analysis of sustained negative BOLD responses showed that voxels with positive and negative BOLD changes have the same delay [Saad et al., 2001] and time courses [Shmuel et al., 2002]. Deactivations and activations are coupled and are similarly correlated with stimuli parameters [Shmuel et al., 2002], which means that these responses are under the influence of the same parameters. This similarity may render less surprising the frequent concomitant occurrence of activation and deactivation.

In some cases deactivations were focal and in good spatial agreement with the likely generator of the epileptic discharge. As we discussed in a large series of temporal lobe epilepsy patients, the focal negative BOLD responses in the probable epileptogenic region are difficult to understand [Kobayashi et al., submitted]. One explanation is that strong local inhibition is playing a role in keeping these discharges from spreading, and therefore could represent the most prominent phenomenon from the metabolic point of view.

About one-third of deactivations occurring with concomitant activation (group AD) involved bilateral mesial and dorsolateral parieto-occipital regions, anterior frontal regions, and the posterior cingulate gyri. These regions were previously implicated in the baseline brain state of activity, supporting the existence of a “default” pattern of brain activity, and would be tonically activated in awake alert resting individuals, showing a task-independent decreased level of activity at the time of a task or stimulus [Raichle et al., 2001]. They were also found to be negatively correlated with the power in the alpha band in the EEG, another

measure of the level of attention [Goldman et al., 2002; Laufs et al., 2003]. Deactivations in areas related to the “default” pattern may indicate a widespread, nonspecific effect of the discharges on the baseline brain state, and as such are not indicative of the region responsible for the generation of the epileptic discharges. Generalized discharges always resulted in deactivations, and the “default” pattern was seen in 43% of these studies, with the other 57% having some involvement of these areas, usually restricted to the posterior aspects. The observation of this deactivation in the “default” pattern in relation to generalized discharges is further evidence for transient cognitive impairment [Aarts et al., 1984] as an effect of interictal discharges on normal brain function. This concept has been raised as a possible factor of morbidity in epilepsy patients, and was recently reviewed by Aldenkamp and Arends [2004]. It is frequently associated with generalized bursts, but also with focal spikes, for which the functional disruption corresponds to the anatomical location of the spike [Shewmon and Erwin, 1988a,b].

Finally, in other cases deactivations were diffuse and did not have a strong relationship with the region of generation of the epileptic discharge, although that region may have been included in the deactivation. These deactivations may result from the effect of the epileptic discharge on the rest of the brain, which may be more widespread than is manifested in the EEG.

Bursts of epileptic discharges are more likely to produce activations combined with deactivations, whereas isolated activation or deactivation result primarily from isolated events. Spike-and-slow waves were always associated with deactivation, which was not observed with spikes not followed by a slow wave. The association of deactivations with the presence of the slow wave component, which may be the electrographic correlate of prolonged inhibition [Gloor, 1978], is an interesting finding. Increased inhibition compared to the baseline should result in increased metabolic demand, and hence in a BOLD activation [Logothetis, 2003]. In this context, a deactivation could result from abnormal coupling between oxygen consumption and blood flow or between blood flow and BOLD signal change. We have shown, however, that these two types of coupling were preserved during epileptic discharges [Stefanovic et al., 2005]. Could it be, then, that increased inhibition results in deactivation? This has been shown during a motor task [Stefanovic et al., 2004] and may be explained by the very low energy required by some types of inhibition and the possible shutting down of action potentials as a result. Even though action potentials are not the primary contributors to the BOLD response, they make a significant contribution to it [Logothetis et al., 2001].

In conclusion, it would seem that in patients with epilepsy deactivations can occur through several mechanisms, and can be directly related to the generation of the epileptic activity or to the effect of the epileptic activity on the brain as a whole. Deactivation occurs as frequently as activation, but more work is needed to determine its true significance.

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