Imaging the Interaction: Epileptic Discharges, Working Memory, and Behavior

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Abstract: Interictal generalized epileptiform discharges may impair cognition. We used simultaneous video-electroencephalography and functional imaging to quantify changes, induced by epileptiform discharges, in the task-related activations during a spatial working-memory paradigm. The number of epileptiform discharges increased during the task with its level of complexity, but were not significantly associated with wrong responses during the task. We observed hemodynamic responses in working-memory related frontal-lobe-network, motor-cortex, precuneus, and parietal lobes in the absence of epileptiform discharges. In the presence of epileptiform discharges during the task, task-related hemodynamic changes were seen only in motor-cortex, precuneus, and parietal lobes. These findings suggest that generalized epileptiform discharges during a high demanding working memory task may change the working memory-related hemodynamic responses in frontal-lobe-network. *Hum Brain Mapp* 34:2910–2917, 2013. © 2012 Wiley Periodicals, Inc.

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INTRODUCTION

The effect of interictal epileptiform discharges (IED) on cognitive function remains controversial [Aldenkamp et al., 1996, 2005]. An impairment of cognitive function during epileptiform discharges was described in 1939 [Schwab, 1939]. Whilst both, generalized and focal discharges were found to impair cognition in up to 50% of patients [Aarts et al., 1984; Binnie et al., 1987; Rugland, 1990; Shewmon and Erwin, 1988], the mechanism by which short lasting IED affects cognition remains unknown [Binnie, 2003]. The nature of the cognitive task is key, as complex tasks with increasing difficulty such as working memory (WM) tasks are more sensitive for detecting cognitive impairment than less demanding tasks [Aarts et al., 1984; Binnie et al., 1987; Hutt and Gilbert, 1980]. Neuropsychological studies indicate that IED and cognition have a complex bidirectional relationship; cognitive tasks may suppress IED, but also may increase the rate of IED with increasing task difficulty [Binnie, 2003; Binnie et al., 1987; Tizard and Margerison, 1963], thus facilitate the detection of IED-related cognitive impairment. Recent functional imaging studies investigating the brain structures involved in the interaction between epileptic discharges and task used simple reaction time tasks under continuous attention [Bai et al., 2010; Berman et al., 2010; Moeller et al., 2010]. We hypothesized that IED during the task may affect well-established WM-related activations in prefrontal cortex. We tested this hypothesis by using a spatial WM-task and testing for regionally specific interactions between IED and haemodynamic responses developed by WM-task using simultaneous video, electroencephalography and functional magnetic resonance imaging (v-EEG-fMRI).

METHODS

We report a 39-year-old, right-handed woman with idiopathic generalized epilepsy (IGE, subtype: childhood absence epilepsy). Birth and early development were normal and there were no learning disabilities. The seizure onset was at age 7 years with typical absences and generalized tonic-clonic seizures. Neurological examination and high resolution structural imaging were normal. Repeat long-term video telemetry EEG recording had shown frequent bilaterally synchronous 2.5–3 Hz generalized spike and wave discharges (GSWDs) with anterior predominance lasting 1–3 s. The discharges were more marked with stressful conditions and lack of sleep and were not increased with hyperventilation. The discharges associated with unresponsiveness were accurately recalled by the patient. Several antiepileptic medications including valproate, carbamazepine, ethosuximide, lamotrigine, clobazam, phenytoin, topiramate, and clonazepam had been tried without any significant improvement to control absences. Written informed consent was obtained and the

study was approved by the local hospital research ethics committee.

A gradient-echo echo planar imaging sequence was used to acquire 240 blood oxygen level dependent (BOLD) sensitive scans using a 3T GE Signa[®] Excite HDX echospeed MRI scanner (GE, Milwaukee, USA) with a standard transmit/receive head coil. The image parameters were as follows: TE = 30 ms; TR = 3,000 ms; Flip angle = 90°; Number of slices = 44; Slice thickness = 2.4 mm; Slice gap = 0.6 mm; FOV = 24 × 24 cm²; matrix: 64 × 64.

During scanning, the patient performed a continuously updating parametric spatial WM task of the *n*-back type with three levels of working memory load: 0-back, 1-back, and 2-back [Vollmar et al., 2011]. During the task dots randomly appeared in one of the four corners of a diamond-shaped box and the patient had to move a joystick with her right hand to the position of the dot. Each dot was displayed for 2 s in one position. The patient was instructed to move the joystick to the position of the current dot in the 0-back condition; to the position of the previous dot in 1-back condition; and to the position of the dot two presentations earlier in the 2-back condition. Performance parameters (“correct,” “wrong,” and “no” responses derived from the movement of joystick) during the task were recorded simultaneously. Each of the three active conditions: 0-back, 1-back, and 2-back, lasted 30 s and was repeated five times (30 × 5 = 150 s) in a pseudorandom order alternating with a 15 s rest condition consisting of a static display of all four dots. The total duration of the task inside the scanner was twelve minutes and the patient underwent task familiarization before scanning.

For the purpose of statistical analysis each 2 s (time for the display of dot at one position) was counted as one event. The numbers of IED and performance parameters (correct responses and wrong/no responses) during different task phases were compared using chi-squared tests in the statistical package Stata/IC 11.1 (StataCorp LP).

Video-EEG recording was performed during fMRI using MR-compatible 64-channel EEG-cap and recording equipment [Chaudhary et al., 2010]. EEG was recorded and processed using Brain Analyzer2 (Brain Products). The IEDs (2.5–3Hz GSWD) identified on inside-scanner EEG were identical with the IEDs on EEG during long-term video telemetry. All IEDs identified on inside-scanner EEG were used for further fMRI analysis.

All fMRI data was pre-processed (realigned, normalized to Montreal Neurological Institute (MNI) space and smoothed) and analysed using SPM5 (www.fil.ion.ucl.ac.uk/spm). A general linear model (GLM) was specified based on factorial design: task × IED (Factor 1 = Task with 4 levels: rest, 0-back, 1-back, 2-back, and Factor 2 = IED with 2 levels: presence, absence). As a result, the GLM (see Supplementary Figure 2 showing design matrix and orthogonality) had eight regressors of interest: rest with

Figure 1.

(a) Mean number of IED with 95% confidence intervals [Mean $\pm$ 1.96*(Standard Deviation/ $\sqrt{n}$)] during each 30-s block of active conditions [0-back (total duration = 150 s), 1-back (total duration = 150 s), 2-back (total duration = 150 s)] and 15-s block of rest (total duration = 270 s). The IED increased from rest to 0-back to 1-back to 2-back which was statistically significantly (Chi-squared test for trend: $Z = 4.25$, $P < 0.001$). (b) Mean number of correct responses

with 95% confidence intervals [Mean $\pm$ 1.96*(Standard Deviation/ $\sqrt{n}$)] during each 30-s block of active conditions [0-back (total duration = 150 s), 1-back (total duration = 150 s), 2-back (total duration = 150 s)]. The correct responses decreased linearly with increasing task complexity from 0-back to 1-back to 2-back (Chi-squared test for trend: $Z = 7.56$, $P < 0.001$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

IEDs, 0-back with IEDs, 1-back with IEDs, 2-back with IEDs, rest without IEDs, 0-back without IEDs, 1-back without IEDs, 2-back without IEDs. IED and stimulus presentation (for 0-back, 1-back and 2-back) were represented as “0” duration stick functions and convolved with canonical hemodynamic response function [Friston et al., 1995; Price et al., 1997]. The six realignment parameters from image preprocessing were included in the GLM as covariates of no interest [Friston et al., 1995], explaining head movement-related MR-signal variance.

The contrasts were defined for the “task” by including the memory load (1-back and 2-back) and the control task (0-back, as it does not have a memory load and represents only motor-related changes), and for the “WM” by comparing task with memory load (1-back and 2-back) against the control task (0-back) [Vollmar et al., 2011]. SPMs of the F -statistic were computed to test for the (simple) main effects of: IED (during rest and task) showing IED-related BOLD changes, and task (with and without IED) showing BOLD responses in task-sensitive brain regions. SPMs testing for main effect of the task were used as an inclusive mask in SPM-contrast building to restrict the search for regions showing an effect (SPMs of the t -statistics) of: task-with-IED, task-without-IED, WM-(excluding motor-related changes)-with-IED, WM-without-IED and the following interactions: task-level (task-without-IED > task-with-IED) and WM-level (WM-without-IED > WM-with-IED). SPMs were thresholded at $P < 0.05$ (family wise error corrected) to test for the main effects of IED and task (with and without IED), and also for $P < 0.001$ (uncorrected for family wise error). The effects: task-with-IED, task-without-IED, WM-(excluding motor-related changes)-with-IED, WM-without-IED and the following interactions: task-level (task-without-IED > task-with-IED) and WM-level (WM-without-IED > WM-with-IED) were tested at a significance of $P < 0.001$ (uncorrected) within the task-sensitive

brain regions (as described above). The results were overlaid on a 3D-rendered normalized brain in MNI space. We confirmed the location of visually identified BOLD clusters using automated anatomical labelling (AAL) atlas in SPM tool box: xjView.

RESULTS

The patient had 52 IED lasting 0.2–2s (mode:0.3, standard error: ± 0.05) during vEEG-fMRI recording session. The number of IED was significantly different (chi-squared test, P -value < 0.001) during the task (43/225 observations) and rest conditions (9/135 observations) and increased with increasing complexity of the task (chi-squared test for trend: $Z = 4.25$, $P < 0.001$) (Fig. 1a). Furthermore, correct responses were significantly different for 2-back (9/75) than 1-back (22/75) than 0-back (58/75) and decreased with increasing complexity of the task (χ^2 test for trend: $Z = 7.56$, $P < 0.001$) (Fig. 1b). We did not find a significant association between presence of IED and the performance parameters, that is, correct and wrong response in either of the active task conditions (0-back, 1-back, 2-back) at the time of stimulus presentation or at the time of actual response corrected for delay in 1-back and 2-back.

The IED recorded during the task and rest conditions were similar (Fig. 2a) to the discharges recorded during standard EEG. The main effect of IED revealed significant BOLD decreases in the precuneus and lateral parietal and frontal lobes (Fig. 2b). (see Supplementary Figure 3 for SPM[F] - maps for IED during rest and task showing similar BOLD changes).

The main effect of task irrespective of the presence of IEDs showed significant BOLD changes in task sensitive areas: bilateral middle and inferior frontal gyrus, bilateral pre- and post-central gyrus, bilateral parietal lobe,

Figure 2.

(a) Representative sample of EEG during rest and task periods. 2.5–3 Hz GSWD during 270 s of rest ($N = 9$) and 450 s ($N = 43$) of task lasting 0.2–2 s were counted, which were significantly higher during the task (Chi-squared test, $P = 0.001$). (b) Main effect of IED: SPM of F -statistics ($P < 0.001$) overlaid on a 3D-rendered normalized brain in MNI space. IED during rest and task were associated with BOLD decreases (green clusters) in precuneus (left sagittal medial surface view), lateral parietal lobes, lateral and basal frontal lobes and small clusters of BOLD increases (red clusters) in frontal and parietal lobe and cerebellum. The crosshair in the medial surface view showing BOLD

changes in precuneus. (c) Main effect of task [memory load (1-back and 2-back) and control condition (0-back)] irrespective of IED: SPM of F -statistics ($P < 0.001$) overlaid on a 3D-rendered normalized brain in MNI space. Significant BOLD changes were seen in bilateral middle and inferior frontal gyrus, bilateral pre and post-central gyrus, bilateral lateral parietal lobe, precuneus, paracentral lobule, supplementary motor area, medial superior frontal gyrus, thalamus and occipital lobe (left sagittal medial surface view). The crosshair in the medial surface view showing BOLD changes in precuneus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

precuneus, paracentral lobule, supplementary motor area (SMA), medial superior frontal gyrus, thalamus, and occipital lobe (Fig. 2c).

Task-related effects (without IED) showed significant BOLD activations in the pre- and post-central gyri bilaterally extending into the middle and inferior frontal gyri,

superior parietal lobes, thalamus, SMA and cerebellum, with BOLD deactivations in the precuneus, lateral parietal, frontal and medial frontal lobes, and right pre-central gyrus (Fig. 3a.i). For the task-related effects during IED, BOLD activations were observed only in the left pre-central gyrus, and bilateral superior parietal lobes, and BOLD

Figure 3.

SPMs of T -statistics ($P < 0.001$) masked by main effect of task and overlaid on 3D-rendered normalized brain in MNI space. Red clusters represent BOLD activations and green clusters represent BOLD deactivations. (a.i) BOLD activations for the task without IED involved bilateral pre and post-central gyri extending into middle and inferior frontal gyri, superior parietal lobes, thalamus, supplementary motor area, and cerebellum. BOLD deactivations involved precuneus, lateral parietal and frontal and medial frontal lobes, and right pre-central gyrus. Left sagittal medial surface view showing BOLD changes in the midline structures and the crosshair in the medial surface view reveals BOLD changes in precuneus. (a.ii) BOLD activations for the task with IED were seen in left pre-central gyrus, and bilateral superior parietal lobes, and BOLD deactivations in precuneus, left lateral parietal and frontal lobes, and right pre-central gyrus. Left sagittal medial surface view showing BOLD changes in the midline structures and the crosshair in the medial surface view reveals BOLD changes in precuneus. (b.i) BOLD activations for the WM without IED were present in bilateral middle and inferior frontal gyri, pre and post-central gyri, superior parietal lobes, superior temporal gyrus, occipital lobes, thalamus and cerebellum, and BOLD deactivations in precuneus and lateral parietal

deactivations in precuneus, left lateral parietal and frontal lobes, and right pre-central gyrus (Fig. 3.a.ii).

The effect of WM-without-IED revealed significant BOLD activations in a fronto-parieto-striato-thalamo-cerebellar network: bilateral middle and inferior frontal gyri extending into pre- and post-central gyri, SMA, superior parietal lobes, superior temporal gyrus, occipital lobes, caudate, globus pallidum, thalamus and cerebellum, and BOLD deactivations in the default mode network (DMN)-related areas: precuneus, lateral parietal and medial frontal lobes (Fig. 3.b.i). For the WM-related effects during IED, smaller clusters of BOLD activations were observed only in the occipital lobes, SMA, parieto-temporo-occipital junc-

tion, and medial frontal lobes. Left sagittal medial surface view showing BOLD changes in the midline structures and the crosshair in the medial surface view reveals BOLD changes in precuneus. (b.ii) BOLD activations for the WM with IED were observed in occipital lobes, supplementary motor area, parieto-temporo-occipital junction, left pre-central gyrus, thalamus and cerebellum, and small clusters of BOLD deactivations in frontal lobes. Left sagittal view showing BOLD changes in left hemisphere and the crosshair points to the BOLD changes in precentral gyrus. (c.i) Interaction between task and IED showed greater BOLD activations for the task-without-IED than task-with-IED in bilateral inferior frontal gyrus extending into pre- and post-central gyrus. Right sagittal view showing BOLD changes in right hemisphere and the crosshair points to the BOLD changes in inferior frontal gyrus. (c.ii) Interaction between WM and IED, showing BOLD activations for WM-without-IED more than WM-with-IED in right inferior and middle frontal gyrus and bilateral parietal lobes. Right sagittal view showing BOLD changes in right hemisphere and the crosshair points to the BOLD changes in inferior/middle frontal gyrus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

tion, bilateral pre/post-central gyrus, thalamus, left inferior frontal gyrus and cerebellum; other smaller clusters of BOLD deactivations were seen in the frontal and parietal lobes (Fig. 3.b.ii).

The interaction between the task and IED (Fig. 3.c.i) revealed activation differences in areas including: bilateral inferior frontal gyri extending into the pre- and post-central gyri. We also plotted the time course of the BOLD signal change for the global statistical maximum cluster in the contrast task-without-IED > task-with-IED (Fig. 3ci, crosshair shows the global statistical maximum cluster). We found greater BOLD changes for task-without-IED than task-with-IED reflecting that these areas were active during different

Figure 4.

Predicted BOLD responses based upon the maximum likelihood parameter estimates of the GLM for regions showing a significant interaction with task. These quantitative estimates demonstrate that these areas are more active during task-without-IED than task-with-IED. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

phases of the task (0-back, 1-back, 2-back) without IED and deactivated for task-with-IED as shown in Figure 4. There were no greater BOLD decreases for task-without-IED than task-with-IED. The interaction between WM and IED (Fig. 3.c.ii) showed greater BOLD activations in right inferior and middle frontal gyri and bilateral parietal lobes for WM-without-IED than WM-with-IED.

DISCUSSION

Our observations suggest a bidirectional relationship that cognitive processing of a high demanding task influences IED which in turn may affect the functional networks active during WM. Consistent with previous reports, WM-task provoked IED in our patient [Aarts et al., 1984; Binnie et al., 1987].

The task and WM-related frontal-lobe-networks were suppressed when IED were present during the task, despite preserved motor-performance and visual-spatial processing as evident by button presses related BOLD changes in motor cortex and visual attention related BOLD changes in occipital lobes and superior parietal lobes [Owen et al., 2005] (Fig. 3). During the task-performance (without-IED), the task and WM-related-network of BOLD activations was consistent with the fronto-parieto-striato-thalamo-cerebellar

network described previously [Kumari et al., 2009; Takeuchi et al., 2011]. Similarly, during the task performance without IED, the task and WM-related BOLD decreases seen in DMN-related areas were also consistent with previous findings [Takeuchi et al., 2011]. Nonetheless, the WM-related frontal lobe network was found to be activated more strongly with the task without IED, than with the task in the presence of IED as shown in Figure 3b,c. It is possible that the presence of IED introduced increased variability in the fMRI signal causing some of the task-related fMRI changes to be more difficult to detect because of their reduced amplitude relative to baseline variability, and thus failed reaching statistical significance. The parametric increase of task-related BOLD response (in the absence of IED) in the WM-related frontal lobe network, as shown in Figure 4, was similar to that observed previously [Kumari et al., 2009]. In addition, the presence of IED during the task was associated with BOLD decreases in the same areas active for the task without IED. This is in agreement with the findings that interictal discharges are associated with focal tissue hypoxia [Geneslaw et al., 2011], which in turn may result in poor performance for a high demanding task.

The effect of IED was also consistent with the previously reported BOLD decreases in the DMN in IGE [Bai et al., 2010; Berman et al., 2010; Moeller et al., 2010]. We did not observe IED-related BOLD signal changes in the thalamus which may be due to the relatively short duration of the discharges in our patient (always less than 3 s). It has been observed previously that thalamic signal changes were seen in patients with discharges of longer durations [Hamandi et al., 2006]. The duration of IED is important when investigating cognitive impairment secondary to IED or seizures [Aarts et al., 1984]. Our findings are supported by recent studies [Bai et al., 2010; Berman et al., 2010; Moeller et al., 2010] investigating the interaction between behavior and epileptiform discharges of longer durations in IGE, using either simple motor or attention tasks. Cortico-thalamic BOLD network changes were noticed in association with behavioral interruptions, i.e. typical absence seizures [Bai et al., 2010; Berman et al., 2010; Moeller et al., 2010]. In our study, we focussed on short lasting discharges without clinical change and a task with high cognitive demand. The differences in the WM-related BOLD network in the presence and absence of IED are in line with the findings that functional changes underlie the impaired interictal attention [Killory et al., 2011].

Increased task complexity was associated with a significant increase in the number of IED (Fig. 1a) and a significant decrease in correct responses (Fig. 1b) [Aarts et al., 1984; Binnie et al., 1987]. It can be argued that the level of statistical significance for correct responses would be different if the three performance parameters (wrong, correct, and no response) were included separately rather combining wrong and no response as one performance parameter. We verified this by comparing the three performance parameters separately and confirmed that there was a significant decrease in correct responses (χ^2 test for trend: $Z = 2.20$, $P = 0.03$) with increased task complexity. It is difficult to

associate the presence of IED with individual behavioral response categories (correct, wrong and no responses) during different task phases for the following reasons: (1) the complexity of the design with a continuously updating working memory task with possible interaction between IED and response to a stimulus occurring 2 s earlier (retrieval) or later (encoding); (2) limited number of discharges during each active condition of the task. Behaviorally, the performance parameters were not significantly different by the occurrence of IED. It is argued that for an IED to produce a measureable behavioral correlate, it needs to be of certain duration (more than 3 s) [Aarts et al., 1984; Aldenkamp et al., 2001]. Our imaging data suggests an interaction between IED and the WM-related BOLD network in the presence of short lasting IED, as compared to the WM-related BOLD network in the absence of IED; despite there was no statistically significant association between wrong responses and the presence of short lasting IED.

Designing such studies, combining three modalities (hemodynamic, electrophysiological, and behavioral), is challenging and can be very demanding on patients who we need to have sufficient numbers of IED during the limited time inside the scanner when performing the task (see Supplementary Figure 1 SPM[T] - maps for multiple patients with or without IED showing BOLD changes for the WM, reflecting there is no obvious cumulative effect of IED during the task). For example we scanned eight IGE patients with frequent IED on repeat standard EEG and only the patient reported here had increased IEDs during task performance inside the scanner. It may be possible that IED were suppressed by the complexity of the task in seven patients, as suggested by other studies that increasing complexity of the task performance may also suppress the focal and generalized interictal and ictal discharges [Aarts et al., 1984; Berman et al., 2010; Binnie et al., 1987; Binnie, 2003; Matsuoka et al., 2000].

Our observations in one patient cannot be generalized, but these findings suggest that the functional networks active during a high demanding cognitive task may change in the presence of shorter lasting IED, generating interesting hypotheses on how interictal discharges may affect cognition, but this requires further testing in larger studies.

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