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Research article

Carbamazepine reduces memory induced activation of mesial temporal lobe structures: a pharmacological fMRI-study

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Abstract

Background and Purpose: It is not known whether carbamazepine (CBZ; a drug widely used in neurology and psychiatry) influences the blood oxygenation level dependent (BOLD) contrast changes induced by neuronal activation and measured by functional MRI (fMRI). We aimed to investigate the influence of CBZ on memory induced activation of the mesial temporal lobes in patients with symptomatic temporal lobe epilepsy (TLE).

Material and Methods: Twenty-one individual patients with refractory symptomatic TLE with different CBZ serum levels and 20 healthy controls were studied using BOLD fMRI. Mesial temporal lobe (MTL) activation was induced by a task that is based on the retrieval of individually familiar visuo-spatial knowledge. The extent of significant MTL fMRI activation was measured and correlated with the CBZ serum level.

Results: In TLE patients, the extent of significant fMRI activation over both MTL was negatively correlated to the CBZ serum level (Spearman $r = -0.654$, $P < 0.001$). Activation over the supposedly normal MTL, i.e. contralateral to the seizure onset of TLE patients, was smaller than the averaged MTL activation in healthy controls ($P < 0.005$). Age, duration of epilepsy, side of seizure onset, and intelligence were not correlated to the extent of the significant BOLD-response over both MTL in patients with TLE.

Conclusions: In TLE patients, carbamazepine reduces the fMRI-detectable changes within the mesial temporal lobes as induced by effortful memory retrieval. FMRI appears to be suitable to study the effects of chronic drug treatment in patients with epilepsy.

Introduction

Functional magnetic resonance imaging of the brain (fMRI) is no longer exclusively used in normal control subjects and highly selected patients, but increasingly applied to large numbers of chronically ill patients in clinical neurology and psychiatry [1]. In these settings, fMRI is used to explore neuronal (dys-)function in or close to brain regions implicated in the assumed disease processes. Recently, fMRI has been applied to patients with chronic epilepsy, mood disorders and chronic pain without systematically exploring possible interactions with pre-existing chronic medication [2–4].

Carbamazepine (CBZ) is a widely used drug in neurology and psychiatry. CBZ was originally introduced as an anticonvulsant and nowadays is used as a first-line drug in patients with localization-related epilepsies [5]. There is good evidence that CBZ is effective in the management of acute mania and prophylaxis of bipolar disorder, and it might have some benefit in the treatment of drug-resistant depression [6]. It is also used in patients with chronic neuralgic facial pain and headaches [7]. The definite modes of action remain unclear in these diverging manifold CBZ usages, as do the causes for the cerebral side effects of the drug (drowsiness, vertigo etc.). There are only single reports on CBZ affecting cerebral metabolism measured with positron emission tomography (PET) [8].

There is no information whether the intravenous concentration of CBZ interferes with task-related contrast changes of fMRI in patients treated chronically with CBZ. Using a recently described memory fMRI paradigm for single case studies we aimed to determine possible interactions between CBZ serum levels and fMRI response in mesial temporal lobe structures of patients with chronic symptomatic temporal lobe epilepsy (TLE) [9].

Subjects and methods

Subjects

We studied 21 consecutive patients with refractory TLE [11 women; mean age 35.7 years; SD 10.1; range 13 to 54 years) who underwent a comprehensive evaluation prior to epilepsy surgery at our institution. All patients fulfilled the following criteria: unilateral seizure onset of temporal lobe origin shown by continuous interictal and ictal video/EEG monitoring with scalp and sphenoidal electrodes, and unilateral lesions within the temporal lobes demonstrated by high resolution routine MRI. In 13 patients a right-sided and in eight patients a left-sided TLE was diagnosed. Ten patients had hippocampal sclerosis, three vascular lesions, two tumors, and six miscellaneous or cryptogenic temporal lobe lesions. The mean duration of epilepsy was 21.6 years (SD 9.4; range 1 to 35 years). Median seizure frequency was 3 complex partial seizures/month (range 0.1–180 seizures/month). The mean full scale IQ (WAIS-R, WCIS-R) was 96.3 (SD 20.6; range 51 to 126). Neither global nor selective cognitive impairment were a criterion for patient exclusion.

All patients received CBZ (mean serum level 7.5 mg / l; range 2.4 to 11.7). Two patients received gabapentine (GBP: 3.8; 2.3 mg / l) and three patients lamotrigine (LTG: 2.3; 3.2; 3.9 mg / l) as comedication.

Twenty healthy controls (10 women, mean age 31.7 years, SD 0.6) were also studied using fMRI.

FMRI task design

The paradigm consisted of 10 activation blocks and 10 baseline blocks. Each block was introduced by spoken commands using the in-build communication device of the commercially available MR scanner. The duration of each block was 30 seconds. During each block, 10 sets of 16 coronal T2*-weighted MR-slices were obtained. During the activation block, retrieval from long-term memory without language was induced by self paced performance of Roland's Hometown Walking task [9,10]. The task were explained to the subjects in detail before scanning. For each subject an individual hometown walk encompassing ten destinations was prepared. If a subject had recently moved, than the most familiar hometown was chosen. The walk started either at home or at a well known central point (e.g. place, station). Then the subjects were asked to select a familiar landmark as destination. This landmark served as starting point for the walk to the next destination. Subjects were instructed to seek destinations within a 300 to 400 meters range. After preparation of ten pairs of starting points and destinations the complete route was presented to the subject to ensure consistency and comprehension of the words denoting the route. During MR-scanning, subjects were asked to mentally navigate through the ten different routes and to imagine as many details as possible while navigating. Subjects were instructed to look around the destination if they reach the destination prior to the beginning of the baseline condition. After 30 seconds each route was interrupted by the baseline task. The baseline condition consisted of covertly counting odd numbers starting with 21. Children and mentally impaired patients counted consecutively if they had difficulties to count fluently odd numbers.

MRI acquisition

MRI scanning was performed on a 1.5 T scanner (Siemens Magnetom Symphony, Erlangen, Germany) equipped with a standard head coil. Scout and sagittal T1-weighted images were obtained in every subject to position the coronal T2*-weighted images perpendicular to the long axis of the hippocampus. For fMRI, 16 contiguous coronal T2*-weighted images covering the temporal lobes with a slice thickness of 5 mm were obtained using a standard EPI sequence (TR = 1600 msec, TE = 50 msec, field of view 192 mm, matrix 64×64).

Image analysis

Online image processing was performed using software provided with the commercially available scanner which recently has been compared to standard offline post-processing software (SPM 99) [11]. The T2*-weighted images were corrected for subject movement using an algorithm for realignment in k-space. Images were smoothed using a Gaussian filter (width 2.0) to prepare

statistical comparisons on a voxel-by-voxel basis. Voxel-by-voxel z tests were performed for each subject, identifying average signal intensity increases as measured during the activation phases, compared to the average signal intensity acquired during baseline conditions. The statistical threshold was chosen to be $z > 4$, $P < 0.00003$ for a single activated voxel. Statistical maps showing activated voxels were projected onto EPI images of the same patient thus using images for display purposes with geometric distortions similar to the fMRI data. To perform group data analysis, two investigators blinded to clinical data counted the numbers of voxels in a predefined region of interest over both MTL. The size of this region of interest was 600 to 800 voxels per person. Counting used the crus of the fornix as the posterior starting point and continued anteriorly until no activated voxels were found. Activated voxels were defined as those voxels that had neighboring activated voxels, i.e. at least one adjacent activated voxel in plane and one neighboring activated voxel on at least one adjacent MR-slice. Clustering removed small and scattered activated regions that were unlikely to represent genuine brain activation. Clustering further reduced the real type I error probability of a $z > 4$ threshold.

Statistical analysis

For each subject the absolute numbers of individual MTL voxel counts were determined. In patients, activated voxels for the MTL ipsilateral and contralateral to the seizure onset were counted. The total voxel number of both MTL was summed up. Spearman's rank correlation coefficients were computed between CBZ serum level, the ipsilateral, contralateral, and total number of activated voxels within MTL. A univariate analysis of variance (ANOVA) was used to study effects of the factor 'side of seizure onset' and of the covariates 'age', 'duration of epilepsy', and 'intelligence'. MTL activation contralateral to the seizure onset of patients was compared to averaged MTL activation of healthy controls using an univariate ANOVA with study group as factor, while age served as covariate. The influence of polytherapy and type of lesion on the number of activated voxels was compared.

Results

Retrieval of hometown routes relative to the listing of odd numbers resulted in significant T2*-contrast differences ($z > 4$) over regions within MTL of all subjects (Fig. 1). Activity was most frequently confined to the parahippocampal gyrus. Clustered significant signal changes projecting onto the hippocampus were not observed at the statistical threshold chosen. Significant signal differences also were noted in several other areas, including bilateral posterior-parietal cortex, retrosplenial cortex, and mesial occipital cortex.

The CBZ serum level was negatively correlated with the number of significantly activated MTL voxels: ipsilateral $r = -0.469$, $P < 0.05$; contralateral $r = -0.642$, $P < 0.002$; bilateral $r = -0.654$, $P < 0.001$). The CBZ epoxide serum level did not further contribute to the explanation of variance of the fMRI activation. There was no Spearman rank correlation between seizure frequency and number of activated voxels in the MTL opposite the seizure onset ($p > 0.1$).

The analysis of variance on the number of bilaterally activated MTL voxels revealed no effect of the factor side of TLE ($P > 0.2$). The covariate CBZ serum level was related to the number of activated voxels ($F = 6.18$, $P < 0.05$) but not the variables age, duration of epilepsy, and intelligence ($P > 0.3$). There was no difference in the number of activated voxels between patients receiving exclusively CBZ and patients with add-on medication. Patients with hippocampal sclerosis showed less ipsilateral activation compared with patients without hippocampal sclerosis ($P < 0.05$).

The comparison of contralateral MTL activation of patients and averaged MTL activation of healthy controls revealed less activation in patients ($F = 10.33$, $P < 0.005$). Age was unrelated to the number of activated voxels.

Discussion

This is the first study correlating the spatial extent of significant, mesiotemporal fMRI activation to intravenous CBZ concentrations in patients with TLE. Thus, this study adds to the ongoing discussion about the role of fMRI in pharmacological research in neurology and psychiatry [12,13]. Levels of antiepileptic drugs (AED) have to be taken into account when interrogating fMRI studies for presurgical fMRI localization of memory [2,14,15] and might even be important for the increasing clinical use of fMRI in language lateralization, in localization of motor function and seizure onset in patients with epilepsy [1,16].

Main advantage of fMRI is that the method has no known biological side effect and uses no radioactive radiation. Thus, it lends itself to pharmacological within-subjects study designs which have been conducted with fast acting compounds like acetazolamide, cocaine, nicotine, metamphetamine and diazepam [17–20]. Repeated, longitudinal studies of the effects of drug administered over a longer interval [21] might be based on cross-sectional data like the findings presented here.

In fMRI, the 'behavioral' measure of interest is a localized T2*-contrast change due and close to neuronal activation. We are not drawing inferences about which part

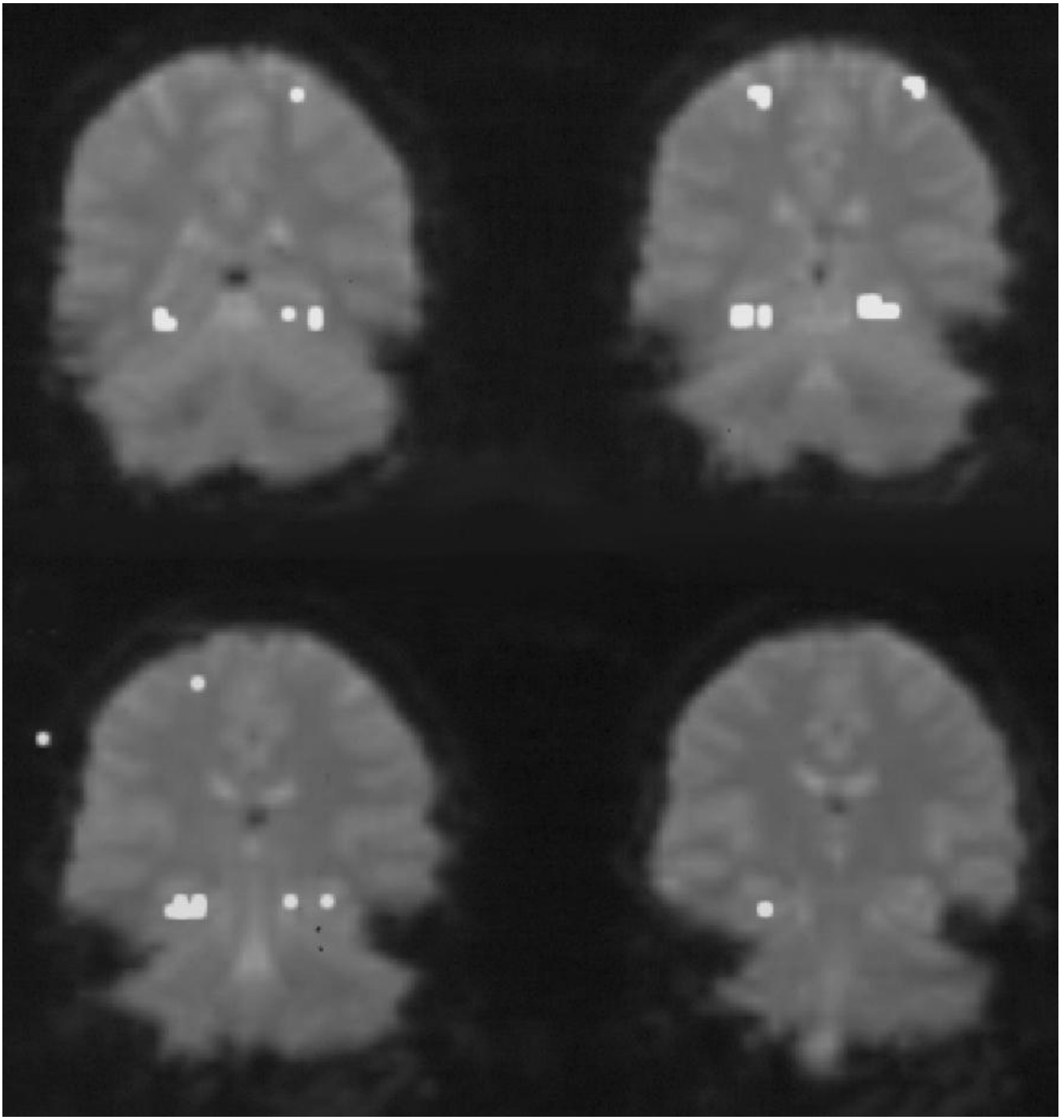

Figure 1
Representative example of functional images of a 31-year-old female patient with left sided hippocampal sclerosis. Those voxels whose signal intensity significantly increased ($z > 4$) in association with the visuo-spatial memory retrieval task are displayed in white. Four consecutive slices of significant voxels superimposed on EPI images are shown. The right, contralateral MTL region shows more significantly activated voxels than the left diseased MTL.

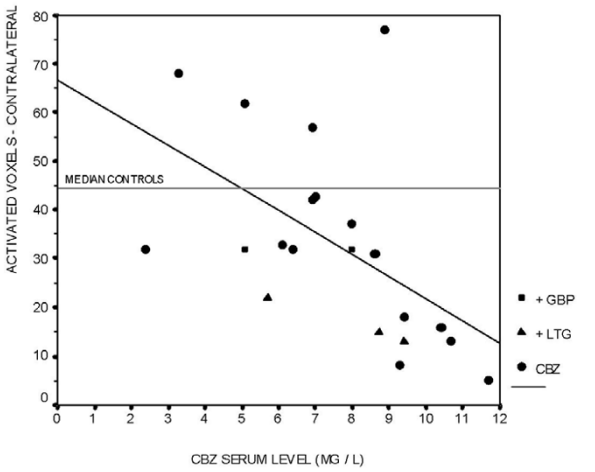

Figure 2
Scatterplot of the number of activated voxels (contralateral to seizure onset in patients with TLE) as a function of the CBZ serum level. Five patients receiving GBP and LTG as add-on therapy are indicated. The linear regression function is shown. The gray line represents the median number of activated MTL voxels (half of total number) of 20 healthy controls. Only four patients had more activated voxels than the median of controls.

of the complex activation paradigm (imagery of visual scenes, landmarks, navigation etc.) is responsible for the mesiotemporal activation. The parahippocampal gyrus underlying the activated voxels is nowadays accepted to be active in response to landmarks and visual scenes of depicted places [22,23]. The resulting bilateral mesiotemporal activation in our experiment was shown relatively homogeneously in all control subjects. In TLE patients the extent of this significant contrast change over both mesial temporal lobes was inversely correlated to the CBZ drug level. The reduction of fMRI cluster size was most marked, when the drug levels were close to toxic levels. There is no behavioral data in our patient group describing memory problems as a function of CBZ drug levels – behavioral data, which by definition would have to be of a longitudinal nature. Side effects like memory decline depending on high CBZ drug levels, however, have been described earlier [24].

The complex nature of task-related fMRI contrast changes (from neuronal activation via neurovascular coupling to T2*-contrast differences in active brain tissue [25] leads to question the origin of the observed inverse correlation between CBZ serum level and size of the cluster of significantly activated voxels in mesiotemporal lobes of TLE. It might be possible that CBZ related changes in fMRI parallel reduced cerebral glucose metabolism as shown by glucose PET in epilepsy patients receiving CBZ [8], and thus represent neuronal dysfunction. To make unspecific vascular effects unlikely, it might be necessary to combine different methods in forthcoming longitudinal studies (ideally covering initiation, chronic administration and withdrawal of AED). Reduced cerebral glucose metabolism has been observed using PET in diseases with impairment of intellectual function [26]. In our study there was no correlation between the extent of significant mesiotemporal fMRI activation and a measure of global intellectual functioning like IQ. There is the possibility that a high CBZ level is associated with a difficult-to-treat epilepsy. All our patients, however, were refractory to medical treatment and there was no correlation between the extent of mesiotemporal fMRI activation and the current seizure frequency.

Conclusions

Pharmacological fMRI may prove useful for monitoring cerebral changes following chronic administration of AEDs. It might help to understand the profile of AED side effects and, eventually, to identify individual patients prone to develop side effects.

Competing interests

None declared.

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