Changes in perfusion underlie negative bold responses (NBR) in epilepsy patients with generalised spike wave activity

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Background: It is unclear whether neurovascular coupling is normal in patients with generalised epilepsy. Blood oxygen level-dependent (BOLD) functional MRI (fMRI) studies have demonstrated negative BOLD responses (NBRs) in frontal, parietal and posterior cingulate cortex during epileptic generalised spike wave activity (GSW) with some evidence of concomitant perfusion decreases[1]. GSW is associated with cortical neuronal inhibition and loss of consciousness. We hypothesise that GSW-related NBR are associated with decreased cerebral blood flow (CBF), suggesting neuronal inhibition (or reduced neuronal activity). To address this, we measured BOLD and cerebral perfusion using simultaneous EEG with arterial spin label (ASL) fMRI at 3T.

Methods: We investigated four patients with frequent GSW. Two had idiopathic generalised epilepsy (IGE) and two had secondarily generalized epilepsy (SGE). 32 channel scalp EEG was recorded in the MR scanner (Brainproducts, Germany). The start and stop of GSW epochs were visually identified on the artifact corrected EEG. Imaging was performed on a dedicated 3T head scanner (Allegra, Siemens, Erlangen, Germany) using a standard head transmit/receive coil. One thirty minute run of a pulsed arterial spin labeling (PASL) sequence (Q2TIPS)[2] with the PICORE labeling scheme (FOV 22.4cm x 22.4cm, matrix 64x64, 6 axial slices (extending superiorly from the top of the corpus callosum), 4mm slice thickness, slice gap 0.5mm, TR 2300ms, TE 30ms, $TI_1/TI_{1stop}/T_{I2}$ 600/1200/1300ms. From the ASL time series both a BOLD weighted (ASL-B) (by summation of adjacent label and control images) and perfusion weighted (ASL-P) time series (a 'surround average' was taken[4] and expressed as a ratio of the control image and non-physiological signal changes were filtered as per Garraux et al[5]) were obtained.

Statistical analysis: GLM analysis was performed in SPM2 (www.fil.ion.ucl.ac.uk/spm) with GSW epochs defined from the EEG convolved with the haemodynamic response function (HRF) and its temporal derivative. These were entered into a design matrix along with a Volterra expansion of the 6 realignment parameters yielding 24 confounds. T-contrasts for positive and negative HRF were used to map GSW associated changes. The resulting statistical parametric maps, SPM{t}, from individual analysis were thresholded at P<0.05 corrected for the BOLD time series, and *P*<0.001 (uncorrected) for the perfusion images given their lower signal to noise ratio[4].

$$r = \frac{Cov(perf, bold)}{\sqrt{Cov(perf, perf), Cov(bold, bold)}} \quad \textbf{eq. 1}$$

Correlation analysis: The correlation at each voxel between the ASL and BOLD signal time course was calculated to establish spatial correspondence between these measurements. To remove confounding variance, a design matrix was created using SPM as described above but omitting the onset and duration of epochs of GSW for both the ASL and BOLD time series. A residual time series of images was calculated using the SPMd toolbox (www.sph.umich.edu/~nichols/SPMd). The correlation between the ASL and BOLD residual time series was calculated for each voxel using eq. 1, where *Cov* is the covariance, *perf* is the residual perfusion time series for a voxel and *bold* is the residual BOLD time series for a voxel. A significant correlation at a voxel level was taken as |r|>0.3 and p<0.05 Bonferonni corrected with voxels not meeting these criteria set to zero (masked). This analysis was carried out separately on data from epochs of EEG showing normal background activity and GSW and for the whole time course.

Results: Focal frontal and thalamic activation were seen in two patients with SGE, concordant with the electro-clinical features of their epilepsy. NBR, which corresponded to regional decreases in CBF occurred in frontal, parietal and posterior cingulate cortex in the patients with both IGE and SGE. Maps of the correlation between BOLD and rCBF were obtained for the whole time series and separately for rest and GSW epochs for each subject (representative slice from one patient are shown in Fig. 1). We found a significant positive correlation between BOLD and perfusion signals for both positive and negative BOLD responses in all cases. This held true when epochs of normal background EEG and GSW were studied separately. The areas showing the highest correlation corresponded to the clusters of significant BOLD (de/)activation. In particular, there was a strong positive correlation between BOLD and rCBF in regions that showed NBR.

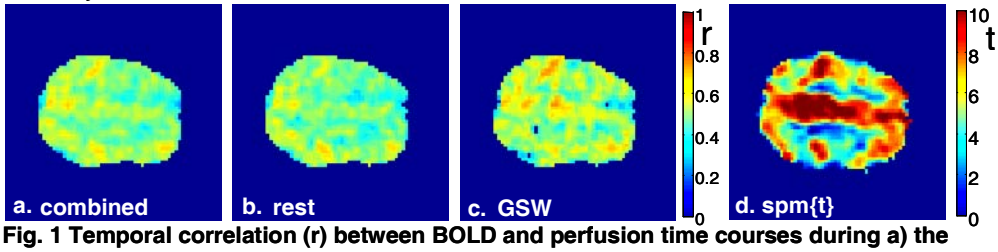

Fig. 1 Temporal correlation (r) between BOLD and perfusion time courses during a) the whole time course b) rest epochs c) GSW epochs compared to d) the spm{t} map from the BOLD time course using a negative HRF (t>3.11 is significant p<0.05 corrected).

Discussion and conclusions: Cortical NBR is a consistent finding in fMRI studies of GSW; we show that these changes were primarily due to decreases in cerebral perfusion. By looking at the temporal correlation from each pixel for BOLD and rCBF, we removed the difficulty of comparing regions obtained using a statistical threshold on data with different noise characteristics[1]. We observed correlation of BOLD and perfusion changes both during periods of GSW and normal background EEG through out the imaged volume, indicating neurovascular coupling of metabolic demand and perfusion across both functional states. Spatially, the BOLD and perfusion decreases were regionally specific involving the frontal, posterior parietal and posterior cingulate cortex. GSW associated haemodynamic changes identified regions in the association cortex in which decreases of activity, compared to the resting state, were detected. This supports the hypothesis that NBR reflects decreased neuronal activity/neuronal inhibition, and that in this state, neurovascular coupling is maintained in GSW patients as in the experimental studies of Shmuel et al[6].

1. Stefanovic B et al, NeuroImage 28, 205-215; 2005. **2.** Luh WM et al, Magn Reson. Med. 41, 1246-1254; 1999. **3.** Aguirre et al, NeuroImage 15, 488-500; 2002. **4.** Loring DW et al, Epilepsy Behav. 3, 539-547; 2002. **5.** Garraux et al, NeuroImage 25, 122-132; 2005. **6.** Shmuel et al, Nat.Neurosci. 9, 569-577; 2006.