Quantification of false negative BOLD response; functional magnetic resonance imaging in brain tumour patients

S. Gevers[1], J. N. van der Meer[2], R. B. Willemse[3], C. B. Majoie[1], and A. J. Nederveen[1]

[1]Radiology, Academic Medical Centre, Amsterdam, Netherlands, [2]Neurology, Academic Medical Centre, Amsterdam, Netherlands, [3]Neurosurgery, Academic Medical Centre, Amsterdam, Netherlands

Purpose/Introduction

Functional magnetic resonance imaging (fMRI) based on the blood oxygenation level dependent (BOLD) signal, is used to assess the spatial relationship between eloquent cortical areas and brain tumour tissue. Within certain limits, fMRI can be used for neurosurgical planning. Its non-invasiveness makes fMRI more attractive than intra-operative brain mapping, the gold standard for identification of eloquent cortical areas.

However, the influence of tumour tissue on cerebral blood volume, perfusion and oxygenation is not exactly known. Accumulating evidence suggests that the BOLD signal in the vicinity of tumour tissue does not reflect neuronal activity as accurately as it does in healthy brain tissue. Moreover, previous studies suggested that altered BOLD physiology might cause false negative activations in fMRI due to an inverse response to stimuli which is missed by conventional fMRI analysis using the general linear model. These false negative activation patterns could undermine the applicability of fMRI in pre-neurosurgical brain mapping. In this study we used spectral analysis to quantify negative BOLD responses (NBR) to stimulation in brain tumour patients.

Subjects and Methods

For studying the NBR we retrospectively analysed a dataset of 23 brain tumour patients. Patients were scanned on a Philips 3.0 T Intera scanner during a block design paradigm (unilateral finger tapping of the right and the left hand). All of the patients had no paresis at the time of examination. Functional T2* weighted images were obtained with an echoplanar imaging (EPI) sequence. Analysis was performed using FSL (motion correction MCFLIRT; slice timing; Gaussian smoothing FWHM 6 mm). We performed spectral analysis to identify voxels displaying signal changes with frequencies corresponding to the frequency of our block design. Spectral peaks were thresholded. Voxels with a phase of ½ π were regarded as displaying a regular, positive BOLD response (PBR) and voxels with a phase of -½ π were regarded as displaying a NBR. We compared the amount of voxels displaying a PBR and a NBR in the motor cortex of the hands of the diseased and healthy hemisphere. We calculated activation ratios for the PBR and NBR by dividing the number of (inversely) activated voxels in the diseased hemisphere by the number of (inversely) activated voxels in the healthy hemisphere. We tested the differences between the mean activation ratios of PBR and NBR for significance, using the non-parametric Mann Whitney test (SPSS version 14.0).

Results

Spectral analysis of fMRI data in our population yielded activation maps of voxels inversely responding to the applied block design. In *Figure 1A* and *B*, we show an example of the false negative response to stimulation in brain tumour tissue. Comparison of the number of inversely activated voxels in the diseased and healthy hemisphere showed that the NBR in the diseased hemisphere tends to exceed the NBR in the healthy hemisphere. *Figure 2A* shows activation ratios for PBR and NBR of all patients at a threshold of 1.5. The mean of the activation ratios of PBR and NBR of all subjects differed significantly (0.84 ± 0.36 and 1.06 ± 0.41 respectively, $P < 0.05$). The mean and median of the activation ratios against threshold is displayed in *Figure 2B*. At thresholds of 1.5 and higher, the NBR activation ratio surpasses the PBR activation ratio.

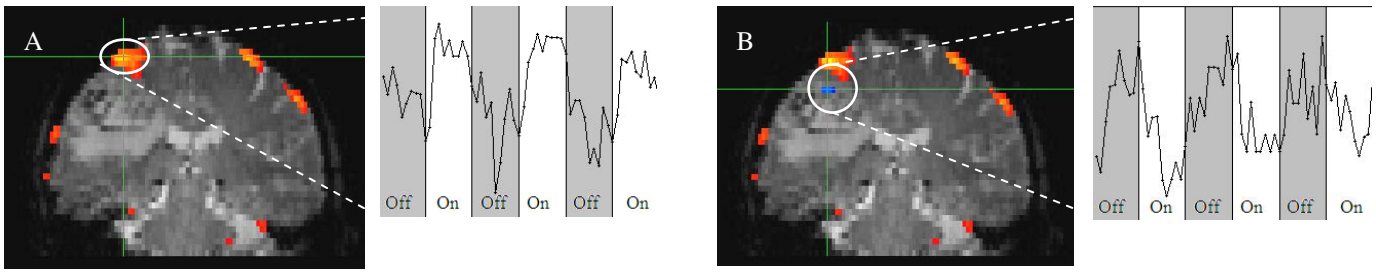

Figure 1: fMRI activity during left hand finger tapping vs. rest in a patient with a glioblastoma multiforme in the right hemisphere, extending partly within the precentral gyrus. *Figure 1A* shows cortical activity (in red) and corresponding time series of the hand knob. There seems to be no activity in the pathologic tissue. However, spectral analysis of MRI signal changes yielded the activation pattern (in blue) and time series indicated in *Figure 1B*. Part of the tumour tissue thus responds inversely to our finger-tapping paradigm.

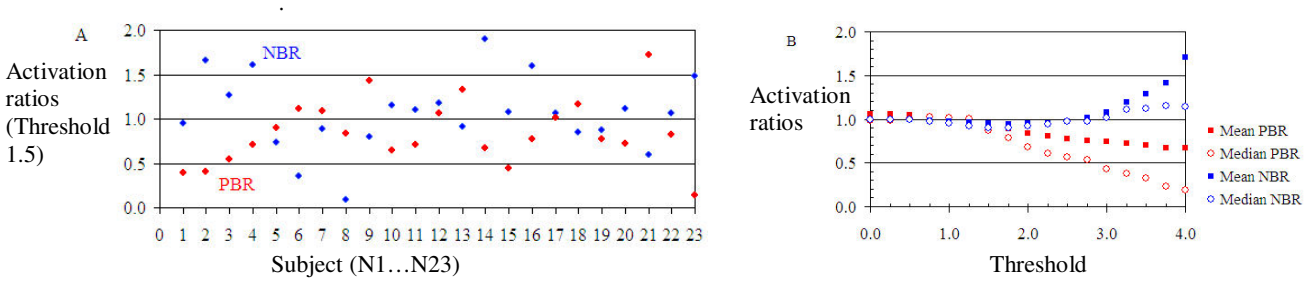

Figure 2: Activation ratios for positive and negative BOLD responses in the diseased/healthy hemisphere for all subjects *(Figure 2A)* and the mean and median of these data against different thresholds for 14 patients with a tumour adjacent to or extending into the hand knob *(Figure 2B)*.

Conclusion

From this study it can be concluded that inverse BOLD responses can be found in or in the proximity of brain tumour tissue. The diseased hemisphere tends to exceed the healthy hemisphere in the number of voxels with a negative response to stimulation. To optimize the applicability of fMRI in pre-neurosurgical brain mapping, these false negative activation patterns must be controlled for.