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QUANTITATIVE ASPECTS OF BRAIN PERFUSION DYNAMIC INDUCED BY BOLD fMRI

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ABSTRACT - The increase of relative cerebral blood flow (rCBF) may contribute for a change in blood oxygenation level dependent signal (BOLD). The main purpose of this study is to investigate some aspects of perfusional alterations in the human brain in response to a uniform stimulation: hypercapnia induced by breath holding. It was observed that the BOLD signal increased globally during hypercapnia and that it is correlated with the time of breath holding. This signal increase shows a clear distinction between gray and white matter, being greater in the grey matter.

KEY WORDS: functional MRI, fMRI, BOLD, perfusion.

Aspectos quantitativos da dinâmica perfusional do cérebro induzida pelo BOLD fMRI

RESUMO - O aumento relativo do fluxo cerebral sangüíneo *(relative Cerebral Blood Flow* - rCBF) pode contribuir para uma mudança no sinal dependente da oxigenação do sangue *(Blood Oxygenation Level Dependent* - BOLD). O objetivo principal deste trabalho foi estudar alguns aspectos da alteração perfusional no cérebro humano em resposta a um estímulo uniforme: hipercapnia, causada por um estado de apnéia induzida. Foi observado um aumento global no sinal BOLD durante a hipercapnia. Este aumento é correlacionado com a duração da apnéia e mostra uma clara distinção entre a substância branca e cinzenta, sendo maior na substância cinzenta.

PALAVRAS-CHAVE: ressonância magnética funcional, fMRI, BOLD, perfusão.

An important discovery of magnetic resonance imaging (MRI) is the recognition that changes in the metabolic state of the brain affect the local MR signal and provide an intrinsic mechanism for detecting brain activation. This mechanism is based on the blood oxygenation level dependent (BOLD) contrast, using the paramagnetic characteristics of deoxyhemoglobin, as an endogenous contrast agent. During brain activation, the regional cerebral blood flow (rCBF) surpasses the cerebral metabolic rate of oxygen (CMRO2). Therefore, the difference between production and consumption of oxygen causes a reduction of deoxyhemoglobin concentration, increasing the signal, and consequently changes the local contrast, of T2* weighted images. This mechanism is the basis of the so called functional MRI (fMRI). fMRI has been increasingly used as a non invasive tool to understand normal and pathological brain function. Beyond mapping cognitive brain function, an increasing number of studies indicate that fMRI techniques could become useful in the clinical set, as a pre-surgical mapping tool[1,2].

The BOLD signal indirectly measures neuronal activity. It actually responds to CBF changes and can be, in principle, used to map brain perfusion. Therefore, recently these techniques have been used to detect rCBF by means of BOLD signal changes, during inhalation of CO_2 gas mixture or injection of acetazolamide[3,4]. During CO_2 inhalation, the increase in pCO_2 leads to vasodilatation and consequently an increase in rCBF. Nevertheless, little or no CMRO2 changes occur, and metabolic activity remains at baseline level of the resting brain state. Hence, this condition decreases the local concentration of deoxyhemoglobin, leading to a decrease in magnetic field distortions and a slightly increase in the local MR signal. In a different set of studies, vasodilatation is induced by the use of acetazolamide, a carbonic anhydrase inhibitor[5]. Carbonic anhydrase catalyzes the conversion of CO_2 to bicarbonate ions, increasing the

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carrying capacity of the blood for removing CO_2. Inhibiting the enzyme, CO_2 concentration may increase in the brain, indicating that the mechanism of action of carbonic anhydrase inhibitors for increase rCBF may be the same for CO_2 itself.

On the other hand, Kastrup et al.[6] have demonstrated that cerebral blood flow and oxygenation changes during breath holding can be detected reliably by means of fMRI at 1.5T. Breath holding has the advantage of being a simpler paradigm for evaluating hemodynamic response, since it requires neither an exogenous source of CO_2 nor an acetazolamide injection, making it a good non-invasive alternative test. Many aspects of such paradigm have nor yet been addressed. Therefore, the main purpose of this study is to investigate quantitatively some aspects of perfusional alterations in the human brain, such as dependency on breath holding duration and brain lateralization of the effect. These changes were mapped by changes in BOLD signal as a result of a global and uniform stimulation: hypercapnia induced by two breath holding paradigms.

METHOD

The methods performed in this study were approved by Ethics Committee in Research. The subjects gave informed consent after having carefully been informed about the study.

This study comprised nineteen asymptomatic volunteers (9 male, 8 female), who were instructed to hold their breath in variable intervals of time, 14 and 27 seconds, after inspiration. The protocol was constituted by eleven alternating periods of hypercapnia and rest for the first protocol, and five periods of hypercapnia versus six normal breaths, for the second. Six exams from the first protocol and five exams from the second were eliminated due to motion artifact. Volunteers were instructed to breath holding after inspiration. Therefore, to obtain maximum response amplitude, the hemodynamic response was delayed 22.5s. To assure the quality of the exams, data was also visually inspected throughout the entire time series.

MRI was acquired in a Siemens 1.5T scanner (Magneton, Vision). High resolution T1-weighted structural images (TR= 9.7 ms; TE=4 ms; flip angle=12°; matrix size=256x256; FOV= 256 mm), using a Gradient Recalled Echo (GRE), MPR sequence, was acquired for anatomical reference. Fast EPI-BOLD fMRI sequences was used for functional imaging (TR=4600ms; TE=60 ms; flip angle=90°; matrix size=128x128). Trial timing was cued by auditory stimulus.

Statistical maps were obtained by Brain Voyager QX™ 1.4 (Brain Innovation Inc, The Netherlands), using the General Linear Model (GLM). Preprocessing of the data included several steps as motion correction, time series image realignment of all images to the first time frame, spatial smoothing (through a Gaussian Filter with FWHM=4 mm) and temporal filtering using a high pass filter of 3 cycle/s.

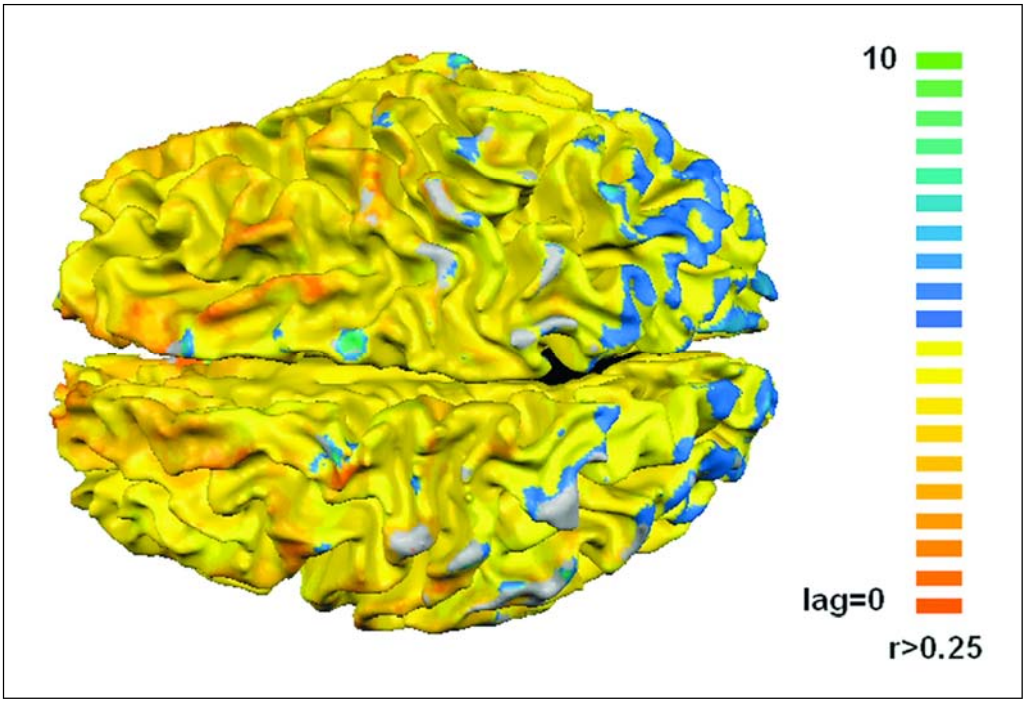

Fig 1. Delay map of the BOLD signal change during 27s of breath holding. The response delay depends on the cerebral region. The color map corresponds to the specific delay of the hemodynamic response function, as reddish brain areas correspond to the ones that responded earlier whereas greenish spots responded later.

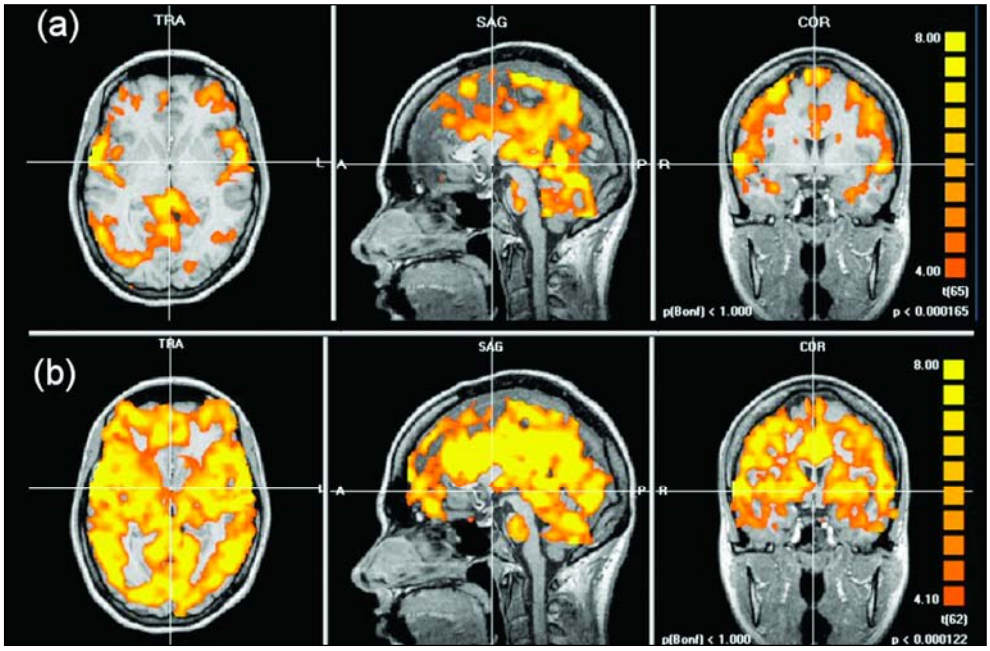

Fig 2. Statistical map of BOLD signal change induced by breath holding. (a) 14s and (b) 27s. The peak of activity demonstrates a global increase in brain perfusion throughout the both hemispheres.

Images were also processed using a cross correlation function map, for different phase shifts in time, in order to obtain the hemodynamic delay for different brain regions. The statistical maps were normalized to Talairach space.

RESULTS

Six subjects had to be excluded due to motion artifact, which exceeded 2 mm in translation or 2 degrees in rotation. BOLD signals were obtained using 27s and 14s breath holding protocols (Fig 1). It shows that, in spite of a global increase of the signal BOLD intensity, the response delay depends on the cerebral region. Phase lag correlation maps indicate an apparent temporal evolution between different cerebral structures (Fig 1). The colors map corresponds to the specific delay of the hemodynamic response function, the reddish brain areas correspond to the ones that responded earlier to the paradigm whereas greenish spots responded later.

Based on the delay, the referring statistical map to the maximum response amplitude was determined (Fig 2). During the period of perfusion peak a global increase in rCBF is observed. Moreover, there is no evidence of cerebral lateralization in response to the paradigm and a clear distinction between gray and white matter can be noticed (Fig 2).

Figure 3 shows the averaged BOLD signal time course in different breath-holding conditions, with duration of 14s and 27s, for the same region of the parietal lobe, selected randomly (Brodmann area 31). The increased signal, induced by breath holding, is correlated with the time of breath holding, i.e., the larger the time, the larger the amplitude of the BOLD signal (Figs 2 and 3).

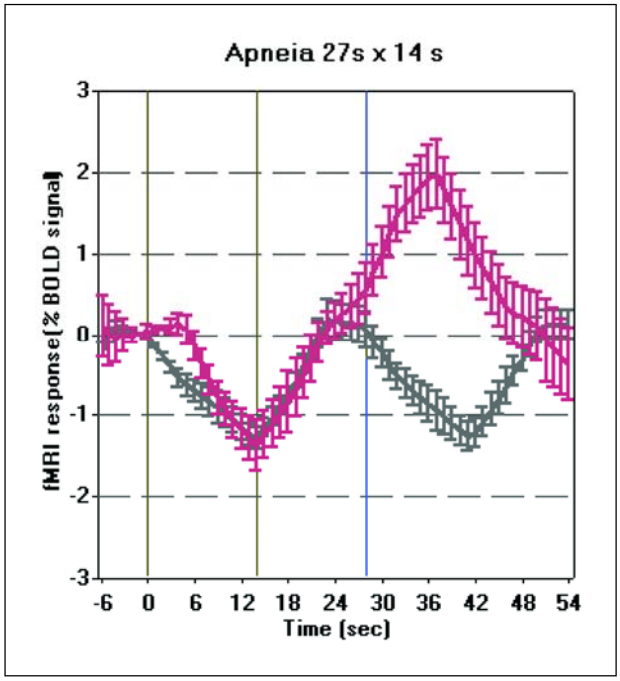

Fig 3. Averaged BOLD signal time course with breath-holding of 14s (grey) and 27s (wine) for (20, -74, 24) on Brodmann area 31. The longer the period of breath holding the greater is the delay amplitude of the hemodynamic response.

DISCUSSION

Here we observed different delays of the BOLD signal depending on the brain region inspected, and may represent differences in the coupling mechanism required in the generation of the BOLD signal.

The amplitude of the BOLD response was dependent on the length of breath holding period, probably since the CBF is regulated to keep a constant ratio of CO_2 and O_2 at the mitochondria, to preserve the thermodynamic free energy available from oxidative metabolism of glucose[7]. Consequently, to increasing the breath holding period implies in a higher CO_2 concentration in the blood, causing cause a more prominent increase of CBF to maintain the relationship between the CO_2 and O_2. Furthermore, the cerebral oxygen extraction fraction will reduce and, in this way, the deoxyhemoglobin concentration will also reduce. As a result, it will lead to a more conspicuous BOLD signal.

Kastrup et al. reported that the longer the breath holding duration, the greater the BOLD signal changes within the voxels[8]. However, such behavior reaches a plateau, as observed by Ho-Ling Liu et al., who found that the number of detected voxel are positively regulated by breath holding periods when the durations are between 10s and 20s[9].

Tie-Qiang Li et al. demonstrated that CBF and changes on BOLD signal intensity also depend on the breath-holding technique employed. BOLD signal and cerebral blood flow decrease initially after deep inspiration, whereas prolonged breath-holding periods lead to increased BOLD signal and blood flow[10]. In contrast, breath holding after expiration leads to an immediate increase of BOLD signal and blood flow after the onset of breath holding. For healthy volunteers, the perfusional pattern is distributed symmetrically, showing no lateralization[9].

In conclusion, the perfusional pattern of healthy volunteers, as measured by the BOLD signal induced by breath holding, is distributed symmetrically, showing no lateralization. Also, there is a relatively clear distinction between gray and white matter, as visualized by the resultants statistical maps. Moreover, there is an apparent linear correlation between period of breath holding and the increase in BOLD signal, up to a certain level. Using relatively simple stimulation like breath holding we demonstrate that the response delay depends on the cerebral region, opening perspectives of a possible non-invasive contrast free mechanism to infer specific patterns of hemodynamic response in a variety of clinical studies. We believe it is possible to apply breath holding paradigms during a routine MR examination to study subjects who have perfusional disorders.

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REFERENCES

1. Moseley ME, Glover GH. Functional MR imaging capabilities and limitations. Neuroimaging Clin N Am 1995;5:161-191.
2. de Araujo DB, Araujo D, Escorsi-Rosset S, et al. fMRI in epilepsy and recent advances in spatial memory mapping. J Epilepsy Clin Neurophysiol 2003;9:213-219.
3. Lythgoe DJ, William SC, Colliname M, Markus HS. Mapping of cerebrovascular reactivity using BOLD. Magn Reson Imaging 1999;17:495-502.
4. Rostrup E, Larsson HB, Toft PB, et al. Funcional MRI of CO_2 induced increase in cerebral perfusion. NMR Biomed 1994;7:29-34.
5. Brown GG, Eyler Zorrilla LT, Georgy B, Kindermann SS, Wong EC, Buxton RB. BOLD and perfusion response to finger-thumb apposition after acetazolamide administration: differential relationship to global perfusion. J Cer Blood Flow Metab 2003;23:829-837.
6. Kastrup A, Li T-Q, Glover GH, Moseley ME, Cerebral blood flow related signal changes during breath holding. Am J Neuroradiol 1990;20: 1233-1238.
7. Buxton, R.B. A hypothesis for cerebral blood flow regulation and the origin of the BOLD effect. 12th ISMRM Scientific Meeting. Kyoto, Japan, 2004.
8. Kastrup A, Li TQ, Takahashi A, Glover GH. Functional magnetic resonance imaging of regional cerebral blood oxygenation changes during breath holding. Stroke 1998;29:2641-2645.
9. Li TQ, Kastrup A, TaKahashi AM, Moseley ME. Functional MRI of human brain during breath holding by BOLD and FAIR techniques. NeuroImage 1999;9:243-249.
10. Liu HL, Huang JC, Wu CTH. Detectability of blood oxygenation level-dependent signal changes during short breath hold duration. Magn Reson Imaging 2002;20:643-648.