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Near-infrared study of the underlying physiology of the functional magnetic resonance signal in humans during hypoxia

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Abstract

We use near-infrared spectroscopy to investigate hemodynamic changes in humans during a breath holding exercise and their influence on the BOLD fMRI signal. We have quantitatively compared the BOLD fMRI signals with the hemoglobin concentration changes using correlation analysis of NIRS and fMRI data.

Keywords

human brain; hypoxia; near-infrared spectroscopy; functional magnetic resonance imaging

Introduction

Functional magnetic resonance imaging (fMRI) of the brain is based on the dependence of the MR signal on the hemoglobin content, which is known as the blood oxygen level dependent (BOLD) effect. A detailed understanding of the underlying physiology of the BOLD effect is particularly important for the correct physiological interpretation of the results of fMRI experiments. The existing physical theory expresses the parenchymal BOLD signal as a function of changes in cerebral blood oxygenation (CBO) and cerebral blood volume (CBV) [1].

Near-infrared spectroscopy (NIRS) is a technique allowing direct measurement of both CBO and CBV. An important advantage of NIRS is that it is mostly sensitive to hemodynamic changes in tissue capillaries rather than in large vessels. In our previous study using NIRS we found that during functional (motor) activation the influence of CBV on the BOLD signal was relatively small. However, other experimental paradigms such as breath holding, may produce different cerebral hemodynamic responses, and therefore they can be used to further investigate the physiological basis of the BOLD signal.

Cerebrovascular reactivity to the hypoxia was previously separately studied both by NIRS [2] and fMRI [3,4]. Studying cerebral vasomotor responses to altered CO₂ tension is clinically important because they can be used to determine the cerebrovascular reserve capacity and to access the autonomic disturbance in a number of clinical syndromes, including neuropathies, sleep disorders, and other diseases. In fMRI study [3] the authors

observed diffuse negative BOLD responding areas at cortical level and a stronger negative response in the main sinuses. They concluded that these phenomena were unrelated to a specific neural activity, appearing to be expressions of a mechanical variation in the hemodynamics. The other study [4] employed both blood oxygenation level dependent (BOLD) and CBF sensitized fMRI techniques. During each vascular challenge BOLD and CBF signals were determined simultaneously with a combined BOLD and flow-sensitive alternating inversion recovery pulse sequence. There was a good correlation between the global BOLD signal intensity changes during breath holding and CO₂ inhalation supporting the notion that the breath holding is equivalent to the CO₂ inhalation in evaluating the hemodynamic reserve capacity with BOLD fMRI.

In the present study we used NIRS to investigate hemodynamic changes in humans during a breath holding exercise and their influence on the BOLD fMRI signal. We have quantitatively compared the BOLD fMRI signals with the hemoglobin concentration changes using correlation and multiple regression analyses of NIRS and fMRI data.

Methods

Magnetic resonance imaging was performed using a 3 Tesla head only MR scanner (Allegra, Siemens). 38 slice gradient-echo echo-planar volumes were acquired using a data matrix of 64×64 complex points, TR=2000 ms, TE = 25 ms, FOV = 220 mm, slice thickness = 3 mm, no inter-slice gap, and flip angle 90°. In order to avoid image artifacts due to the sinuses we used an oblique slice orientation, so that slices spanned the slab, which included the optical sensor attached to the forehead near the hair edge.

For NIRS measurements we used a frequency-domain (250 MHz modulation frequency) Imager (ISS, Champaign, IL), which had 16 laser diode sources at each wavelength of 690 and 830 nm, and four photomultiplier tube detectors. The acquisition cycle for 32 light sources was 94 ms. Light emitted by laser diodes was guided to the tissue through 6.5 m long multi-mode silica optical fibers. 6.5 m long glass fiber bundle collected the scattered light and guided it to the detector. The optical sensor covered area 2.5×4 cm² and included 56 source-detector pairs at 10 evenly spaced distances between 3 and 30 mm. To obtain hemoglobin concentrations we used the frequency-domain method based on spatially-resolved measurements of signal's AC and phase described in [1].

In order to control the arterial oxygen saturation we used the pulse oximeter NONIN 8600FO. The MRI-compatible sensor of the pulse oximeter was attached to the left index finger of the subject. The arterial saturation readings (SpO₂) were recorded with the repetition rate of 1 s via the serial port of the same computer as the one recording NIR data.

Experimental paradigm included three 20 s long breath holding trials during each BOLD data set acquisition, beginning at 20, 100, and 180 seconds after the beginning of the recording. Subjects were instructed to hold their breath at the end of the normal expiration after they received a command through the speaker, and to resume breathing normally without deep inhale. To reduce motion artifacts subjects worn an adjustable posture collar.

Additionally, subject's head and neck were immobilized by means of foam padding. Three data sets were acquired for each subject.

The near-infrared data was processed using the standard user library supplied with the Imager (ISS, Champaign, IL). The fMRI data was processed using the AFNI software. After standard preprocessing procedures, such as the blasting noisy voxels, motion correction (3D registration), detrending, and temporal smoothing, the fMRI data was cross-correlated with the total hemoglobin (tHB), and deoxyhemoglobin (hHb) concentration signals obtained from the NIR data, and with the SpO2 signal obtained using the pulse oximeter.

Results

Fig. 1 shows typical changes in the total- and deoxyhemoglobin concentration ([tHB] and [hHB], respectively, and SpO2. Since different intracranial tissues significantly bias the absolute values of [tHB] and [hHB], the changes are shown in arbitrary values.

In Fig. 1 one can see that at every of the three trials, the breath holding causes a very prominent increase in the cerebral blood volume almost synchronous with the decrease in the deoxyhemoglobin concentration. One can also see that cerebral hemodynamic response begins during the breath holding, and significantly precedes the SpO2 response measured using the finger sensor.

Fig. 2 shows a map of fMRI BOLD signal changes correlated with the negative of the [hHB] signal. The figure shows four slices closest to the location of the sensor, which is indicated by the radiological marker attached to the sensor (a bright stain outside the head in Fig. 2). The threshold correlation value for maps in Fig. 2 equals to 0.5

One can see that the topology of the "activated" regions follows the sulcus furrows, and that only a relatively small fraction of grey matter exhibits BOLD signal highly correlated with the negative of the [hHB] signal. Reduction of the correlation threshold leads to the expansion of the "activated" regions along the sulci.

As Fig. 1 shows, the changes in [tHB] and [hHB] are almost synchronous. Therefore, correlation of the BOLD signal with [tHB] produces the "activation" maps with the topology very similar to the one shown in Fig. 2. However, the typical correlation values for [tHB] are slightly lower than for the negative of the [hHB] signal.

Cross-correlation of the BOLD and SpO2 signals shows no statistically significant values of the correlation coefficient.

Discussion

The results shown in Fig. 1 agree with the previous findings for normal subjects obtained using NIRS. The interpretation of hemodynamic changes shown in Fig. 1 is that they reflect the normal cerebrovascular reactivity to hypoxia, i.e. the dilation of arterioles causes the increased blood flow in order to compensate the reduction of the oxygen saturation.

The “activation” map shown in Fig. 2 is similar to those previously obtained in fMRI studies by correlation with the delayed paradigm boxcar function []. This result shows that the deoxyhemoglobin signal measured using NIR technology is strongly related to the BOLD fMRI signal. However, unlike the functional activation, such as the finger-tapping [], hypoxia causes blood volume changes strongly correlated with the deoxyhemoglobin changes. The reason for that could be the accumulation of SO₂ in the blood. However, the fact that the brain does not “wait” for the SpO₂ decline, indicates that cerebral tissue utilizes a regulation mechanism different from the rest of the body.

The fact that only a relatively small fraction of the brain tissue exhibits high correlation with the NIR signal show a high sensitivity of the optical methods.

Conclusion

Using simultaneous fMRI and NIRS we have shown that the signal measured by NIRS during hypoxia originates from the relatively small fraction of the cerebral tissue spread along the brain sulci. A higher BOLD-[hHB] than BOLD-[tHB] correlation leads to a preliminary conclusion that, similar to the case of the functional activation, during the hypoxia the deoxyhemoglobin plays more important role in the BOLD signal formation than the cerebral blood volume. The ultimate clarification of this issue requires a more extensive study on large number of subjects and using quantitative techniques allowing measuring not only relative, but absolute hemodynamic changes. Currently we develop a method based on the MRI-aided inverse problem solution, which should allow such quantitative measurements.

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Fig.1.

Changes in cerebral total ([tHB]) and deoxyhemoglobin ([hHB]) concentration and in the arterial saturation (SpO2).

Fig. 2.
Cerebral “activation” maps showing regions of high correlation between BOLD fMRI and the negative of [hHB] signal.