Interaction between gCBF and rCBF and normalization of language BOLD fMR maps using breath holding

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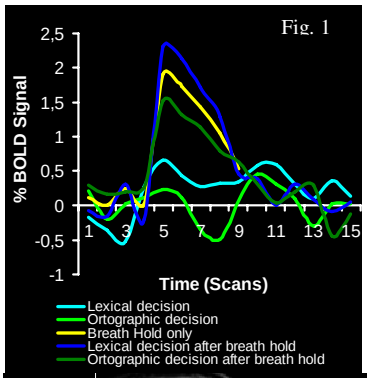
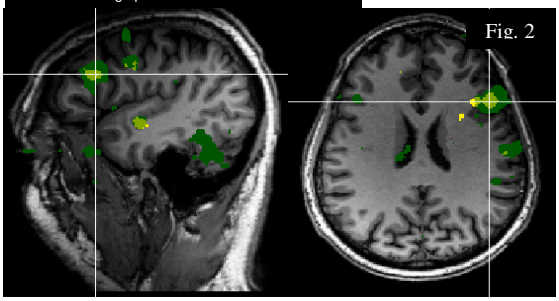
Introduction

Blood oxygen level dependent (BOLD) functional MR (fMR) is based on regional cerebral blood flow (rCBF) and volume changes (rCBV) due to neurovascular coupling. However, strong BOLD MR signal is also induced by the continuous global CBF (gCBF) adjustments mediated by specific brain vascular reactivity mechanisms that are sensitive to systemic CO2 modifications. The amplitude of gCBF modulation vary largely among brain areas [1]. Thus, interpretation of cognitive BOLD fMR studies could be strongly distorted if gCBF and rCBF interaction is not addressed. Critical questions are: 1) how concurrent gCBF and rCBF modulation is reflected in the BOLD signal and 2) how differences in vascular reactivity among brain regions maybe normalized. Previous studies demonstrated that, when modulated concurrently, gCBF and rCBF interact in an additive way [2]. Other studies suggested that spatial specificity of BOLD fMR could be significantly improved normalizing BOLD signal change induced by rCBF response to BOLD signal change induced by gCBF response due to hyprcapnia [3,4]. Nevertheless, all these studies have been conducted by means of region of interest analysis only in primary motor and visual areas engaged by simple tasks. The aim of this study was to evaluate if these results would hold also for associative brain areas involved in higher cognitive functions, such as language, and verify if an estimation of brain vascular reactivity induced by mild and transient hypercapnia due to short breath holds could be used to normalize BOLD fMR data in the entire brain.

Methods

Ten subjects (mean age: 28.3, range 20-42; 5 males and 5 females; 1 left handed) participated in the study. Subjects were asked to press a button with their right hand to indicate if visually presented stimuli were words or pseudowords (lexical decision) or to indicate if presented stimuli were italian consonants or Japanese strings (orthographic decision). The two tasks alternated twice within each run with 15 stimuli presented every 2 s during each block. At the beginning and at the end of each run subjects rested for 30 s fixating a cross in the center of the visual field. Each subject underwent 5 runs. During two of them, visual cues instructed the subject to hold the breath for 15 sec for two times prior to either the lexical or the orthographic decision task. The timing of the apnea phases were calibrated so that the predicted hemodynamic response (HRF) due to the increase of the systemic CO2 would be superimposed with that due to either the lexical or the orthographic decision tasks. During the last run no language task was performed and the subject was visually instructed to just hold breath for 15 s alternating it for five times with periods of normal breathing lasting 42 s each. Data were acquired on a 4 T Bruker MedSpec using echoplanar imaging (TR:3000 s; TE:33ms; FA:81; FOV:192x192; 64x64 acq. matrix). Pre-processing and general linear model statistical analysis were performed with BrainVoyager QX (Brain Innovation, The Netherlands). Activation maps were computed contrasting the lexical decision with the orthographic decision task separately for condition, preceded by either a breath hold or a normal breathing period. For each subject, we computed also the voxel by voxel average maximum percentage signal change due to breath holds performed in alternation with normal breathing (MPCC) as described for the last run of each session. For those runs where the language task was performed without breath modulation, whole brain normalization of BOLD signal was computed dividing all regressors' beta values of each voxel, obtained with a standard GLM fitting, by the corresponding MPCC. Contrasts and inferences were then performed separately using either normalized or non-normalized beta values.





Results

All subjects performed the tasks without discomfort. Statistically reliable lateralized activation of the inferior frontal gyrus and/or of temporo-parietal areas was obtained in 8 out of 10 subjects. Within these areas breath hold task induced a positive signal change ranging from 0.5 and 2%. This variation summed with that induced by the language task when it was performed concurrently (Fig 1 show data for the inferior frontal area in a representative subject). The interaction between language task and breathing modulation was not significant. This finding supports the hypothesis that the interaction between gCBF and rCBF is additive in these areas and could be subtracted once the exact timing of the gCBF modulation is known. Comparison of activation maps obtained with and without beta values normalization showed a better spatial definition of inferior frontal and temporal-parietal language areas without any loss of statistical significance in all subjects. On the contrary, a significant reduction of statistical significance was observed in many other non-language related areas which, overall, resulted in cleaner activation maps for any given statistical threshold at which normalized and non-normalized maps were inspected (Fig. 2: superimposition of non-normalized [green] and normalized [yellow] map in one representative subject).

Discussion

These preliminary results suggest that the interaction between gCBF and rCBF is additive in associative brain areas similarly to what has been demonstrated within primary motor and visual areas (cita). Moreover, it is suggested that vascular reactivity maps, obtained by modulation of gCBF induced by short breath holds, may be used to normalize BOLD fMR activation maps in space. Results of the normalization of GLM beta values are in line with what has been demonstrated in previous studies with a region of interest approach and provide a method for whole brain BOLD signal normalization.

References

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