Improved Localization of BOLD Activation in Patients with Brain Tumors using Vasoreactivity Maps

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Objectives

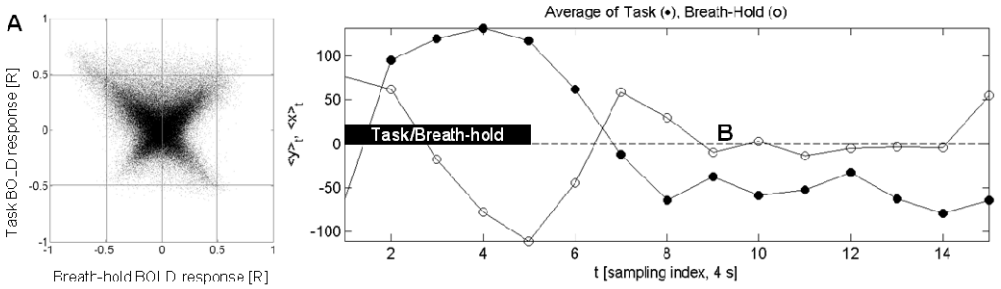
In subjects with brain tumors the BOLD response to a task is influenced by the tumor's local and remote effects on neurovascular response characteristics [1] and often the BOLD signal is weakened [2]. Therefore, a global hemodynamic response function may not be sufficient to yield the most accurate maps of eloquent cortical areas in presurgical planning fMRI [3]. We propose to assess local vasoreactivity [4] by using a breath-holding paradigm that has the same timing as the subsequent fMRI tasks. We derive vasoreactivity maps and find that in most areas of task response vasoreactivity is correlated with the task block design function. Therefore, under the assumption of a linear relationship between task response and vasoreactivity we derive a model that takes altered hemodynamics into account. We carefully adjust statistical test thresholds before comparing conventional modeling and our approach, and obtain altered task response maps as compared to maps obtained without breath-holding information, in particular adjacent to tumors, in half of the studied cases.

Methods

Functional MRI scanning: The institutional review board at MSKCC approved the study. Patients reported with high grade glioblastoma multiforme (N = 9), grade III glioma (N = 3), grade II glioma (N = 3), or kidney cancer metastasis (N = 1). MRI was performed on a 3.0 Tesla GEMS (Waukesha, WI) clinical MRI system with an 8-channel head coil using echo-planar functional MRI (TR=4 s; TE=40 ms; 90° flip angle; 128×128 matrix; 240 mm FOV; 4.5 mm slice thickness). Six on/off blocks of 15 samples each were used in both breath-holding and functional MRI (5 samples on (corresponding to inhalation and breath holding, or task, respectively), 10 samples off (corresponding to normal breathing or resting, respectively). During fMRI, patients either performed a motor and/or up to three language tasks, following oral instructions. For breath holding, patients were instructed to take a deep breath and then hold their breath for the rest of the 20 s.

Analysis and modeling: First, vascular reactivity maps were generated by correlating the breath-hold response time series x_t voxelwise with the block design function I_t (I_t = 1 for breath holding or task and 0 for normal breathing or rest). Task response maps were generated in three different ways: 1. Conventional analysis: Correlation of task BOLD response y_t with I_t. 2. Coherence based conventional analysis: The spectral coherence between two signals is ≤ 1 and = 1 for linear dependence. The maximum value of the coherence between y_t and I_t in an interval centered at the block design task frequency was used as test statistics. Significance thresholds were determined by matching the number of active voxels in the well-controlled first method using a nonlinear optimization algorithm. 3. Coherence based analysis including vasoreactivity information obtained from breath-hold data: We assumed the basic linear model $y_t = a\, h_t + \varepsilon_t$, in which h_t is the hemodynamic response, a is a coefficient to be estimated from y_t , and ε_t is noise not captured by the model. To take into account possible dependence of h_t on location in the brain, which is necessary to assess the impact of altered vascular reserve by the presence of tumors, here we assumed that h_t varies depending on brain location and can be modeled from measuring the vasoreactivity x_t, obtained from breath-holding scans with the same timing as the task in an additional fMRI experiment on the same subject. This assumption is motivated by the observation that the task response y_t and the breath-hold response x_t were very often simultaneously correlated or anti-correlated to I_t in voxels in which significant task activation was observed (Fig. A). For this unknown dependence between task response and breath-hold response (vasoreactivity), we assumed the model $h_t = L_0[X_t]$, where X_t is a local vasoreactivity template derived from the breath-hold signal x_t by block averaging and subsequent repetition and L_0 a linear functional. This relationship takes into account, for example, possible latencies between x_t and y_t . The task response model can now be written as $y_t = L[X_t] + \varepsilon_t$ with again an unknown general linear dependence L. The degree of dependency can thus be estimated by the coherence between x_t and y_t , analogous to the second method.

Results



We found that very often a significant positive task response is associated with either a positive or negative breath-hold response. A significant task response was defined in this abstract for $p < 0.05$ (corrected for multiple testing by Sidak method [5]); Fig. A shows typical correlation coefficients R of task response with block design function and breath-hold response with block design function for all voxels in a brain. Lines indicate significance thresholds. Fig. B shows one example for an anti-linear dependency between task and breath-hold response. These observations motivated our approach to quantify task response using additional information from breath-hold response. Fig. C shows BOLD response (correlation map) in a language task in a patient with grade II oligoastrocytoma. The tumor is anterior/superior to the dashed circle; Fig. D shows the corresponding coherence map; Fig. E shows a correlation or vasoreactivity map of the breath-hold response (blue negative R, red positive R, not thresholded). Finally, Fig. F shows the coherence of the task response with the breath-hold template, or in other words, the activation map that utilizes information from vasoreactivity. Activation in Heschl's gyrus and additional activation in Wernicke's area is evident, which were both not visible in conventional analysis (C) and weaker in the coherence map without breath-hold information (D). Note the strong vasoreactivity (E) seen in the areas of activation. In summary, we found significant changes in activation when vasoreactivity is utilized in 8 of 16 subjects.

Discussion and Conclusion

To map eloquent cortical areas in patients with brain tumors, we attempted to correct for altered hemodynamics by performing a simple breath-hold assessment and incorporated this information into the modeling of the BOLD response. The method proposed here is one of probably several possible ways to incorporate vasoreactivity data and showed differences in activation in half of the patients studied. Whether a difference is observed might be related to the proximity of eloquent areas to the tumor and the kind of pathology, but more experiments are necessary to clarify this. However, our results suggest that the inclusion of vasoreactivity data could enhance BOLD detection in patients with compromised hemodynamics secondary to pathology. To better evaluate our results we plan to use cortical stimulation mapping or to derive heuristic methods [6].

References

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