Brain Atrophy Accounts for Age-Related Differences in Hemodynamic Impulse Response Function from Auditory Cortex

Raphael T Gerraty[1], David B Parker[2], Alayar Kangarlu[3], and Qolamreza R Razlighi[2,4]

[1]*Psychology, Columbia University, New York, NY, United States,* [2]*Biomedical Engineering, Columbia University, NY, United States,* [3]*Psychiatry, Columbia University, NY, United States,* [4]*Neurology, Columbia University, New York, NY, United States*

Introduction

One of the major challenges of aging research using BOLD fMRI is possibility of age-related alteration in hemodynamic impulse response function (HRF). Evidence of cerebrovascular changes throughout the life span highlight the importance of this potential confound, and there is an extensive body of literature suggesting age-related alterations in the hemodynamic response[1]. Even though these studies show mixed results, but they have been used as evidence that differences in neurovascular coupling represent a significant confound in fMRI studies of aging[2]. These differences would present a difficulty in interpretation of standard GLM-based fMRI analysis results.

In this study we aimed to investigate issues associated with these mixed and often conflicting results. We first investigated different deconvolution methods and then we compared the effects of extracting time series of the fMRI data from subject's native space or from standard space after spatial normalization. Almost all the existing reports on age-related alteration of HRF were performed after spatial normalization. By extracting the time series in subject native space we aim to eliminate brain atrophy as another confounding factor in aging studies which makes co-registration of older brain to template space even more challenging.

Materials and Methods

Thirty-five right handed healthy subjects (17/18 young/old; female percentage: 0.53/0.61, age mean$\pm$std: 25.5/64.9$\pm$2.4/2.2 years) were presented with visual (flashing checker boards) and auditory (tones) stimuli with random onset and duration (event related design) while undergoing fMRI scanning. To ensure attention to the stimuli, subjects were asked to respond with a button press at the conclusion of each visual stimulus. Participants were scanned for 5.5 minutes, with at least 37 events of visual and auditory stimuli. FMRIB software library (FSL) standard motion correction, slice timing correction, smoothing with an 5 mm^3 non-linear kernel, intensity normalization, and high-pass filtered using a Gaussian kernel and cut-off frequency of 0.008 Hz were performed. For group-level analysis in standard space, spatial normalization was performed by linear registration to an EPI template in MNI space. Both the native space and spatially normalized fMRI data were linearly modeled by fitting voxels' time series to multiple regressors of interest (visual, auditory, and motion stimuli, each convolved with both the canonical HRF and its first derivative) and nuisance regressors (6 sets of motion parameters and an intercept). All terms in this linear model were "pre-whitened" using an autocorrelation matrix given by an first-order autoregressive (AR(1)) model of residuals from a preliminary GLM.

Second level linear analysis was performed only on the spatially normalized activation maps to obtain group level map for each age group. Group level activation maps were FWE corrected for multiple comparisons using Gaussian random field theory and binarized to be used as Region of Interest (ROI) masks for deconvolution analysis. For the native space analysis the group level ROI mask was transformed back to each subject's native space and a conjunction mask was generated as the intersection of the transformed mask and a native space uncorrected ($p < 0.01$) activation map. Three deconvolution schemes (Wiener Filtering[3], FLOBS[4], and FIR[5]) were examined in this study. All of these methods have been widely used in the literature to extract the HRF from fMRI time series.

Results and Discussion

Group-level averages between young and old subjects revealed robust activation of primary visual and auditory cortices for their respective stimuli. Younger and older subjects showed robust differences in activation to auditory stimuli. This difference survived whole-brain correction (FWE $p<0.05$). No significant difference was found using the same method for visual cortex. Using the spatially normalized data, all three deconvolution techniques showed no age related difference in the extracted HRF for visual stimuli (Fig. 1A), whereas there were a significant delay and reduction in the amplitude of the extracted HRF for auditory stimuli in the older group (Fig. 1B). These results suggest that older subjects' hemodynamic response to auditory stimuli is not only slower, but also of lower magnitude than their younger counterparts. This is consistent with previous evidence of the cerebrovasculature deterioration with age. Using the times series extracted from native space, none of the three deconvolution techniques exhibited age-related differences in the extracted HRF for either visual or auditory stimuli (Fig. 1C &D). This indicates that the difference apparent in the auditory HRF using the spatially normalized time series might be a direct effect of inaccurate registration resulting from extensive brain atrophy in old subjects.

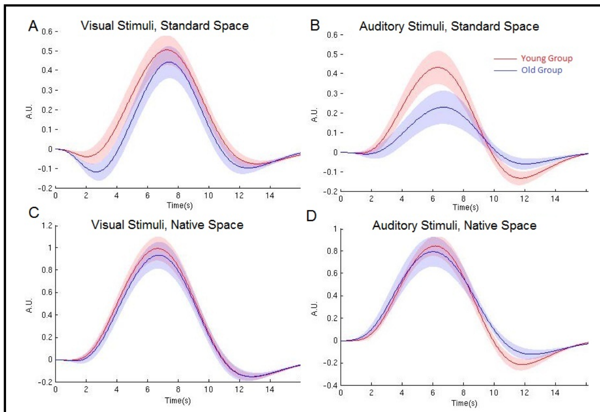

Figure 1: The deconvolved HRF from visual and auditory stimuli using time series extracted after spatial normalization and in subject native space. only results for FLOB are represented.

Conclusions

A direct comparison of BOLD activation between young and old adults using a canonical HRF revealed bilateral significant differences in the auditory cortex. Interpretation of this result would be challenging given significant age-related variabilty in the shape of HRF. Previous claims about the importance of this hemodynamic variability have not considered the effect of registration to template space, which may be problematic for older subjects who exhibit irregular patterns of atrophy, especially in regions of the temporal cortex. In fact, most rely on ROI defined in template space, either from functional or structural atlases, in order to extract time series for deconvolution. Here we deconvolved HRF from ROIs defined in both template- and subject- space, using multiple deconvolution methods. Our findings indicate that many of the reported HRF differences are more pronounced when considering time-series derived after registration to template space than when using ROIs generated in native space from subjects' individual activation maps.

References

1. Huettel, S. A., Singerman, J. D., & McCarthy, G. (2001). The effects of aging upon the hemodynamic response measured by functional MRI. *Neuroimage*,*13*(1), 161-175.
2. D'Esposito, M., Deouell, L. Y., & Gazzaley, A. (2003). Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. *Nature Reviews Neuroscience*, *4*(11), 863-872.
3. Glover, G. H. (1999). Deconvolution of impulse response in event-related BOLD fMRI. *NeuroImage*, *9*(4), 416-429.
4. Woolrich, M. W., Behrens, T. E., & Smith, S. M. (2004). Constrained linear basis sets for HRF modelling using Variational Bayes. *NeuroImage*, *21*(4), 1748-1761.
5. Henson, R., Rugg, M. D., & Friston, K. J. (2001). The choice of basis functions in event-related fMRI. *Neuroimage*, *13*(6), 149-149.