Identification of neurovascular changes in cerebral amyloid angiopathy by modeling subject-specific hemodynamic response functions

Rebecca J Williams[1,2], Bradley Goodyear[1,2], Stefano Peca[3], Cheryl R McCreary[1,2], Richard Frayne[1,2], Eric E Smith[1,2], and G Bruce Pike[1,2]

[1]Radiology and Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada, [2]Seaman Family MR Research Centre, Alberta Health Services, Calgary, Alberta, Canada, [3]Tom Baker Cancer Centre, University of Calgary, Calgary, Alberta, Canada

Target Audience Researchers and clinicians with interests in cerebrovascular disease; hemodynamic response modelling; functional magnetic resonance imaging.

Purpose Cerebral amyloid angiopathy (CAA) is an age-related disease characterized by deposition of the β-amyloid peptide within the media and adventitia of small blood vessels. The loss of vascular integrity resulting from this deposition may lead to intracerebral haemorrhages and microbleeds[1]. It is therefore essential to characterize the early vascular changes resulting from CAA to guide intervention and treatment. CAA-related injury is preferentially localized to the occipital regions of the brain, with the posterior circulation showing decreased vascular reactivity[2]. Vascular changes resulting from CAA have been detected using functional MRI, characterized by reduced response amplitude to visual stimulation[3,4]. However modelling the hemodynamic response function (HRF) may provide further information regarding neurovascular changes than BOLD signal amplitude alone. The time-to-peak (TTP) and full-width at half-maximum (FWHM) of the HRF reflects timing and duration of hemodynamic changes associated with neural activity. In this study, we characterized the HRF to visual stimulation in CAA patients and healthy controls.

Methods The data analysed were acquired as part of a prospective longitudinal cohort study. Data from 14 patients with a diagnosis of probable CAA (mean age = 73.1 ± 7.0 years, 8 male) and 13 healthy control (HC) participants (mean age = 70.2 ± 5.5 years, 6 male) were included. Visual stimulation (black and white checkerboard reversing contrast at 8 Hz) was interspersed with a grey blank baseline condition. A central fixation cross was consistently present. A total of 4 visual stimulus blocks of 40 seconds each, interspersed with 40 s rest blocks, were used. All images were acquired on a 3 T MR scanner (Signa VHi, GE Healthcare, Waukesha, WI) with a 12-channel head coil. For each participant, 180 sets of EPI data sensitized to BOLD contrast (TR = 2000 ms, TE = 30 ms, flip angle = 70, 3.75 × 3.75 × 4mm) were acquired continuously. A 3D T_1-weighted structural image was also acquired. Images were analysed in SPM8. HRFs were estimated using routines established for block designs[5] running in MATLAB. Pre-processing involved slice-timing correction, realignment and reslicing, coregistration of the structural to the mean functional image for each participant. Segmentation of the coregistered structural image was performed, with resultant deformation fields used to transform an atlas-based region-of-interest (ROI) corresponding to the primary visual cortex (V1)[6] from MNI to subject space on an individual basis. First-level statistical analyses were performed using the finite impulse response (FIR) basis functions, to allow variability in the shape and timing parameters of the impulse response without imposing an *a priori* functional form. For every participant, contrast images identifying the effects of the visual stimulation ($p < .05$ FDR corrected) were inclusively masked with the V1 ROI. Signals from all activated voxels within the ROI were extracted and averaged for HRF estimation. Subject-specific HRFs were estimated by modelling the fMRI time course as the convolution of the HRF (generated using the sum of two gamma functions) and a boxcar stimulus function. The TTP and FWHM of the positive response were calculated from each subject-specific HRF and compared using independent samples *t*-tests.

Results The HRFs estimated from the CAA patients were significantly wider: FWHM in CAA was 4.7 ± 1.5 s compared to 3.8 ± 0.7 s in HC, $p = 0.04$. The TTP was delayed in the CAA group relative to the controls, however this difference did not reach statistical significance, TTP = 4.9 ± 1.9 s; 3.7 ± 1.1 s (for CAA and HC groups respectively), $p = 0.18$. Figure 1 shows the group-averaged HRFs for both CAA and HC groups.

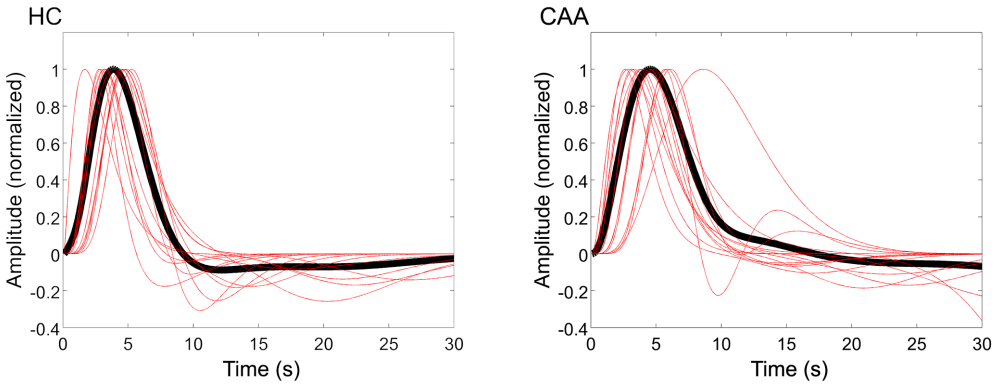

Figure 1. *Group-averaged HRFs (black lines) for healthy controls (HC, left) and CAA patients (CAA, right). Superimposed over subject-specific HRFs shown in red. Amplitudes normalized to a maximum value of 1*

Discussion We estimated the HRFs to visual stimulation in patients with CAA and healthy controls. We found that the positive response was significantly wider in the CAA group relative to the controls, however the TTP was less sensitive to group differences. This is in contrast to previous research[3] demonstrating a significant delay in the TTP of CAA patients compared to controls. Methodological differences between our study and the previous research may explain this discrepancy. While the previous authors extracted TTP directly from the fMRI time-course, we estimated subject-specific HRFs in order to calculate the TTP. The previous work included a larger sample size and thus had greater power to detect group differences. Here we show that the FWHM of subject-specific HRFs may be a more sensitive marker of group differences than the TTP, and provide further information about neurovascular changes associated with CAA. **Conclusion** The width of the hemodynamic response may provide a sensitive marker of CAA-related neurovascular changes.

References [1] Smith EE & Greenberg SM. (2009). Stroke, 40:2601-2606. [2] Smith EE, Vijayappa M, Lima F, *et al*. (2008). Neurology, 71:1424-1430. [3] Dumas A, Dierksen GA, Gurol ME, *et al*. (2012). Ann Neurol, 72(1):76-81. [4] Peca S, McCreary CR, Donaldson E *et al.* (2013). Neurology, 81(19):1669-1665. [5] Shan ZY, Wright MJ, Thompson PM, *et al*. (2013). JCBFM, 34:316-324. [6] Maldjian, J.A., Laurienti, P.J., Burdette, J.B. & Kraft, R.A. (2003). NeuroImage, 19:1233-1239.