Verification of impaired vasoreactivity in subjects with Cerebral Amyloid Angiopathy: A post-hoc analysis of visual-stimulus fMRI

James A Goodman[1], Mark R Austin[2], Andrea S Les[2], Zhiyong Xie[1], Yao Zhang[3], and Claire Leurent[4]

[1]*Precision Medicine - Clinical and Translational Imaging, Pfizer Inc, Groton, CT, United States,* [2]*IXICO plc, London, United Kingdom,* [3]*PharmaTherapeutic Statistics, Pfizer Inc, Cambridge, MA, United States,* [4]*Neuroscience Research Unit, Pfizer Inc, Cambridge, MA, United States*

Target audience: This work benefits neurologists and imaging scientists interested in validation of novel techniques for characterizing neurodegenerative disorders that impair cerebrovascular reactivity.

Purpose: Cerebral amyloid angiopathy (CAA) is characterized by deposition of amyloid in the walls of leptomeningial and cerebrocortical vessels.[1] Probable CAA is diagnosed clinically in patients over age 55 by the presence of multiple otherwise unexplained lobar, cortical, or corticosubcortical microhemorrhages in MRI or CT scans.[2] Subjects with probable CAA have recently been shown to exhibit an fMRI-BOLD response to visual stimulus that has reduced amplitude and increased time-to-peak response compared to age-matched healthy controls.[3] This observation of an impaired hemodynamic response to physiological challenge is interpreted as reduced cerebrovascular reactivity due to the deposition of vascular amyloid, an observation previously made directly in transgenic mouse models.[4] In a separate study performed at 3 T by Peca *et al.*,[5] a similar observation was made with respect to reduced amplitude of the hemodynamic response in CAA subjects. The purpose of this work is to extend the analysis of the data reported in Peca *et al.*[5] to include assessment of the temporal *and* amplitude characteristics of the hemodynamic response, as estimated by modeling the ascending slope, to determine whether or not the initial observation of Dumas *et al.*[3] can be replicated in an independent cohort.

Methods: Research was conducted on images acquired from a 3rd party that has been verified as compliant with Pfizer policies, including Research Ethics Board approval. The images had been acquired previously, as described in Peca, et al.[5] Briefly, BOLD fMRI (TR/TE = 2000/30 ms, 3.75 mm^2 in-plane resolution, 4 mm thick) was performed on CAA (n=18) and age-matched healthy controls (n=18) at 3T. Subjects were shown an 8-Hz flashing checkerboard that was on for 40 s, off for 40 s, and was repeated over 4 blocks. Activation masks ($p < 0.02$) were generated for each subject and were used to define an ROI in which at least 50% of the CAA subjects activate. The mean signal timecourse from within this ROI was then generated for each subject using the FLOBS tool within FSL. This timecouse was then fit to a trapezoid in order to characterize the ascending slope of the hemodynamic response. This fit was motivated by the work of Dumas et al.[3], which applied a trapezoid fit to the raw data in order to infer vasoreactivity from the amplitude and the time-to-peak response.

Results: Of the 36 original fMRI data sets, 14 healthy control and 13 CAA data sets passed all pre-established quality control criteria, and only these data sets were analyzed. CAA subjects and healthy controls had an ascending slope of the hemodynamic response of 0.17 +/- 0.02 and 0.29 +/- 0.02 %BOLD/second (mean +/- standard error of the mean, $p < 0.001$), respectively. Mean hemodynamic response curves are shown in figure 1.

Discussion: The Dumas et al.[3] values, which were acquired at 1.5T, cannot be directly compared to the those reported here because of the differences in the amplitude of the BOLD response at 1.5T and 3T. However, the significantly reduced hemodynamic response, reported therein of the group differences in both amplitude and time-to-peak ($p < 0.05$ and $p < 0.001$, respectively) between CAA and healthy subjects, is consistent with what has been observed in the reanalysis of the Peca *et al.*[5] data reported here.

Conclusion: These results confirm previously-reported differences in the temporal characteristics of the occipital hemodynamic response in subjects with CAA compared to age-matched healthy control subjects. As the data were acquired in an independent cohort at a different field strength with different acquisition parameters, and analyzed with a different pipeline than the initial report of Dumas *et al.*,[3] this technique is robust in its sensitivity to the biological determinants of the physiological response to stimulus that are particular to CAA versus control subjects.

Acknowledgement: The study dataset was provided without compensation by Prof. Eric E. Smith.

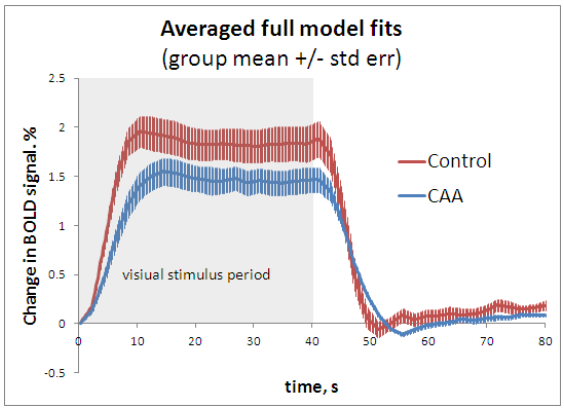

Figure 1. Shown above are mean hemodynamic responses from CAA and control subjects. The ascending slope of the hemodynamic response differed significantly between the two groups ($p < 0.001$).

References:

1. Vonsattel J, Myers R, Hedley-Whyte E., et al. Cerebral Amyloid Angiopathy Without and With Cerebral Hemorrhages: A Comparative Histological Study. *Ann Neurol*. 1991;30(5):637-649.
2. Greenberg S, Rebeck G, Vonsattel J, et al. Apolipoprotein E ε4 and cerebral hemorrhage associeiated with amyloid angiopathy. *Ann Neurol*. 1995;38:254-259.
3. Dumas A, Dierksen G, Gurol E, et al. Functional Magnetic Resonance Imaging Detection of Vascular Reactivity in Cerebral Amyloid Angiopathy. *Ann. Neurol*. 2012;72:76-81.
4. Han B, Zhou M, Abousaleh F, et al. Cerebrovascular Dysfunction in Amyloid Precursor Protein Transgenic Mice: Contribution of Soluble and Insoluble Amyloid-B Peptide, Partial Restoration via g-Secretase Inhibition. *J. Neurosci*. 2008;28(50):13542–13550.
5. Peca S, McCreary C, Donaldson E, et al. Neurovascular decoupling is associated with severity of cerebral amyloid angiopathy. *Neurology*. 2013;81:1659-65.