fMRI of Delayed Albumin Treatment during Stroke Recovery in Rats: Implication for Fast Neuronal Habituation in Recovering Brains

Y. R. Kim[1], M. P. van Meer[1], J. B. Mandeville[1], E. Tejima[2], G. Dai[1], K. Topalkara[3], J. Qui[3], R. M. Dijkhuizen[4], M. A. Moskowitz[3], E. H. Lo[2], B. R. Rosen[1]

[1]Athinoula Martinos Center for Biomedical Imaging/ Massachusetts General Hospital, Charlestown, MA, United States, [2]Neuroprotection Research laboratory/ Massachusetts General Hospital, Charlestown, MA, United States, [3]Stroke and Neurovascular Regulation Laboratory/ Massachusetts General Hospital, Charlestown, MA, United States, [4]Image Sciences Institute, University Medical Center Utrecht, The Netherlands, Charlestown, MA, United States

ABSTRACT Accumulating experimental and clinical data suggest that albumin may be neuroprotective for stroke. Here, we use functional magnetic resonance imaging (fMRI) to evaluate the therapeutic efficacy of albumin and its effects on the recovery of stimuli-induced cerebral hemodynamics. For this purpose, fMRI activity in the ipsilesional somatosensory (SS) cortex was assessed using a well established rat model of transient 90 min focal ischemia and electrical forelimb stimulation. Rats were treated with either saline or albumin via intracerebroventricular injections at 12 hrs post-stroke onset. Despite this delayed treatment time, when compared to the saline-treated rats (n=7), there were significant enhancements of the fMRI activation in the albumin-treated rats (n=6) for both blood oxygenation level dependence (BOLD) and functional cerebral blood volume (fCBV) responses. Interestingly, the temporal characteristics of the ipsilesional SS BOLD responses in the albumin-treated rats appeared considerably altered compared to those of contralesional responses while such temporal alterations were not pronounced for the fCBV responses. These characteristic fMRI temporal profiles of the albumin-treated brains may be due to altered neuronal responses rather than altered neurovascular coupling, which implies an unusually fast habituation of neuronal responses in the lesional SS cortex. The correlation between various MRI-derived structural parameters and the fMRI response magnitude was also characteristic for albumin and control groups. Taken together, these data suggest that restoration of fMRI response magnitudes, temporal profiles, and correlations with structure may reveal the extent and specific traits of albumin treatment associated stroke recovery.

MATERIALS AND METHODS 12 hours after a transient middle cerebral artery occlusion (90min), the rats received a single intracerebroventricular (ICV) injection of bovine serum albumin (BSA) solution alone (1μg/l0μl/rat: n=6), or the same volume of normal saline (0.9 % NaCl l0μl: n=7). On day 15 following the MCAO, fMRI was performed in both stroke and control groups. The fMRI activation of both BOLD and fCBV responses (Gradient Echo Planar Imaging, TR/TE = 3700/15 ms for BOLD, TR/TE = 3700/11 ms for fCBV, FOV = 2.5x2.5 cm^2; nine 1 mm slices, and 80x80 matrix zero filled to 128x128) was acquired using a horizontal bore 9.4T Bruker/Magnex system, equipped with a home-built surface coil. An unilateral electrical stimulation paradigm, consisting of 3 periods of 37 sec 'stimulation on' separated by 185 sec 'stimulation off,' was alternated between the left and right forepaw and was repeated at least 2 up to 5 times. Following BOLD fMRI, MION was intravenously administered (36mg (FeO_2)/kg), and the stimulation paradigm was repeated for fCBV fMRI. Functional activation maps were generated by a voxel by voxel t-test between the on and off stimulus periods. Simulations of the fMRI time courses were performed using Matlab (The Mathworks Inc. Natick MA) by convolving an assumed fMRI impulse response function (IRF) with the time-dependent neural transfer function: $S(t)=h(t)*n(t)$ where * denotes convolution and $h(t)$ and $n(t)$ represent impulse response and neural transfer functions, respectively. The BOLD and MION IRF's were assembled from a series of exponential basis functions, $h(t)=\Sigma_k a_k/\tau_k \exp(-t/\tau_k)$, as described previously by Leite et al.[1] The neural transfer function ($n(t)$) was modified from a step function in which $n(t)$ is assumed to be exponentially decreasing during the stimulus with varying time constant (τ_c): $n(t)=C_o\exp(-1/\tau_c)$.

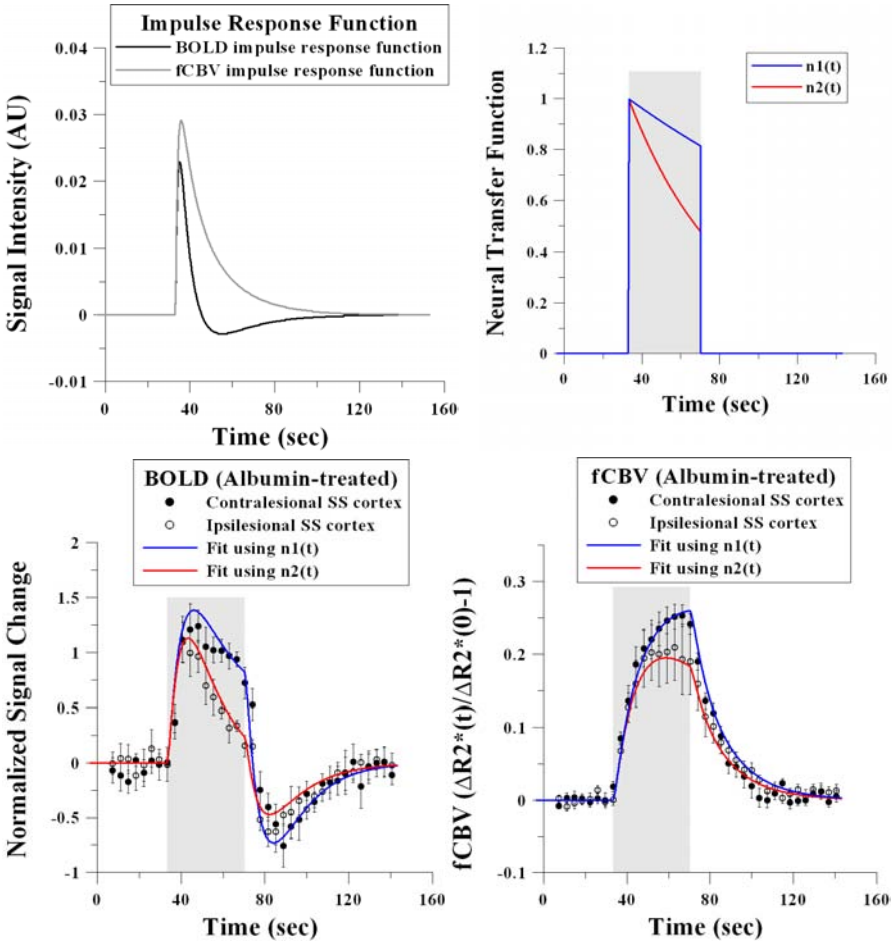

Figure 1. BOLD and fCBV impulse response functions (top left), neural transfer functions (top right), simulated BOLD (bottom left) and fCBV fMRI responses (bottom right) using the convolution of time dependent neural ($n(t)$) and impulse response ($h(t)$) functions.

RESULTS AND DISCUSSION We observed that ischemic brains responded to the delayed ICV administration of albumin, as assessed by fMRI measurements. A dramatic restoration of fMRI response in the ipsilesional SS cortex was detected in albumin-treated animals as compared to the saline-treated controls. Further evidences suggest that the neurohemodynamic linkage was *not* altered in ipsilesional cortex, but restoration of activation was accompanied by a stronger neural habituation in the temporal domain. In conclusion, we demonstrated that quantified fMRI responses can be used for defining recovery traits of albumin-treated stroke animal models and for providing insights into the detailed recovery process of neurovascular function.

REFERENCES

1. Leite, F. P., Tsao, D., Vanduffel, W., Fize, D., Sasaki, Y., Wald, L. L., Dale, A. M., Kwong, K. K., Orban, G. A., Rosen, B. R., Tootell, R. B. & Mandeville, J. B. (2002) *Neuroimage* **16,** 283-94.