Orthogonal diffusion measurements in the mouse hypothalamus by MRI reveal cerebral activity in the fed or fasted states

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INTRODUCTION: Cerebral activation is associated to intracellular, extracellular and transcellular ion fluxes between neural cells, accompanied by water movements and potentially cellular swelling. Notably, translational diffusion of water molecules in the brain, as observed by diffusion weighted MRI (DWI), has been shown to decrease in the activated brain cortical areas. This finding reveals a relative redistribution of water diffusion compartments between the Fast Diffusion Pool (FDP) and the Slow Diffusion Pool (SDP) and implies a certain degree of cellular swelling during brain activation (1). Additionally, DWI methods may be sensitized to detect flow contributions using reduced b values (IVIM), a possibility that could enable to monitor blood flow changes during activation (2). In this study, we report on the use of DWI and IVIM as novel biomarkers to explore cerebral hypothalamic activation during a feeding-fasting paradigm.

EXPERIMENTAL: *Animal model:* Adult C57 mice (n=8), drinking water *ad libitum* were imaged in two consecutive experimental conditions, fed *ad libitum* and fasted (48 h). *MRI studies:* Mice were maintained anesthetized with 1% isofluorane/oxygen through a nose cap during MRI protocols. We used a 7T Bruker Pharmascan scanner equipped with a 90mm gradient coil insert (36 G/cm, max intensity) and a mouse head resonator. Diffusion weighting was achieved using the Stejskal-Tanner spin-echo sequence (3) with 4 shot EPI-read gradient and 3 different directions defined by the read, phase and slice encoding gradients. Acquisition conditions were: $\delta = 4ms$ Δ=20 ms, TR=3000 ms, TE= 51 ms, FOV=38 mm, axial slices (1.5 mm thickness). We obtained 5 "high b" value acquisitions (200<b<1200 s/mm^2) and 6 "low b" value acquisitions (10<b<90 s/mm^2**)** across an imaging plane containing the hypothalamus. *Data analysis:* The complete data set was analyzed using either (i) a monoexponential diffusion decay $S(b)/S(0)=f\cdot\exp(-bD)$, (ii) a biexponential diffusion decay $S(b)/S(0)=SDP\cdot\exp(-bD_{slow})+FDP\cdot\exp(-bD_{fast})$, with slow (SDP) and fast (FDP) diffusion phases characterized by slow (D_{slow}) and fast (D_{fast}) diffusion coefficients, respectively. Mono and biexponential models were analyzed using three approaches; A- fitting the signal attenuation of the 5 high b values only (with no flow contribution expected as b>200 s^2/m); B- fitting the signal attenuation of the complete 11 b values collection (thus including flow sensitation); and C- fitting the signal attenuation of the 6 low b values only (flow sensitized, Fig. 1 left panel). Parameter values were obtained by pixel by pixel fitting of the image data set using home made MATLAB v7a libraries and compared between fed and fasted states (Fig.1 central panel).

RESULTS AND DISCUSSION

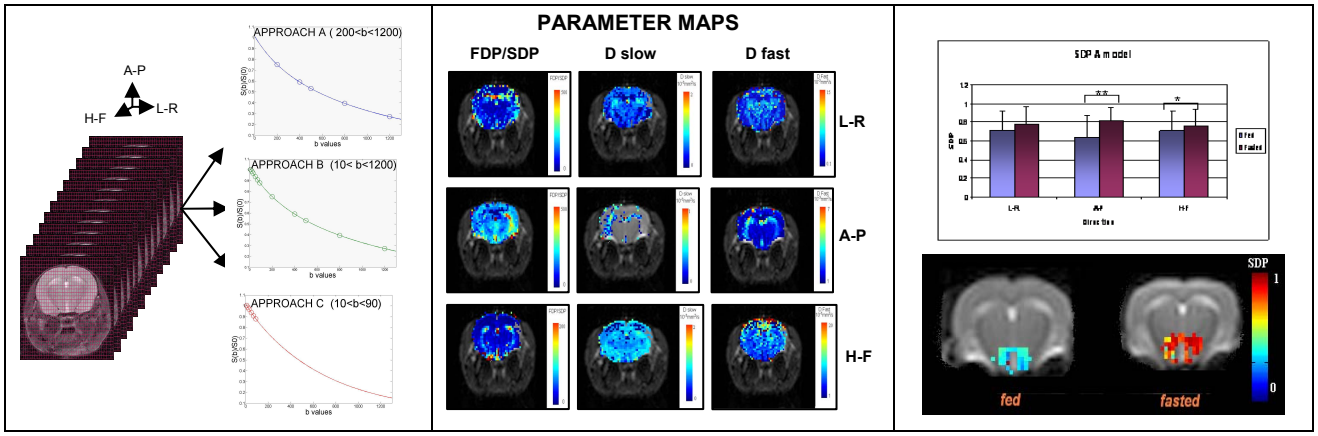

Figure1. Left: Approaches A, B and C). Centre: Representative parameter maps for the coefficients of the biexponential model in a fed mouse, note the different parameter values in the three orthogonal directions. Right: Comparison of average values of SDP in the hypothalamus of fed and fasted mice (upper panel) and comparison of representative parameter maps of SDP in the same mouse, in the fed and fasted states (lower panel)

We found significant changes of the mean values of SDP, FDP/SDP, D_{slow}, D_{fast}, in the hypothalamus of fed and fasted mice between the two feeding conditions. Those differences were larger in the SDP and FDP/SDP parameters, using in the biexponential model as applied to high b value acquisitions (Fig.1 right panel). Our findings agree well with previous DWI studies of activation in the human visual cortex (3) reporting an increase in the contribution of the slowly diffusing water pool upon visual activation. In addition, our results reveal anisotropy in these effects, detecting more important differences in A-P directions. The contribution of flow effects tends to mask the changes observed. In conclusion, we report that hypothalamic activation by fasting, results in an increase in the contribution of the Slow Diffusion Phase, compatible with activation-induced intracellular swelling.

BIBLIOGRAPHY

(1) Le Bihan D, Urayama S-i, Aso T, Hanaakawa T and Fukuyama. Direct and fast detection of neuronal activation in the human brain with diffusion MRI Proc. Natl Acad.Sci 2006; *103:8263-68*

(2) Le Bihan D Intravoxel Incoherent Motion Perfusion MR Imaging: A Wake-Up Call. Radiology 2008;249(3):748-52

(3) Stejskal, E. O. & Tanner, J. E. Spin diffusion measurements: spin echoes in the presence of a time dependent field gradient. J.Chem. Phys. 1965; 42, 288–292

(4) Niendorf T, Dijkhuizen RM, Norris DG, VanLookeren Campagne M, Nikolay K. Biexponential diffusion attenuation in various states of brain tissue: implications for diffusion-weighted imaging. Magn Reson Med 1996; 36:847-857.