

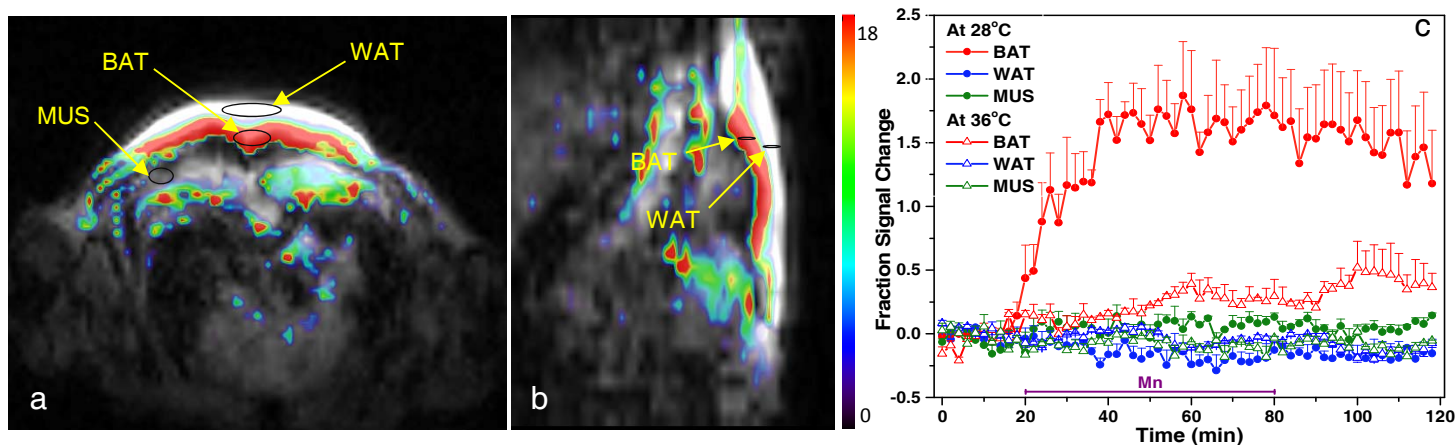
## Differentiation of Brown Adipose Tissue using Manganese Enhanced MRI

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**Introduction:** The brown adipose tissue (BAT) is a type of fat that modulates both basal and inducible energy expenditure in mammals. Its presence in adult human has recently gained much interest due to its implication in the development of obesity [1,2,3] and made it a new target for treatments [2]. Compared to white adipose tissue (WAT), BAT has multilocular lipid droplets, increased number of mitochondria, and is more metabolically active. Despite its importance and implications in obesity, BAT detection is challenging and mostly done by radioactive fluorodeoxyglucose (FDG) PET, which is limited by its low resolution and radioactivity. Recently BOLD and blood volume-based fMRI was proposed for imaging active BAT [4,5], though their susceptibility-based contrast may suffer from artifacts in body imaging. In this work, we investigate the potential of Manganese Enhanced MRI (MEMRI) to map increased  $\text{Ca}^{2+}$  flux of active BAT in the mouse model *in vivo* [6].

**Methods:** All animal experiments were approved by the local Institutional Animal Care and Use Committee. C57BL/6 (21  $\pm$  0.1 g, 8-12 weeks) female mice were used in this study. Anesthesia was induced by 3% isoflurane and then maintained at 0.5-1.5 % throughout the imaging session in 100%  $\text{O}_2$  via a nose cone. Body temperature was measured via a rectal probe and maintained with a MRI-compatible feedback heating system throughout the whole experiment at either 36  $\pm$  0.1  $^\circ\text{C}$  for the control group (n=2) or at 28  $\pm$  0.2  $^\circ\text{C}$  for the cold exposure group (n=3). MRI were acquired using a 9.4T (Agilent, USA) scanner with a quadrature volume coil for RF transmission and a single-loop surface coil (1.5 cm in diameter) for receiving. The coil was carefully positioned above the interscapular BAT depot. Dynamic T<sub>1</sub>-weighted MRI was acquired using 3D-MPRAGE (TR 8 ms, TE 2.5 ms, 1 mm slice thickness, 128x128x32 matrix, FOV 3.0x3.0 cm) for 2 hr. After 20 min of baseline acquisition, 5.93mg/kg/h of  $\text{MnCl}_2$  was continuously infused i.v. for 60 min. Mean signal intensity was then extracted from ROIs drawn in the BAT, WAT, and muscle (MUS) tissue.

**Results:** Fig. 1a and b represent  $\text{Mn}^{2+}$  enhancement maps whereby high uptake of  $\text{Mn}^{2+}$  is observed in the subcutaneous fat in the interscapular area under cold exposure. The average time courses show significant  $\text{Mn}^{2+}$  uptake in BAT under cold but not thermoneutral condition. The signal was specific to BAT as no  $\text{Mn}^{2+}$  uptake was detected in the surrounding muscle or WAT (Fig. 1c).



**Fig. 1** Enhancement map show high manganese uptake in BAT on (a) axial and (b) sagittal views. Arrows in yellow point to the different subtypes of tissue. (c) Mean signal timecourse from ROIs in BAT (red), WAT (blue) and muscle (green) at 28  $^\circ\text{C}$  and 36  $^\circ\text{C}$ .

**Discussion and Conclusion:** We demonstrated MEMRI as a functional imaging method to detect brown fat activation in the mouse. Taken advantage of the increased  $\text{Ca}^{2+}$  flux in BAT by adrenergic activation,  $\text{Mn}^{2+}$ , as a  $\text{Ca}^{2+}$  analog, provides a sensitive way to detect functional activation at high resolution. An insignificant uptake of  $\text{Mn}^{2+}$  seen in mice maintained at normal temperature suggests the induced  $\text{Mn}^{2+}$  uptake following cold exposure. Besides, the slightly higher  $\text{Mn}^{2+}$  uptake than WAT under normal temperature indicates that resting BAT may also be detectable. Together with other anatomical imaging of fat, MRI could be a powerful tool to study BAT in animal models of metabolic diseases.

**References:** [1] Nedergaard et al, Cell Metab 11(4) 2010; [2] Nedergaard et al, Am J Physiol Endocrinol Metab 293(2) 2007; [3] Nedergaard et al, Ann N Y Acad Sci. 2010; [4] Khanna et al, MRM 68(4) 2012; [5] Chen et al, Obesity 20(7) 2012; [6] Lee et al, Am J Physiol 264(1 Pt1) 1993.