Measuring Human Brown Adipose Tissue Volume and Activity by Quantitative and Functional MRI

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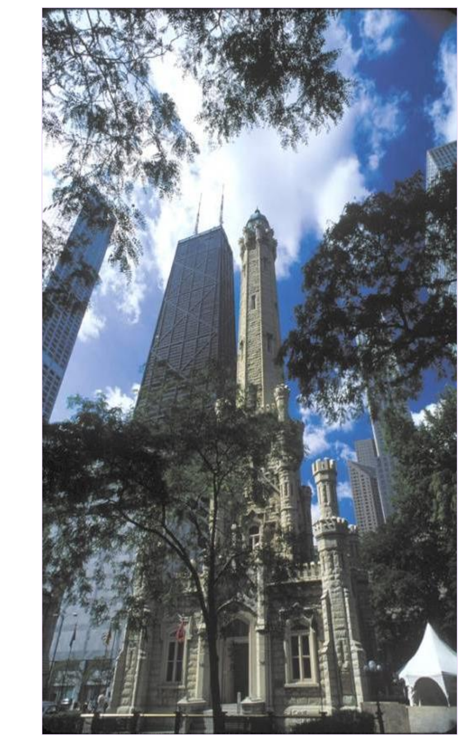

Background

- In the search for potential therapies for obesity and diabetes, brown adipose tissue (BAT) has emerged as a potential target of interest.
- In rodents, BAT is the tissue responsible for adaptive thermogenesis, or increased energy expenditure and heat generation during cold exposure and overfeeding.
- Emerging data indicates that BAT plays a similar role in humans, suggesting a mechanism by which human BAT may protect against obesity development.
- Increasing evidence suggests that BAT may play a role in glucose metabolism and insulin sensitivity. Potential mechanisms include 1) acute increases in glucose and fatty acid utilization in metabolically active BAT depots, 2) increased thermogenesis leading over time to changes in body composition, particularly decreases in body fat, and 3) paracrine or endocrine actions of adipokines secreted by BAT, such as interleukin-6 (IL-6) or fibroblast growth factor-21(FGF-2).
- PET/CT after cold exposure is the current gold-standard technique for imaging activated BAT. However, the utility of PET/CT is limited due to potential underestimation of BAT with insufficient tissue activity levels, ionizing radiation exposure, and the inability to determine the composition of tissues that contain a mixture of brown and white adipocytes.
- Magnetic resonance imaging (MRI) is a non-ionizing radiation modality with superior spatial resolution and soft tissue contrast with which adipose tissues can be well delineated. Unlike PET/CT, MRI has the potential to identify inactive as well as active BAT.
- The ability to quantify inactive BAT could facilitate future studies investigating methods to activate and recruit BAT, with a goal of increasing energy expenditure or improving metabolic parameters, such as blood sugar.
- In this study, multi-parametric quantitative MRI methods will be utilized to characterize BAT at both quiescent and activated status; the gold-standard PET/CT will also be utilized to image cold-activated BAT.

Hypotheses

- BAT activation results in tissue property changes in tissue fat content, fatty acid composition, and/or physiological changes in diffusion, blood flow, and oxidative metabolism which can be detected with MRI.
- MRI will be a useful imaging modality for the characterization of BAT, including the study of its composition and functionality.

Methods

Subjects: 15 lean (BMI 18.5-24.9) and 15 overweight/obese (BMI 25.0-50.0) male subjects, ages 18-24, will be recruited.

- Some inclusion criteria: Subjects must be within 3% of their maximal body weight and weight stable (+/- 3%) over the last three months
- Some exclusion criteria: Thyroid conditions, diabetes, medications that might affect BAT activity, and implanted metal devices that might interfere with the MRI

Screening visit: Subject fasts for eight hours. Visit includes a history, physical exam, and labs (TSH, free T4, hemoglobin A1C, insulin, glucose, lipids)

Imaging visit: (Figure 1)

1. Subject fasts for five hours.
2. DXA scan for body composition
3. Baseline (pre-cold) MRI at thermoneutrality (TN)
4. Subject sits in a cold room (19°C) wearing a temperature –controlled, MRI-safe water suit. Suit temperature is lowered until subject starts to shiver, then raised by 1°C every 4 minutes until shivering stops: this is the non-shivering cold temperature (NST).
5. ^{18}F-fluorodeoxyglucose (FDG) is injected intravenously at a dose of 0.075mCi/kg (max 10mCi). Subject sits in the cold room for another hour in the water suit at NST.
6. FDG-PET/CT scan while wearing the water suit at NST
7. Final MRI while wearing the water suit, first at NST, and then the water temperature is warmed to 30°C for the final imaging at thermoneutrality (WM).

Statistical analyses were performed with SAS 9.3. Friedman repeated measure statistics were used to determine whether MRI parameters were different under the three thermal conditions. Pairwise tests were done for further comparisons. Temperature-induced differences between thermal conditions were correlated with BAT volume and activity as measured by PET/CT using Spearman correlation.

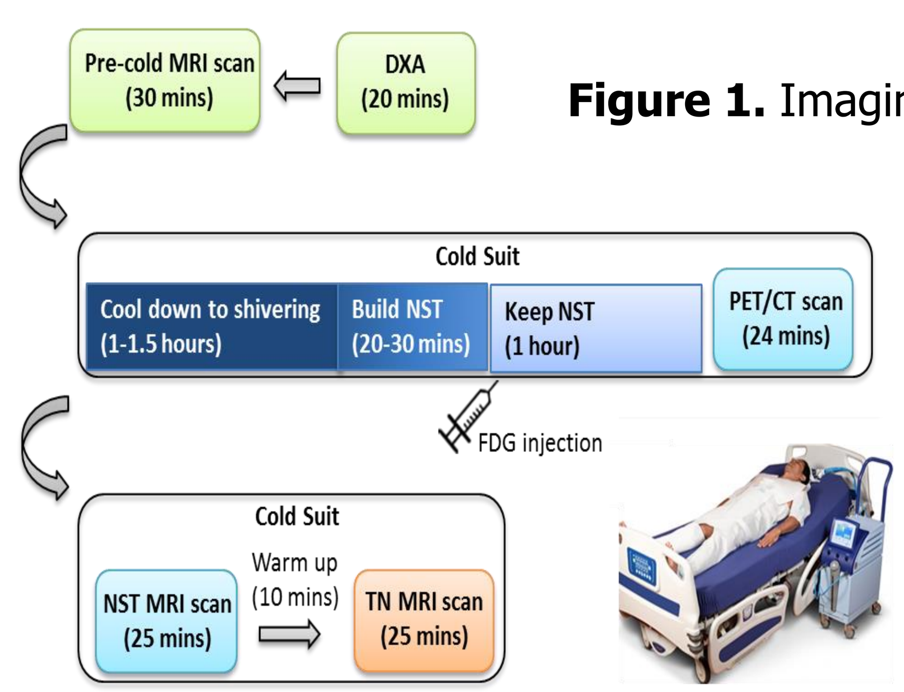

Figure 1. Imaging protocol.

Preliminary Results

- 15 lean subjects (BMI: 18.5 - 24.9 kg/m2) have completed the study. Data collection on overweight and obese volunteers is ongoing. Analysis of metabolic data (e.g. glucose, insulin) will be conducted at study conclusion.
- PET/CT scans for the completed lean subjects are shown in **Figure 2**. All 15 subjects had active BAT, but SUVmax (standard uptake value) varied widely (3.99 to 39.9 g/mL; mean 18.5 ± 10.9). The volume of metabolically active BAT also varied widely (3.1-189.3 ml; mean100 ± 57.3 ml).
- MRI parameter changes were detectable at NST and WM, in comparison with the baseline TN condition. In this study, activation of BAT was detected on MRI scan by:
  1) Combustion of the fatty acids led to depletion of lipids within adipocytes and decreased unsaturated fatty acid synthesis. Decreased tissue fat percentage (FP) was observed in BAT at NST, likely due to fat depletion during BAT activation. Fatty acid double bonds measurements ndb, nmidb and chain length cl all tended to decrease after cold exposure (NST). (**Figure 3**)
  2) Oxygen consumption due to increased metabolism resulted in increased blood flow to provide oxygen supply to the tissue. With increased oxygen consumption, the level of deoxyhemoglobin in the blood increases resulting in decreased T2*. Increased blood flow can also bring with it more oxyhemoglobin, and thus a decrease in regional deoxyhemoglobin and an increase in T2*. In this study, T2* maps showed a heterogeneous response to cold exposure, with increasing T2* in some regions but decreasing T2* in others. **(Figure 4)** Overall, thermal changes significantly affected T2* (p = 0.038) **(Figure 3)**
- T2* differences between TN and WM were correlated with SUVmax (r = 0.53, p = 0.041) and BAT activity (r = 0.54, p = 0.037); T2* difference between NST and WM were correlated with SUVmax (r = 0.54, p = 0.04), BAT volume (r = 0.59, p = 0.02), and BAT activity (r = 0.62, p = 0.01)

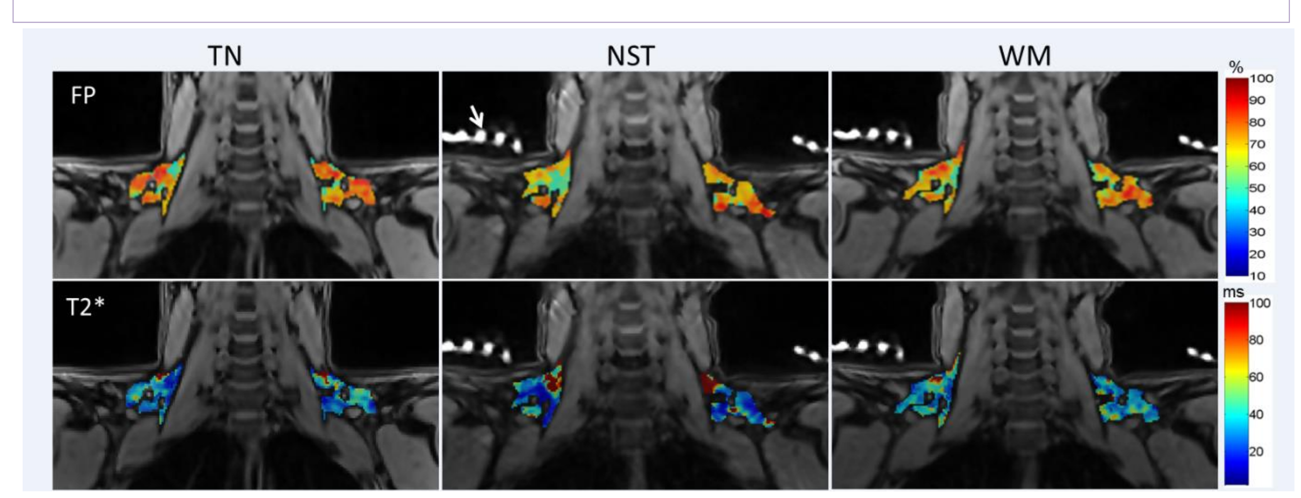

Figure 4. Representative MRI scan showing changes in Fat Percent (FP) and T2* from baseline (TN), at non-shivering thermogenesis (NST), and after warm-up (WM).

Conclusions

- This study demonstrated that multi-parametric quantitative MRI images acquired under three thermal conditions provide multi-dimensional measurements for detecting BAT activation in lean subjects.
- These techniques can be exploited to investigate changes in BAT functionality in an obese population.
- Use of MRI techniques will enhance future studies targeting BAT activation and recruitment as a potential intervention for obesity and diabetes.

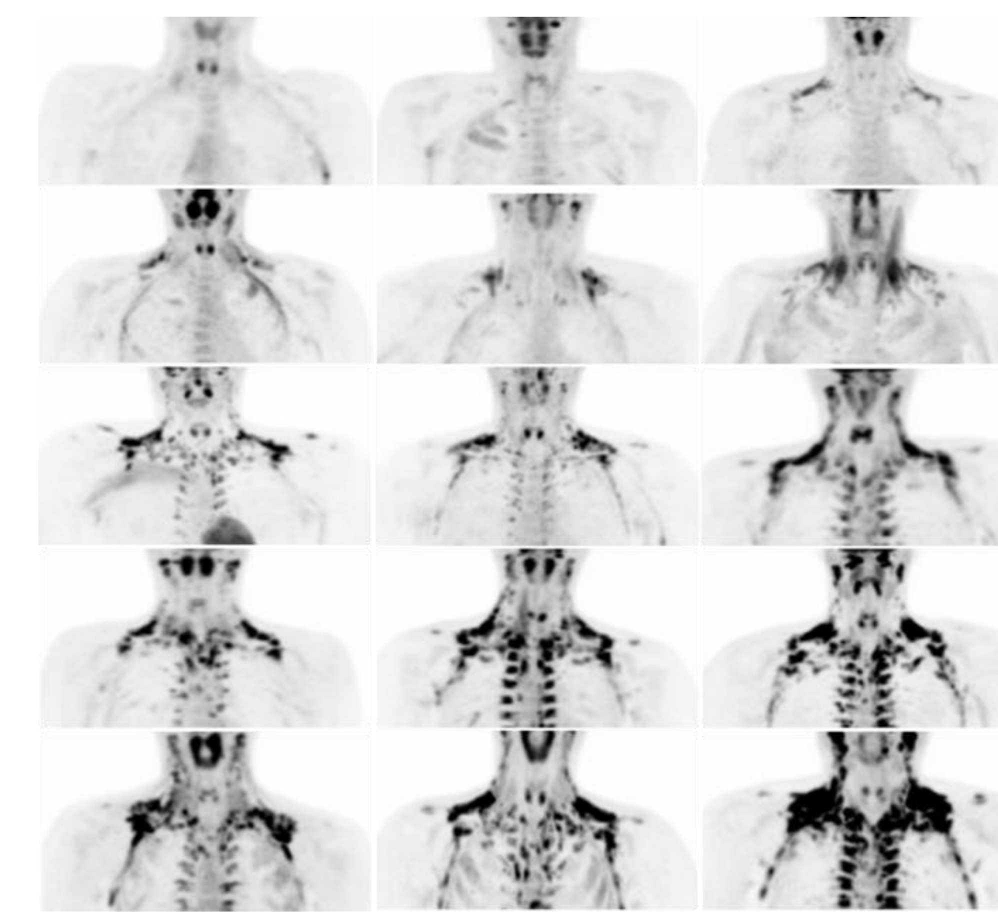

Figure 2. Glucose uptake in BAT detected by PET imaging after cold exposure in 15 lean subjects.

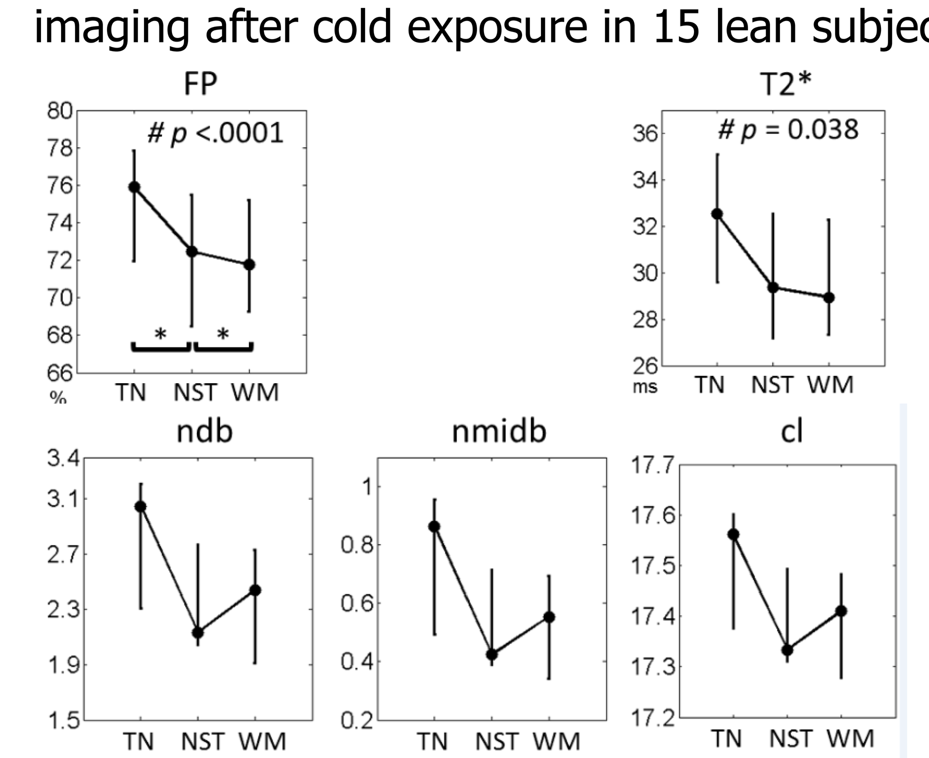

Figure 3. MRI parameters prior to cold (TN), at non-shivering thermogenesis (NST), and after warm-up (WM). FP: fat percent; ndb: number of double bonds; nmidb: number of methylene-interrupted double bonds; cl: fatty acid chain length