BROWN FAT - TOWARDS SAFER QUANTIFICATION IN THE COMBAT AGAINST OBESITY & DIABETES

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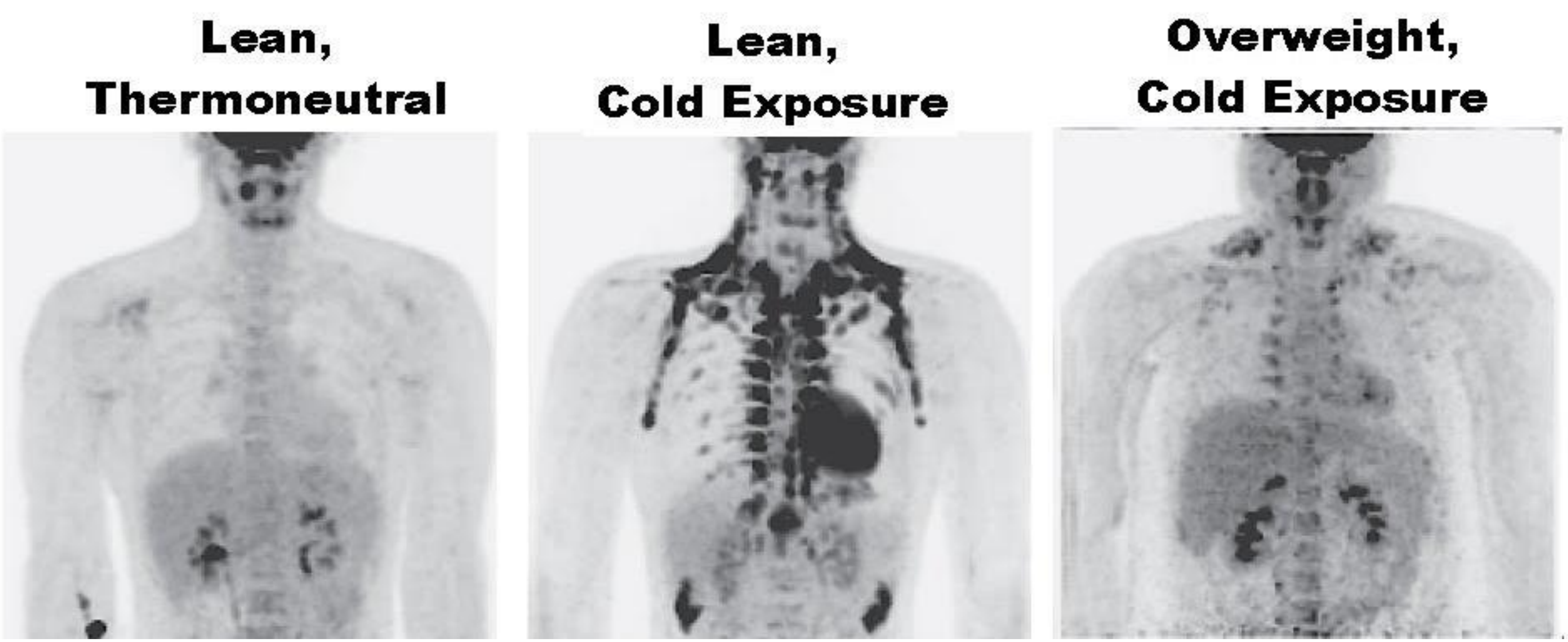
NMRC CSA (INV) 2015-2018

The NEW ENGLAND JOURNAL of MEDICINE

NEJM 2009; 360:1509

Identification and Importance of Brown Adipose Tissue in Adult Humans

Aaron M. Cypess, M.D., Ph.D., M.M.Sc., Sanaz Lehman, M.B., B.S., Gethin Williams, M.B., B.S., Ph.D., Ilan Tal, Ph.D., Dean Rodman, M.D., Allison B. Goldfine, M.D., Frank C. Kuo, M.D., Ph.D., Edwin L. Palmer, M.D., Yu-Hua Tseng, Ph.D., Alessandro Doria, M.D., Ph.D., M.P.H., Gerald M. Kolodny, M.D., and C. Ronald Kahn, M.D.

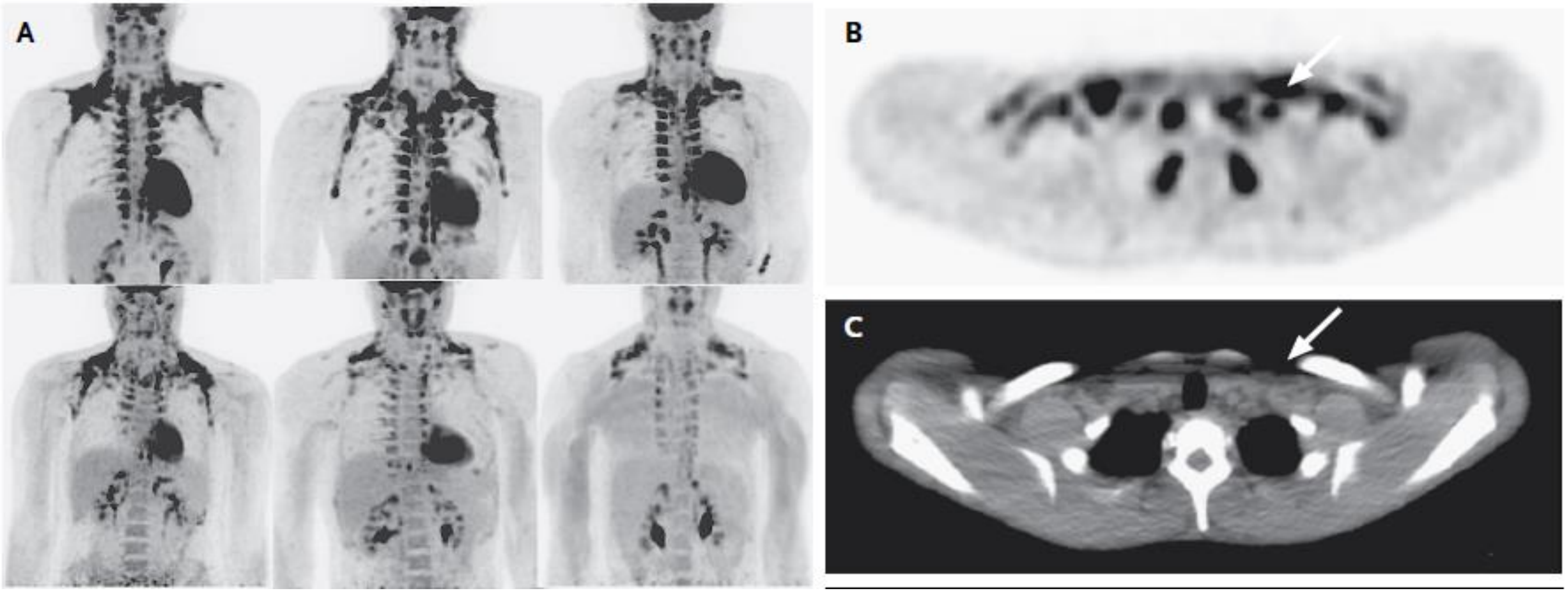


The NEW ENGLAND JOURNAL of MEDICINE

NEJM 2009; 360:1500

Cold-Activated Brown Adipose Tissue in Healthy Men

Wouter D. van Marken Lichtenbelt, Ph.D., Joost W. Vanhommerig, M.S., Nanda M. Smulders, M.D., Jamie M.A.F.L. Drossaerts, B.S., Gerrit J. Kemerink, Ph.D., Nicole D. Bouvy, M.D., Ph.D., Patrick Schrauwen, Ph.D., and G.J. Jaap Teule, M.D., Ph.D.



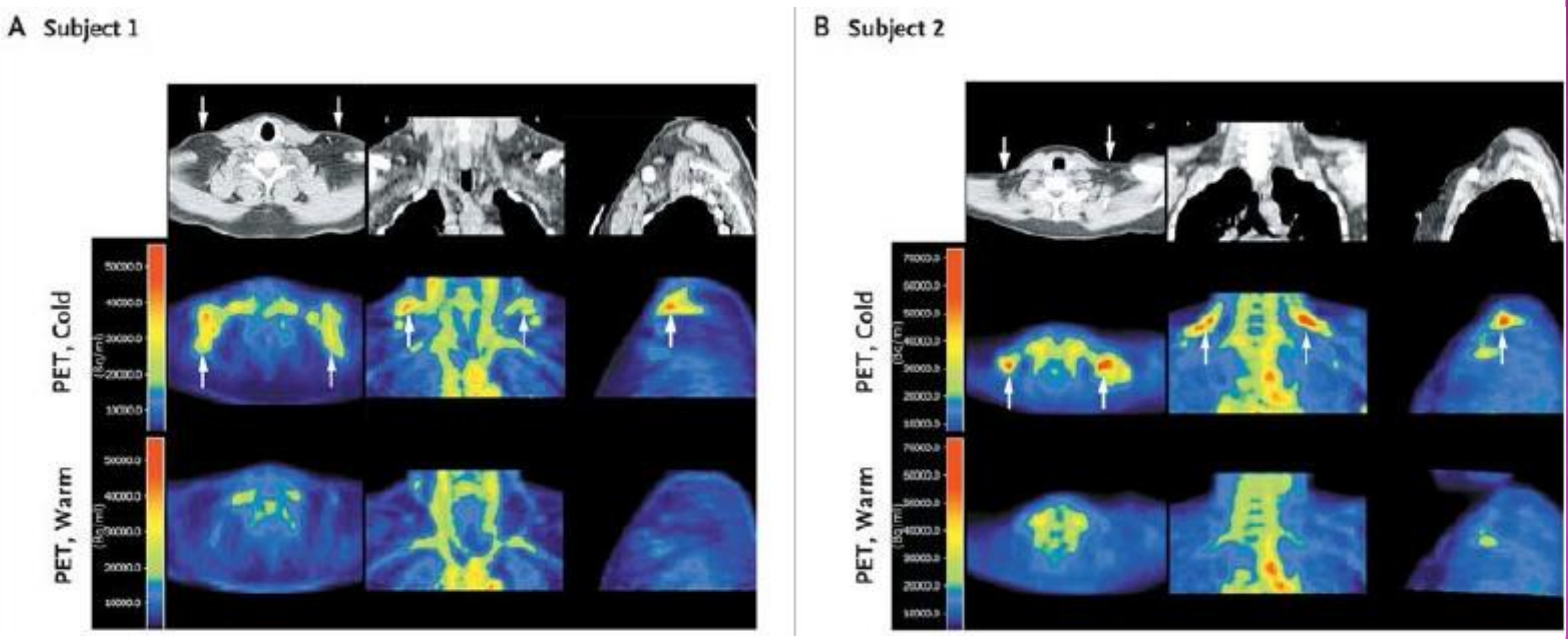
The NEW ENGLAND JOURNAL of MEDICINE

NEJM 2009; 360:1518

ORIGINAL ARTICLE BRIEF REPORT

Functional Brown Adipose Tissue in Healthy Adults

Kirsi A. Virtanen, M.D., Ph.D., Martin E. Lidell, Ph.D., Janne Orava, B.S., Mikael Heglind, M.S., Rickard Westergren, M.S., Tarja Niemi, M.D., Markku Taittonen, M.D., Ph.D., Jukka Laine, M.D., Ph.D., Nina-Johanna Savisto, M.S., Sven Enerbäck, M.D., Ph.D., and Pirjo Nuutila, M.D., Ph.D.et al.



The NEW ENGLAND JOURNAL of MEDICINE

NEJM 2009; 360:1553

Brown Adipose Tissue — When It Pays to Be Inefficient

Francesco S. Celi, M.D.

Obesity has reached epidemic proportions, and complications related to obesity contribute substantially to health care costs and mortality. Since the accumulation of fat is the net result of a prolonged state of imbalance between energy intake and energy expenditure, one would think that an ideal fat mass in obese persons could be achieved relatively simply by either decreasing food intake or increasing energy expenditure, ultimately causing a sustained negative energy balance. Unfortunately, this is not so easy to achieve, because evolutionary pressure has rewarded those individuals and species able to store sufficient energy to survive famines; also, the unrestricted availability of food represents an unnatural condition.[1] Currently, most interventions, whether behavioral or pharmacologic, are aimed at the energy-intake side of the equation and result in only moderate, often temporary improvements, with the notable exception of bariatric surgery.

Interventions designed to increase energy expenditure are relatively limited. An increase in physical activity, although effective, is not easy to sustain. The pharmacologic approach has also been disappointing. Supraphysiologic doses of thyroid hormones or adrenergic agonists result in an increase in energy expenditure, but their systemic adverse events preclude their use for the treatment of obesity.

Brown adipose tissue represents a natural target for the modulation of energy expenditure. This tissue is far from being a fat depot. When activated, it requires the uptake of substrate from the circulation, mostly free fatty acids, but also glucose (Fig. 1). The physiologic role of brown adipose tissue in small mammals (and human newborns) is the maintenance of core temperature. In brown adipose tissue, mitochondria release chemical energy in the form of heat by means of the uncoupling of the oxidative phos-

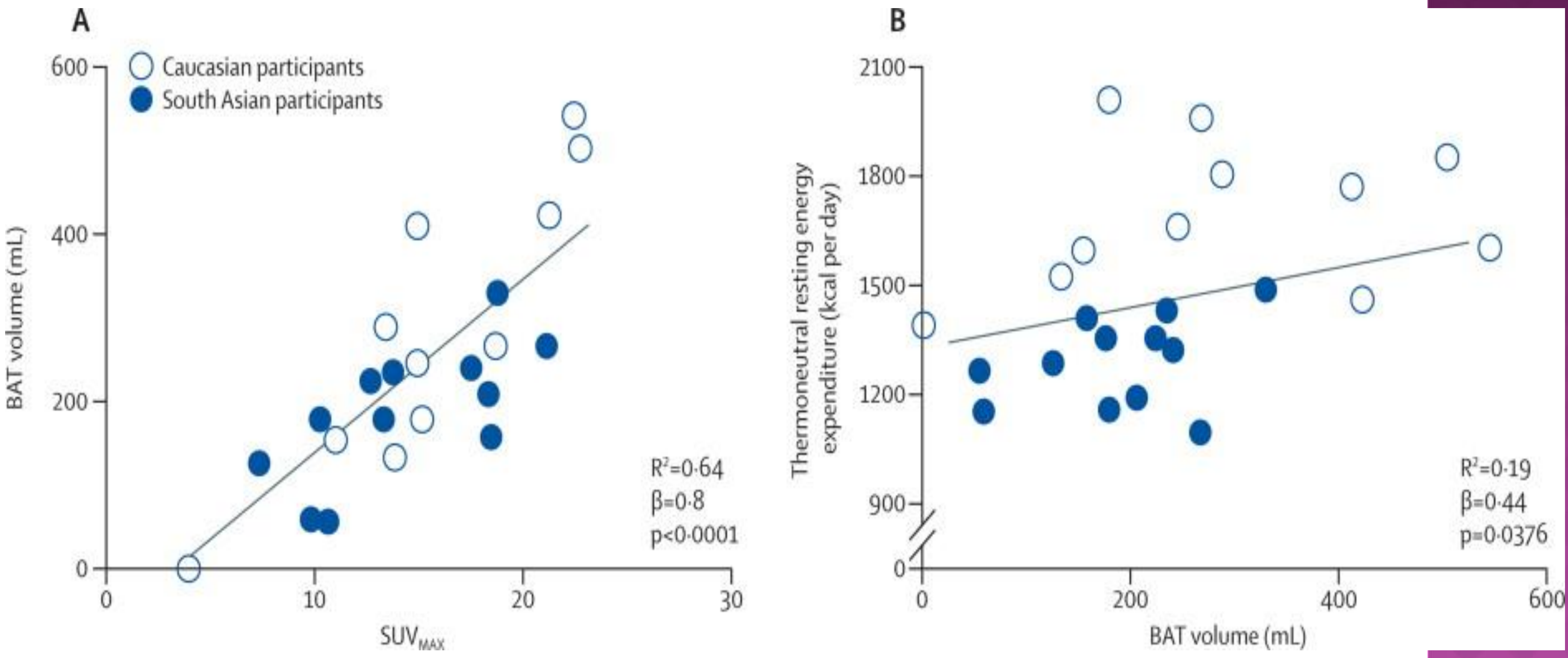
TERMINOLOGY

- Brown adipose tissue (BAT) collectively refers to
  - Classic brown fat (constitutively expressing UCP-1 in mitochondria)
  - Beige fat (brown fat-like adipose tissue derived from white fat with induced UCP-1 expression); otherwise also known as ‘Brite’ fat (brown-in-white)
- White adipose tissue (WAT)

WHY STUDY BROWN ADIPOSE TISSUE?

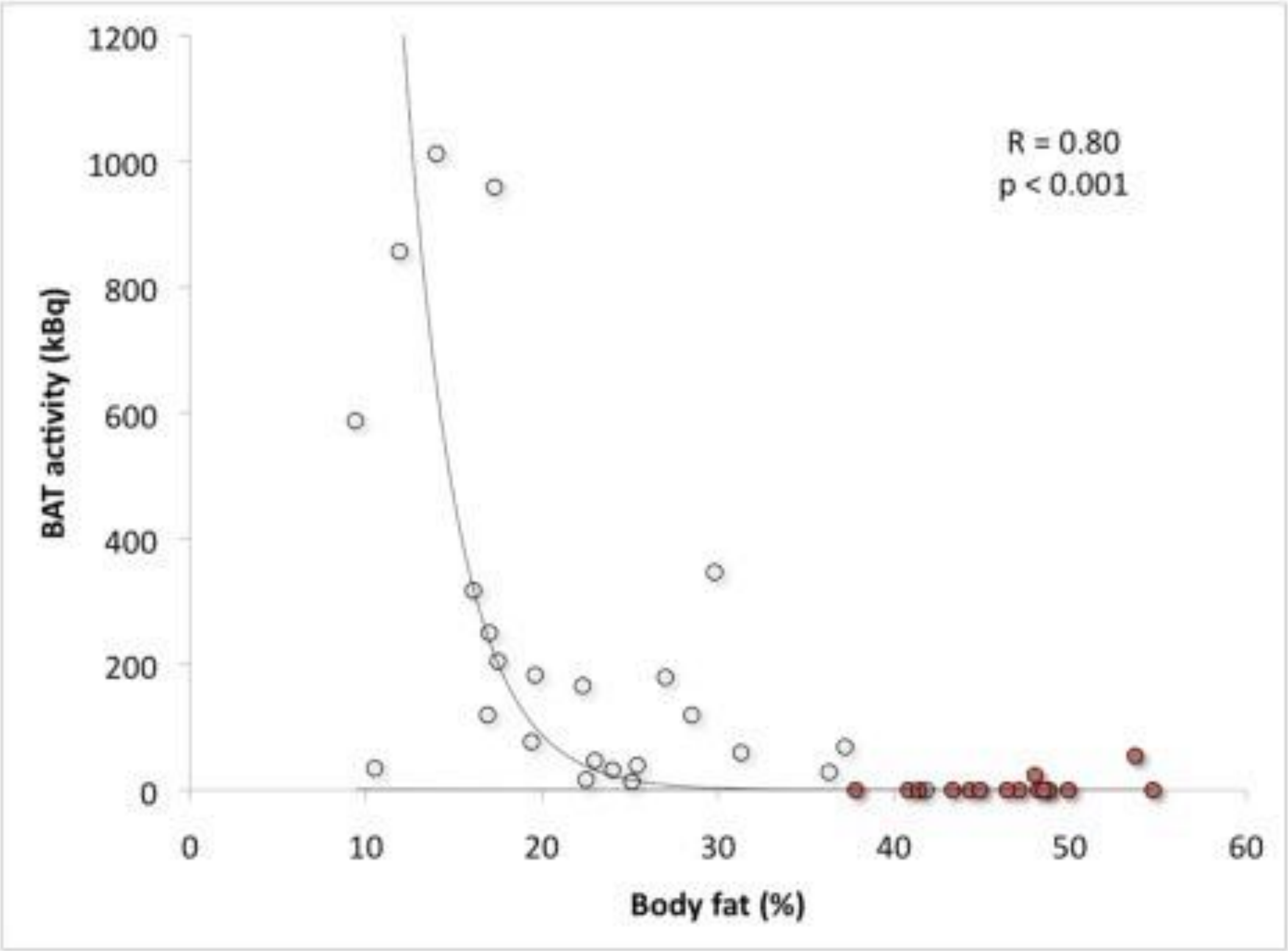
- **When maximally activated, BAT can generate up to 300W/kg of tissue (**Cannon and Nedergaard, 2004**)**
- **Adults possess BAT that may be critical for normal energy expenditure and body weight (**Symonds, 2013**,** van Marken Lichtenbelt et al., 2009**,** Cypess et al., 2009**,** Lidell and Enerback, 2010**,** Stephens et al., 2011**,** Saito, 2013**,** Carey and Kingwell, 2013**)**
- **WAT is a potential depot for transformation into BAT-like fat (beige/brite) via browning (**Wu et al., 2012**,** Spiegelman, 2013**,** Bostrom et al., 2012**)**
- **Browning and BAT activation occur via both endogenous (eg. thyroid hormone) and exogenous (eg. cold, capsinoids, exercise) triggers which can potentially tackle metabolic syndrome and obesity (**Young et al., 1984**,** Bostrom et al., 2012**,** Rao et al., 2014**)**

RESTING METABOLIC RATE & BAT



Lancet Diabetes Endocrinol 2014; 2: 210-217.

BAT INVERSELY RELATED TO BODY FAT



The open dots indicate the study group ranging from lean to morbidly obese obese (age range: 18–32 years; van Marken Lichtenbelt et al., 2009) and the red dots indicate a second group of morbidly obese subjects (age range: 25–51 years; Vijgen et al., 2011).

ENDOGENOUS BROWNING PATHWAYS

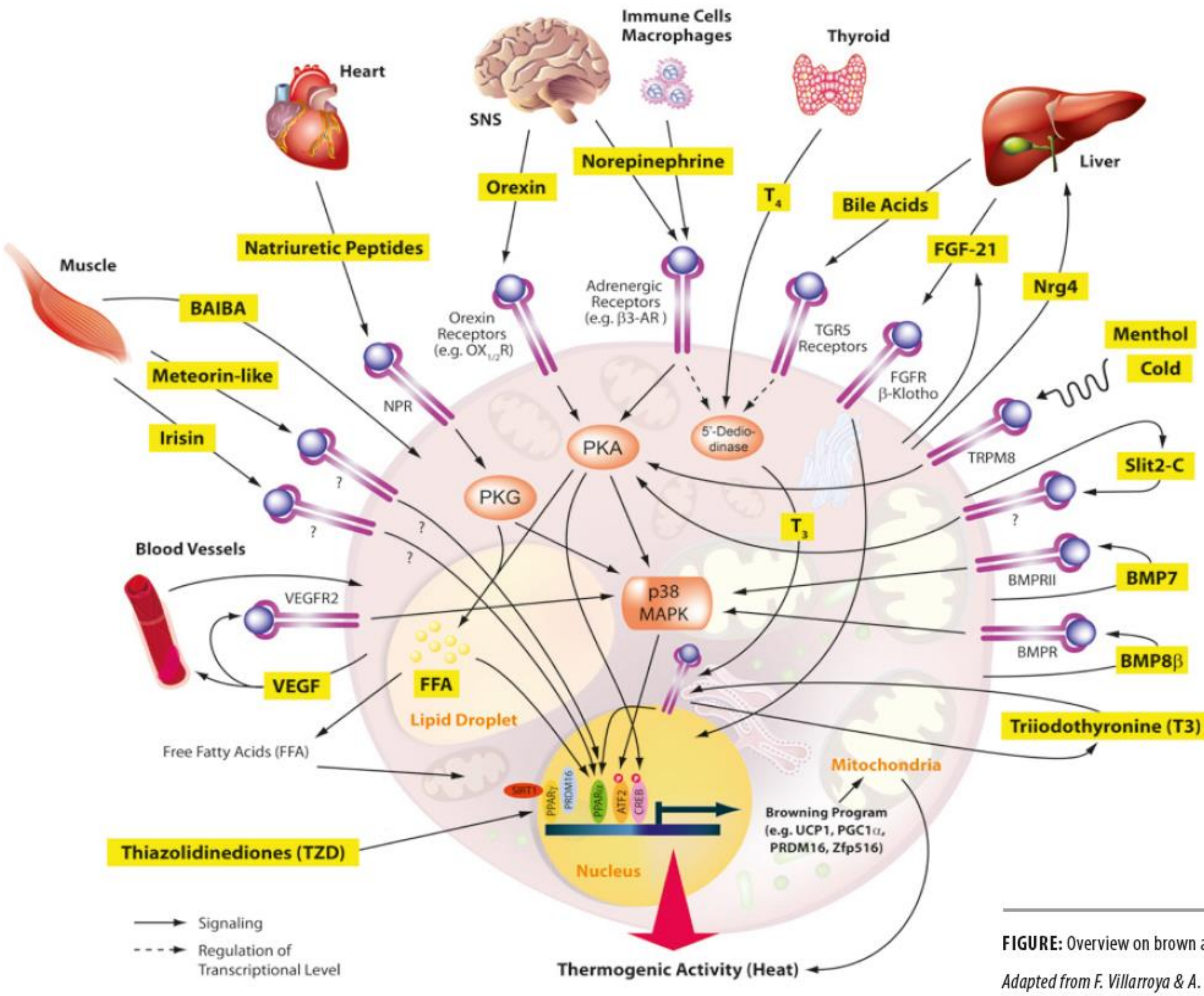
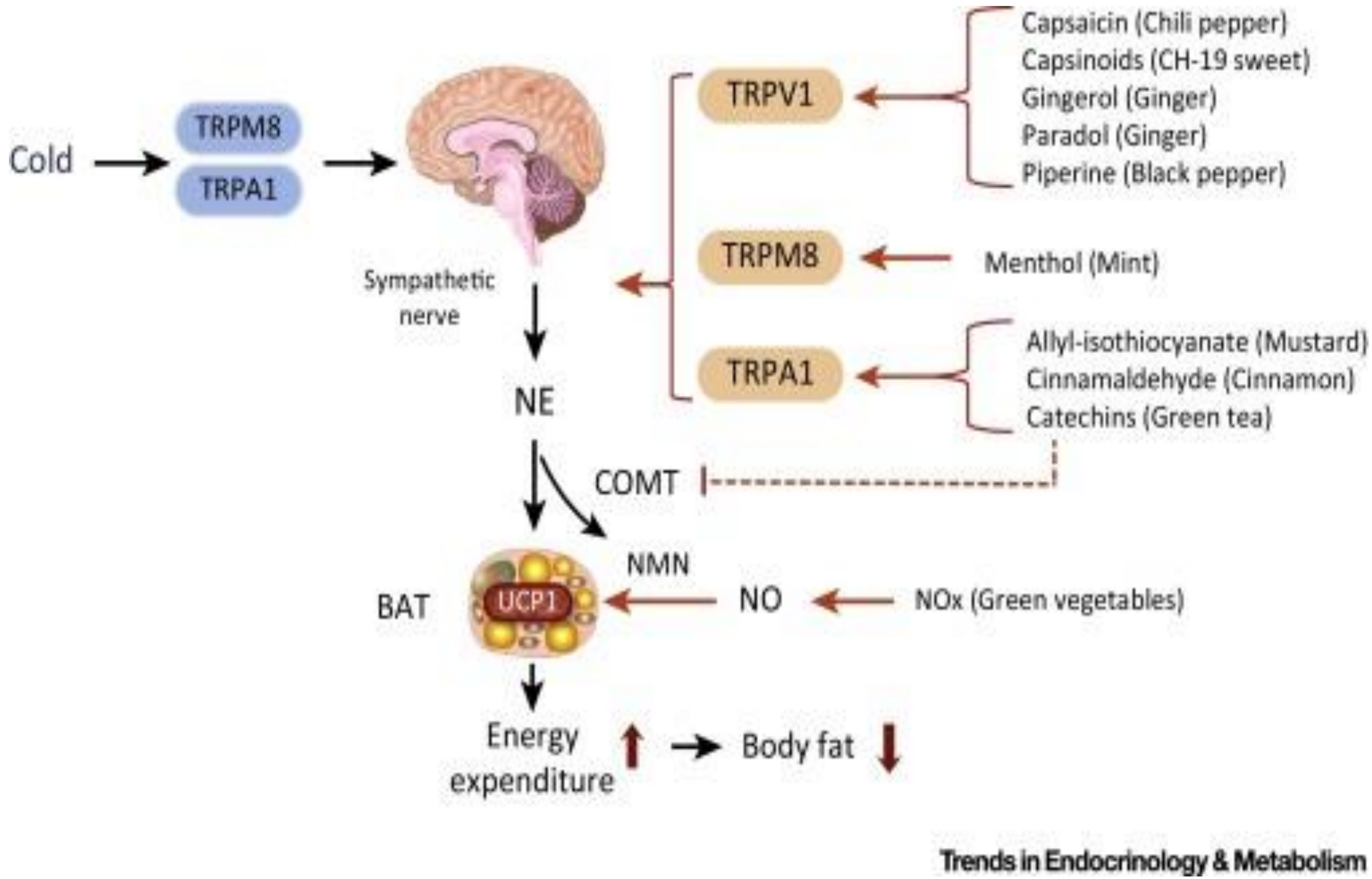


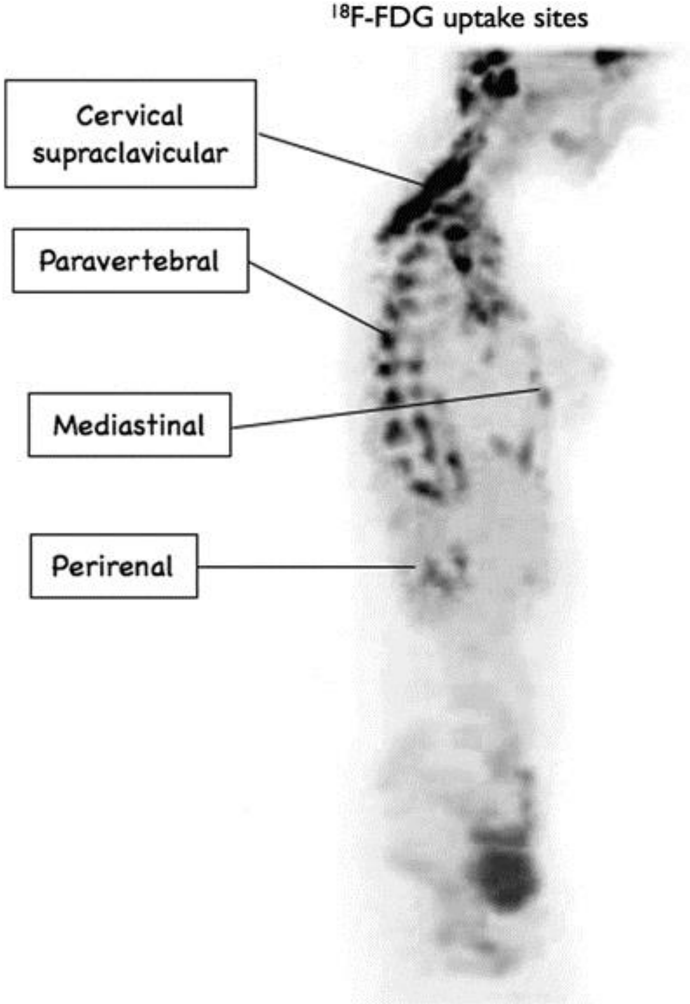
FIGURE: Overview on brown and beige fat activators.

Adapted from F. Villarroya & A. Vidal-Puig; Cell Metab. 17, 638 (2013)

EXOGENOUS BAT-ACTIVATING & BROWNING PATHWAYS

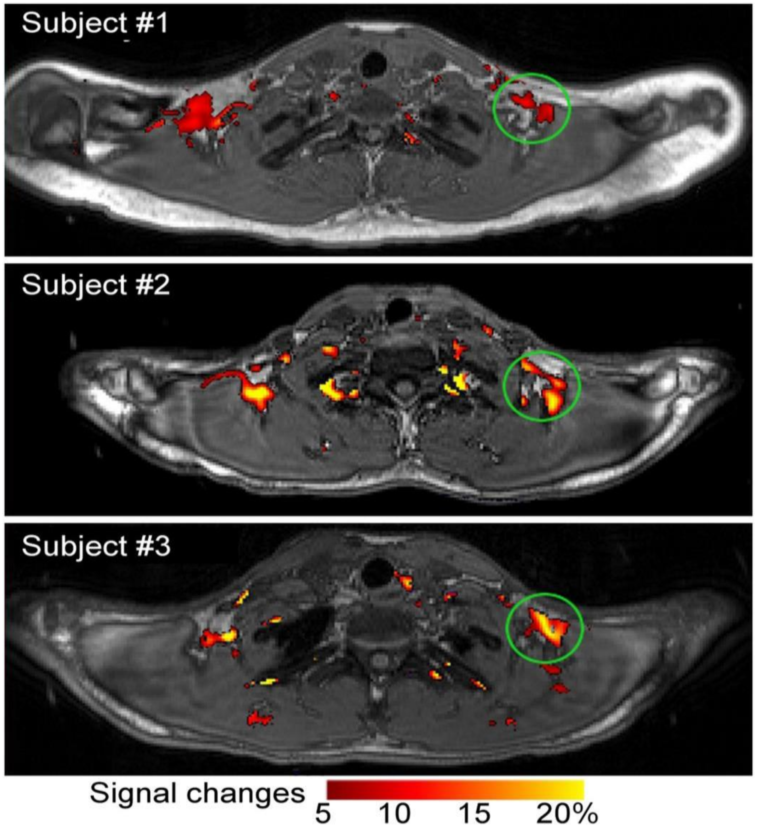


PET-CT HINDERS BAT RESEARCH

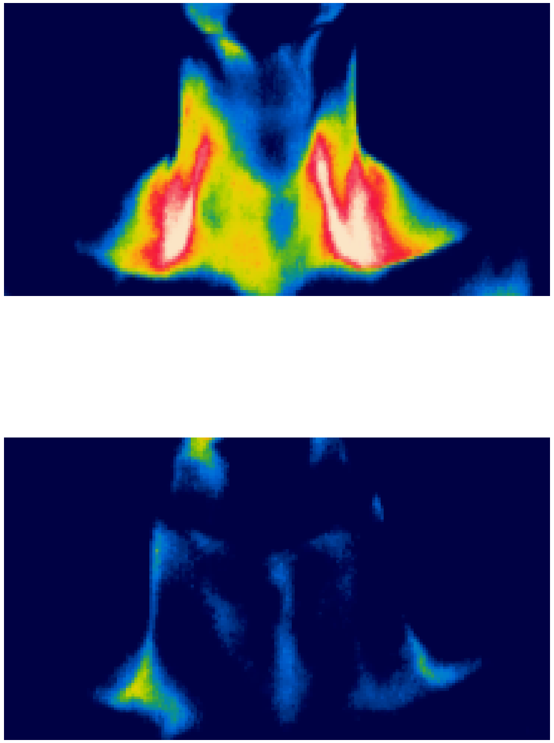


- 18-FDG PET/CT is current 'gold-standard' of assessing BAT activity, but limitations:
  - High ionizing radiation exposure
  - Prohibitively high cost
- Infrared thermography (IRT)
  - Non-invasive, cheap, safe
  - Effective alternative for detecting human BAT in vivo
- Captures heat-producing capacity of BAT

OTHER METHODS OF BAT IMAGING



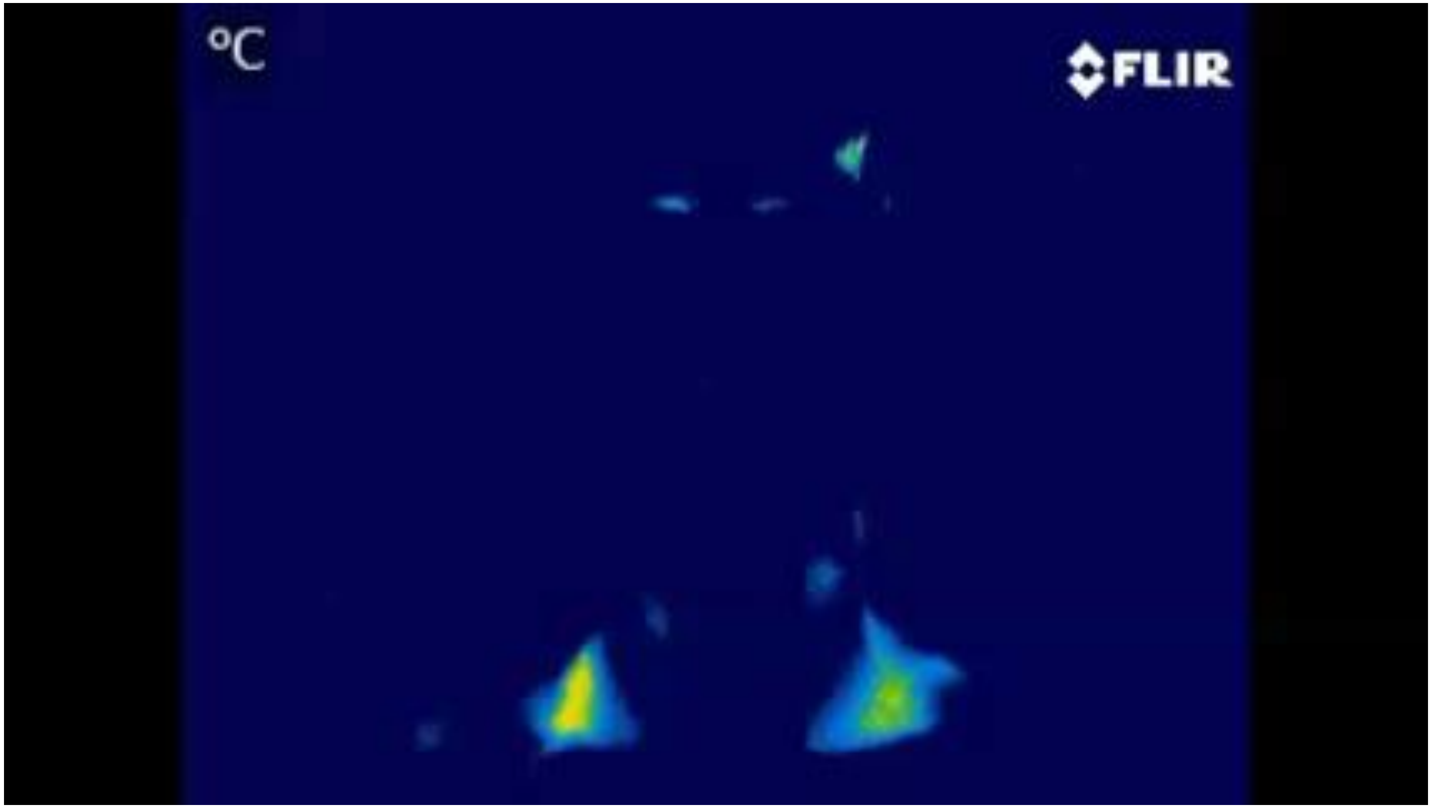
Functional MRI



Infrared Thermography (IRT)

Ideally, aim for Faster, Better, Cheaper & Safer method – IRT satisfies these criteria!

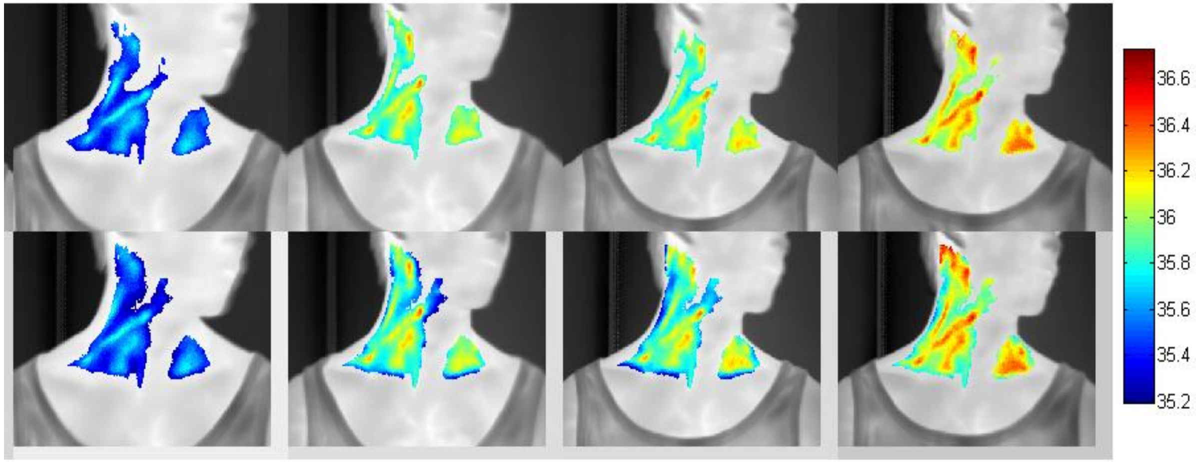
FLIR THERMAL CAMERA FOR IRT



- Infrared thermogram video showing human BAT activation by cold stimulation over 10 mins

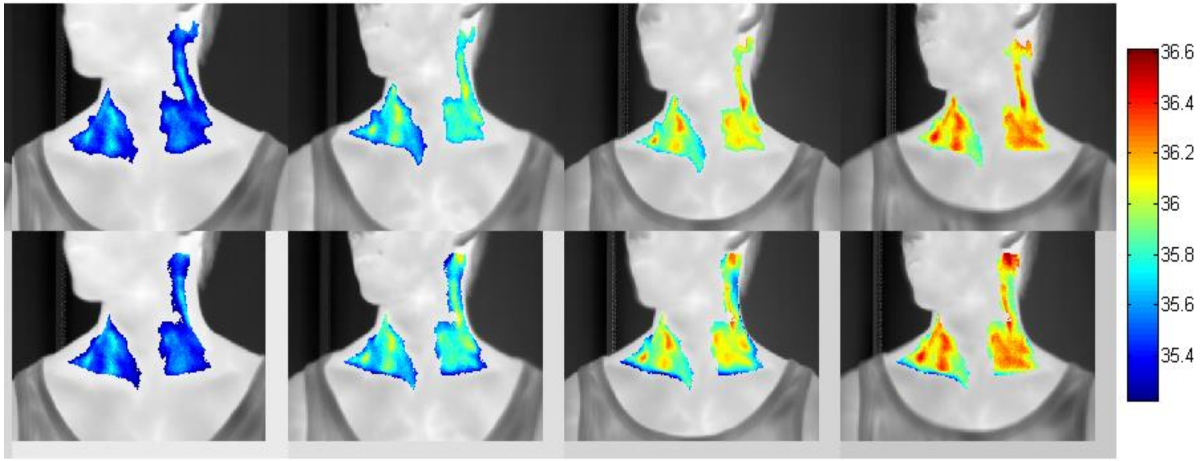
BAT IMAGE SEGMENTATION

Right Lateral

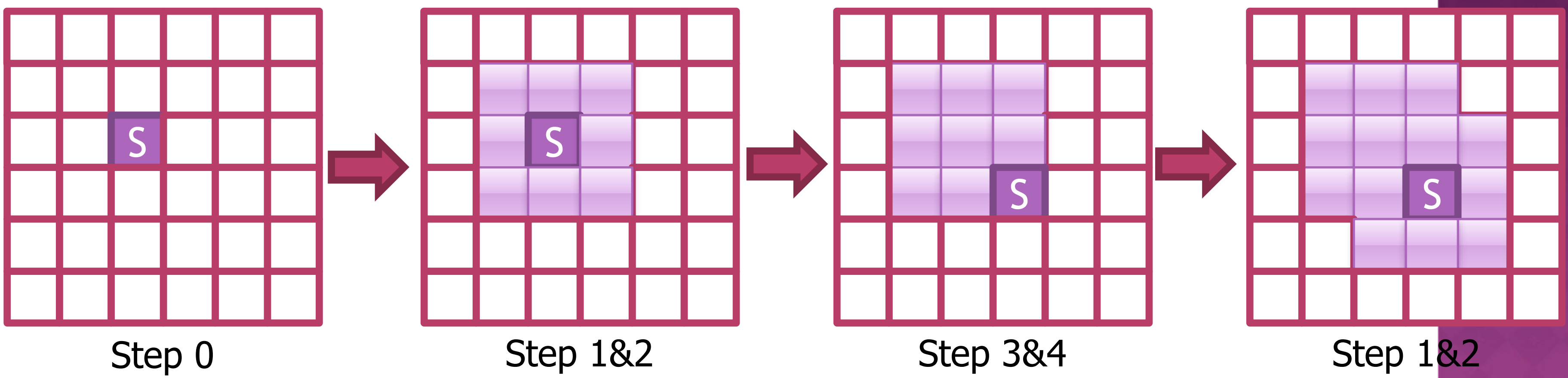


Time: = 0 min 5 min 10 min 15 min

Left Lateral

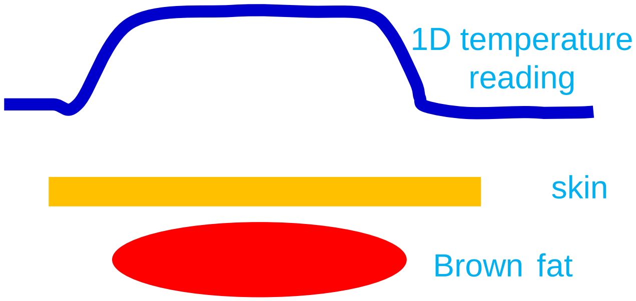


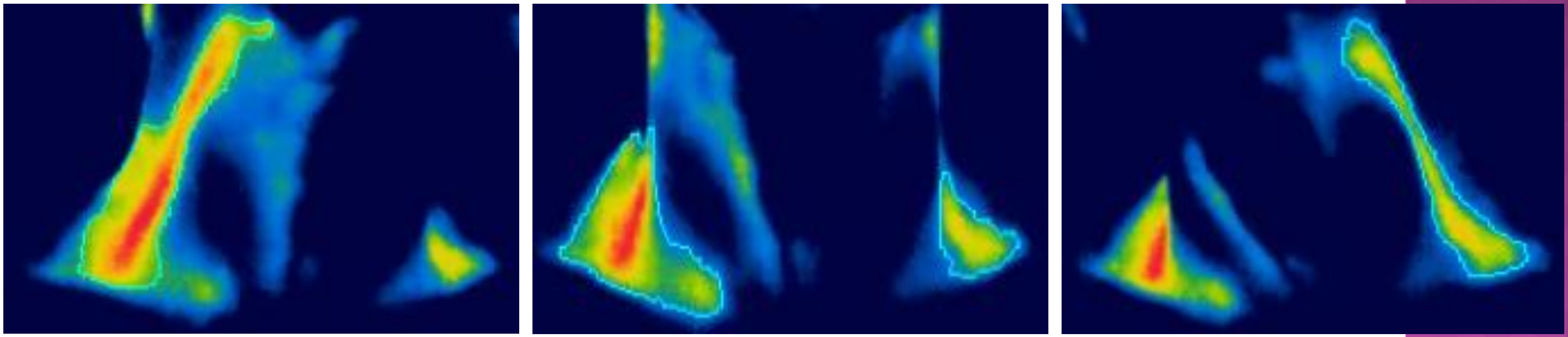
NOVEL SEED REGION GROWING ALGORITHM (SRG)



- Image processing algorithm – Seed Region Growing (SRG); collaborated with I^2R scientists
- Peak temp pixel identified – grow & define ROI over supraclavicular BAT
- Allows quantification of area and average temperature of ROI

REGION OF INTEREST (ROI)





Right lateral **Anterior** **Left Lateral**

IRT SET UP IN WHOLE BODY CALORIMETER – TEMP OF ROOM CAN BE COOLED DOWN TO 16 DEG C

THERMOGRAPHY FOR BAT STIMULATION BY CAPSINOIDS AND COLD (TACTICAL)

J Physiol Sci
DOI 10.1007/s12576-016-0472-1

CrossMark

ORIGINAL PAPER

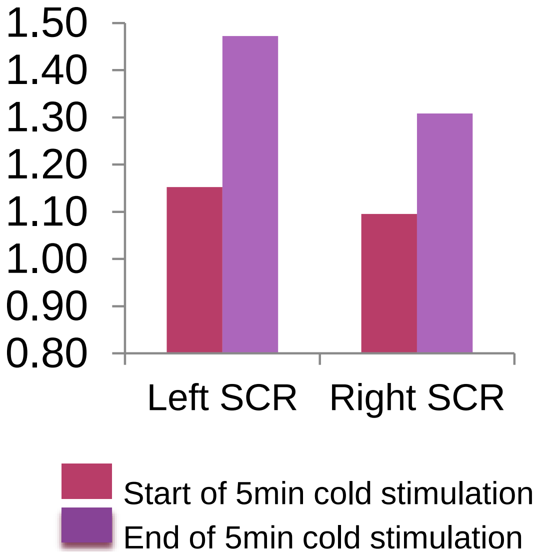
A new method of infrared thermography for quantification of brown adipose tissue activation in healthy adults (TACTICAL): a randomized trial

Qi Yan Ang[1] · Hui Jen Goh[1] · Yanpeng Cao[2] · Yiqun Li[2] · Siew-Pang Chan[3,4] · Judith L. Swain[1,3] · Christiani Jeyakumar Henry[1,5] · Melvin Khee-Shing Leow[1,3,6,7,8]

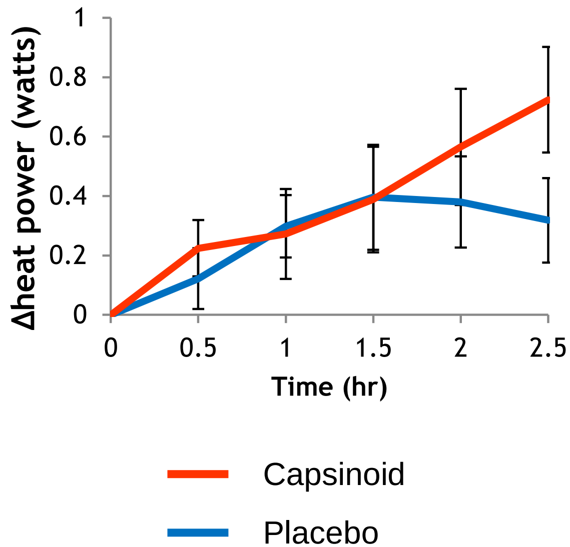
Received: 24 February 2016 / Accepted: 7 July 2016

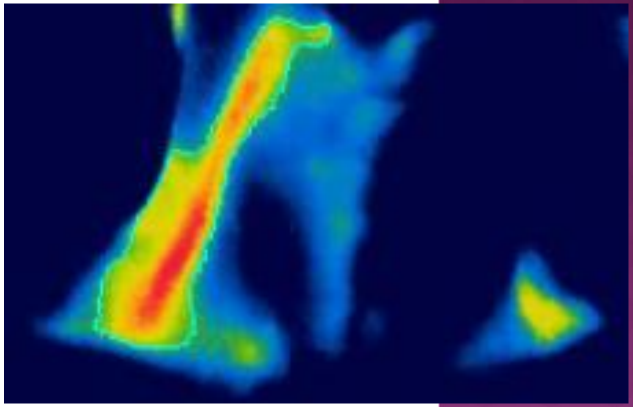
IRT QUANTIFICATION OF BAT THERMOGENESIS VIA COLD & CAPSINOIDS STIMULATION (TACTICAL)

Heat power (watts)



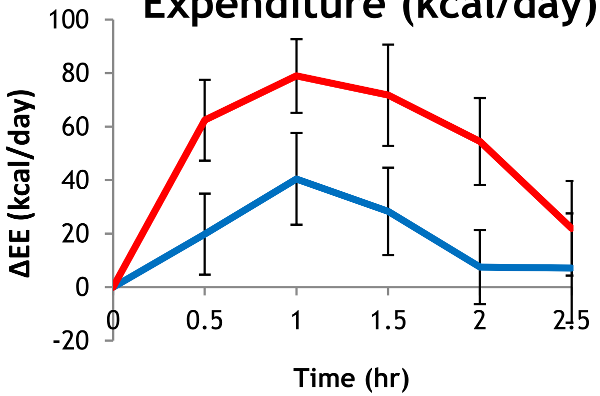
Δheat power (watts)



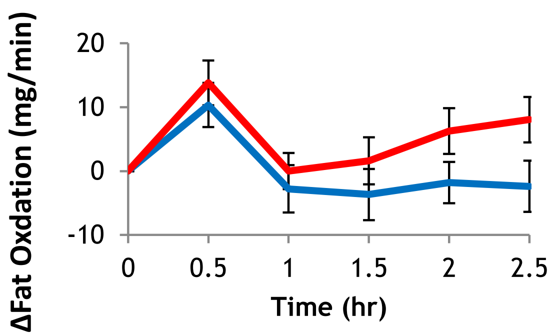


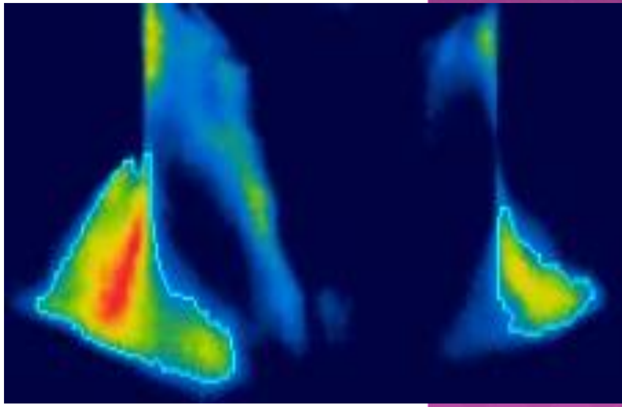
Right

Change in Energy Expenditure (kcal/day)

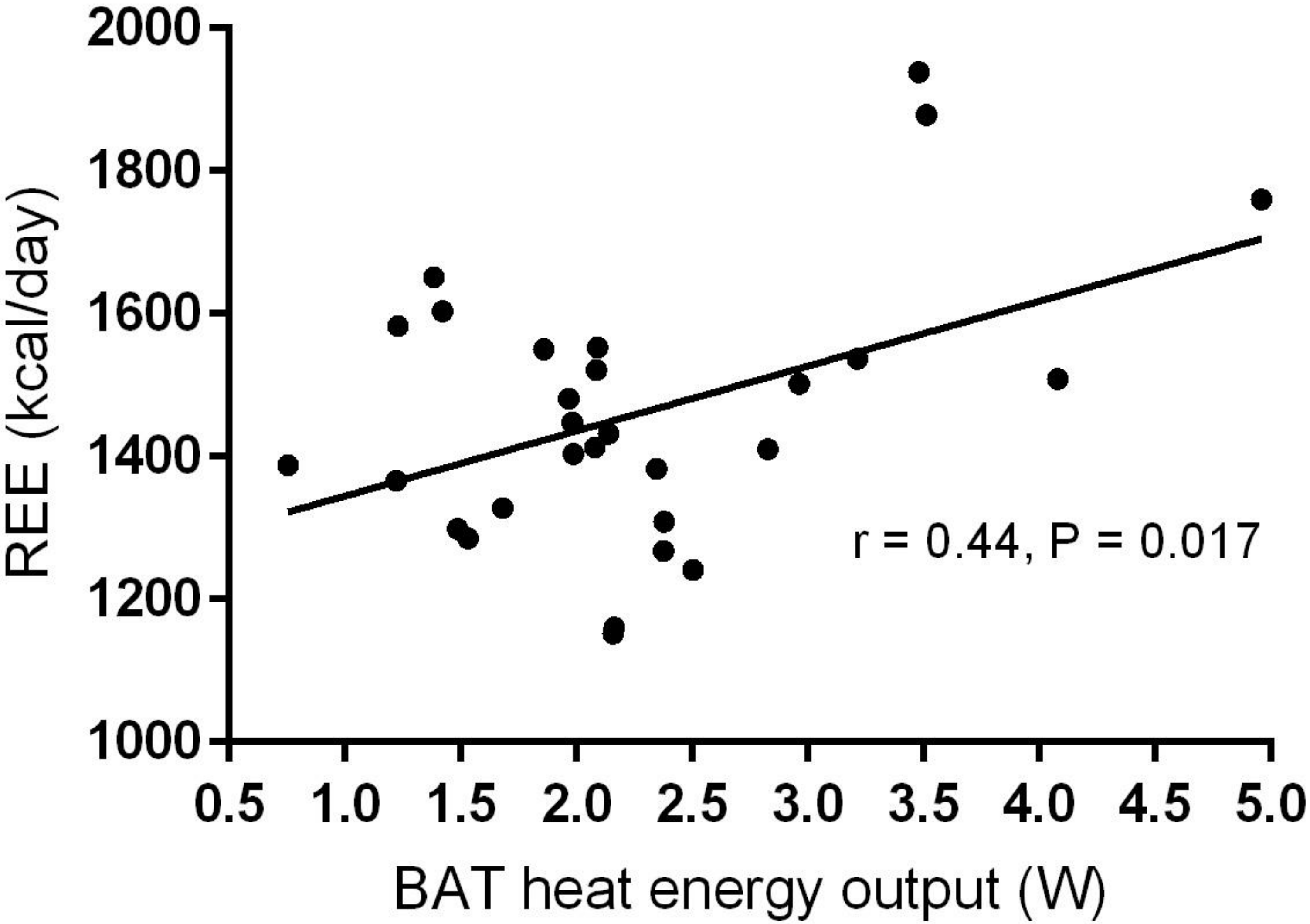


Change in Fat Oxidation (mg/min)

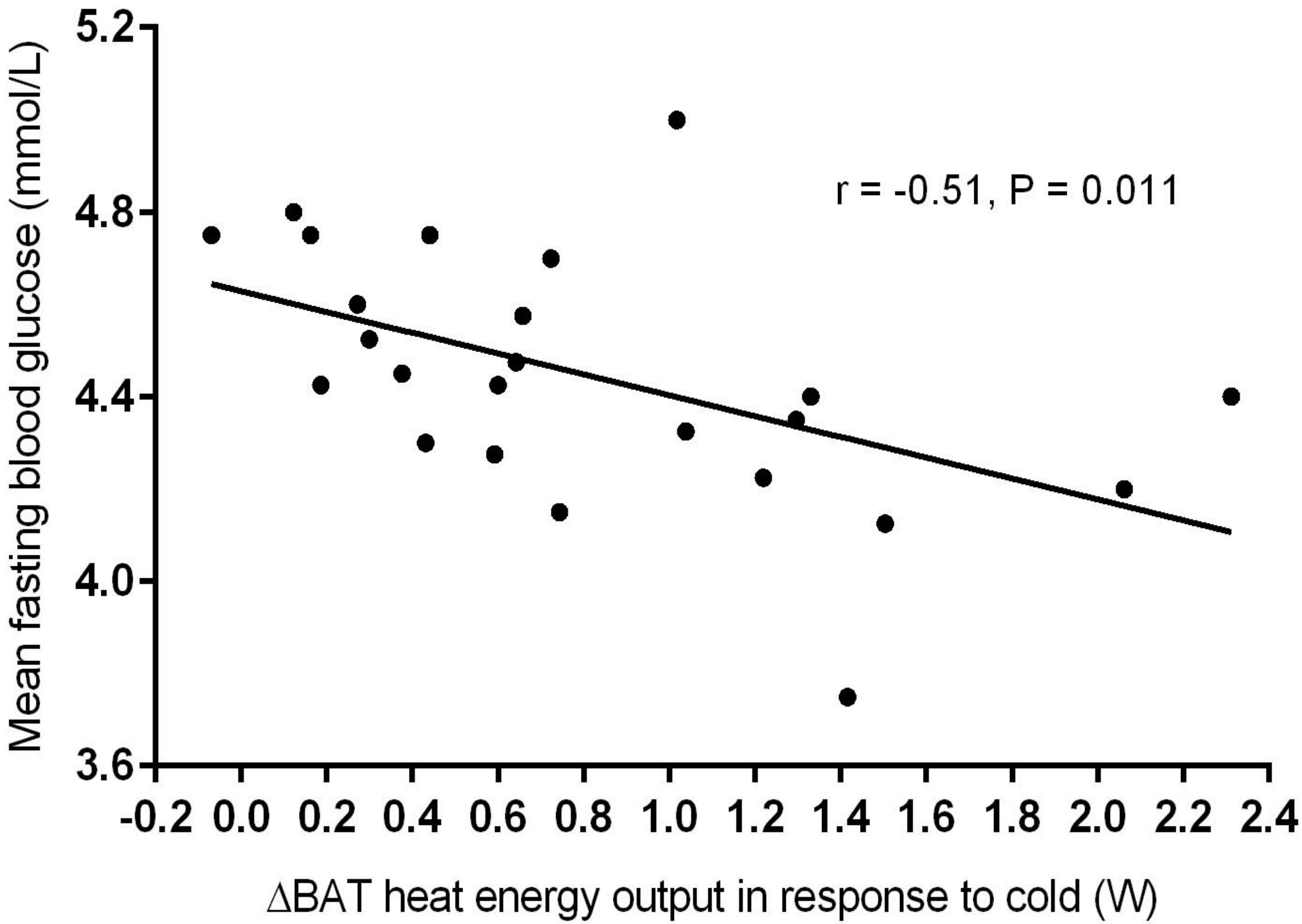




Front



Ang QY, …, Leow MK. J Physiol Sci 2016



Ang QY, …, Leow MK. J Physiol Sci 2016

BAT Activation & Energy Expenditure by Cold & Capsinoids Stimulation – Trimodality Imaging using PET, MRI & IRT (TACTICAL-II)

- IRT + MRI validation against 18-FDG-PET
- N=20 healthy euthyroid lean to obese
  - (BMI 18.5 to 30 kg/m2)
  - Age 21-65 yo
  - Males & Females without a history of thyroid disease
  - No ethnic restrictions (Chinese, Malays, Indians, Caucasians)

TACTICAL-II STUDY

- 20 healthy subjects
- Age: 25.9 ± 4.1 years
- M:F = 8:12
- BAT-positive by FDG-PET = 12

	All subjects	Male	Female	P value
n	20	8	12	
Age (years)	25.9 ± 4.1	25.8 ± 4.1	25.9 ± 4.3	NS
Height (cm)	168.5 ± 8.9	175.0 ± 5.4	164.2 ± 8.2	0.004
Weight (kg)	62.5 ± 12.6	70.5 ± 12.7	57.1 ± 9.8	0.015
BMI (kg/m^2)	21.7 ± 2.5	22.9 ± 3.0	20.9 ± 1.8	NS
Body fat (%)	29.2 ± 8.0	23.4 ± 6.6	33.2 ± 6.3	0.004
Fat Mass (kg)	18.4 ± 7.5	17.1 ± 7.6	19.3 ± 7.6	NS
Fat free Mass (kg)	43.6 ± 9.5	53.0 ± 6.9	37.4 ± 4.3	<0.001
RMR (kcal/day) ^	1533 ± 271.0	1752.5 ± 245.5	1386.7 ± 173.6	0.001

STUDY DESIGN PROTOCOL

Visit 1 (screening)

↓

Informed consent

Do renal, liver, thyroid function tests

Visits 2 and 3

↓

Confirm euthyroid:
1. Normal renal and liver function
2. Normal thyroid function

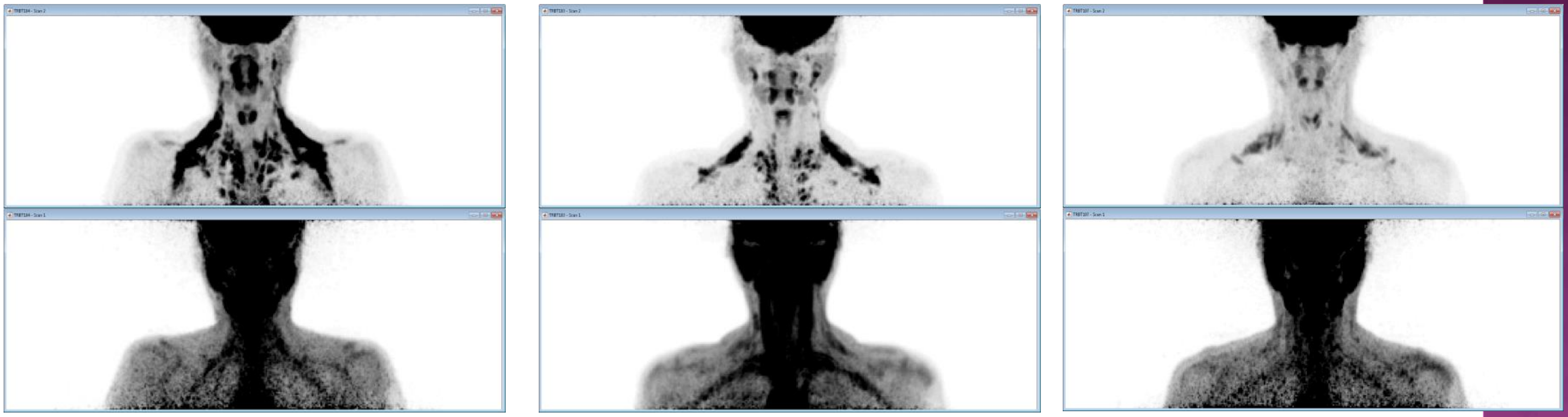
+

<u>Baseline</u>

Visit 2:
Labs/DXA +
MRI/MRS of WAT +
PET/fat fraction MRI of BAT
(no capsinoid)

Visit 3:
BMR/IR x 45 min (no capsinoid), then
BMR/IR x 150 min (with capsinoid), then
PET/fat fraction MRI (with capsinoid)

RESULTS



3 BAT positive subjects via FDG-PET by cold stimulation (upper half panels); SUV of capsinoid stimulation (lower half panels) was below the cutoff for definition of BAT positivity but clearly showing BAT FDG uptake when re-windowed through varying the greyscale values of the displayed window without adjusting the SUV thresholding

TACTICAL-II PAPER PUBLISHED

- **Capsinoids activate BAT with increased energy expenditure associated with subthreshold ^{18}F-FDG uptake in BAT-positive humans confirmed by PET scan.**

Sun LJ, Goh HJ, Govindharajulu P, Camps SG, Velan SS, Schaefferkoetter J, Totman J, Townsend DW, Sun L, Sze NS, Lim SC, Boehm BO, Henry CJ, Leow MK.

- ***Am J Clin Nutr 2017***

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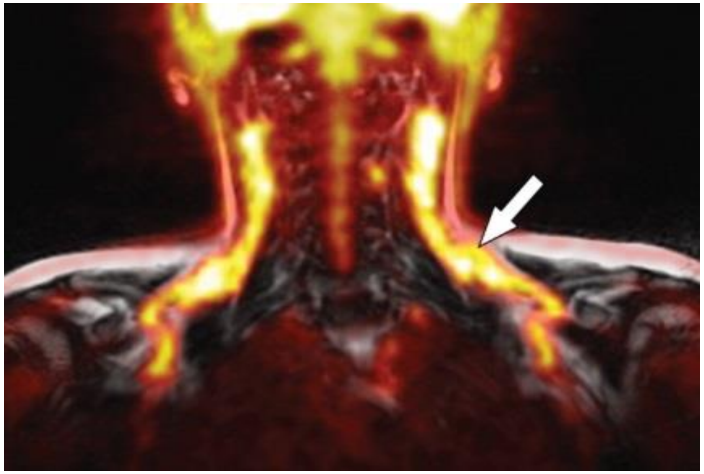
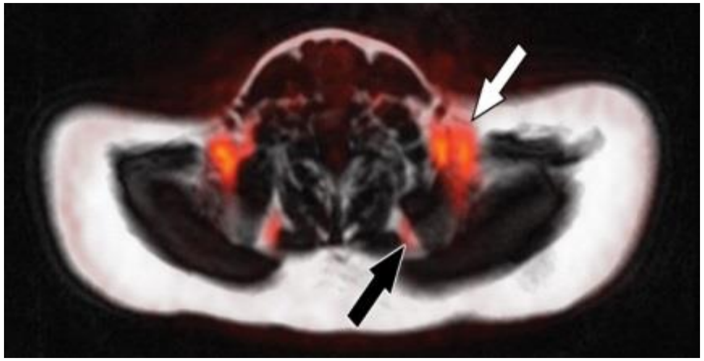
A Publication of the American Society for Nutrition

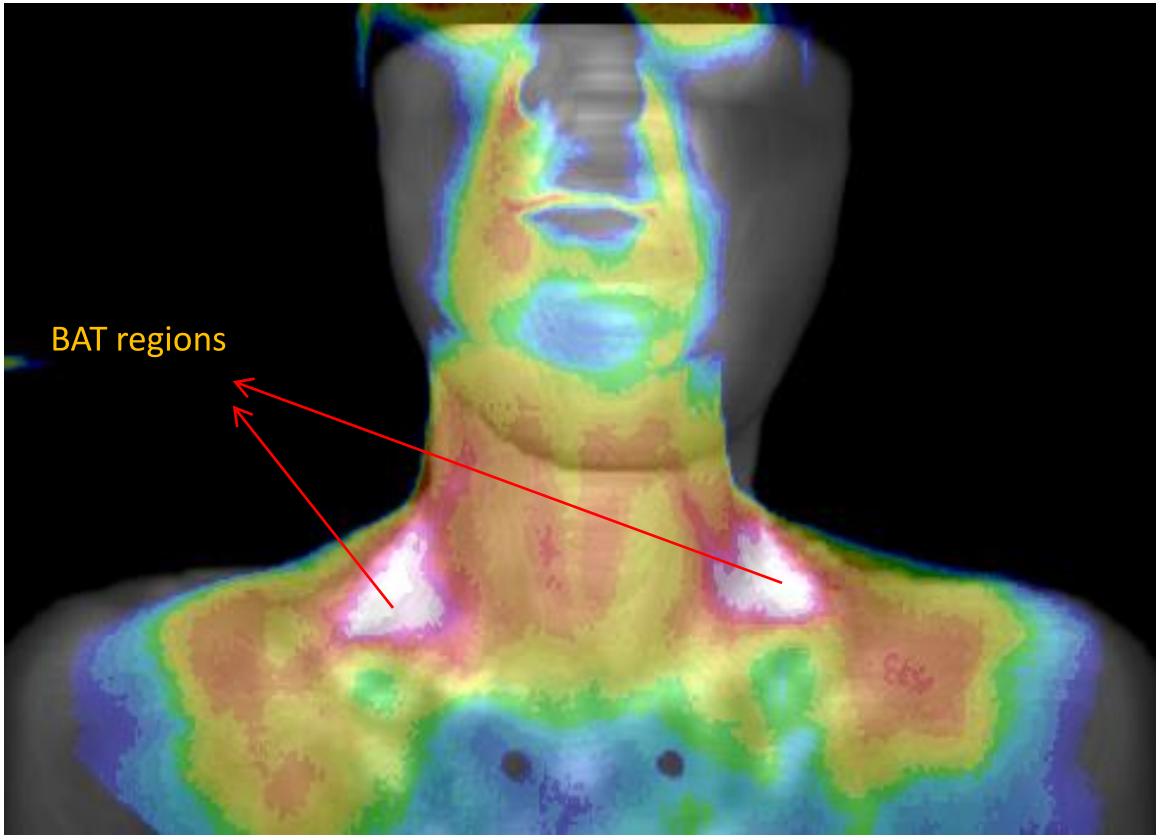
MARCH 2018 • VOLUME 107 • NUMBER 3 http://ajcn.nutrition.org/ ISSN 0002-9165

PET-MRI FUSION

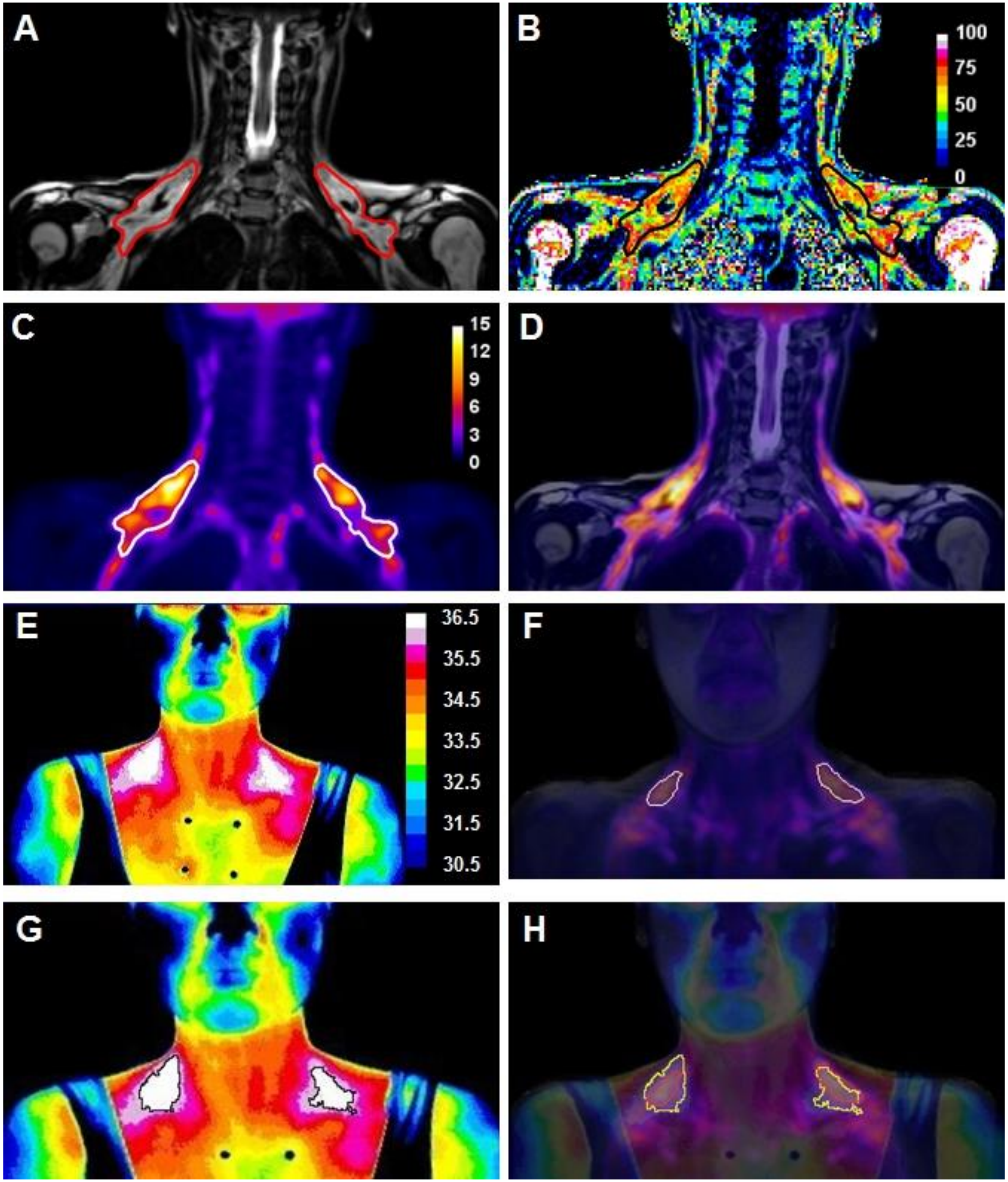




PET-IRT FUSION



18F-FDG-PET image co-registered with IRT thermogram of a healthy volunteer proven BAT-positive. Both images are superimposed upon each other with the help of the maximum intensity projection (MIP) algorithm


A
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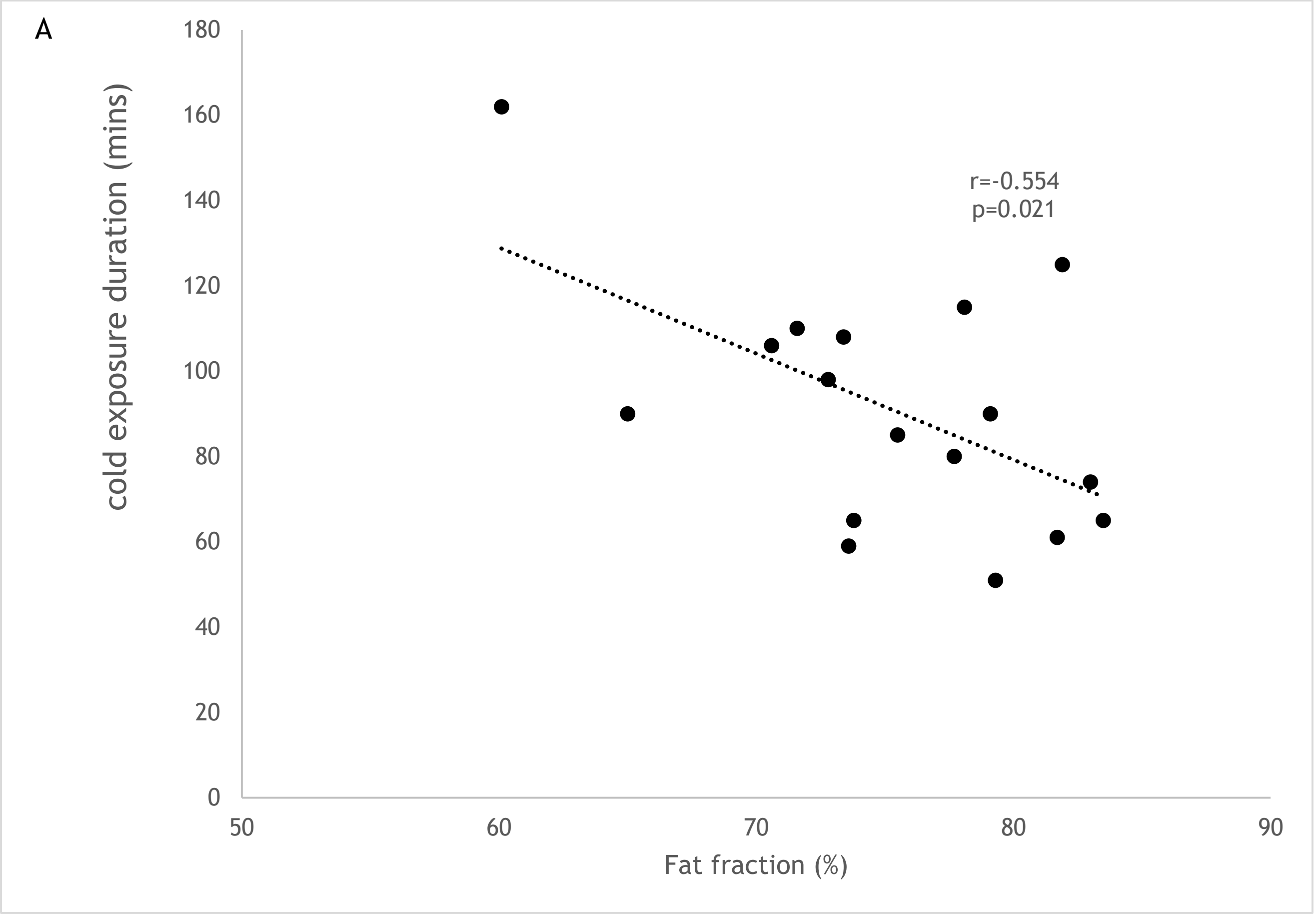
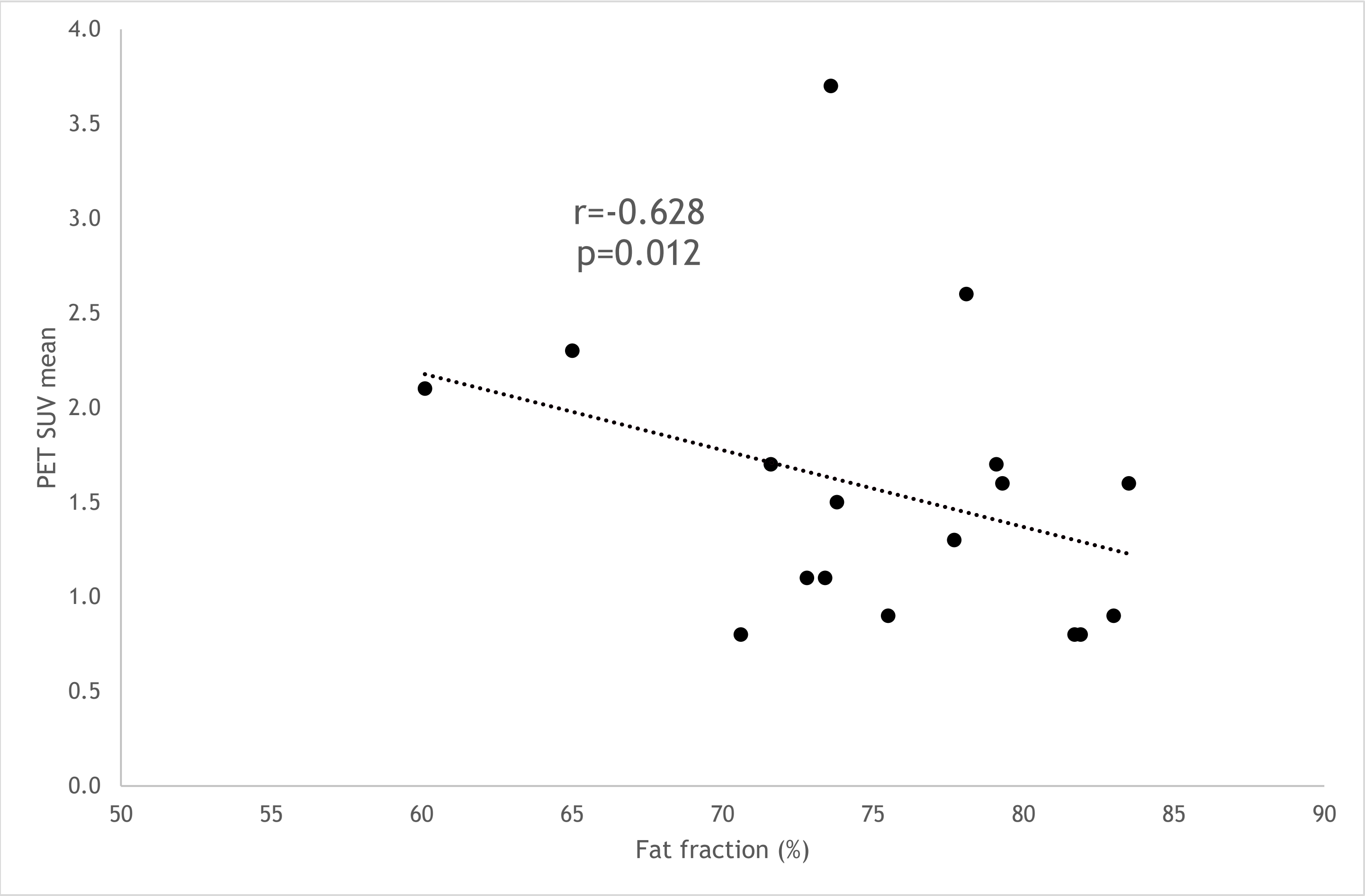
33.5
32.5
31.5
30.5
F
G
H

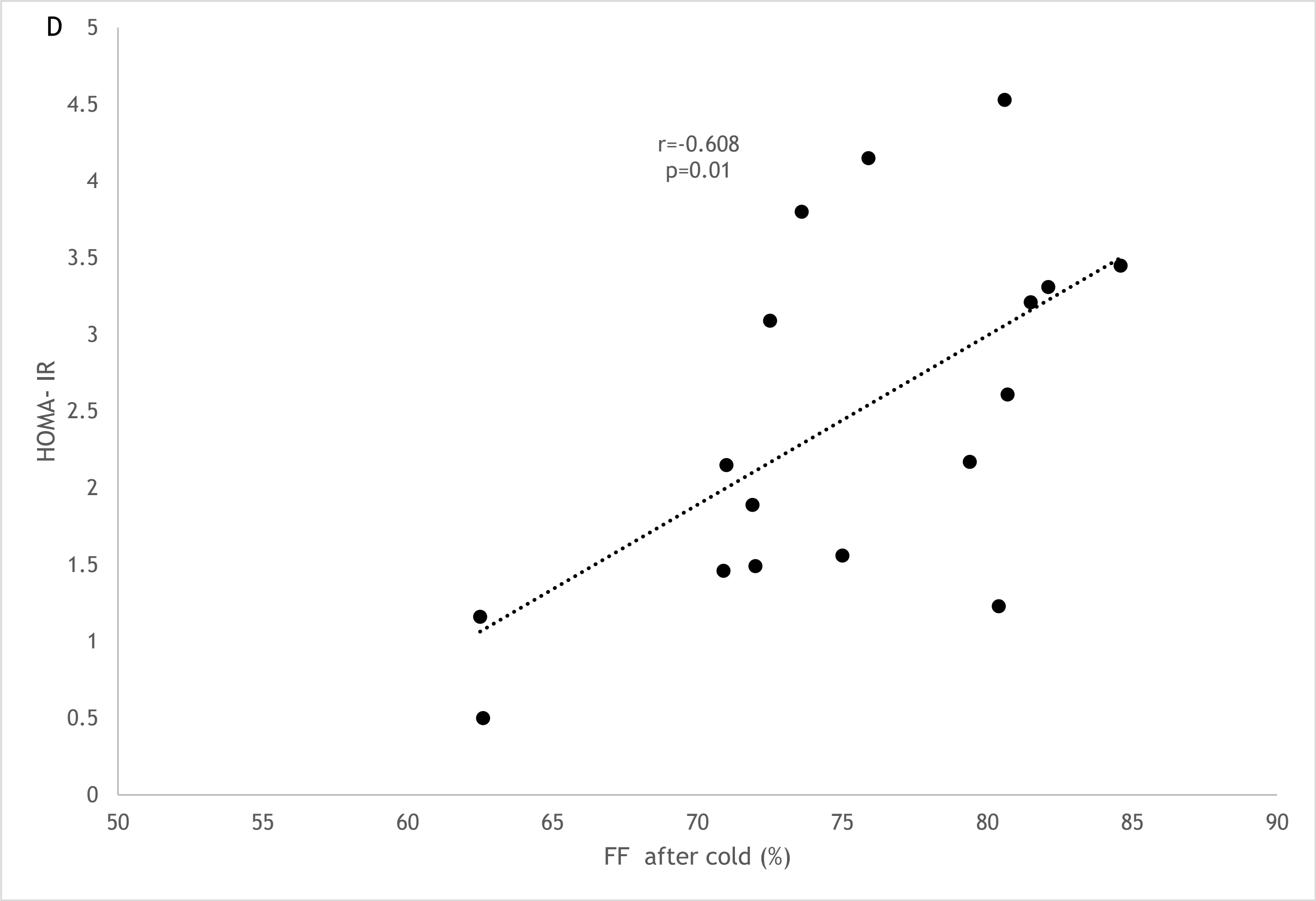
FAT FRACTION AND COLD EXPOSURE



FAT FRACTION CORRELATES WITH PET SUV



CORRELATION BETWEEN FAT FRACTION AND HOMA-IR



FINDINGS

- PET SUV was significantly higher after cold stimulation than capsinoids ingestion (P=0.02).
- EE post-cold stimulation was significantly higher than post-capsinoids stimulation (P<0.01).
- Tscv post-cold was strongly correlated with EE (coefficient=198, P=0.025).
- PET SUV was significantly inversely correlated with FF (r= 0.628, P=0.012).

FINDINGS

- The supraclavicular hotspot identified on IRT closely corresponds to the area of maximal FDG uptake on MR-PET images.
- Greater increase in Tscv and higher PET SUV were associated with higher increase in EE response after cold exposure.
- IRT is a promising method to study BAT activity noninvasively.

ACKNOWLEDGMENTS

- Team Members (CNRC)
  - Stefan Camps
  - Sun Lijuan
  - Goh Hui Jen
  - Priya Govindharajulu
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  - Prof. Cao Yanpeng (I2R, A*STAR)
  - A/Prof. Sendhil Velan (SBIC)
  - Dr. Sanjay Verma (SBIC)
  - Dr. Suresh Sadanantham (SBIC)
  - Prof. David Townsend (CIRC)
  - Dr. Joshua Schaefferkoetter (CIRC)
  - Dr. John Tottman (CIRC)