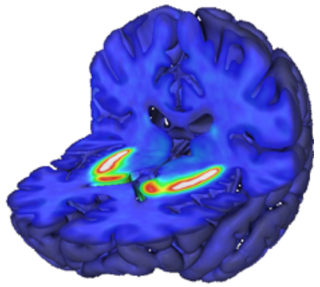


Principles and Applications of Brain Positron Emission Tomography

Lauri Nummenmaa

Turku PET Centre

ACADEMY OF FINLAND

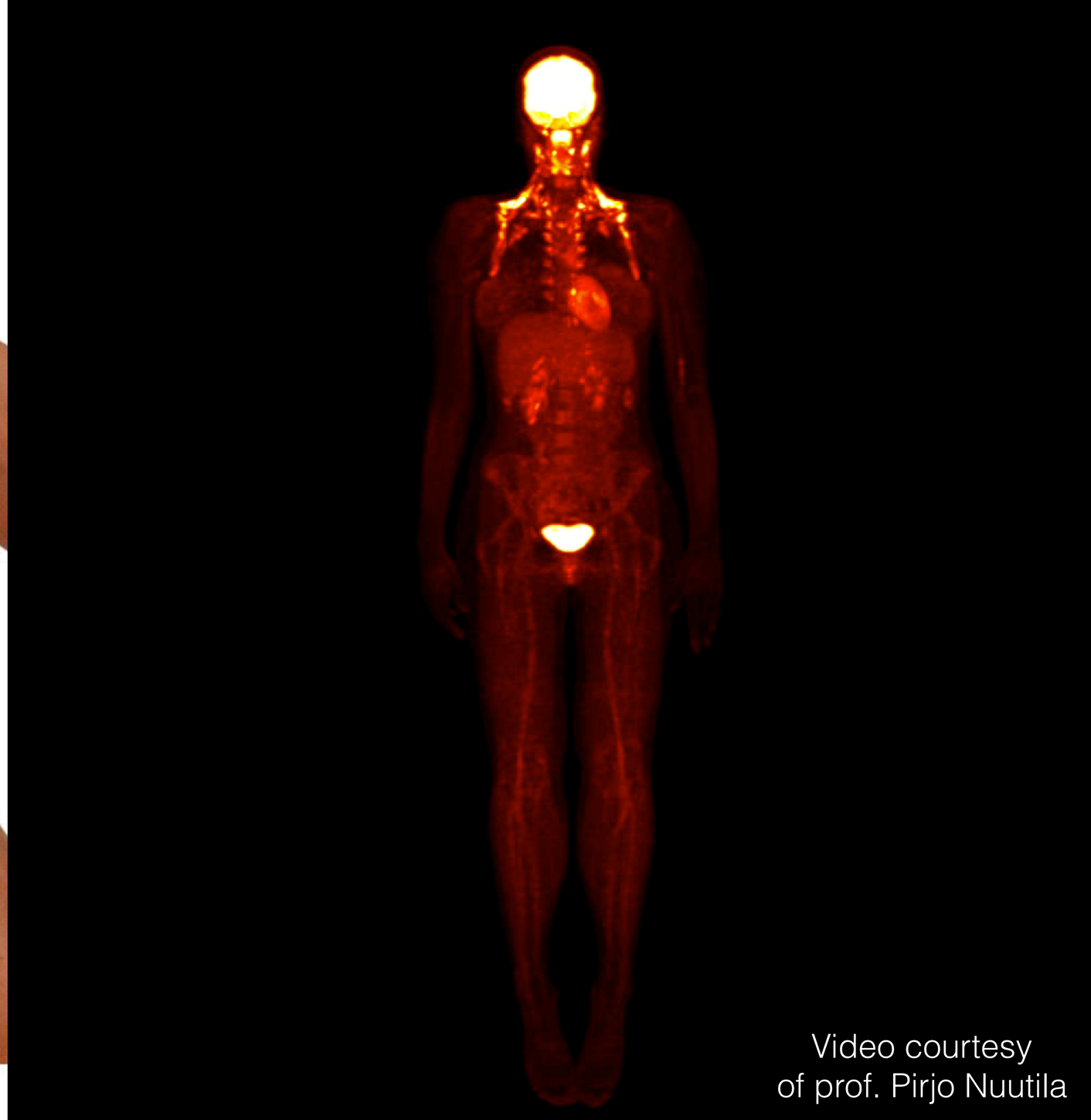
TURKU MEDICAL CYCLOTRON PROJECT

erc

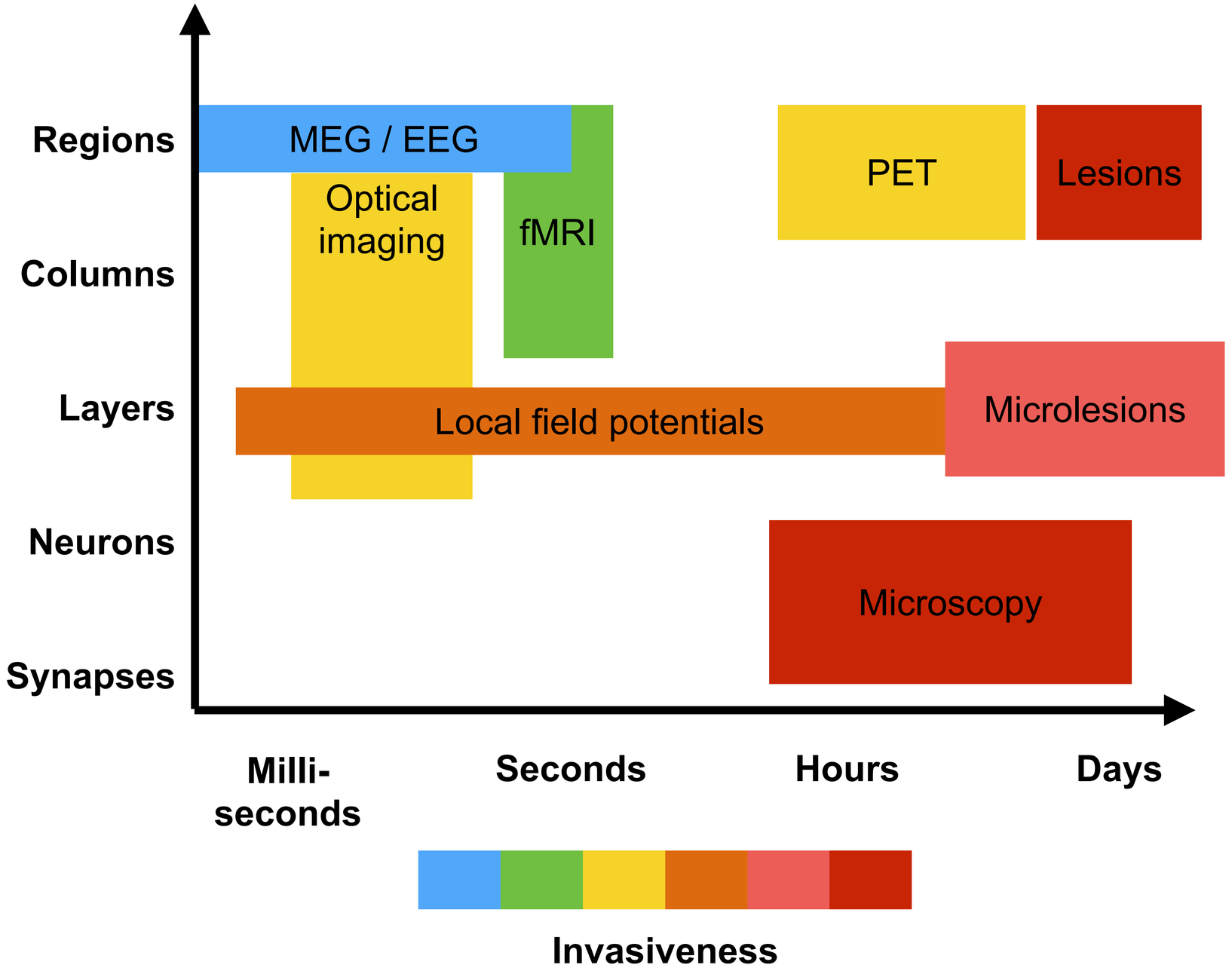
JUSELIUS SIGRID STIFTELSE

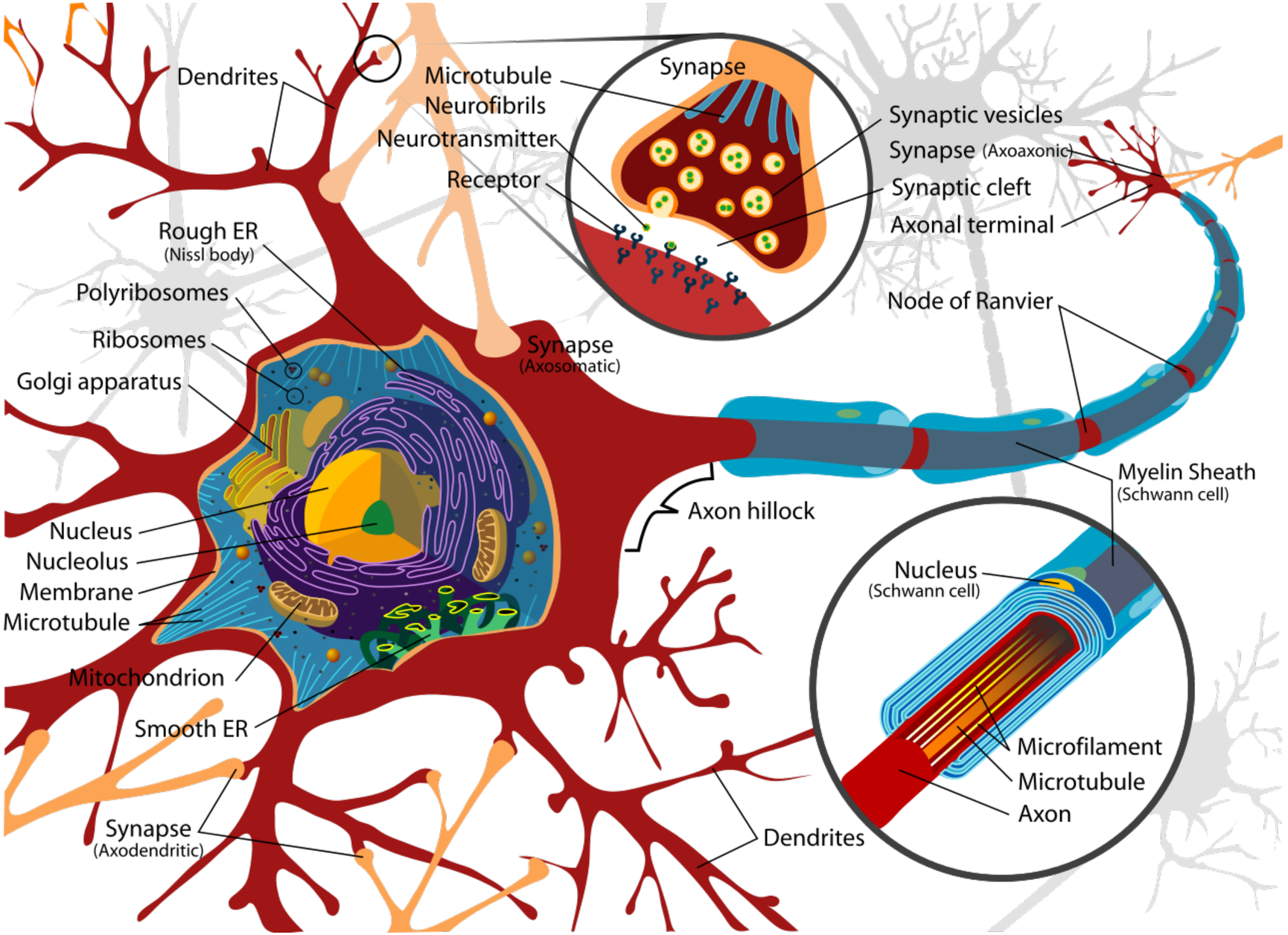
PET RUNS ON NUCLEAR POWER

Turun yliopisto
University of Turku



Video courtesy
of prof. Pirjo Nuutila


Regions
Columns
Layers
Neurons
Synapses
MEG / EEG
Optical imaging
fMRI
PET
Lesions
Local field potentials
Microlesions
Microscopy
Milli-seconds
Seconds
Hours
Days
Invasiveness


Dendrites
Microtubule
Neurofibrils
Neurotransmitter
Receptor
Synapse
Synaptic vesicles
Synapse (Axoaxonic)
Synaptic cleft
Axonal terminal
Rough ER
(Nissl body)
Polyribosomes
Ribosomes
Golgi apparatus
Synapse
(Axosomatic)
Node of Ranvier
Myelin Sheath
(Schwann cell)
Axon hillock
Nucleus
Nucleolus
Membrane
Microtubule
Mitochondrion
Smooth ER
Synapse
(Axodendritic)
Dendrites
Nucleus
(Schwann cell)
Microfilament
Microtubule
Axon

Radiochemistry

- Radioligands: Biologically active, unstable isotopes
- Decay via positron emission
- Short half-life required for sufficient SNR and reasonable scan duration
- Need to be synthesised close to PET camera
- Radiochemistry allows investigation of any biological circuit as long as it can be radiolabeled
- Radiochemistry is the “pulse sequence design for PET”

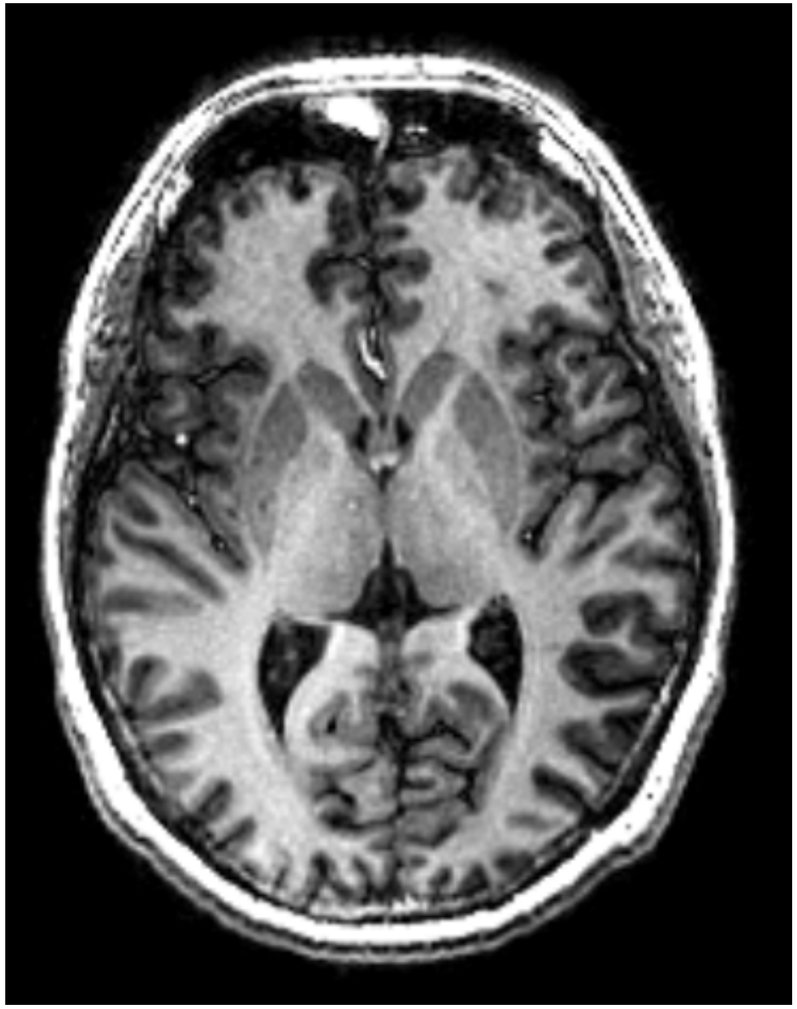
What makes a good radioligand?

- Optimal target density and ligand affinity: Density x Affinity ≈5
- High brain uptake
- Optimal lipophilicity (LogP=2.5–4); sufficiently high to cross blood-brain barrier but not too high to cause non-specific binding
- Not substrate for efflux transporters at BBB (e.g., P-gp)
- High pharmacological selectivity
- No brain-penetrant radiometabolites
- Quantifiable plasma protein binding
- Amenability to rapid labelling with high specific activity
- Fast enough kinetics to allow measurement in a few hours

Common molecular brain-PET targets

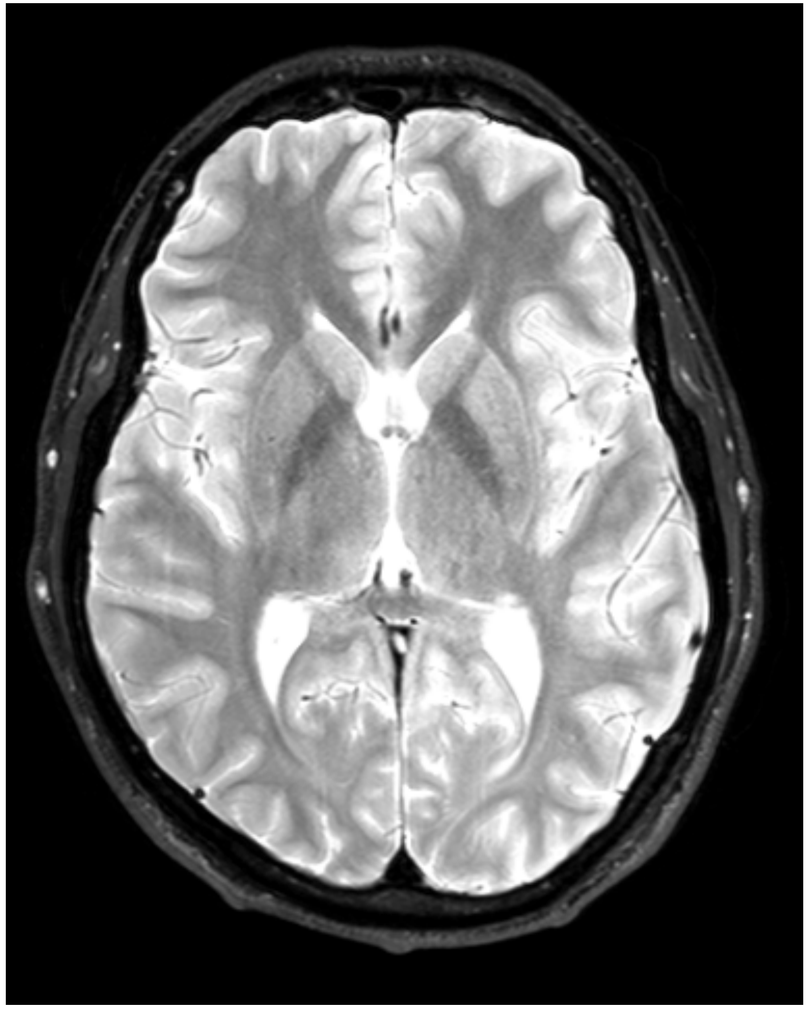
Target	Typical tracer	Stable molecule	Isotope	Half-life
Perfusion	[13N] ammonia	Nitrogen [N]	[13N]	10 min
Perfusion	H2O15	Oxygen [O]	[O15]	2 min
Glucose uptake	[18F]FDG	Fluoride [F]	[18F]	118 min
Beta-amyloid plaques	[11C]-PIB	Carbon [C]	[11C]	20 min
Opioid receptors	[11C]carfentanil	Carbon [C]	[11C]	20 min

T1-weighting



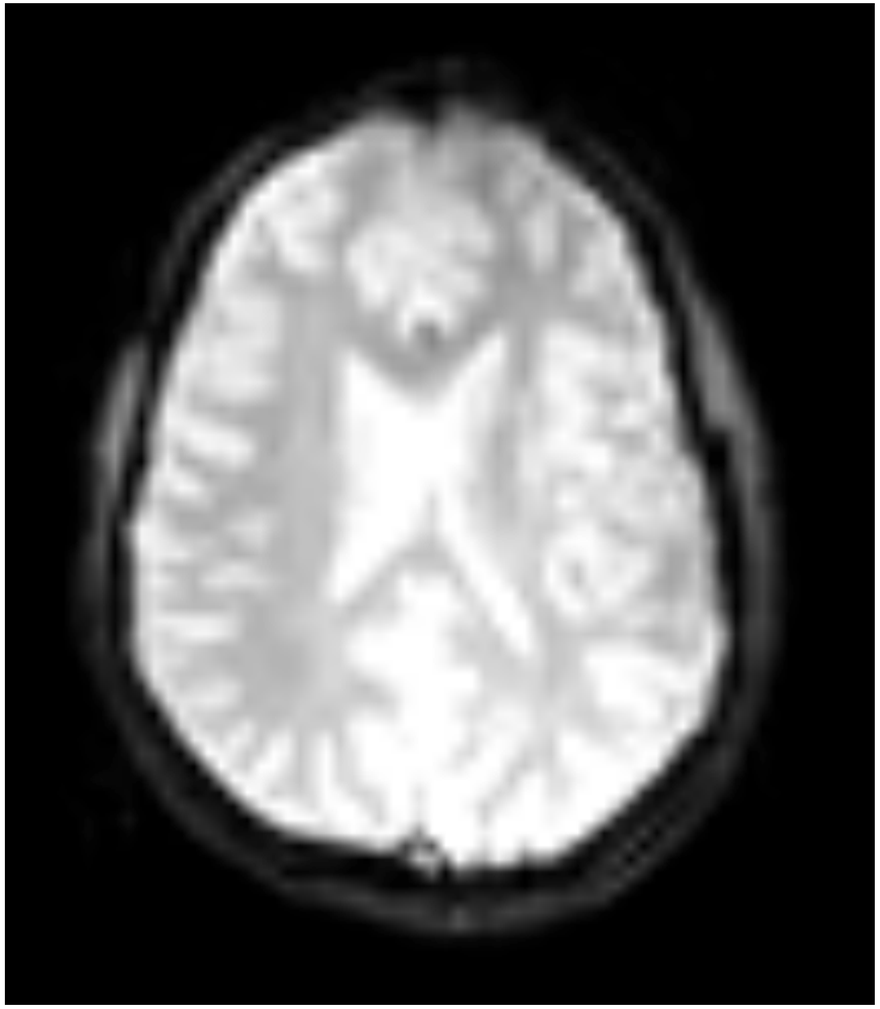
1 mm isotropic voxel

T2-weighting



1 mm isotropic voxel

T2*-weighting (EPI)

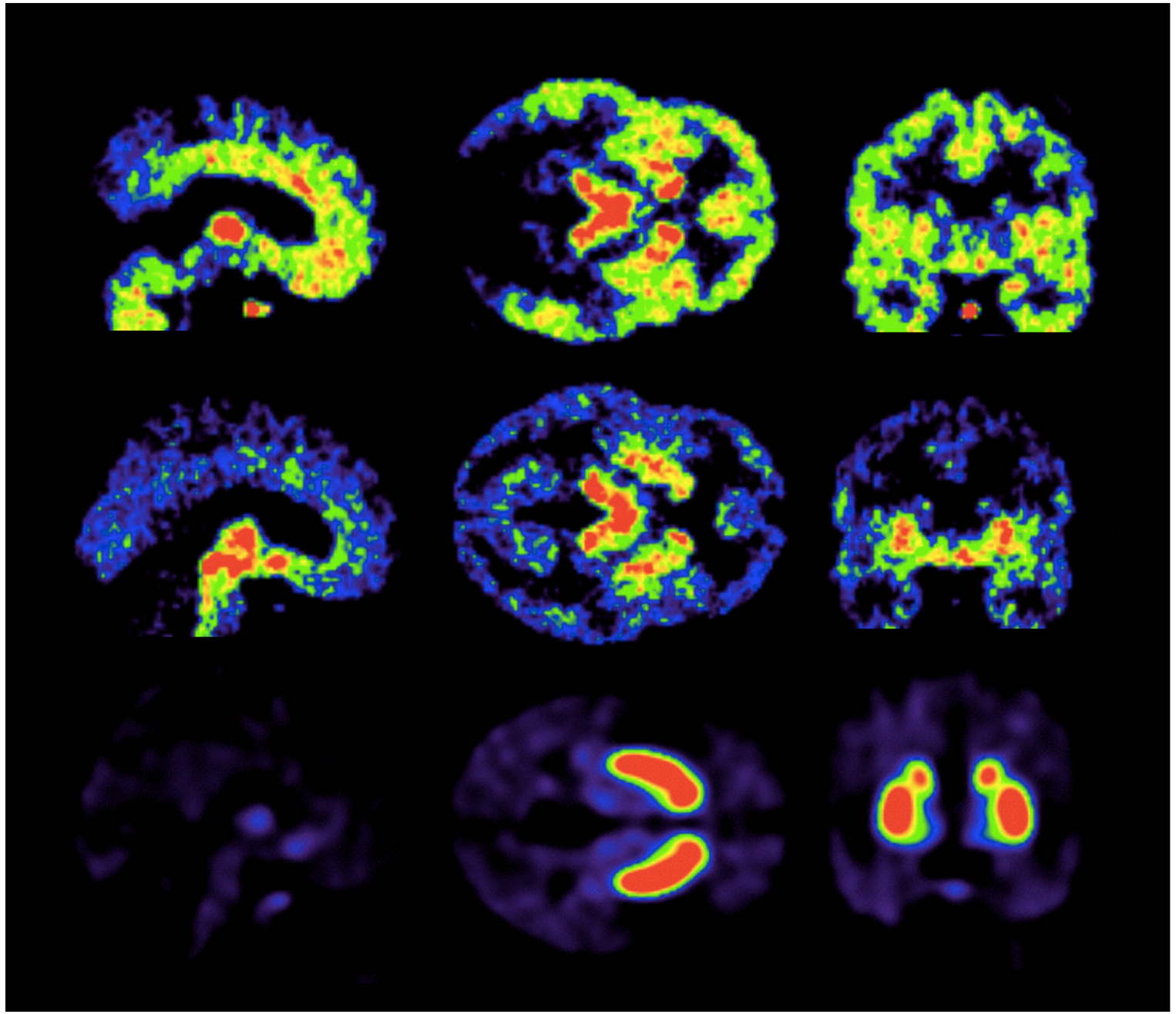


3 mm isotropic voxel

[11C]carfentanil
MOR tracer

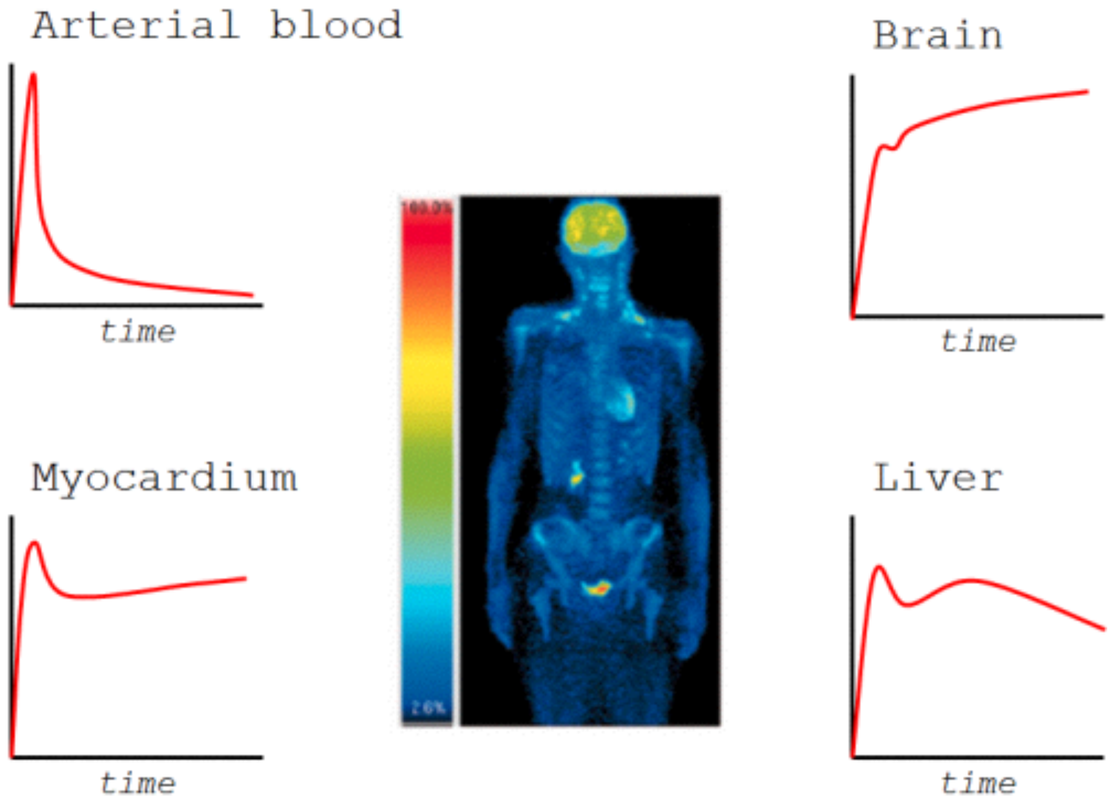
[11C] MADAM
SERT tracer

[11C] raclopride
D2R tracer



Modelling

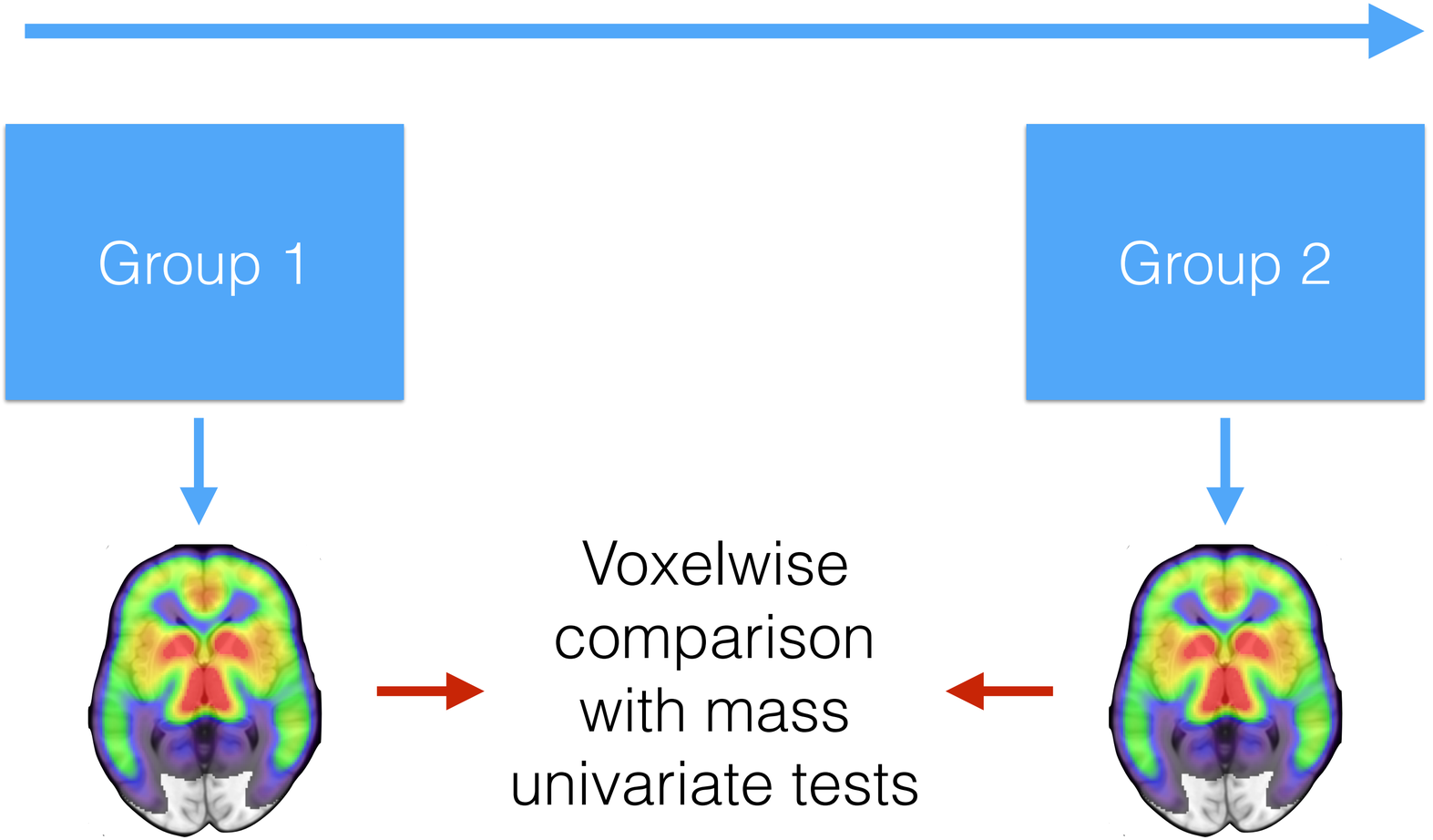
- Modelling transforms radioactivity concentration into biologically relevant pharmacokinetic information
  - **No modeling** (‘raw’ radioactivity)
  - **Standardised uptake value** (SUV; control for injection and weight)
  - **Kinetic modeling** (arterial plasma as input)
  - **Reference tissue model** (reference tissue as input; not always possible as e.g. with H2O)



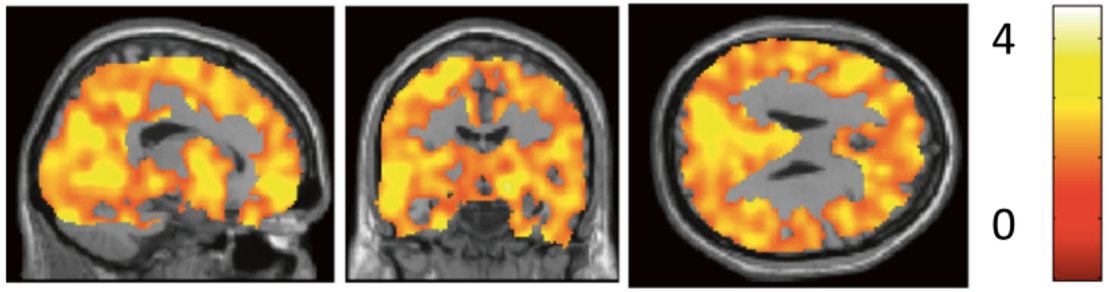
Oikonen (Turku PET Centre)

Experimental designs for PET

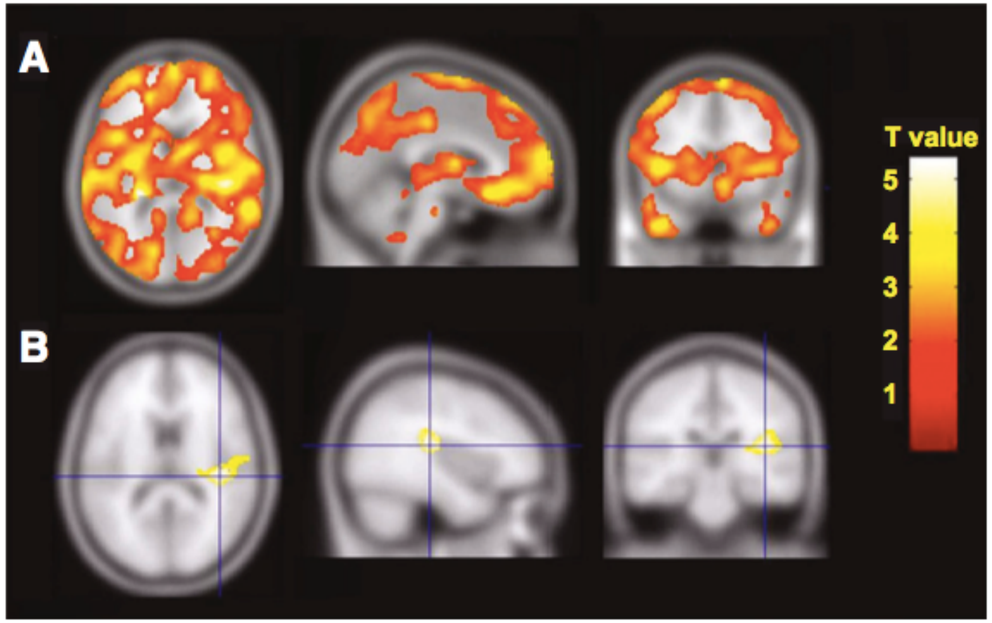
Establishing group differences



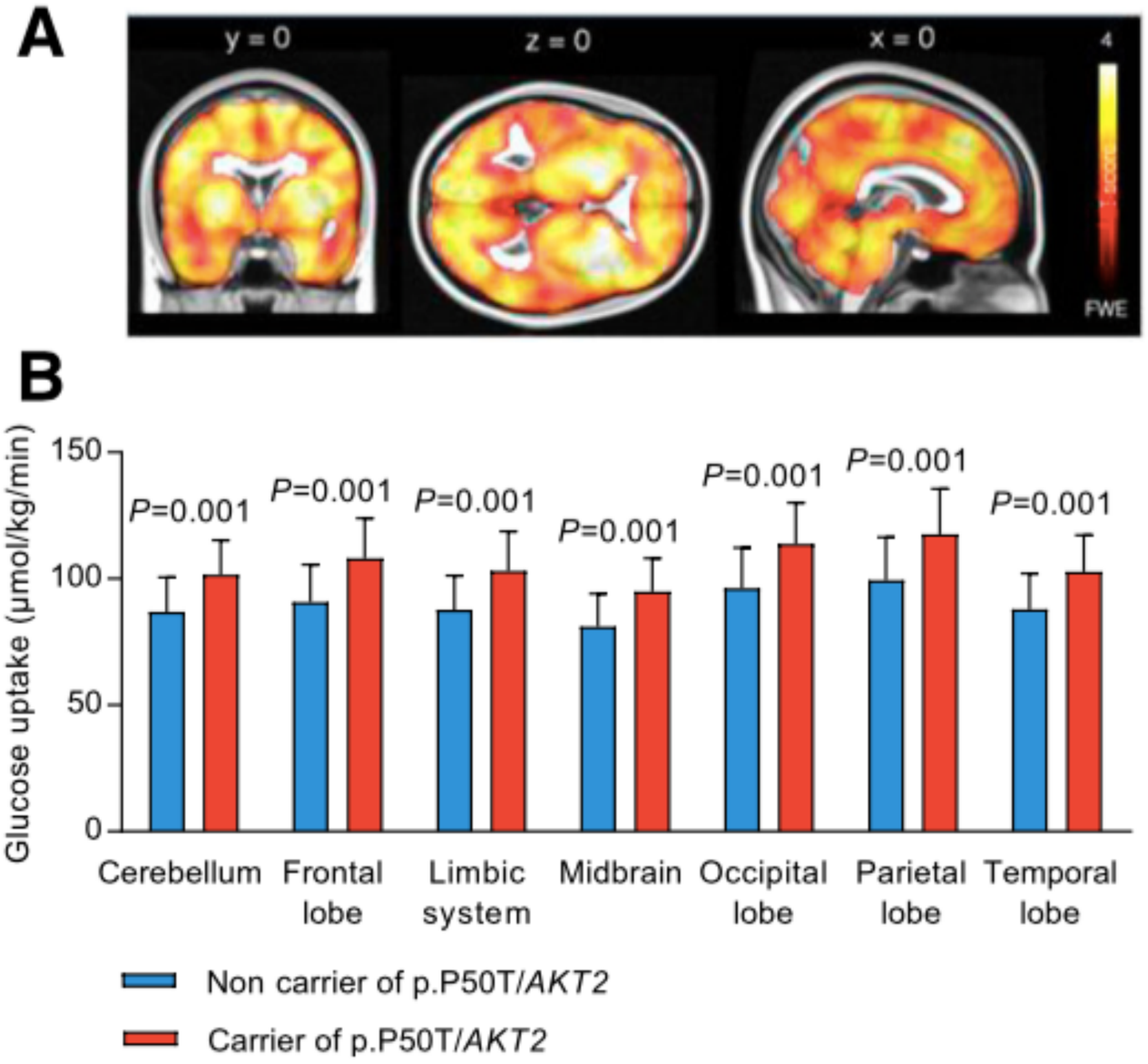
1. Obese versus lean subjects



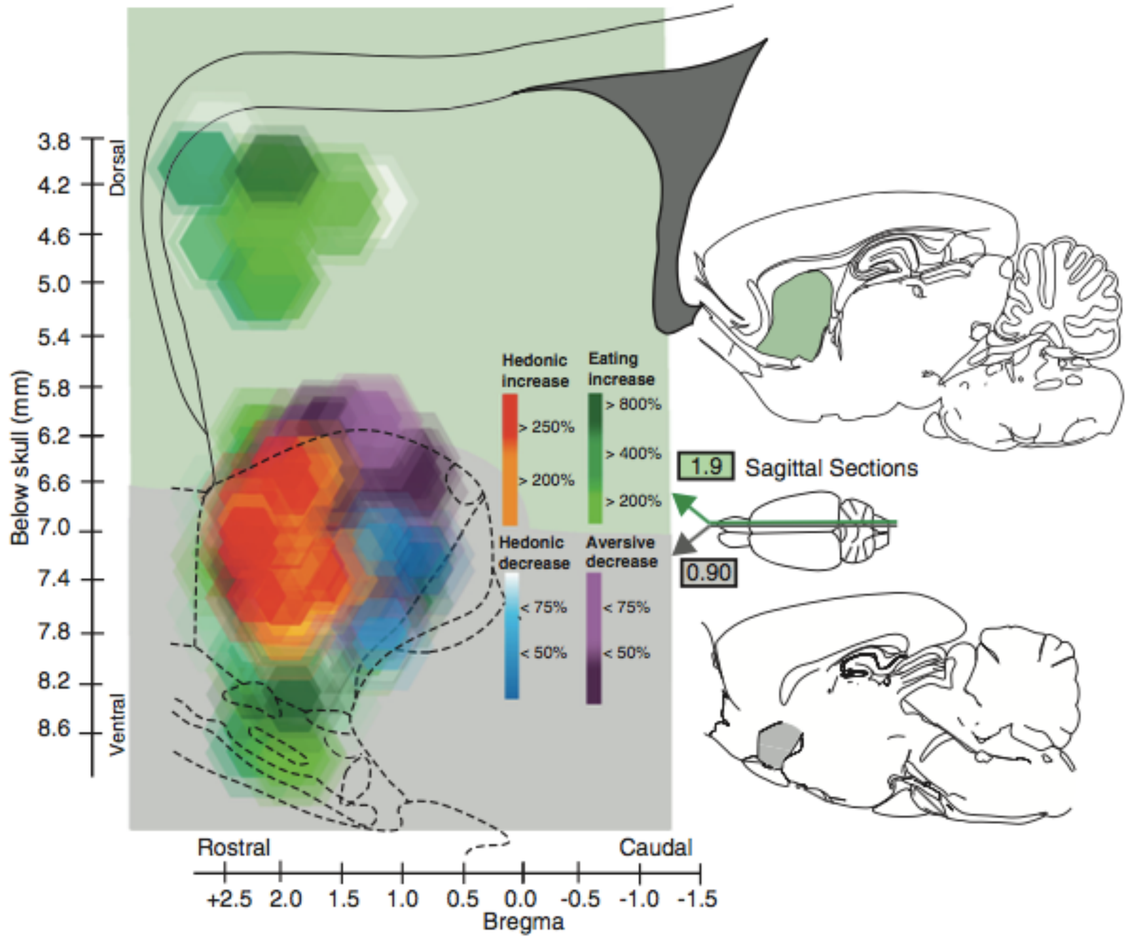
2. IGT versus controls



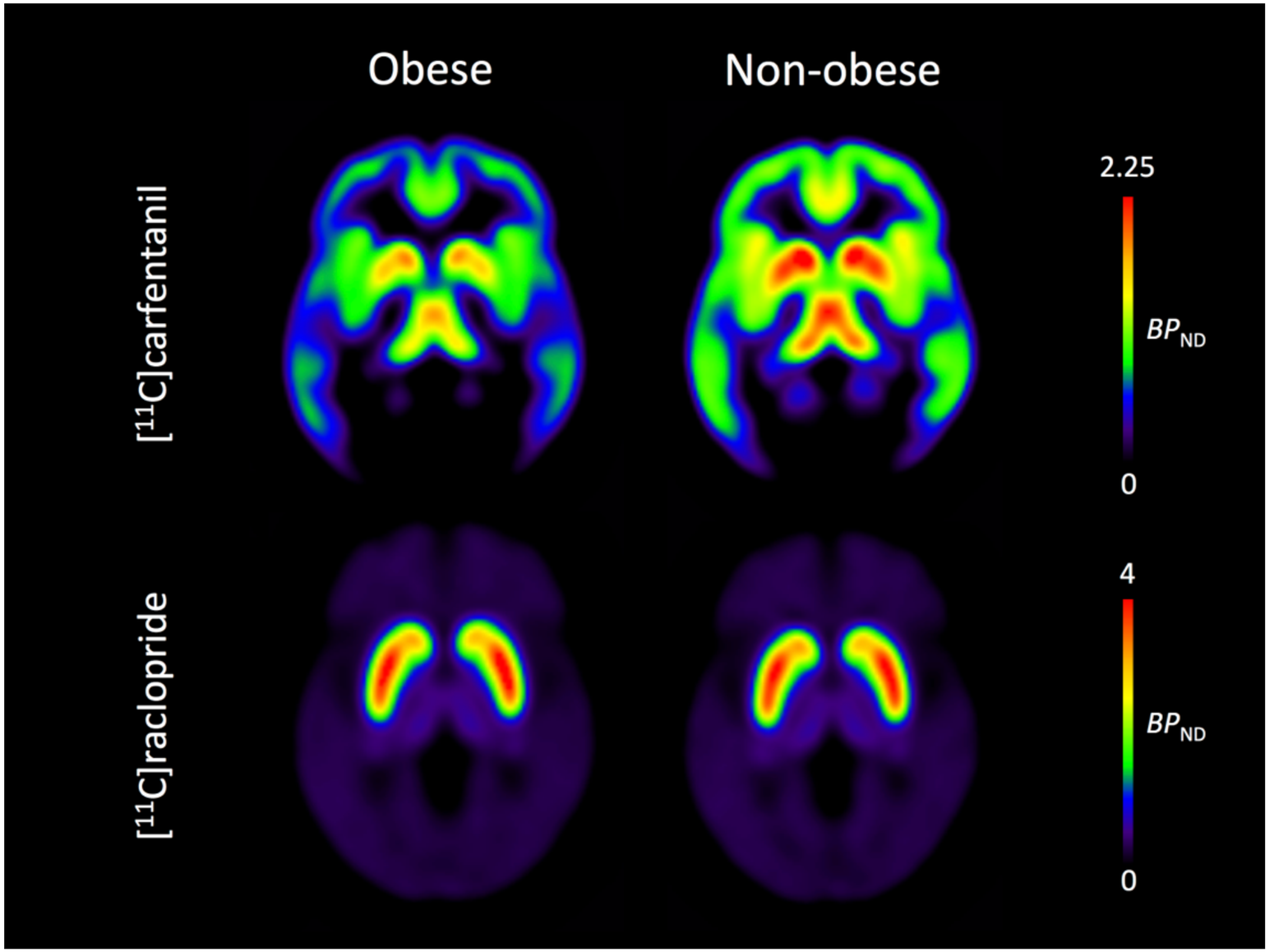
3. p.P50T/AKT2 carrier vs. non-carrier



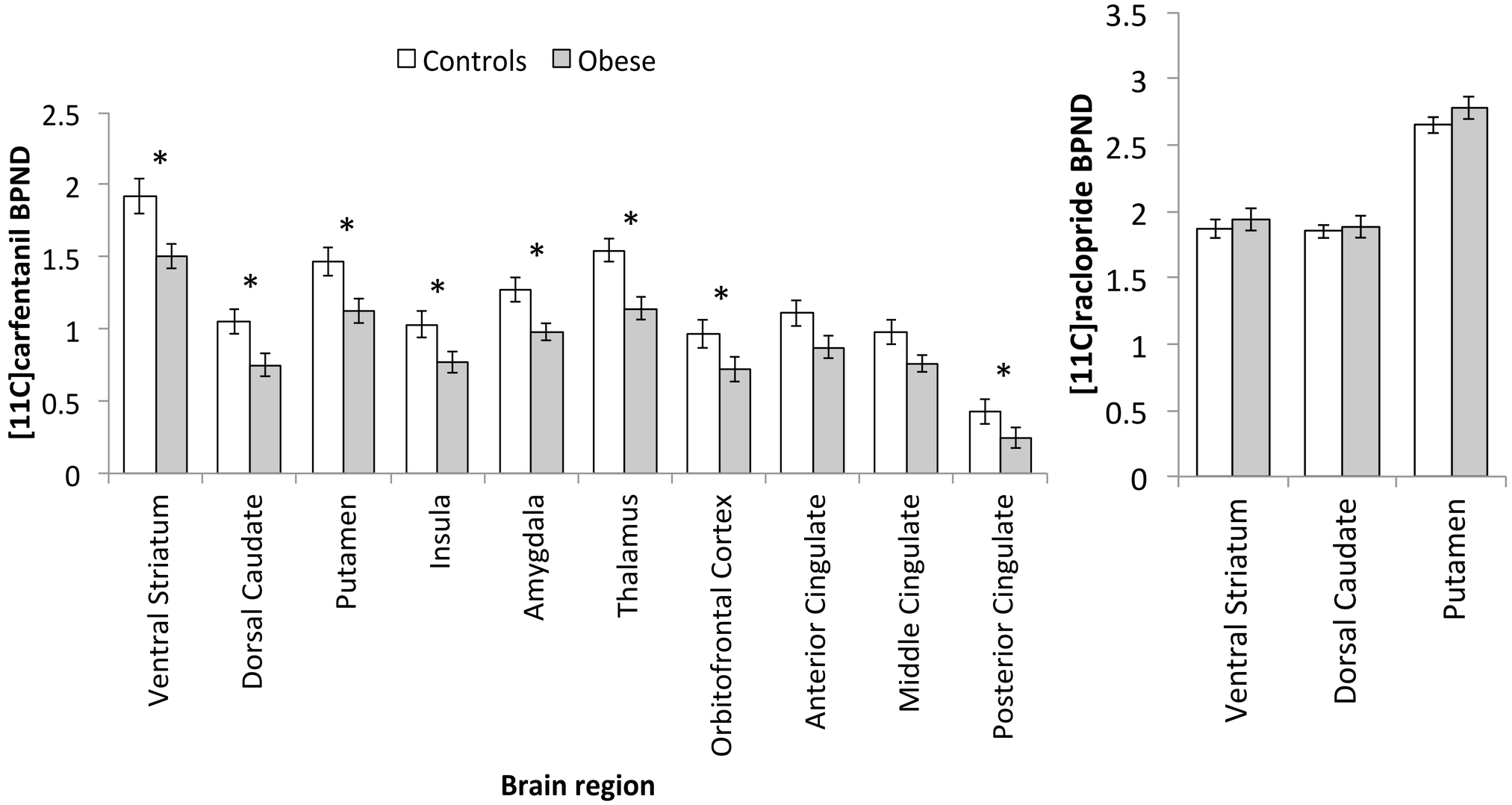
Tuulari et al (2013 Diabetes); Hirvonen et al (Diabetes 2012); Latva-Rasku et al (2018 Diabetes)



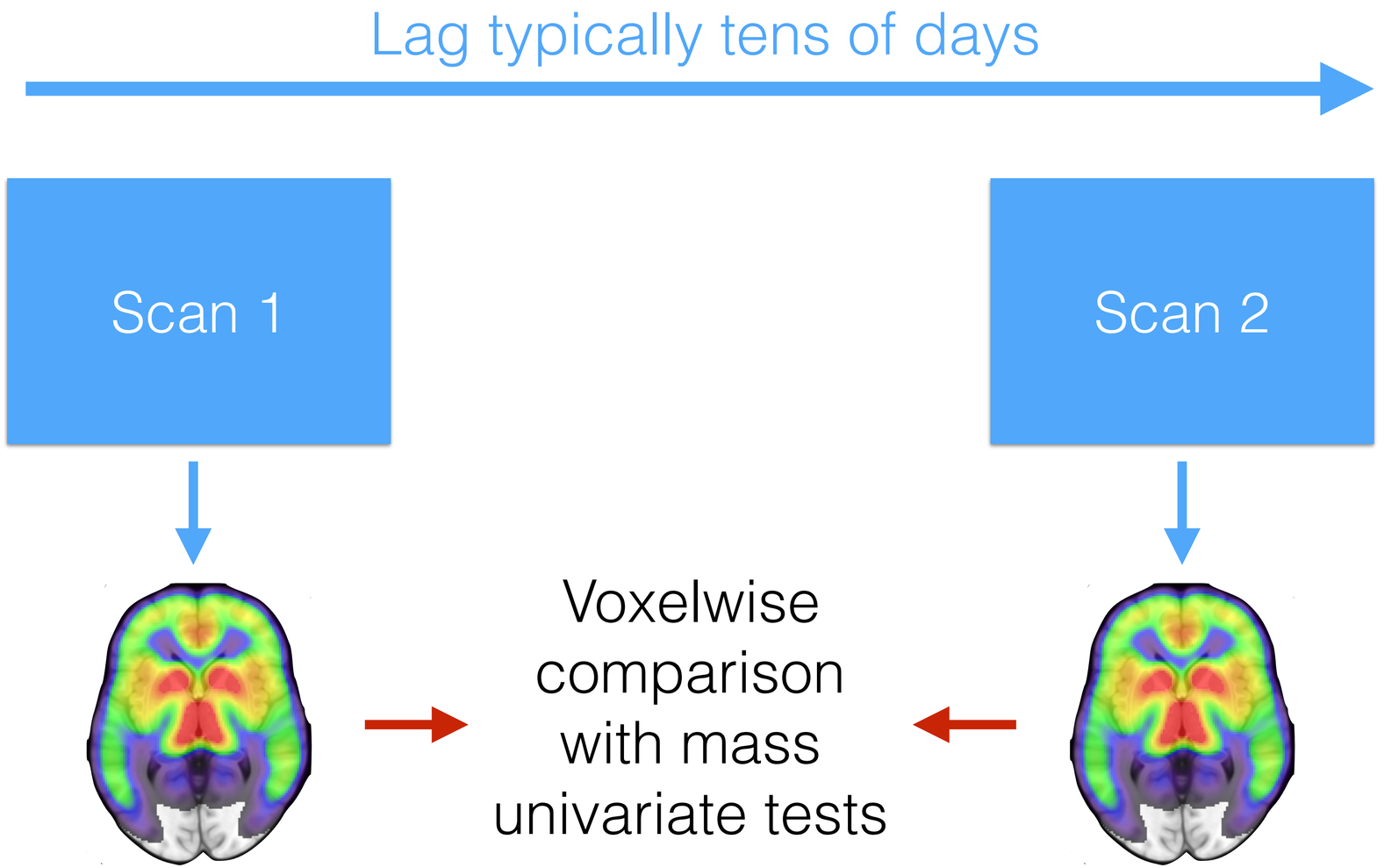
Berridge & Kringelbach (2013 CiN)

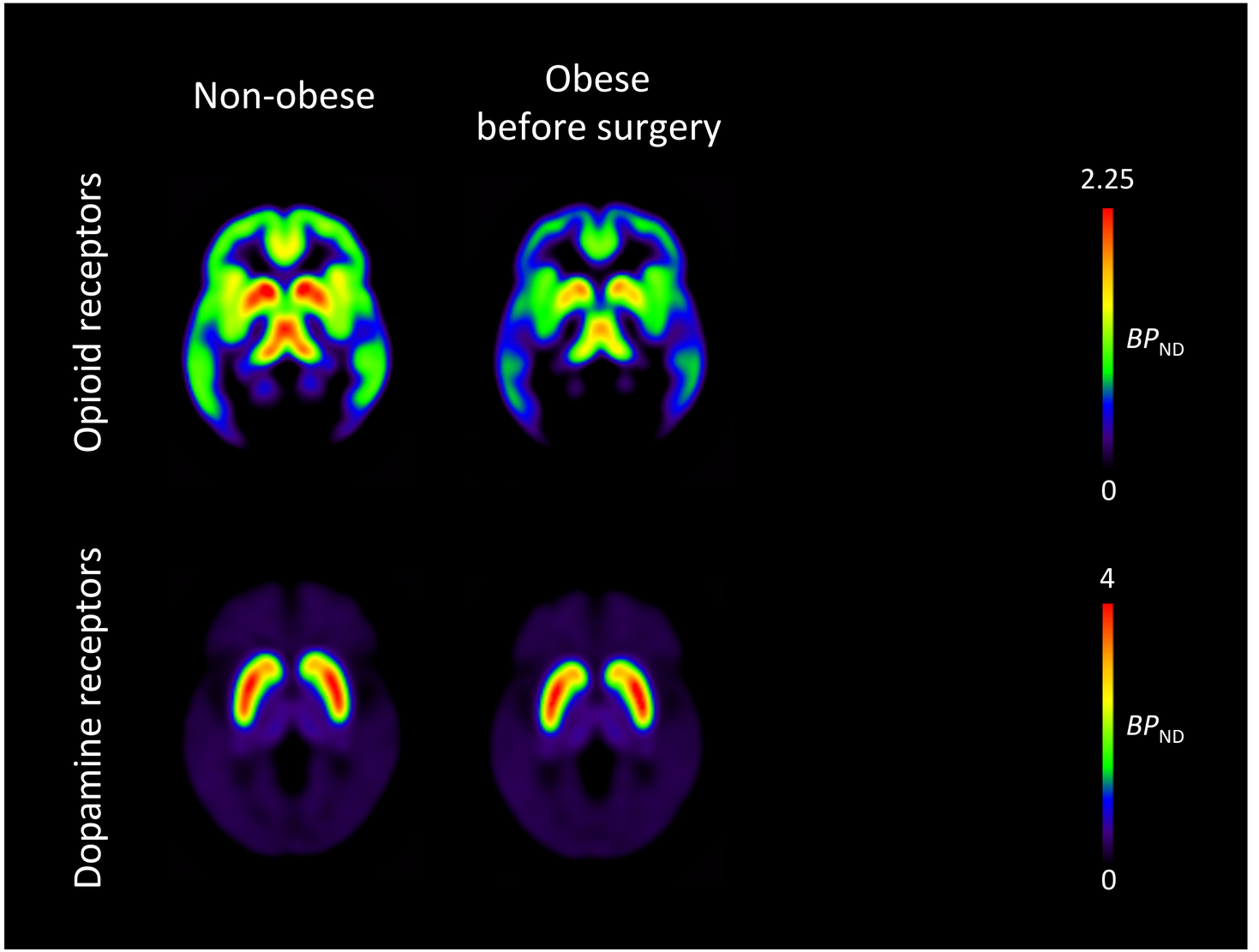


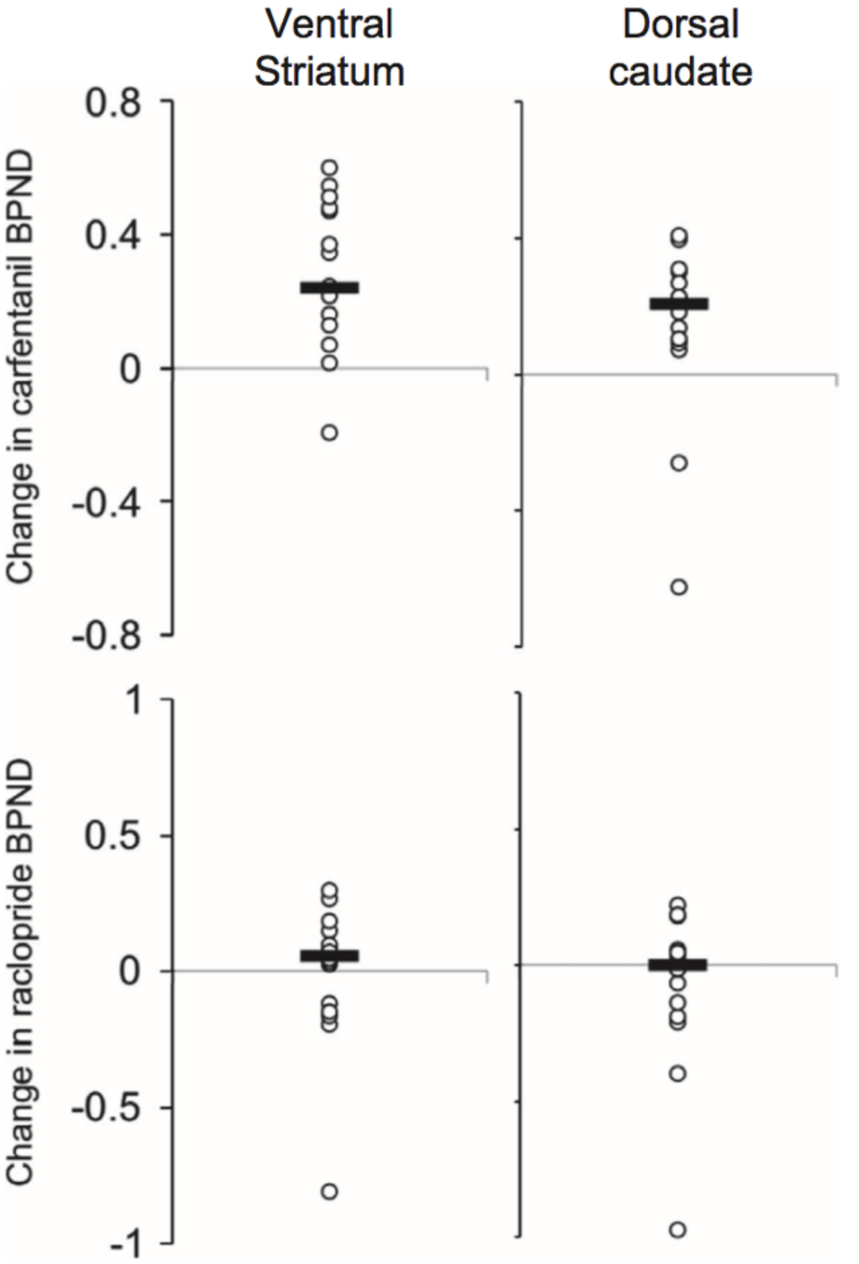
Karlsson et al (2015 J Neurosci)


Controls
Obese
[11C]carfentanil BPND
2.5
2
1.5
1
0.5
0
*
Ventral Striatum
Dorsal Caudate
Putamen
Insula
Amygdala
Thalamus
Orbitofrontal Cortex
Anterior Cingulate
Middle Cingulate
Posterior Cingulate
Brain region
[11C]raclopride BPND
3.5
3
2.5
2
1.5
1
0.5
0
Ventral Striatum
Dorsal Caudate
Putamen

Measuring change







Karlsson et al (2015 Mol Psych)

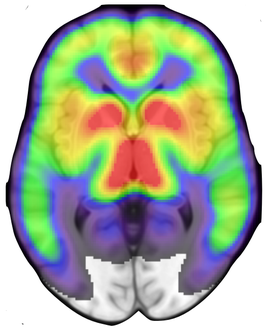
Functional PET (challenge paradigm)

Temporal resolution tens of minutes

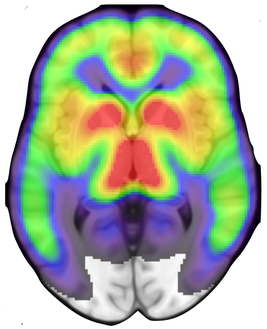
Task 1

Decay break

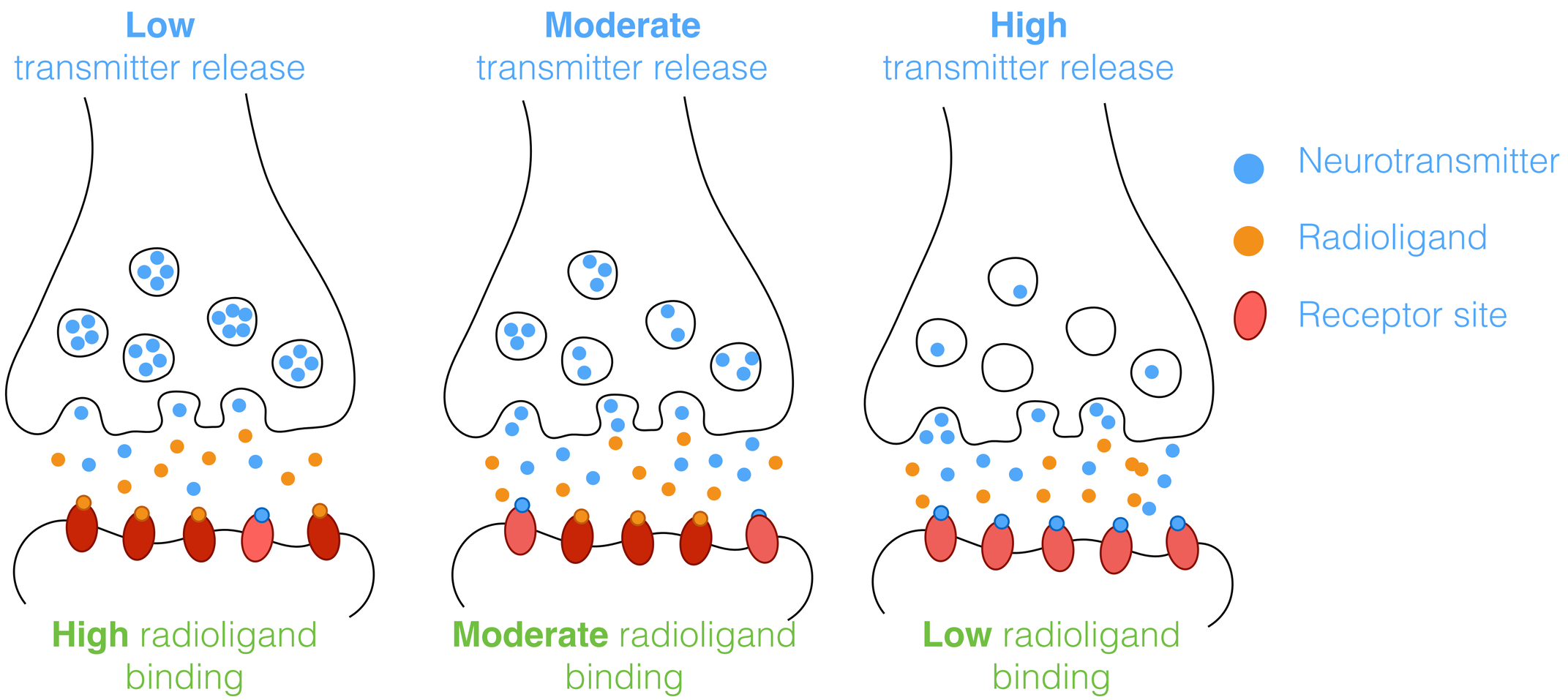
Task 2



Statistical comparison (cognitive subtraction)



Challenge paradigm



Nummenmaa et al (2018 ACS Chemical Neuroscience)

1. Nutridrink

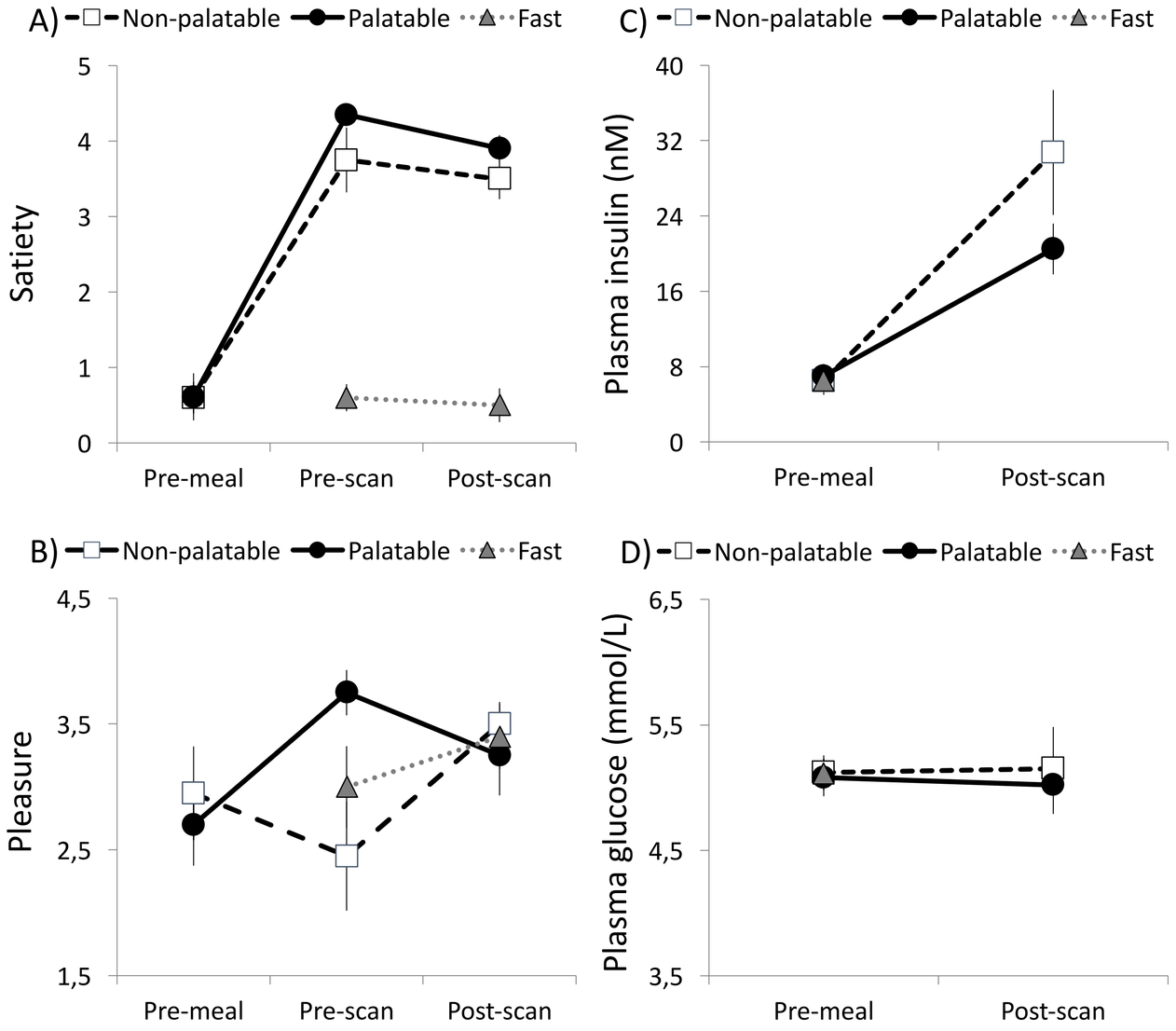
Non-palatable food
Liquid meal
Energy content matched with pizza

2. Pizza

Palatable food
Pizza; with toppings chosen by subject. Energy content matched with non-palatable food

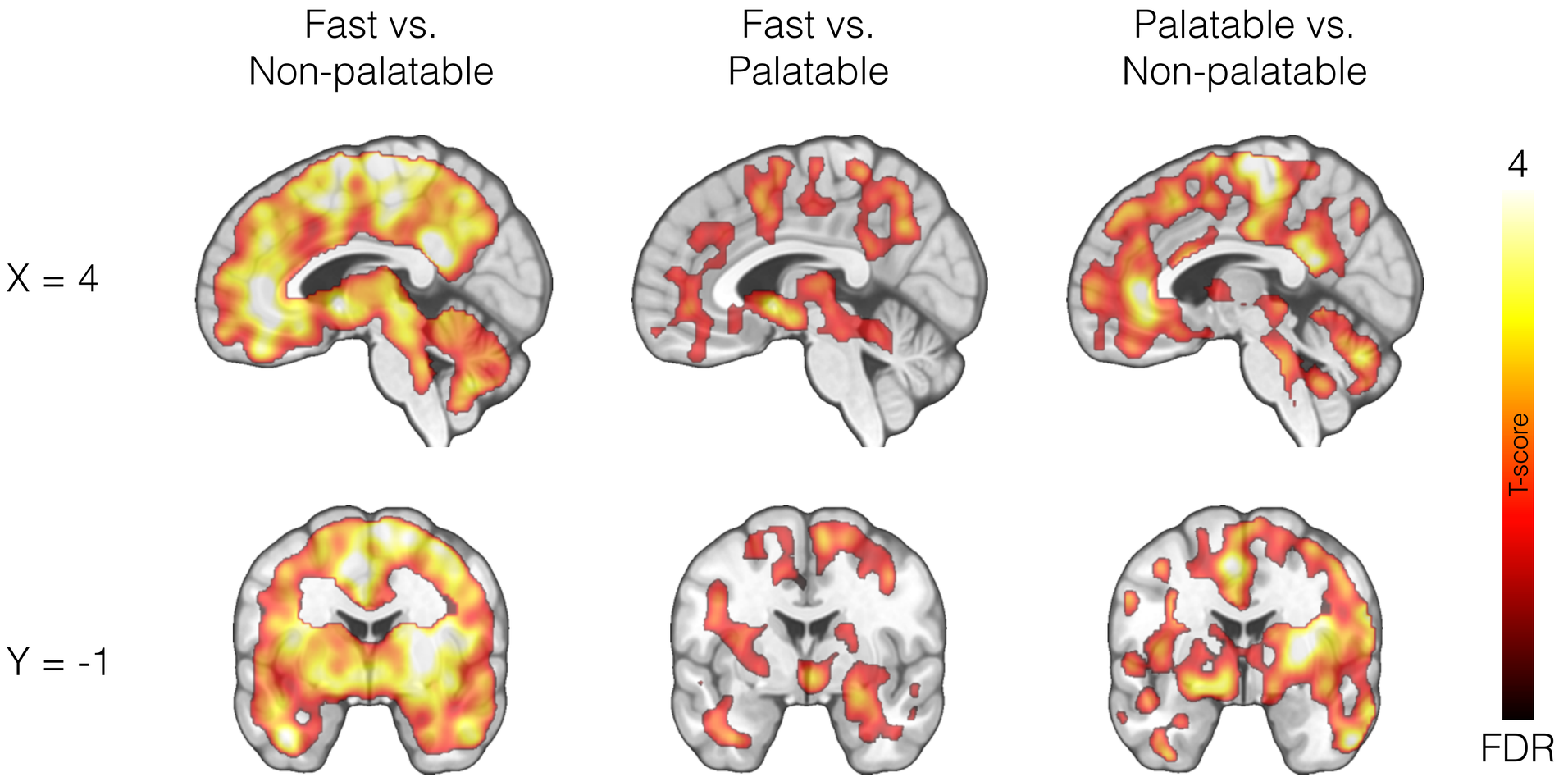
3. Fasting

12 hour fasting
before PET scan



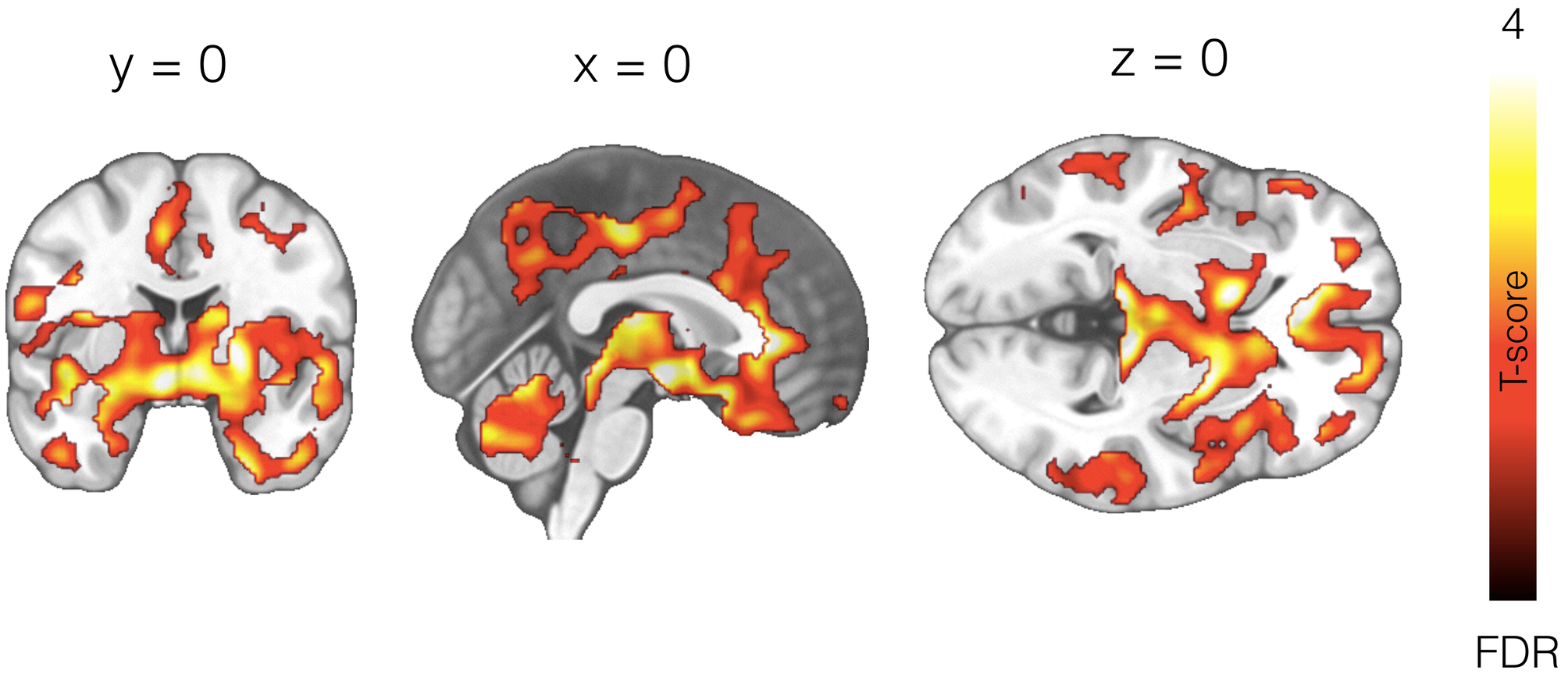
Tuulari et al (2017 J Neurosci)

Feeding releases endogenous opioids



Tuulari et al (2017 J Neurosci)

Strenuous physical exercise triggers opioid release



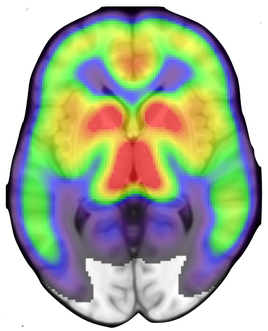
Saanijoki et al (2018 Neuropsychopharmacology)

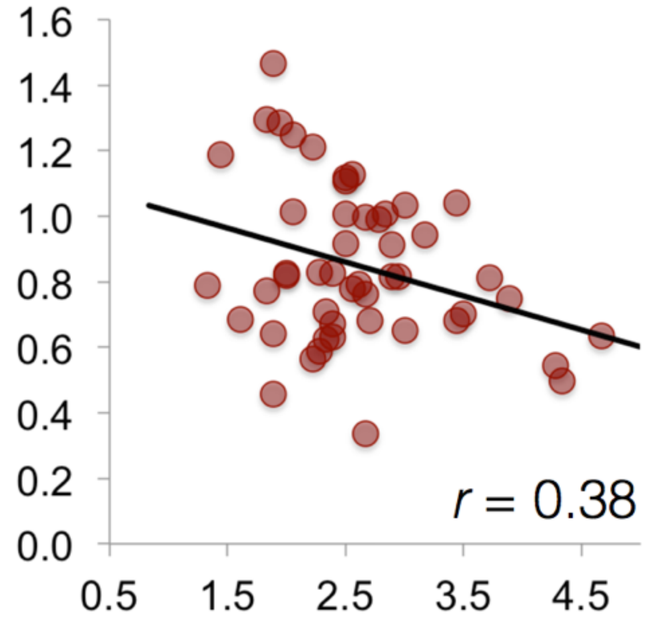
Saanijoki et al (under revision, Hum Brain Mapp)

Correlational design

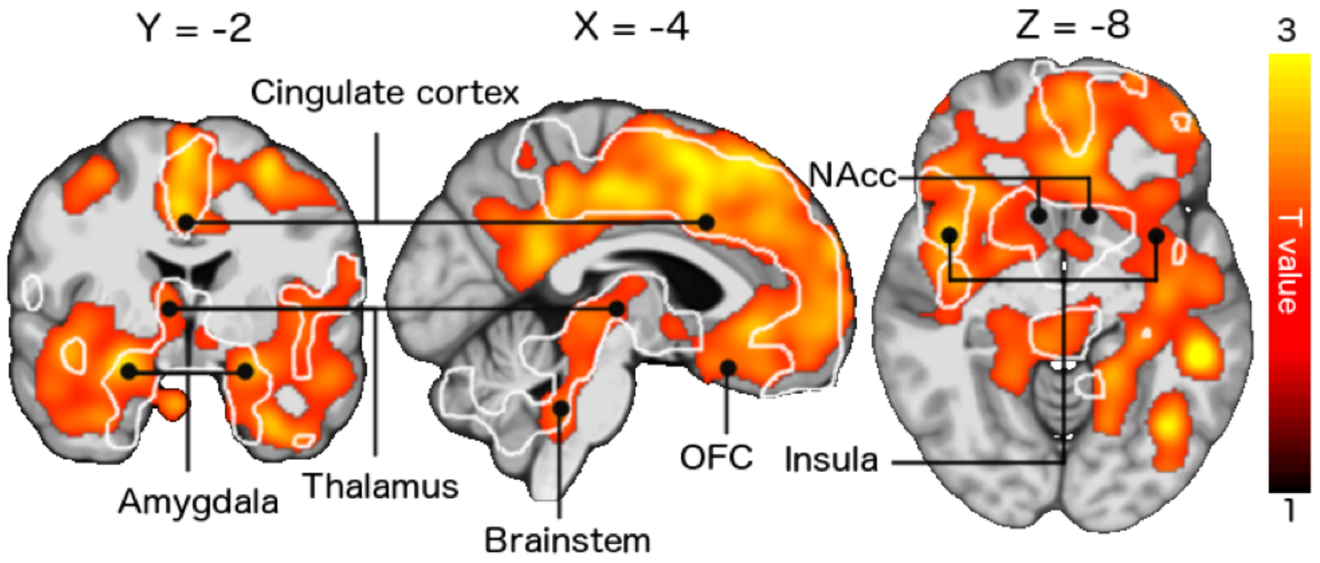
Baseline scan

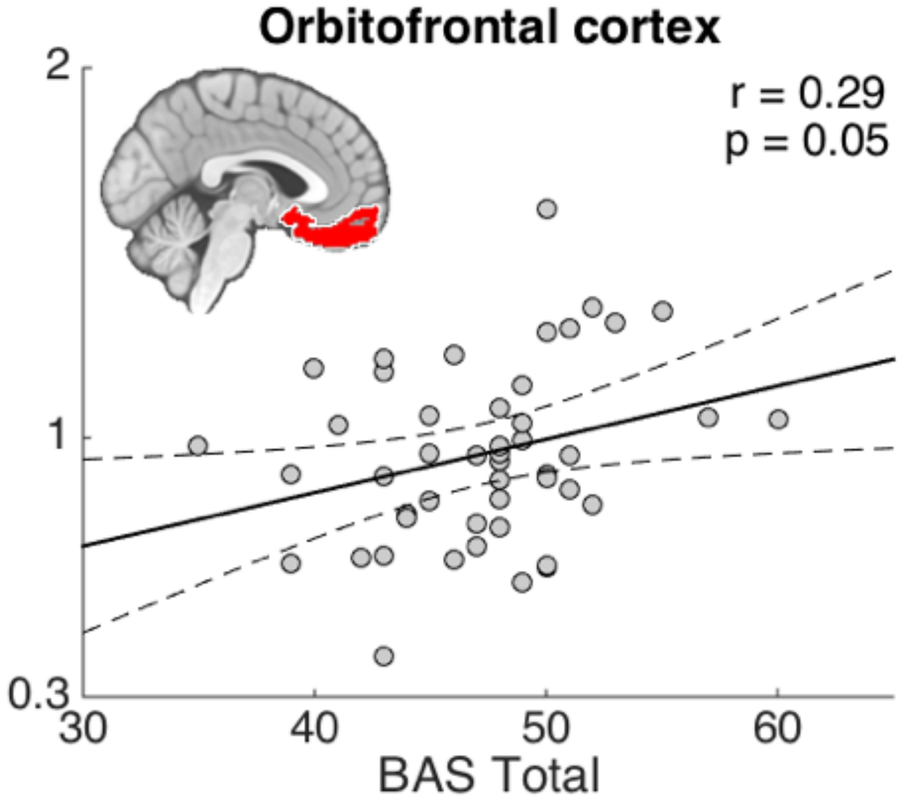
Physiological / Behavioural assay



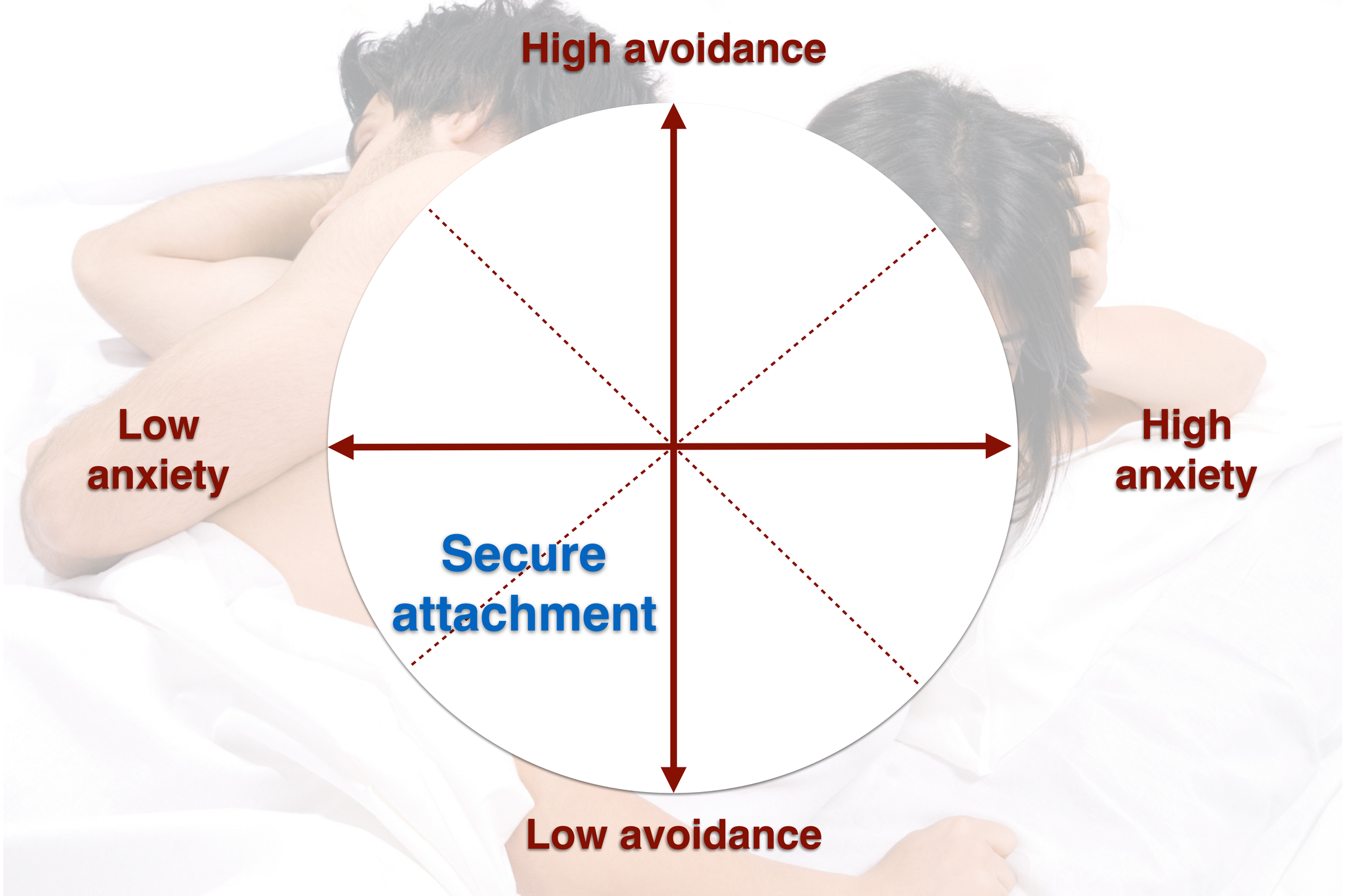


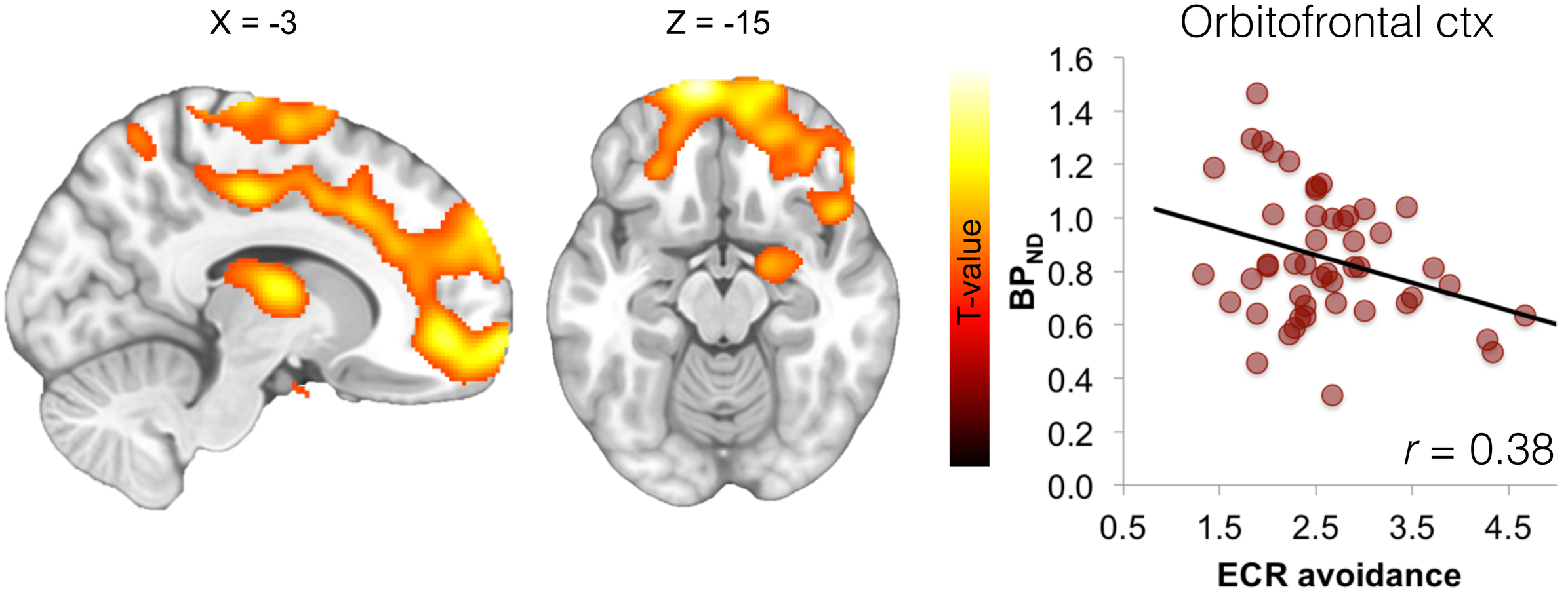
MOR tone is associated with reward sensitivity





Karjalainen et al (2016; Soc Cogn Affective Neurosci)


High avoidance
Low anxiety
High anxiety
Secure attachment
Low avoidance



Nummenmaa et al (2015 Hum Brain Mapp;)

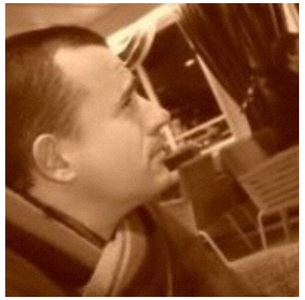
Summary - Brain-PET

- Based on radiolabeled tracers
- Allows quantification of any biological system as long as it can be radiolabeled
- Excellent chemical resolution
- Spatial resolution limited due to positron scattering
- Temporal resolution depends on tracer kinetics; typically from minutes to hours and often not relevant (no functional imaging)

Human Emotion Systems Laboratory

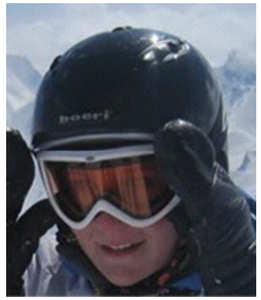

Lauri

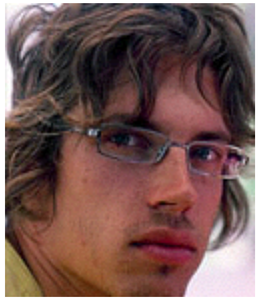

Enrico


Matthew

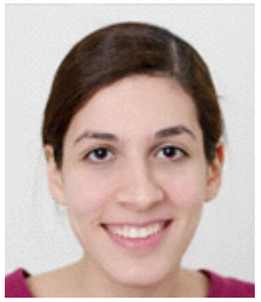

Iskä

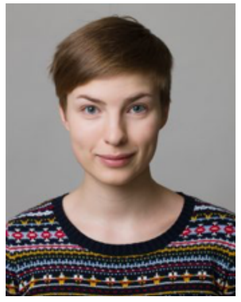

Juulia


Sandra


Mikko


Yngwie


Lara


Sonya


Kerttu


Tomi


Severi

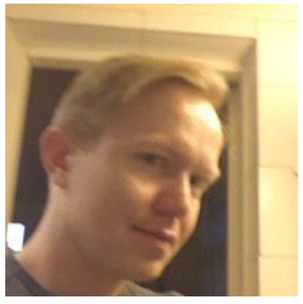

Tatu


Tuulia


Tullijohtaja


Marco


Lihua


Janne


Vesa


Sanaz


Matias


"That's all Folks!"