The Role Of Contemporary MR Imaging Techniques in Early CNS Drug Development

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South London and Maudsley NHS Foundation Trust


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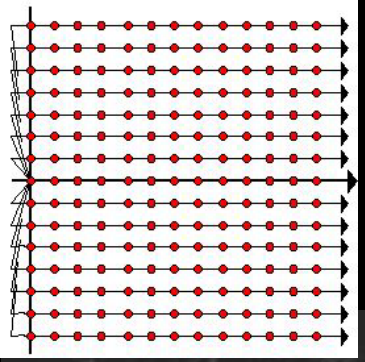
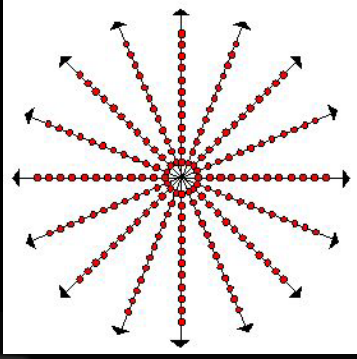
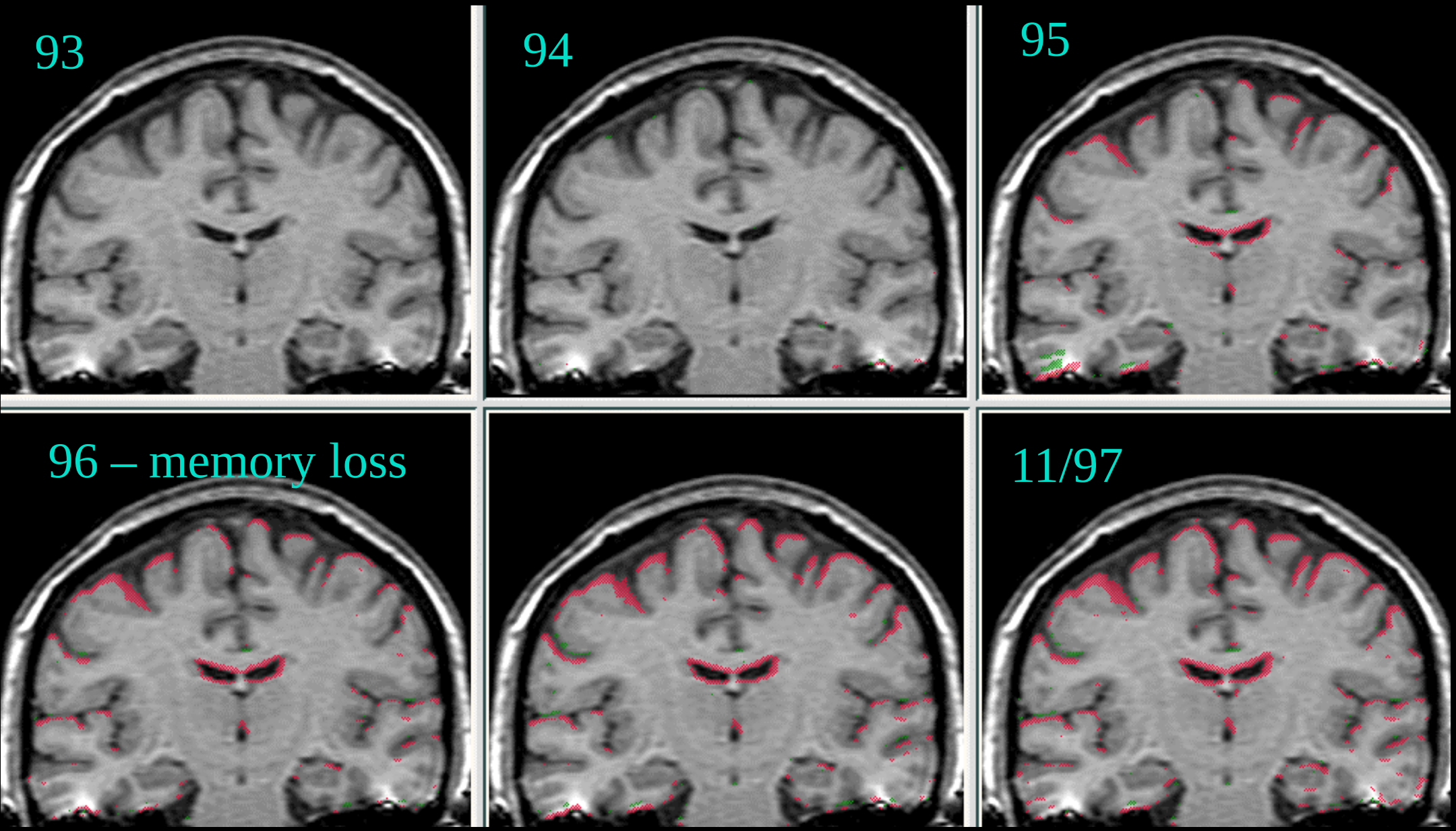
"First we're going to run some tests to help pay off the machine."

High Resolution Structural MRI

Motion Insensitive Imaging



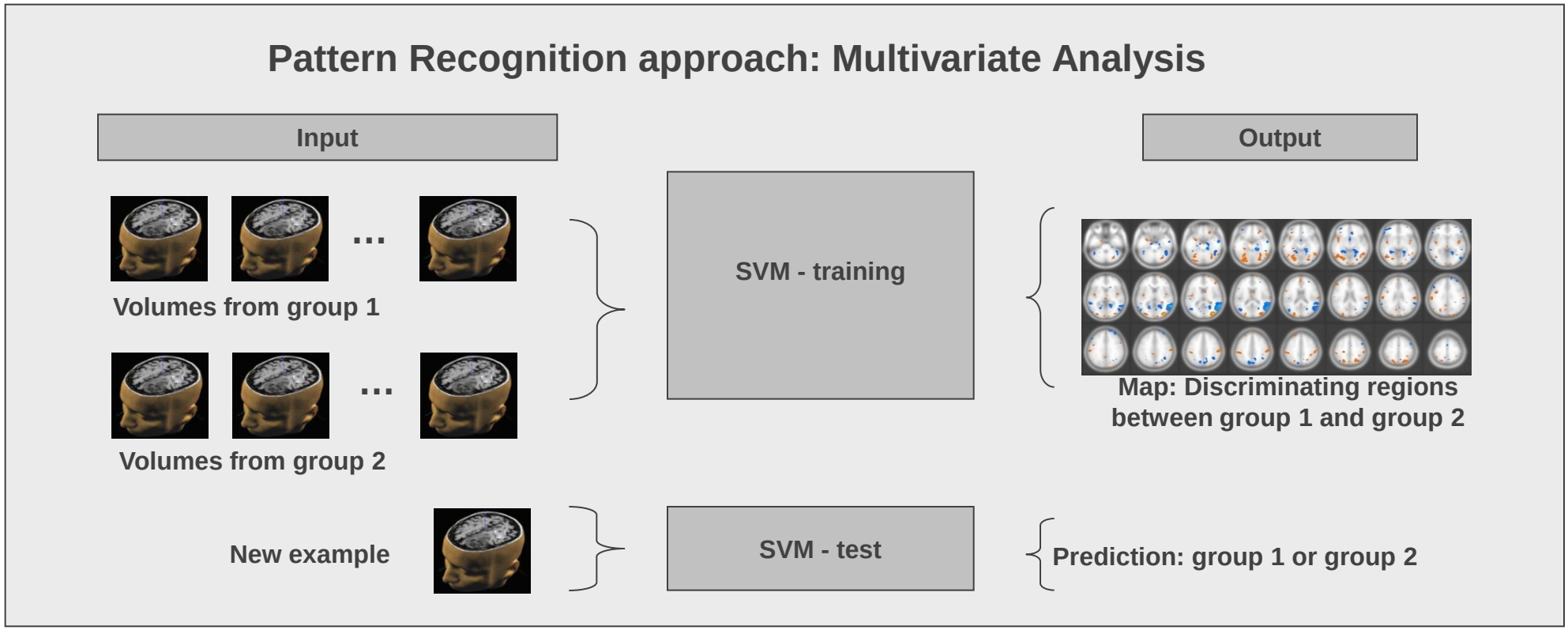




Progressive cerebral losses in early AD. Red = loss

Fox DRG

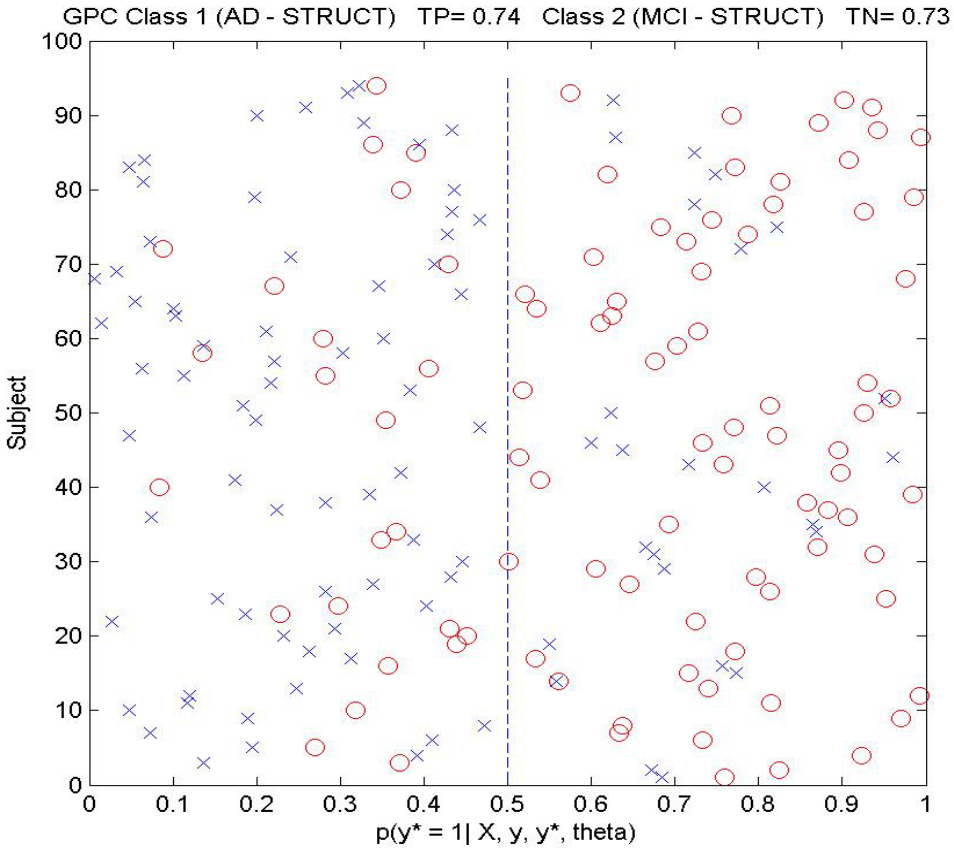
Applying Machine Learning Methods to Brain Images

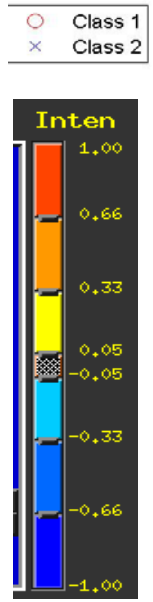


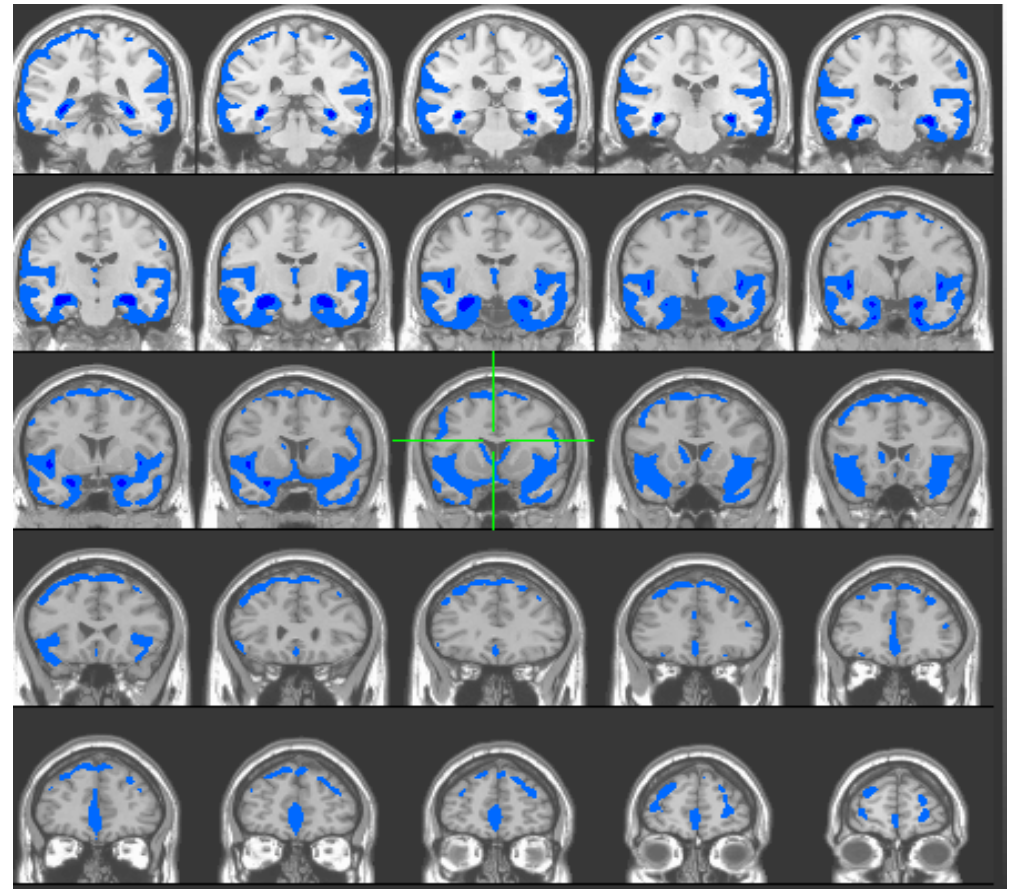
P.R. takes into account information distributed across the whole brain

AD versus MCI

No genetic information







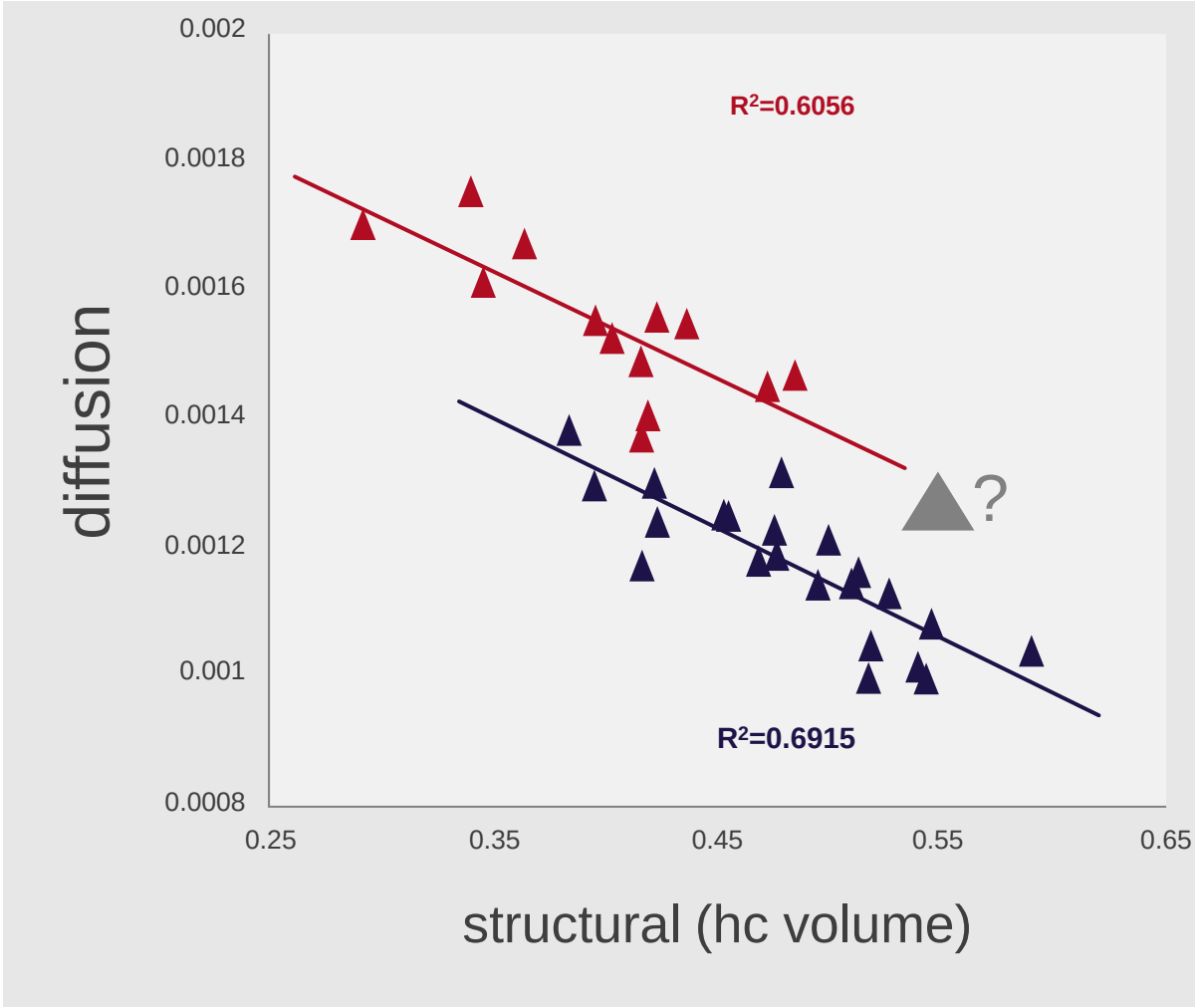
	ADxMCI
TP	0.74
TN	0.73
Accuracy	0.74
p value	0.001

Discrimination map for gray matter classification. Relative increases in gray matter volume in the Alzheimer group compared with the MCI group are displayed in red, while deficits are displayed in blue.

PREDICTION OF TRANSITION FROM MCI TO AD

- Structural MRI (66% accuracy)
- Diffusion MRI (77% accuracy)
- CSF amyloid (74% accuracy)

"Combining these measures can predict conversion to Alzheimer's, two years in advance, with 91% accuracy"



Gwenaëlle Douaud et al., *J. of Neuroscience*, 33(5):2147-2155

Pre-Clinical 7T MR in the J.B.C.

Visualization of β-Amyloid Plaques in a Transgenic Mouse Model (Tg2576) of Alzheimer's Disease Using MR Microscopy Without Contrast Reagents

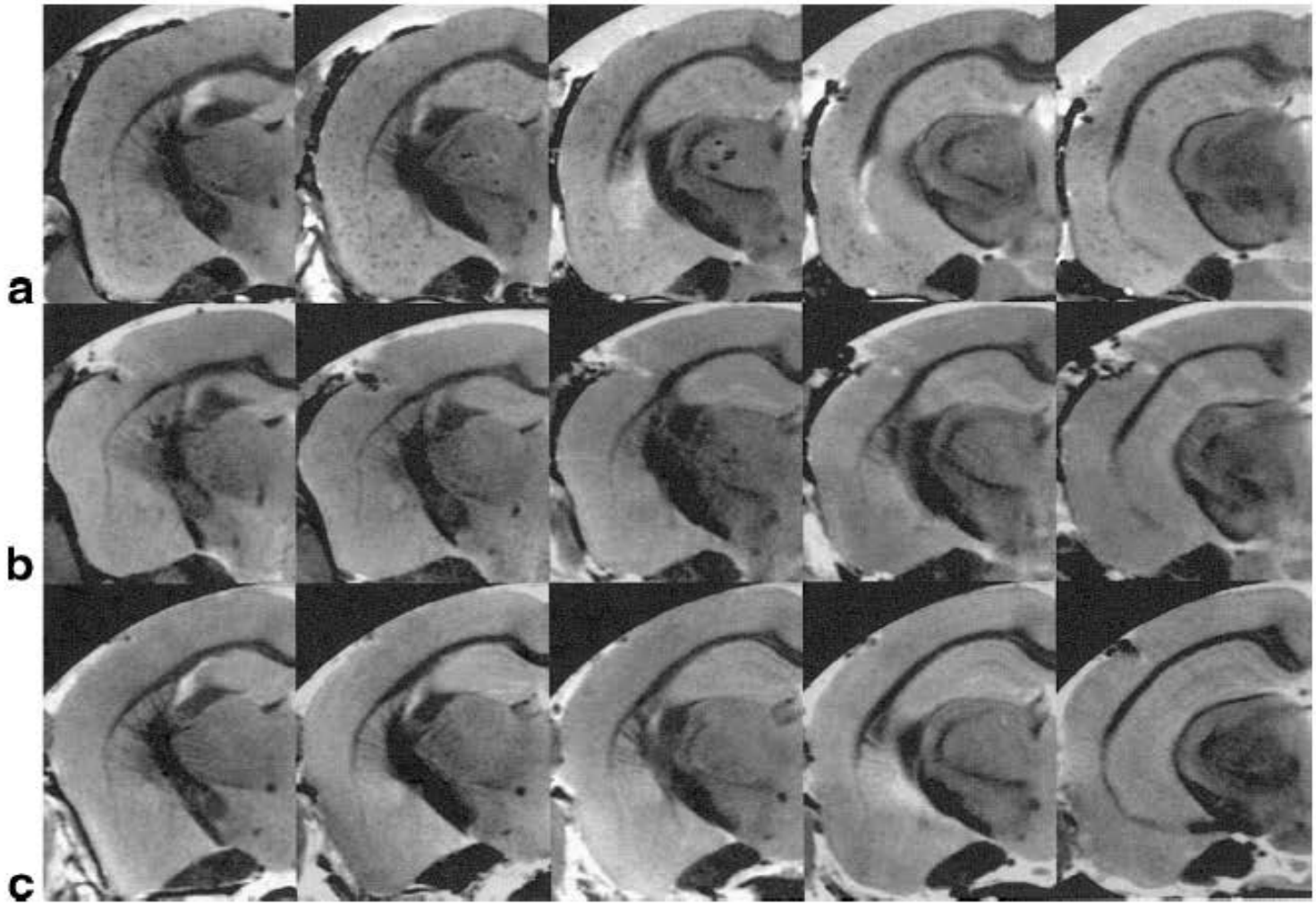
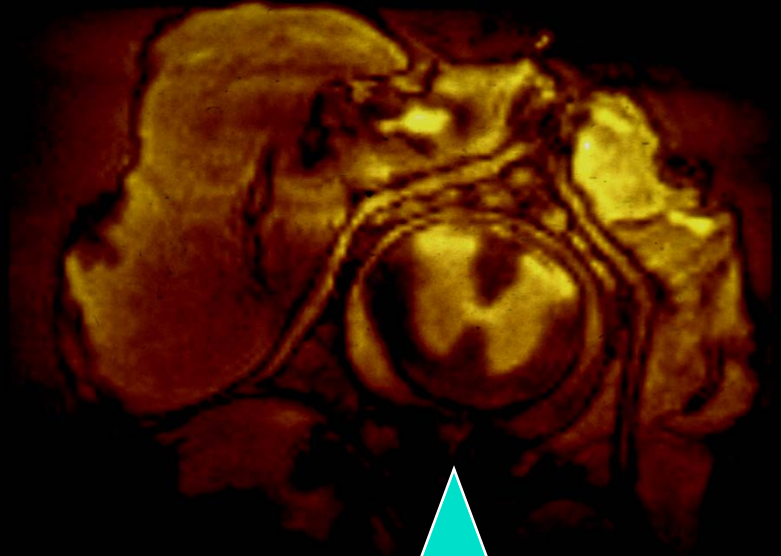
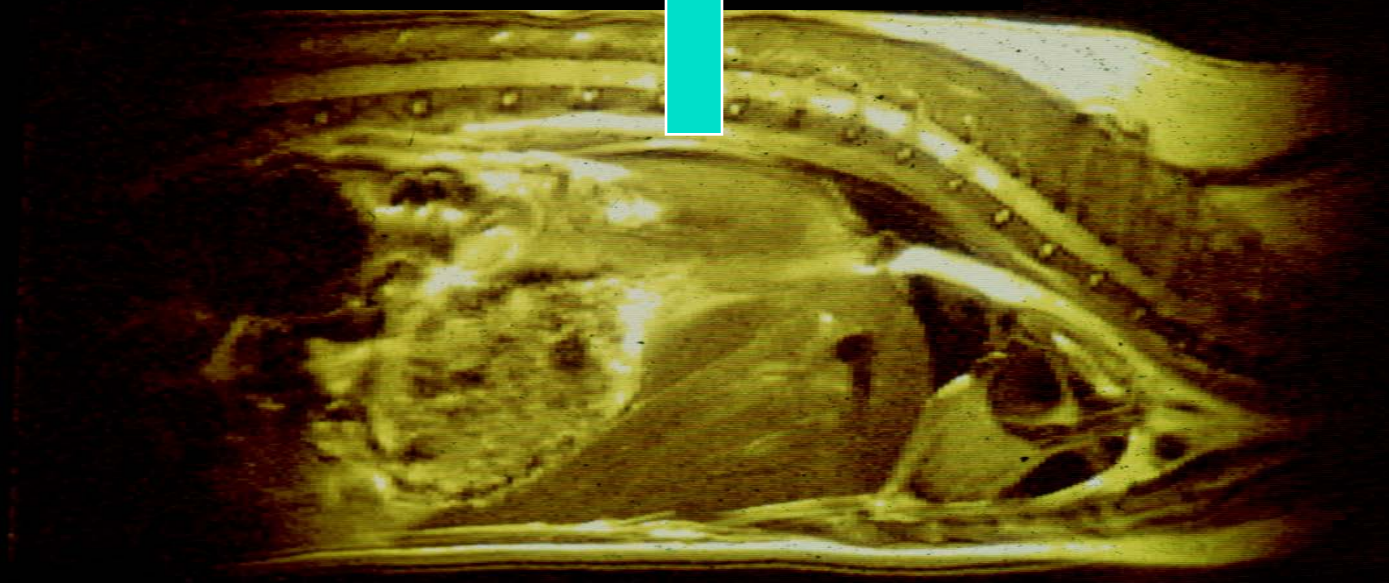


FIG. 2. MR microscopy of fixed mouse brains with PBS perfusion. MR microscopy images of fixed brains of a PS/APP mouse (a) and a PS mouse (b) and an NTg mouse (c) with spatial resolution of $54 \times 58 \times 200\ \mu m^3$ (TR = 5–6 sec, TE = 10 ms, total scan time = 10–11 hr). Numerous circular signal hypointensities can be seen in the areas of cortex and hippocampus of the PS/APP mouse brain (a), whereas no distinctive signal hypointensities are visible in PS (b) and NTg (c) mouse brains.

S-P Lee et al , Magnetic Resonance in Medicine 52:538–544 (2004)

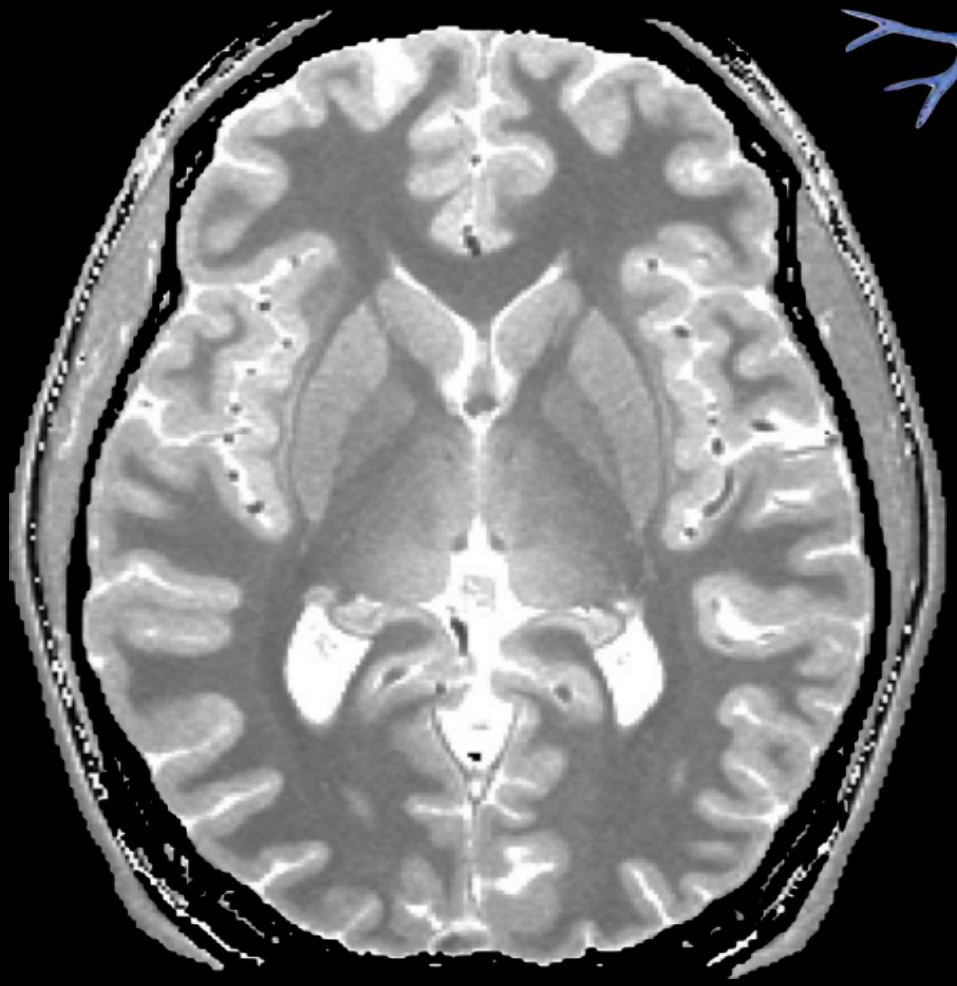


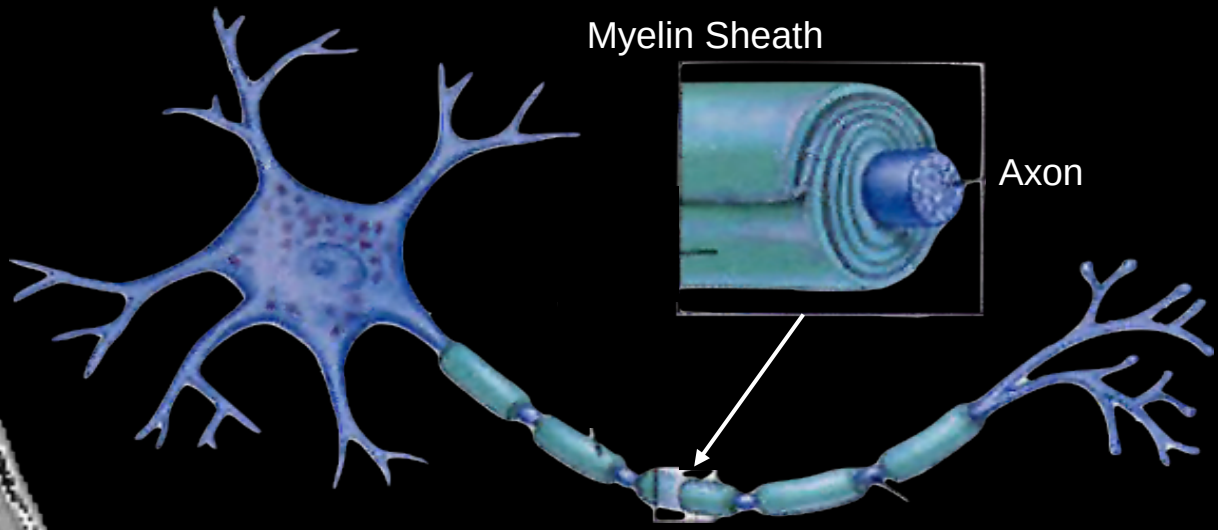
Spinal Cord MR Image

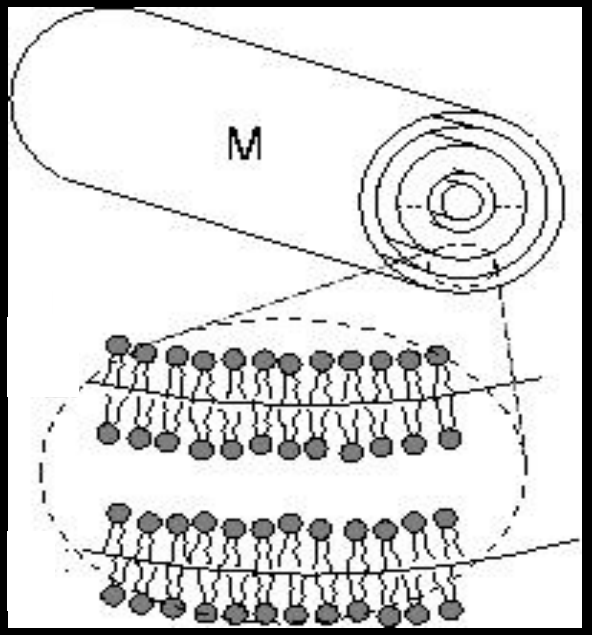


Sagittal
Body Section

Stomach Liver Heart







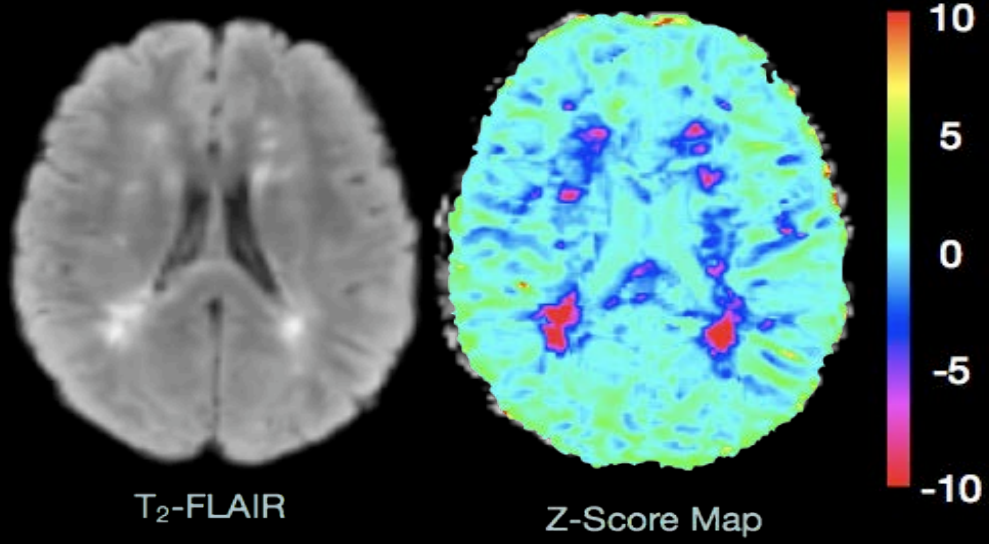
Intra-Axonal Water

Myelin Water

Extra-cellular Water

Multiple Sclerosis

Relapsing-Remitting (RRMS) Patient #1

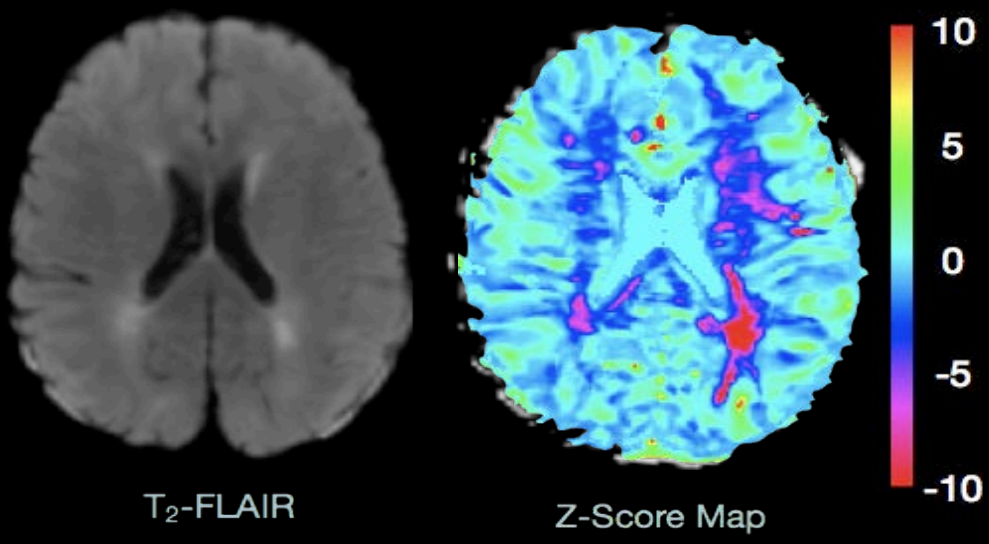


T_2-FLAIR

Z-Score Map

EDSS Score: 1.0

Relapsing-Remitting (RRMS) Patient #2

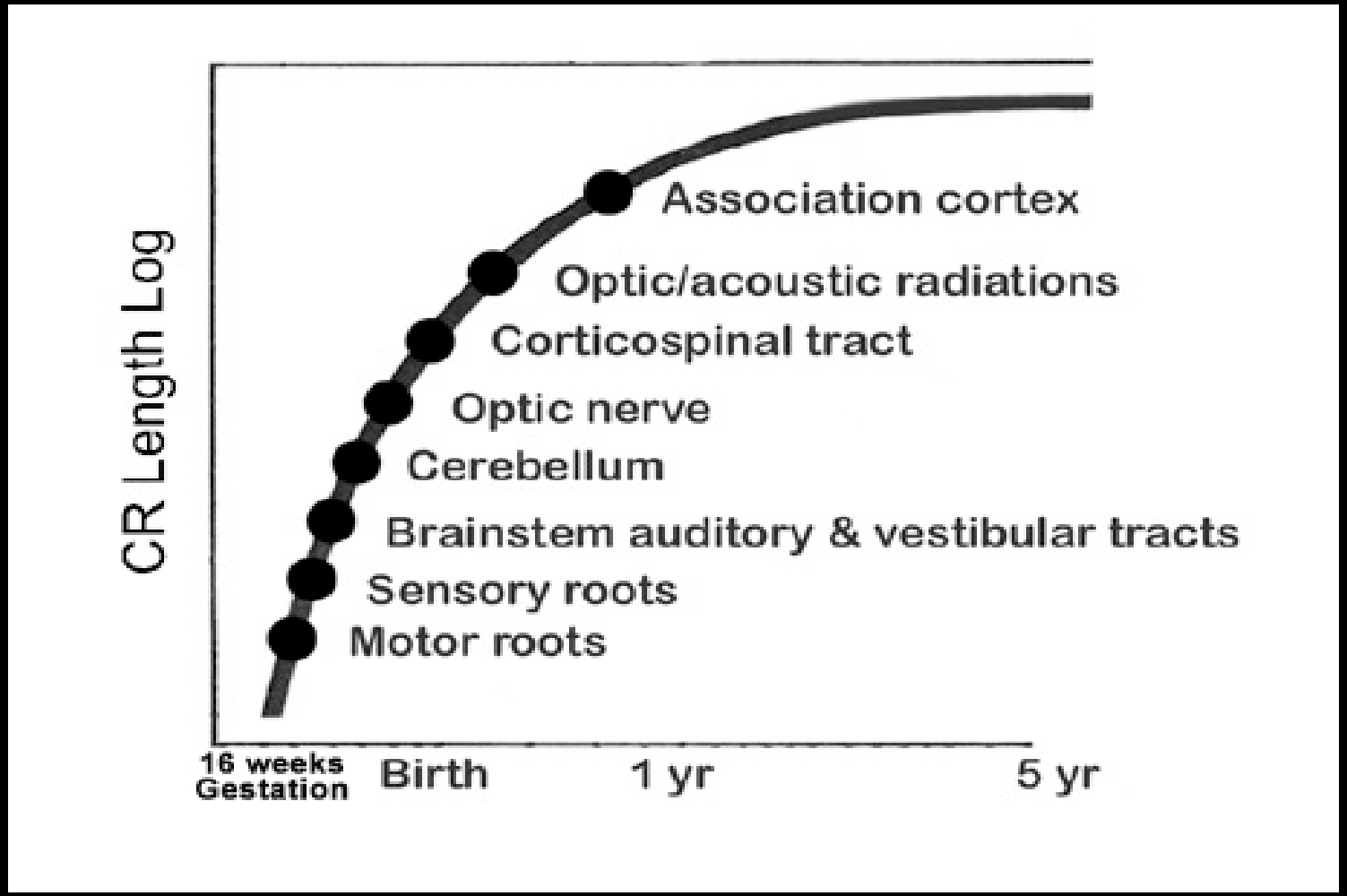


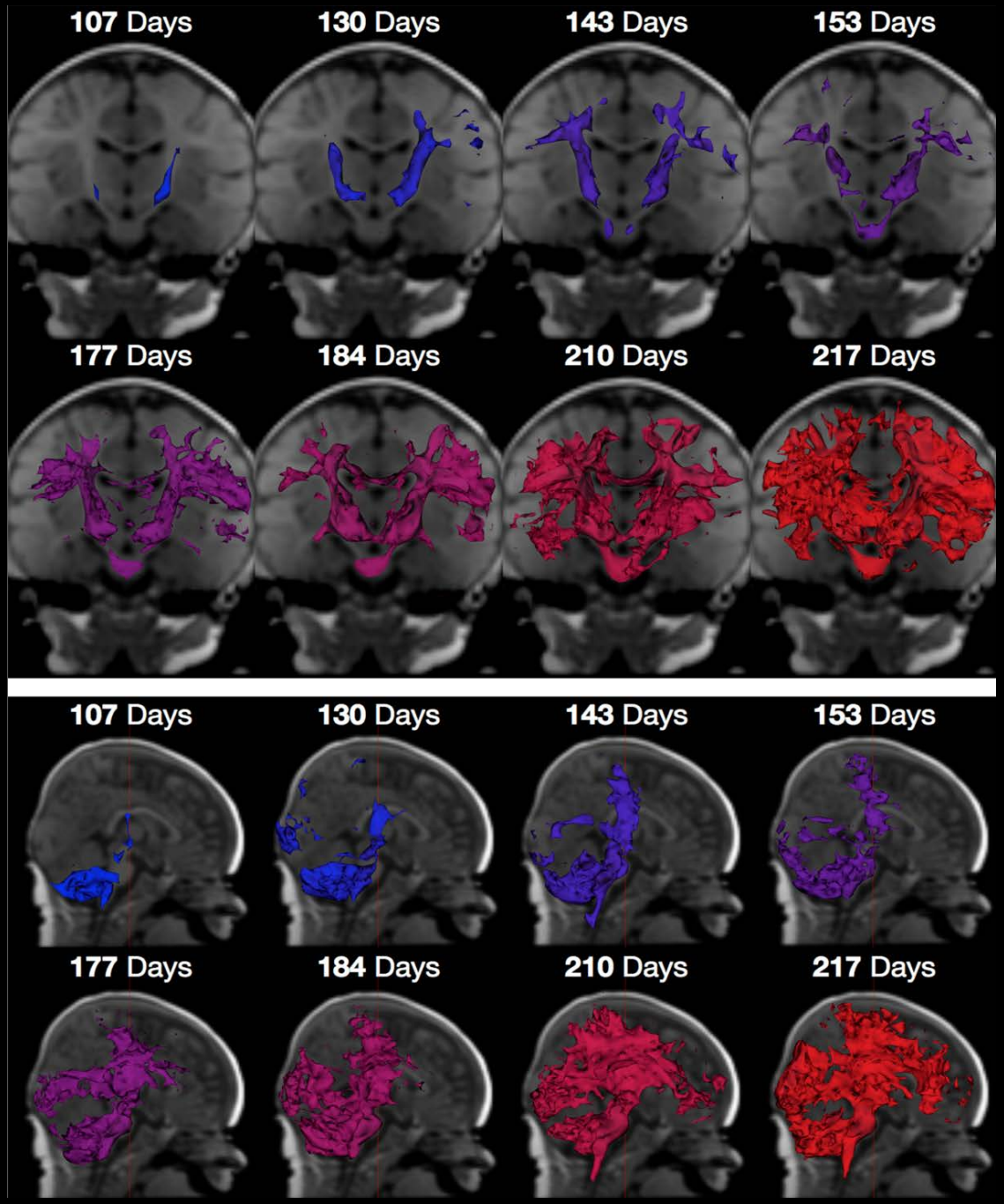
T_2-FLAIR

Z-Score Map

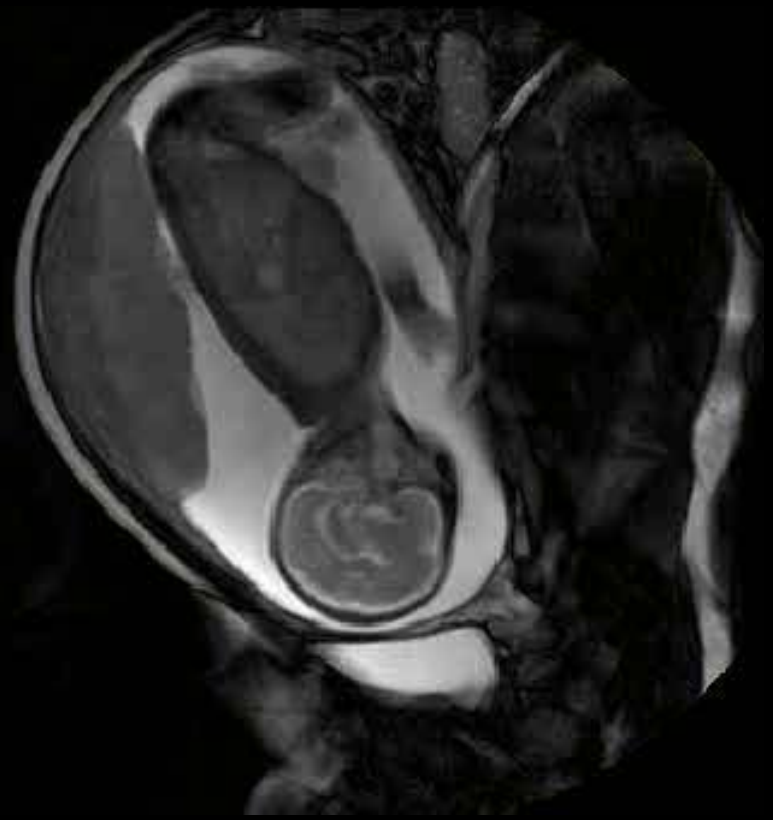
EDSS Score: 6.5

Myelination Trajectory – During Early Development

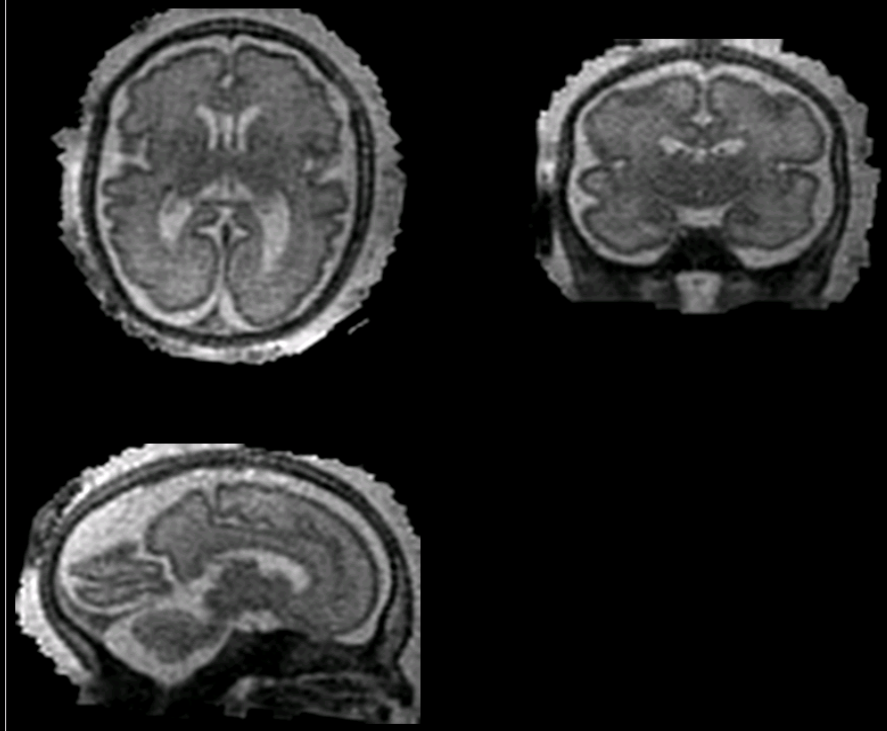



107 Days
130 Days
143 Days
153 Days
177 Days
184 Days
210 Days
217 Days
107 Days
130 Days
143 Days
153 Days
177 Days
184 Days
210 Days
217 Days

28 week foetus imaged *in utero*



Real time observation



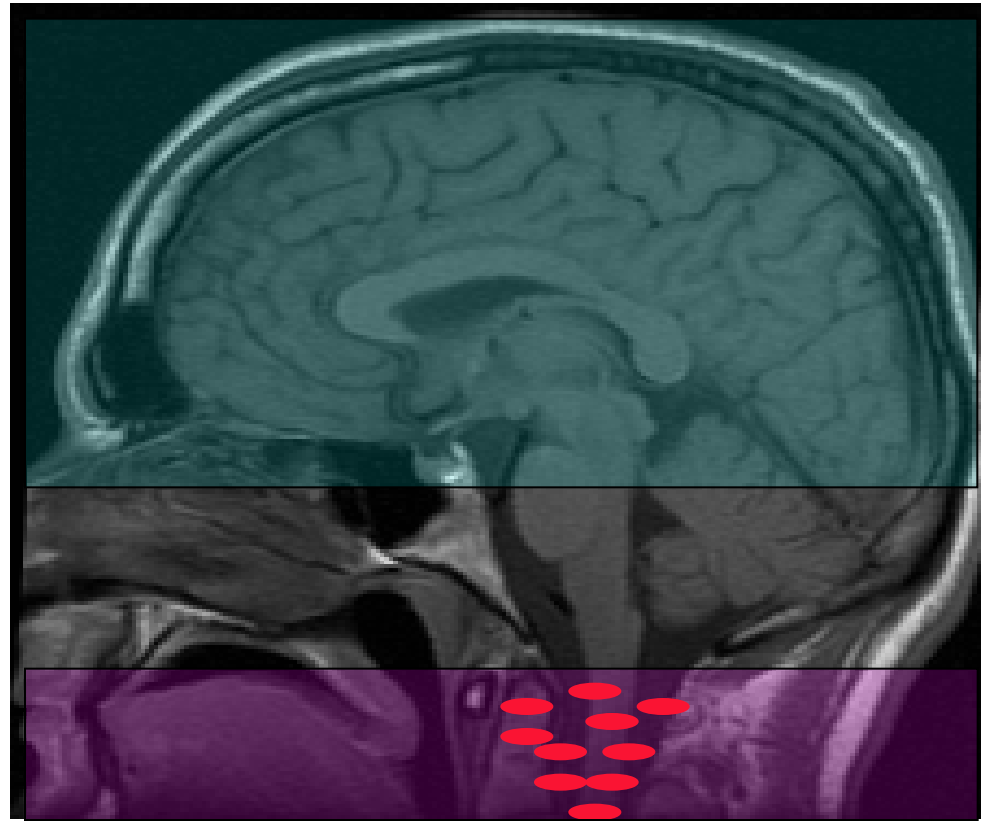
SVReconstructed 3D brain images

Jiang, S. et al. IEEE Trans Med Imaging, 26(7), 967-980 (2007)

Arterial Spin Labelling (cASL)

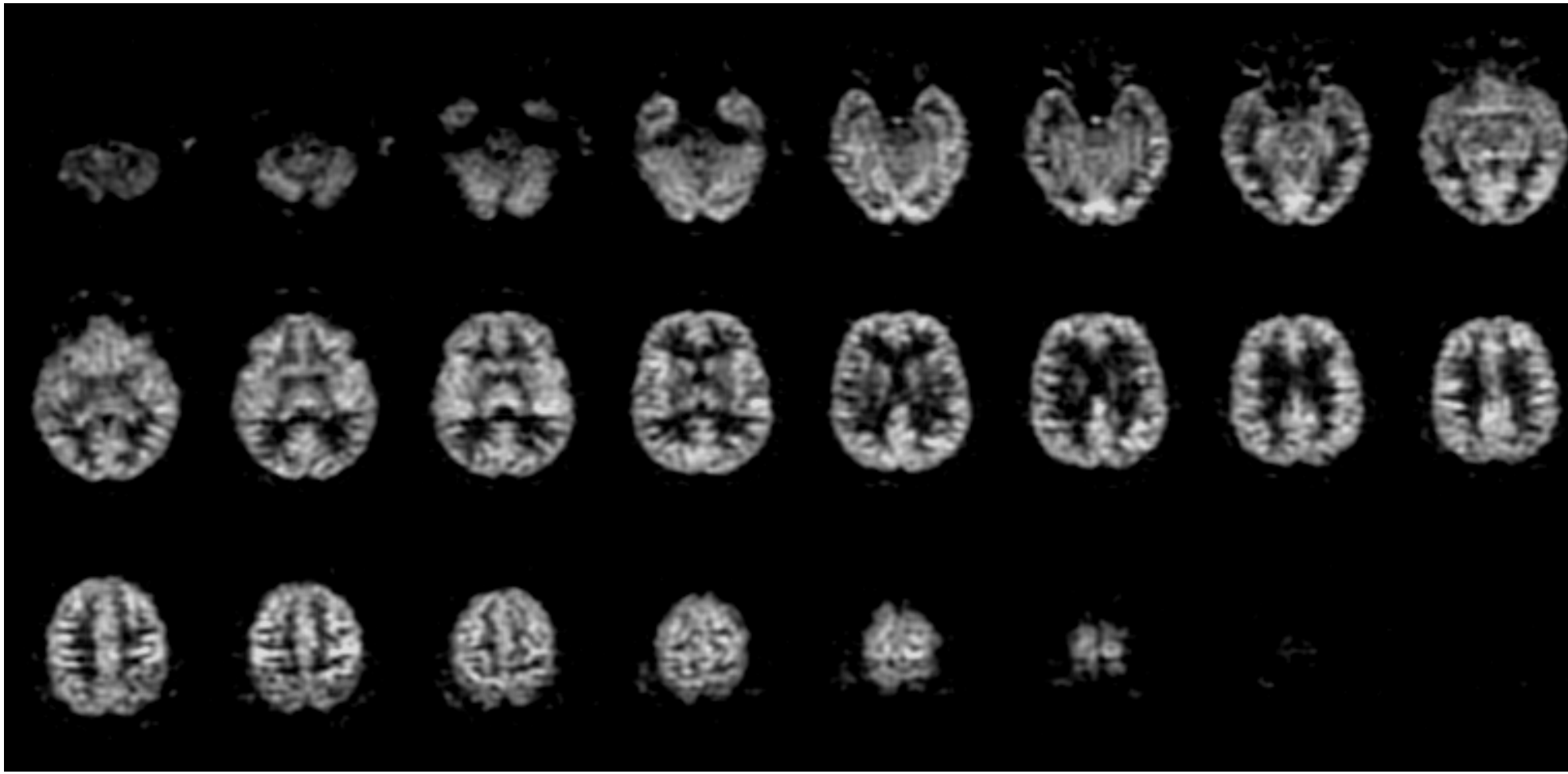
IMAGE ACQUISITION

MAGNETISATION OF BLOOD

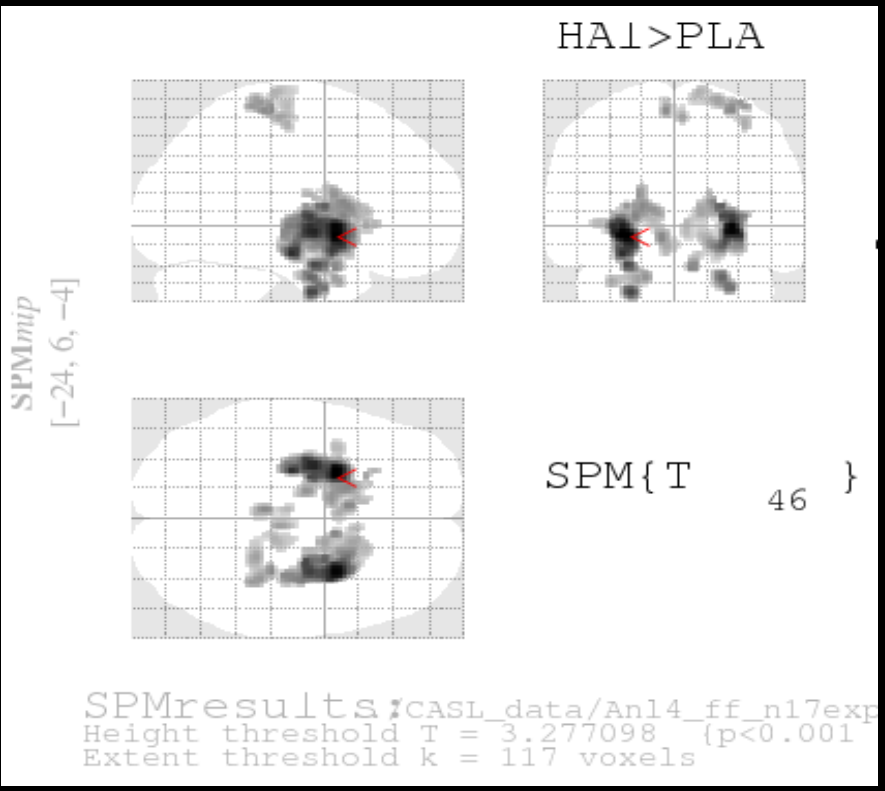


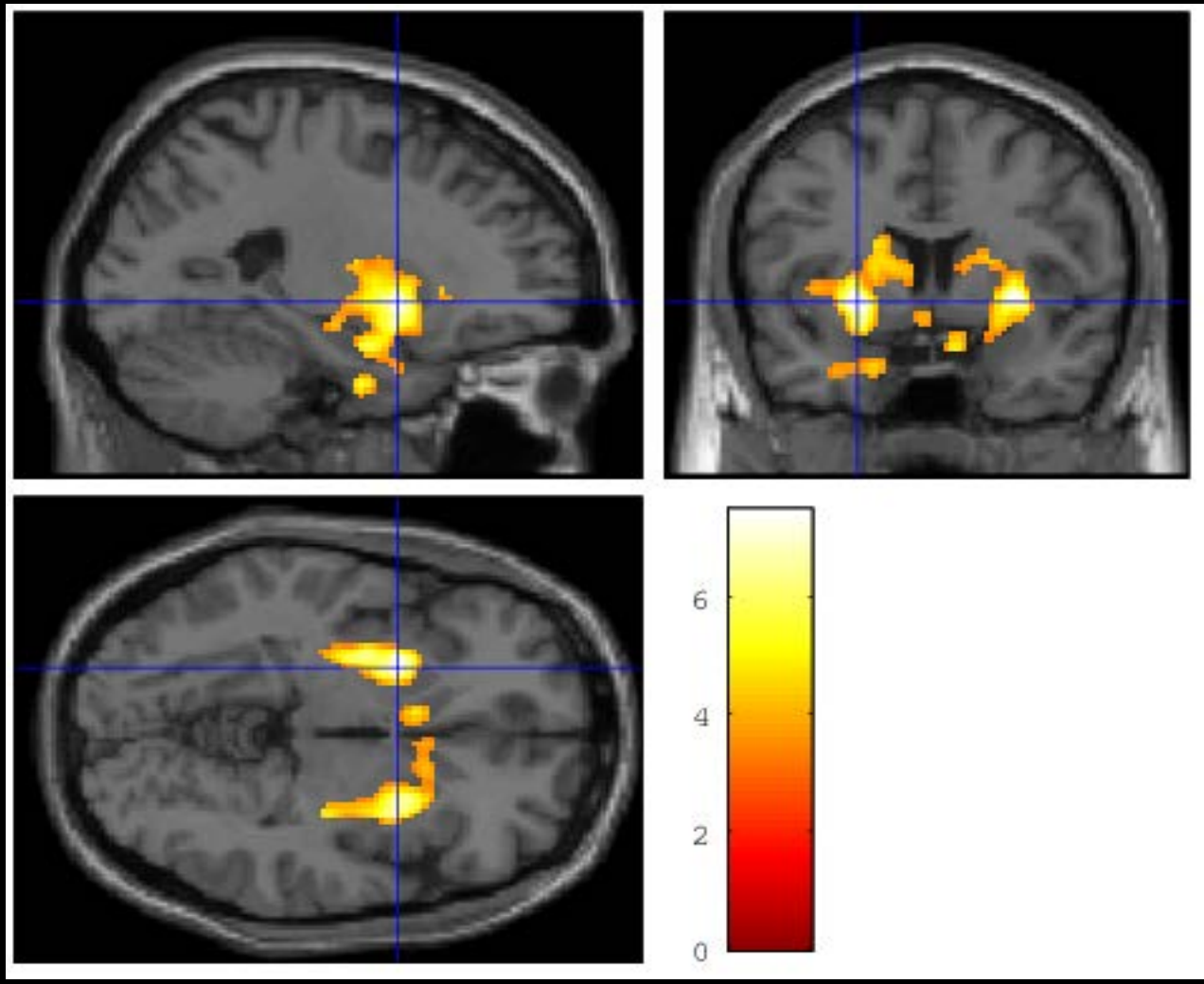
Allows us to quantify cerebral blood flow (CBF) changes

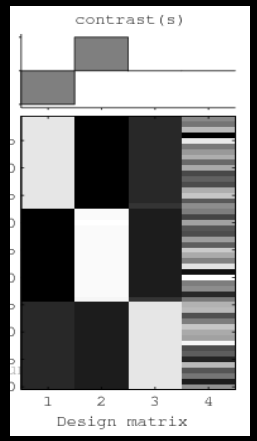
Quantitative CBF maps (ml/100g/min)



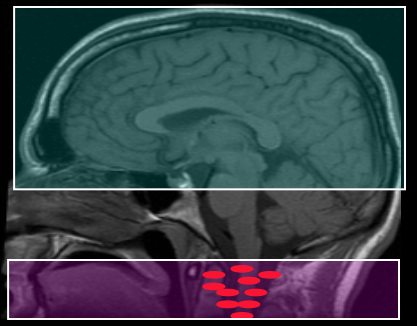
ASL : haloperidol > placebo

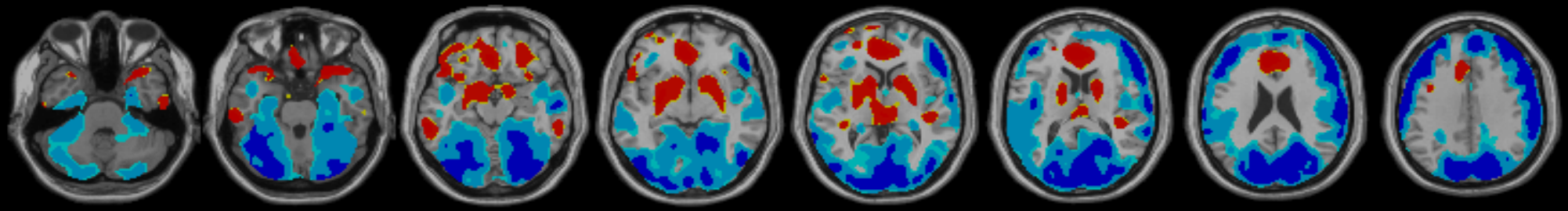






Drug Discrimination in ADHD



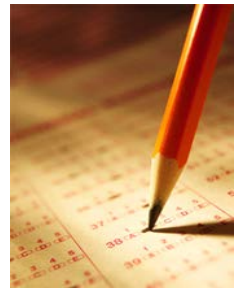


Methylphenidate / Placebo (100%)

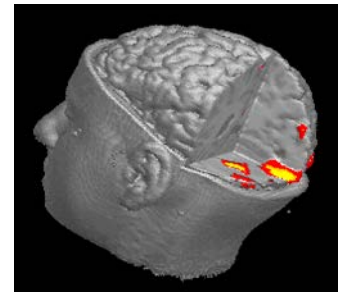
Atomoxetine / Placebo (93%)

Marquand et al. Neuoimage 2012

Pre-surgical visits



Ψassessment & screening



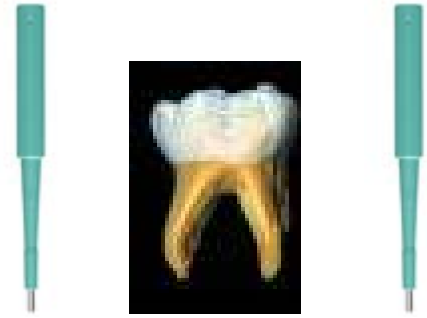
cASL assessment

post-scan RNA

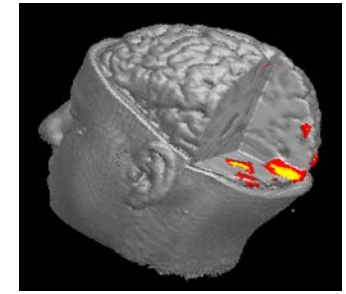
Surgical visits

Ψassessment & screening

pre-surgery RNA



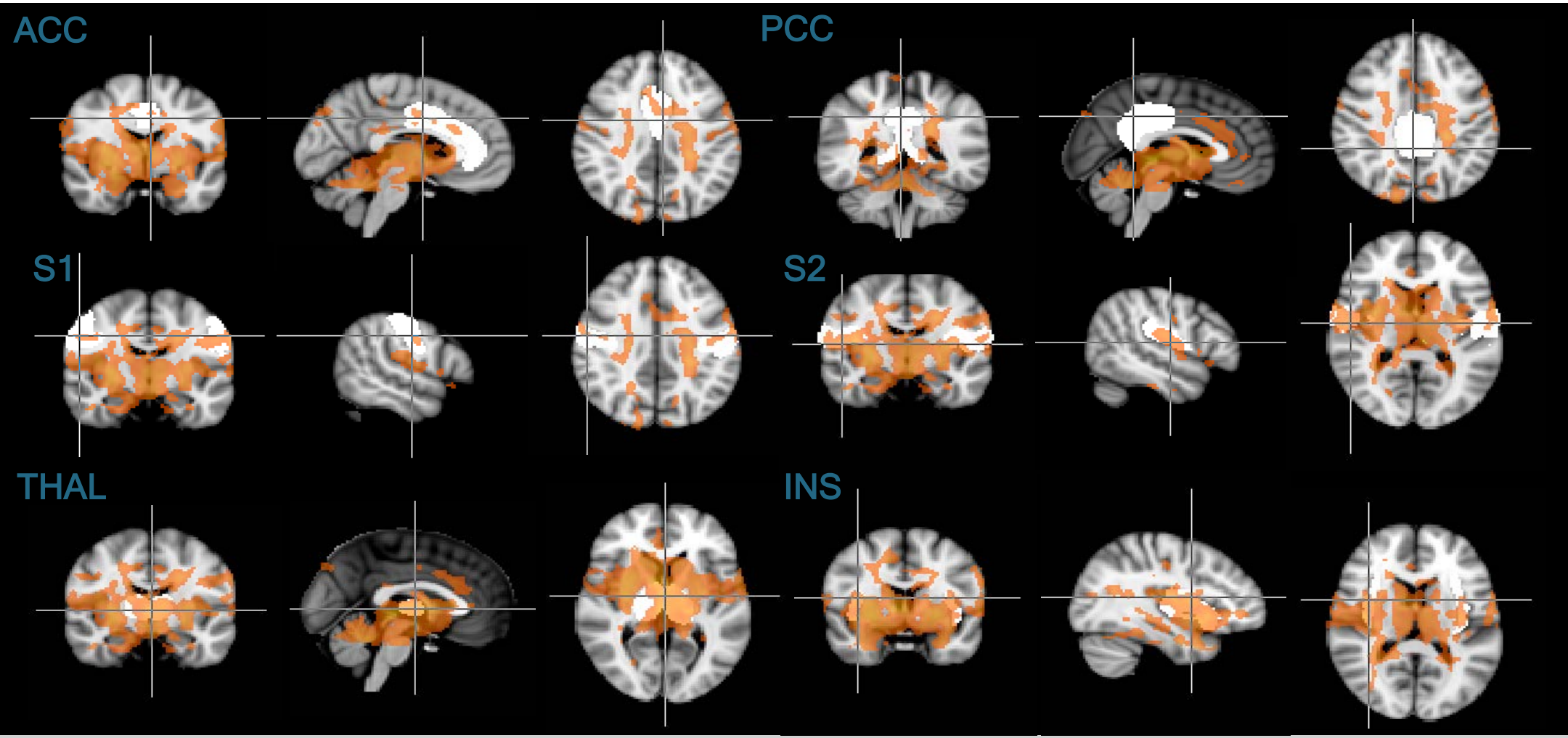
wisdom tooth extraction & mucosa sampling



cASL assessment

post-scan/surgery RNA

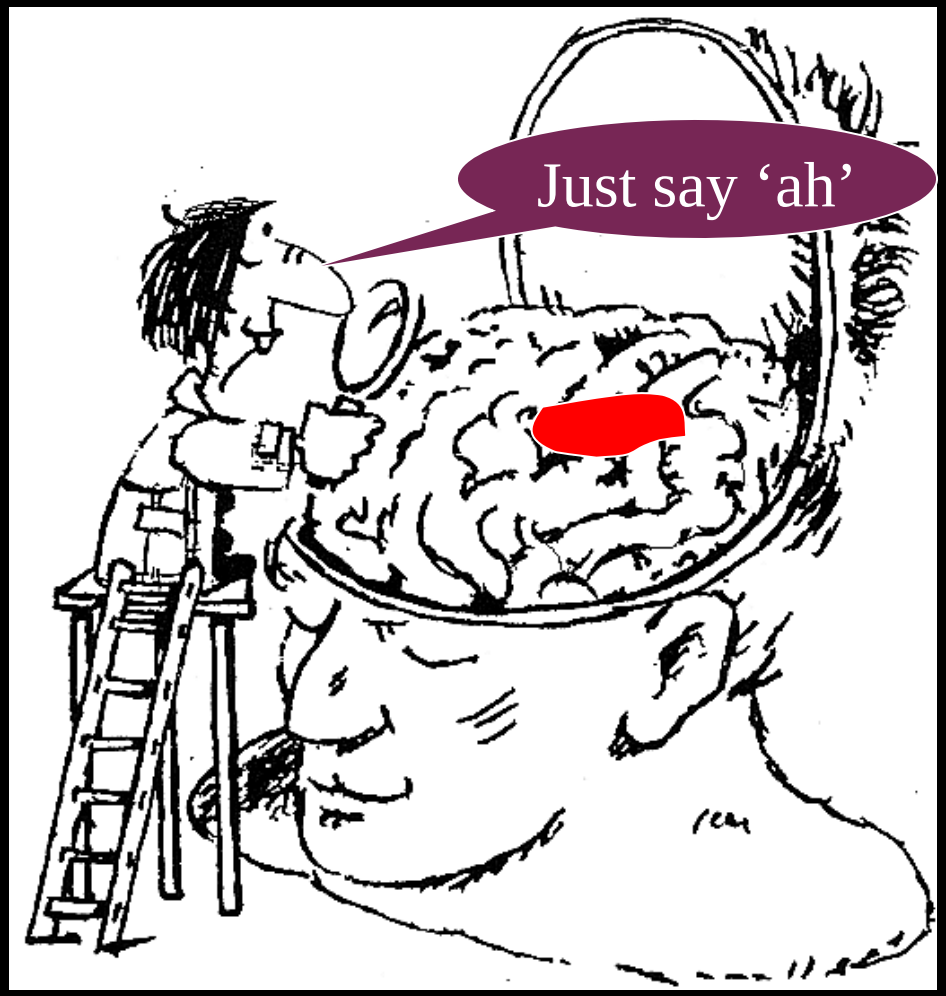
Dental Pain after 3rd Molar extraction



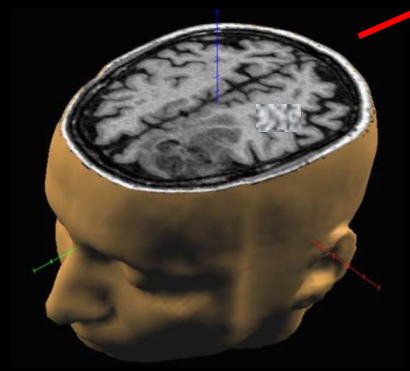
Whole brain imaging of on-going pain – a new biomarker for analgesia

Tara Renton, Matt Howard & Pfizer

FMRI – A Window into the Mind

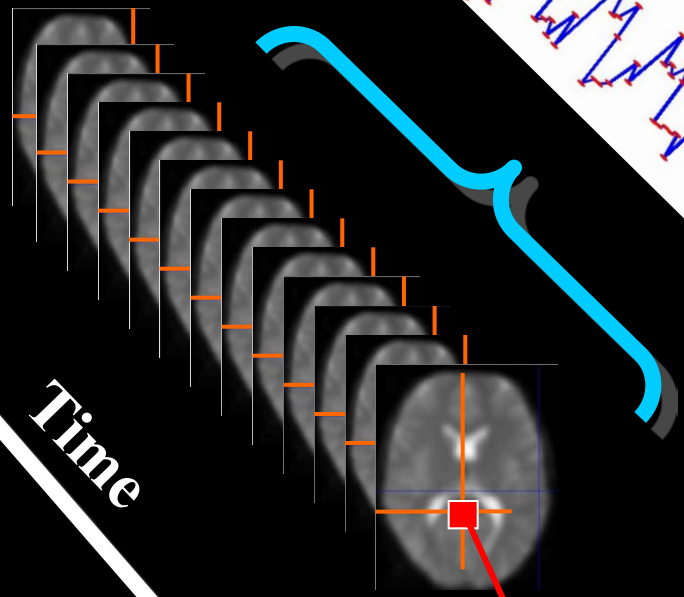


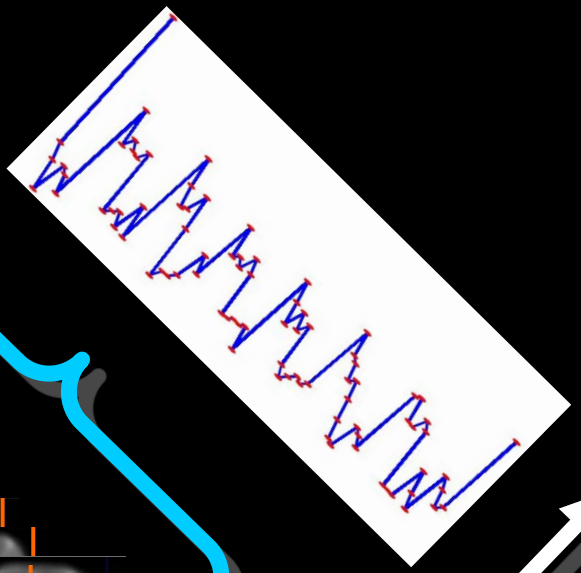
Classical Approach to FMRI collection and analysis: mass-univariate



Slice

fMRI Data



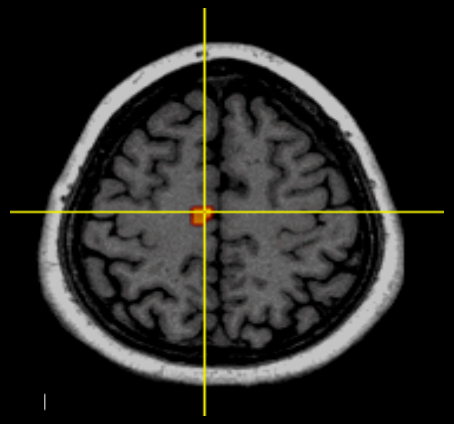


Time

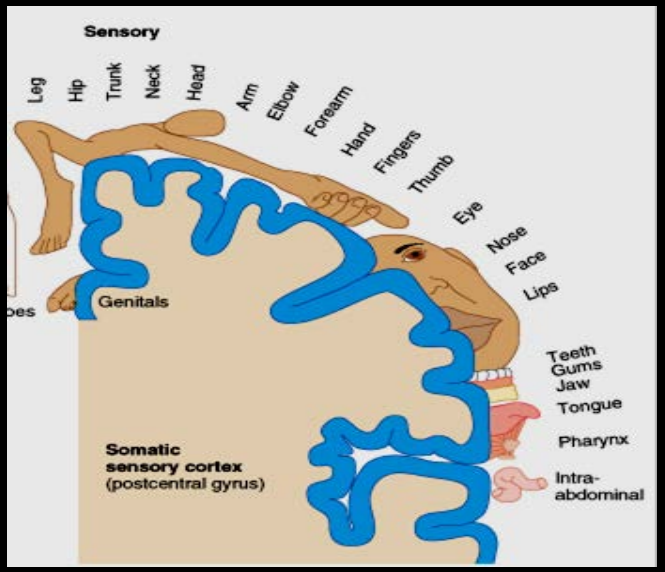
Intensity
BOLD signal

Voxel

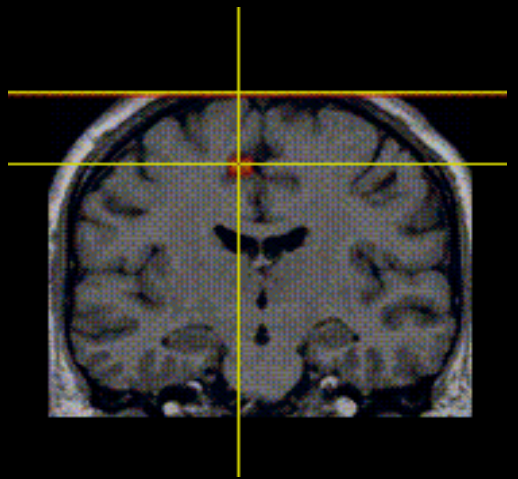
Somatic Stimulation and fMRI



Tal: X= -6, Y= -12, Z= 52

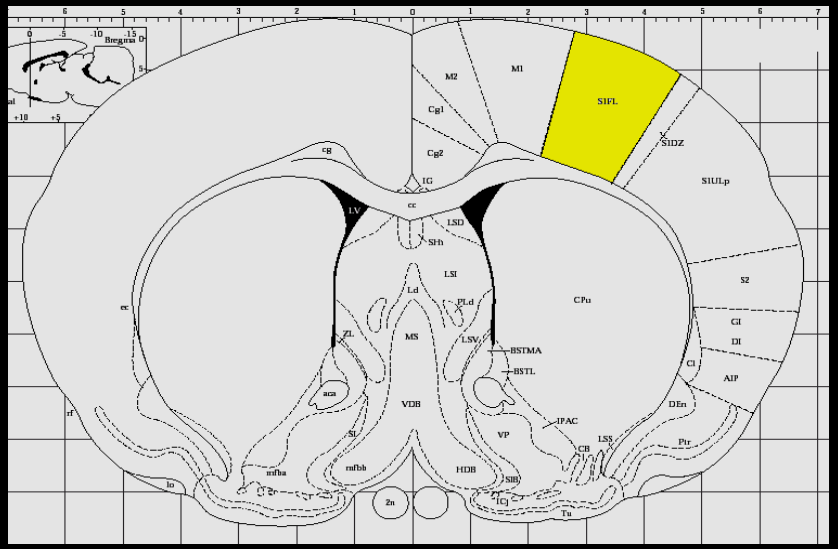


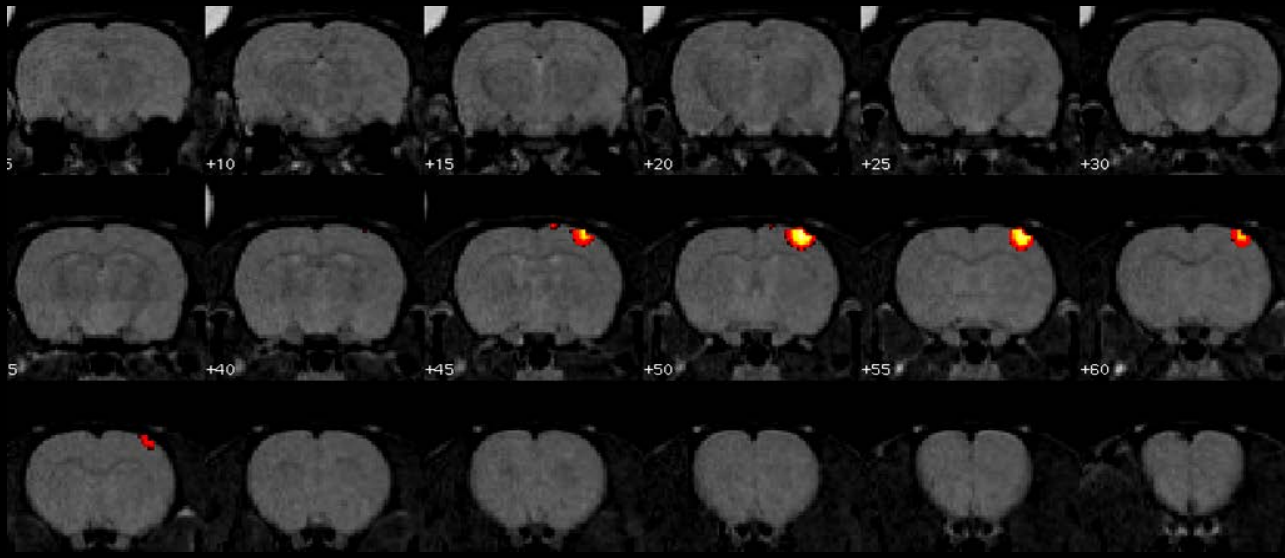
Somatotopic Organization of the Human Cerebrum



Tal: X= -6, Y= -12, Z= 52

Sensory MRI in the Rat

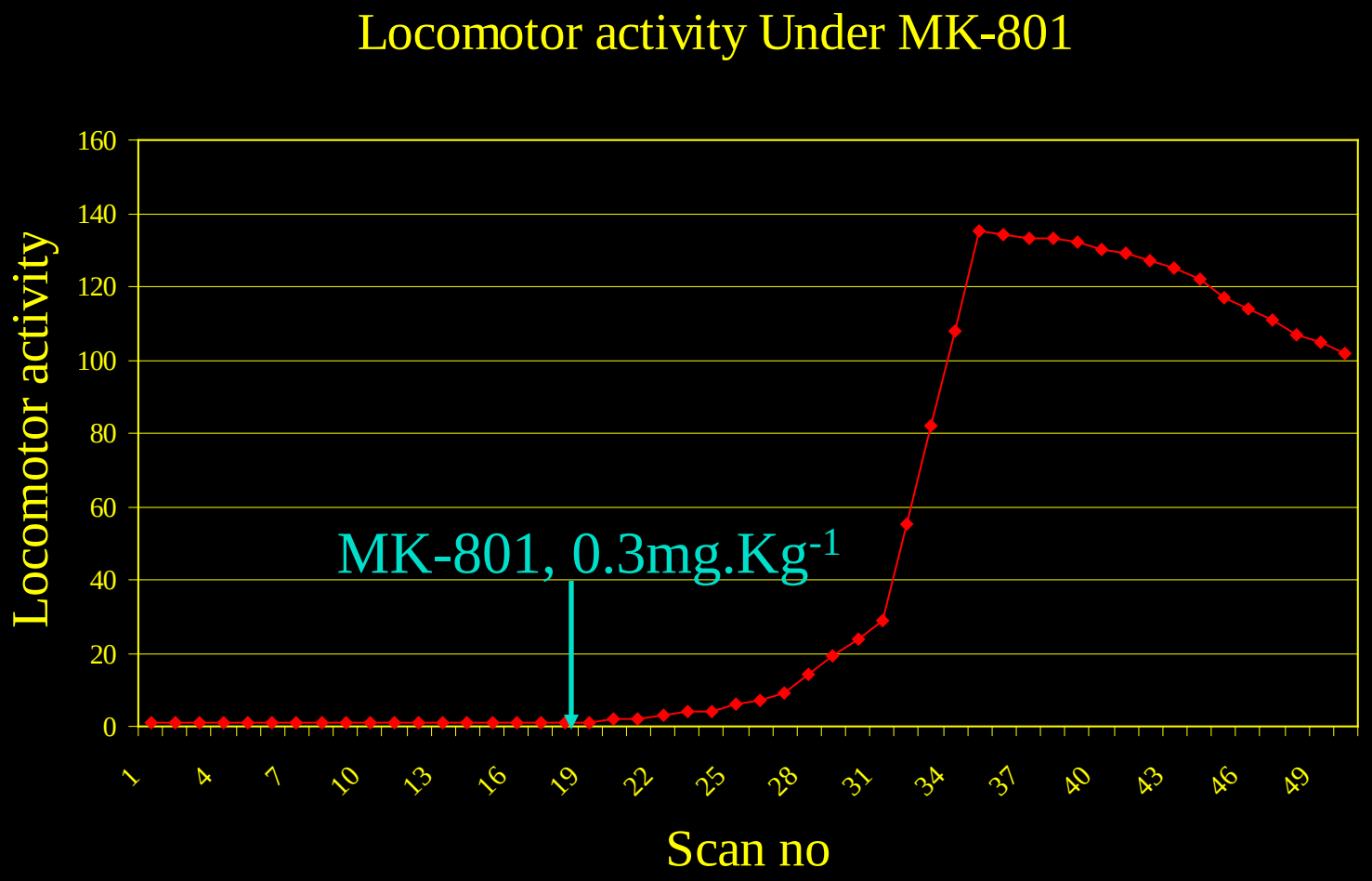


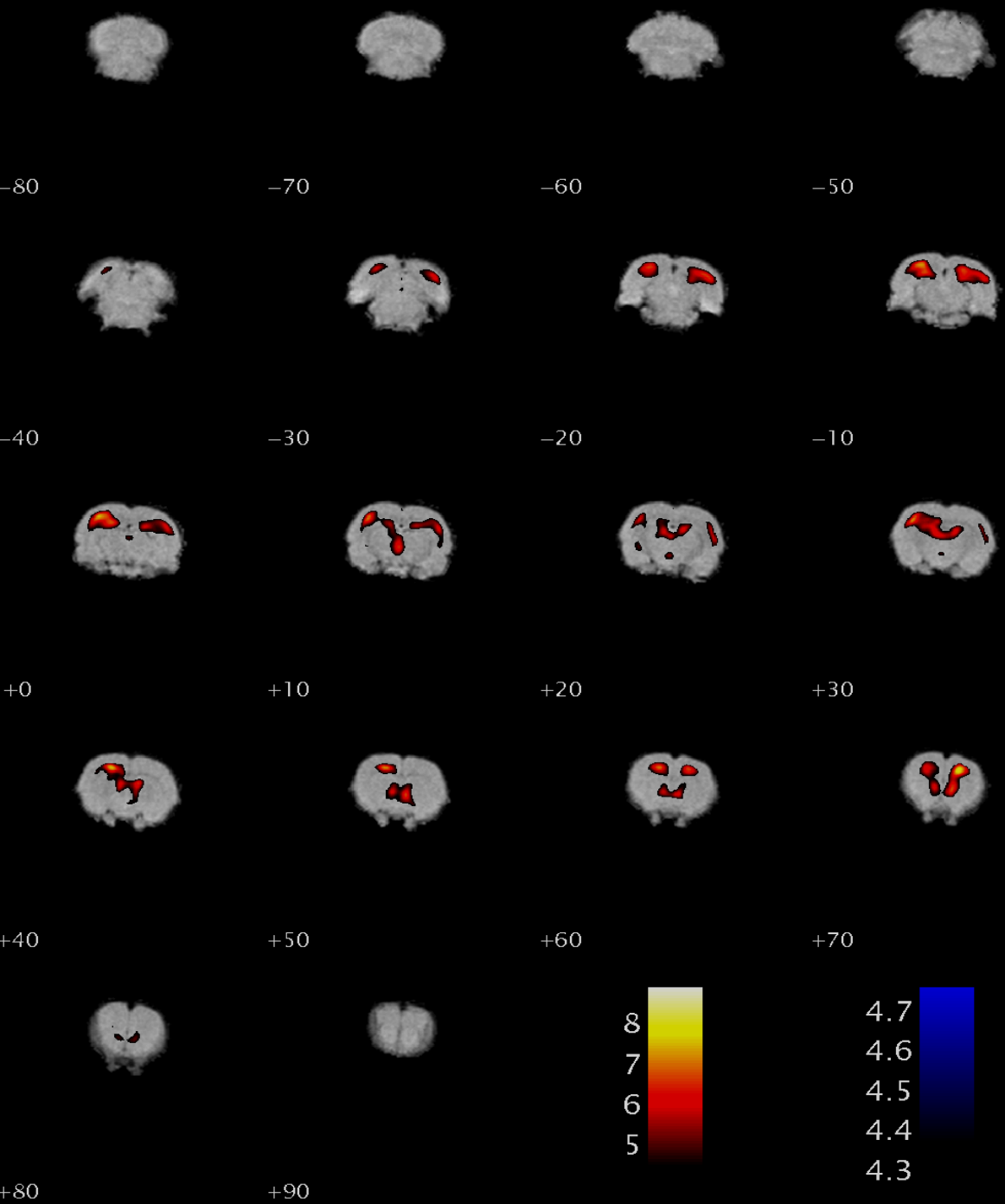


Paxinos & Watson representation of forepaw somatosensory cortex

Activation after electrical forepaw stimulation

Pharmacological MRI (phMRI)

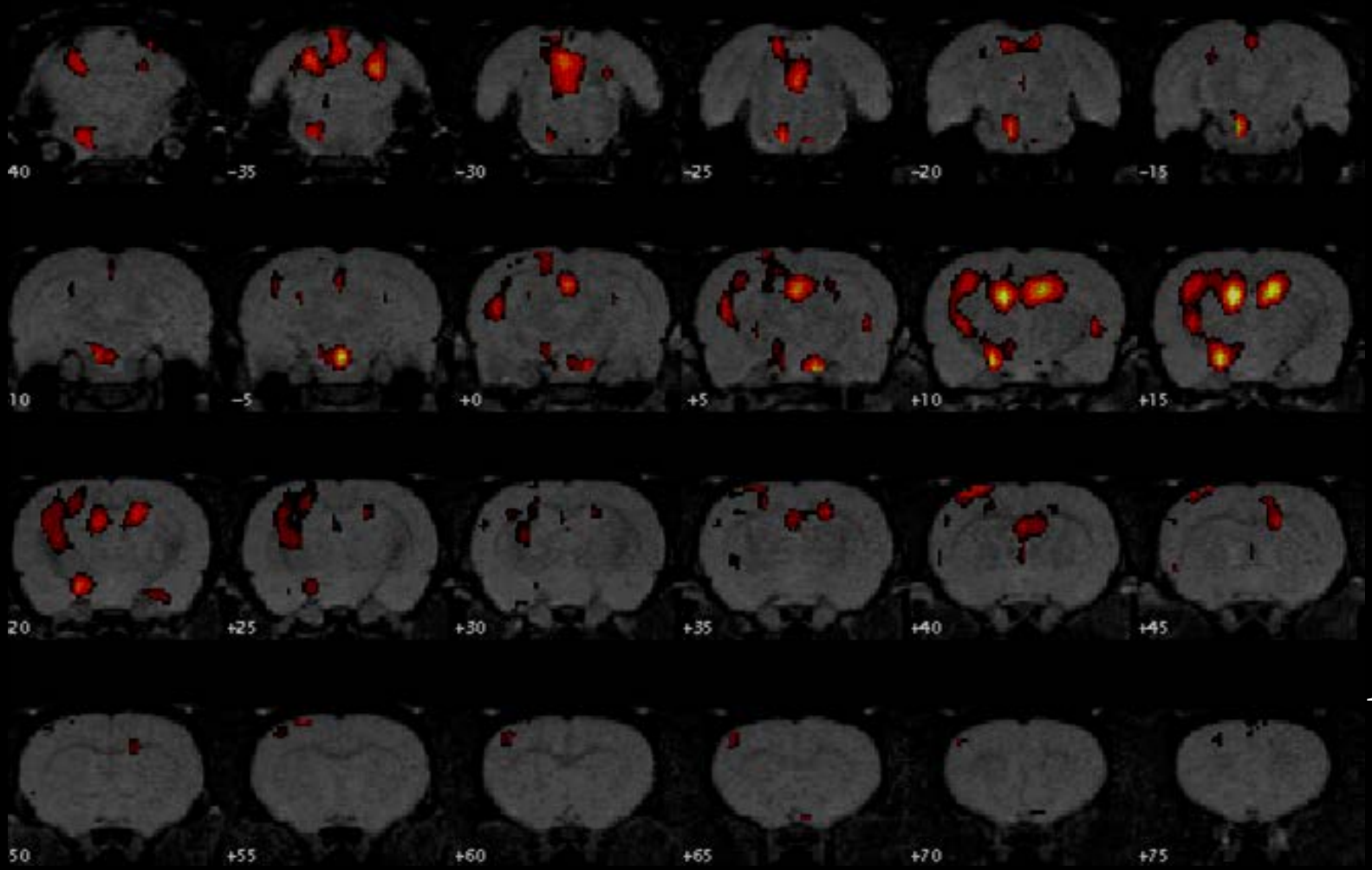




Main effect of the NMDA antagonist MK-801 (modelled to the animal behaviour for n=5)

Toby Roberts

Main effect of LY404187 - an AMPA potentiator



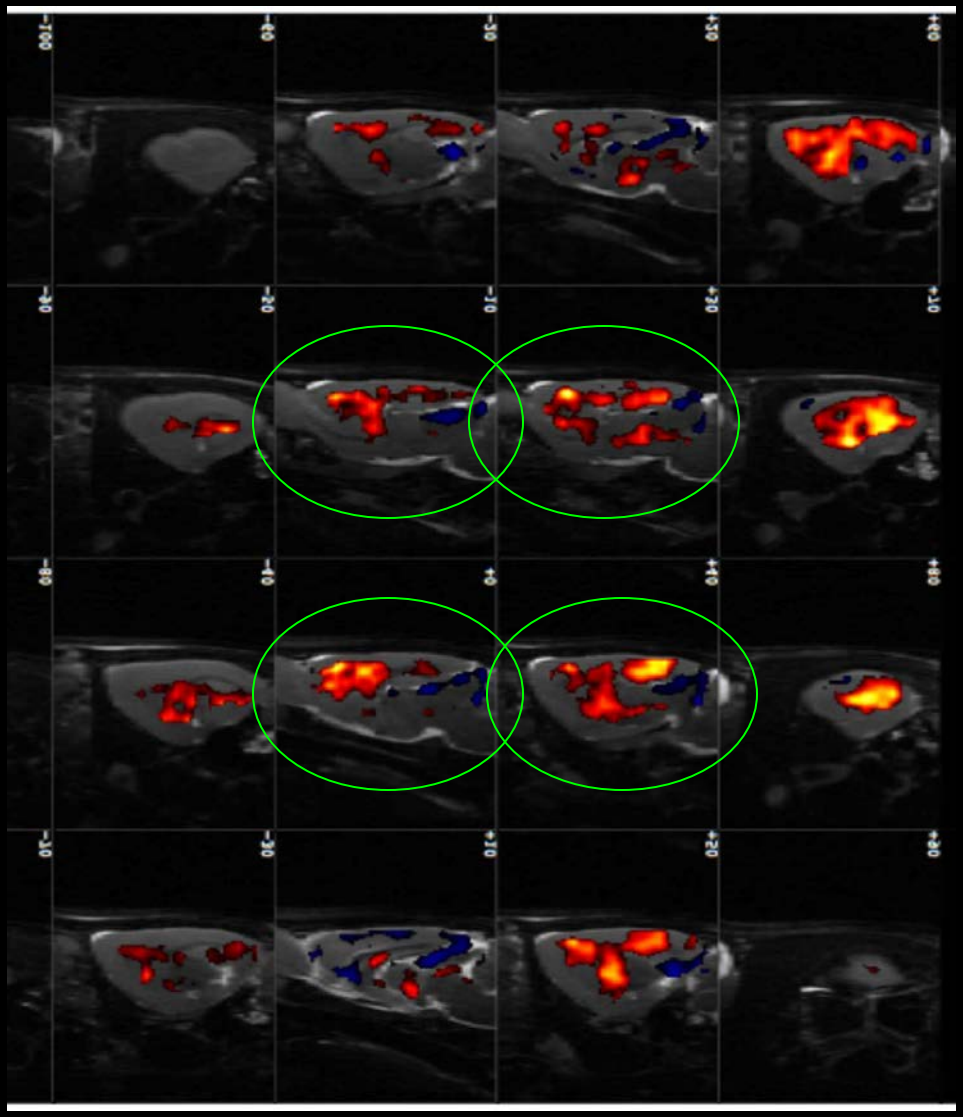
n = 7
0.5 mg/kg s.c.
hippocampus,
habenulae
and colliculi

blocked by
selective
AMPA antagonist
LY293558

Nick Jones

Correspondence to autoradiography (H3 antagonist)

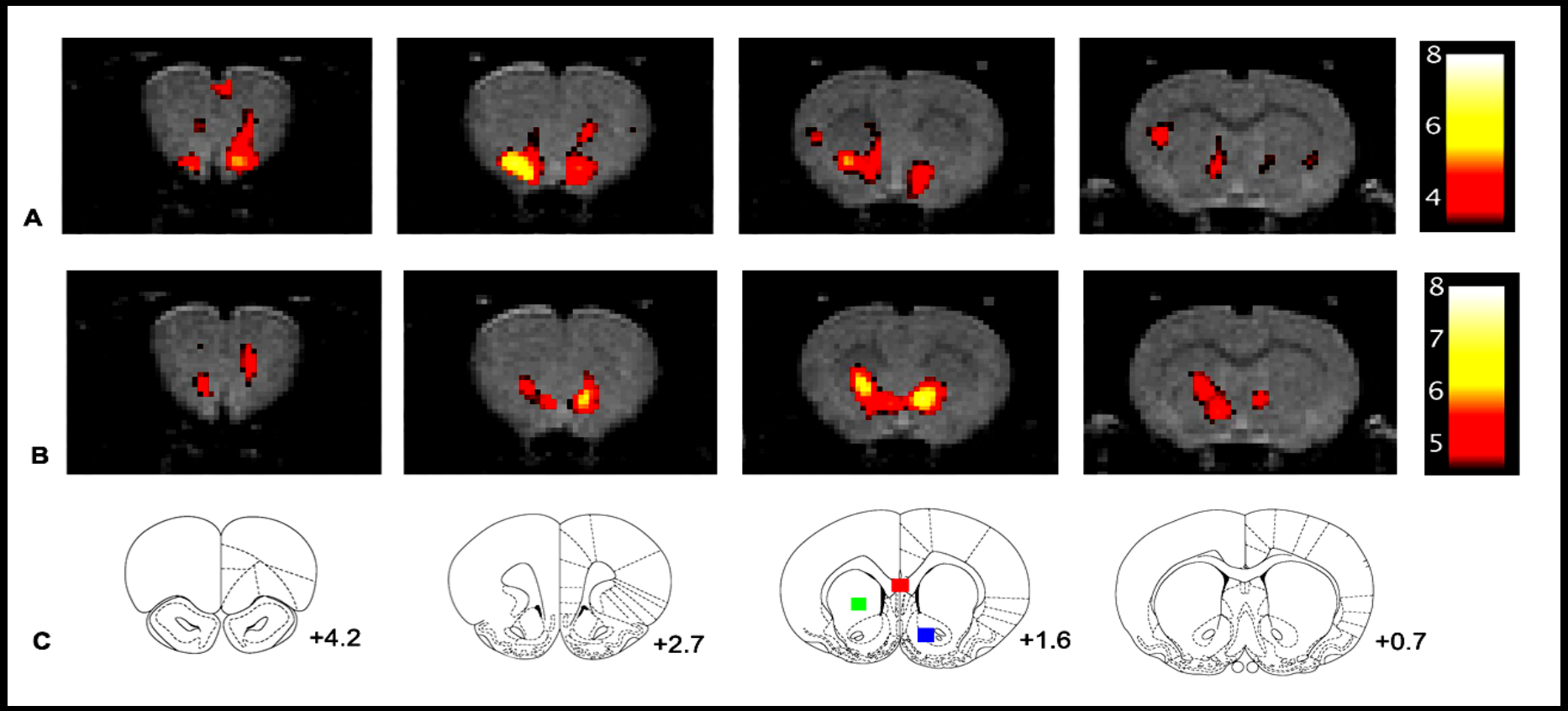
1nM 3H-GSK189254-A
Sagittal section



Pharmacological MRI of Quinelorane

D3

D2/3



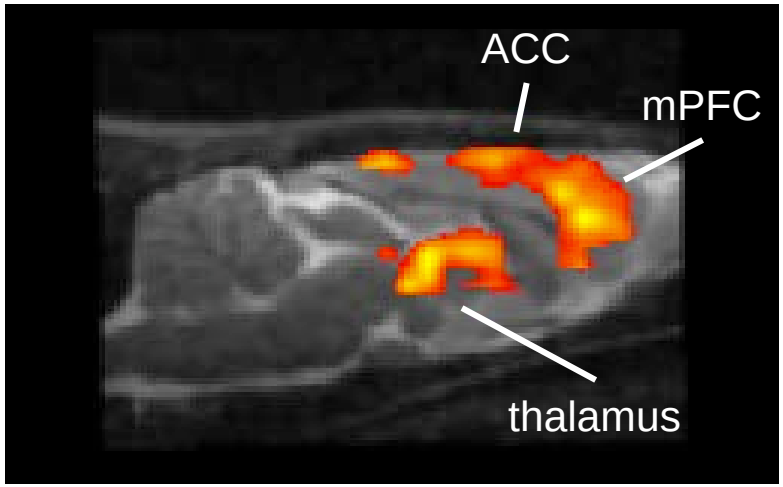
Group statistical parametric maps showing statistically significant increases in BOLD contrast after administration of 3µg/kg quinelorane (A), or 30µg/kg quinelorane (B) and corresponding rat brain atlas diagrams and co-ordinates relative to Bregma (C) (Paxions and Watson, 1996).

green=caudate-putamen, blue=nucleus accumbens, red=corpus callosum.

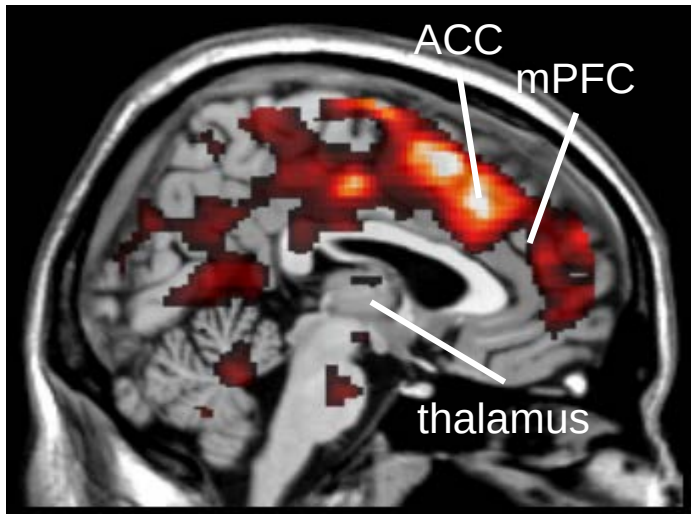
M.Ireland

Ketamine phMRI – rat vs man

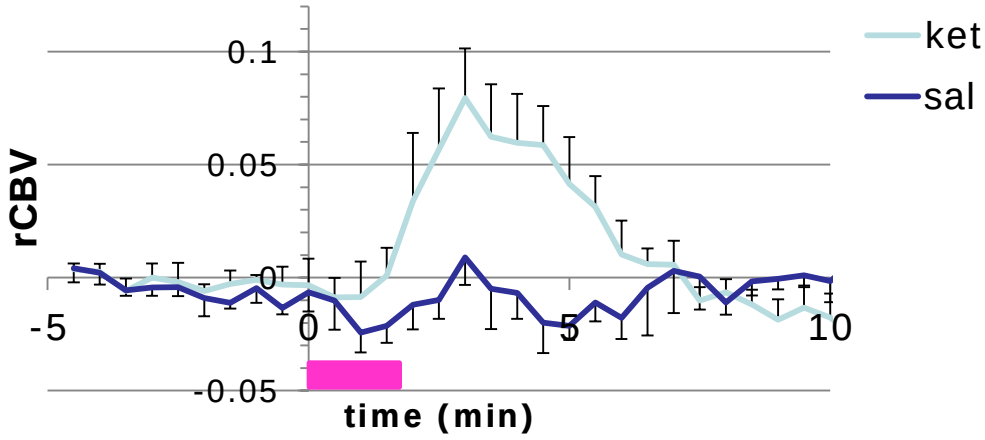
Rat



Human

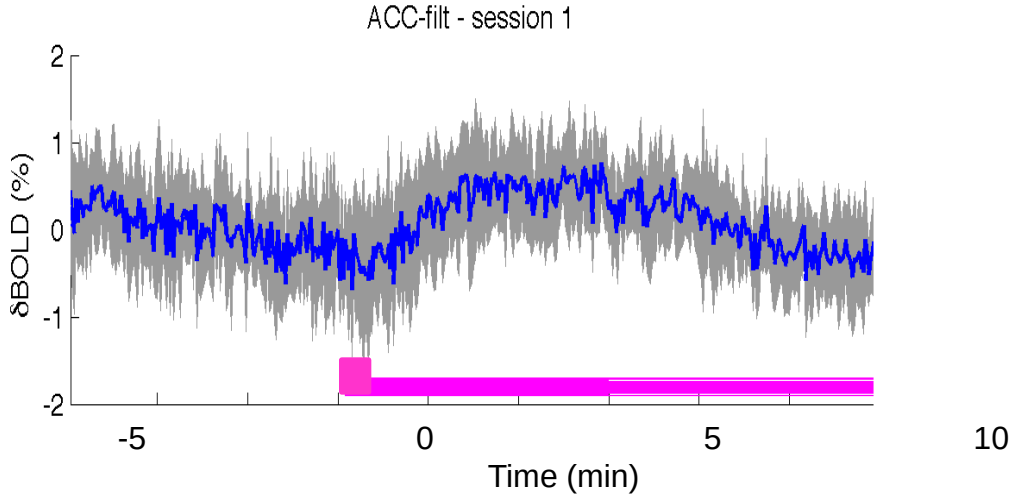


Cingulate cortex (N=5)



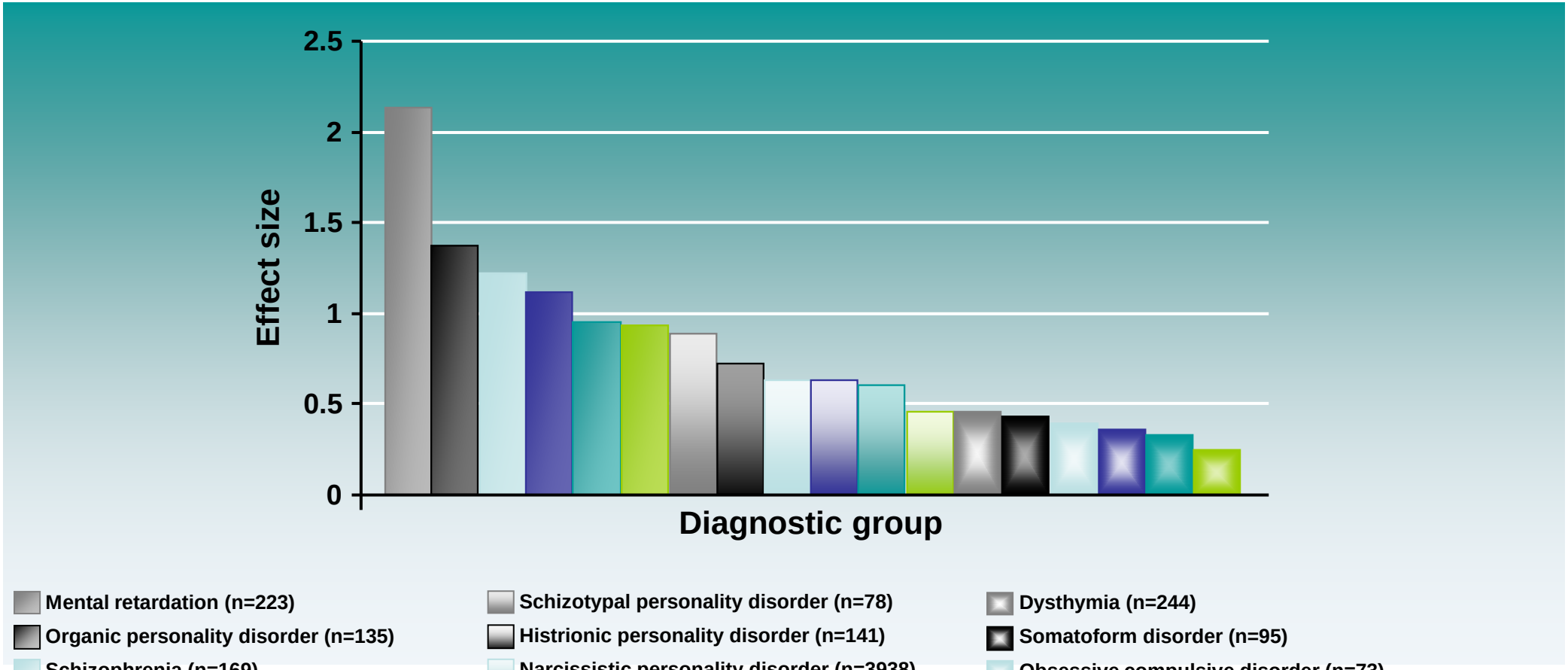
1mg/kg IV

Anterior cingulate cortex (ACC)



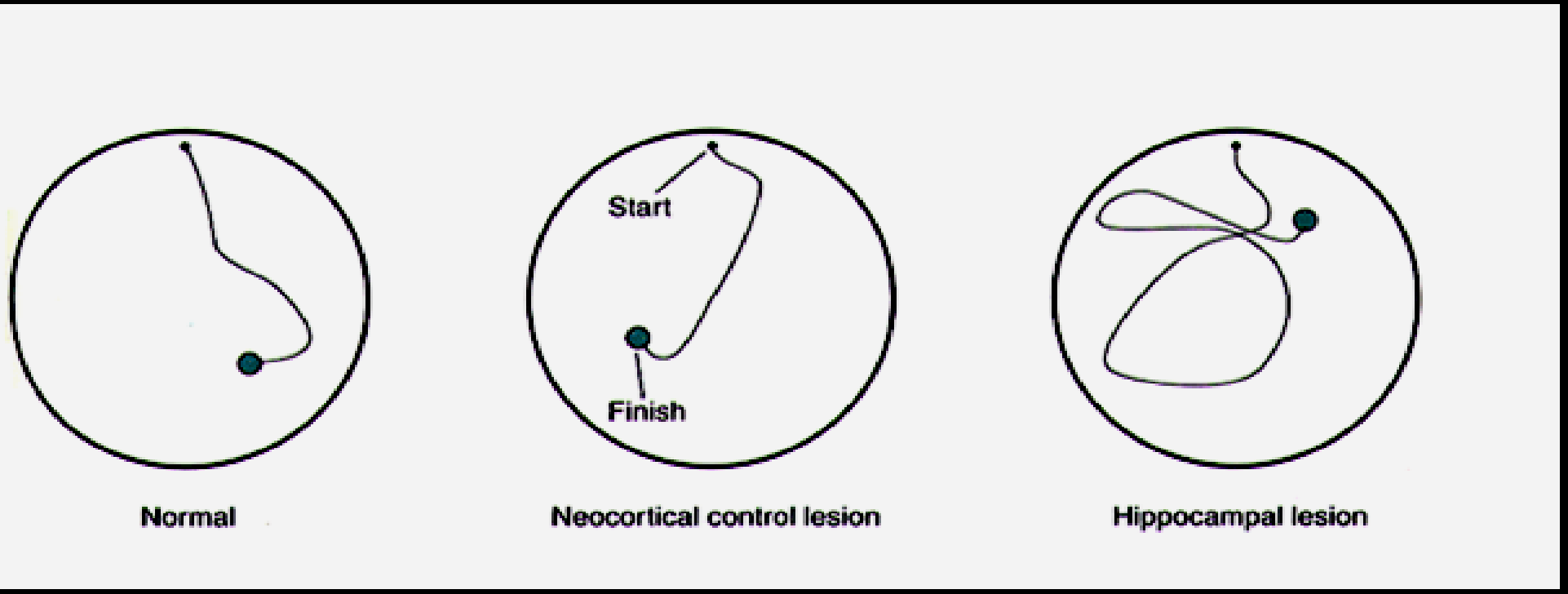
Clements Model → 75ng/ml

Cognitive impairment across all mental illnesses

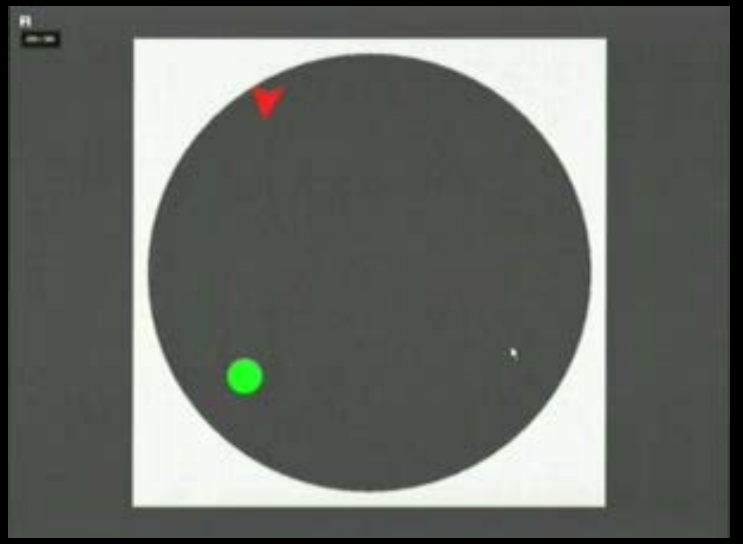


Mark Weiser, Michael Davidson et al., 2004

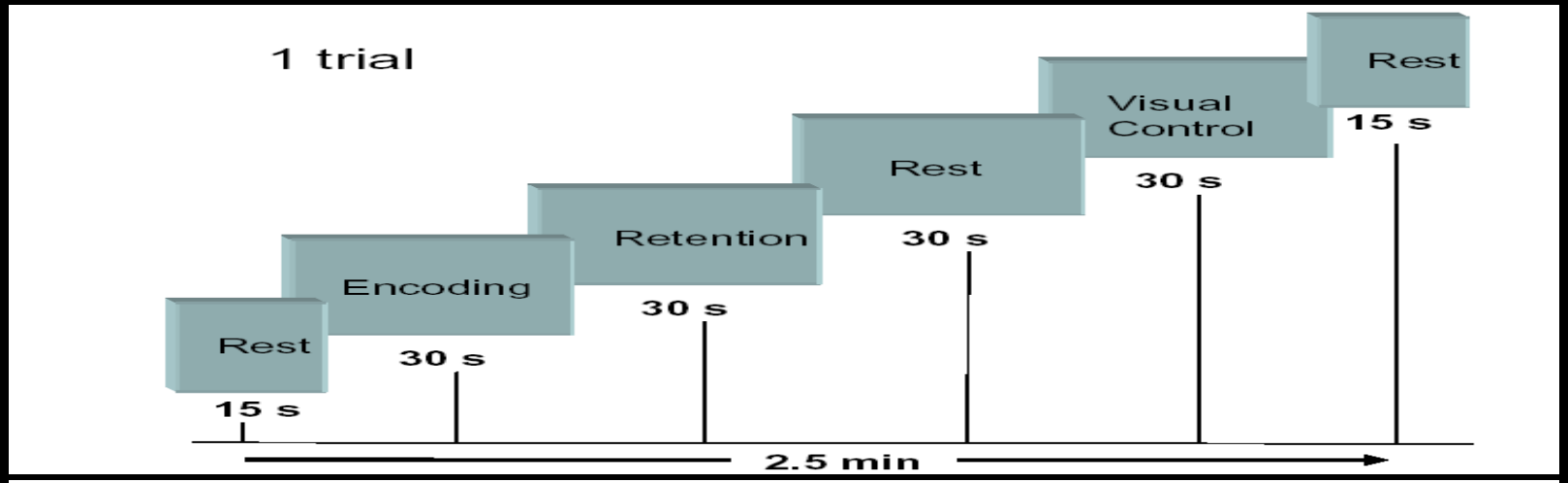
Morris Water Maze

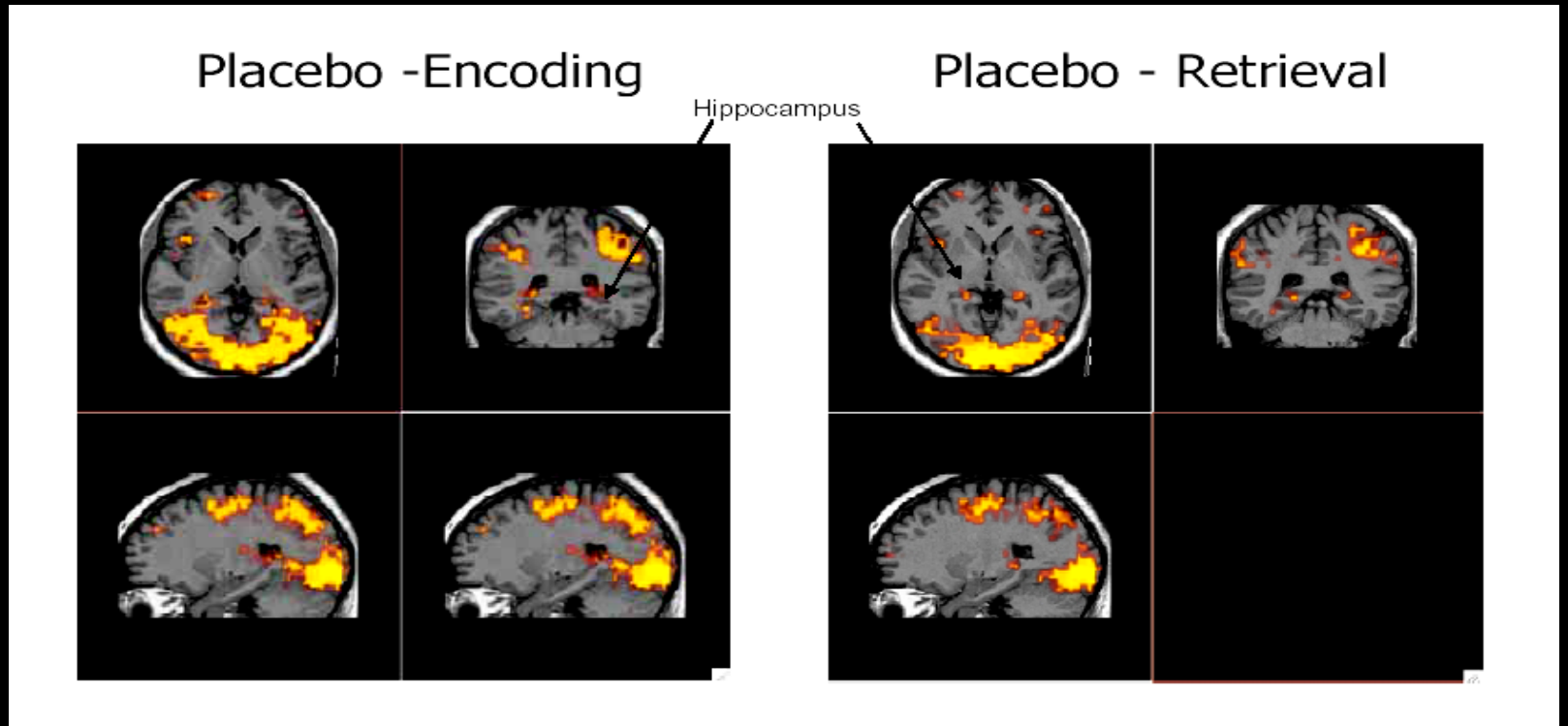


The Arena Task in the Scanner



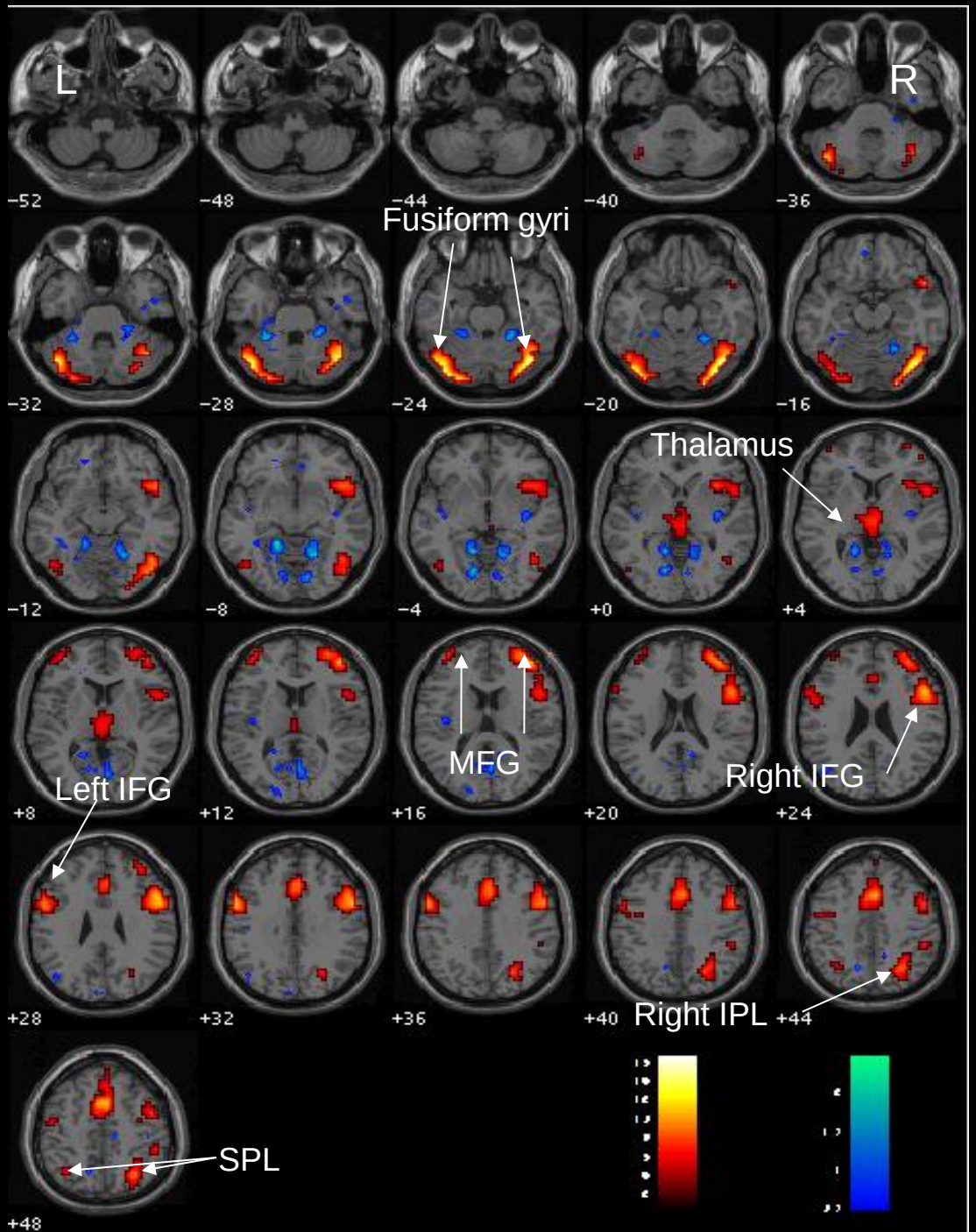
FMRI allows discrete investigation of encoding and retrieval in a human analogue of the Morris Water Maze

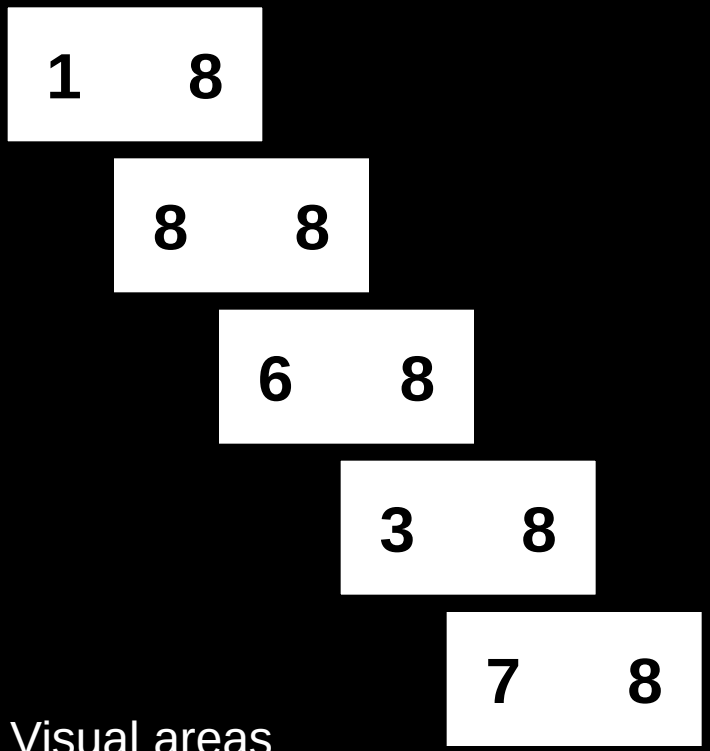





Time: 0.09
Crisps & Sn

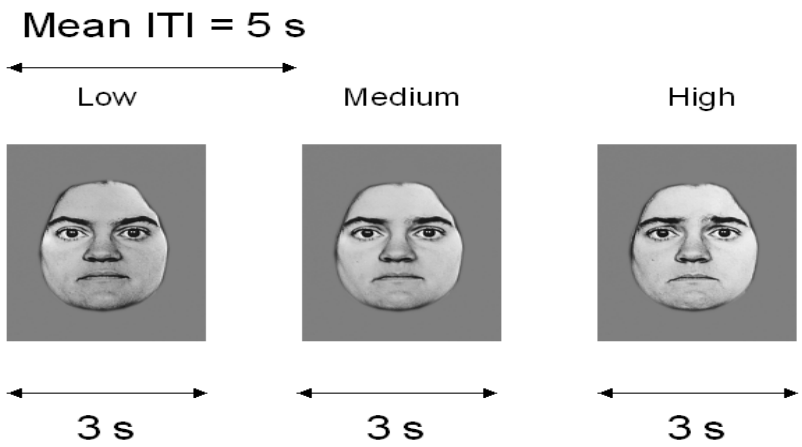
CDR – Digit Vigilance

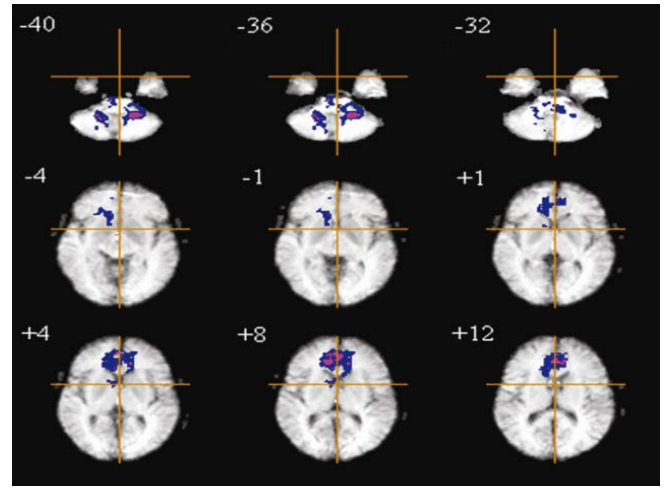




- Visual areas
- Bilateral inferior frontal gyrus
- Bilateral middle frontal gyrus
- Bilateral superior parietal lobule
- R inferior parietal lobule
- Thalamus (medial dorsal nuc)

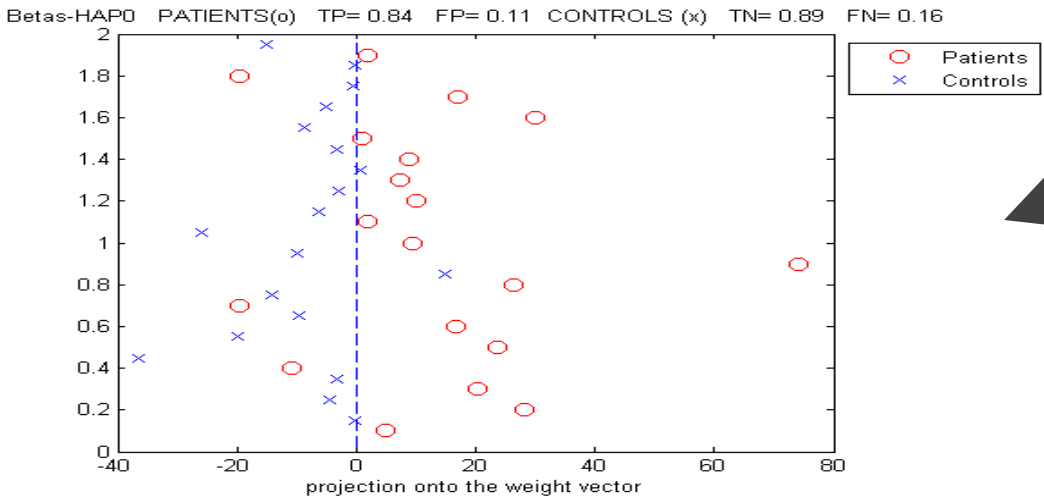
Automated Classification of Depression





"Look at the Face....Is it Male or Female?"

FMRI Response



Sensitivity 84%

Specificity 89%

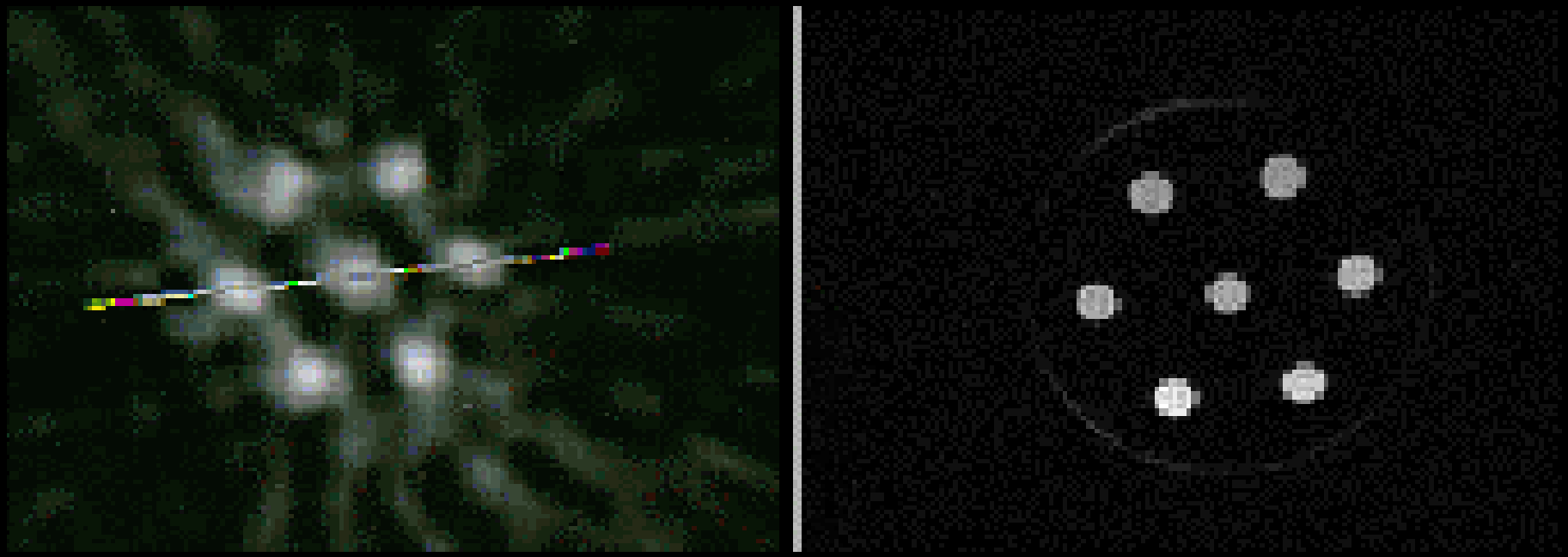
Mean Accuracy ~85%

C.H. Fu et al, Biol Psychiatry. 2008 Apr 1;63(7):656-62

Resting Metabolism

“PANDA” - Simultaneous PET and MRI

PET *MRI @ 4.7 T*



Paul Marsden, Diana Cash, Simon Cherry & Daniel Struhl

BUT :

MRI has limited spatial and temporal resolution !