

MR Neuroimaging from Mouse to Man – Facilitating the Pharmaceutical R & D Process



Institute of Psychiatry, Psychology & Neuroscience (IoPPN)

steve.williams@kcl.ac.uk

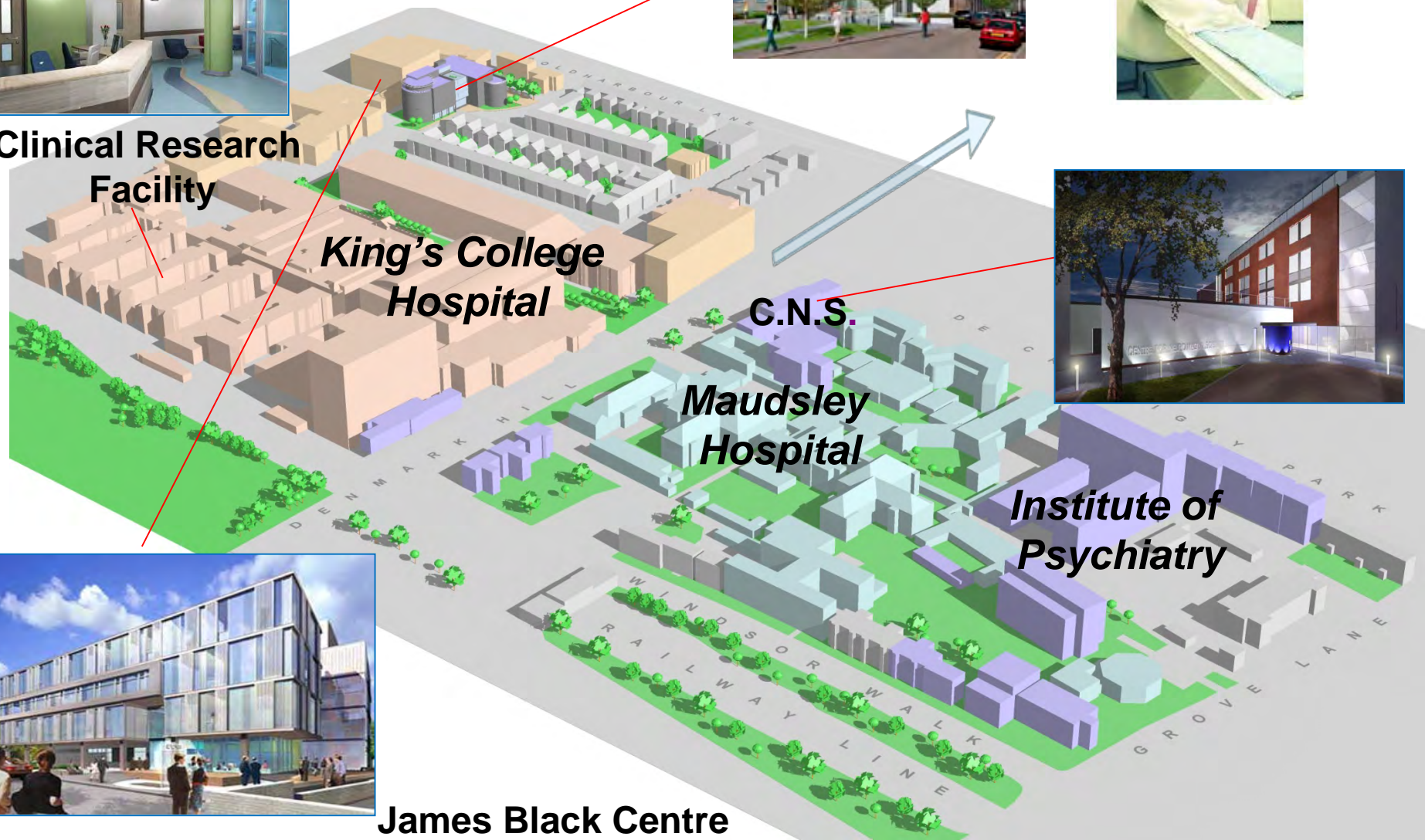
Imaging at Denmark Hill

St. Thomas' PET Centre

Maurice Wohl Clinical Neuroscience Institute



Clinical Research Facility



King's College Hospital

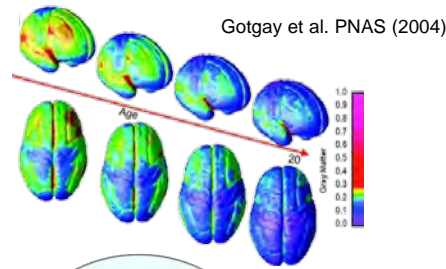
C.N.S.

Maudsley Hospital

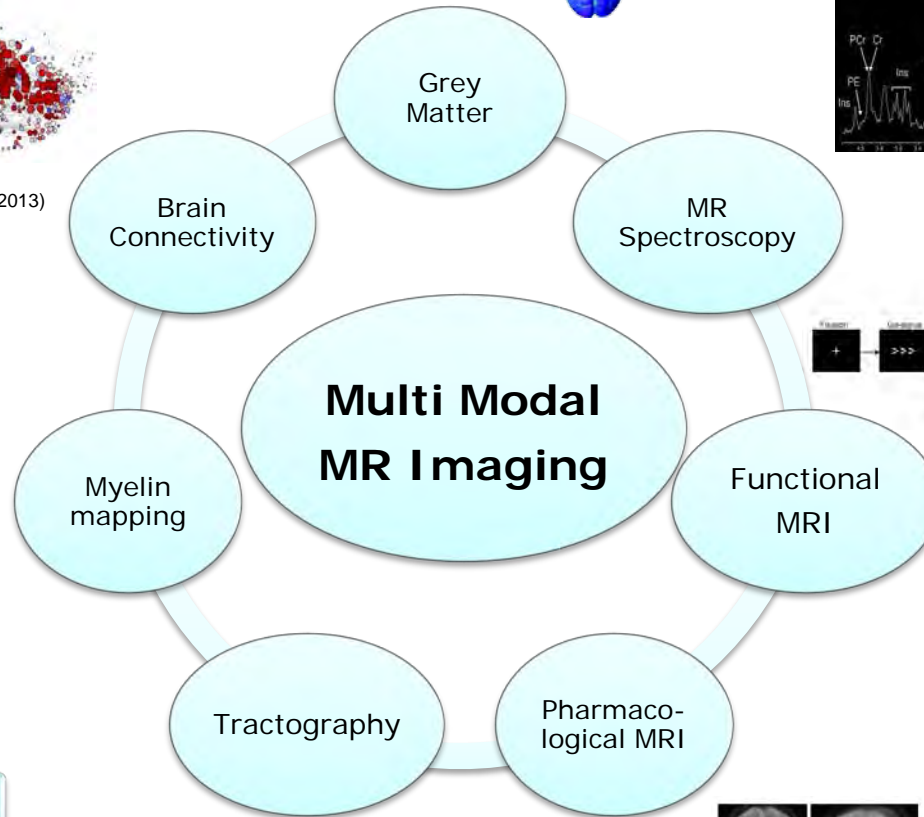
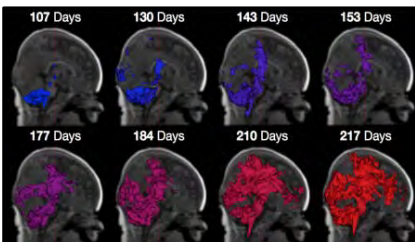
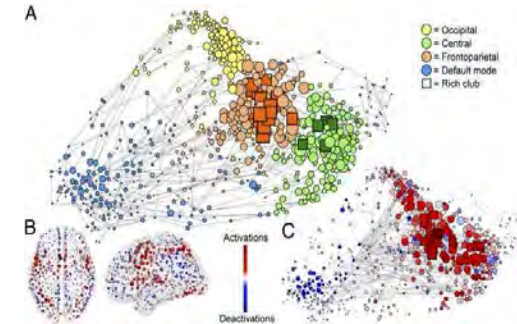
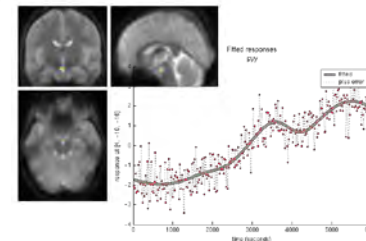
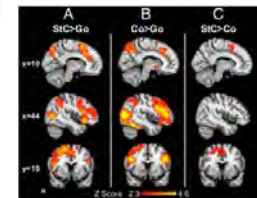
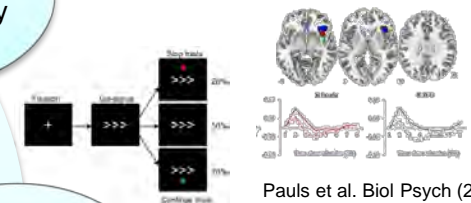
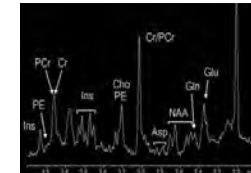
Institute of Psychiatry



James Black Centre



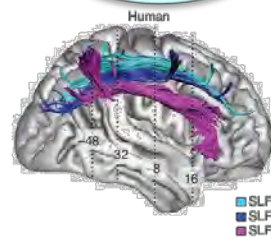
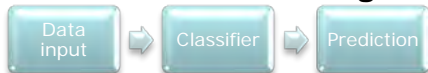
Stone et al. Mol Psych (2012)



Classical analysis



Machine Learning

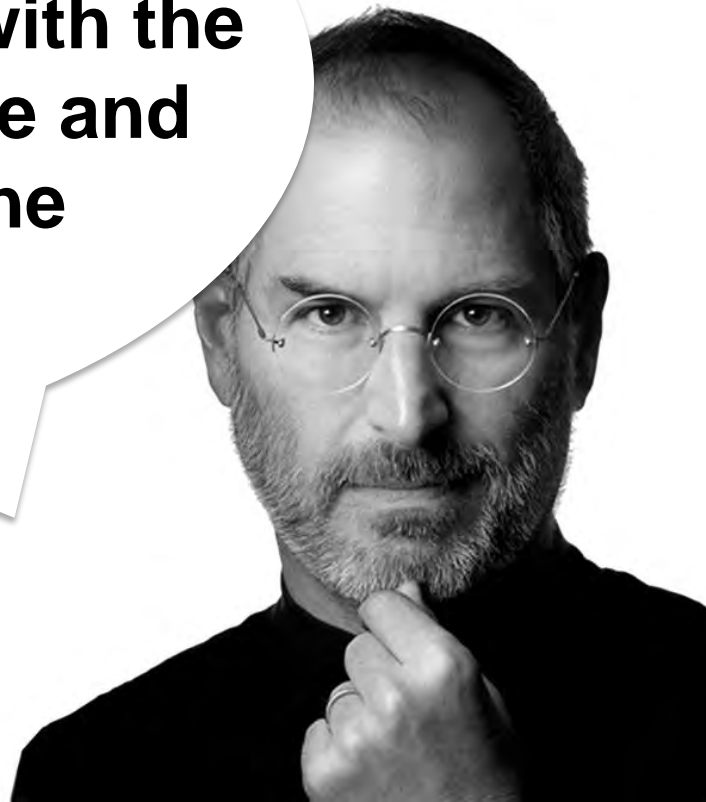


Doyle et al. J Clin Invest (2015)

Thiebaut de Schotten et al. Nat Neurosci (2011)

The Secret to Successful Design & Innovation

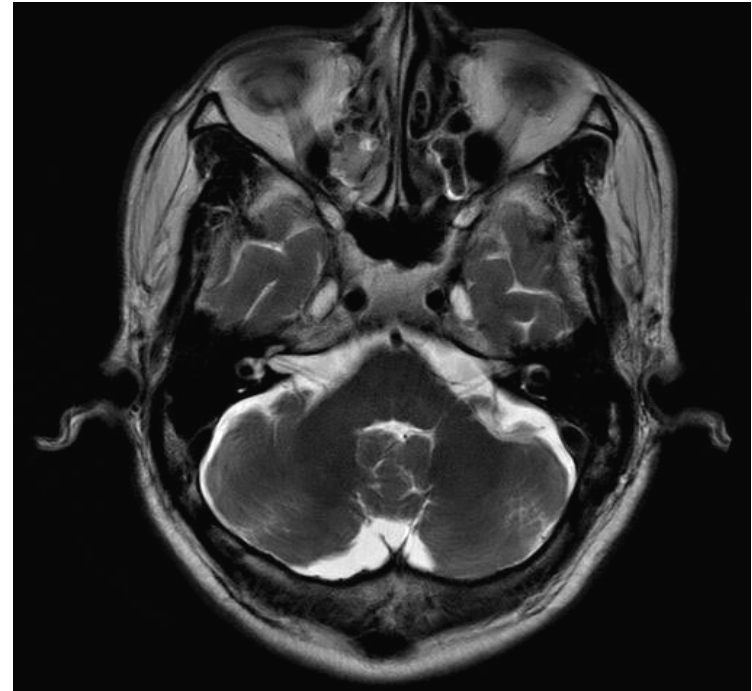
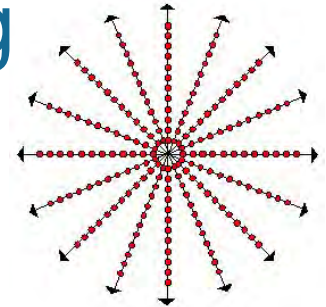
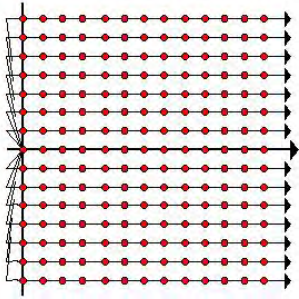
“You’ve got to start with the customer* experience and work backwards to the technology”



***for customer : see Williams family – 7 months to 7 years to 47 years to 70 years old**

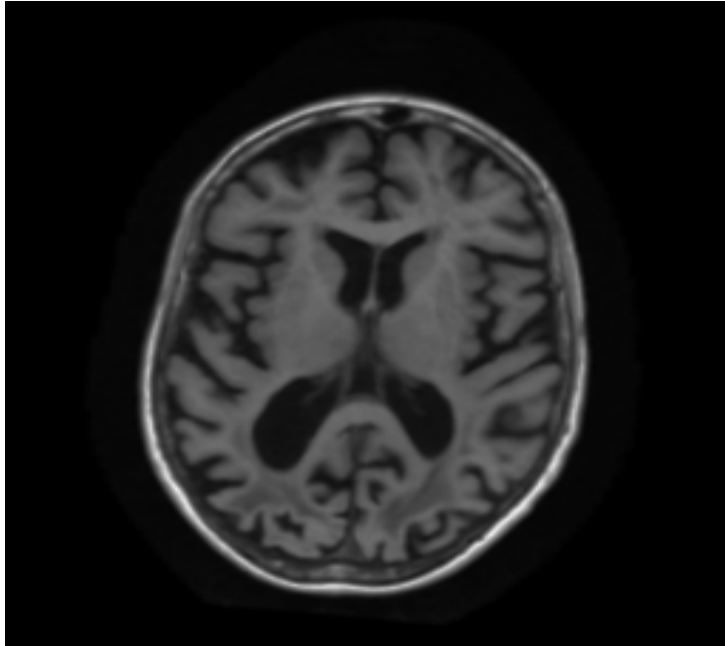
“ I’m struggling to lie still ”

Motion Insensitive Imaging

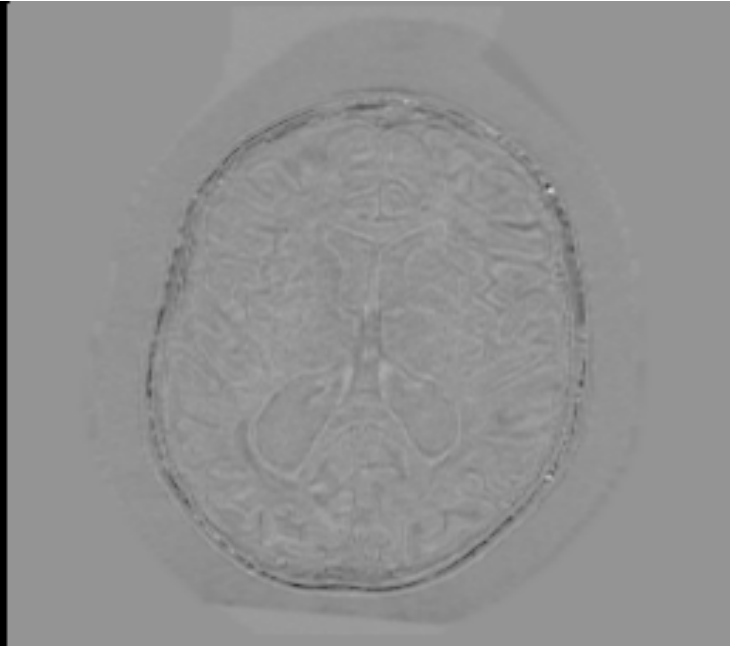


Jim Pipe

Brain changes in Alzheimer's Disease over 24 months.

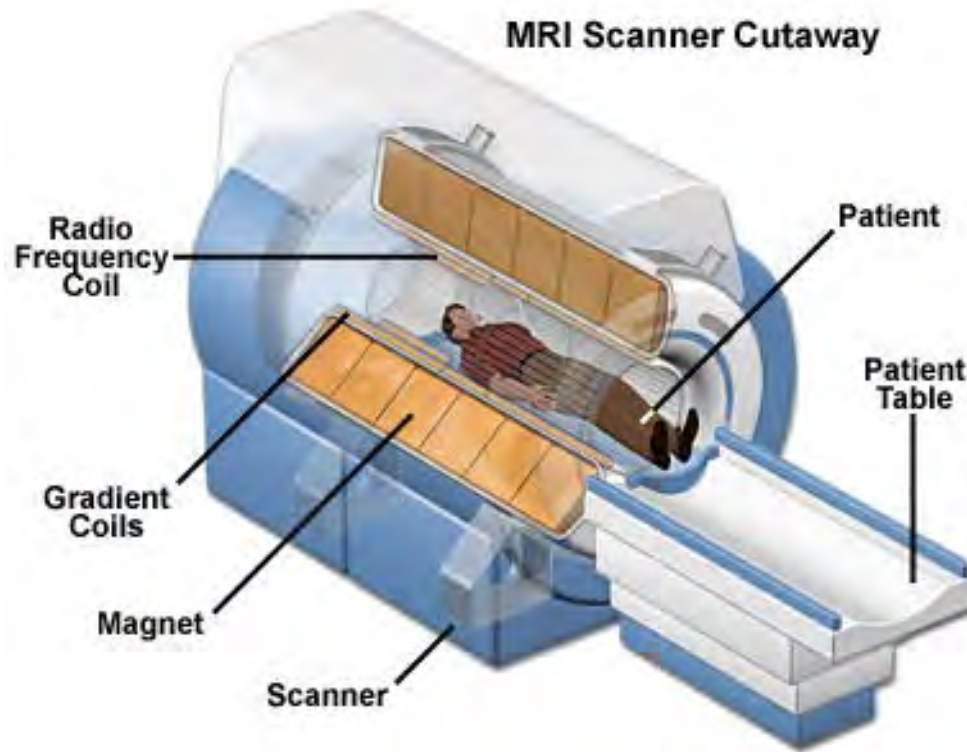


Changing Brain

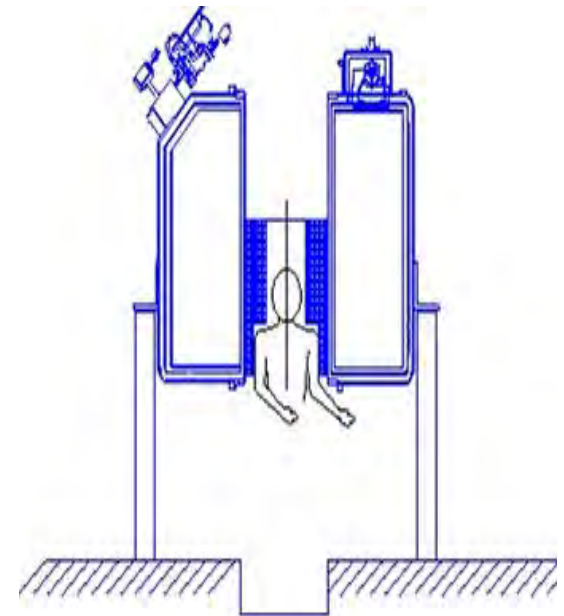


Evolving Differences

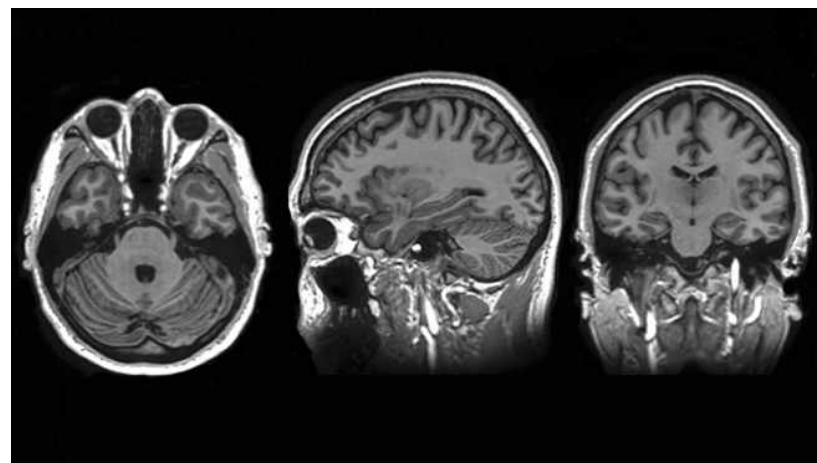
“ Why am I up to my ankles in it ? ”

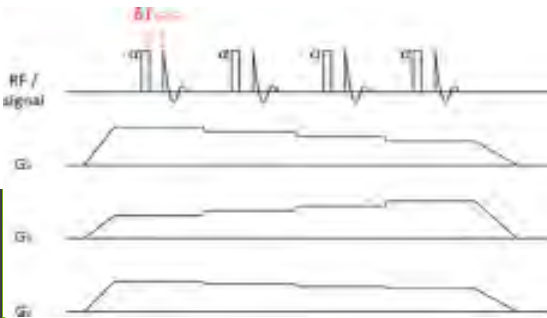


**“ Why do I have to lie down ? ”
(with my bad back)**

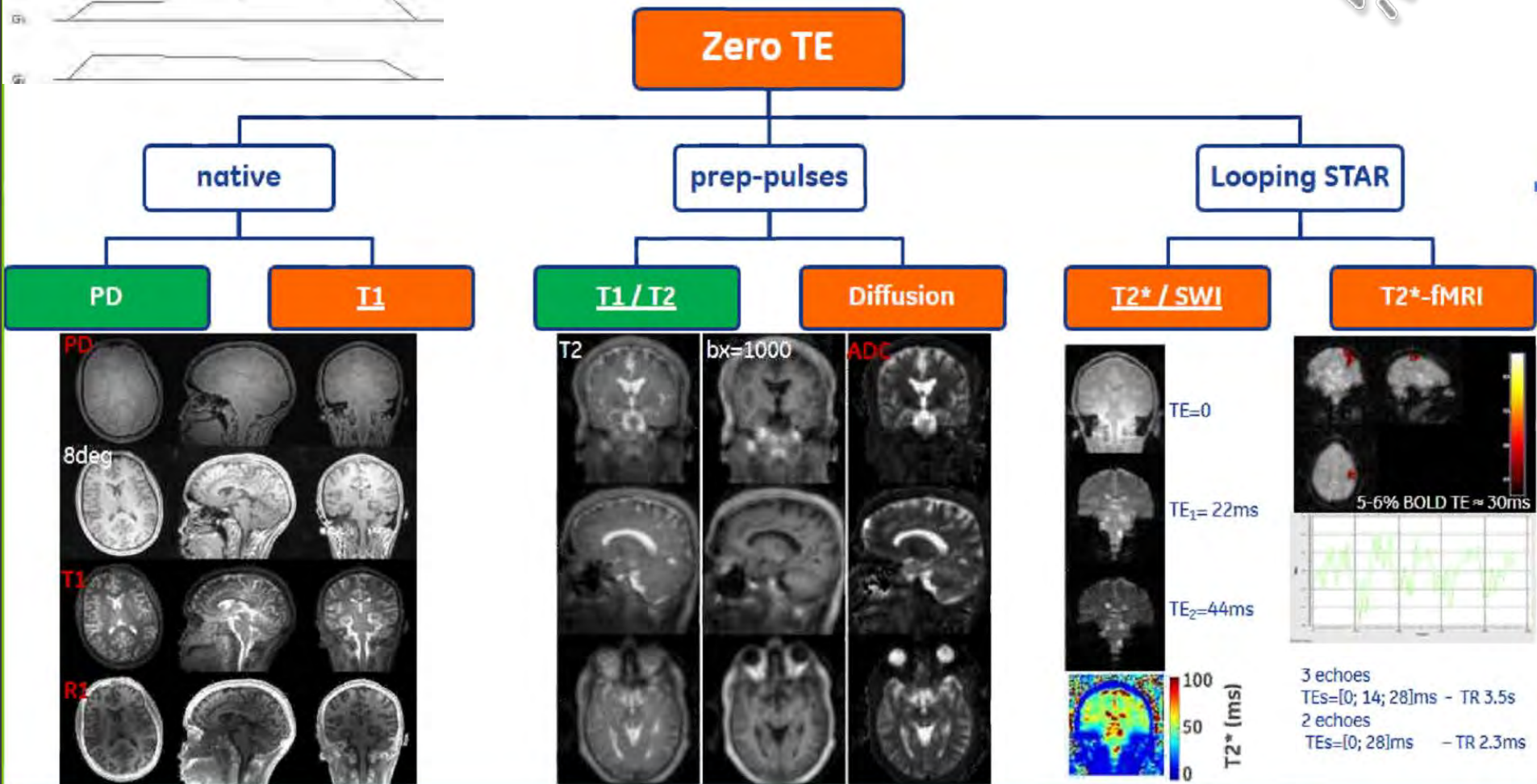


The first prototype – Mayo Clinic





“It’s too noisy”



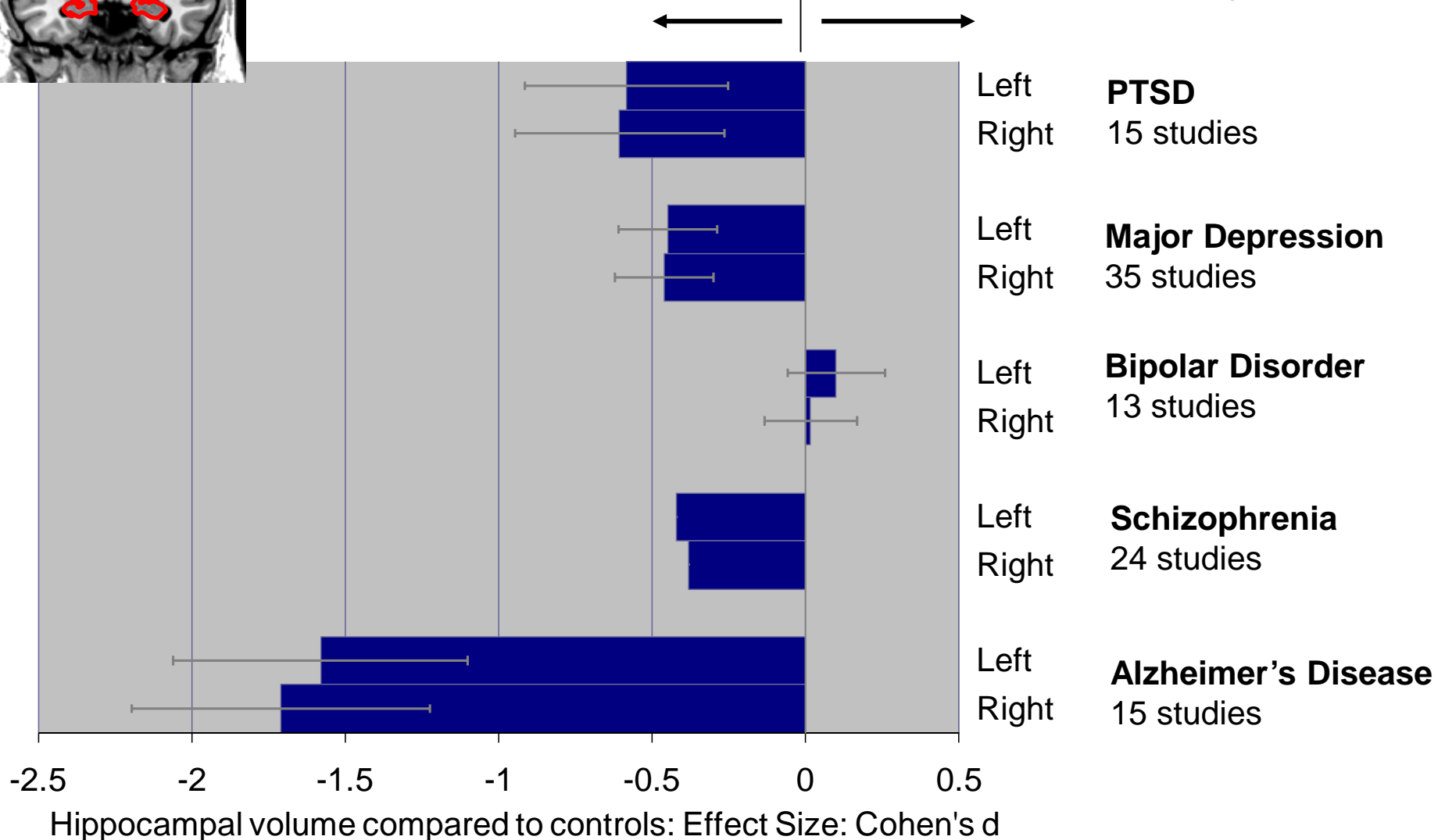
AnaBea Solana et al ,
 Quiet and distortion-free, whole brain BOLD fMRI using T2 -prepared RUFIS.
 Magn Reson Med. 2016 Apr;75(4):1402-12.

“Mental Illness - It’s all in the mind !”

Hippocampal volume in Psychiatric Disorders: Meta-analyses

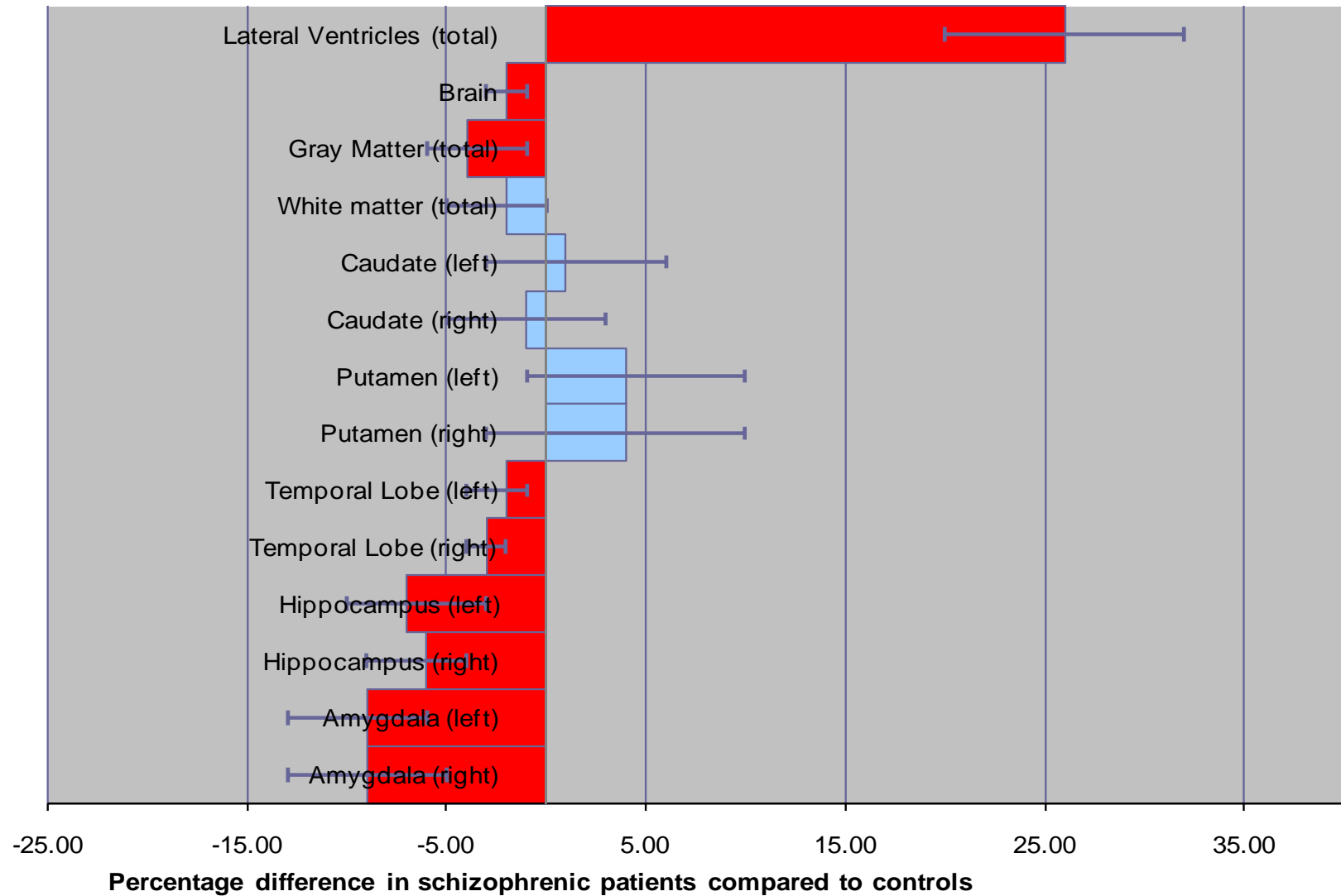
Hippocampus smaller in patients

Hippocampus larger in patients



Sources: Karl et al 2006, Kempton et al 2008,2011, Wright et al 2000, Zakzanis et al 2003

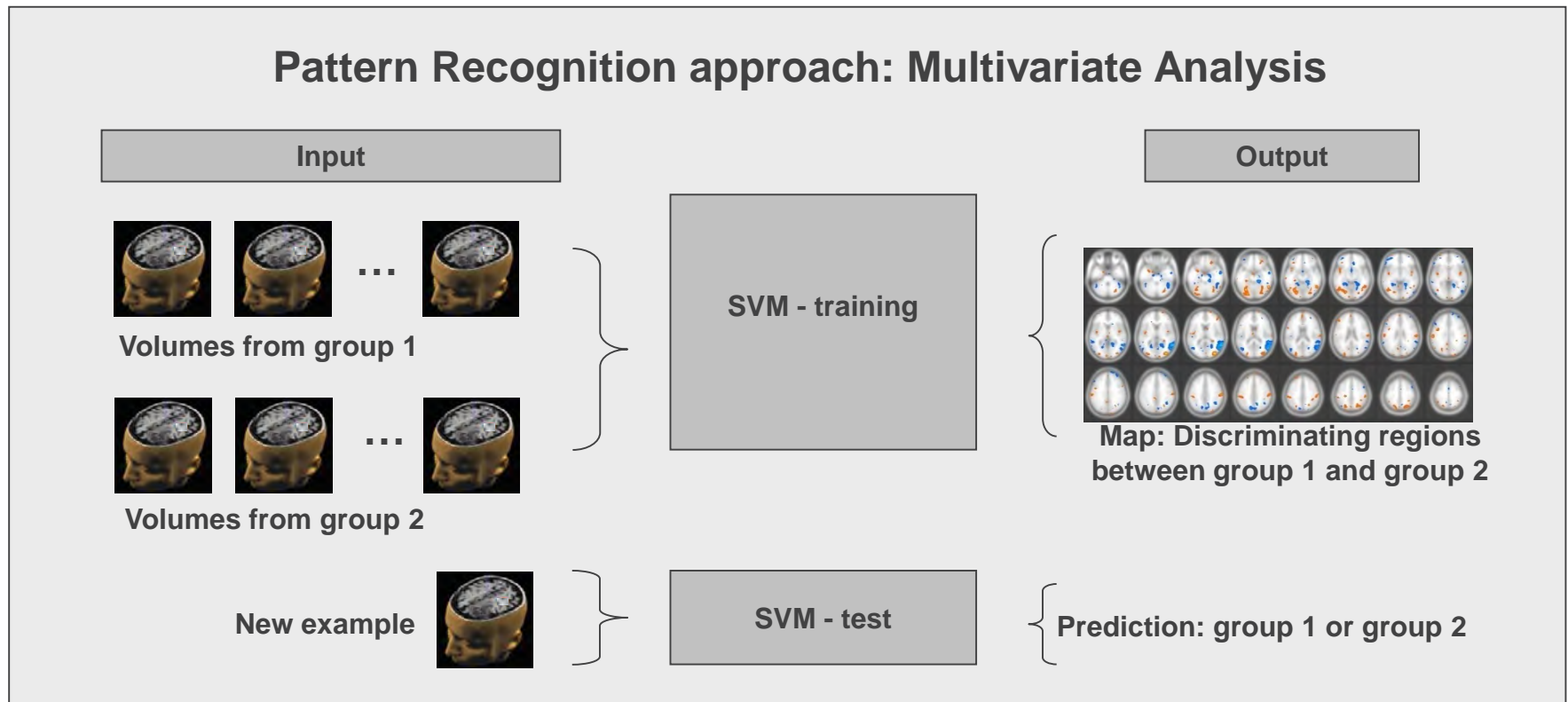
Schizophrenia vs Controls



Ian Wright et al 2000



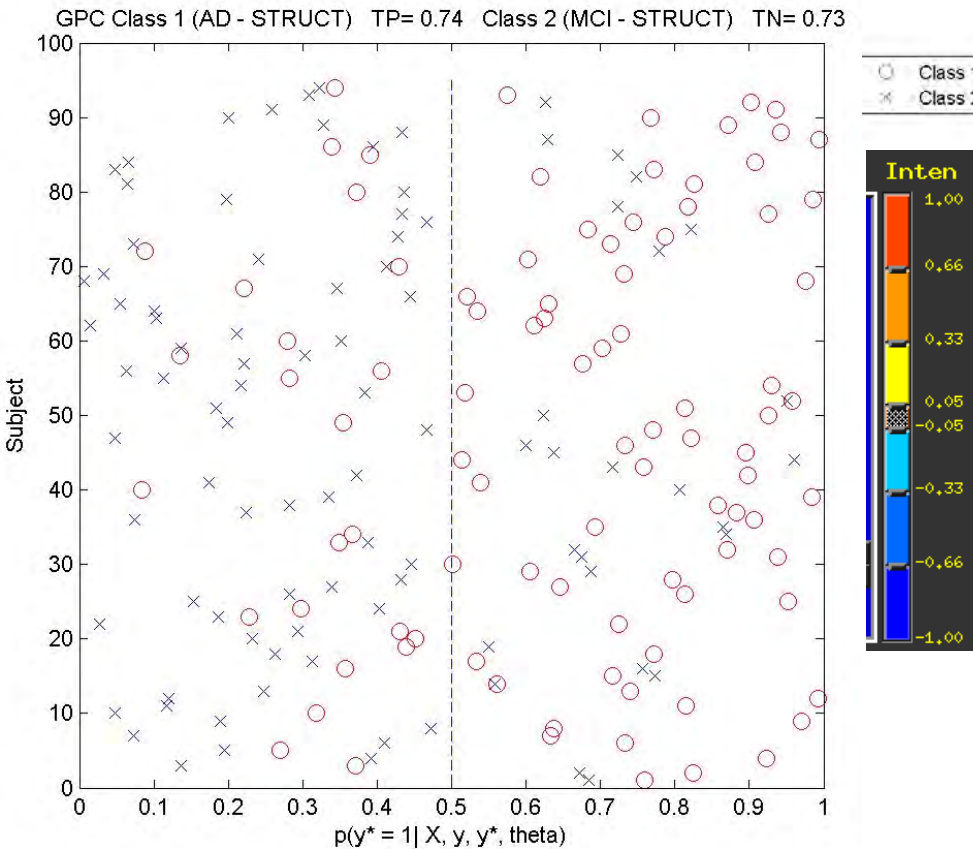
Applying Machine Learning Methods to Brain Images



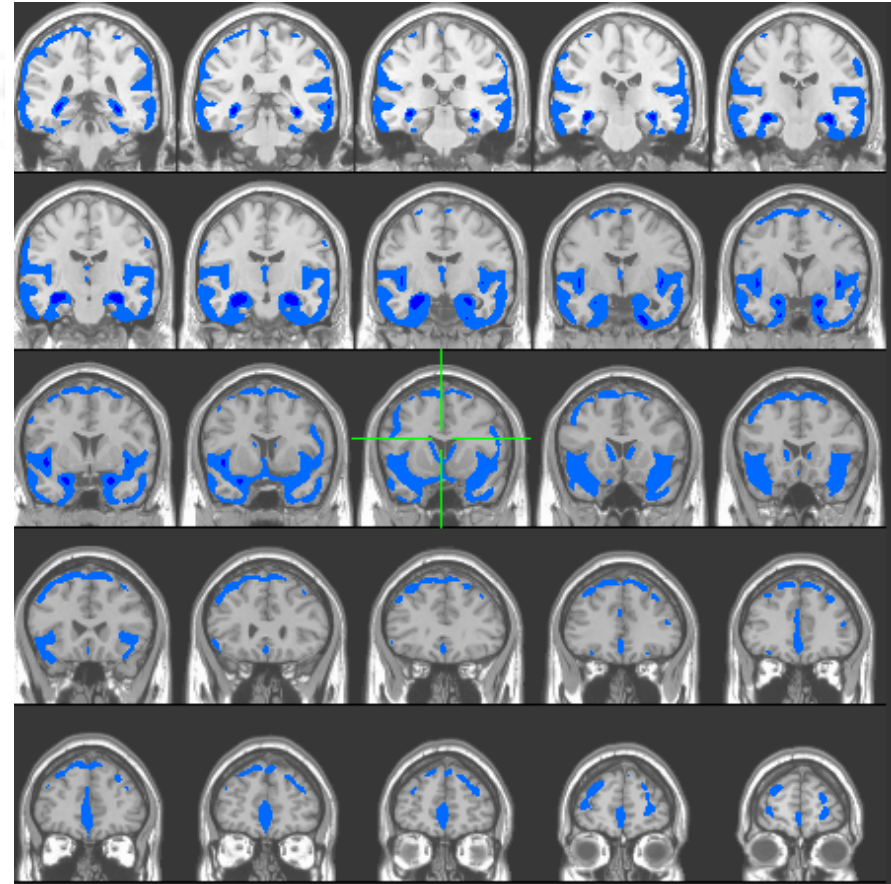
P.R. takes into account information distributed across the whole brain

AD versus Controls

No genetic information



	AD x Control
TP	0.74
TN	0.73
Accuracy	0.74
p value	0.001

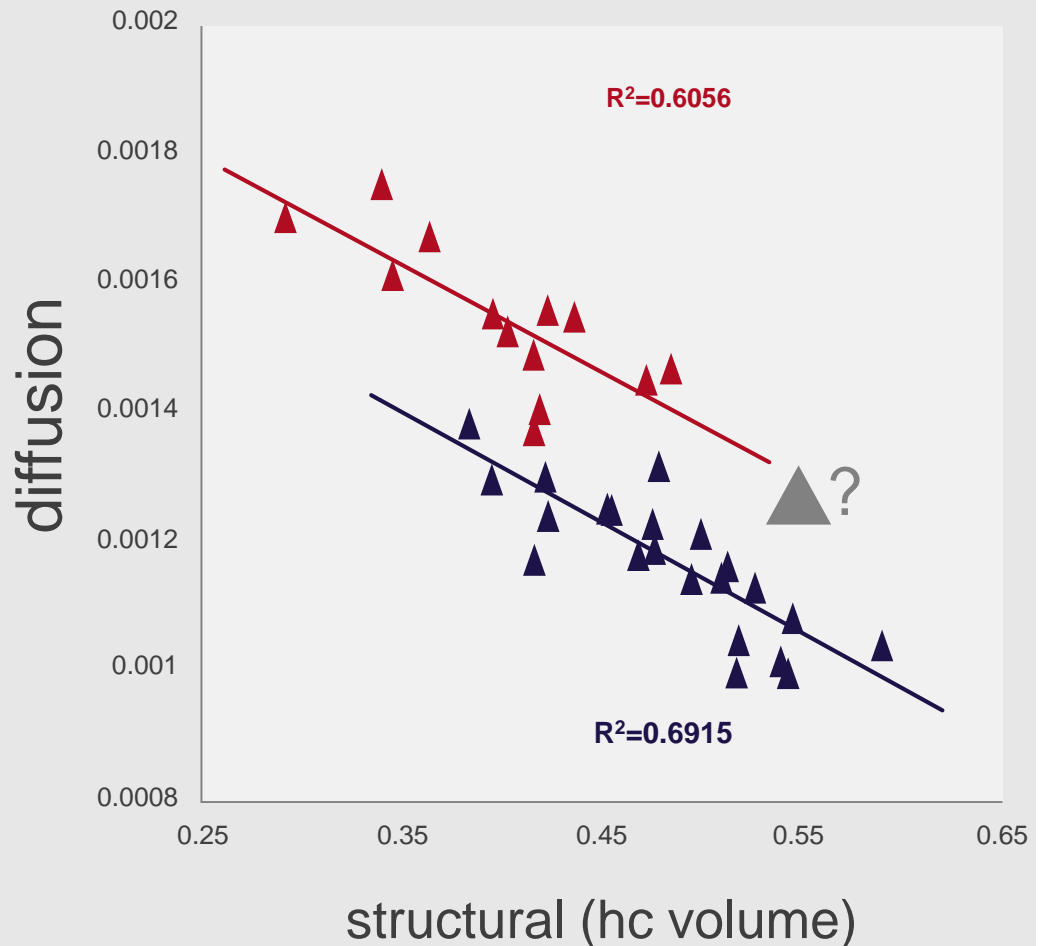


Discrimination map for gray matter classification. Relative increases in gray matter volume in the Alzheimer group compared with the Control group are displayed in red, while deficits are displayed in blue.

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”



At Risk Mental State (ARMS)

'someone on the train was laughing at me'

Persecutory Ideas

'peoples voices and noises sound different'

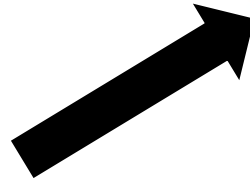
Perceptual Abnormalities

'I don't seem to be able to talk as clearly as before'

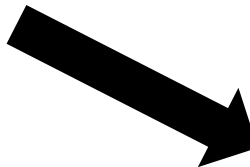
Disorganised speech



At Risk Mental State



~15%
Psychotic



Non-Psychotic

'MI5 have put a microphone in my head'

Delusions

'a voice comments on my every move'

Hallucinations

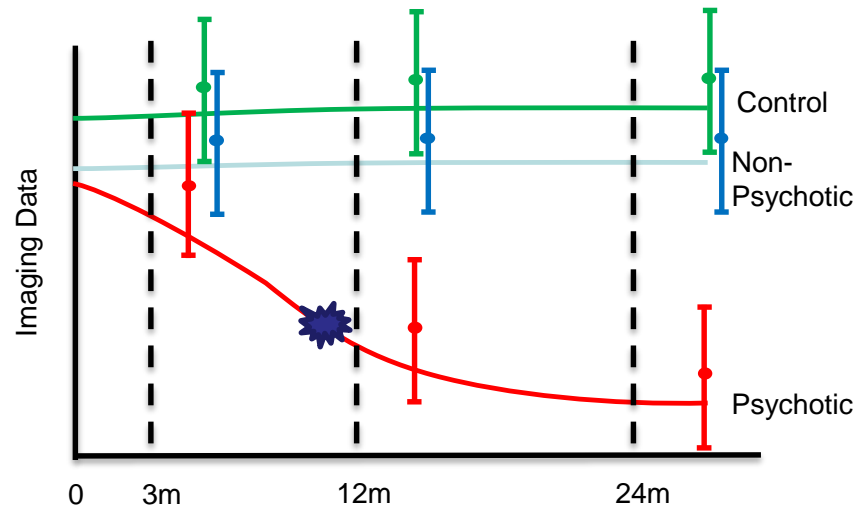
'isn't lettuce brave? I like lunch, hello now'

Incoherence

Psychosis

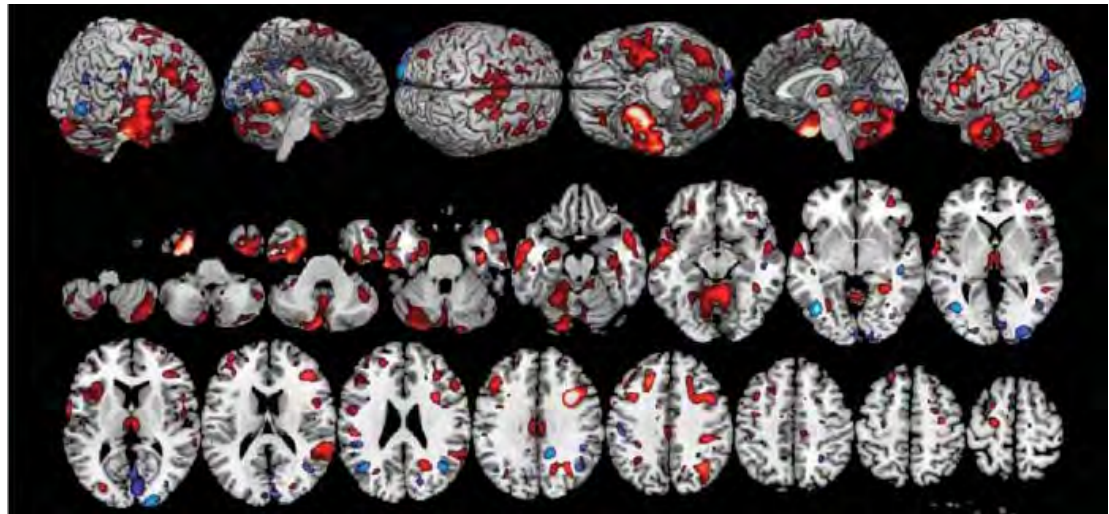
At Risk Mental State

Prediction of Transition to Psychosis



ARMS-T
vs
ARMS-NT

82% accuracy



Nikolaos Koutsouleris et al Arch Gen Psychiatry. 2009;66(7):700-712

Early Differential Diagnosis of **Movement Disorders**

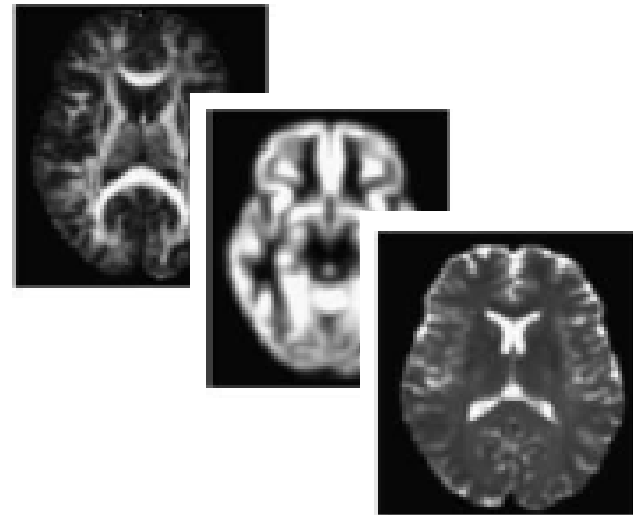
Multi-Modal, Multi-Class Disease Discrimination

Automatic differential diagnosis of :

Parkinson's disease (PD)

Multiple System Atrophy (MSA)

Progressive Supranuclear Palsy (PSP)



true	PSP	15	3	0
	IPD	1	13	0
	MSA	0	0	19
		PSP	IPD	MSA
		predicted		

92% accuracy

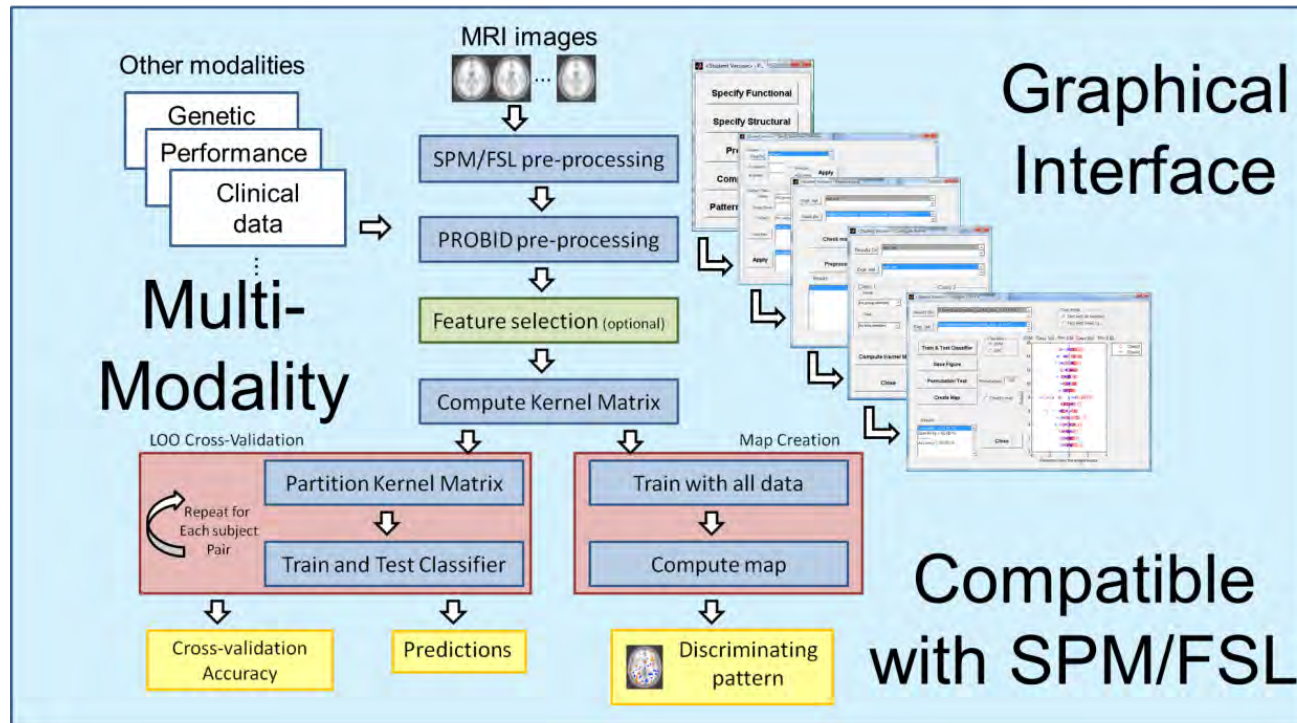
M. Filippone et al, Ann Appl Stat. 2012 27;6(4):1883-1905

A. Marquand et al, PLoS One. 2013 Jul 15;8(7):e69237

A Machine Learning Approach to the Analysis of Neuroimaging Data

*A software toolkit which makes pattern recognition methods available to neuroimaging researchers: **Pattern Recognition of Brain Image Data (PROBID)**.*

PROBID Architecture



Applications include:

- Autism
- Alzheimer's disease
- Bipolar disorder
- Depression
- Pain
- Parkinson's disease
- Schizophrenia
- Social Anxiety

PROBID has been used as the primary analytical tool for >100 peer-reviewed publications.
Open source software available at: www.brainmap.co.uk/probid.htm



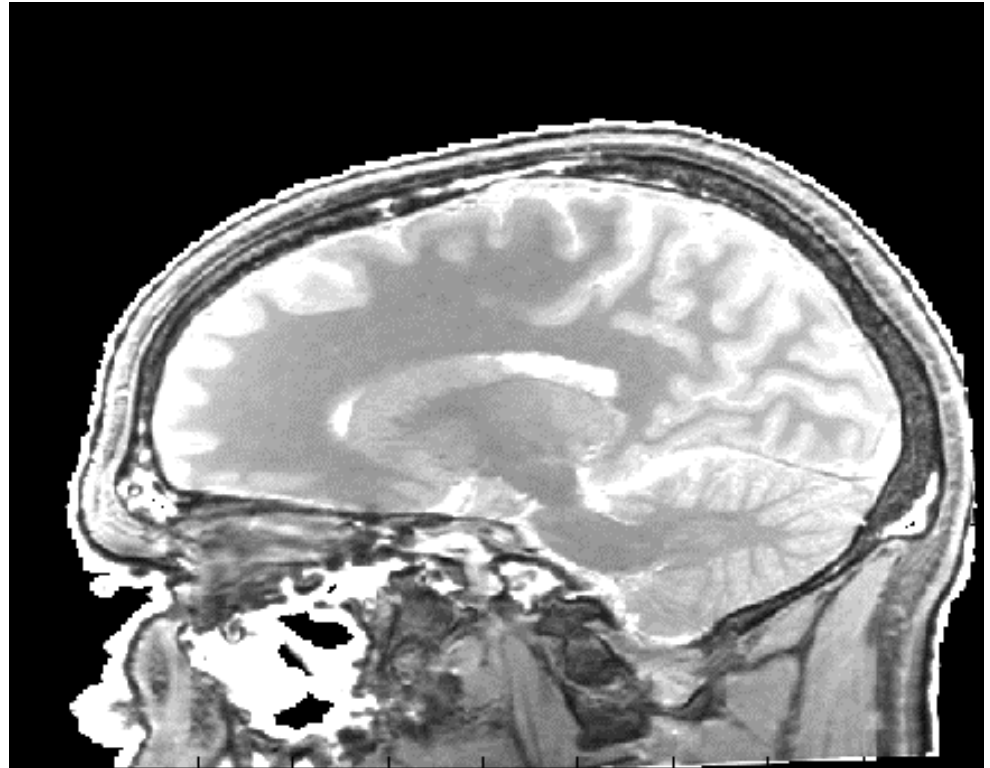
"First we're going to run some tests to
help pay off the machine."

“ What’s the best picture ? ”

www.CartoonStock.com

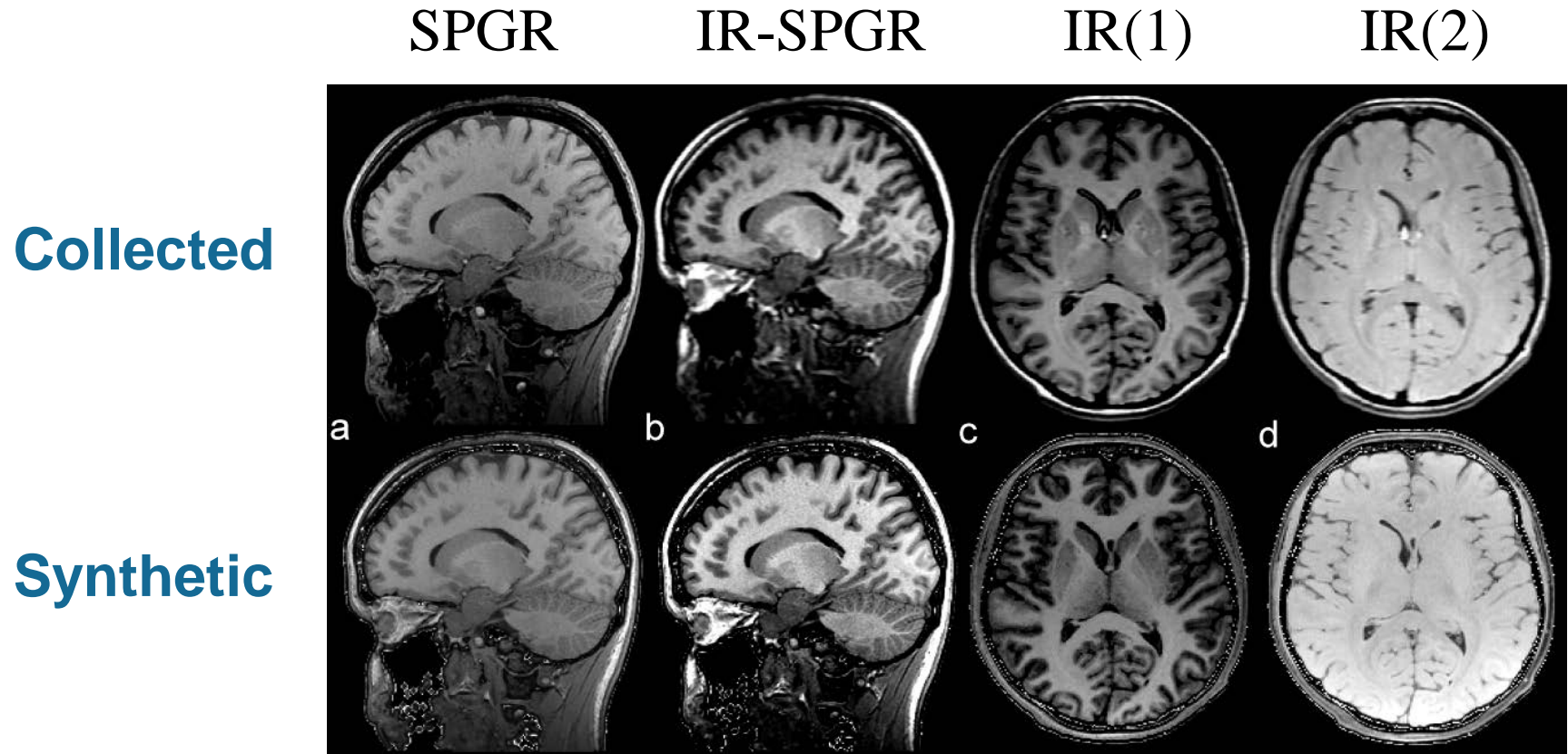


"We've given you a brain scan and
we can't find anything."



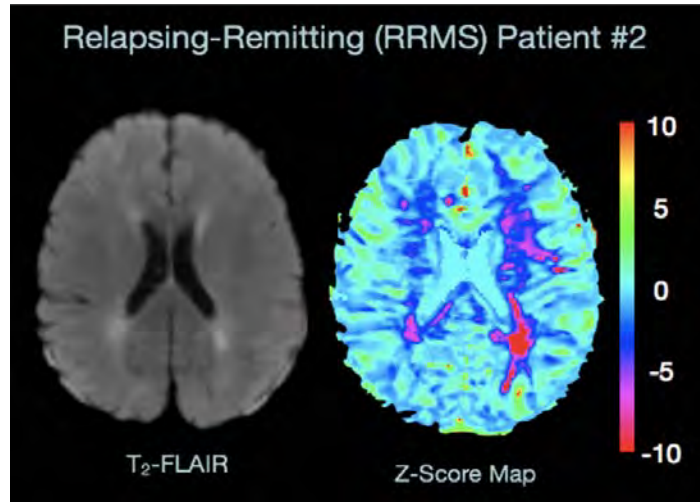
Sean Deoni et al

“ Can’t you share data ?”



Collect Future-Proof (Big) Data
Synthesise Desired Images

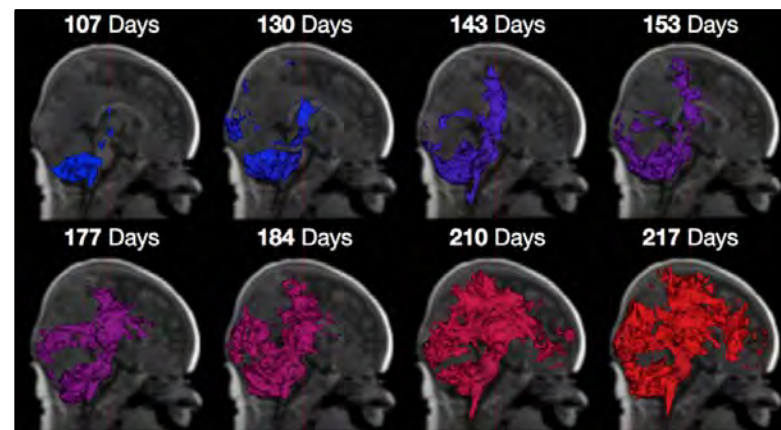
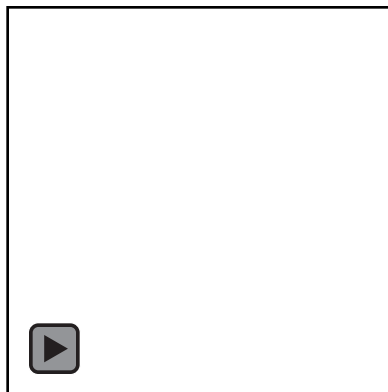
Myelin Mapping using mcDESPOT



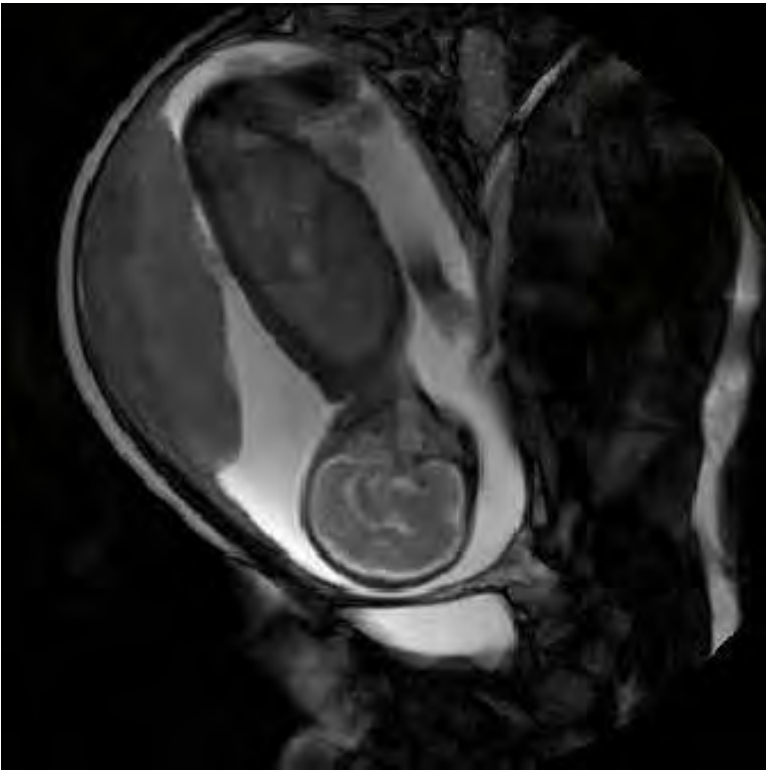
T₂-weighted MRI



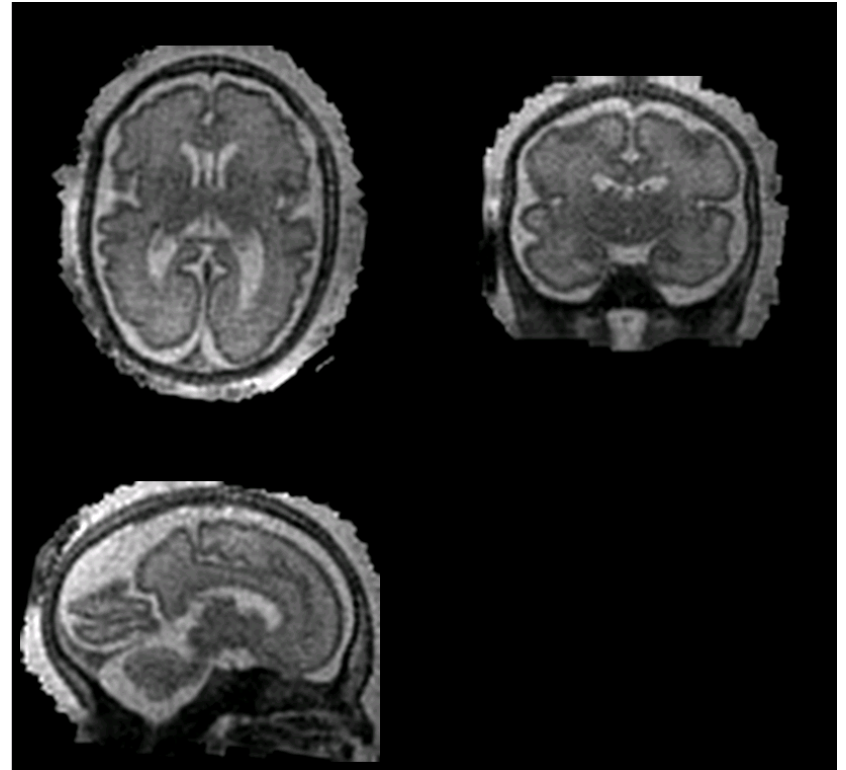
Myelin Water Fraction



28 week foetus imaged *in utero*



Real time observation

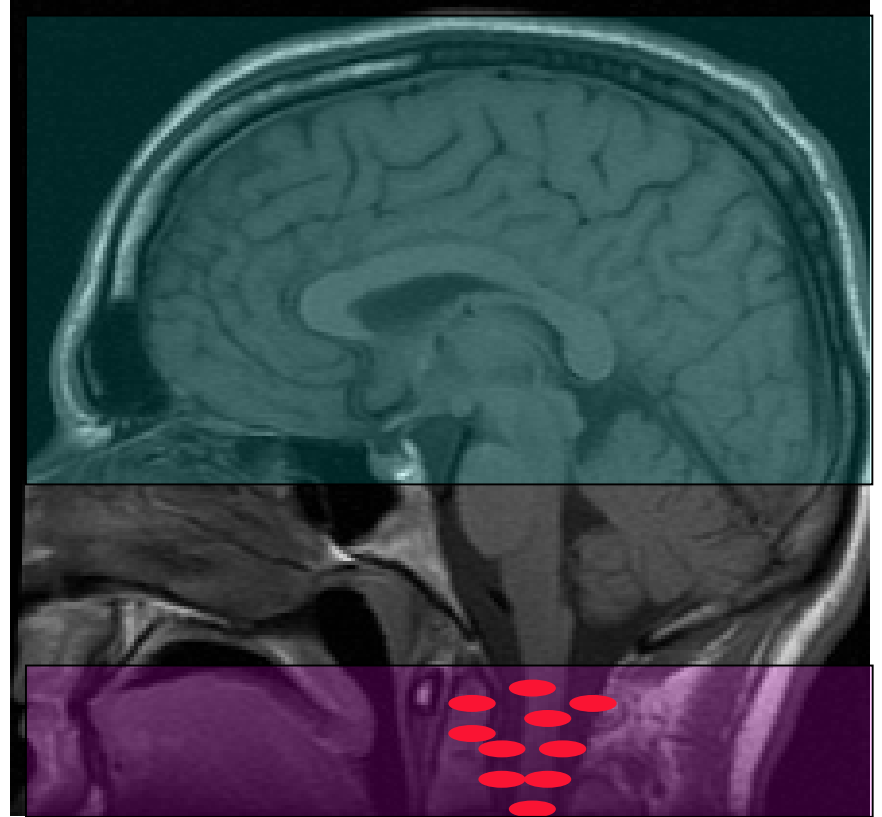


SVReconstructed 3D brain images

Jo Hajnal et al

Arterial Spin Labelling (cASL)

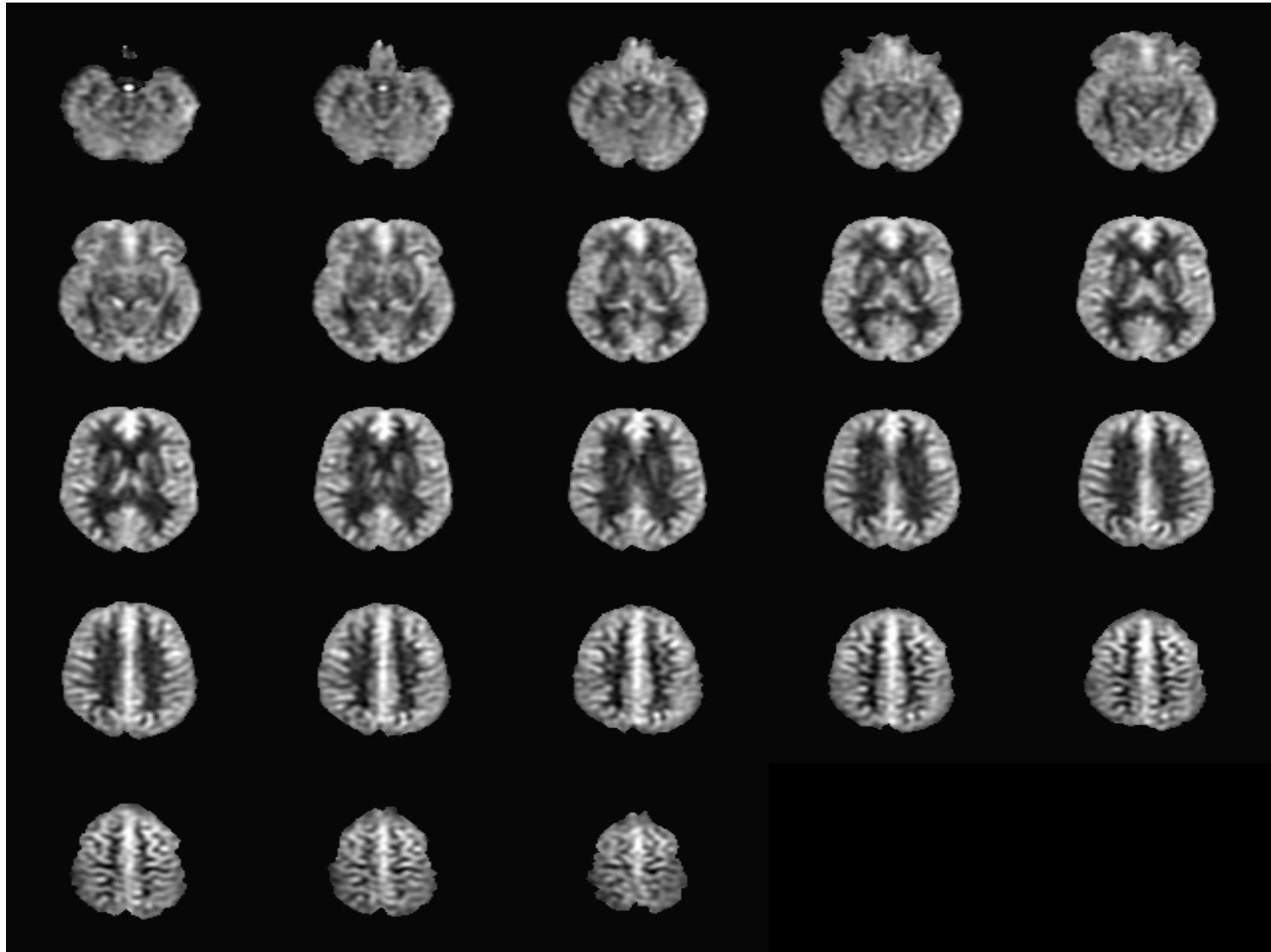
IMAGE ACQUISITION



MAGNETISATION OF BLOOD

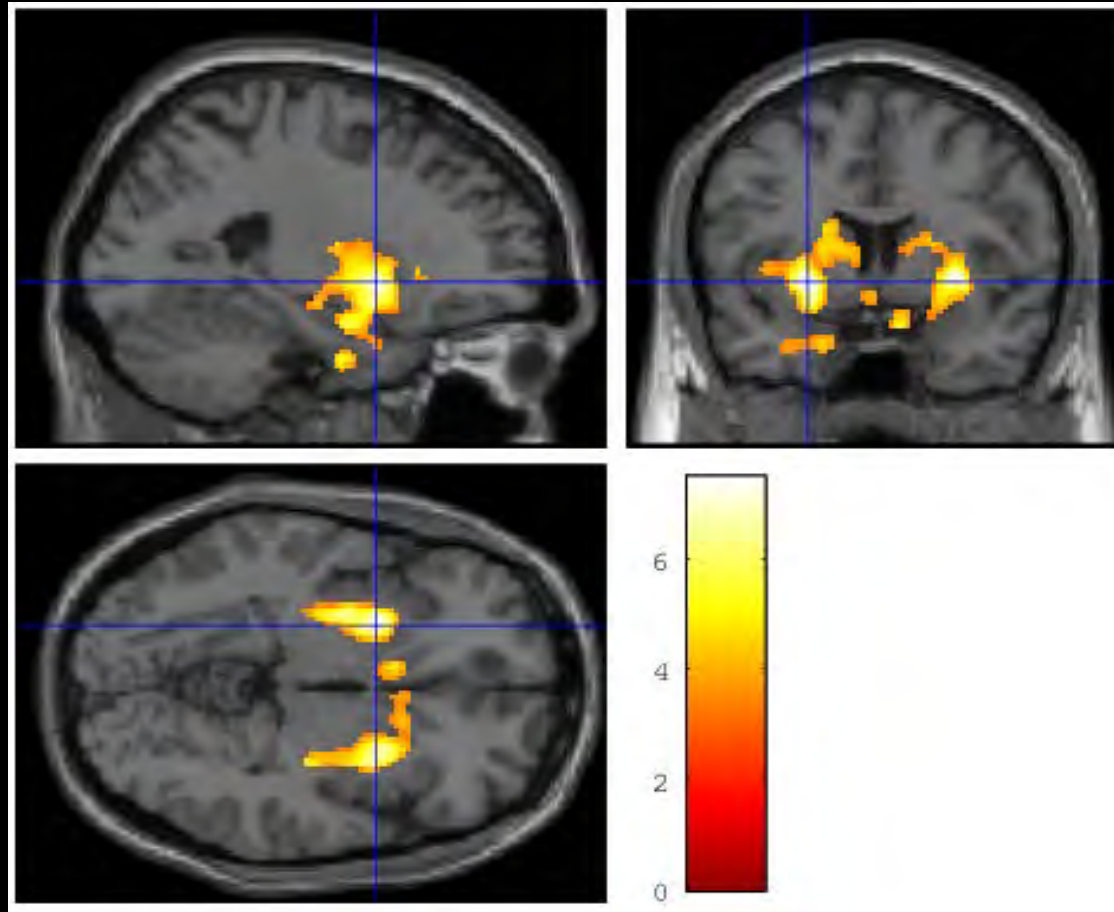
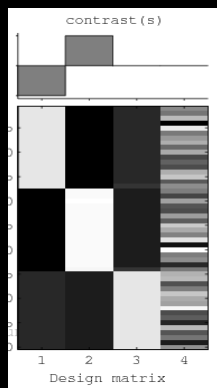
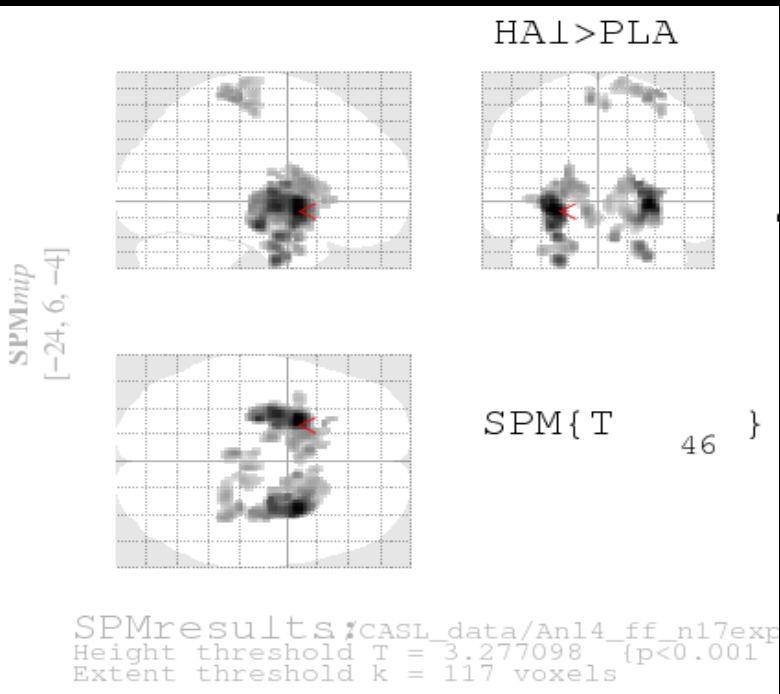
Allows us to quantify cerebral blood flow (CBF) changes

Quantitative CBF maps (ml/100g/min)



Fernando Zelaya

ASL: haloperidol > placebo

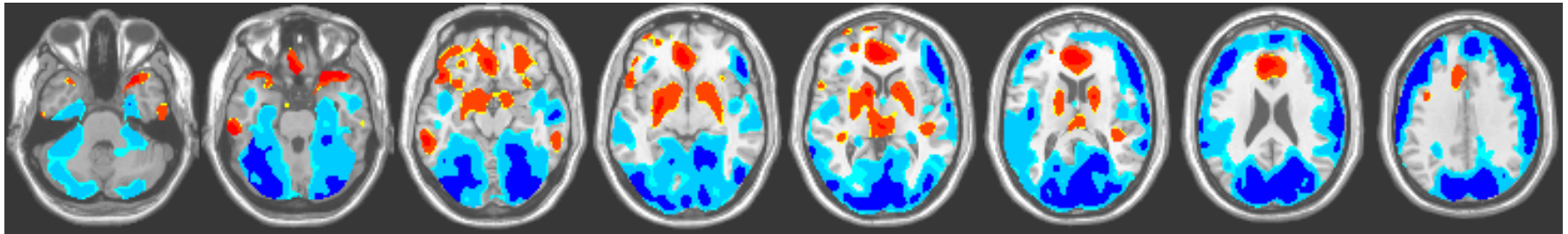
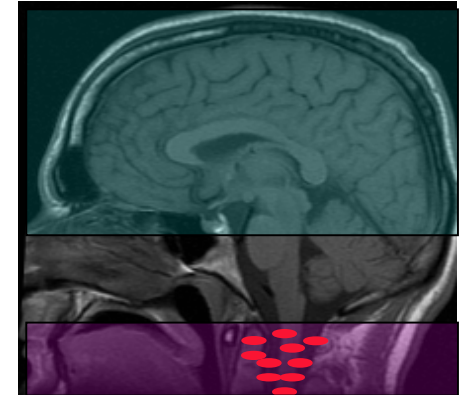


Informing Treatment Development in ADHD

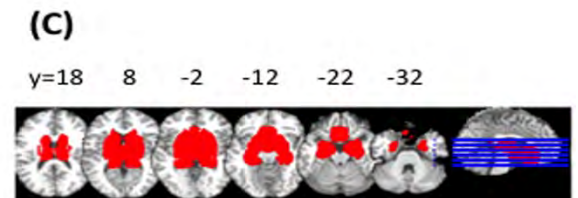
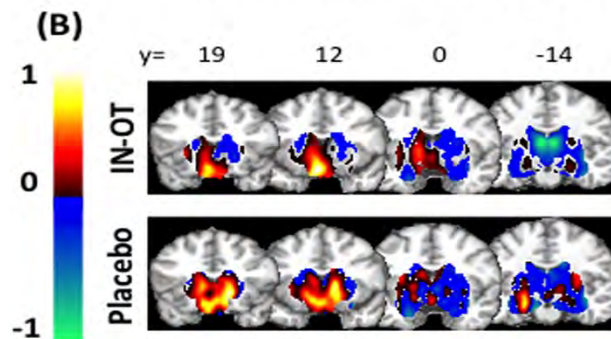
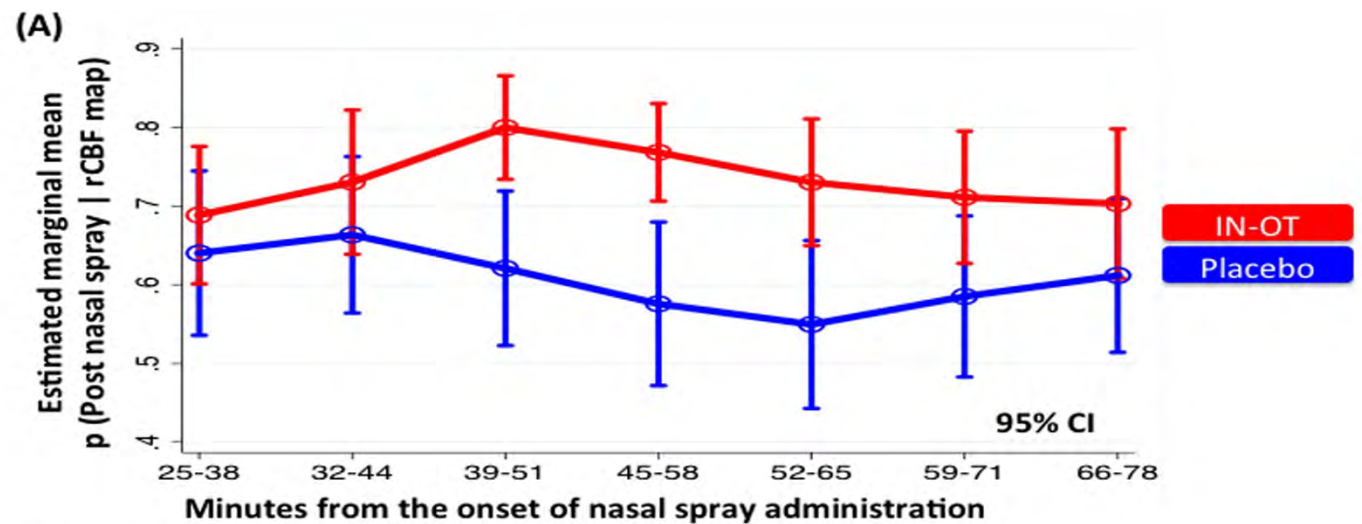
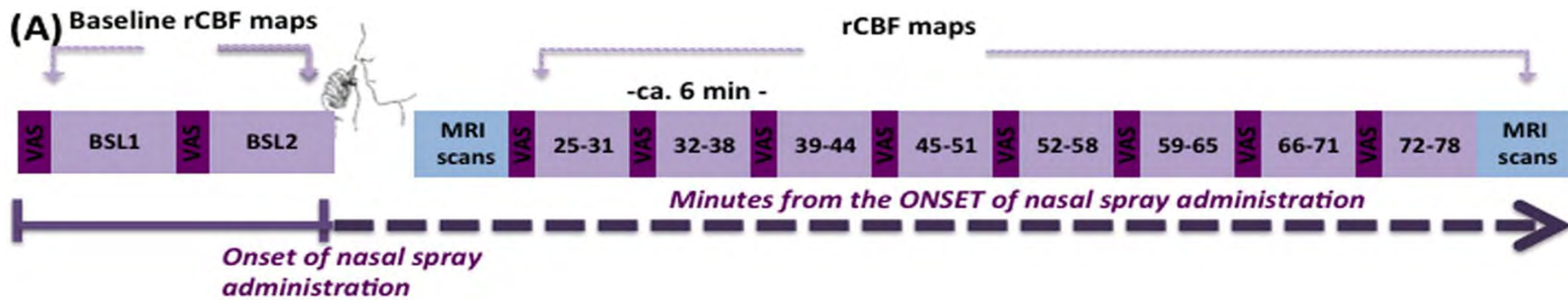
Quantitative Perfusion MRI (pCASL)

Existing Treatment - Methylphenidate

Potential New Medication - Atomoxetine



Excellent Discrimination Accuracy 85%

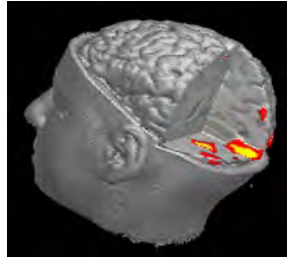


O
X
Y
T
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N

Pre-surgical visits



Ψ assessment &
screening



cASL
assessment



post-scan RNA



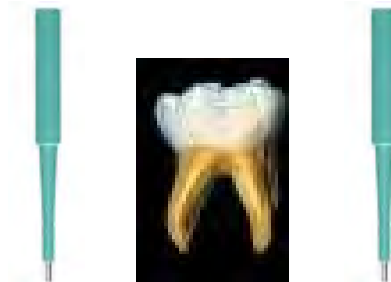
Surgical visits



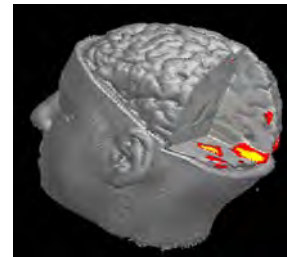
Ψ assessment &
screening



pre-surgery
RNA



wisdom tooth
extraction &
mucosa sampling



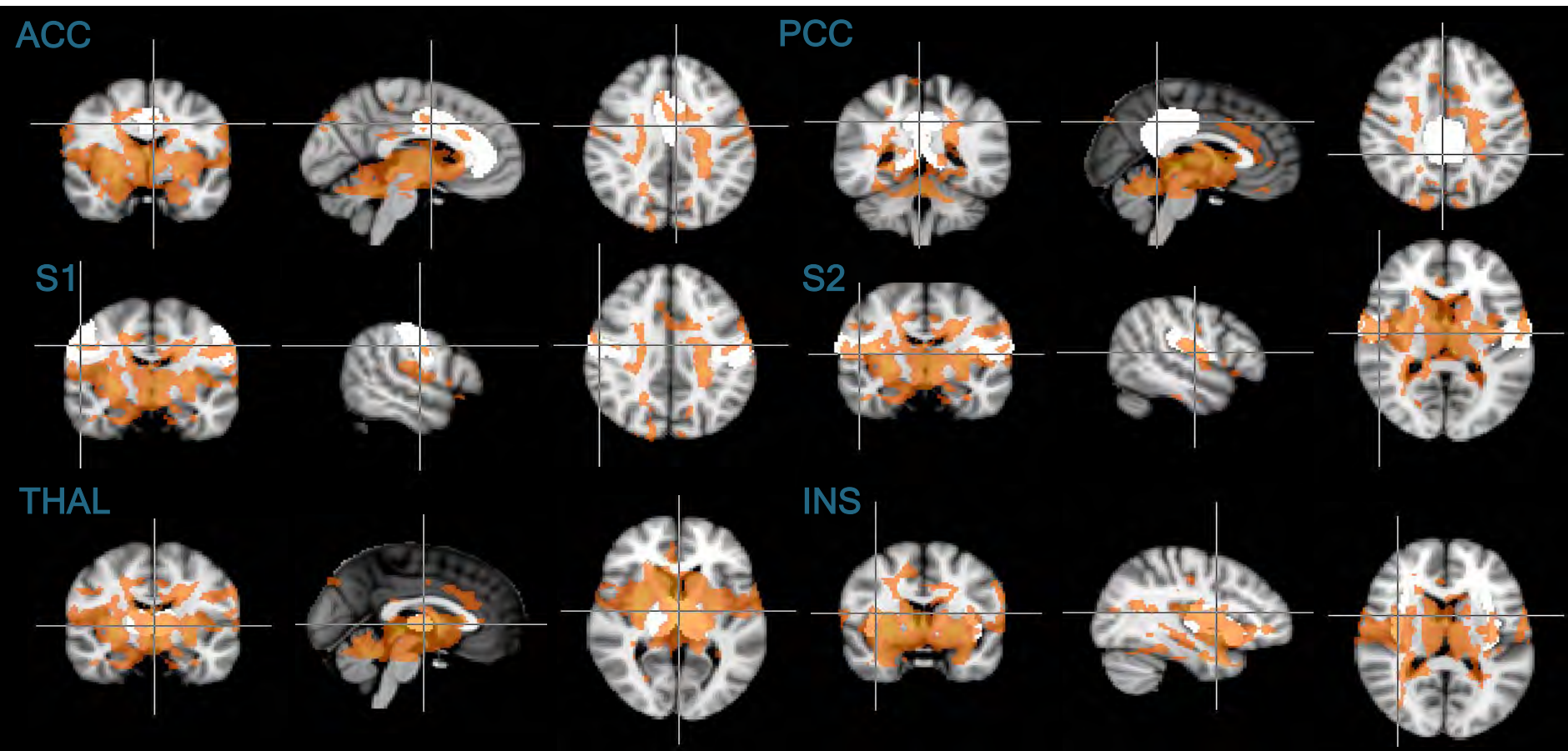
cASL
assessment



post-scan/surgery
RNA



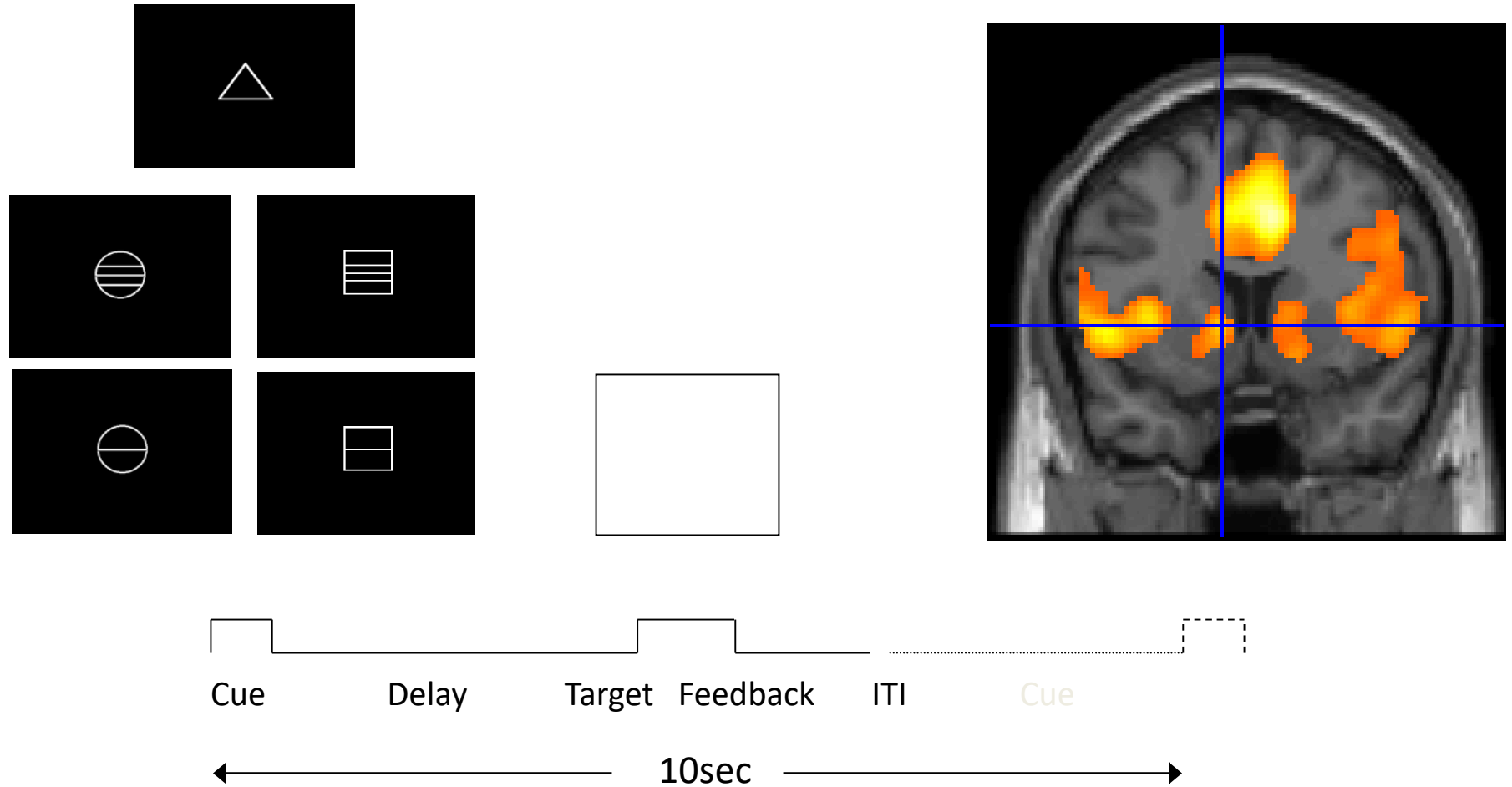
Dental Pain after 3rd Molar extraction



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

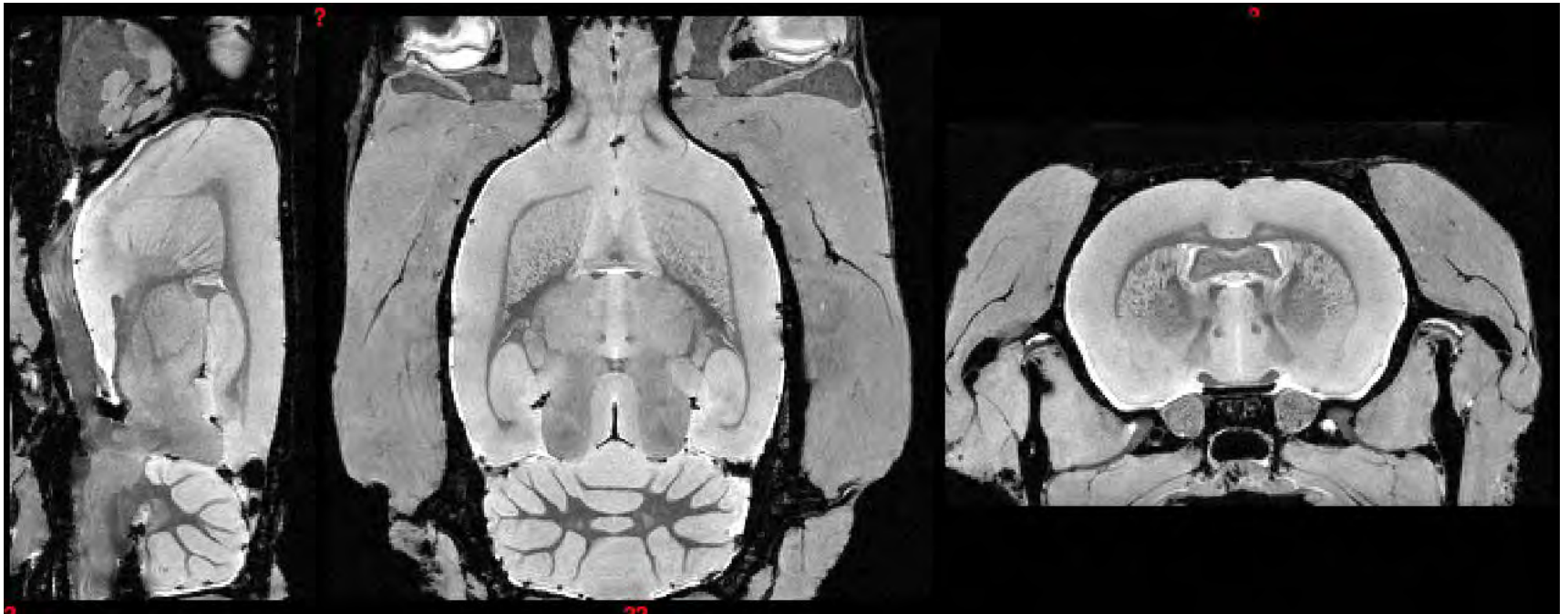
Tara Renton, Matt Howard & Pfizer

Addictions - Monetary Incentive Delay Task

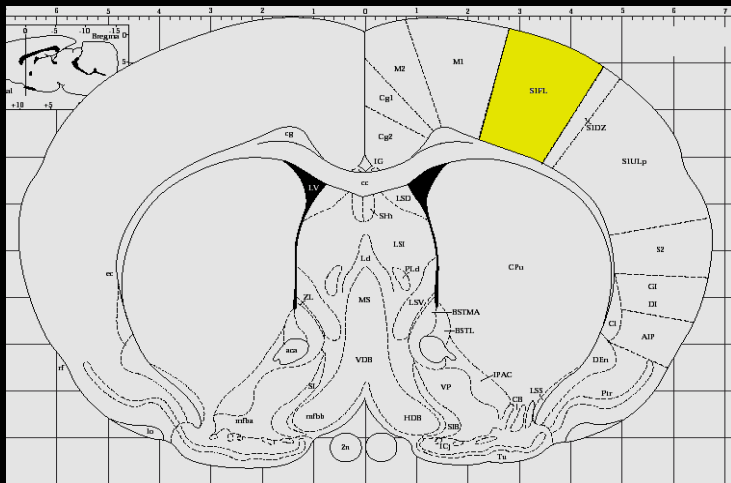


Brian Knutson et al. (2001) J Neurosci

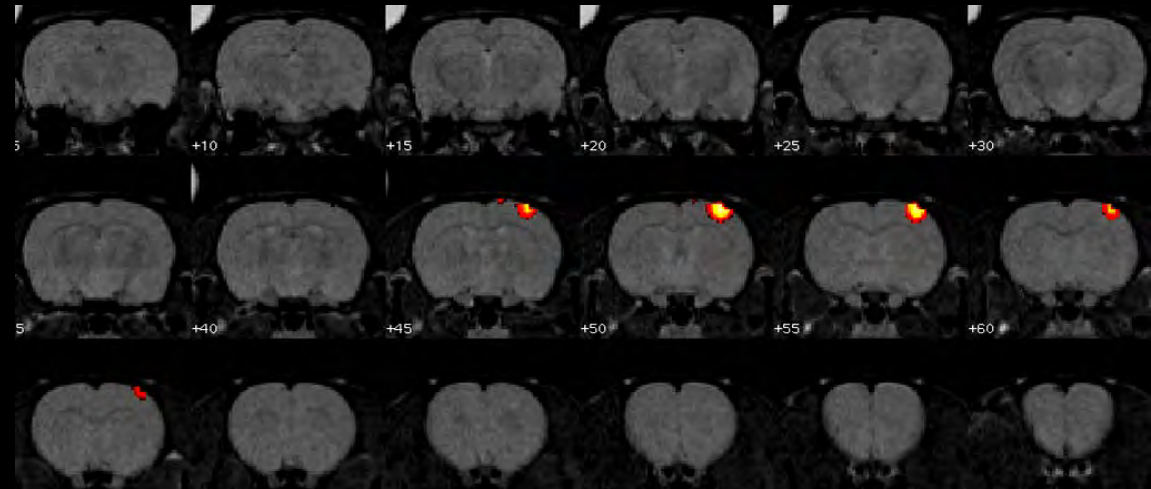
MRI is even safe for our mice



Sensory FMRI in the Rat



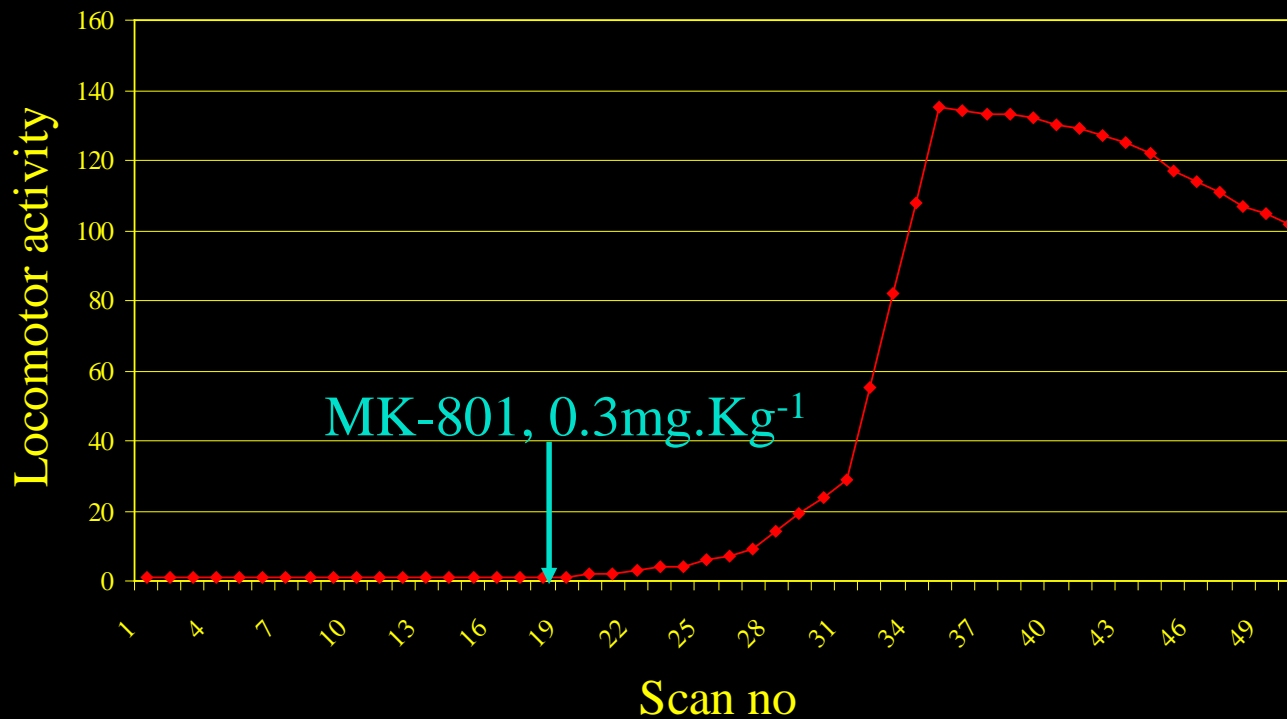
Paxinos & Watson
representation of forepaw
somatosensory cortex



Activation after electrical forepaw
stimulation

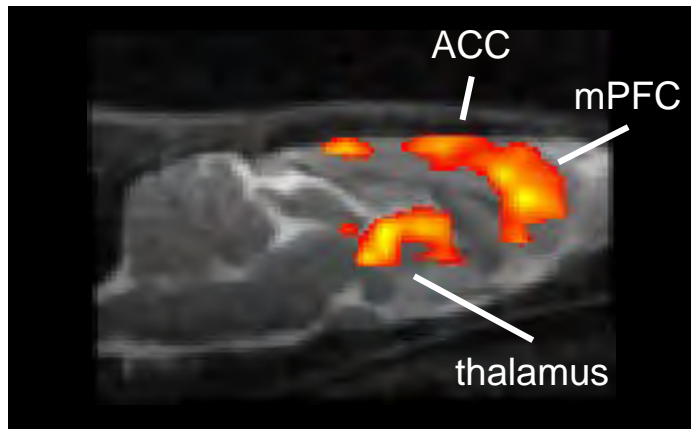
Pharmacological MRI (phMRI)

Locomotor activity Under MK-801

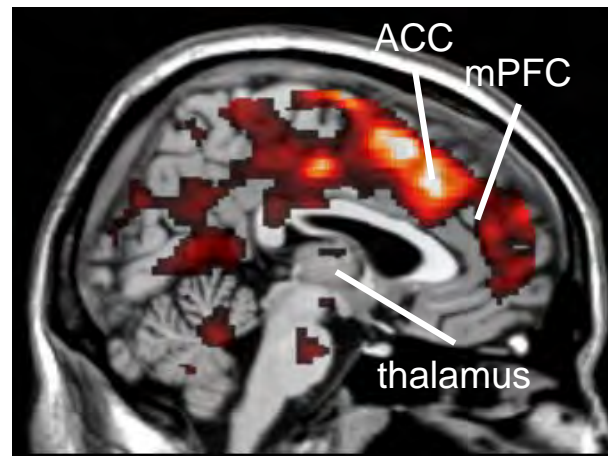


Ketamine phMRI – rat vs man

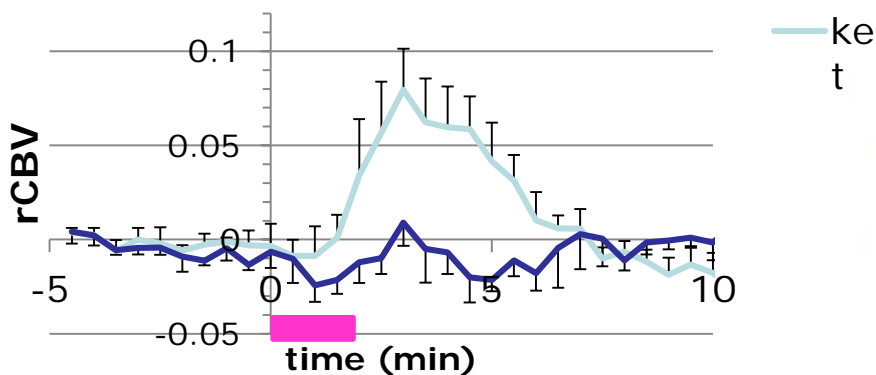
Rat



Human



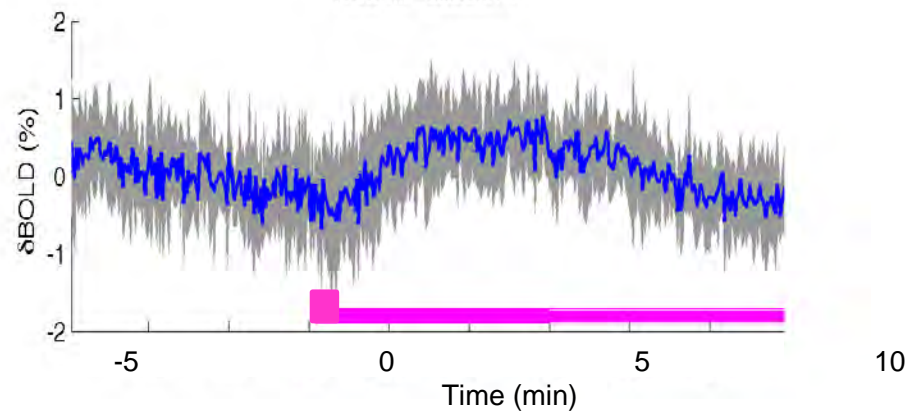
Cingulate cortex (N=5)



1mg/kg IV

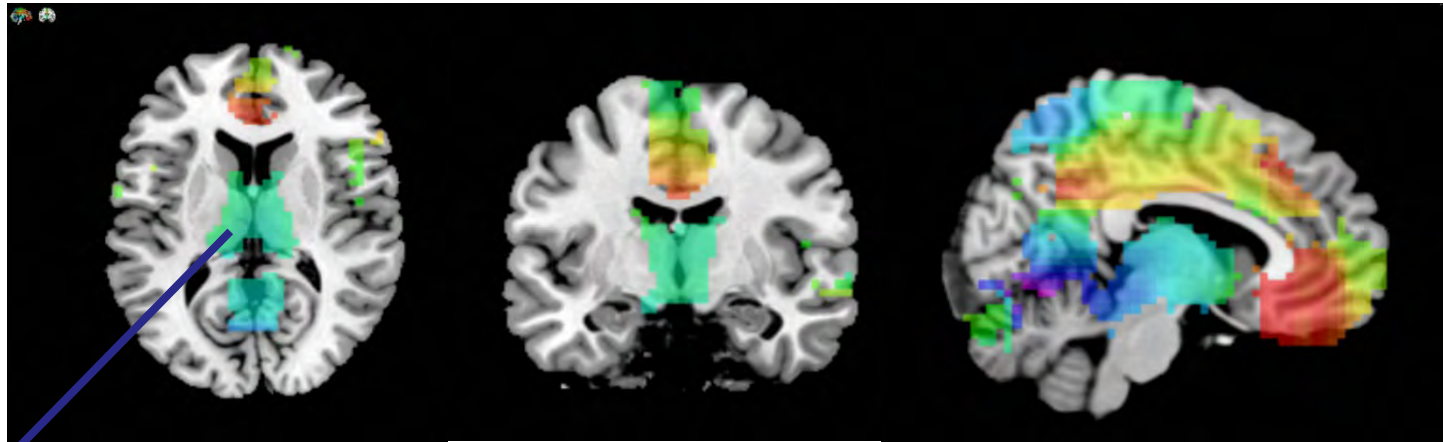
Anterior cingulate cortex (ACC)

ACC-filt - session 1

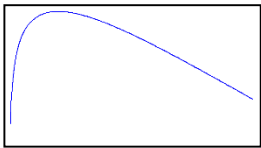


Clements Model → 75ng/ml

Temporal Characteristics (Brain T_{max}) of Ketamine



BOLD signal



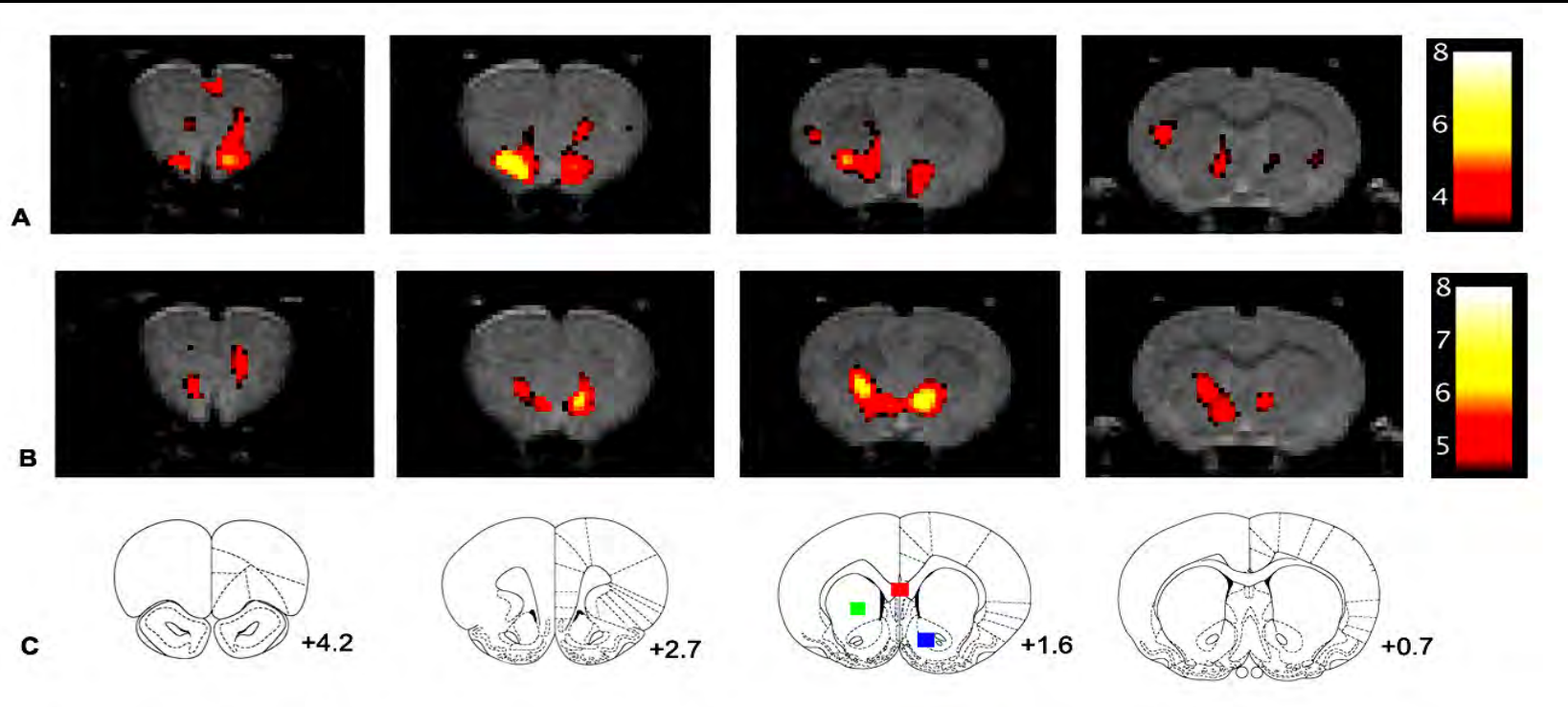
Time



Orla Doyle et al. (2012) NiPS

Pharmacological MRI of Quinelorane

D3



Group statistical parametric maps showing statistically significant increases in BOLD contrast after administration of 3 µg/kg quinelorane (A), or 30 µg/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

Correspondence to autoradiography (H3 antagonist)

1nM 3H-GSK189254-A
Sagittal section



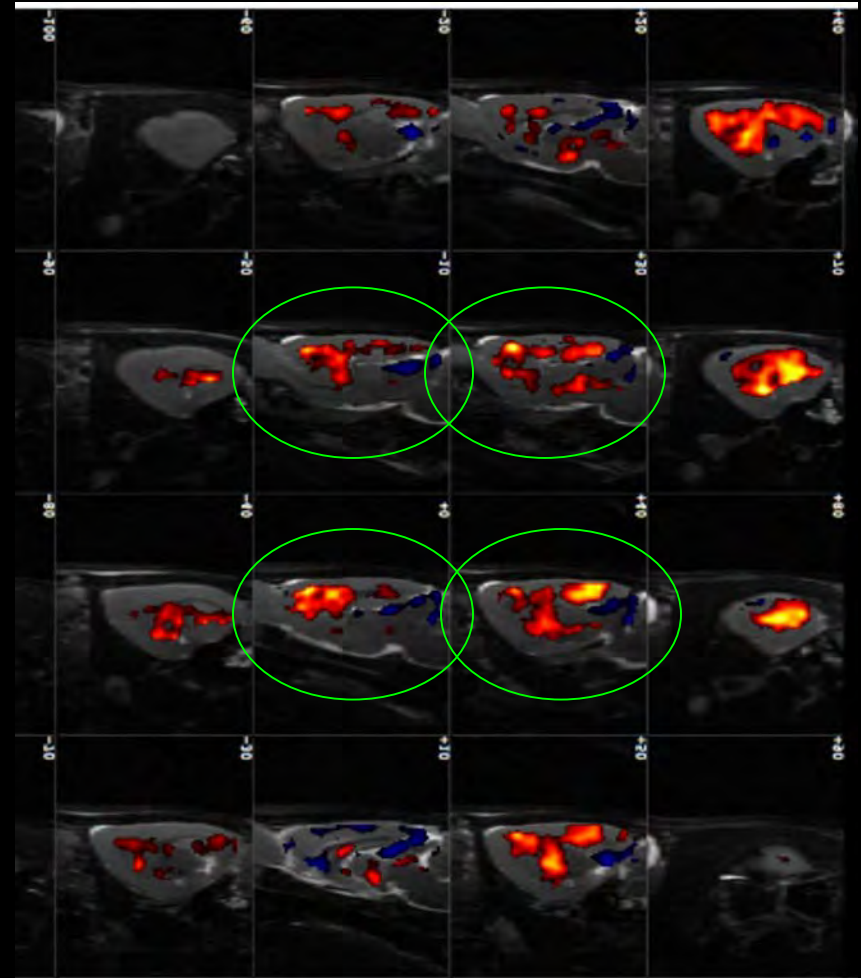
Cortex

Cerebellum

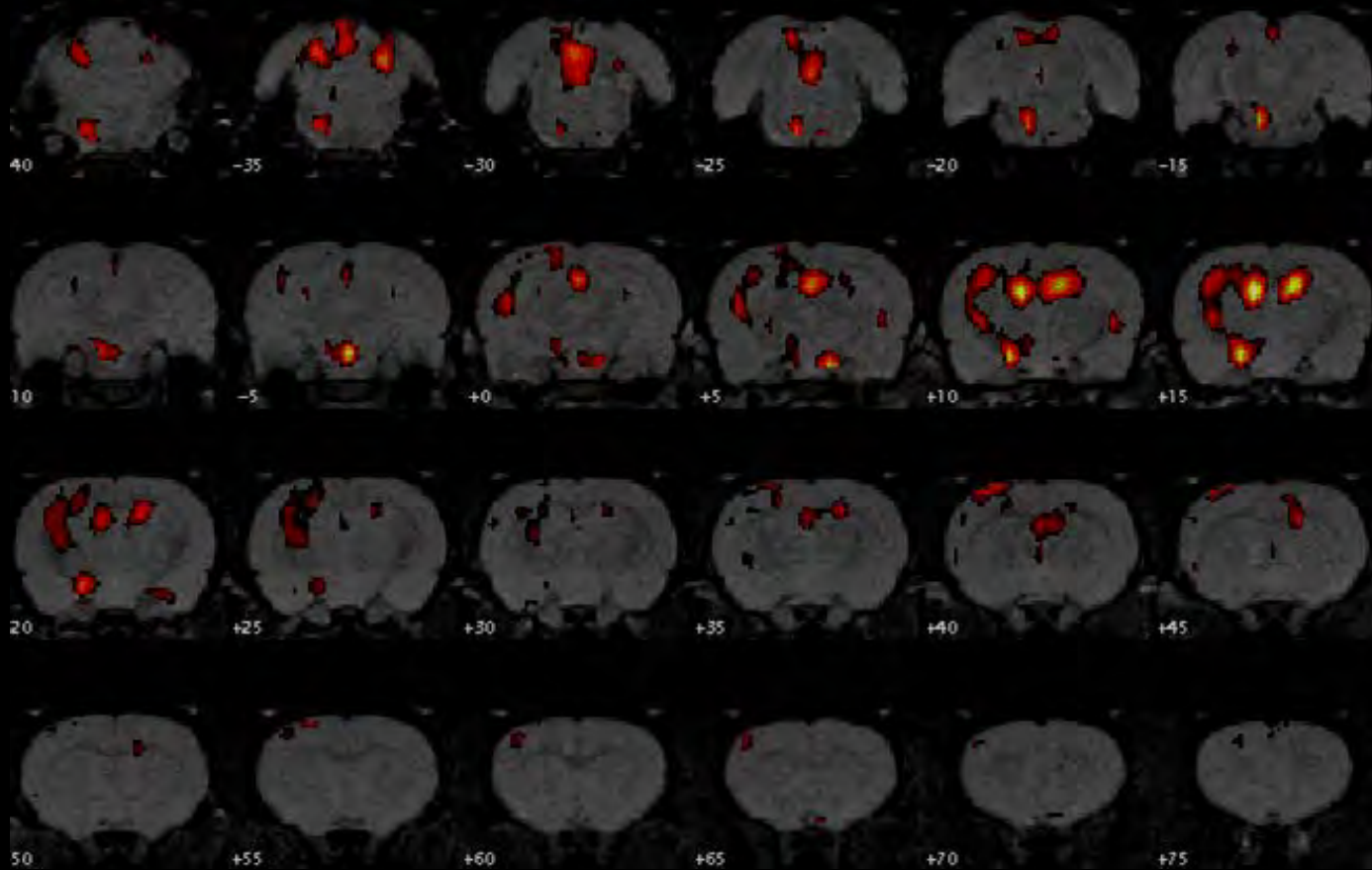
Caudate
Putamen

Nucleus accumbens

Substantia nigra



Main effect of LY404187 - an AMPA potentiator



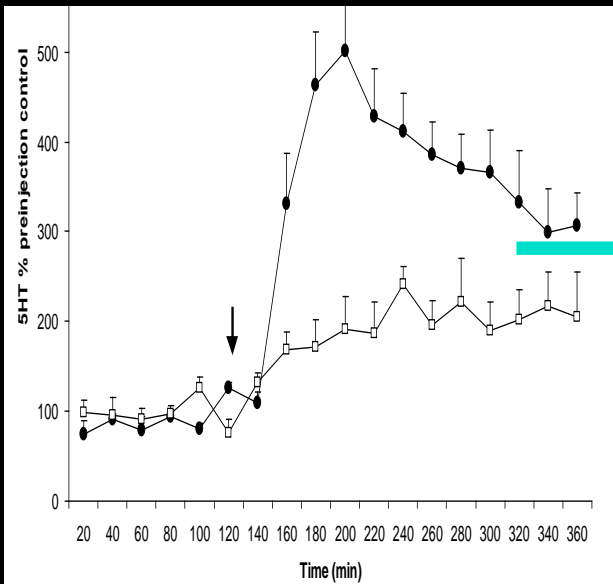
n = 7

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

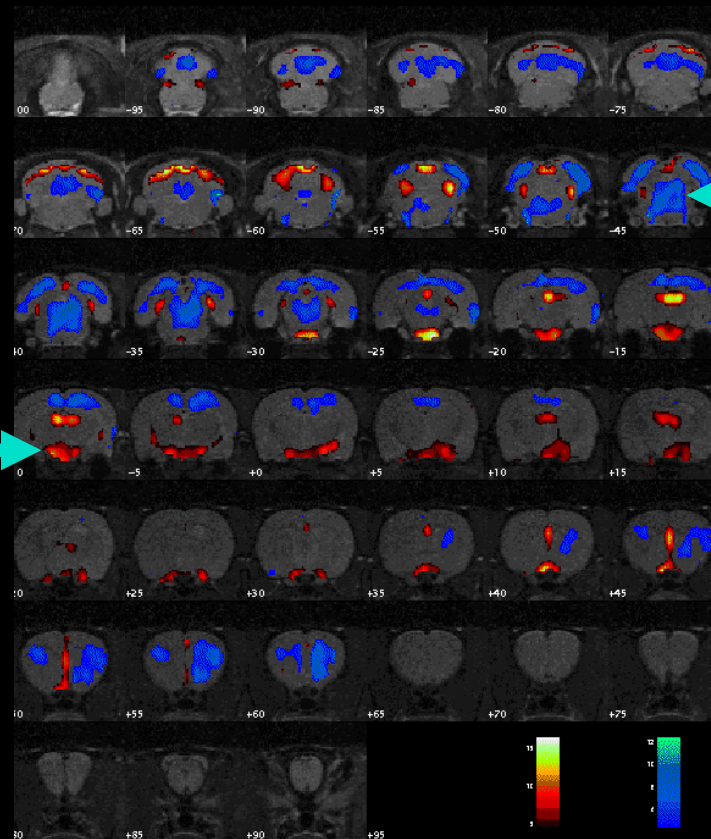
blocked by
selective
AMPA antagonist
LY293558

Nick Jones

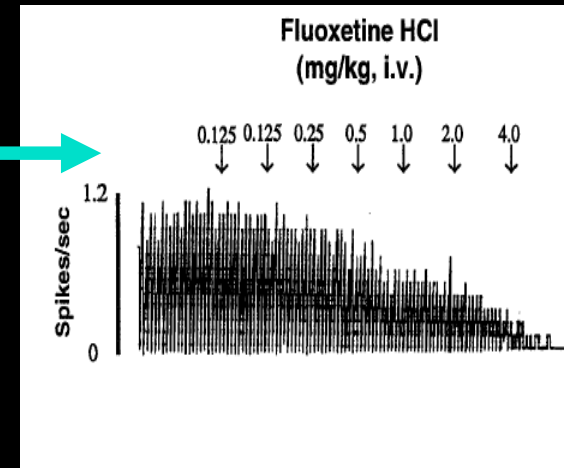
Functional Response to Acute Fluoxetine



Extracellular Levels of 5-HT
in the Hypothalamus

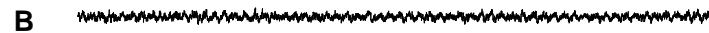
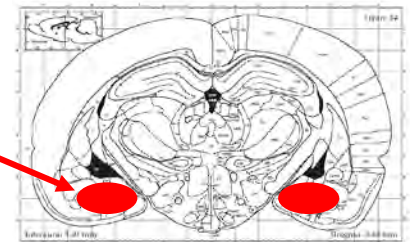
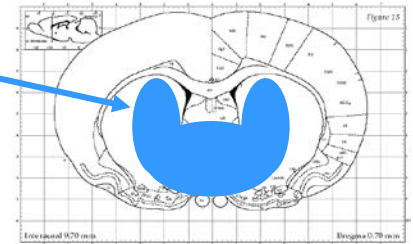
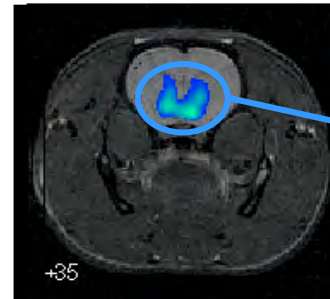
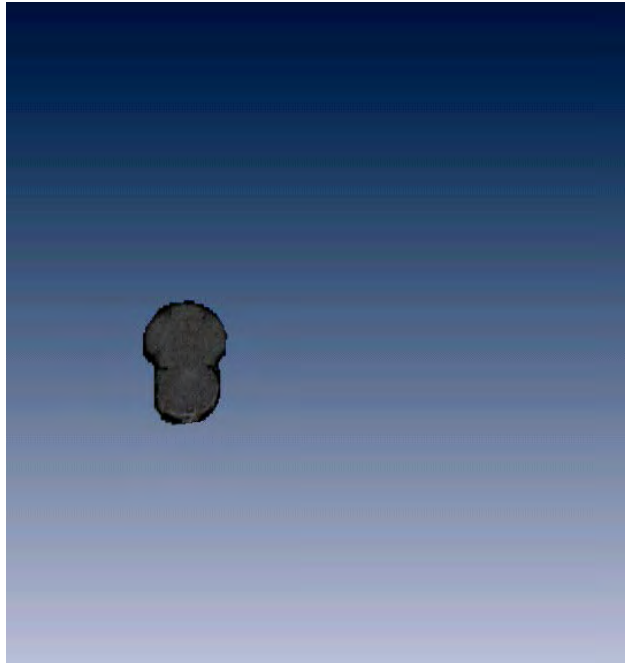


BOLD MR images



Single-unit, extracellular
recordings of serotonergic
neurons in the dorsal
raphe nucleus

fMRI - Picrotoxin v Control

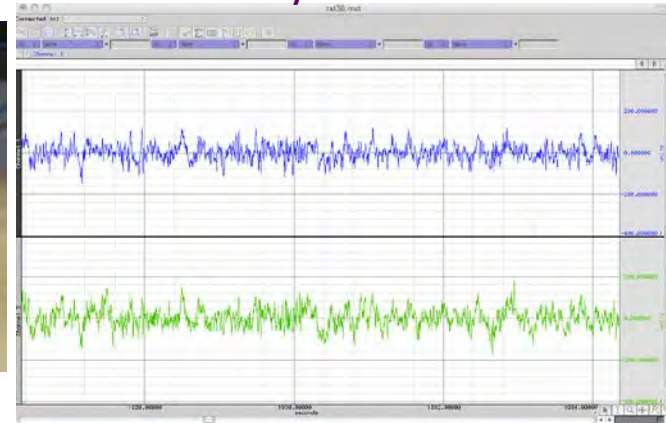
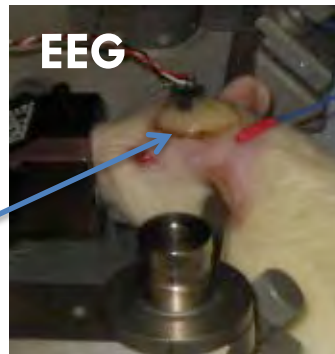
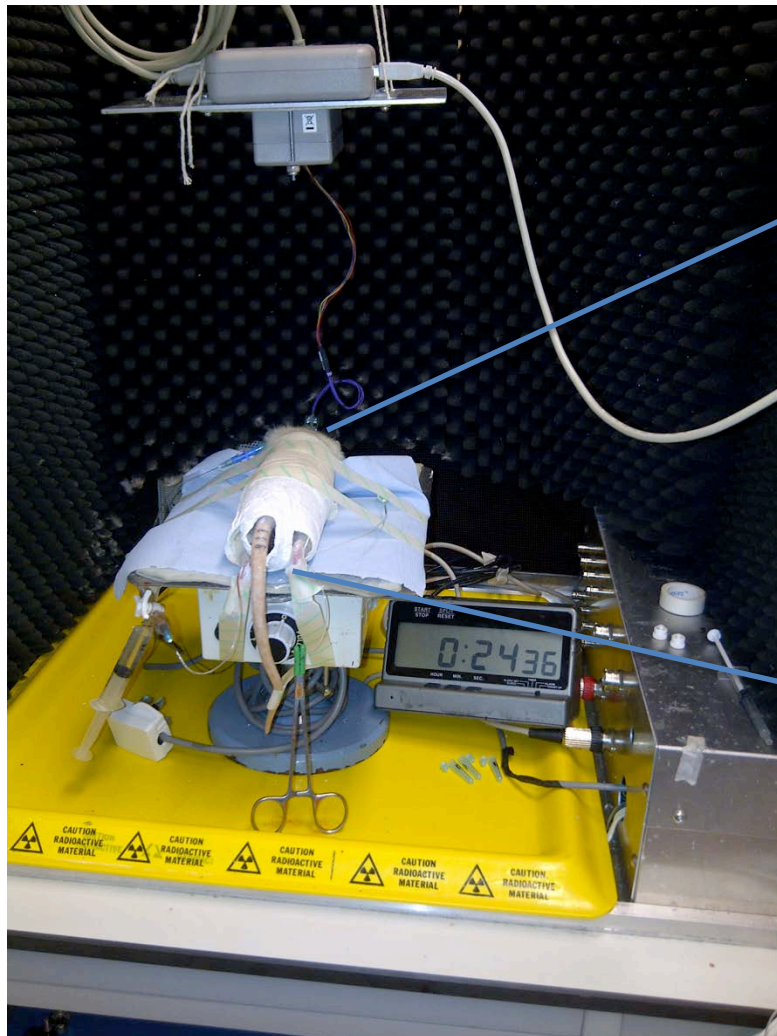


5 sec

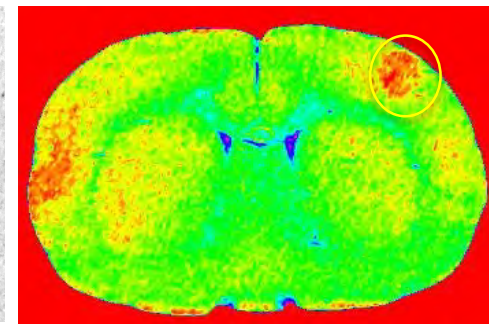
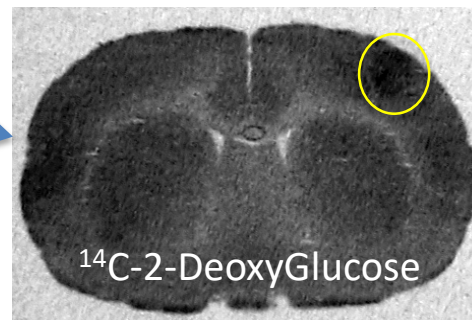
1 V

Bench techniques to corroborate fMRI: autoradiography (2DG) & EEG

Timecourse of neural activity

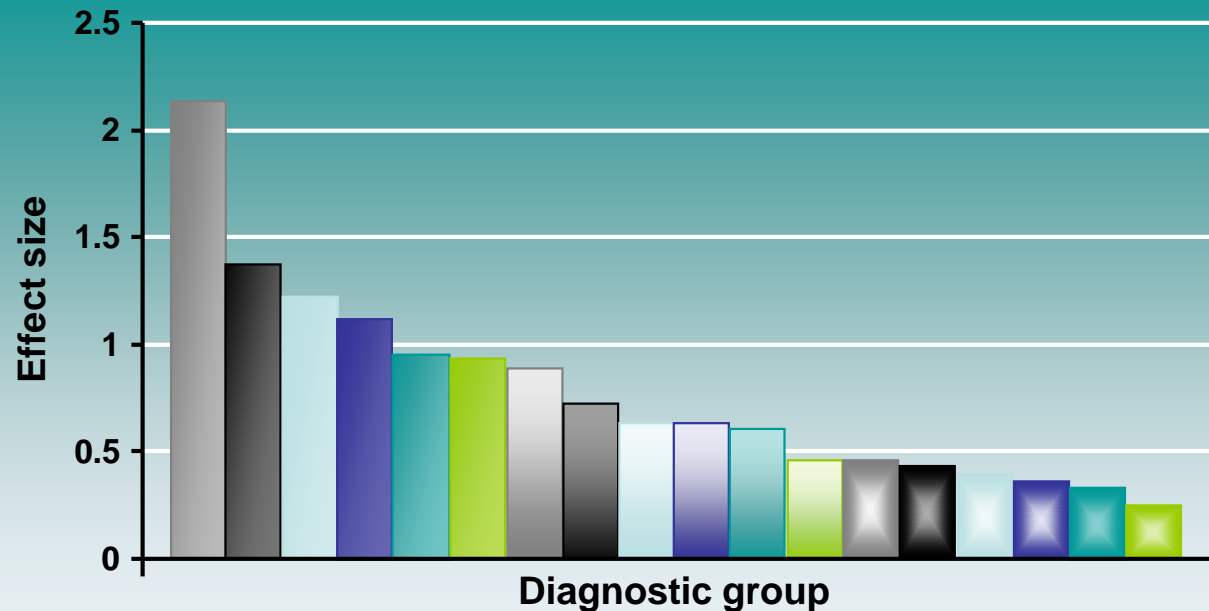


Snapshot of brain metabolism



Camilla Simmons, Michel Bernanos, KCL

Cognitive impairment across all mental illnesses



Mental retardation (n=223)

Organic personality disorder (n=135)

Schizophrenia (n=169)

Antisocial personality disorder (n=222)

Schizophreniform disorder (n=30)

Post-traumatic stress disorder (n=111)

Schizotypal personality disorder (n=78)

Histrionic personality disorder (n=141)

Narcissistic personality disorder (n=3938)

Dependent personality disorder (n=3642)

Drug abuse (n=29)

Affective disorder (n=97)

Dysthymia (n=244)

Somatoform disorder (n=95)

Obsessive compulsive disorder (n=73)

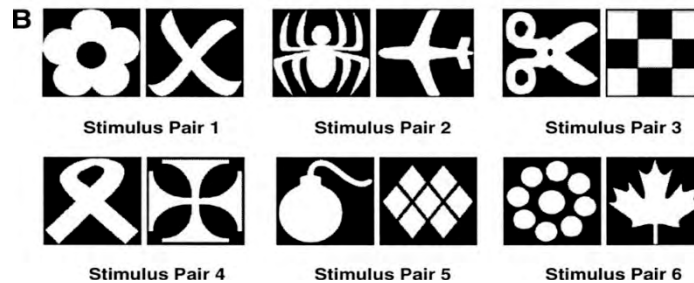
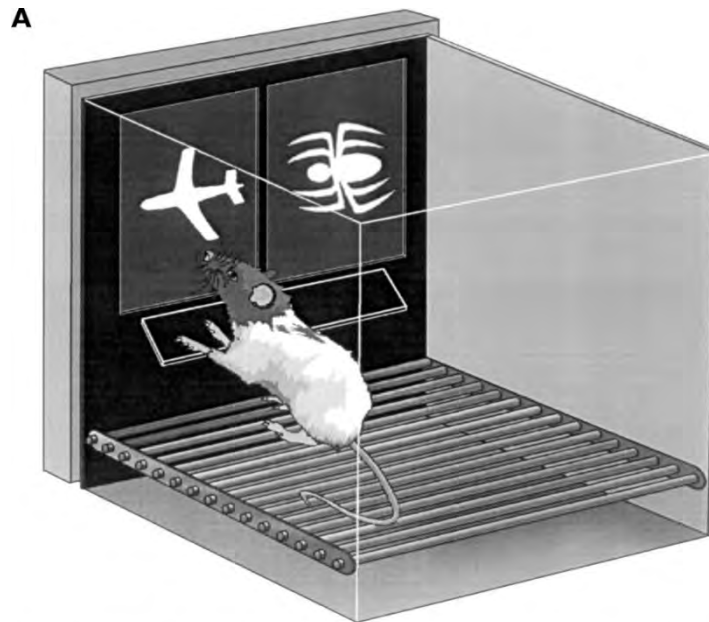
Anxiety disorder (n=693)

Adjustment disorder (n=417)

Obsessive compulsive personality disorder (n=96)

Mark Weiser, Michael Davidson et al., 2004

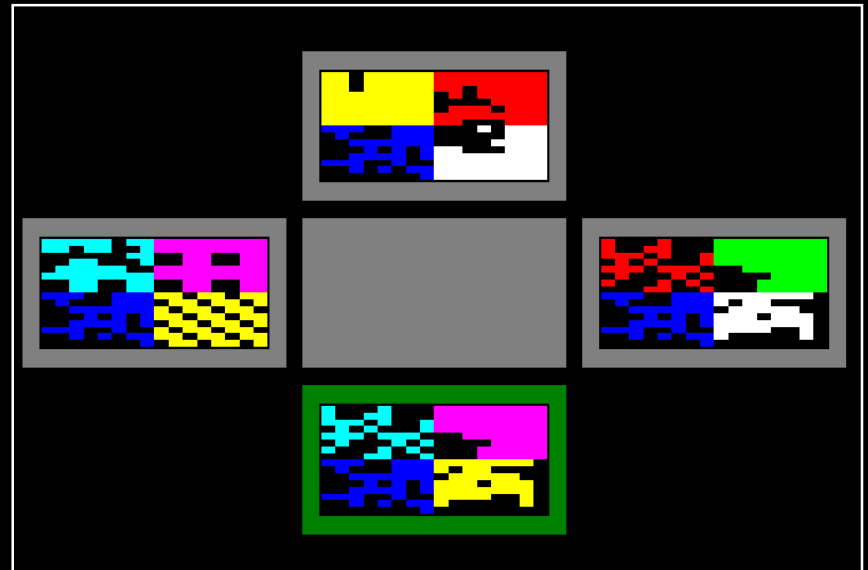
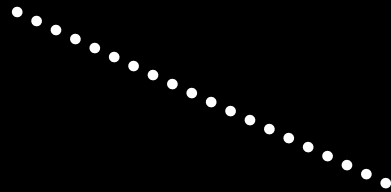
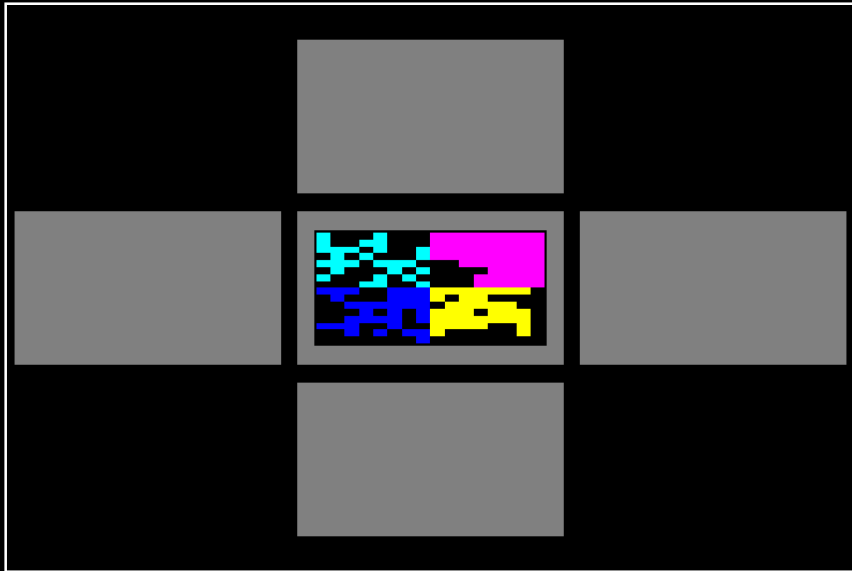
(A) The rat touchscreen apparatus.



Bussey T J et al. Learn. Mem. 2008;15:516-523



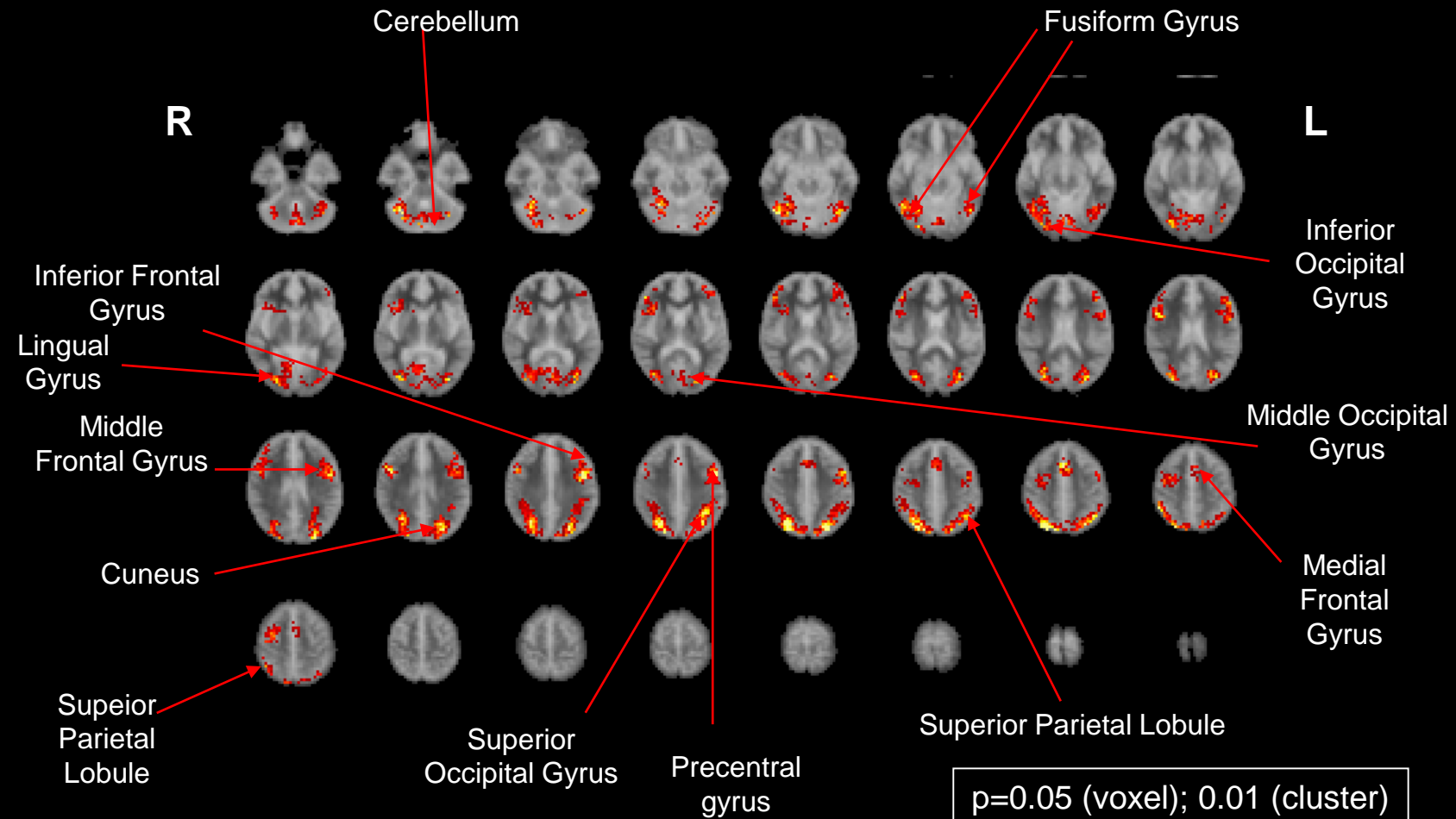
Delayed Match To Sample



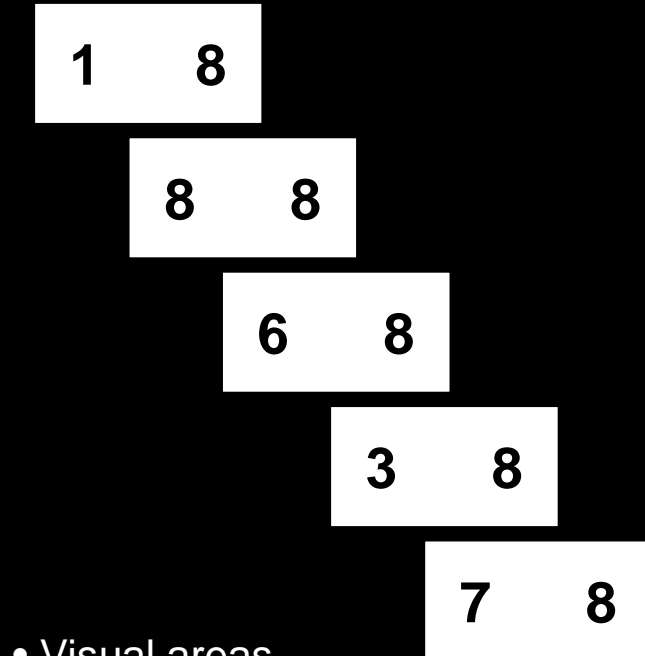
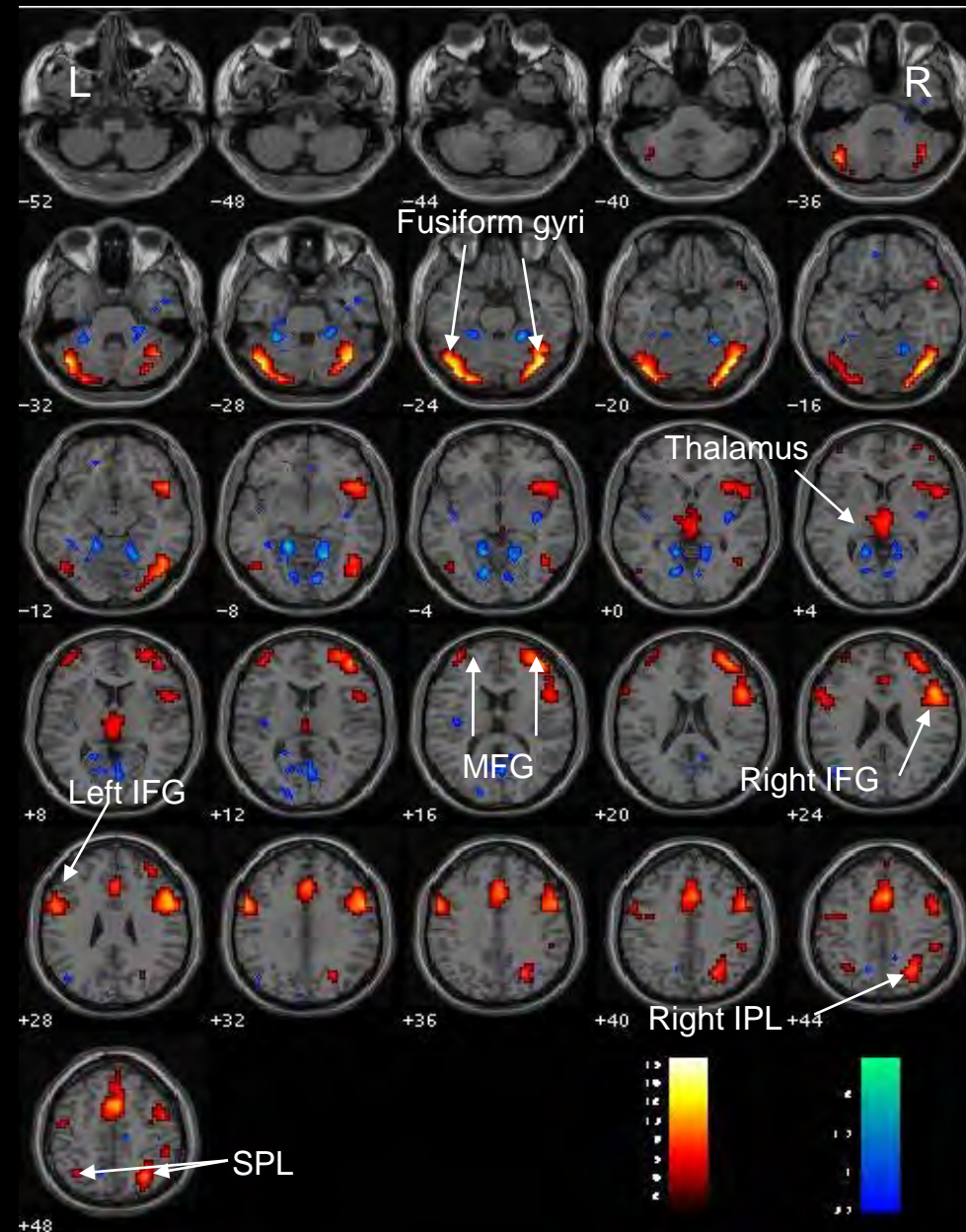
Mitul Mehta

D.M.T.S. - Group Map (n=14)

3 second delay vs control condition



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)

Morris Water Maze



Normal



Neocortical control lesion

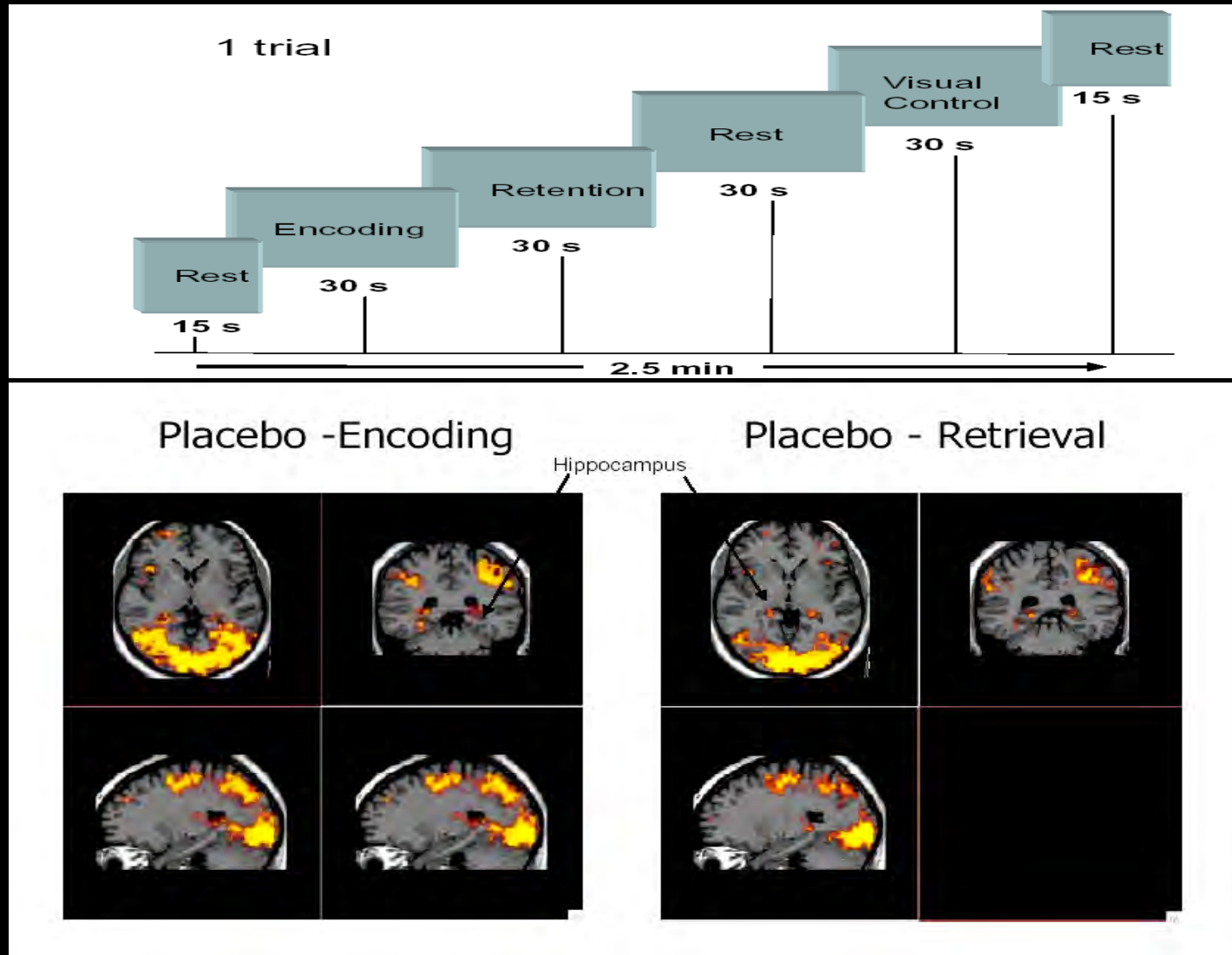


Hippocampal lesion

The Arena Task in the Scanner



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



Precision Psychiatry – Aiding Depression Management

FMRI Task – “Is the Face Male or Female?”



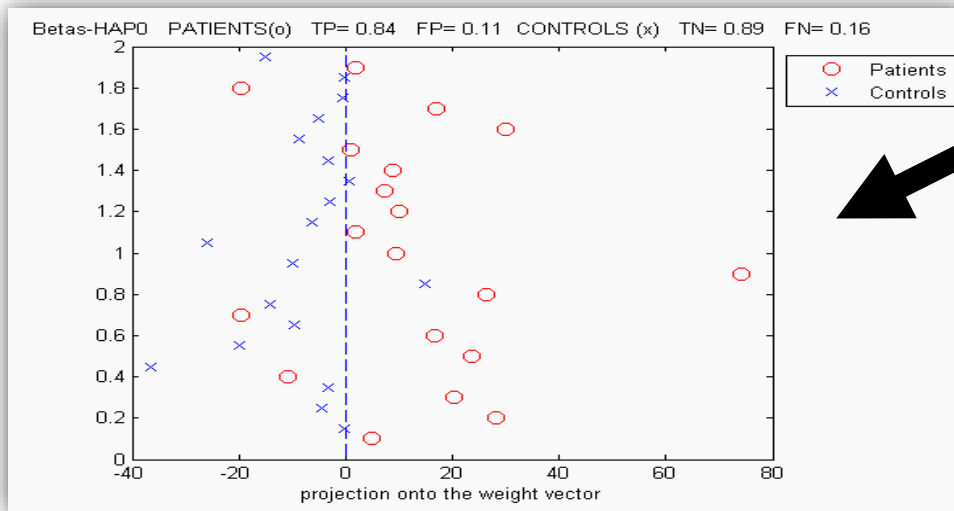
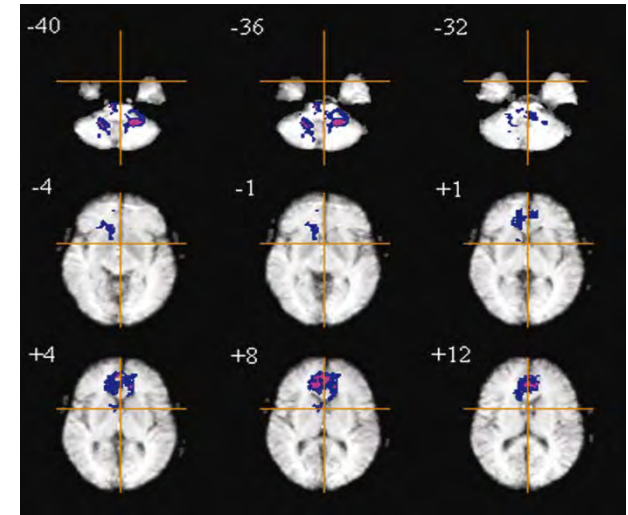
Neutral



Sad



Sadder



85% Accuracy of Diagnosis

82% Accuracy of Treatment Response

Why bother with Neuroimaging (phMRI) in Drug Development?

- Visualise central effects of drug - dose ranging
- Fingerprint may inform potential indication(s)
- Inform clinical (imaging) protocol
- Serial assessment – reduce n, reduce cost
- Neurobiological correlation with behaviour
- Pharmacodynamic profiling – acute and chronic
- Drug discrimination
- Add on therapies – drug-drug interaction
- Abuse liability

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