
# From Neurons to Perception: ***How Physics Opened the Black Box***

Irene Tracey

Head of Nuffield Department Clinical Neurosciences
& Nuffield Chair of Anaesthetic Science,
University of Oxford,
England UK

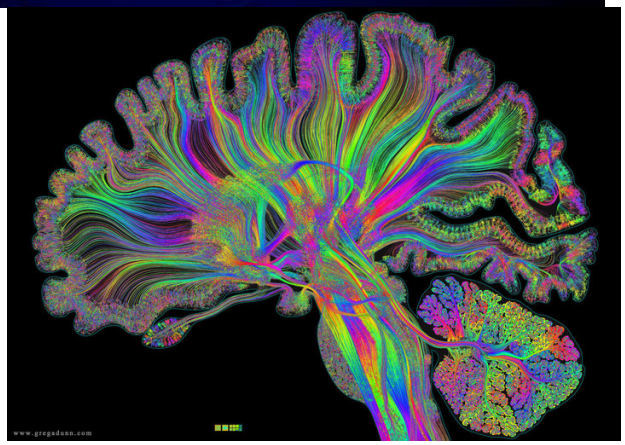
NUFFIELD DEPARTMENT OF
CLINICAL NEUROSCIENCES

# The Early Years…



# The Human Brain

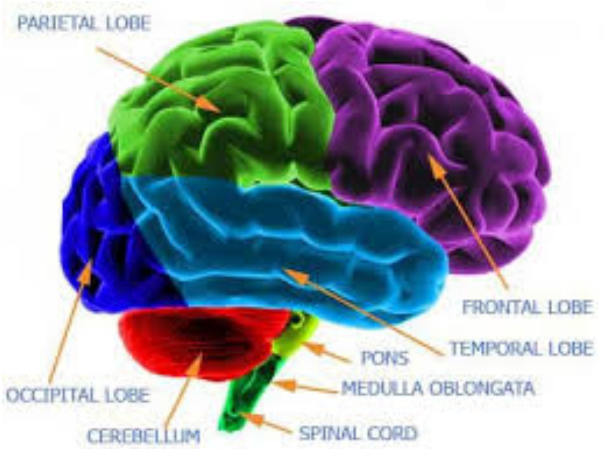
- Neurons are computational elements
- White matter connects the neurons
- The connection is called the synapse

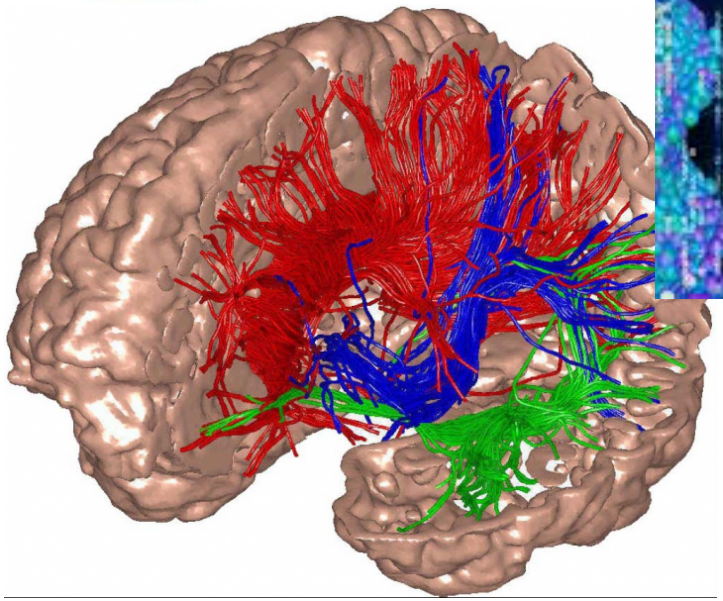


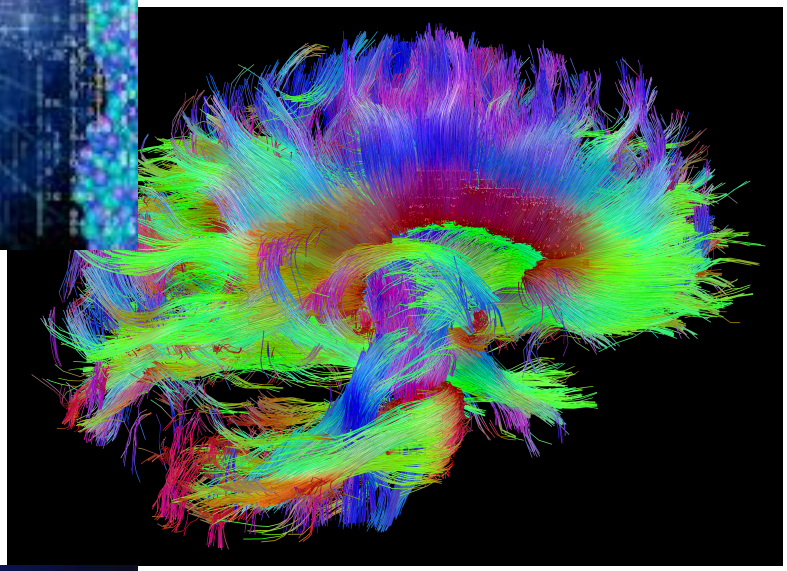
**Weighs:** 1.4 Kg
**Neurons:** 100 billion (and >100 billion glial cells)
**Synapses/neuron:**1000-10,000
**Most connections:** local (10-100 μm); some span many centimetres
**Neurons multiply at a rate 250,000 neurons/min during early pregnancy!**

200-400 billion stars in Milky Way

# The Human Brain



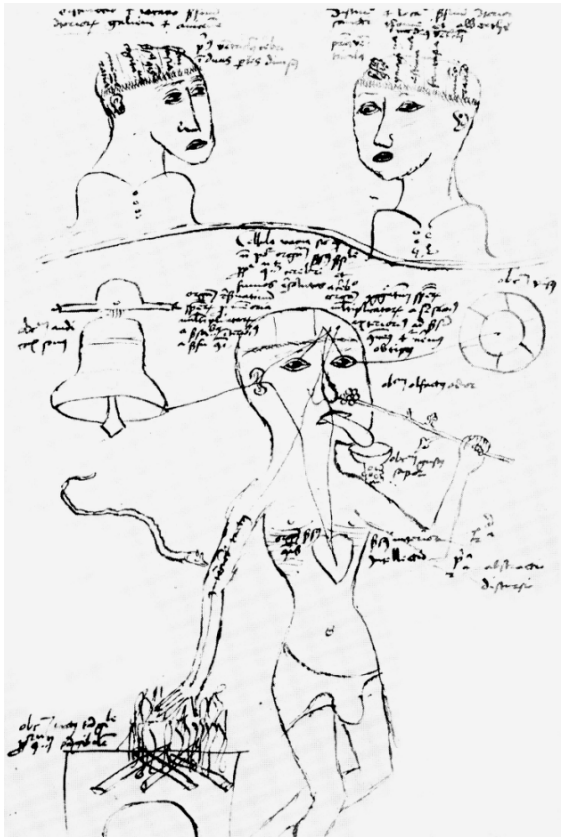





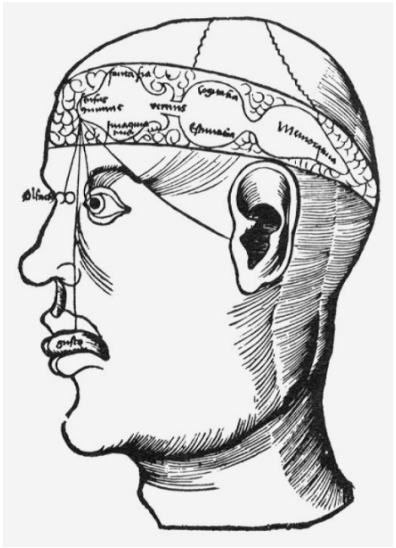
Hippocratic School of physicians (400 BC) first challenged ancient supernatural concepts of illness:

*"Not only our pleasure, our joy and our laughter but also our sorrow, pain, grief and tears arise from the* ***brain****, and the* ***brain alone****. With it we think and understand, see and hear, and we discriminate between the ugly and the beautiful, between what is pleasant and what is unpleasant and between good and evil"*

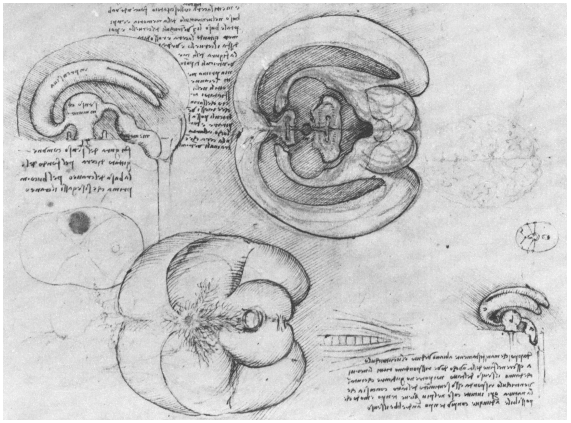
# Early attempts - antiquity



Arrangement of brain ventricles known from the great Greek anatomist, Galen (130-200 A.D.)



From ***sensus communis***, images created and passed onto middle ventricle - seat of reason (**ratio**), thought (**cognatio**) or judgement (**aestimatio**). Final step was memory itself (**memoria**), in last ventricle.



By 1506, Leonardo made wax cast of ventricles. He wrote ***"sensus commune"*** not on banana-shaped first pair of ventricles but on the middle one.

This scheme persisted until 17th century – questioned in Renaissance – two men in particular: **Leonardo da Vinci and Rene Descartes.**

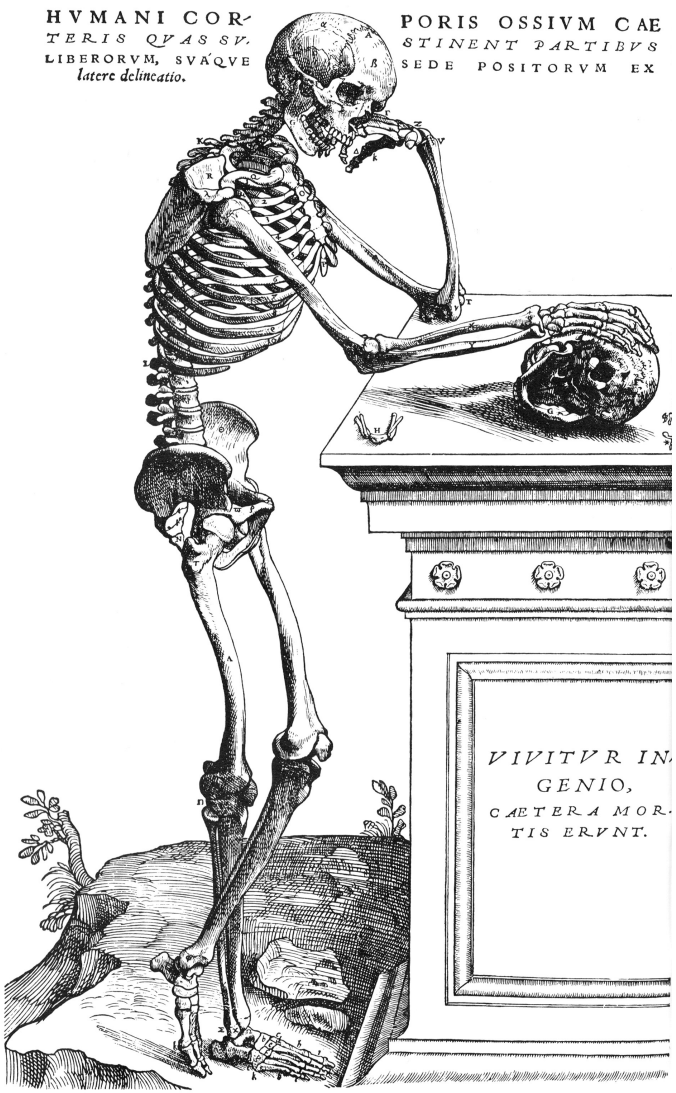
*“Copying the round shape of the universe, they confined the two divine revolutions in a spherical body – the head, as we now call it – which is the divinest part of us and lord over all the rest.”*

**Plato, Timaeus**

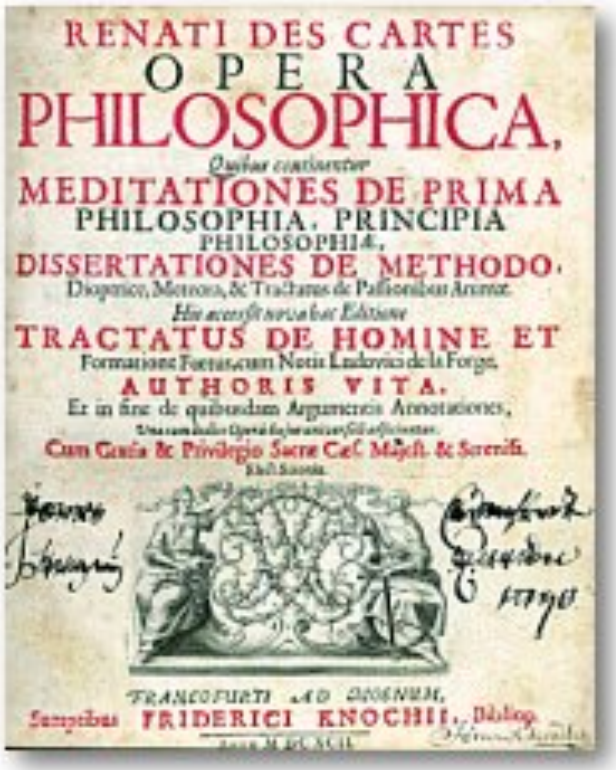
BUT controversy waged throughout Classical Antiquity, the Middle Ages and beyond as to whether the soul was sited in the brain or heart:

*“Tell me where is fancie bred,*
*Or in the heart, or in the head”*

**Merchant of Venice, 1596**



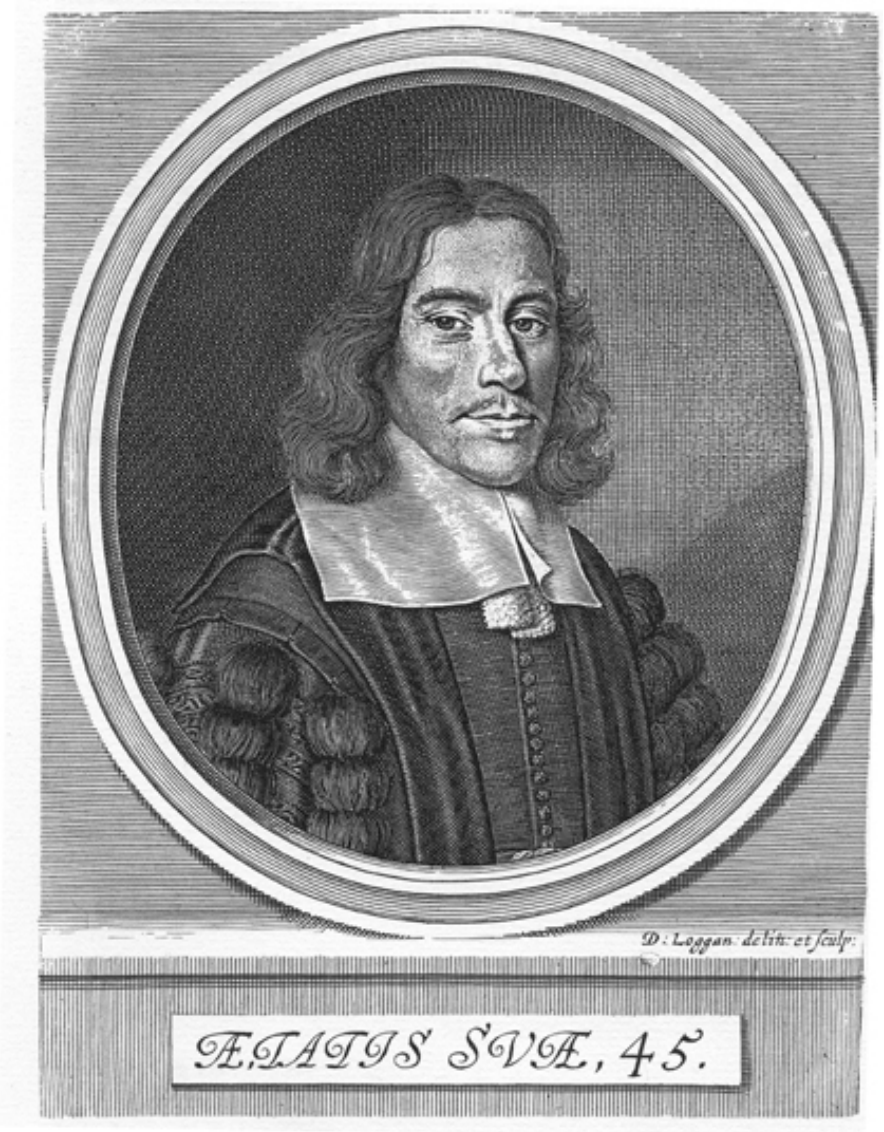

A skeleton contemplates a skull. *From De Fabrica (1543) by* ***Andreas Vesalius,*** perhaps the greatest anatomist of all time




Descartes contribution (1596-1650) - radical distinction between a mind and a body – made explicit principle of ***dualism*** – freed men, even devout ones, to speculate about working substance of brain without treading in footprints of God.

# Thomas Willis

Oxford's Sedleian Professor of Natural Philosophy (1660-1675)




Behold Gods
Providence.

# The Chang Mai Thai Restaurant

Imprimatur,

Jan. 20. 1663. THO. GRIGG R. in Christo Pat. ac Dno D. *Humfr.* Episc. *Lon.* à sac. Domesticis.

CEREBRI
# ANATOME:

CUI ACCESSIT

*NERVORUM DESCRIPTIO*

ET USUS.

STUDIO

THOMÆ WILLIS, ex *Æde Christi* *Oxon.* M. D. & in ista Celeberrima Academia Naturalis Philosophiæ Professoris *Sidleiani.*

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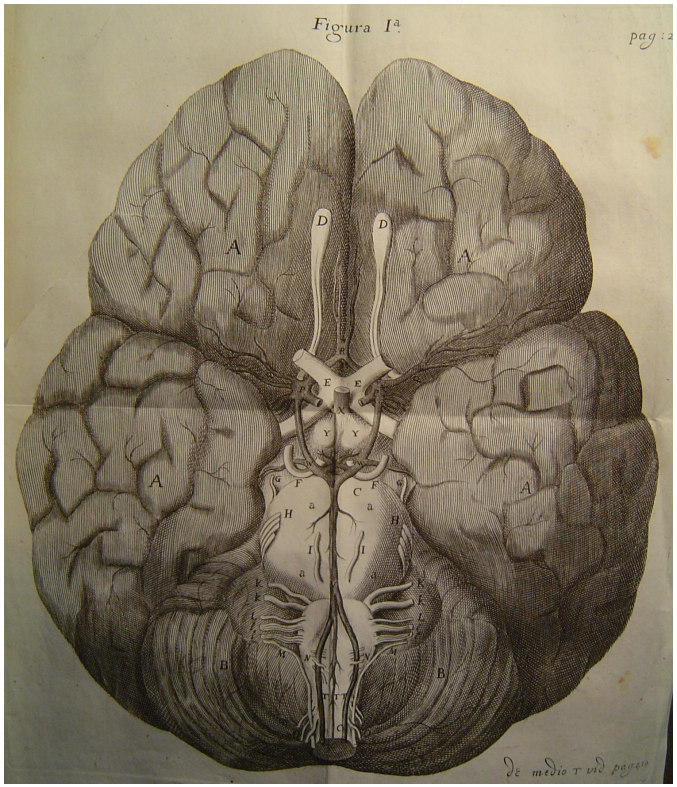
*LONDINI,*

Typis *Ja. Flesher*, Impensis *Jo. Martyn* & *Ja. Allestry* apud insigne Campanæ in Cœmeterio *D. Pauli.* MDCLXIV.

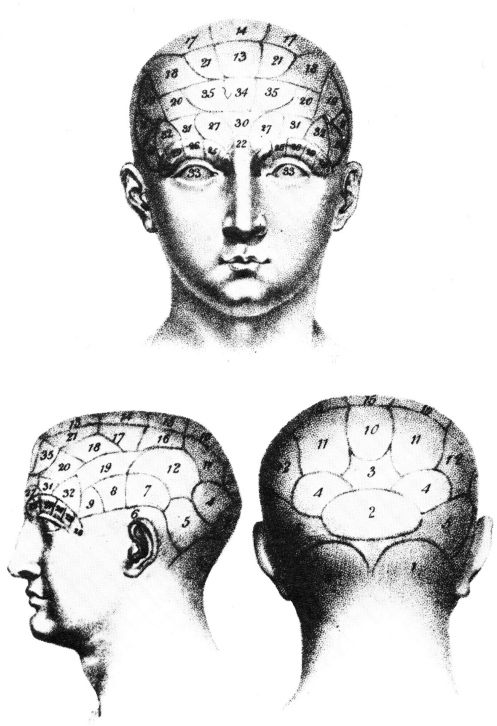


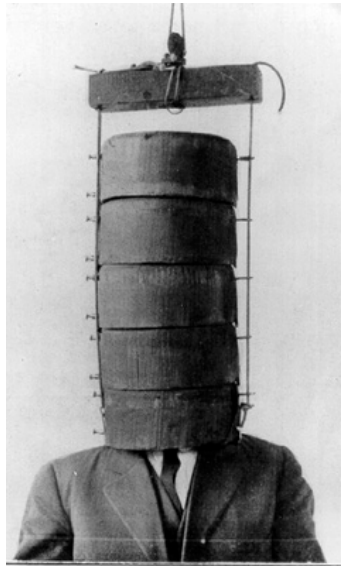
# Circle of Willis




"The cerebrum is the primary seat of the rational soul in man, and of the sensitive soul in animals. It is the source of movements and ideas."

# The Era of Folly



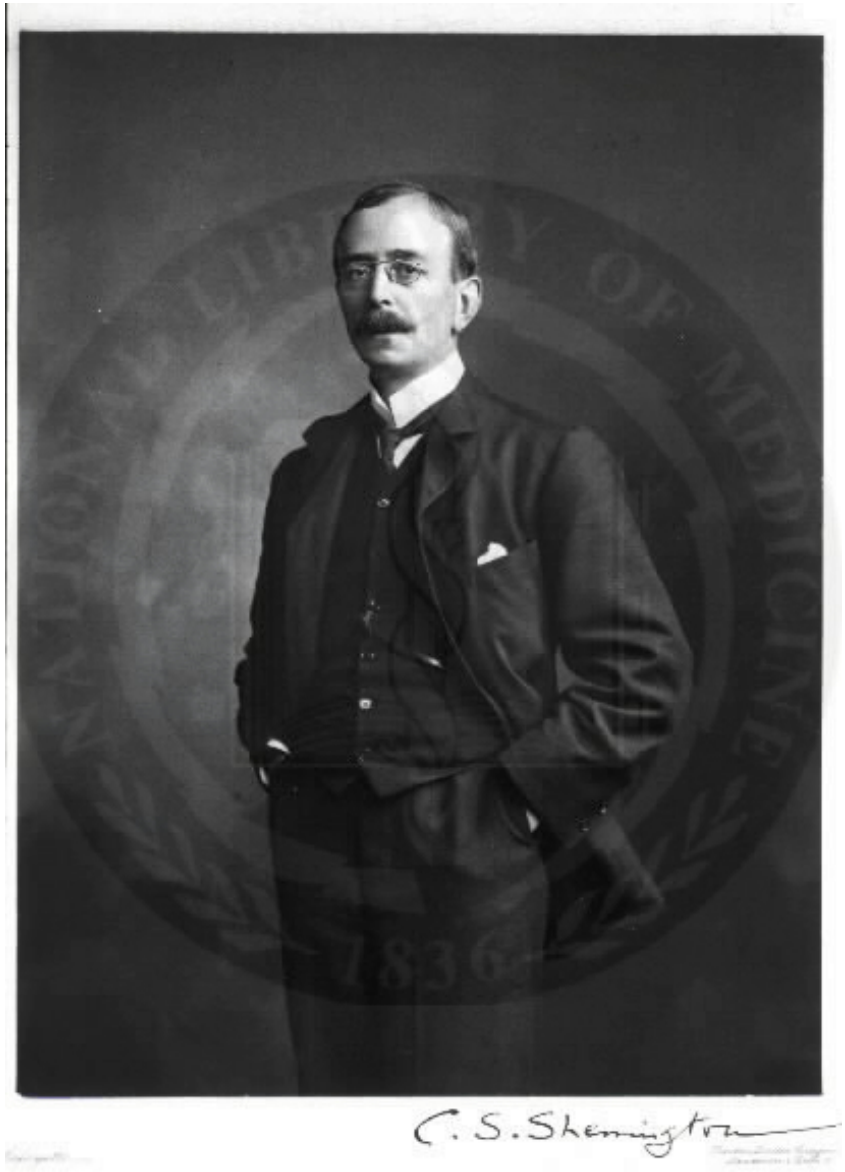


Early Transcranial Magnetic Stimulation

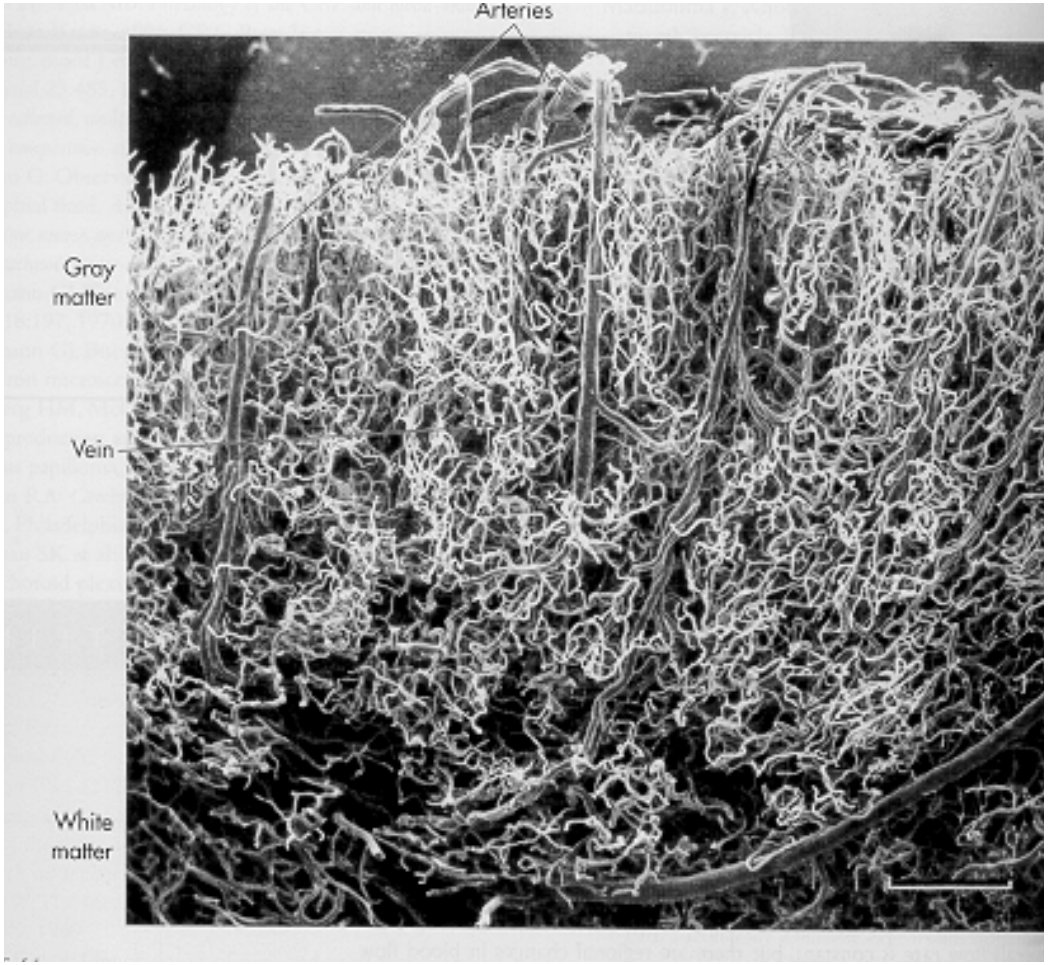
Franz Joseph Gall (Viennese physician, 1758-1828)
*"….number of acquaintances with particularly good memories also had, large protruding eyes. I was forced to idea that eyes so formed are the mark of an excellent memory…why should not other faculties also have their visible external characteristics?"*

# Sir Charles Scott Sherrington

1857-1952




# The Human Brain is a highly perfused organ




Historical Perspective:
Roy and Sherrington, 1890 proposed coupling of cerebral blood flow to metabolism

# Brain Blood Flow and Oxygen Consumption Coupling

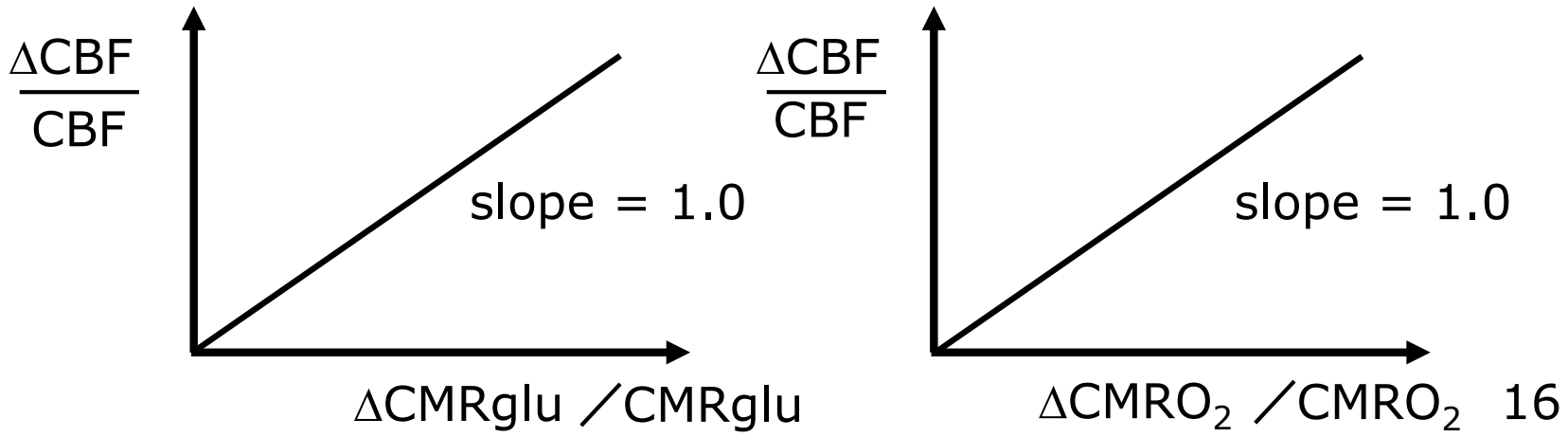
**ON THE REGULATION OF THE BLOOD-SUPPLY OF THE BRAIN.** By C. S. ROY, M.D., F.R.S., *Professor of Pathology, University of Cambridge,* AND C. S. SHERRINGTON, M.B., M.A., *Fellow of Gonville and Caius College. Lecturer on Physiology in the School of St Thomas's Hospital, London.* Plates II., III. and IV.

*From the Cambridge Pathological Laboratory.*

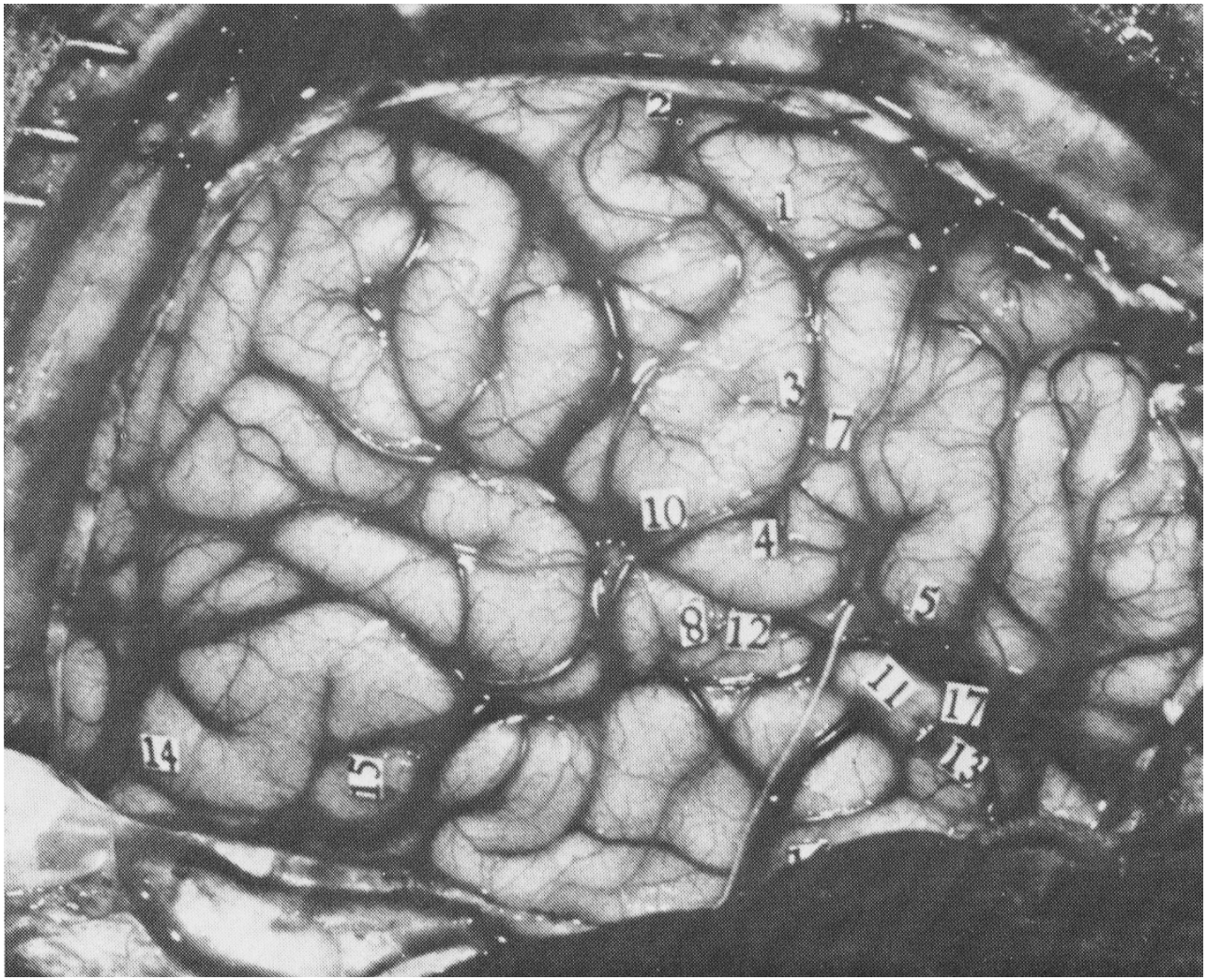
ONE marked characteristic of the literature dealing with the cerebral circulation is, we think, the contradictory nature of the results which have been obtained by different investigators.

Coupling confirmed in resting brain 1970s–1980s. Almost all neuronal energy derives from oxidative glucose metabolism

Journal of Physiology 1890;11(1-2):85-158.17



# …..open surgery – ethics?



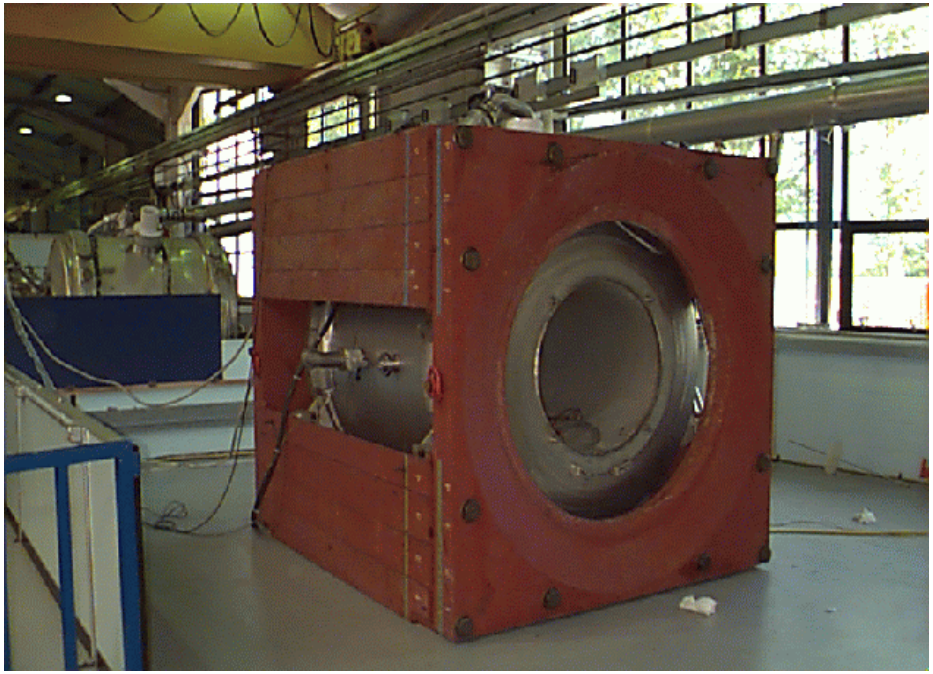

***Wilder Penfield (1891-1976).***

During one operation - electrically stimulated places marked with numbers.

**The woman fully conscious - described curious sensations:** recollection of woman calling her child evoked by stimulation at spot marked 11, and a circus from spot marked 13.

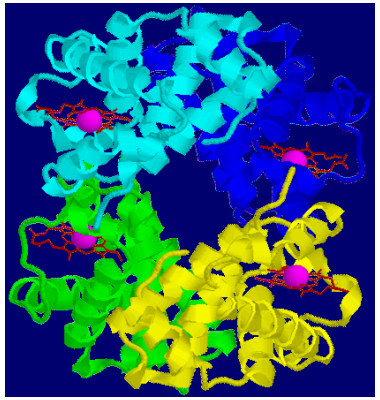
# The Era of Magnets

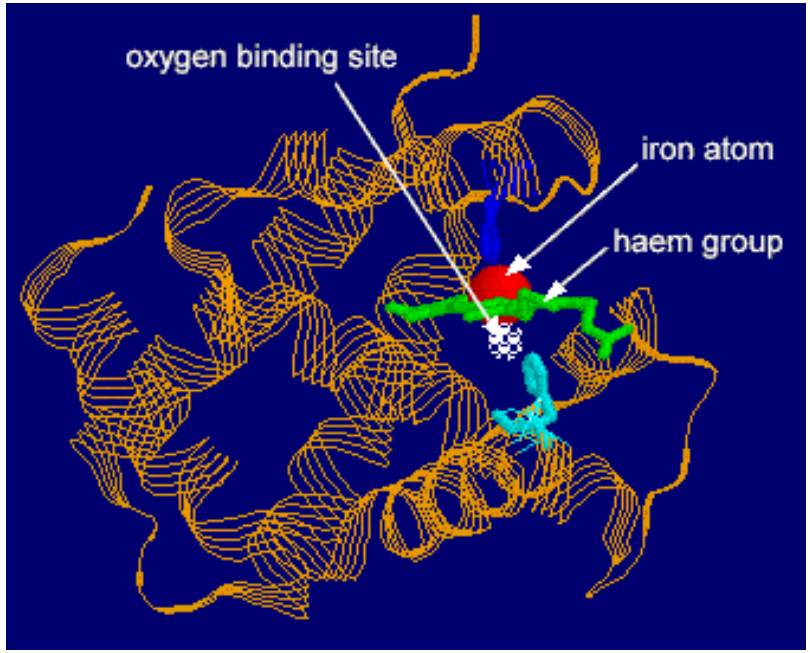
Sir Martin Wood – Oxford Instruments 1960's
(superconducting)



# Magnetic Properties of Hemoglobin

- The oxygen is supplied by the blood.
- Since oxygen is not very soluble in water it is bound to haemoglobin.
- Haemoglobin is an organic molecule with an iron atom bound in the centre.





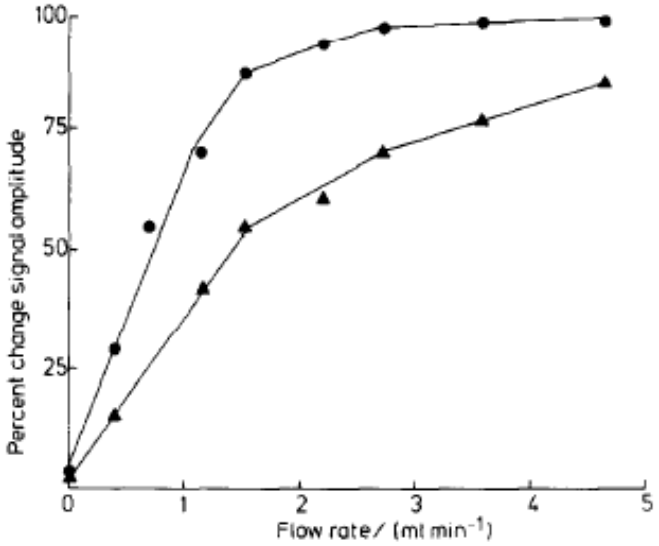

Oxy-hemoglobin
Diamagnetic
(same as tissue)

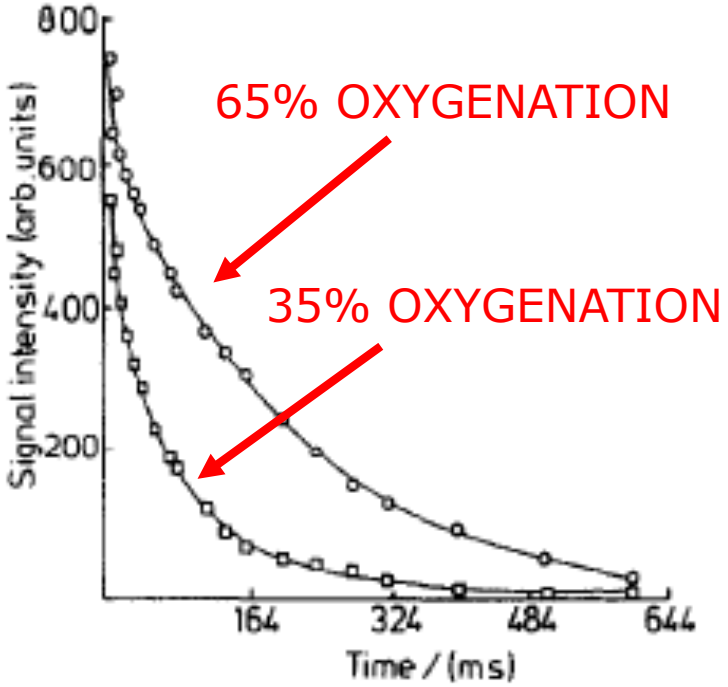
Deoxy-hemoglobin

Paramagnetic

$\Delta\chi \approx 0.08$ ppm

# Using Magnetic Resonance to measure Blood Flow and Oxygen Consumption

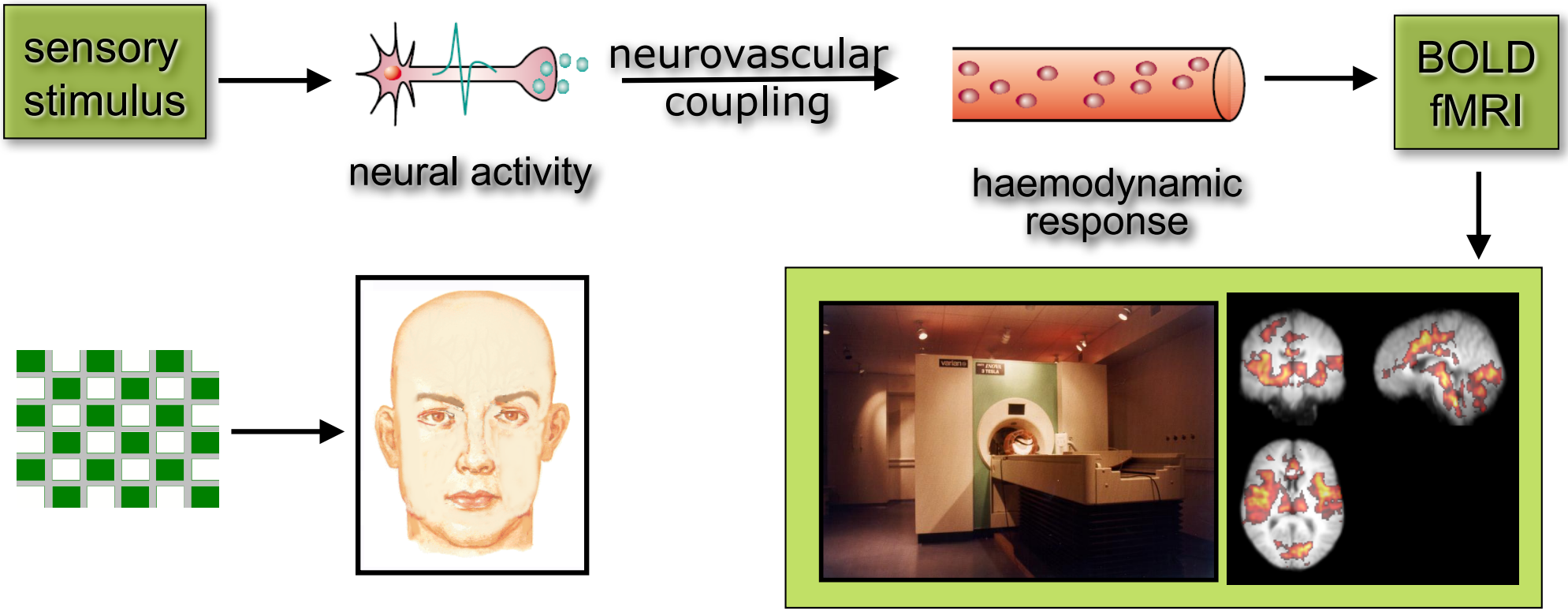



Thulborn, Waterton & **Radda**, J.Mag.Res. 1981
Biochemistry Department, Oxford

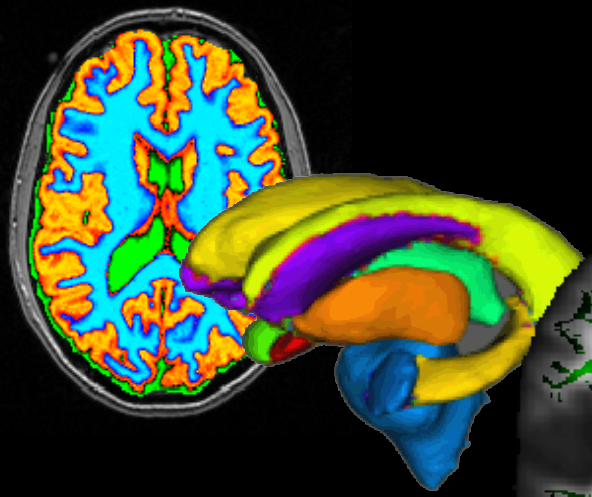
# Physiological Correlate of FMRI

- Hemodynamic response to a stimulus
- Indirect measure of neuronal activity
- Spatial resolution: millimetres
- Non-invasive = longitudinal studies (ideal for
  - assessing drug-related effects, patients, etc)
- No radioactivity involved

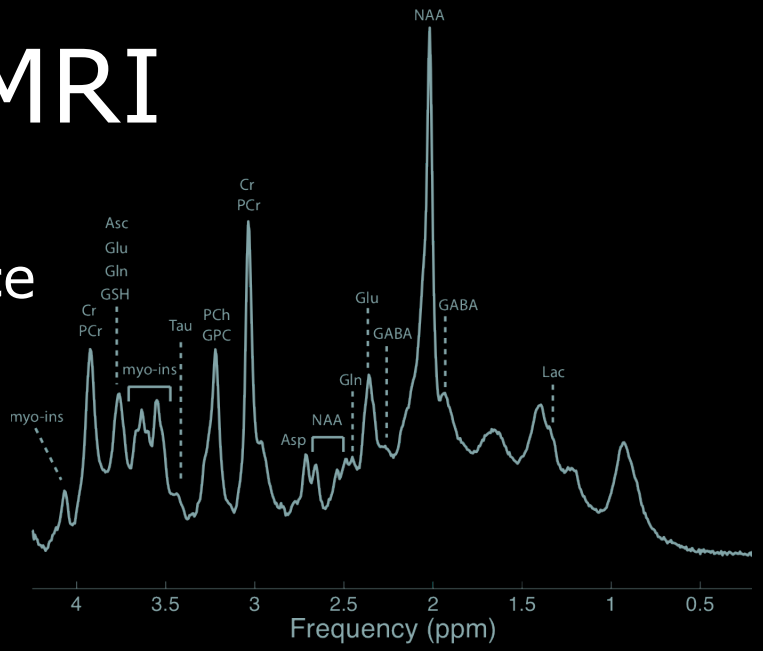


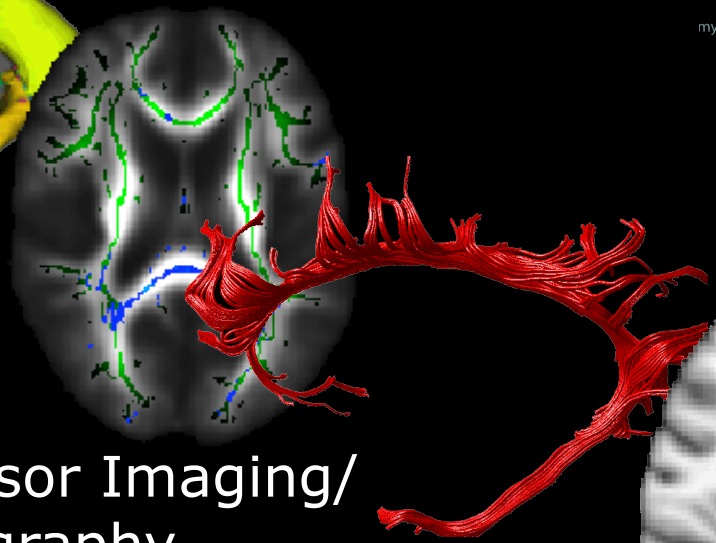
# Advanced MRI

Volumetric measures

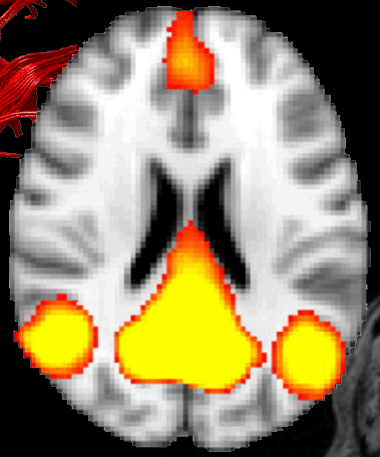


Magnetic Resonance Spectroscopy

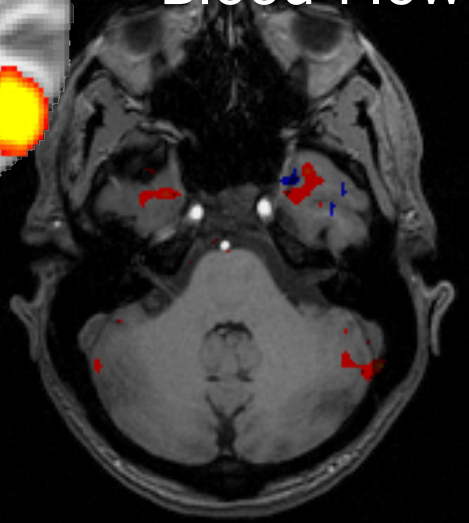


Diffusion Tensor Imaging/ Tractography



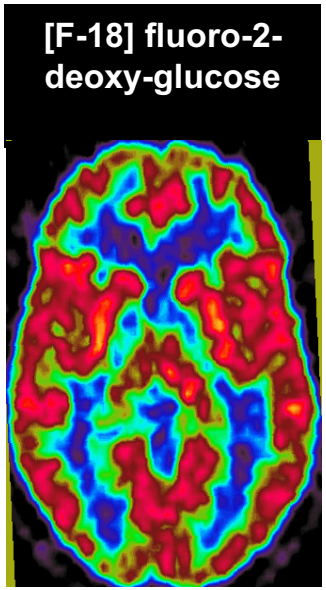
Task FMRI/Cerebral Blood Flow

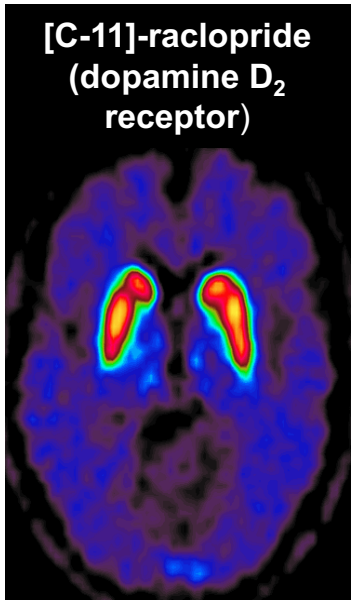


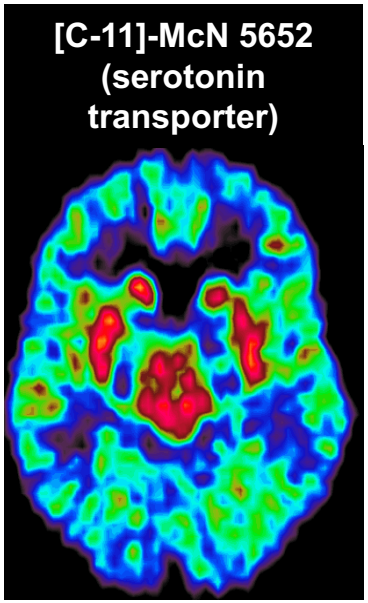
Resting FMRI

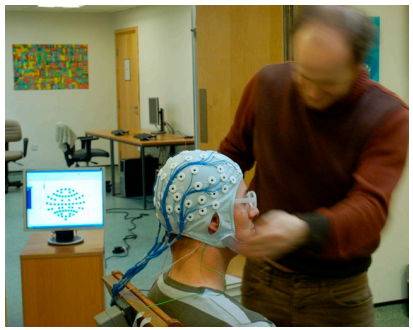
# Other Imaging Tools Available

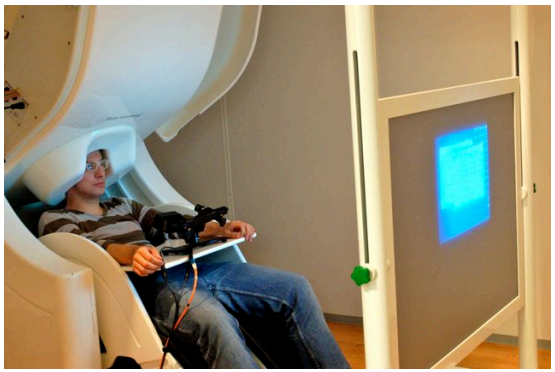
## MEG, EEG, PET

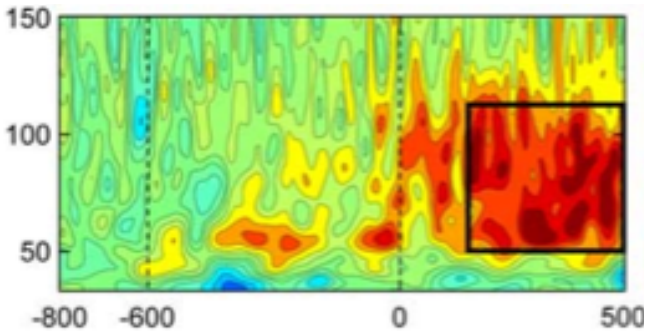


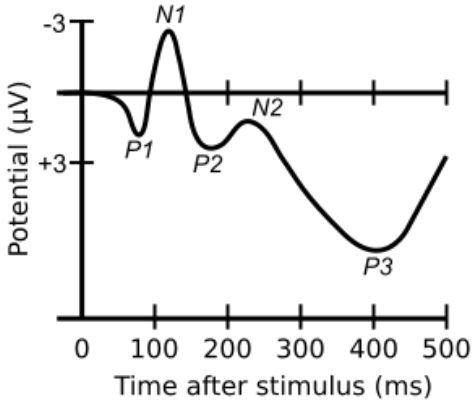



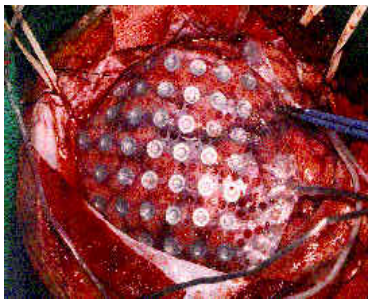





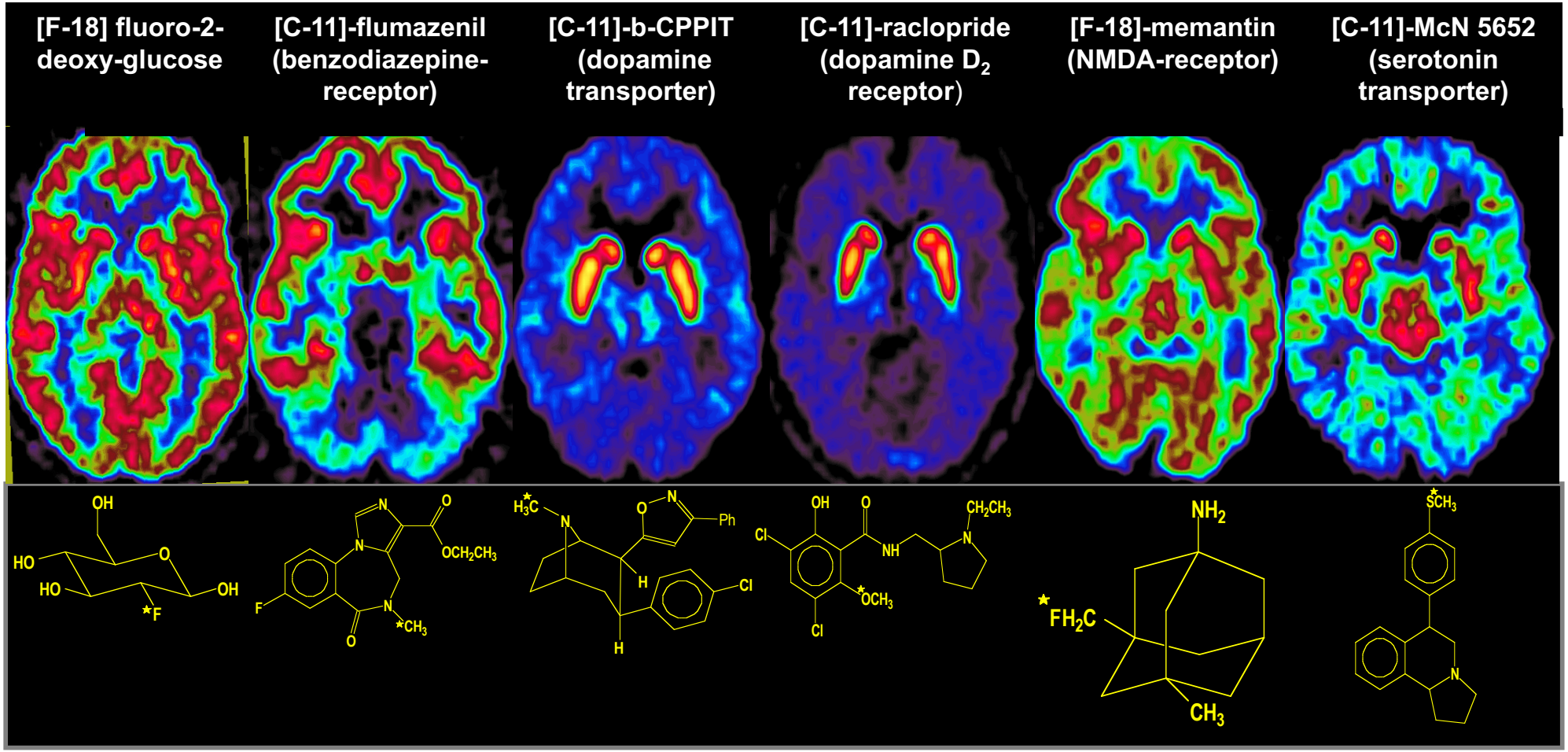


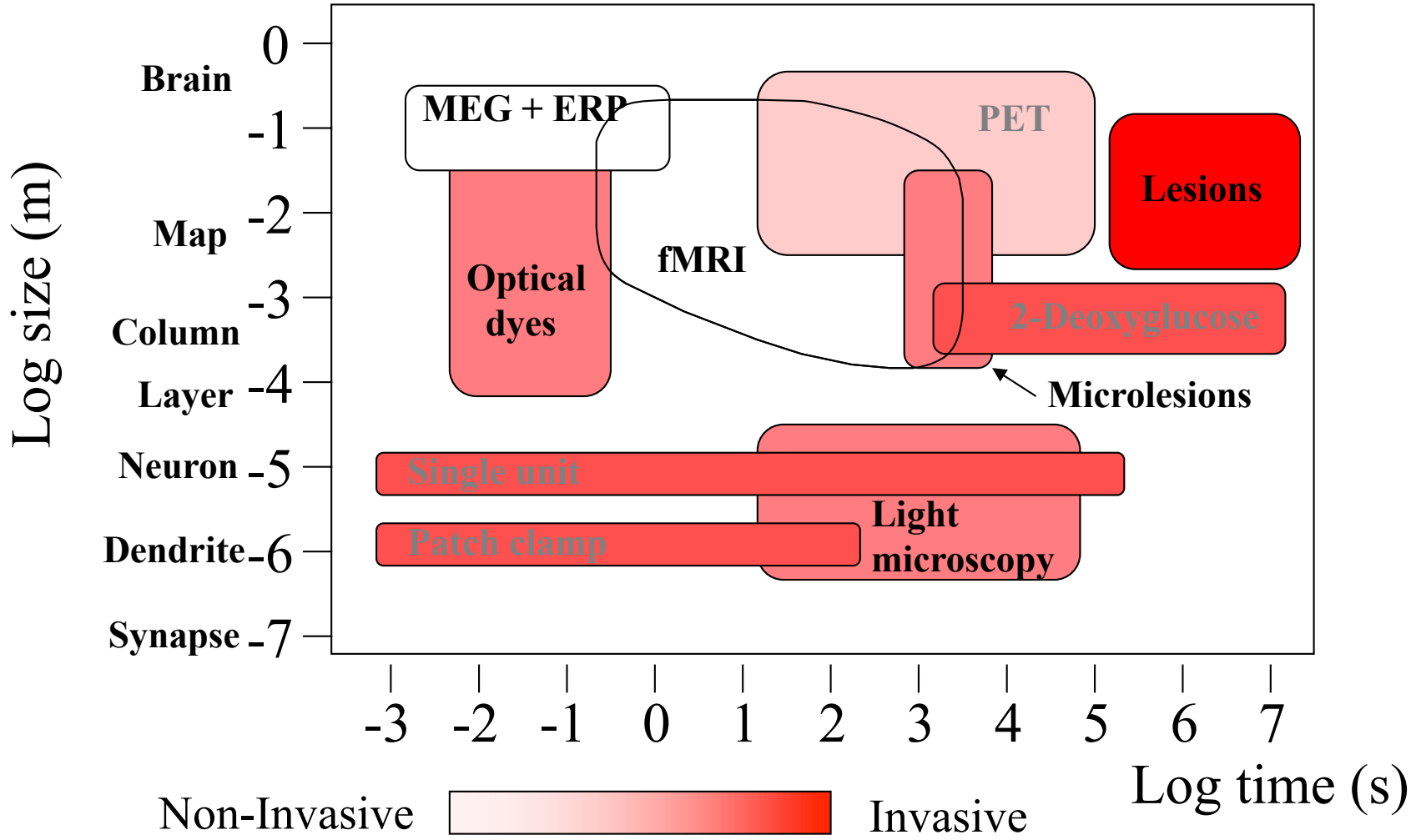



Implanted electrodes

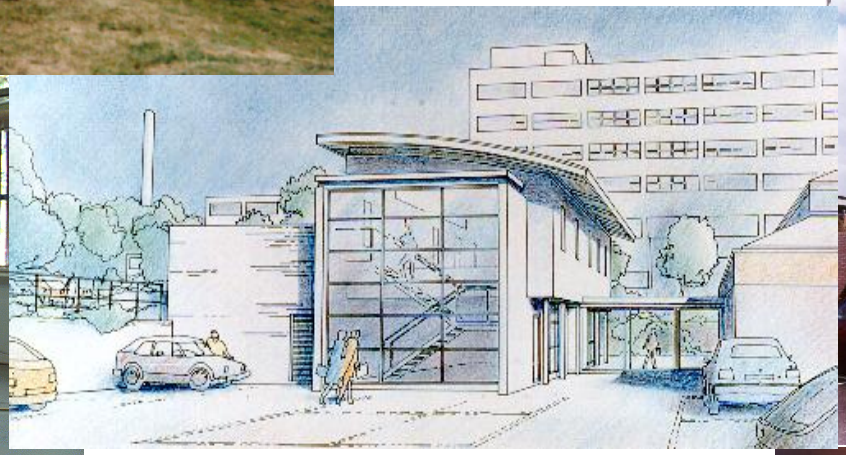
# Brain Receptor System Images

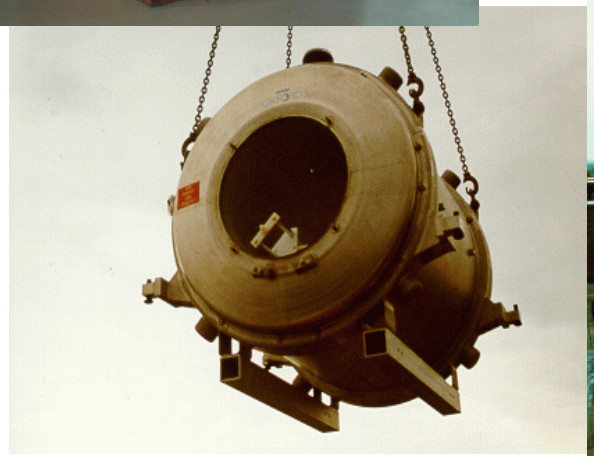


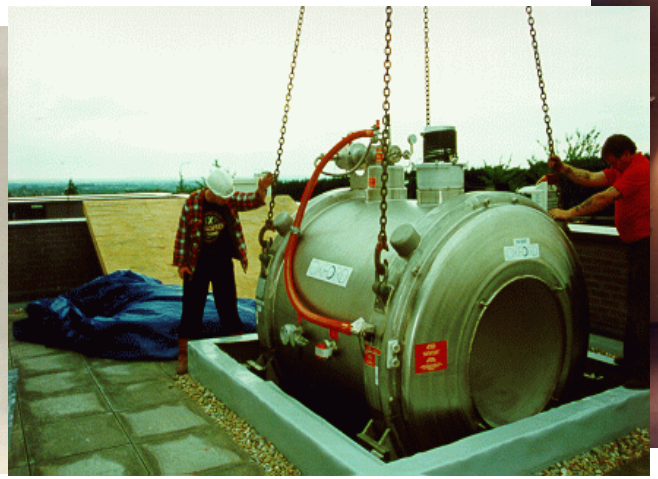
# Functional Mapping Methods:
## cost/balance between resolution and invasiveness

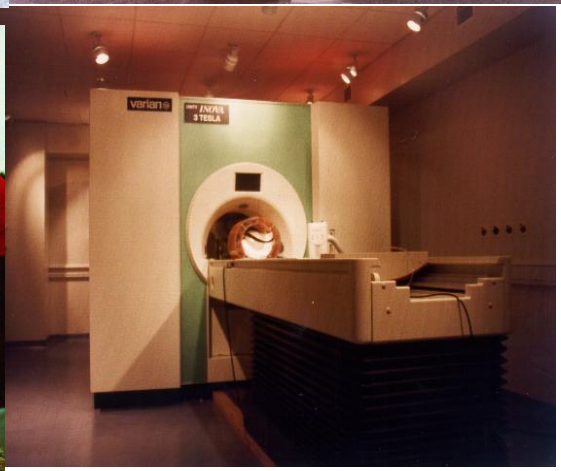


# Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) 1997









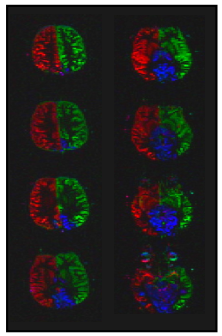
# FMRIB Centre

From this (1996)…3 expansions later…to FMRIB

# Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB)

Neuroimaging 'hub' for University – rich environment

130 clinicians and scientists conducting full-time **inter-disciplinary** translational neuroscience research: **3 T and 7 T MR Systems**

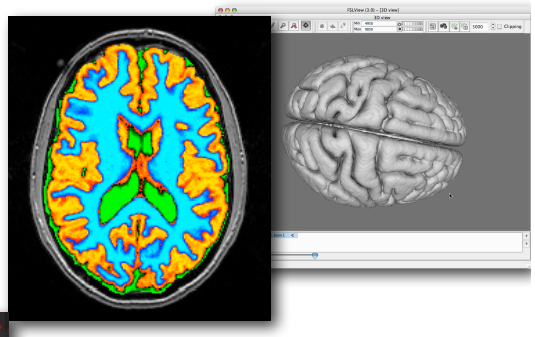



## Applications

- Pain
- Stroke
- Plasticity
- Multiple Sclerosis
- Respiration
- Epilepsy
- Language
- Cognition
- Computational Neuroscience
- Neurodegeneration
- Vision

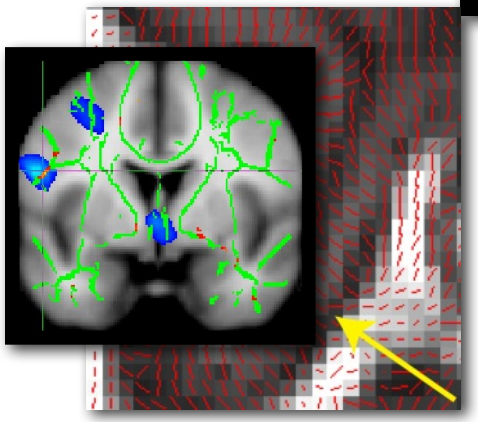
## Image Analysis

- FSL software
- Data modelling
- Segmentation
- Xmodal integration



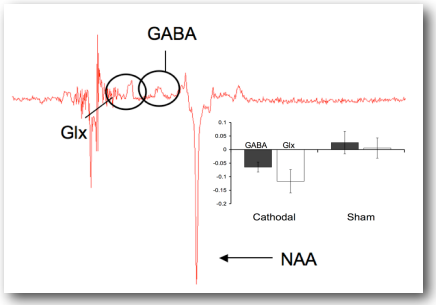
## Imaging Physics

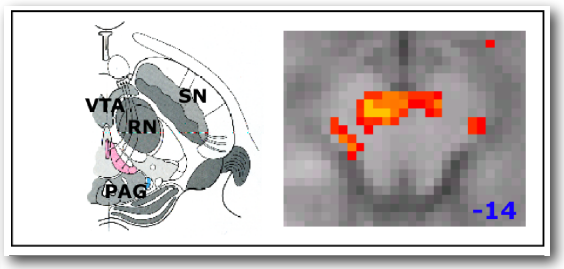
- Functional imaging
- Quantitative perfusion imaging
- Diffusion imaging
- Spectroscopy



## White Matter Tracts

- Connectivity
- Parcellation
- Validation
- Tract-based morphometry

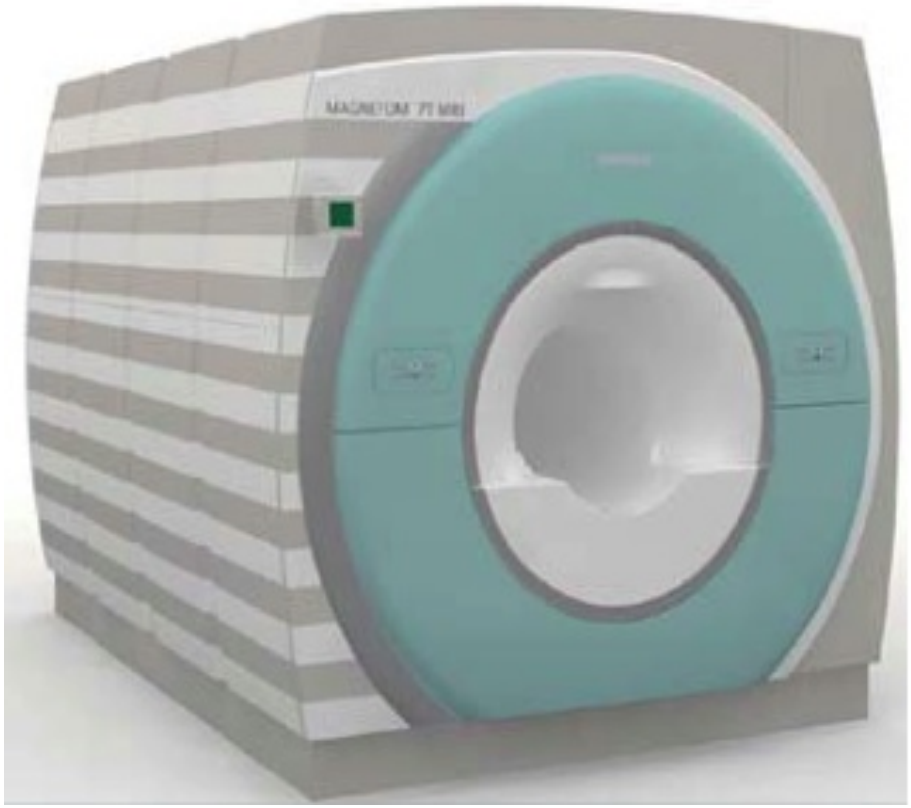


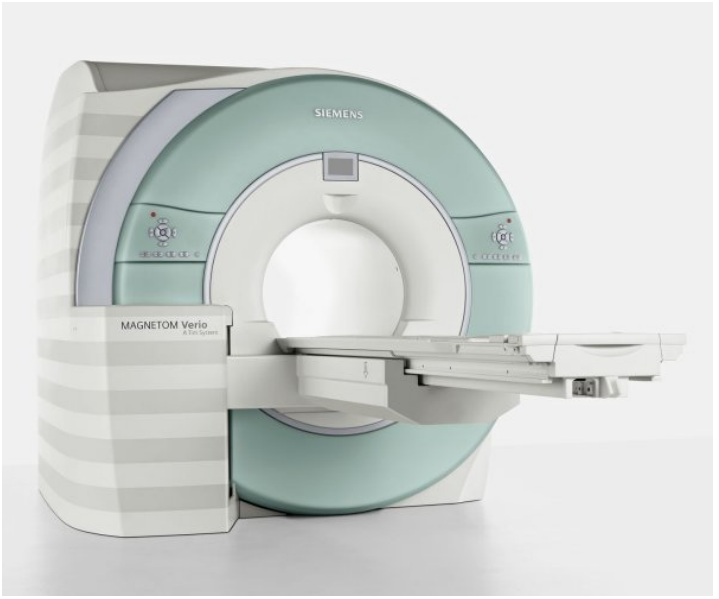



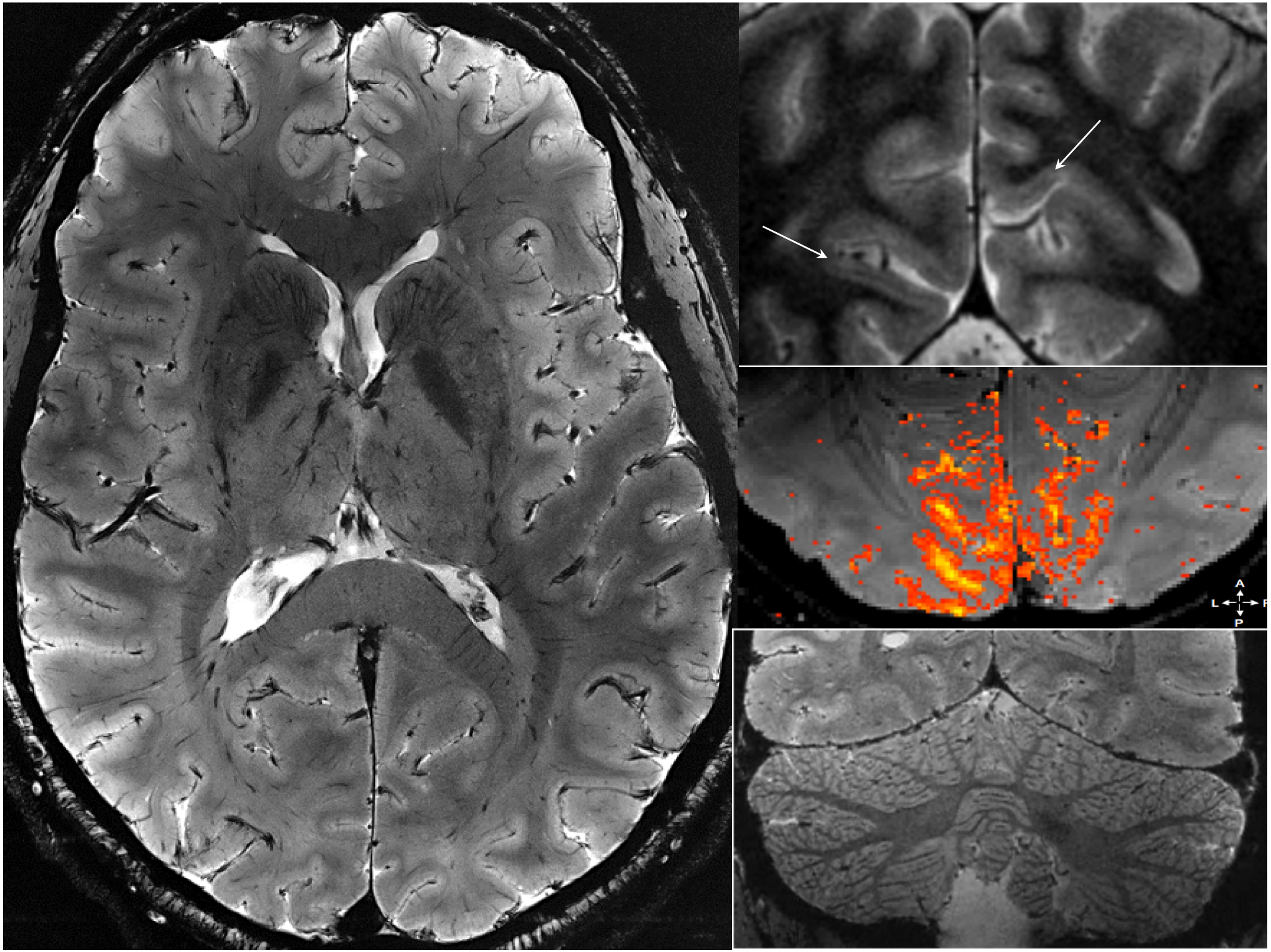

## Integrating Modalities

- Transcranial stimulation
- Electro-encephalography
- Direct current stimulation

Secured £8.4 million research funds (MRC, EPSRC, Wolfson Foundation, University of Oxford) to purchase and install whole body 7 Tesla MR scanner and whole body, neuro-optimised 3 Tesla MR scanners






A
L
R
P

# We love physicists (and mathematicians and engineers!)

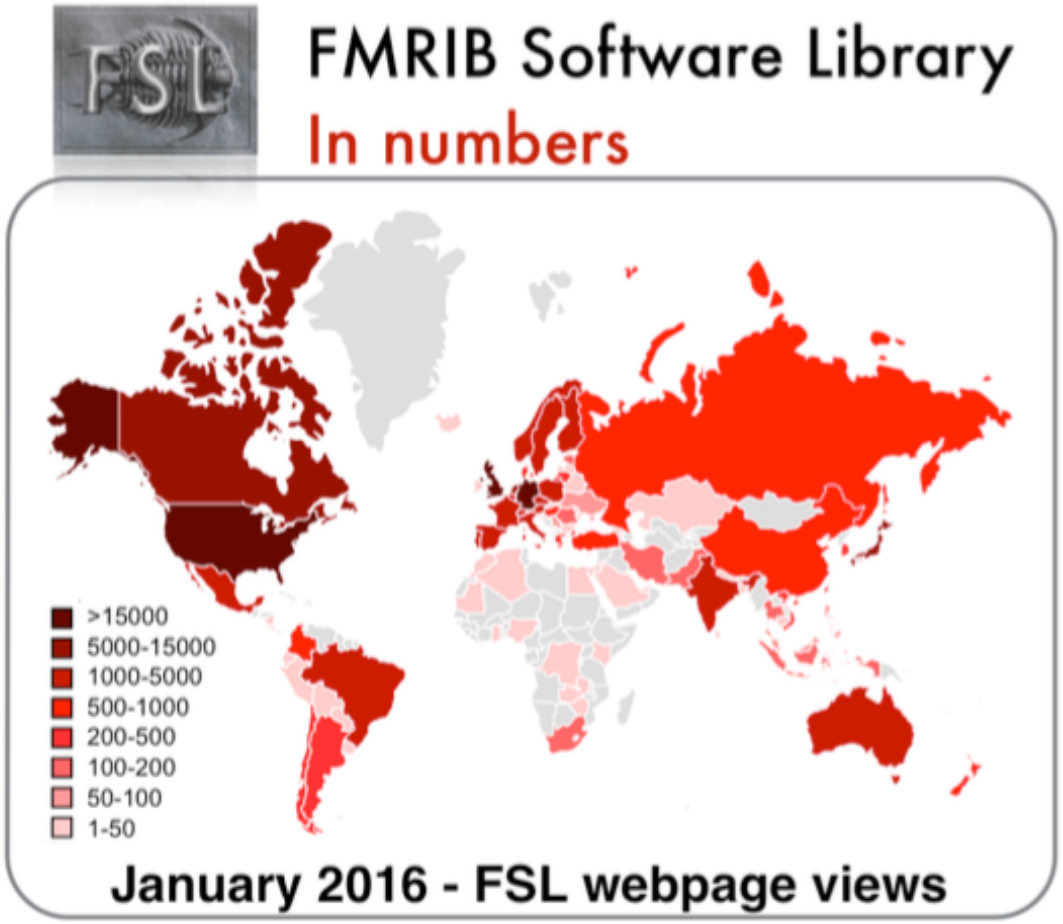








# FMRIB Software Library




**4.8 Million** website page views in 2015

downloads in the last 5 months **10,000**

citations for the main FSL publication **5,000**

used in **1,000** labs worldwide

**Figure 1: FSL global reach**

# Training

# Our Physics Research Achieves Impact Through Technology Innovation and Sharing of Expertise

## Industrial partnerships

SIEMENS

RESONANCE RESEARCH

Fraunhofer MEVIS

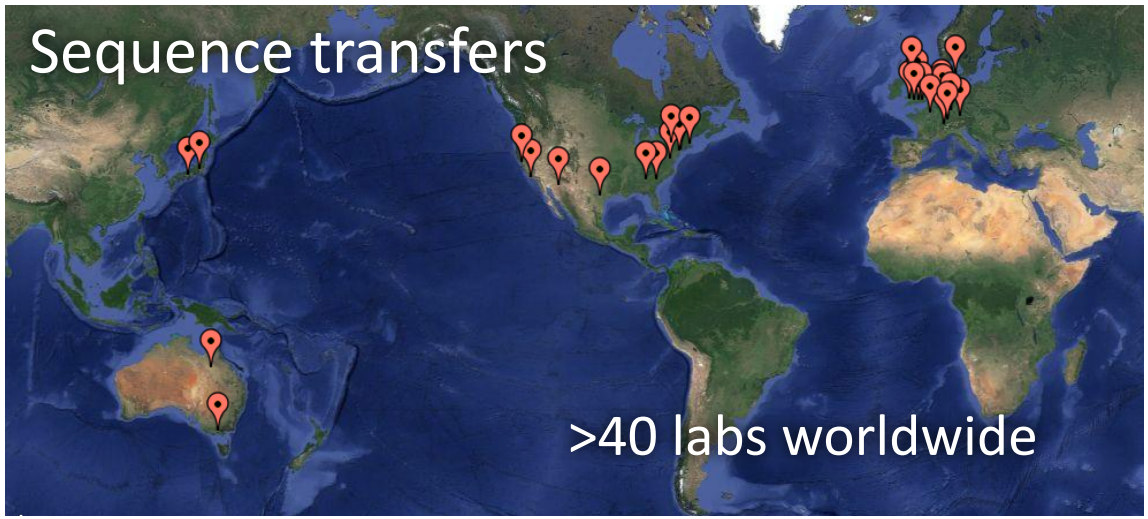
ZMT

Flywheel

Pulse Teq

GE Global Research

ACUITAS medical




## UK 7T Network

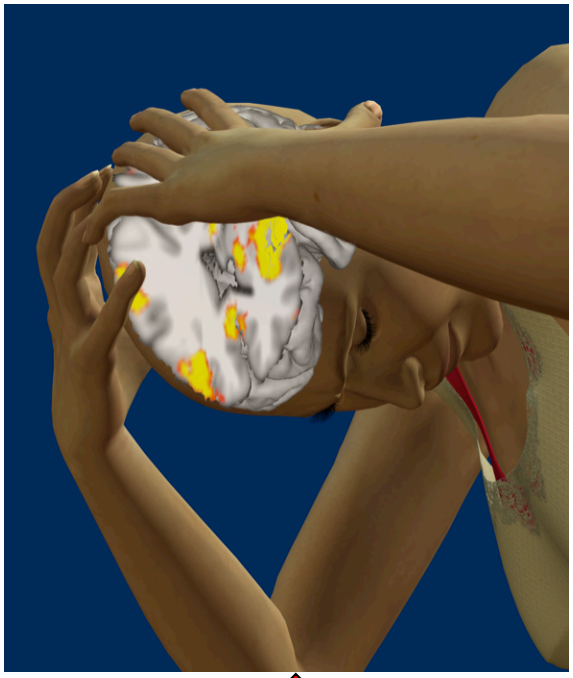
**Existing**
Oxford
Nottingham

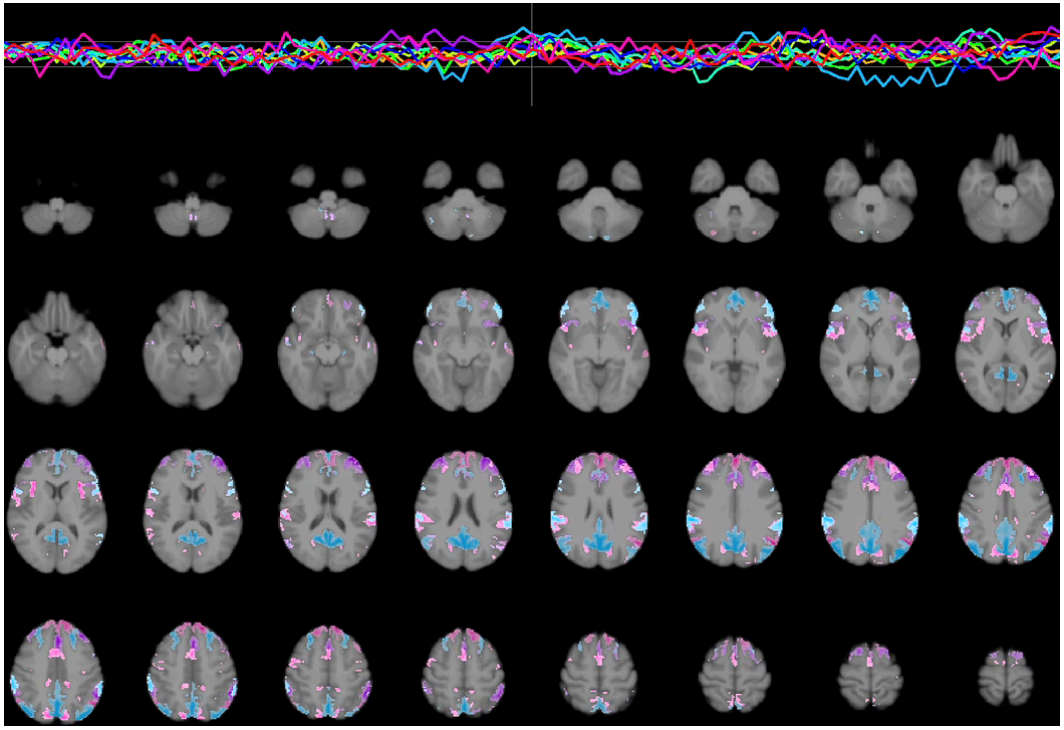
MRC Medical Research Council

**Online 2016**
Cambridge
Cardiff
Glasgow

**Funded 2016**
London

# How the Brain Works – 21st Century knowledge and current thoughts…..





The brain is NOT a simple 'receipt' organ producing perceptions and experiences by processing bottom up sensory inputs as sole contributor:

**Bottom up:** Light, sound, taste, touch, smell, nociception…..

The Concept of:

***Priors and a Bayesian view of the Brain***

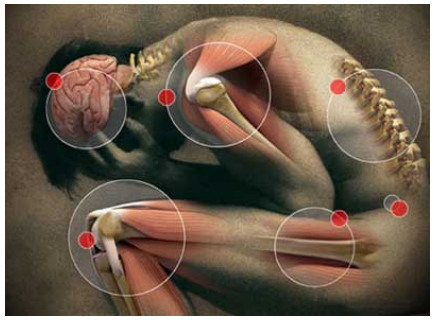
# Priors and Pain

**Correspondence**

## Influence of prior information on pain involves biased perceptual decision-making

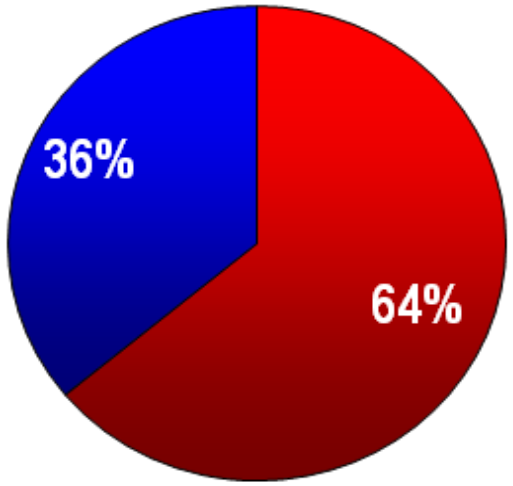
Katja Wiech[1,2],
Joachim Vandekerckhove[3,4],
Jonas Zaman[4], Francis Tuerlinckx[4],
Johan W.S. Vlaeyen[4,5],
and Irene Tracey[1,2]


Current Biology, 2014



# Chronic Pain: a widespread unmet clinical need

- 1:5 people suffer from chronic pain
- On average, sufferers live with chronic pain for 7 years (20% >20 years)
- One in five reports losing a job or have been diagnosed with depression as a result of their pain
- Conservative estimate annual costs $560-635b USA/€200b Europe




*Relieving Pain in America. IOM. 2011*

*www.painineurope.com*

# WHAT HOLDS PEOPLE IN CHRONIC PAIN?



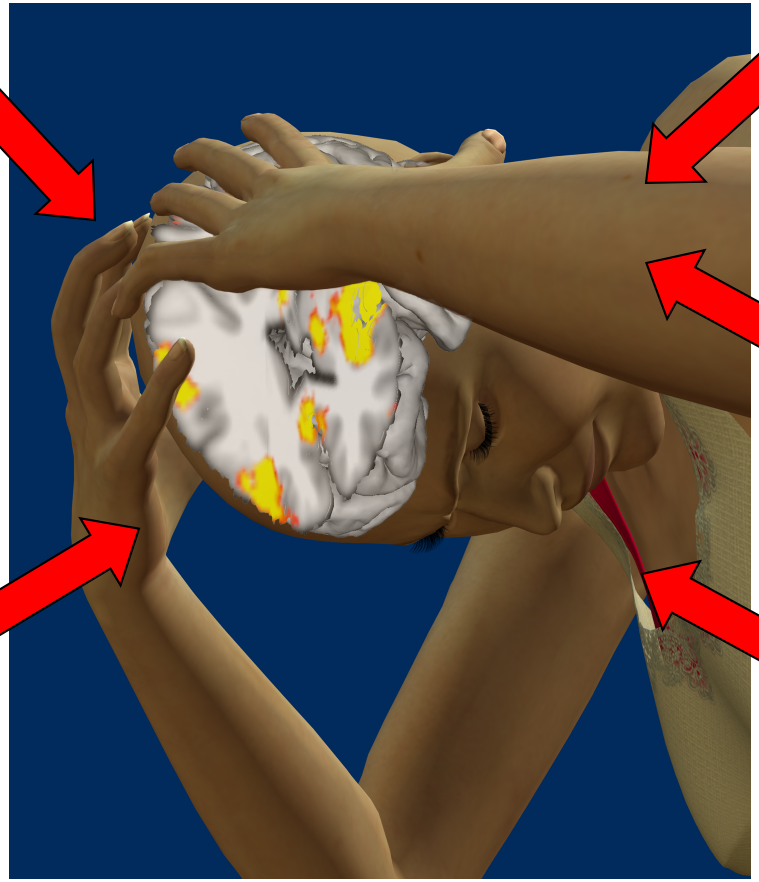


1. Constant firing of 'pain nerves'

2. Amplification of signals in central nervous system

3. Maladaptive plasticity

# Understanding Pain

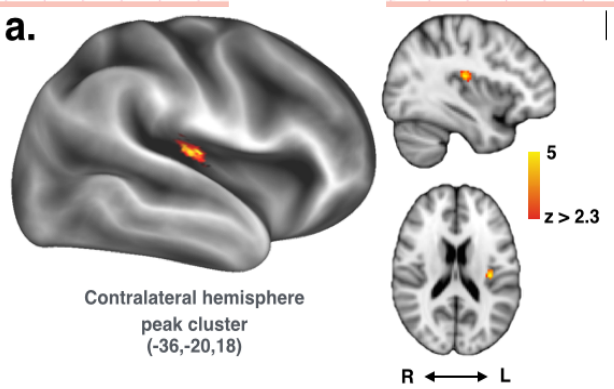


Verification & new target

Mechanism

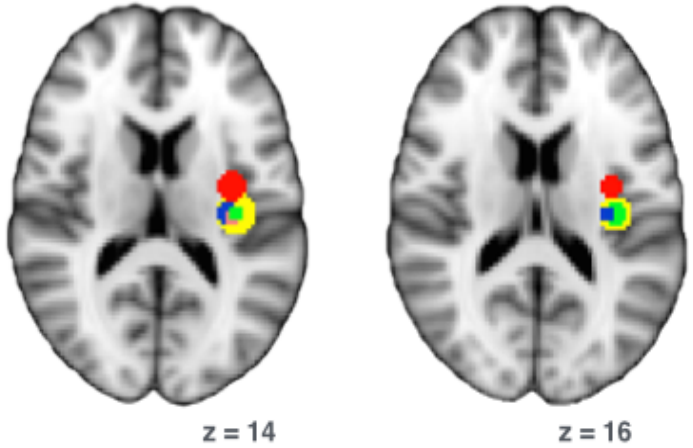
Observation

Behavioural readout
= challenging




# Imaging Tonic Pain:

## Quantitative Cerebral Blood Flow




**Direct electrical stimulation of posterior insula:**

Mazzola, L. *et al.* (2009)

- Face pain: (-35 ± 4 , -6.4 ± 6, 11 ± 8)
- Lower limb pain: (-36 ± 5 , -19 ± 11, 8 ± 3)

**Tracking ongoing tonic heat pain:**

Current study

- Peak active cluster: (-36,-20,18)

**Acute pain somatotopy of posterior insula:**

Brooks, JCW. *et al.* (2005)

- Thermal stimulus applied to foot: (-35 ± 4 , -20.8 ± 6, 11 ± 5)

Baumgärtner, U. *et al.* (2010)

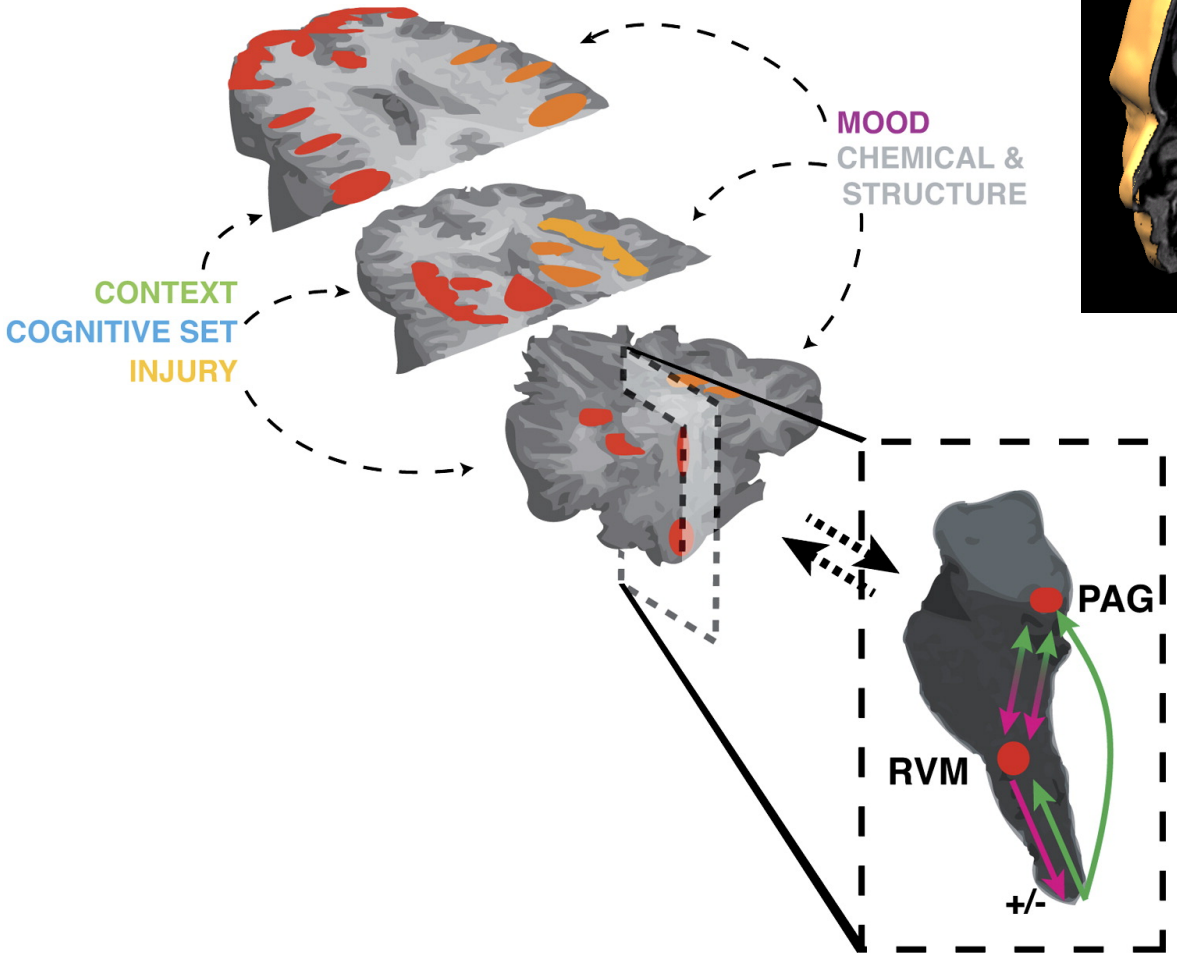
- Laser stimulus applied to foot: (-32 ± 2 , -20 ± 1.8, 12 ± 2.4)

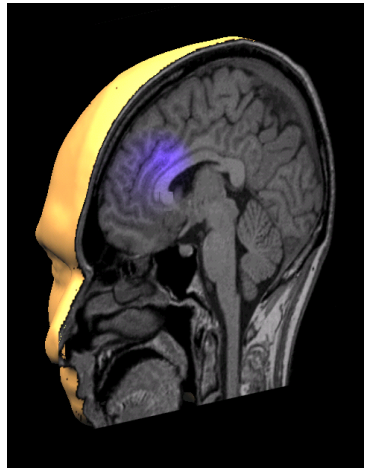
Segerdahl A*, Mezue M.* Okell, Farrar, Tracey. Nature Neuroscience 2015

# The Descending Pain Modulatory System:

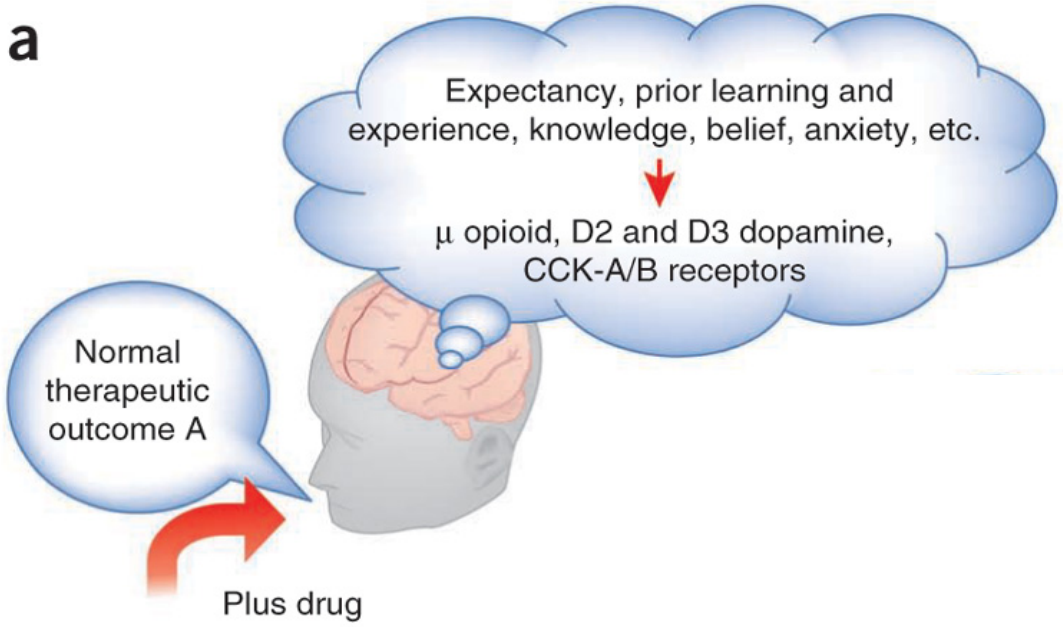
## cortical-subcortical-brainstem network with anti- and pro- influences on dorsal horn nociceptive processing

Tracey & Mantyh, Neuron 2008



# Expectation in the therapeutic setting: don't underestimate the patient-physician interaction




***Hippocrates:*** "Make frequent visits and enquire into all particulars"

***Galen:*** "He cures most successfully in whom the people have the most confidence"

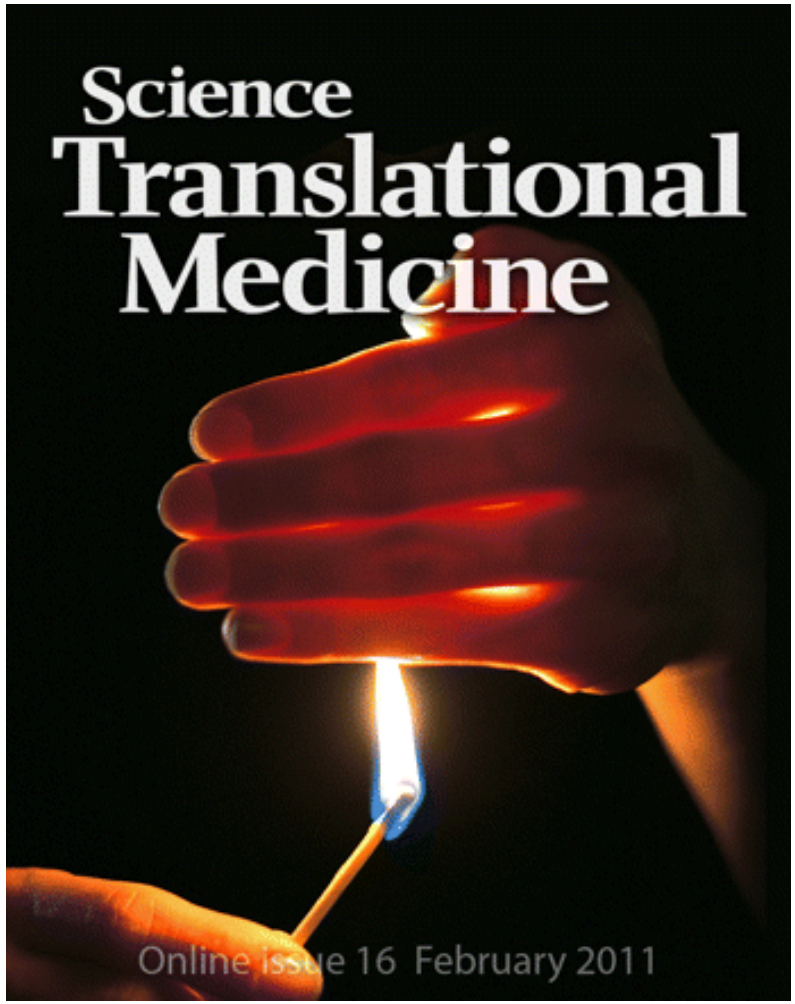
I. Tracey: Getting the Pain you Expect. Nature Medicine, 2010

DRUG EFFICACY

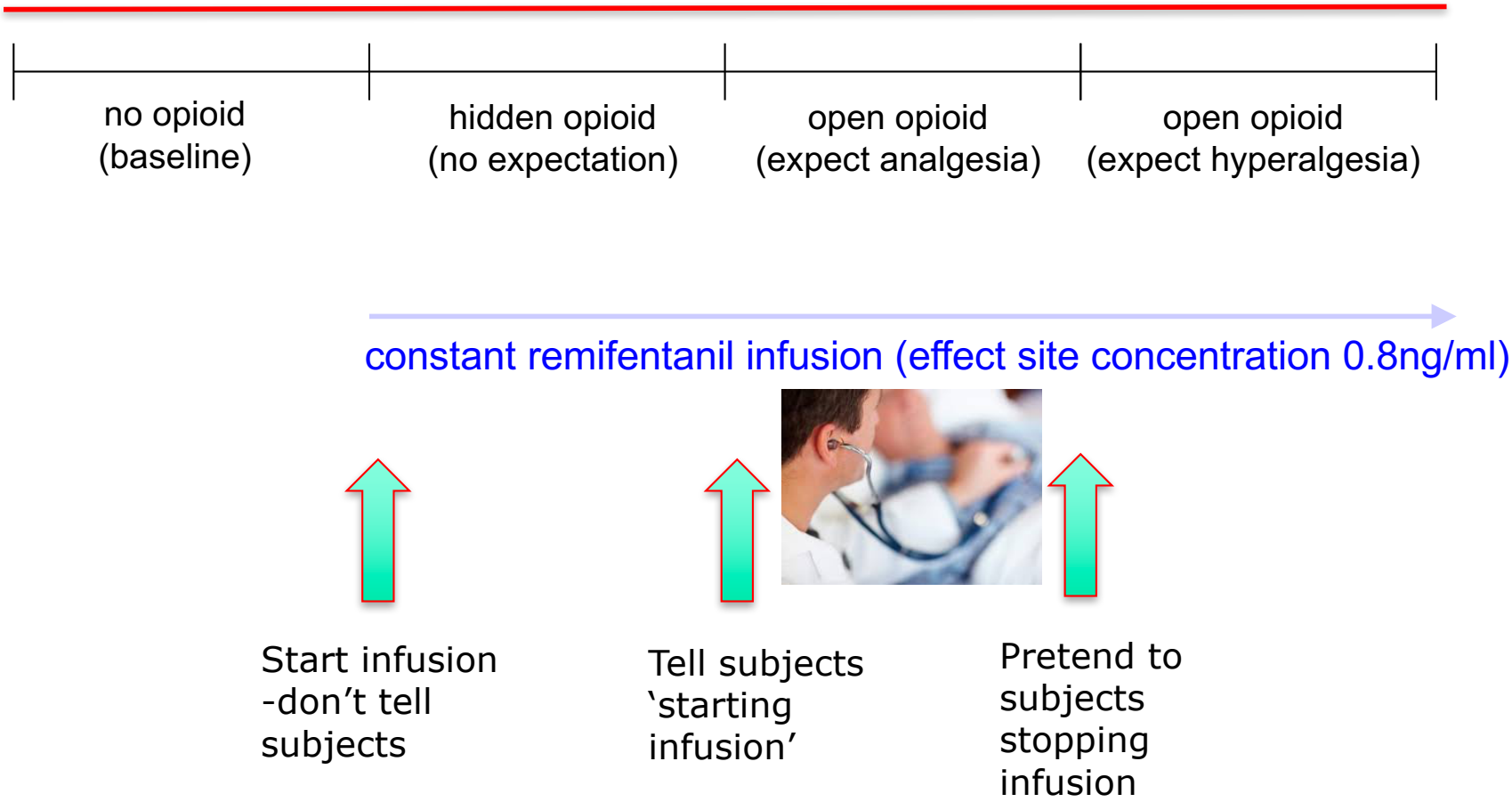
Science Translational Medicine AAAS

# The Effect of Treatment Expectation on Drug Efficacy: Imaging the Analgesic Benefit of the Opioid Remifentanil

Ulrike Bingel,[1,2]* Vishvarani Wanigasekera,[1] Katja Wiech,[1] Roisin Ni Mhuircheartaigh,[1] Michael C. Lee,[3] Markus Ploner,[4] Irene Tracey[1]



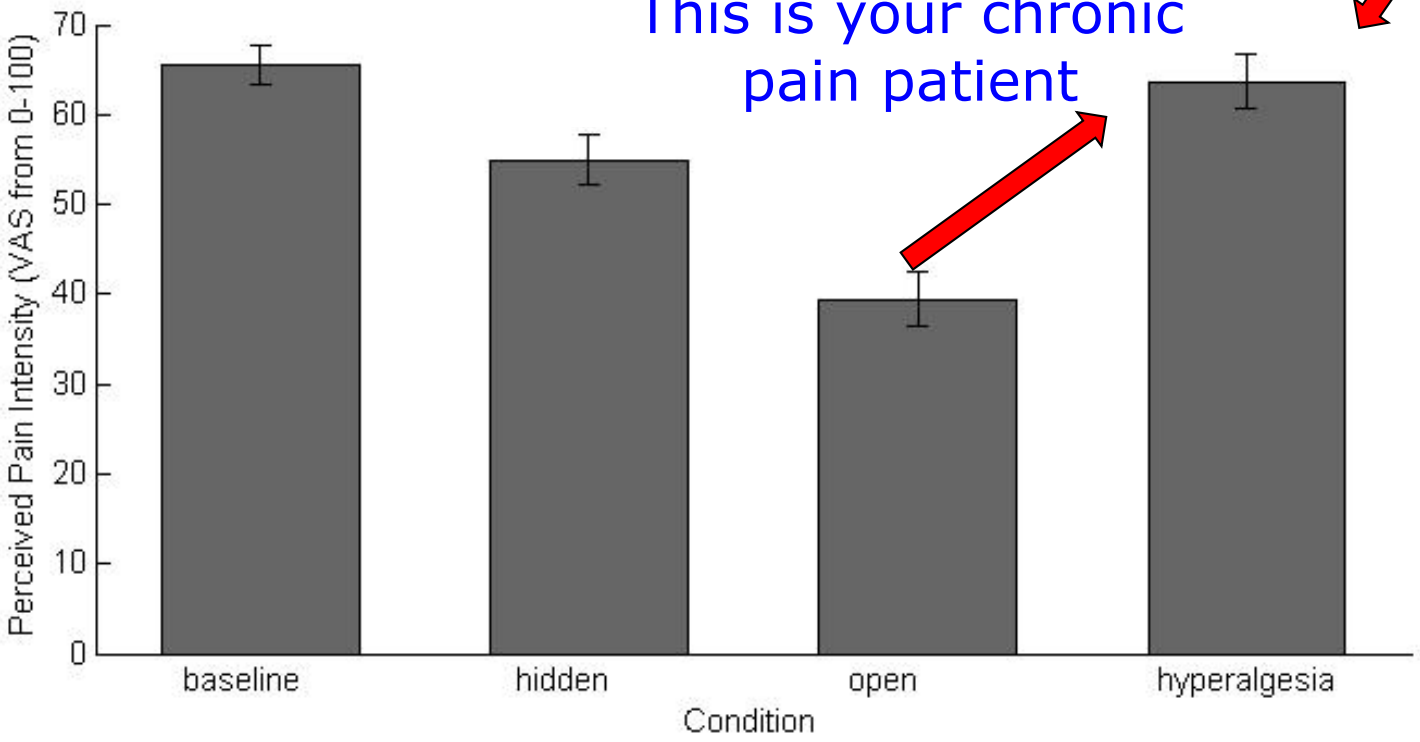
# Repeated constant thermal painful stimuli applied throughout entire experiment while imaging the brain response



# Pain Ratings

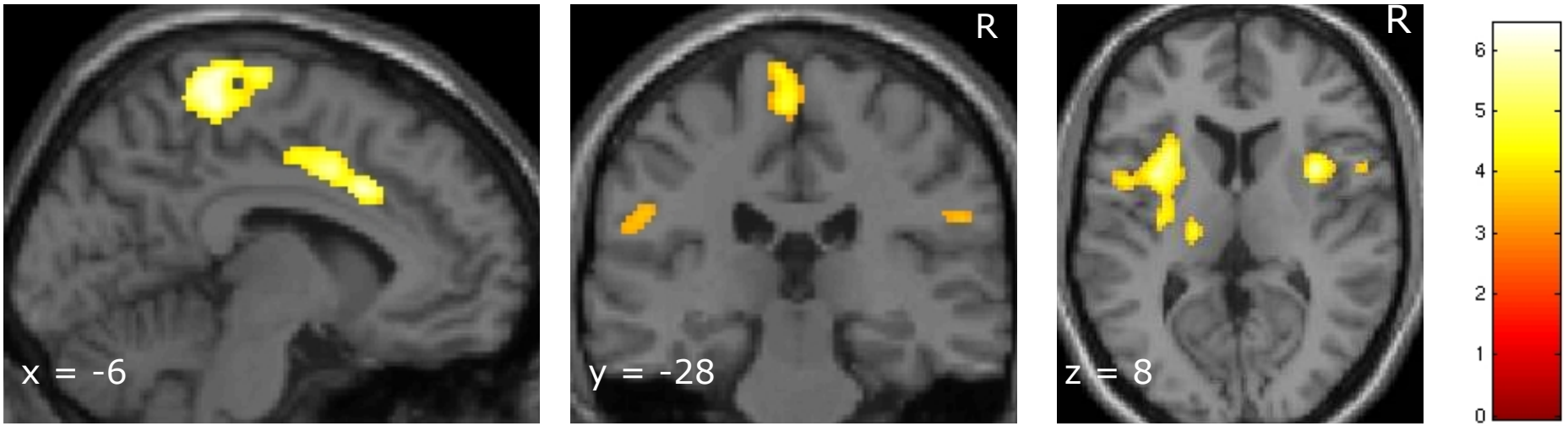
Not controlling for this leads to another failed drug….

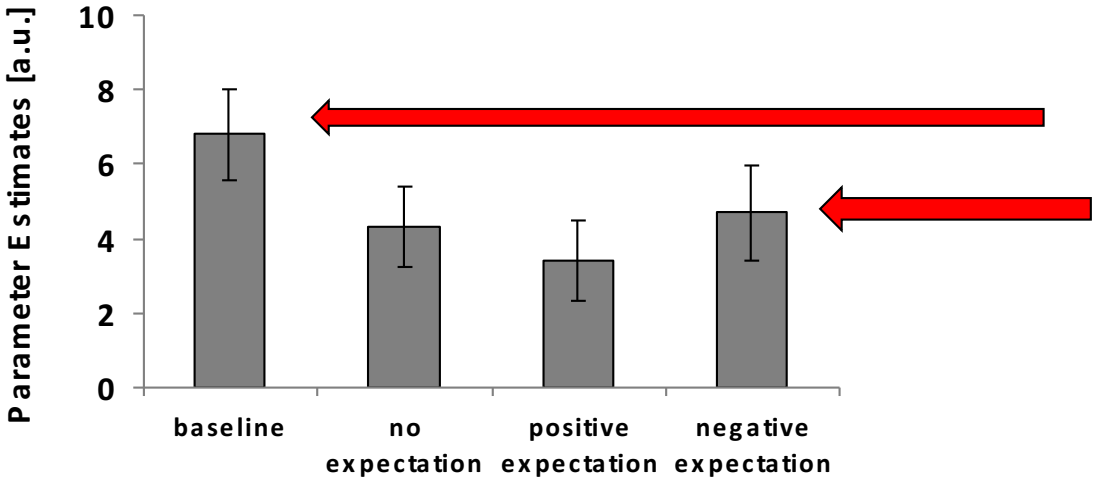
This is your chronic pain patient



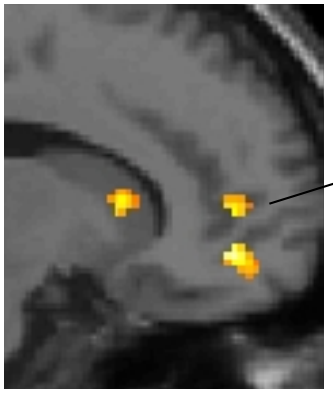
# Contextual Modulation of Opioid Analgesia is Reflected in Areas of the Brain's pain processing regions:

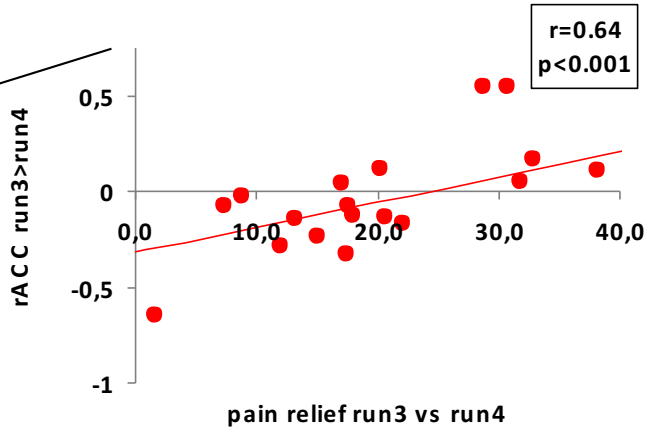
## NOT report bias AND imaging never lies…



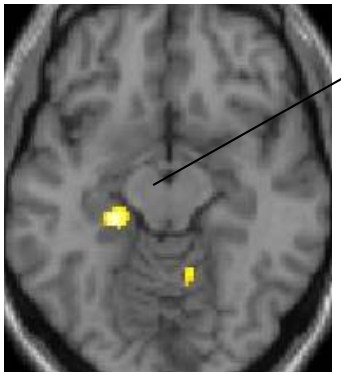



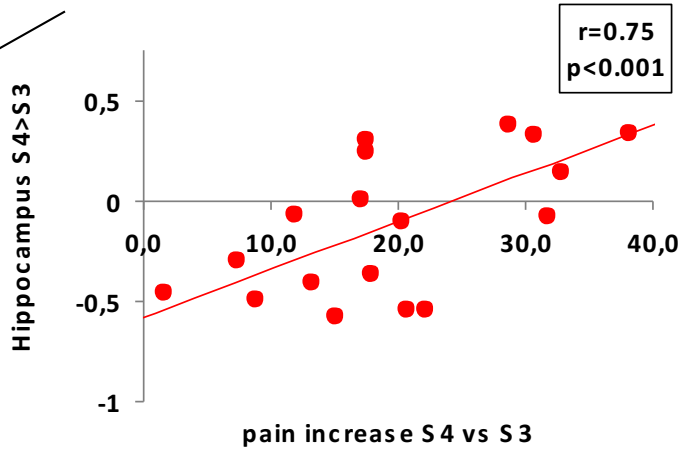
# Anti-nociception with positive expectancy






# 'Anxiety amplifier' with negative expectancy (nocebo)






Anxiety Amplifies Pain: Ploghaus et al., Science 1999; PNAS 2000; J. Neuroscience, 2001

# Arthroscopic subacromial decompression for subacromial shoulder pain (CSAW): a multicentre, pragmatic, parallel group, placebo-controlled, three-group, randomised surgical trial

*David J Beard, Jonathan L Rees, Jonathan A Cook, Ines Rombach, Cushla Cooper, Naomi Merritt, Beverly A Shirkey, Jenny L Donovan, Stephen Gwilym, Julian Savulescu, Jane Moser, Alastair Gray, Marcus Jepson, Irene Tracey, Andrew Judge, Karolina Wartolowska, Andrew J Carr, on behalf of the CSAW Study Group**

Articles

www.thelancet.com **Published online November 20, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32457-1**

doi:10.1093/brain/awx337 BRAIN 2018: 141; 357–364 | 357

BRAIN
A JOURNAL OF NEUROLOGY

REPORT

# A brain-based pain facilitation mechanism contributes to painful diabetic polyneuropathy

Andrew R. Segerdahl,[1] Andreas C. Themistocleous,[2] Dean Fido,[1] David L. Bennett[2] and Irene Tracey[1]

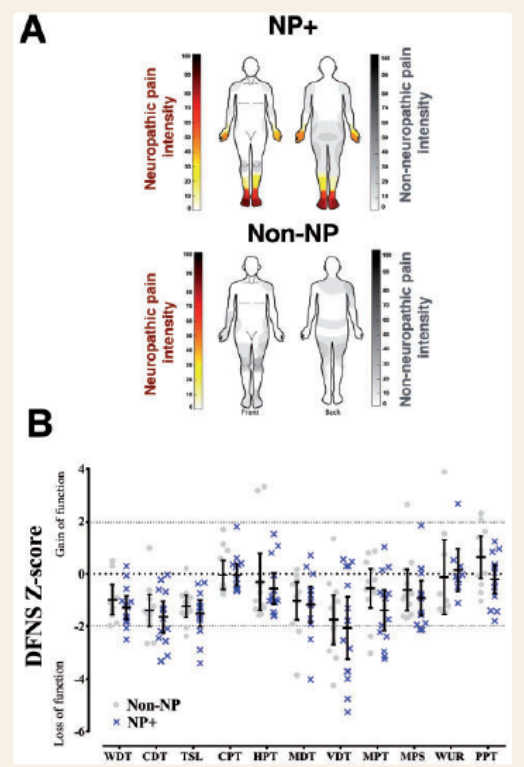
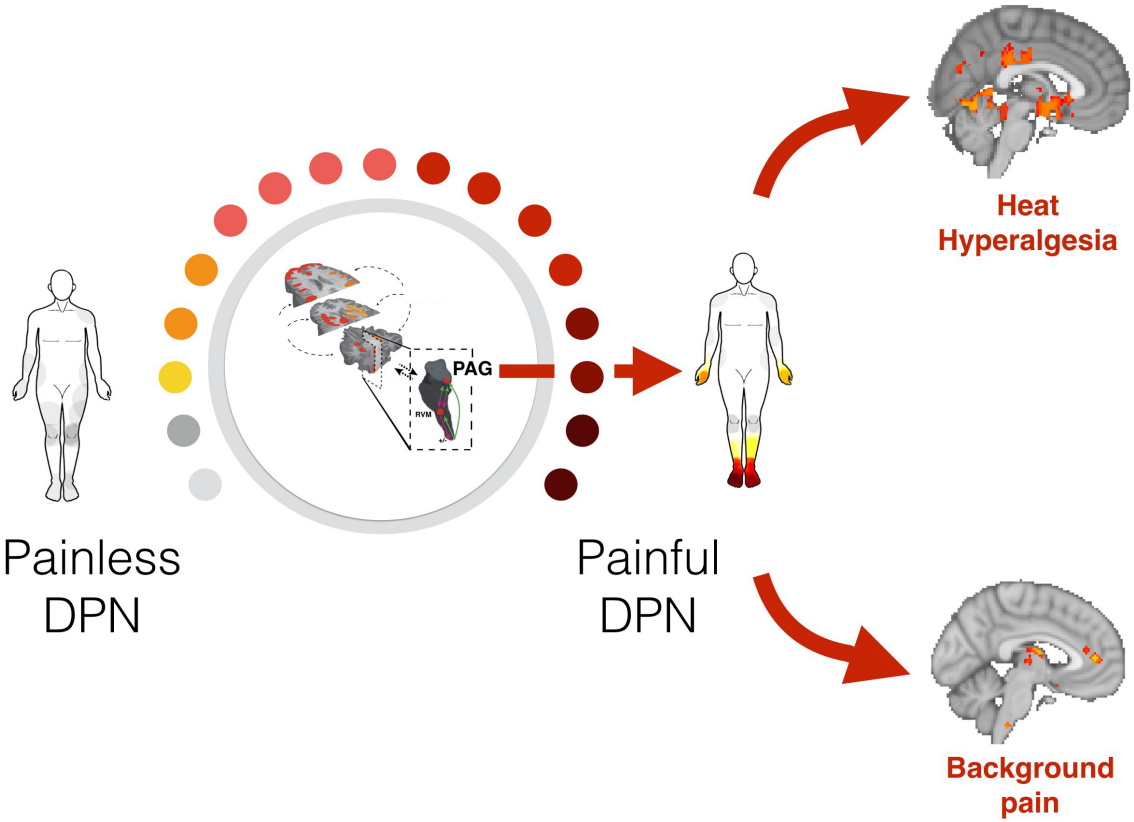
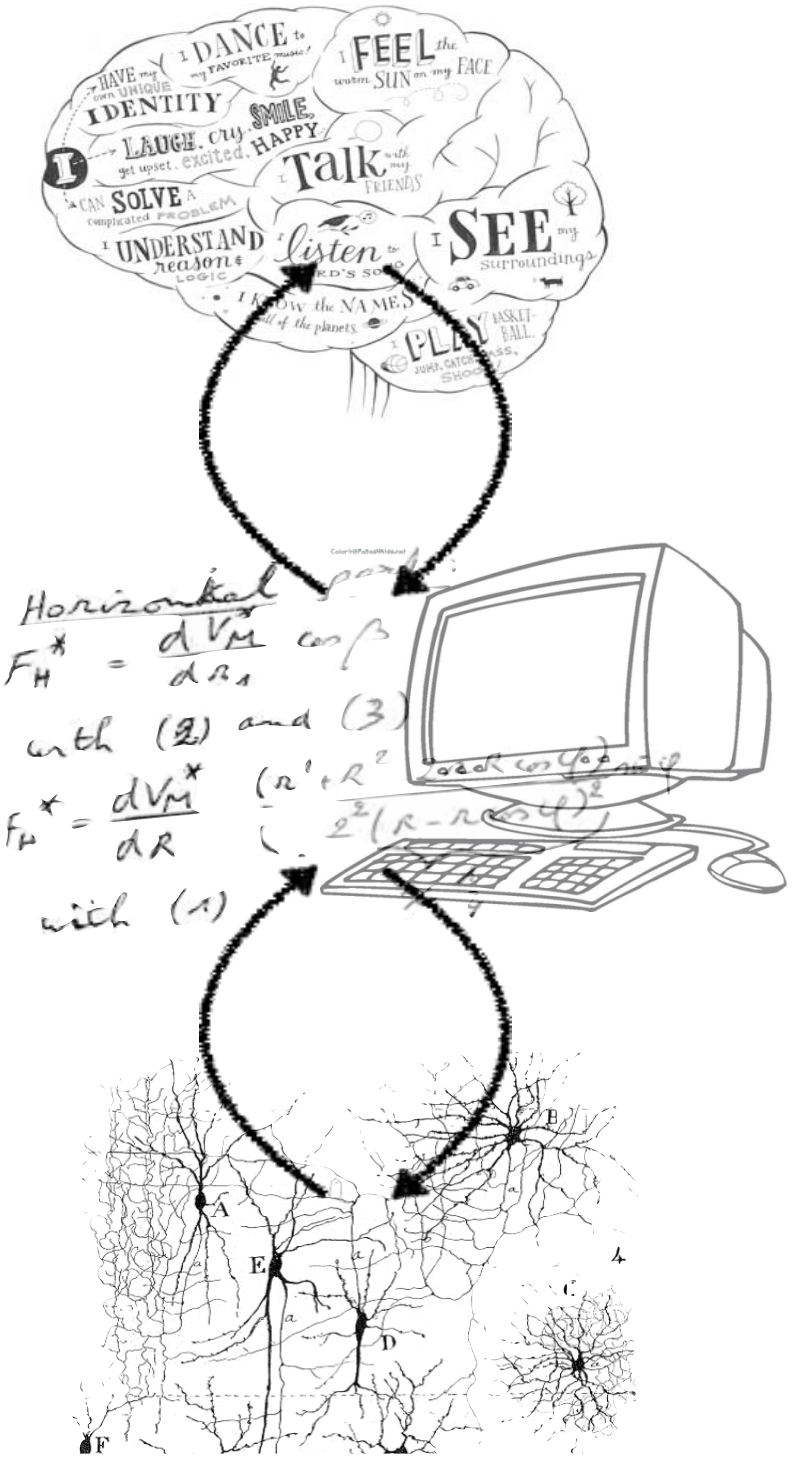



Figure 1 Neuropathic pain severity. (A) Heat maps summar-

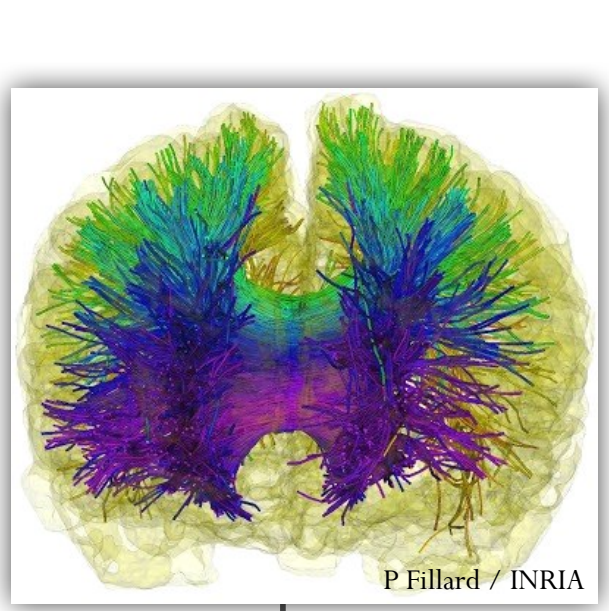


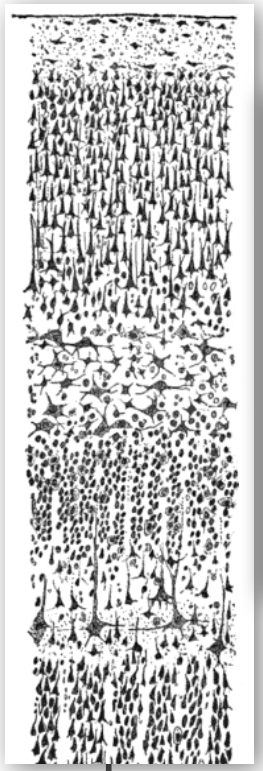
wellcome centre integrative neuroimaging

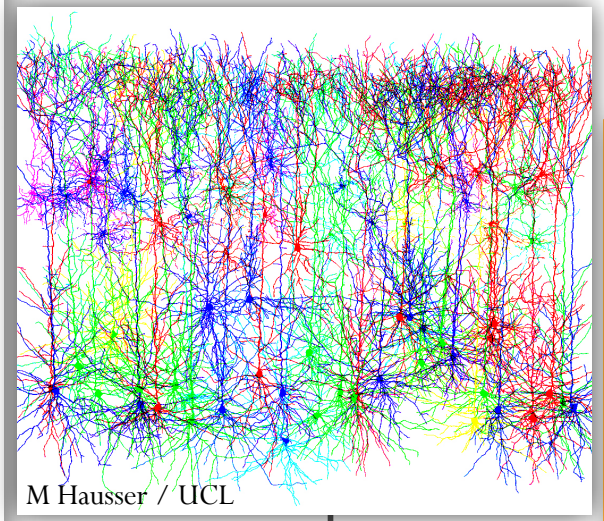
Cross-species
Cross-scale
Patients
Populations
Open neuroimaging

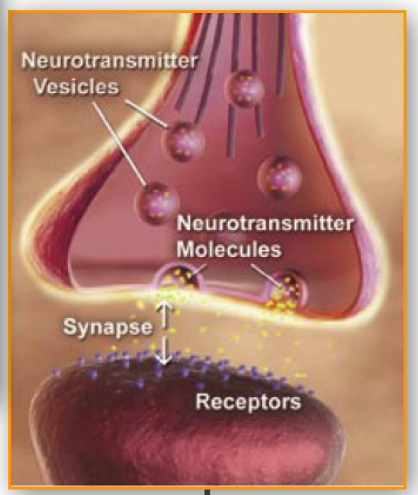


# Challenges of Scale



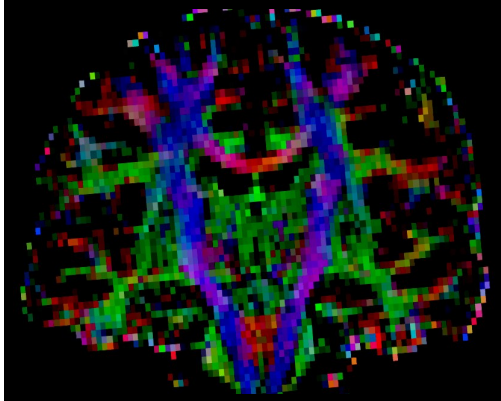
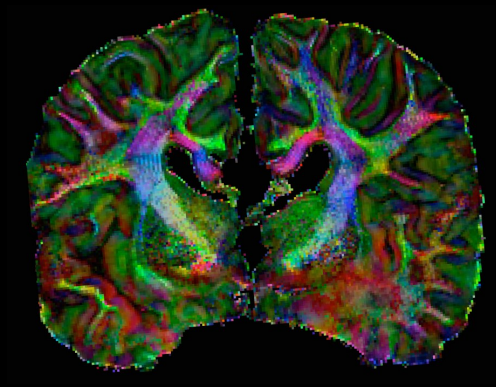
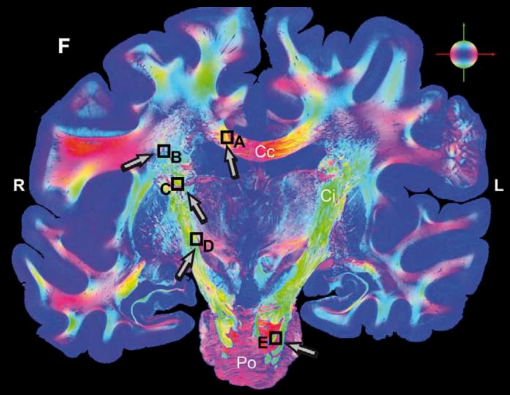
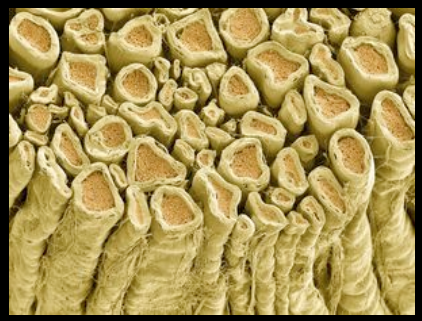



$10^{-1}$ m $10^{-3}$ m $10^{-5}$ m $10^{-7}$ m

Structure relates to function over 6-8 orders of magnitude

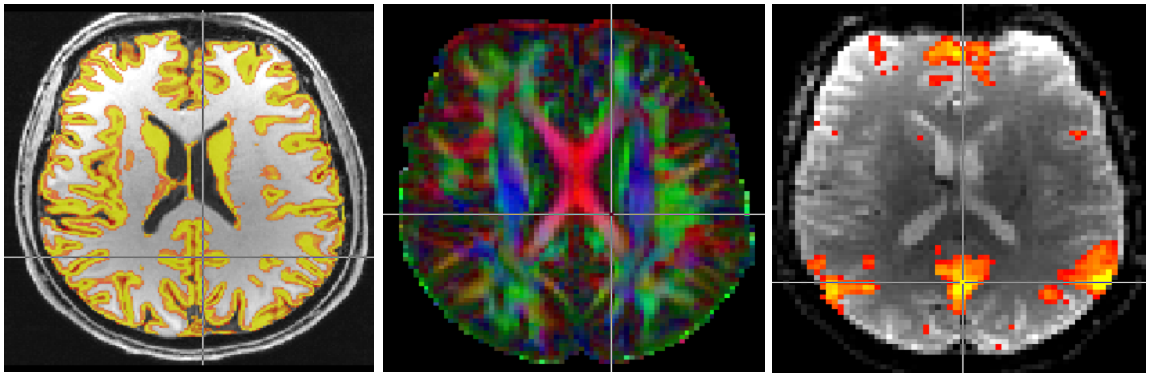
Increasing resolution

| ~1 mm | ~0.1 mm | ~1 µm | ~1 nm |
|---|---|---|---|
|  |  |  |  |
| In-vivo MRI | Post-mortem MRI | Optical Microscopy | Electron Microscopy |
| 100,000 | 100 | 10 | 1 |

Increasing population

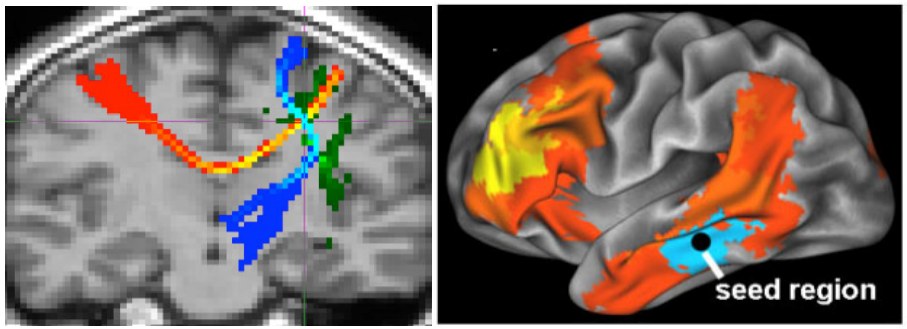
# UK Biobank Imaging

- Large prospective epidemiological study: 500,000, 45-70y
- Imaging Extension: bring back **100,000** for MRI



# NIH Human Connectome Project (HCP)

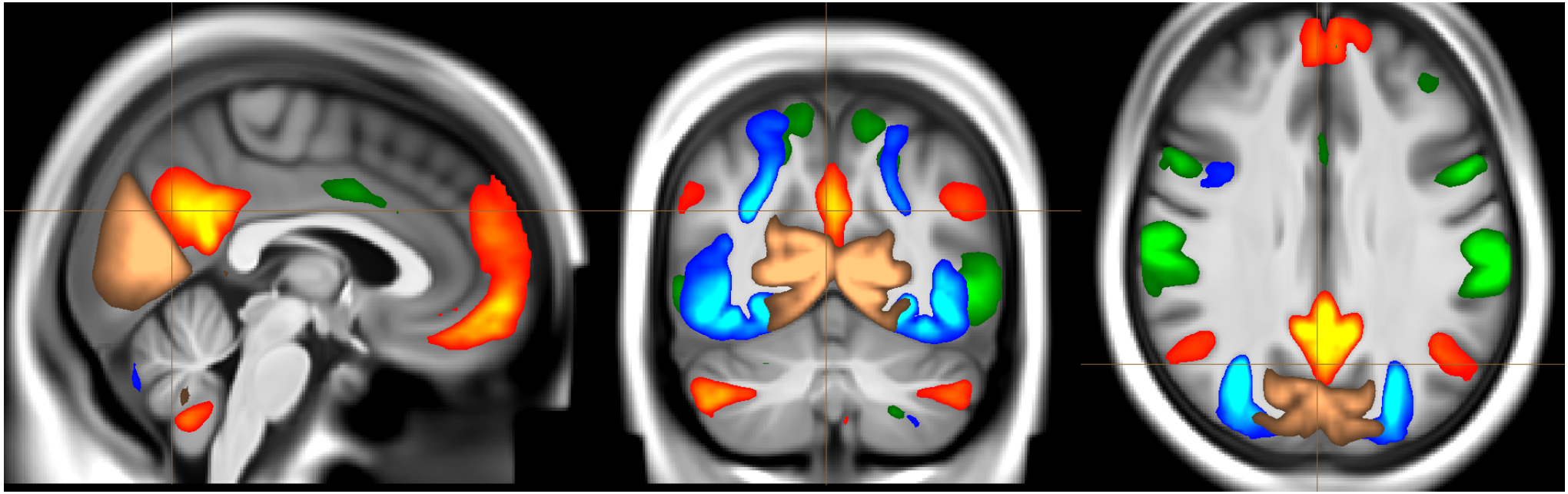
- $30m NIH: best possible in vivo human macro-connectome mapping
- Main groups:WashU, UMinn & Oxford
- 1200 subjects: **dMRI**, **rfMRI**, tfMR, MEG, behaviour, genetics



biobank uk
Imaging study

- Brain imaging scientific direction:
  Stephen Smith, Karla Miller (Oxford)
- Brain imaging analysis pipeline:
  Fidel Alfaro Almagro, Stephen Smith (Oxford) and many others

- Prospective epidemiological study: 500,000, 45-70y
- Imaging: bring back **100,000** (20,000 already scanned)
  - » Brain, heart, body imaging
- Discover early imaging markers & risk factors of disease



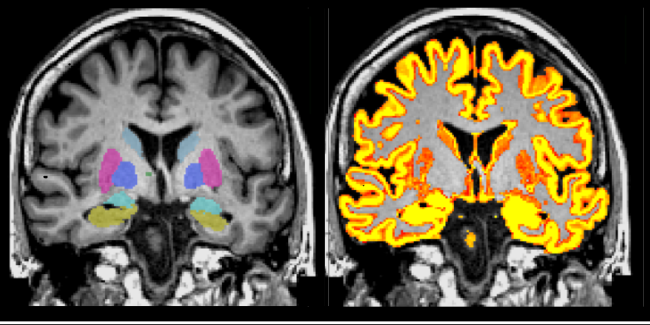
wellcome centre integrative neuroimaging

wellcome trust

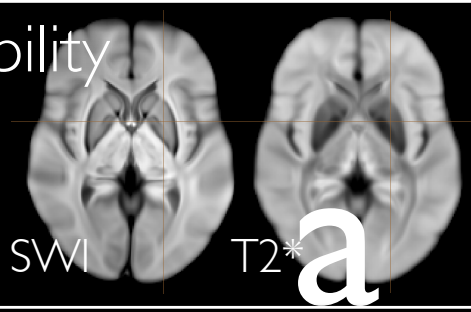
MRC Medical Research Council

biobank uk
Imaging study

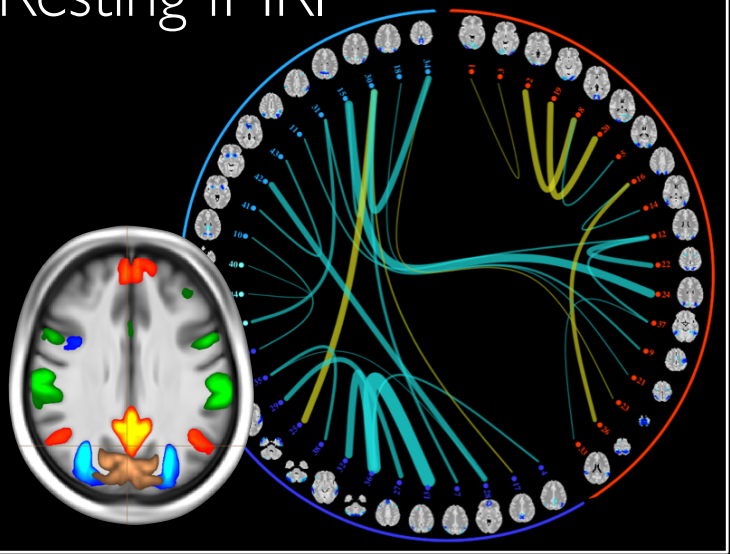
## T1-weighted



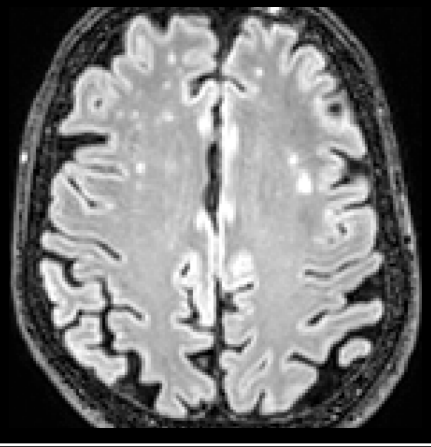
## Susceptibility contrast




## Resting fMRI

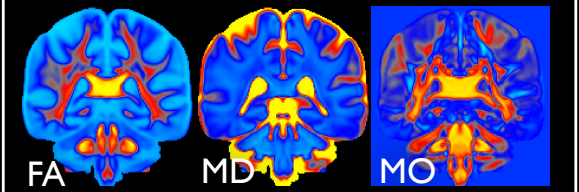


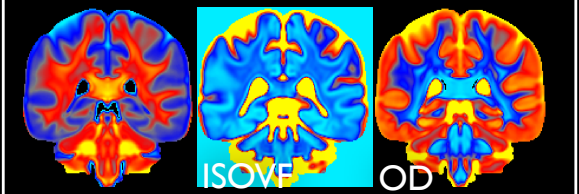
## T2 FLAIR

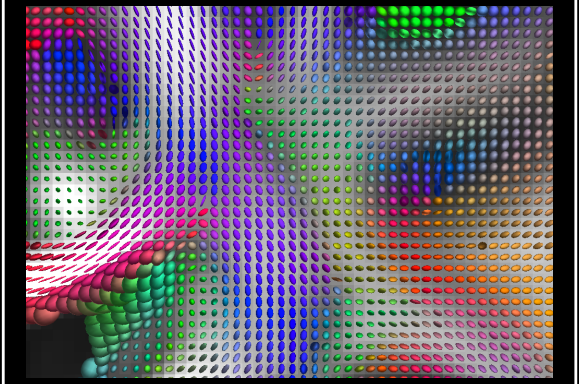


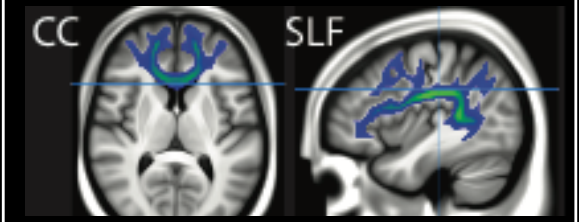
## Task fMRI


## Diffusion MRI

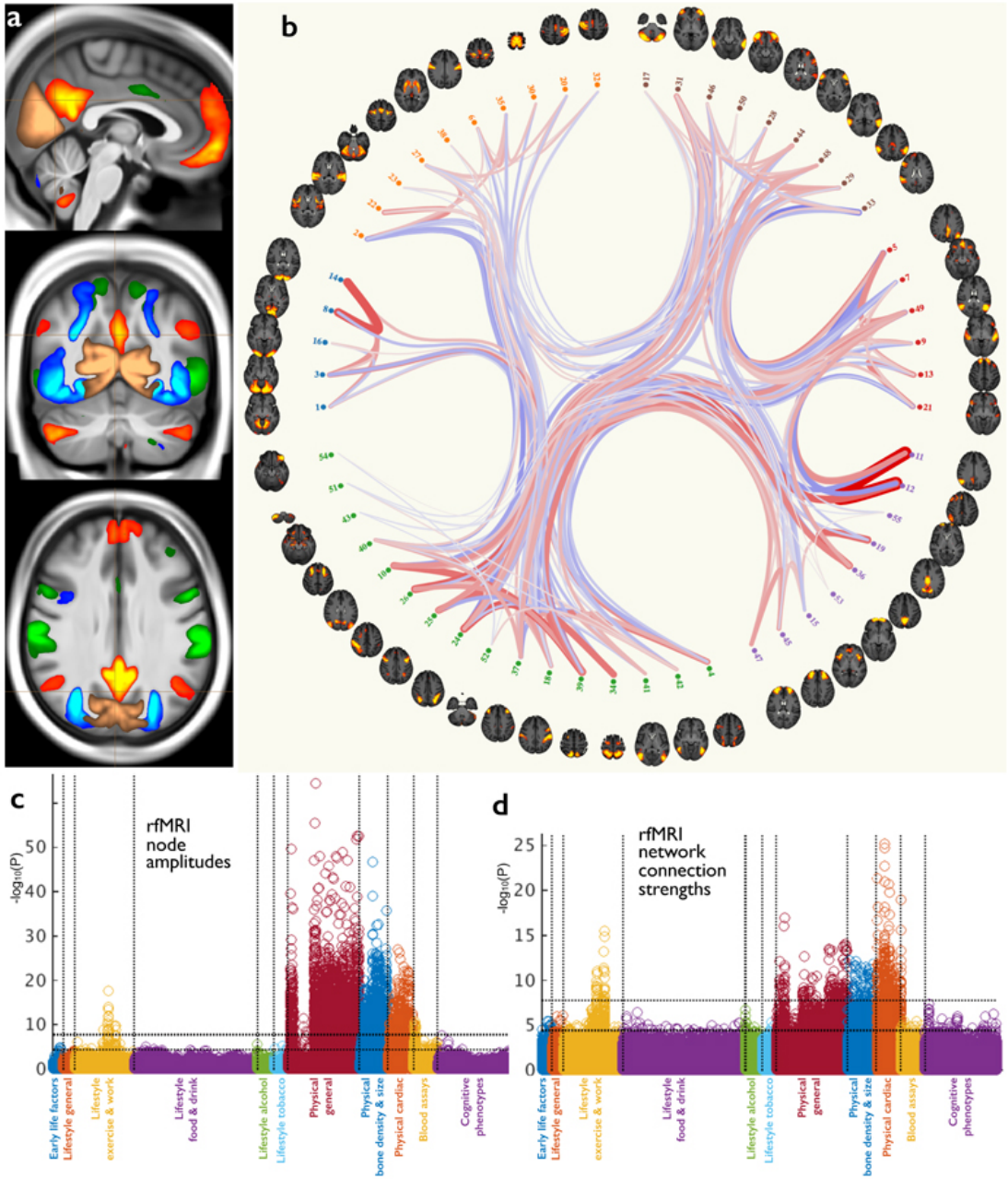




# Miller et al. Nat. Neuroscience 2016

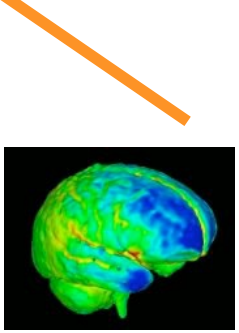


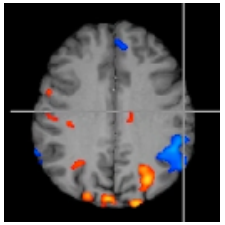
environment
& lifestyle

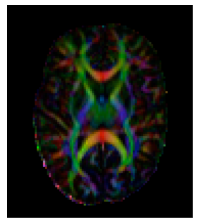

long-term health
outcomes

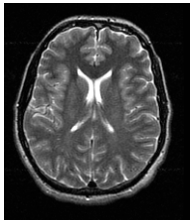

*learn*

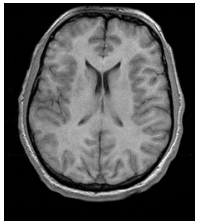
blood chemistry

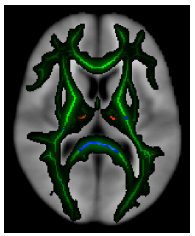


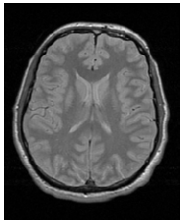


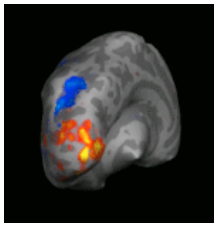












imaging
phenotypes

genetics

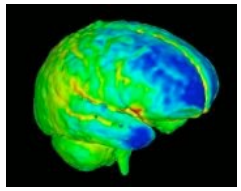
environment
& lifestyle

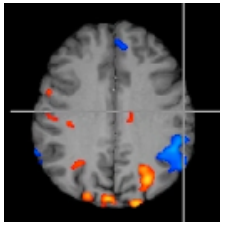

predict

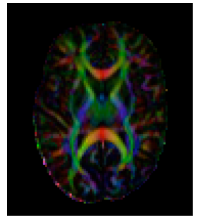
long-term health
outcomes

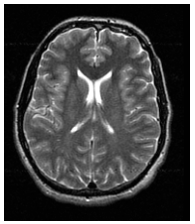
blood chemistry

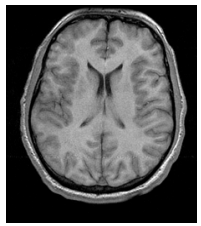
genetics

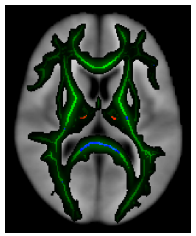


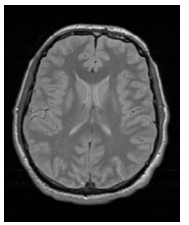


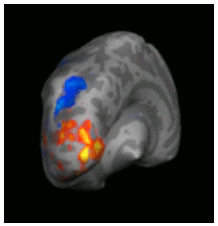












imaging
phenotypes

# 100,000s of general anaesthetics given daily worldwide

BUT when does an individual under anaesthesia stop perceiving the outside world?

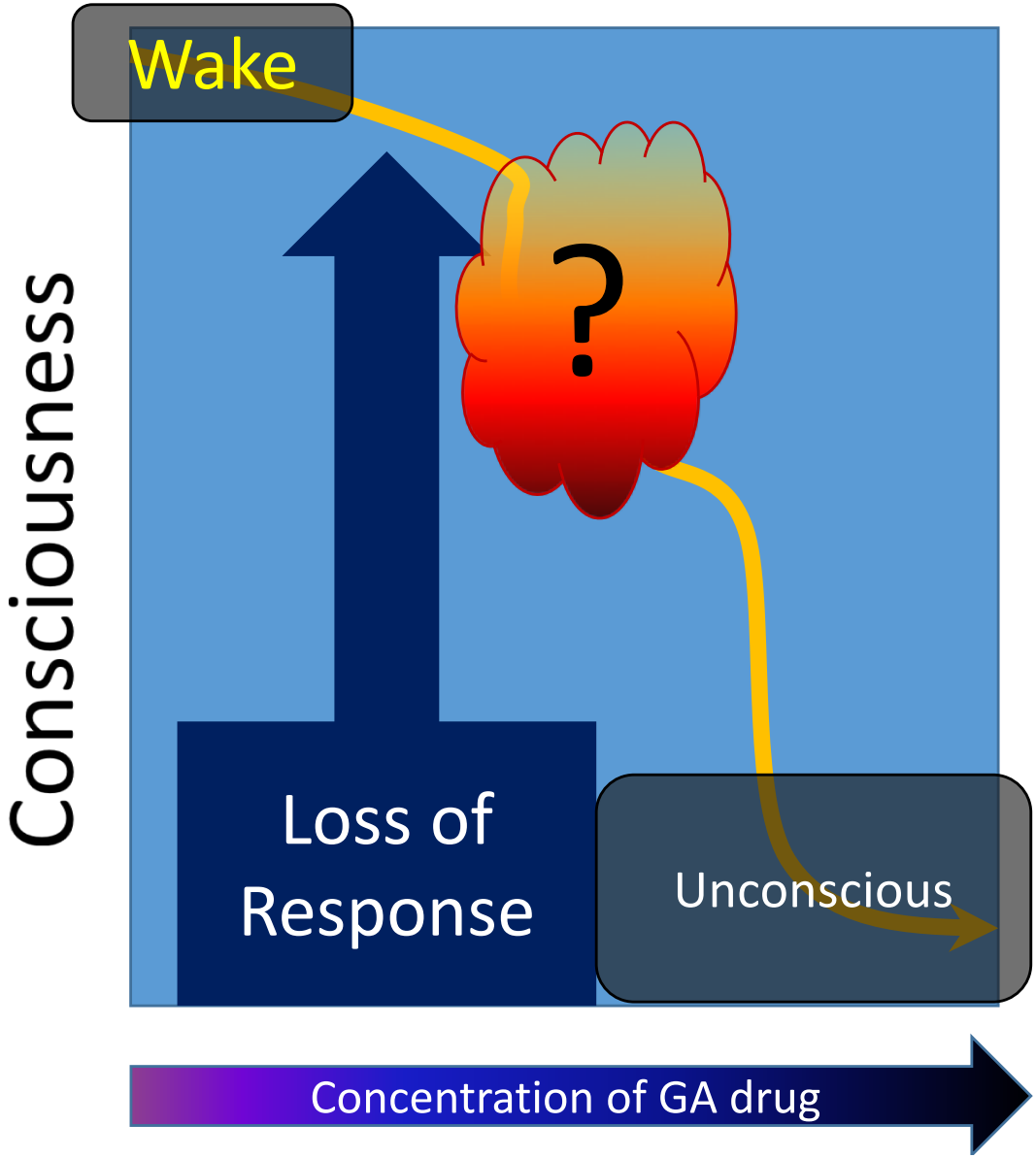
# Continuum of anaesthesia-induced unconsciousness

Alert wakefulness

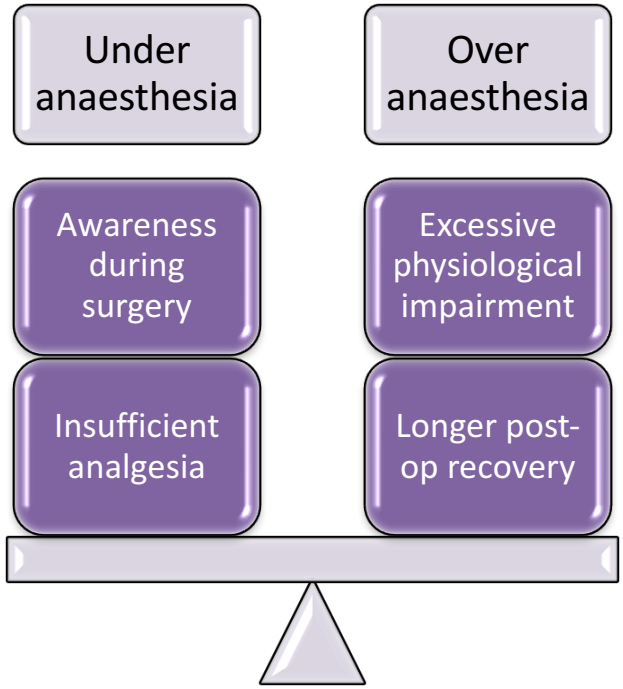
Loss of responsiveness

Indeterminate state

Deeply unconscious

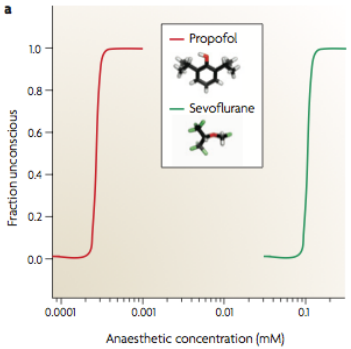


# Finding the Balance is difficult and current methods limited…




**POPULATION DOSE RESPONSE**

=



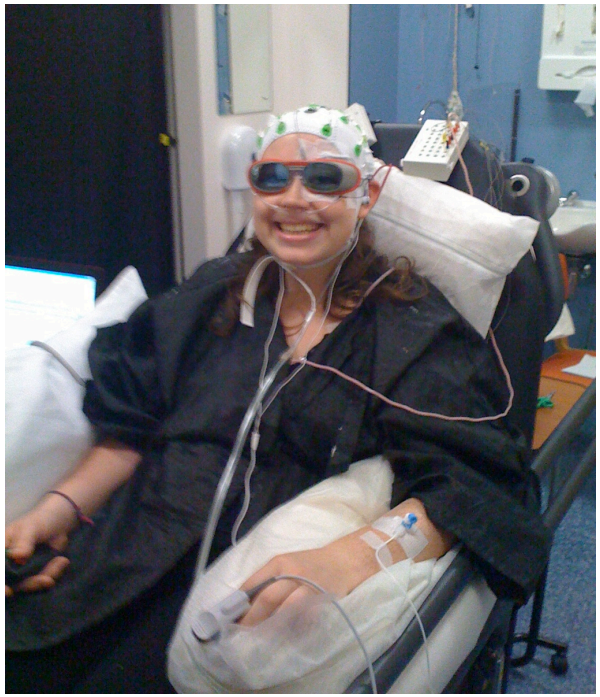

**MONITORING OF VITAL SIGNS**

+

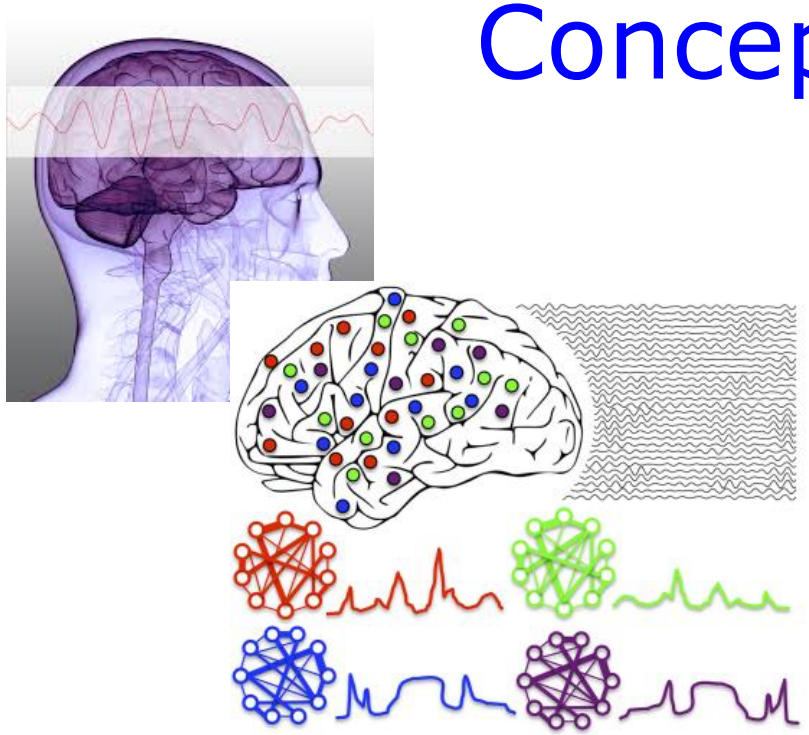

**DEPTH OF ANAESTHESIA MONITORING**

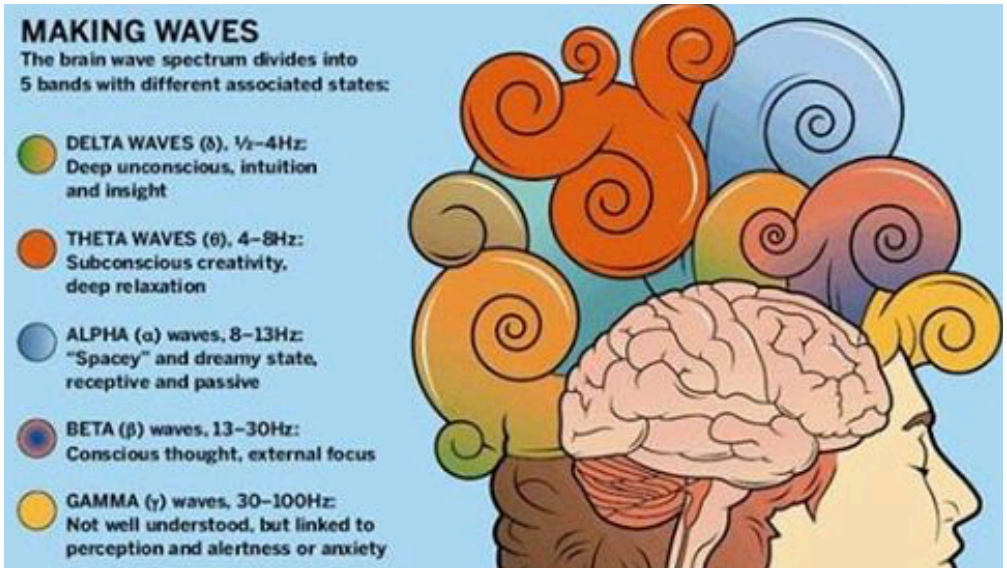
±

# Not easy experiments



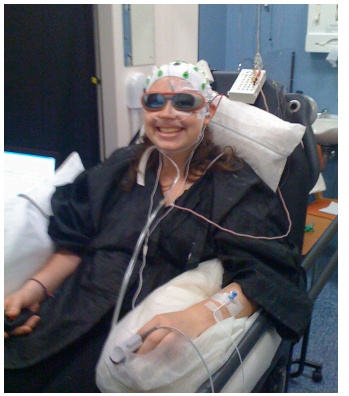
# Concept of Brain Waves

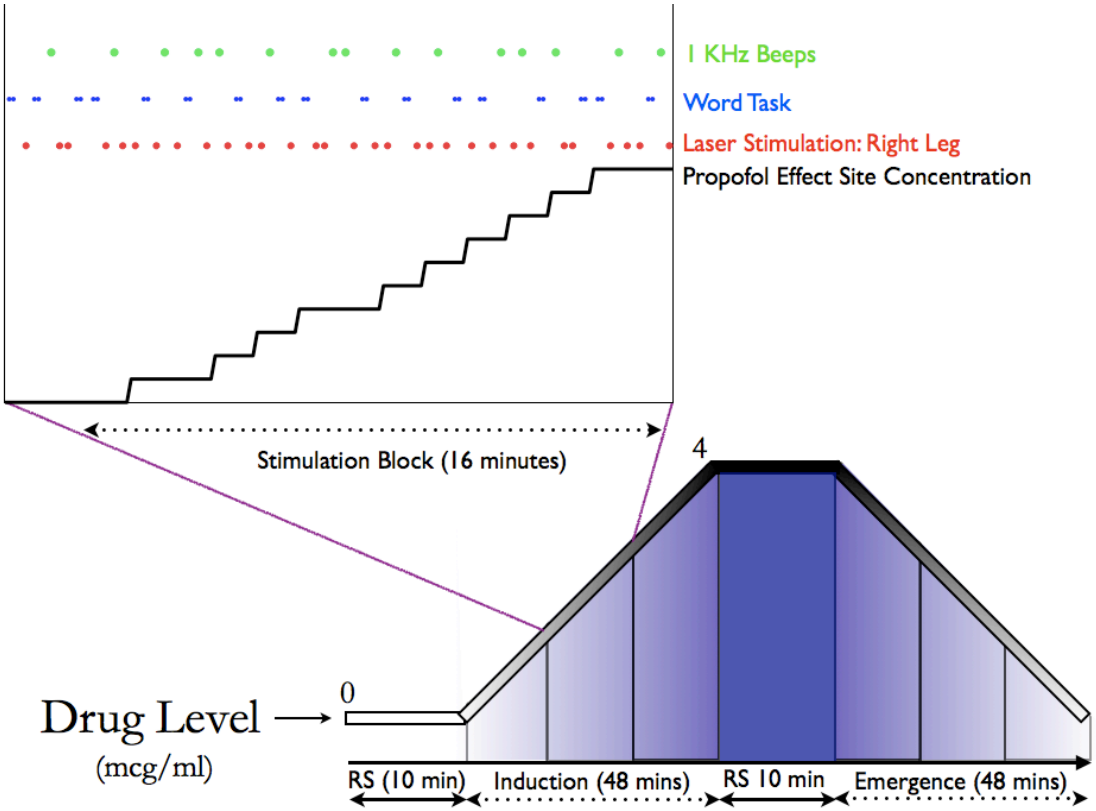


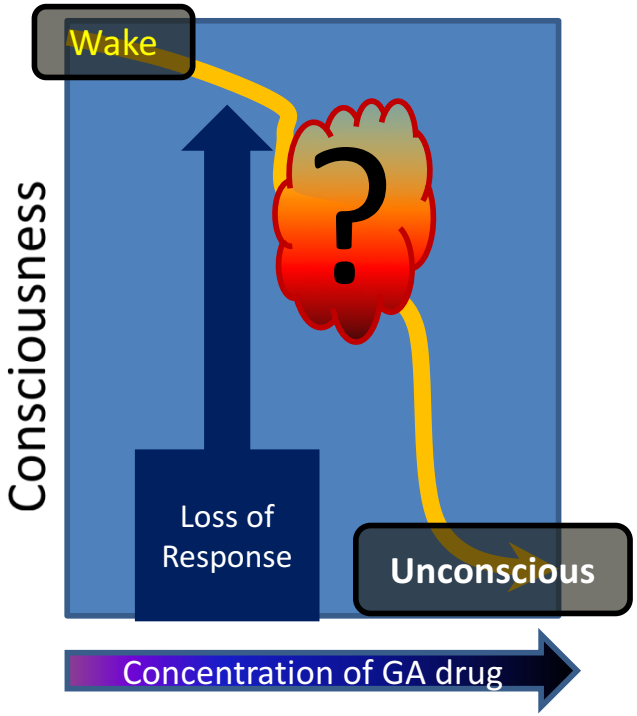


# Interrogating the anaesthesia continuum

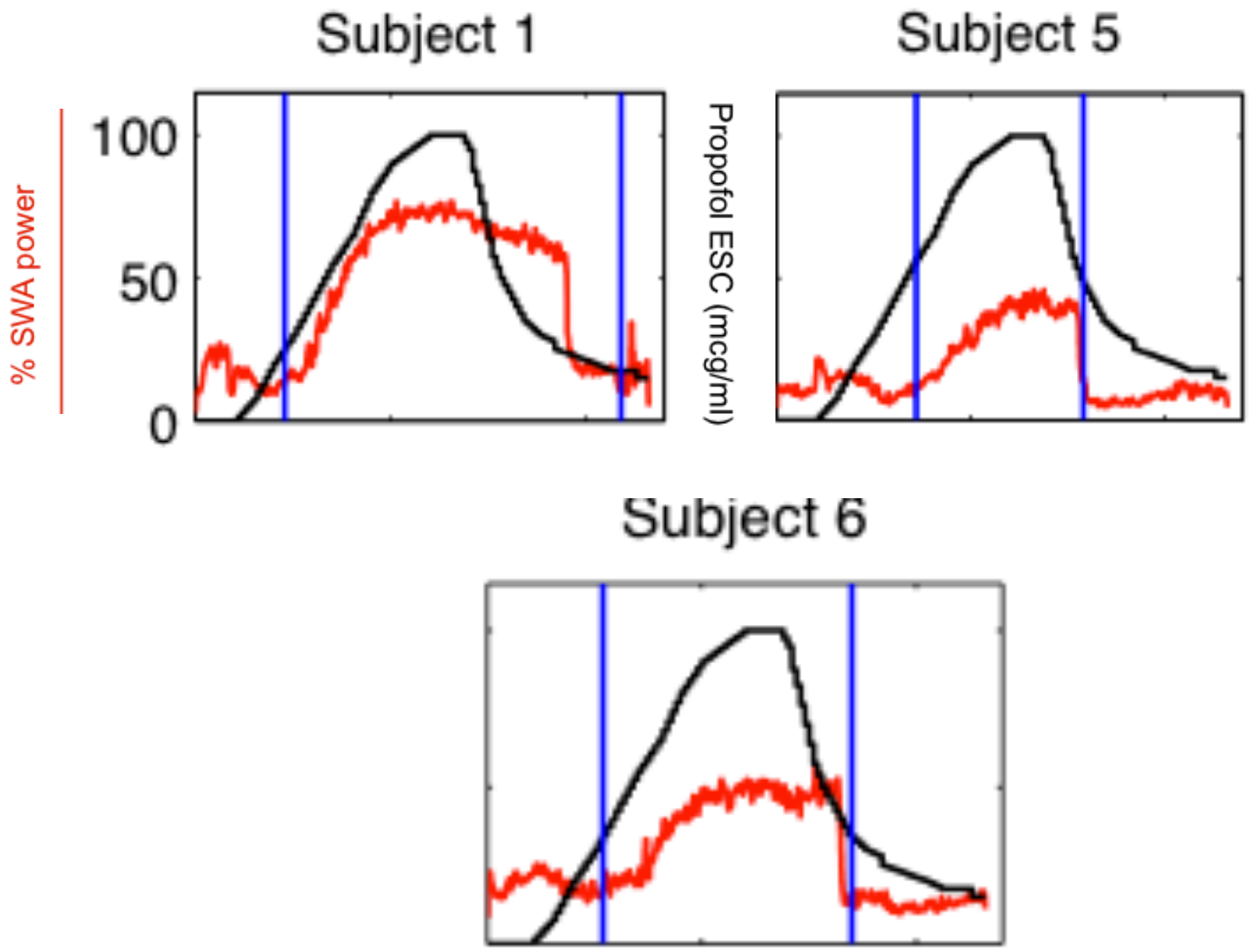
Use an ***ultraslow induction*** to observe precise point where each ***individual becomes unresponsive*** to external stimuli





# Slow wave activity ONSET and SATURATION (SWAS) is unique to each person (0.5-1.5Hz)

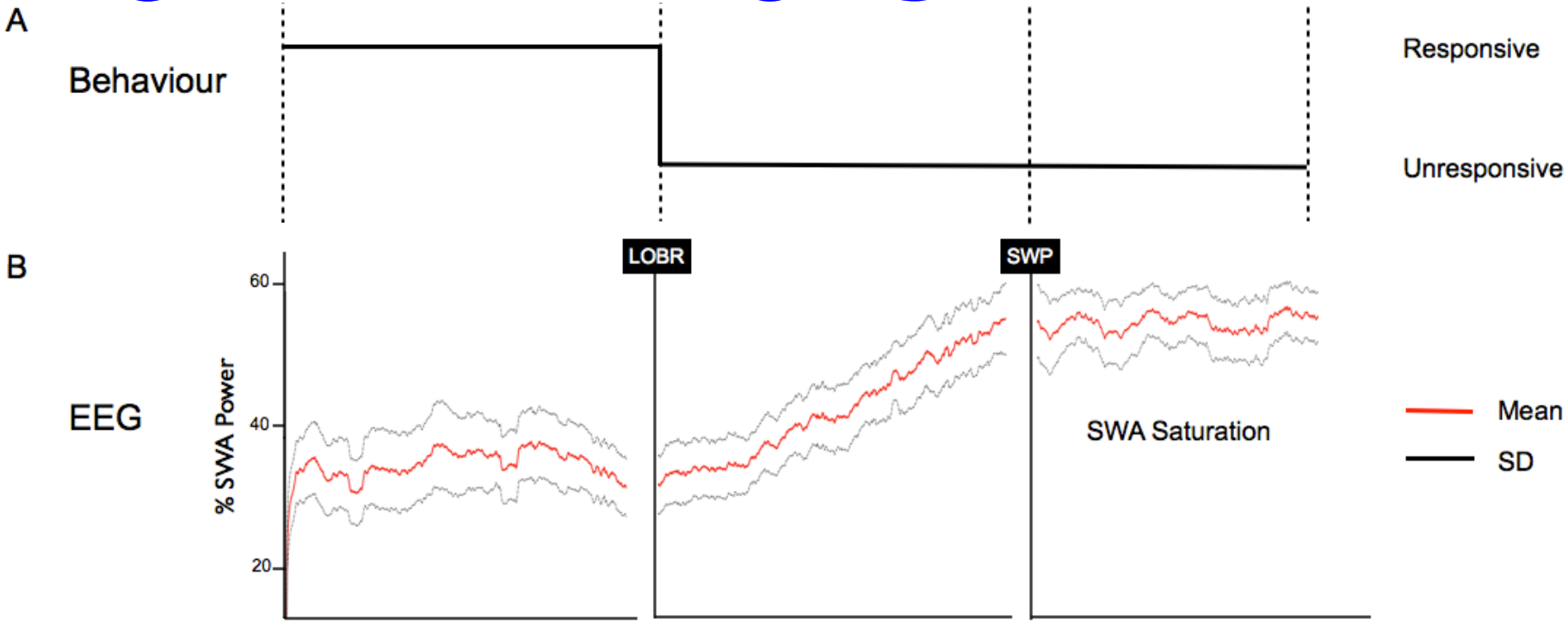



**Red:** Relative slow wave power

**Blue:** loss and recovery of behavioural response

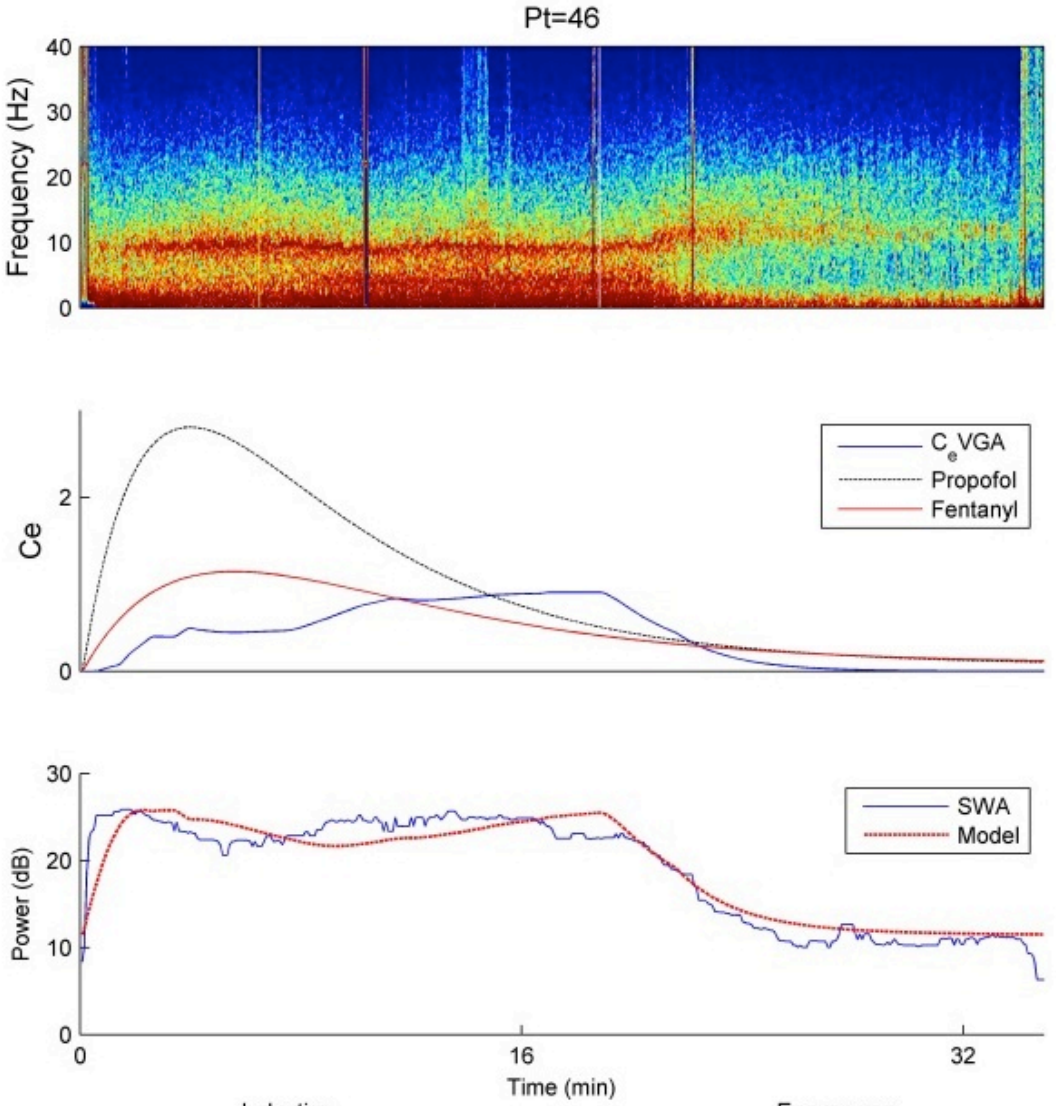
**Black:** Propofol

# BUT WHAT DOES IT MEAN?



# Does SWAS occur clinically?

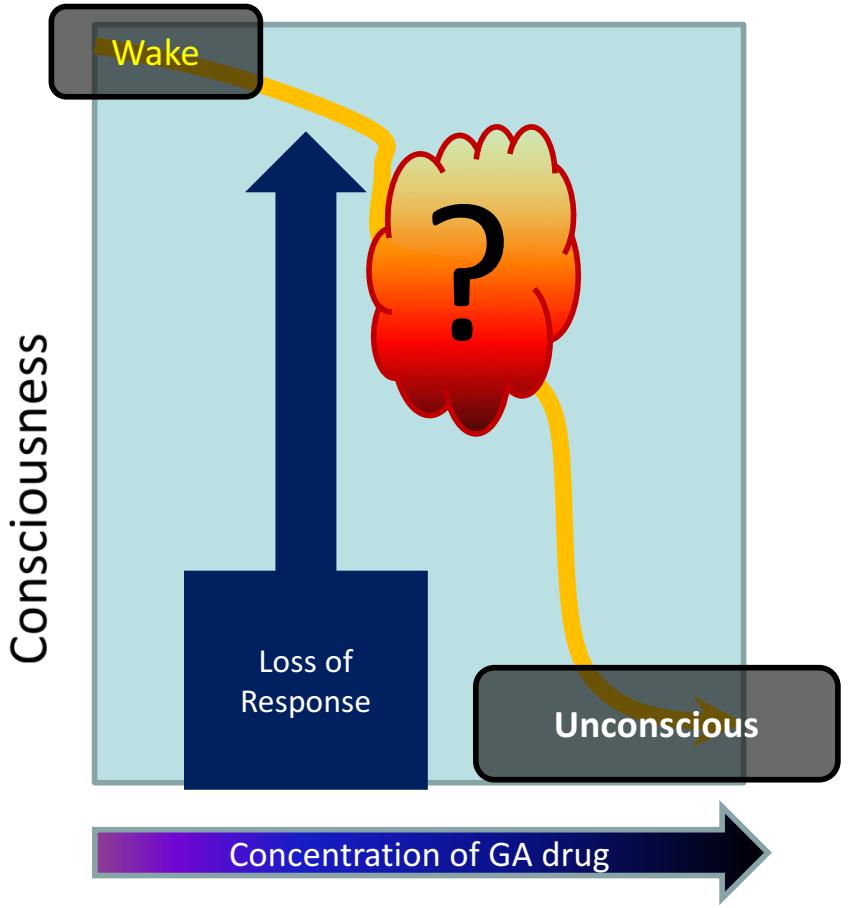
- For inhalational and intravenous anaesthetic agents?
- In presence of anaesthetic co-induction agents?
  - opioids
  - muscle relaxants
- With different EEG recording systems?
- 393 individual EEG datasets from 4 studies (3 clinical + experimental)



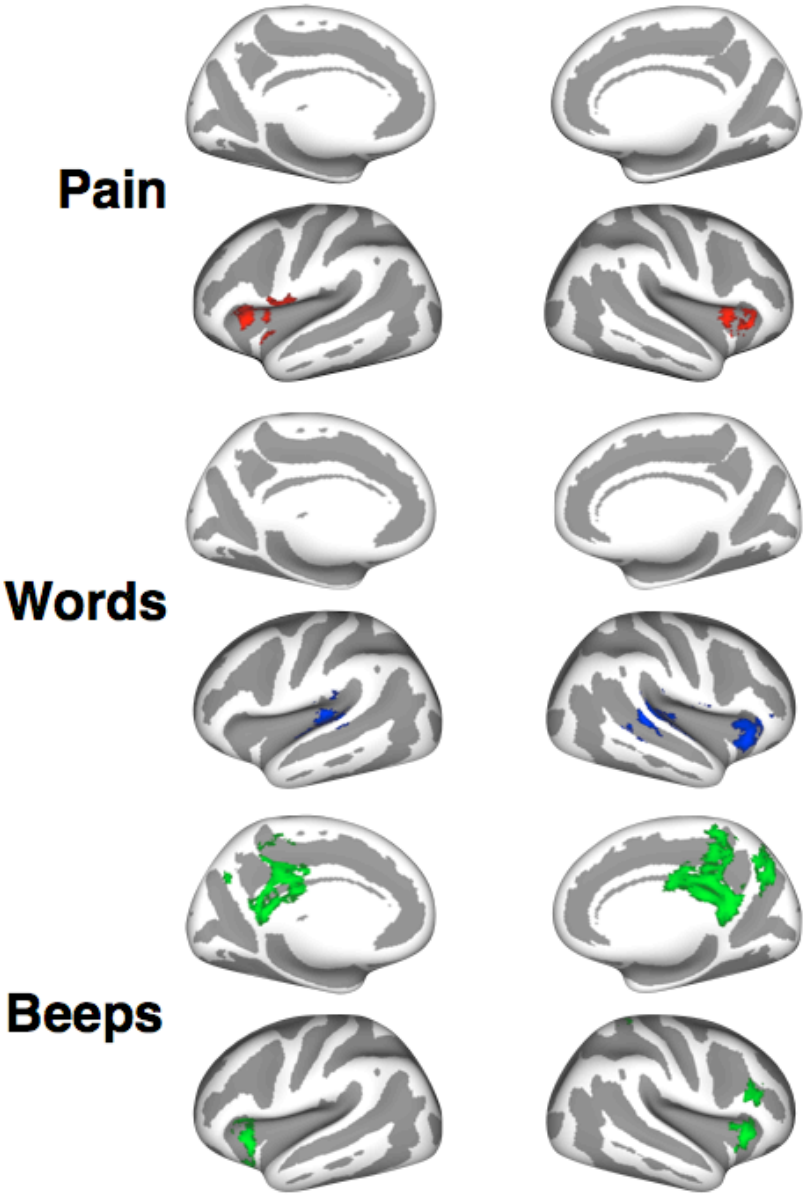

Warnaby et al., Anesthesiology 2017

So **what is lost** at loss of responsiveness?

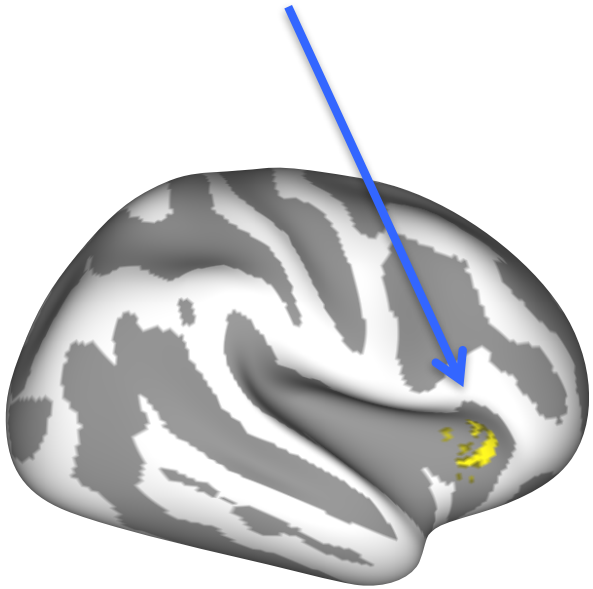
Why are individuals no longer willing to engage?



## Altered stimulus-evoked activity
## pre-LOBR > post-LOBR




# Activity in dorsal anterior insula (dAIC) is lost to all stimuli at LOBR



**Conjunction**
**pre-LOBR > post-LOBR**

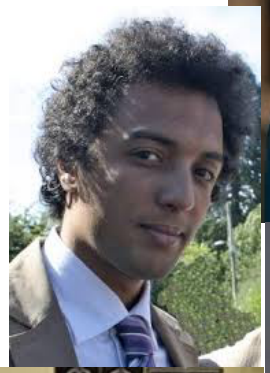
Mixed effects group analysis (n=15) , cluster thresholded at Z=2.3, $p < 0.05$

Warnaby et al., Anesthesiology 2016

# The Current Team & Collaborators

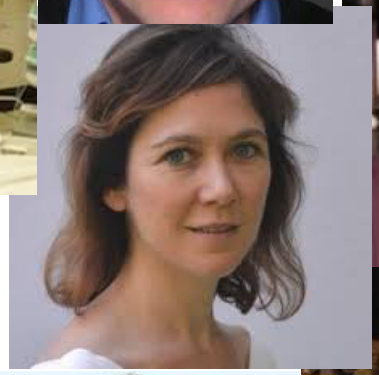
## Ongoing Pain - ASL


## Anaesthesia





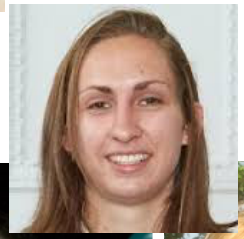


## Spinal Cord



## Clinical & Analgesia

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AIN

FMRIB
Oxford Centre for Functional MRI of the Brain

## Group – Present

- Falk Eippert
- Katie Warnaby
- Vishvarani Wanigasekera
- Andrew Segerdahl
- Melvin Mezue
- Min-Ho Lee
- Jennifer Brawn
- Sarah Waldman
- George Tackley
- Jo Kong
- Anushka Soni

## Current Collaborators

FMRIB Centre Analysis, Physics & Plasticity Groups
Andy Carr & Andrew Price (NDORMS, Oxford)
Dr Marta Seretny (University of Edinburgh)
Professor Jamie Sleigh (University of Auckland)
Richard Rogers, Jane Quinlan (NDA, Oxford)
Stephen Kennedy (Gynaecology Department, Oxford)
Jackie Palace & David Bennett (Neurology, Oxford)
David Menon (Anaesthetics, Cambridge, UK)
Bill Vennart (Pfizer, UK)
Steve McMahon, Tony Dickenson, Dave Bennett, Andrew Todd, Giandomenico Iannetti, Allan Basbaum (UCL/Imperial/Kings, London, Glasgow, UK and UCSF, USA)
Markus Ploner (Munich, Germany)
Ulrike Bingel (Hamburg, Germany)
Improving Medicines Initiative Consortium (Europain)
John Farrar (University Pennsylvania, USA)
John Brooks (Bristol, UK)

# Acknowledgments (cont)…all volunteer subjects and patients participated in studies

## Past Group Members

- Richard Lin
- Chantal Berna
- Jon Brooks
- Markus Ploner
- Ulrike Bingel
- Stephen Gwilym
- Kyle Pattinson
- Karl Ward
- Ricardo Governo
- Andy Brown
- Woong Tsang
- Merle Fairhurst
- Siri Leknes
- John Keltner
- Giandomenico Iannetti
- Laura Zambreanu
- Petra Schweinhardt
- Paul Dunckley
- Richard Wise
- Manu Goyal
- Sarah Longe
- Brandon Lujan

## Past Group Members

- Elisa Favaron
- Ajit Itty
- Amy Godinez
- Susy Bantick
- Alex Ploghaus
- Emily Johns
- Asma Ahmad
- Katie Fairhurst
- Chia-Shu Lin
- Karolina Wartolowska
- Mike Lee
- Roisin Ni Mhuirchearta
- Daniella Siexas
- Katy Vincent
- Katja Wiech
- Line Loken
- Janet Bultitude
- Tamar Makin

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