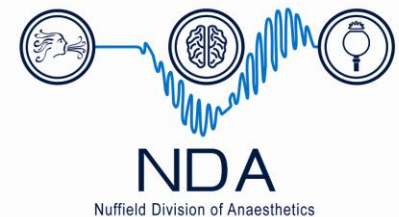# What is the role of imaging in analgesic clinical trials and the development of improved analgesic treatments?

Irene Tracey
Nuffield Professor of Anaesthetic Science &
Director of Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB),
Head, Nuffield Division Anaesthetics,
Nuffield Department Clinical Neurosciences
University of Oxford
England UK

UNIVERSITY OF OXFORD

FMRIB
Oxford Centre for Functional MRI of the Brain

NLO
Nuffield Laboratory of Ophthalmology

DCN
Division of Clinical Neurology

NDA
Nuffield Division of Anaesthetics

So Why is Record So Bad?

Problems with translating efficacy from pre-clinical models to man - Why?

• Behavioural and alternative measures from animal models need improving:

– ongoing (tonic or spontaneous) pain
– affective components
– over-reliance on nociceptive/reflexive measures?

–Means too many FALSE POSITIVES

–More 'reverse-translation' needed

…cont.

Experimental pain models in man or patient studies need improving:

– ethical limitations limit experimental models

– over-reliance on coarse, subjective rating scales in patients

– inadequate understanding of what constitutes placebo effects/other emotional/cognitive mechanisms that drive therapeutic outcomes

– lack of patient stratification or measures to 'baseline' predict high/low responders means 'pool' analgesic responses so effect to low to 'beat' placebo arm

–All lead to yet another FAILED TRIAL

Pain is an emergent experience
- it is a perception so malleable and subject to many influences
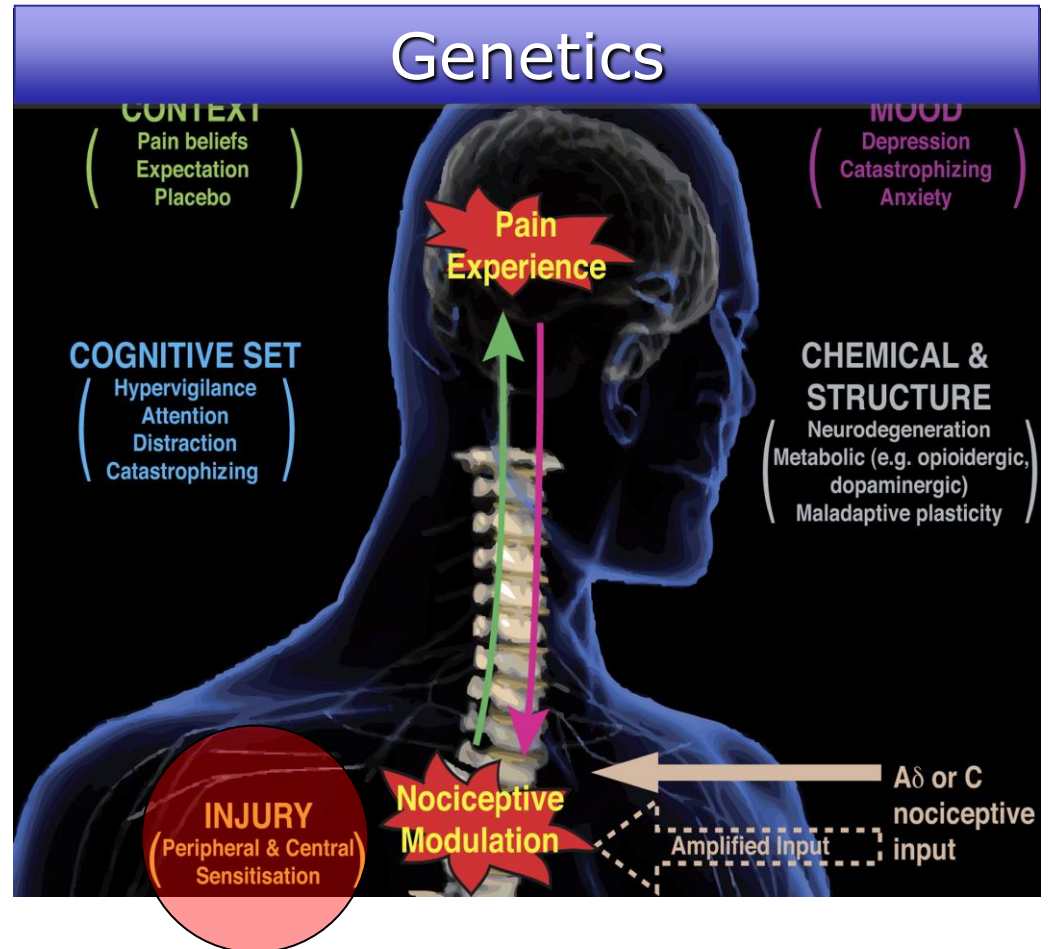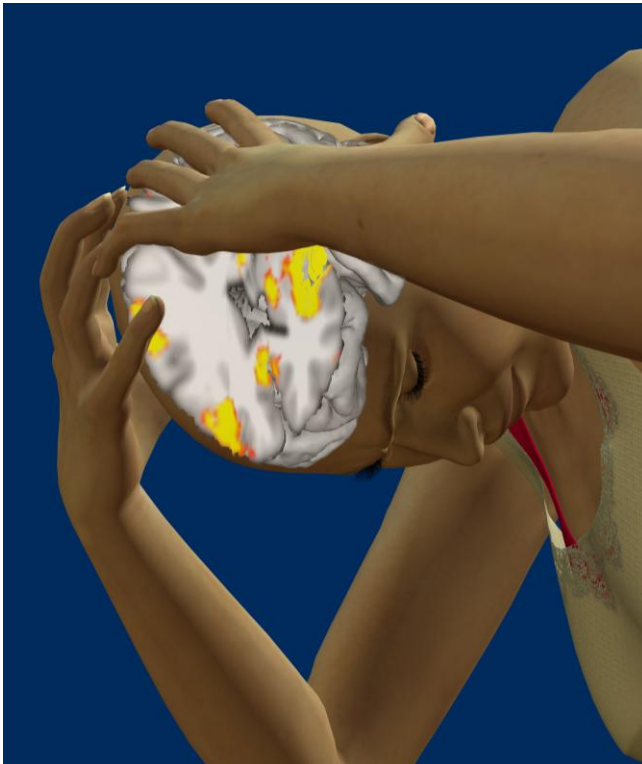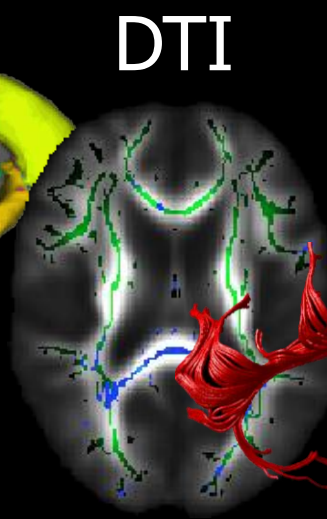
Relief..not simply pain intensity reduction

A multifactorial phenomenon that is context and personality dependent
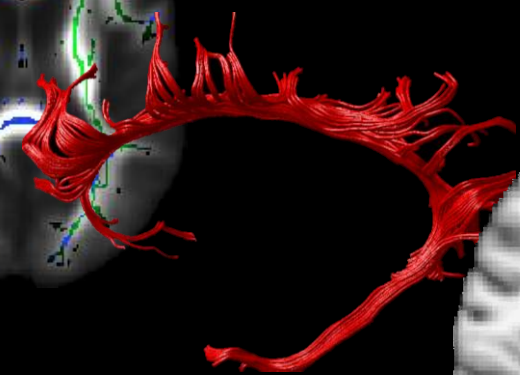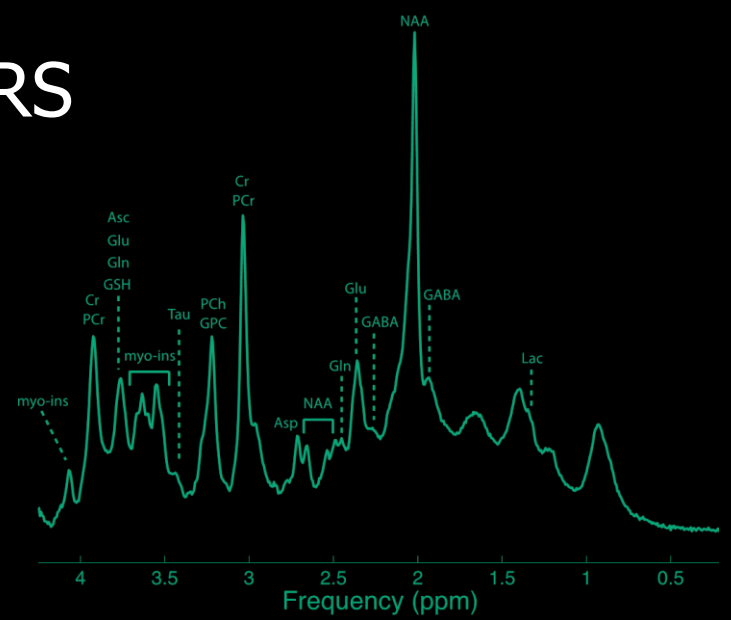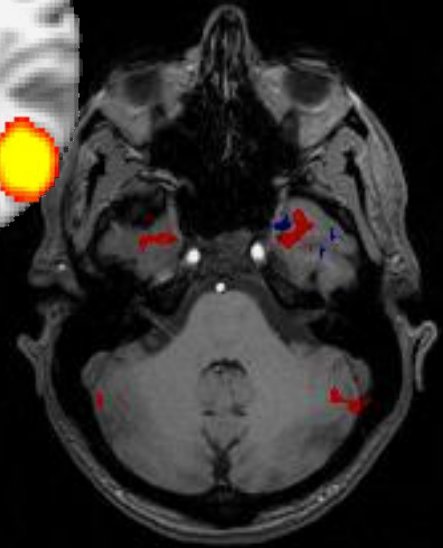
Advanced MRI

MRS
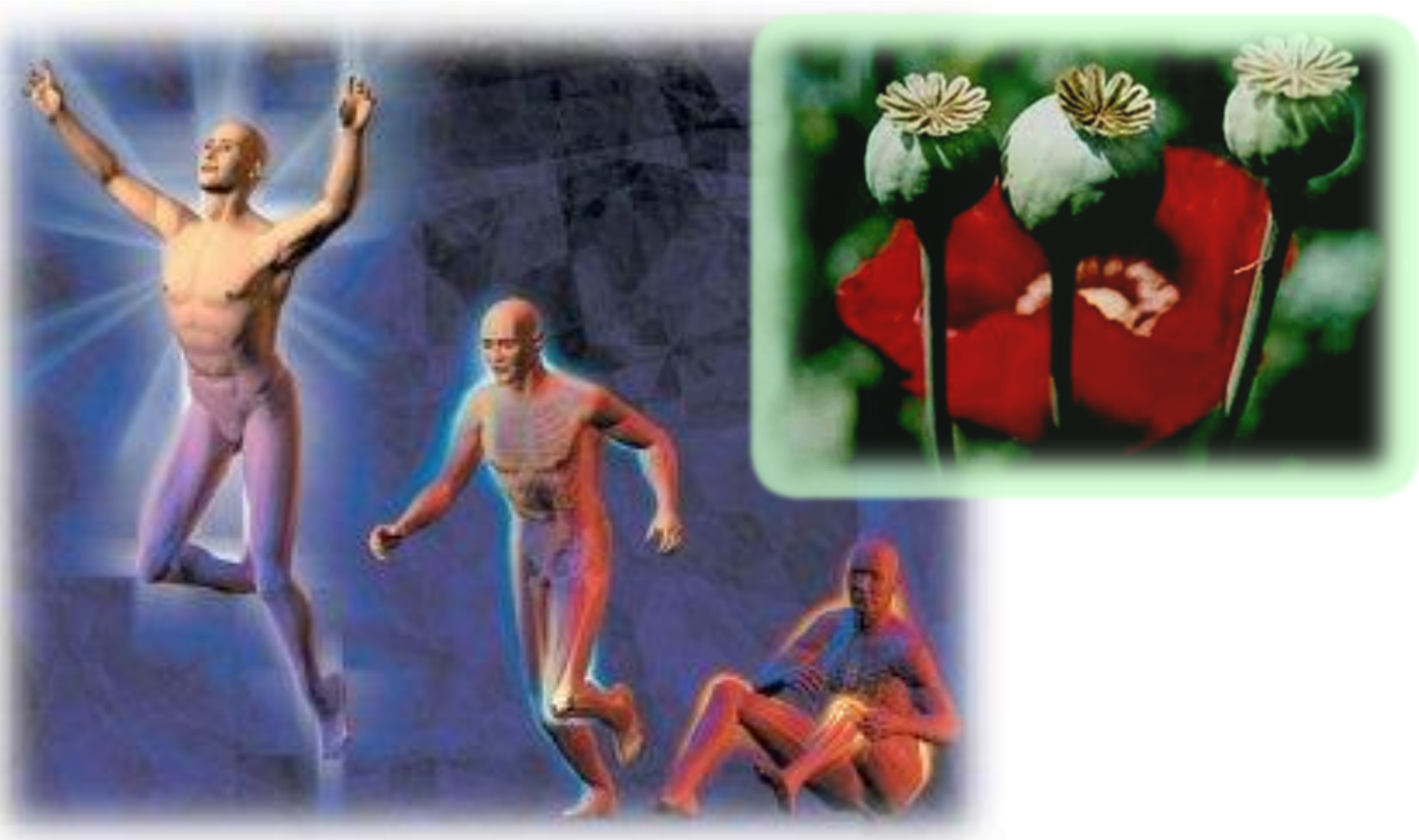
DTI
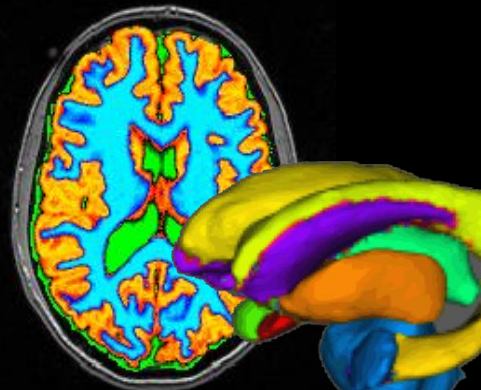
Volumetric
measures

Diffusion
tractography

Task
FMRI

Resting
FMRI

What is advanced MRI good for?

- New insight into disease processes and normal brain function

- Intermediate outcome measure in trials

- Use in everyday clinical (and increasingly legal) practice

- **NOTE:** we do NOT image the process of subjective report but the process 'behind the scenes' = tells you 'additional' things (so don't assume it's a surrogate biomarker of "pain" – biomarker of processing and chronification - yes….)
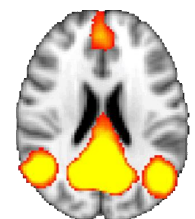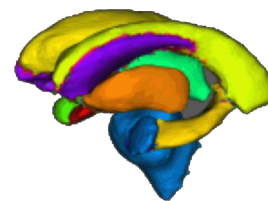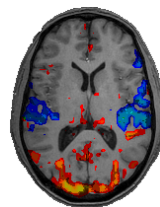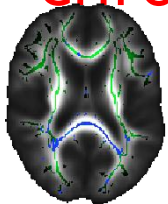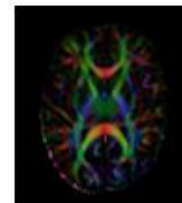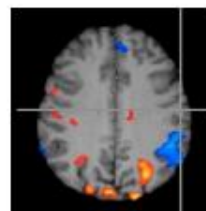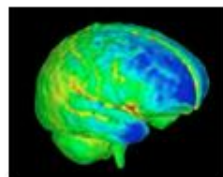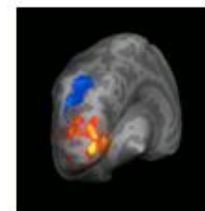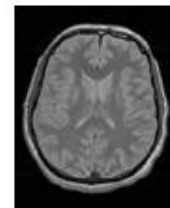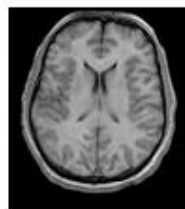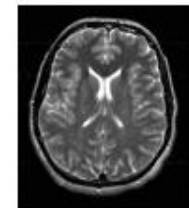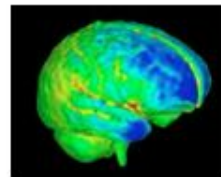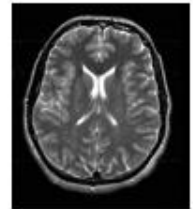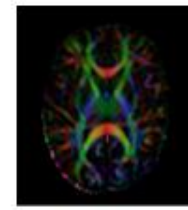
environment / lifestyle

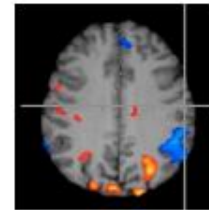long-term health outcomes

learn

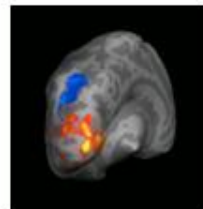genetics

neuro imaging phenotypes
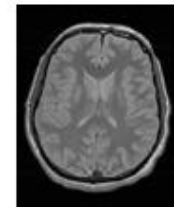
environment / lifestyle
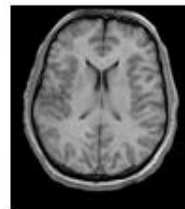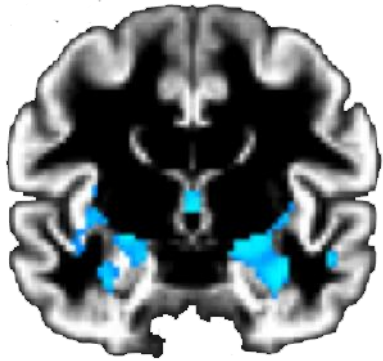
long-term health outcomes
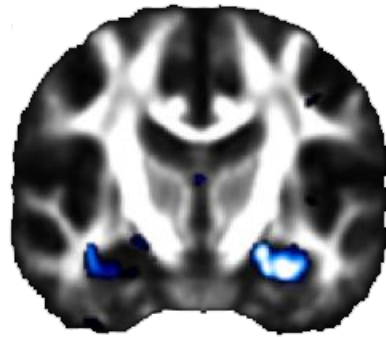
predict

genetics

neuro imaging phenotypes

Predicting conversion to Alzheimer's Disease

- Patients with Mild Cognitive Impairment given multi-modal MRI 2 years before some converted to AD and others did not

Hippocampal volume

Hippocampal diffusivity
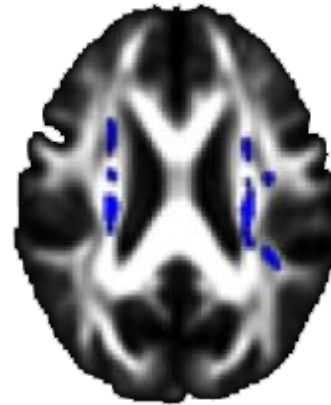
WM paths anisotropy

Beta-amyloid in CSF

Douaud et al; Oxford; GSK; Basel

Predicting conversion to AD

(hippocampus volume)
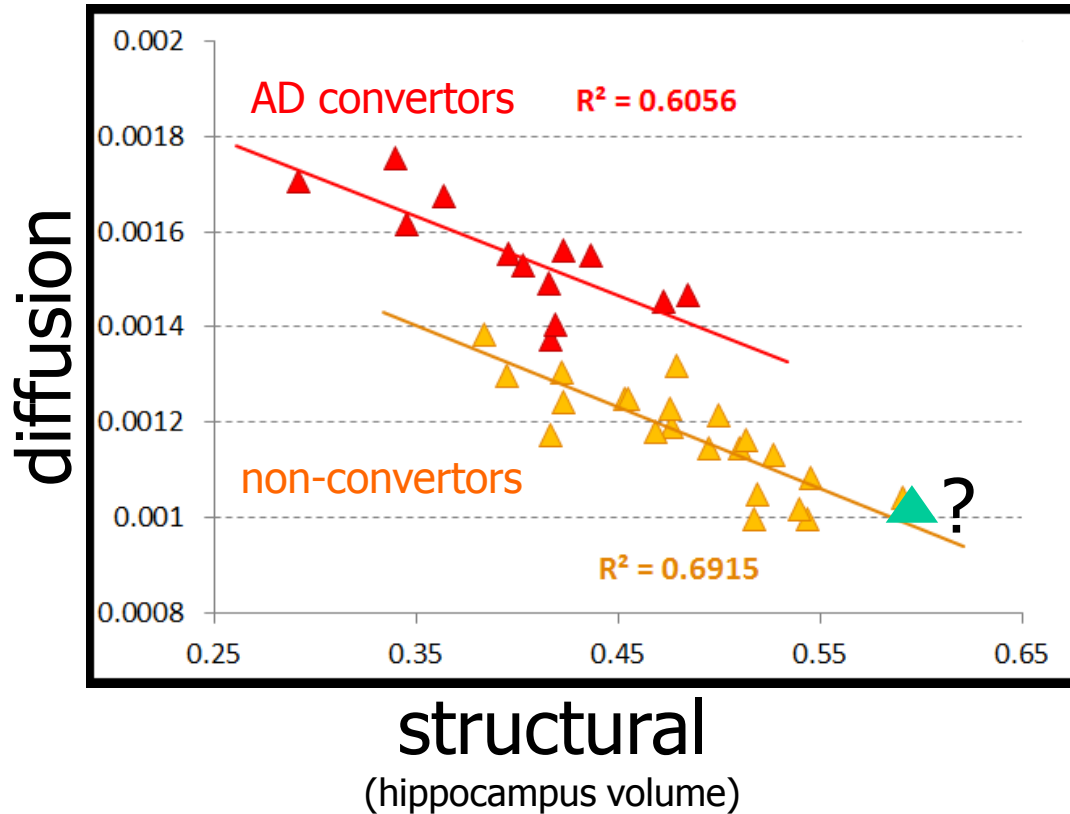
Multimodal multivariate discriminant analyses separates the groups better than any individual measure - **predict conversion to Alzheimer's more than two years in advance with 92% accuracy**
(cf 66-77% with any single modality)

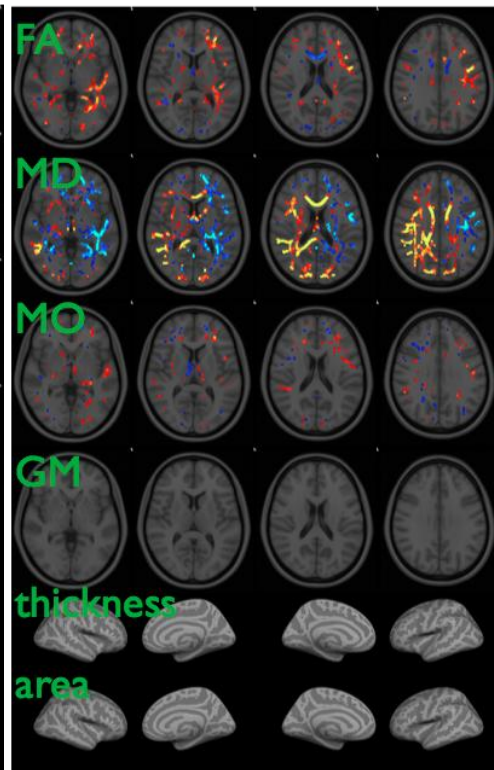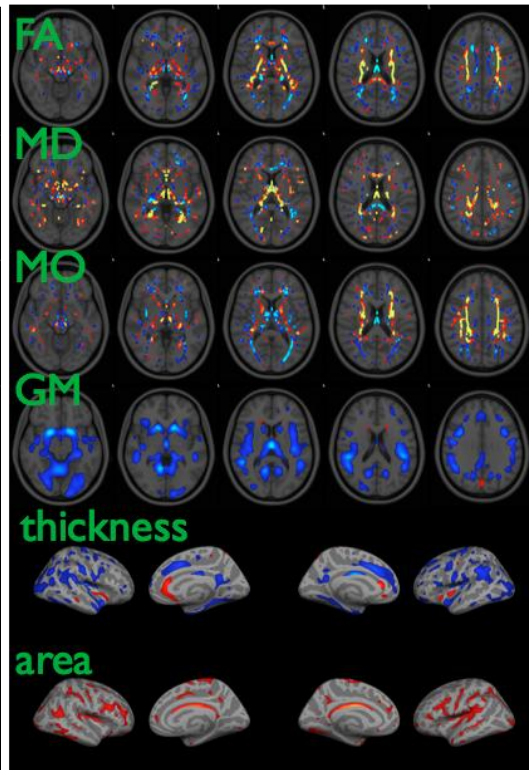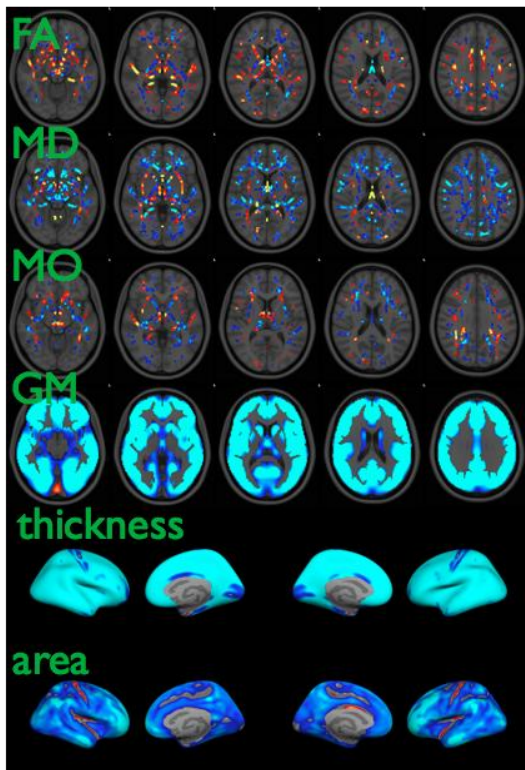# Exploratory multivariate, multimodal, Bayesian ICA
(Groves & Woolrich)
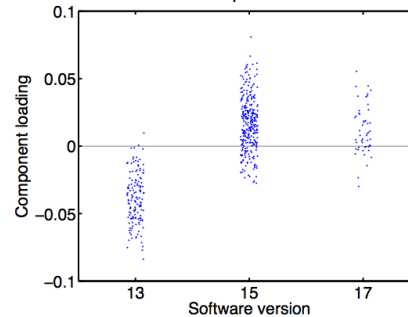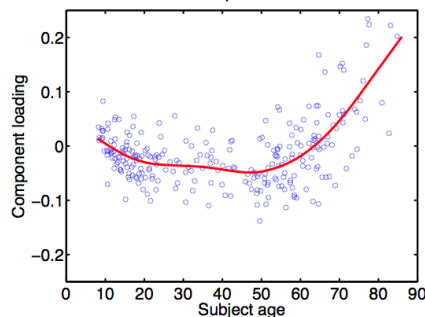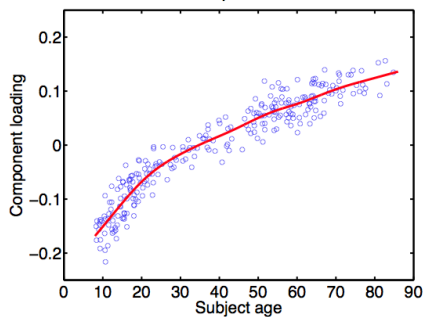
484 healthy subjects, ages 8-85y, from collaborators in Oslo (Fjell et al.)

Neuroanatomy of Acute and Persistent Pain Processing:
Unique Cerebral Signatures

Tracey & Mantyh, Neuron 2007
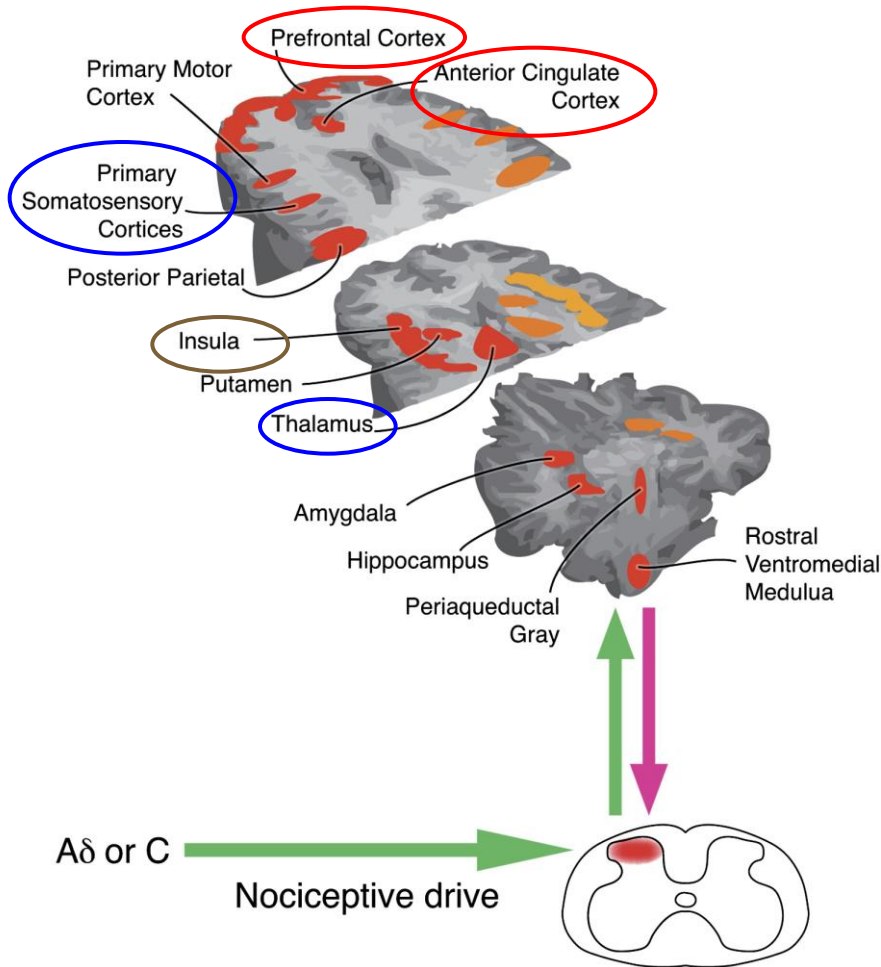
The Hard Core = "analgesic" network

sensory/discriminatory + affective/cognitive/motivational?

- Thalamus
- S1/S2
- Insula (several divisions)
- ACC (several divisions)
- Prefrontal

1. Can we use this analgesic "network" as sensitive read-out and/or target = aid drug discovery?

2. Can you have analgesia without modulating these regions = research

Is there merit in non-patient studies?

- Quicker, cheaper and potentially 'cleaner' mechanistically

- But ethical limitations on models of symptoms – so few available options plus pharmacokinetics makes life tricky, nevertheless……
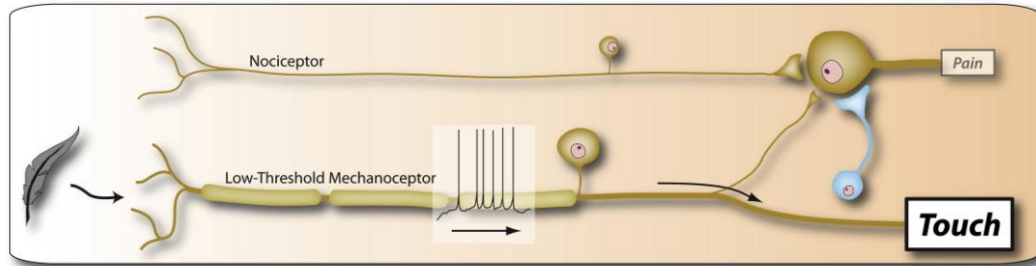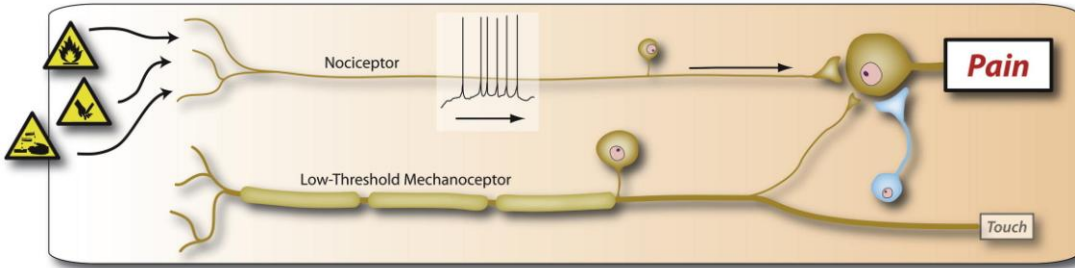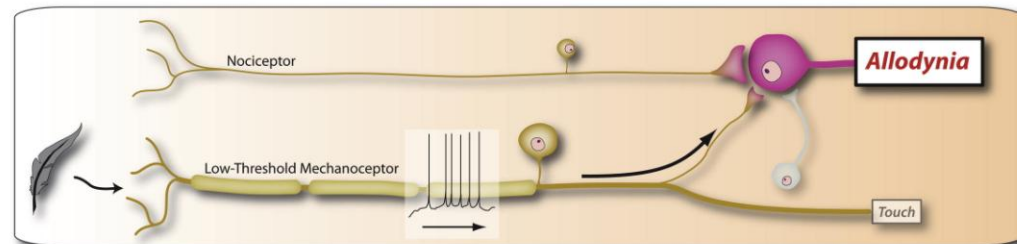
Relevance of Central Sensitisation for Chronic Pain
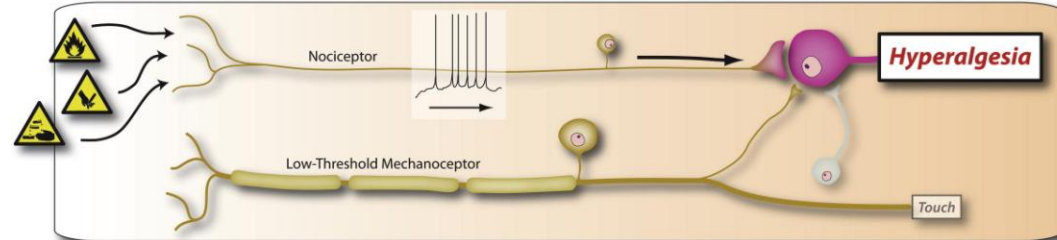
From: Woolf CJ Pain 2011

The brainstem plays key role influencing dorsal horn processing

Increasing pre-clinical/clinical evidence for pivotal role in chronic pain – i.e. pro-nociceptive mechanisms maintain central sensitisation and poor anti-nociceptive mechanisms contribute to pain experiences

The Descending Pain Modulatory System:
Anti- (good) and Pro- (bad) nociceptive mechanisms

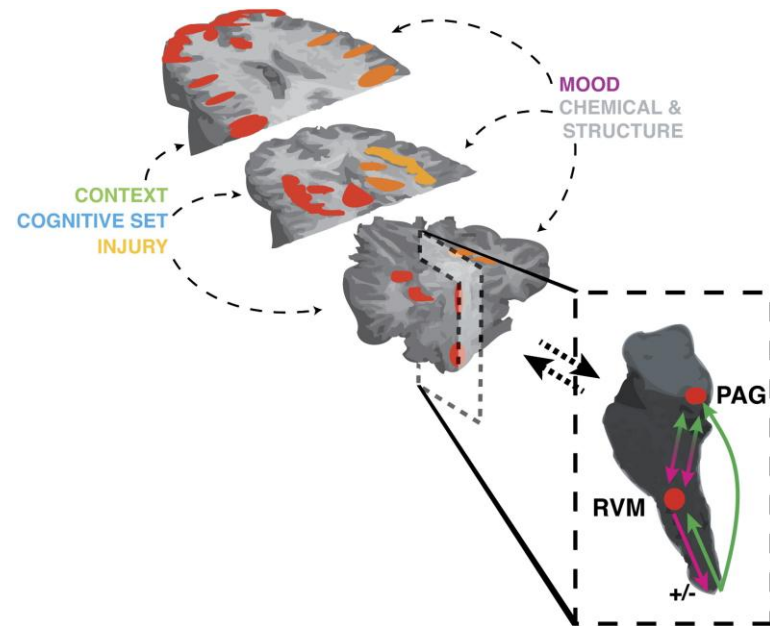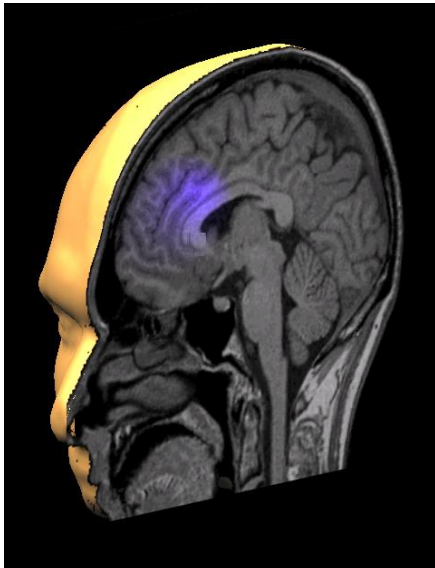# Engagement of descending inhibition from the rostral ventromedial medulla protects against chronic neuropathic pain

Milena De Felice [a,1], Raul Sanoja [b,1], Ruizhong Wang [c,1], Louis Vera-Portocarrero [d], Janice Oyarzo [a], Tamara King [a], Michael H. Ossipov [a], Todd W. Vanderah [a], Josephine Lai [a], Gregory O. Dussor [a], Howard L. Fields [e], Theodore J. Price [a,□], Frank Porreca [a,□]

A

B Number of OFF cell pauses of more than 10sec

C Number of ON cell bursts of more than 10sec

SD ON Cell   HZ ON Cell

D   E

4Hz   4Hz

time (min) post formalin injection

F SD OFF Cell   G HZ OFF Cell

5Hz   10Hz
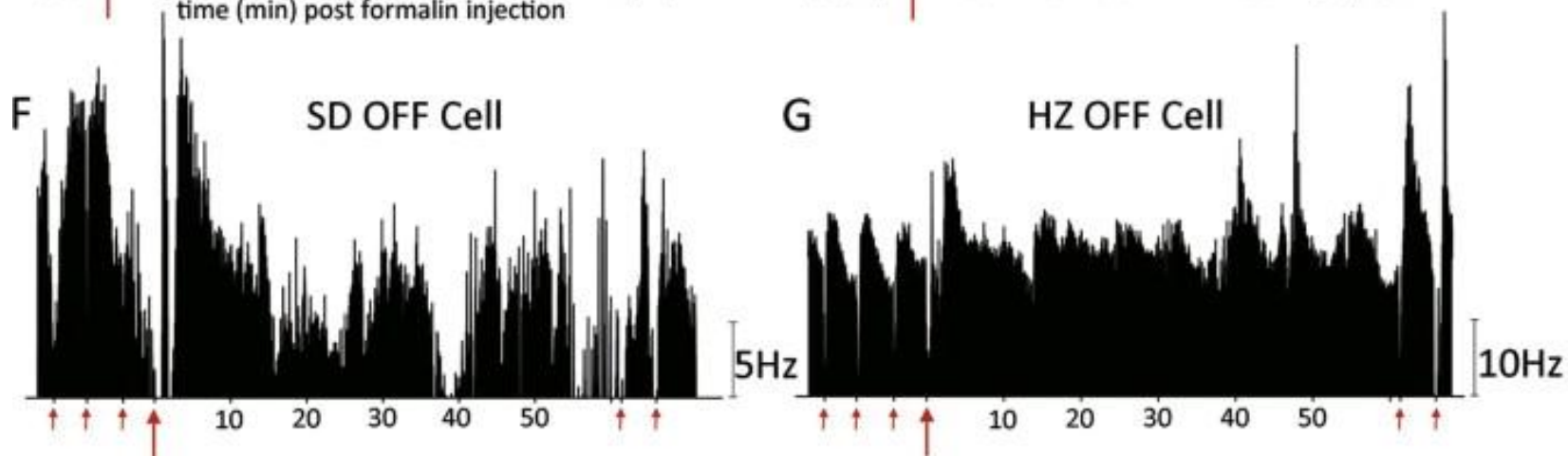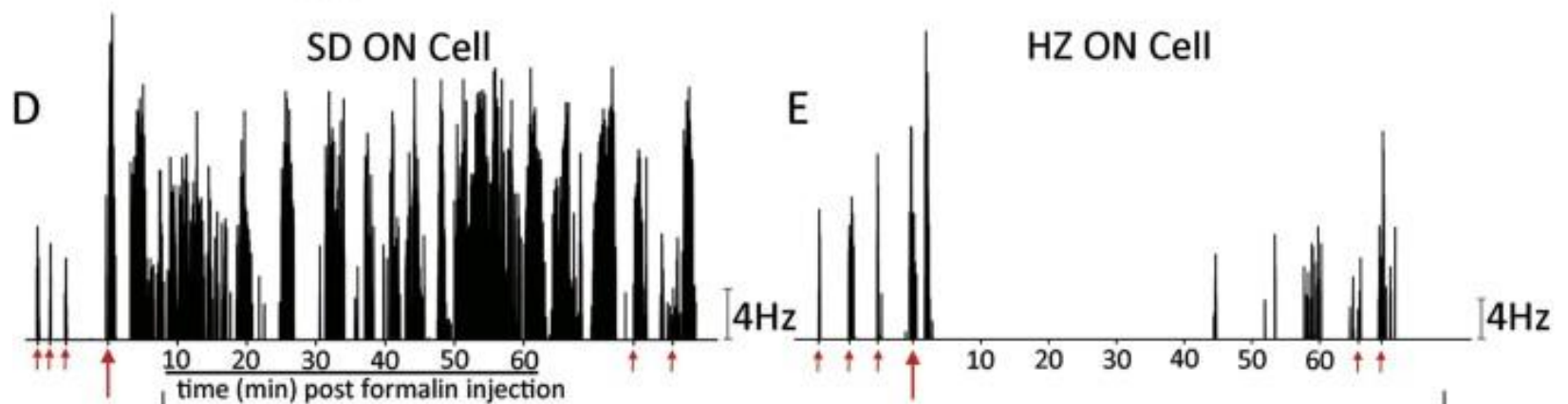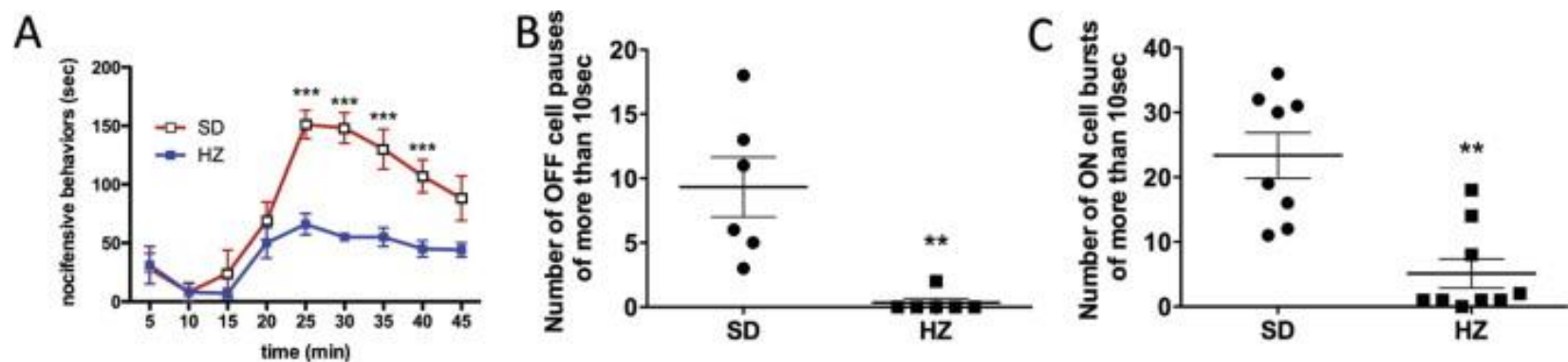
Developing a Biomarker for Central Sensitisation

Capsaicin:

Model of central sensitisation
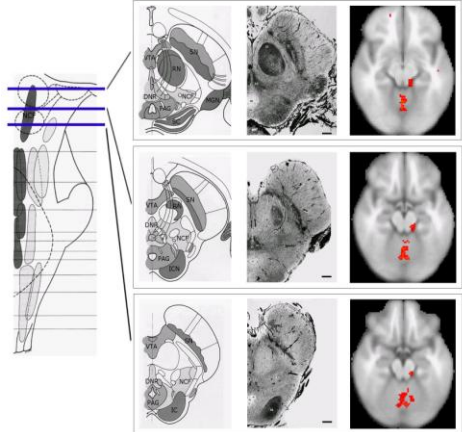
Zambreanu et al., PAIN 2005

VAS
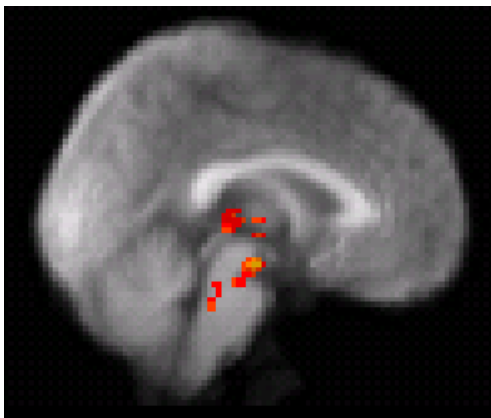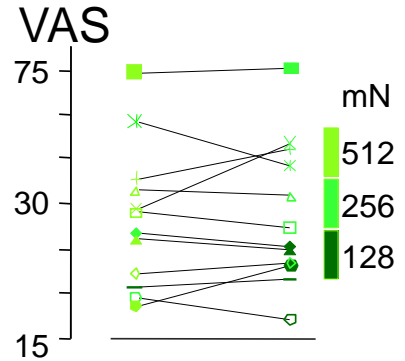
Lee et al., J. Neuroscience 2009

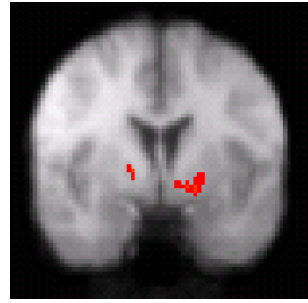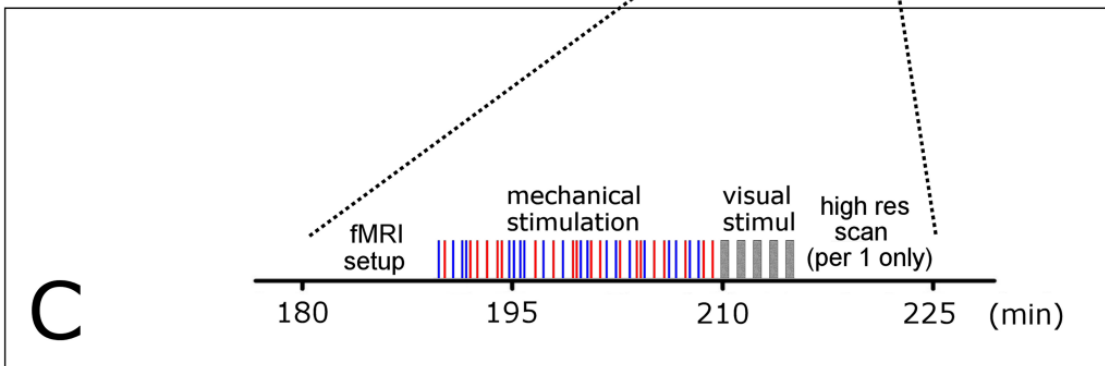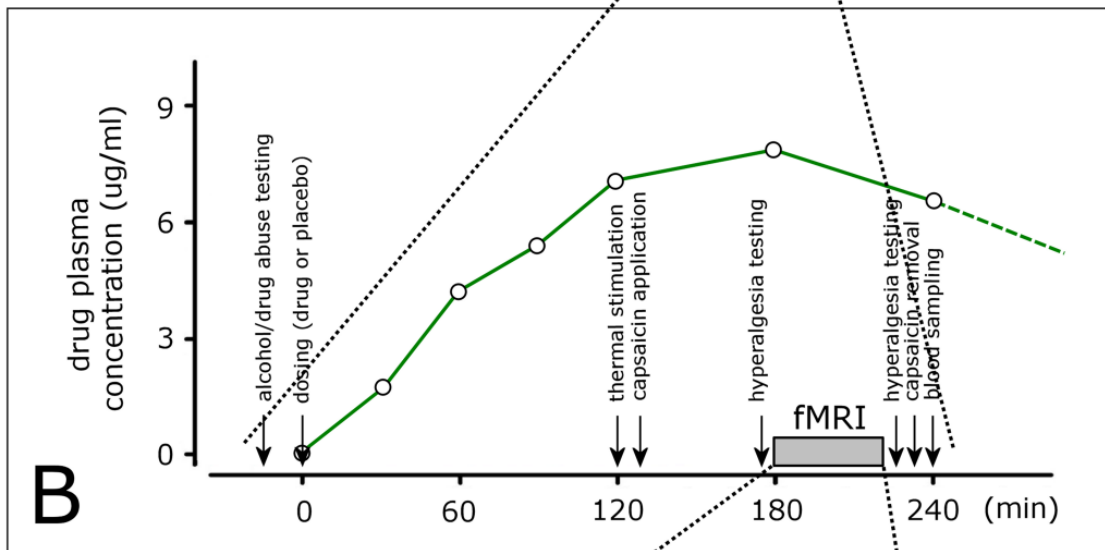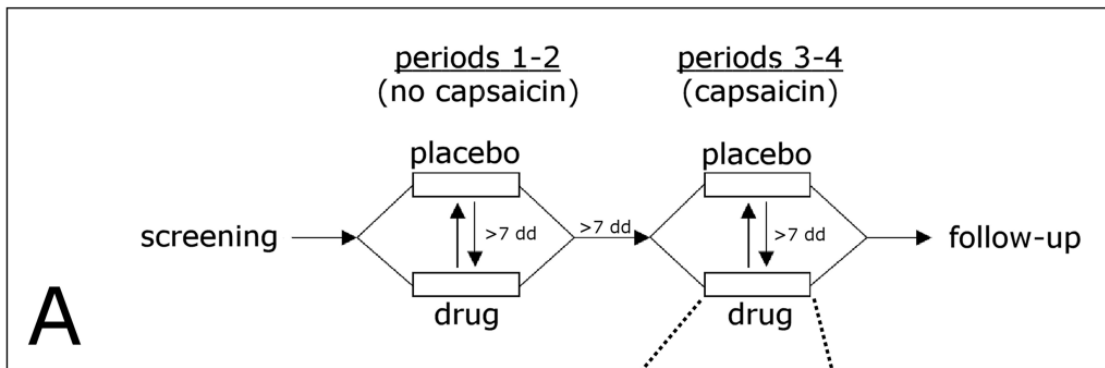Gabapentin modulation of pain-related brain activity during normal and central sensitisation states in humans
(collaboration with Pfizer)

1800 mg given orally as a single dose. Expected blood peak 3 hr later – time point of FMRI data collection

PSYCHOPHYSICS - ns

Iannetti, Zambreanu et al., PNAS., 2005

1: normal state   P: placebo
2: central sensitisation   D: drug
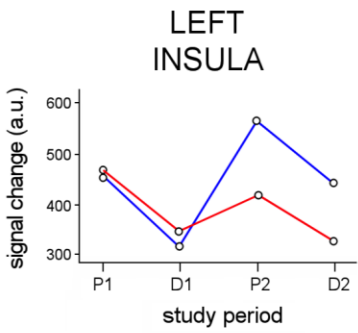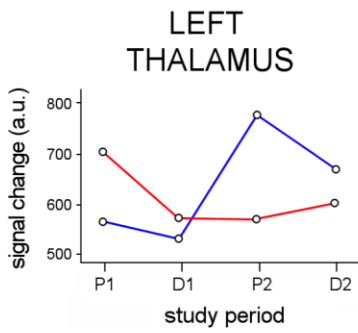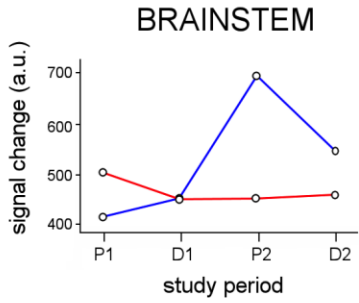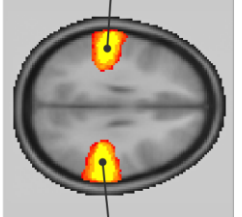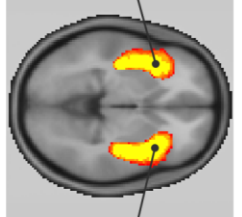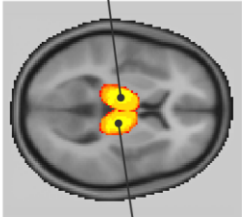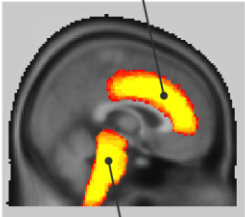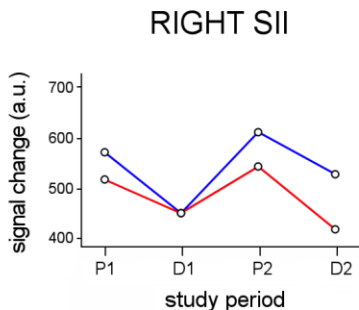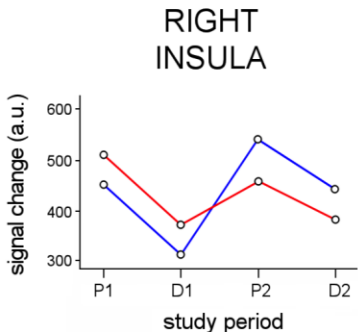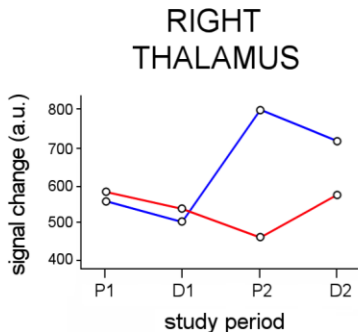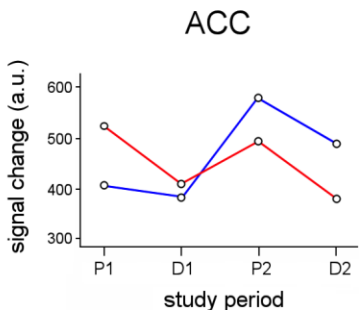
Gabapentin abolishes normal brain deactivation during nociceptive transmission - measure of its side effects?
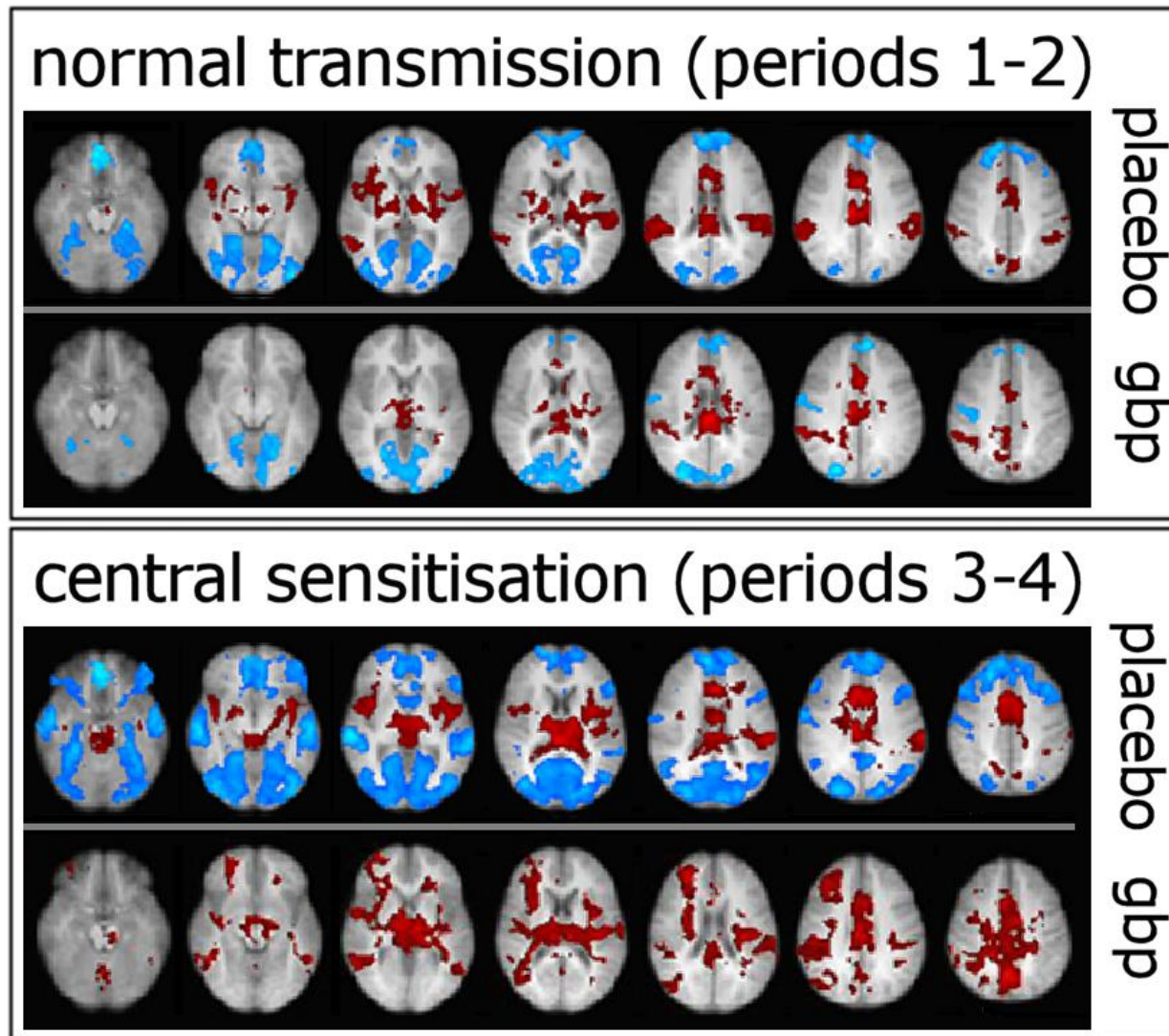
Identifying Neural Correlates of Non-nerve Injury Model of Hyperalgesia in Humans: The post-opioid induced hyperalgesia model

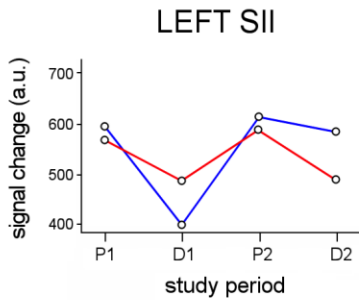## relevance for functional pain syndromes and withdrawl effects of opioids?

(Wanigasekera et al., J. Neuroscience 2011)
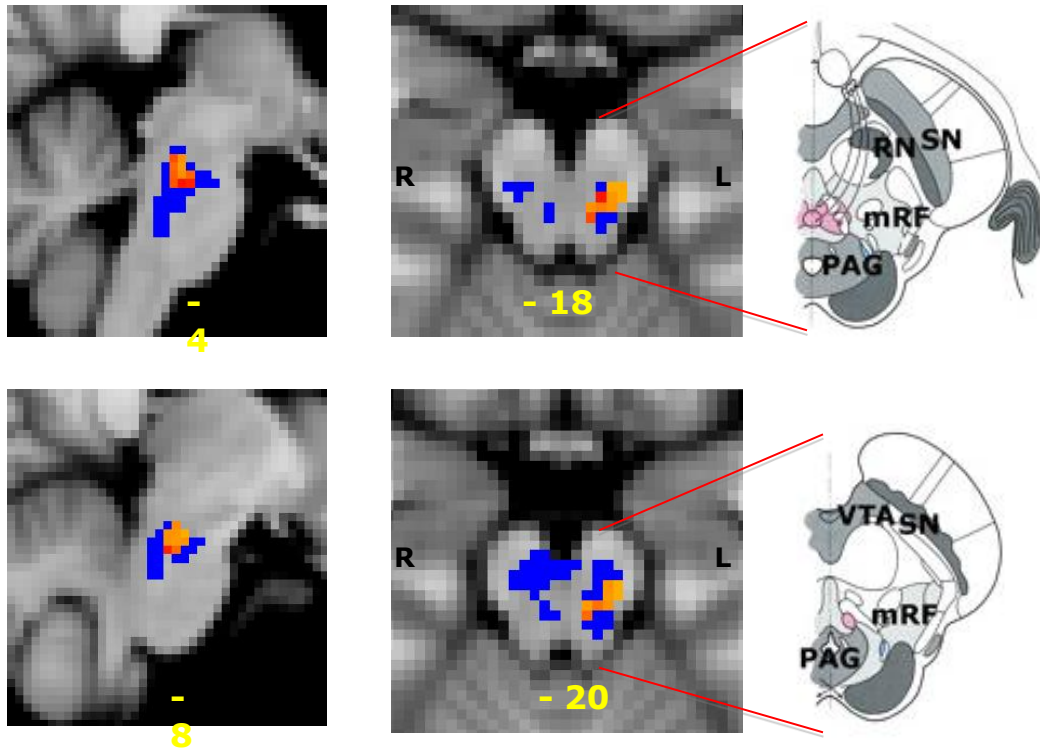
Effect of opioid withdrawal on BOLD activity within the mesencephalo-pontine reticular formation (MPRF)

Innovative Medicines Initiative = pan European academic-industry partnership – Oxford determining whether our 'biomarker' assay is a predictive tool for drugs known to work/not work in clinic

Study drug (gabapentin 1200 *tablets*; ibuprofen 600mg *tablets;* placebo
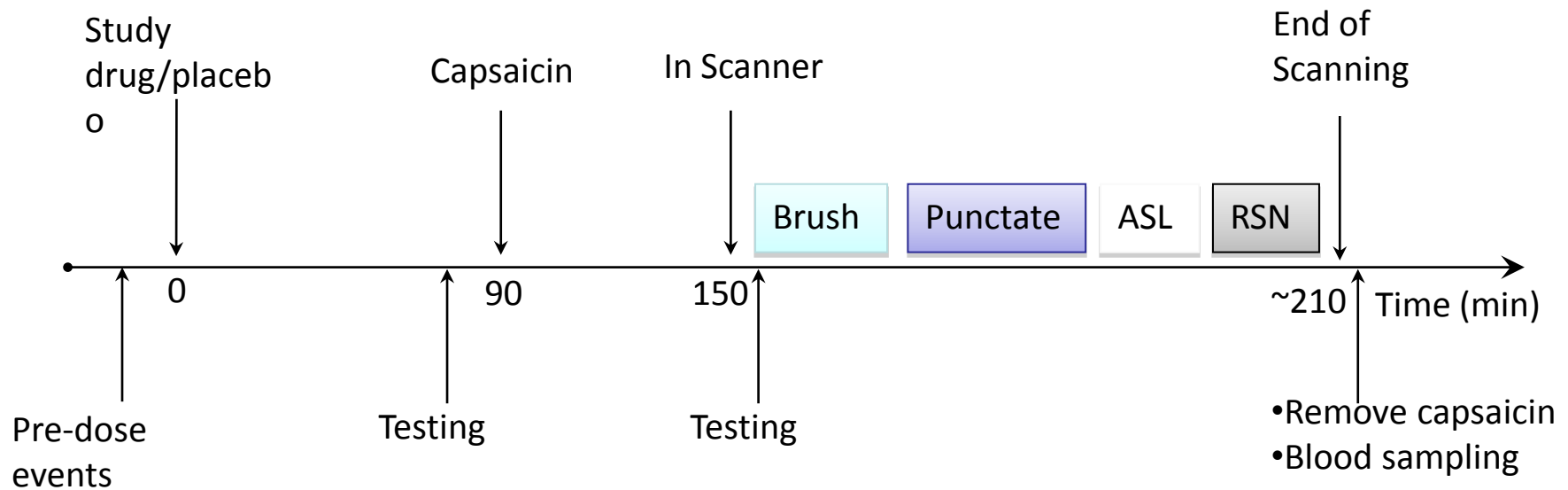
Decision-making using fMRI in clinical drug development: revisiting the NK-1 receptor antagonist for pain

(Borsook et al., Drug Discovery Today 2012)
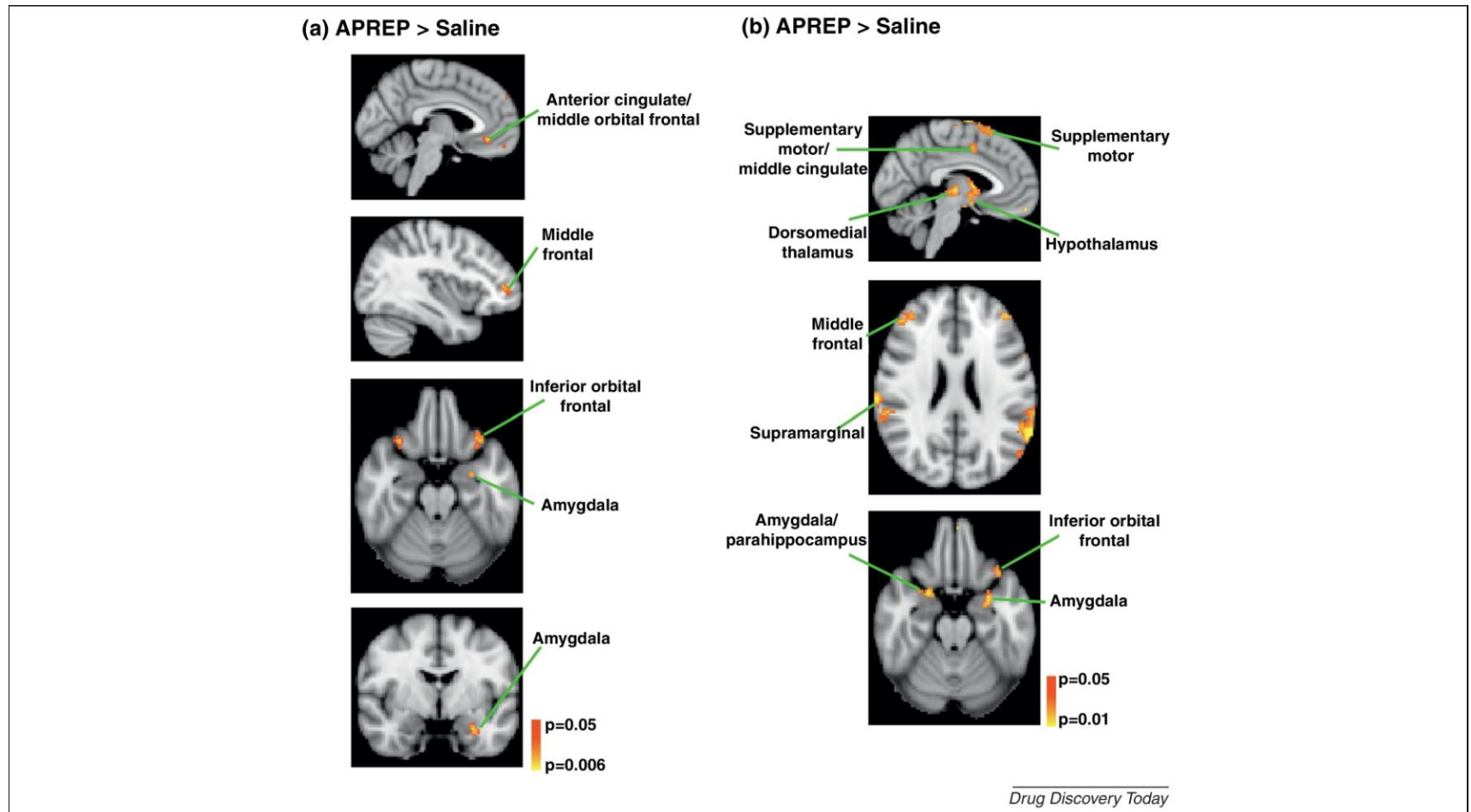
Determining the neural basis of cannabinoid analgesia in humans
(Lee et al., in revision 2012.)
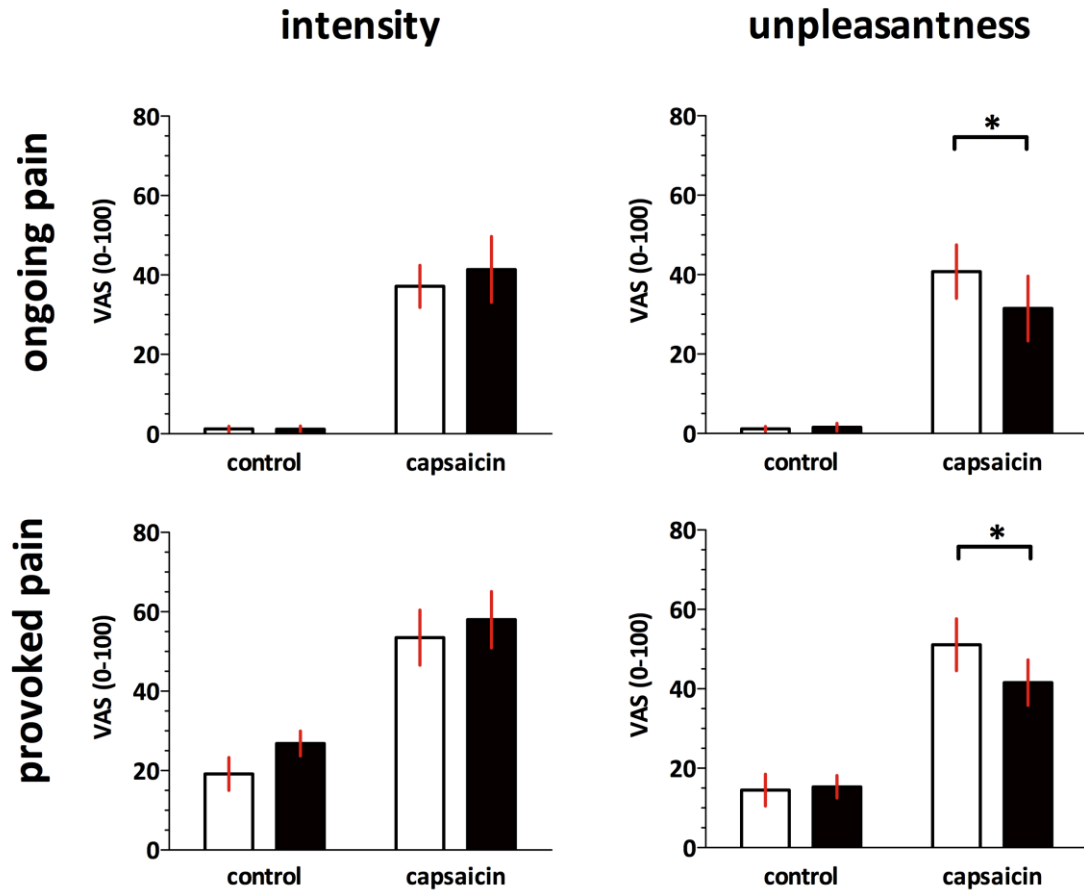
THC specifically reduced unpleasantness of hyperalgesia

THC increased amygdala reactivity to noxious stimulation
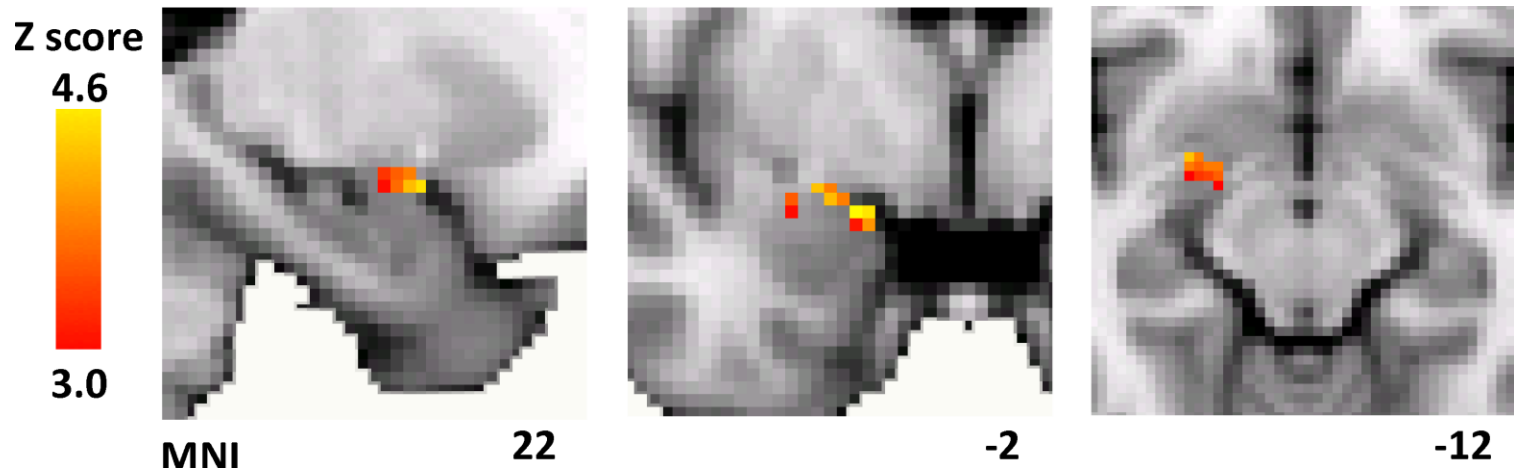
Amygdala reactivity was correlated with analgesic effect
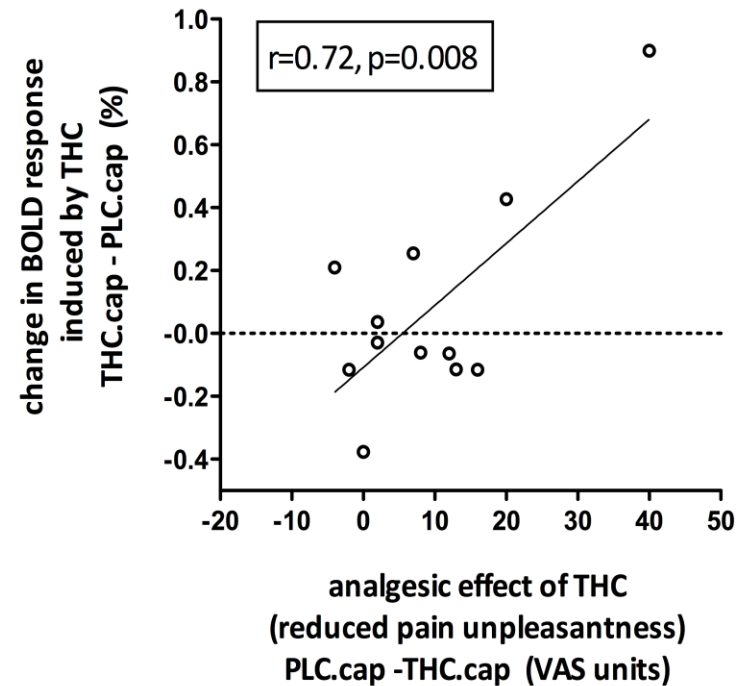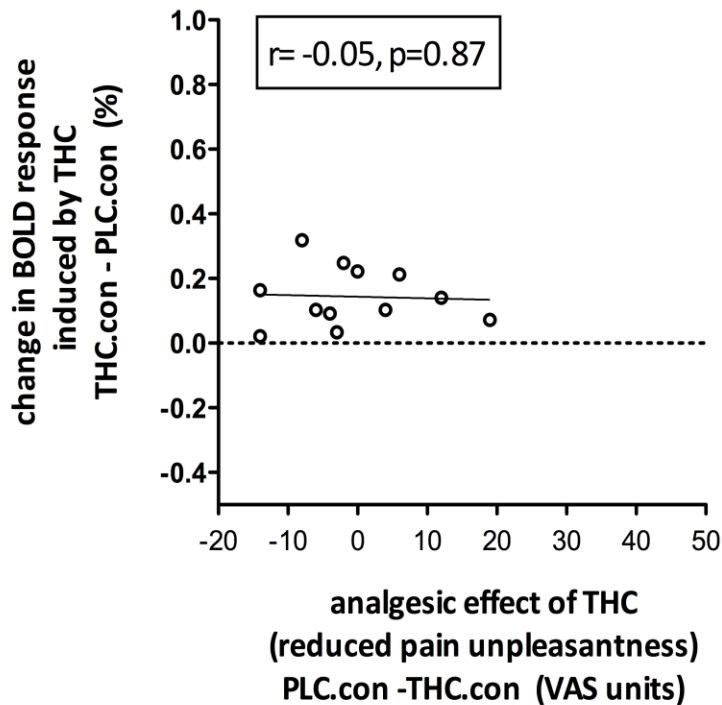
THC uncoupled limbic-sensory activity producing a 'pain asymbolia' like state

functional amygdala

fMRI signal

reduced correlations with somatosensory areas

Z score

-2   -5.2
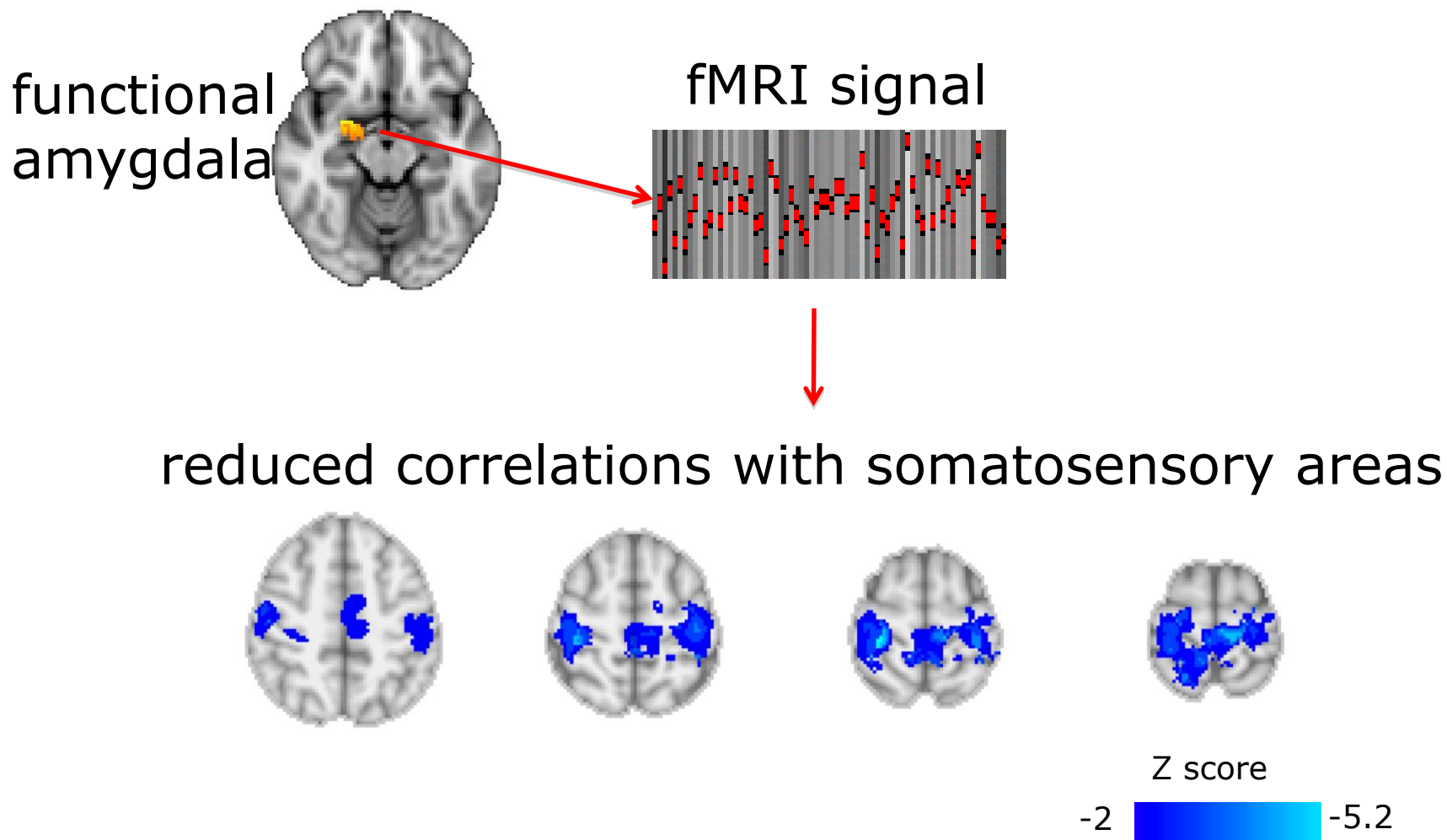
Limbic-sensory uncoupling explained the differential effect of THC on pain intensity and unpleasantness
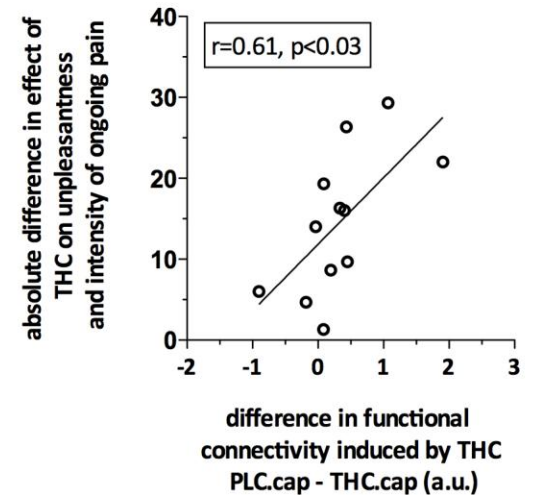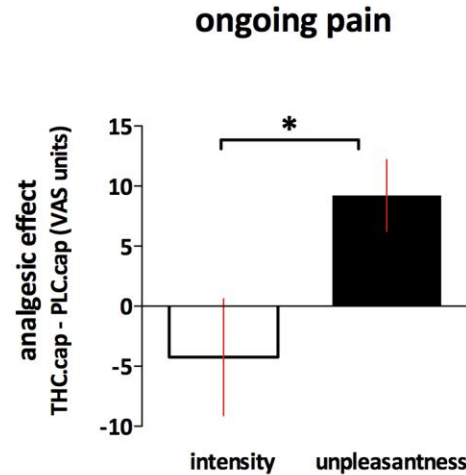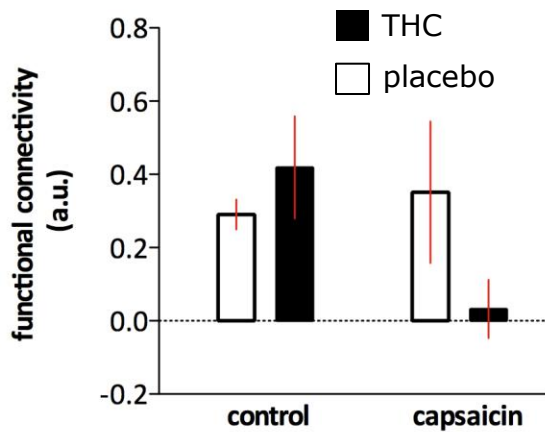
Simulating Pharma's Go/No-Go Decision Making Point:
Wartolowska et al., 2012 (in prep)

FMRI "head-to-head" study examining pregabalin, tramadol, placebo in small cohort of Neuropathic Pain Patients (n=16) – in collaboration with Pfizer and clinical colleagues from Birmingham and Portsmouth
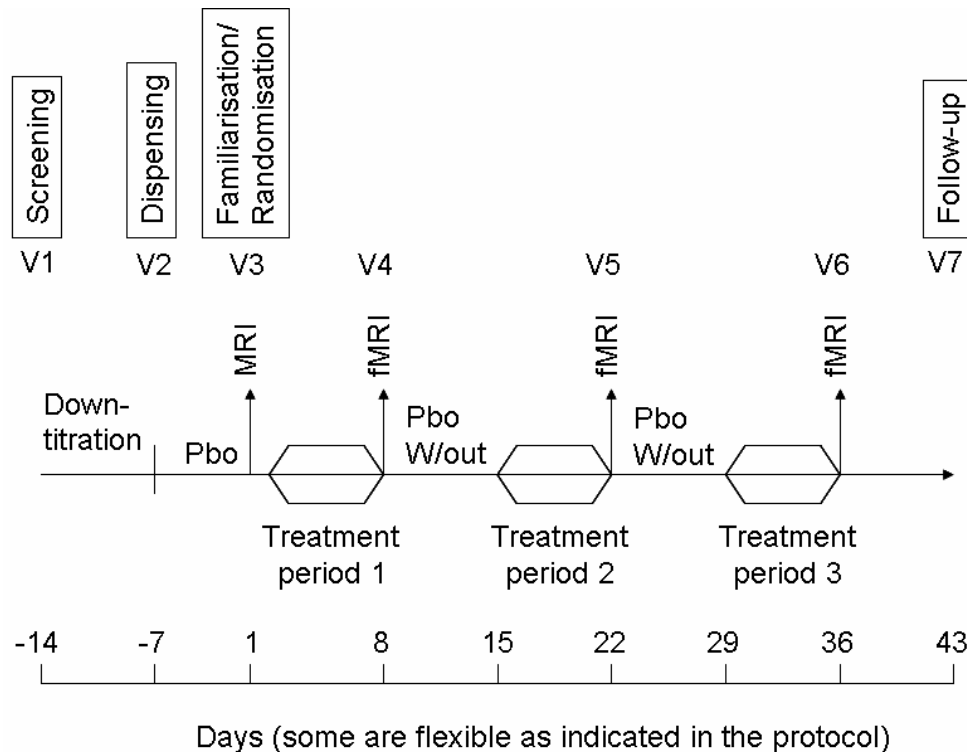
Randomized, double-blinded, placebo-controlled, three-period, crossover study.

3 periods with subjects randomized to receive 7 days of dosing with:

Placebo, or
Pregabalin (titrated to 150 mg BID),
Tramadol SR (titrated to 200 mg BID).

7-day washout periods

DMAa

6.6	5.7	6.0
A	B	C
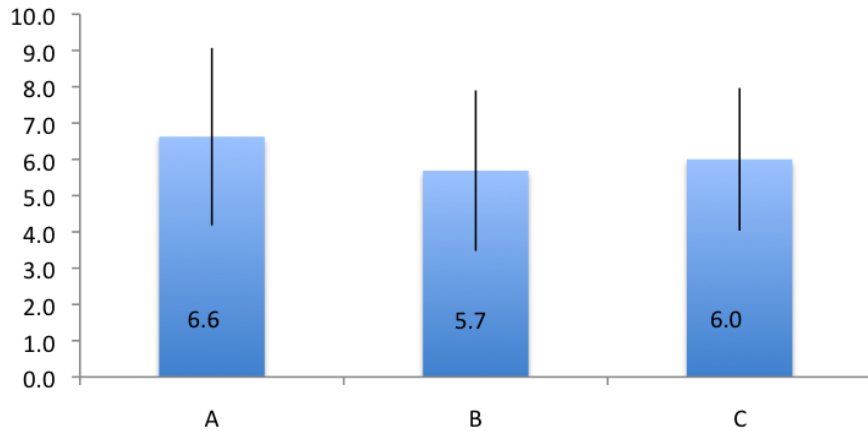
Dynamic Mechanical Allodynia Pain Ratings – no difference between groups

Present pain intensity

5.8	4.6	5.6
A	B	C
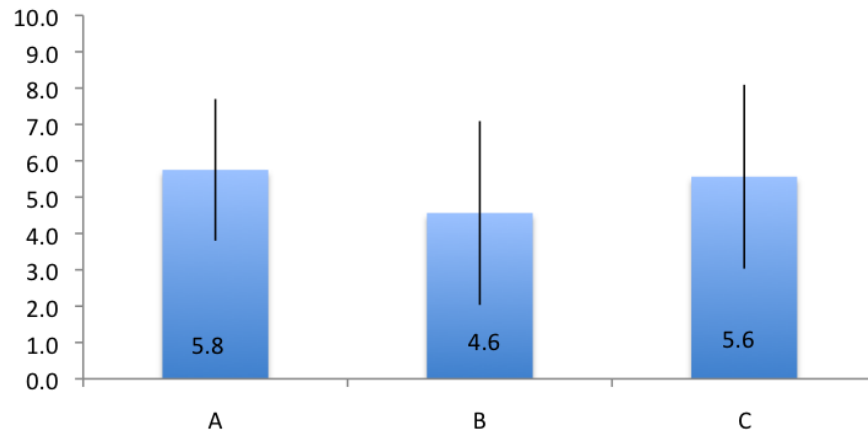
Ongoing pain ratings – no difference between groups

Treatment effect on brain patient-reported scores. Mean within-subject differences and confidence intervals (95%CI) for the dynamic mechanical allodynia ratings (DMAa), Neuropathic Pain Syndromes Inventory (NPSI) scores, present pain intensity (PPI) and Daily Pain Score on the day of the scan (DPS1), for the following comparisons placebo minus pregabalin (PLAPRE), placebo minus tramadol (PLATRA) and tramadol minus pregabalin (TRAPRE).
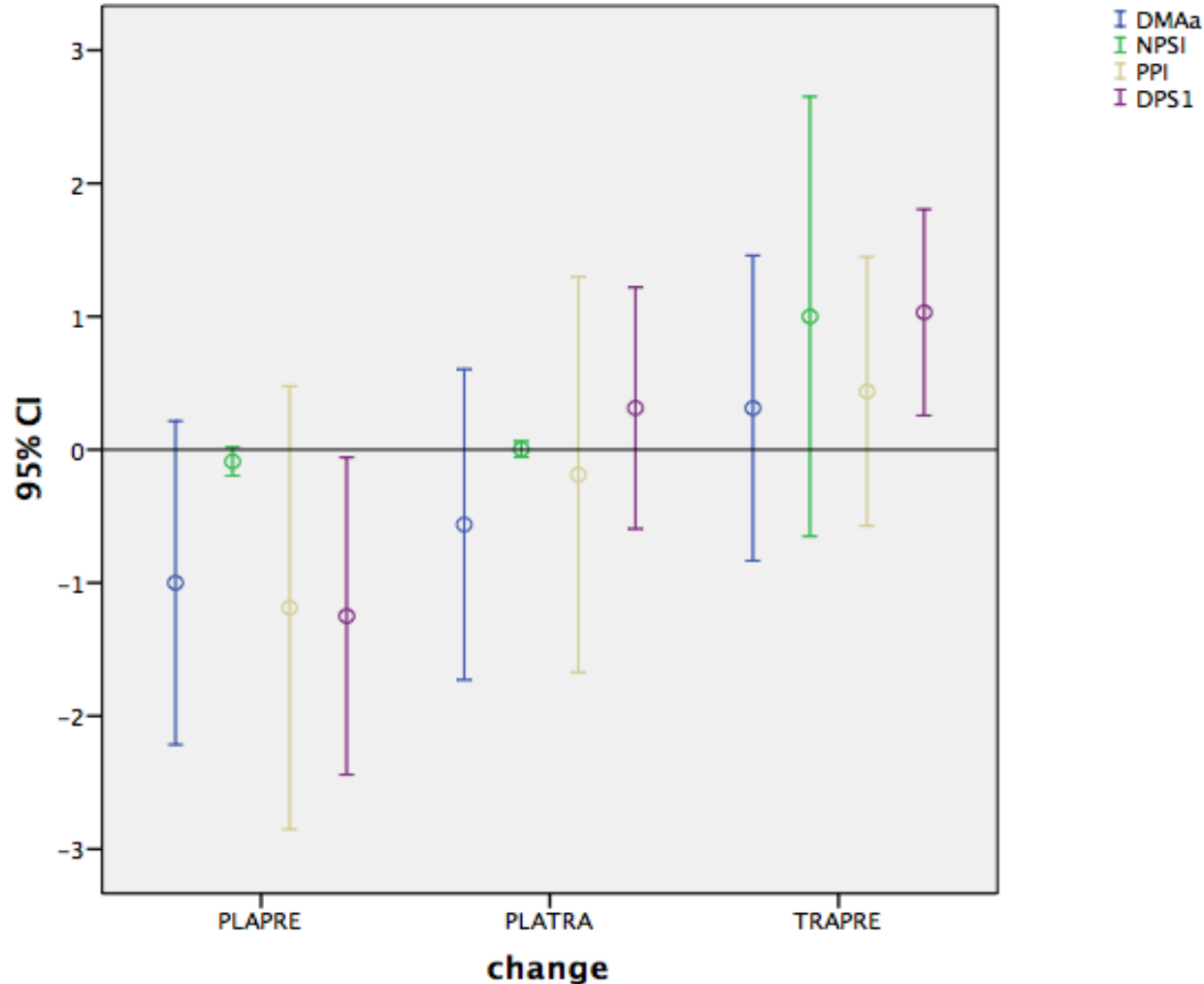
Brain activity in response to dynamic mechanical allodynic stimulation – DOES show significant group differences
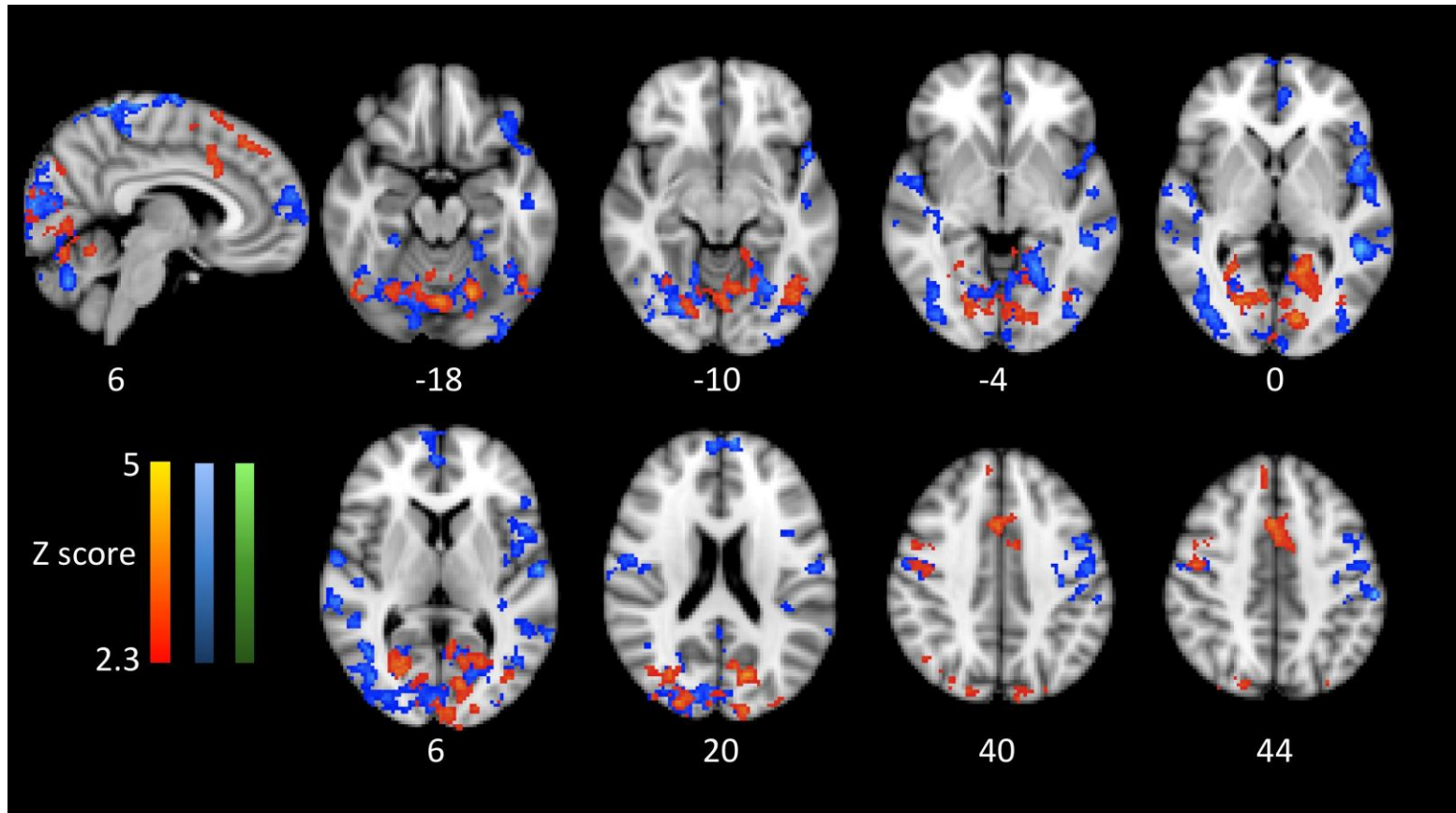
Treatment effect on brain response related to the dynamic mechanical allodynia (DMAa). Paired differences between treatment periods: contrast C minus A shown in blue, C minus B in green and B minus A in red. Mixed-effects, cluster-based thresholding with Z threshold at Z>2.3 and significance level p=0.05.

Placebo and opioid analgesia share a neuronal network
(Petrovic et al., Science 2002)

Context

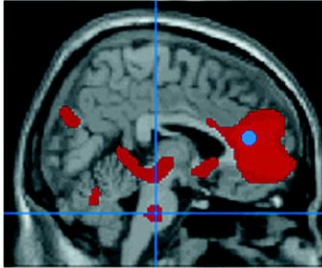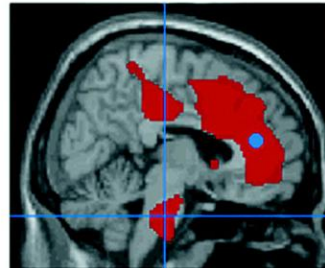- i.e. the placebo effect

Pain + Opioid Treatment   Pain + Placebo Treatment

PAG
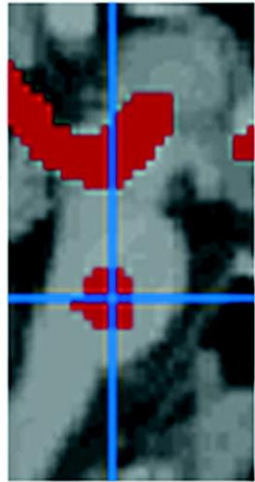
Pons   Pons
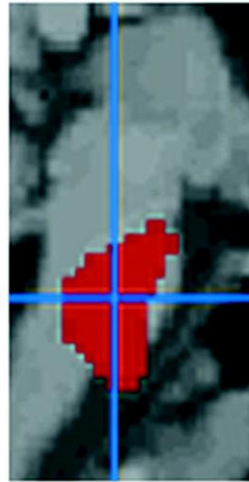
…..also high responders to placebo mirrored their ability to respond to real opioid injection cf. low placebo responders

– possibly reflects genetic variance in opioid receptors?

Wager et al., Science 2004 – EXPECTATION of placebo effect – neural correlates defined – prefrontal cortex influences brainstem and descending inhibitory pathways

Zubieta et al., J. Neuroscience 2005 - Placebo effects mediated by endogenous opioid activity on mu-opioid receptors

Activation of the Opioidergic Descending Pain Control System Underlies Placebo Analgesia

Eippert et al. Neuron 2009

Reduced coupling
rACC-PAG

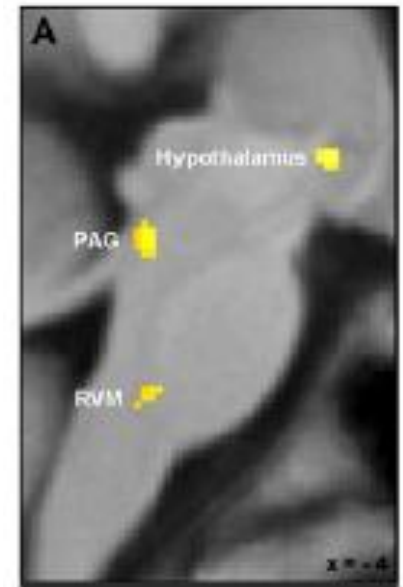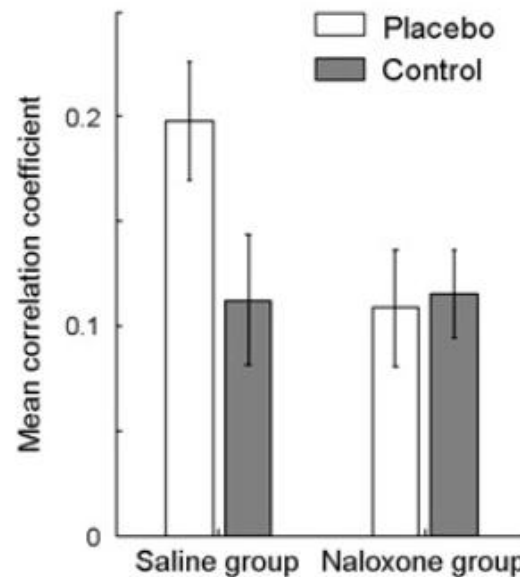Reduced activity
Hypothalamus, PAG, RVM

Reduced placebo related activit
with nlx

Placebo Analgesia - Mechanisms

Eippert et al. Science, 2009

C6 ipsilat to stimulation

➡️ Direct evidence for spinal cord involvement in placebo analgesia

Emotions and Mood

- as central amplifiers to the pain experience
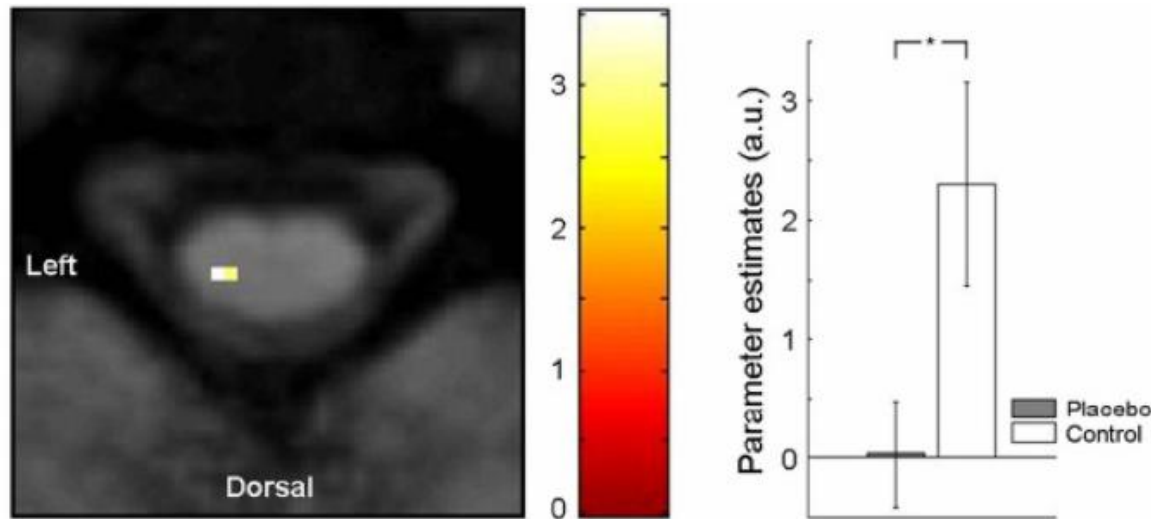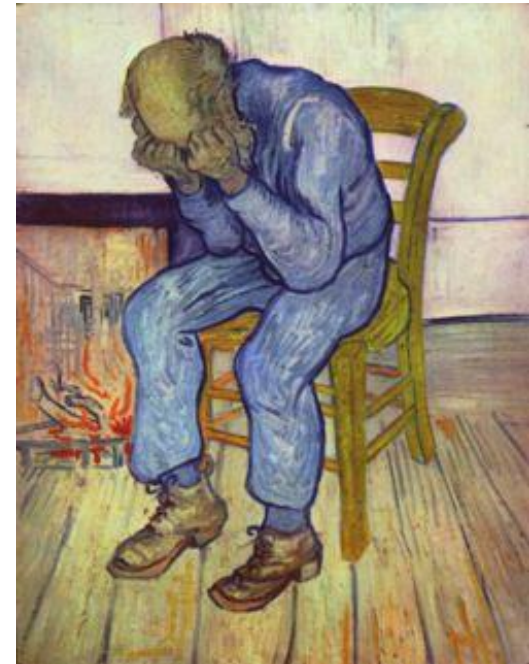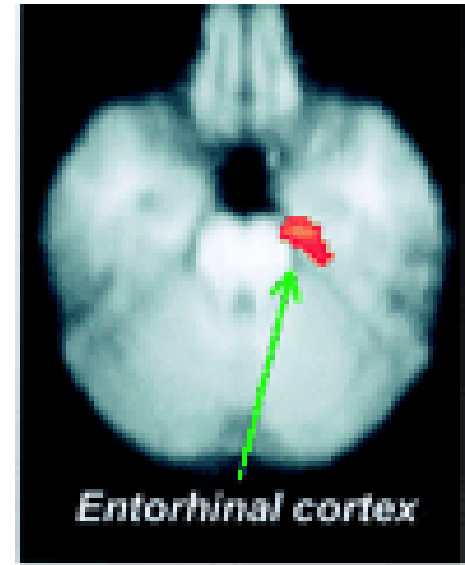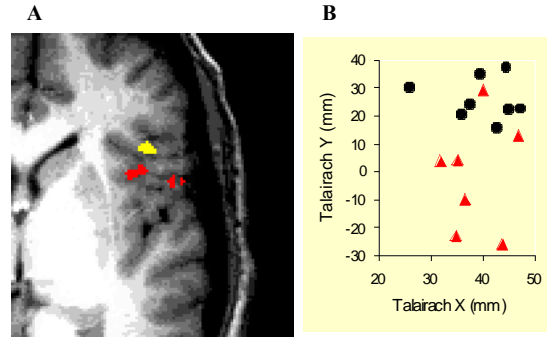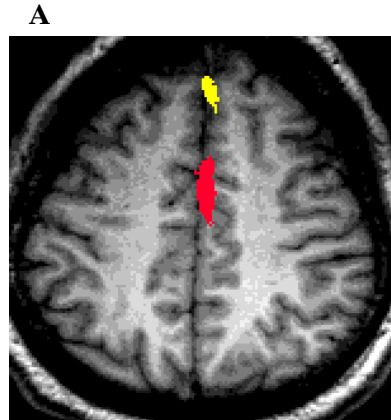

Anxiety & Depression – does it makes things worse?
Common clinical and experimental observation that anxiety and depression exacerbate the pain experience

Expecting and being anxious about pain can have adaptive and maladaptive consequences NOT report 'bias'

Expectation of Pain
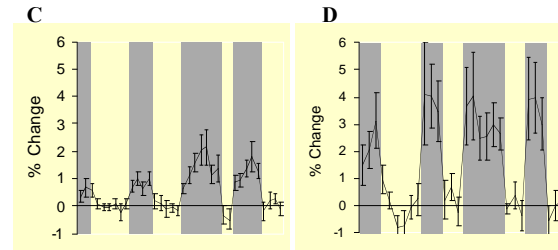
Anxiety about Pain

Entorhinal cortex

Ploghaus et al.,

Dissociating pain from its anticipation in the human brain. Science, 1999

Learning about pain: the neural substrate of the prediction error for aversive events. PNAS 2000

Exacerbation of pain by anxiety is associated with activity in a hippocampal network J. Neuroscience, 2001

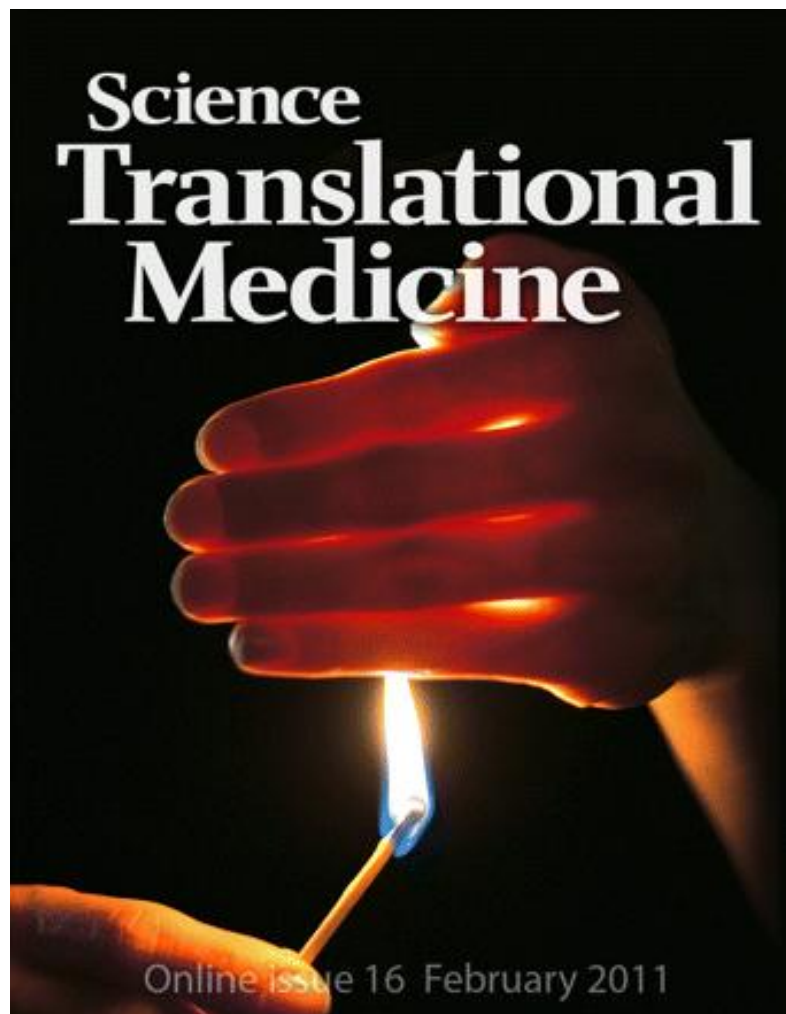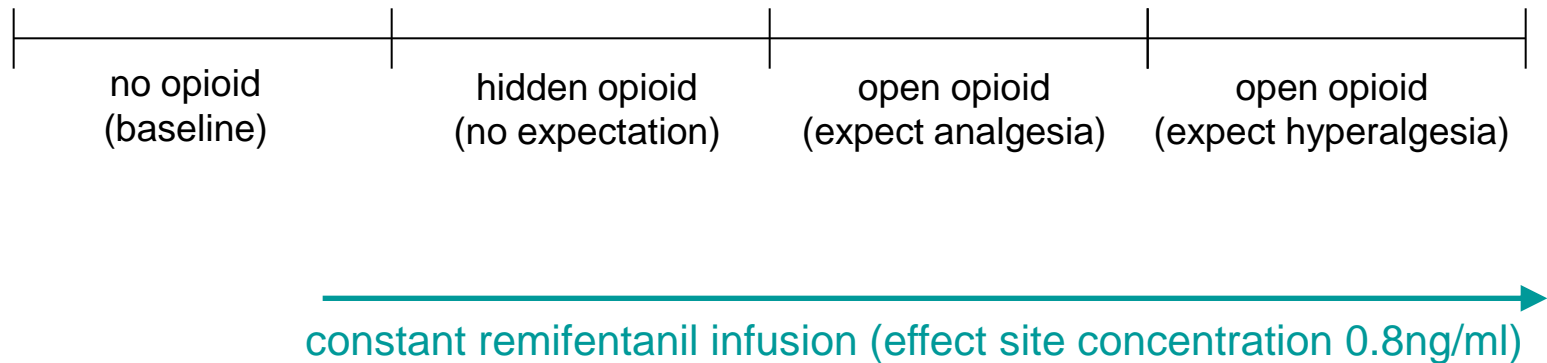# The Effect of Treatment Expectation on Drug Efficacy: Imaging the Analgesic Benefit of the Opioid Remifentanil

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

Science Translational Medicine

Online issue 16 February 2011

Experimental Paradigm: Opioid & Expectancy

| no opioid (baseline) | hidden opioid (no expectation) | open opioid (expect analgesia) | open opioid (expect hyperalgesia) |

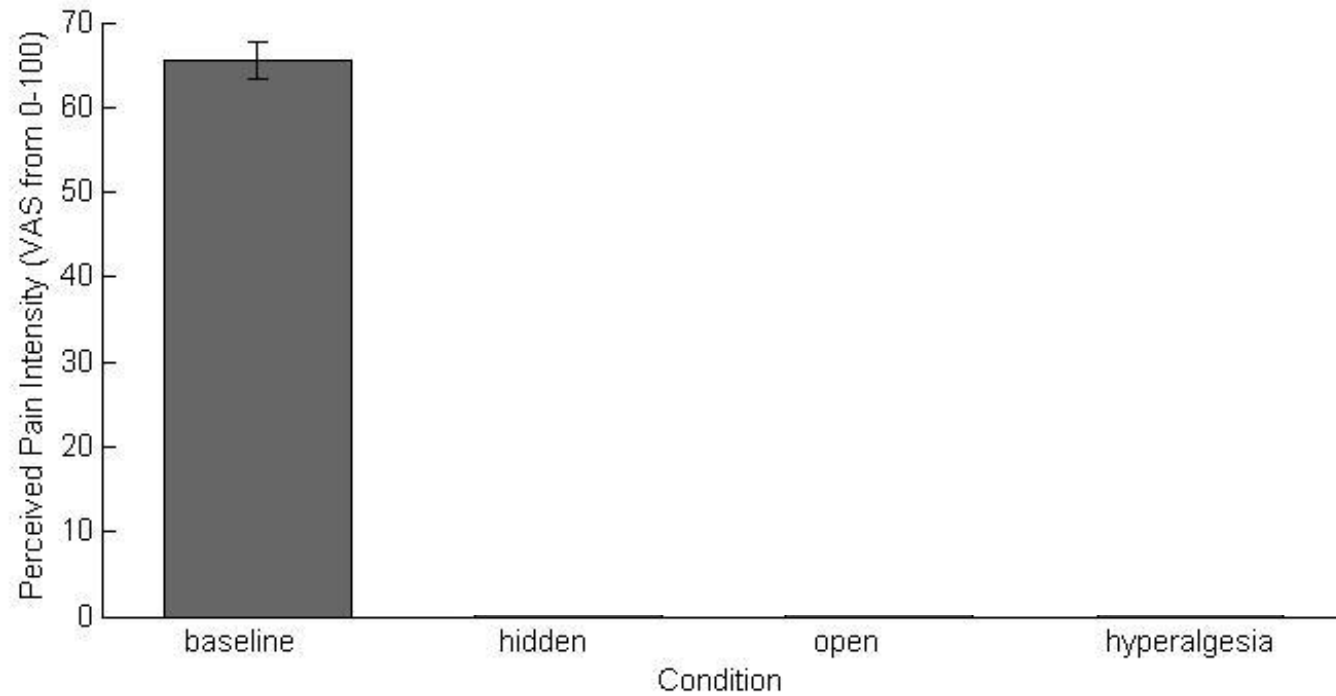constant remifentanil infusion (effect site concentration 0.8ng/ml)
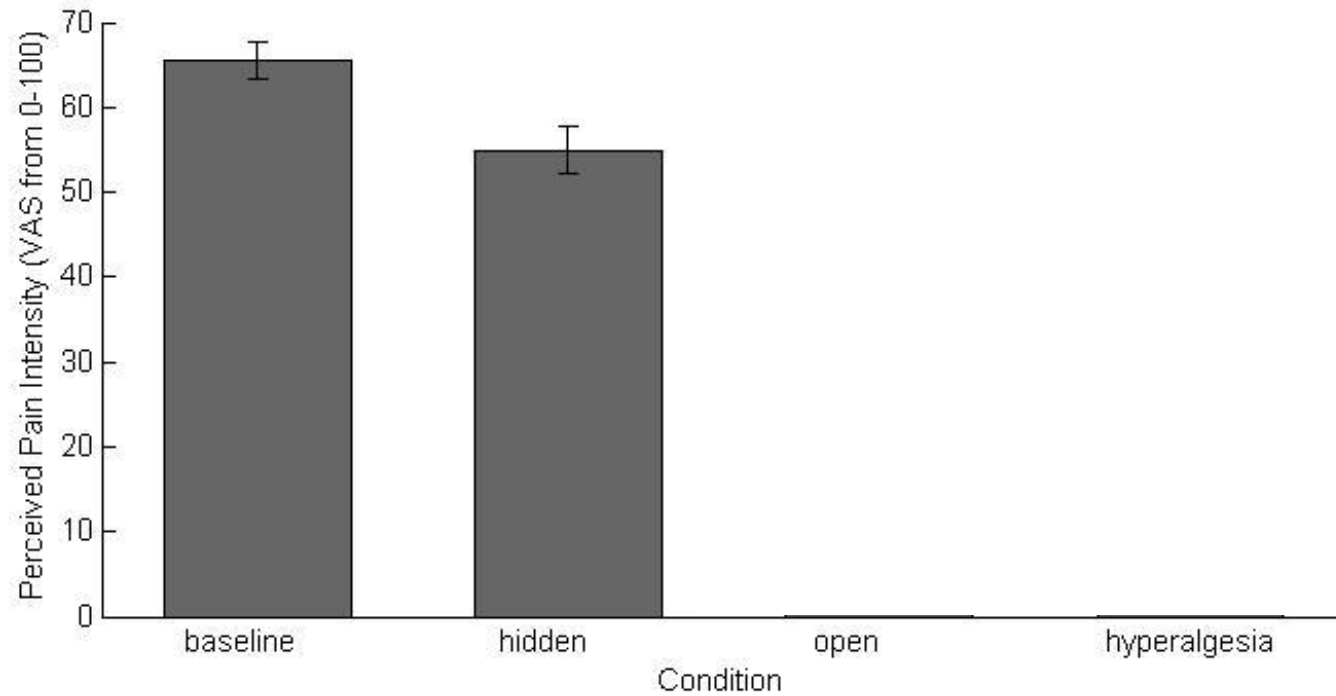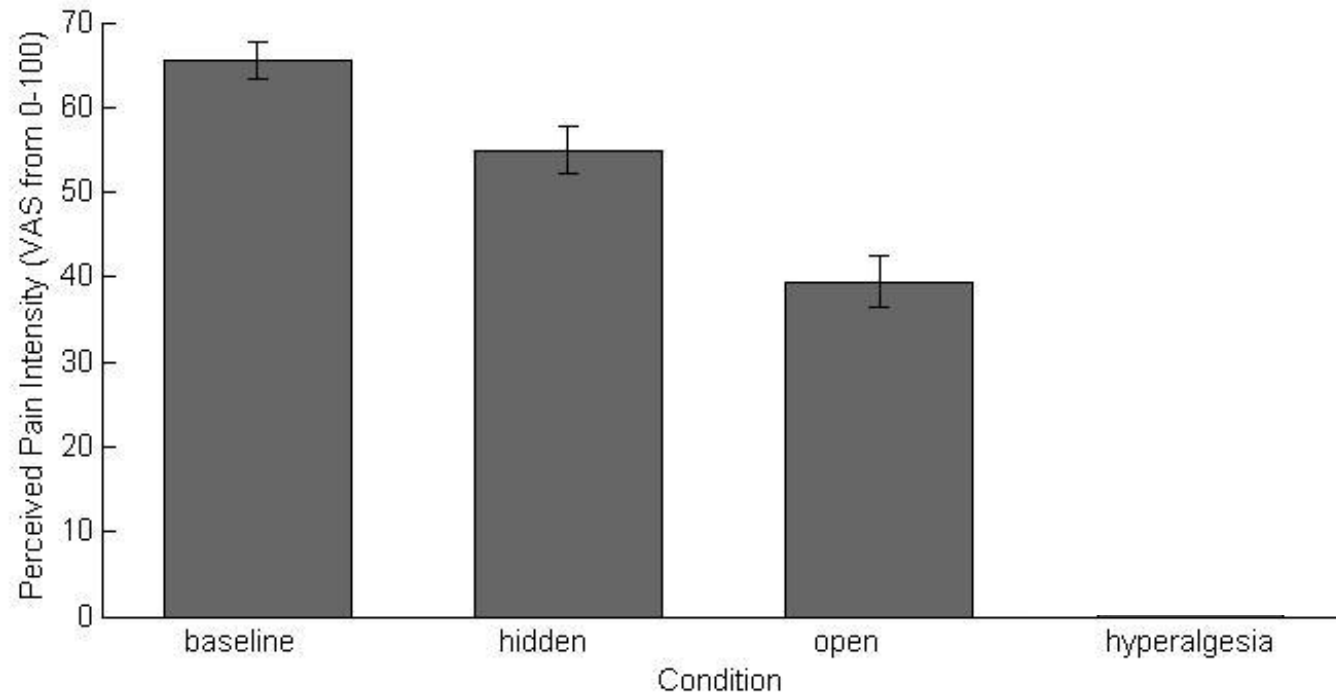
Opioids & Expectancy

Pain Ratings

Opioids & Expectancy
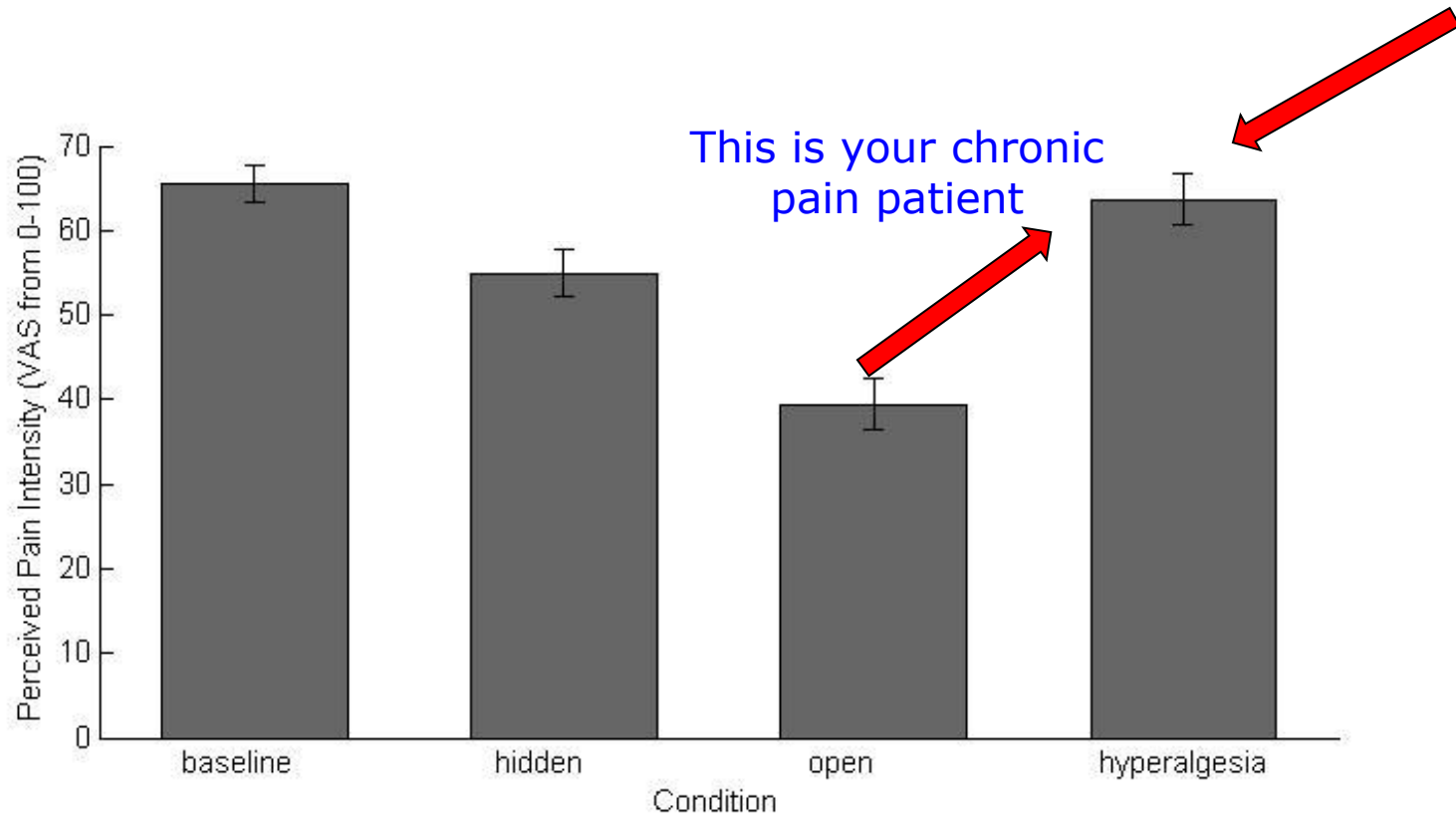
Pain Ratings

Opioids & Expectancy

Pain Ratings

Opioids & Expectancy

Pain Ratings
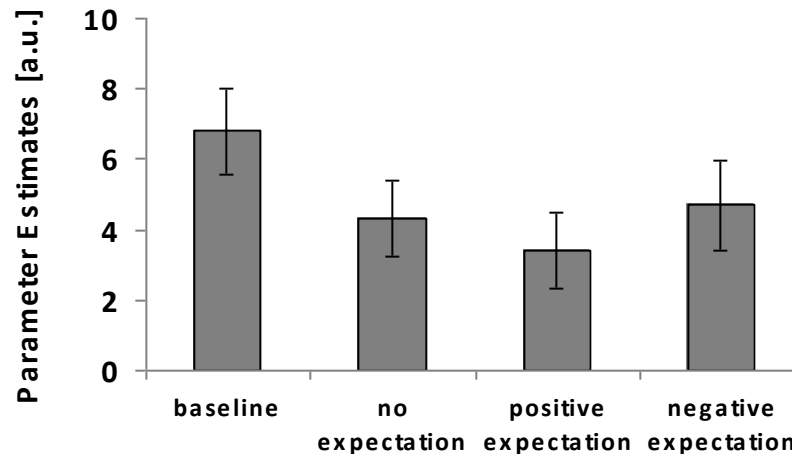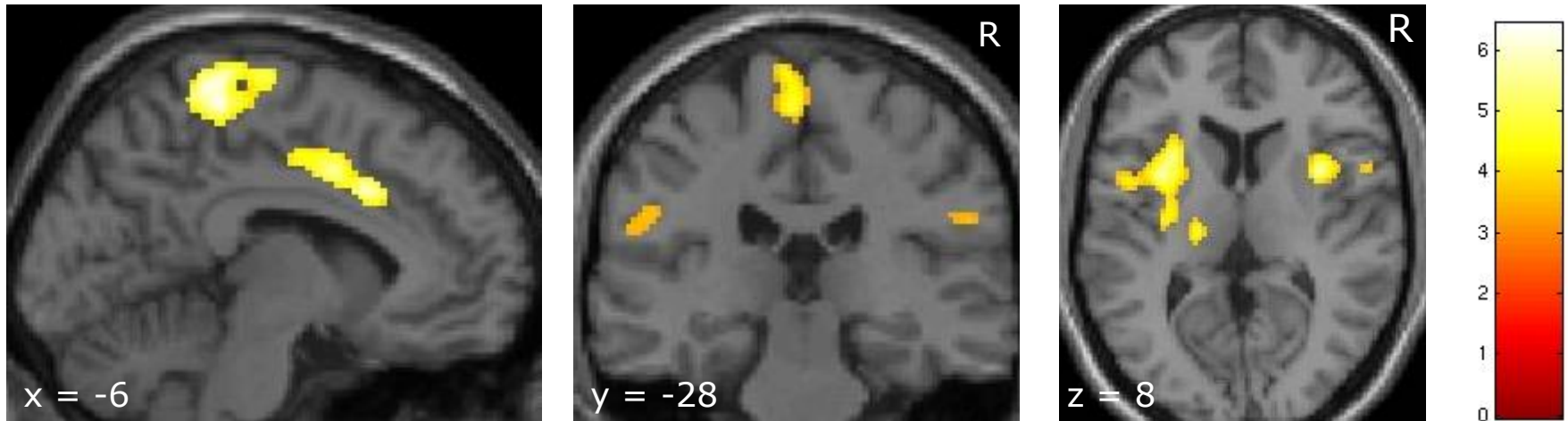
Not controlling for this would lead to failed trial and INCORRECT assumption remifentanil non-efficacious analgesic
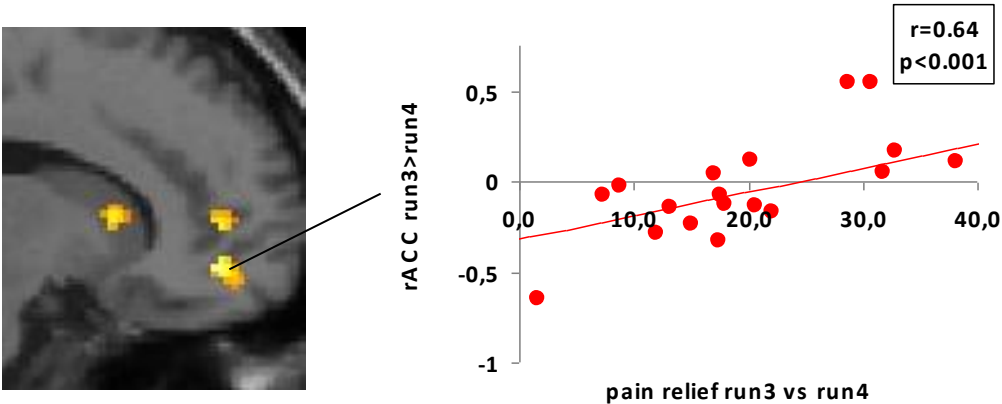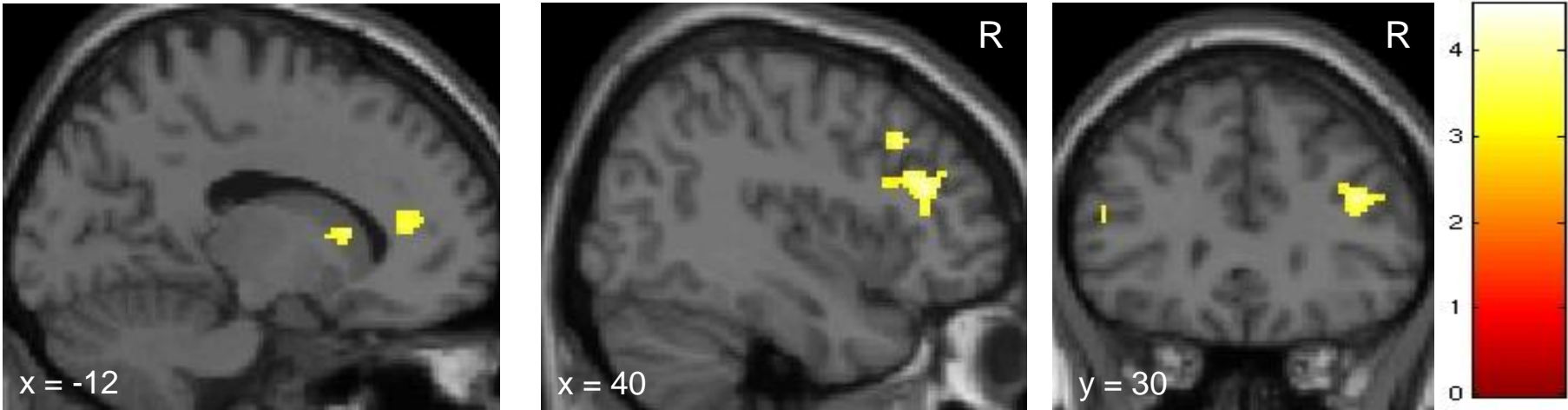
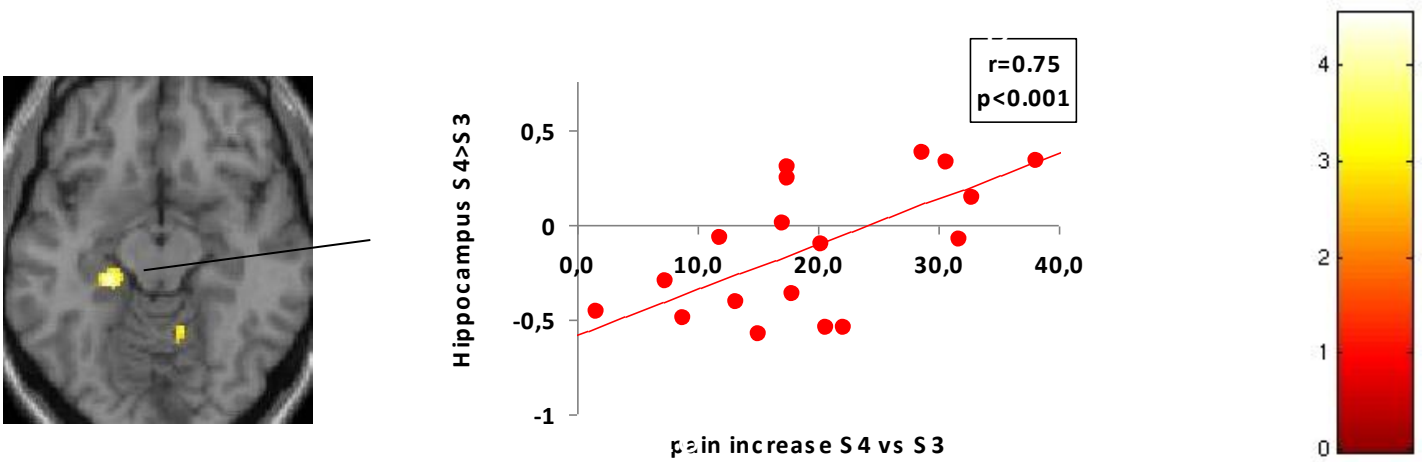This is your chronic pain patient

Contextual Modulation of Opioid Analgesia is Reflected in Areas of the Pain Neuromatrix:
NOT report bias

Recruitment of descending pain modulatory system with positive expectancy

The impaired analgesia during negative expectation is associated with hippocampus activity

r=0.75
p<0.001

Hippocampus S 4>S 3

pain increase S 4 vs S 3

Supplementary Figure 3

Parameter estimates [a. u.] Hippocampus [18, -24, -14]

No expectancy   Positive expectancy   Negative expectancy

Parameter estimates [a. u.] sgACC [6, 16, -14]

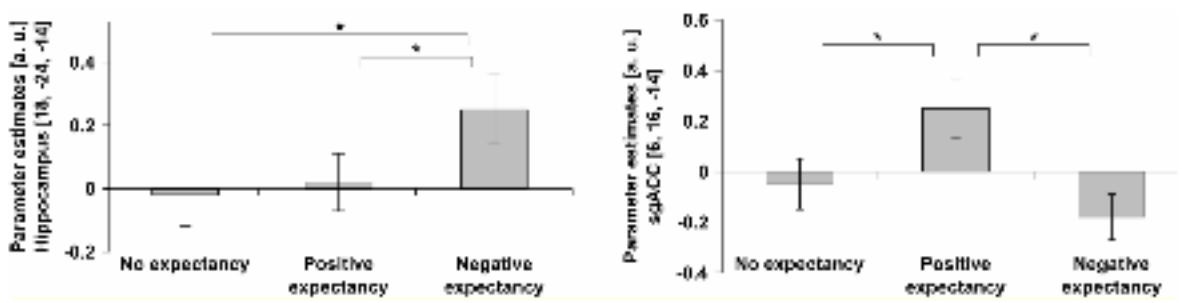No expectancy   Positive expectancy   Negative expectancy

Fig. S3. Brain areas mediating the effects of positive and negative expectancy. (Left)
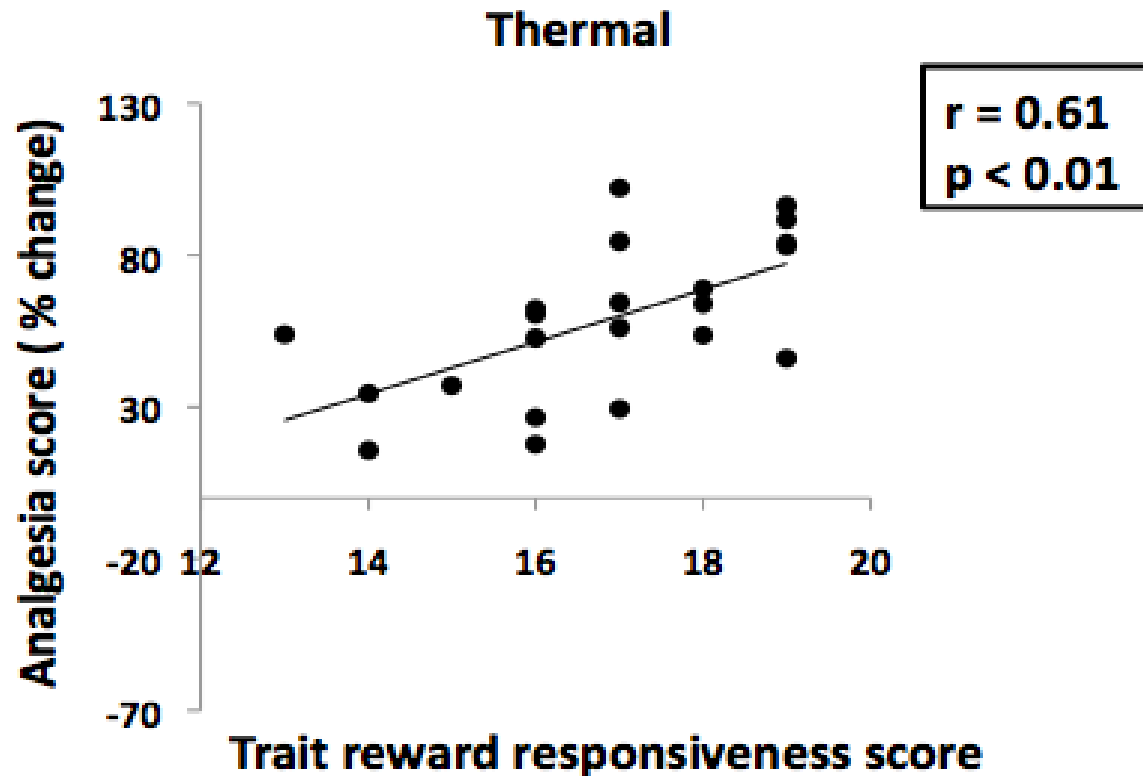
Patient Stratification at Baseline: new opportunities and future era

Can we define at baseline neuroimaging responses that are predictive of treatment outcome and side effects
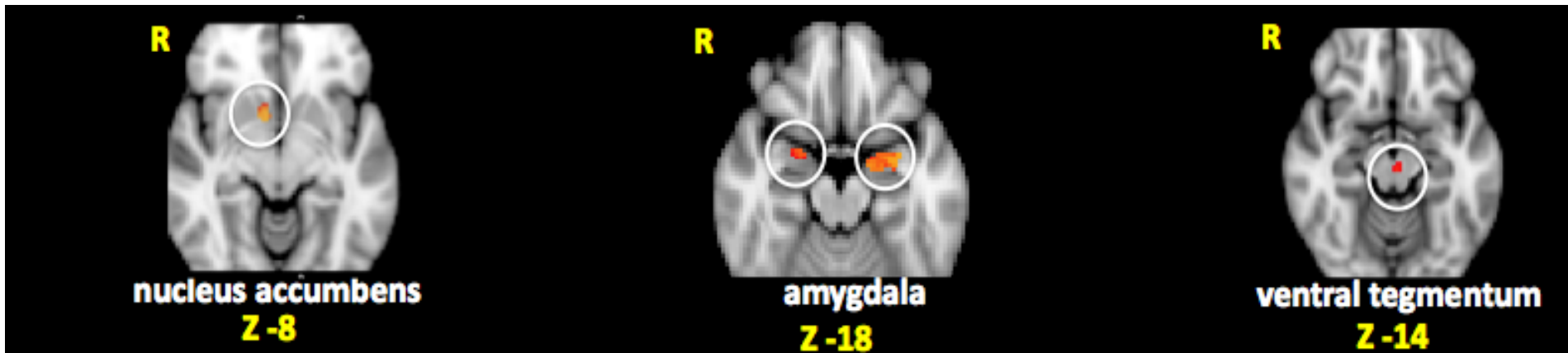
predicting responders and non-responders

Predicting who benefits from opioid analgesia – baseline responses and trait factors
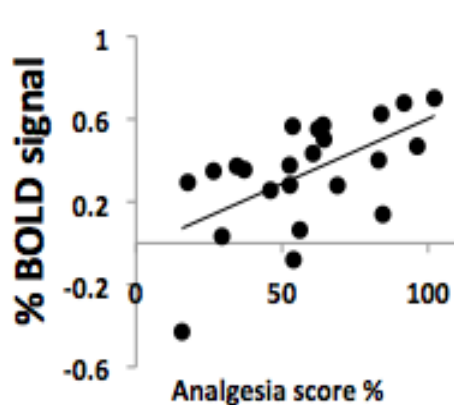
(Wanigasekera et al., in revision 2012)

Regions of interest analysis (ROI) of reward processing areas of the brain where baseline neuronal response to noxious stimuli predict opioid induced analgesia
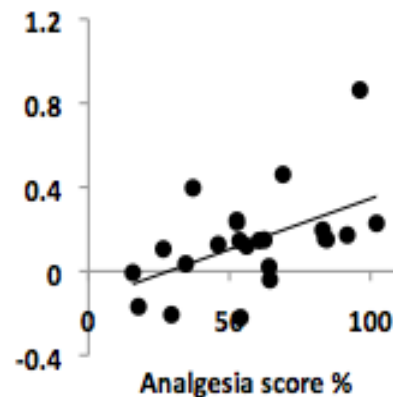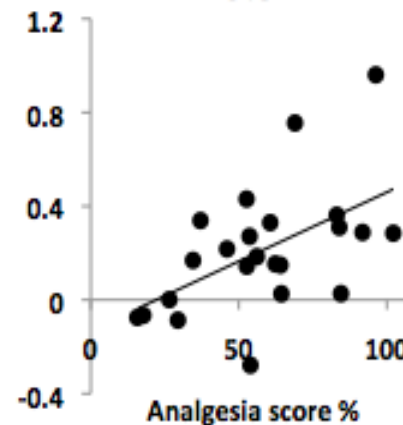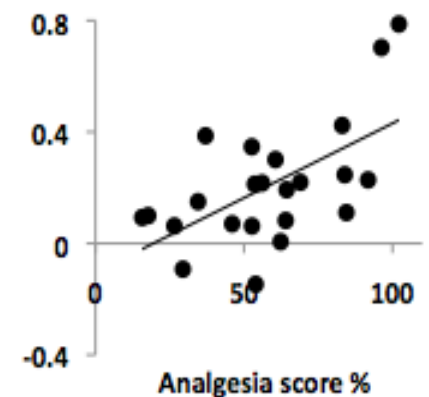
Broderson et al., 2012 (in revision)

Decoding:
multivariate pattern analysis

univariate analysis

pain

no pain

multivariate pattern
analysis
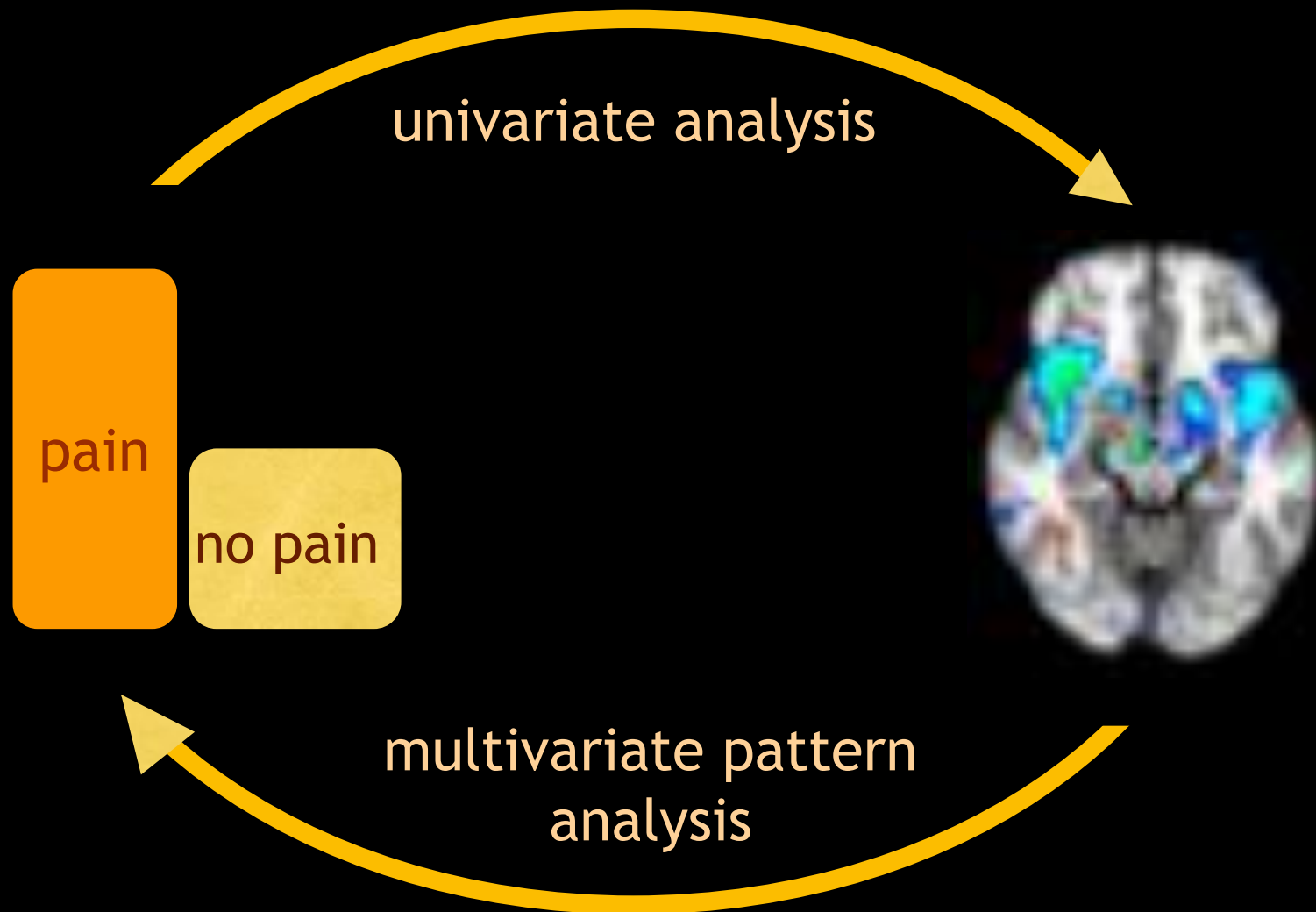
Multivariate pattern analysis:
principles
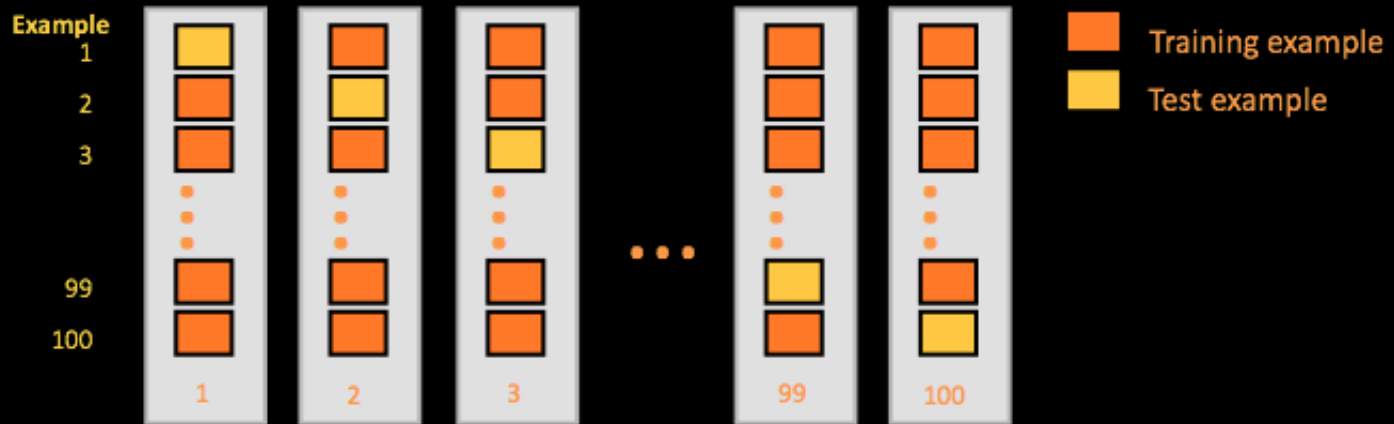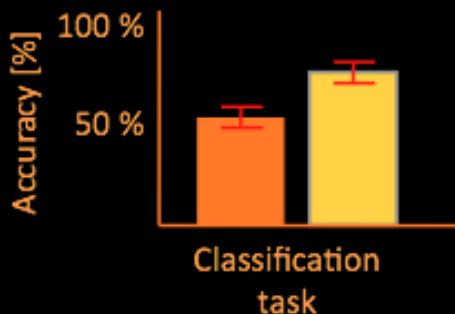
Using past FMRI studies to enable novel inferences on new data - application to drug development (Duff et al., 2012 (in prep)
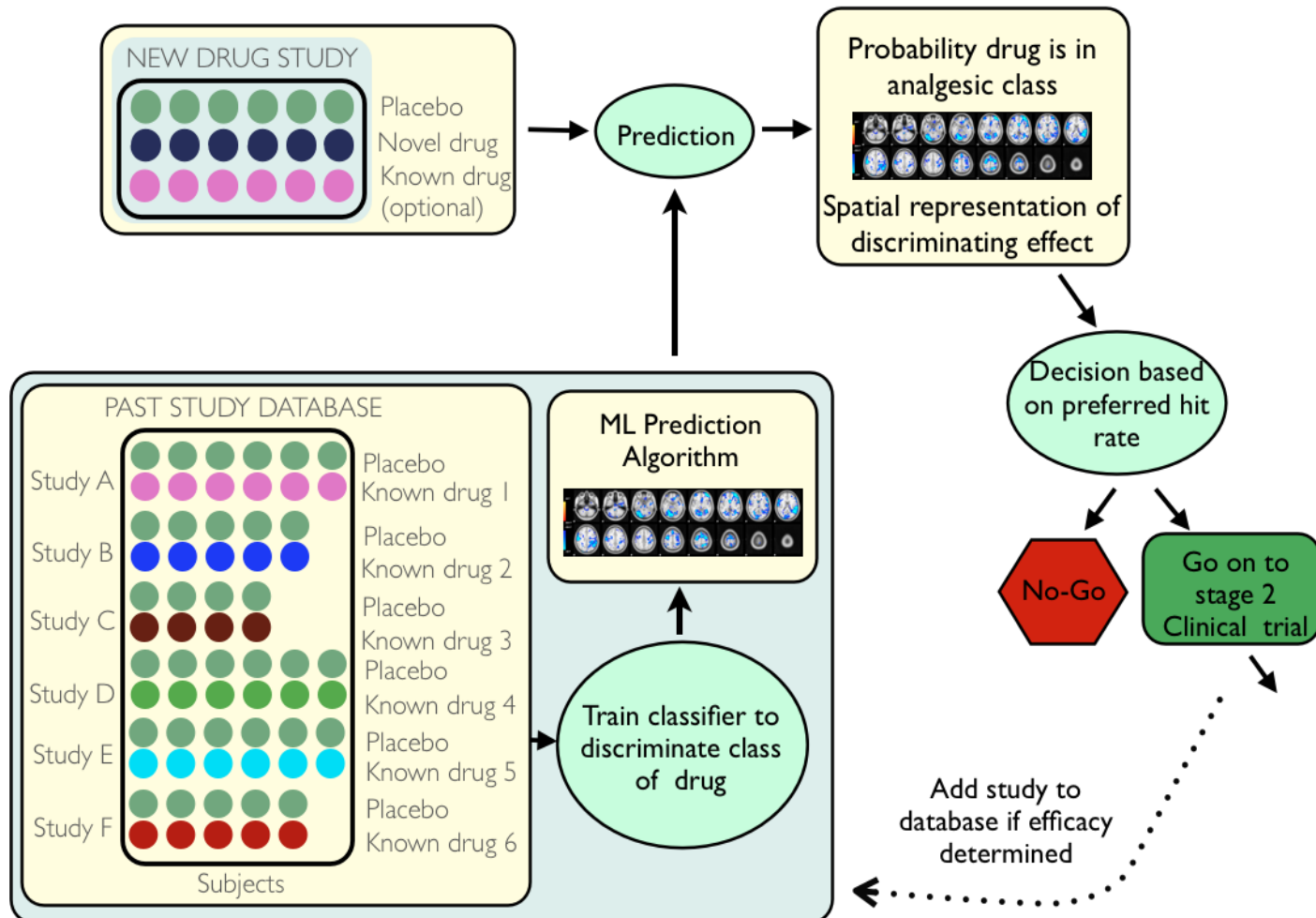
Neuroimaging Biomarkers for Drug Development

Wise and Tracey (2006)

Borsook et al., Drug Discovery Today (2012)

Drug Discovery Today

ARTERIAL SPIN LABELING [1]
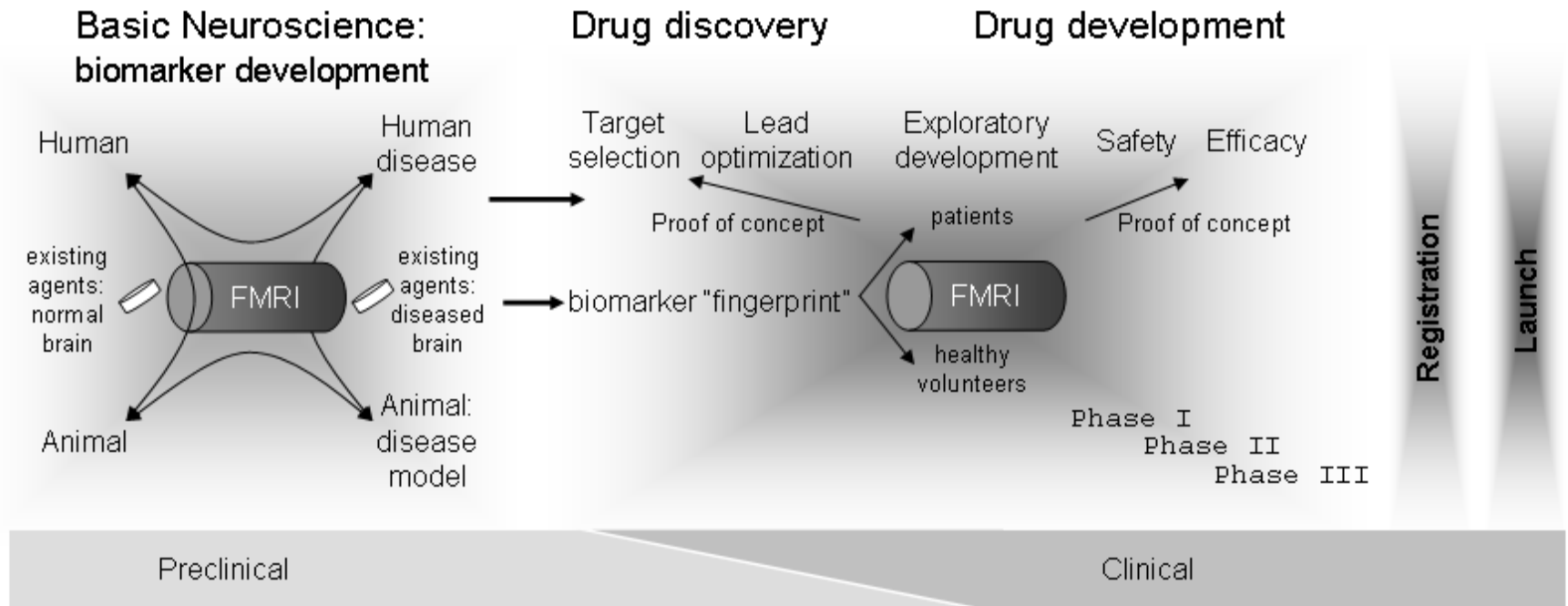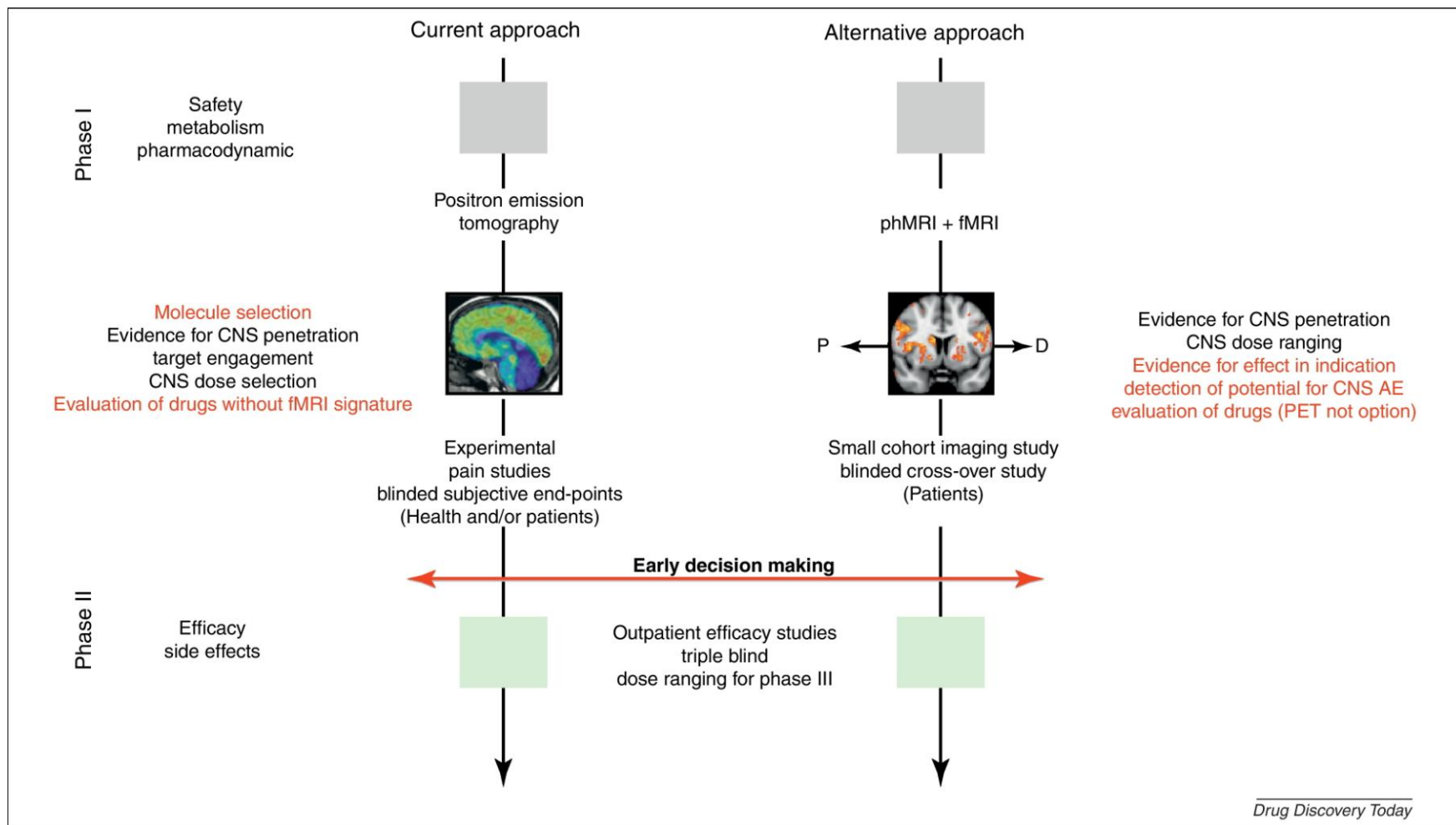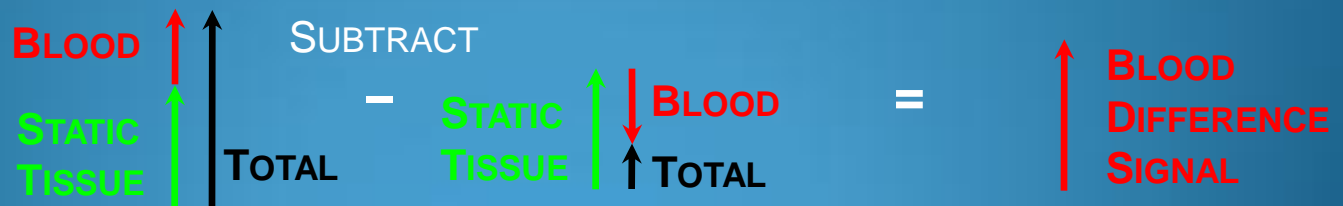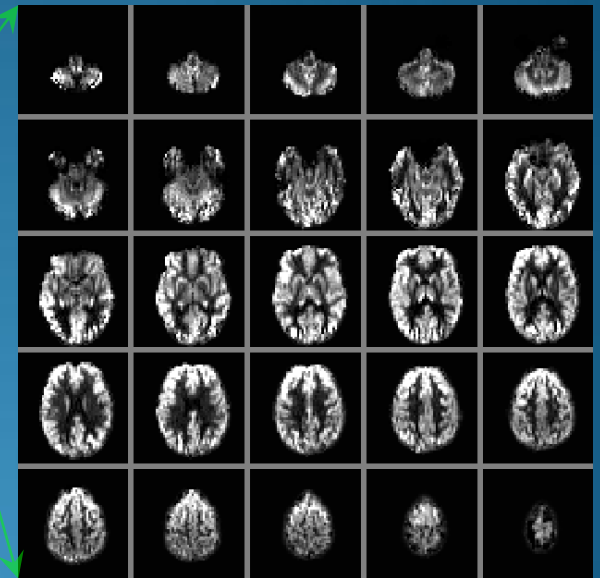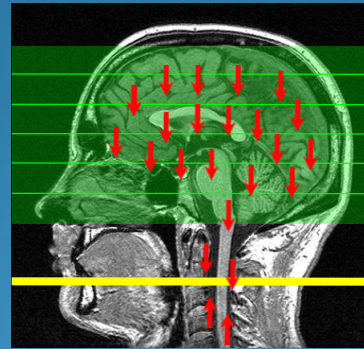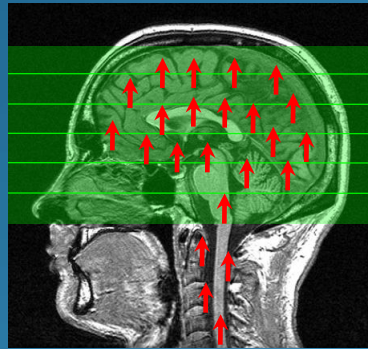
CONTROL − TAG = PERFUSION WEIGHTED IMAGES

BLOOD
STATIC TISSUE
TOTAL

SUBTRACT

− STATIC TISSUE
BLOOD
TOTAL

=

BLOOD DIFFERENCE SIGNAL

[1] Detre et al, MRM 1992;23:37
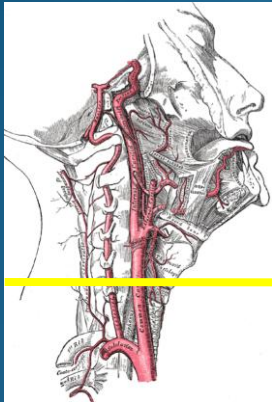
Imaging the neural correlates of ongoing pain with ASL

Segerdahl et al., PAIN 2012

In Healthy Controls

a)

Stimulus: Force calibrated probes
Site: Hand

b)

c)
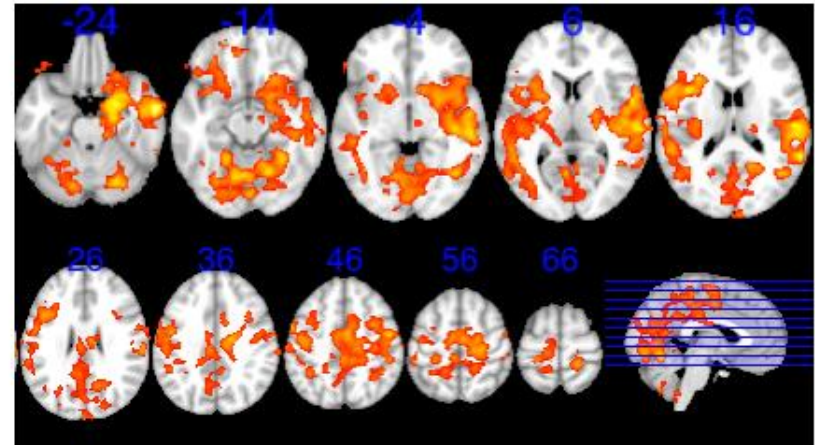
Mixed Effects, z>2.3, p<0.01 (Cluster Corrected)

In Neuropathic Pain Patients

a)

PAIN ON : 5.0 minutes Skin Temp Water Perfusion ON
PAIN OFF : 5.0 minutes Cold Water Perfusion ON

b)

c)

Fixed Effects, z>2.0, p<0.05 (Cluster Corrected)

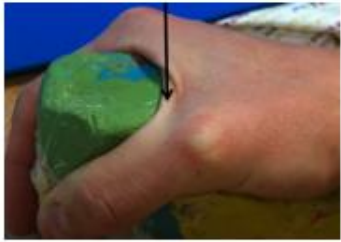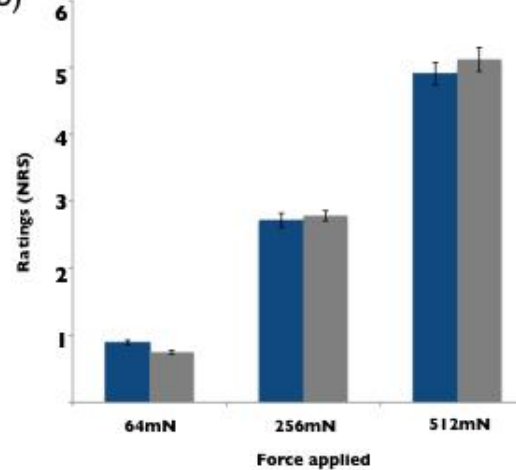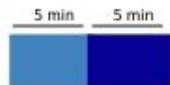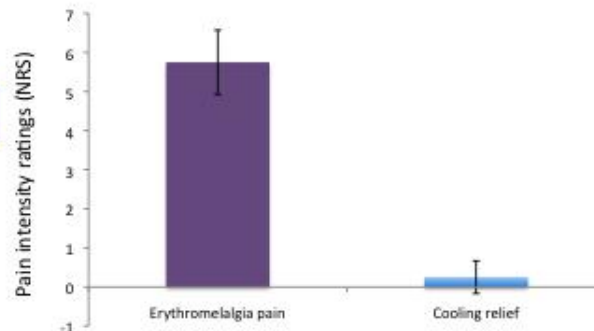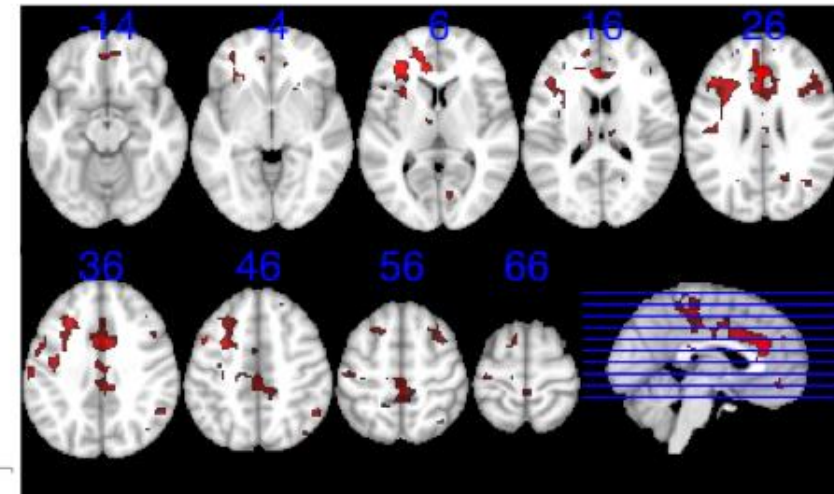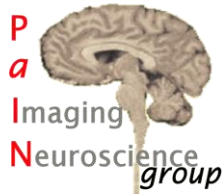# Pain Imaging Neuroscience Group

Group – Present

- Katja Wiech
- Falk Eippert
- Rebeccah Slater
- Jon Brooks
- Katie Warnaby
- Karolina Wartolowska
- Mike Lee
- Line Loken
- Vishvarani Wanigasekera
- Roisin Ni Mhuircheartaigh
- Andrew Segerdahl
- Richard Lin
- Chantal Berna
- Daniella Siexas
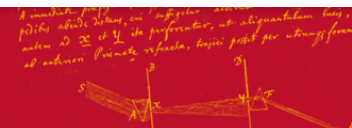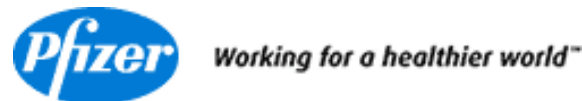- Katy Vincent
- Melvin Mezue

Current Collaborators

FMRIB Centre Analysis, Plasticity and Physics Groups – especially Heidi Johansen-Berg, Steve Smith and Peter Jezzard
Andy Carr & Paul Wordsworth (NDORMS, Oxford)
Pain Relief Unit, (NDA, Oxford)
Richard Rogers, Jane Quinlan (NDA, Oxford)
Stephen Kennedy (Gynaecology Department, Oxford)
Guy Goodwin, Emily Holmes (Psychiatry Department, Oxford)
David Menon (Anaesthetics Department, Cambridge, UK)
Bill Vennart, John Huggins (Pfizer, UK)
Steve McMahon, Tony Dickenson, Dave Bennett, Andrew Rice, John Wood (UCL/Imperial/Kings, London, UK)
Markus Ploner (Munich, Germany)
Ulrike Bingel (Hamburg, Germany)
Robert Edwards (Johns Hopkins, USA)
Rolf Detlef-Treede (Germany)
Improving Medicines Initiative Consortium (Europain)

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

Past Group Members

- 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
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- Amy Godinez
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- Alex Ploghaus
- Emily Johns
- Asma Ahmad
- Katie Fairhurst
- Chia-Shu Lin