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
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
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

Volumetric measures

DTI

Diffusion tractography

Resting FMRI

Task FMRI

MRS

Volumetric measures

Diffusion tractography

Resting FMRI

Task FMRI

MRS
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....)
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

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)

early-age development
aging
artefact

diffusion MRI
structural MRI

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,1
Developing a Biomarker for Central Sensitisation

Capsaicin: Model of central sensitisation

Zambreanu et al., PAIN 2005

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  
2: central sensitisation  
P: placebo  
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 withdrawal 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)

- **Pre-dose events**
- **Study drug/placebo**
- **Capsaicin**
- **In Scanner**
  - Brush
  - Punctate
  - ASL
  - RSN
- **End of Scanning**
  - Remove capsaicin
  - Blood sampling
- **Time (min)**
  - 0
  - 90
  - 150
  - ~210
Decision-making using fMRI in clinical drug development: revisiting the NK-1 receptor antagonist for pain
(Borsook et al., Drug Discovery Today 2012)

(a) APREP > Saline

(b) APREP > Saline
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
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
Dynamic Mechanical Allodynia Pain Ratings – no difference between groups

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 alldynia (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)

.....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?


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 activity with nlx
Placebo Analgesia - Mechanisms

Direct evidence for spinal cord involvement in placebo analgesia

Eippert et al. Science, 2009
Emotions and Mood
- as central amplifiers to the pain experience

Anxiety & Depression – does it make 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

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,3 Katja Wiech,3 Roisin Ni Mhuircheartaigh,1 Michael C. Lee,3 Markus Ploner,4 Irene Tracey1
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

Perceived Pain Intensity (VAS from 0-100)

Condition

baseline  hidden  open  hyperalgesia
Opioids & Expectancy

Pain Ratings

Perceived Pain Intensity (VAS from 0-100)

Condition: baseline, hidden, open, hyperalgesia
Pain Ratings

- Opioids & Expectancy

Perceived Pain Intensity (VAS from 0-100)

- Baseline
- Hidden
- Open
- Hyperalgesia
Opioids & Expectancy

Pain Ratings

This is your chronic pain patient

Not controlling for this would lead to failed trial and INCORRECT assumption remifentanil non-eficacious analgesic
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

$r = 0.64 \quad p < 0.001$

$r_{ACC} \text{ run3 > run4}$

$r = 0.64 
 p < 0.001$
The impaired analgesia during negative expectation is associated with hippocampus activity.

Supplementary Figure 3

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.
Decoding: multivariate pattern analysis

univariate analysis

pain

no pain

multivariate pattern analysis

Broderson et al., 2012 (in revision)
Multivariate pattern analysis: principles

- **Pattern discrimination**
  - “Is there information about pain?”

- **Spatial pattern localization**
  - “Where is the information?”

- **Pattern characterization**
  - “How is the information encoded?”

![Diagram](image)
Using past FMRI studies to enable novel inferences on new data - application to drug development (Duff et al., 2012 (in prep))
**Arterial Spin Labeling**

$\text{CONTROL} - \text{TAG} = \text{PERFUSION WEIGHTED IMAGES}$

$\text{BLOOD} \uparrow \text{STATIC TISSUE} \uparrow \text{TOTAL} - \text{STATIC TISSUE} \uparrow \text{TOTAL} = \text{BLOOD DIFFERENCE SIGNAL}$

Imaging the neural correlates of ongoing pain with ASL

Segerdahl et al., PAIN 2012

In Healthy Controls

Stimulus: Force calibrated probes
Site: Hand

In Neuropathic Pain Patients

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

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

Fixed Effects, z>2.0, p<0.05 (Cluster Corrected)
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
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David Menon (Anaesthetics Department, Cambridge, UK)
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John Wood (UCL/Imperial/Kings, London, UK)
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- Woong Tsang
- Merle Fairhurst
- Siri Leknes
- John Keltner
- Giandomenico Iannetti
- Laura Zambreanu
- Petra Schweinhardt
- Paul Dunckley
- Richard Wise
- Manu Goyal
- Sarah Longe
- Brandon Lujan
- Elisa Favaron
- Ajit Itty
- Amy Godinez
- Susy Bantick
- Alex Ploghaus
- Emily Johns
- Asma Ahmad
- Katie Fairhurst
- Chia-Shu Lin