



# Can Imaging Dissect Analgesic versus Placebo Responses?

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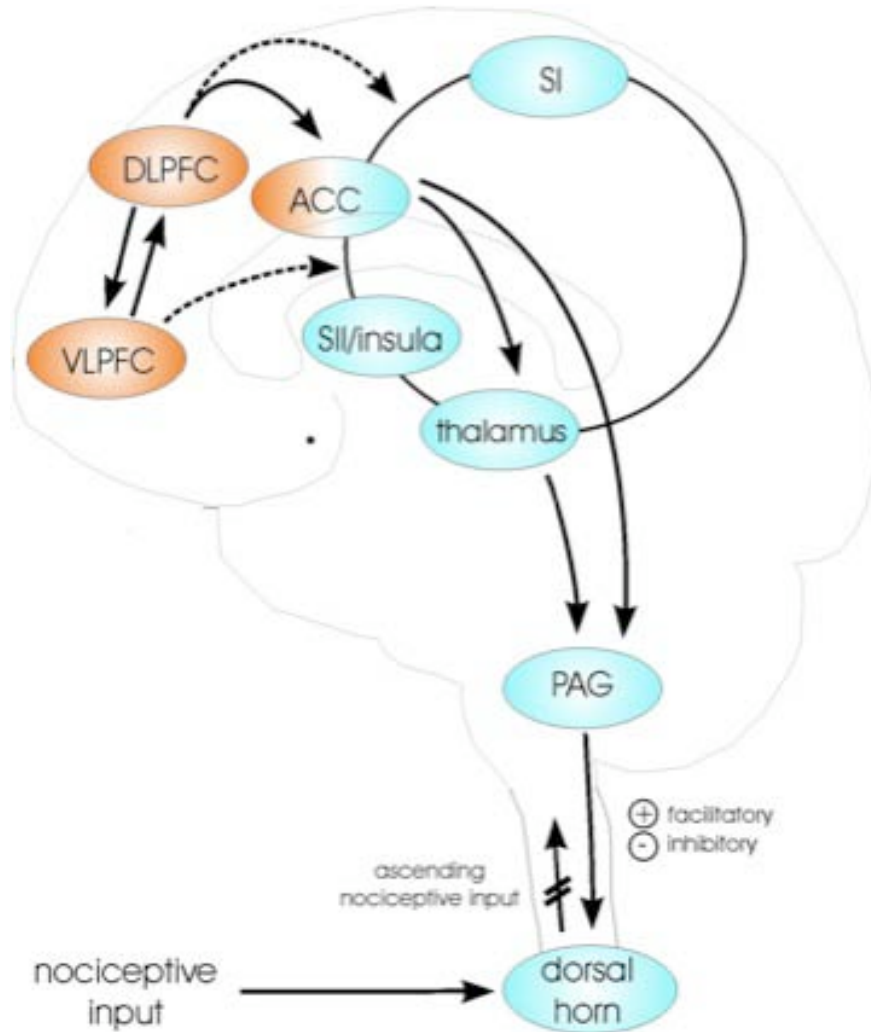


# What Can Functional Imaging Deliver For Analgesic Drug Discovery?

1. Simple, objective correlate of subjective report that potentially indicates efficacy (i.e. analgesia) with greater sensitivity than current behavioural measures - aids go/no-go decision making - and SMALL N needed (so cost-effective)
  - Helps with problem of too many false-positives coming from preclinical models - as get information in humans (models/patients) therefore probably will translate to wider clinical trials in Phase 3?
2. Potential information regarding mechanism of action (or successful targeting of intended mechanism of action = reverse-translate to preclinical development)

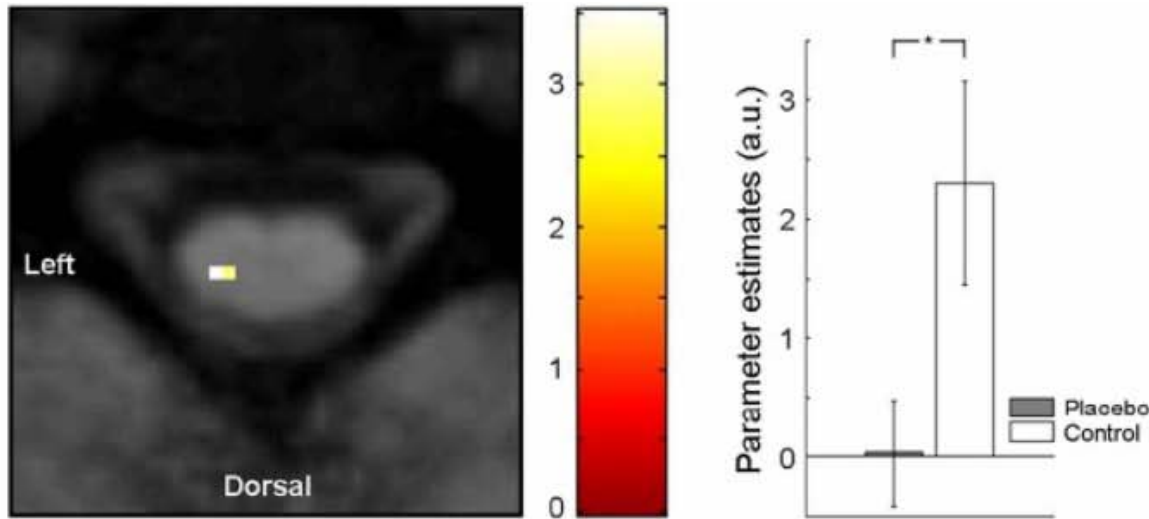
# Cognition and Pain: attention, distraction, expectation, control and reappraisal

Wiech, Ploner & Tracey, TICS 2008



# Placebo Analgesia - Mechanisms

Eippert et al. Science, 2009



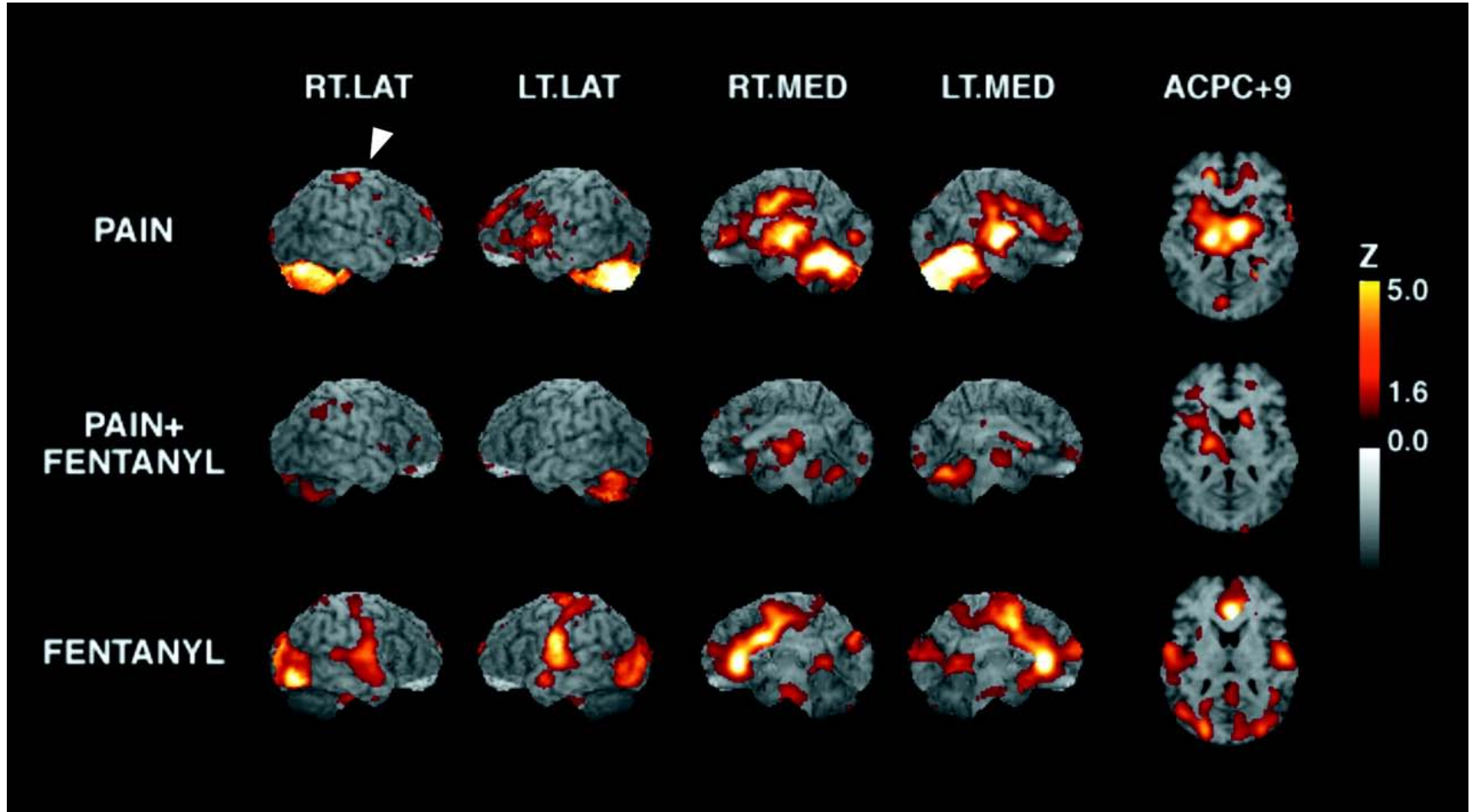
C6 ipsilat to stimulation



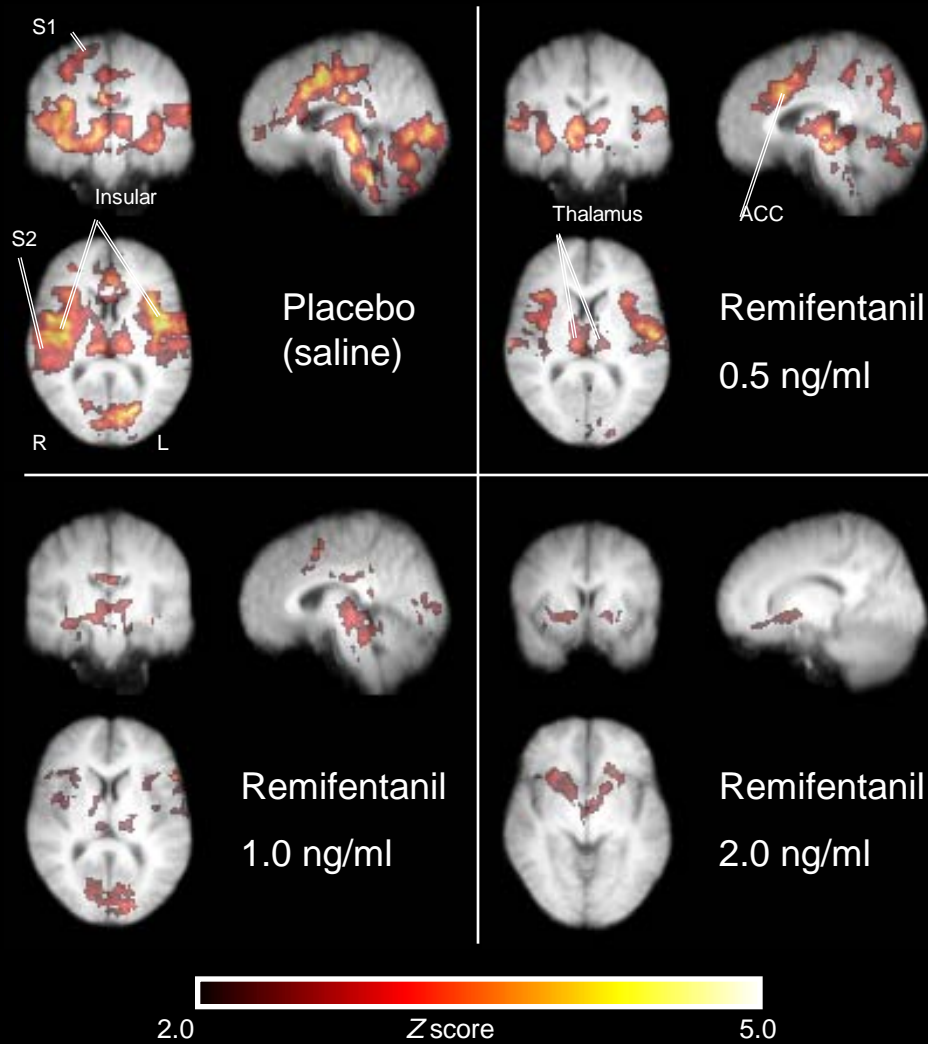
Direct evidence for spinal cord involvement in placebo analgesia

# Early PET Study -

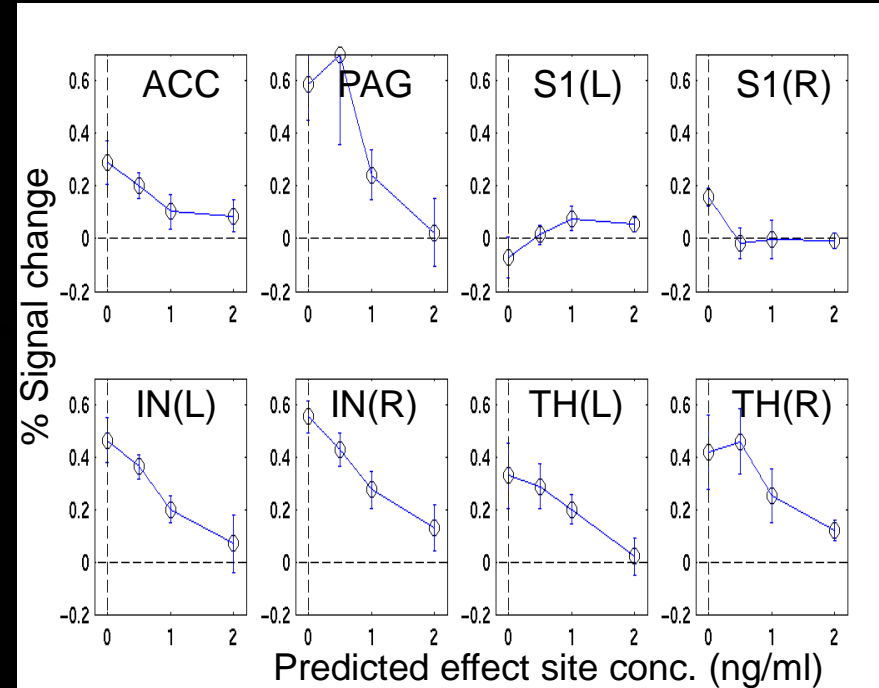
(Casey J. Neurophysiology 2000)



# Remifentanyl Analgesia



## FMRI "dose-response curves"



# Recently Completed Collaboration with Pfizer

(J.Huggins, B. Vennart & Sandwich Team)

Simulating Go/No-Go Decision Making Point:

FMRI “head-to-head” study examining pregabalin,  
tramadol, placebo in small cohort of Neuropathic  
Pain Patients

# Expectancy and Money



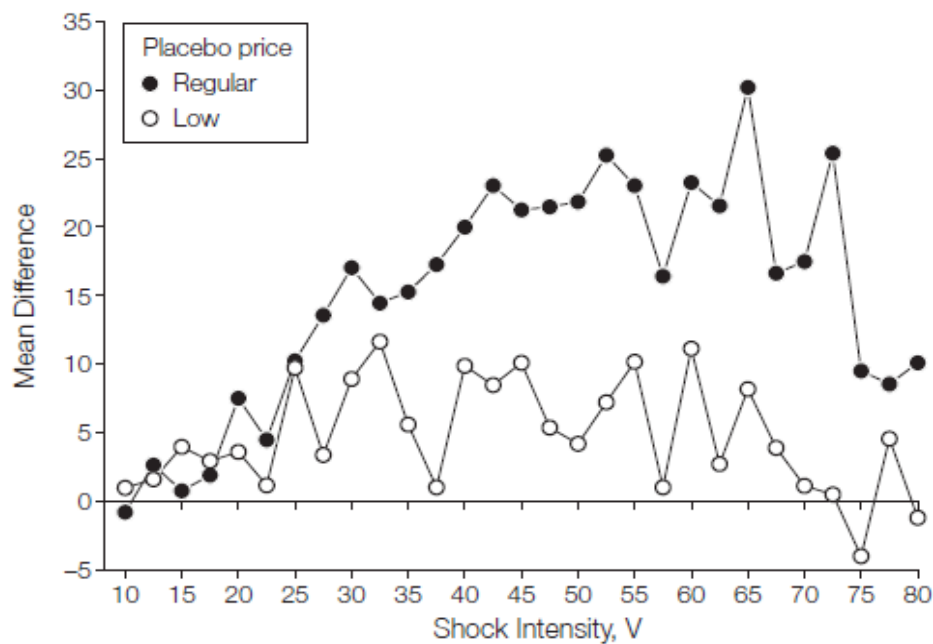
Online article and related content current as of October 4, 2008.

## Commercial Features of Placebo and Therapeutic Efficacy

Rebecca L. Waber; Baba Shiv; Ziv Carmon; et al.

*JAMA*. 2008;299(9):1016-1017 (doi:10.1001/jama.299.9.1016)

**Figure.** Pain Ratings by Voltage Intensity

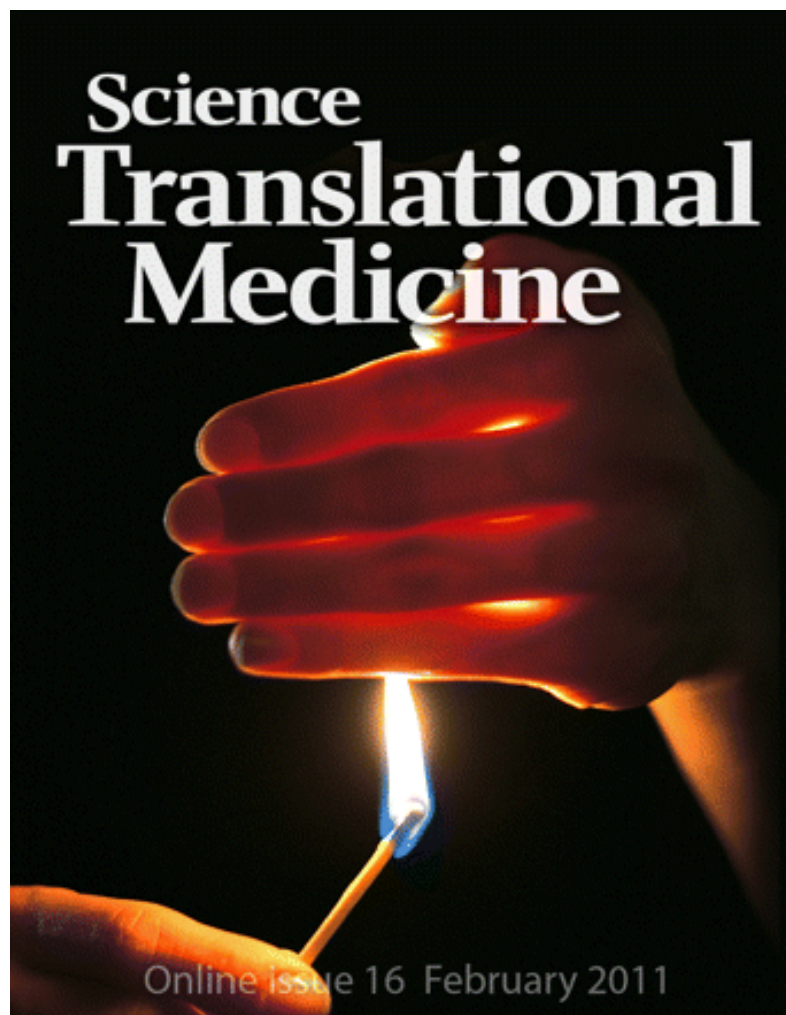




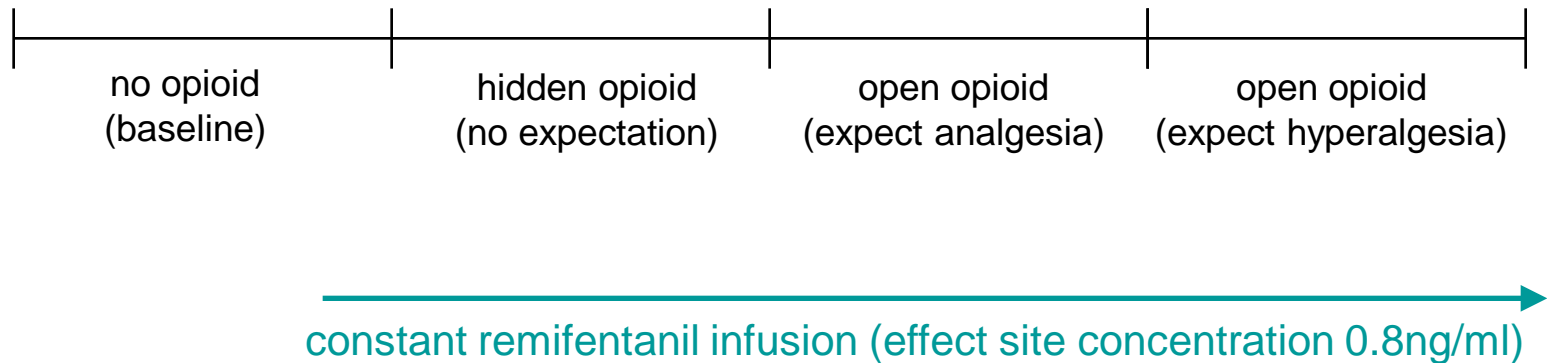
## DRUG EFFICACY

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

Ulrike Bingel,<sup>1,2\*</sup> Vishvarani Wanigasekera,<sup>1</sup> Katja Wiech,<sup>1</sup> Roisin Ni Mhuircheartaigh,<sup>1</sup> Michael C. Lee,<sup>3</sup> Markus Ploner,<sup>4</sup> Irene Tracey<sup>1</sup>

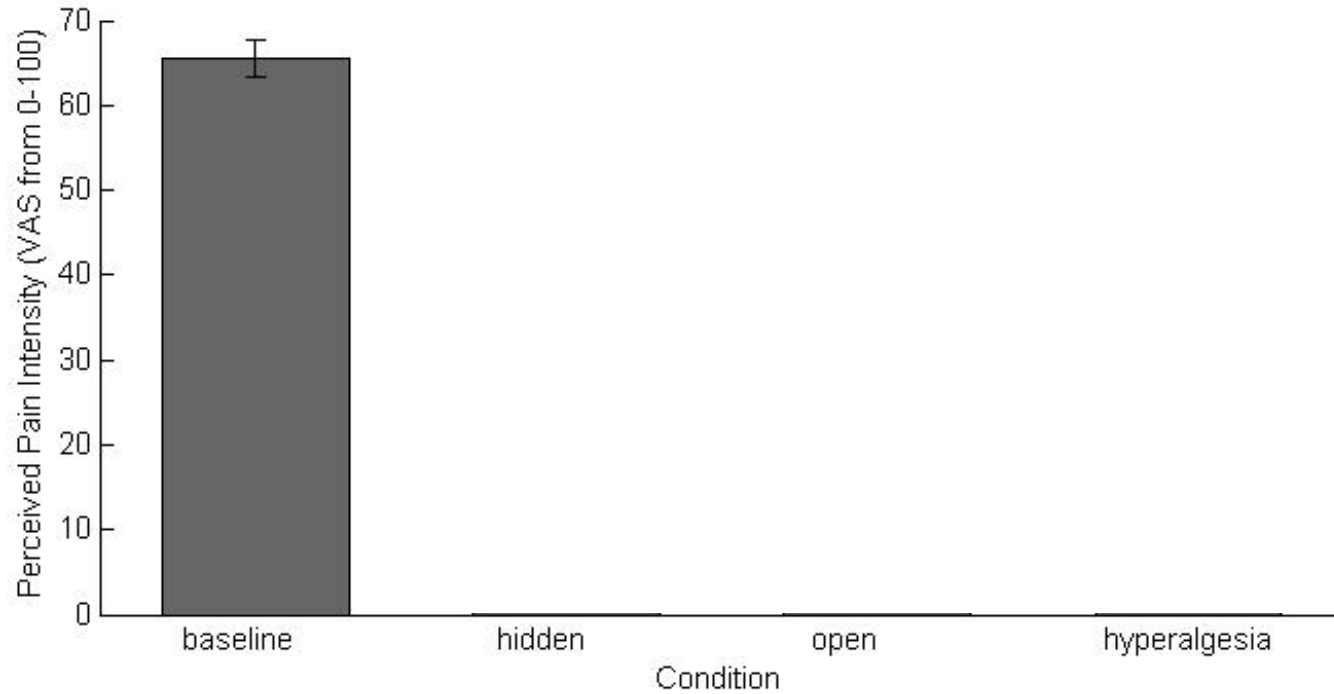


# Experimental Paradigm: Opioid & Expectancy



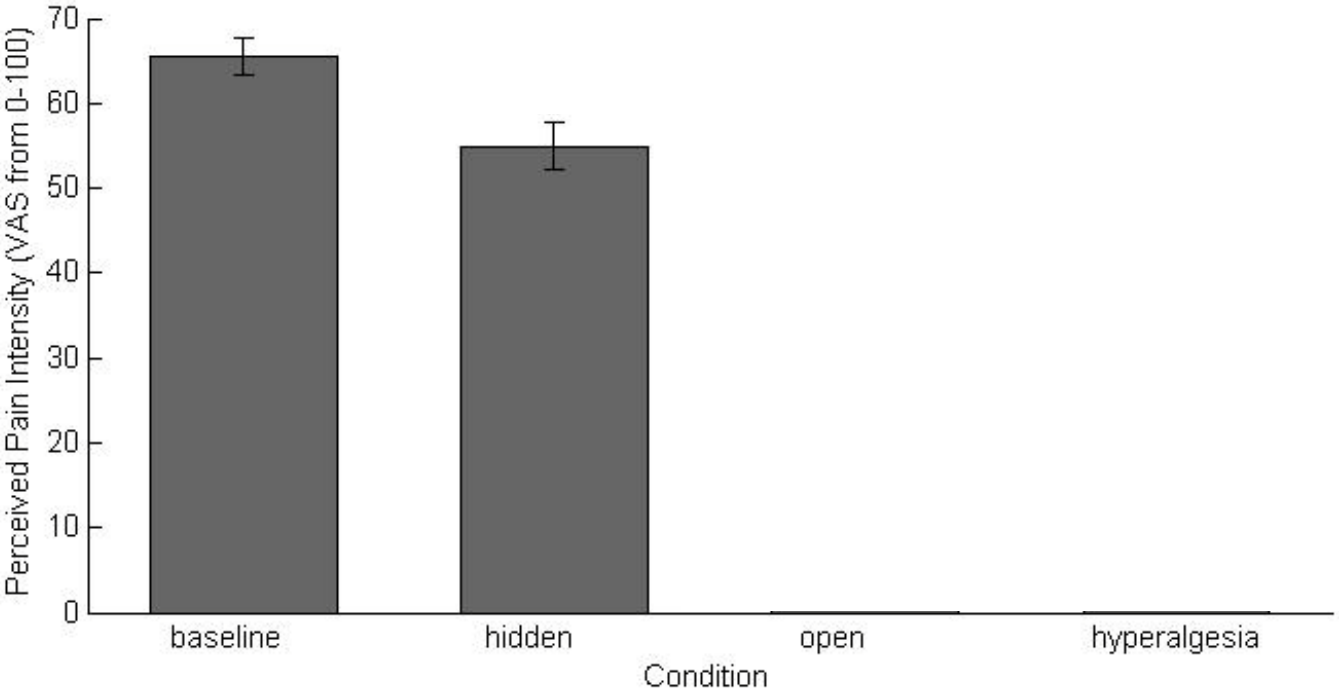
# Opioids & Expectancy

## Pain Ratings



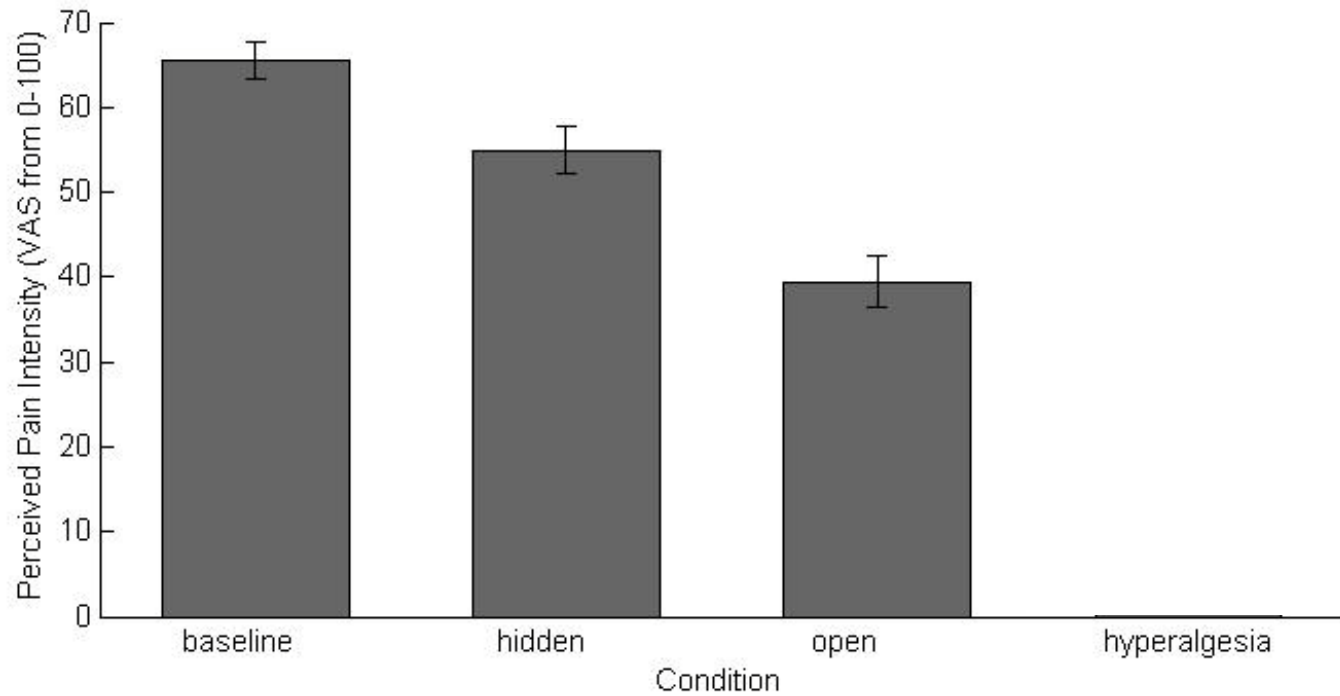
# Opioids & Expectancy

## Pain Ratings



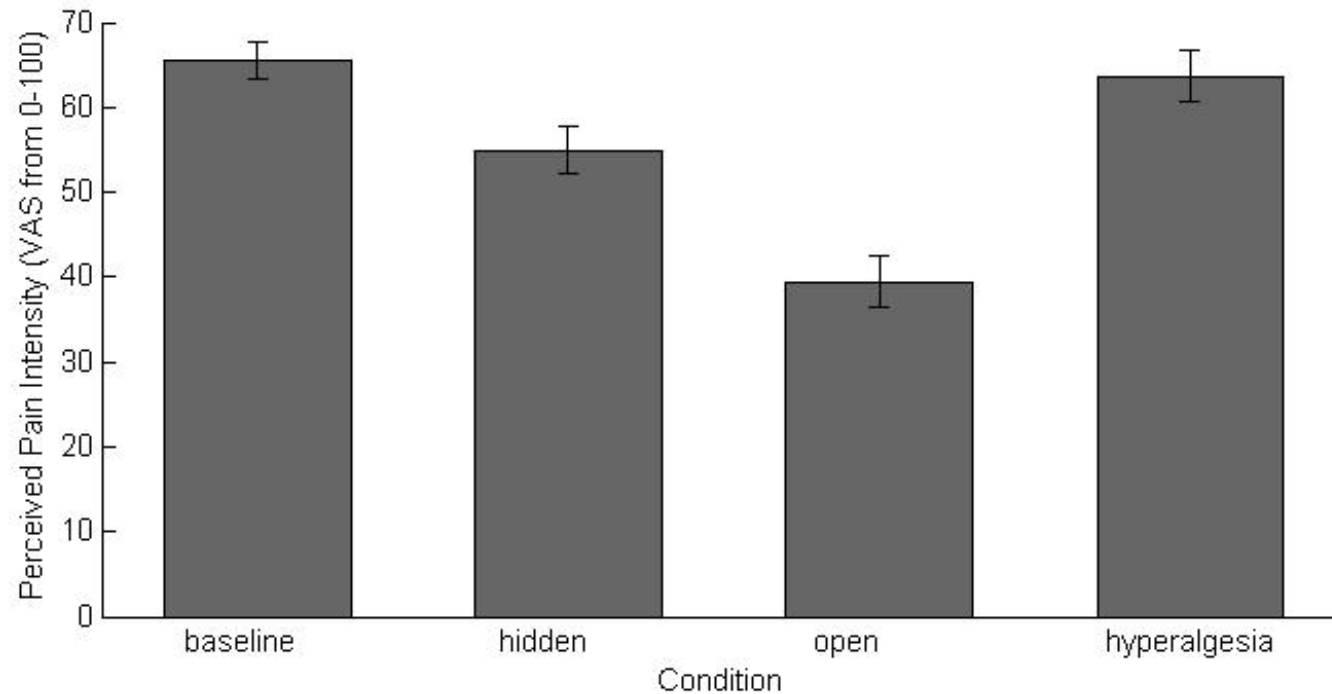
# Opioids & Expectancy

## Pain Ratings

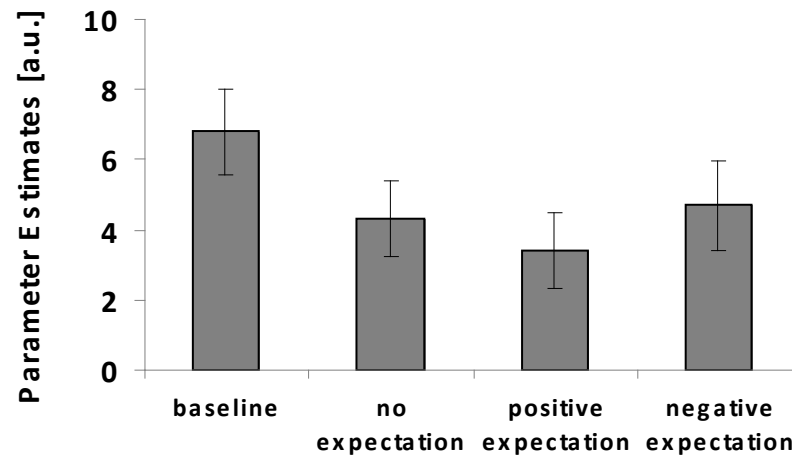
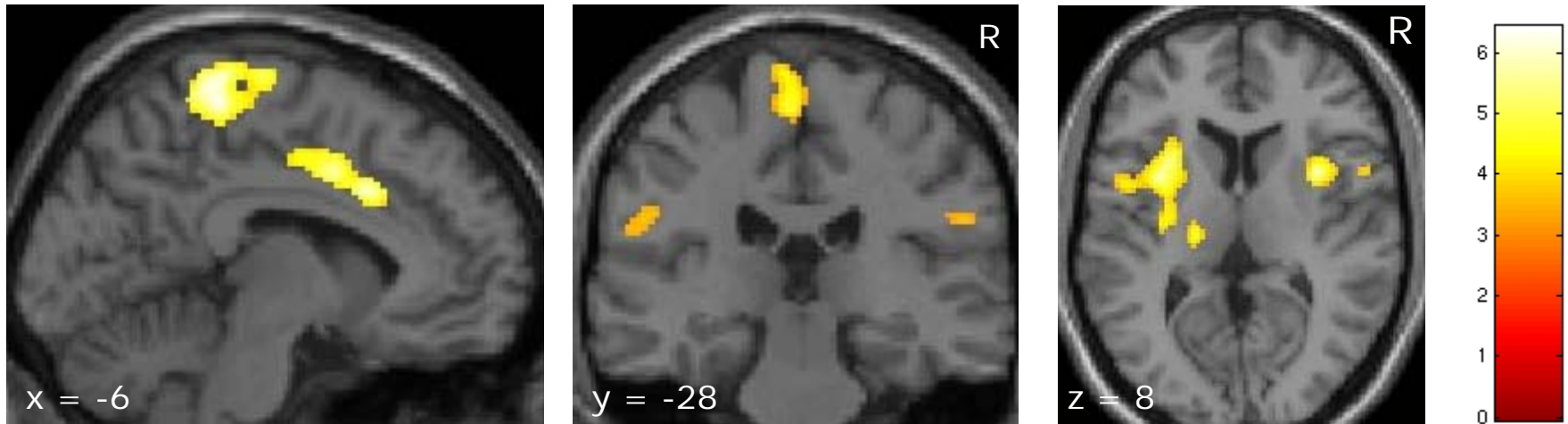


# Opioids & Expectancy

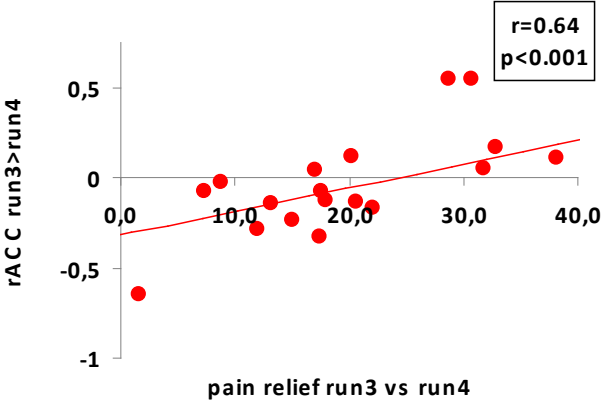
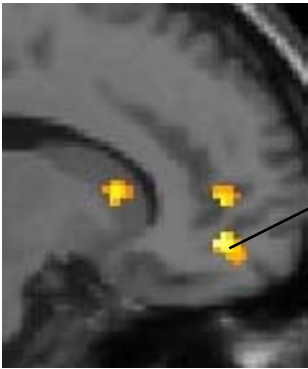
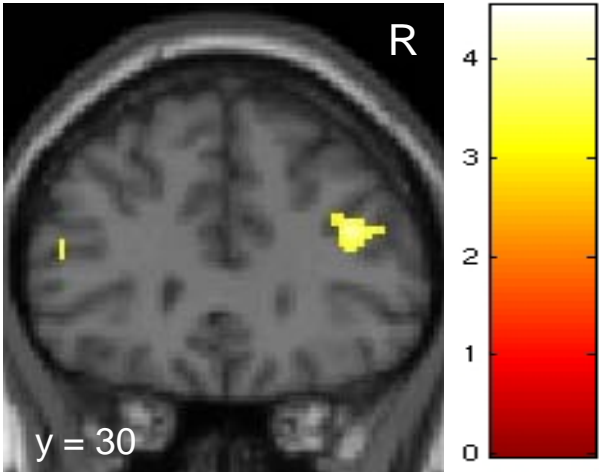
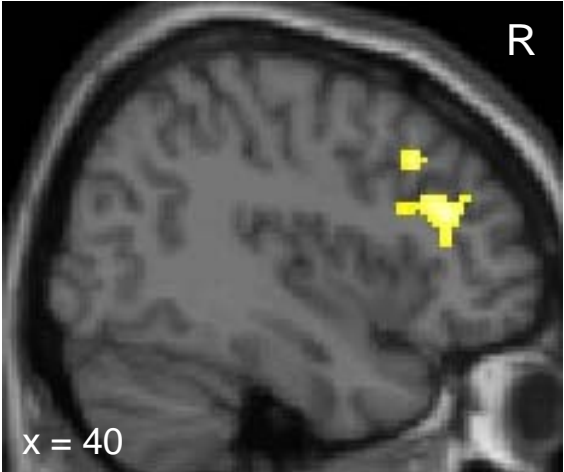
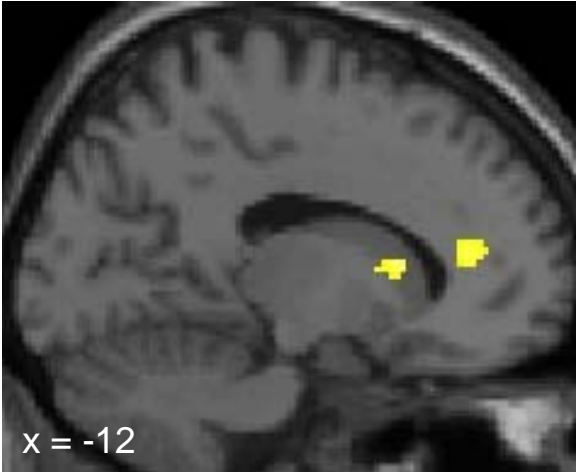
## Pain Ratings



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

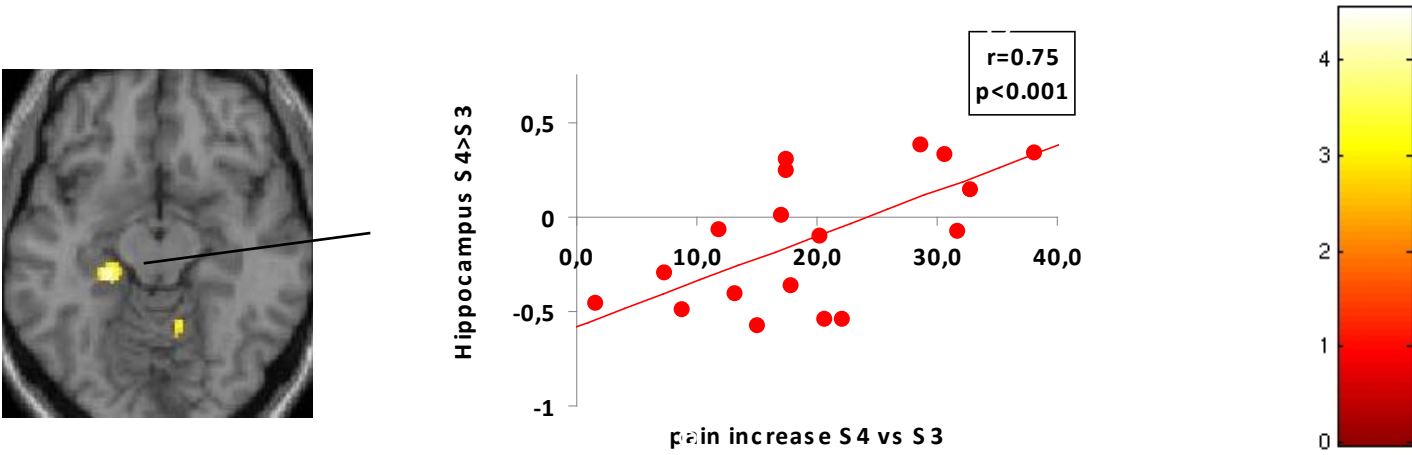


# Recruitment of descending pain modulatory system with positive expectancy





# The impaired analgesia during negative expectation is associated with hippocampus activity



Supplementary Figure 3

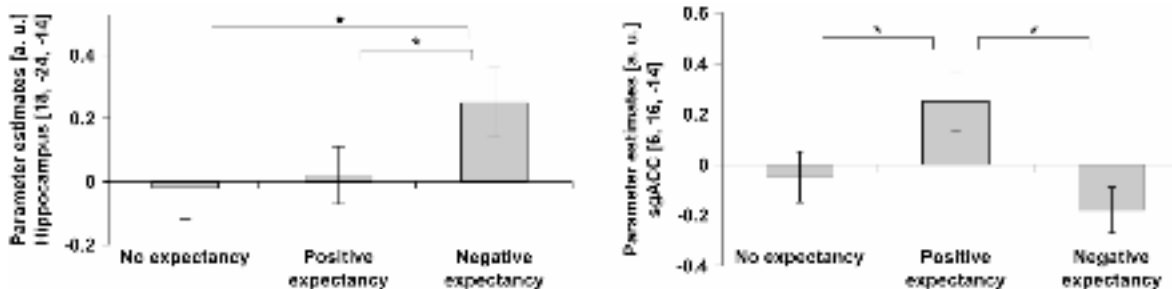


Fig. S3. Brain areas mediating the effects of positive and negative expectancy. (Left)

## Supplementary Figure 4

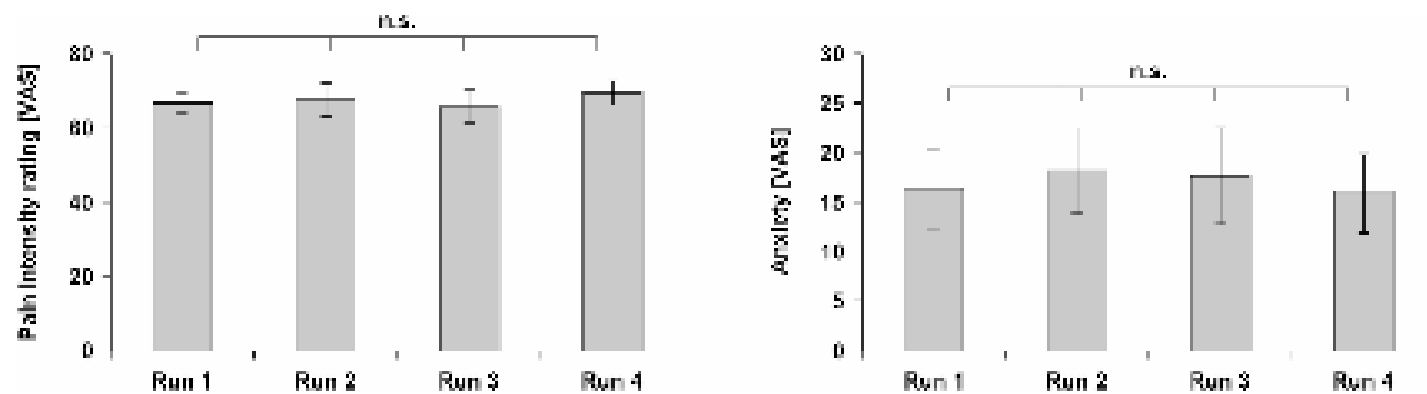


Fig. S4: Control experiment I—exclusion of habituation or sensitization effects. Mean

## Supplementary Figure 5

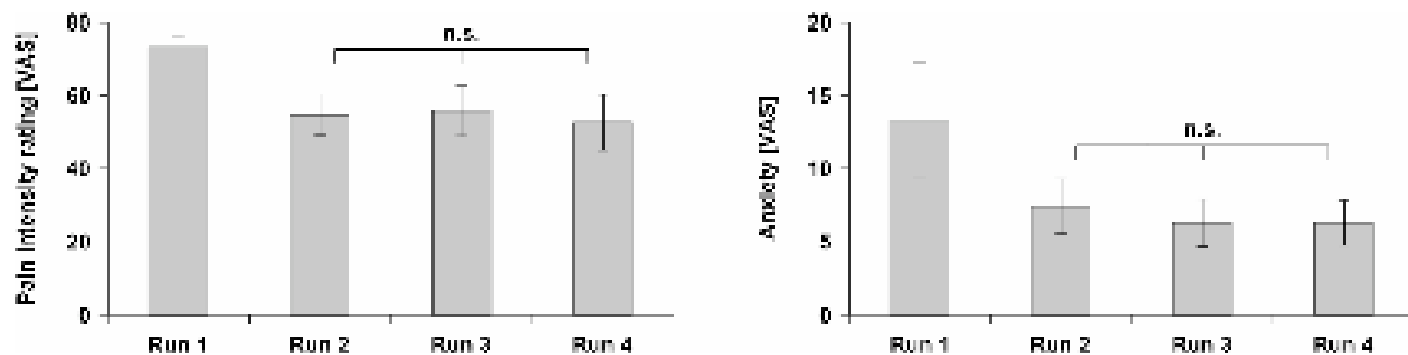
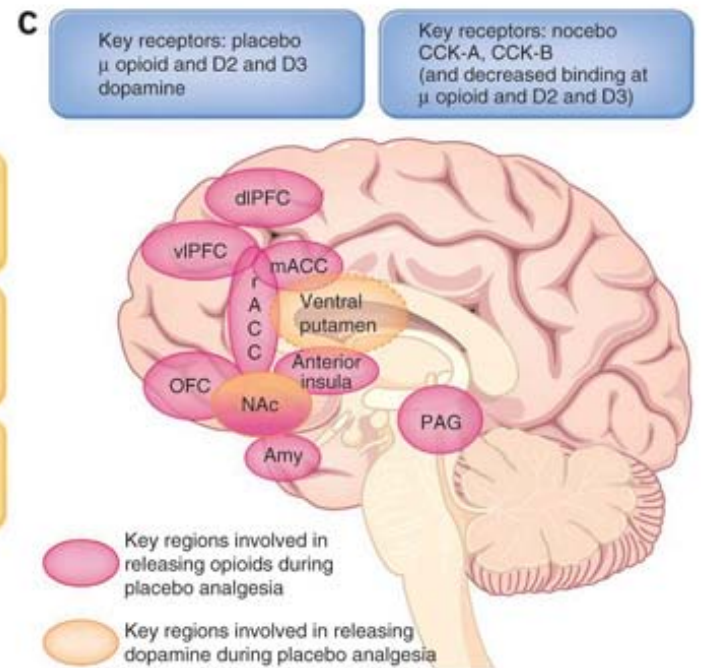
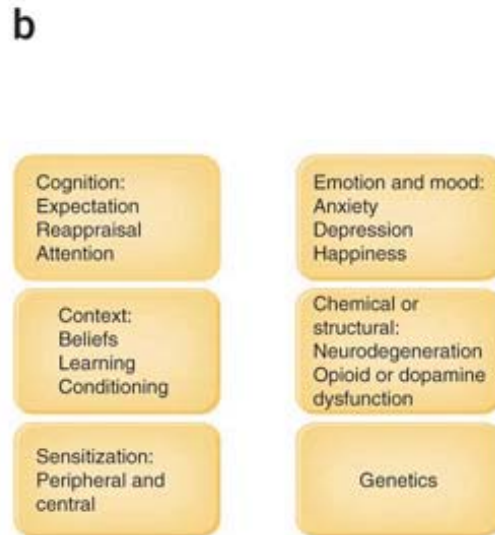
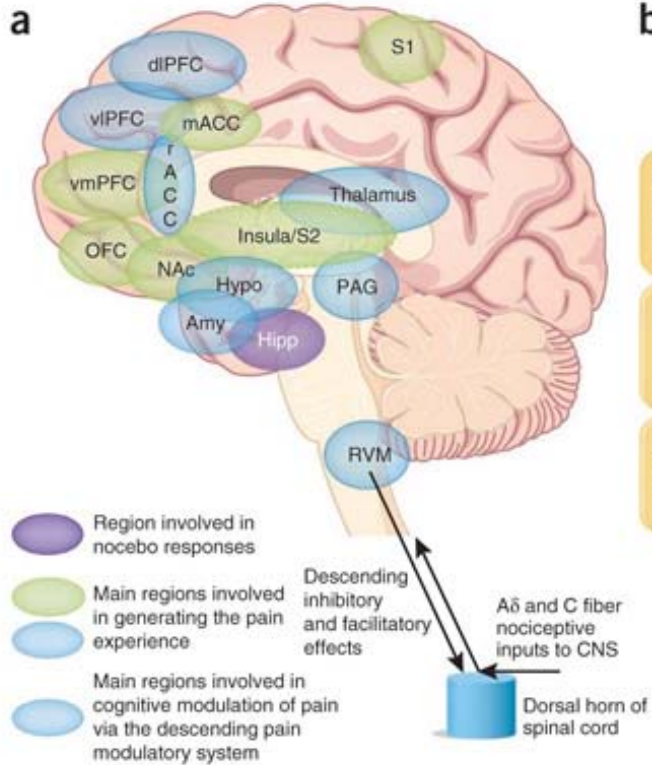


Fig. S5: Control experiment II—the natural time course of remifentanyl analgesia without expectancy manipulation. Mean pain intensity ratings (left panel) and anxiety

# Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans

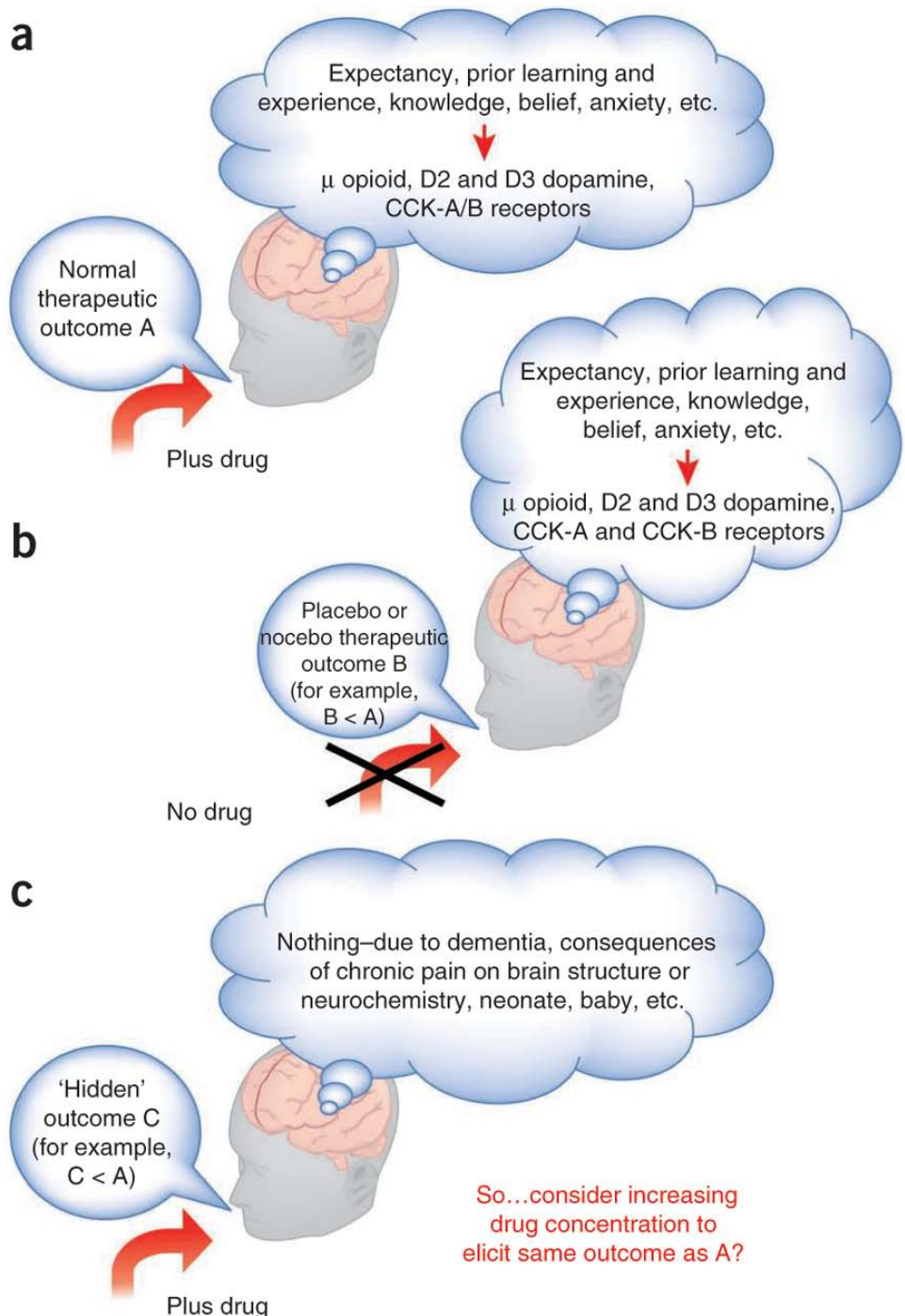
Irene Tracey

**The perception of pain is subject to powerful influences. Understanding how these are mediated at a neuroanatomical and neurobiological level provides us with valuable information that has a direct impact on our ability to harness positive and minimize negative effects therapeutically, as well as optimize clinical trial designs when developing new analgesics. This is particularly relevant for placebo and nocebo effects. New research findings have directly contributed to an increased understanding of how placebo and nocebo effects are produced and what biological and psychological factors influence variances in the magnitude of the effect. The findings have relevance for chronic pain states and other disorders, where abnormal functioning of crucial brain regions might affect analgesic outcome even in the normal therapeutic setting.**

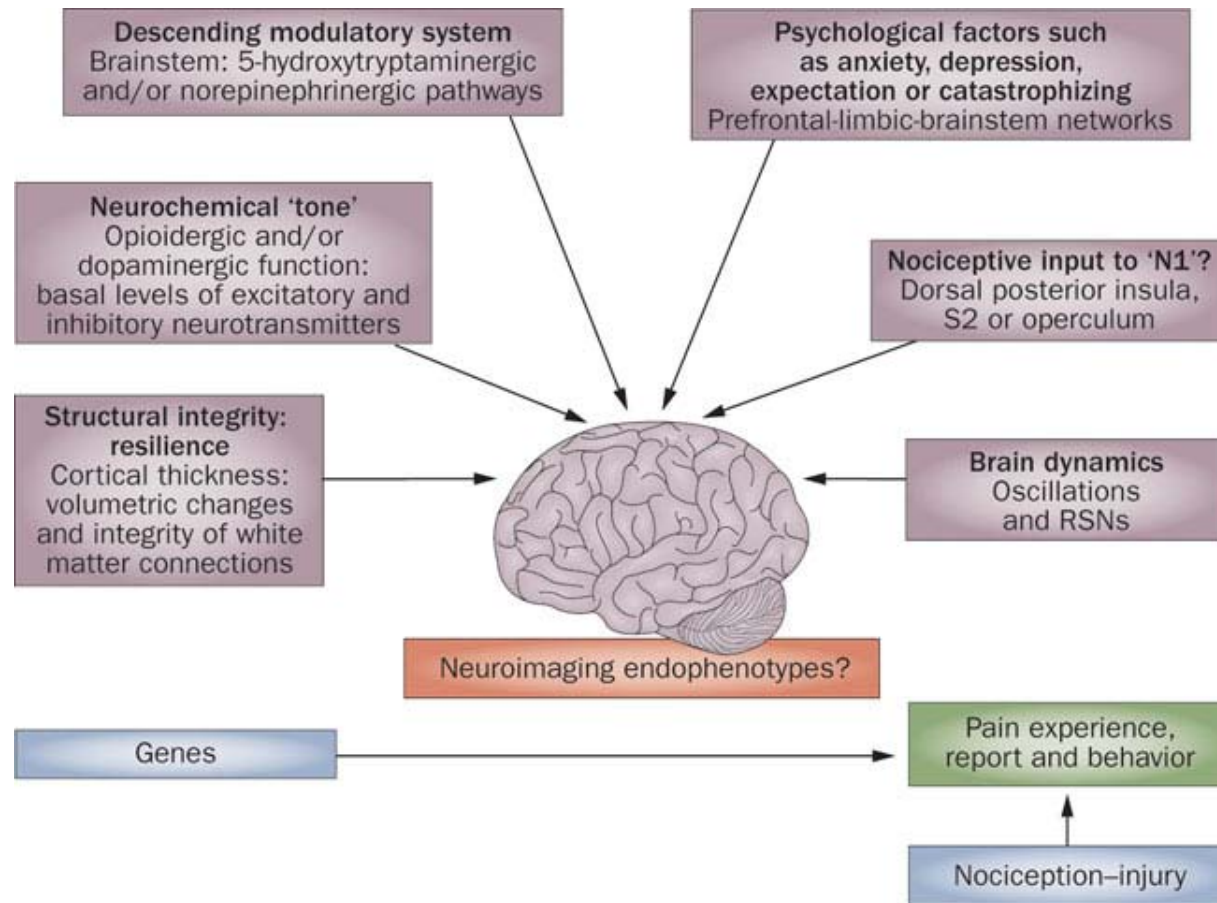


# The Patient Environment

Tracey I. Nat. Medicine 2010



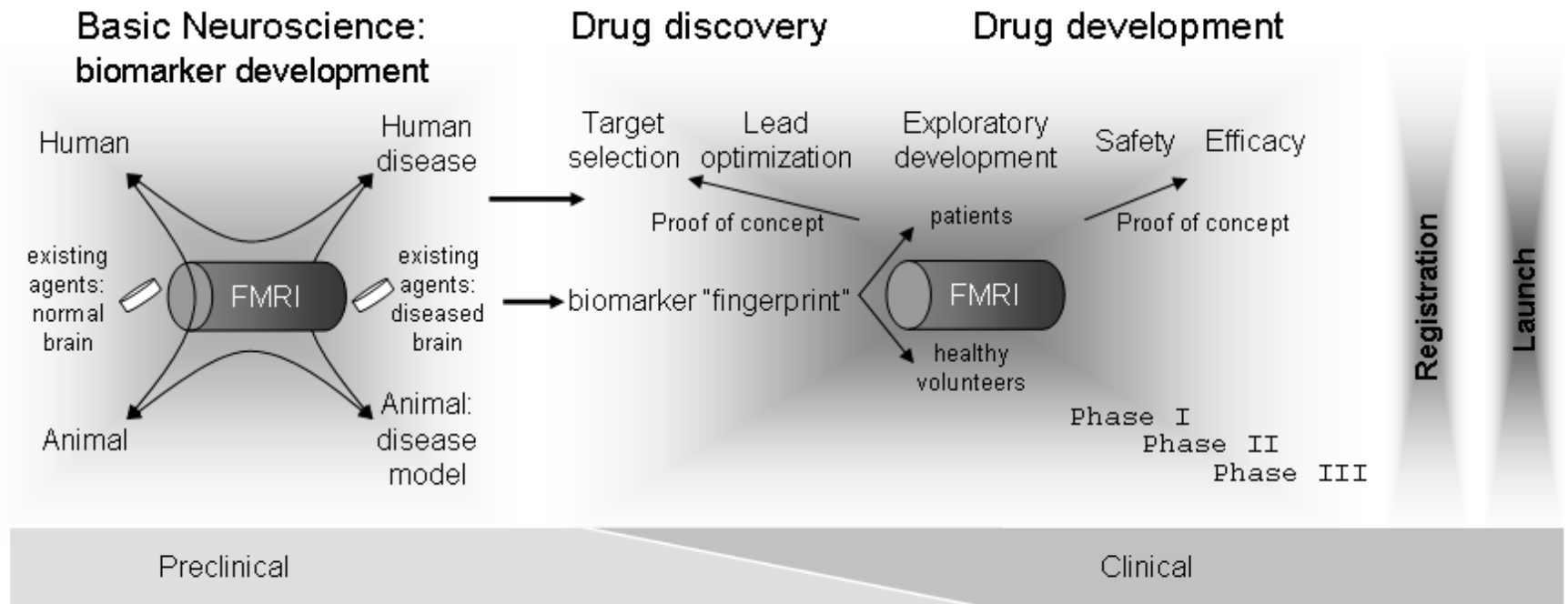
# Figure 1 Factors involved in generating and influencing pain perception



Tracey, I. (2011) Can neuroimaging studies identify pain endophenotypes in humans?  
*Nat. Rev. Neurol.* doi:10.1038/nrneuro.2011.4

# Neuroimaging Biomarkers for Drug Development

Wise and Tracey (2006)





# Pain Imaging Neuroscience Group



## Group – Present

- Katja Wiech
- Jon Brooks
- Katie Warnaby
- Rebeccah Slater
- Karolina Wartolowska
- Line Loken
- Chantal Berna
- Emily Johns
- Daniella Siexas
- Katy Vincent
- Asma Ahmad
- Katie Fairhurst
- Chia-Shu Lin
- Vishvarani Wanigasekera
- Roisin Ni Mhuircheartaigh
- Andrew Segerdahl
- Richard Lin
- Melvin Mezue
- Sue Field

## Current Collaborators

FMRI Centre Analysis and Physics Groups  
Andy Carr (Nuffield Orthopaedic Hospital, Oxford)  
Paul Wordsworth (Rheumatology Department, Oxford)  
Pain Relief Unit, Oxford  
Richard Rogers, Jane Quinlan (NDA, Oxford)  
Stephen Kennedy (Gynaecology 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)



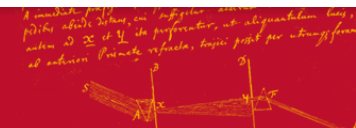
*We aim to bring a systems understanding to pain processing within the human central nervous system in health and disease*



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

## Past Group Members

- Stephen Gwilym
- Markus Ploner
- Ulrike Bingel
- Mike Lee
- 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
- Elisa Favaron
- Ajit Itty
- Amy Godinez
- Susy Bantick
- Alex Ploghaus



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