Advances in pain made by a better understanding of neuroscience

Irene Tracey

Head of Nuffield Department Clinical Neurosciences & Nuffield Chair of Anaesthetic Science, University of Oxford, England UK
More confidence in mechanism if...

Cross-species
Cross-scale
Patients
Populations
Open neuroimaging
A Key Role for Neuroimaging in Understanding Acute and Chronic Pain

I. Tracey

Neuroimaging Mechanisms in Pain: From Discovery to Translation.
Pain 2017
Increasingly imaging tells you something unexpected: can drive new measures for diagnosis/intervention.
What Holds People in Chronic Pain?

1. Constant firing of ‘pain nerves’
2. Amplification/Sensitisation of signals in central nervous system
3. Maladaptive plasticity
4. Vulnerability towards developing chronic pain

Targeting the periphery proving challenging

Commonality
ONGOING PAIN

Target brain function for pain relief?
How We Currently “Measure” Pain:

Self-report

Observe behaviour and *infer*

Indirect physiology

Subjectivity leads to limitations in diagnosis and treatment, failed clinical trials, legal disputes/claims, etc…
Pain is Multidimensional, Malleable and Subject to Mood, Cognitive and Contextual Influences: there is not a simple one-to-one brain mapping between nociception and perception.
Amplification/Sensitisation

> hyperalgesia
> allodynia

BOLD FMRI

Spontaneous pain

Tonic pain

BOLD FMRI

“functional connectivity”

How tightly correlated are A & B?

“Stimulus vs Baseline”

Arterial Spin Labelling FMRI

Measure activity over time

Tjandra et al., Neuroimage 2005; Owen et al., Pain 2010; Tracey & Johns Pain 2010; Segerdahl et al., Pain 2012; Mezue et al., JCBFM 2014; Segerdahl et al., Nat. Neuro 2015; Zhao et al., Neuroimage 2017
The Early Days: anatomical 'blobs' - trying to find the 'hurt'

Multiple Representations of Pain in Human Cerebral Cortex

JEANNE D. Talbot, SEAN Marrett, ALAN C. Evans, ERNST Meyer, M. CATHERINE Bushnell, GARY H. Duncan*

Cortical and subcortical localization of response to pain in man using positron emission tomography


MRC Cyclotron Unit, Hammersmith Hospital, London W12 0HS, U.K.


Printed in Great Britain
Anticipating pain has **adaptive and maladaptive consequences**

Learning about pain: The neural substrate of the prediction error for aversive events (Ploghaus et al., PNAS 2000)
Can the Spinal Cord ‘Learn’ about pain? Yes

Maixner et al., 1989, J Neurophysiol

Using Pavlovian conditioning design show that predictive visual stimuli can elicit spinal cord responses (Eippert et al., 2018 in prep.)
The Gate Theory & Beyond


Modulation of Pain by Nonpainful Events

Patrick D. Wall

Department of Anatomy, Cerebral Functions Research Group, University College, London WC1E 6BT, England

The Gate Theory predicted pain could be modulated


The Role of Substantia Gelatinosa as a Gate Control

Patrick D. Wall
Relevance of Central Sensitisation for Chronic Pain: role of the dorsal horn

Woolf CJ Pain 2011
Functional imaging of human spinal cord: not for the faint hearted

- Special hardware
- Small size
- Signal dropout

Physiological noise

Brooks et al., Neuroimage 2008, Kong et al., 2012; Finsterbusch et al., Neuroimage 2012
Spinal Cord Imaging: Sensorimotor

Motor responses

Maieron et al., J. Neuroscience 2007

Laterality pain responses

Brooks et al., J. Neuroscience 2012
The spinal cord is never at rest

Even when we are at rest, our spinal cords show spontaneous, yet well organised, fluctuations of activity that might reflect sensory and motor networks.

FALK EIPPERT AND IRENE TRACEY

Barry et al., eLife 2014
Kong et al., PNAS 2014
Eippert et al., Neuroimage 2017
7T spinal cord imaging
High-resolution anatomical imaging

Functional Imaging Challenges: The $B_0$ field fluctuates with breathing cycle → ghosting artefacts, apparent motion in functional imaging time series

Develop physics to compensate for field fluctuations
(Vanessjo et al., Neuroimage 2018)
Modulating the Perception of Pain: Mood, Cognition & Context
Nociceptive driven vs. ‘non-physical’ Pain

Empathising vs. ‘physical’ Pain

green = self red=other

(Singer et al., Science 2004)

Hypnosis vs. ‘physical’ Pain

Raij et al., PNAS 2005
Emotional Pleasure then Pain....

(Leknes & Tracey Nature Reviews Neuroscience 2008; Leknes et al., PAIN 2013)
Anterior cingulate and insula: Shared representations of “pain?”

Physical pain

Anterior cingulate

Anterior Insula

Tracey 2001; Apkarian 2005; Atlas 2010, 2012; Many others

Social pain (rejection)


Pain empathy (observed pain)

Green = self, red = other

Singer 2004; Jackson 2005; Fan 2012; Lamm & Decety; others
100,000 voxels

One voxel:
5.5 M neurons

Multiple functional circuits

Anterior cingulate:
• Separate neurons respond to mechanical and thermal pain (25% overlap); Sikes and Vogt (1982)
• Separate circuits for reward onset and offset in foraging; Kvitsiani et al. (2013), Nature
Decoding what brain regions are essential for pain: **machine learning**

Neurologic Pain Signature
(Wager et al. 2013, NEJM)

- Negative predictive weights
  -2.95 - 3.35 + Z

- Positive predictive weights
  2.95 3.35 + Z

- Dorsal anterior cingulate
- Somatosensory
  - SII
  - Post. insula
- Insula
  - Ventrolateral
  - Medial
- Thalamus

Krishnan et al., eLIFE 2016

Lopez-Sola et al., Towards a neurophysiological signature for fibromyalgia Pain 2017
Learning to identify CNS drug action and efficacy using multi-study fMRI data

Duff et al., 2015
Remember, pain is old and shared

We infer pain in others by analogy to our own experiences and behavior: *this can be problematic too*
because we can get it wrong
Can sleeping babies help us?

fMRI used to compare the neural activity overlap between adult and infant pain

Williams et al., Acta Paediatr. 2015; Goksan et al., eLife 2015
Degrading the Perception of Pain via Anaesthesia

100,000s of general anaesthetics – rarely look at the brain

The Descending Pain Modulatory System: Pro- & Anti-nociceptive mechanisms – imbalance is key in chronic pain.
The Good Cop: Anti-nociception

Confirmation ‘free analgesia’ utilised in everyday situations (including placebo): some people able/others not – can we target using noninvasive brain stimulation? Yes


(Segerdahl et al., Nat. Neuro 2015)
Ipsilesional anodal tDCS enhances the benefits of rehabilitation in patients

Claire Allman,‡* Ugwechi Amadi,‡* Anderson M. Winkler,† Leigl
Udo Kischka,‡ Charlotte J. Stagg,†* Heidi Johansen-Berg†‡

Increased fMRI activity and gray matter volume in the anodal TDCS group compared to sham

Upper Extremity Fugl-Meyer Assessment; Research Arm Test; Wolf Motor Func
Brain plasticity

- Learning
- Change in sensory input
- Recovery from brain injury
White Matter Plasticity in the Adult Brain

Cassandra Sampaio-Baptista and Heidi Johansen-Berg
1Oxford Centre for Functional MRI of the Brain, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, UK
*Correspondence: cassandra.sampaiobaptista@ndcn.ox.ac.uk
https://doi.org/10.1016/j.neuron.2017.11.026

The study of brain plasticity has tended to focus on the synapse, where well-described activity-dependent mechanisms are known to play a key role in learning and memory. However, it is becoming increasingly clear that plasticity occurs beyond the synapse. This review focuses on the emerging concept of white matter plasticity. For example, there is growing evidence, both from animal studies and from human neuroimaging, that activity-dependent regulation of myelin may play a role in learning. This previously overlooked phenomenon may provide a complementary but powerful route through which experience shapes the brain.

Figure 3. Neuroimaging Findings of White Matter Plasticity in Humans and Rodents with Spatial and Motor Skills
(A) Learning a spatial navigation task results in rapid decreases in MD in the fornix (Hofstetter et al., 2013).
(B) Morris water maze task acquisition results in changes in WM and higher myelination (Blumenfeld-Katzir et al., 2011).
(C) Learning a new motor skill results in increases in FA (Schödl et al., 2009).
(D) Skill learning results in higher FA and higher myelination (Sampaio-Baptista et al., 2013).
Error bars represent SE.
New Imaging Observations: Plasticity

Pons et al., Science 1991

Flor et al., Nature 1995
Phantom Limb Pain – Poster Child for Maladaptive Plasticity

We find: preserved hand representation AND…….

↑ deprivation > ↑ reorganisation > ↑ pain > ↓ missing hand representation

Makin et al., Nature Communications 2013; Makin et al., eLife 2013; Makin et al., Neuroimage 2014; Makin et al., Brain 2015; eLife 2016

↑ pain > ↑ missing hand representation
Using tDCS to relieve phantom pain

Kikkert et al., in revision, 2018

1. Sham  
2. Anodal deprived  
3. Cathodal Deprived  
4. Anodal Intact

Long-term pain effects (t=\sim1 week)

Kikkert et al., in revision, 2018
The Descending Pain Modulatory System: Pro- & Anti-nociceptive mechanisms – imbalance is key in chronic pain
Evidence of Placebo Mechanism in Neuropathic Pain Patients During Clinical Trial

Nothing special about placebo analgesia

Wanigasekera et al., BJA 2018

It hijacks the Anti-nociception Brainstem Pathway

But challenges assumption of additivity in clinical trials: begs question why do all pain drugs fail?

Eippert et al., Neuron 2009
Spinal Cord Imaging: cognitive & contextual influences – outcome of good cop?

Placebo effects

Eippert et al., Science 2009

Distraction

Sprenger et al., Current Biology 2012
Interacting nociceptive cord medialisation: nocebo hypothesis

A. Tinnermann, S.
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
The Power of Expectations
(Bingel et al., Sci. Trans Med 2011)
Arthroscopic subacromial decompression for subacromial shoulder pain (CSAW): a multicentre, pragmatic, parallel group, placebo-controlled, three-group, randomised surgical trial

Beard et al., Lancet 2017
Figure 2: Oxford Shoulder Score in the intention-to-treat analyses
Data are mean (95% CI) shown at follow-up timepoints. OSS = Oxford Shoulder Score.

Enhancing treatment of osteoarthritis knee pain by boosting expectancy: A functional neuroimaging study

Jian Kong\textsuperscript{a,b,y}, Zengjian Wang\textsuperscript{a}, Jaclyn Leiser\textsuperscript{a}, Domenic Minicucci\textsuperscript{a}, Robert Edwards\textsuperscript{c,d}, Irving Kirsch\textsuperscript{e}, Ajay D. Wasan\textsuperscript{f,g}, Courtney Lang\textsuperscript{a}, Jessica Gerber\textsuperscript{b}, Siyi Yu\textsuperscript{a}, Vitaly Napadow\textsuperscript{b}, Ted J. Kaptchuk\textsuperscript{b}, Randy L. Gollub\textsuperscript{b,h,i}
How the Brain Works – 21st Century knowledge and current thoughts…..

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

The brain is NOT a simple ‘receipt’ organ producing perceptions and experiences by processing bottom up sensory inputs as sole contributor: The Concept of: *Priors and a Bayesian view of the Brain*
Reframing Old Data: Priors & Pain

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

Katja Wiech¹,², Joachim Vandekerckhove³,⁴, Jonas Zaman⁴, Francis Tuerlinckx⁴, Johan W.S. Vlaeyen⁴,⁵, and Irene Tracey¹,²

Figure 1

A. Drift diffusion model

B. Influence of prior information on pain-related perceptual decision-making

- change in drift rate
- shift in starting point
- high pain
- low pain
- time

- 80% hi stim
- 20% lo stim period
- high pain
- low pain

- 20% hi stim
- 80% lo stim
- stim period
- high pain
- low pain

- hi stim following 20% hi stim/80% lo stim
- cue
- stim period
- high pain
- low pain
The Descending Pain Modulatory System: Pro- & Anti- nociceptive mechanisms – imbalance is key in chronic pain
The Bad Cop: pro-nociception

Maintains central sensitisation
(Zambreanu et al., Pain 2005; Lee et al., Journal of Neuroscience 2009)

Aberrant activity identified across a range of pain conditions
(Gwilym et al., Arthritis and Rheumatism 2009; Wanigasekera et al., J. Neuroscience 2011; Segerdahl et al., Brain 2018; Soni et al., 2018 (in revision).

Biomarker drug discovery
(Iannetti et al., PNAS 2005; Lee et al., Pain 2013; Wanigasekera et al., Anaesthesiology 2016; BJA 2018)

Mayer et al., PAIN 2005; Becerra et al., 2006; Edwards 2005; Goadsby 2007; Sandrini et al., 2006; Seifert & Maihofner 2007; Mainero et al., 2007; Mainero et al., Annals of Neurology 2011
A brain based pain facilitation mechanism contributes to painful diabetic polyneuropathy (Segerdahl et al., Brain 2018)
Risk Factors for Chronic Pain Conditions

Denk, McMahon & Tracey
Nature Neuroscience 2014

Baliki et al., Nat. Neurosci 2012;
Ploner et al., PNAS 2010
• 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

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
T1-weighted

Susceptibility contrast

T2 FLAIR

Diffusion MRI

Resting fMRI

T2 FLAIR

Task fMRI

shapes>faces
imaging phenotypes
genetics
blood chemistry
environment & lifestyle
long-term health outcomes
predict
Pain Biomarkers

Preclinical studies, abattoirs, vets, etc

Insurance firms, lawyers, etc

Anaesthetized or comatose patients

Neonates, infants, non-verbal or demented elderly

Analgesic drug discovery, novel therapeutics and interventions

Drug Discovery

Diagnosis in the clinic
The Current Team & Collaborators

Ongoing Pain - ASL

Anaesthesia

Spinal Cord

Clinical & Analgesia
Group – Present

-Vishvarani Wanigasekera
-Andrew Segerdahl
-Sarah Waldman
-George Tackley
-Katie Warnaby
-Anushka Soni
-Min-ho Lee

Current Collaborators

FMRIB Centre Analysis, Physics & Plasticity Groups
Andy Carr & Andrew Price (NDORMS, Oxford)
Marta Seretny (University of Edinburgh)
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 Mhuircheartaigh
- Daniella Siexas
- Katy Vincent
- Katja Wiech
- Line Loken
- Janet Bultitude
- Tamar Makin
- Melvin Mezue
- Min-Ho Lee
- Jennifer Brawn
- Jo Kong
- Falk Eippert
Imaging has the potential to unravel the neural basis of pain, relief and CNS mechanisms important for predisposing, maintaining and worsening chronic pain states.

Certainly more than ‘fantasy labels’