Imaging the placebo response



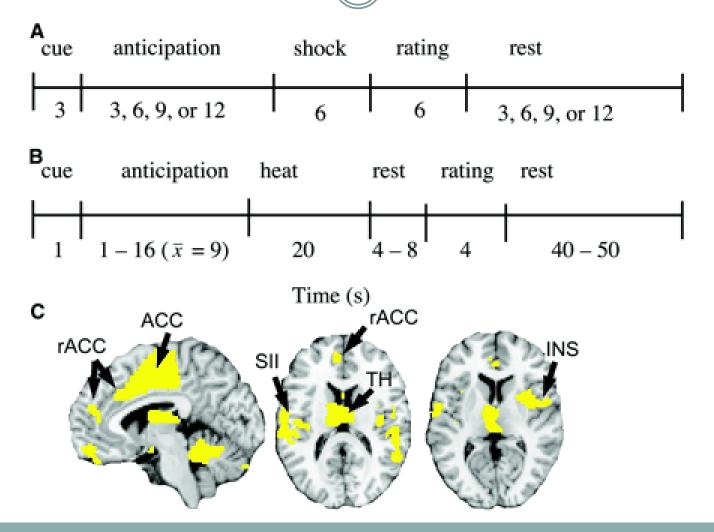
M CATHERINE BUSHNELL MCGILL UNIVERSITY

How is placebo effect created? 1. Before conditioning 2. Before conditioning response response Food Salivation Tuning fork No salivation Unconditioned Unconditioned Neutral No conditioned stimulus stimulus response response 4. After conditioning 3. During conditioning response response Food Salivation Tuning fork Salivation Tuning fork Unconditioned Conditioned Conditioned stimulus response response

Expectation

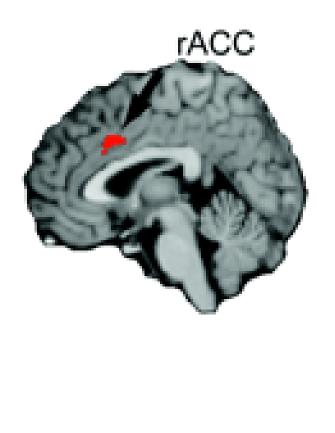
Conditioning

Imaging placebo analgesia

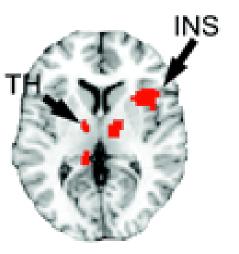


Wager et al 2004 *Science*

Imaging placebo analgesia



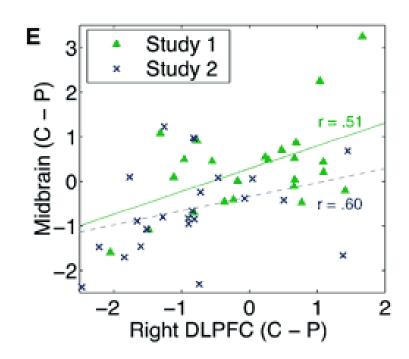
Placebo reduces painevoked activity in ACC, insula and thalamus



Wager et al 2004 Science

Imaging placebo analgesia

DLPFC Midbrain

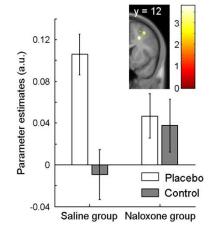


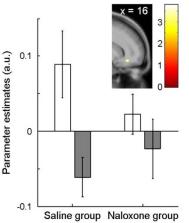
Placebo increased prefrontal and midbrain activity in anticipation of pain

Wager et al 2004 Science

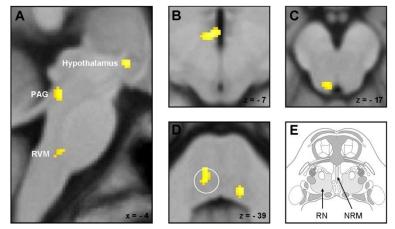
Naloxone disrupts rACC-PAG functional connectivity

DLPFC and rACC active during placebo



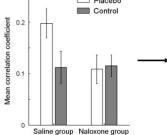


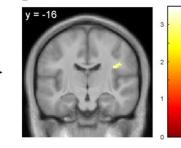
Mid-brain and brainstem activations

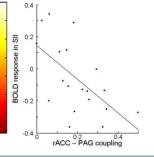


rACC-PAG functional connectivity disrupted by naloxone

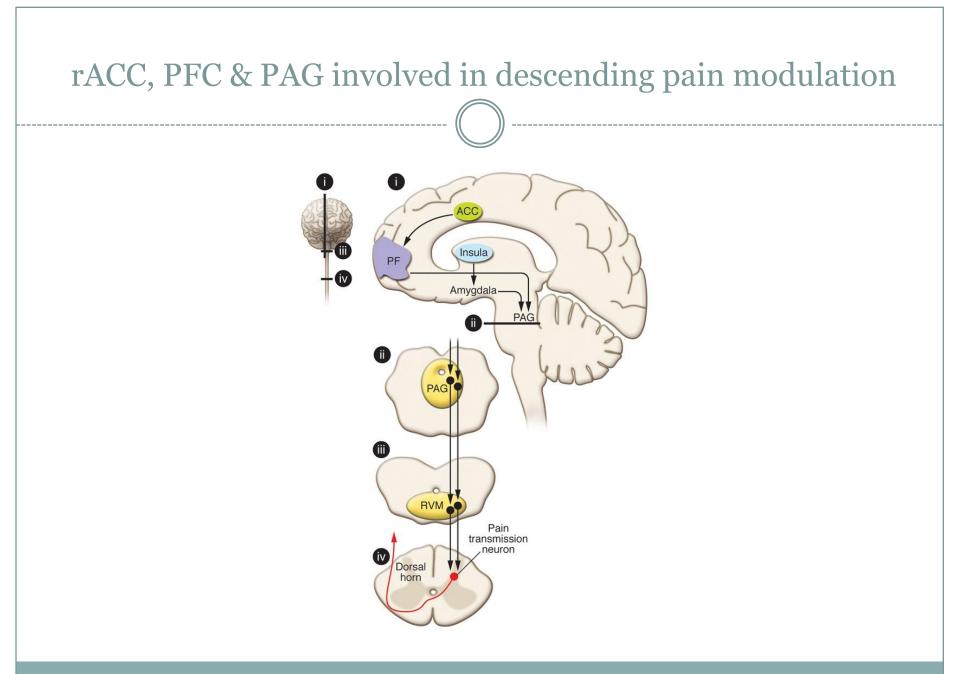








Eippert et al 2009 Neuron

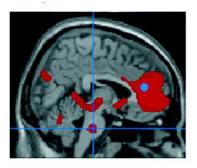


Schweinhardt and Bushnell, J. Clin. Investigation, 2010.



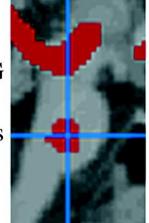
Both opiates and expectation-induced placebo activate rACC-brainstem circuit

Pain + opiate

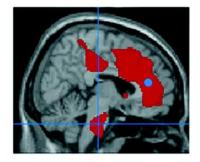


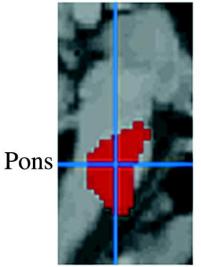
PAG

Pons



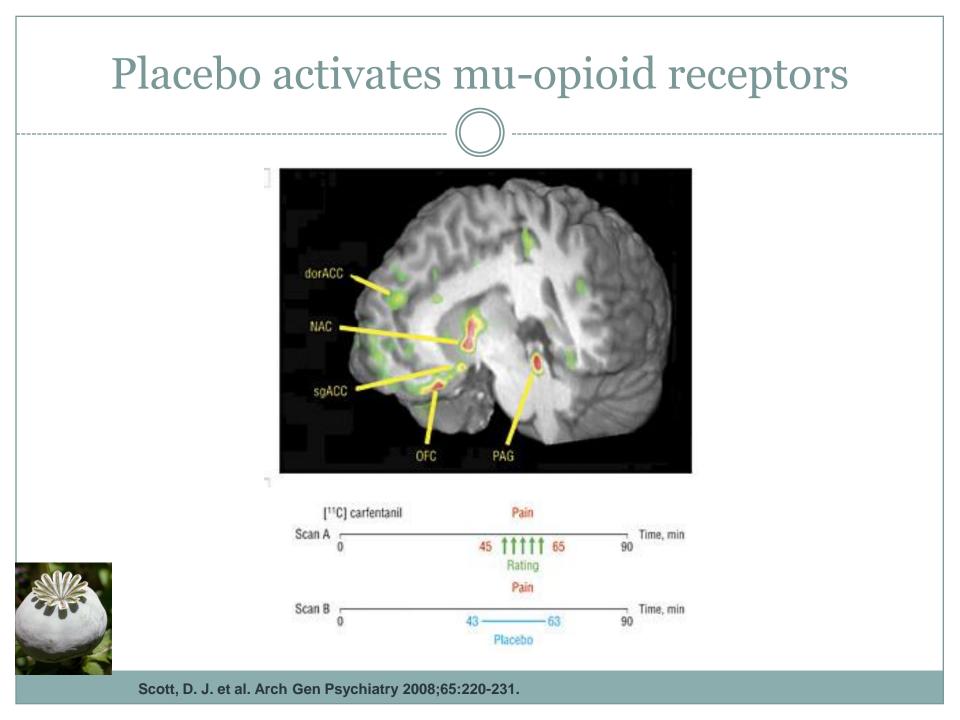
Pain + placebo





Petrovic et al 2002

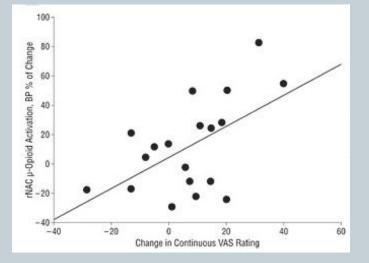


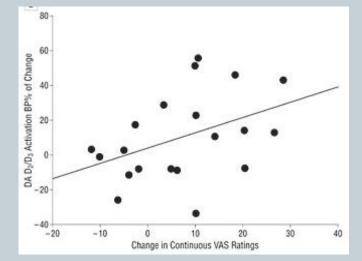


Placebo activates dopamine D2/D3 receptors A CAU NAC PUT [¹¹C] raclopride Pain Scan A Time, min 65 0 45 90 Rating Pain Scan B Time, min 43--63 0 90 Placebo

Scott, D. J. et al. Arch Gen Psychiatry 2008;65:220-231.

Placebo-induced opiate and dopamine activations related to analgesia



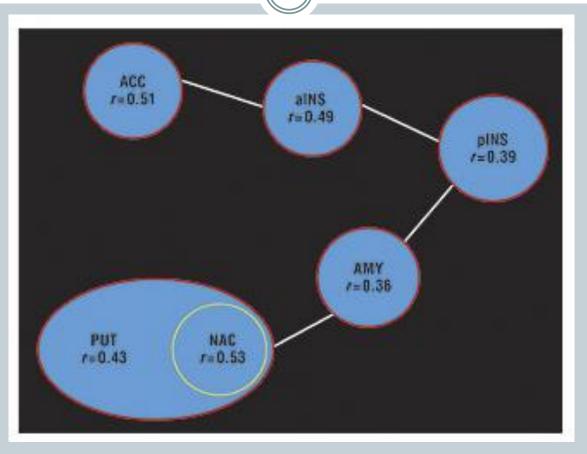






Scott, D. J. et al. Arch Gen Psychiatry 2008;65:220-231.

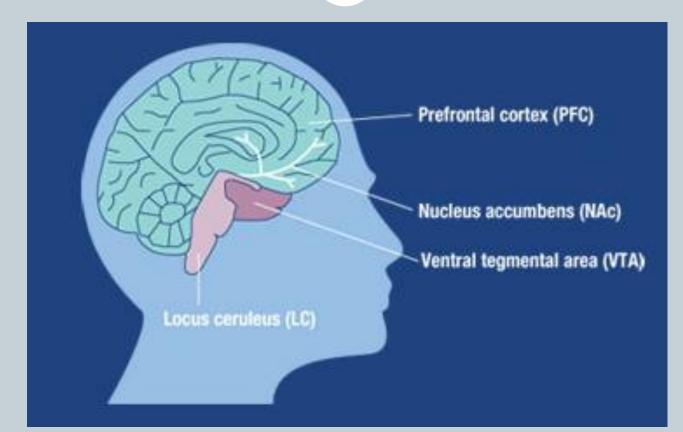
Imaging allows us to look at how opiate and dopamine systems may work together in producing placebo effect



Correlation between placebo-related dopamine activation in nucleus acumbens and opiate activations

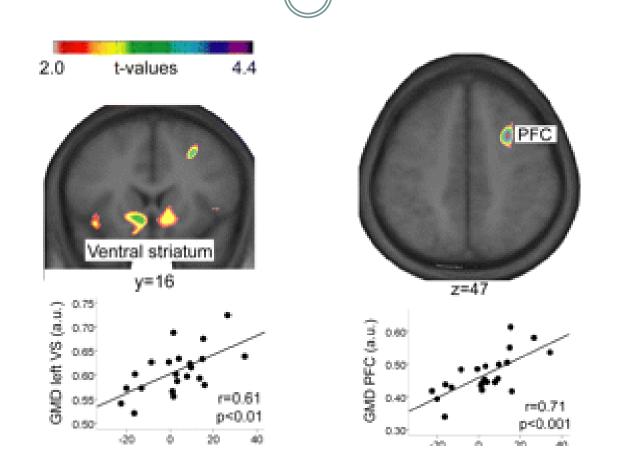
Scott, D. J. et al. Arch Gen Psychiatry 2008;65:220-231.

Anticipation of clinical benefit may be a type of reward anticipation



Placebo effect may involve dopamine mesolimbic reward system

Anatomical imaging shows that magnitude of placebo analgesia correlates with gray matter density in parts of reward system



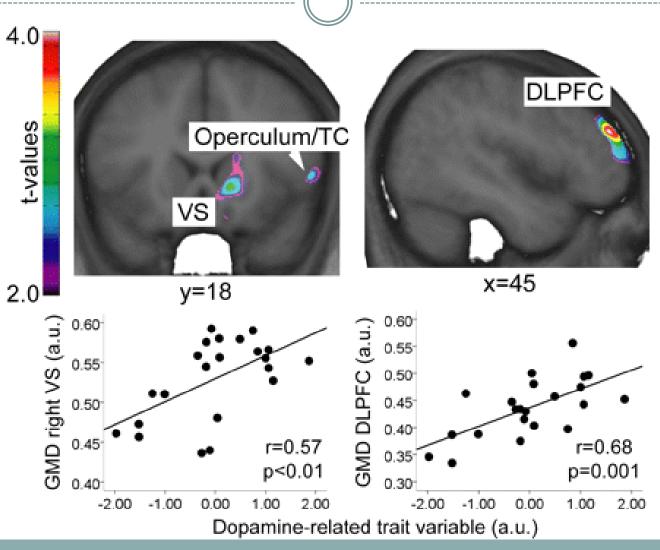
Placebo analgesic response (AUC, %)

Schweinhardt, P. et al. J. Neurosci. 2009;29:4882-4887

Dopamine-related traits explain ~30% of the variance of placebo-induced analgesia

- Traits related to dopamine neurotransmission:
 - Novelty seeking
 - Behavioral drive
 - Fun seeking
 - Reward responsiveness
 - Harm avoidance (negatively correlated)

Dopamine-related trait correlates with gray matter density in ventral striatum and prefrontal cortex



Schweinhardt, P. et al. J. Neurosci. 2009;29:4882-4887

Summary

- Functional MRI reveals that expectation-related placebo analgesia activates descending modulatory systems.
- PET imaging shows how both opiate and dopamine systems are involved in placebo analgesia.
- Anatomical imaging reveals that individuals high in dopamine-related traits may be better placebo responders.