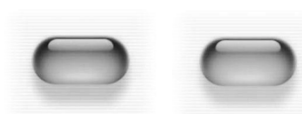

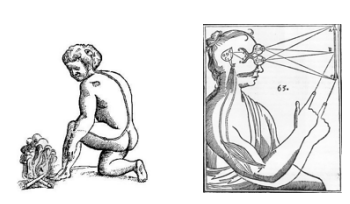


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Expectations, Beliefs
and the origins of the Placebo effect

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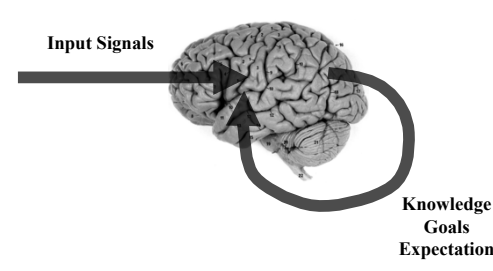
René Descartes

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Salvador Dalí

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Input Signals

Knowledge
Goals
Expectation

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Prof. Richard Gregory, University of Bristol

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Placebo effect

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Placebo effect

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Same underlying mechanism?

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Expectations

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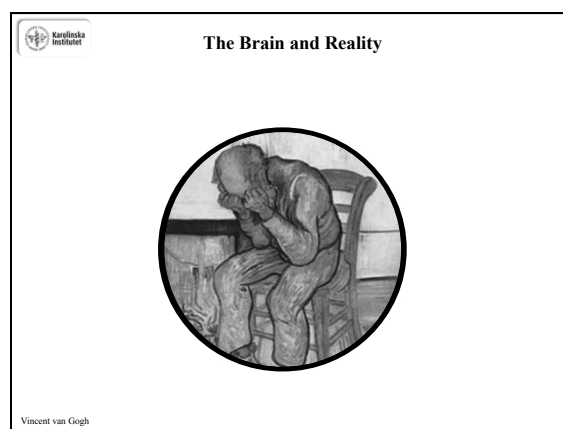
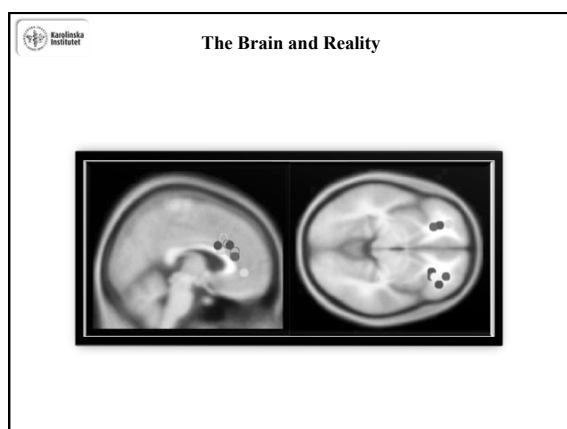
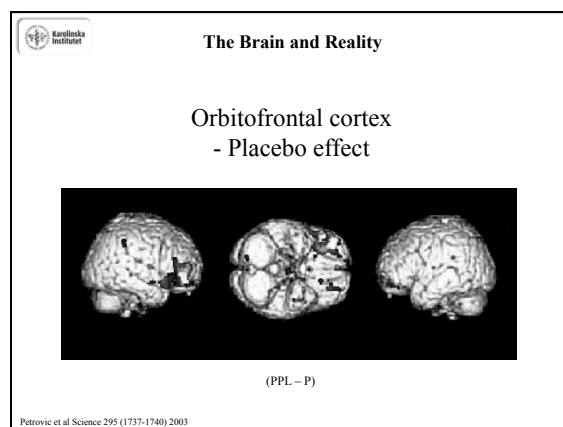
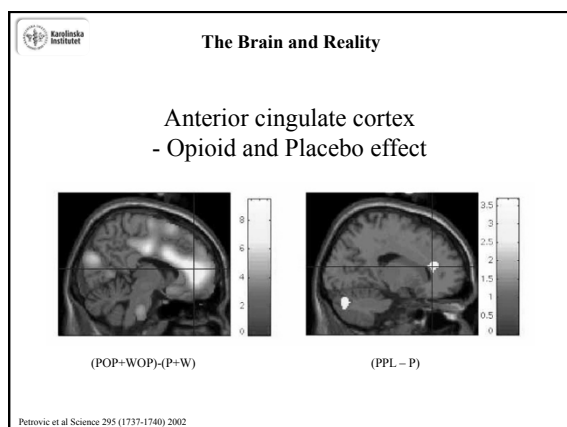
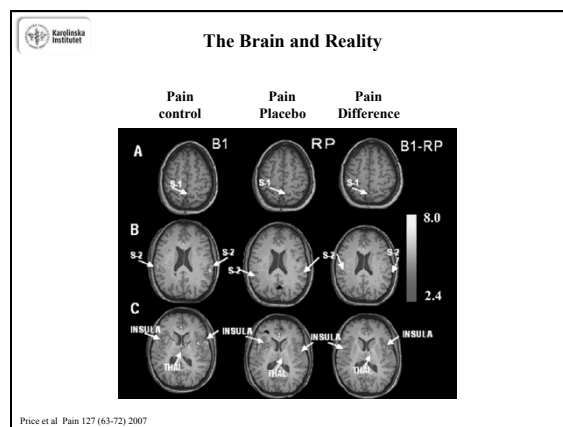
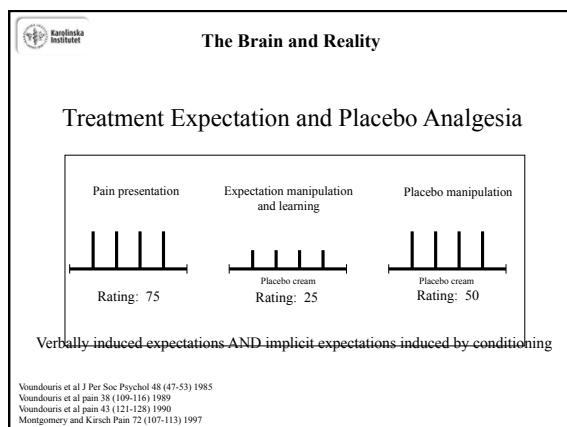
Frida Kahlo

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The opioidsystem and placebo analgesia

Naloxon
(opioid-receptorblocker)

Levine et al. The Lancet 2 (654-657) 1978



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Study of Emotional Placebo

International Affective Picture System (IAPS)

Petrovic et al Neuron 46, (957-969) 2005

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Study of Emotional Placebo

Day 1 – expectation modulation

Unpleasantness rating

Petrovic et al Neuron 46, (957-969) 2005

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Study of Emotional Placebo

Day 2 – The brain and the placebo effect

Unpleasantness rating

Petrovic et al Neuron 46, (957-969) 2005

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Study of Emotional Placebo

Decreased emotional processing in placebo condition

Placebo dependent increased activity

Unpleasantness processing

Placebo decrease in unpleasantness

Petrovic et al Neuron 46, (957-969) 2005

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Rostral anterior cingulate cortex

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Opioid- and Placebo analgesia

(POP+WOP)-(P+W)

(PPL - P)

Petrovic et al Science 295 (1737-1740) 2003

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Petrovic et al Science 295 (1737-1740) 2003

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Cortical opioid system

Anterior cingulate cortex

Willloch et al 1999

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Opioid receptor imaging of Placebo Analgesia

Placebo Effect

Z scores and BP

RACing DLPPC
Ins NAcc
NAcc RACing
Ins

Zubieta et al Journal of Neuroscience, 25 (7754-7762) 2005

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POP PPL P Naloxone

Regression analysis

Fields et al Nature Reviews Neuroscience 2004
Petrovic et al Science 295 (1737-1740) 2002
Eippert et al Neuron 63 (533) 2009

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Anterior Cingulate and Attention

Emotional Stroop Task

Cognitive task
Emotional task

Congruent Incongruent

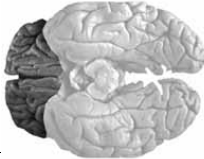
rACC

Bush et al Journal of Neuroscience, 4 (215-225) 2000
Etkin et al Neuron 21 (871-882) 2006

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rACC in placebo analgesia:
Interaction between attentional processes and opioid system

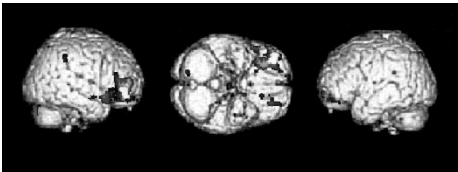
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Orbitofrontal cortex

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Orbitofrontal cortex

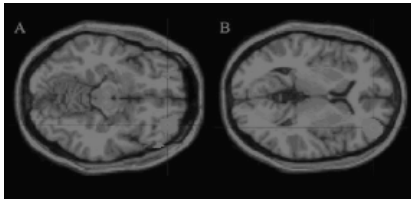


(PPL - P)

Petrovic et al Science 295 (1737-1740) 2003

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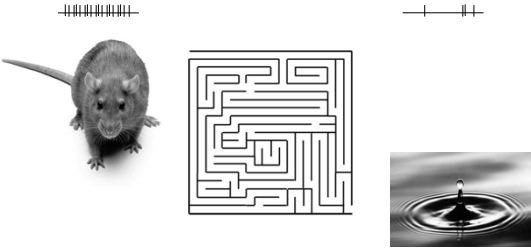
Placebo analgesia vs. opioid analgesia



Petrovic et al Pain 150 (59-65) 2010

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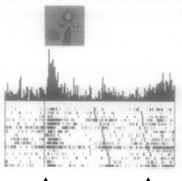
Motivational and homeostatic goals in Obfc



Schoenbaum Neuron 47 (633-636) 2005

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Expected reward and Obfc

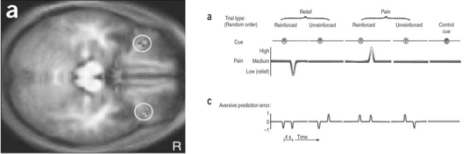


Reward expectation Reward

Tremblay and Schultz Progress in brain research 126 (193-215) 2000

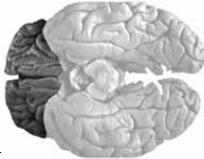
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Aversive error-signal



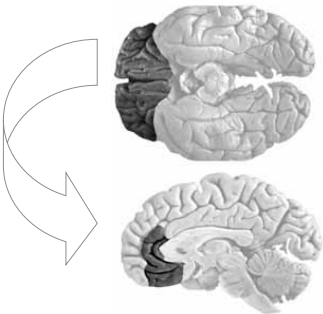
Seymour et al Nature Neuroscience 8 (1234-1240) 2005

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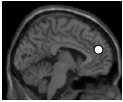


Orbitofrontal cortex in placebo analgesia:
Cognitive processes including emotional goals, expectations, emotional tracking and aversive error signals.

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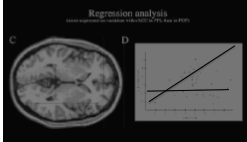


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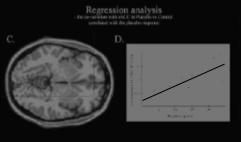


rACC-ROI
used in the
PPI
correlation

Placebo analgesia (PET-study)



Emotional placebo (fMRI-study)

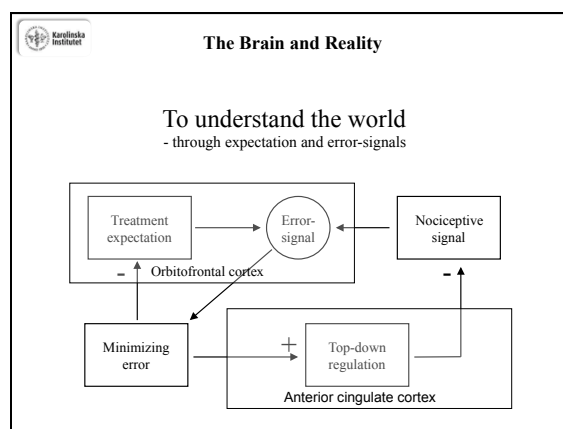
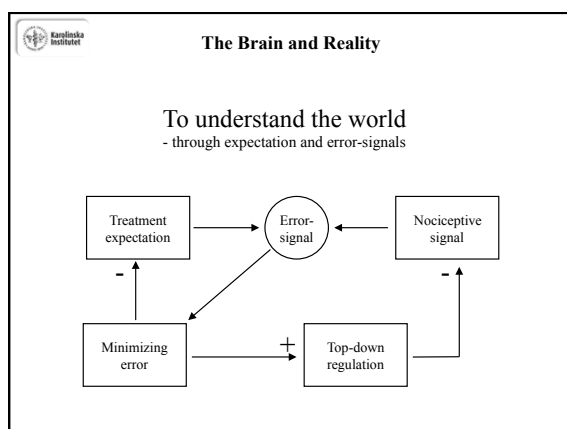


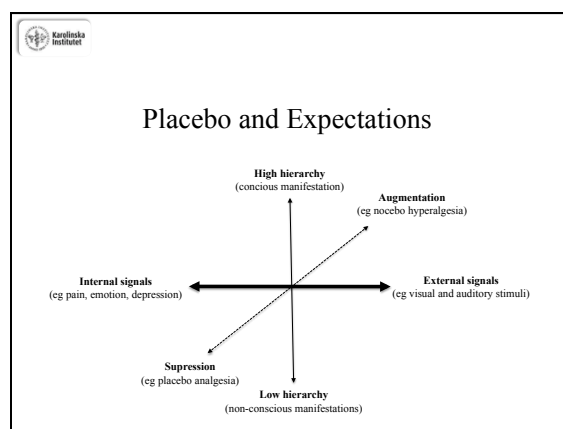
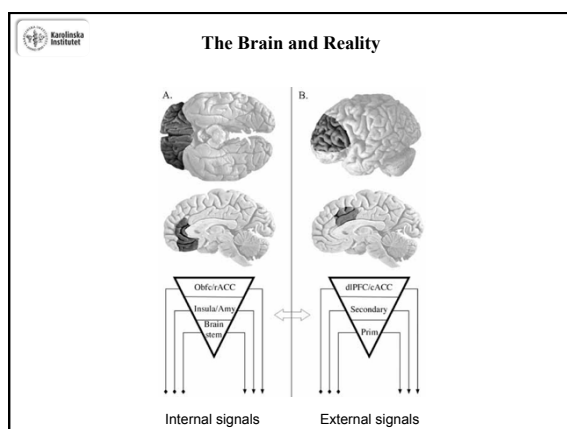
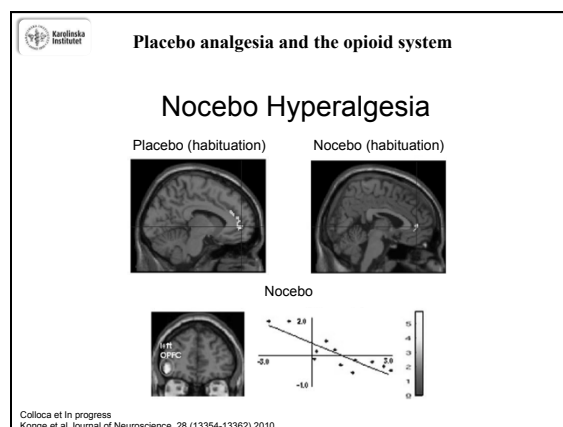
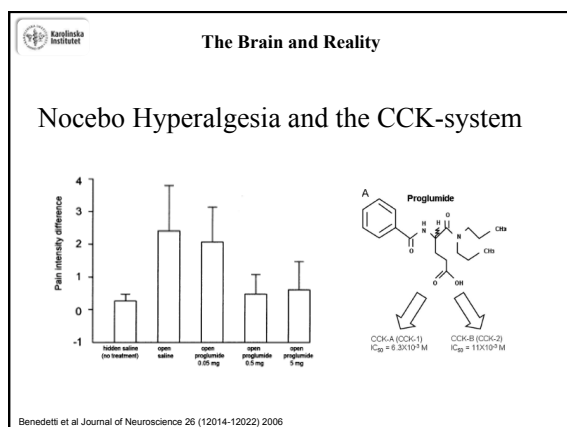
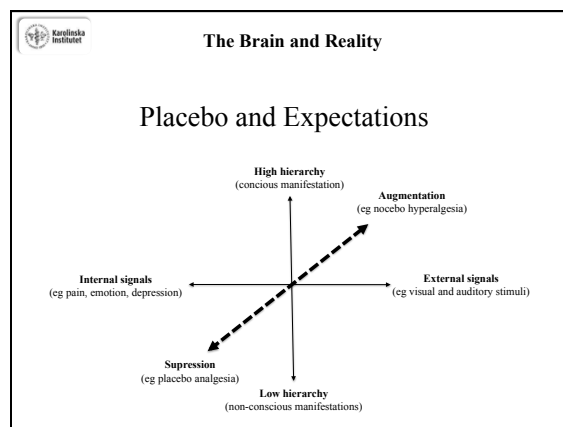
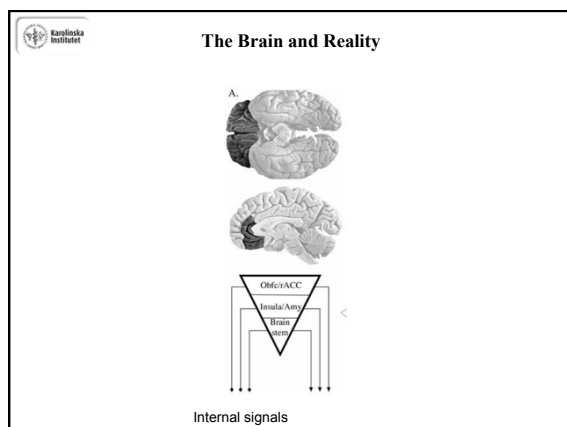
Petrovic et al Pain 150 (59-65) 2010

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Why do we have the placebo effect ?

Hypothesis: The placebo effect is just a consequence of a system trying to understand and predict the world.





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Magic glasses

Phase	Condition	Left (Dark)	Right (Light)
Baseline start	no glasses	~0.8	~0.8
	glasses	~0.4	~1.2
Learning	no glasses	~1.2	~0.4
	glasses	~0.8	~1.2
Test	no glasses	~0.8	~1.2
	glasses	~1.2	~0.8
Baseline end	no glasses	~0.8	~0.8
	glasses	~0.8	~0.8

Sterzer, Frith and Petrovic Current Biology 18 (697-8) 2008

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Complex associative learning - Expectations and error-signals

Turner et al Cerebral Cortex 14(872-880) 2004

The Brain and Reality

Schizophrenia and expectations / error signals

Corlett et al Brain 130 (2387-2400) 2007

The Brain and Reality

Placebo and Expectations

High hierarchy (conscious manifestation)
 Low hierarchy (non-conscious manifestations)
 Internal signals (eg pain, emotion, depression)
 External signals (eg visual and auditory stimuli)
 Suppression (eg placebo analgesia)
 Augmentation (eg nocebo hyperalgesia)

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Placebo and Conditioning effects

Amanzio et al Journal of Neuroscience 19 (484-494) 1999

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Placebo and Conditioning effects

Benedetti et al Journal of Neuroscience 23 (4315-4323) 2003

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Placebo and Conditioning effects

Benedetti et al Journal of Neuroscience 23 (4315-4323) 2003

Consciousness vs. Non-consciousness

T1 Conscious high strength and attention
 T2 Preconscious high strength, no attention
 T3 Subliminal weak strength

Dehaene et al TICS 10 (204-211) 2006

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Lower cortical areas
 Synaptic plasticity
 $\mu_{ij}^L = -\alpha_{ij} \xi^L \xi^L$

Higher cortical areas
 Synaptic gain
 $\mu_{ij}^H = \beta_{ij} \alpha_{ij} [\xi^L - \mathbb{I}(\mu_{ij}^H)]$

Friston Nature Reviews Neuroscience 11 (127-138) 2010

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De La Fuente-Fernandez and Stessel TINS 25 (302-306) 2002
 Pollo and Benedetti Progress in Brain Research 175 (283-294) 2009

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Midbrain dopamine system

Reward processing, expectations and error signaling.

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Placebo och Amphetamine

Boileau et al Journal of Neuroscience 27 (3998-4003) 2007

The Brain and Reality

Opioid and Dopamine involvement in placebo analgesia

Scott et al Arch Gen Psychiatry 65 (220-231) 2008

Placebo and Expectations

High hierarchy (conscious manifestation)
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 Augmentation (eg nocebo hyperalgesia)

