

# Mechanisms of the placebo response

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# OVERVIEW

Definition

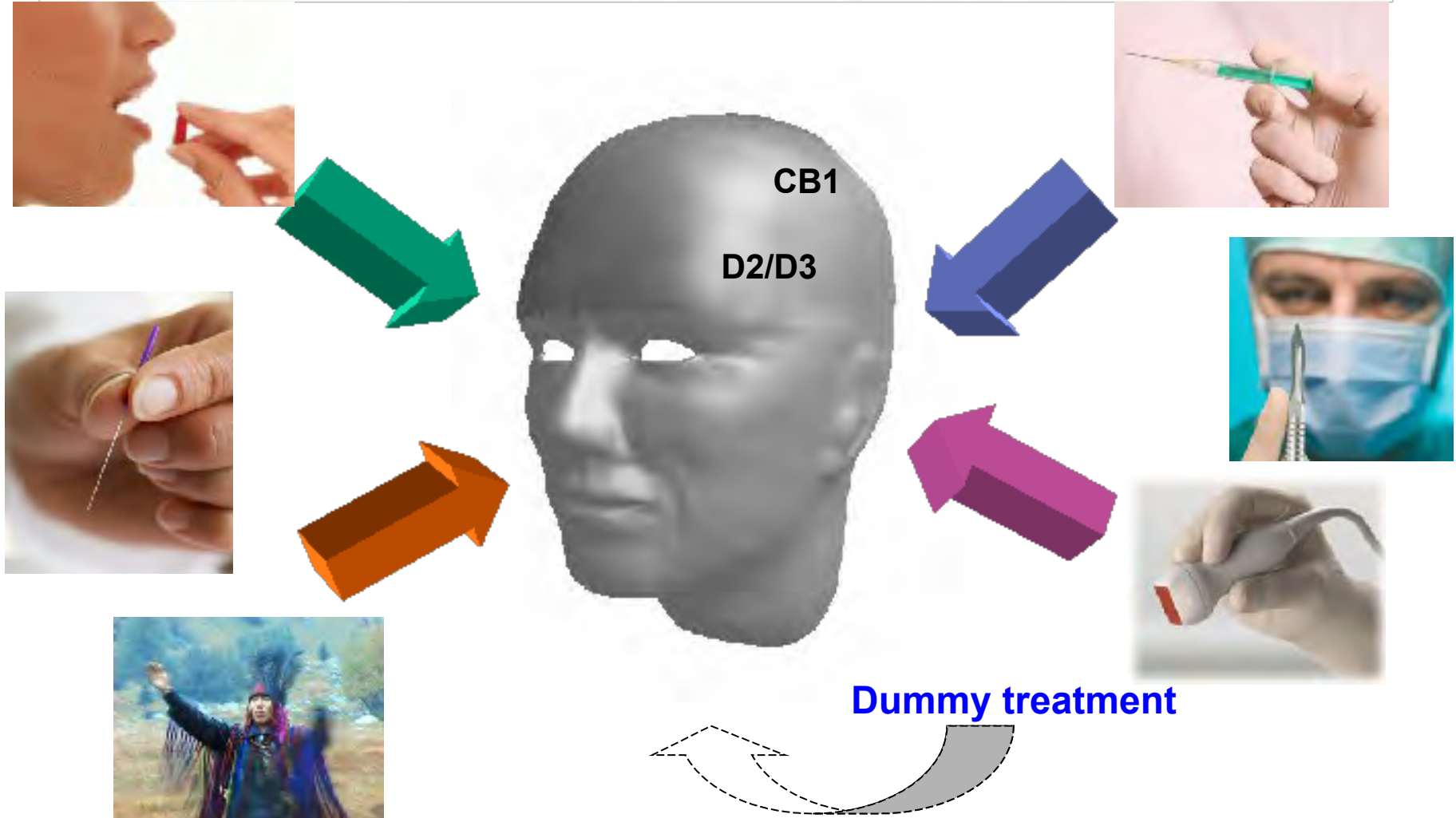
Mechanisms in pain

Mechanisms in Parkinson's disease

Why are there responders and nonresponders?

Clinical implications

# Ritual of therapeutic act



<b>DISEASE/SYSTEM</b>	<b>MECHANISMS</b>
<b>Pain</b>	<b>Activation of endogenous opioids and dopamine (placebo). Activation of CCK and de-activation of dopamine (nocebo)</b>
<b>Parkinson's disease</b>	<b>Activation of dopamine in the striatum and changes in activity of neurons in basal ganglia and thalamus</b>
<b>Depression</b>	<b>Changes of electrical and metabolic activity in different brain regions, e.g. ventral striatum</b>
<b>Anxiety</b>	<b>Changes in activity of the anterior cingulate and orbitofrontal cortices. Genetic variants of serotonin transporter and tryptophane hydroxylase 2</b>
<b>Addiction</b>	<b>Changes of metabolic activity in different brain regions</b>
<b>Autonomic responses to DBS</b>	<b>Change of neuronal excitability in limbic regions</b>
<b>Cardiovascular</b>	<b>Reduction of <math>\beta</math>-adrenergic activity of heart</b>
<b>Respiratory</b>	<b>Conditioning of opioid receptors in the respiratory centres</b>
<b>Immune system</b>	<b>Conditioning of some immune mediators (e.g., IL-2, IFN-<math>\gamma</math>, lymphocytes)</b>
<b>Endocrine system</b>	<b>Conditioning of some hormones (e.g., growth hormone, cortisol)</b>
<b>Physical performance</b>	<b>Activation of endogenous opioids and increased muscle work</b>
<b>Alzheimer's disease</b>	<b>Prefrontal executive control and functional connectivity of prefrontal areas</b>

**Finniss, Kaptchuk, Miller and Benedetti (2010) *Lancet*, 375: 686-695**

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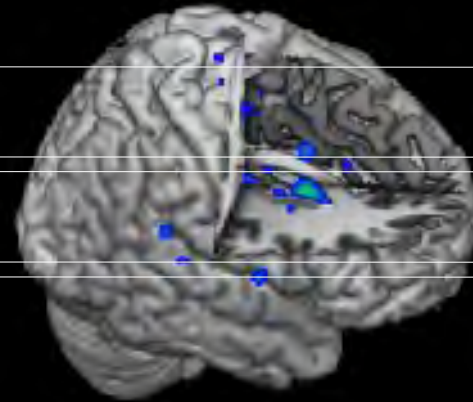
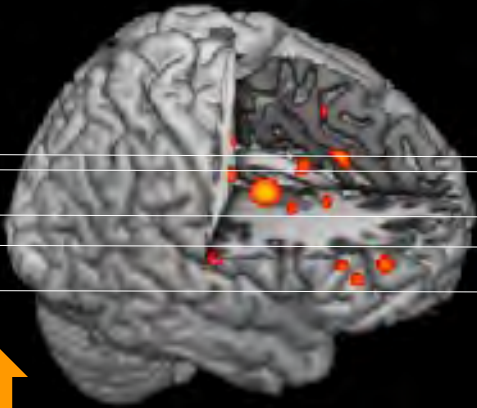
**Range of movement  
after thoracotomy**



**Placebo  
Analgesia**

**Placebo - Expectation**

**Pain**



**Activation**



**Inhibition**



**DLPFC**

**rACC**

**PAG**

**Inhibition**

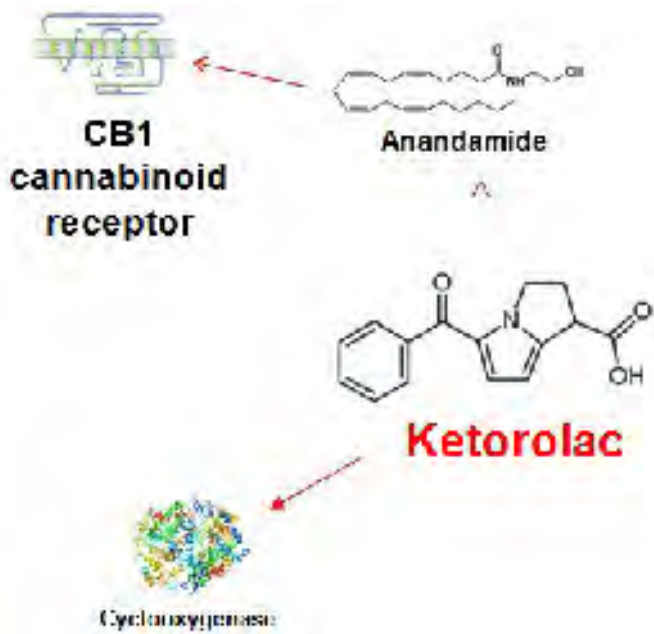
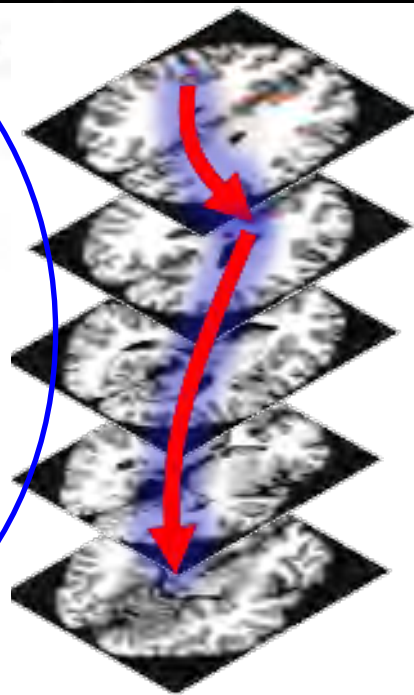
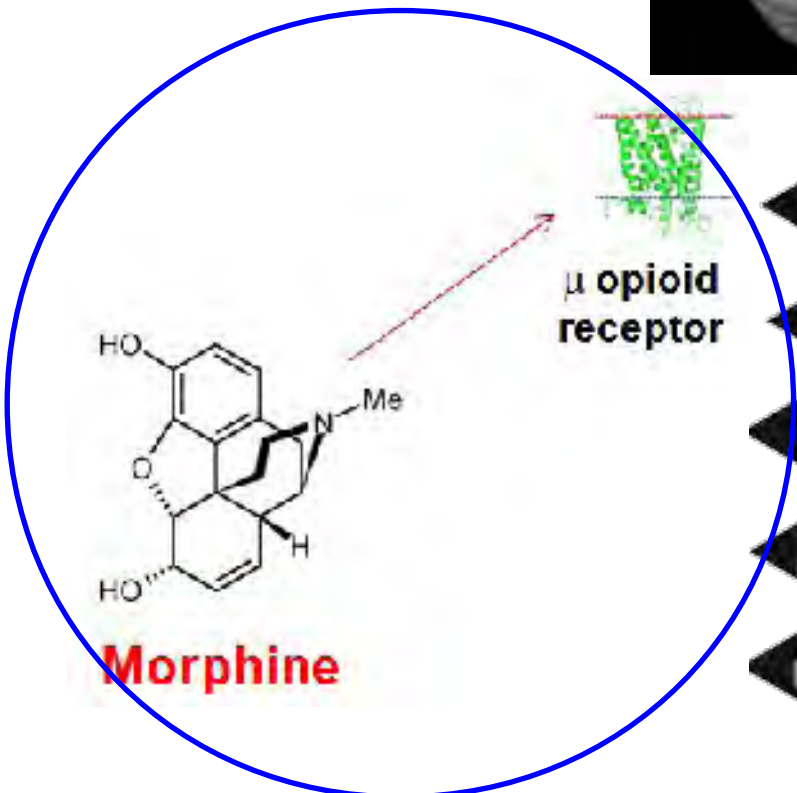
**PCC  
MCC**

**Caudate  
Thalamus**

**Putamen  
Insula**

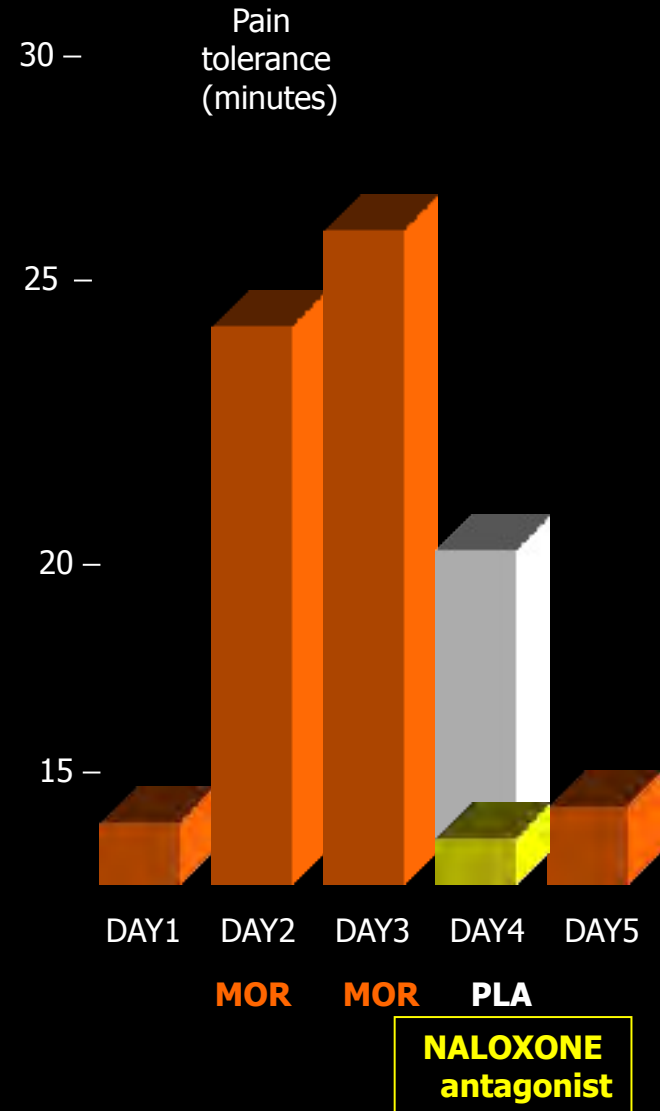
# Ritual of therapeutic act Psychosocial context

**Learning  
is crucial**



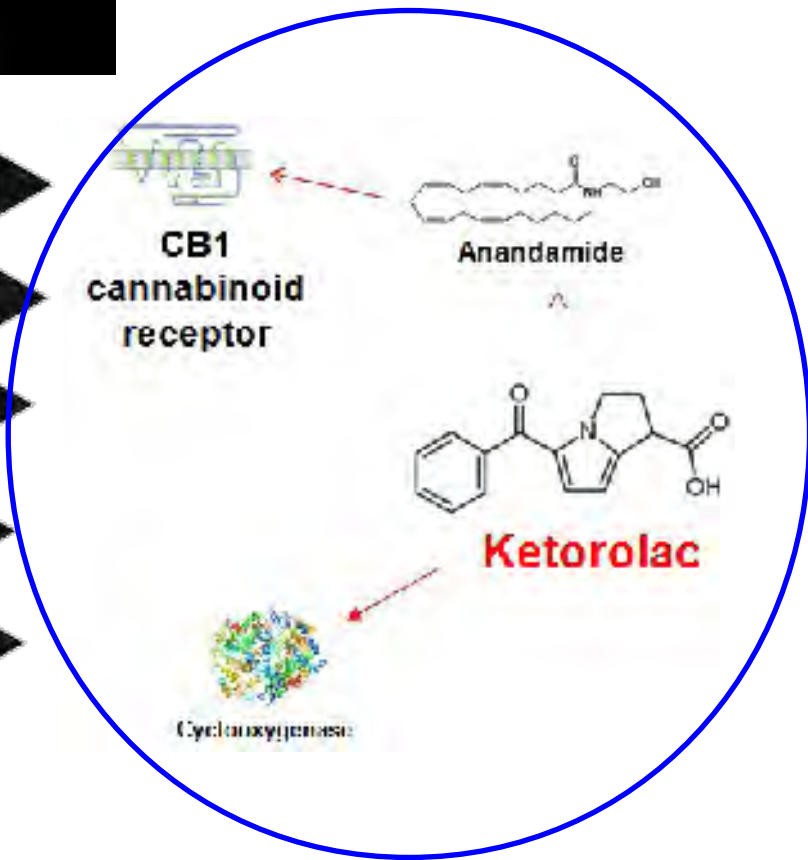
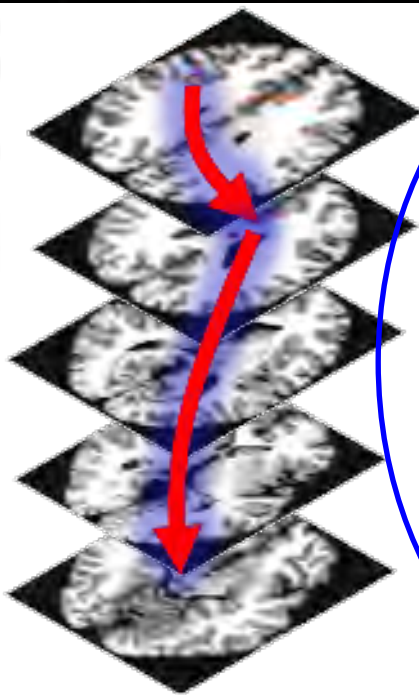


# Experimental ischemic arm pain





# Ritual of therapeutic act Psychosocial context



# Experimental ischemic arm pain

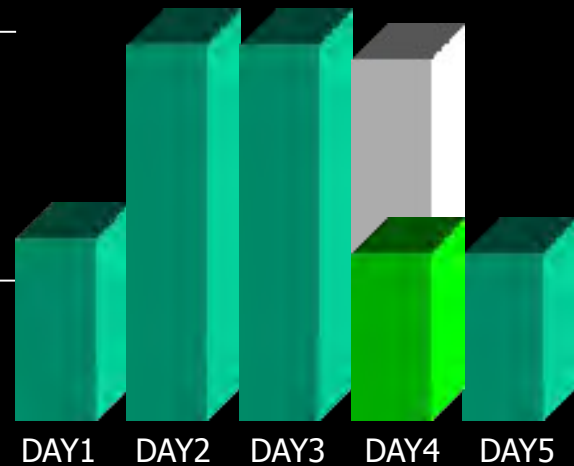


Pain  
tolerance  
(minutes)

20 –

15 –

10 –



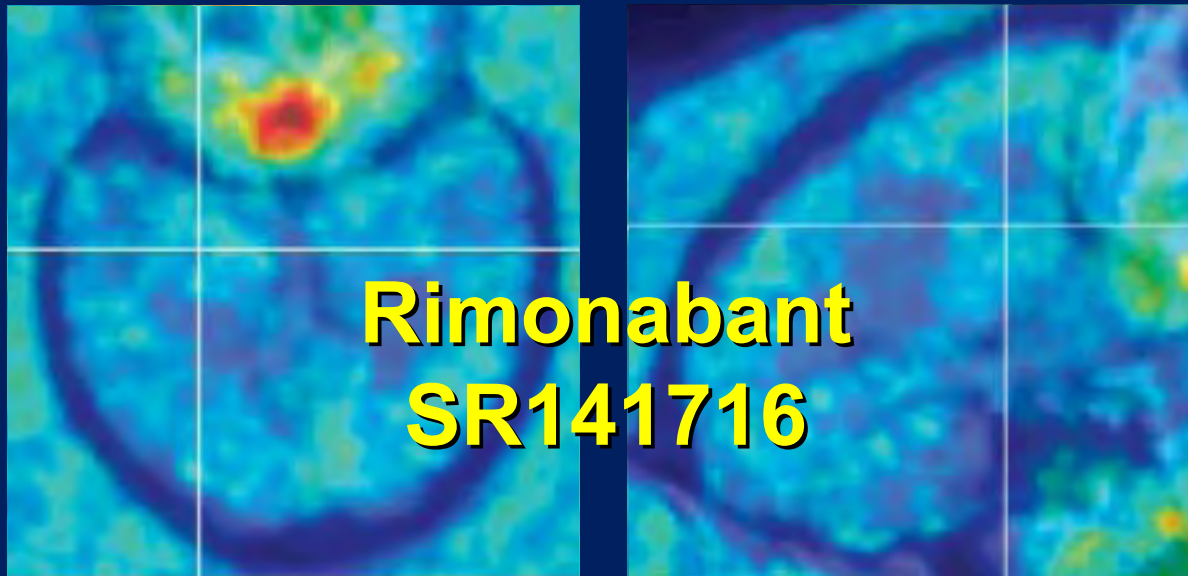
KET

KET

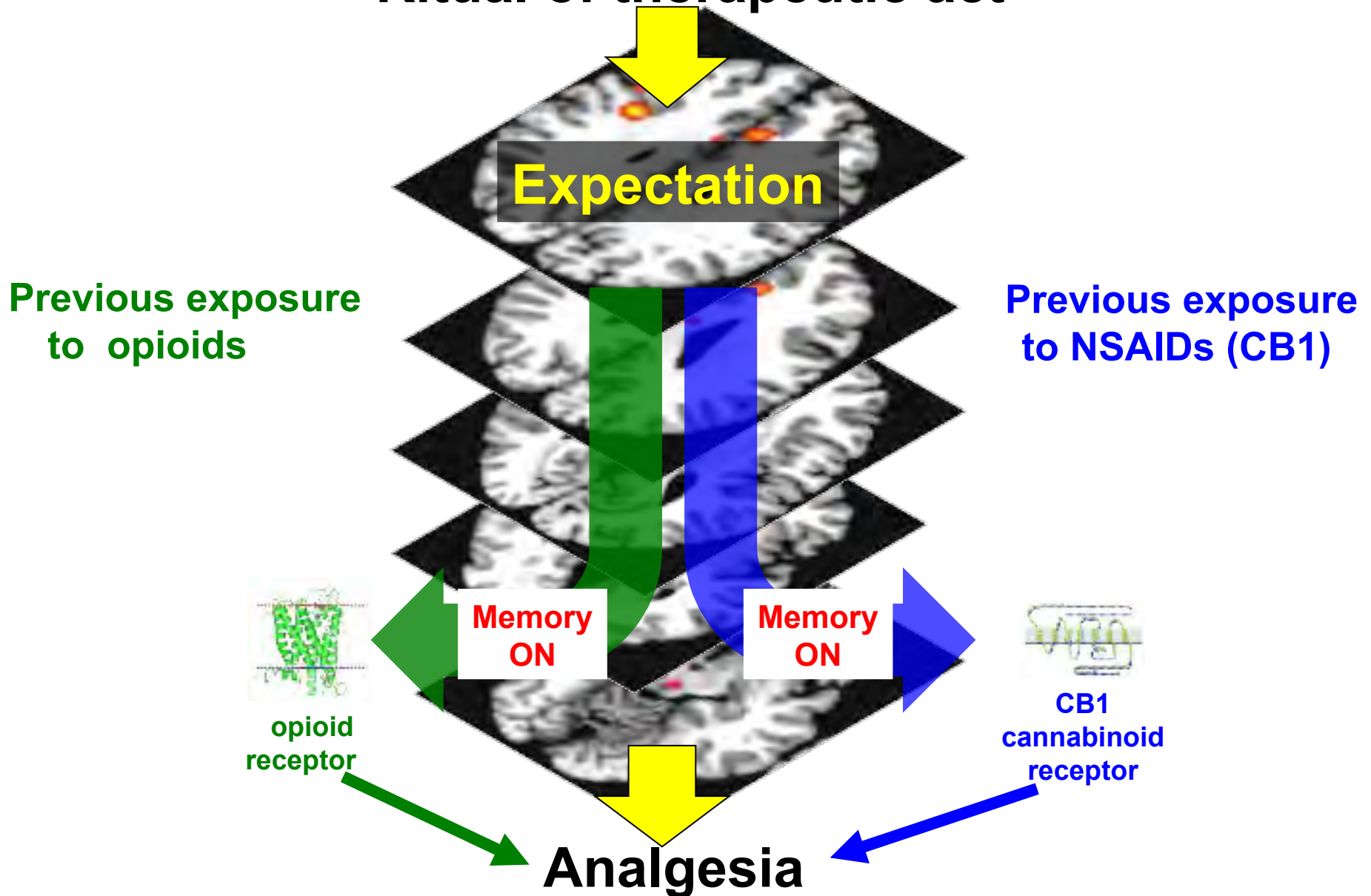
PLA

**RIMONABANT  
CB1 antagonist**

**CB1 cannabinoid receptors distribution with  $^{11}\text{C}$ -JHU75528 radiotracer  
in the baboon**



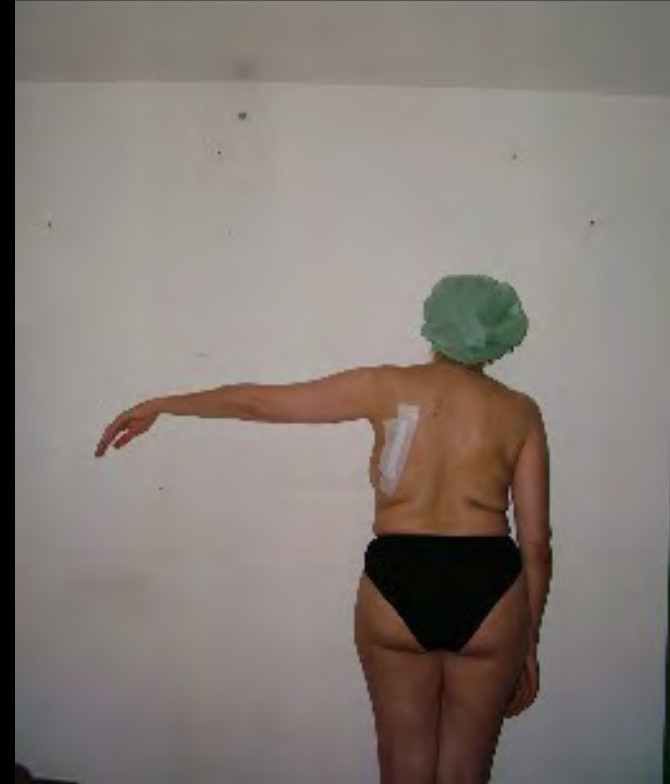
# Ritual of therapeutic act



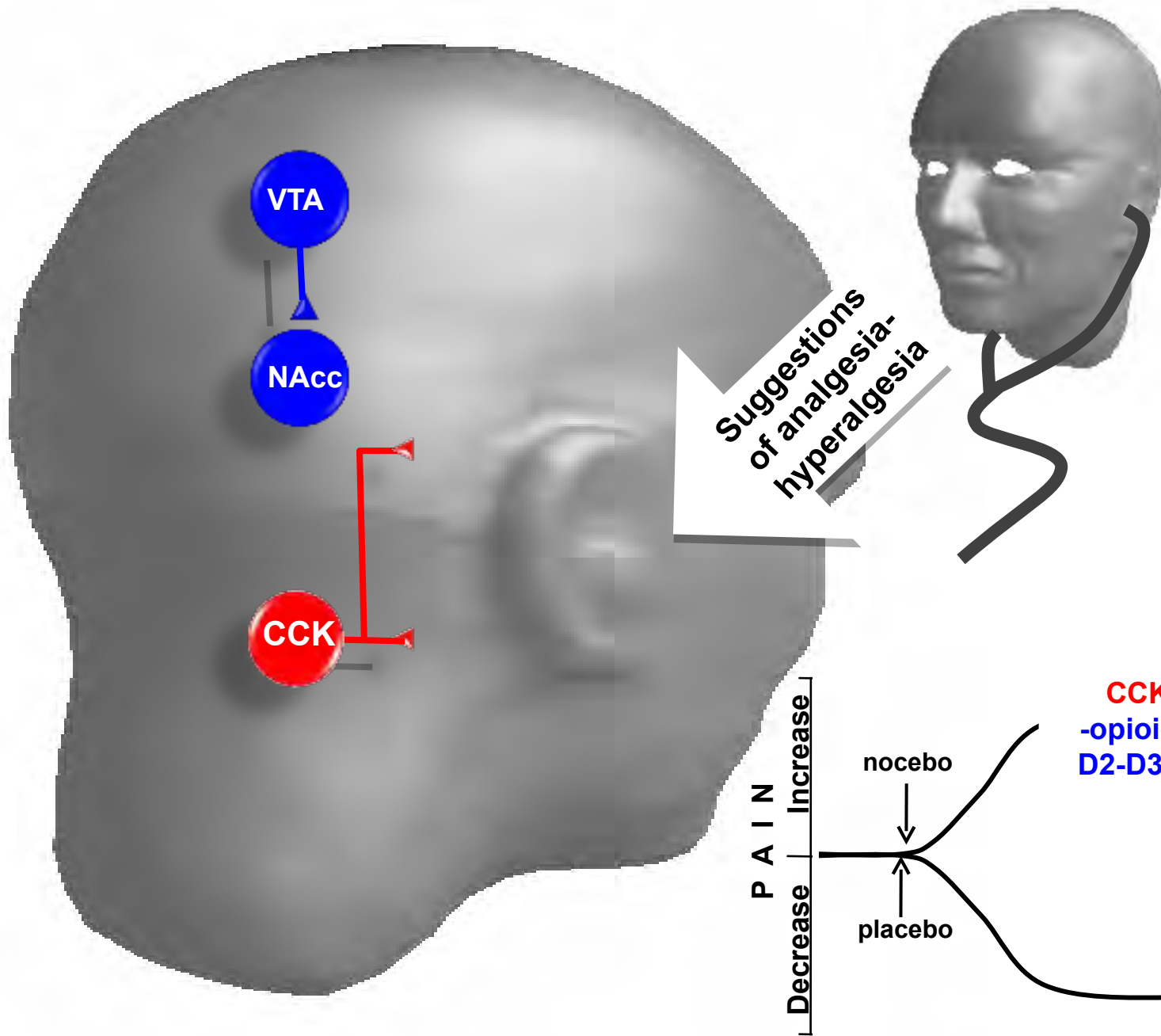




**Range of movement  
after thoracotomy**



**Nocebo  
Hyperalgesia**





# OVERVIEW

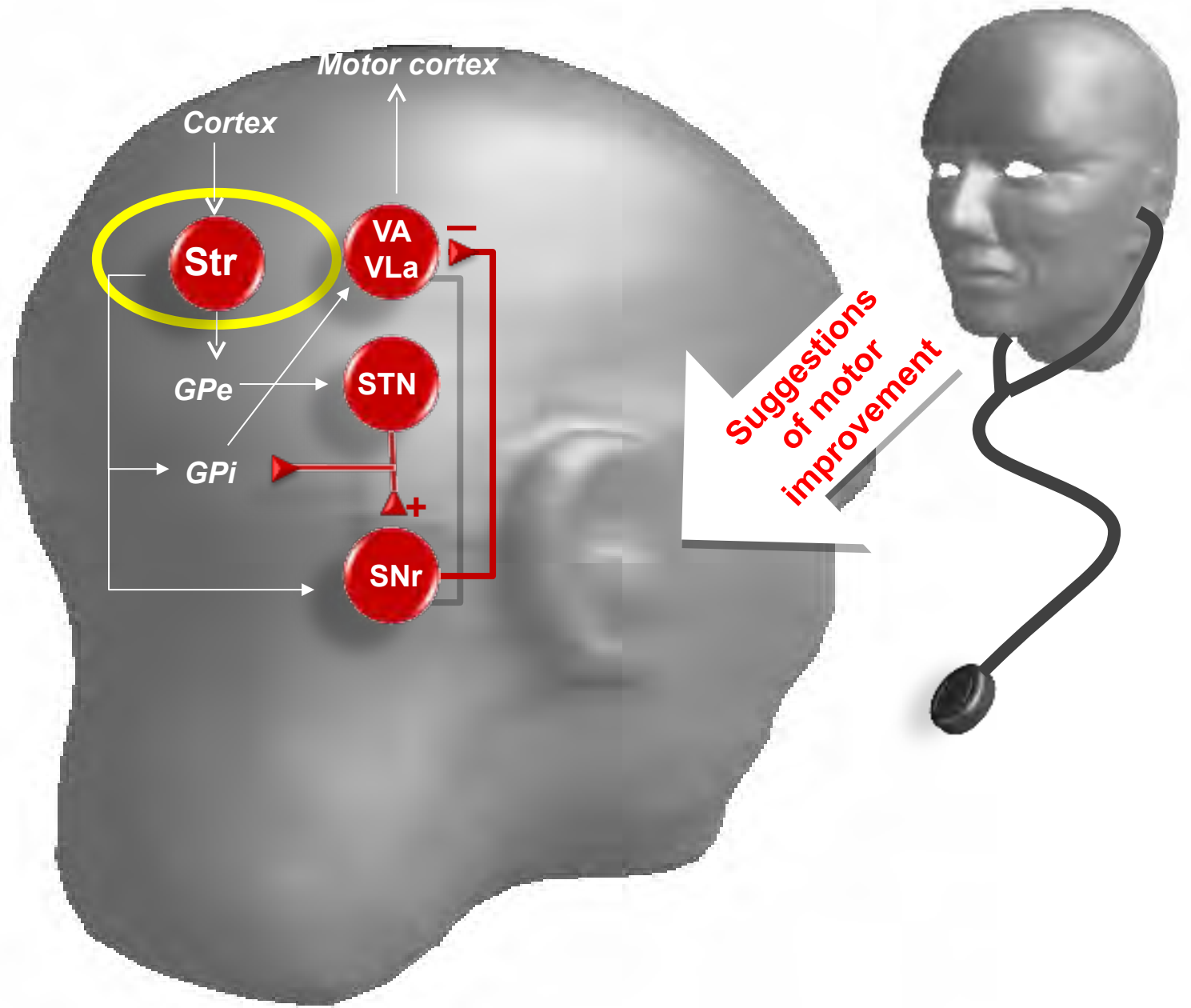
Definition

Mechanisms in pain

Mechanisms in Parkinson's disease

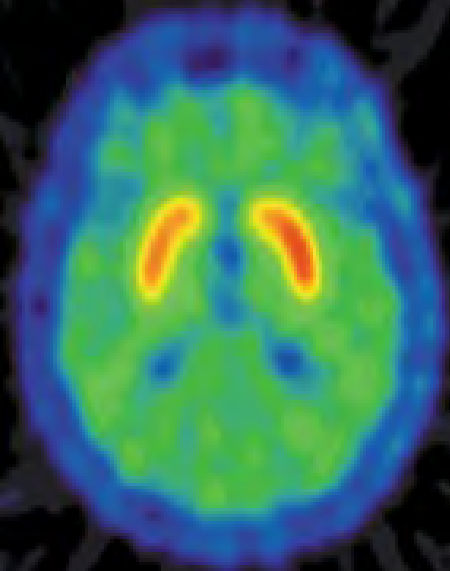
Why are there responders and nonresponders?

Clinical implications

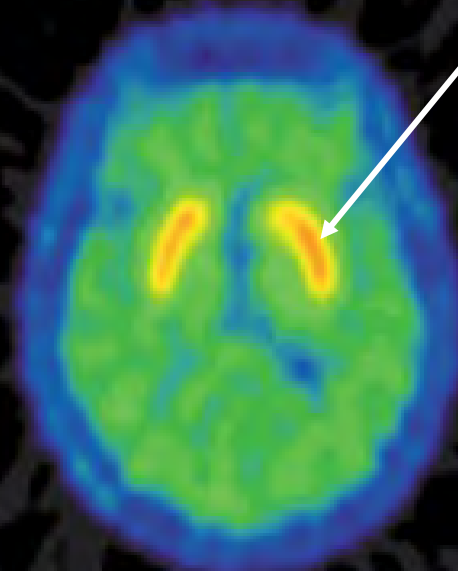




## Parkinson's disease

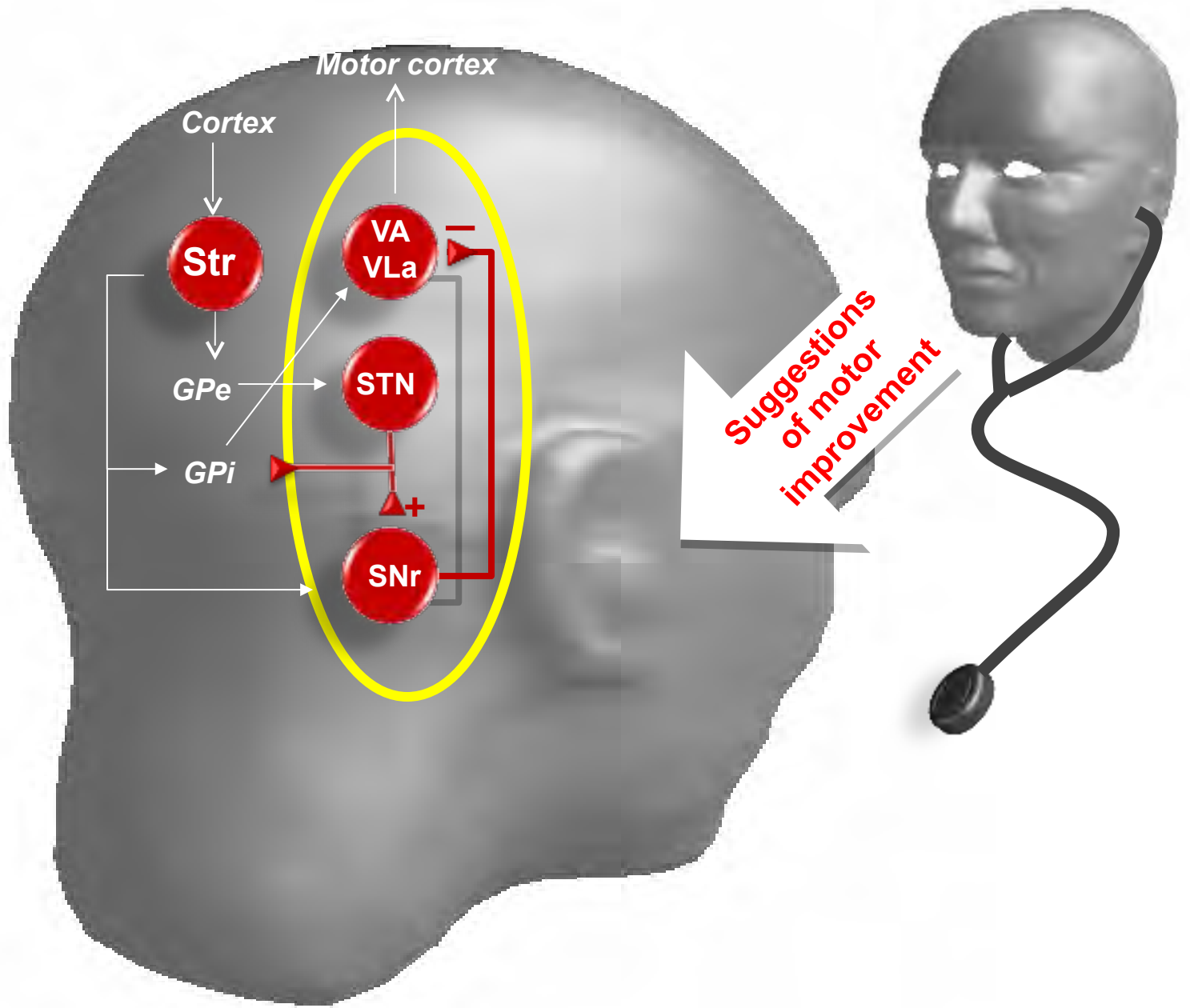


Baseline

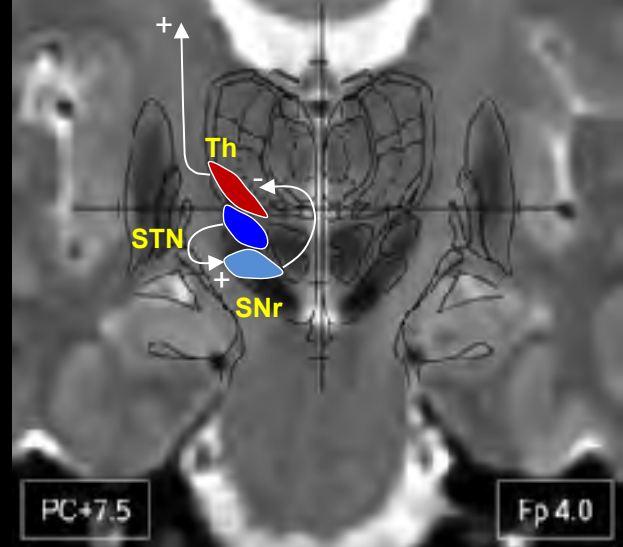
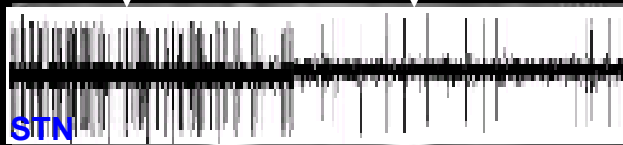
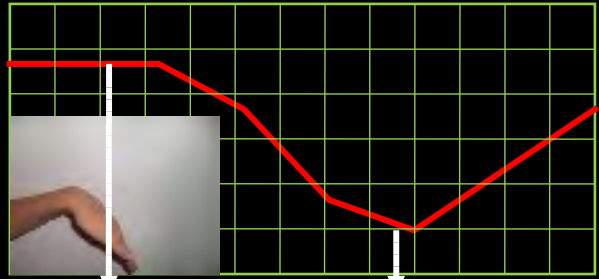


200% increase in  
dopamine =  
One dose of  
amphetamine

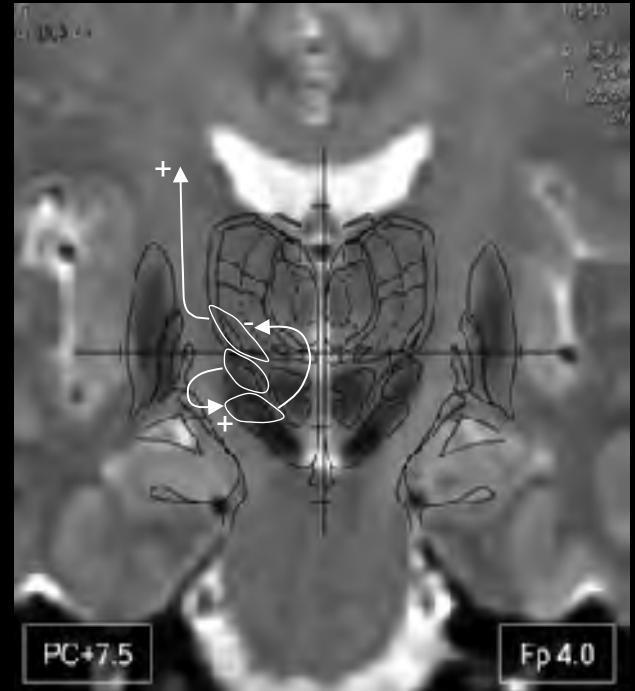
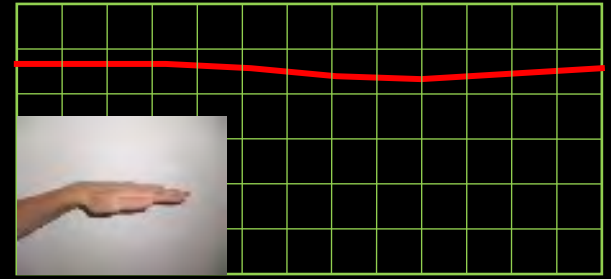
After placebo



**Placebo responder**



**Placebo non-responder**



decrease increase

$\frac{\text{pre} - \text{post}}{\text{pre}}$  Neuronal firing rate (Hz)

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Clinical implications

**PLACEBO  
(social stimuli)**



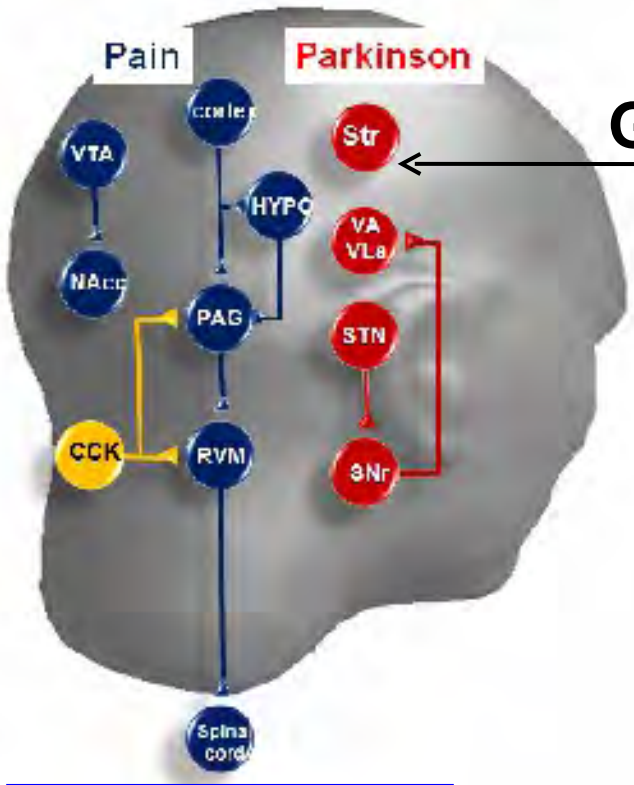
**Learning**



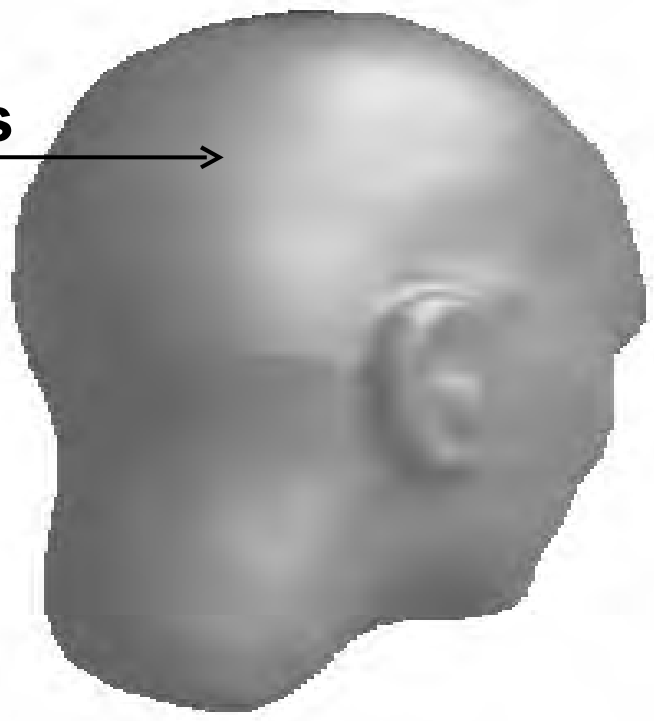
**PLACEBO  
(social stimuli)**



**Genetics**



**Placebo responders**



**Placebo non-responders**

# OVERVIEW

Definition

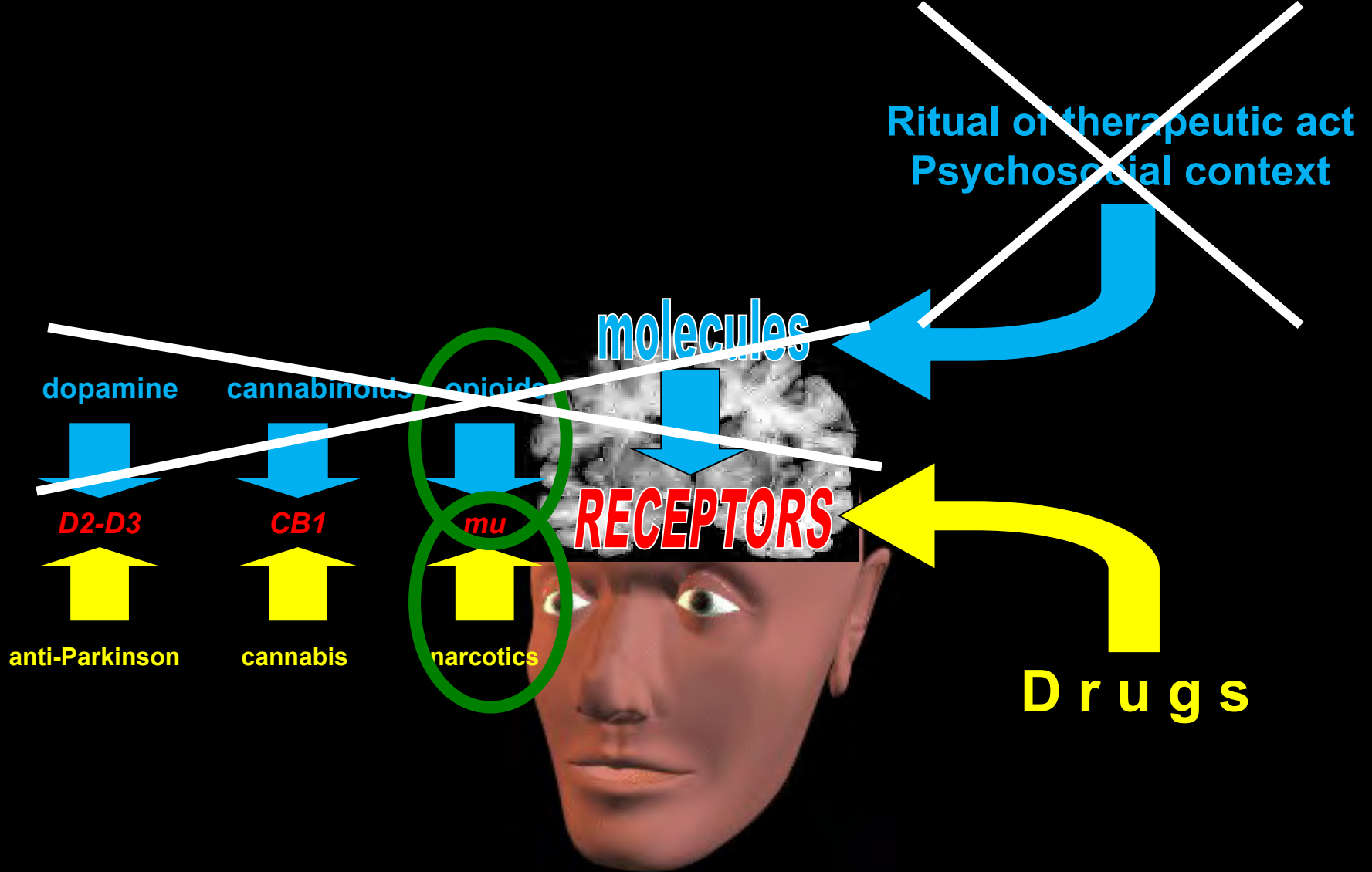
Mechanisms in pain

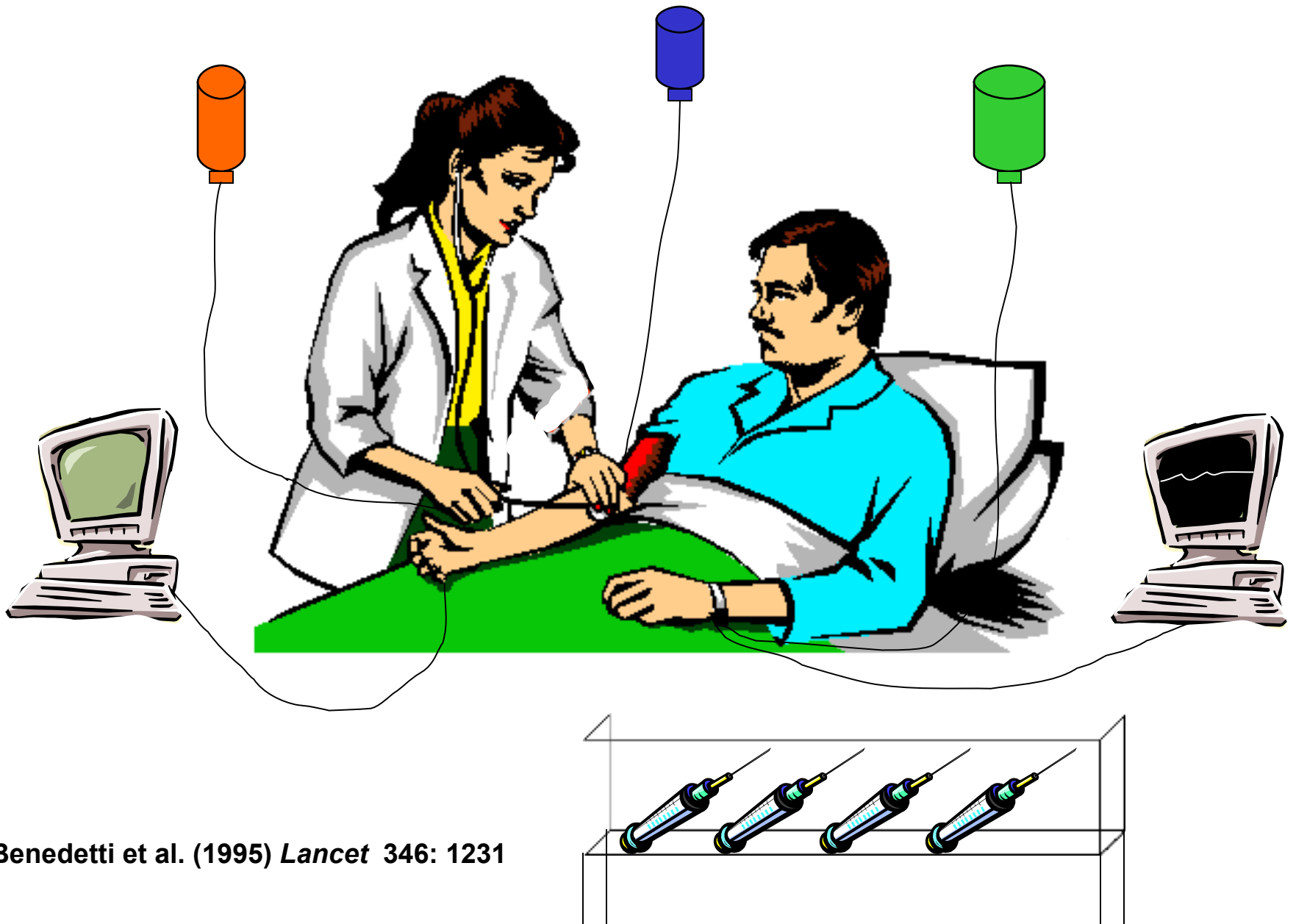
Mechanisms in Parkinson's disease

Why are there responders and nonresponders?

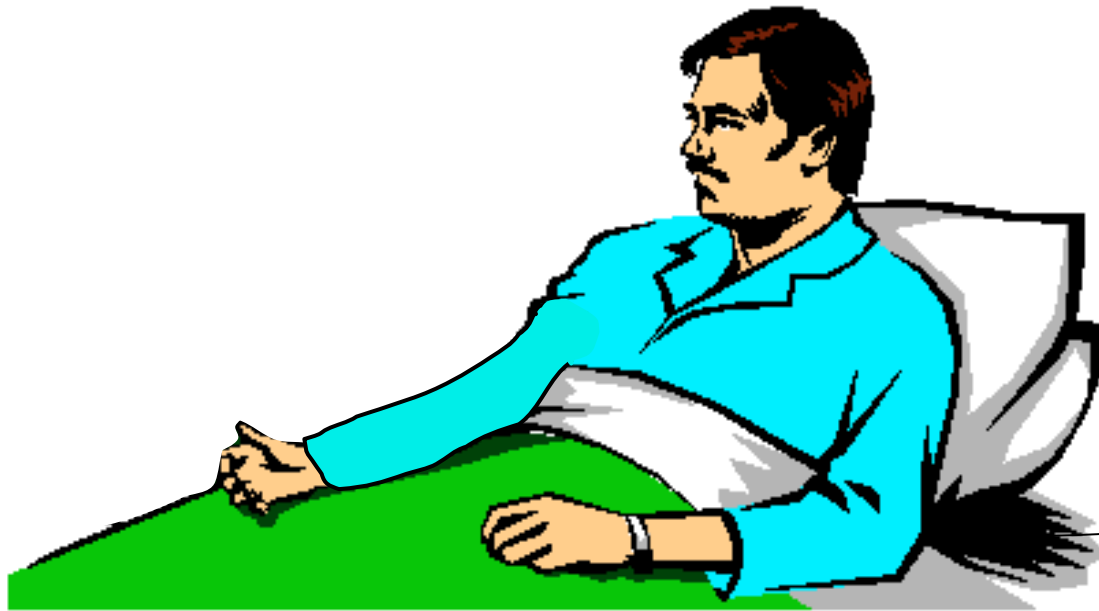
Clinical implications







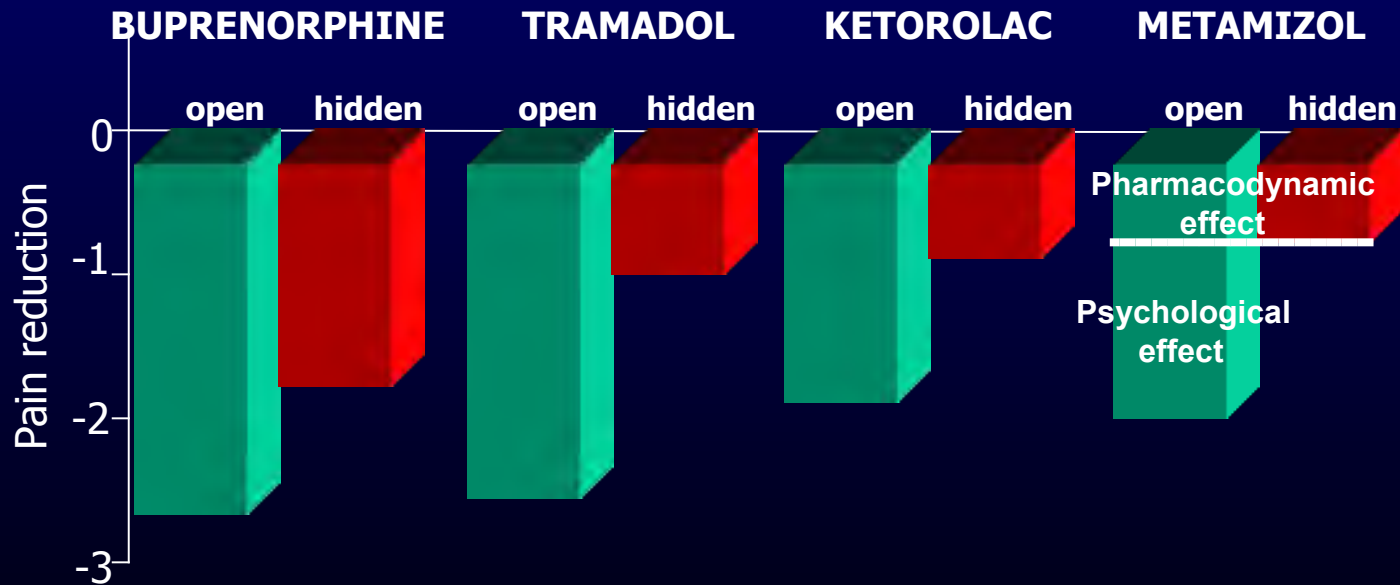
Benedetti et al. (1995) *Lancet* 346: 1231



hidden drug



computer



Amanzio et al (2001) *Pain* 90:205-15

Benedetti et al (1995) *Lancet* 346: 1231  
 Colloca et al (2004) *Lancet Neurol.* 3: 679-684

# TRIAL Met#2

(Colloca and Benedetti, *Nature Rev Neurosci* 6: 545-552, 2005)

Is metamizol (300 mg) effective in post-thymectomy pain?



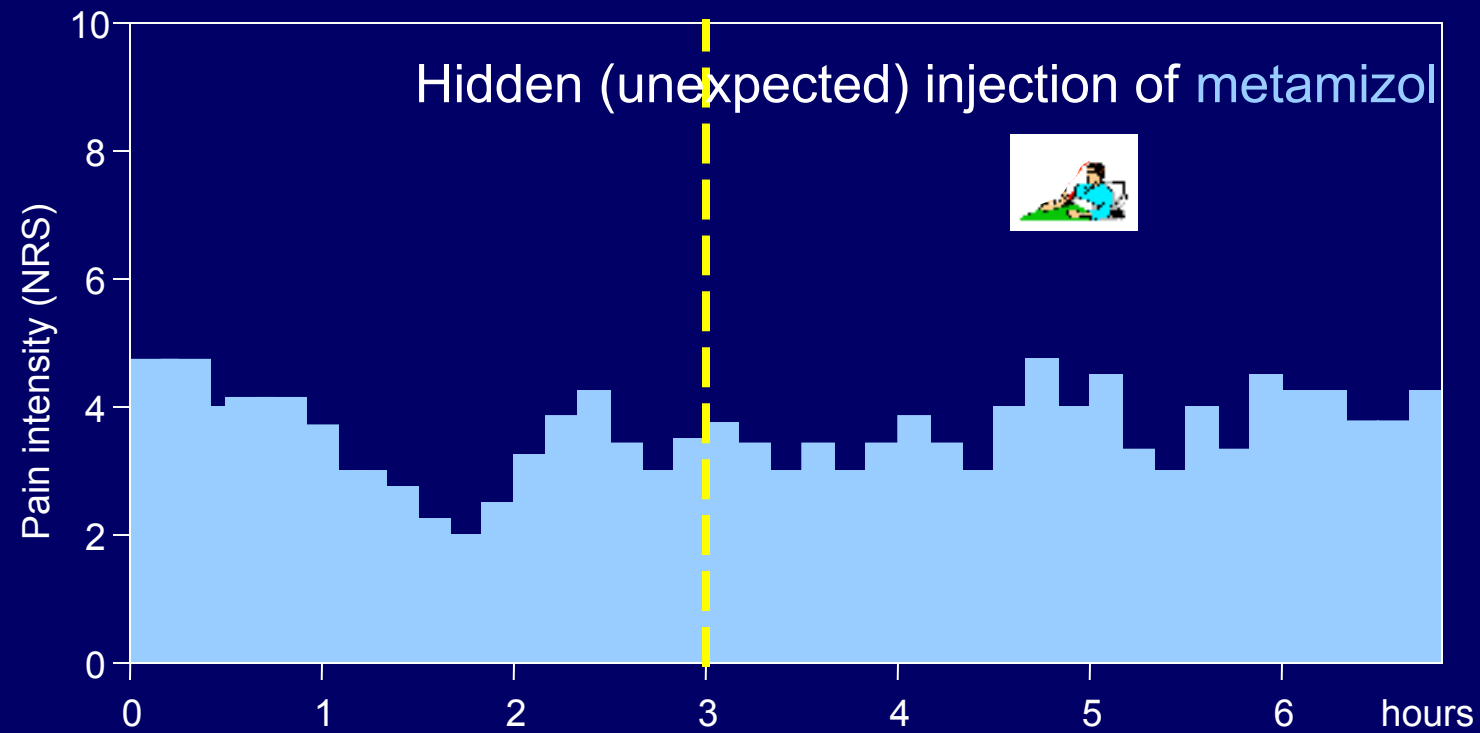
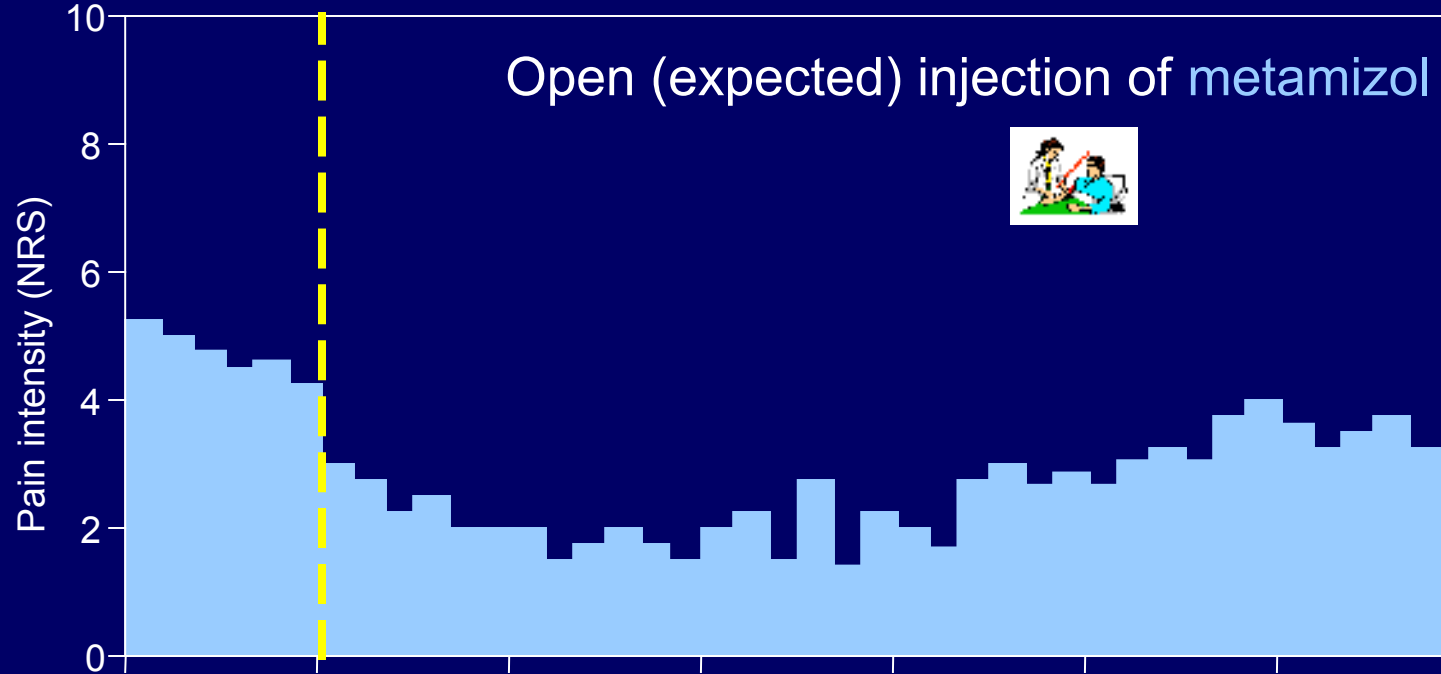
Open metamizol injection group (N=10)



Hidden metamizol injection group (N=10)

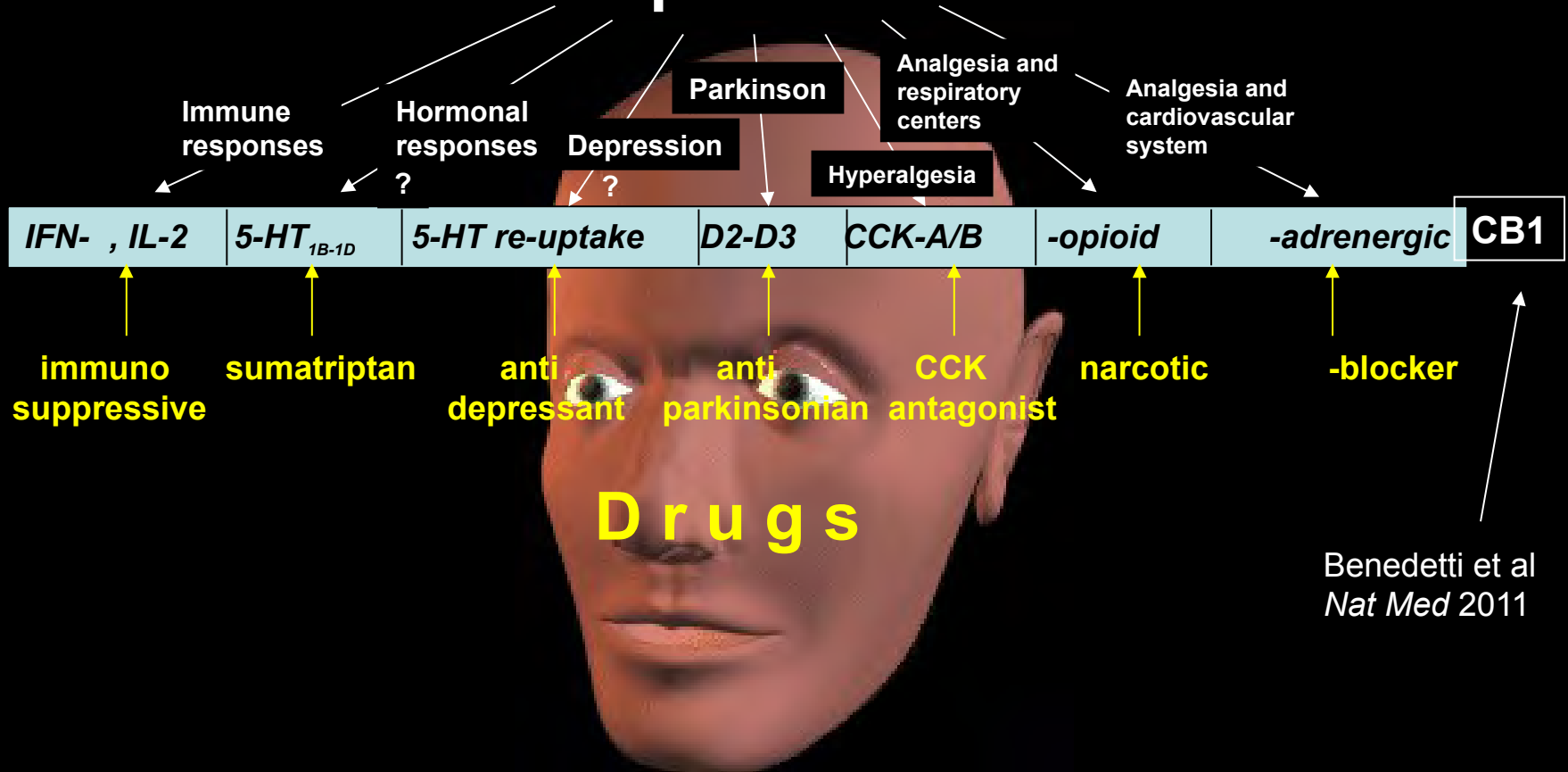
Informed consent “You will receive metamizol but you don’t know when”

Double blind





# Therapeutic rituals



Benedetti et al  
*Nat Med* 2011

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