

Modulazione del dolore: cosa abbiamo imparato dall'effetto placebo e nocebo

Fabrizio Benedetti

Università degli Studi di Torino



Plateau Rosa Labs, Switzerland



OVERVIEW

Definizione di farmaco e definizione di placebo

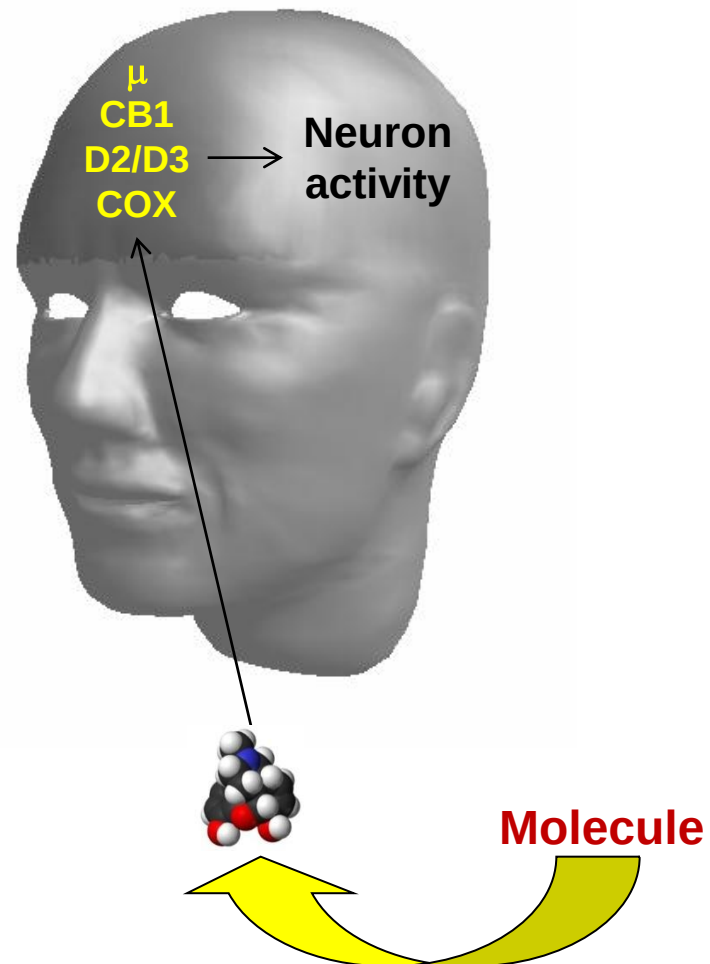
Similarità tra farmaci e placebo

- Il sistema oppioide
- Gli endocannabinoidi
- La via della cicloossigenasi
- I recettori della dopamina

La risposta nocebo

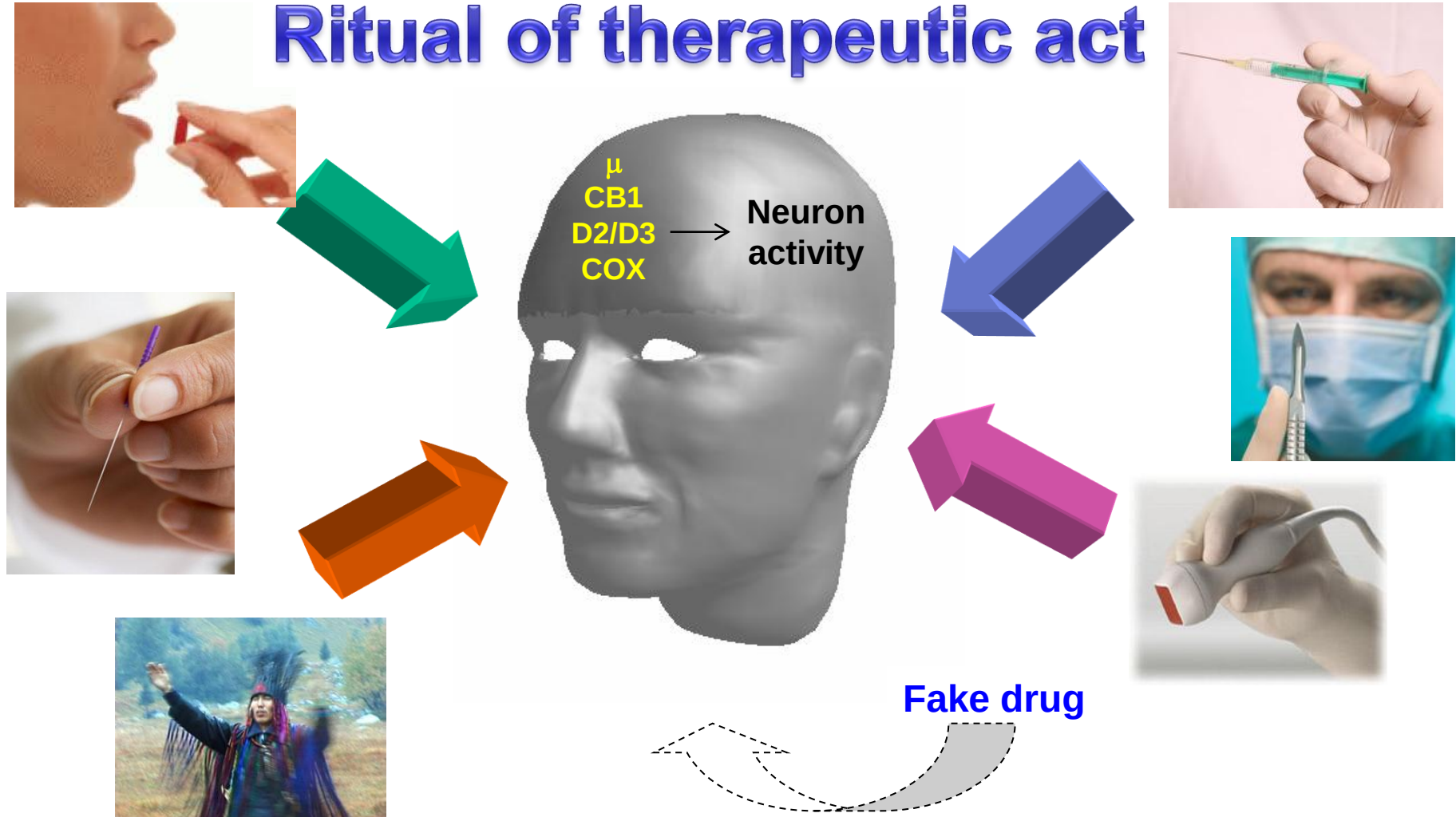
Il modello emergente: implicazioni cliniche

Cos'è un farmaco?



Cos'è un placebo?

Ritual of therapeutic act



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

Finniss, Kaptchuk, Miller and Benedetti (2010) *Lancet*



**Range of movement
after thoracotomy**

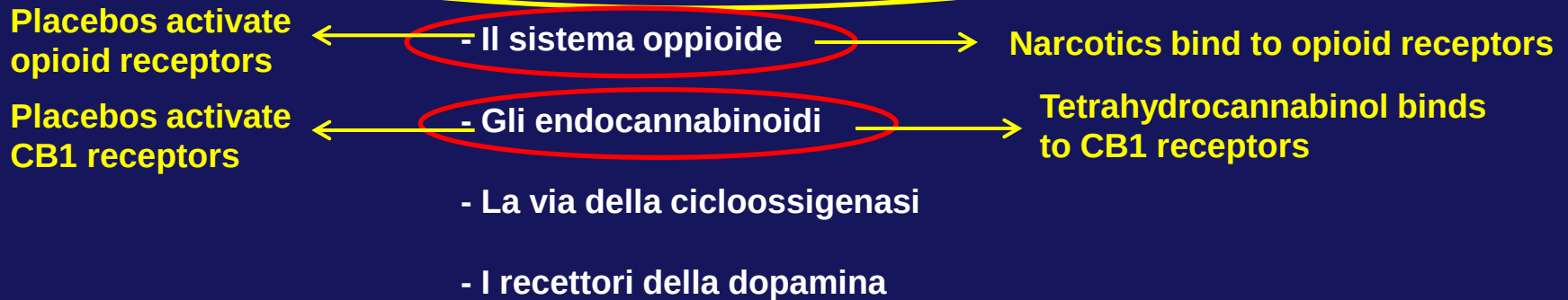


**Placebo
Analgesia**

OVERVIEW

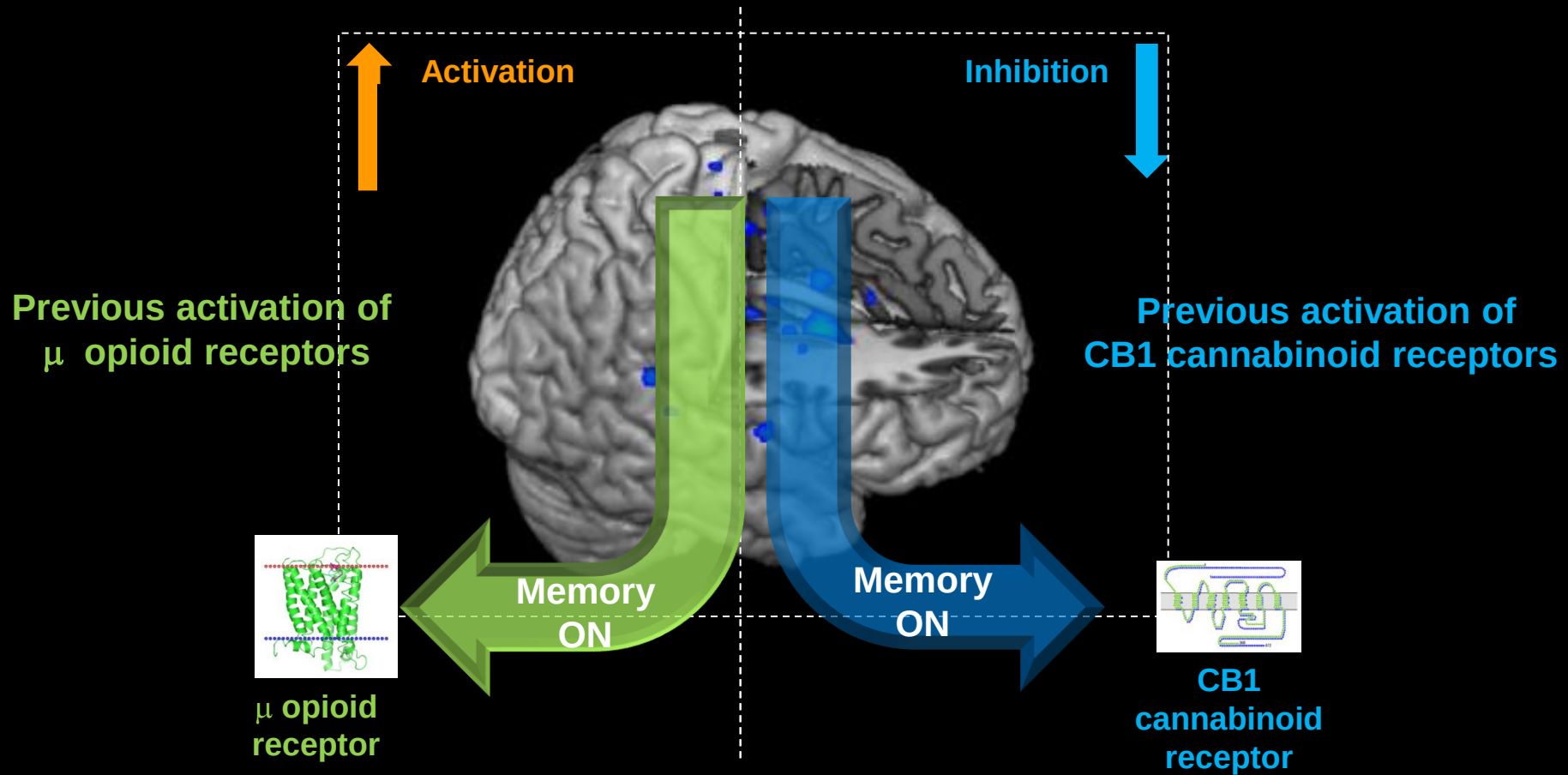
Definizione di farmaco e definizione di placebo

Similarità tra farmaci e placebo



La risposta nocebo

Il modello emergente: implicazioni cliniche



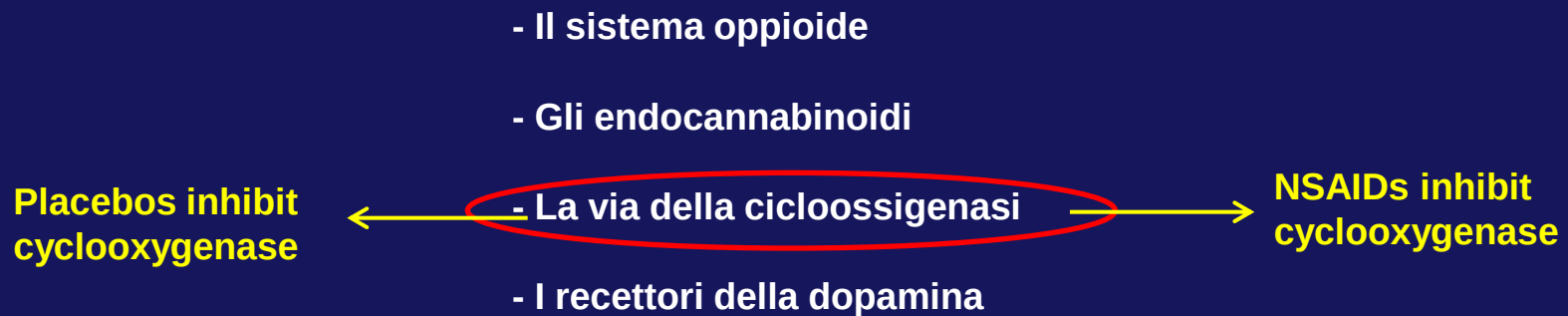
Amanzio et al (2011) *Hum Brain Map*

Benedetti et al. (2011) *Nature Med*

OVERVIEW

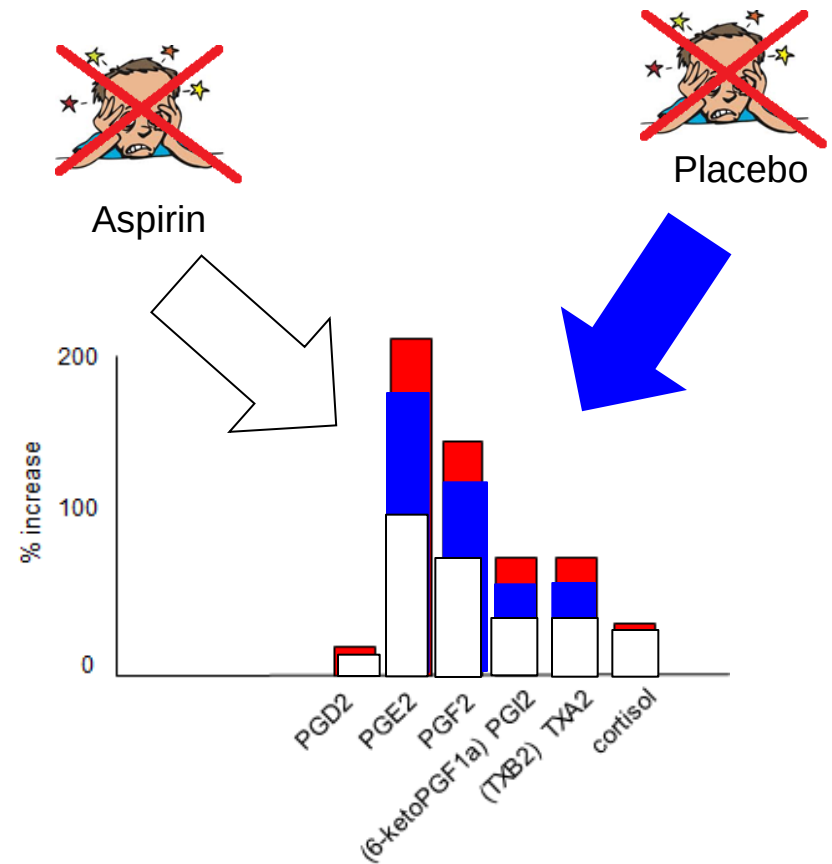
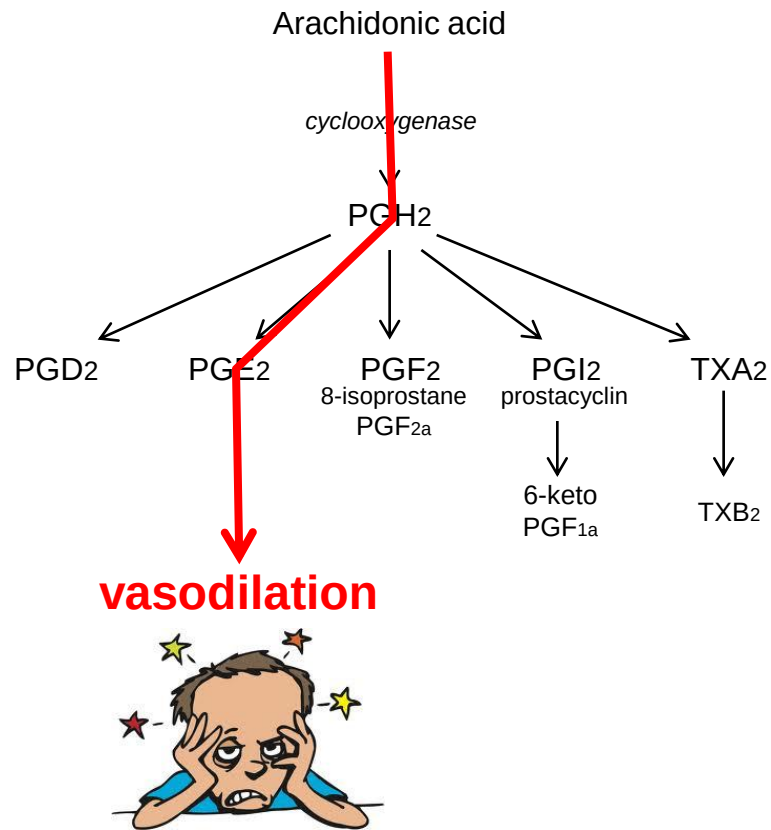
Definizione di farmaco e definizione di placebo

Similarità tra farmaci e placebo



La risposta nocebo

Il modello emergente: implicazioni cliniche



Benedetti et al (2014) *Pain*
 Benedetti (2014) *Neuron*
 Benedetti et al (2016) *Lancet Neurol*

OVERVIEW

Definizione di farmaco e definizione di placebo

Similarità tra farmaci e placebo

- Il sistema oppioide
- Gli endocannabinoidi
- La via della cicloossigenasi

Placebos activate
dopamine receptors

- I recettori della dopamina

Anti-Parkinson dopaminergic
drugs bind to dopamine receptors

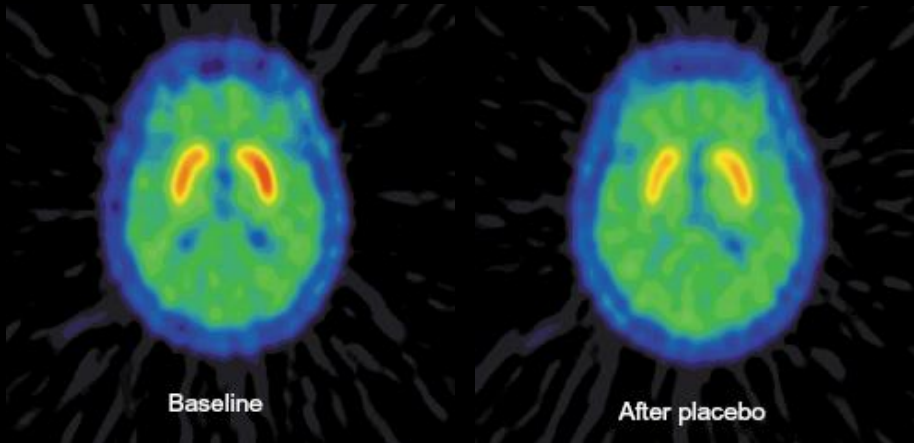
La risposta nocebo

Il modello emergente: implicazioni cliniche

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

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

Parkinson's disease



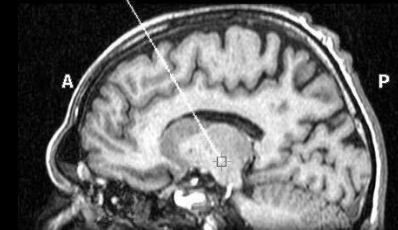
200% increase in dopamine
=
One dose of amphetamine

de la Fuente-Fernandez et al. (2001) *Science*



Sagittal 289/512 109.4 (mm)

S



I



↑
placebo

Benedetti et al. (2004) *Nature Neurosci*

OVERVIEW

Definizione di farmaco e definizione di placebo

Similarità tra farmaci e placebo

- Il sistema oppioide
- Gli endocannabinoidi
- La via della cicloossigenasi
- I recettori della dopamina

La risposta nocebo

Il modello emergente: implicazioni cliniche

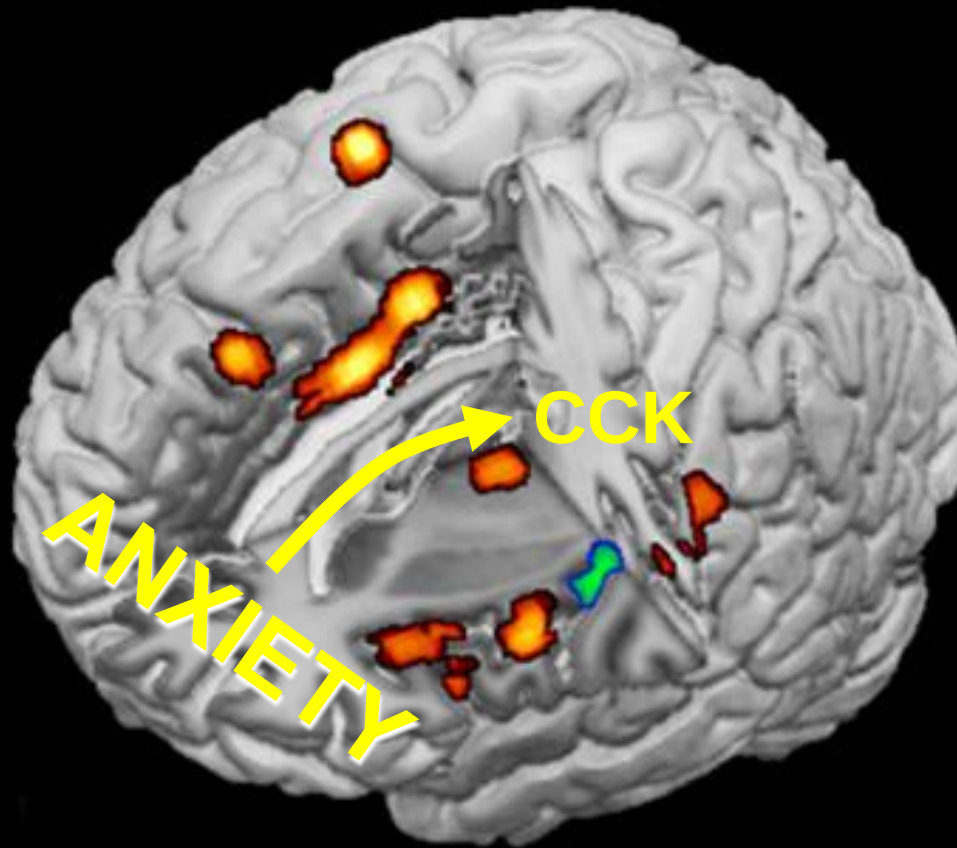


**Movement
after thoracotomy**



**Nocebo
Hyperalgesia**

The nocebo effect



Palermo et al. (2015) *Hum Brain Mapp*

Benedetti et al. (2006) *J Neurosci*

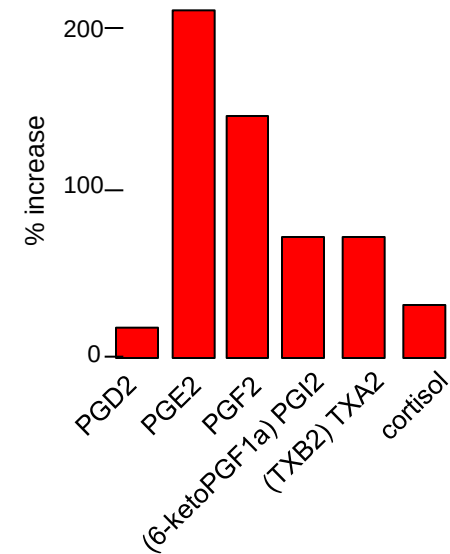
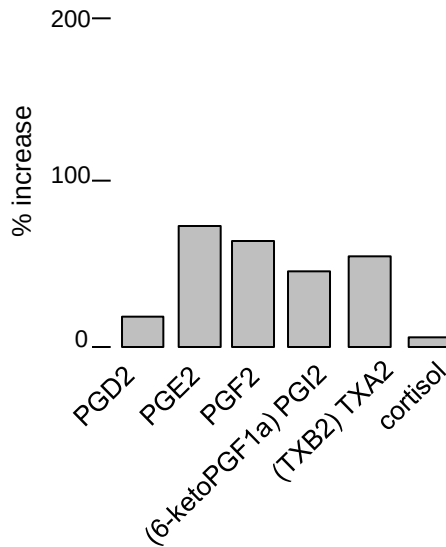
Hypobaric hypoxia headache



Control
(no expectations)



nocebo
(negative expectations)



Benedetti et al (2014) *Pain*
Benedetti (2014) *Neuron*
Benedetti et al (2016) *Lancet Neurol*

OVERVIEW

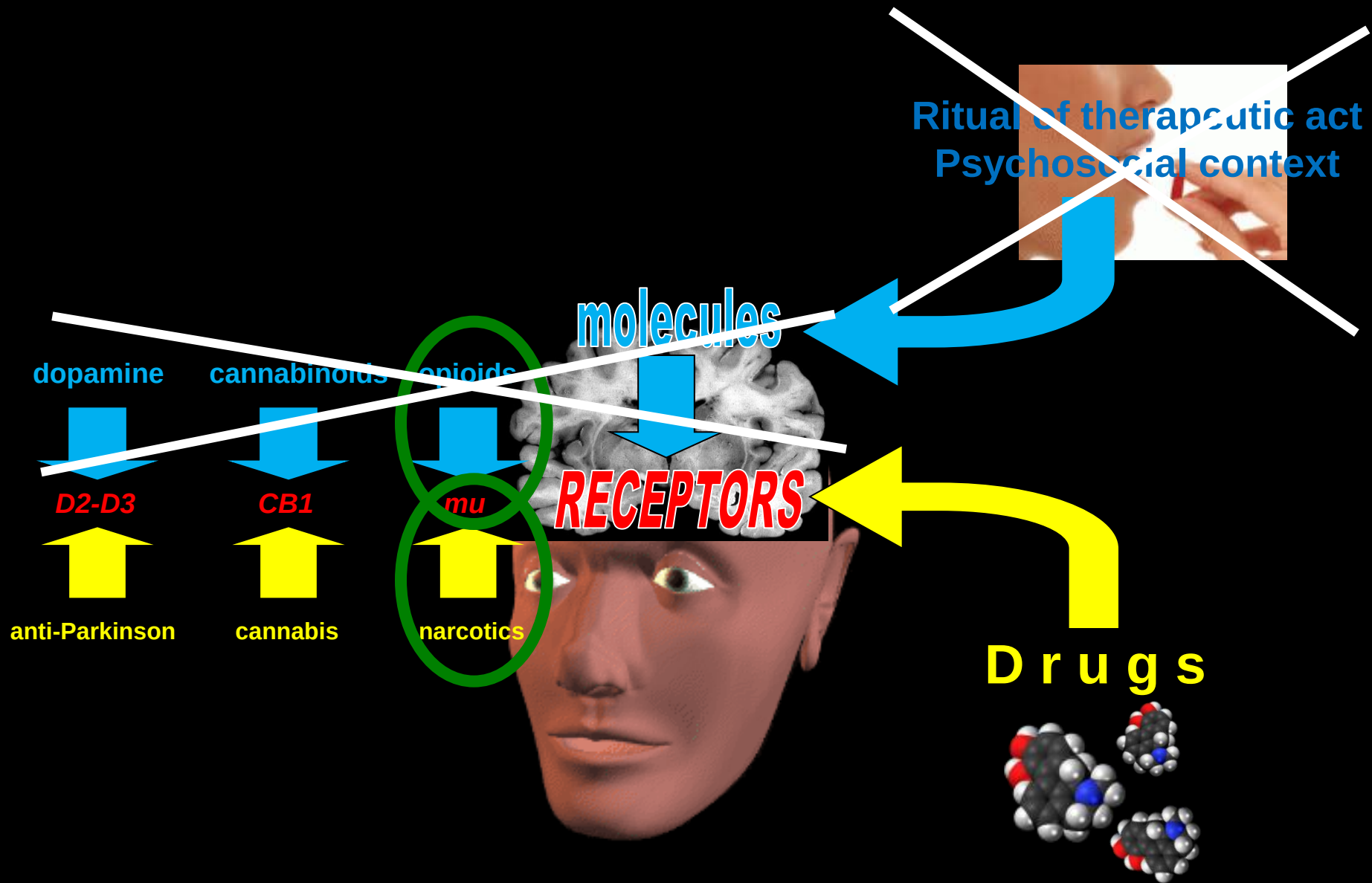
Definizione di farmaco e definizione di placebo

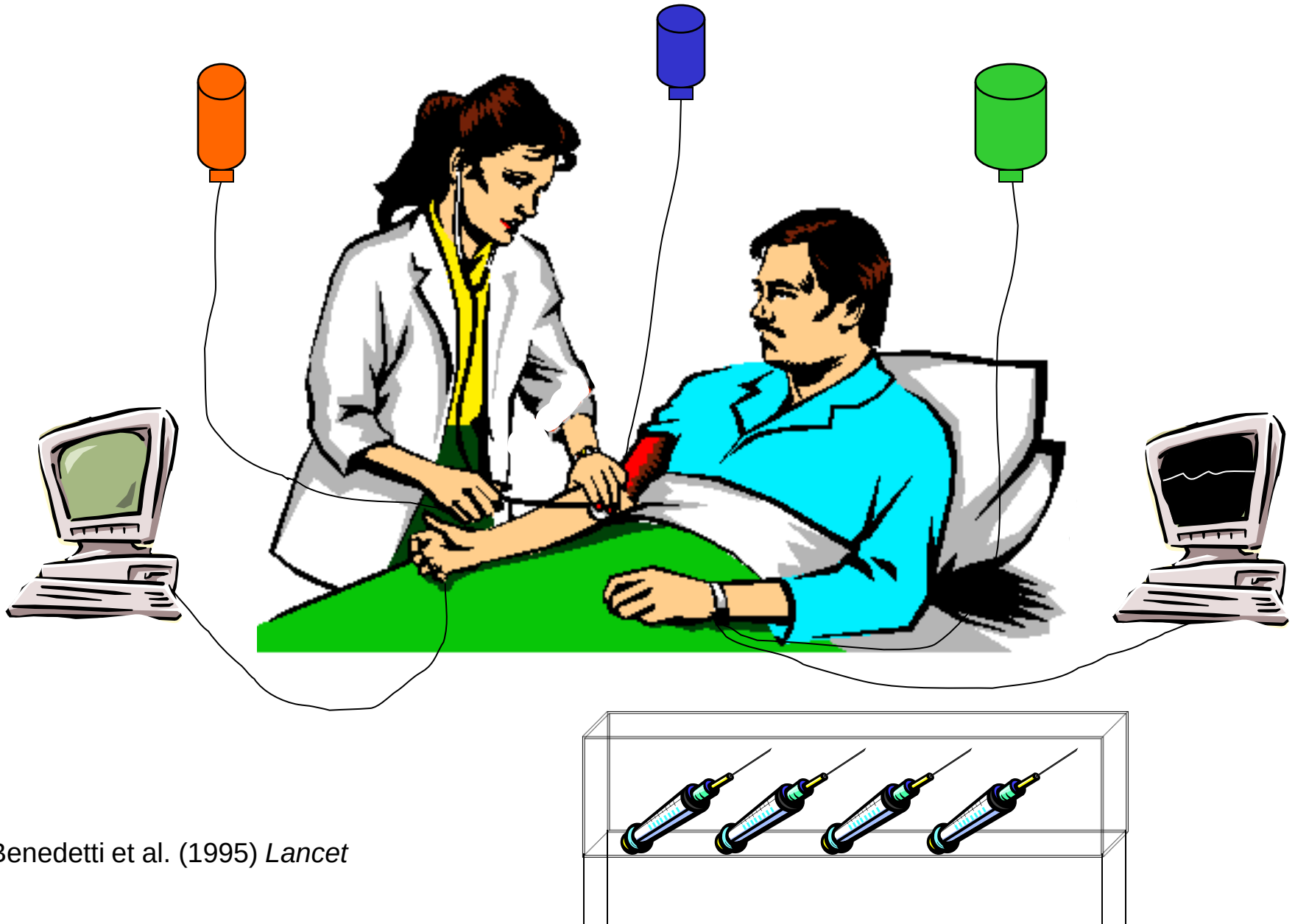
Similarità tra farmaci e placebo

- Il sistema oppioide
- Gli endocannabinoidi
- La via della cicloossigenasi
- I recettori della dopamina

La risposta nocebo

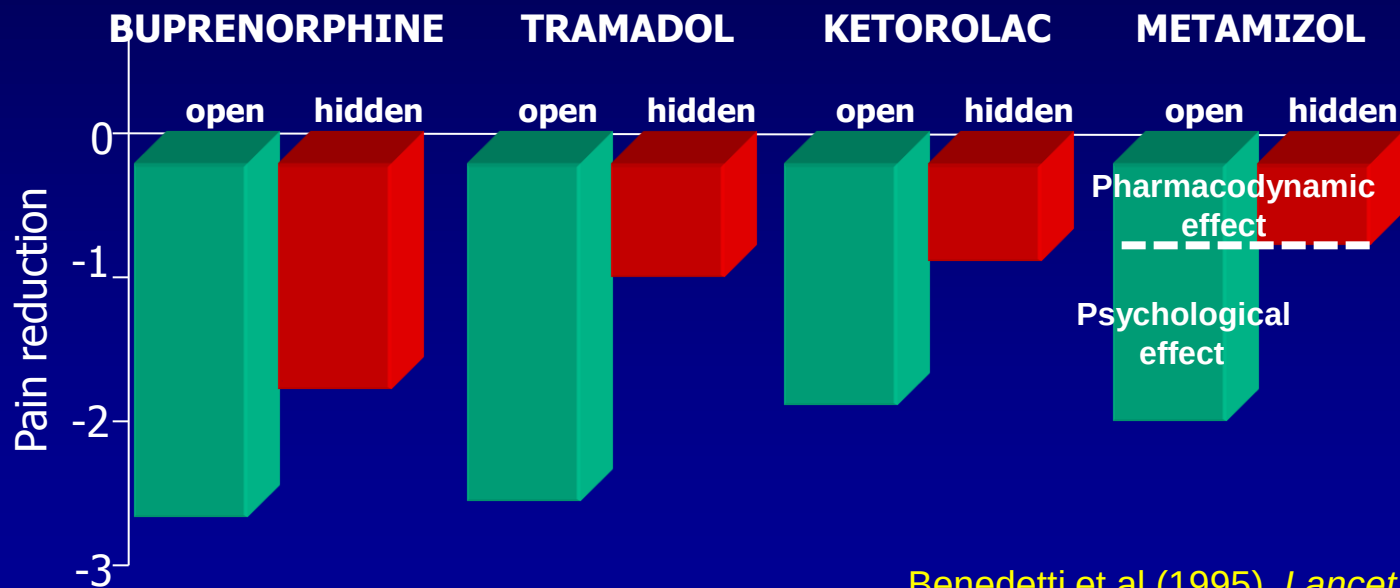
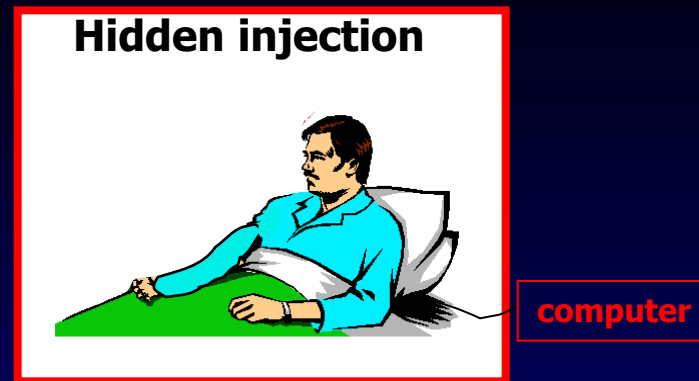
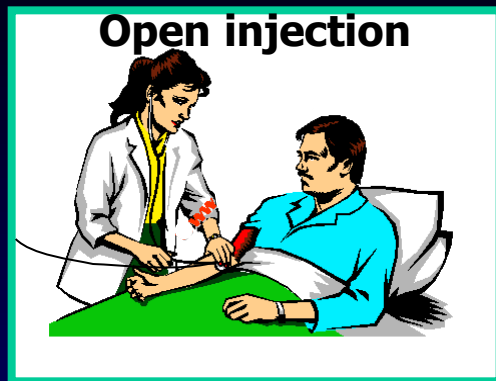
Il modello emergente: implicazioni cliniche





Benedetti et al. (1995) *Lancet*





Benedetti et al (1995) *Lancet*
 Colloca et al (2004) *Lancet Neurol*
 Benedetti et al (2016) *Lancet Neurol*

TRIAL Met#2

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

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



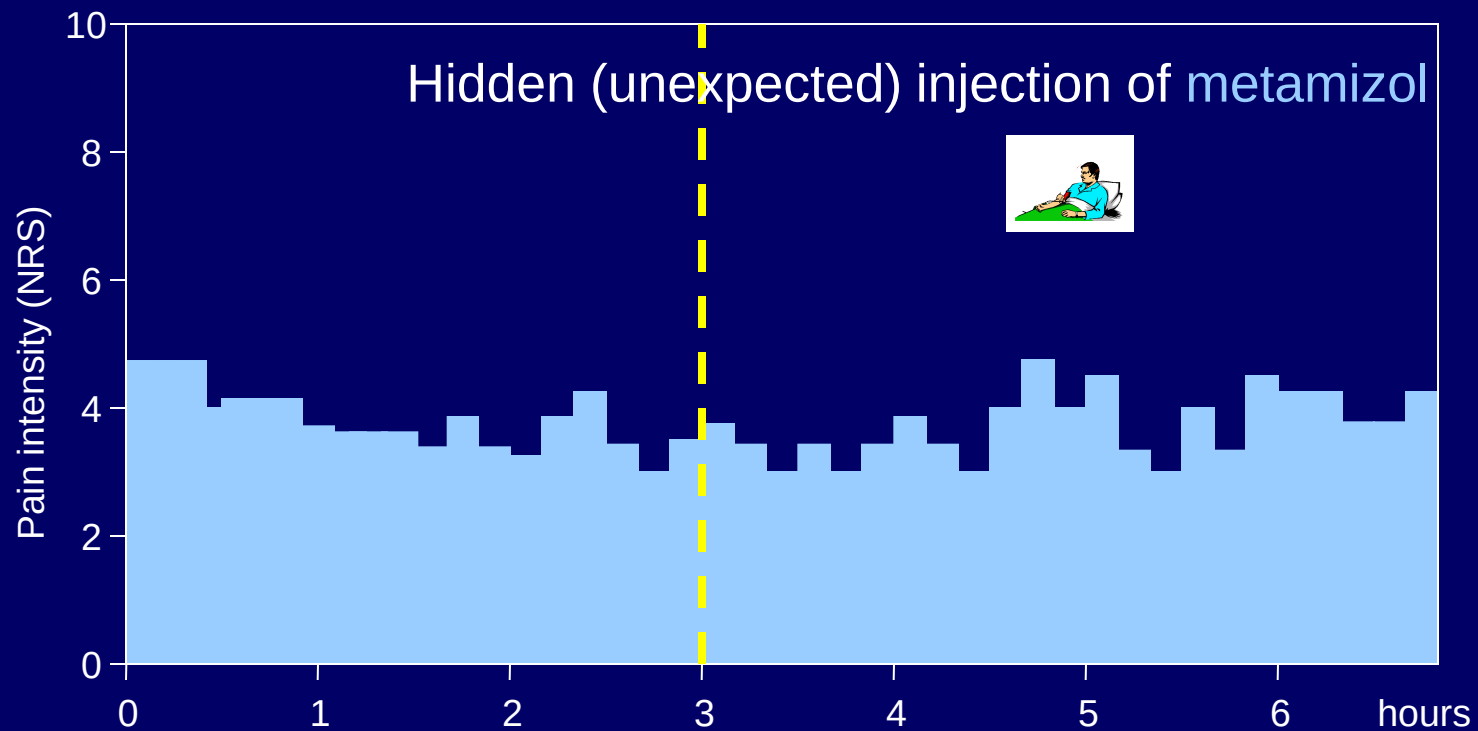
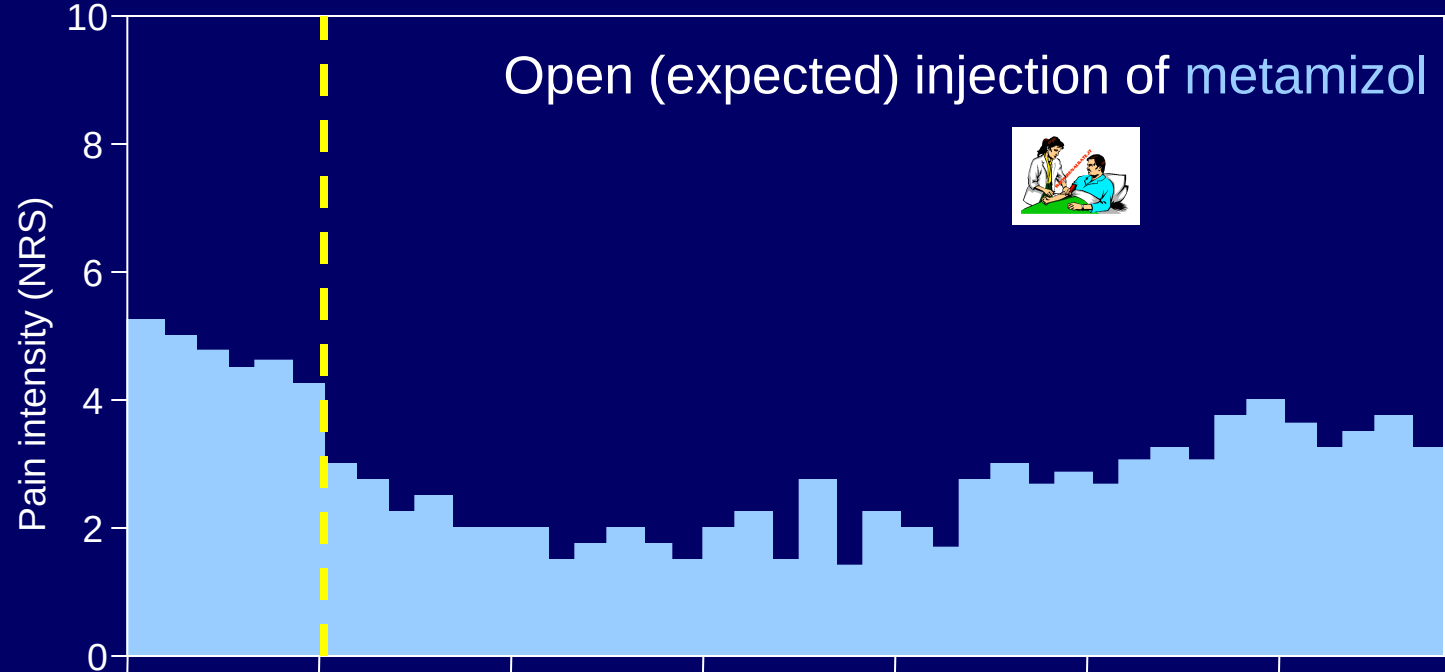
Open metamizol injection group (N=10)



Hidden metamizol injection group (N=10)

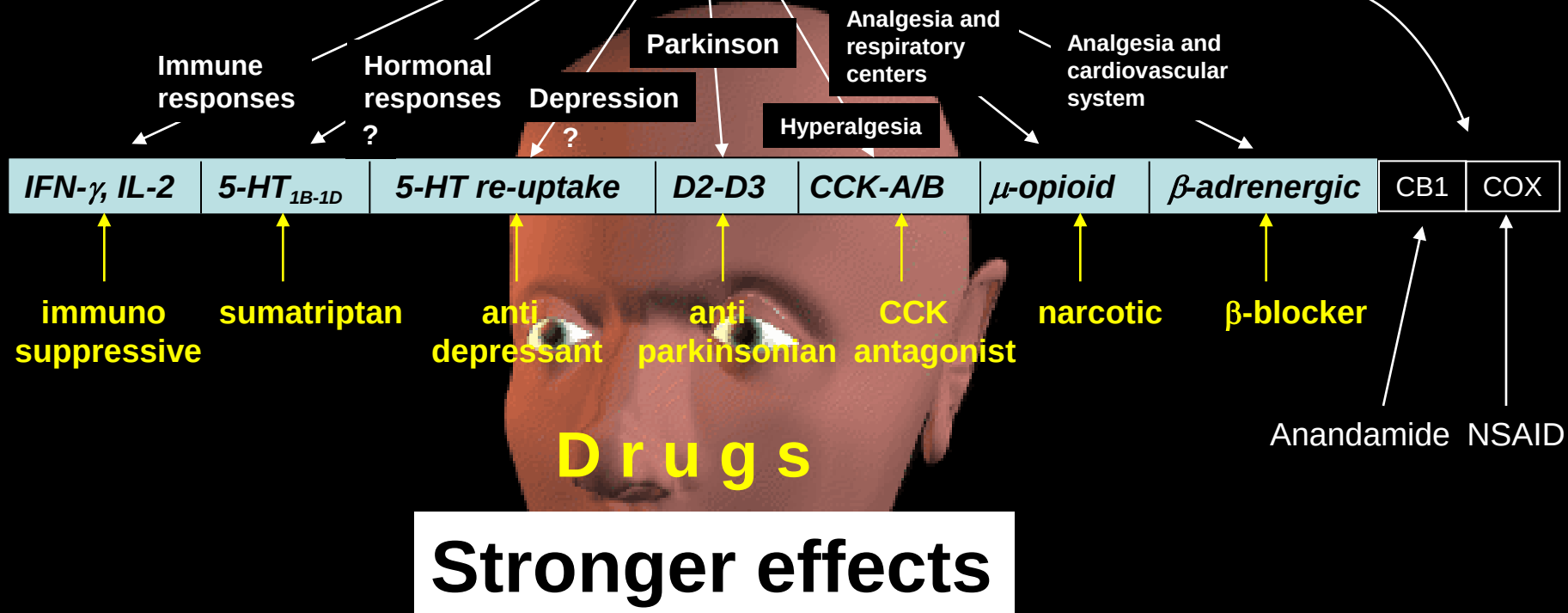
Informed consent “You will receive metamizol but you don’t know when”

Double blind





Placebos Therapeutic rituals



NEUROPHYSIOLOGY

Antonella Pollo

Luana Colloca

Elisa Frisaldi

Jennifer Durando

Sergio Vighetti

PSYCHOLOGY

Martina Amanzio

Elisa Carlino

Claudia Arduino

Rosalba Rosato

Sara Palermo

Alessandro Piedimonte

NEUROLOGY

Leonardo Lopiano

Innocenzo Rainero

Giovanni Asteggiano

NEUROIMAGING

Carlo Porro

Fausta Lui

Franco Cauda

ENDOCRINOLOGY

Catherine Blanchard

Wilma Thoen

Sara Dogue

THORACIC SURGERY

Giuliano Maggi

Caterina Casadio

NEUROSURGERY

Michele Lanotte



University of Turin Medical School, Italy



Plateau Rosa Laboratories, Switzerland