



Dalle molecole del cervello al farmaco,
fra passato, presente e futuro.

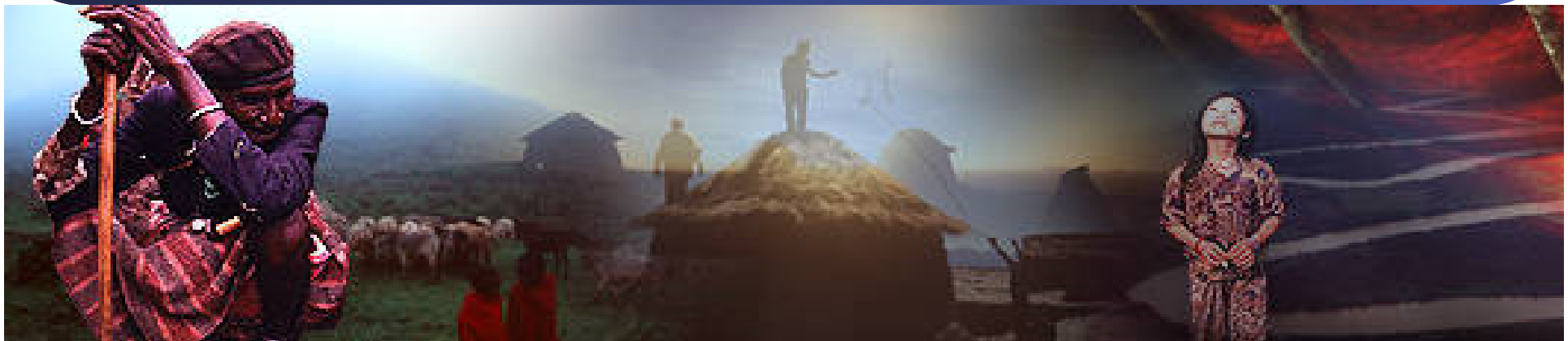
Sviluppare un farmaco per la mancanza di motivazioni.

Una prospettiva di psicofarmacologia evoluzionistica Darwiniana

Luca Pani, M.D.



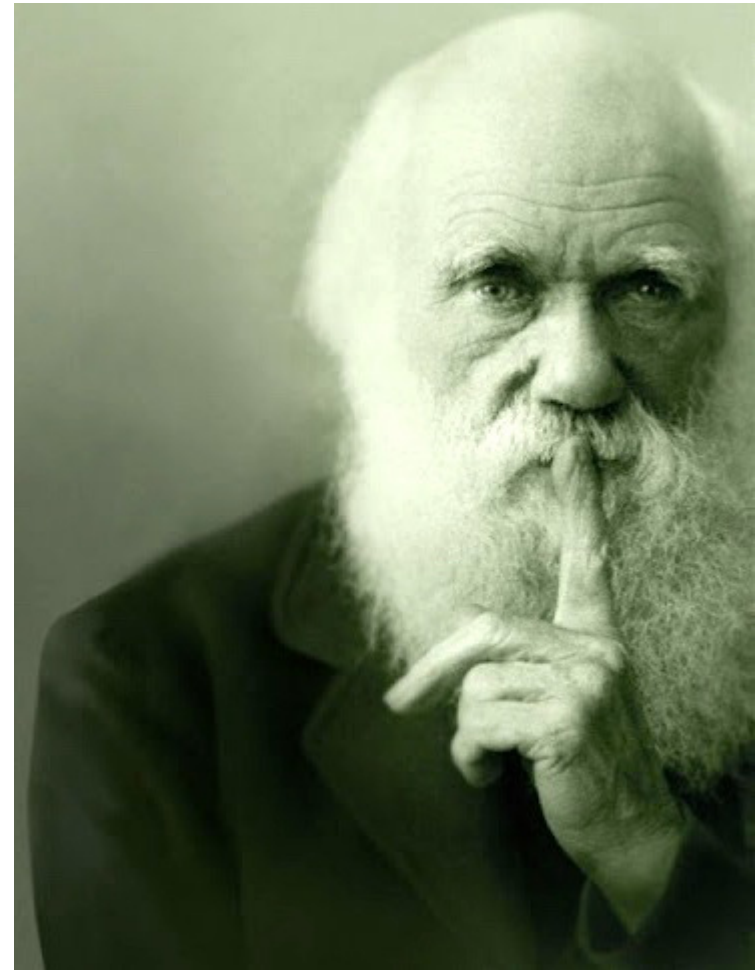
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A talk in the context of human ethology

Nothing in Biology makes sense
except in light of evolution

(T. Dobzhansky, 1973)



Sir Charles Darwin
(1809-1882)

Evolution in De Rerum Naturae (100 BC)

Mutat enim mundi Naturam totius ætas [...]
Nec manet ulla sui similis res: omnia migrant,
Omnia commutat Natura, et vertere cogit.
(Lucretius, V, 828-831)

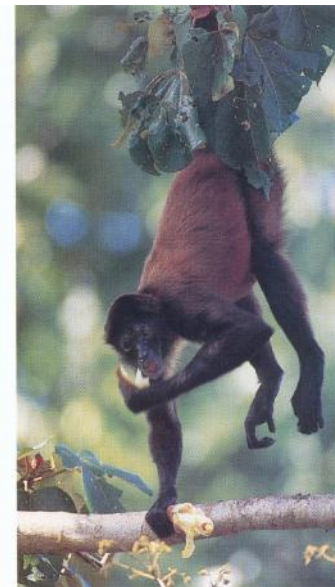
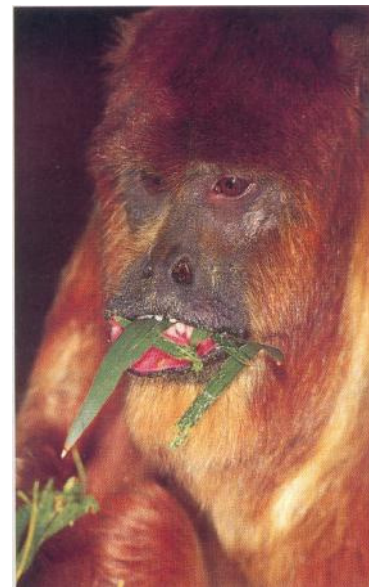
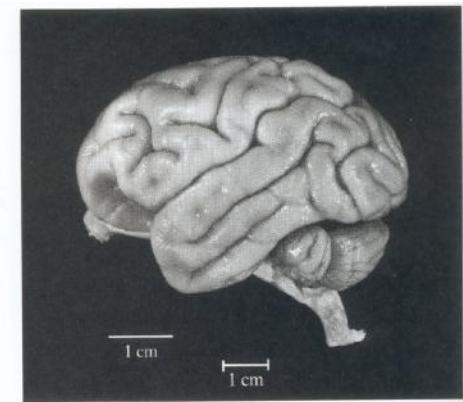
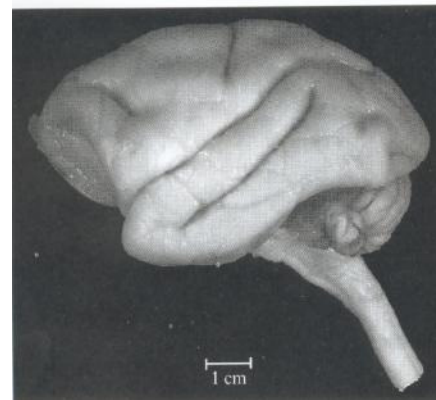
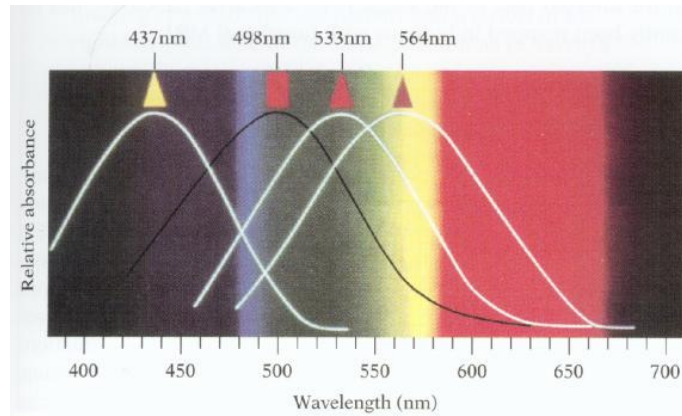


Problem is we cannot “picture” evolution. Can we picture a 3BY time scale?

- If every year is a letter then you could write 1000 giant books of 1000 pages each
- These books would build an 80 m tower
- The divergence between non-human and human primates starts at the end of page number 332 of the book number 999
- We and Aristotle are on the same last page



A single-point mutation can change everything



Colors ah? Let's try

The Stroop Test

(Italian Version)

ROSSO

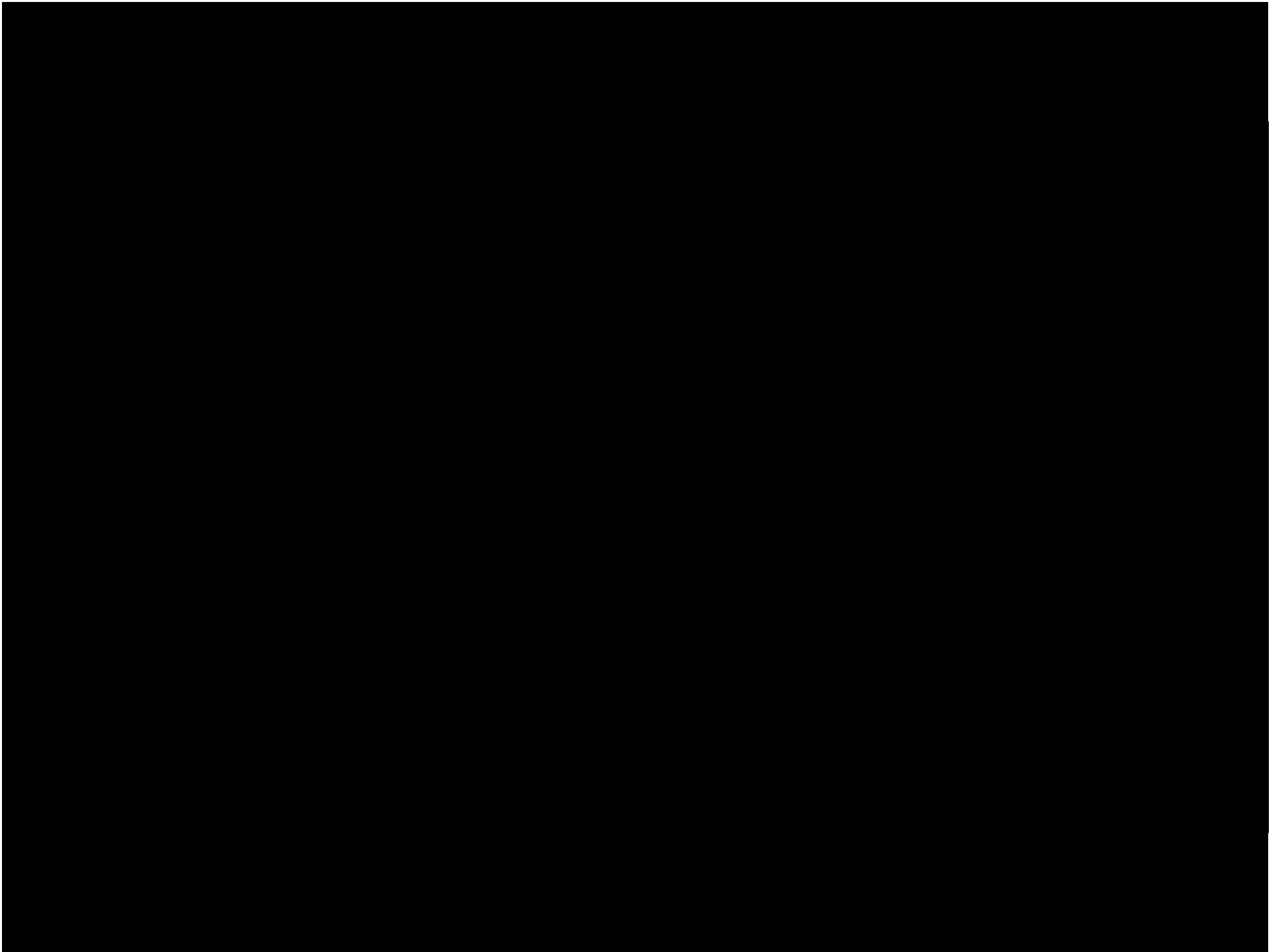
VERDE

GIALLO

ROSSO

ROSA

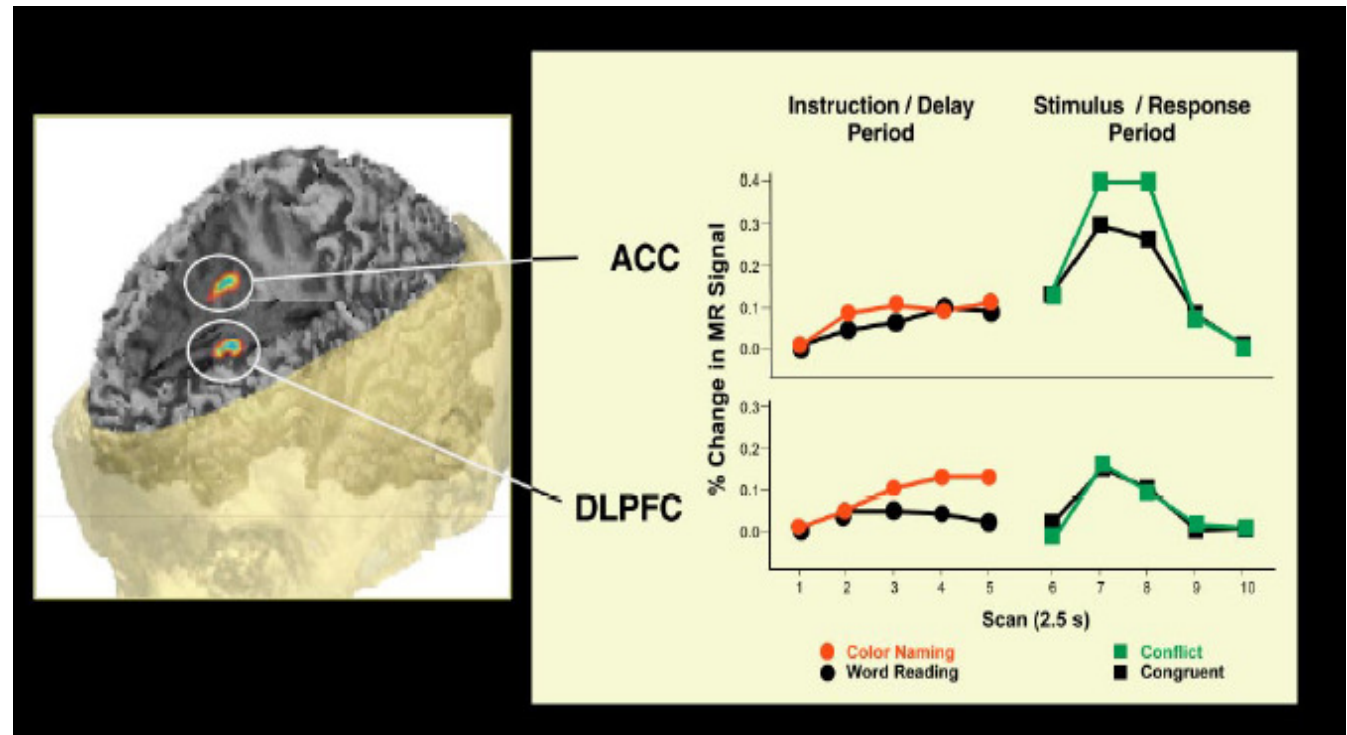
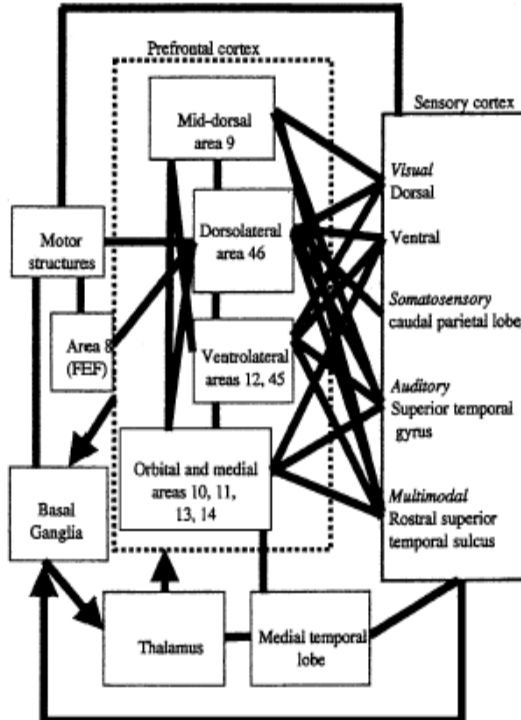
VIO LA



BIANCO

Conflicting circuits: colors/names

red white green brown
 green red brown white
 white brown green red
 red white green brown
 brown green white red
 white brown red green
 green white brown red
 red brown green white



Divergence from reptiles occurred about 300 MYA with three key developments

1) Nursing and maternal care

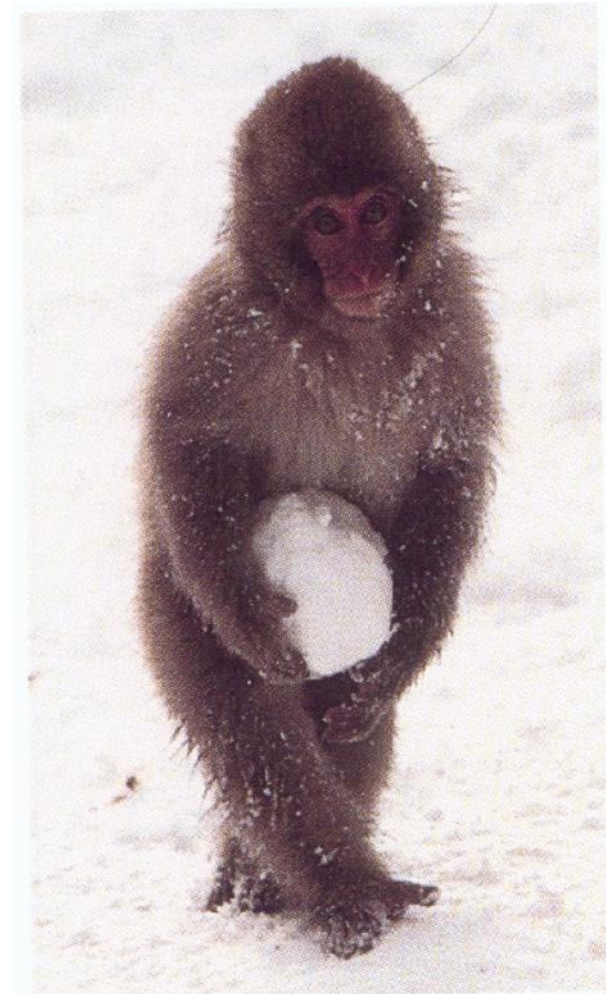
2) Separation call

3) Play



Disorder of Motivation: special forms of basic behaviors

- Establishing a “territory”
- Showing place preference
- Hunting
- Greeting
- Social grouping
- Feeding and drinking
- Grooming
- Courtship
- Mating
- Breeding
- Maternal behaviour
- Play (mammals only)



All of them depend on the perfect functions of the extended limbic system

Dopamine, motivation and evolutionary mismatch

MILLENIUM ARTICLE

Is there an evolutionary mismatch between the normal physiology of the human dopaminergic system and current environmental conditions in industrialized countries?

L Pani

Table 1 Steps in brain evolution with increasing environmental interaction

1. Bipedalism
2. Development of a cooling system
3. Trichromatic vision
4. Hemispheric dominance/use of tools
5. Nursing and maternal care
6. Voluntary control of speech
7. Separation call
8. Self/other feelings awareness
9. Development of syntactic ability
10. Pressure to speak

Anno di invenzioni significative o avanzamenti tecnologici	
1550	Cacciavite
1690	Motore a Vapore
1770	Batteria Elettrica
1853	Ago Ipodermico
1876	Telefono
1885	Motore a scoppio
1886	Coca-Cola
1903	Aeroplano
1920	Trasmissioni Radio
1926	Televisione
1948	Transistor
1962	Minicomputer
1969	Uomo sulla Luna
1972	Videogiochi
1978	Bambino in Provetta
1988	Brevetto Vita Animale
1992	Internet Globale
2000	Sequenza del Genoma Umano
2010	IPad
2015	Prima terapia approvata da cellule <u>staminali</u>

Table 4 The Italian market for psychotropic compounds

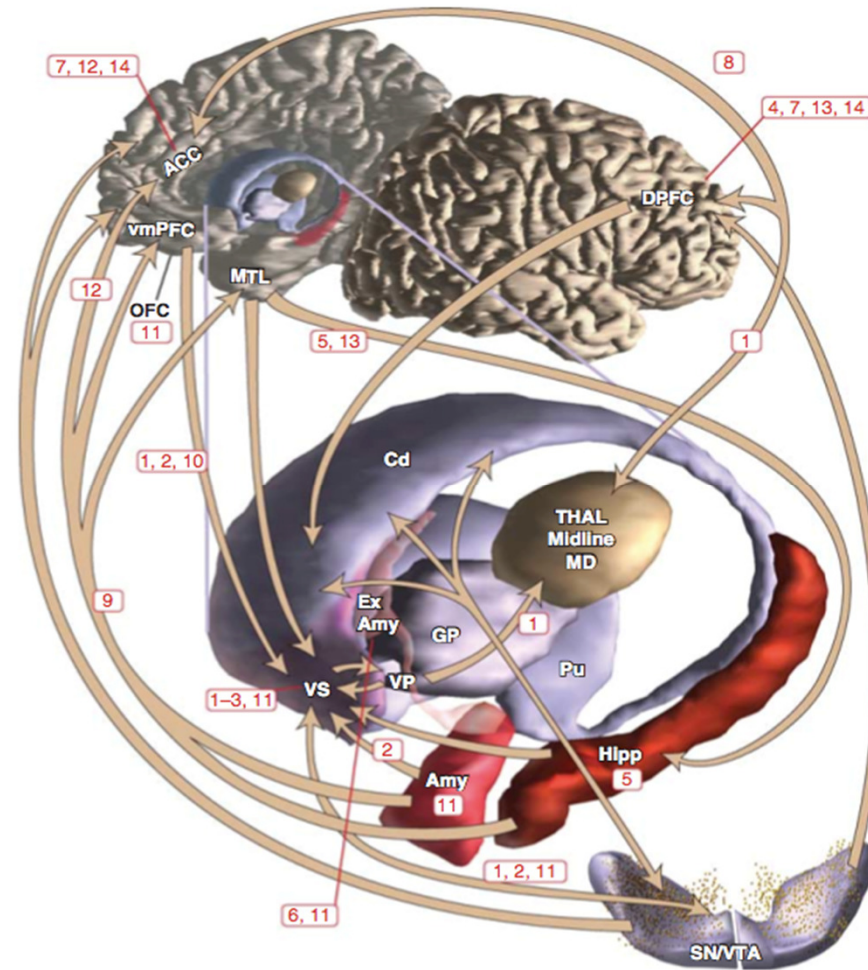
	<i>Millions of prescriptions per year</i>				
	1995	1996	1997	1998	1999
Antipsychotics	11 675	12 432	12 468	12 940	13 428
Antidepressants	16 750	18 275	19 413	20 524	22 493
Anxiolytics	33 143	34 589	34 093	34 917	34 487

Changes throughout recent evolution which interfere with the normal physiology of the dopaminergic system

- Chronic emotional reactions
- Chronic sleep deprivation
- “Stress”
- Chronic antidepressants
- Drugs of abuse
- Withdrawal from various drugs
- Overstimulation from technology



Dopaminergic circuitry subserving motivation



Striatal neurons, motivation and choices

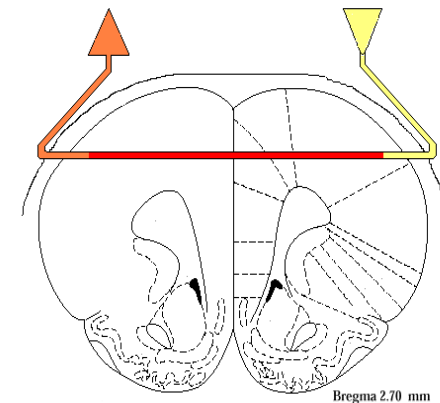
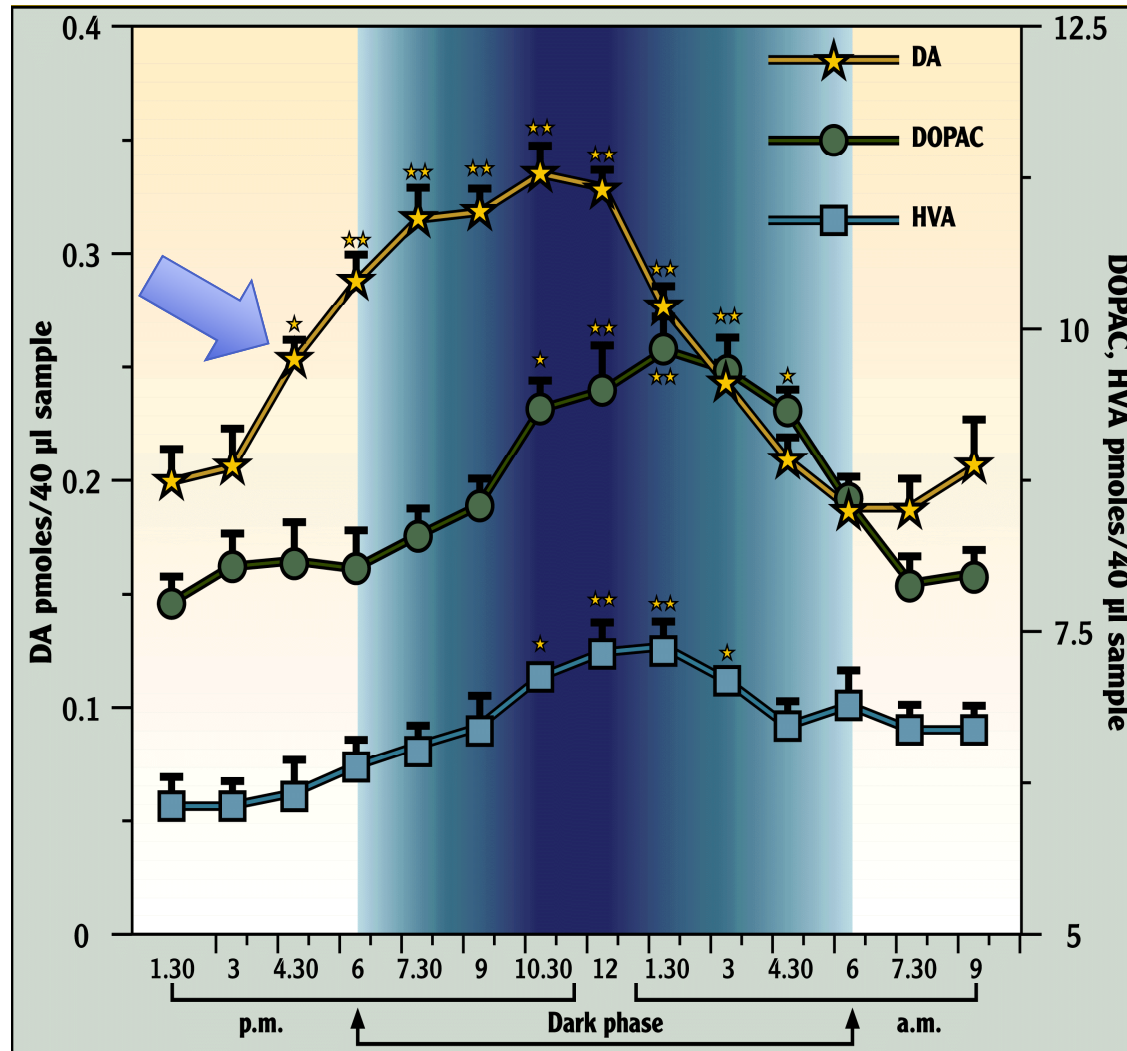
Successful prediction of individual action choices by estimated action values suggests involvement of striatal action-value neurons in the process of selection of an action under a reinforcement learning algorithm.

Whereas a large population of striatal neurons encoded action values, a much smaller population of neurons encoded forthcoming action during a pre-movement delay period.

Striatum? Movement? Indeed....

Moveo ut acto = I move to act (combined etymology of the word motivation)

Circadian rhythm of dopamine release and motivation



Brain Micro-Dialysis

Conditions producing increased dopaminergic transmission and motivation

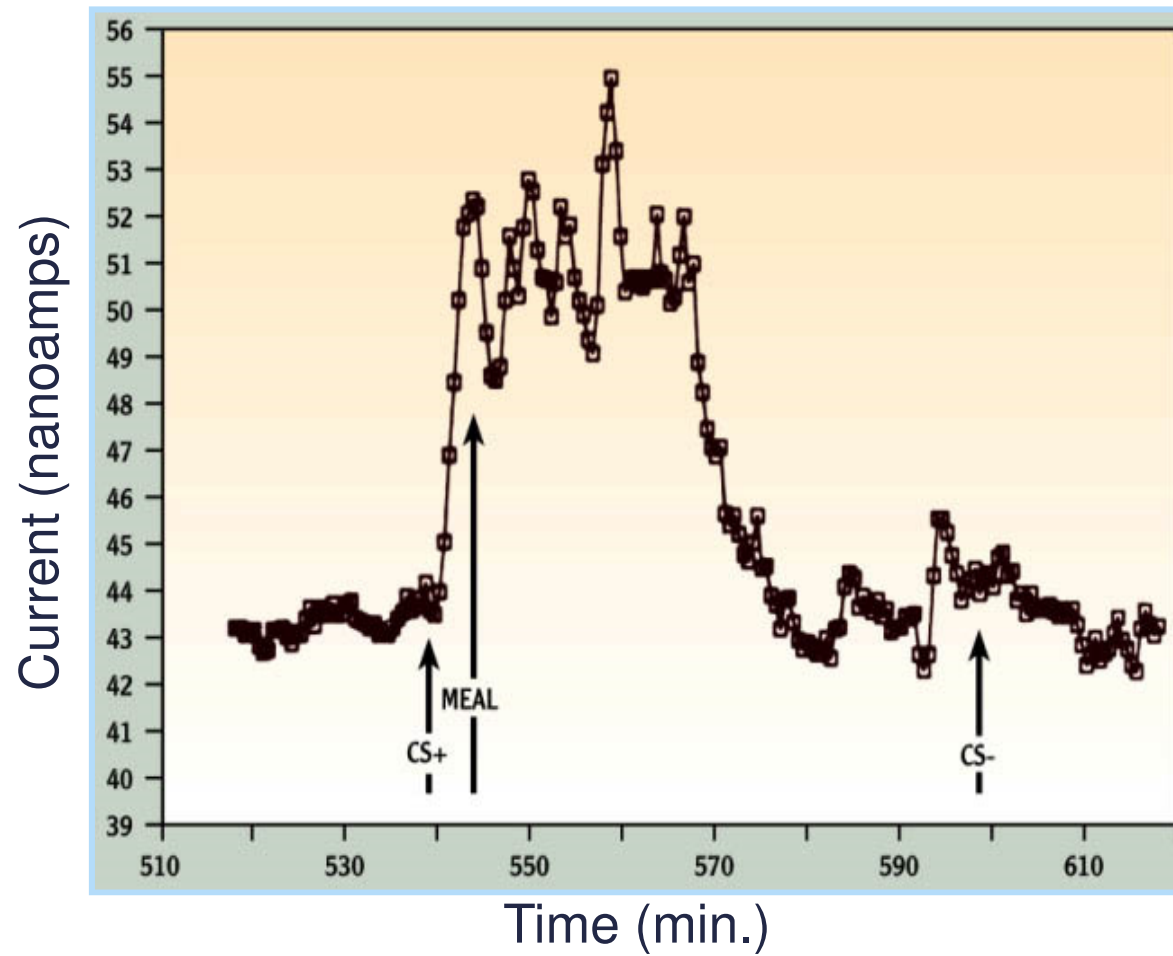
Food & sweets

Sexual stimuli

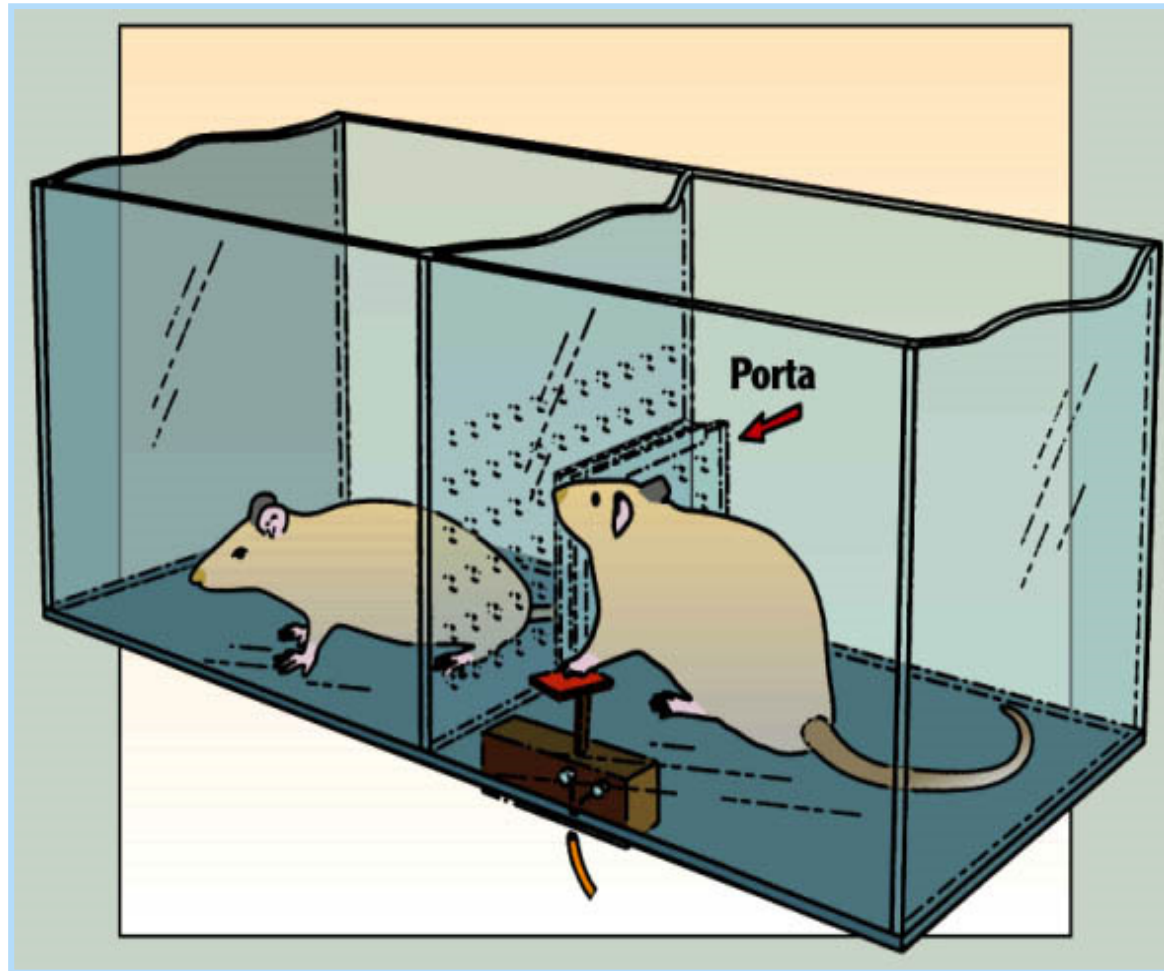
Drug self-administration

Intracranial self-stimulation

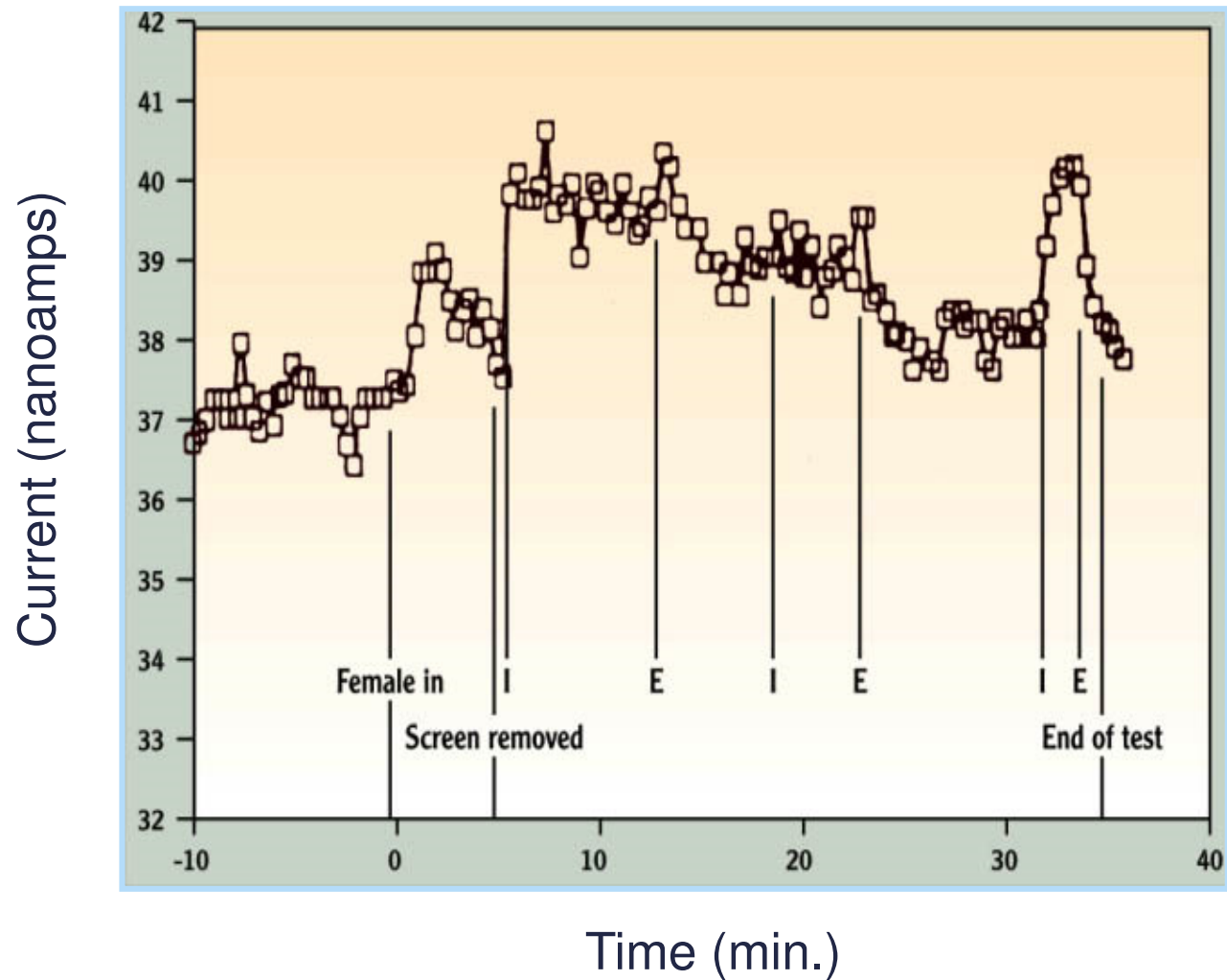
NAcc dopaminergic transmission & food intake



Sexual behaviour and motivation

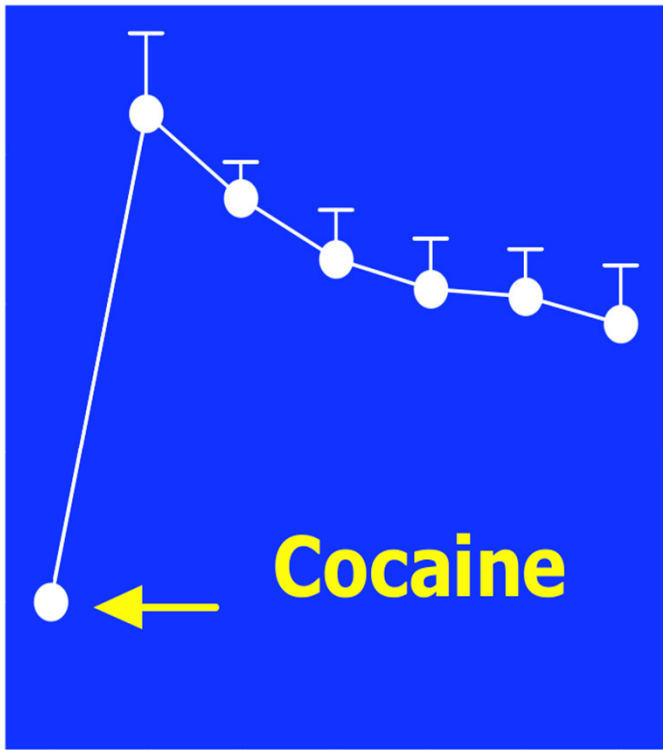


NAcc dopaminergic transmission & sexual behaviour



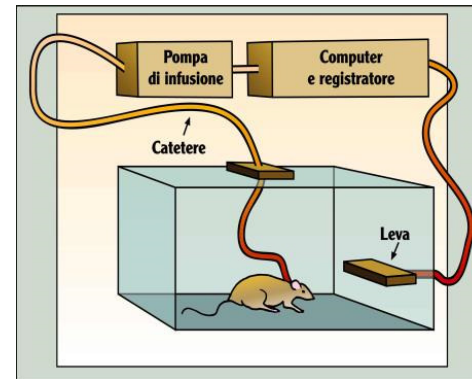
Drug self administration and motivation

Level of Dopamine with respect to baseline

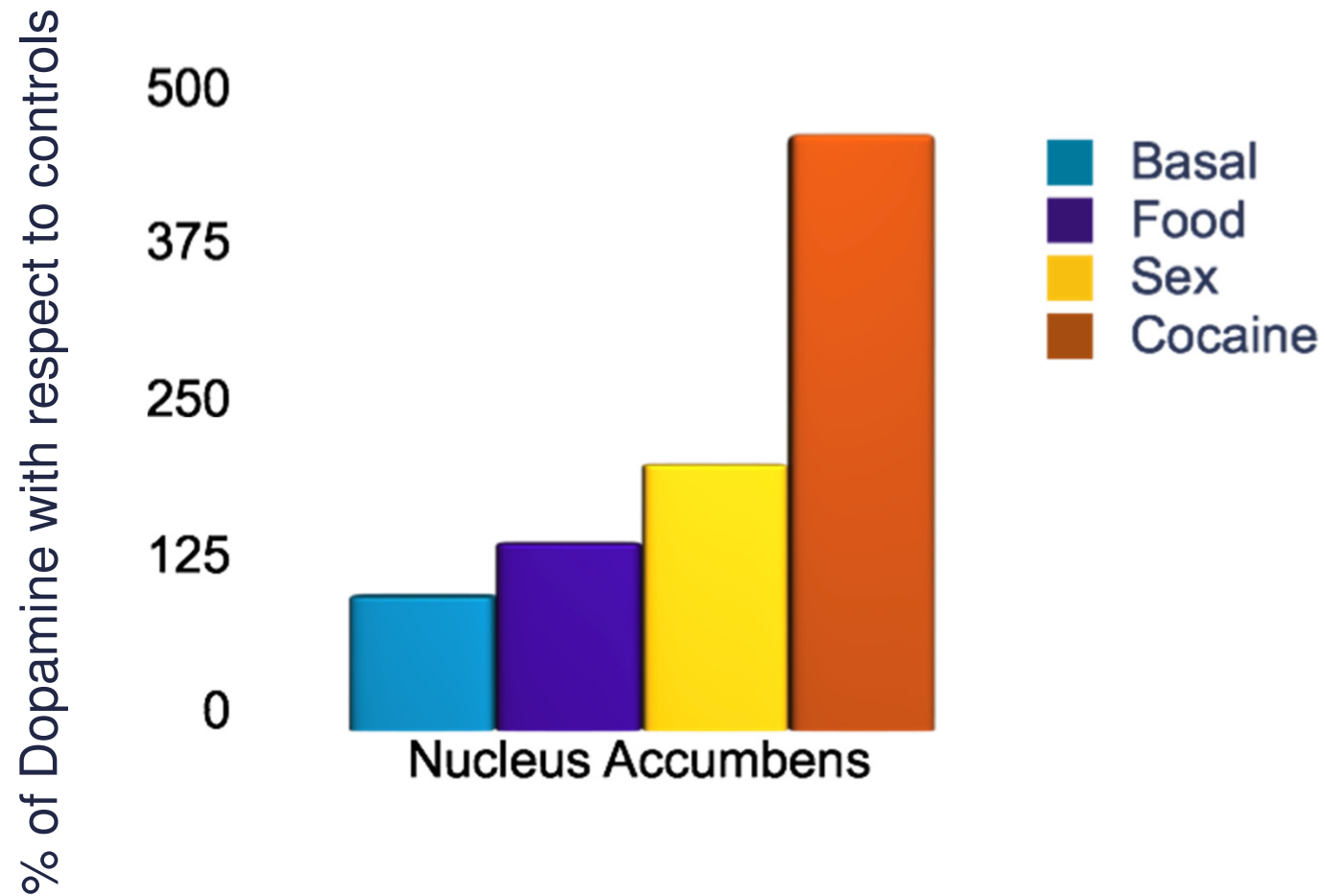


Time (every point is 20')

Nucleus Accumbens



Comparison between rewards & levels of dopamine



Conditions associated with reduced dopaminergic transmission and lack of motivation

Behavioural despair

Learned helplessness

Chronic mild stress

Withdrawal from heroin, cocaine, amphetamine, alcohol

Chronic use of cannabinoids (Amotivational syndrome)

Animal models: learned helplessness

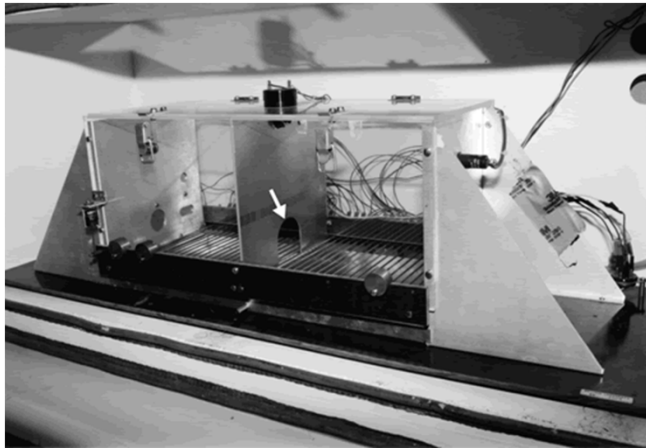
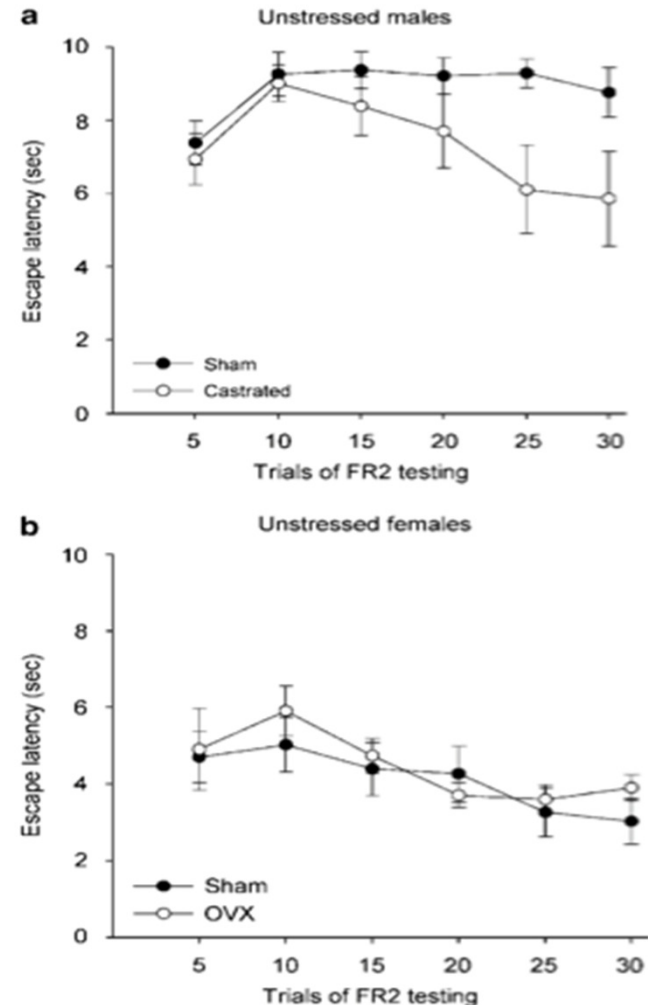


Table 1 General Motor Activity Levels

Sex	Condition	Horizontal activity	Vertical activity
Male	Sham	16007 127	1907 28
	Castrated	15467 82	1457 14*
Female	Sham	16907 184	2337 31
	OVX	17907 129	1717 24*
Female	Vehicle	25077 122	3307 94
	Testosterone	19907 94**	2277 29*

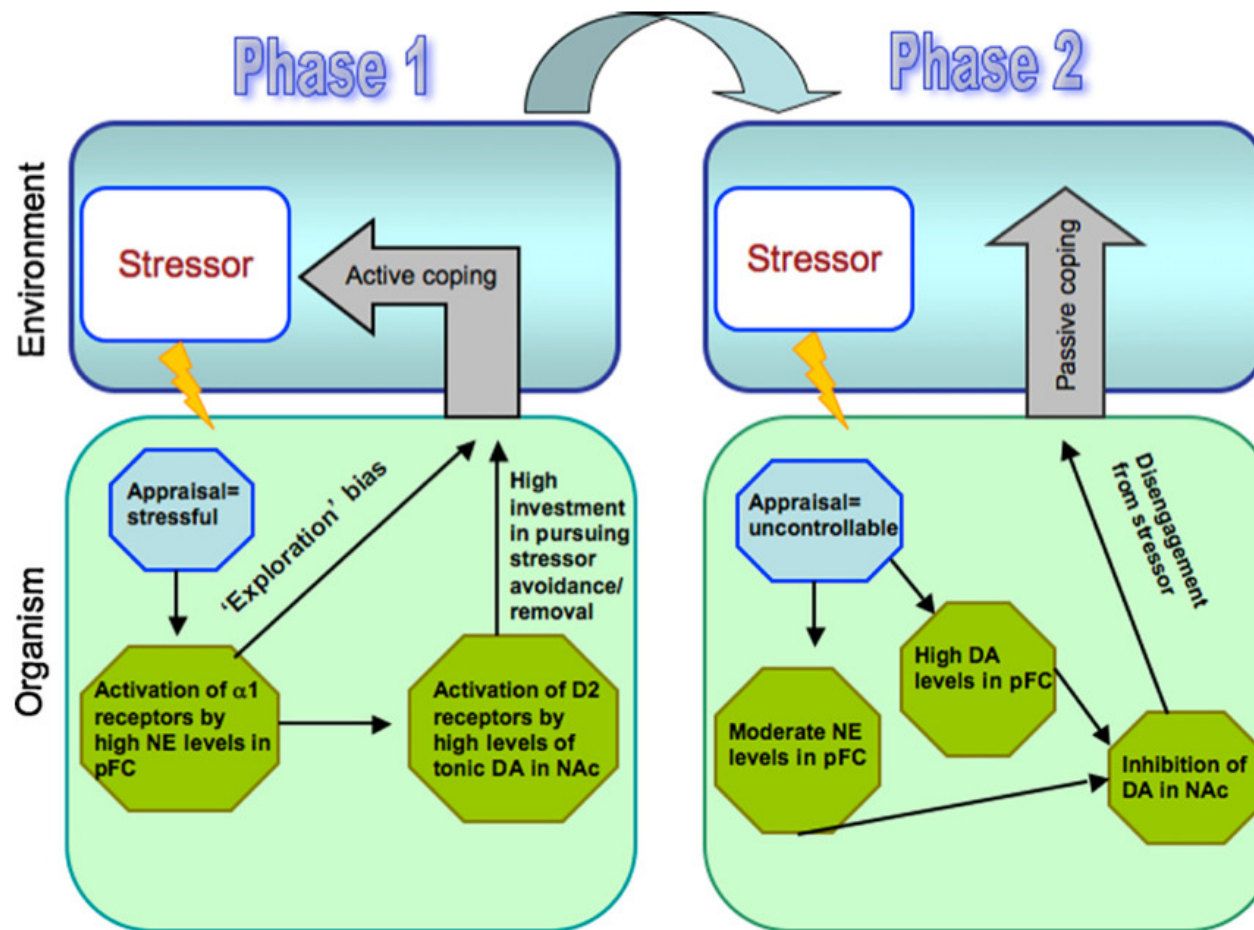
In rats with dopaminergic system depletion there is no motivation to avoid a painful event. An important gender effect exists: in females this model is not useful to study an effect on motivation to escape.



Symptom profile: Chronic mild stress (CMS) model

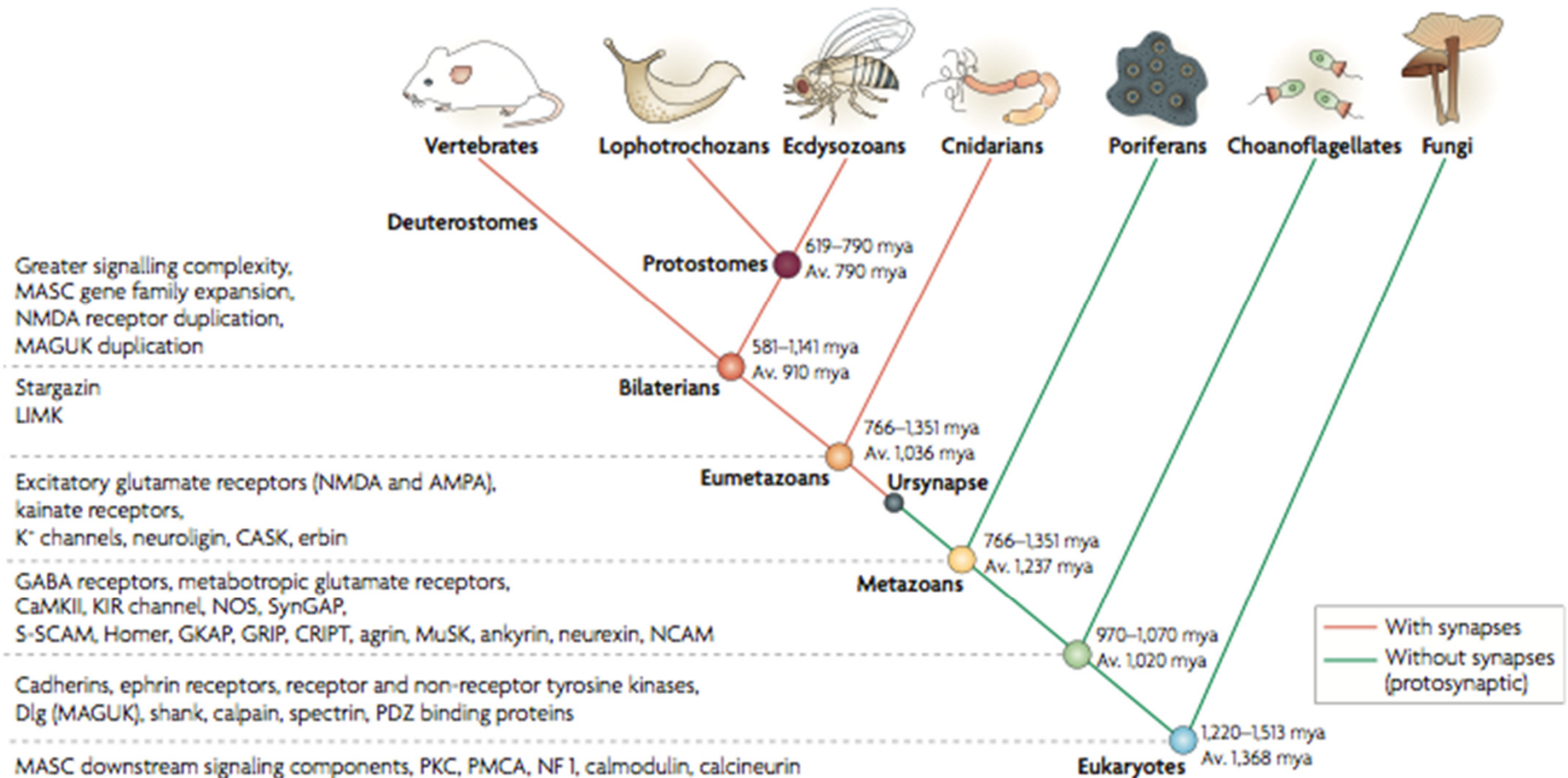
Depression	CMS
A. DSM-IV major depressive episode	
Duration	
At least 2 weeks	Effects of CMS persist for up to 3 months
Core symptoms	
Depressed mood	N/A
Markedly diminished interest/pleasure	Decreases in sexual and investigative behaviours decreased responses to rewards
Other symptoms	
Significant weight loss	Weight loss typically around 5%
Insomnia or hypersomnia	Disrupted sleep patterns
Psychomotor agitation or retardation	Decreased locomotor activity
Fatigue or loss of energy	Decreased “active waking” in EEG
Feelings of worthlessness or excessive or inappropriate guilt	N/A
Diminished ability to think or concentrate or indecisiveness	(Not tested)
Recurrent thoughts of death or suicide	N/A
B. DSM-IV melancholia	
Core symptom	
Loss of pleasure or lack of reactivity to pleasurable stimuli	Generalized decreased in responses to rewards
Other symptoms	
Distinct quality of depressed mood	N/A
Depression worst in morning	Effects worst at start of dark phase
Early morning awakening	Phase advance of diurnal rhythm of locomotor activity
Psychomotor agitation or retardation	Decreased locomotor activity
Significant anorexia or weight loss	Weight loss typically around 5%
Excessive or inappropriate guilt	N/A

Mesoaccumbens dopamine in coping with stress and progressive disease of motivation



Remember that during evolution we all have had a motive to grow (or to move)

Translational pharmacology: Evolution of synapse and point of therapeutic interest



Trans-nosographic dysfunctions of human motivation

- Depressive or Cyclothymic temperament
- Minor depression and the “dysthymias”
- Unipolar depression (if it exists??)
- Major depression and depressive episodes in BP
- Anxiety-depressive neurosis (NOT mixed states)
- Chronic drug abuse and/or withdrawals
- Negative/depressive syndromes in psychosis
- Neurological conditions (e.g. Parkinson’s; post stroke)
- Mental retardation
- Attention-Deficit-Hyperactivity Disorder
- Age-related cognitive impairments

Search for a dysfunction in motivation associated with:

- Depressive feelings
- Pessimism
- Anhedonia
- Low self-esteem
- Gloominess
- Inadequacy
- Cognitive impairment
- Asthenia
- Hypersomnia
- ...

Regulatory (but personal!) conclusions

When searching a new claim for a novel indication and/or an undefined disorder ensure:

- To use regulatory validated scales
- To accurately define the population
- To carefully select the endpoint(s)
- To choose – if possible – an adequate comparator
- To conduct the trial for a significant amount of time
- To show an effect on function
- To run statistics in line with the clinical significance of the claim(s) you want to make

This has been an ethological-regulatory talk, so ...

Are the organization and the flexibility of the human brain still compatible with the evolution of an environment that he can control only partially ?

It is very doubtful.

Jean-Pierre Changeux, 1983

