

# Neurobiologia da Ansiedade: ansiedade normal versus patológica e sistemas de defesa



*"Goethe's Der Erlkönig" Lili  
Bernard (detalhe)*

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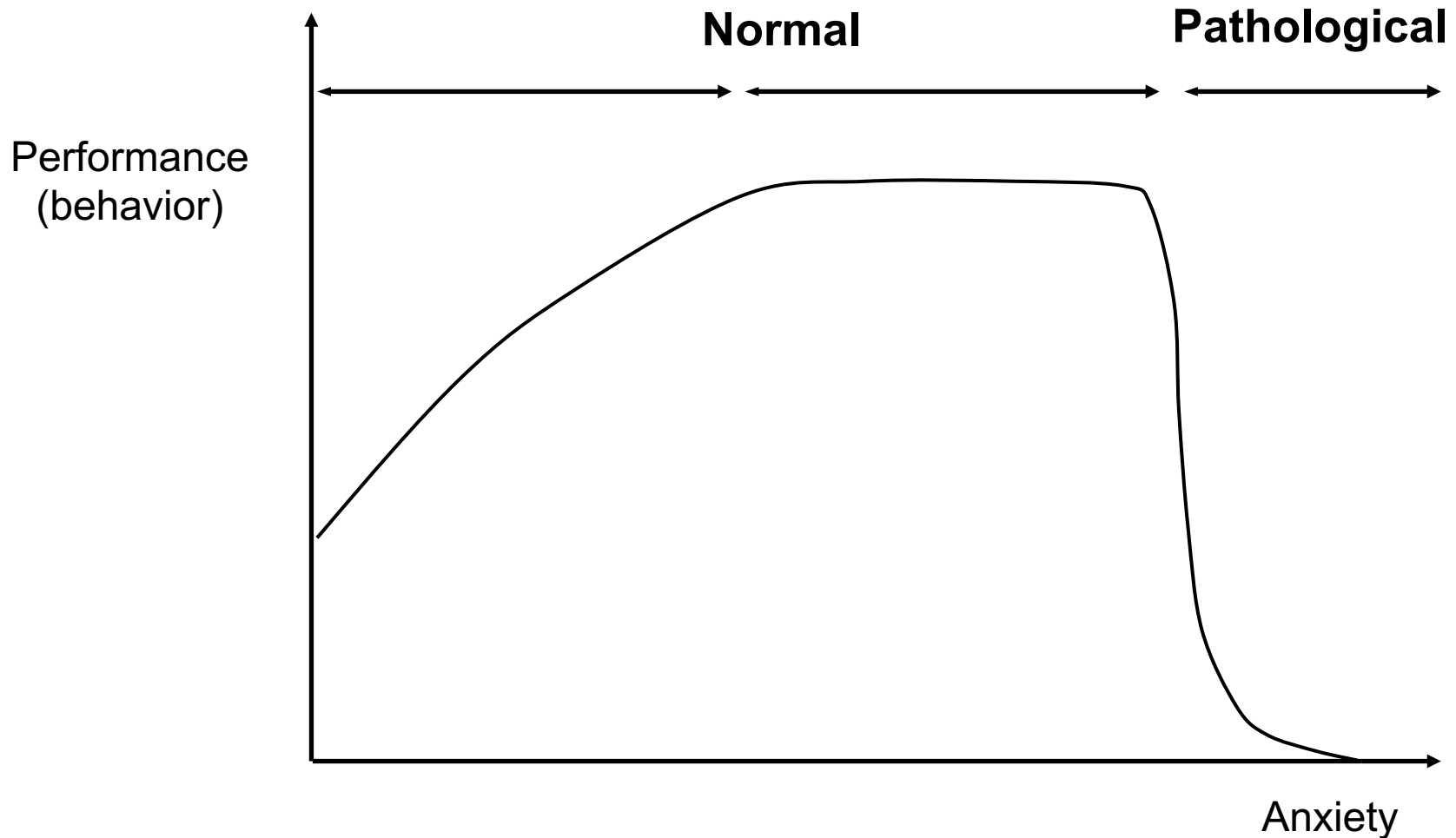
- Animais que não o Homem também apresentam emoções manifestadas por meio de expressões

*The Expression of the Emotions in Man and Animals*

*Charles Darwin, 1872*

**Presuposto básico: As bases biológicas da  
ansiedade humana encontram-se nas  
reações defensivas que os animais mais  
primitivos apresentam frente a estímulos  
ameaçadores**

# Ansiedade normal versus patológica

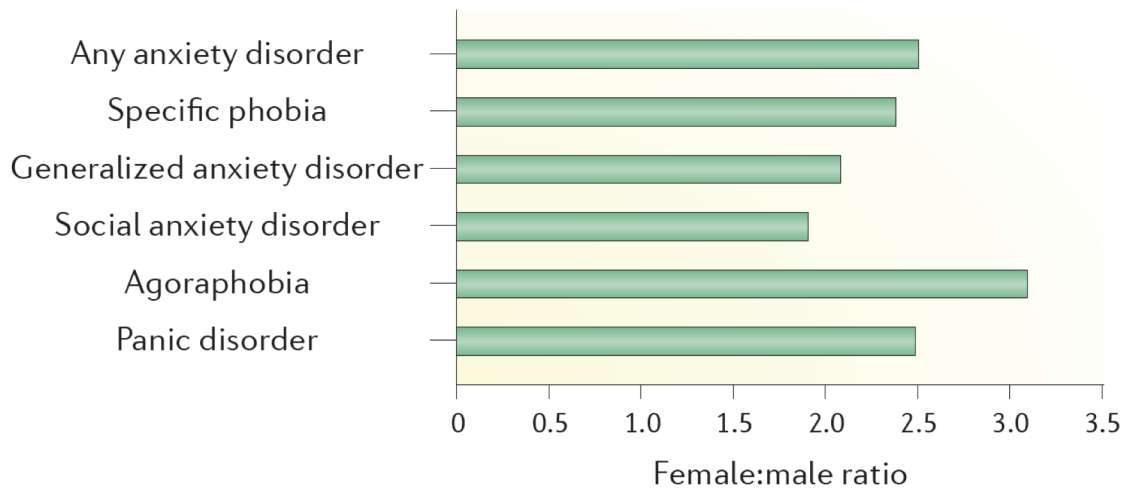
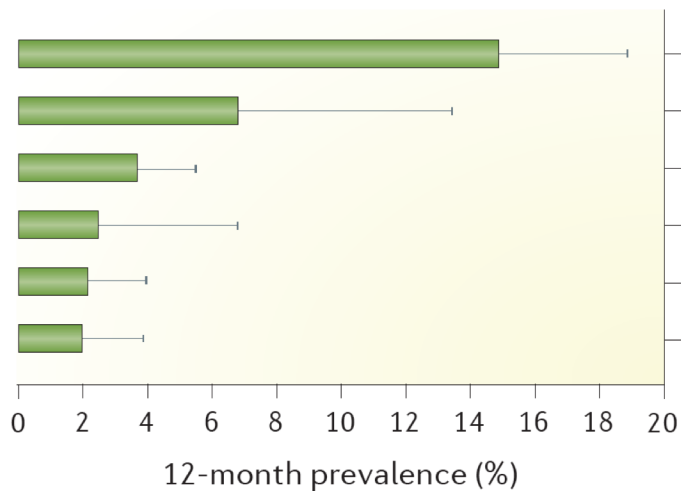
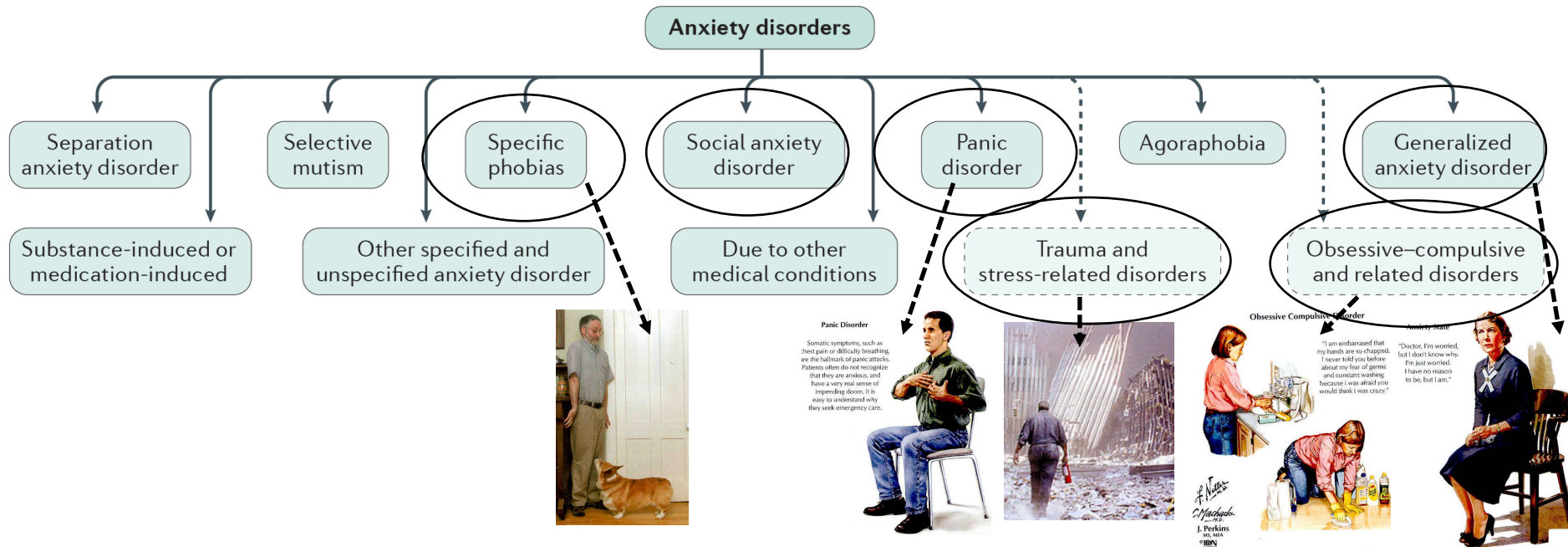


## Disorders of the brain in Europe (as of 2010) (Kondziella D 2016)

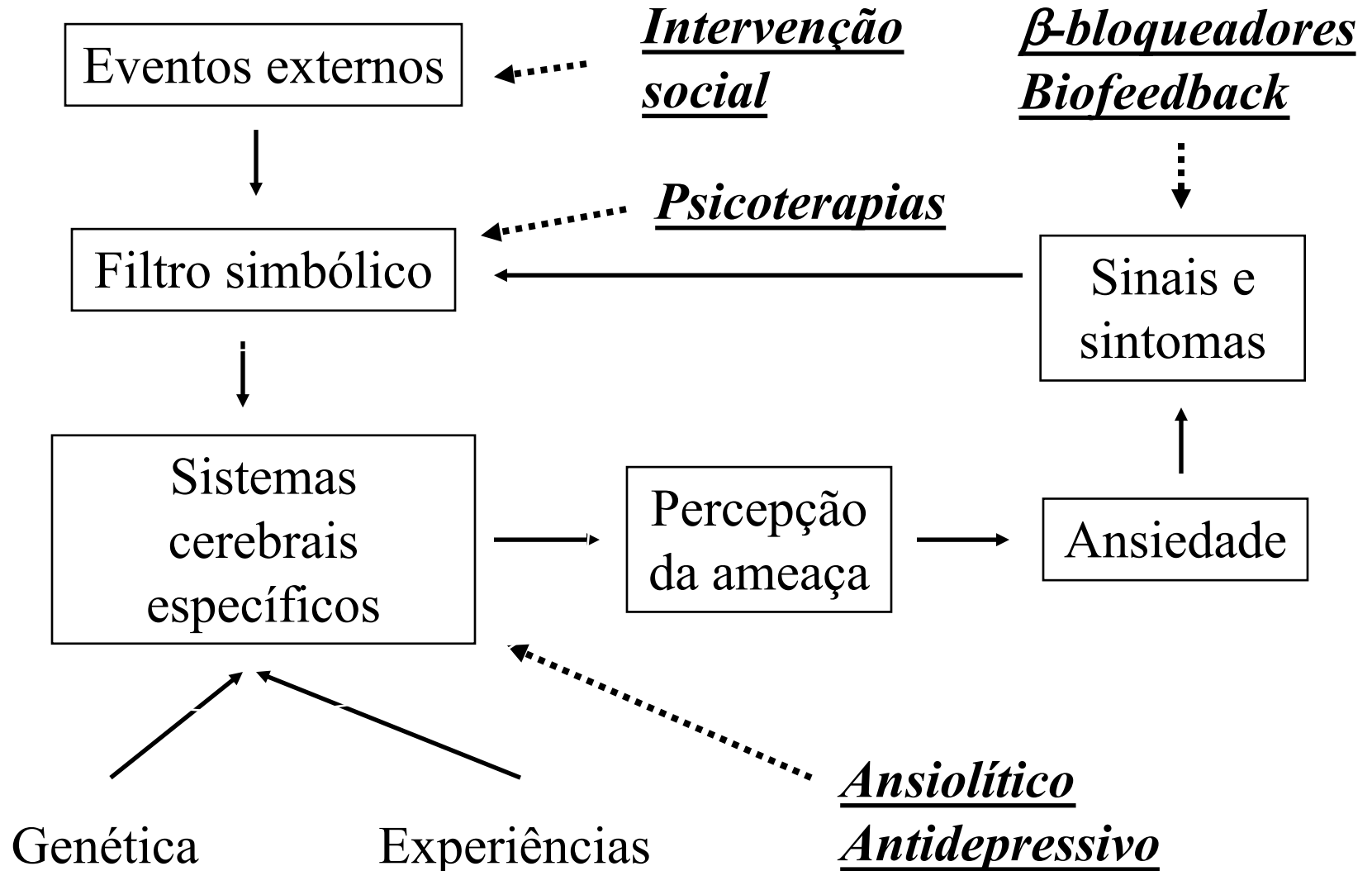
	<b>Number of subjects (in million)</b>	<b>Total costs (in billion €)</b>
Migraine	49.9	18.5
Dementia	6.3	105.2
Epilepsy	2.6	13.8
Stroke	1.3 <sup>a</sup>	64.1
Parkinson's disease	1.2	13.9
Traumatic brain injury	1.2 <sup>a</sup>	33.0
Multiple sclerosis	0.54	14.6
Neuromuscular disorders	0.26	7.7
Brain tumors	0.24	5.2
<b>Mood disorders</b>	<b>33.3</b>	<b>113.4</b>
<b>Anxiety disorders</b>	<b>61.3</b>	<b>74.4</b>
<b>Psychotic disorders<sup>b</sup></b>	<b>5.0</b>	<b>93.9</b>

Costs and incidence of neurological disorders in Europe as of 2010 (data adapted from Gustavsson et al. [2]). Three major psychiatric conditions (mood, anxiety and psychotic disorders) are listed for comparison. <sup>a</sup>Includes only incident cases in 2010; <sup>b</sup>includes schizophrenia

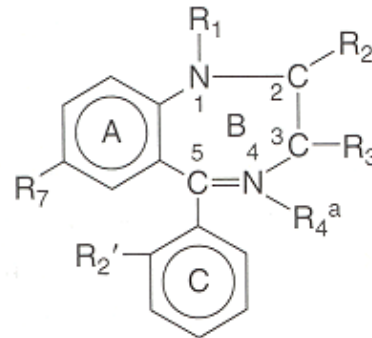
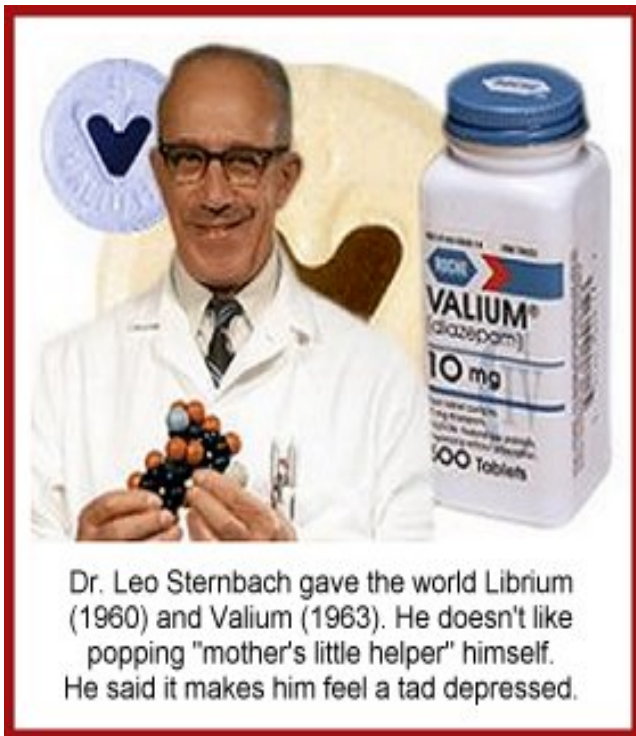
# Classification (DSM-V) and annual prevalence of anxiety disorders



# Visão conceitual da ansiedade humana



# Descoberta das drogas ansiolíticas benzodiazepínicas foi grande incentivo ao desenvolvimento dos modelos animais de ansiedade



Randal 1960



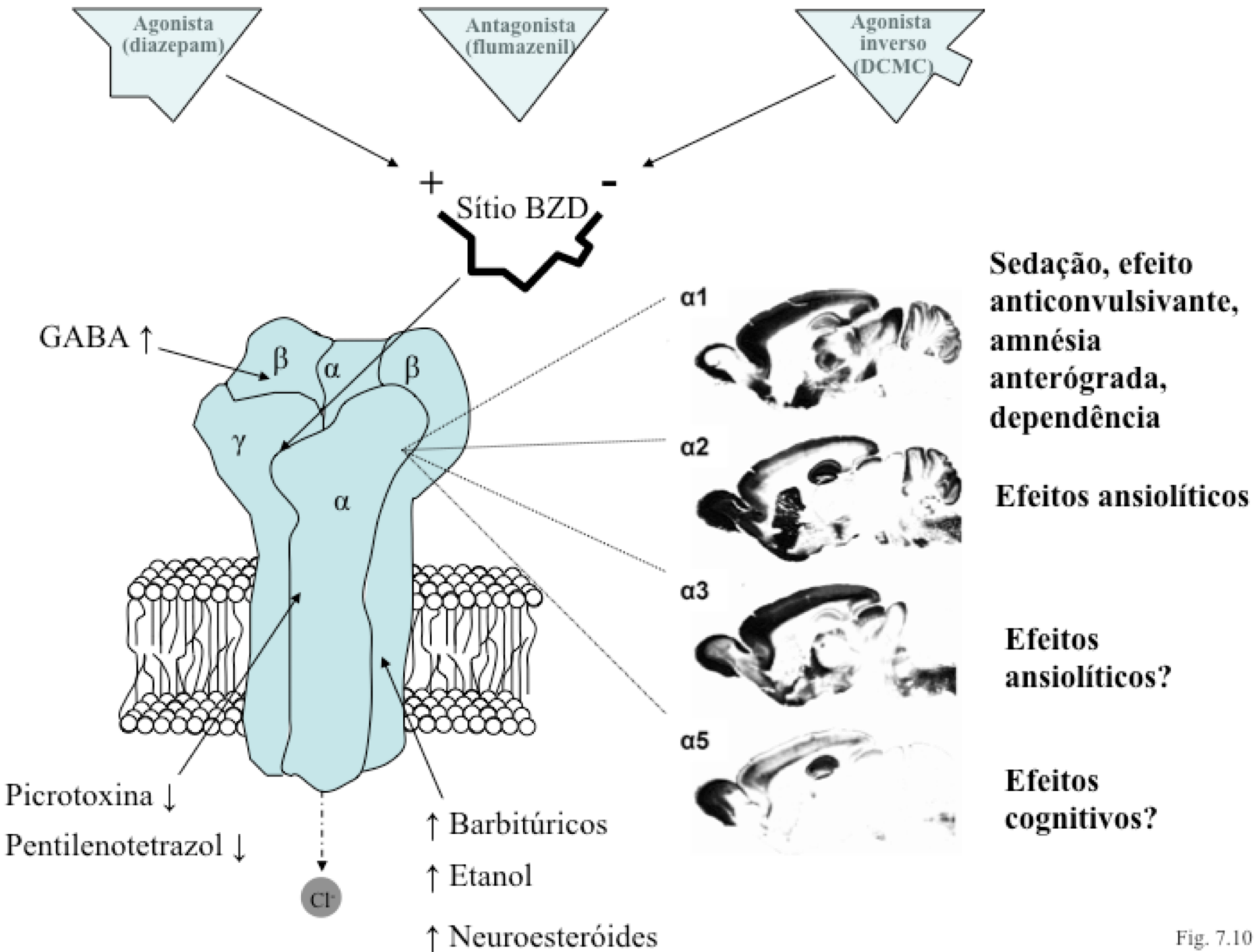
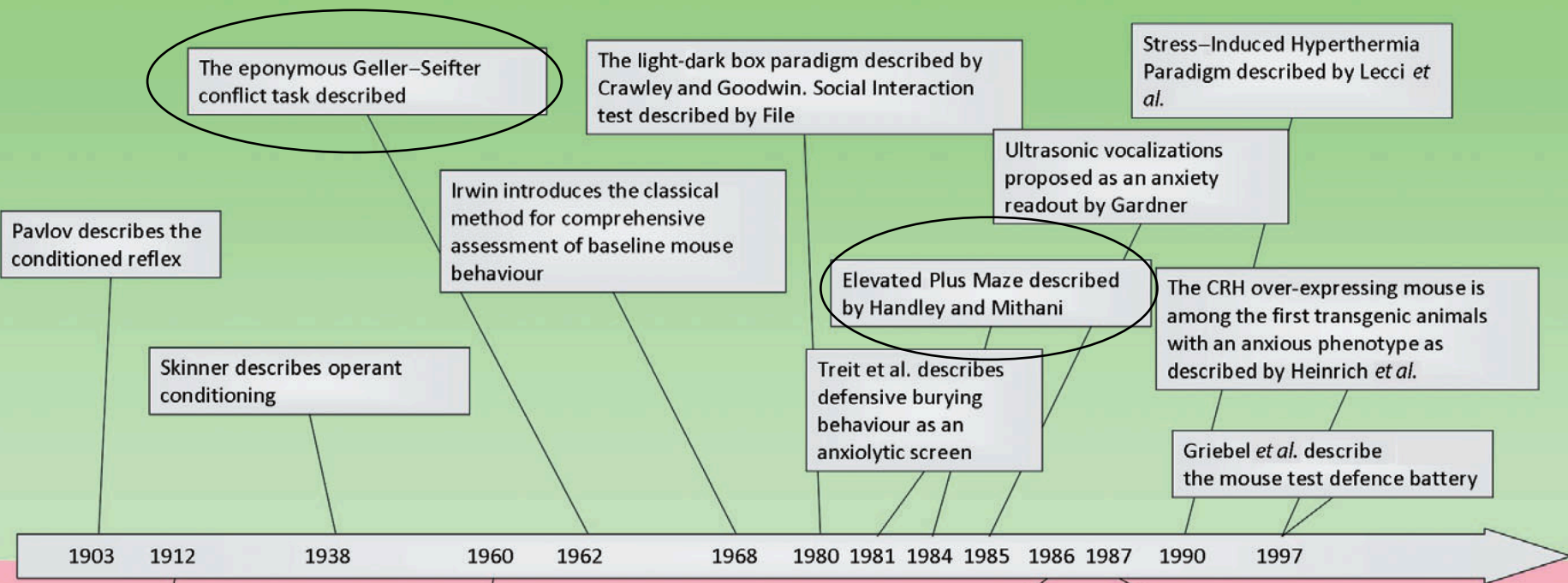


Fig. 7.10

# Evolução dos modelos de ansiedade

## Advances in Animal Modelling of Anxiety Disorders



First clinical use of phenobarbital as a hypnotic

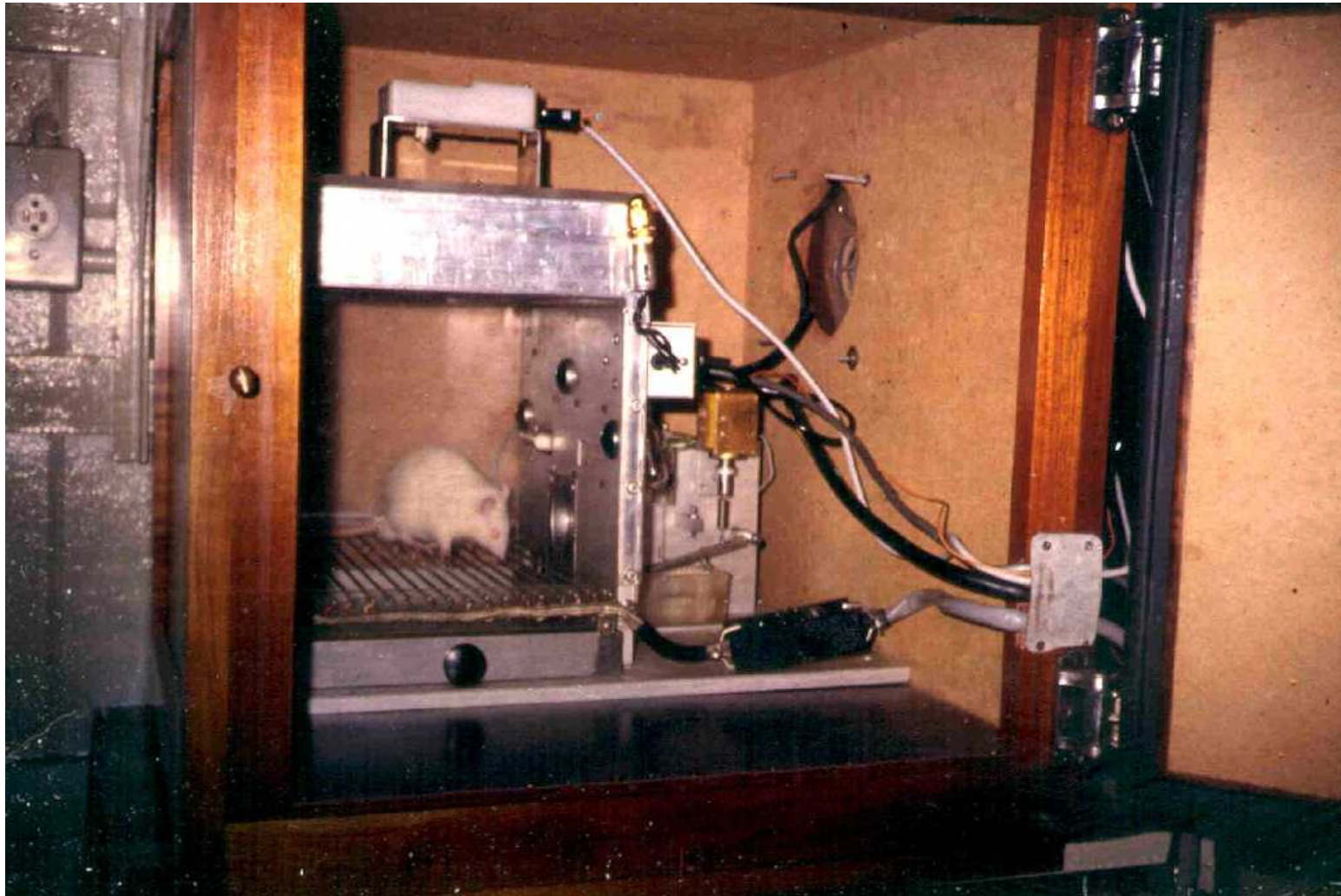
Chlordiazepoxide (Librium®) the first benzodiazepine is launched by Hoffman-LaRoche (circled)

Buspirone receives FDA approval (circled)

Fluoxetine (Prozac®), the first SSRI antidepressant receives FDA approval (circled)

## Anxiolytic Drugs in Clinical Use

# Os modelos animais de ansiedade: O teste de conflito-punição e a inibição comportamental

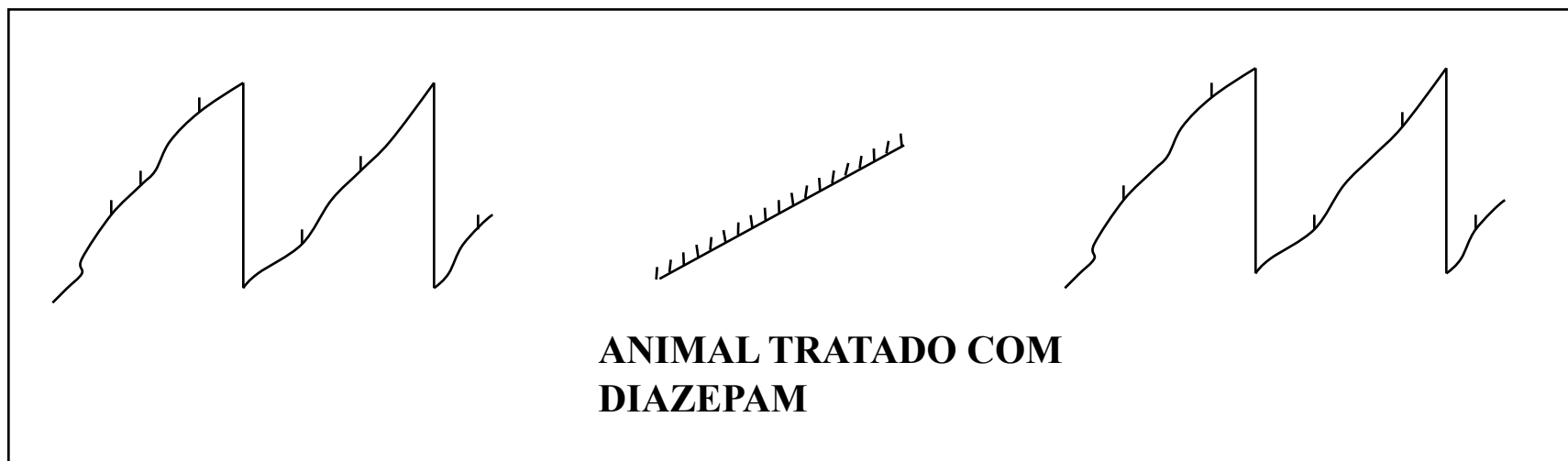
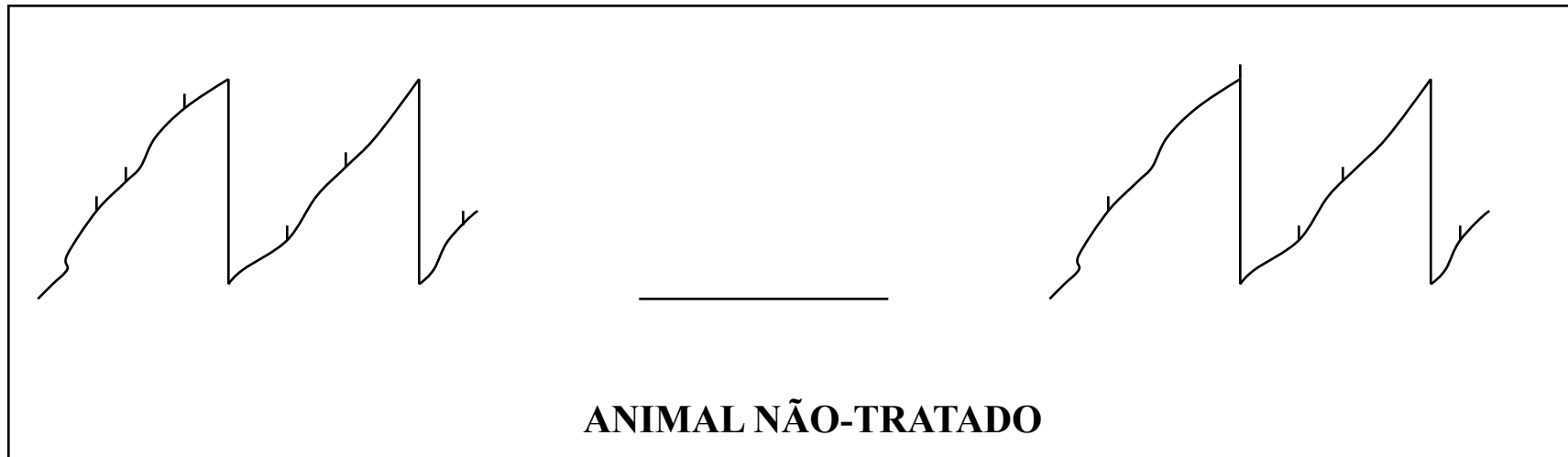


*Geller & Seifter, Psychopharmacology 1:482, 1960*

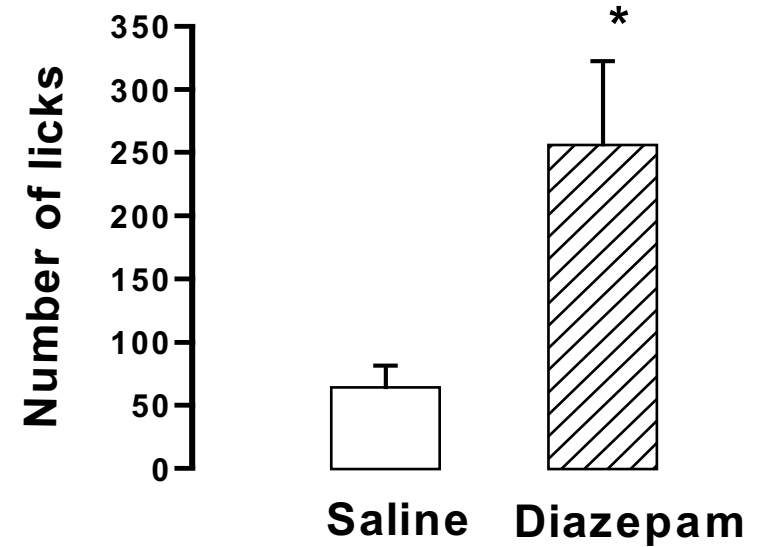
*PERÍODO NÃO-PUNIDO*

*PERÍODO PUNIDO*

*PERÍODO NÃO-PUNIDO*



# Teste de conflito de Vogel



*Jardim M, 2003*

# *Sistema de Inibição Comportamental (Gray, 1982)*

Sinais de punição ou frustração

Novidade

Estímulos ameaçadores inatos



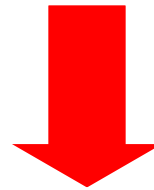
***Sistema de inibição comportamental***



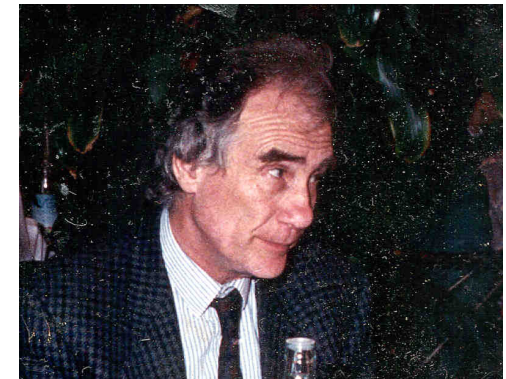
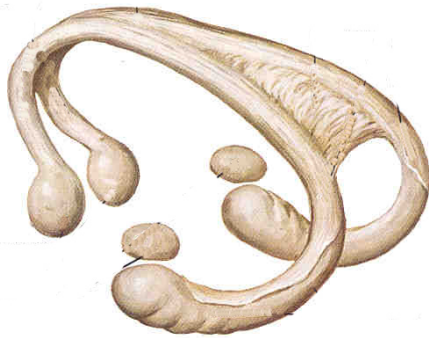
Inibição comportamental

Aumento da vigilância

Aumento na atenção seletiva



***Sistema septo-hipocampal***



Ansiolíticos

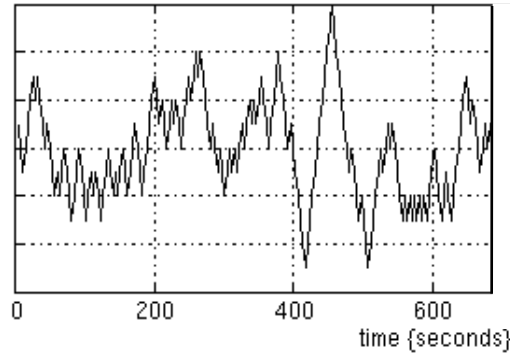


?

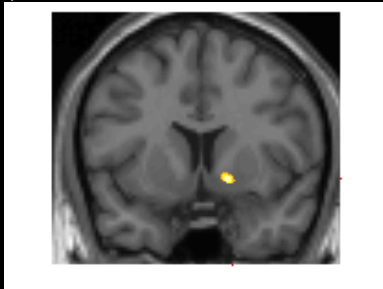
*The task:*



*Height of reward bar over time:*



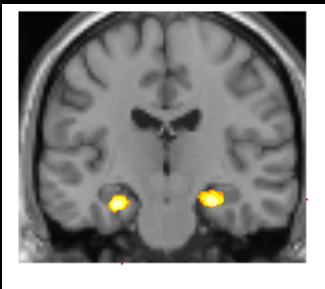
(a)



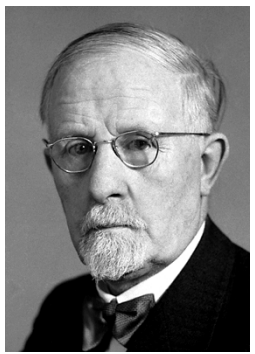
(b)



(c)



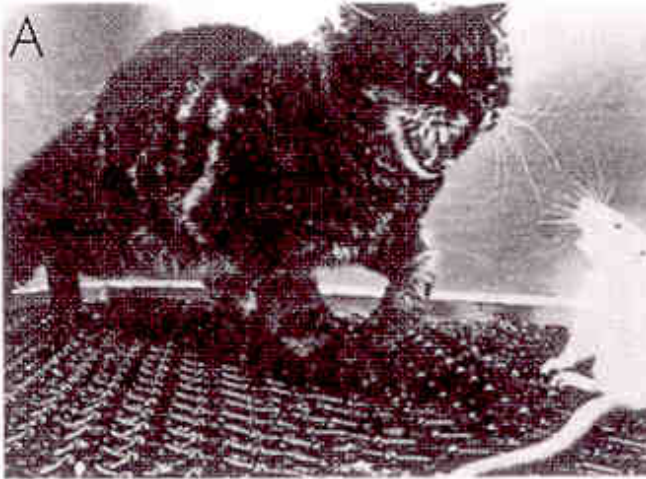
- \* *Subjects perform a series of two choice guesses*
- \* *Reward bar shows cumulative reward across trials*
- \* *fMRI used to measure evoked haemodynamic response*
- \* *Height of bar used as model for activity changes*
- \* *Overall height of bar correlates with activation in nucleus accumbens and substantia nigra (a)*
- \* *Where height is increasing most rapidly increased activation is seen in dorsal striatum and subgenual cingulate (b)*
- \* *Height of the bar correlates negatively with activation in hippocampus (c). Thus hippocampal blood flow seen when reward is removed.*



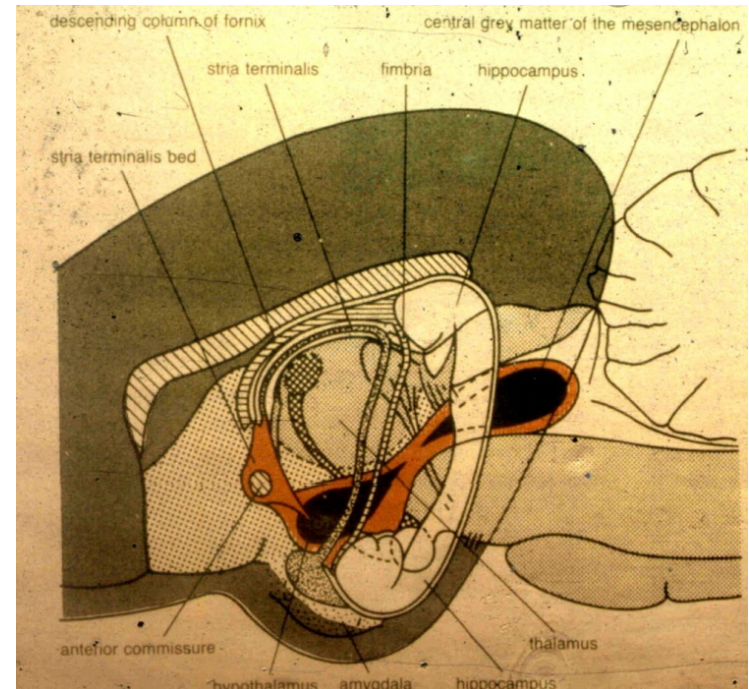
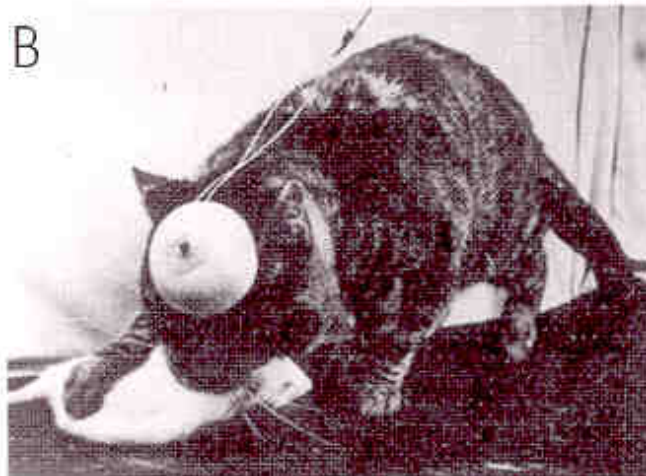
# Outros modelos: Reação de “defesa afetiva” x ataque ofensivo

*Hess 1943*

Estimulação  
Hipotálamo  
medial



Estimulação  
Hipotálamo  
lateral

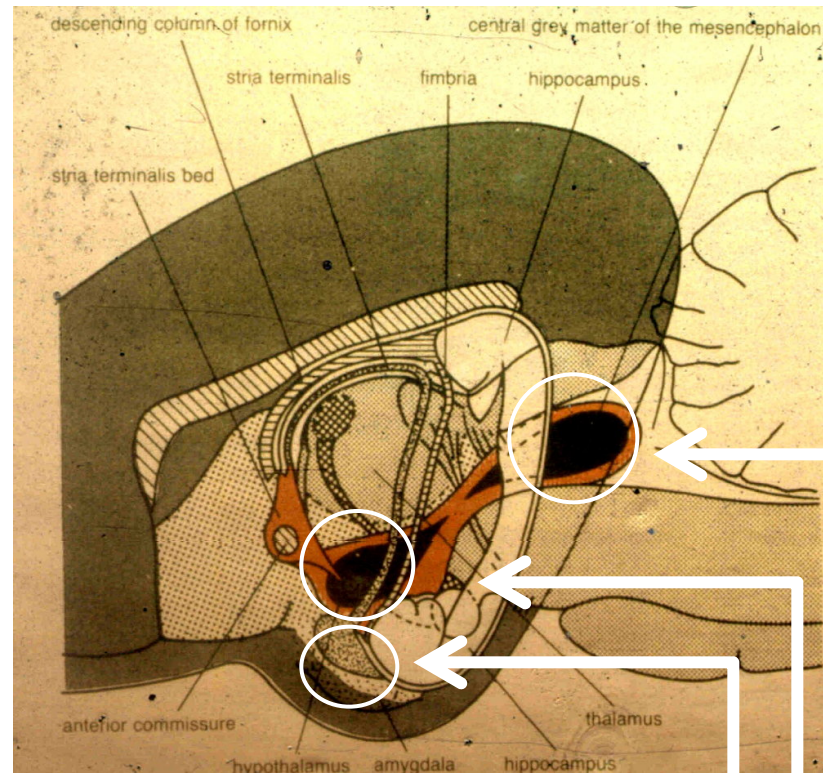
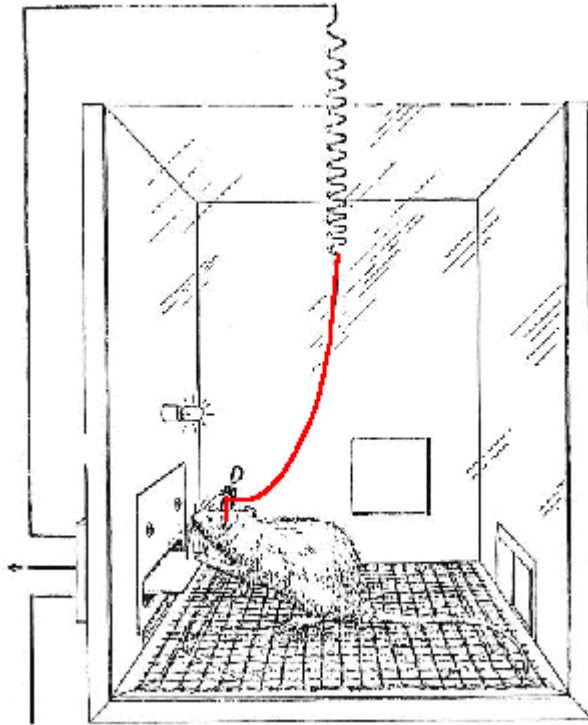


Hunsberger and de Molina:  
incluíram a amígdala e  
substância cinzenta  
periaqueductal





**Estimulação  
elétrica da  
SCPD de  
roedores**

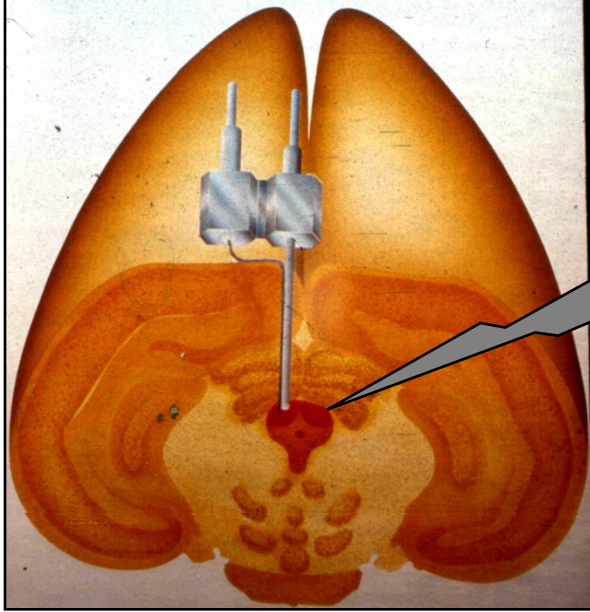


## Estimulação cerebral aversiva



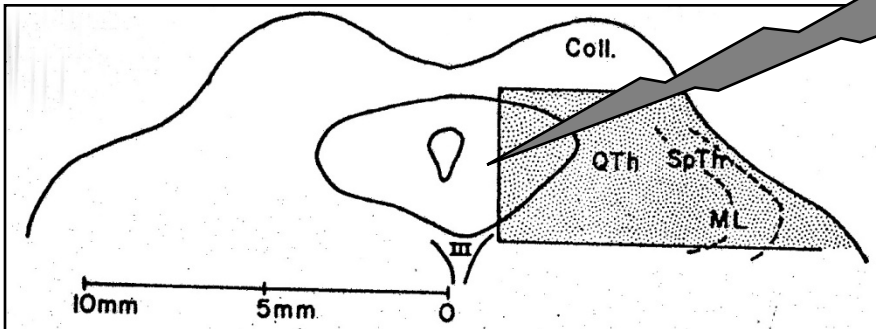
*Graeff 1981:*  
*sistema cerebral*  
*aversivo*

**Amígdala**  
**Hipotálamo**  
**medial**  
**Substância**  
**Cinzenta**  
**periaquedutal**



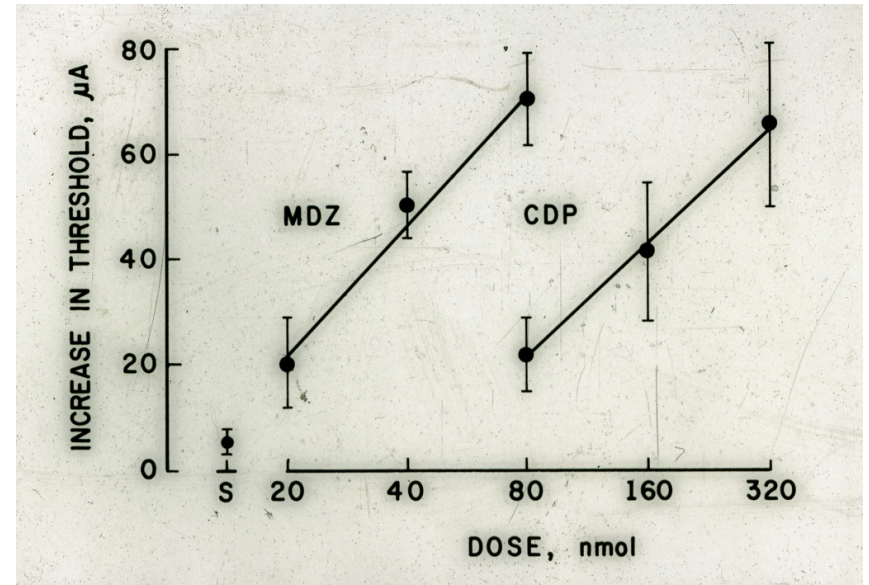
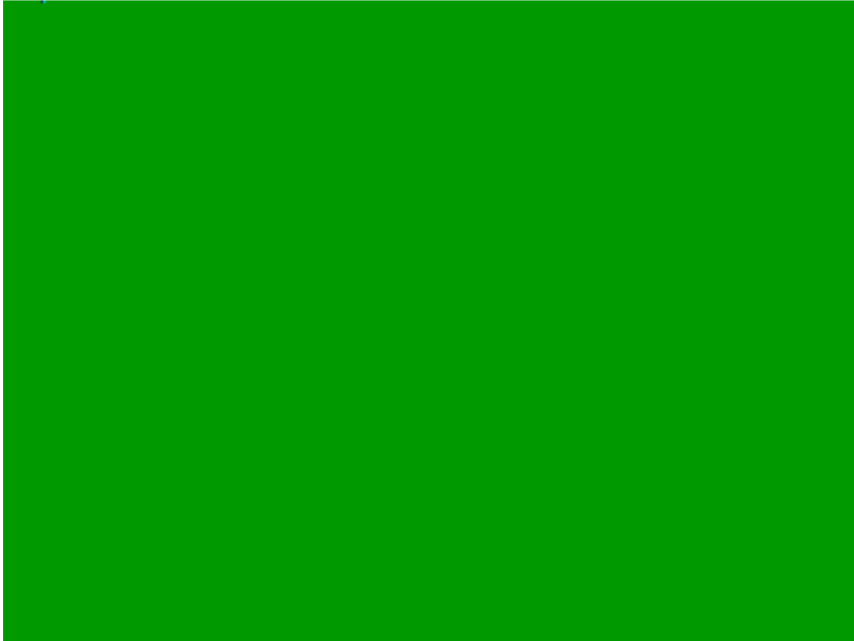
*Estimulação cerebral  
aversiva*

**Pânico (?)**



Terror, medo, aversão  
Sensação de morte iminente  
Taquicardia, alterações  
ventilatórias, dor, parestesias

# Ansiolíticos atenuam os efeitos da estimulação cerebral aversiva



*Audi e Graeff 1984*

Estimulação do “sistema cerebral aversivo” produz reação semelhantes àquelas apresentadas frente a predadores



Microinjeção de NMDA na SCPD



Gato de brinquedo



Gato de verdade

*Bejamini V, 2003*



Efeito da inibição da SCPD na resposta a predadores



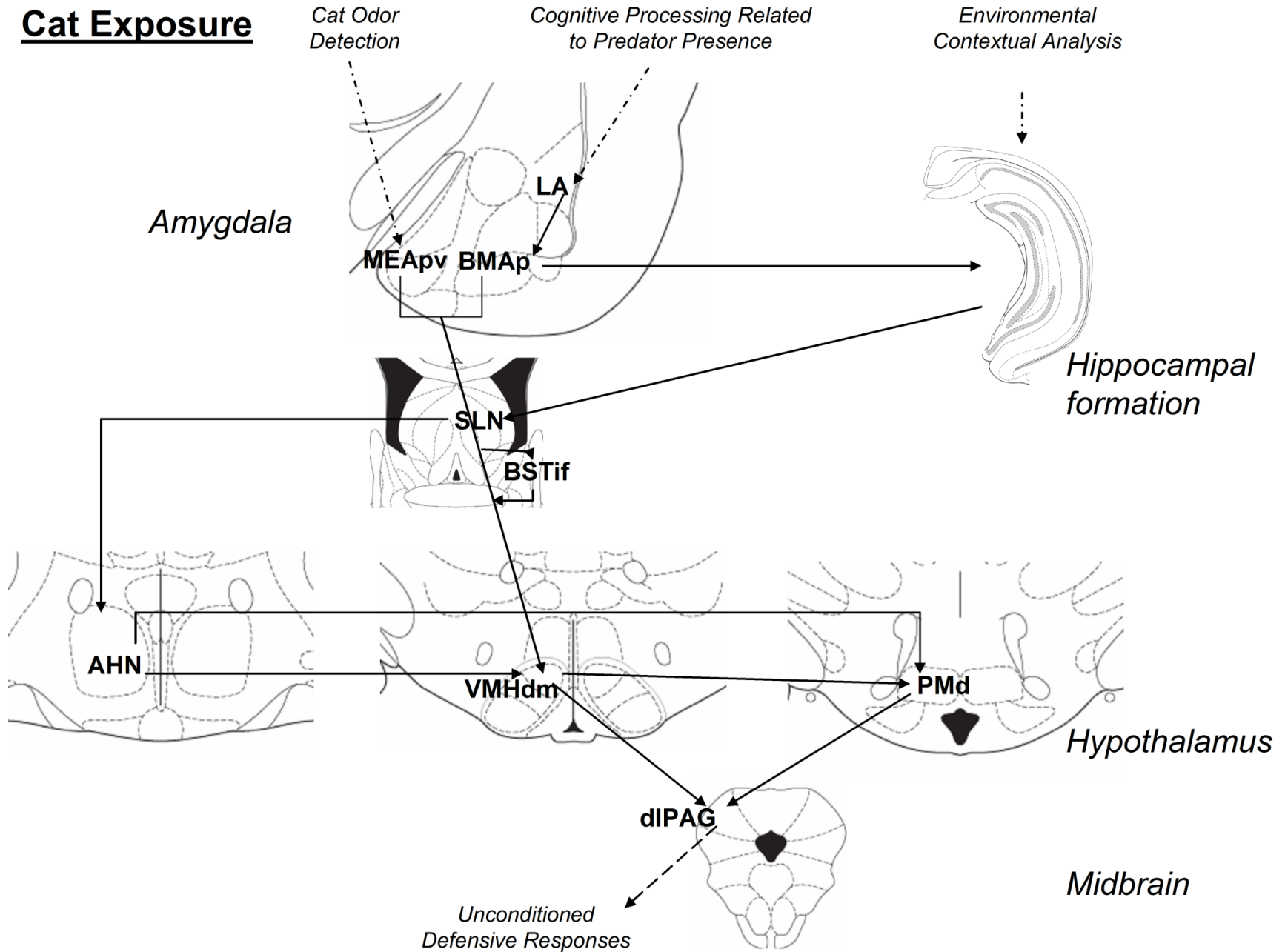
**controle**



**Inibição da substância cinzenta  
periaquedutal dorsal**

# Principais estruturas envolvidas em reações inatas de defesa

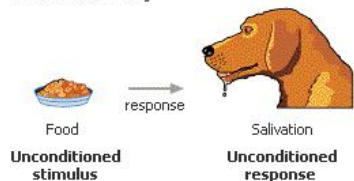
## Cat Exposure



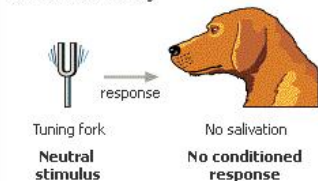


# Como aprendemos a ter medo: condicionamento aversivo

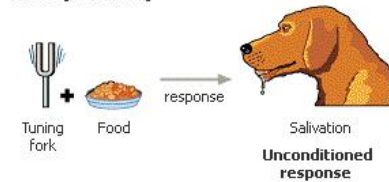
1. Before conditioning



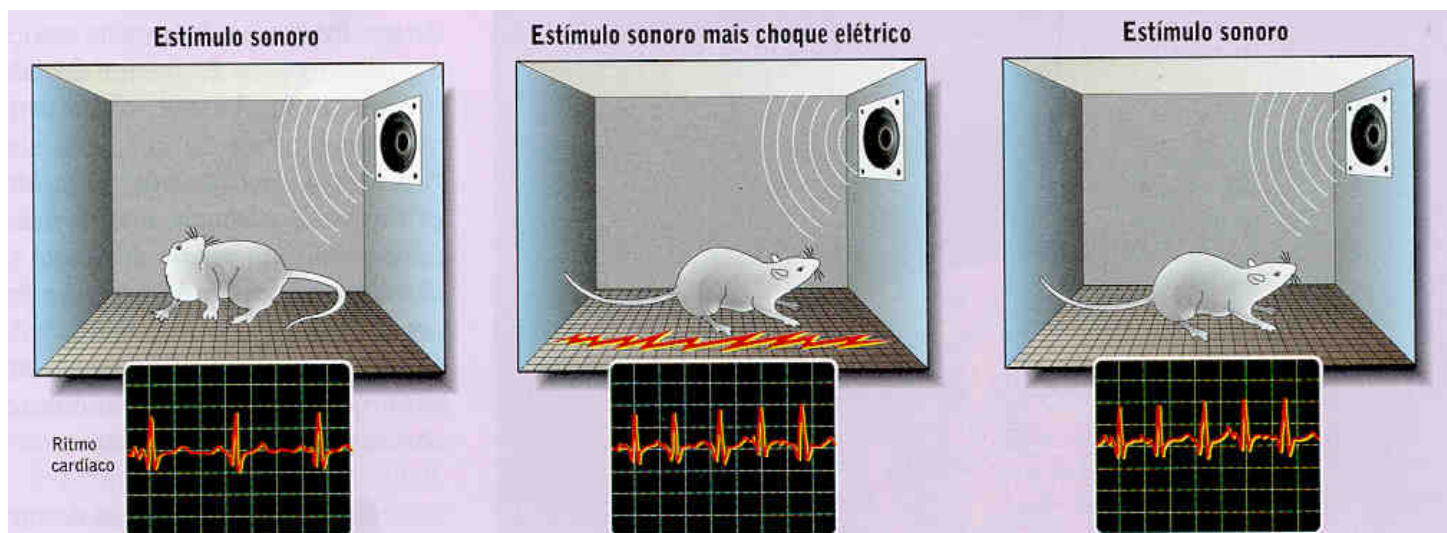
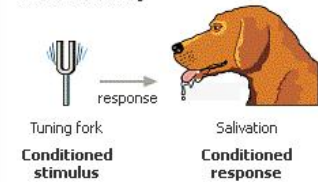
2. Before conditioning



3. During conditioning



4. After conditioning



## Stanley Kubrick: A laranja mecânica



Lá pelo sexto ou sétimo malchique  
rindo e esmecando...

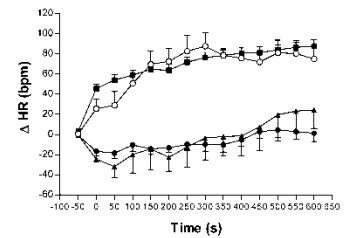
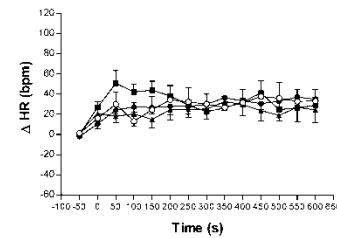
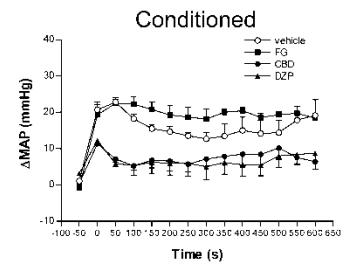
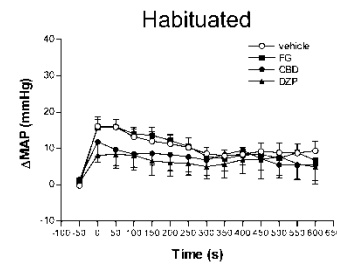
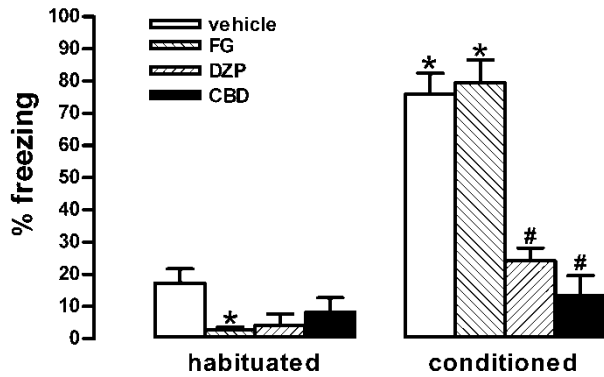
# Condicionamento aversivo contextual



Veículo



Diazepam

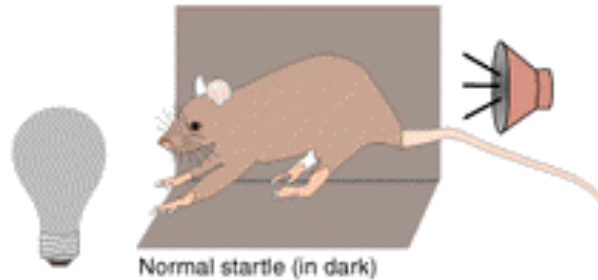


# O susto potencializado pelo medo

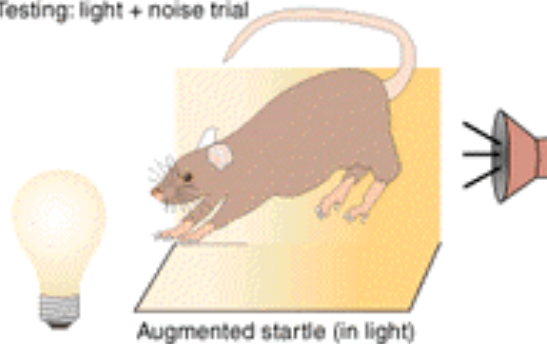
Training: light and shock paired

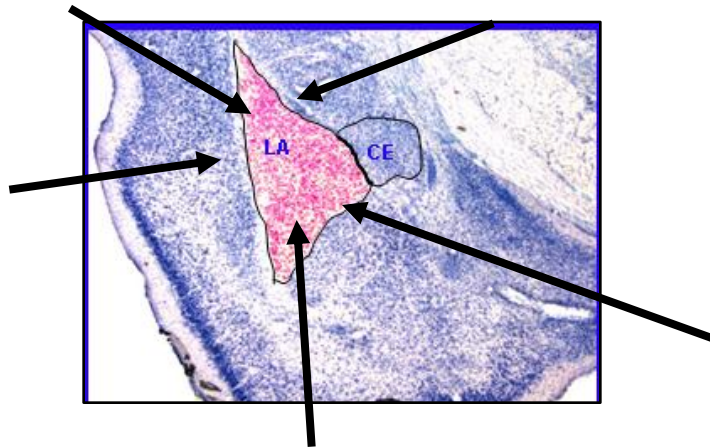


Testing: noise-alone trial



Testing: light + noise trial





**Complexo  
amigdalóide: recebe  
informação sensorial  
processada**

# Projeções da amígdala para áreas de defesa

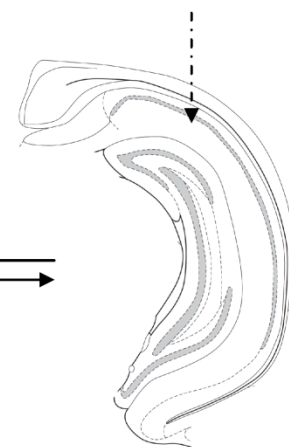
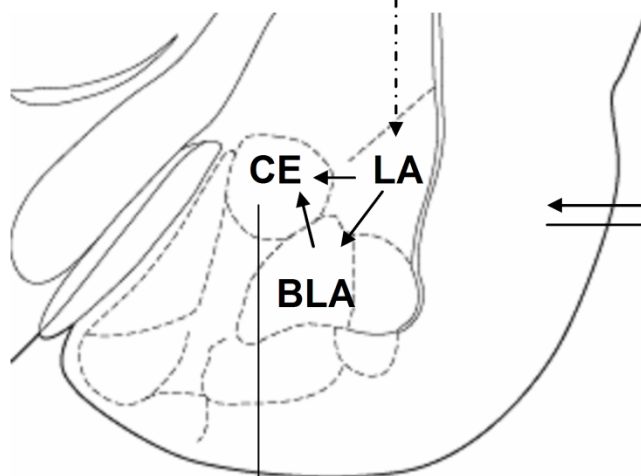
## Fear Conditioning

CS + UCS

Associative learning

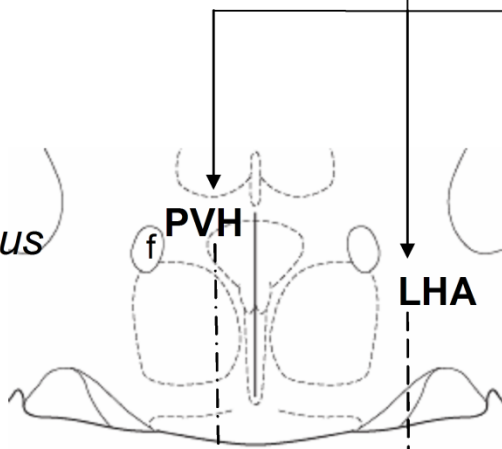
Environmental Contextual Analysis

Amygdala



Hippocampal formation

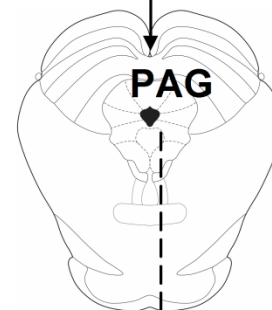
Hypothalamus



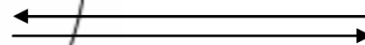
Neuroendocrine Responses

Autonomic Reactions

Midbrain



Conditioned Freezing



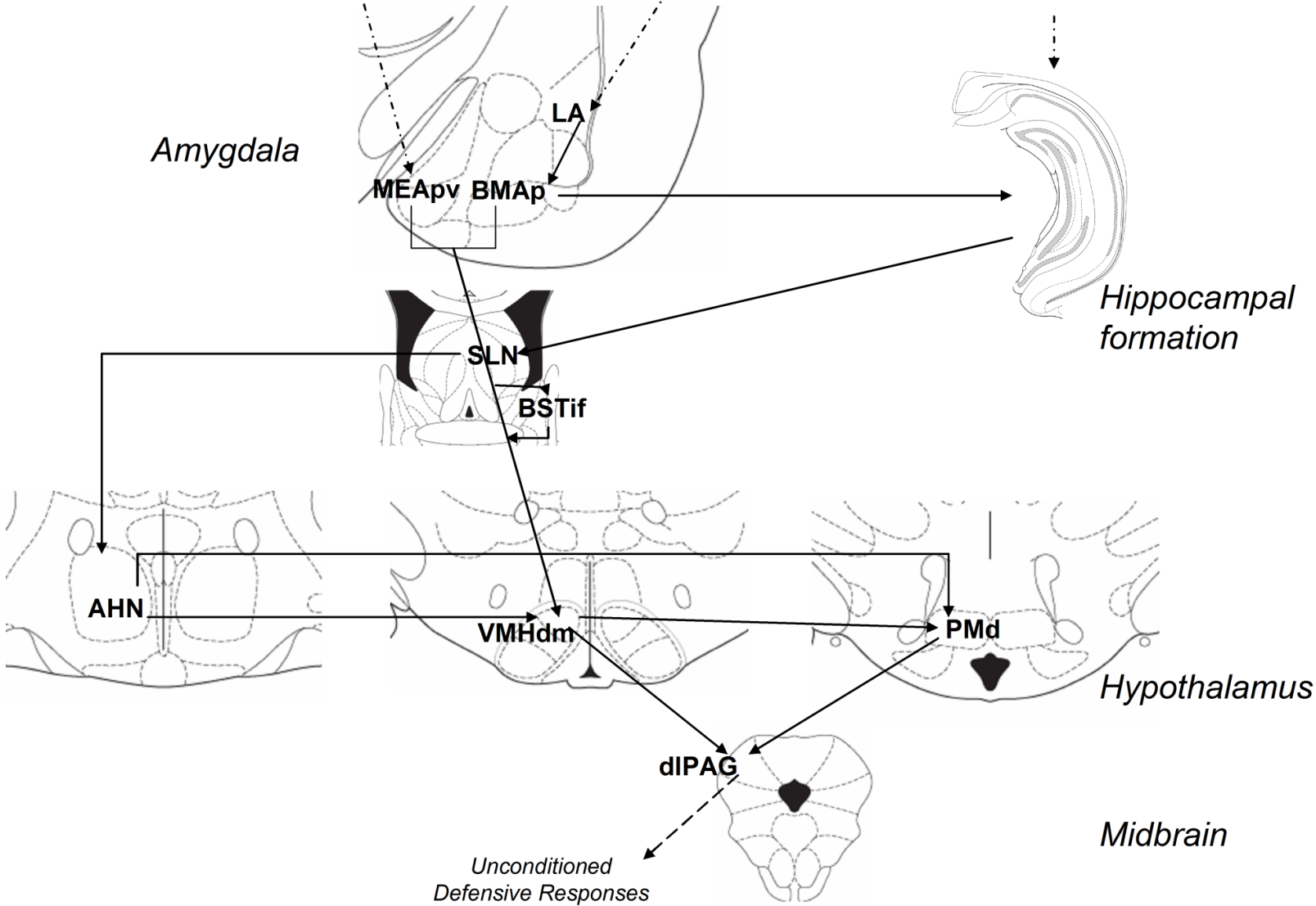
# Amígdala também está envolvida em reações inatas de defesa

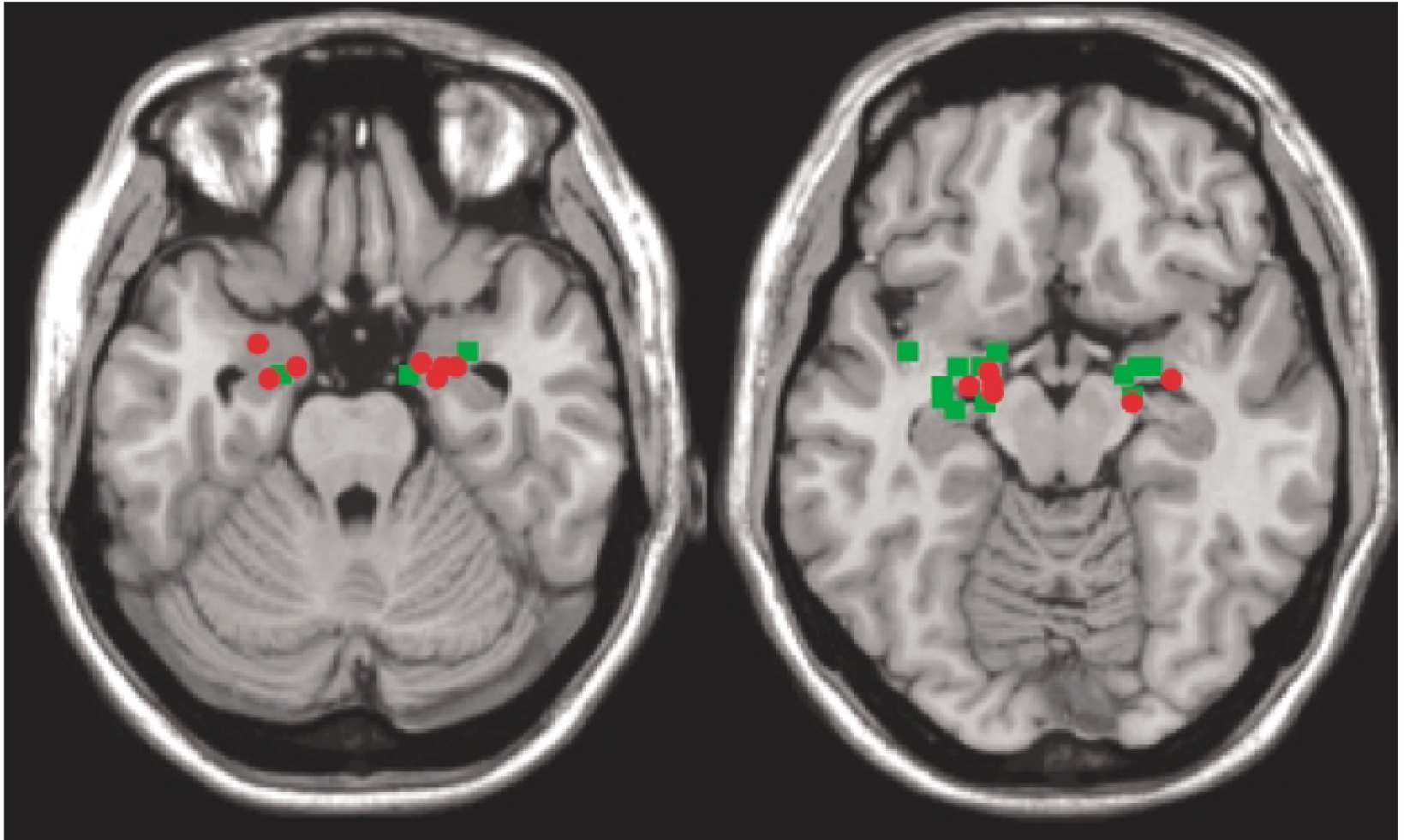
## Cat Exposure

Cat Odor Detection

Cognitive Processing Related to Predator Presence

Environmental Contextual Analysis

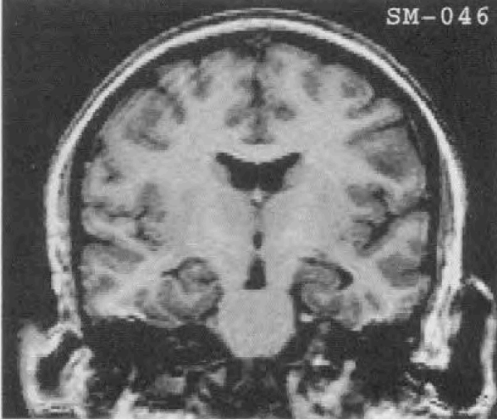




**Expressões faciais de medo (quadrados verdes): ativação dorsal esquerda**

**Medo condicionado (círculos vermelhos): ativação bilateral ventral e dorsal**

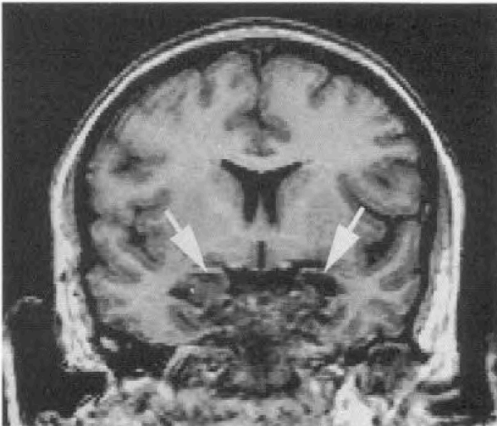




## Fear and the Human Amygdala

Ralph Adolphs,<sup>1</sup> Daniel Tranel,<sup>1</sup> Hanna Damasio<sup>1,2</sup> and Antonio R. Damasio<sup>1,2</sup>

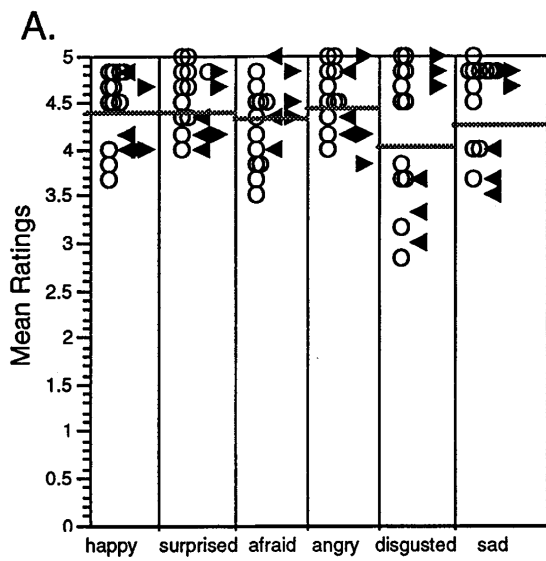
<sup>1</sup>Department of Neurology, Division of Cognitive Neuroscience, University of Iowa College of Medicine, Iowa City, Iowa and <sup>2</sup>The Salk Institute for Biological Studies, La Jolla, California



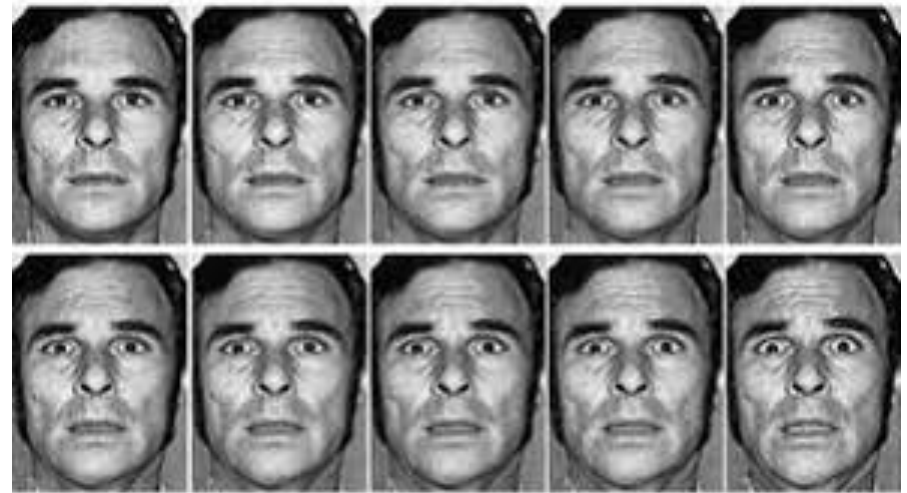
**SM: paciente feminina, 30 anos, com doença genética autossômica recessiva rara chamada de **Urbach-Wiethe**, que resulta em calcificação e atrofia progressiva da amígdala**



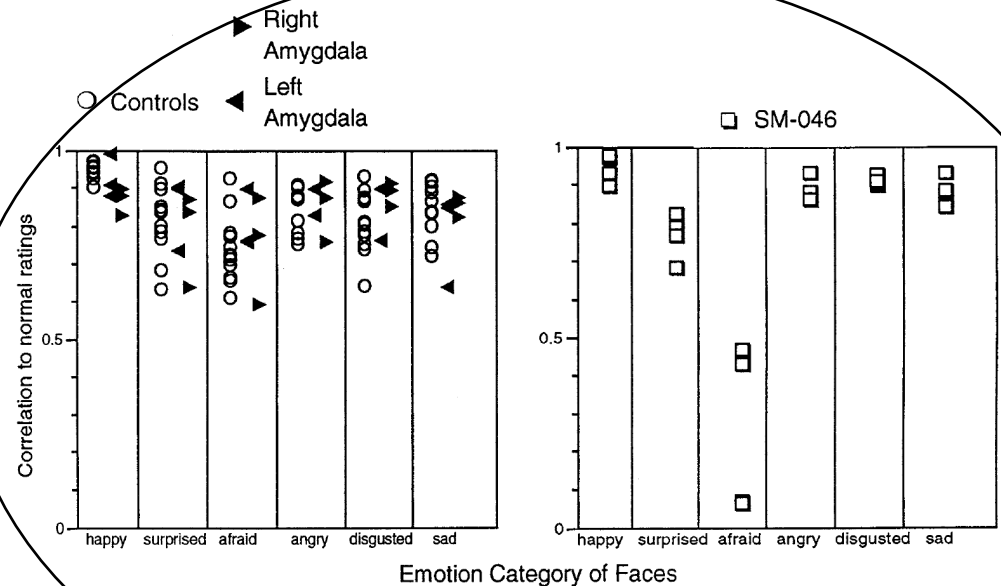
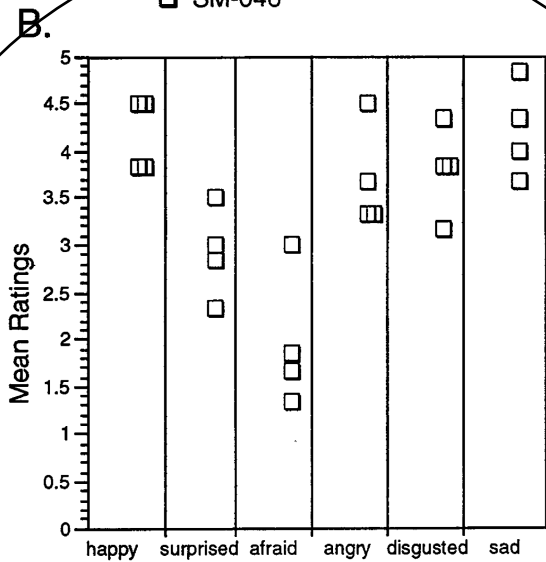
Paciente com QI médio baixo, com educação superior, **sem dificuldade de reconhecimento de objetos e faces**



- Brain-damaged controls
- Normal controls
- ◀ Left Amygdala damage
- ▶ Right Amygdala damage
- SM-046



Ex.: medo



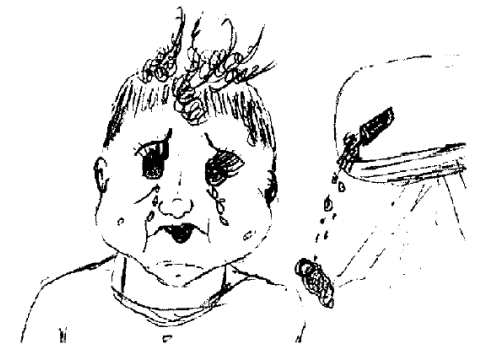
Intensidade das emoções

Categoria das emoções

# Desenho pela paciente SM de expressões emocionais



**HAPPY**



**SAD**



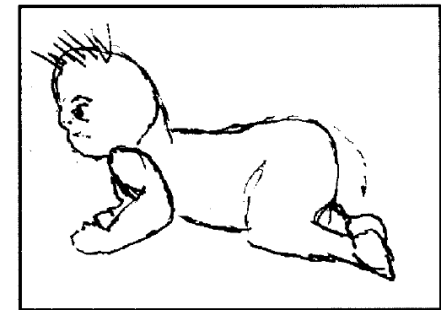
**SURPRISED**



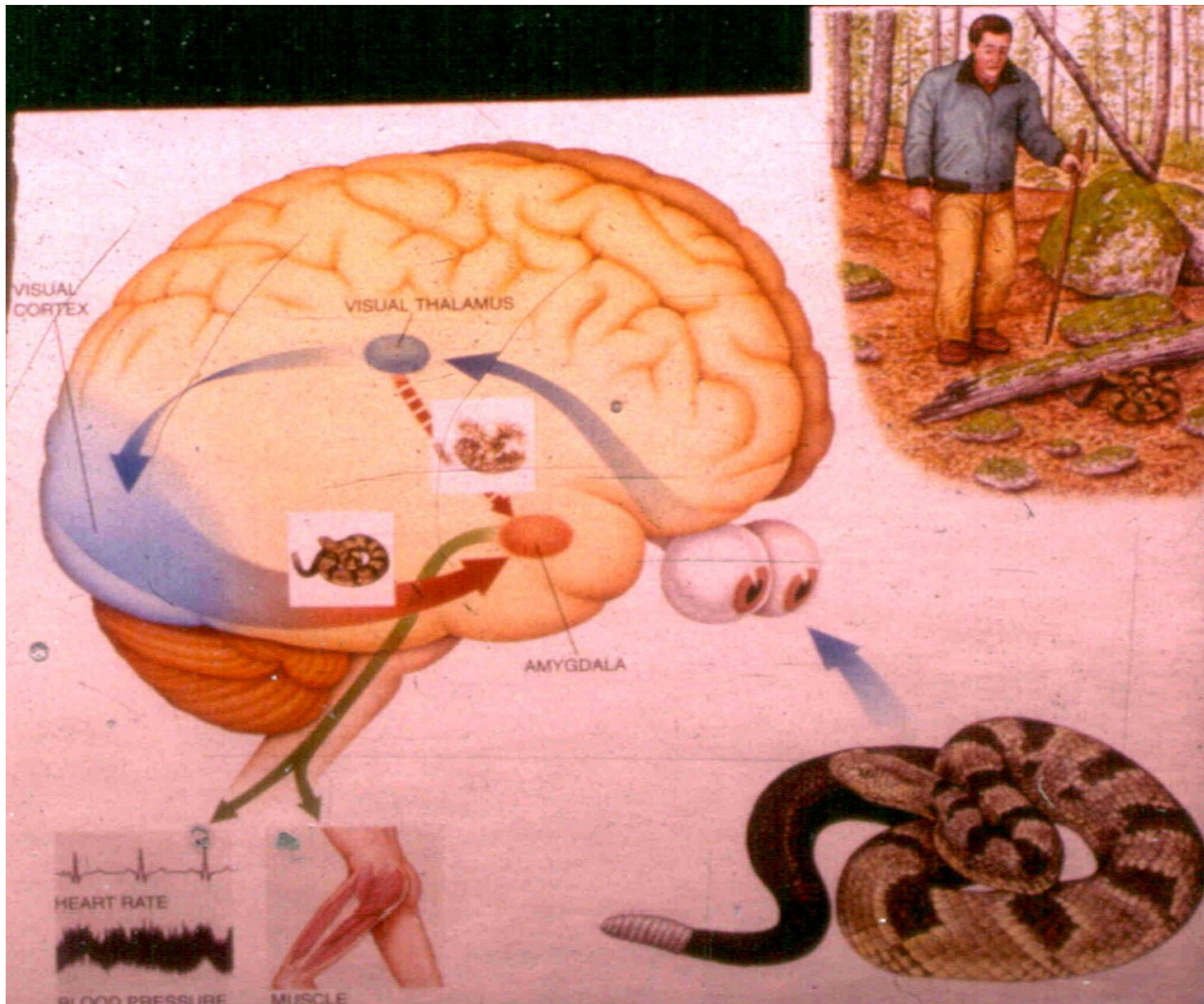
**DISGUSTED**



**ANGRY**



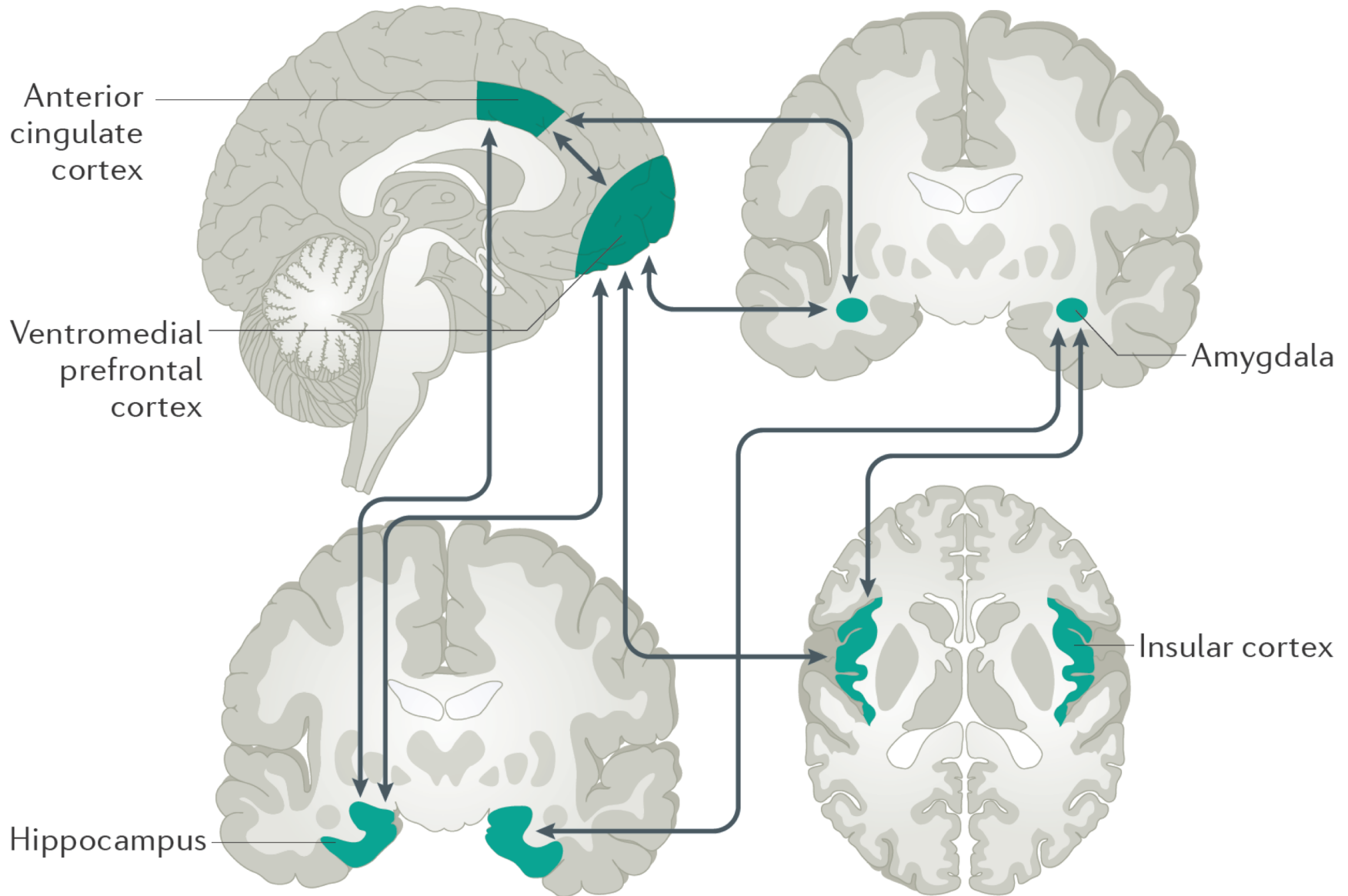
**AFRAID**



***Amídala  
também é  
envolvida  
em sistema  
rápido de  
detecção  
do perigo***

***Joseph E.  
LeDoux***

# Estudos de neuroimagem em humanos tem confirmado o envolvimento de várias destas estruturas na ansiedade



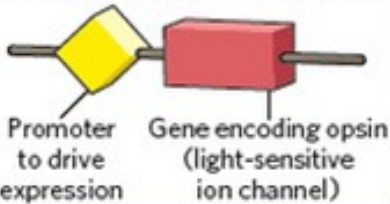
# A optogenética trouxe novas importante abordagens metodológicas para o estudo da ansiedade

## SIX STEPS TO OPTOGENETICS

With optogenetic techniques, researchers can modulate the activity of targeted neurons using light.

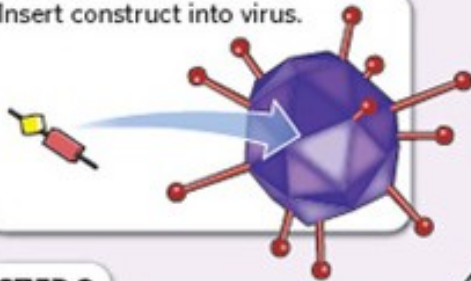
### STEP 1

Piece together genetic construct.



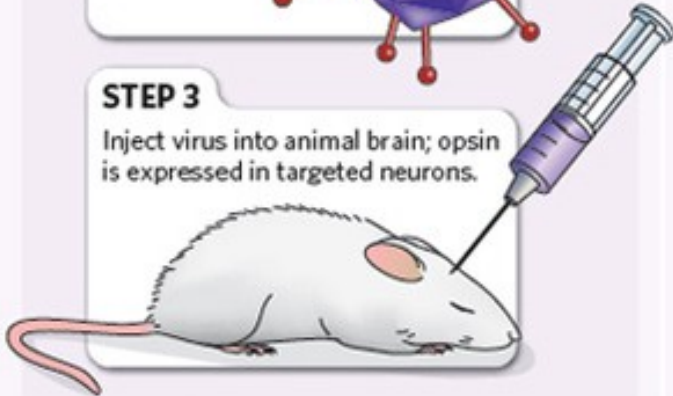
### STEP 2

Insert construct into virus.



### STEP 3

Inject virus into animal brain; opsin is expressed in targeted neurons.



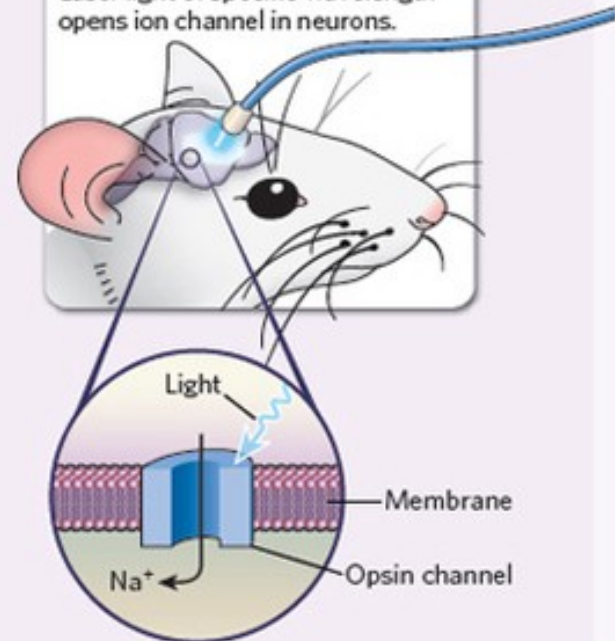
### STEP 4


Insert 'optrode', fibre-optic cable plus electrode.



### STEP 5

Laser light of specific wavelength opens ion channel in neurons.

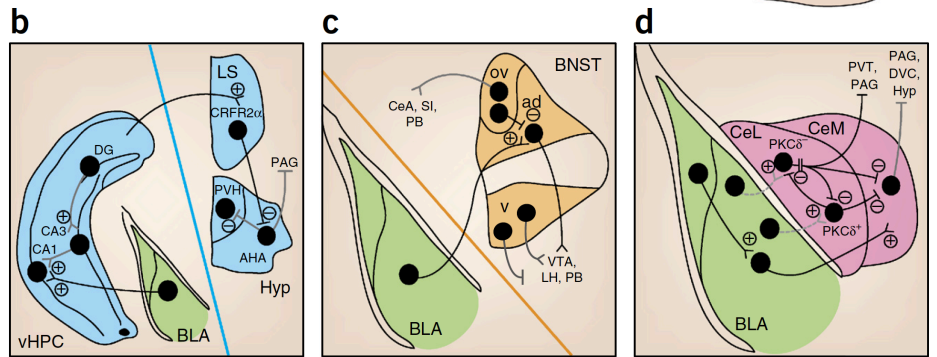
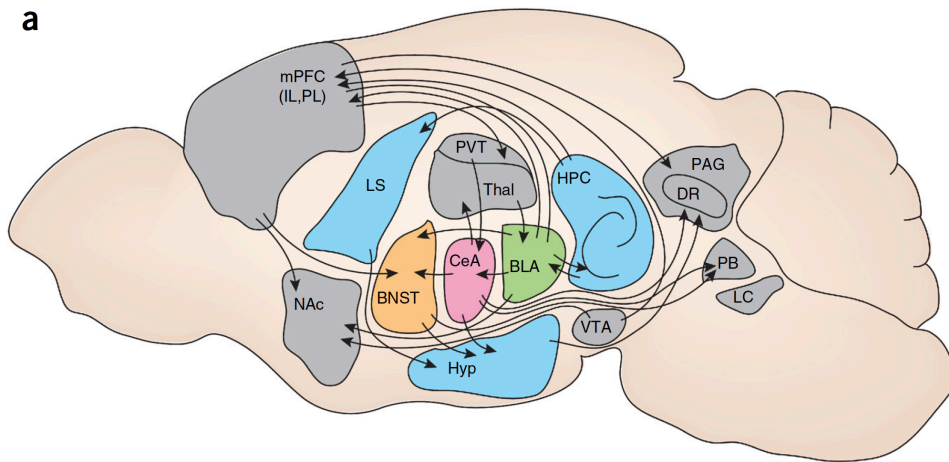




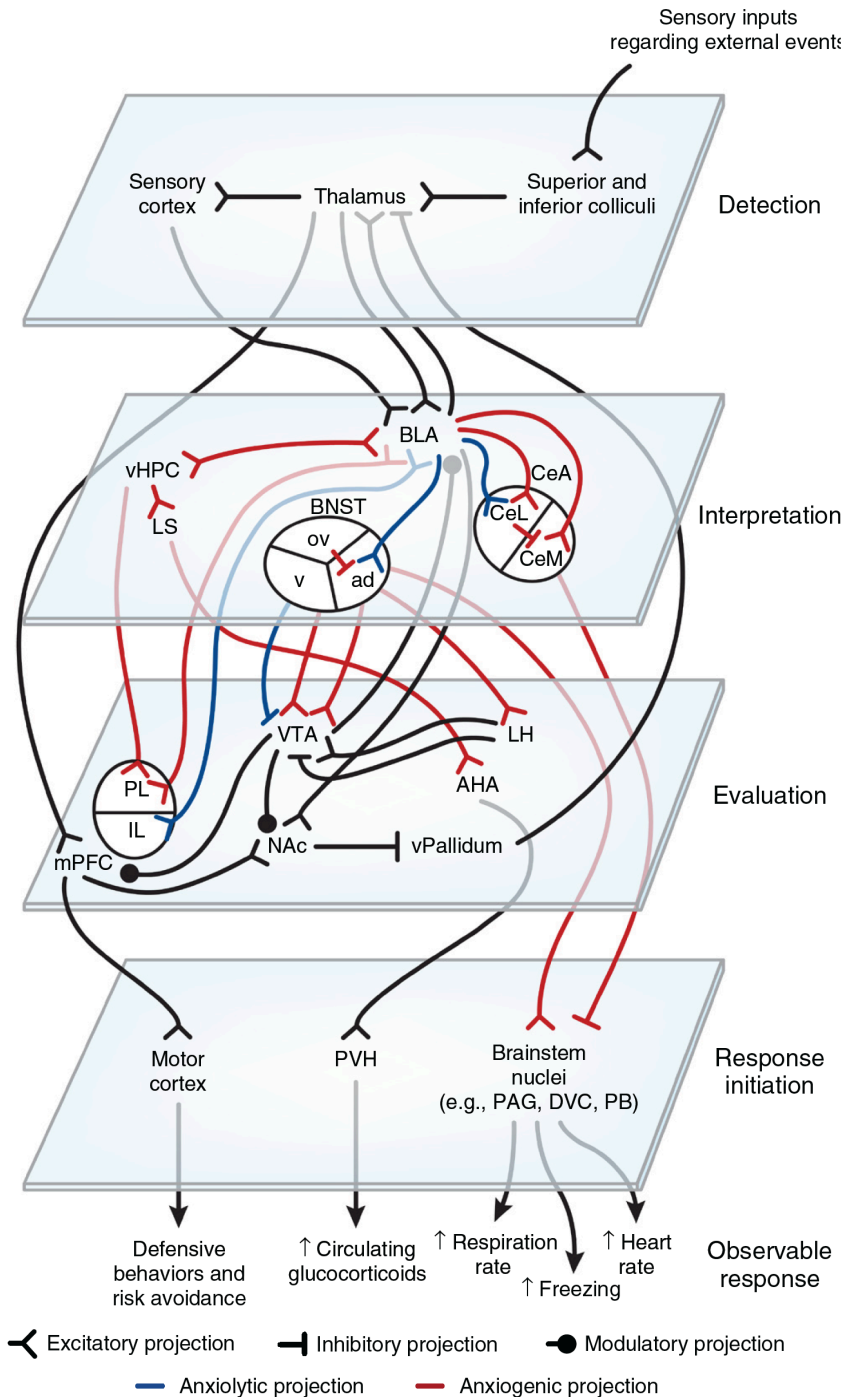
## Uso de optogenética para estimulação aversiva (habênula lateral)

([https://www.youtube.com/watch?v=ChogEq7fBgE&feature=emb\\_logo](https://www.youtube.com/watch?v=ChogEq7fBgE&feature=emb_logo))

# Estudos optogenéticos recentes tem detalhado os microcircuitos destas áreas associadas com a ansiedade



— Projection confirmed with optogenetics    - - - Projection identified with other techniques    ···· Hypothetical projection



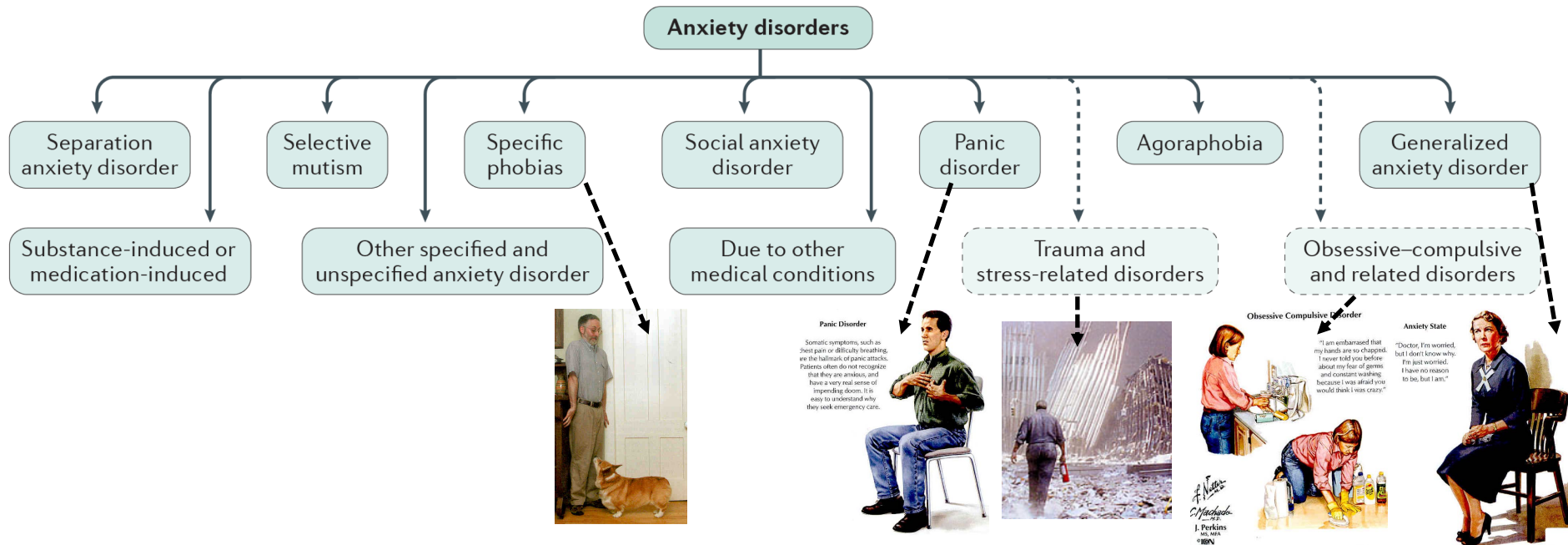
Resolving the neural circuits of anxiety

Nature Neurosc 2015

Gwendolyn G Calhoun & Kay M Tye



# A ansiedade patológica humana pode se apresentar sob diferentes formas

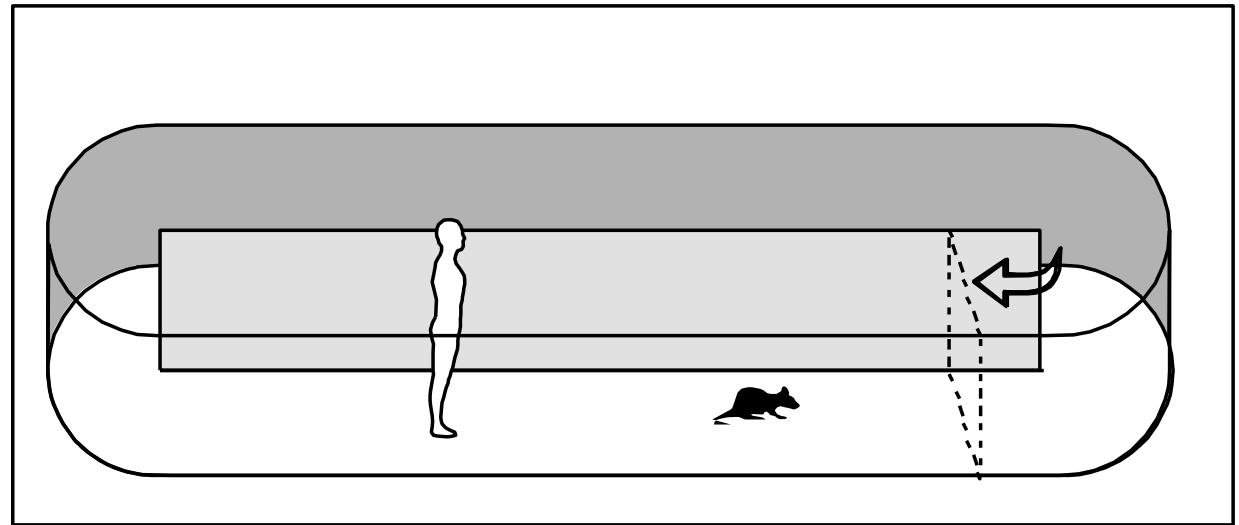


## Porquê?

# Será que a existência de diferentes modelos de ansiedade e sistemas relacionados estaria refletindo isso?



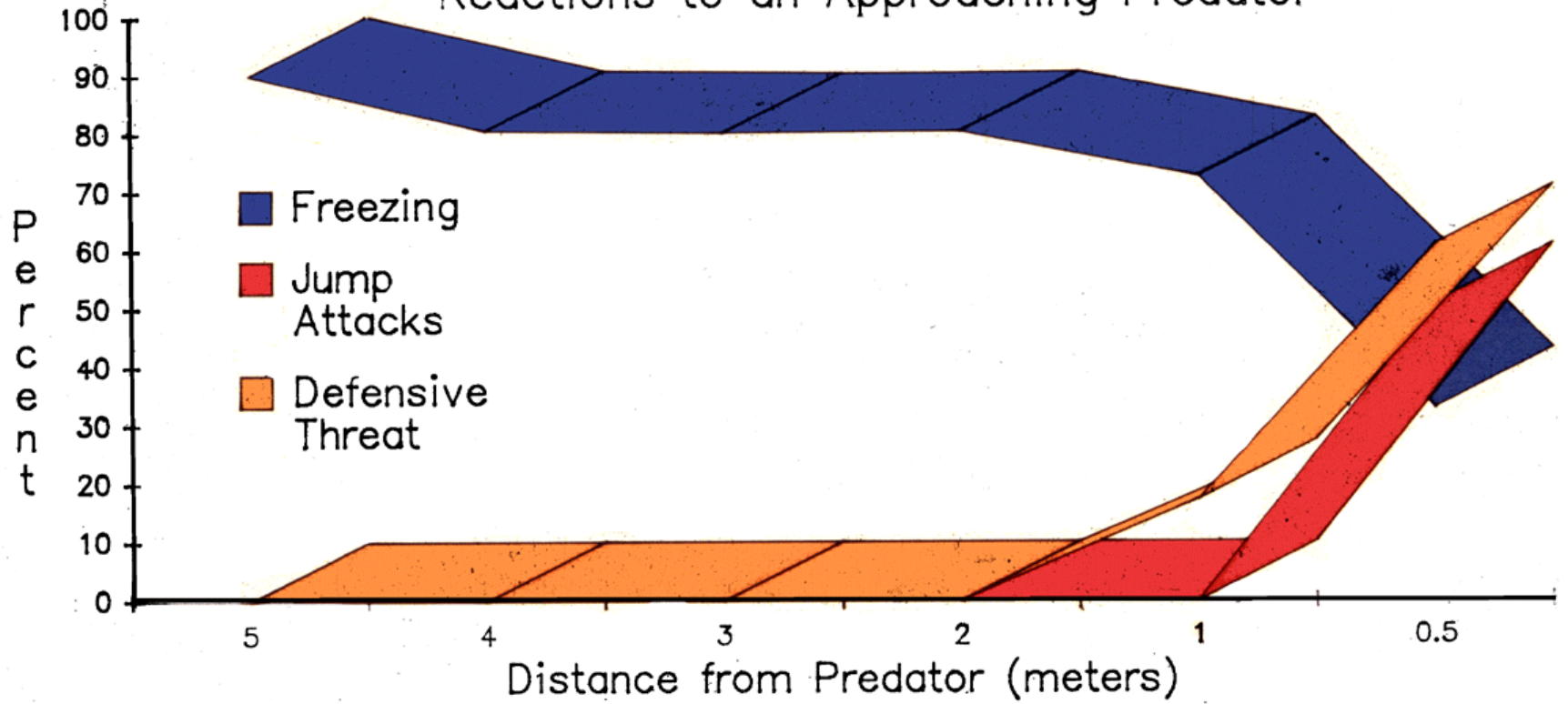
## Bob e Caroline Blanchard: Níveis de defesa (1990)



**Medidas:**

- Esquiva (“avoidance”), fuga (“flight”) e congelamento (“freezing”)

# Reactions to an Approaching Predator



# ***Níveis de Defesa***

***Robert e Caroline Blanchard***

## ***1) Perigo potencial ou incerto***

Investigação cautelosa ou

Avaliação de risco

## ***2) Perigo distal***

Inibição comportamental

Congelamento

## ***3) Perigo proximal***

Imobilidade / Fuga / Luta

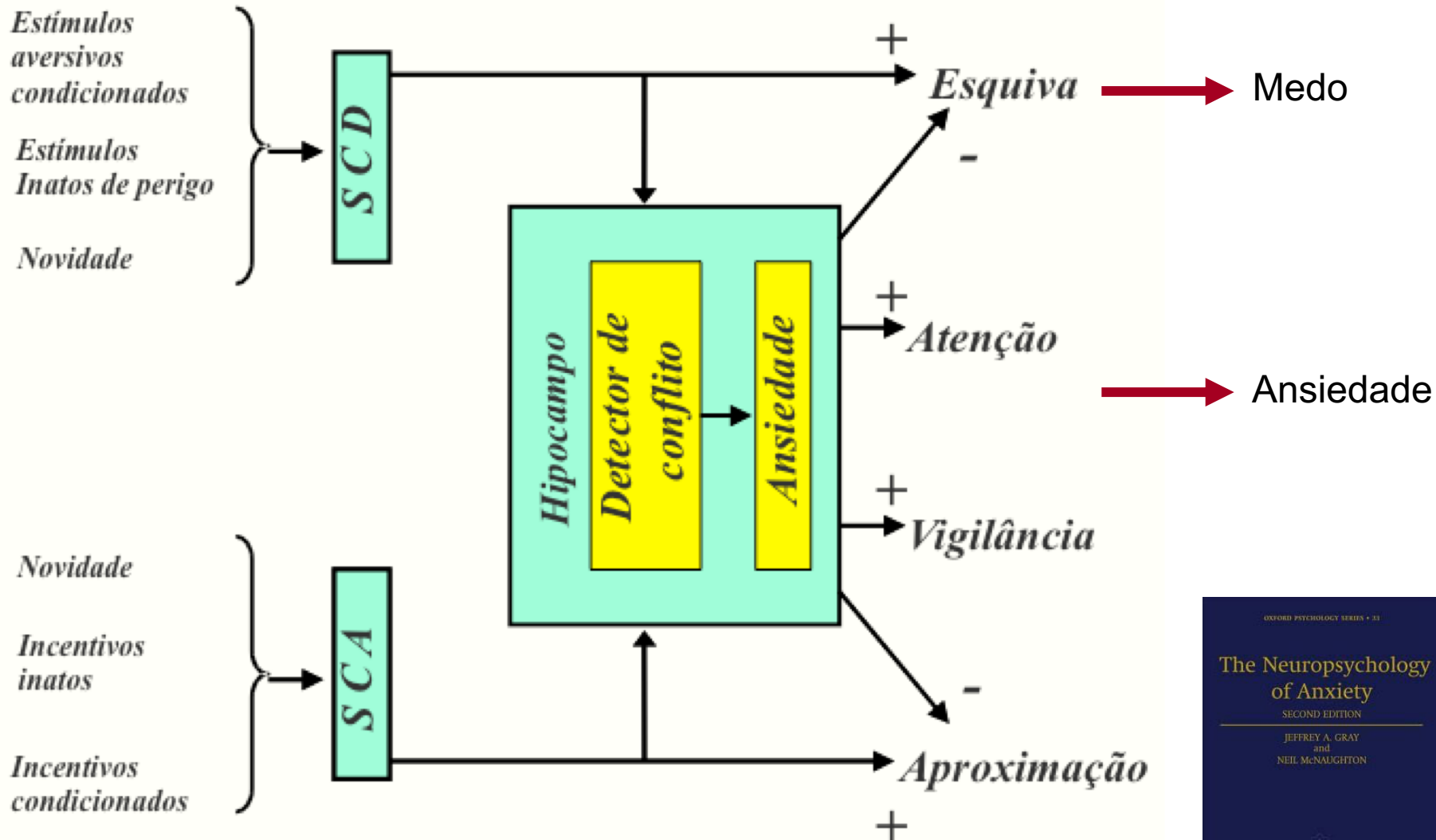
# Estratégias de defesa

Perigo	Defesa	Estrutura	Emoção	Patologia
<u>Incerto</u>	<u>Avaliação de risco</u>	<u>Septo-hipocampo</u>		
<u>Conflito</u>	<u>Inibição comportamental</u>	<u>Amígdala</u> e	<u>Ansiedade</u>	<u>Transtorno de ansiedade generalizada</u>
<u>Antecipado</u>	<u>Congelamento</u>	Amígdala SCPV	<u>Ansiedade antecipatória</u>	
	<u>Esquiva</u>	Amígdala	Medo condicionado	Fobia específica
<u>Distal</u>	<u>Fuga</u>	Hipotálamo medial	Medo incondicionado	Fobia específica
<u>Proximal</u>	<u>Fuga</u> <u>Imobilidade</u>	<u>SCPV</u>	<u>Pavor</u>	<u>Transtorno de pânico</u>

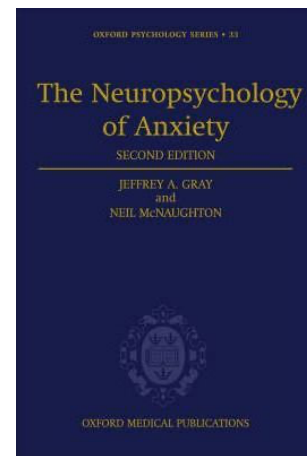
Deakin e Graeff, 5HT and mechanisms of defense. J. Psychopharmacology 5:305, 1991



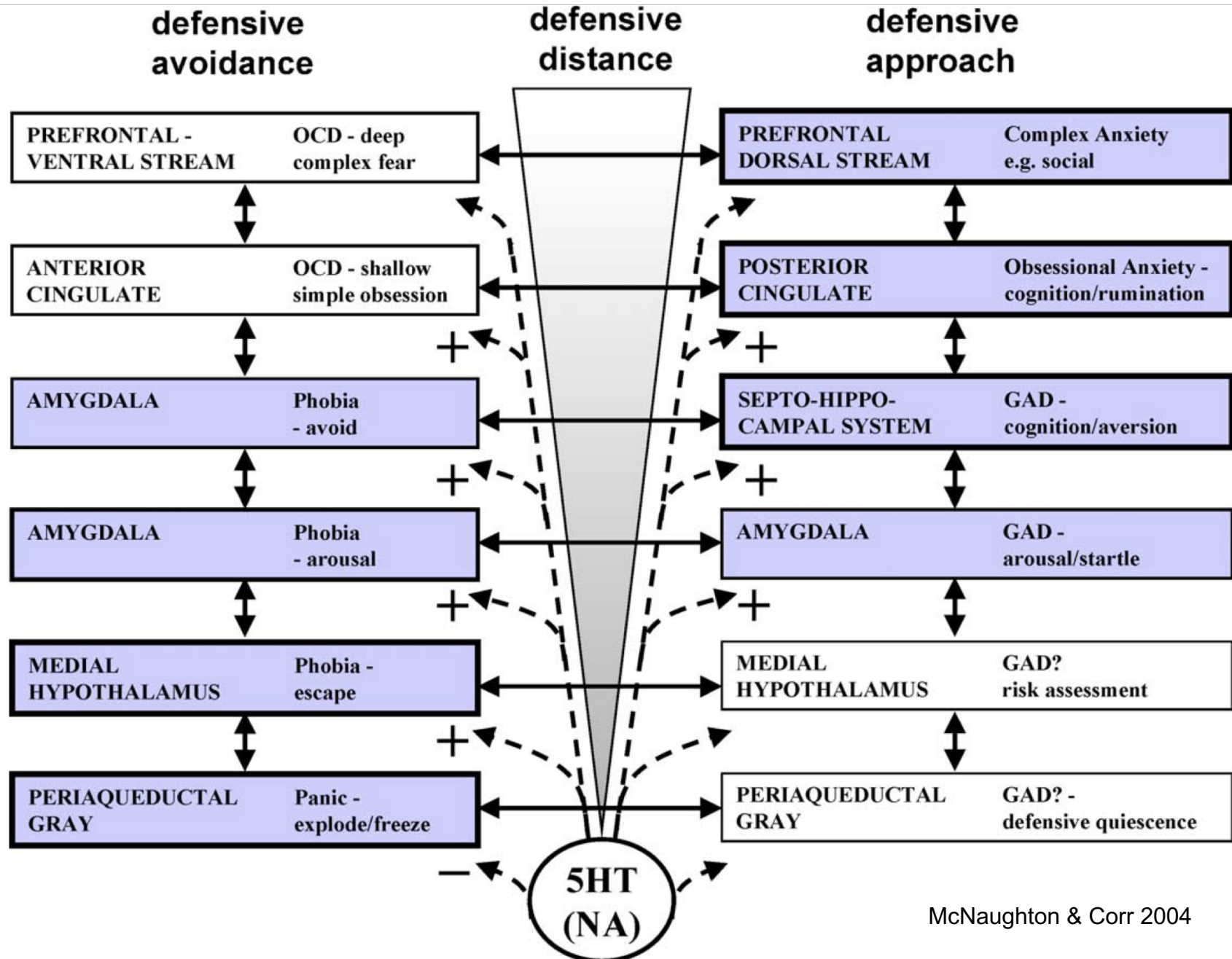
# Convergência de idéias (medo versus ansiedade)



Gray e McNaughton, 2002



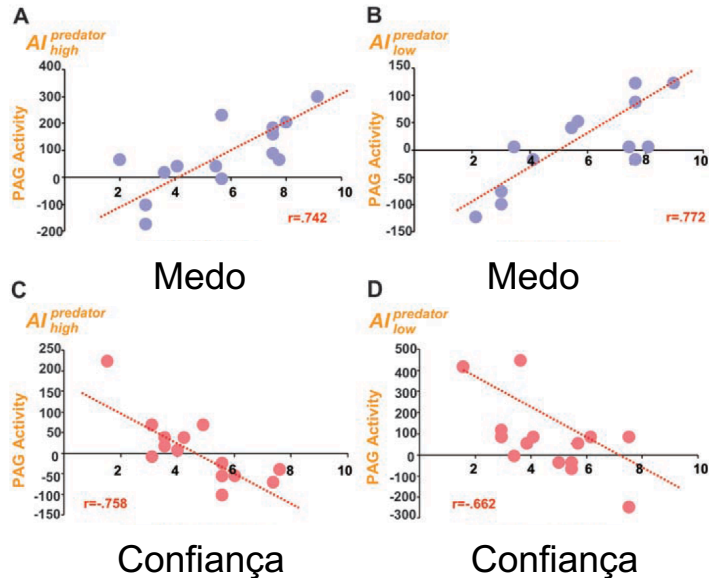
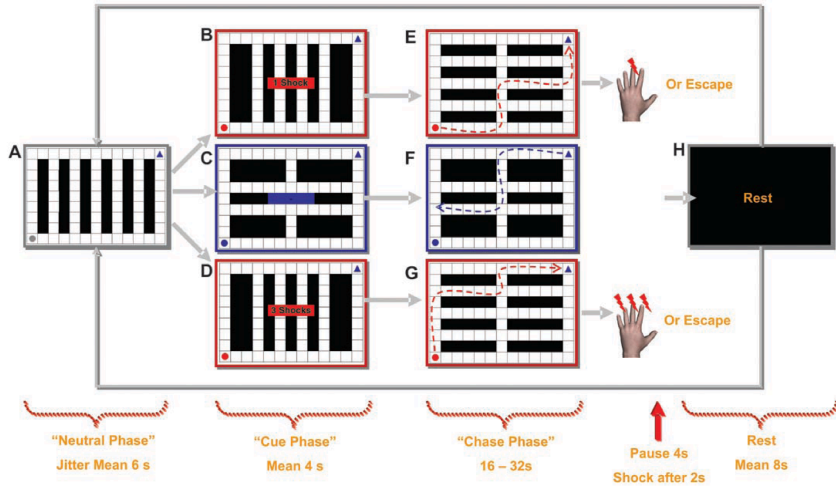
# Visão mais recente: sistemas paralelos com representações distintas



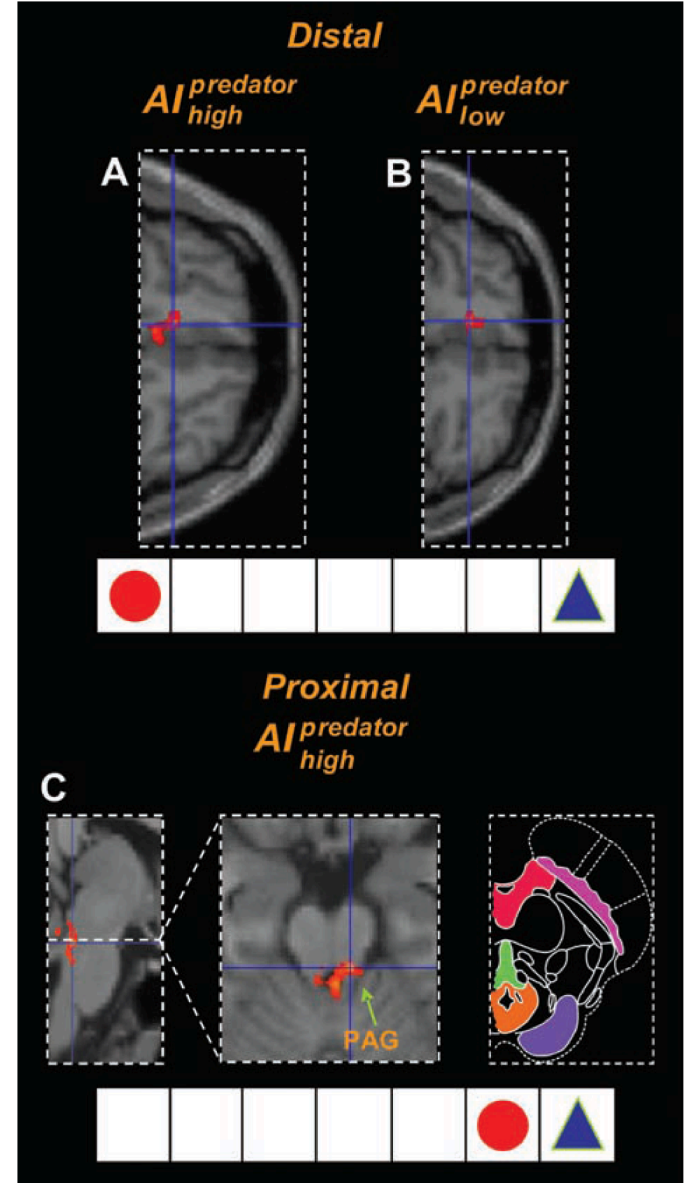
# Teste da proposta dos Blanchards

## When Fear Is Near: Threat Imminence Elicits Prefrontal– Periaqueductal Gray Shifts in Humans

Dean Mobbs,\* Predrag Petrovic, Jennifer L. Marchant, Demis Hassabis, Nikolaus Weiskopf,  
Ben Seymour, Raymond J. Dolan, Christopher D. Frith  
Science 2007



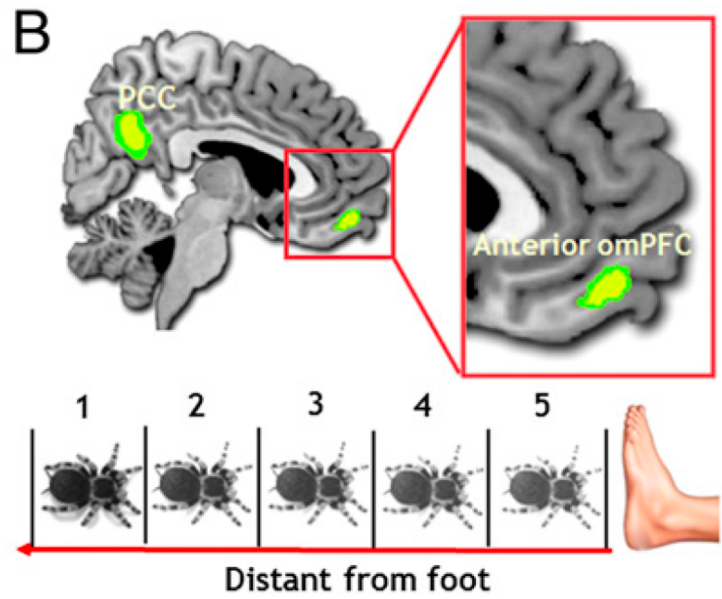
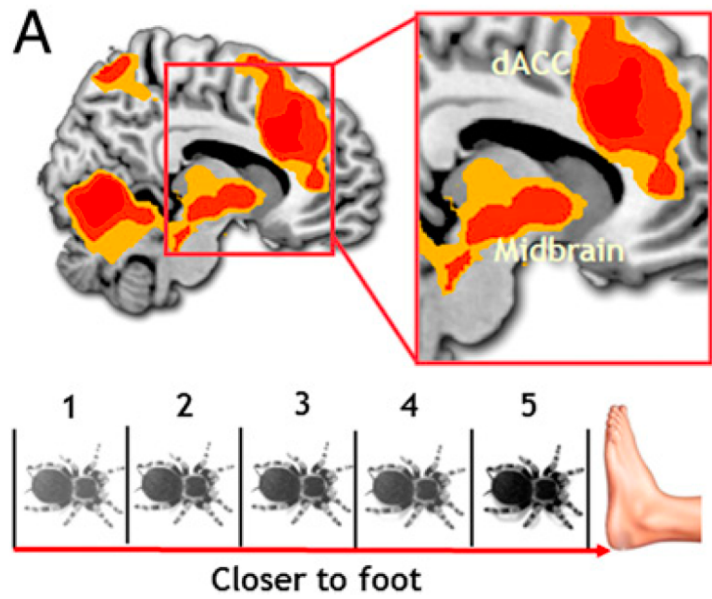
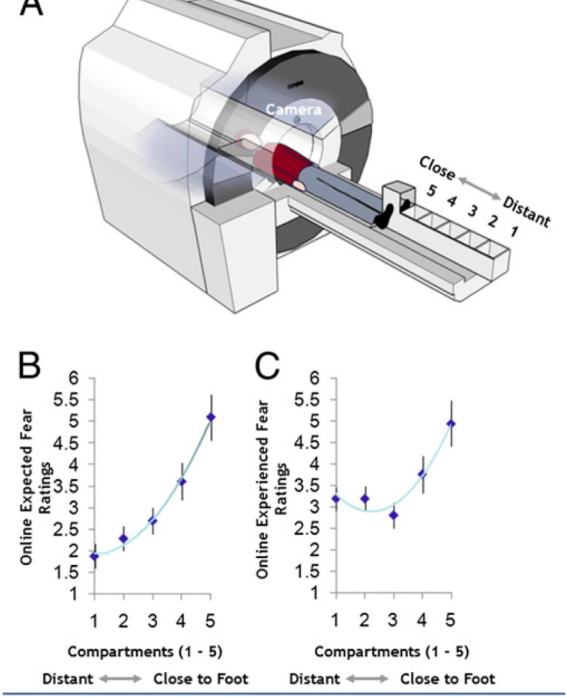
Atividade PAG





# Neural activity associated with monitoring the oscillating threat value of a tarantula PNAS 2010

Dean Mobbs<sup>a,1</sup>, Rongjun Yu<sup>a</sup>, James B. Rowe<sup>a,b</sup>, Hannah Eich<sup>a</sup>, Oriel FeldmanHall<sup>a</sup>, and Tim Dalgleish<sup>a</sup>

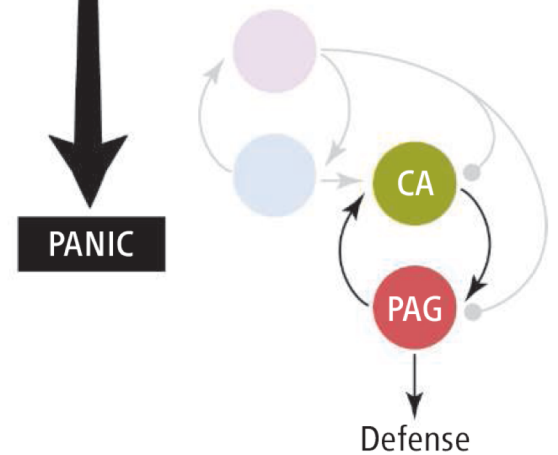
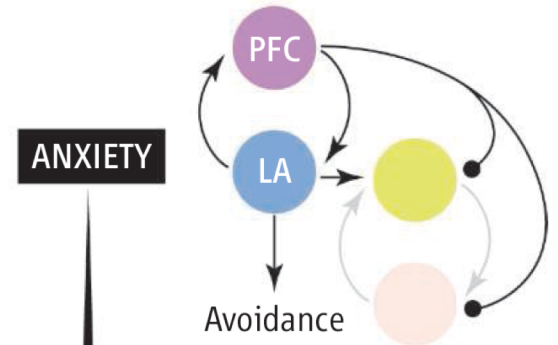
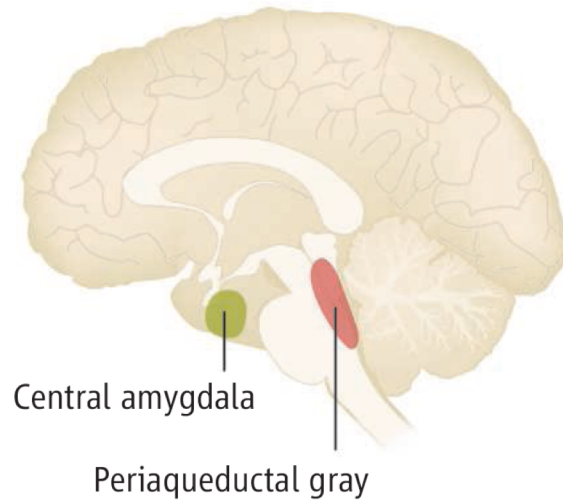
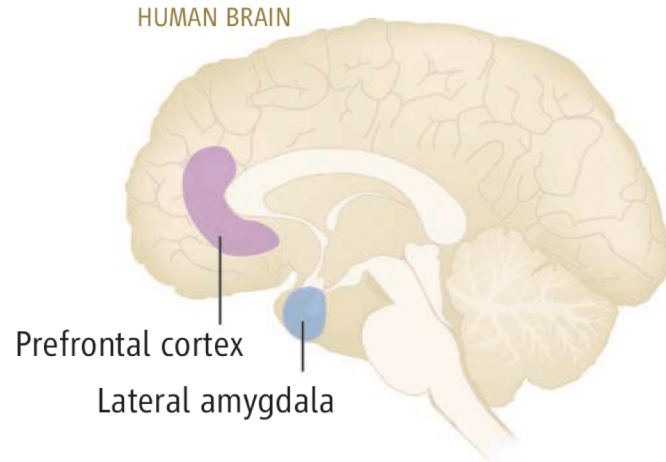


# The threatened brain

Distal



Proximal



# Neuroimagem funcional dos transtornos de ansiedade

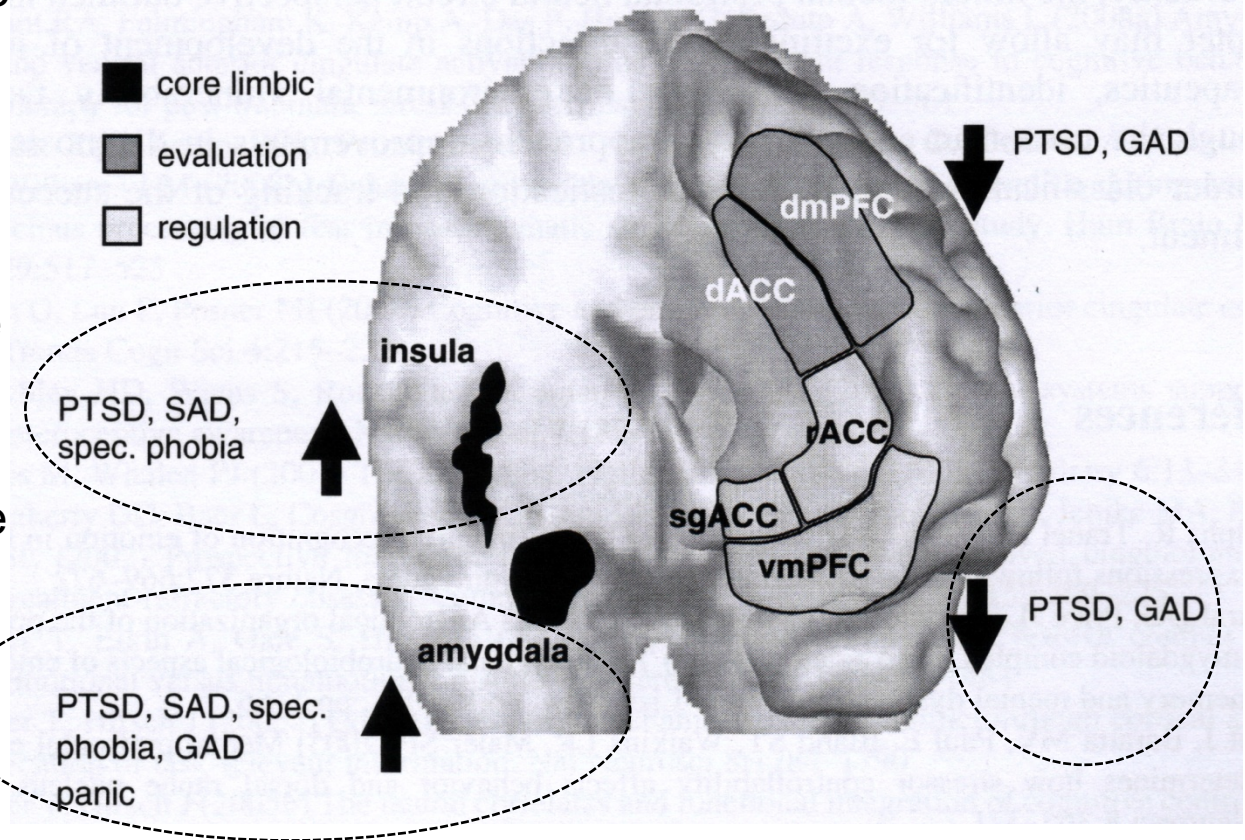
GAD: T. de ansiedade generalizada

Panic: T. do pânico

PTSD: T. de estresse postraumático

SAD: T. de ansiedade social

Spec. phobia: Fobia específica



# Transtorno Obsessivo-compulsivo (principais obsessões e compulsões)

Table 1. Common Obsessions and Corresponding Compulsions in Obsessive-Compulsive Disorder

Obsessions <sup>a</sup>	Specific Examples	Compulsions <sup>b</sup>	Specific Examples
Fear of contamination <sup>c</sup>	Preoccupation or disgust with bodily waste; repetitive concern of spreading illness	Cleaning or washing	Excessive hand washing or cleaning of household items (long after they are reasonably clean)
Persistent doubting	Anxiety that the house door is unlocked despite having just locked it, or that the oven is turned off despite having just turned it off	Checking	Repeatedly checking that oven is off, doors are locked; driving back along a road to ensure that no one was injured; excessively checking writing to ensure no error was made
Violent or sexual intrusive thoughts	Intrusive, unwanted violent or horrific images; unwanted sexual images of strangers, family, friends	Repetitive “undoing” thoughts	Repeated, “neutralizing” thoughts (eg, “I am not a violent person,” repeated asking for reassurance that one did not commit a violent or unwanted sexual act)
Fears of causing harm	Intrusive fears of dropping an infant one is holding; fear of inadvertently hitting pedestrians when driving	Repeated behaviors, checking	Repeatedly driving past crosswalks to check for injured pedestrians
Symmetry	Excessive worry and distress if items on a bookshelf are not arranged symmetrically	Ordering or arranging	Repeatedly arranging books on a bookshelf so that the spines are exactly aligned
Religious scrupulosity	Excessive concern with “right vs wrong”	Religious compulsions	Excessive prayer or apologies to God; need to tell or confess
Superstitions	“Lucky” or “unlucky” numbers or colors	Superstitious behaviors	Avoiding writing unlucky numbers; repeating activities a certain “lucky” or “right” number of times

<sup>a</sup> Obsessions are unwanted, repetitive thoughts.

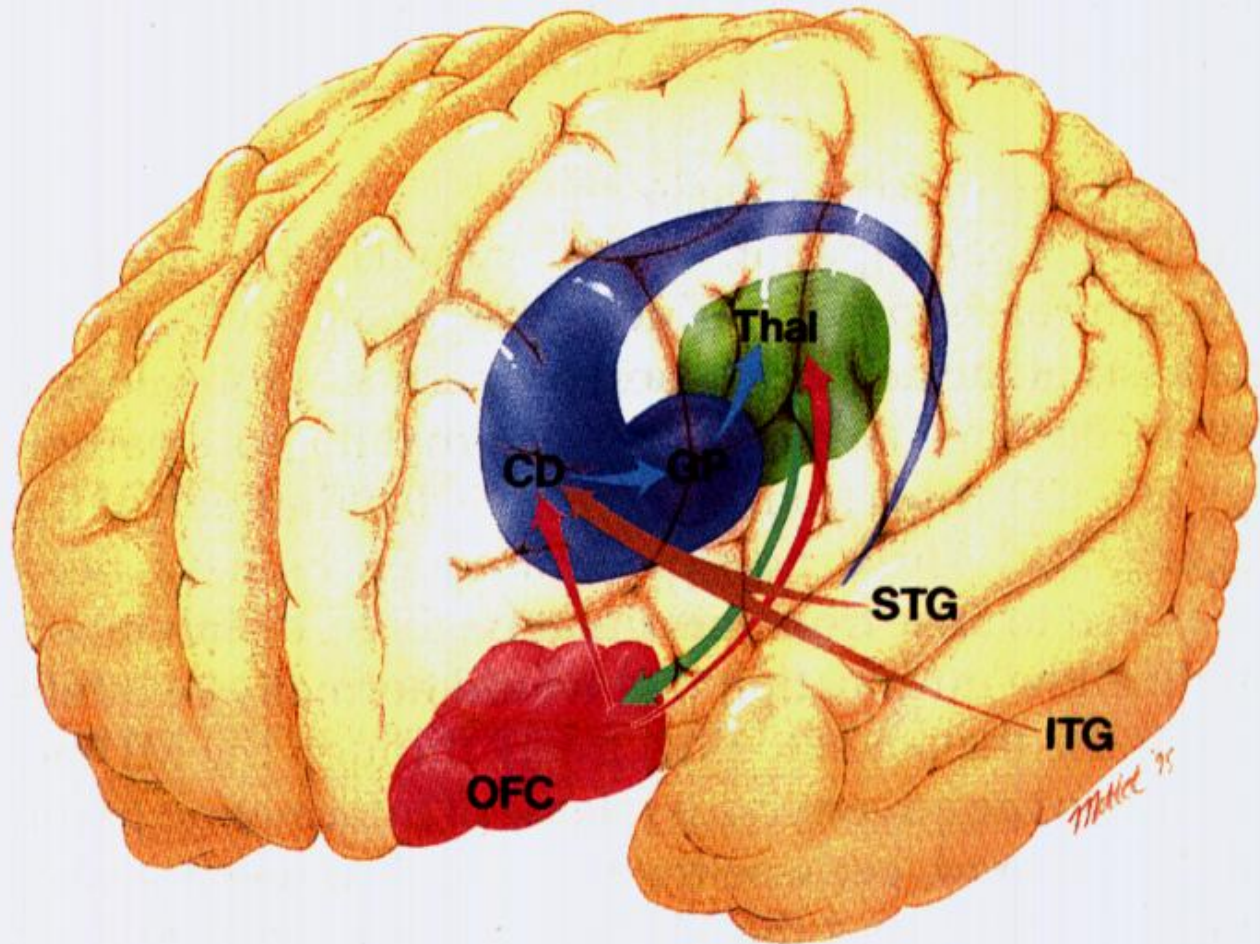
<sup>b</sup> Compulsions are repetitive behaviors or thoughts. Often, but not always, performed to address anxiety associated with obsessions. Avoidance behaviors are also common in response to many obsessions. For example, an individual

with an obsessive fear of dropping infants may avoid interacting with children altogether.

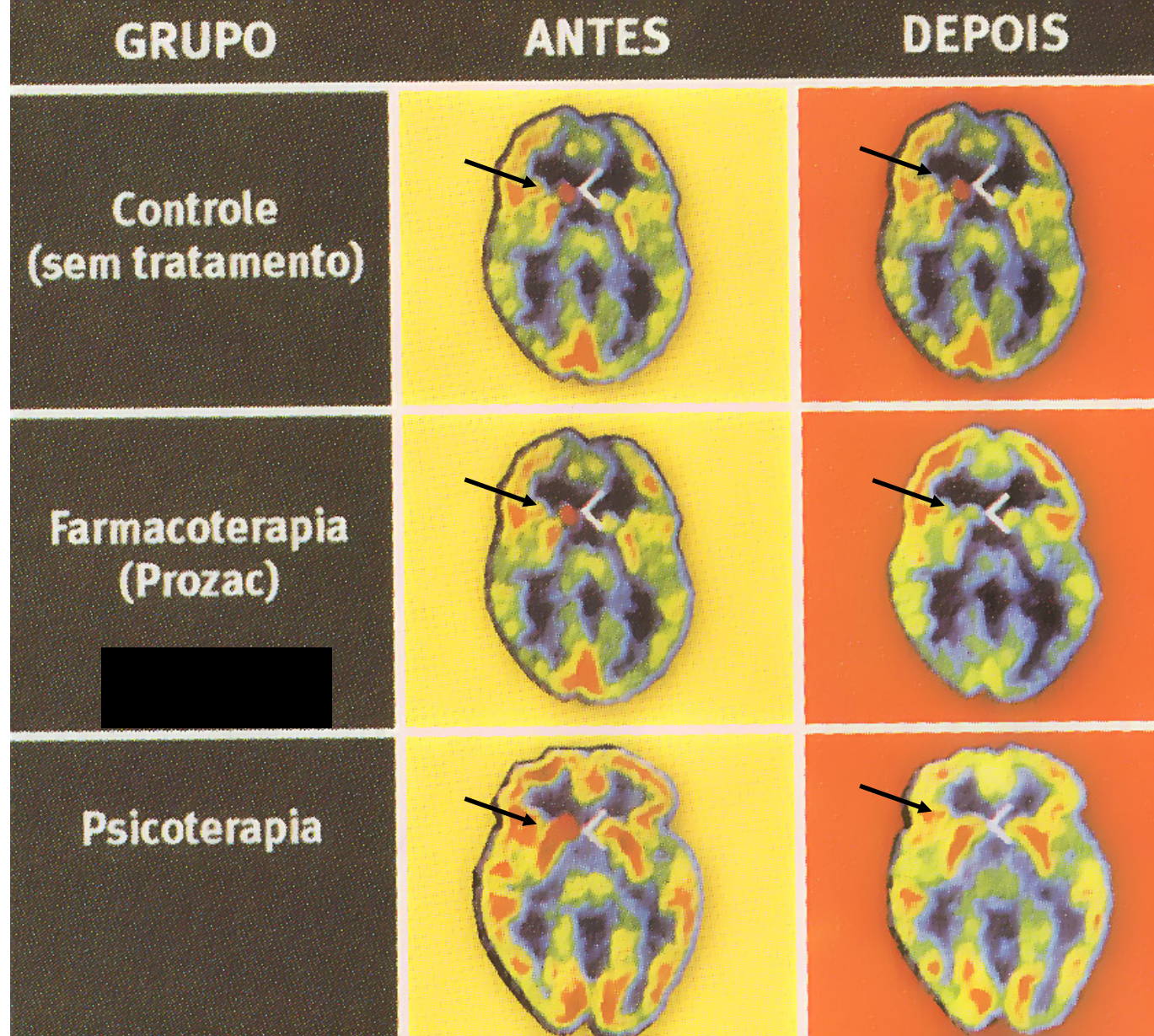
<sup>c</sup> Individuals with contamination fears may not use public bathrooms or public transportation.

# Circuitos do TOC

**FIGURE 9.** The lateral OFC–basal ganglia loop. CD = caudate nucleus; GP = globus pallidum; ITG = inferior temporal gyrus; OFC = orbital frontal cortex; STG = superior temporal gyrus; Thal = thalamus.



Circuito cortico-límbico-estriado



TOC: Existe aumento da atividade do caudato (vermelho)  
 Normaliza com farmacoterapia ou psicoterapia comportamental

De Lewis Baxter et al., modificado por  
 Cruz e Landeira Fernandez, 2001

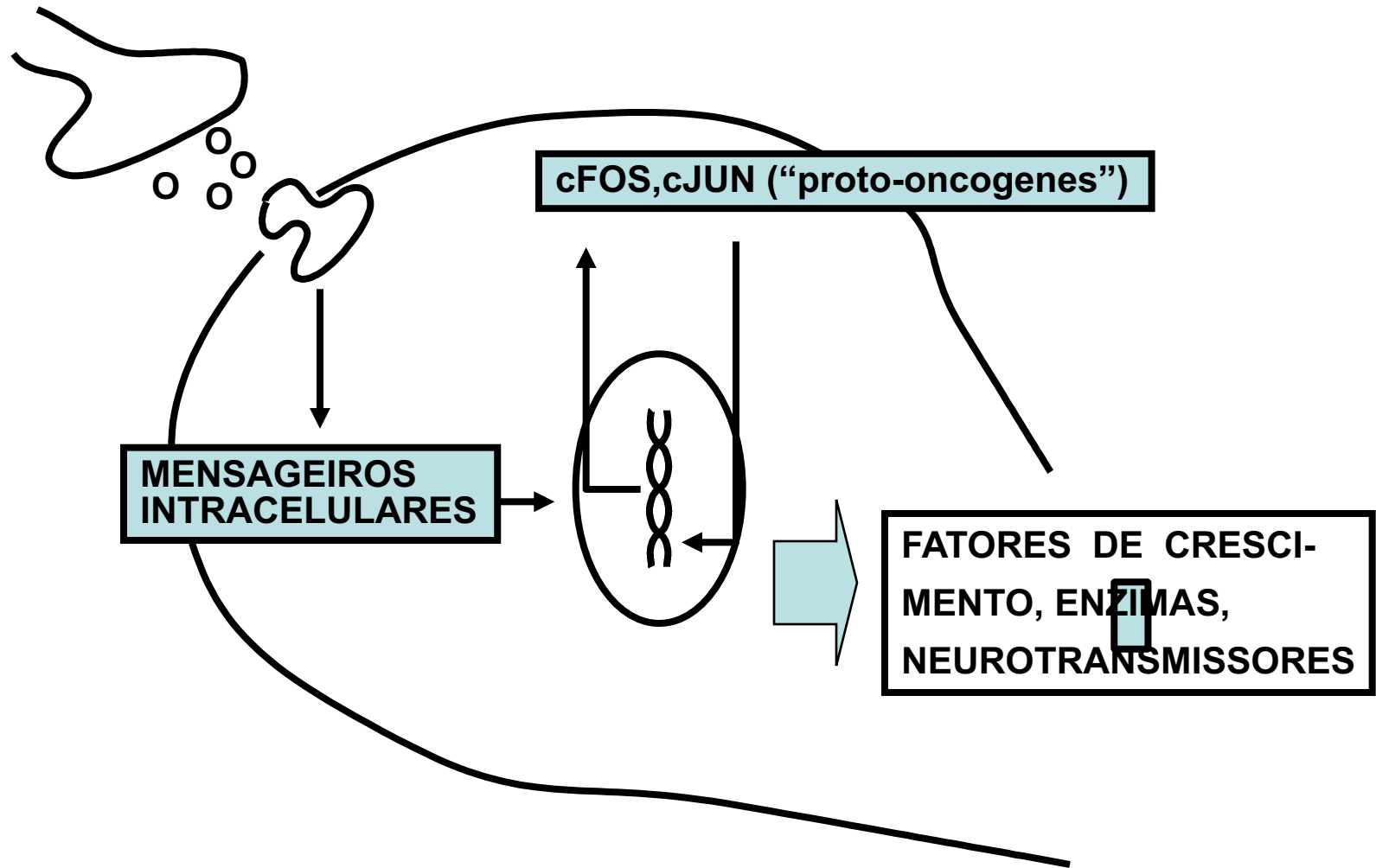
# Perspectiva evolutiva: transtornos de ansiedade como disfunções dos sistemas de defesa



Frederico Graeff

1. ansiedade generalizada, pânico e fobias específicas teriam relação com a defesa predatória
2. ansiedade social estaria relacionado com submissão em resposta a ameaça intra-específica
3. O transtorno obsessivo-compulsivo (TOC) à defesa contra germes e proteção territorial (a ansiedade pode ser encarada como manifestação secundária, e o TOC não seria ligado à defesa)
4. O PTSD estaria relacionado a déficits de extinção de memórias aversivas

# Contribuições de métodos morfo-funcionais em animais de laboratório: ex. cFos

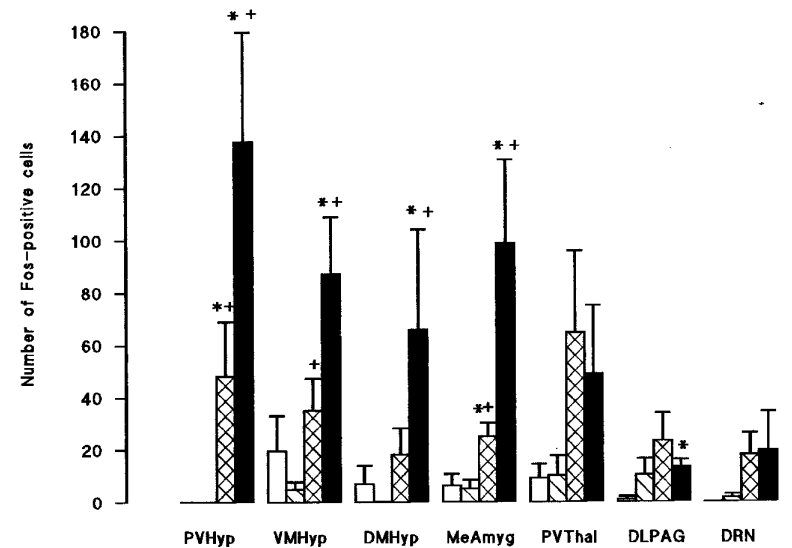
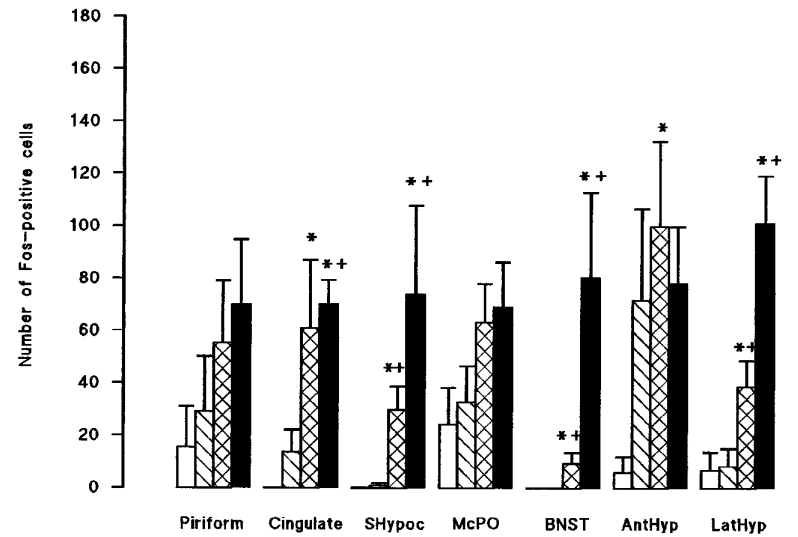
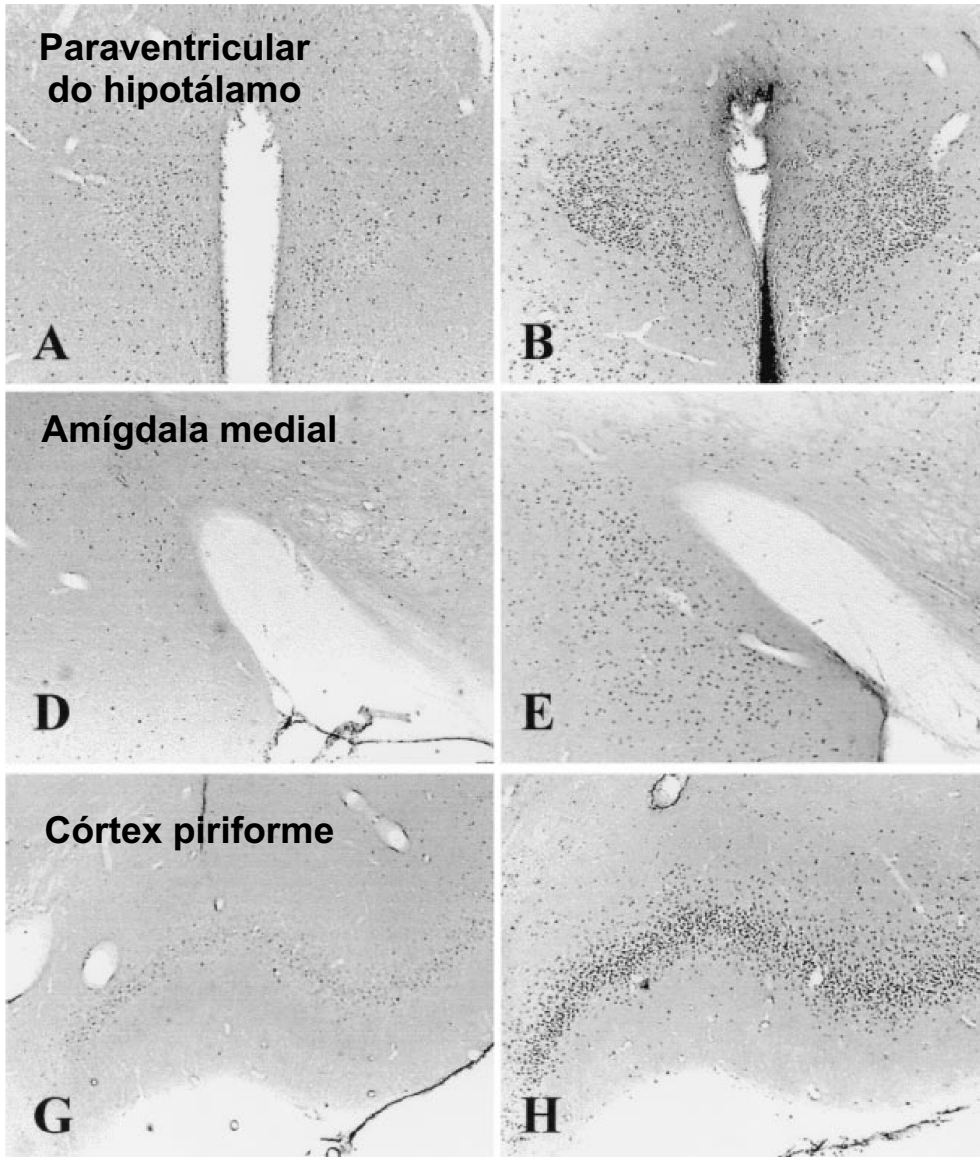


*Morgan & Curran, Mapping patterns of c-fos expression in the central nervous system after seizures. Science 237:192, 1987*



**Controle**

**Estimulação  
PAG**



□ saline    ▨ saline + arena    ▩ SIN-1 150    ■ SIN-1 300

*De Oliveira et al., 2000*

# “Neuroquímica da ansiedade”

