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**SEMMELWEIS
UNIVERSITY**



Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

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BEVEZETÉS A FUNKCIONÁLIS NEUROBIOLÓGIÁBA

INTRODUCTION TO FUNCTIONAL NEUROBIOLOGY

By Imre Kalló

Contributed by: Tamás Freund, Zsolt Liposits, Zoltán Nusser, László Acsády, Szabolcs Káli, József Haller, Zsófia Maglóczky, Nórbert Hájos, Emilia Madarász, György Karmos, Miklós Palkovits, Anita Kamondi, Lóránd Eröss, Róbert Gábrriel, Kisvárdai Zoltán

Psychiatric Disorders

Imre Kalló & József Haller

Pázmány Péter Catholic University, Faculty of Information Technology

Anxiety

**Operation and operation failures
of complex systems**

Depression

Behavior, behavioral disturbances

Behavior

Actions and reactions of the individual (human or animal) under the influence of internal and external stimuli

Behavioral disturbance

Abnormal behavior developing under the influence of internal and/or external stimuli

Abnormal behavior

- inadequate for the situation
- involves suffering
- persistent

Serious injury and/or functional disturbance of the CNS

Behavioral disturbances in humans

neurological disturbances (dementia, epilepsy, Alzheimer disease, brain injury, etc.)

psychiatric disorders

personality disorders (eg. psychopathy)

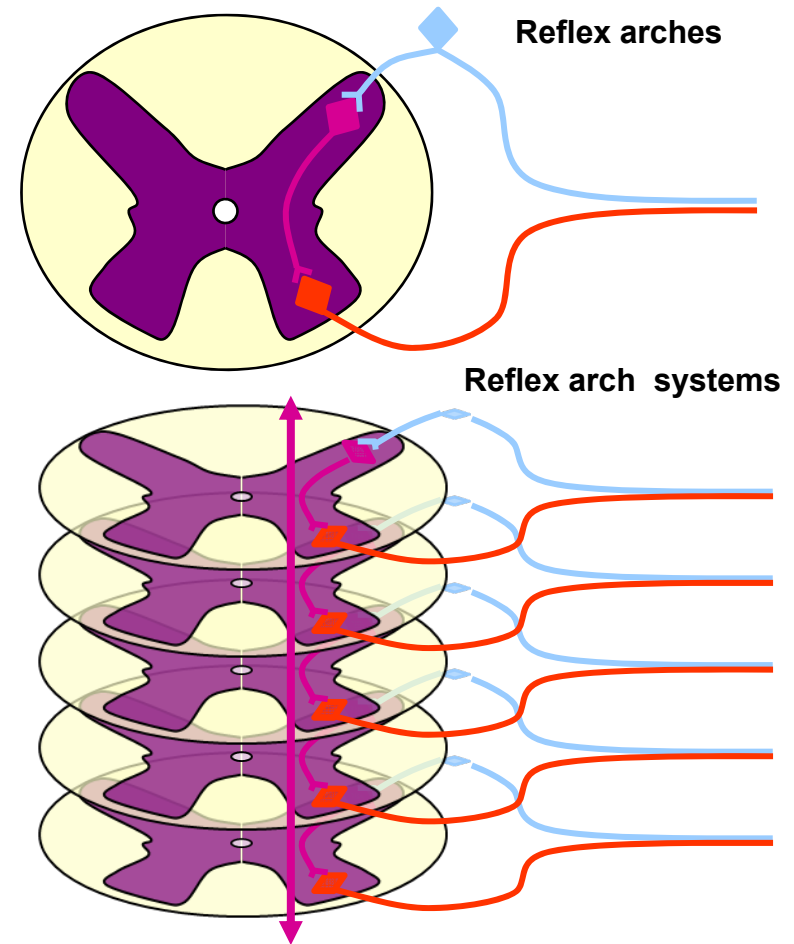
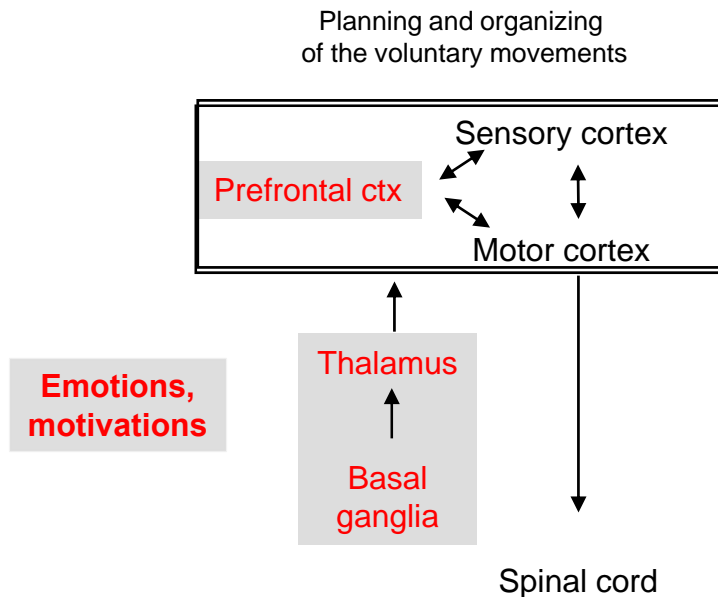
clinical disorders (eg. anxiety and depression)

Mild developmental malformations, functional deficit of CNS

Mild functional deficits developing in response to stimuli of the CNS

How can behavioral disturbances be corrected? - 1st hypothesis

If behavior is action (or reaction), then it is related to movement
 ...consequently, if there was something wrong with behavior
 than movement-control needed correction



Behavior is not just movement; it is emotion-driven movement

Behavior, behavioral disturbance - corrected definitions, 2nd hypothesis

Behavior

The individual (human, animal) is emotionally motivated; emotions, actions and reactions are under the influence of internal and external stimuli

Behavioral disturbance

Abnormal behavior and abnormal emotions developing under the influence of internal and external stimuli

- Mismatch with the situation
- Cause sufferings (equal with sufferings)
- Chronic

Emotional changes are expressed at the level of behavior

2nd hypothesis:

Emotions need to be "corrected", and the behavioral disturbance will be rectified

Behavior, emotion, function

Anxiety

Emotions

Depression

Definite or uncertain fear

Depression, dejectedness

Circumstances of formation

Novel situations

Hopeless crisis

Behavioral consequences

Avoidance of risky places, and behaviors

Behavioral reactions reduced to minimum

Biological function

Avoidance of un-necessary risks

Ensuring survival

Both emotions are "self-defensive"

Both can be abnormal if:
(1) are expressed in inadequate situations
(2) last too long, or occur frequently
(3) involve suffering

Behavioral disturbance, emotion, function

Anxiety

Types:

generalized anxiety

(context-independent fear)

panic

(short-term fear attacks)

PTSD, ATSD

(trauma-induced fear accompanied by many other symptoms)

phobia (agoraphobia, zoophobia, horror of height, etc)

(fear of well-defined objects, living beings or situations)

obsessive-compulsive disorder

(obsessive-compulsive actions driven by anxiety)

Behavioral consequences:

normal lifestyle hindered

Prevalence

men: 6-8%

women: 10-15%

The two disorders are often comorbid

Depression

Types:

Minor

(hopelessness, self pityness, irritability, pessimistic view of future, symptoms of diseases without illness)

Major

(extreme sadness, self reproach, lack of self-esteem, avoidance of pleasant experiences, memory-, sleeping-, and eating problems)

Bipolar: Major + Maniac

(euphoria, feelings of urgency, excitement, aggression, etc.)

Behavioral consequences:

normal lifestyle hindered

suicide risk

Prevalence

men: 10-12%

women: 15-20%

Function: unknown



Behavioral disturbance, emotion, function

Anxiety

Depression

Types:

Types:

generalized anxiety

(context-independent fear)

panic

(short-term fear attacks)

PTSD, ATSD

(trauma-induced fear accompanied by many other symptoms)

phobias

(agoraphobia, zoophobia, claustrophobia, etc.)

obsessive-compulsive disorder

(obsessive-compulsive actions driven by anxiety)

Behavioral consequences:

normal lifestyle hindered

Prevalence

men: 6-8%

women: 10-15%

Minor

(hopelessness, self pityness, irritability, pessimistic view of future, symptoms of diseases without illness)

Major

(extreme sadness, self reproach, lack of interest in life, pleasure, experiences, etc.)

atypical + melancholic

(atypical symptoms of urgency, excitement, aggression, etc.)

Behavioral consequences:

normal lifestyle hindered

suicide risk

Prevalence

men: 10-12%

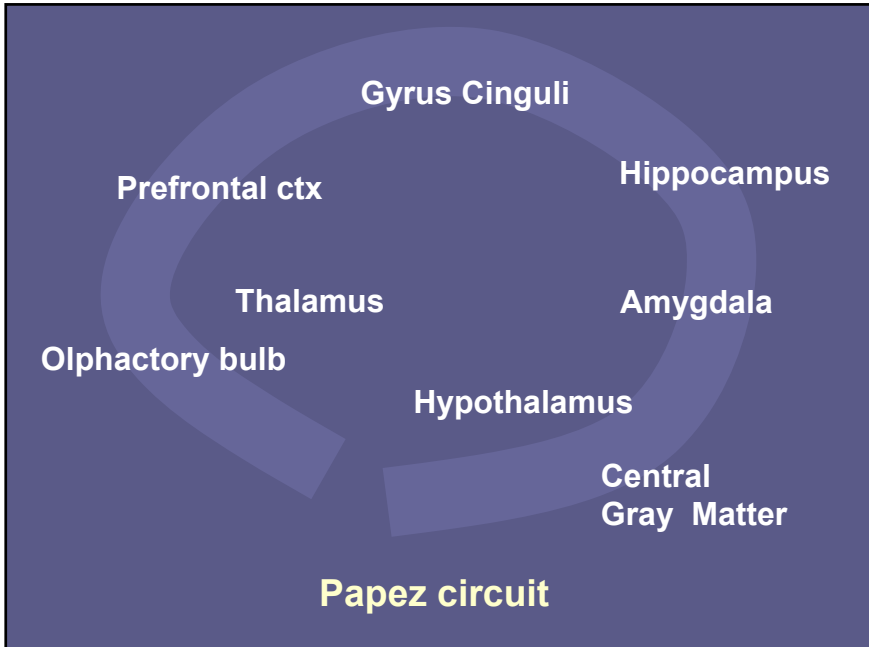
women: 15-20%

Function: unknown

How can these be rectified?

The two disorders are often comorbid

Mechanisms of emotional control – major components and functions



Prefrontal cortex

- control of voluntary movements
- processing of informations
- attention
- emotional attitude
- „personality“

Cingular cortex

- coordination of perception and emotions
- (eg. emotional component of pain)

Thalamus

- control of movement
- processing of sensory informations and relay to the cerebral cortex

Hippocampus

- spatial orientation and memory
- navigation
- emotions, emotional memory

Amygdala

- vigilance, movement control
- emotional responses (fear, aggression, reward)
- control of hormonal responses

Hypothalamus

- action programs of emotional behaviors
- endocrine functions
- autonomic control

Periaqueductal grey matter

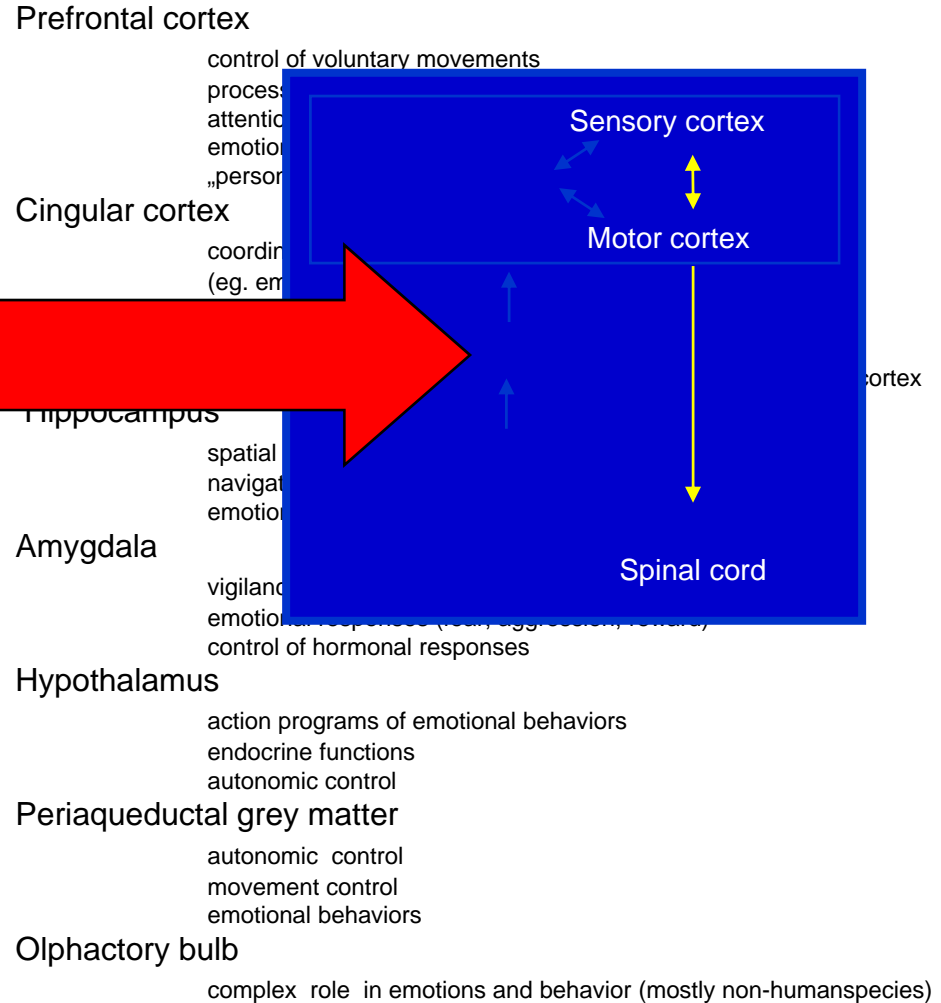
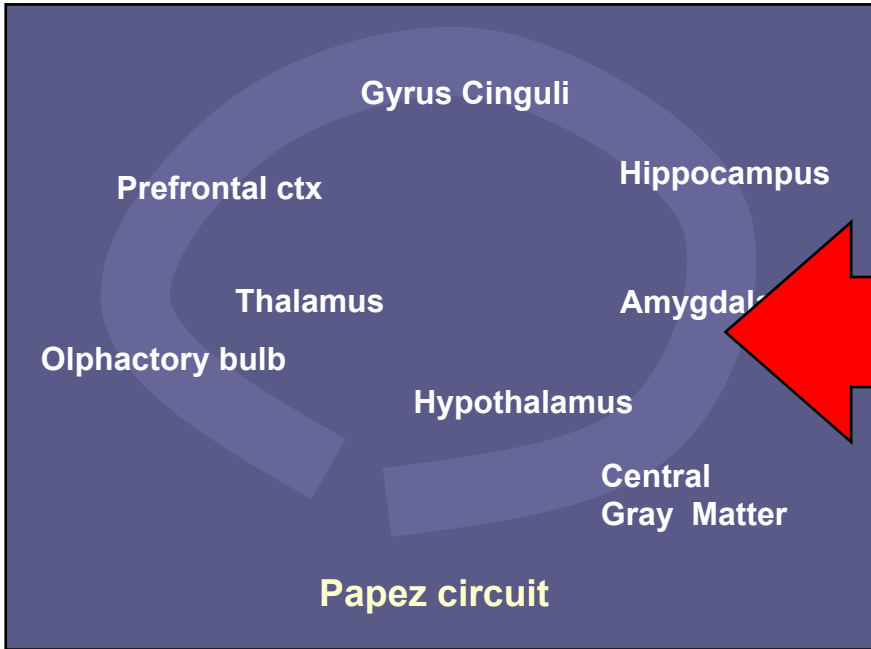
- autonomic control
- movement control
- emotional behaviors

Olfactory bulb

- complex role in emotions and behavior (mostly non-humanspecies)

How will all these result in emotions and movement?

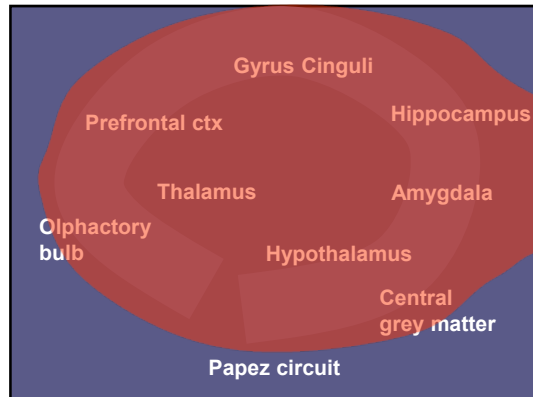
Mechanisms of emotional control – major components and functions



How will all these result in emotions and movement?

System of the emotional control - diffuse effects

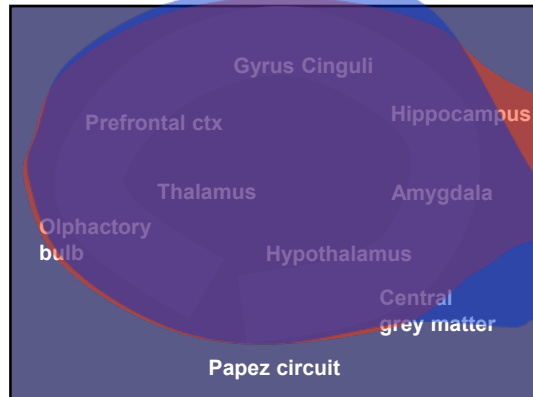
limbic system



raphe
(serotonin)

System of the emotional control - diffuse effects

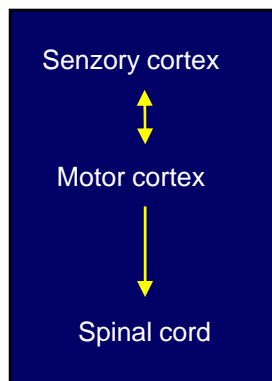
limbic system



raphe
(serotonin)

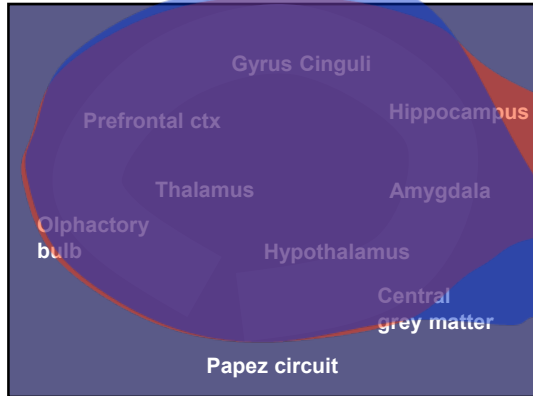
locus coeruleus
(noradrenalin)

motoros rendszer



System of the emotional control - diffuse effects

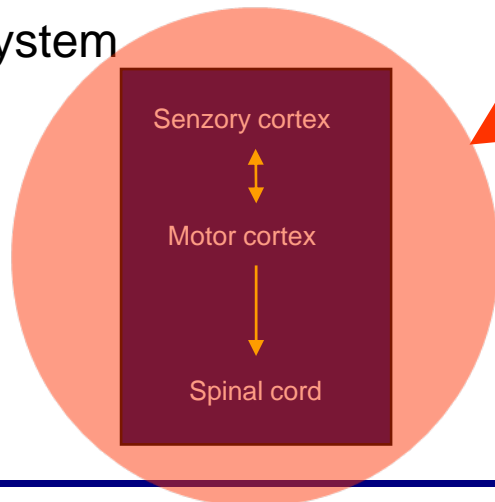
limbic system



raphe
(serotonin)

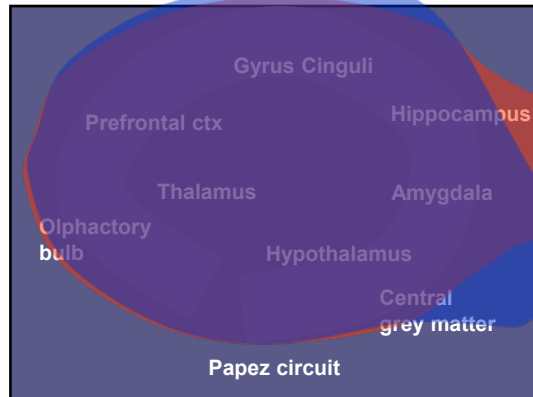
locus coeruleus
(noradrenaline)

motor system



System of the emotional control - diffuse effects

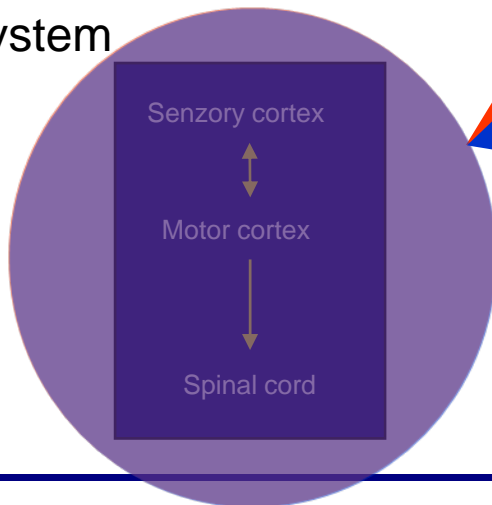
limbic system



raphe
(serotonin)

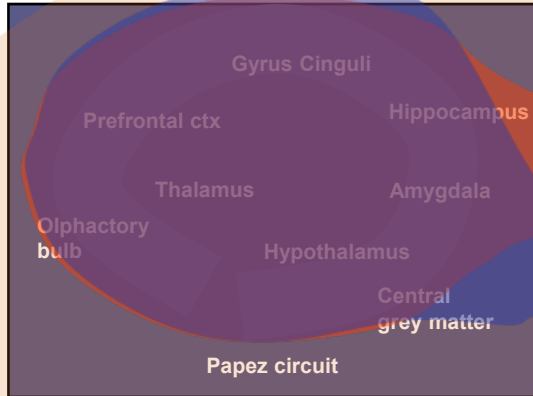
locus coeruleus
(noradrenaline)

motor system



System of the emotional control - diffuse effects

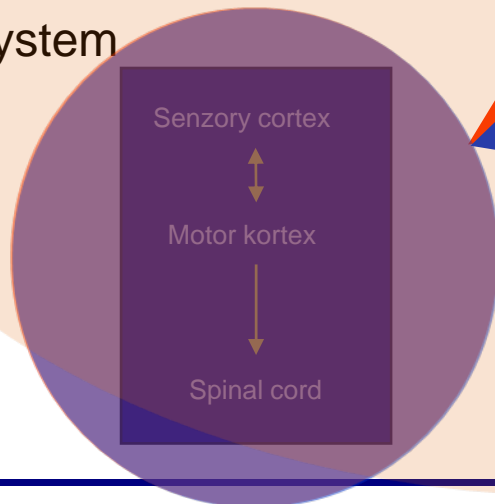
limbic system



raphe
(serotonin)

locus coeruleus
(noradrenaline)

motor system



(Stress)hormones

How does a complex system operate well? – a systems theory approach

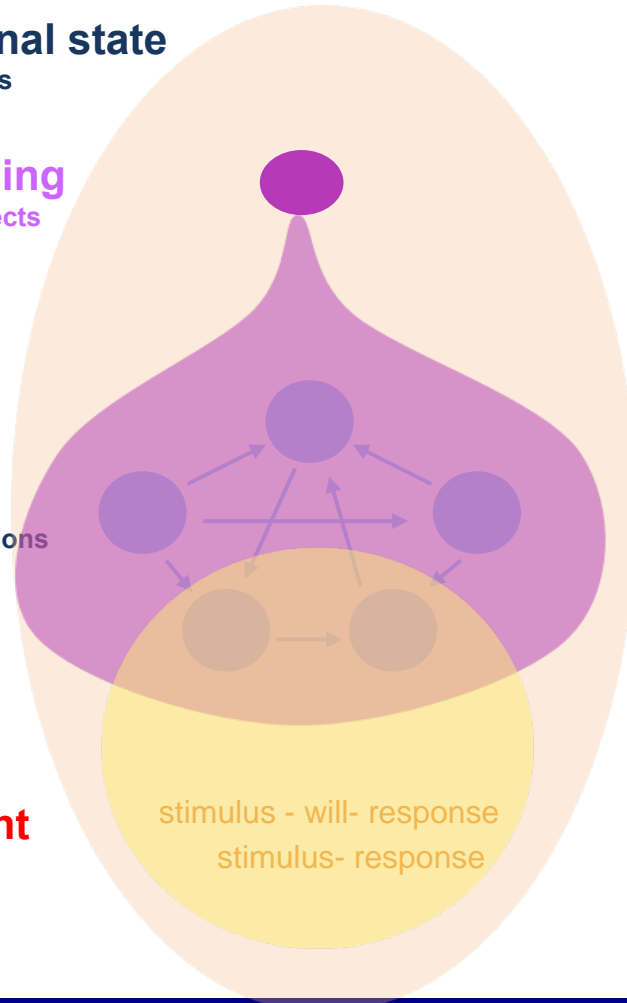
General functional state

Global effects

Fine tuning
diffuse effects

Emotion
complex interactions

Movement
„wiring”



Treatment options

Hormones, hormone antagonists
(testosterone, estrogen, cortizol)

Compounds modifying serotonergic,
norenergic, and dopaminergic
neurotransmission

Compound stimulating GABA neurotransmission
Partial glutamate receptor agonists

How does a complex system operate well? – systems theory approach

General functional state

Global effects

Main risk: interference from bodily functions

Fine tuning

diffuse effects

The most frequently used option

Emotion

complex interactions

Limited possibilities

Movement

„wiring“

stimulus - will- response
stimulus- response

High risk approach, not recommended

Treatment options

Hormones, hormone antagonists
(testosterone, estrogen, cortisol)

Compounds modifying serotonergic, norenergic, and dopaminergic neurotransmission

Compound stimulating GABA neurotransmission
Partial glutamate receptor agonists

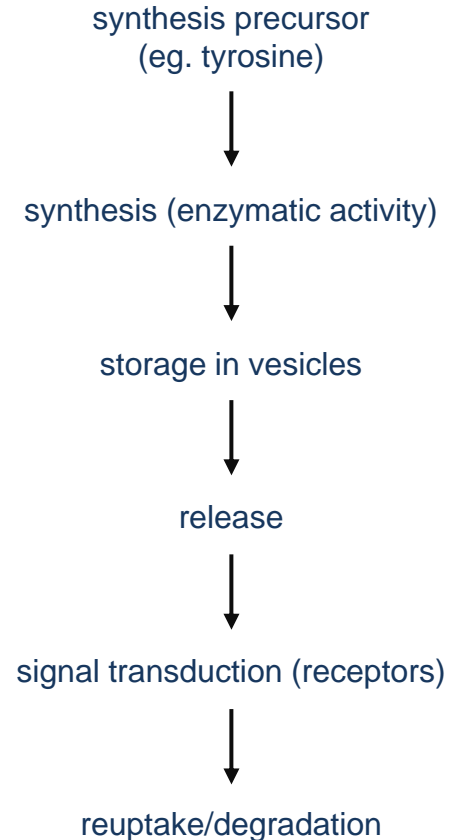
Drug targets and treatment options

Inhibition:

- lesions
- neurotoxins
- inhibition of synthetic enzymes
- inhibition of vesicular uptake
- stimulation of reuptake
- receptor antagonists

Stimulation:

- increasing the amount of precursors
- facilitation of depletion
- inhibition of reuptake
- inhibition of degradation
- receptor agonists



Challenge, anxiety, depression

Systems theory approach



Trouble

real, potential,
or hypothetical

Precaution:

Avoid risks
(precaution "turned on")

Anxiety

Mobilising „dormant” energies:

Energy stores mobilized
Active behavioral programs turned on
(eg. fight or flight)

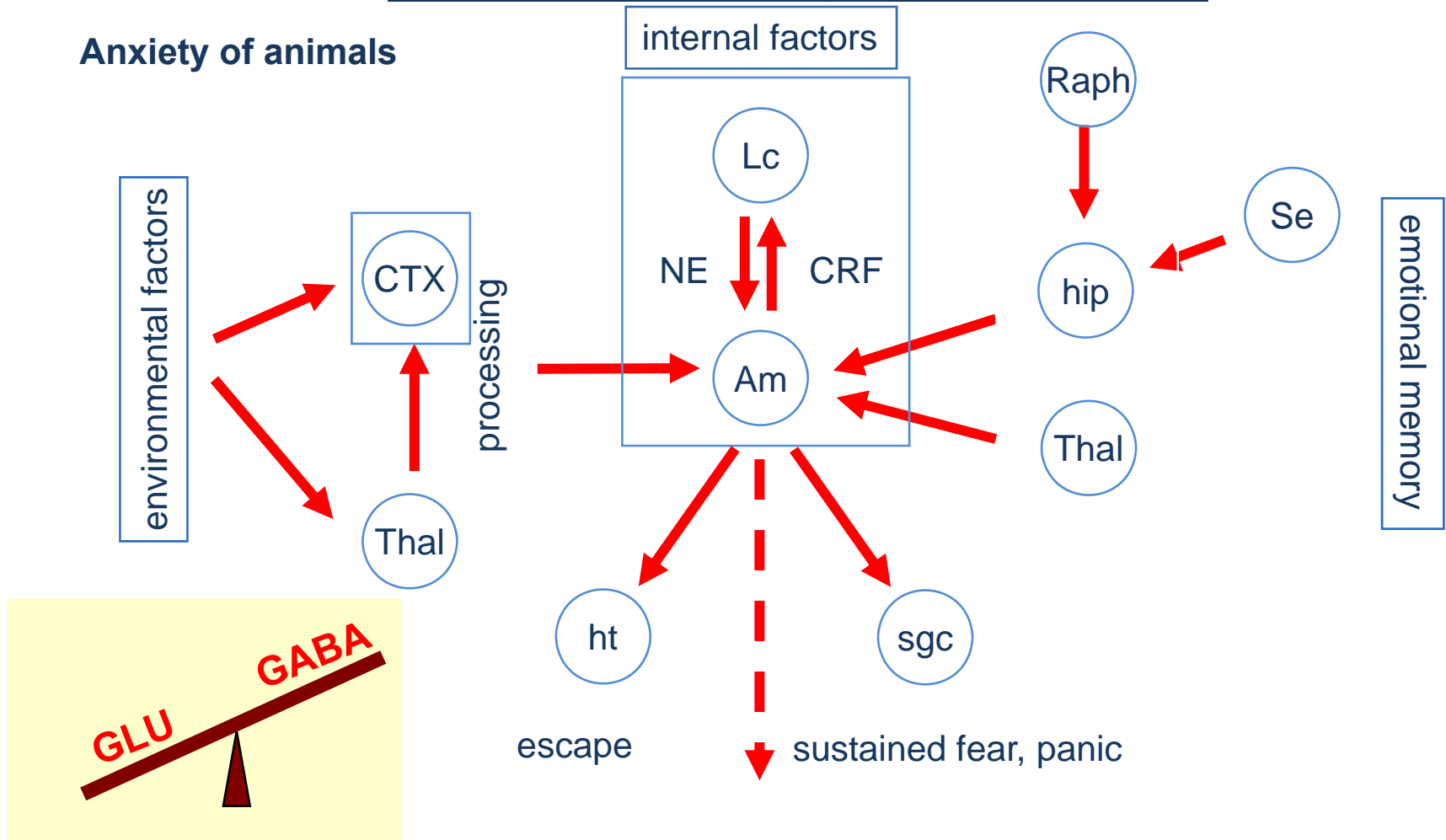
Alarm

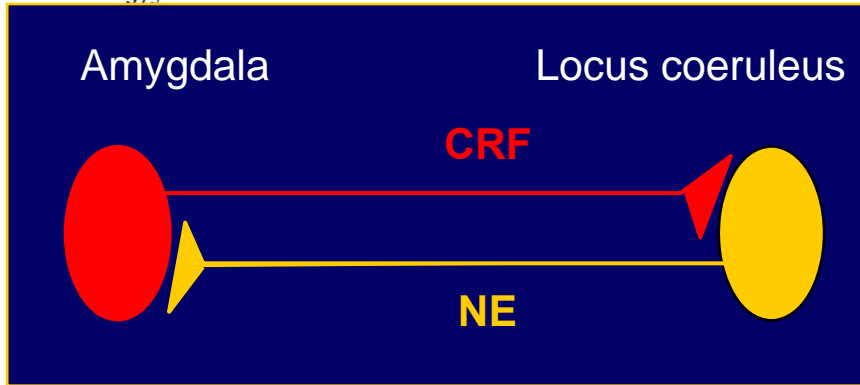
Activity cutback :

Some programs run at minimum
Other programs suspended

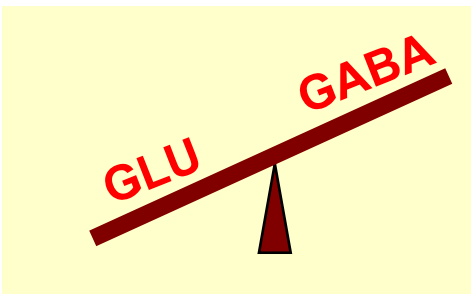
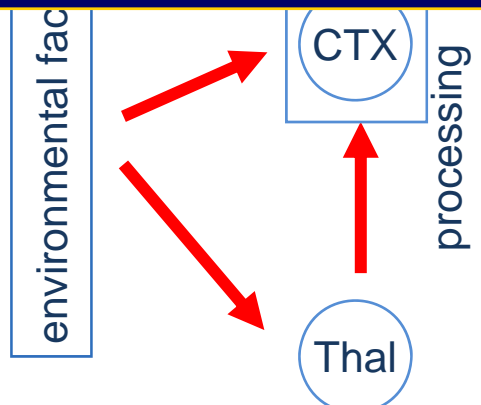
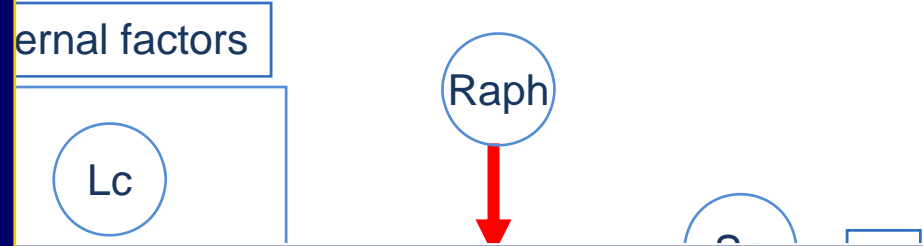
Depression

Neuronal pathways of anxiety

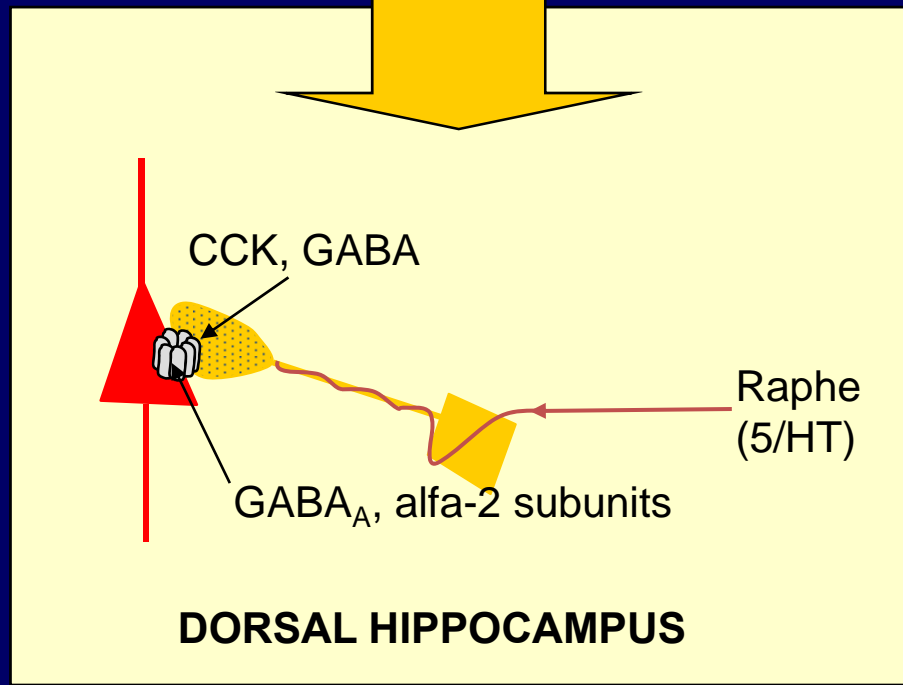




Pathways of anxiety



Benzodiazepines, serotonergic anxiolytics



Aminoacids

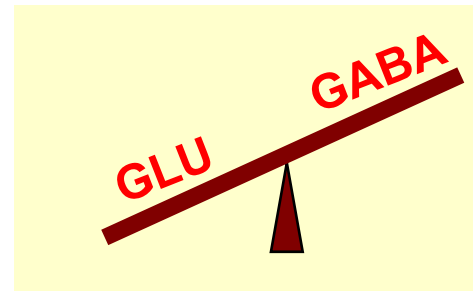
GABA complex

Benzodiazepines
modulation of
channel-opening
frequency

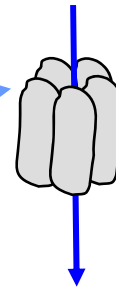
agonists
inhibition of anxiety

antagonists
preventing the effects
of anxiolytics

inverse agonists
increase of anxiety



CL⁻



Barbiturates
small doses
opening probability increases
inhibition of anxiety

large doses
opening the channel
hypnotic effect
toxicity

Human:
The most frequently used anxiolytics are the benzodiazepines, although they are addictive. Barbiturates are still used (relatively rarely).

Excitatory amino acids

Glutamate, aspartate (glycine)

Agonist effects: increase of anxiety
sustain anxiety states (posttraumatic stress disorder; SGC, NMDA/glycine)
inhibition of benzodiazepine effects

Hope: partial antagonism

Most important benzodiazepine anxiolytics (thousands were synthesized)

<u>Compound</u>	<u>Half life*</u>	<u>Effects**</u>
Triazolam	2-4	hypnotic
Lorazepam 8-12		anxiolytic, hypnotic
Oxazepam		
Temazepam		
Lormetazepam		
Alprazolam 6-12		anxiolytic, antidepressant
Nitrazepam 16-40		
Diazepam	20-40 (Nordiazepam 60)	anxiolytic, anticonvulsive
Chlordiazepoxide	4-5	
Flurazepam	1	anxiolytic,
Clonazepam	50	anticonvulsive, anxiolytic,

*Effect can be significantly longer

** All reduce aggressiveness

Side effects

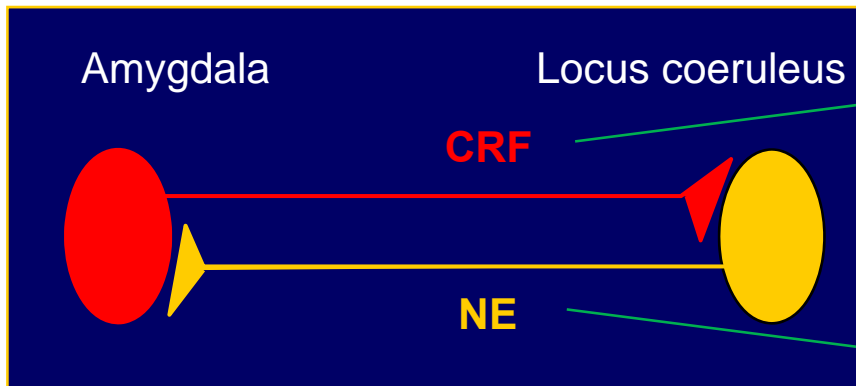
sedation

muscle tone relaxation, movement coordination problems

addiction

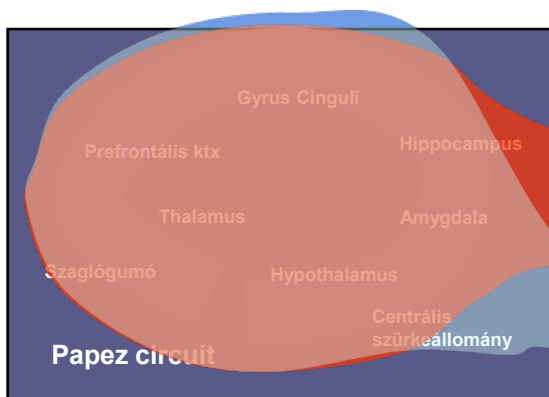
Flumezanil: competitive benzodiazepine antagonist

used to overcome the effects of overdosed benzodiazepines



Hope

Beta adrenergic antagonists



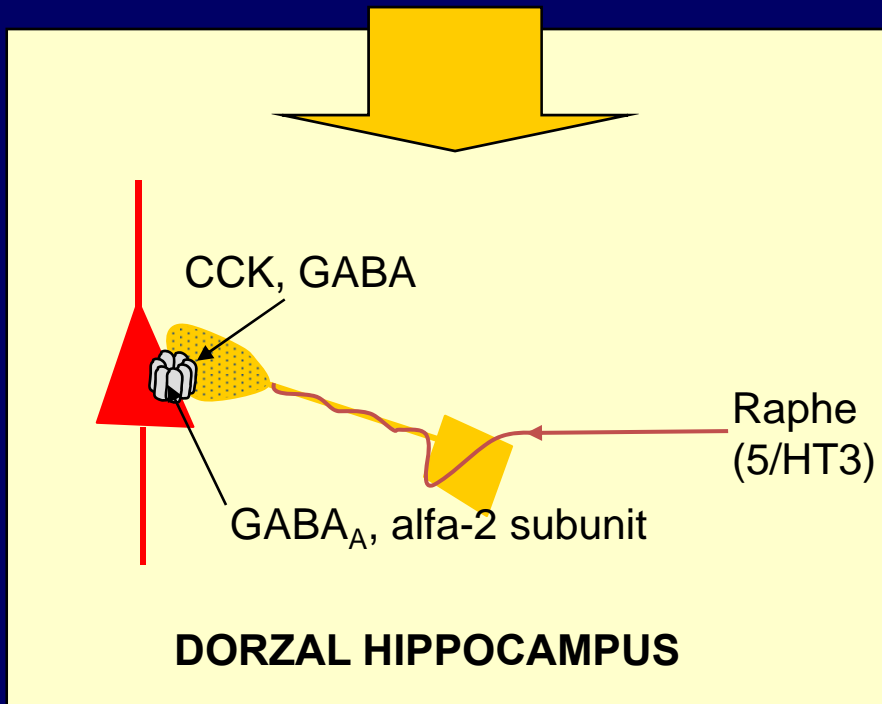
Anxiolytics

raphe
(serotonin)

locus coeruleus
(noradrenaline)

Serotonergic anxiolytics
Beta adrenergic antagonists

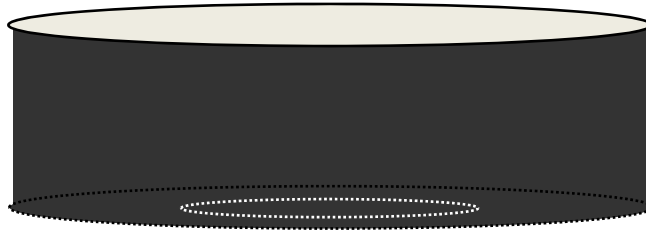
Benzodiazepines, serotonergic anxiolytics



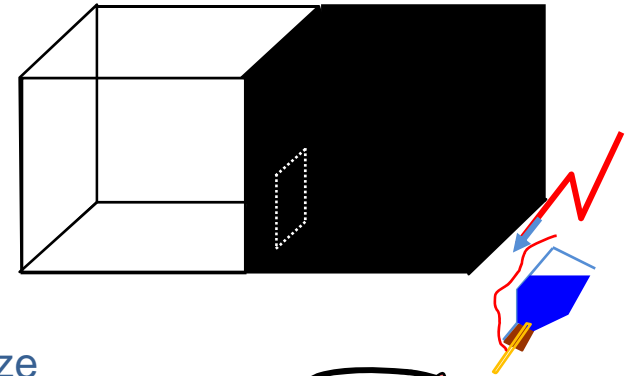
Hope
hope
hope
...

Experimental modelling of anxiety

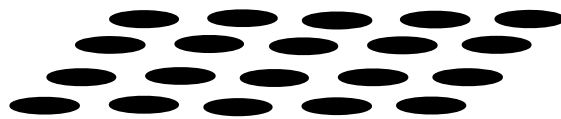
open field



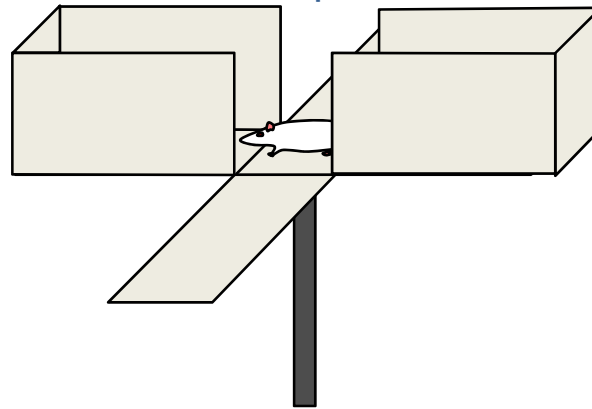
light/dark box



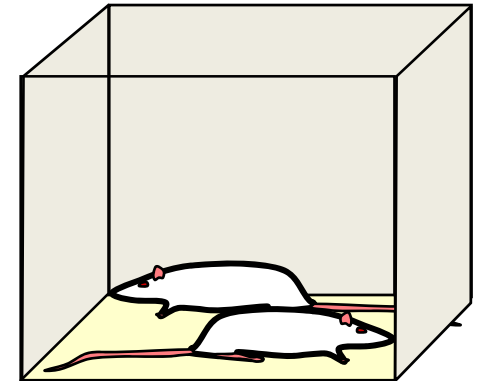
hole board



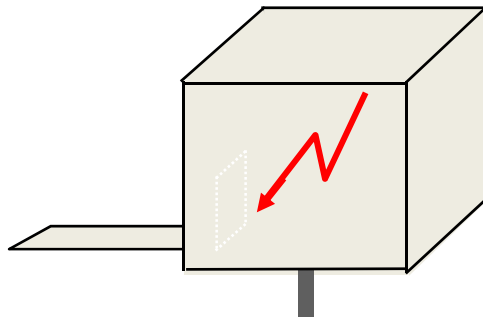
elevated plus maze



Vogel-test



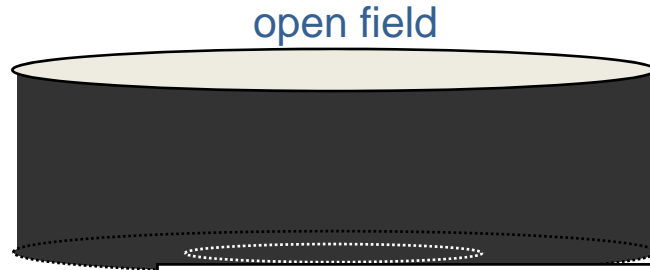
passive avoidance



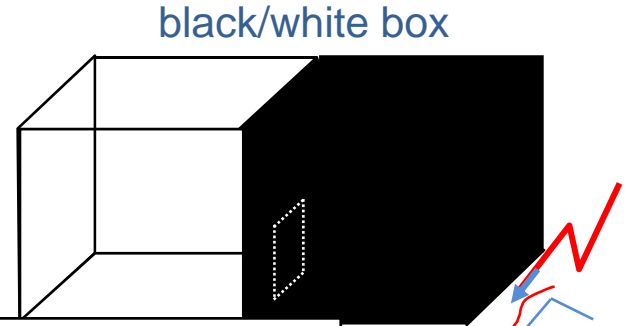
other, eg. shock-prod

social interaction

Experimental modelling of anxiety

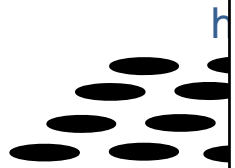


open field



black/white box

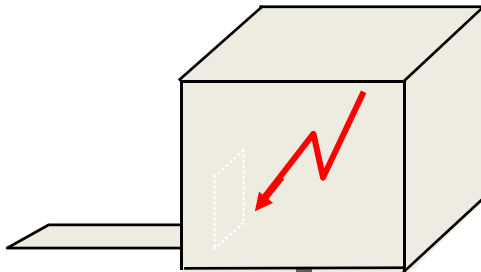
Such tests and models are used to develop novel anxiolytics as the available ones have important shortcomings



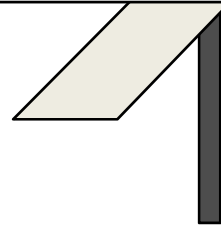
passive avoidance



Vogel-test

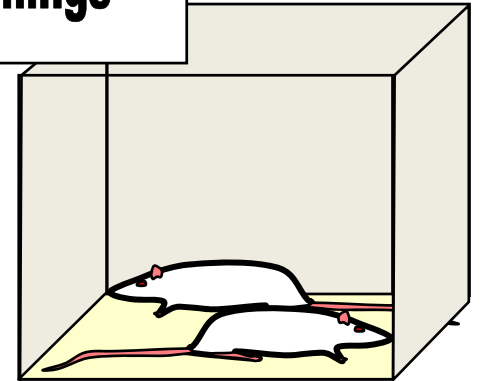


passive avoidance



elevated plus-maze

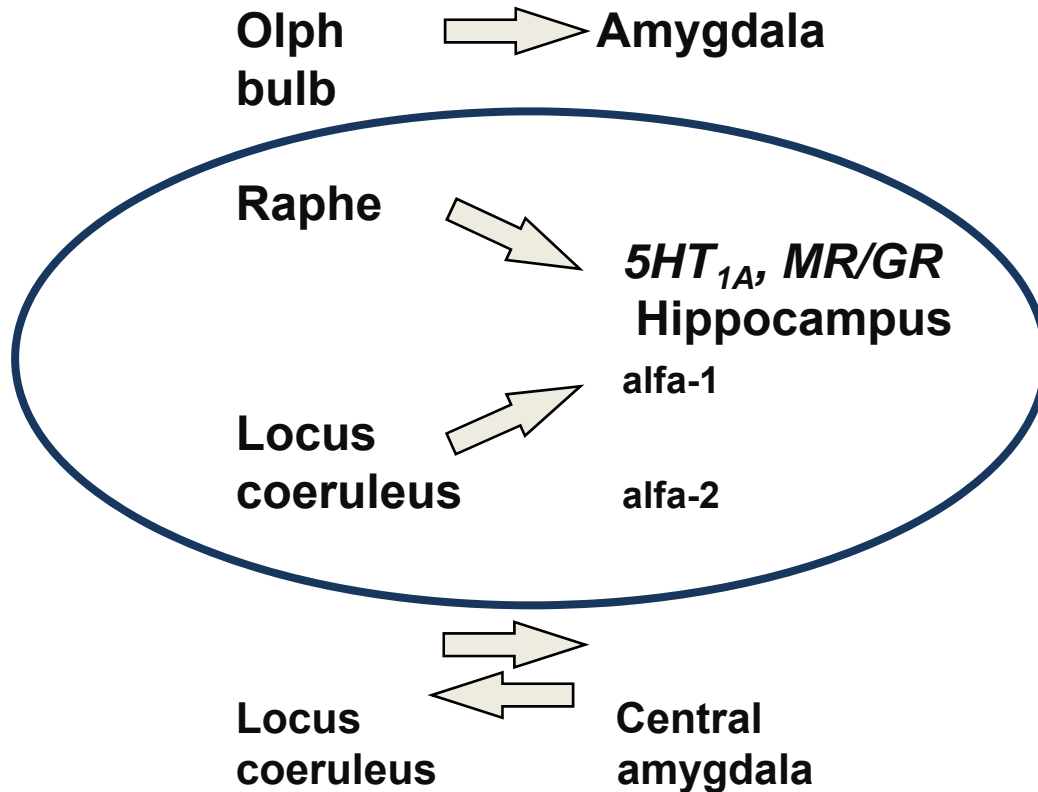
other, eg. shock-prod



social interaction

Neuronal pathways of depression

Pathway



Neuronal pathways of depression

Pathway

Olf bulb → Amygdala

Raphe
Locus
coeruleus → alpha-2

Locus
coeruleus ↔ Central
amygdala

The monoamine theory of depression

The monoamine theory of depression

Depression can be traced back to reduced monoamine (noradrenergic and serotonergic) functions in the brain.

Arguments:

- Depression has a strong genetic component (biochemical abnormality)
- Symptoms of depression are reduced or blocked by compounds, which stimulate the monoaminergic system
- Norepinephrine metabolites are reduced in the blood and cerebrospinal fluid of depressive patients
- Serotonin metabolites are reduced in the cerebrospinal fluid of depressive patients
- Serotonin uptake is reduced in platelets

Counter arguments:

- Biochemical effects of monoaminergic antidepressants are fast while behavioral effects develop slowly
- Data on monoamine metabolism are controversial
- Based on biochemical activity, certain compounds (e.g. amphetamine, cocaine) should decrease symptoms of depression but they do not have such effects
- Certain compounds decrease depression without affecting the monoaminergic system

Conclusion:

- Compounds that stimulate monoaminergic neurotransmission also decrease the symptoms of depression;
- Their behavioral effects are not necessarily direct consequences of their primary biochemical effects.

Antidepressants

Tricyclic antidepressants (TCA)

compounds: imipramine, amitriptillin, clomipramine, desipramin, nortryptillin, protriptillin, doxipramin

effects: inhibition of NE, 5-HT reuptake

side effects: sedation, disturbed motor coordination (weakens with time), dry mouth, constipation, urine retention

Monoamine oxidase inhibitors (MAOI)

compounds: phenelzine, tranylcypramine, iproniazid

effects: reduction of enzymatic degradation of NE, 5-HT, DA

side effects: reduction of blood pressure, tremor, excitation, insomnia, weight increase, hepatotoxicity (rare)

Selective Serotonin Reuptake Inhibitors (SSRI)

compounds: fluoxetine, fluvoxamine, paroxetine, sertraline, nefopan

effects: inhibition of 5-HT reuptake

side effects: nausea, insomnia, weight increase

Selective Noradrenaline Reuptake Inhibitors (SNRI)

compounds: nomifensine, maprotiline

effects: inhibition of NE reuptake

side effects: sedation, dry mouth, disturbed vision, etc

Alpha-2 adrenergic blockers

compounds: mianserine

effects: increase of NE release

side effects: sedation, dry mouth, disturbed vision, etc

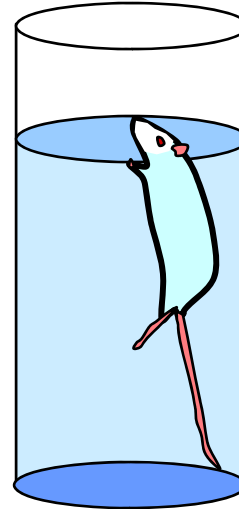
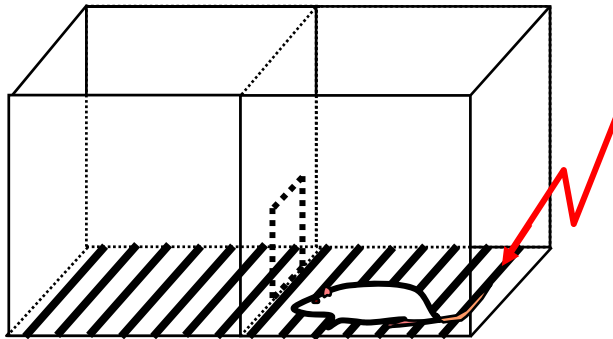
Tyaneptin

lprindole

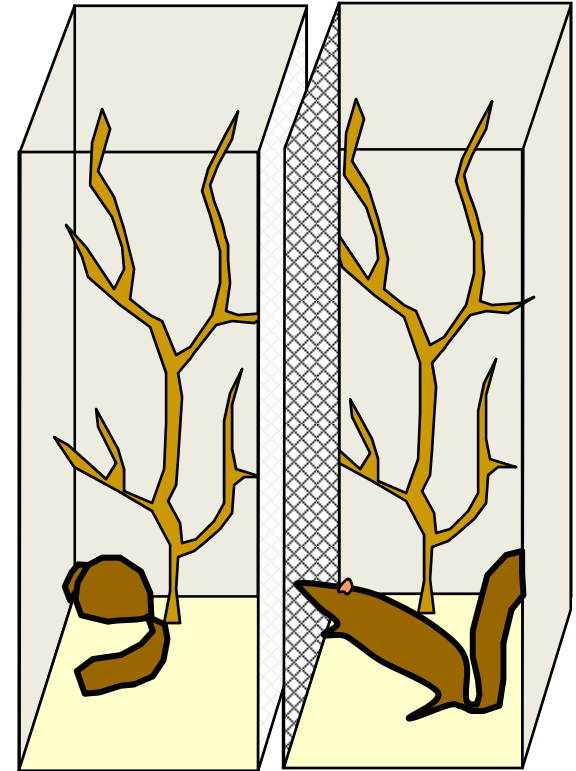
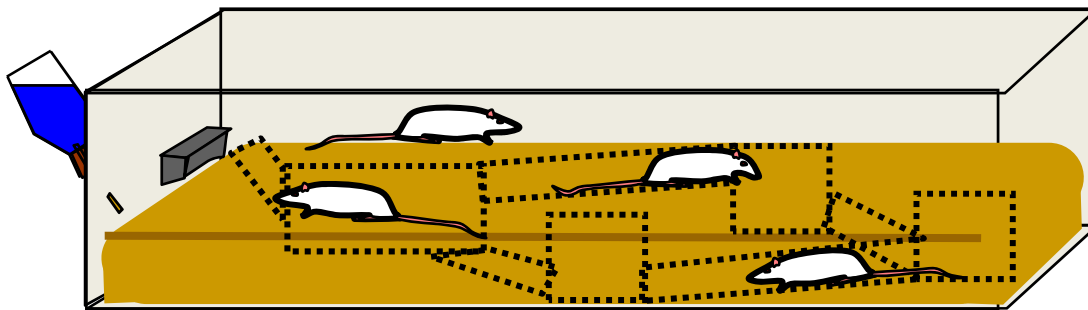
Litium

Electroshock

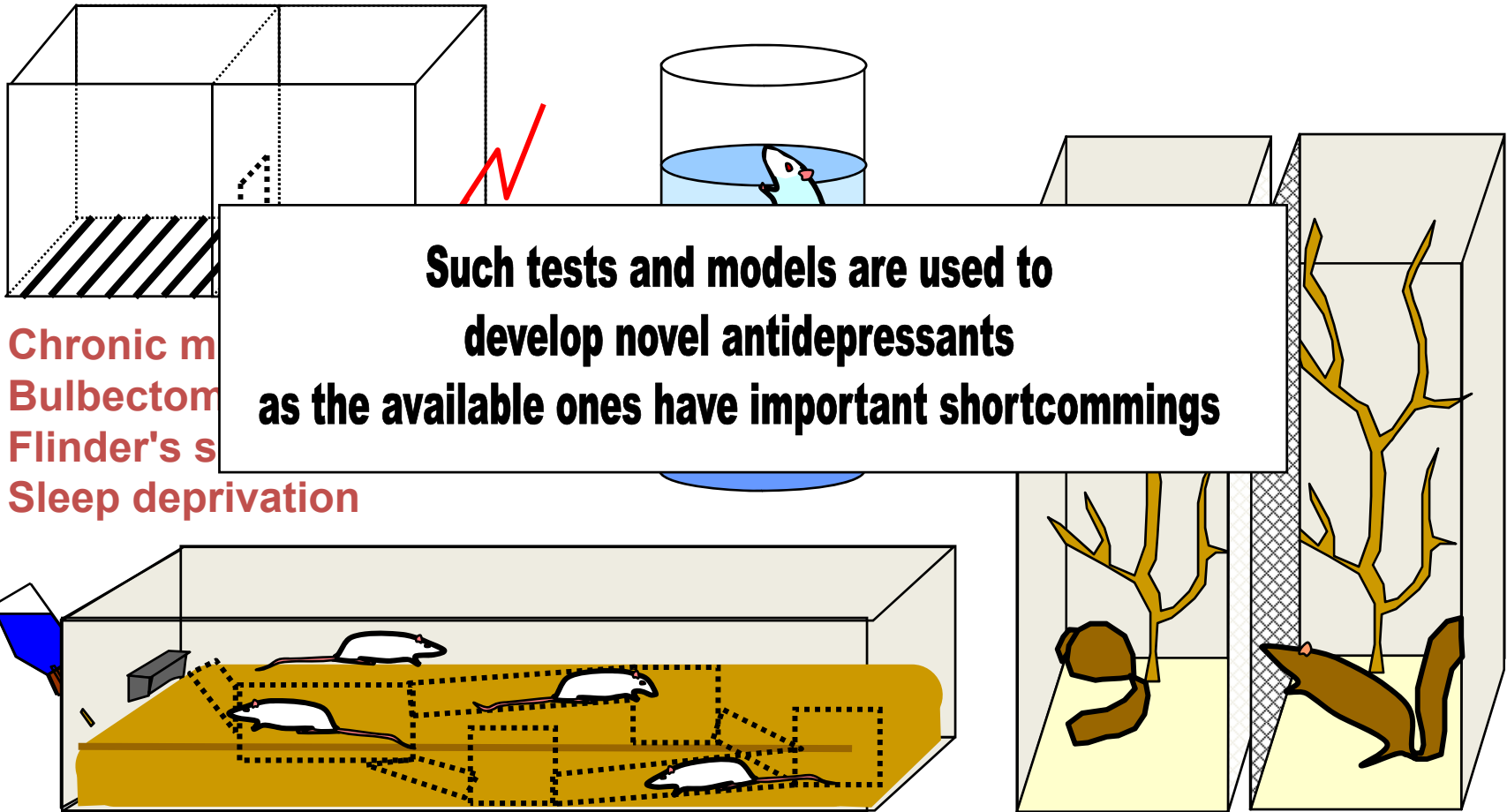
Experimental modelling of depression



Chronic mild stress
Bulbectomy
Flinder's sensitive line
Sleep deprivation



Experimental modelling of depression



General functional state

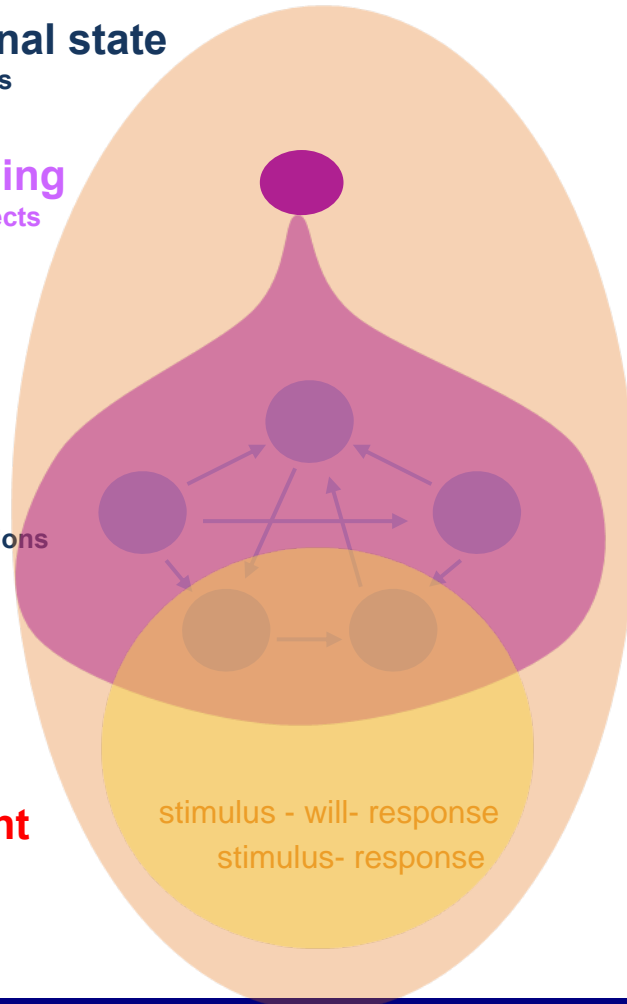
Global effects

Fine tuning

diffuse effects

Emotion
complex interactions

Movement
„wiring”



Subcellular/molecular mechanisms

