Stress Biomarkers: from Adaptation to Disorder

brain cortisol receptors

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Defining Stress

Input (stressor) → Processing information → **Output** (stress response)

- A **stressor** is perceived as any stimulus- either real or imagined- which threatens the integrity of the individual

- The **most severe stressor** is psychological**.**

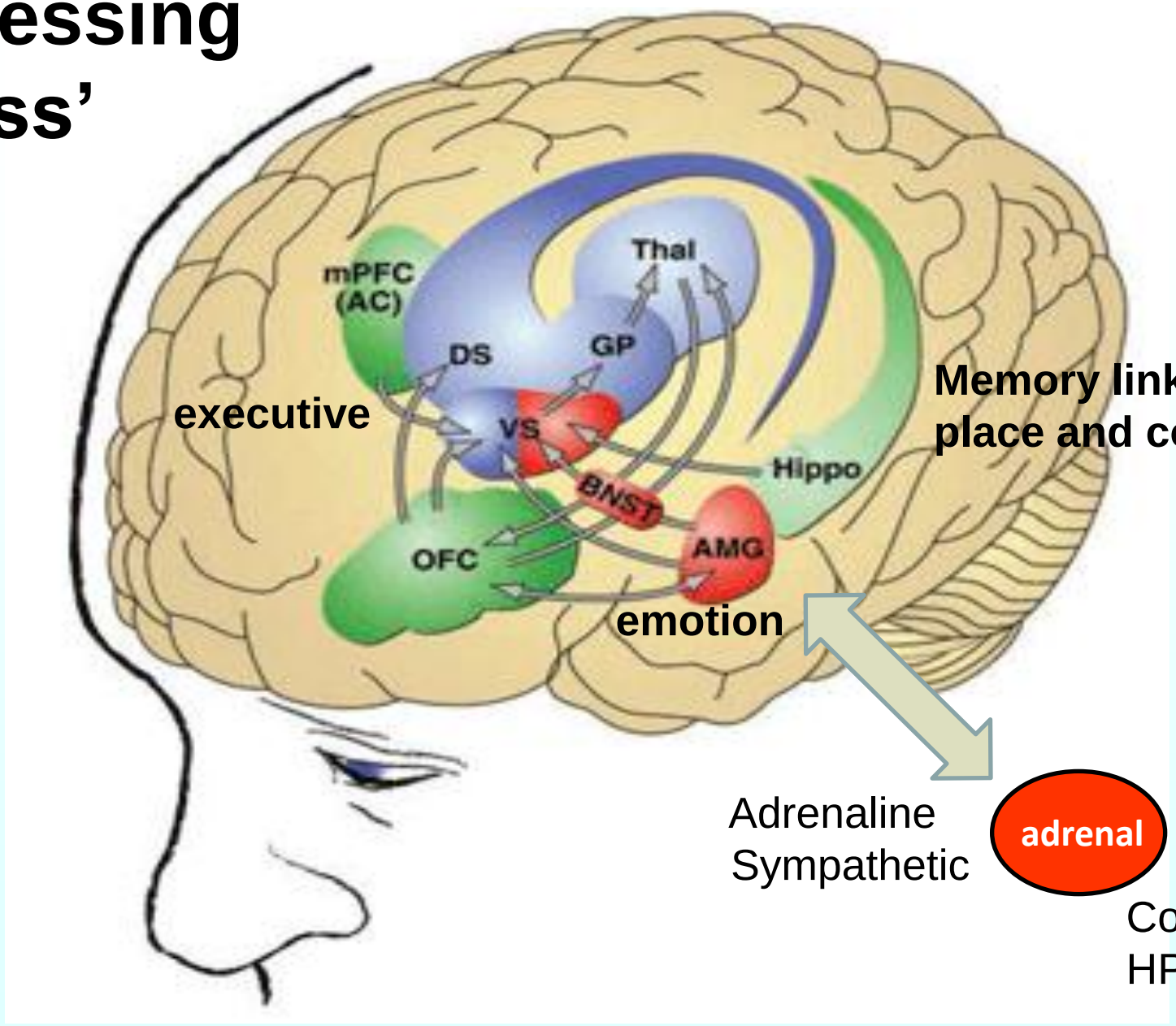
No sense of control, inability to predict, uncertain, fearful

- Homeostasis - stable equilibrium (pH, electrolytes etc)
- Allostasis - labile equilibrium (anticipation, brain)

- BRAIN is the organiser and target of the stress response

Levine, 2005

Processing ‘stress’



Acute stress

Enhances cognition, motivation, adaptation
Energy replenishment,
Enhances immune and cardiovascular function

Chronic Stress

Impairs cognitve function & adaptation
Energy depletion, muscle atrophy
Osteoporosis, suppression immune function,
Cardiovascular problems
Metabolic syndrome

stress mediators in blood

- Psychological & environmental stressors
- Excessive exercise
- Inadequate nutrition

Negative energy balance

Low carbohydrate intake

Dehydration

Increase

(nor) adrenaline

ACTH, endorphins

Cortisol

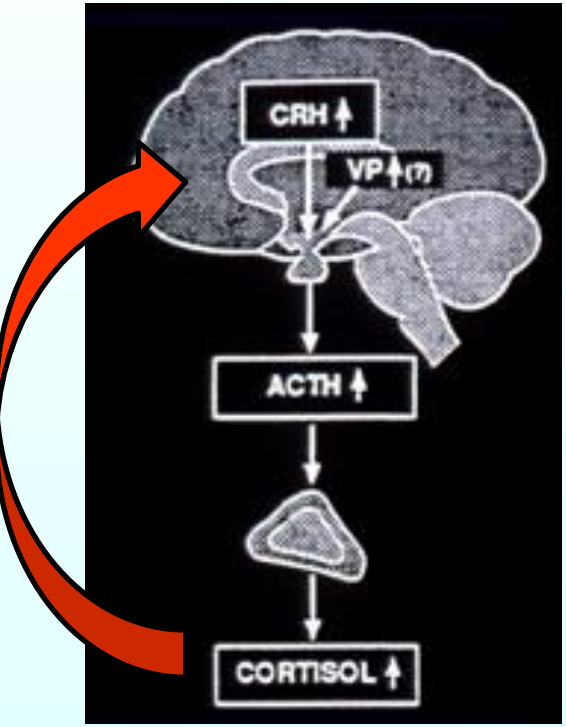
Glucagon

Decrease

Testosterone

Insuline (blockade glucose uptake except brain)

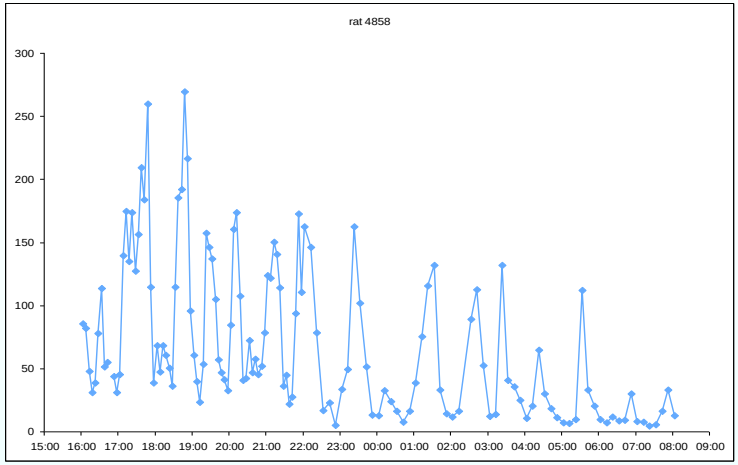
Cortisol
Corticosterone



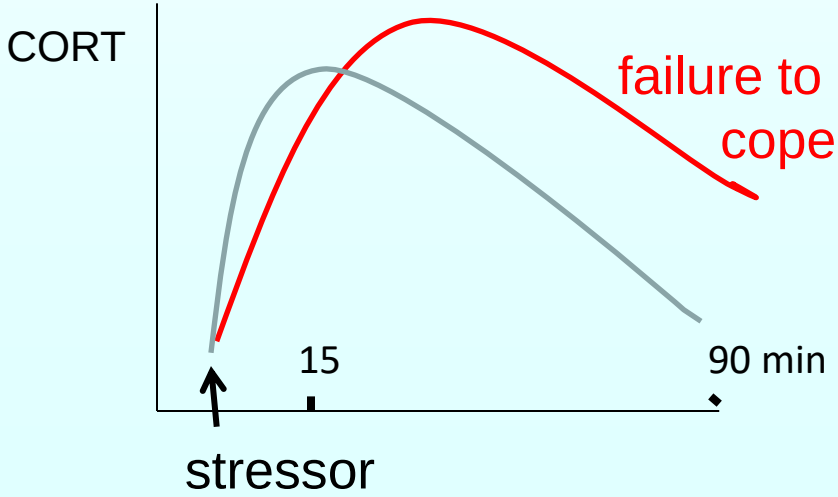
- Energy
- Stress - Adaptation

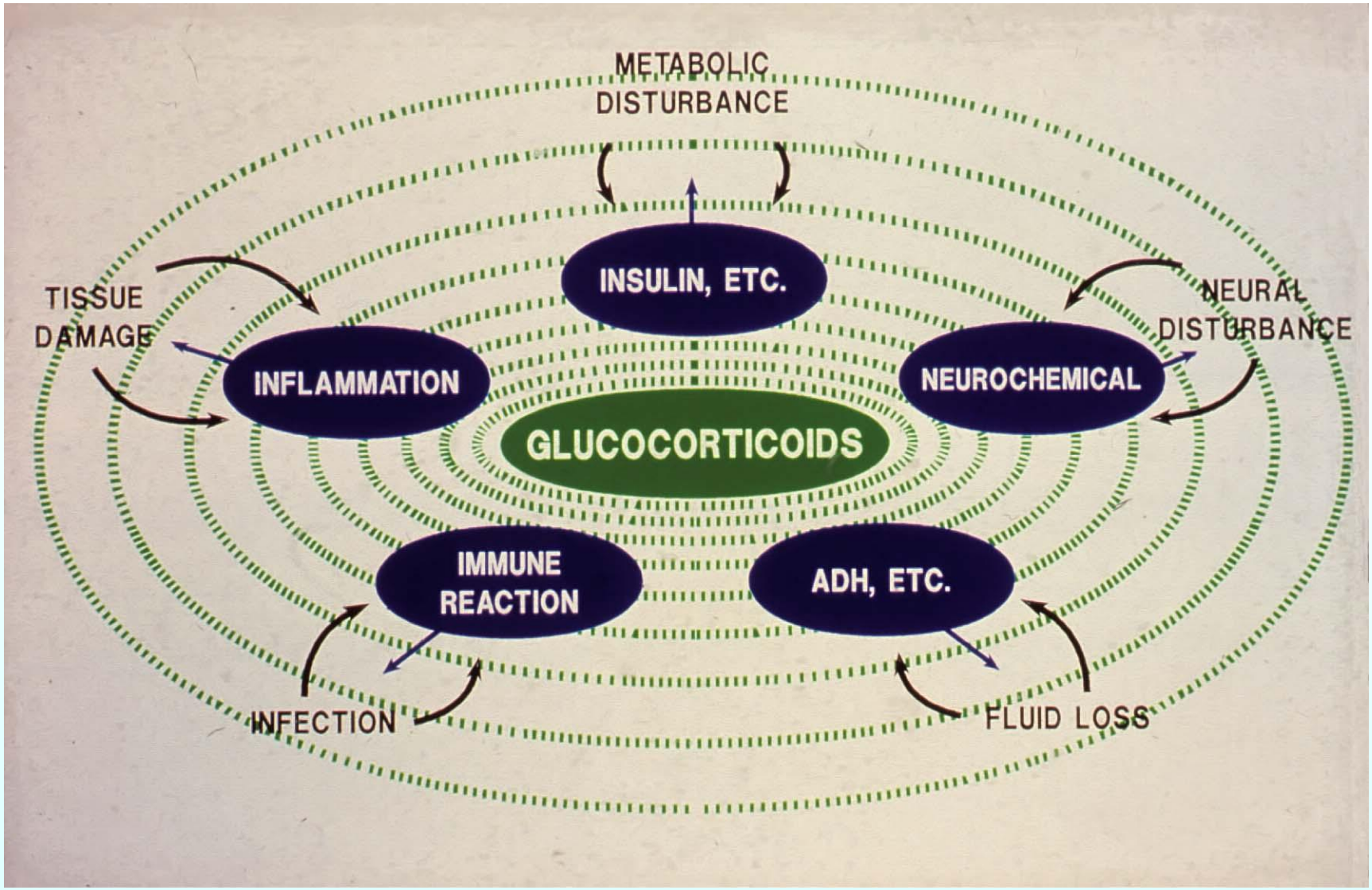
Hypothalamus – Pituitary – Adrenal axis

Basal pulse pattern synchronizes daily and sleep-related events

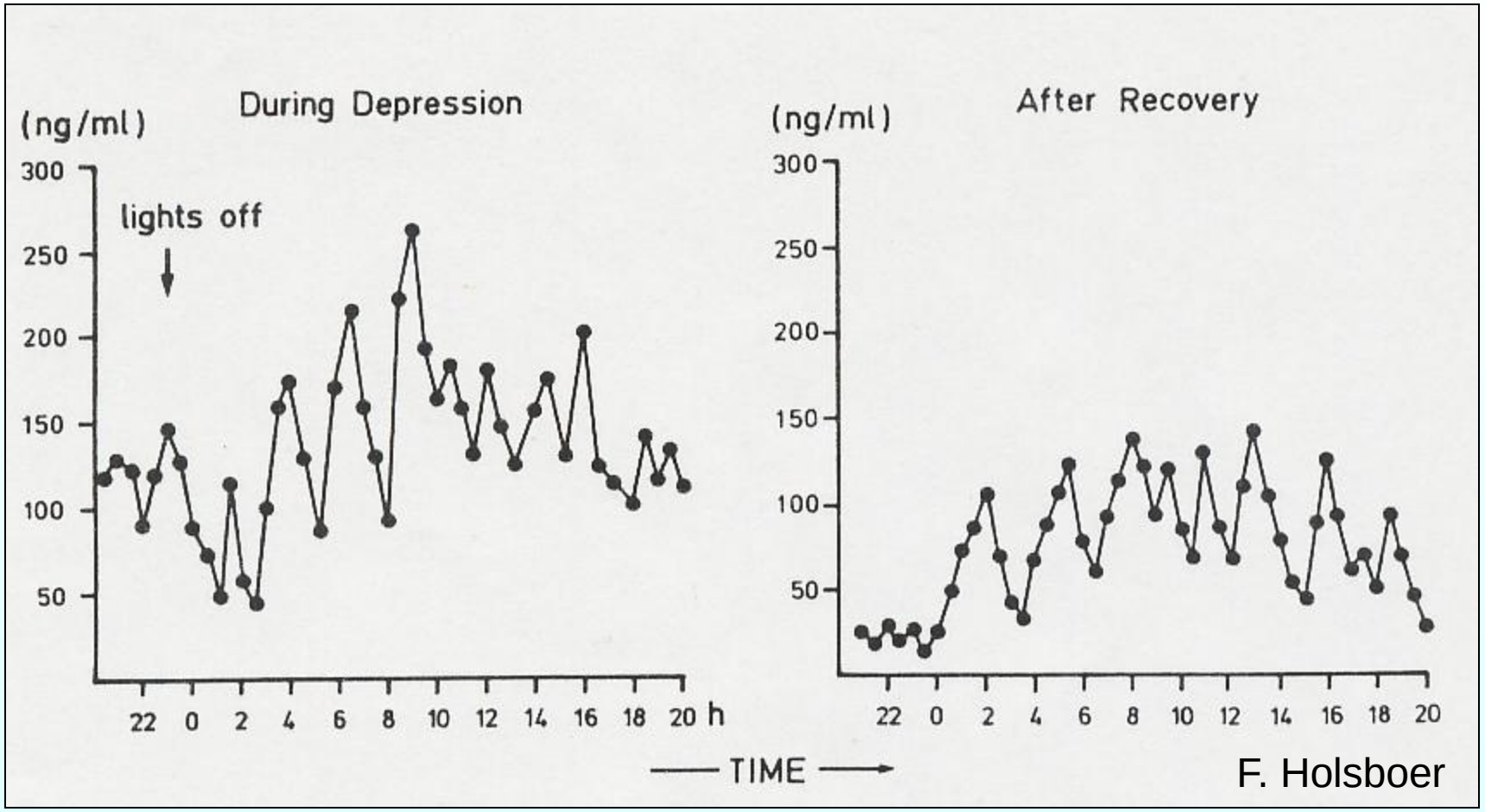


Stress response coordinates the ability to cope and adapt




METABOLIC
DISTURBANCE
INSULIN, ETC.
TISSUE
DAMAGE
INFLAMMATION
NEURAL
DISTURBANCE
NEUROCHEMICAL
GLUCOCORTICOIDS
IMMUNE
REACTION
ADH, ETC.
INFECTION
FLUID LOSS

DEPRESSION - elevated cortisol, flattened rhythm



PATTERNS MATTER RATHER THAN ABSOLUTE LEVELS

Disorders Linked to Over- and Under exposure to Cortisol

Over - exposure

Cushing syndrome
Hyperthyroidism
•Major depression
•Psychotic depression
Anorexia nervosa
Sleep deprivation
Malnutrition
Chronic alcoholism
Childhood abuse
Excessive exercise

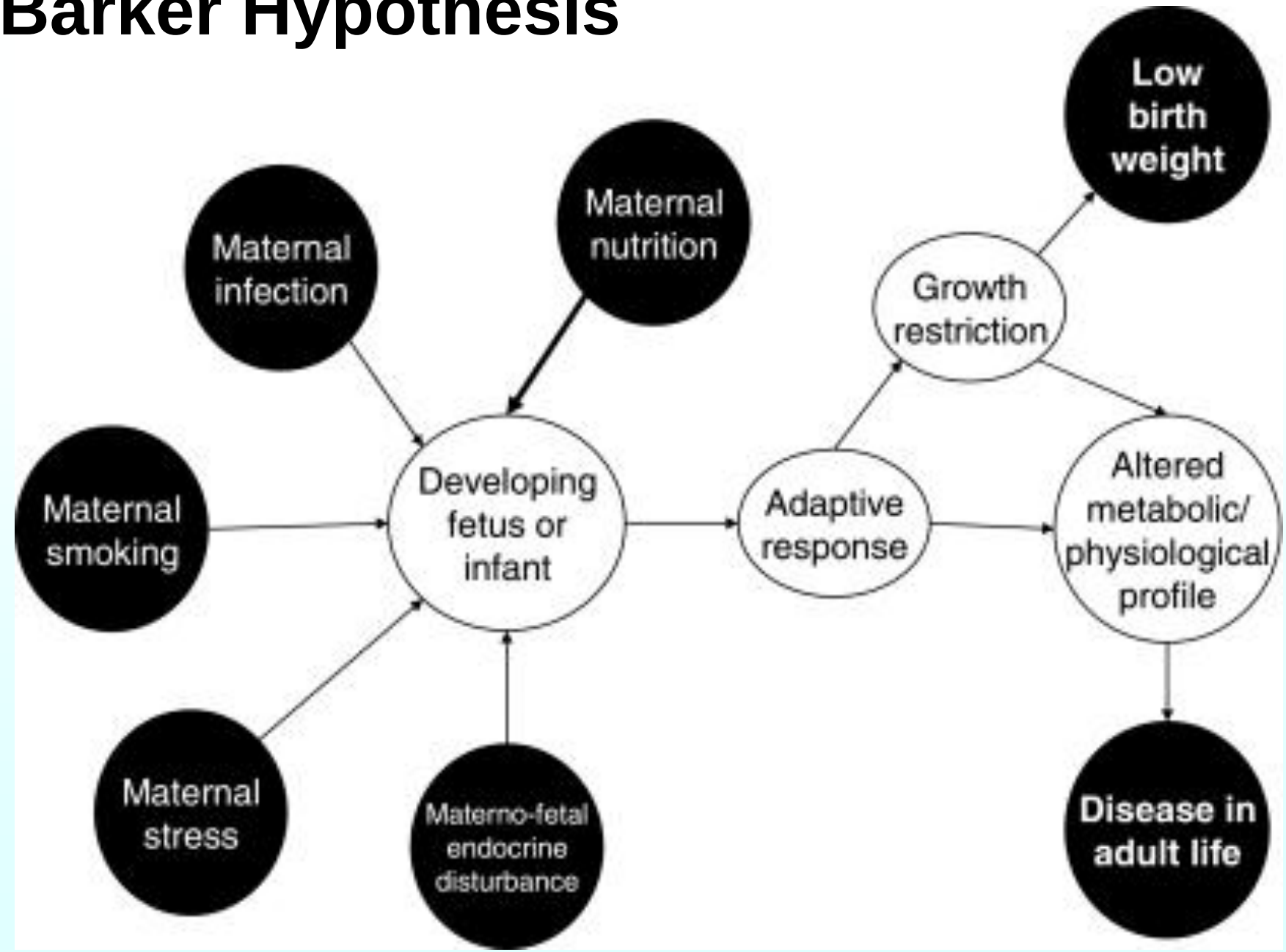
Under - exposure

- Atypical depression
- Chronic fatigue syndrome
- Fibromyalgia
- Post traumatic stress disorder
- Schizophrenia
- Panic disorder
- burnout

Hypothyroidism
Rheumatoid arthritis
Allergies
Asthma

GP Chrousos & PW Gold, 1992

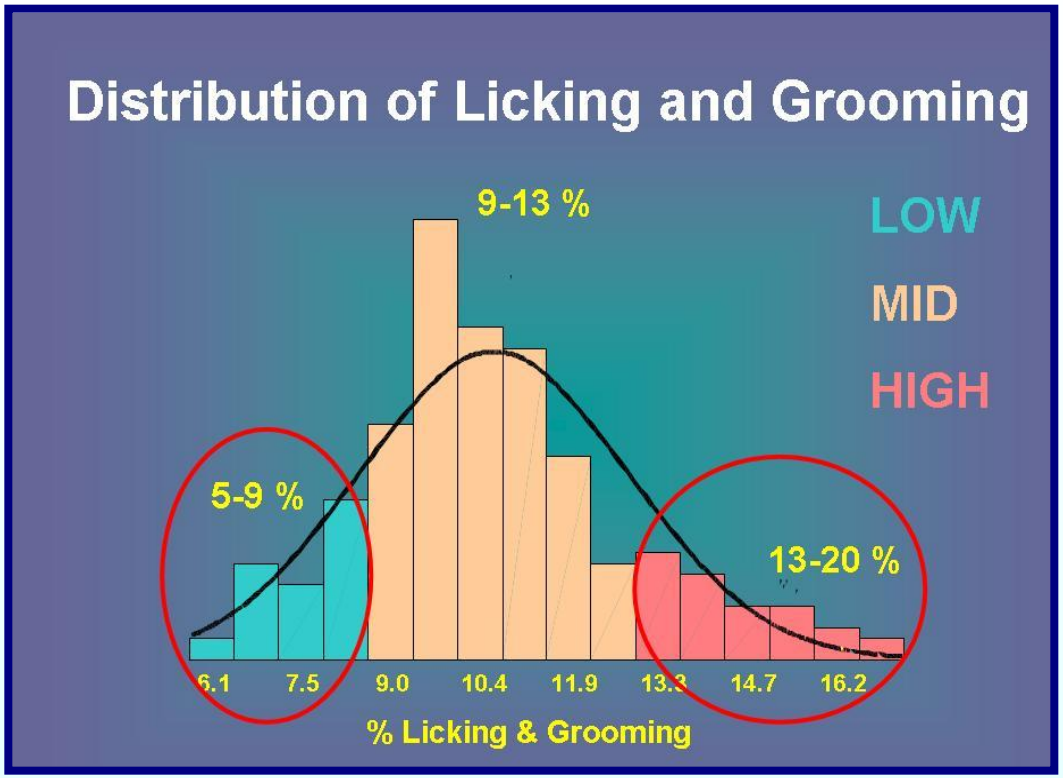
Barker Hypothesis

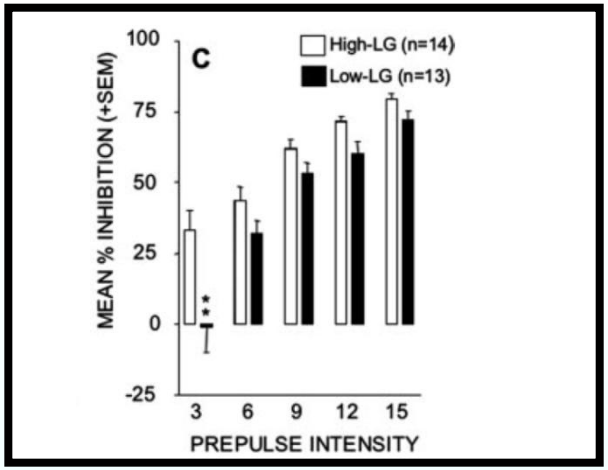


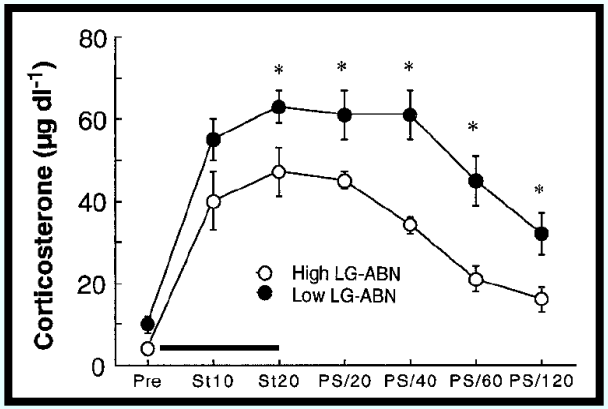
Langley Evans

Passive Nursing

Early-life environment: low maternal care







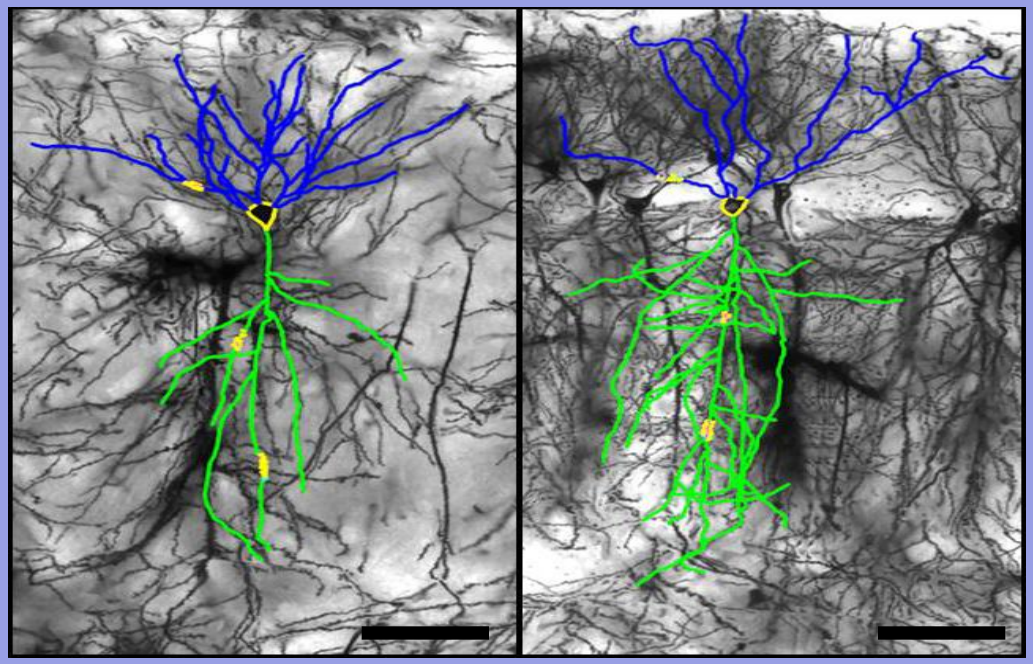
Long Evans rats; Liu et al. 1997, Champagne et al. 2003, Zhang et al. 2005

Low Maternal Care (Low LG):

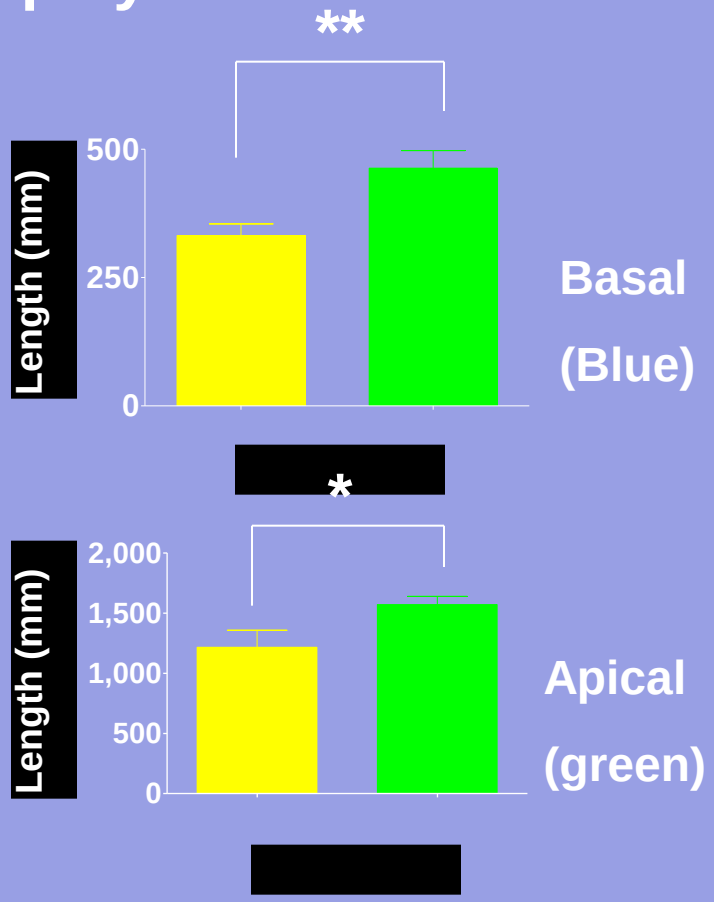
↓pre-pulse inhibition↑emotional stress (CORT) response. ↓ spatial learning & memory

Daskalakis et al, Claessens et al.

Adult offspring who received low amount of maternal care during infancy display lower dendritic length



Low LG High LG

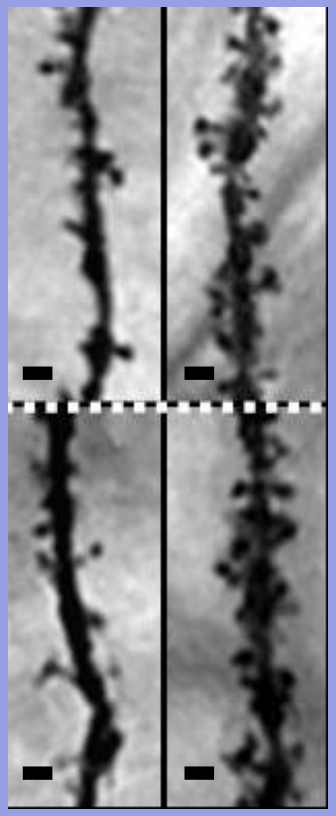


Scale bar: 200mm

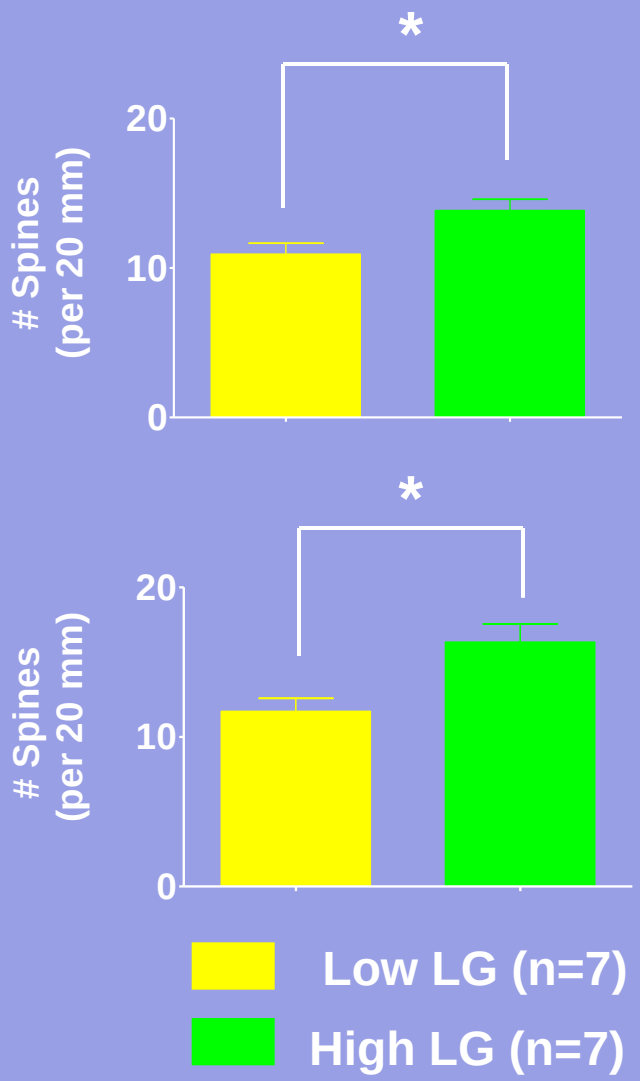
Adult offspring who received low amount of maternal care during infancy display lower spine density

Basal

Apical

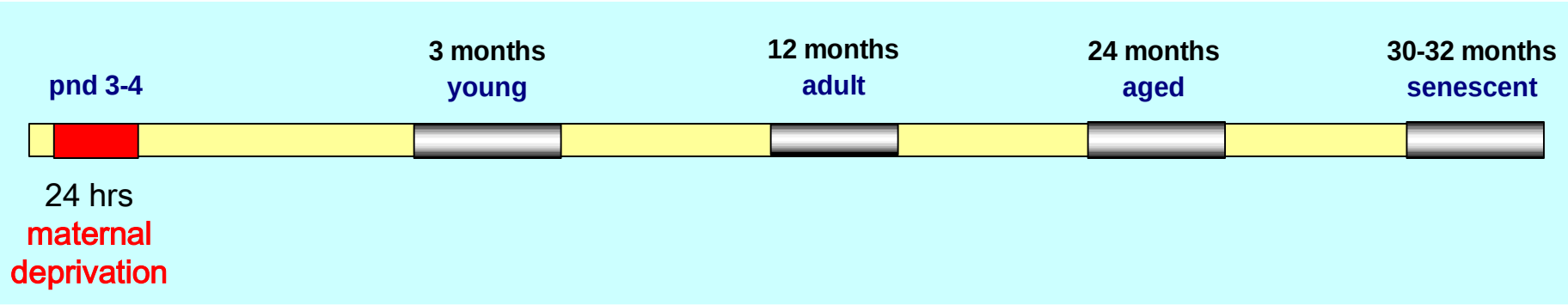


Low LG High LG



Scale bar: 25 mm

Long-lasting effects of mother-pup interaction

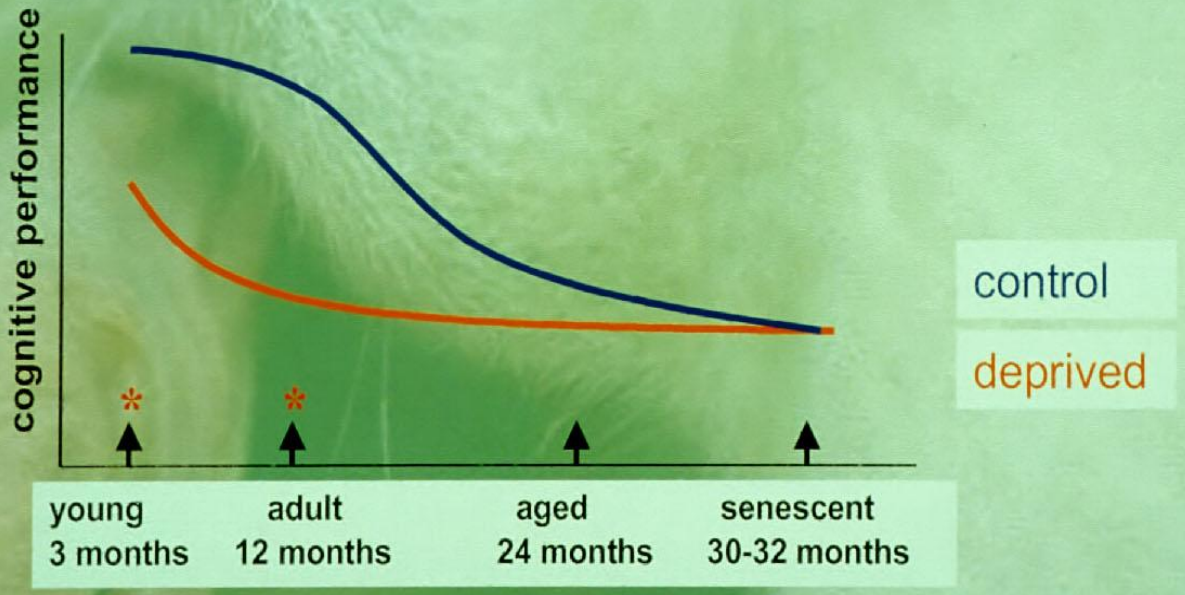


Behaviour, neuroendocrine markers, genes

Deprivation of maternal care a

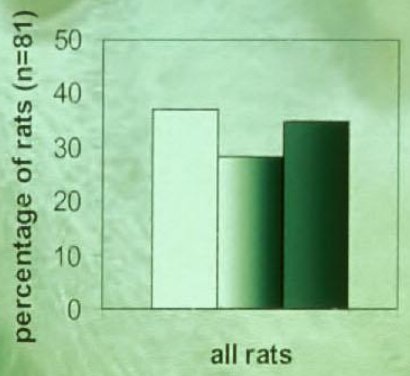
laboratory model for neglect

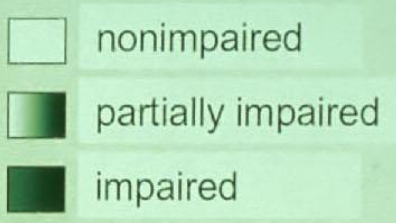
Impaired cognitive abilities of young and adult maternally deprived rats



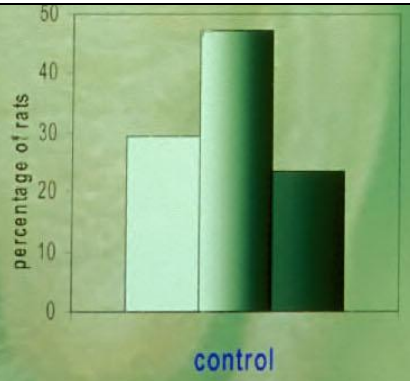
Melly Oitzl 2000

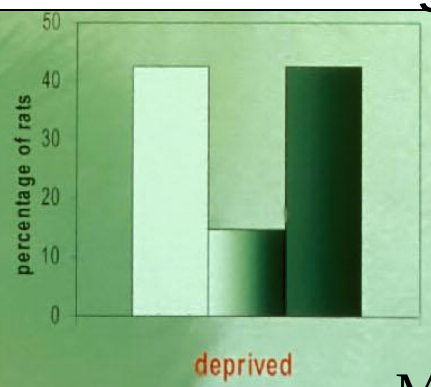
Increased inter-individual variability of cognitive performances **at senescence**





Aging drives in deprived animals performance to the extremes at the expense of the average

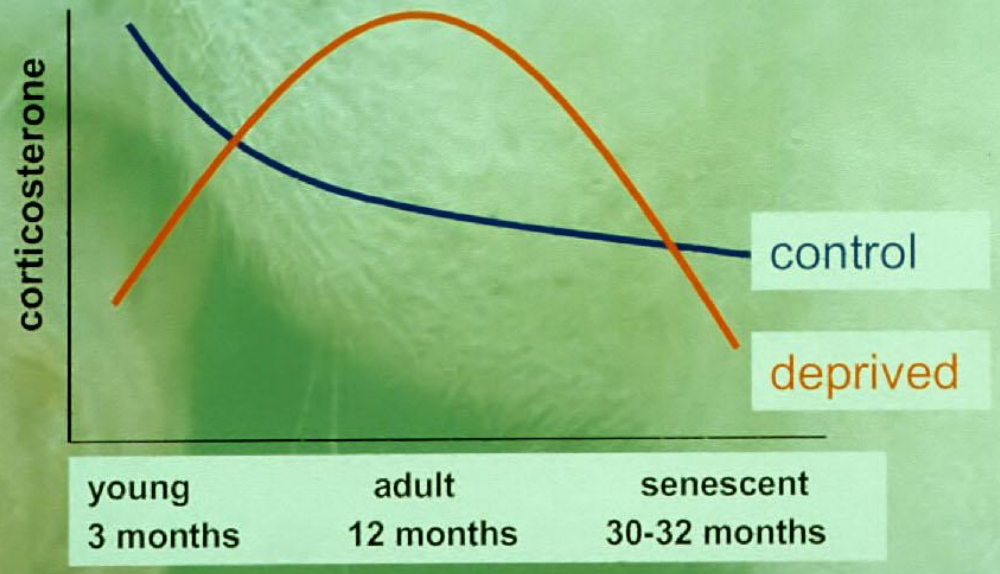




Melly Oitzl 2000

Outcome of an early adverse experience cannot be generalized

Life-long change of corticosterone responses to stress: midlife surge in maternally deprived rats



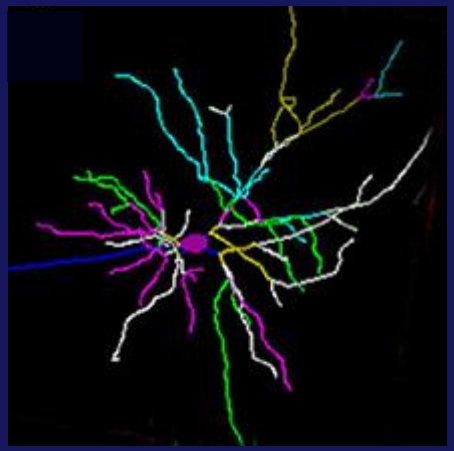
Male Brown Norway rats had been separated from the dam from pnd3-4.

Judith Workel 2001

Chronic Stress causes neurons to shrink or grow

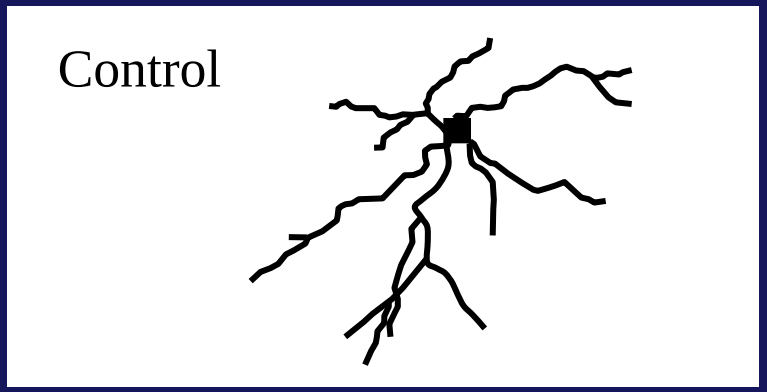
…but not necessarily to die

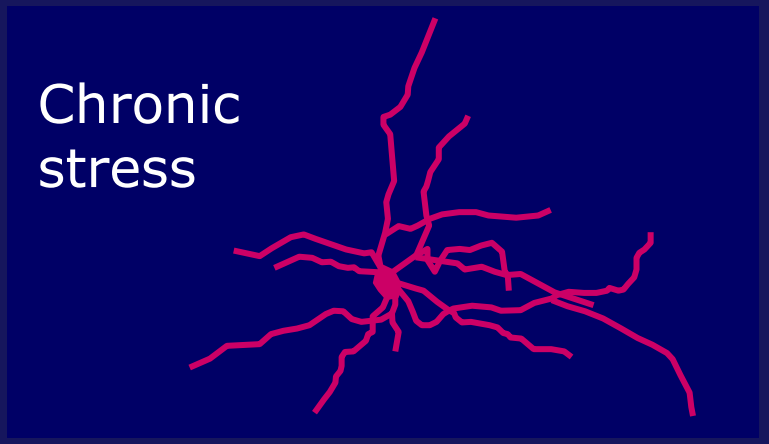
Control



Chronic stress

Prefrontal Cortex
And Hippocampus



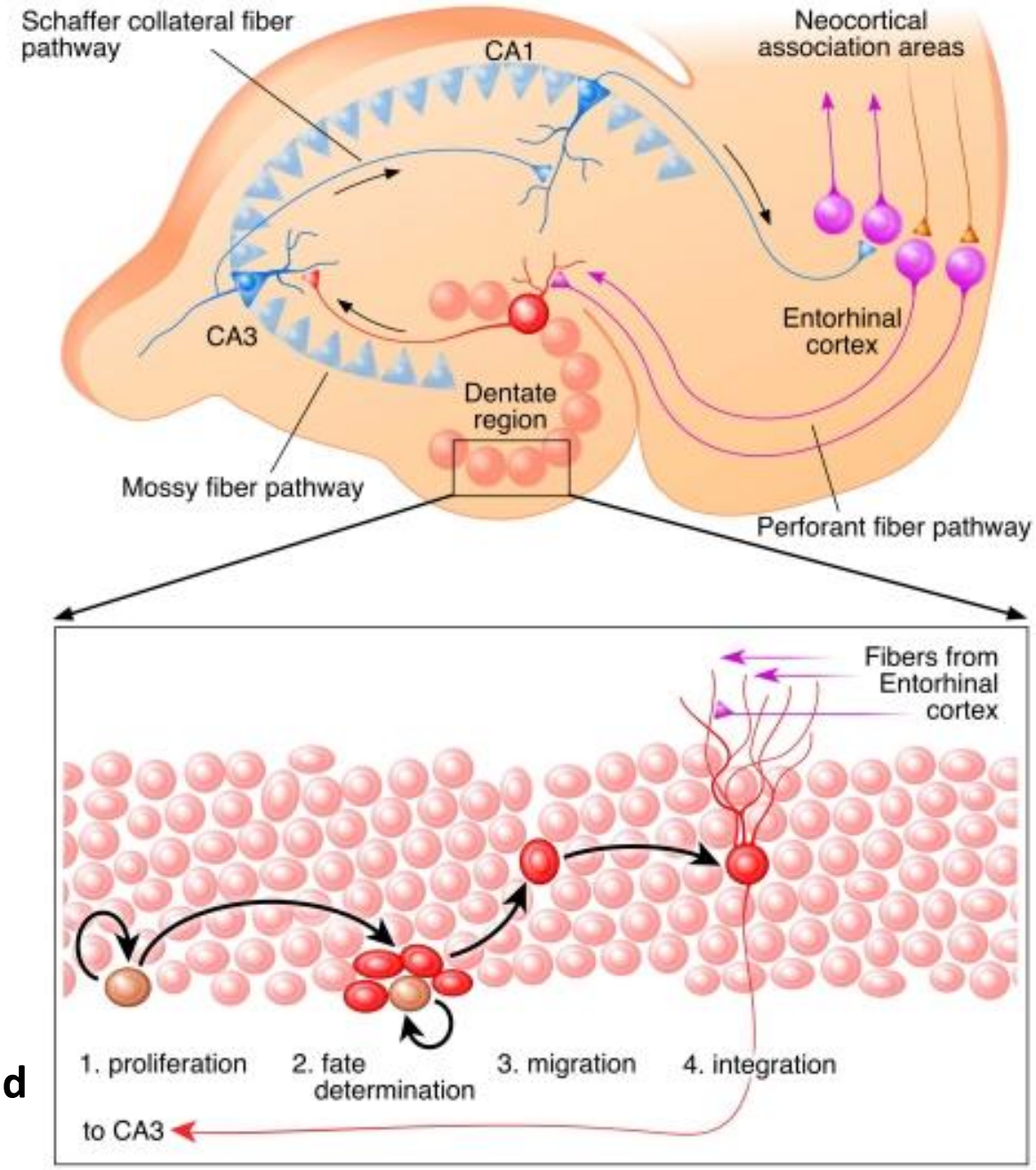


Amygdala
OFC

McEwen

Gene products that modulate integration of newborn neurons in network:

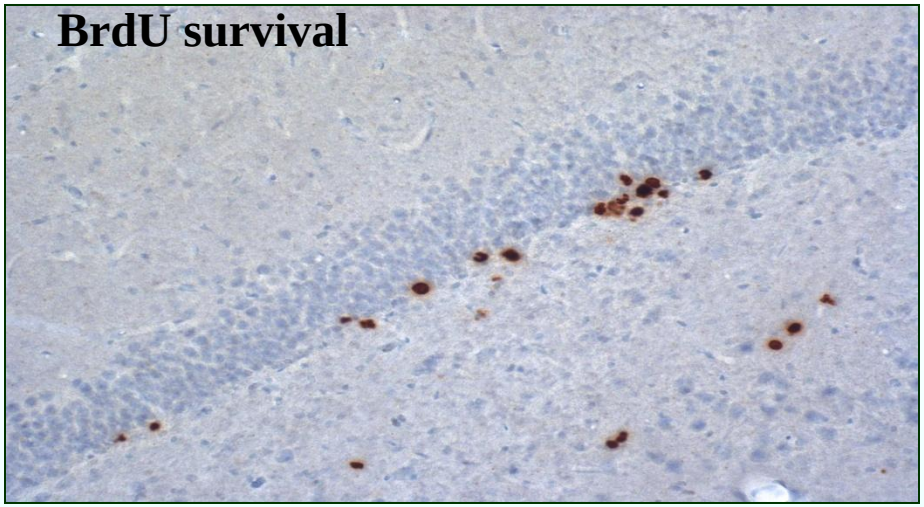
DISC-1, Glucocorticoid receptors

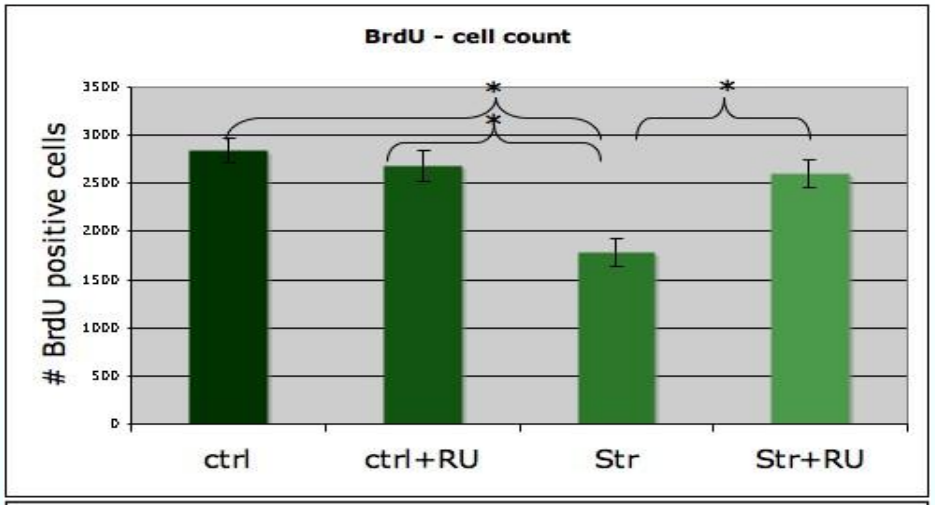


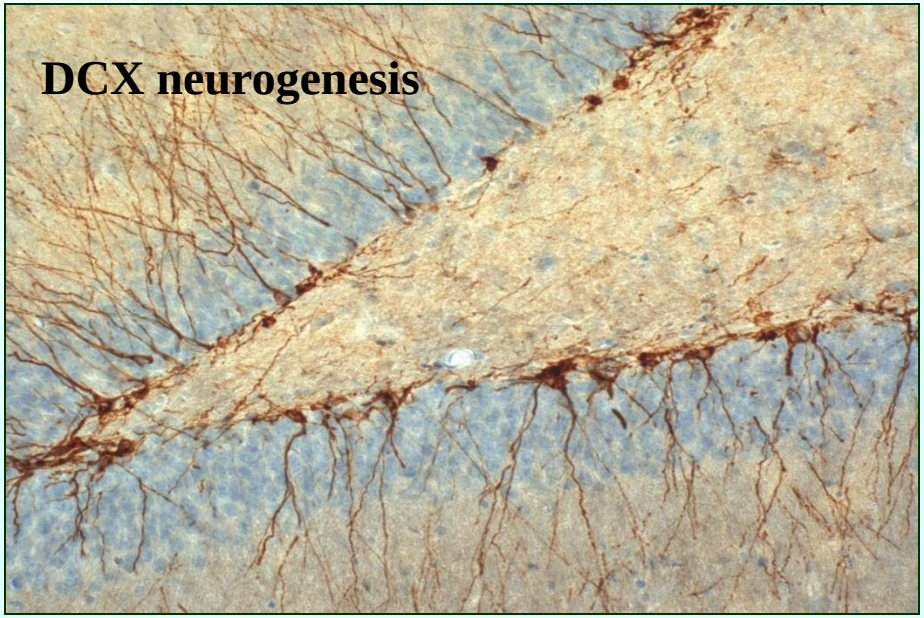
Ftizsimons/Van Hooydonk et al Mol Psychiatry, 2013

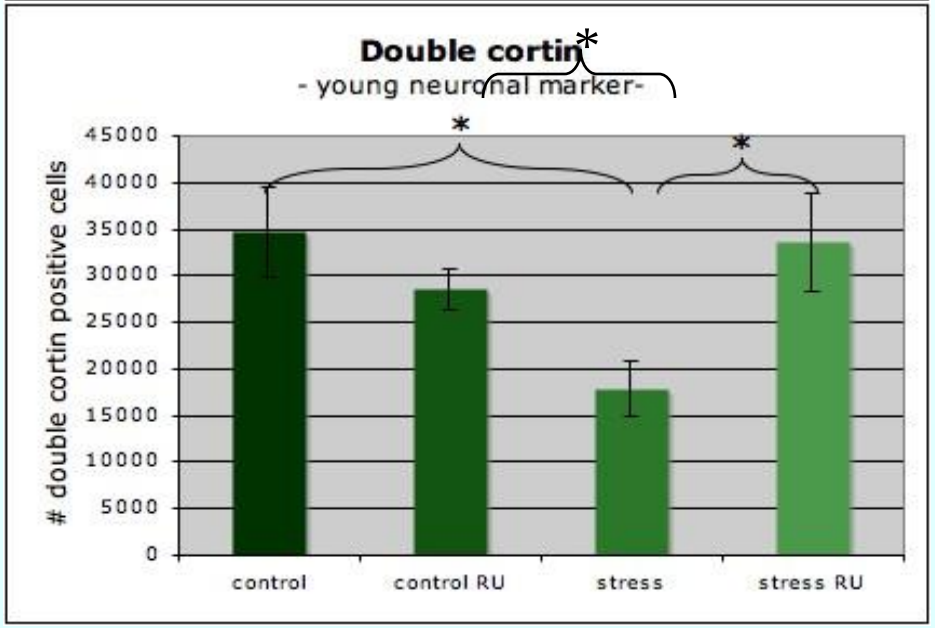
(rat) 3 weeks of chronic stress;

4 days CORT Antagonist day 17 - 21: rapid recovery neurogenesis

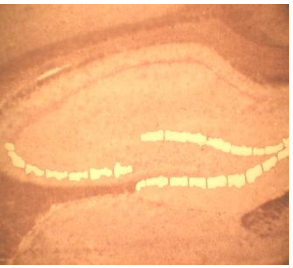




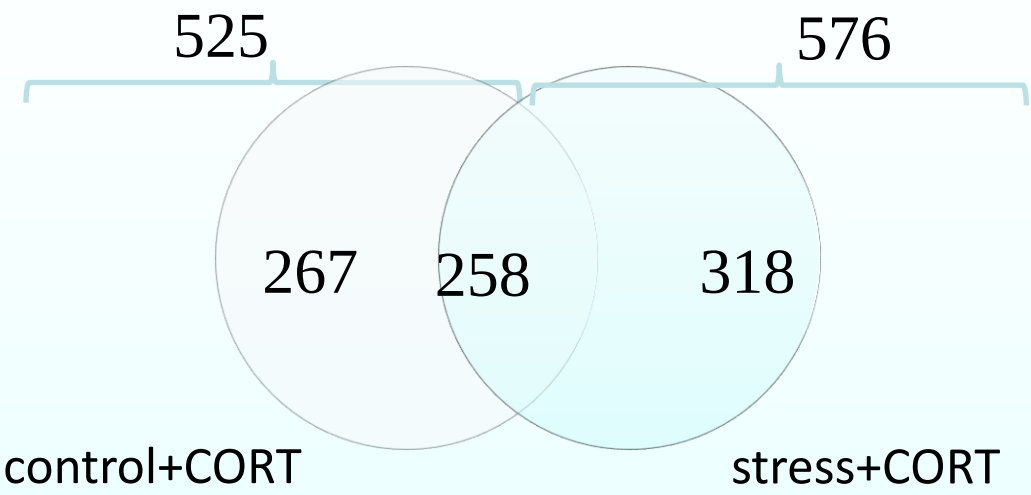




Oomen, Joels, de Kloet,Lucassen, Eur JN 2007



Laser dissection
dentate gyrus



- Corticosterone to controls and chronically stressed rats
- 3 hrs later differential gene expression patterns, but also overlap.
- Some genes are suppressed by cort, others enhanced.

Datson et al. Endocrinology, july 2013.

Question

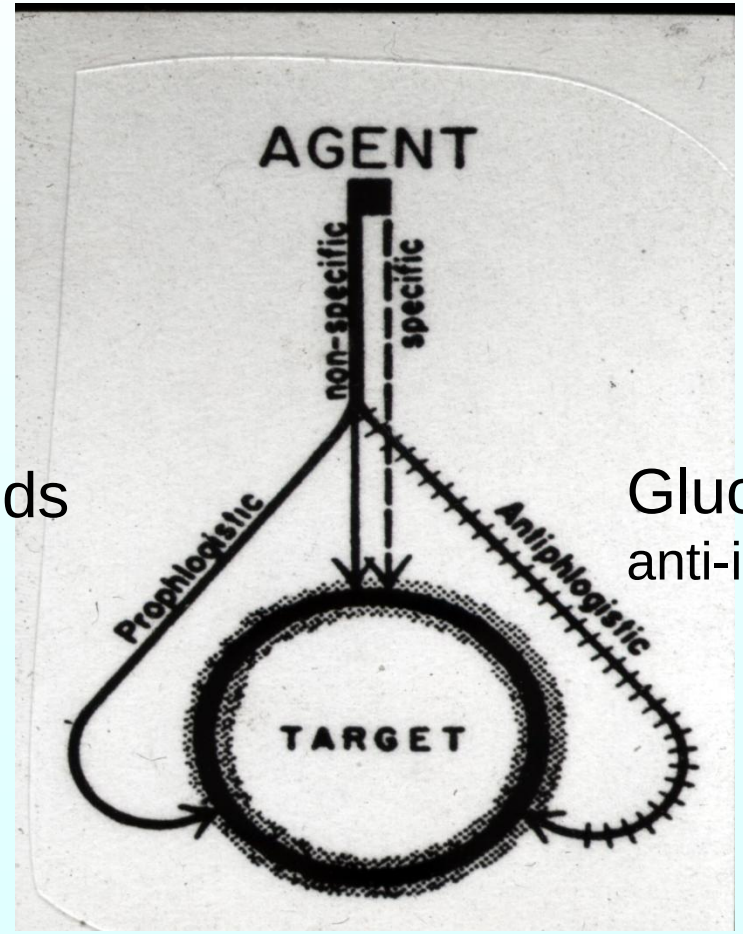
- How does corticosteroid action change from *protective* into *damaging ?*

- What is the cause?
- What are the consequences?

The story of the adaptation syndrome (selye)

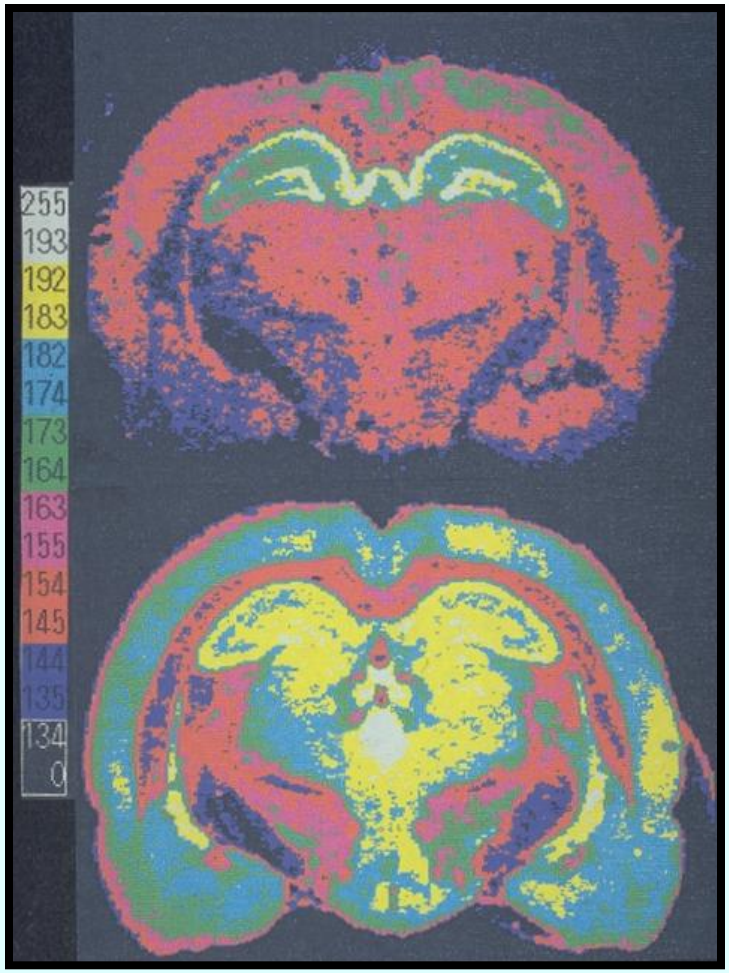
Mineralocorticoids
pro-inflammatory

Heart failure
(antagonist is
life saver)



Glucocorticoids
anti-inflammatory

Not one, but <u>two</u> corticosteroid receptor types in Brain



<u>'Mineralocorticoid' Receptor</u>

- high affinity for Aldo + Cort
- restricted to hippocampus
- always occupied

CORT inactivated in kidney, not in brain

<u>Glucocorticoid Receptor</u>

- 10-fold lower affinity Cort
- widespread, PVN
- occupied after stress

Reul/de Kloet 1985

One hormone - enormous diversity in action

cortisol

CBG

Marie-Pierre Moisan

Membrane receptor **Marian Joëls**

e.g. neurotransmitters, growth factors, inflammation

11HSD

MR GR p23 hsp90 FKBP5

MR

GR

GR MR

activation of TFs:

AP1, CREB, STAT, NFκB

CREB STAT AP1 NFkB

interplay

nuclear translocation

Homo - heterodimers

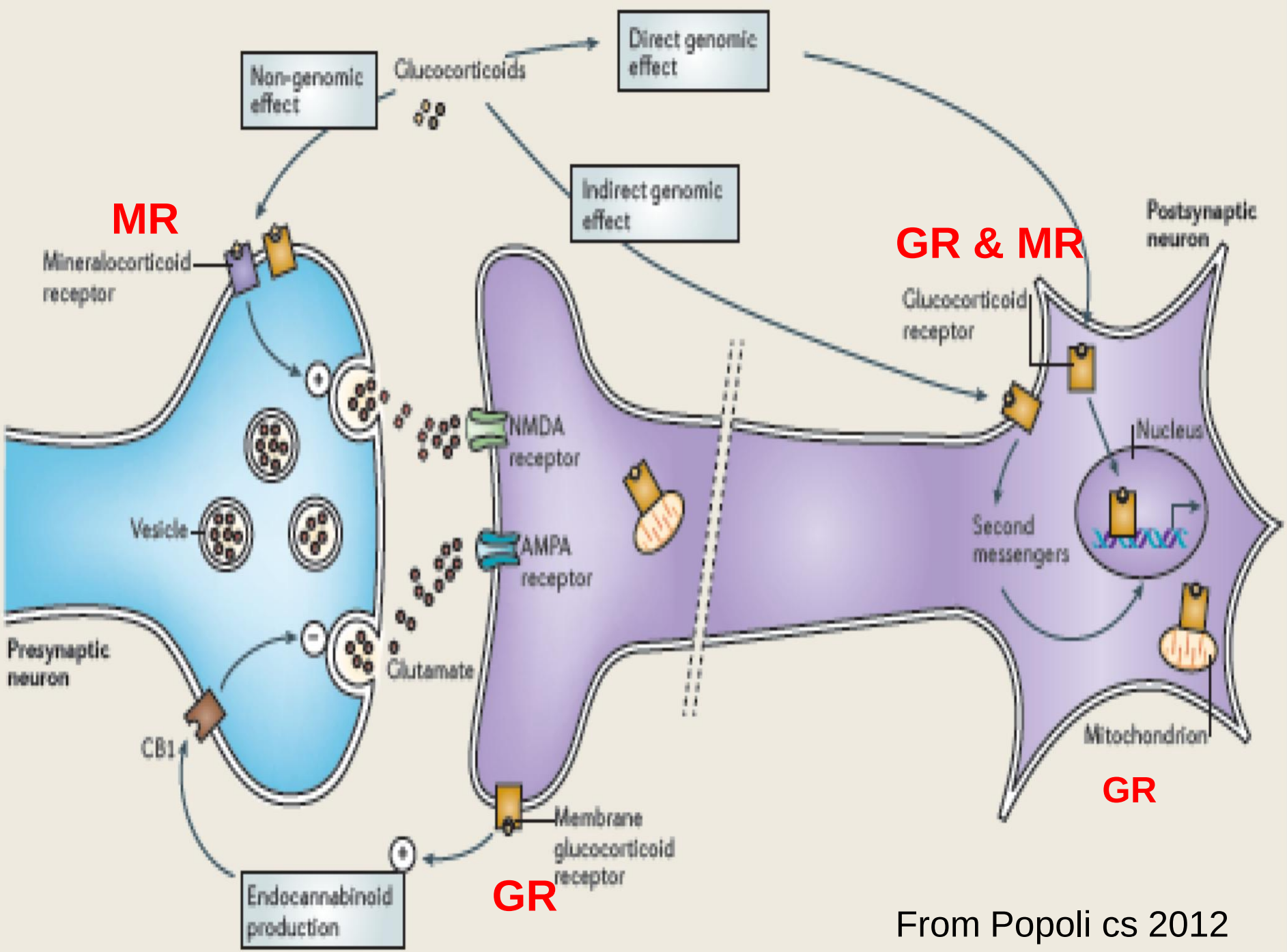
AP1

GRE

transrepression

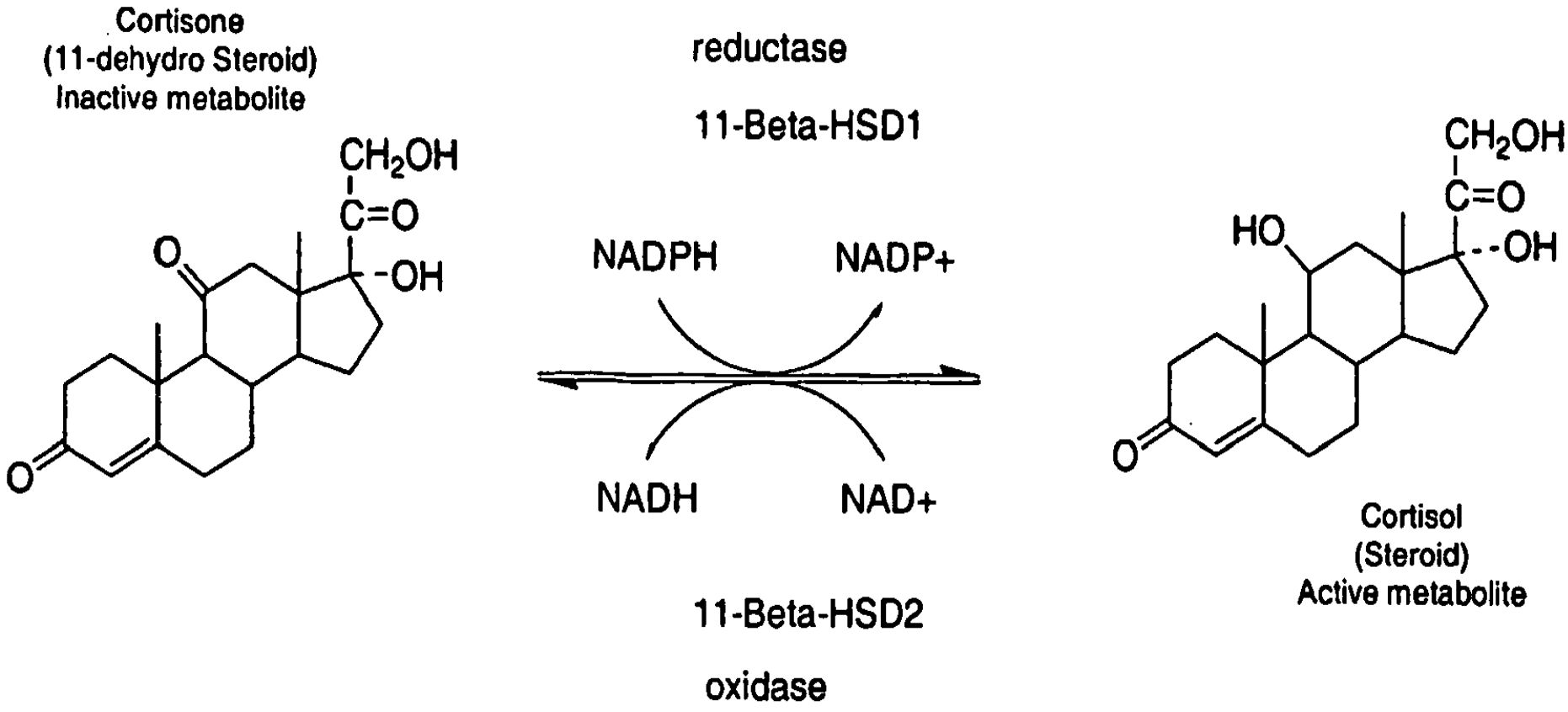
transactivation

Co-regulator cocktails modulate transcription. SGRM, **Onno Meijer** .



From Popoli cs 2012

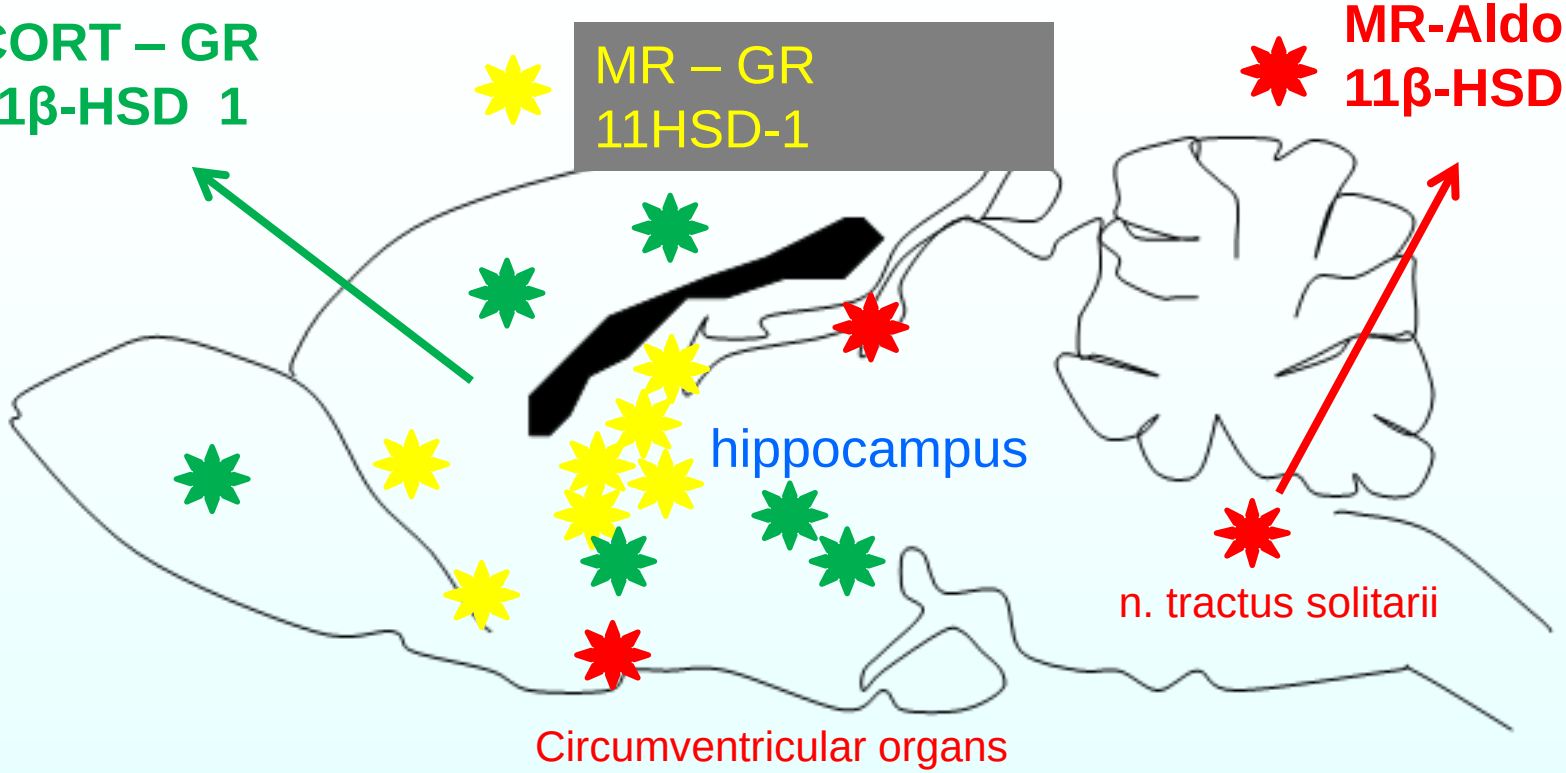
Figure 1: 11 Beta-hydroxysteroid Dehydrogenase
Redox Equilibrium of Corticosteroids



Kidney tubular and other epithelial cells
HSD-2

Heart, fat, brain non-epithelial cells
HSD-1

Brain MR & GR

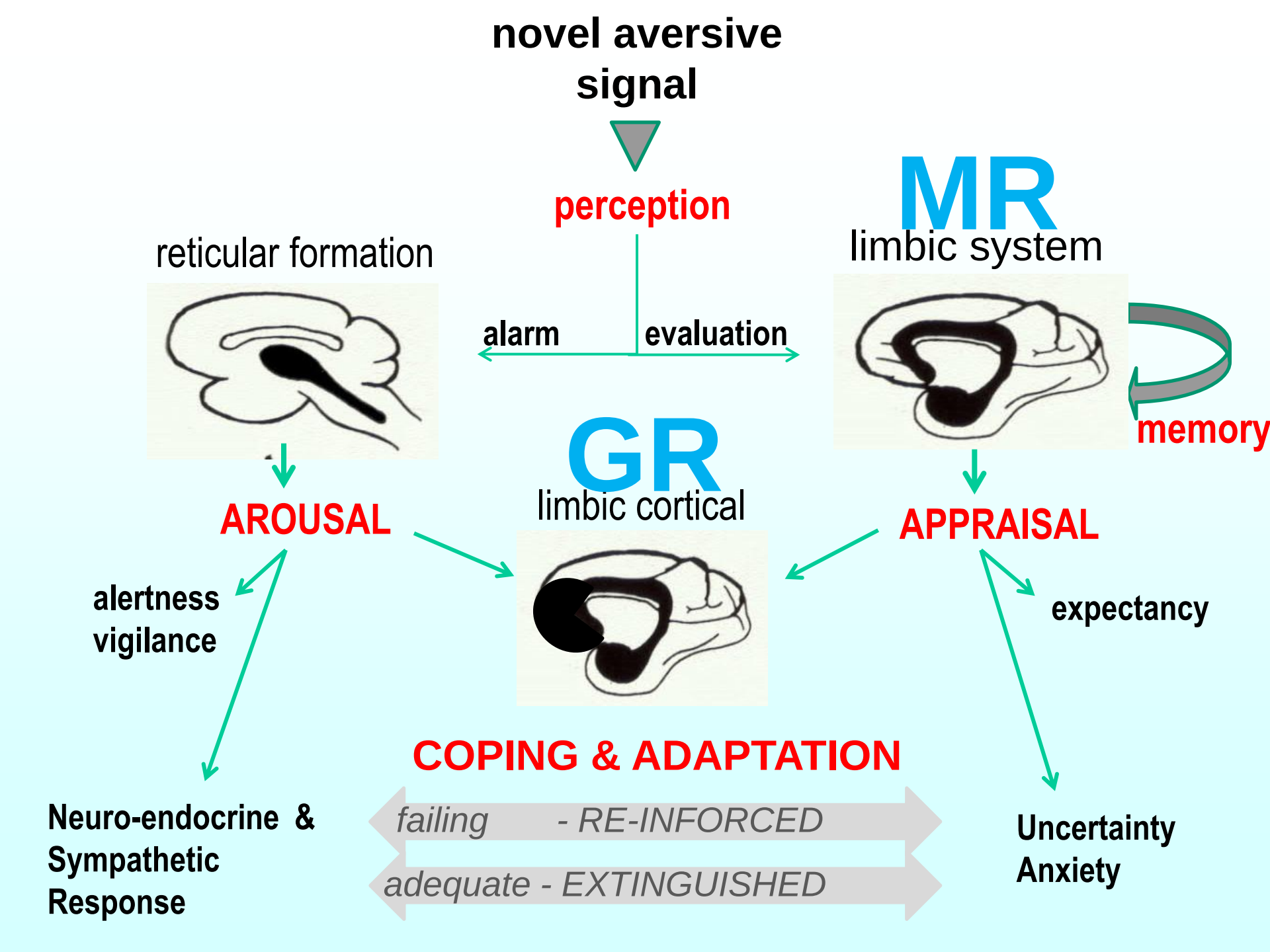


MR - Cortisol/corticosterone
Aldosterone, progesterone, DOC

MR - Aldosterone

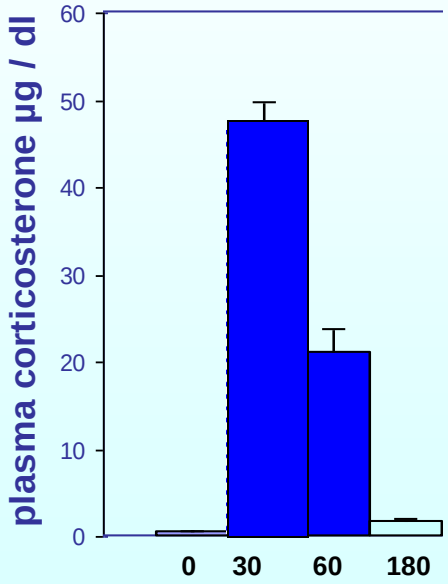
- Salt appetite
- Cardiovascular regulation
- NTS innervates forebrain

De Kloet, Joels and Holsboer Nature Reviews Neuroscience 6: 463-475 (2005)


novel aversive signal
perception
MR
limbic system
reticular formation
alarm
evaluation
memory
GR
limbic cortical
AROUSAL
APPRAISAL
alertness
vigilance
expectancy
COPING & ADAPTATION
failing - RE-INFORCED
adequate - EXTINGUISHED
Neuro-endocrine & Sympathetic Response
Uncertainty
Anxiety

The Morris Water Maze finding a hidden platform

Rat / mouse learns by finding shortest path to platform using either global spatial cues or local contextual clues

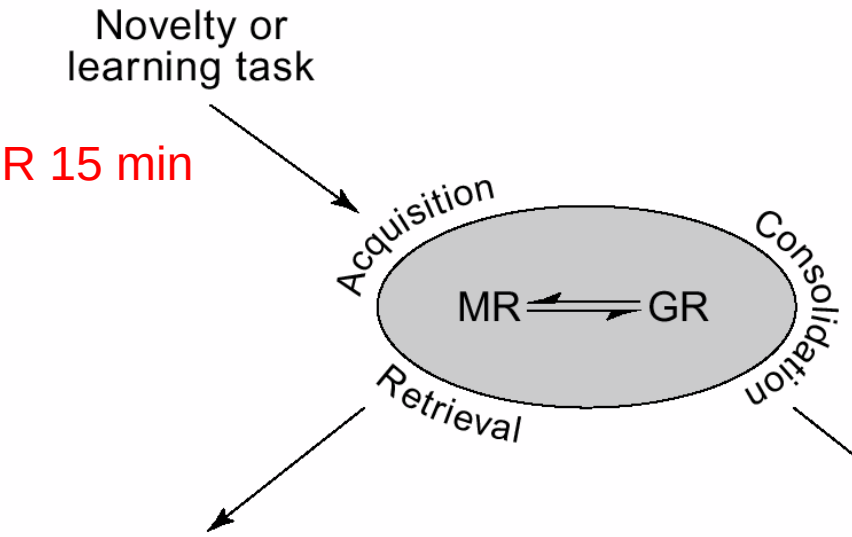


Melly Oitzl

Oitzl / de Kloet 1992, 1994, 1997, 2001, 2005, 2013

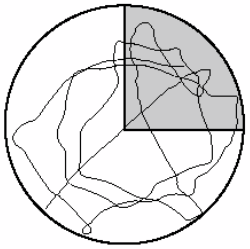
Blockade MR 15 min for retrieval

Fast effect

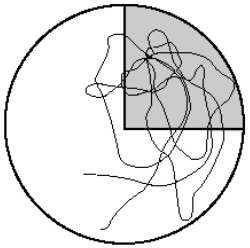


Blockade GR at consolidation; longlasting test 24 uur later.
Same result GR dim/dim GR knockout/knockdown

MR block:
altered swim pattern

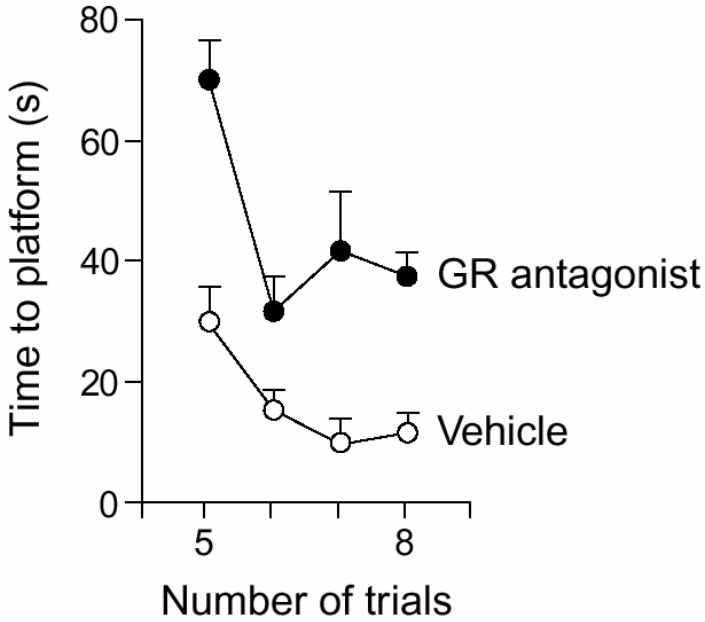


MR antagonist

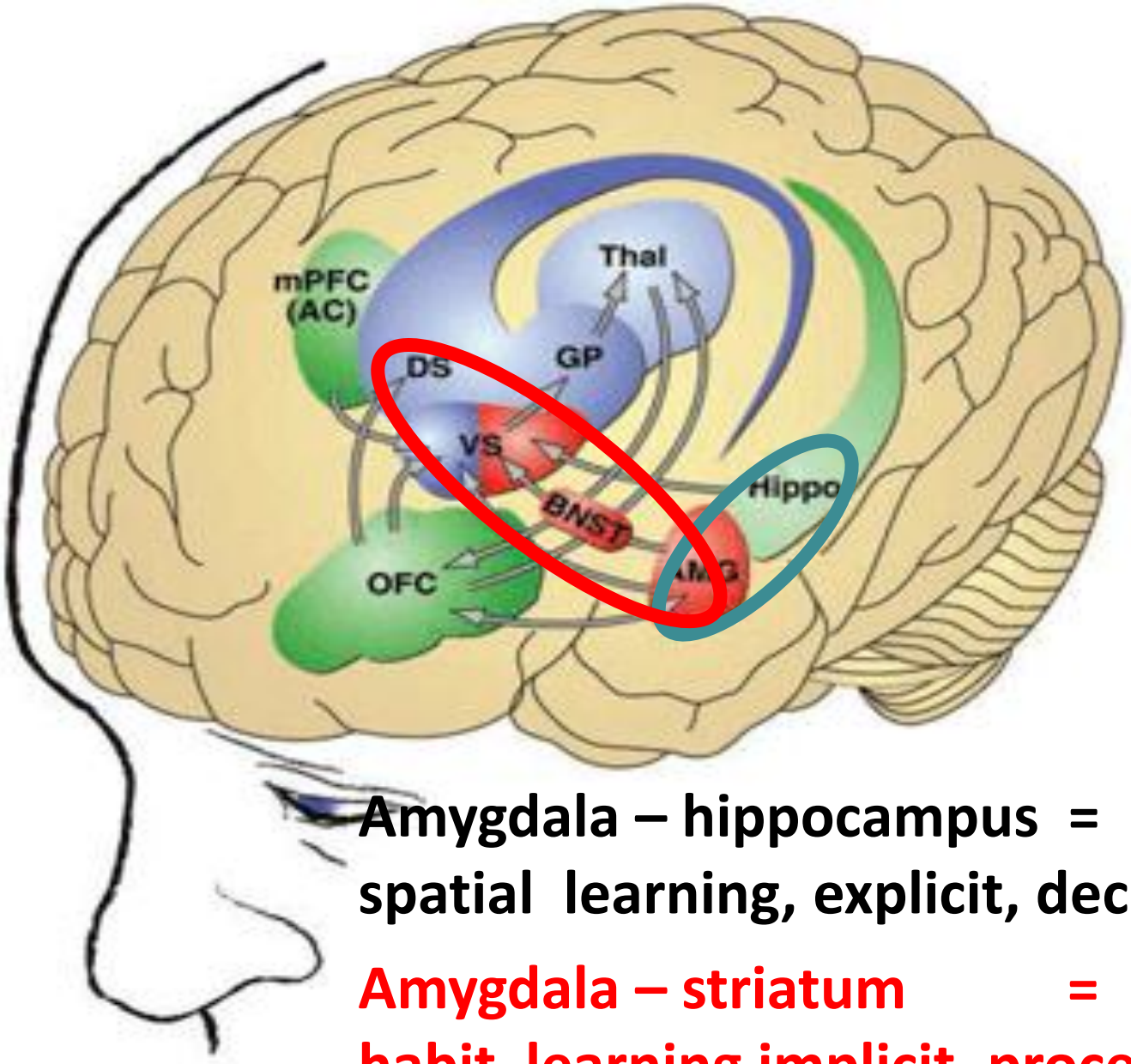


Vehicle

GR block:
impaired consolidation



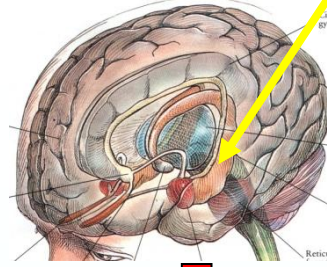
Oitzl/de Kloet



Amygdala – hippocampus =
spatial learning, explicit, declarative

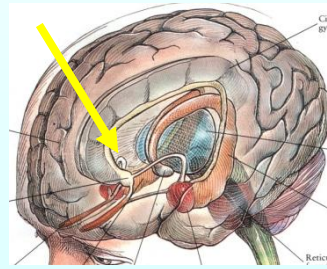
Amygdala – striatum =
habit learning implicit, procedural

Spatial learning and memory



Requires complex association between
multiple distal stimuli

Stimulus-response learning



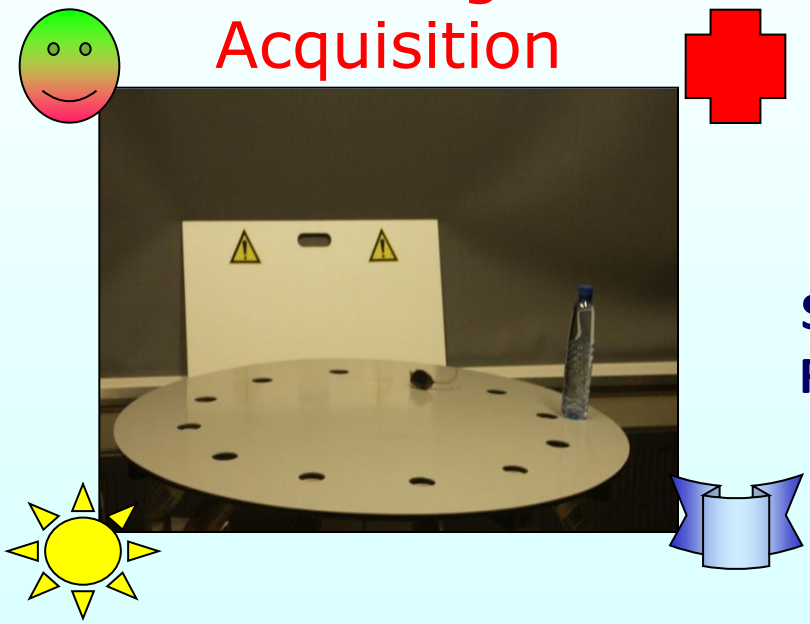
“ habit learning”

- formation of stimulus-response association

“simple” solutions, - one proximal stimulus

Two strategies are possible
Spatial ***and*** Stimulus-Response

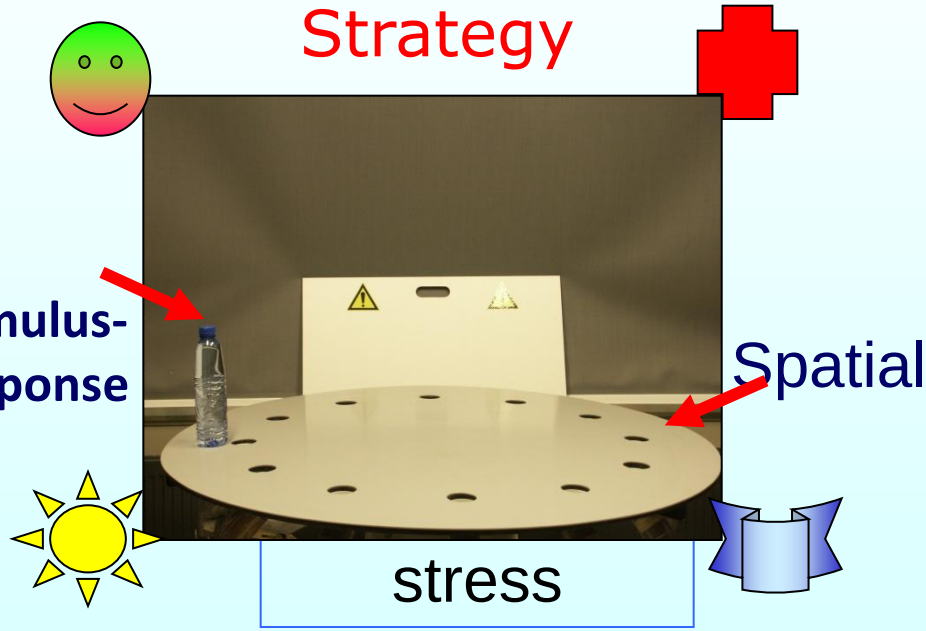
Trials 1-6:
Learning -
Acquisition



STRATEGY unknown

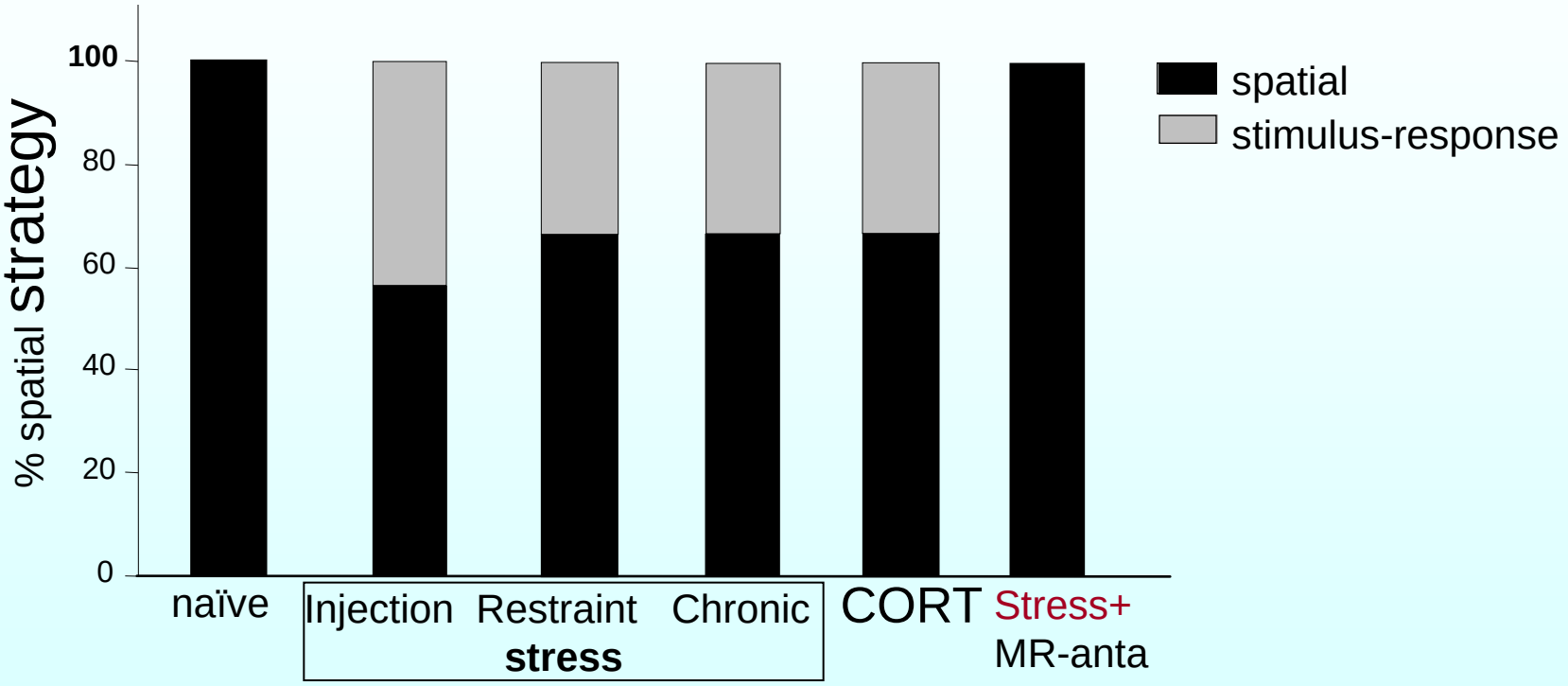
Stimulus-response?
Spatial?

Trial 7:
Strategy



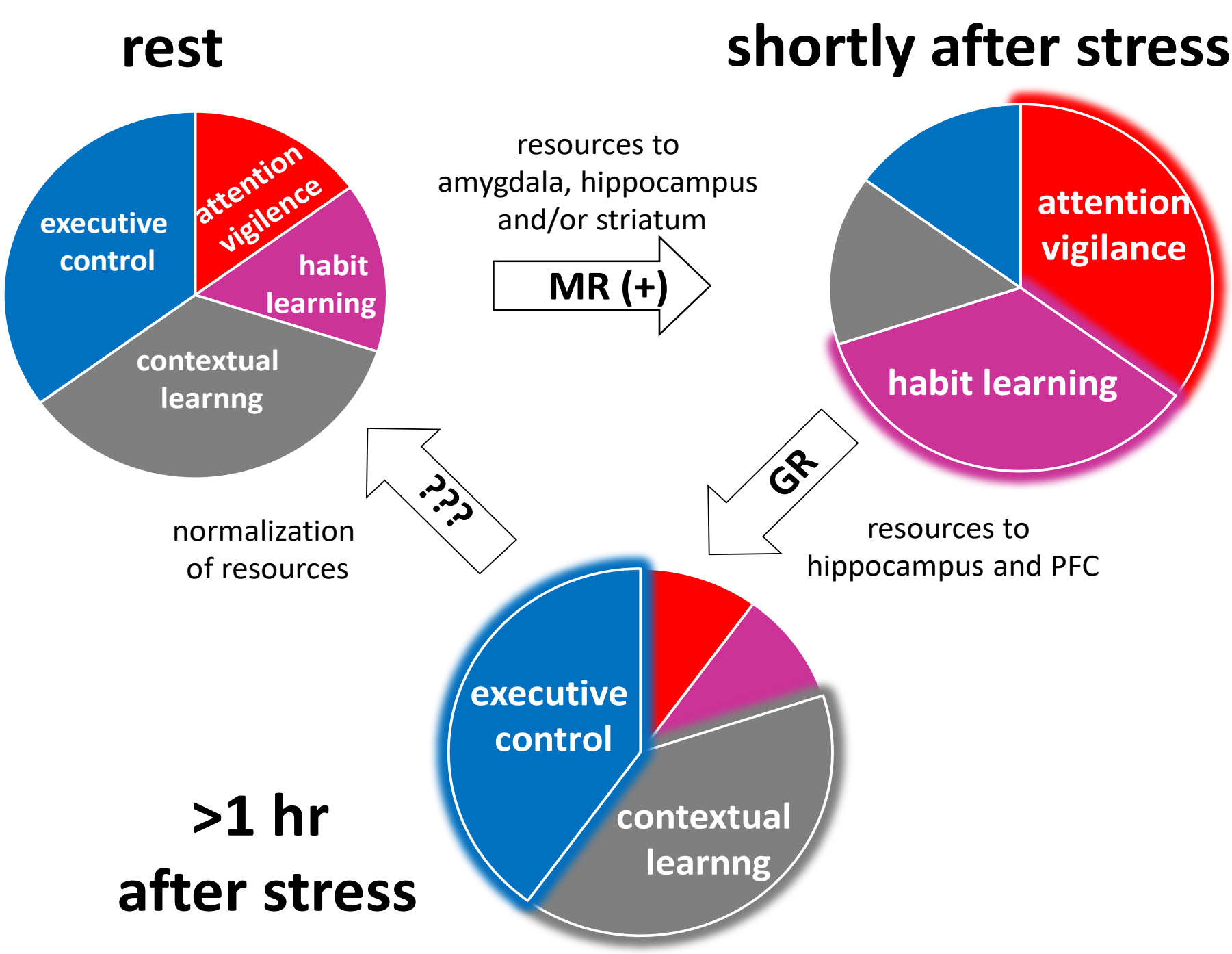
STRATEGY revealed

Switch: spatial to S-R-strategy

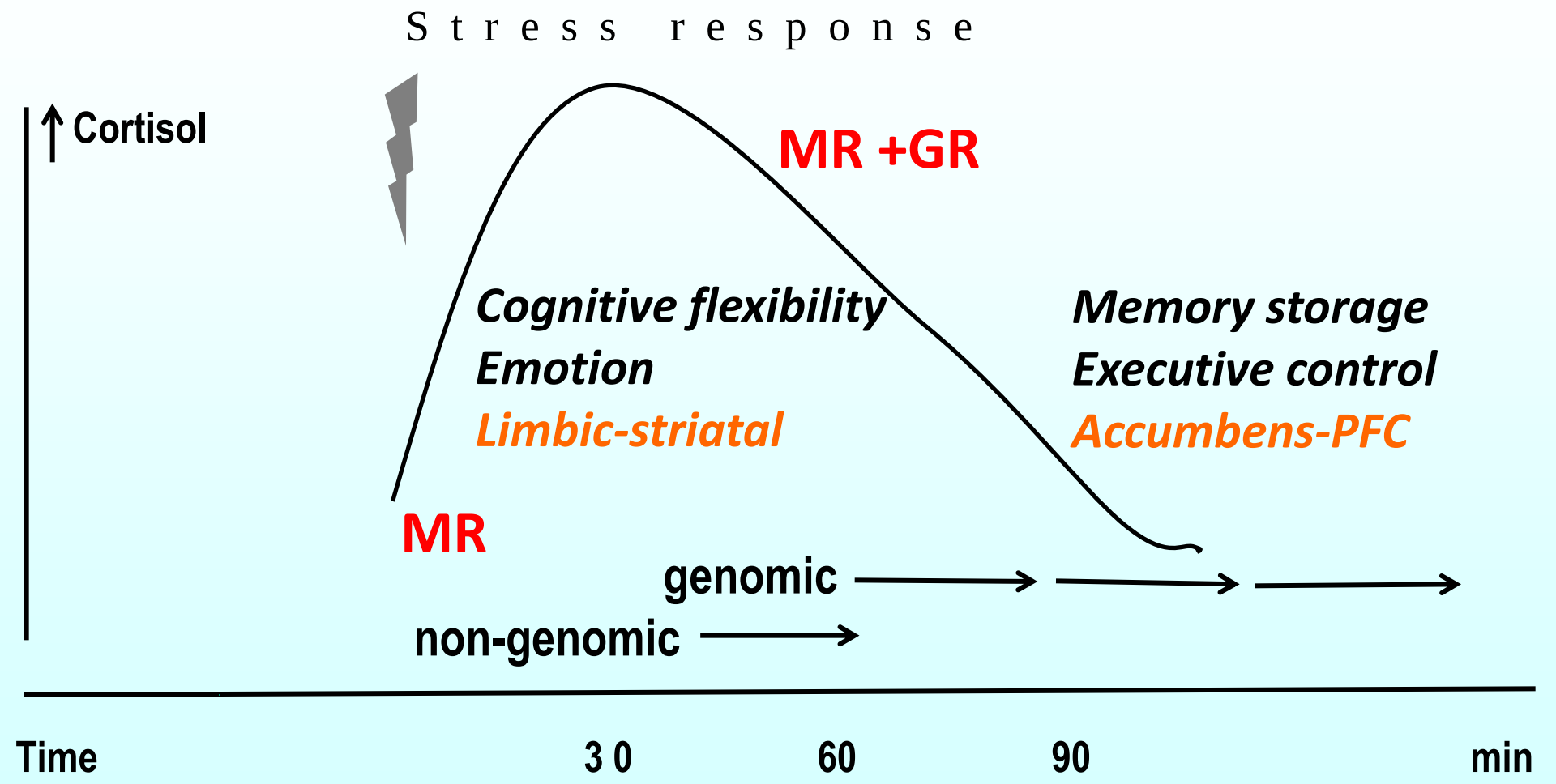


>>> Blockade of MR prevents the switch

Schwabe, Oitzl et al 2009, 2010


rest
shortly after stress
executive control
attention vigilence
habit learning
contextual learnng
resources to amygdala, hippocampus and/or striatum
MR (+)
attention vigilance
habit learning
GR
resources to hippocampus and PFC
???
normalization of resources
executive control
contextual learnng
>1 hr after stress

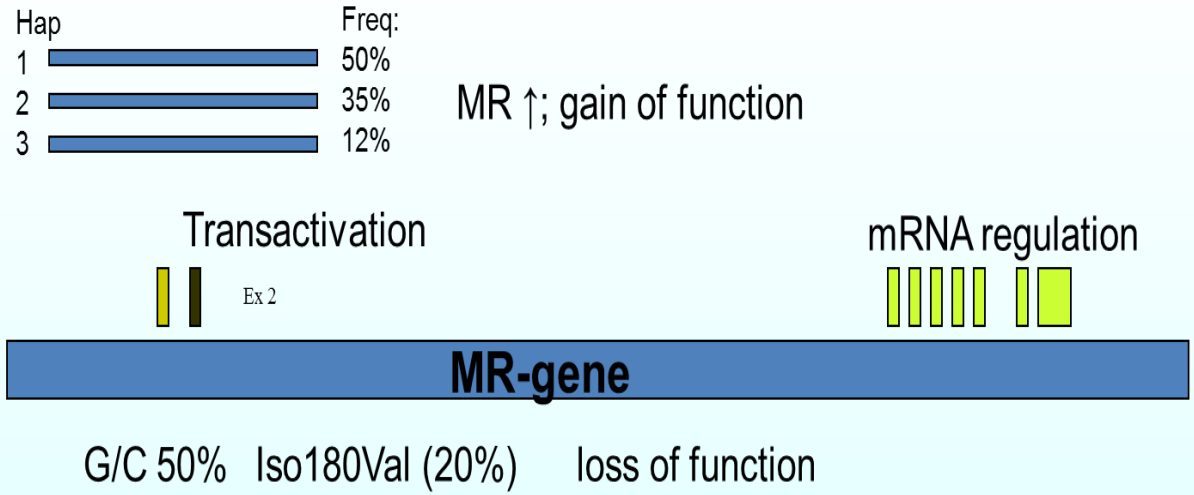
Anticipation **Appraisal/Coping Style** **Adaptation**



MR:GR imbalance

- Genetic variants
- Chronic stress – genomic reorganization
  - cell-circuit remodeling
- Early life adversity – altered brain development
  - programming behaviour
- Puberty – sex prevalence
- Depression
- Dexamethasone treatment

Effects of MR haplotypes

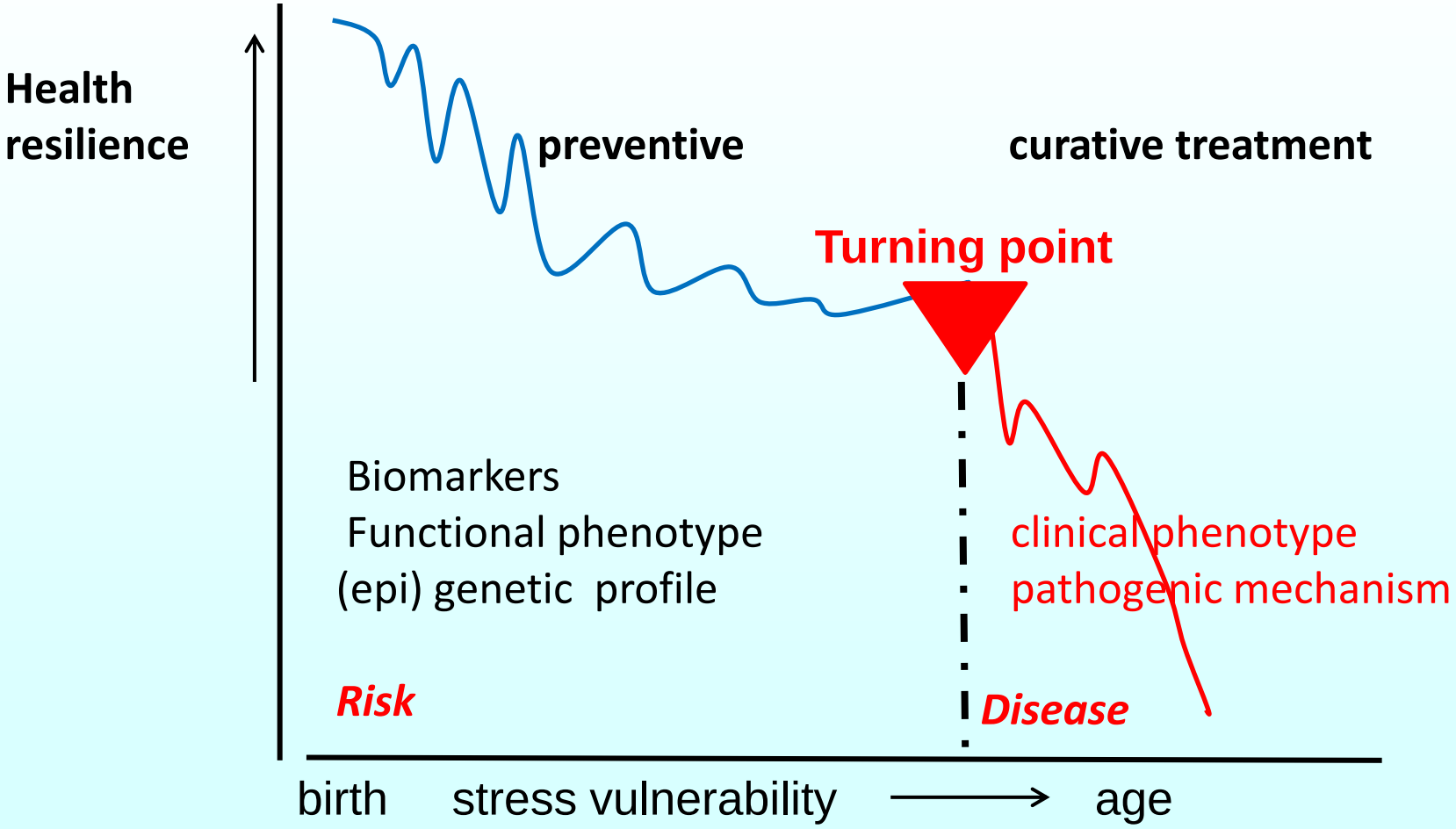


Haplotype 2

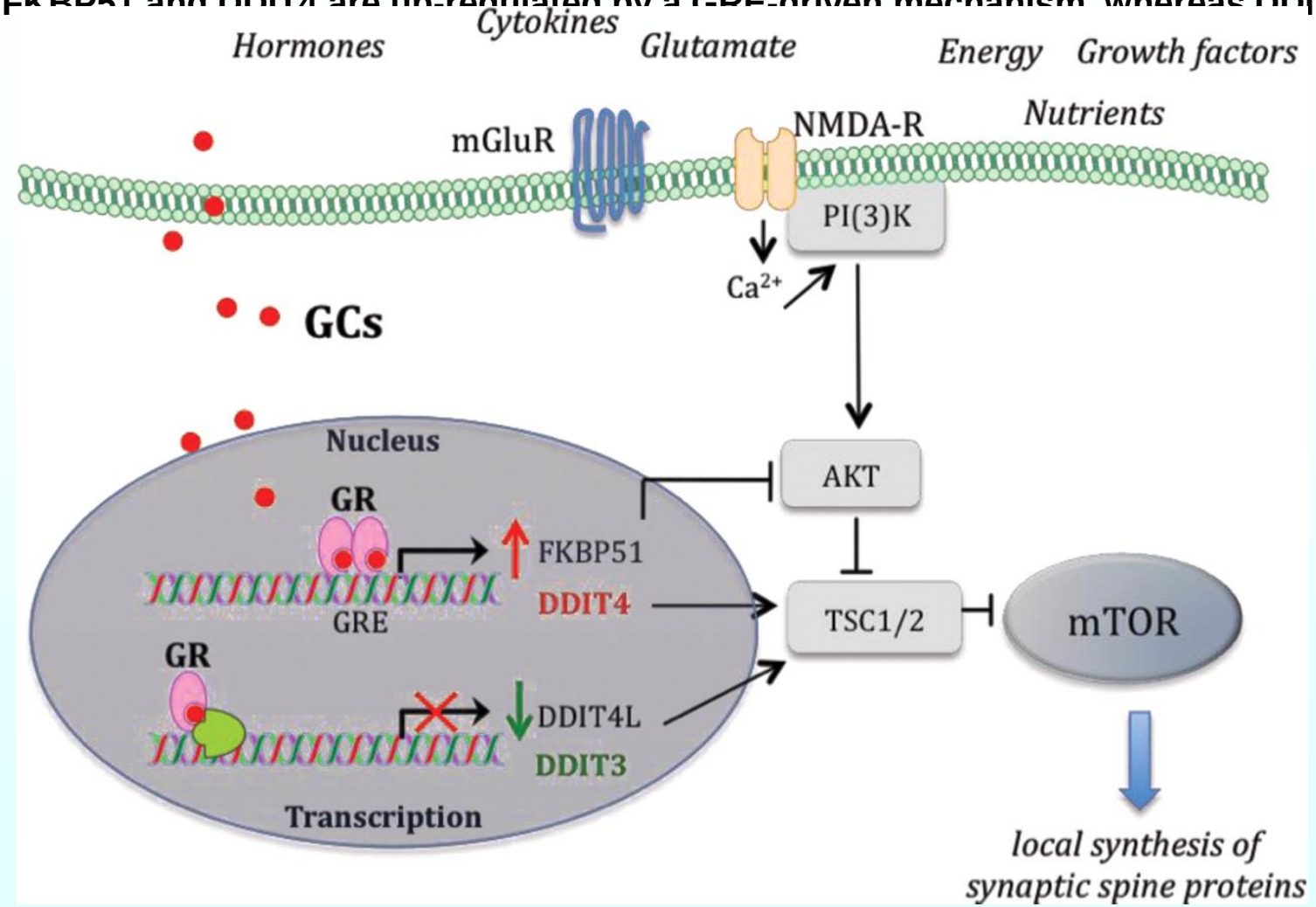
- Enhanced dispositional optimism
- Decreased rumination
- Protection to depression
- Prediction of recurrent depression
- Enhanced response to antidepressants

(Klok et al Transl Psychiatry 2011)

Stress - related disorder



Schematic overview of key components of the mTOR pathway and a number of its physiological and molecular regulators in the brain, indicating a role for GC. After GC binding to GR, FKBP51 and DDIT4 are up-regulated by a GRE-driven mechanism, whereas DDIT4L a...



Polman J A E et al. Endocrinology 2012;153:4317-4327

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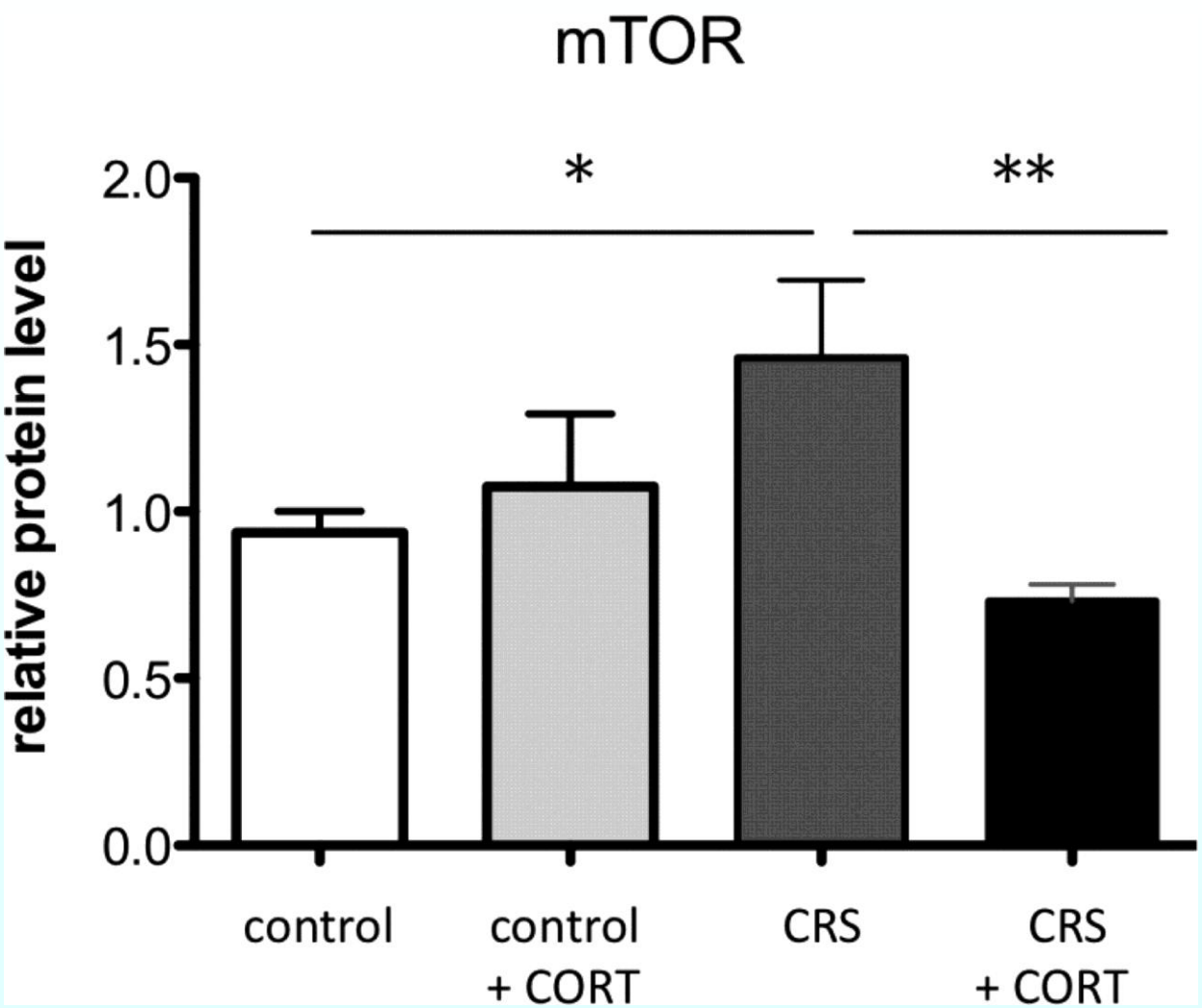
mTOR protein levels in the hippocampus measured by Western blotting. mTOR protein levels were normalized against α-tubulin expression levels.



Polman J A E et al. Endocrinology 2012;153:4317-4327

Endocrinology

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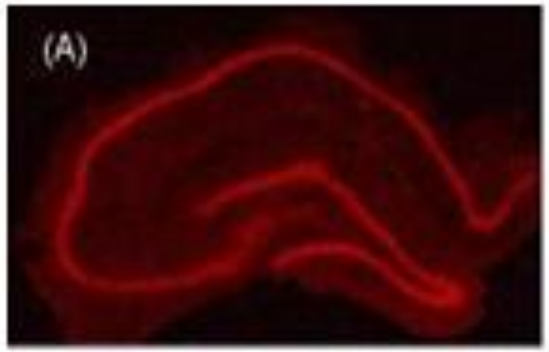
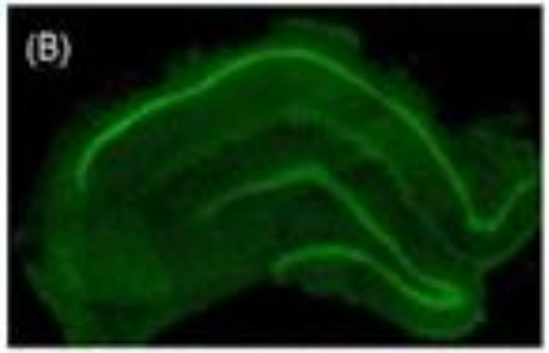
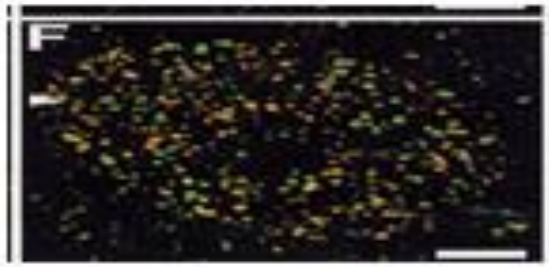
Two corticosterone/cortisol receptor types



MR



GR



Cell nucleus

'Mineralocorticoid' Receptor

high affinity for Aldosterone & Cortisol

Cortisol not degraded in brain, as in kidney

restricted to limbic structures, **11β-HSD 1**

Hippocampus, amygdala, septum, PFC

Glucocorticoid Receptor

10-fold lower affinity for Cortisol

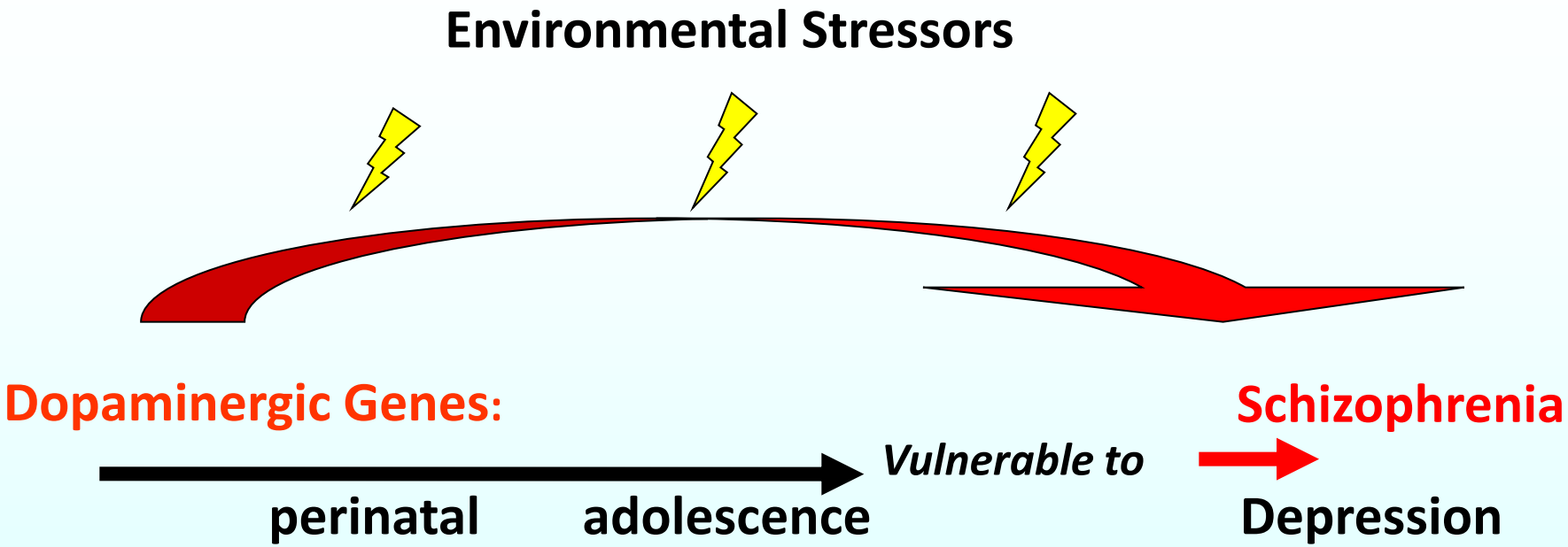
widespread, PVN, amine, limbic-cortical

occupied after stress & at circadian peak

Confocal image

Reul & de Kloet Endocrinology, 1985 Van Eekelen et al J Neurosci Res 1988, Van Steensel et al. J Cell Sci 1996; Groeneweg et al. Plos One, 2014

Genes X Environment



- **Early stressors program - amygdala fear pathway**
- **Hypothalamus – pituitary – adrenal axis: cortisol/corticosterone (Sullivan/Moriceau, 2006; Daskalakis et al.2014)**

Cools et al. 2002 *Daskalakis et al, 2013*

- **glucocorticoids: cortisol & corticosterone**
  - Energy metabolism
  - Dampen initial stress reactions
  - Motivation, arousal, cognition
  - Behavioural adaptation

- **mineralocorticoid: aldosterone**
  - Salt homeostasis: salt appetite to volume control
  - less known: mineralocorticoids amplify initial stress reactions