

EARLY EXPERIENCE: BE PREPARED !



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Founder Marcé Society



Ramesh 'Channi' Kumar
Professor of Perinatal Psychiatry
Institute of Psychiatry, London
1938-2000

- Causes, consequences and treatment of post-natal mental illness
- Impact of mother's postnatal illness on their children's development
- Oestrogen-related augmented dopaminergic activity in brain, importance for post-partum psychosis

Mercy Pregnancy and Emotional Well-being Study (MPEWS)

Understanding maternal mental health, fetal programming and child development.

Study design and cohort profile - *Megan Galbally, Andrew Lewis et al*



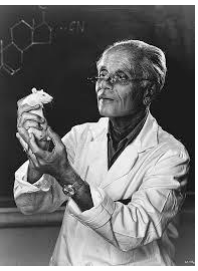
Trans-generational stress regulation: mother-infant cortisol and maternal mental health across the perinatal period.

Megan Galbally et al. Psychoneuroendocrinology 2019, in press

Stress, Cortisol, Oxytocin, Receptors, DNAm

Coming up

- Cortisol as master regulator of the stress response
- Cortisol receptors mediate stress effects on DNA
- Cortisol programs brain circuits in perinatal life



Hans Selye

STRESS



Physical stressors & Psychological stressors:
any stimulus that disturbs homeostasis and causes a response;

Stress response = spectrum of physiological and behavioral adaptations

Processing of information and stress response is modulated by

- *Fear, Love*
- *Social competence*
- *Social support*
- *Reward*
- *Sense of safety*
- *Self esteem*

The most severe stressor

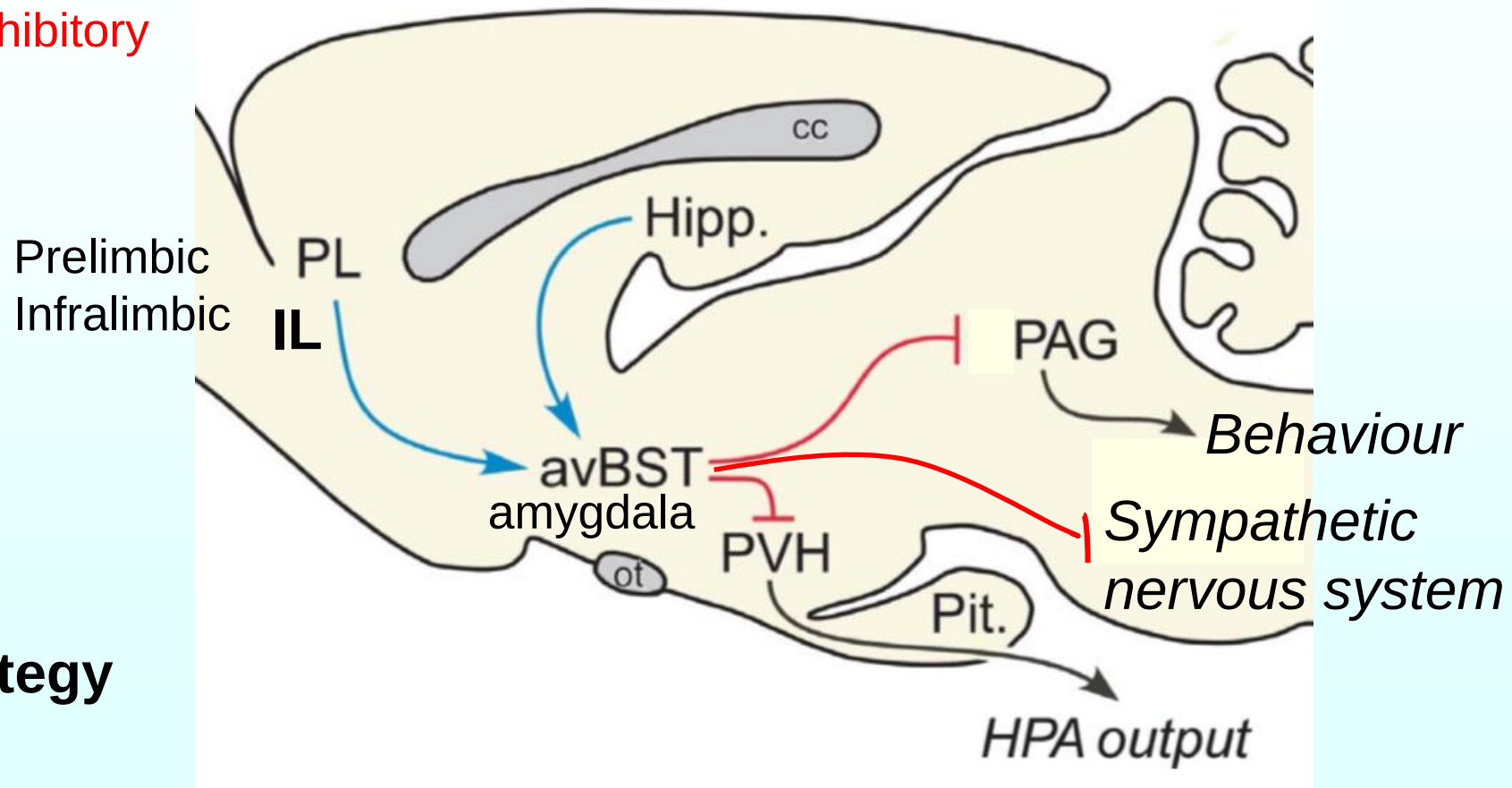
Uncertainty

No information, No control, No prediction possible

Threats to integrity, social competence & self-esteem

Coping with Stressors

Excitatory
Inhibitory

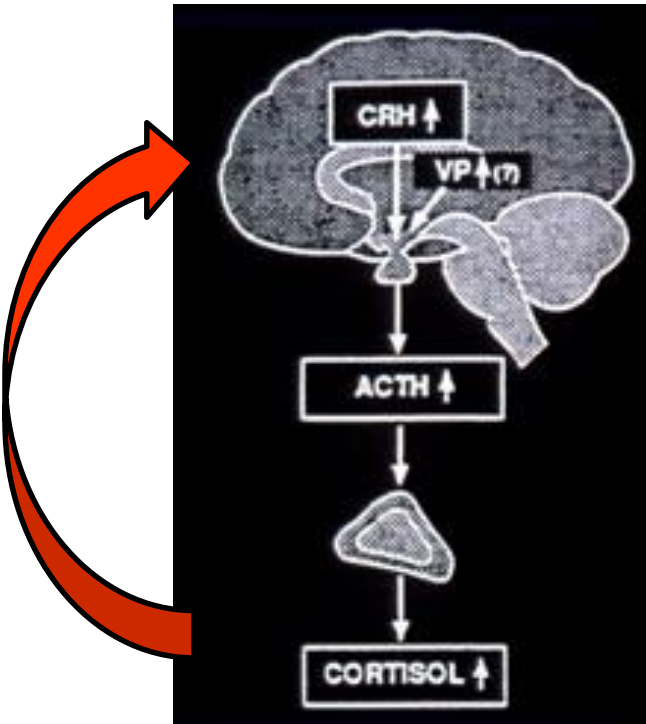


Coping strategy

Males: fight or flight

Females: tend and befriend

Cortisol and corticosterone are glucocorticoids



Hypothalamus –
Pituitary –
Adrenal axis

Energy mobilization
Energy storage

Control of stress reaction

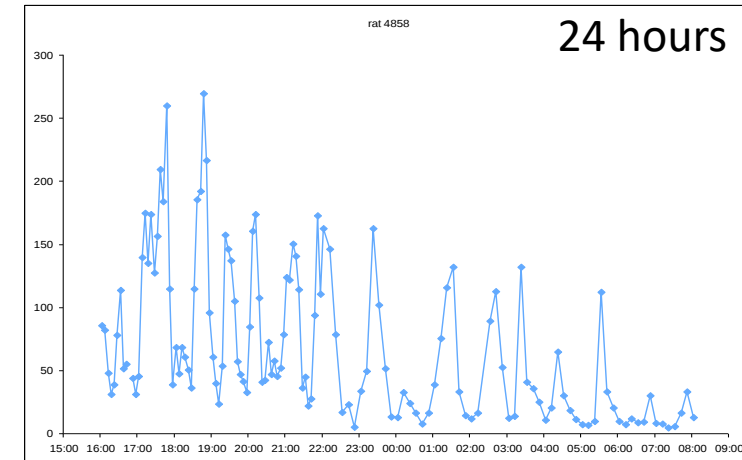
Promotes

Coping, Adaptation

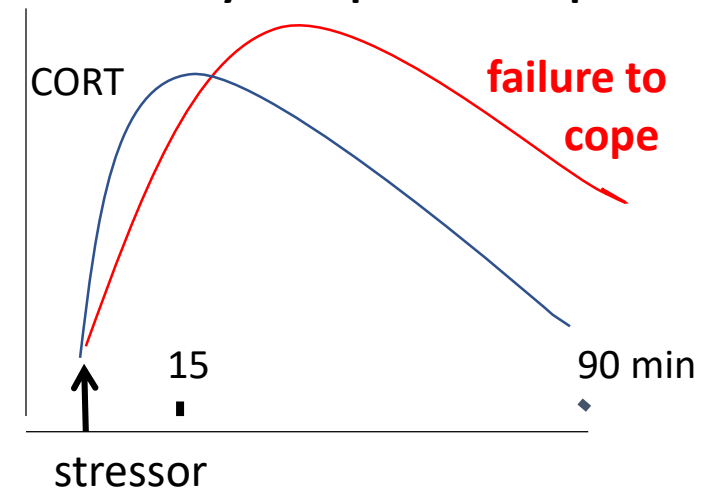
Emotional expression

Memory storage

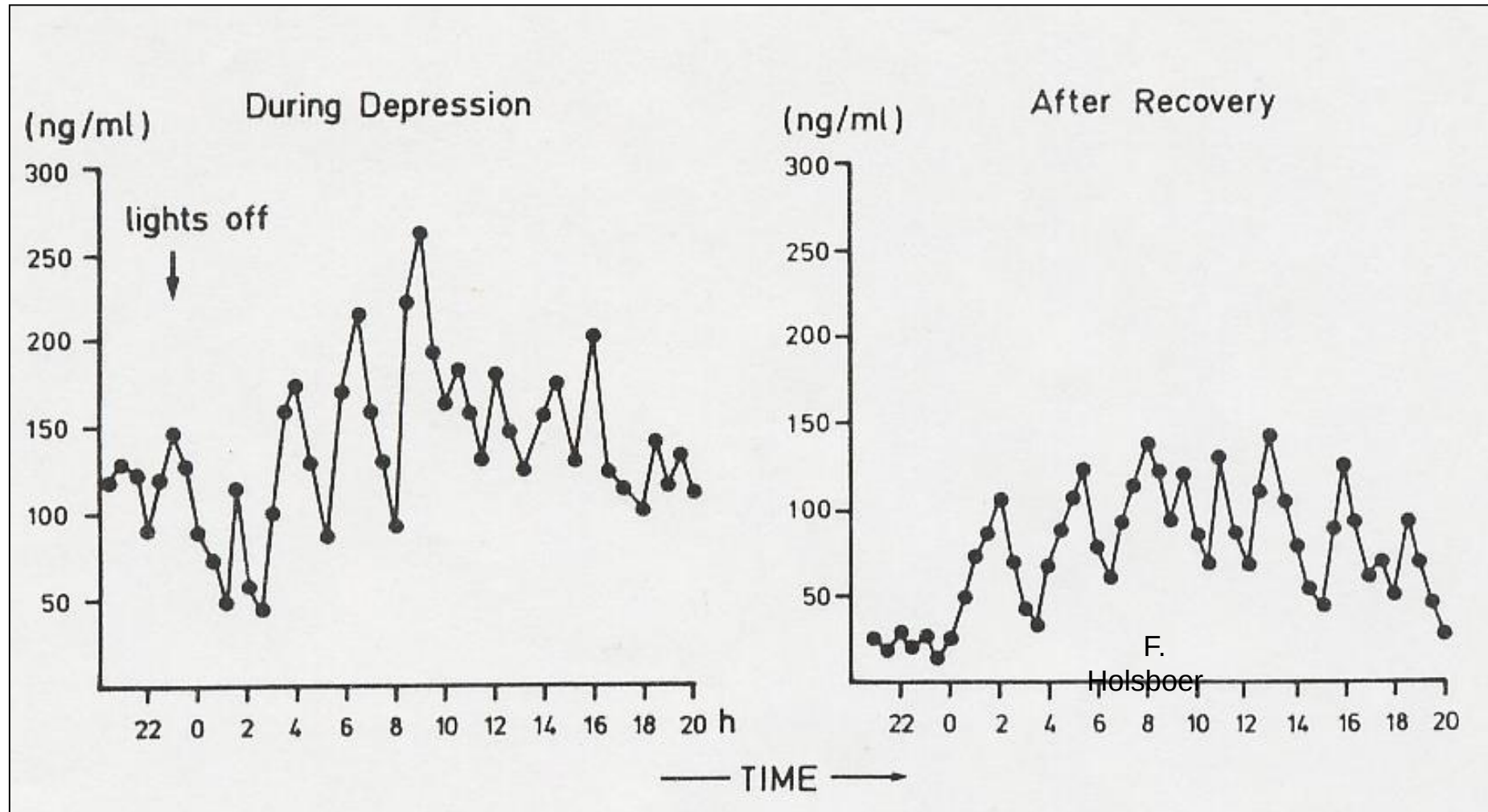
Basal pulse pattern synchronizes
daily and sleep-related events



Stress response coordinates the
ability to cope and adapt



DEPRESSION - elevated cortisol, flattened rhythm



PATTERNS MATTER RATHER THAN ABSOLUTE LEVELS

Disorders Linked to Over- and Under exposure to Cortisol

Over - exposure

- Major depression
- Psychotic depression

Anorexia nervosa

Sleep deprivation

Malnutrition

Childhood abuse

Excessive exercise

Under - exposure

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

Rheumatoid arthritis

Allergies

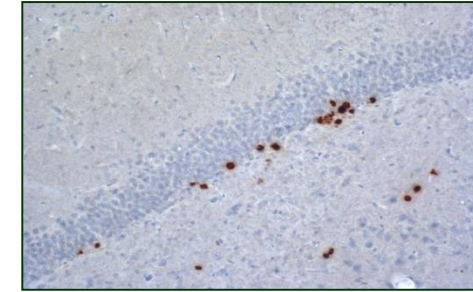
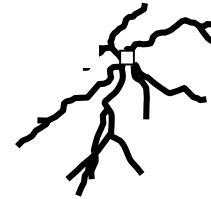
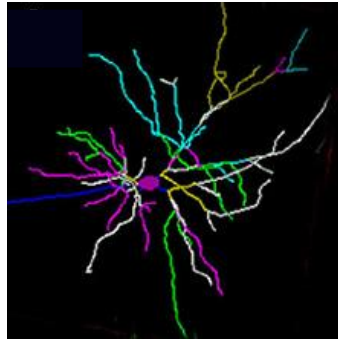
Asthma

Chronic Stress and Excess Cortisol

neurons **shrink** **grow**

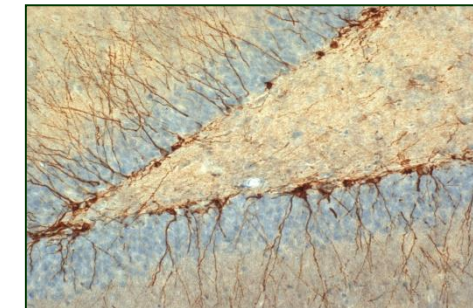
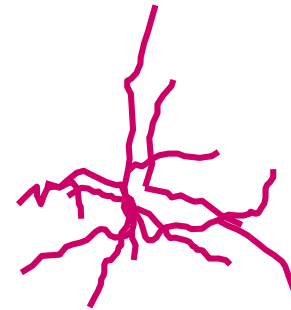
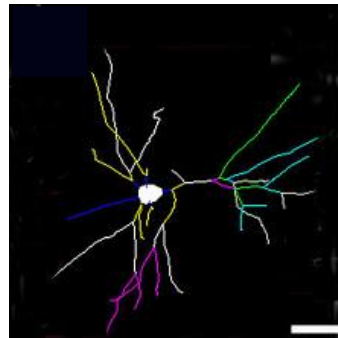
Birth of new neurons
is suppressed

Control



BrdU survival

Chronic stress



DCX neurogenesis

Dentate gyrus

Prefrontal Cortex
Hippocampus

Cognition

Amygdala
Orbital fr cortex

Emotion

Emotional
reactivity

Cognition
performance

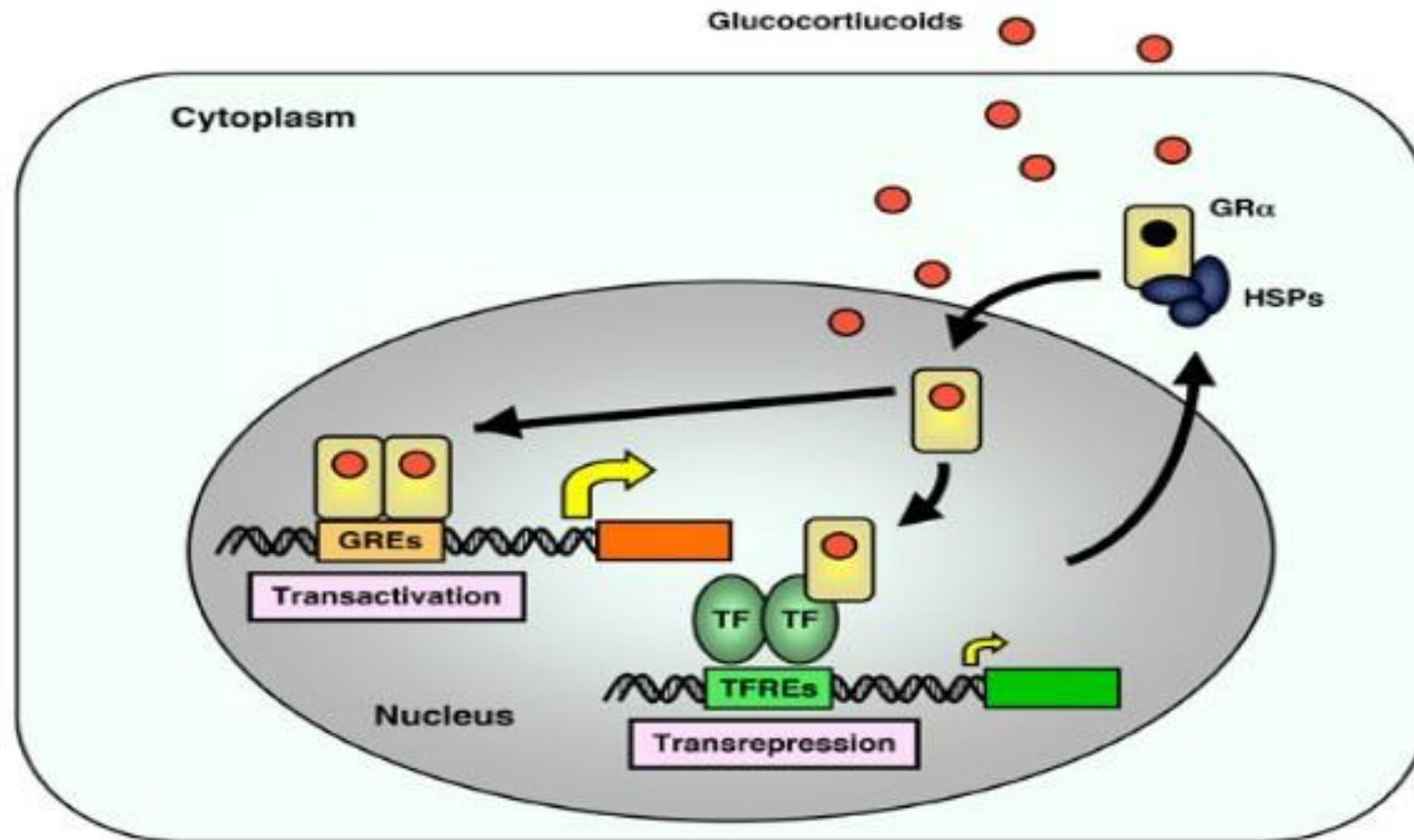


Question

- How does cortisol action change from *protective* to *harmful*?
- What is the cause?
- What are the consequences?

Cortisol mediates stress effects on DNA

Stress increases cortisol which binds to receptor



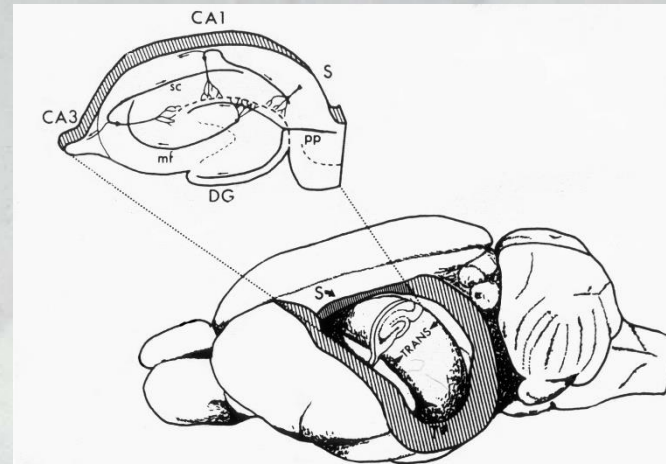
Discovery -1

^3H - corticosterone
Adrenalectomised rat



HIPPOCAMPUS

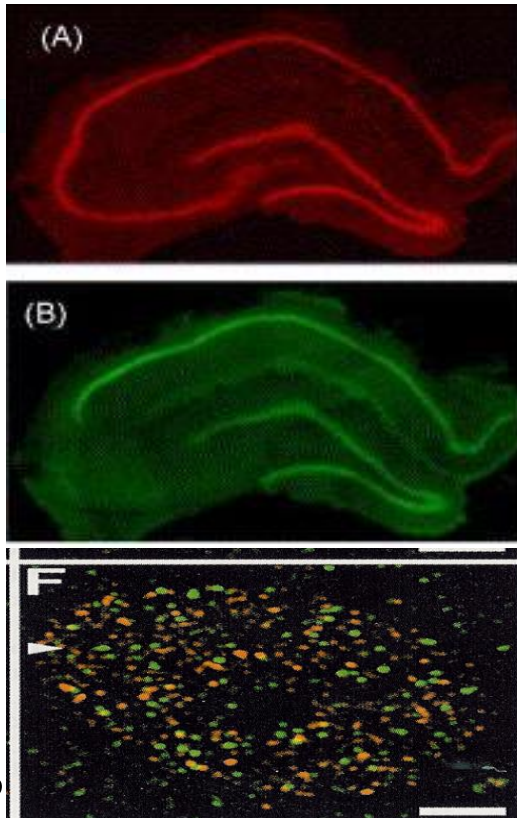
Bruce McEwen &
Ron de Kloet 2016



McEwen et al. 1968

Discovery - 2

Two receptor types (entries) for cortisol



Reul & de Kloet, 1985

Cell nucleus nerve cell

MR red; GR green

Receptor 1: *high affinity*, if something new happens, searches in the memory, appraises and helps to find a coping strategy.

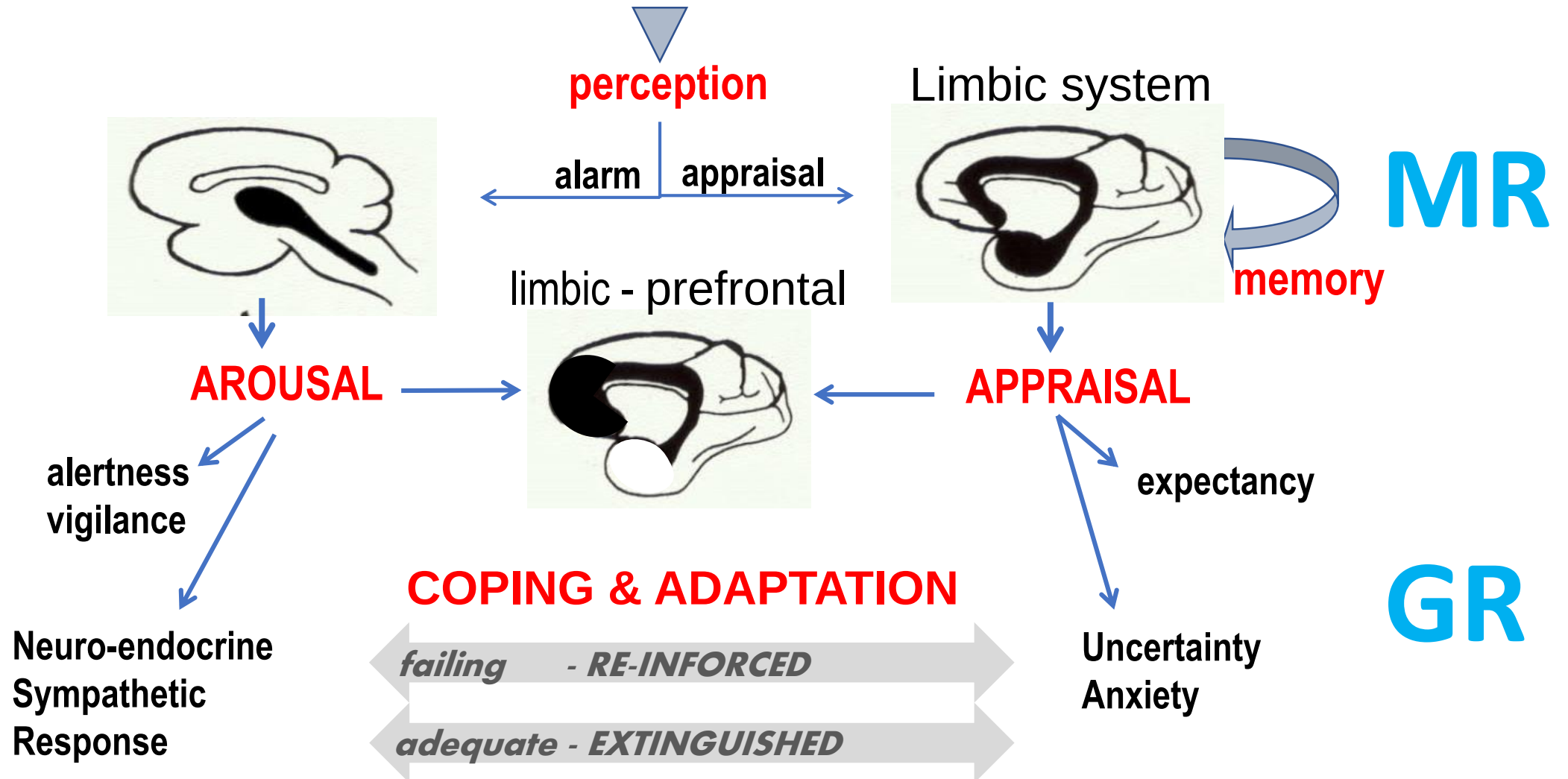
Receptor 2: *low affinity*, stores experience in the memory, helps to adapt and to prepare for the future

For the experts

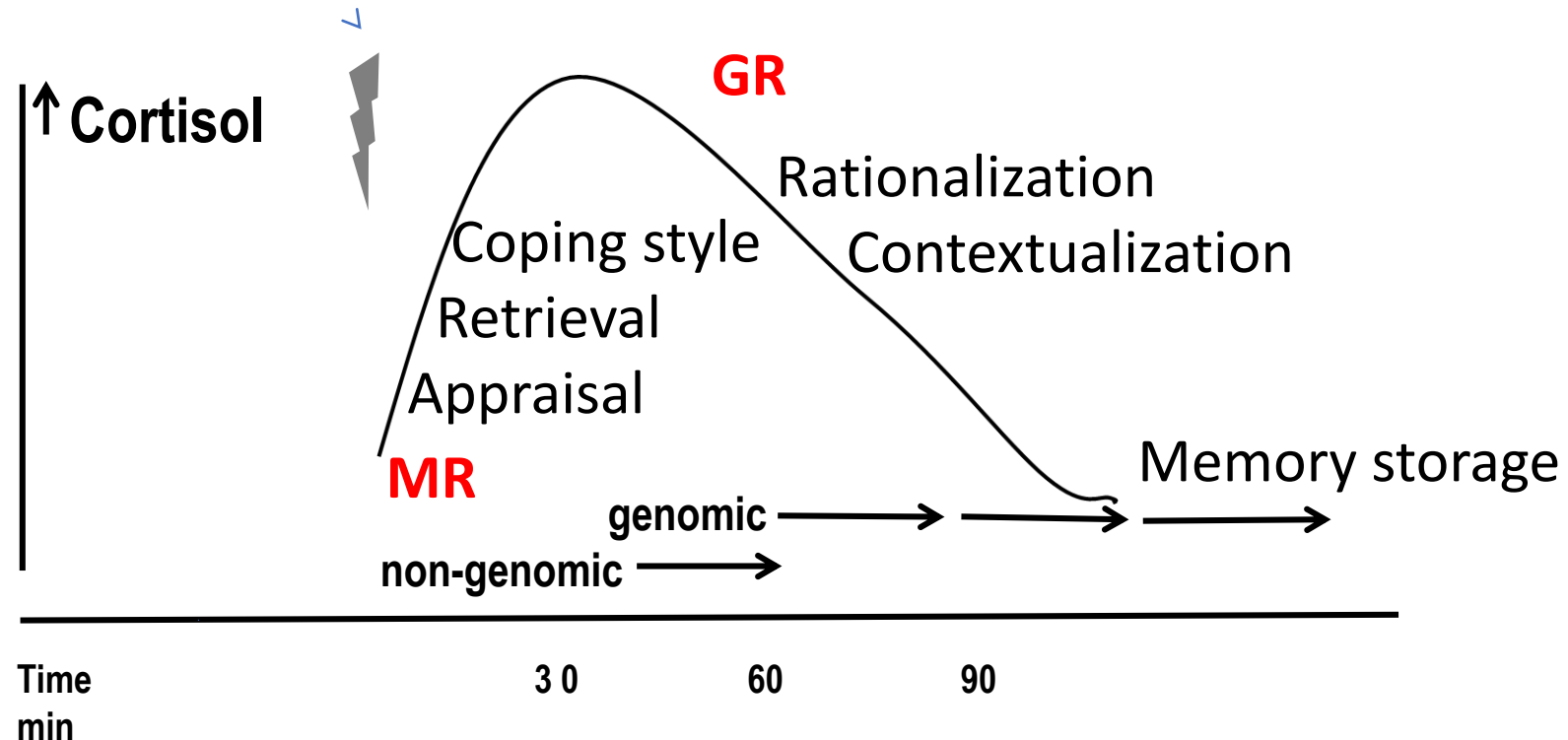
Receptor 1 = MR = mineralocorticoid receptor

Receptor 2 = GR = glucocorticoid receptor

Stressor

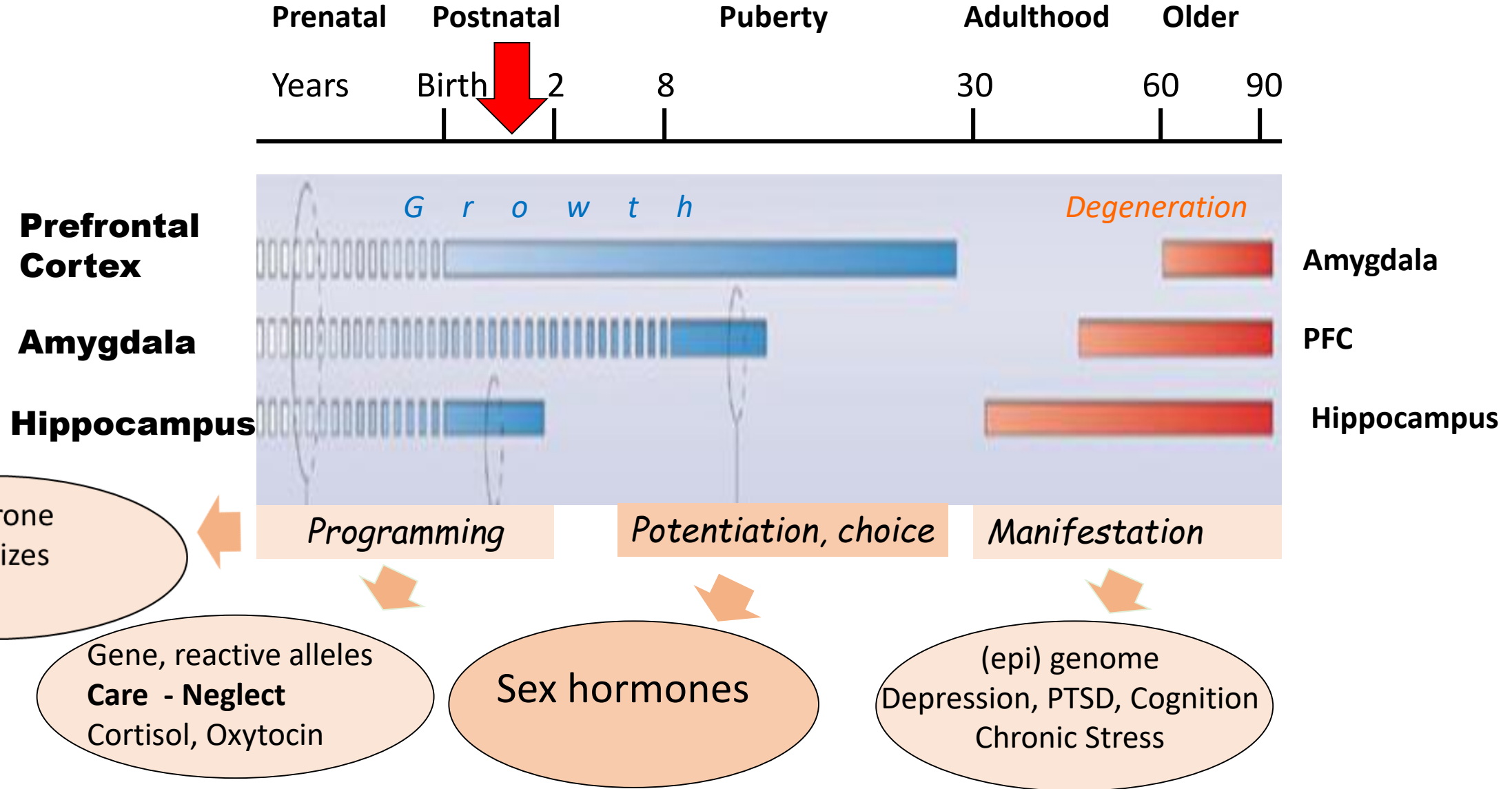


Stress-induced Cortisol secretion

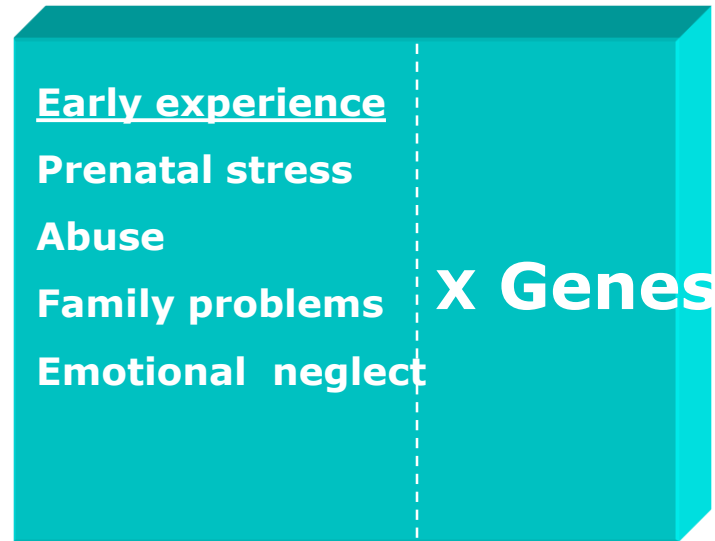


- Genetic predisposition
- (early) life experience (epigenetic)

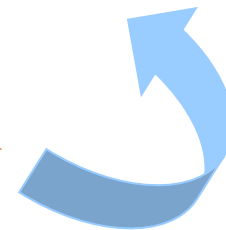
brain development



Epidemiology: humans



**Individual differences in neural &
endocrine response to stress**

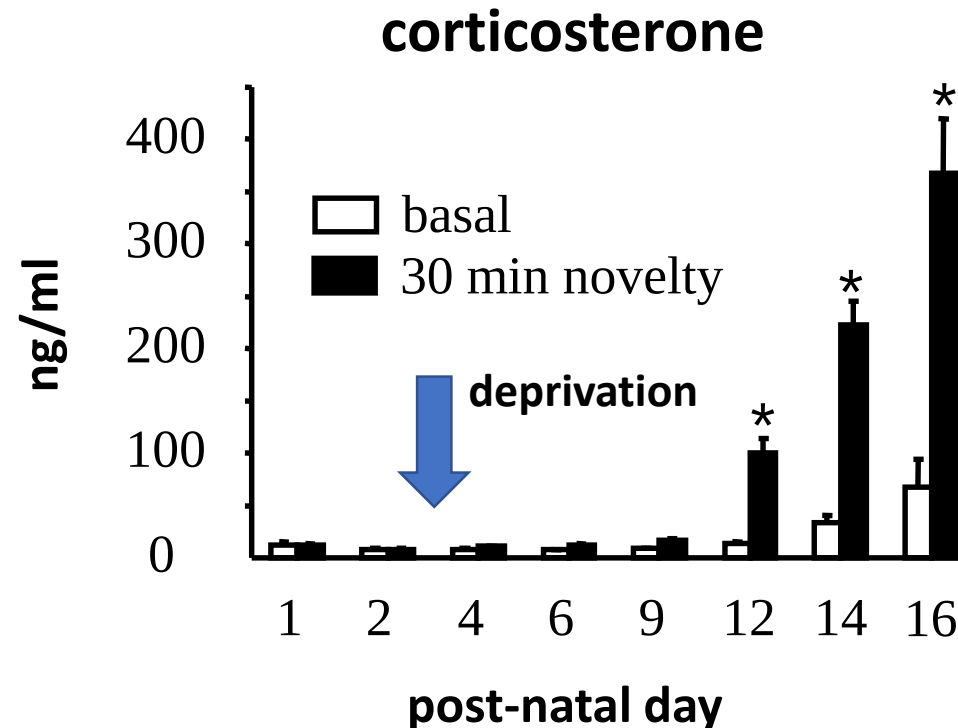


Stress hyporesponsive period

- from postnatal day 1-12
- low basal corticosterone (CORT)
- no CORT response following mild stress



Altricial species
Prematurely born

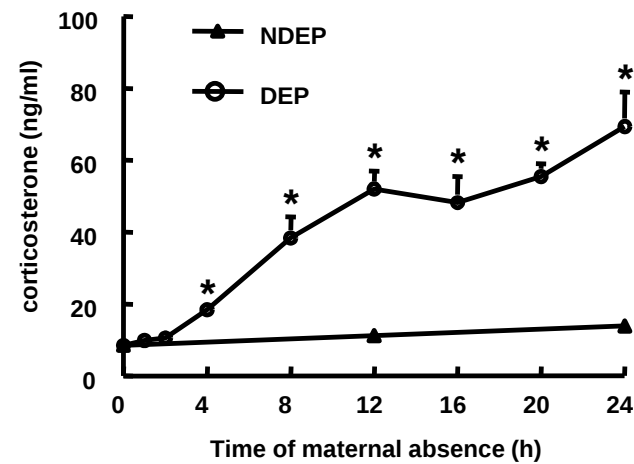


If cortisol is increased,
then the hormone
activates the
amygdala fear circuit

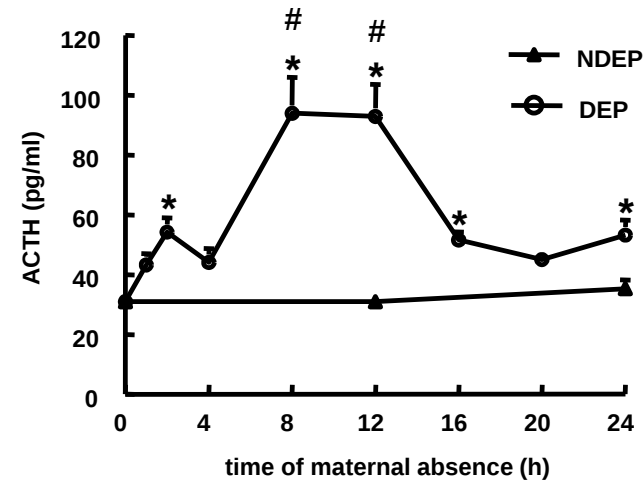
Effect of Maternal deprivation (24h)

Dam is removed, pups stay home

corticosterone

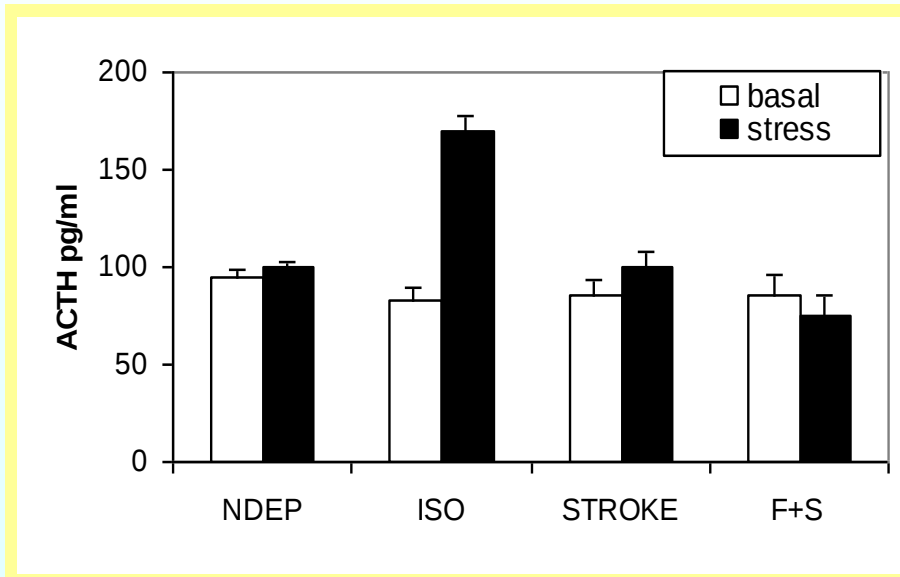


ACTH

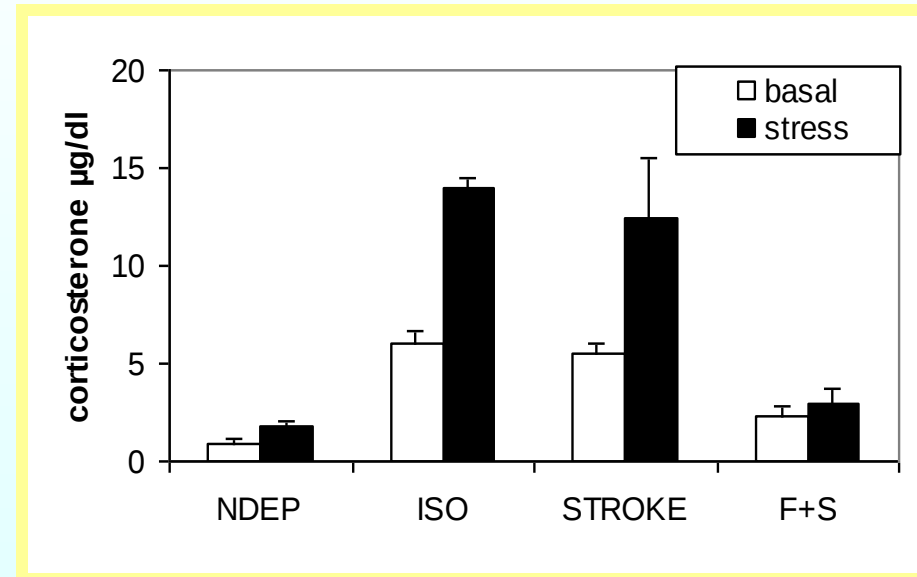


Mimicking elements of maternal care *eliminates* effects of maternal deprivation

stroking (3x45 sec/24 h, every 8 hrs) normalizes brain function (ACTH, CRH, cfos)

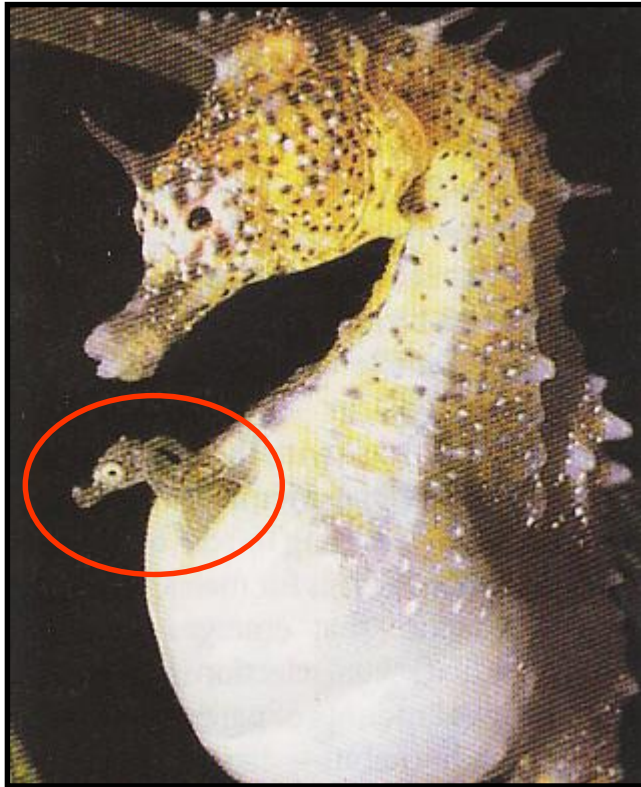


stroking + feeding normalizes adrenal function (corticosterone)



NDEP = non-deprived
ISO = deprived from maternal care

Early life animal models



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Seahorses and their occasional sex-role reversal and would-be- female males

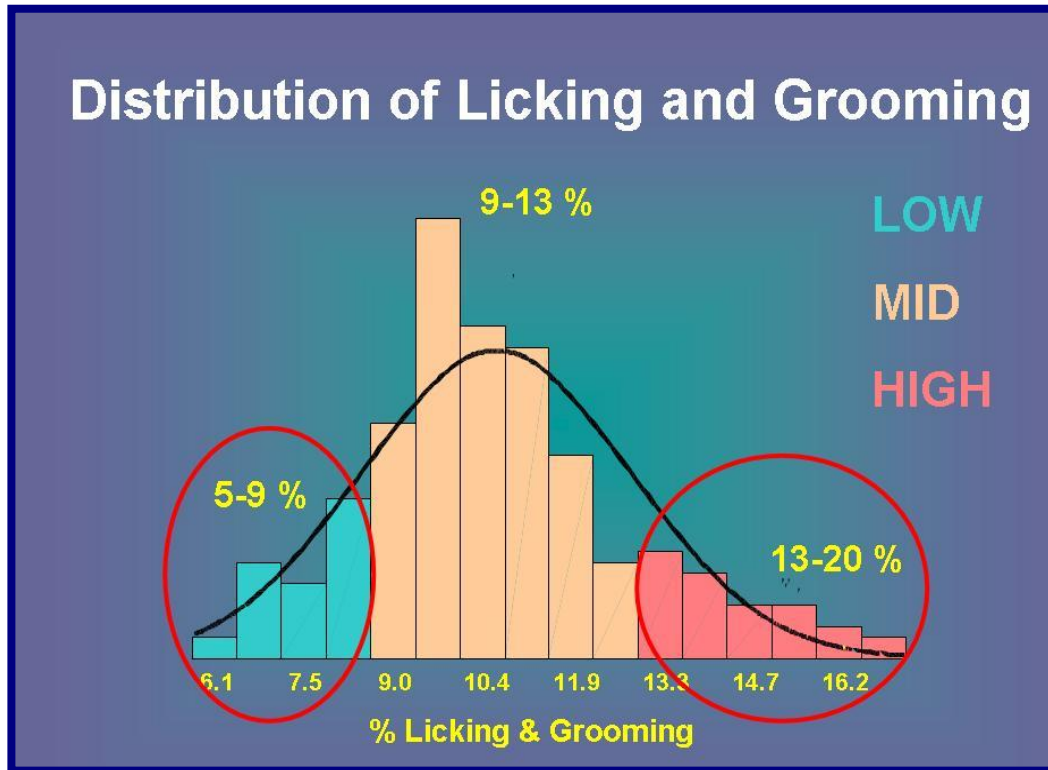
Early life animal models

- Single and repeated mother-pup separation procedures
 - depends on duration, frequency and timing of separation
 - pups rapidly learn to predict return of the dam
- Fragmented and unpredictable maternal signals (limited bedding)
- Select animals by maternal care received

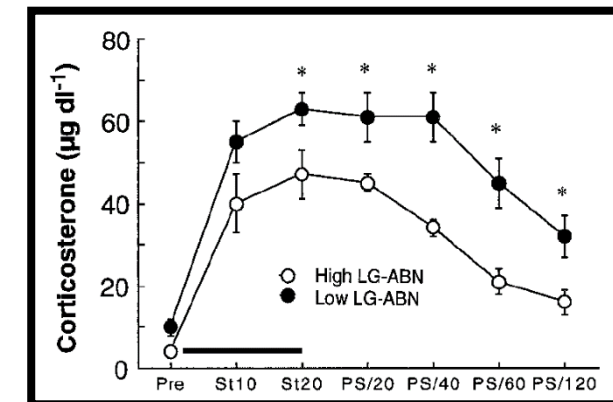
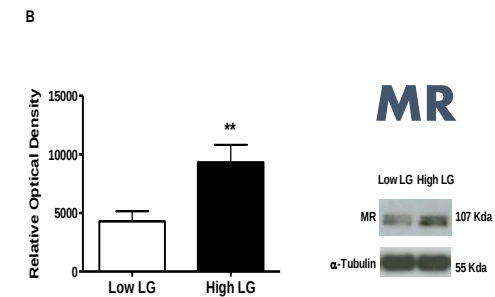
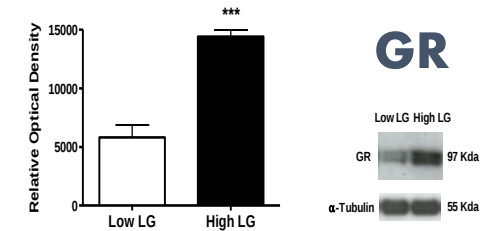


Passive Nursing

Early-life environment: maternal care



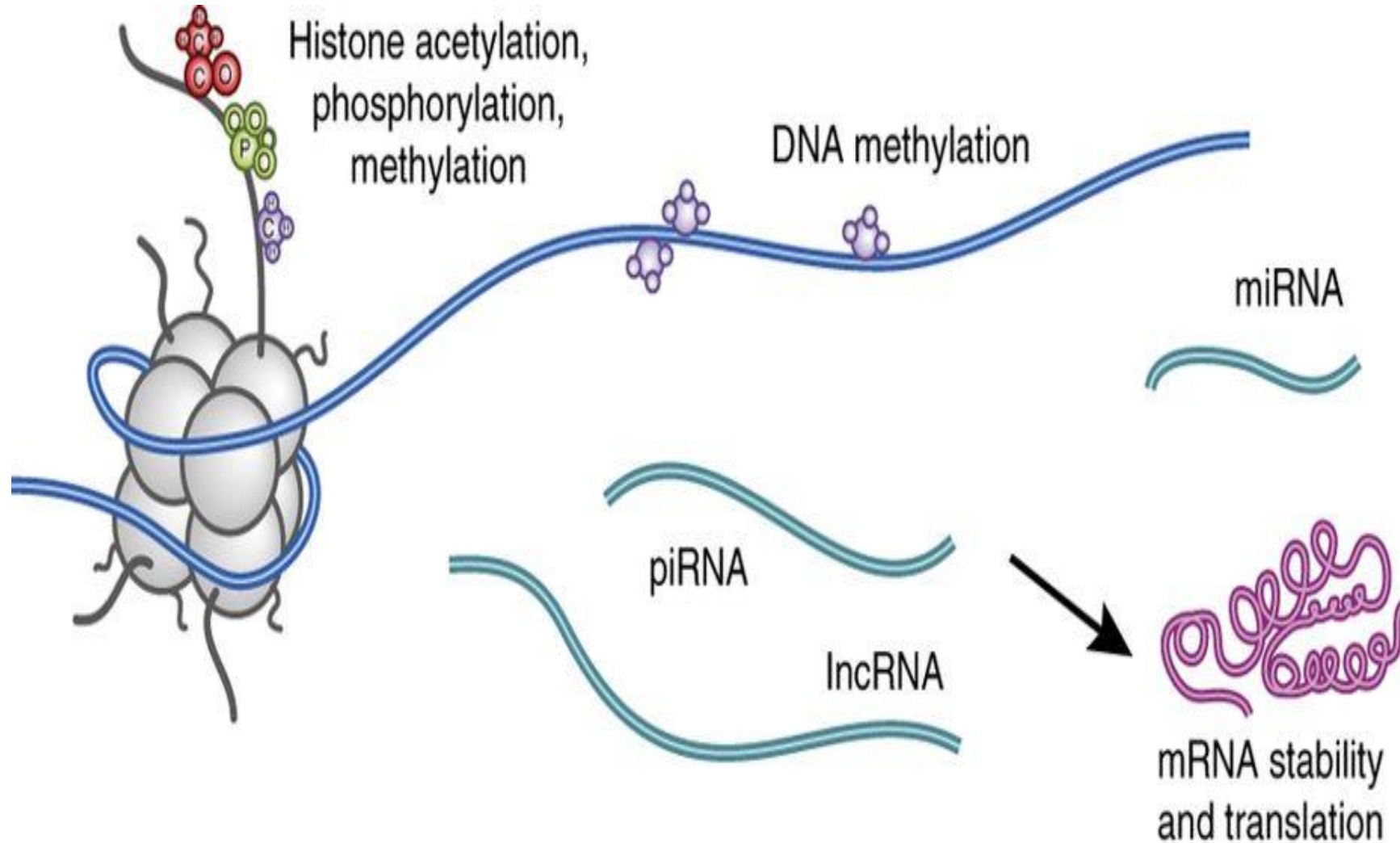
Long Evans rats; Liu et al. 1997, Champagne et al. 2003, Zhang et al. 2005



Low Maternal Care (**Low LG**):

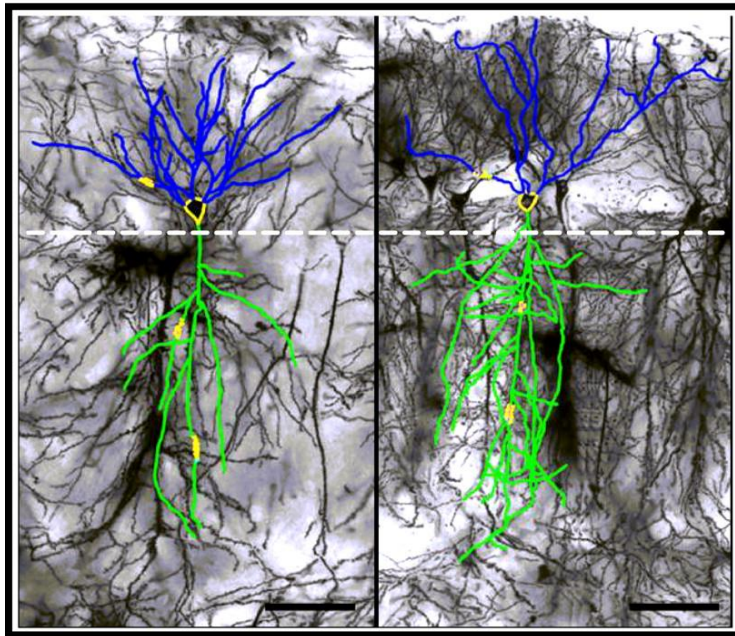
↓ pre-pulse inhibition ↑ emotional stress (CORT) response. ↓ spatial learning & memory

EPIGENETIC REGULATION



Quantitative morphological analysis of dendritic length.

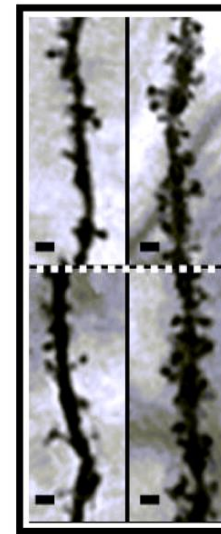
A



Low LG

High LG

B



Low LG

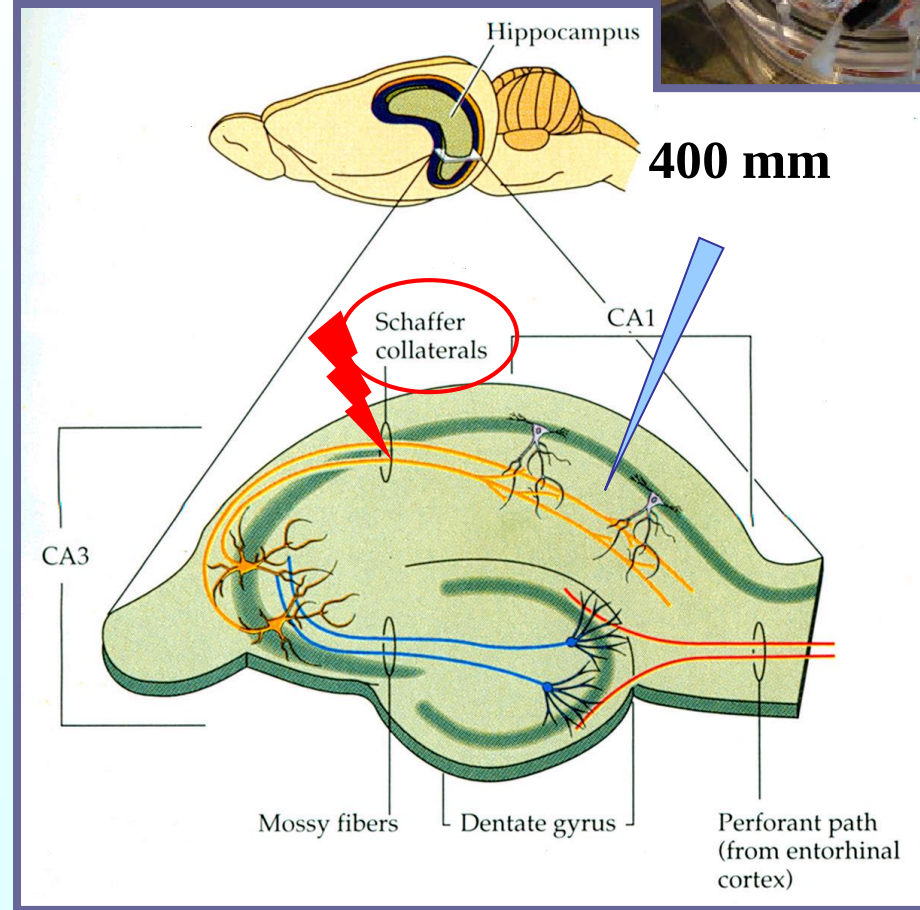
High LG

Low LG = low licking & grooming score
= little maternal care

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Slide Preparation

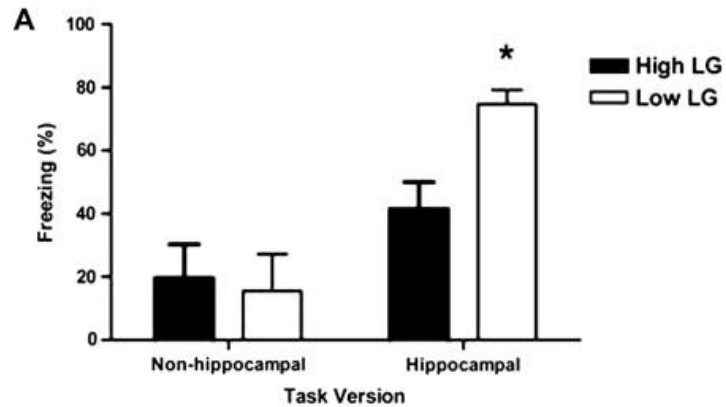
- **Tetanic stimulation: 900 pulses of 10 Hz each over a span of 2 minutes**
- **Synaptic LTP is assessed for 60 minutes**
- **VEH: Artificial CSF**
- **CORT: 100 nM (20 min)**



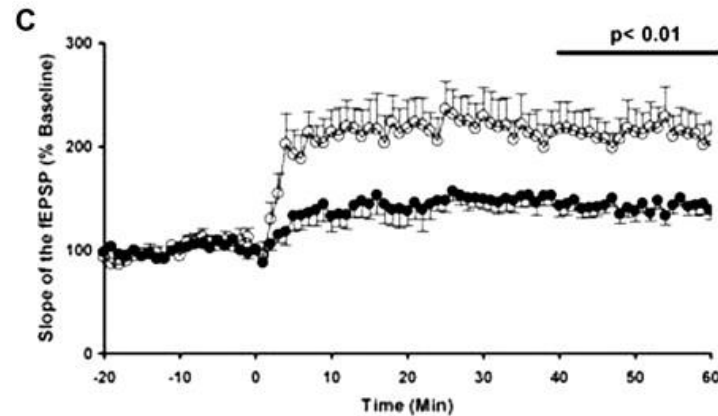
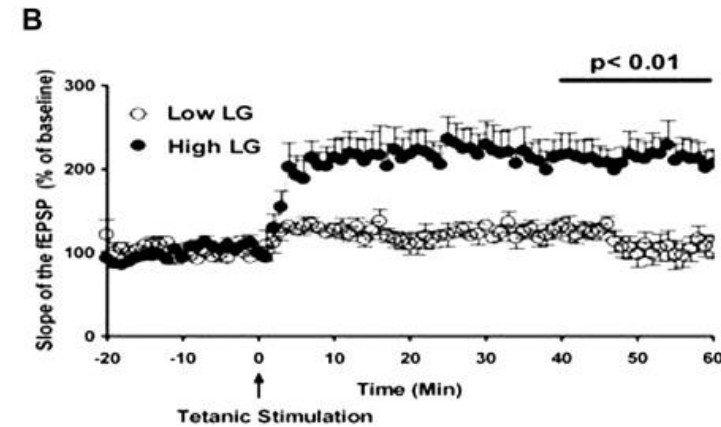
Maternal care

Long term potentiation and fear-motivated behavior

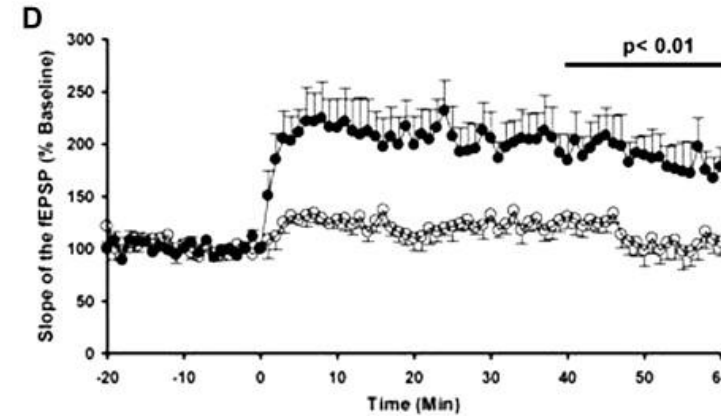
Memory for stress



LTP



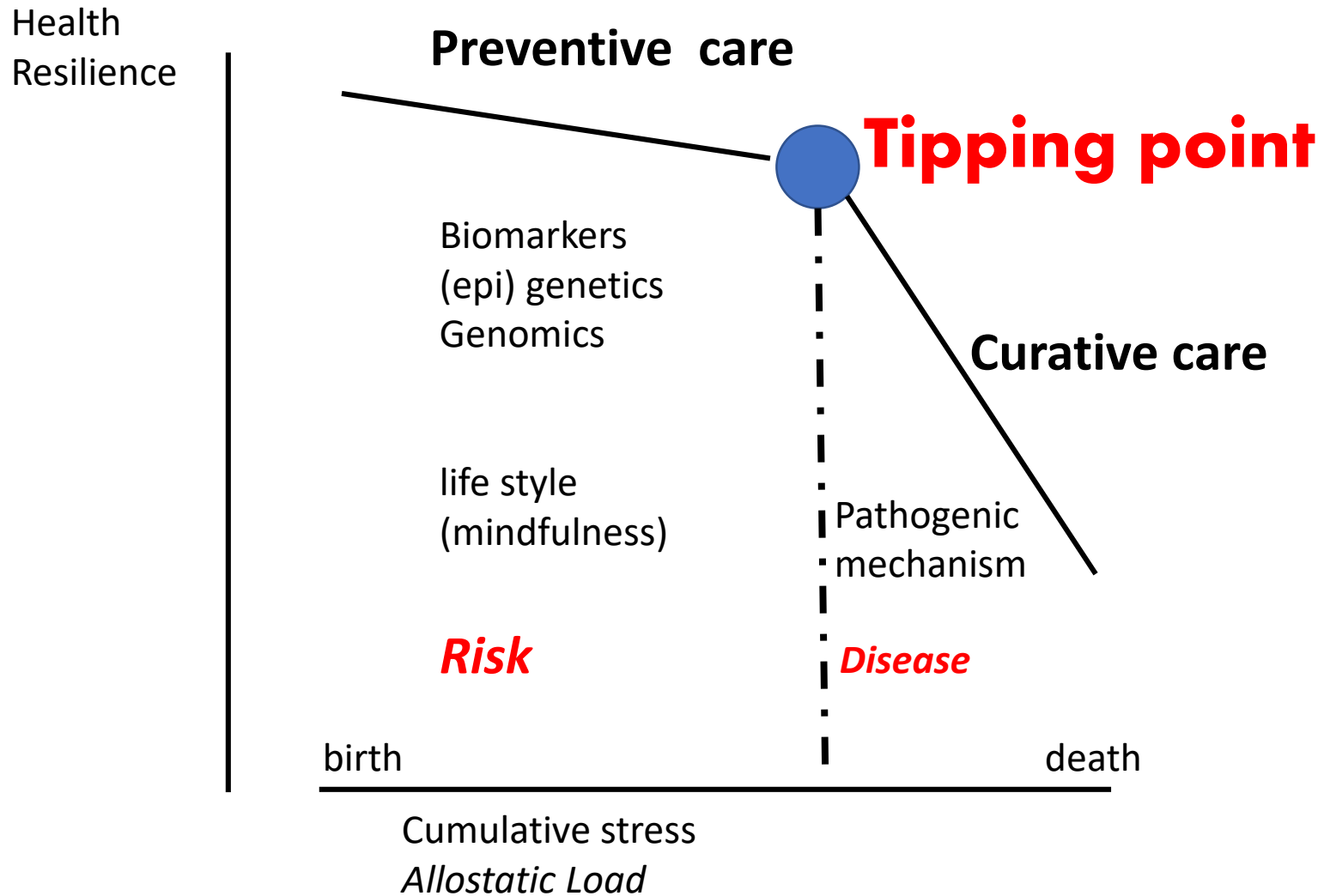
High LG + CORT

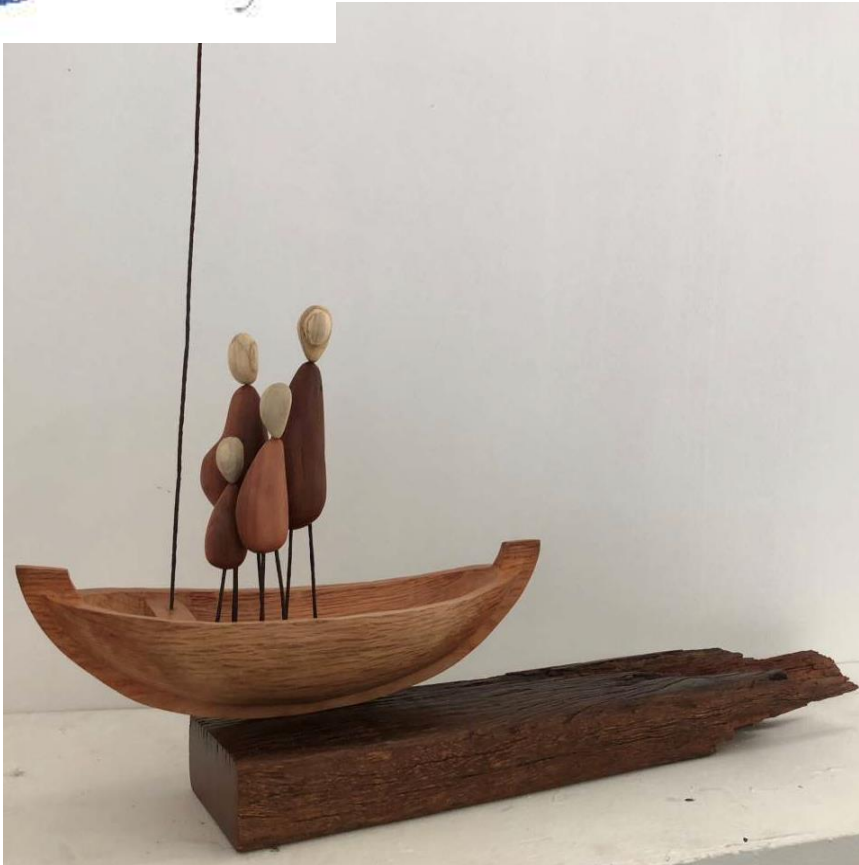


Low LG + CORT

- Predictive adaptive (match/mismatch – stress inoculation) concept (Champagne et al., 2008; Hanson & Gluckman, 2014; Nederhof & Schmidt, 2012). DOHAD
- Cumulative stress concept – or classical diathesis stress theory (Daskalakis et al. 2013)
- Differential susceptibility (biological sensitivity to context) concept (Ellis, Boyce et al. 2011)

Challenge





Perth



Netherlands

Thank You !