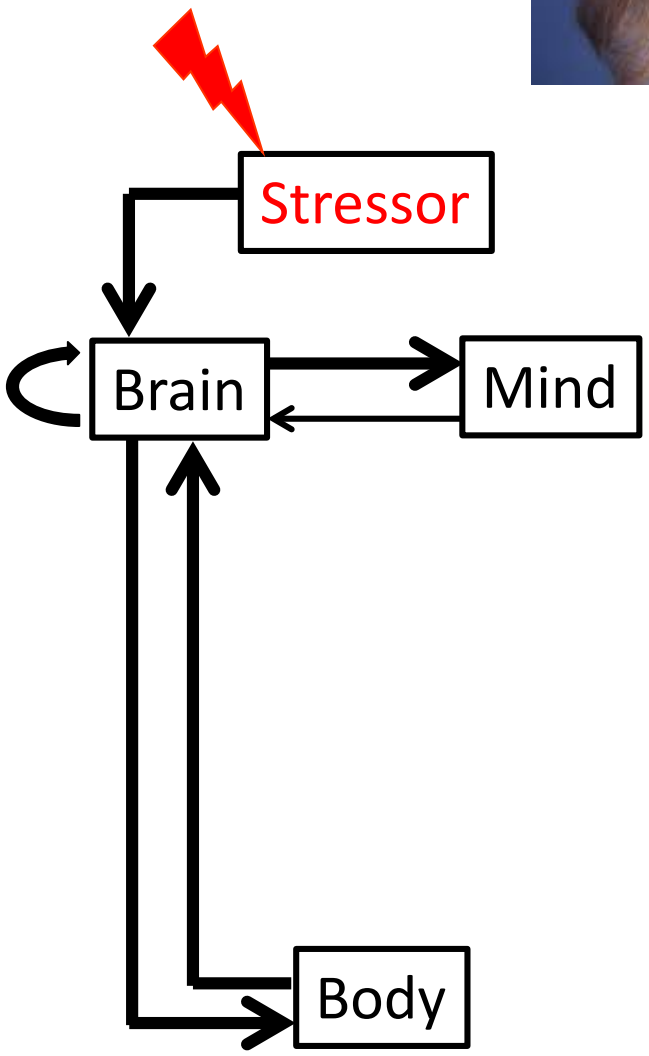
Animal models of human affective disorders: Immune system and depression

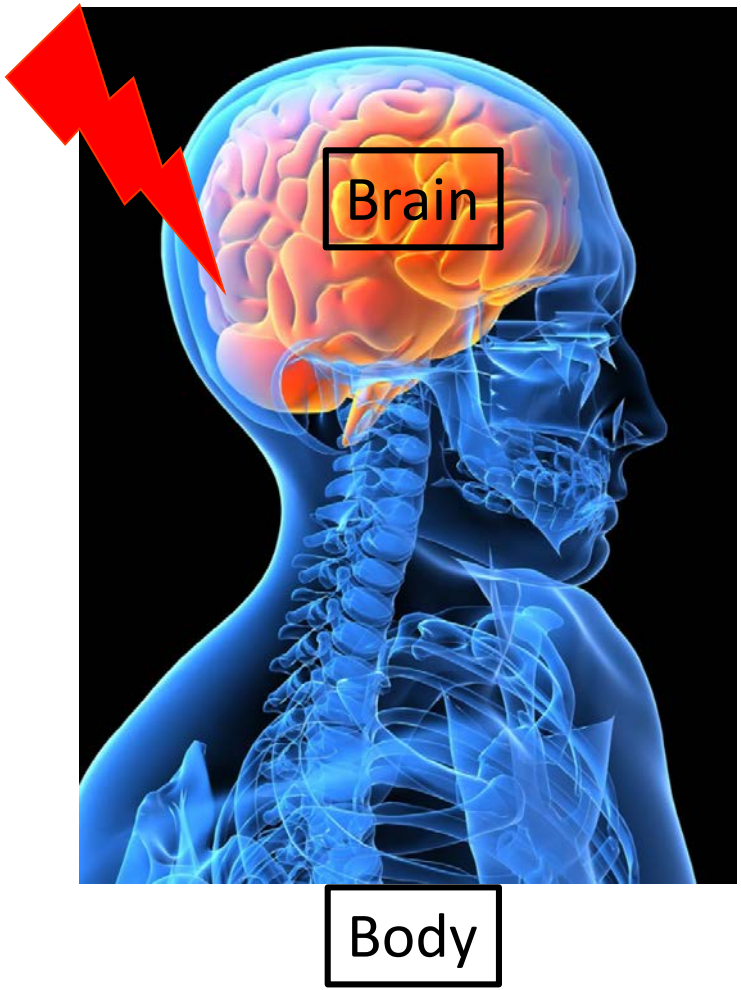
- Brain-Body-Brain interactions
- Stress, sympathetic Autonomic Nervous System and Pro-inflammation
- Cytokines: the messengers of the immune system
- Peripheral inflammation leading to CNS inflammation
- Inflammation aetio-pathophysiology of depression: the evidence
- Sickness behaviour syndrome (SBS) and Depression-relevant behaviour
- Rat/Mouse model of Lipopolysaccharide, SBS and Depression-relevant behaviour
- Rat/Mouse model of CUMS, Inflammation and Depression-relevant behaviour
- Mouse model of CSD, Inflammation and Depression-relevant behaviour
- Stress-Cytokine-Kynurenine pathway
- Exercise reduces Kynurenine pathway activity (Resilience against Stress)
- Kynurenine pathway and dopamine and serotonin neurotransmission

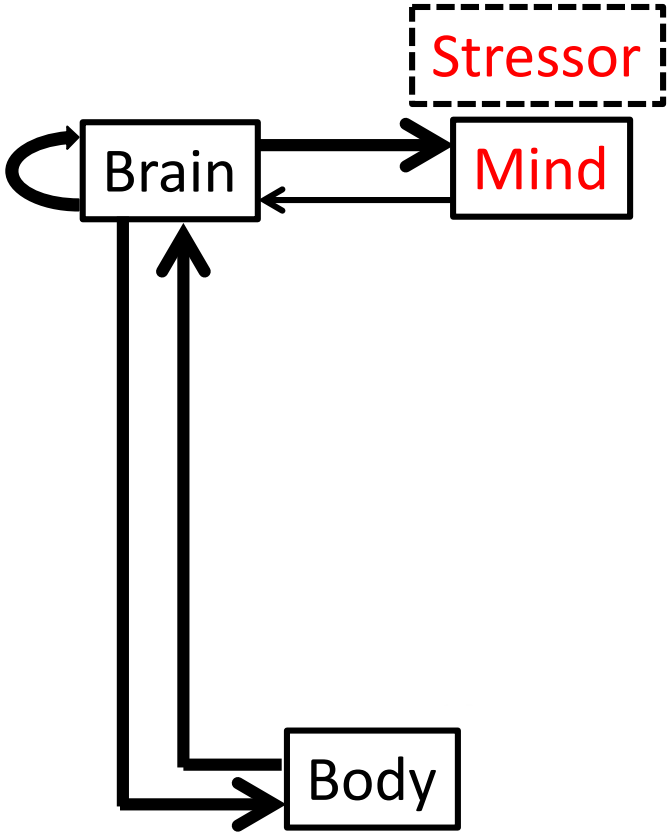
Depression Aetiology: Environment-Brain-Body-Brain-Mind

humans can keep a stressor. animals don't (maybe), since stressor passes simply
it is not known if a memory of stressor is made and can be activated later.
but it is thinkable that brain cellular strucutre is modified which infleunces long term brain function (brain has a different morphology but may gradually recover)

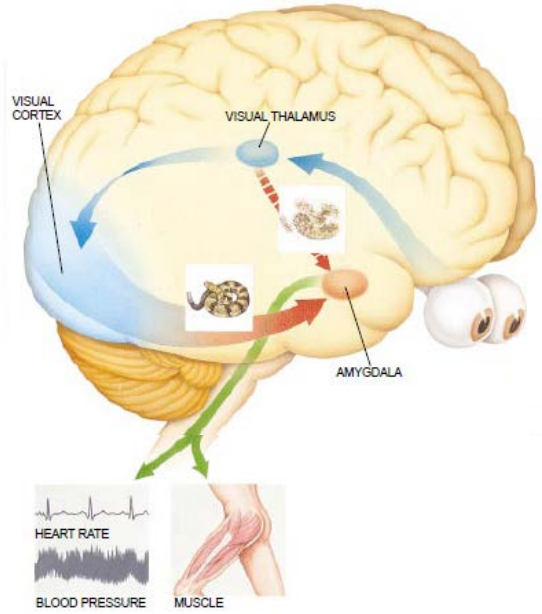
Mind

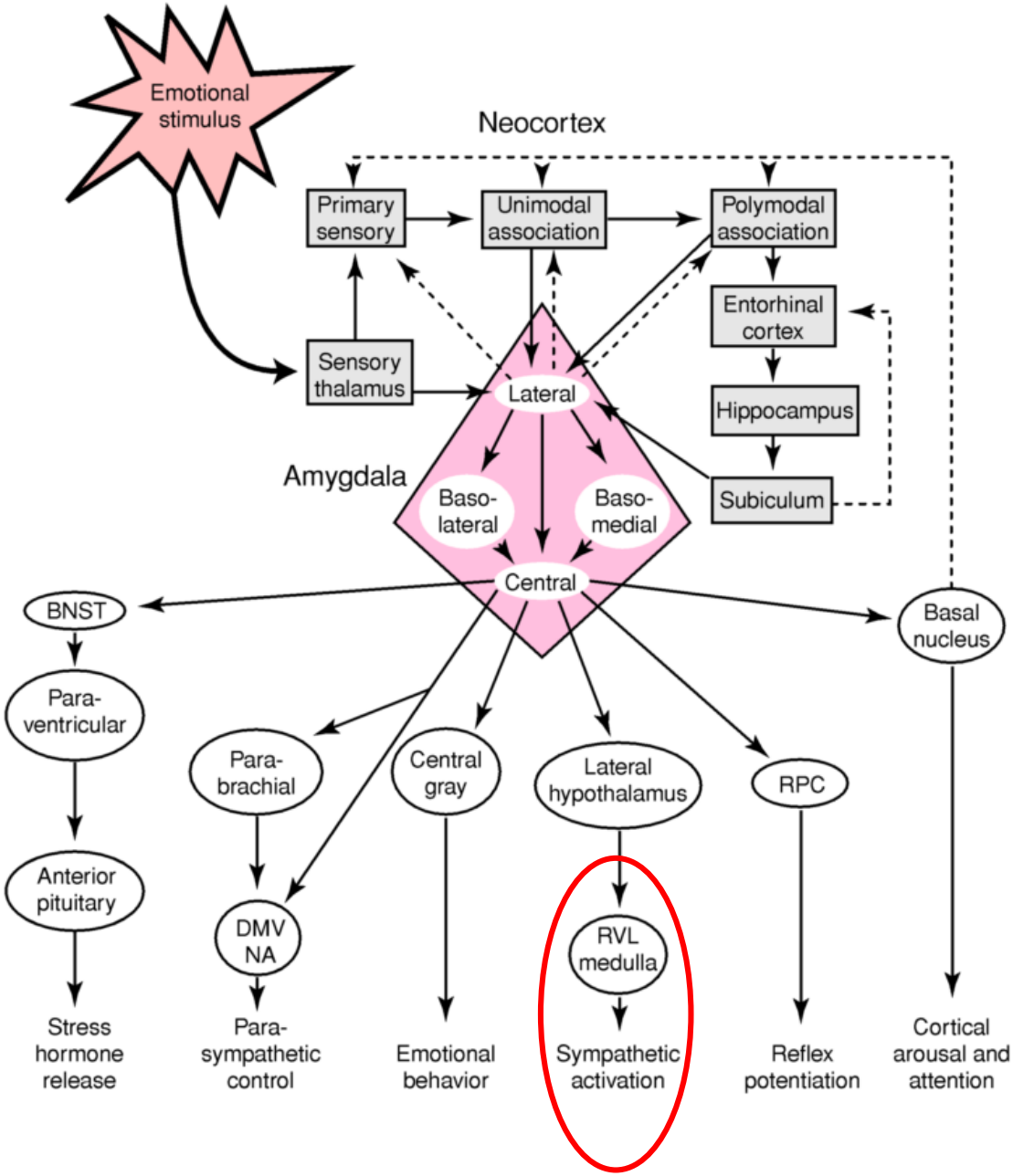




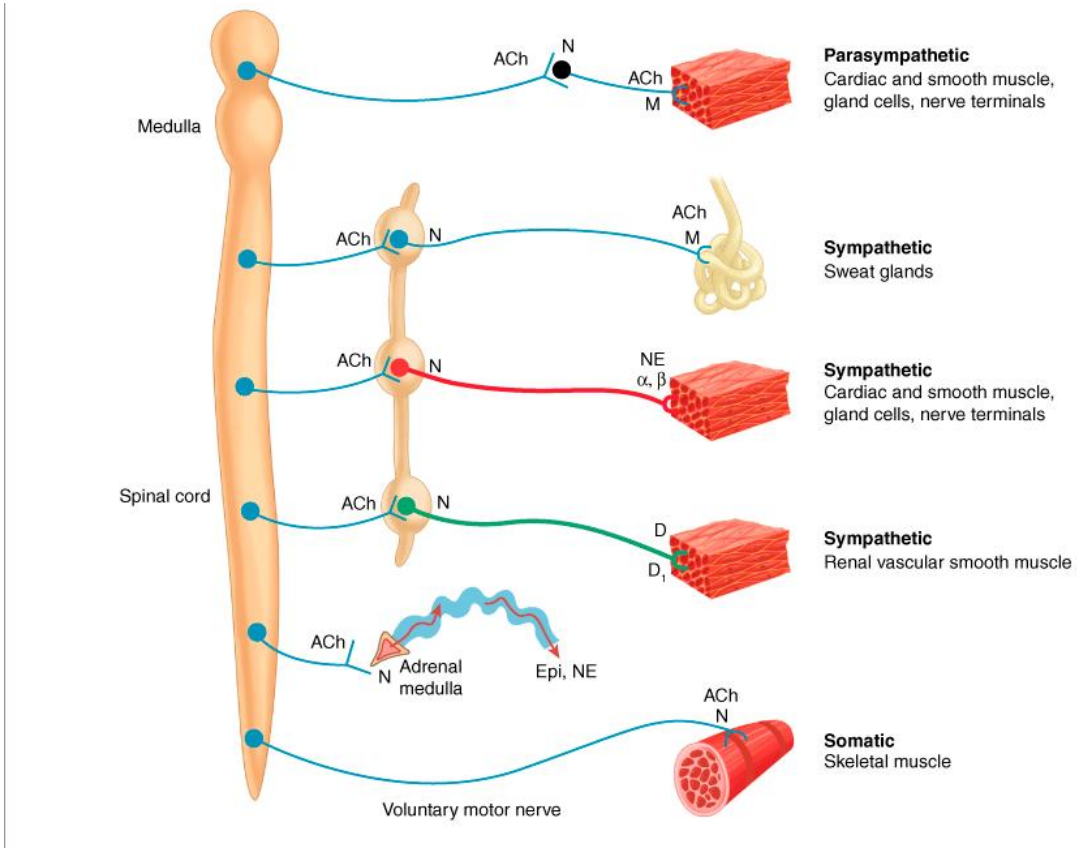


The amygdala: at the interface of emotional-cognitive input and emotional output

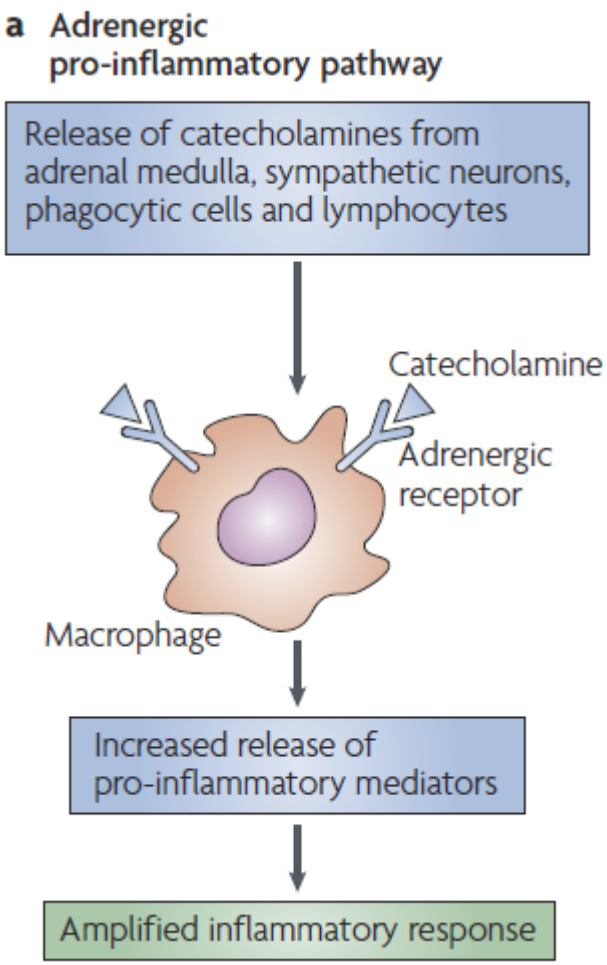




Stress-induced activation of the inflammatory response and CNS effects: Important roles for Noradrenaline and Nuclear Factor-κB



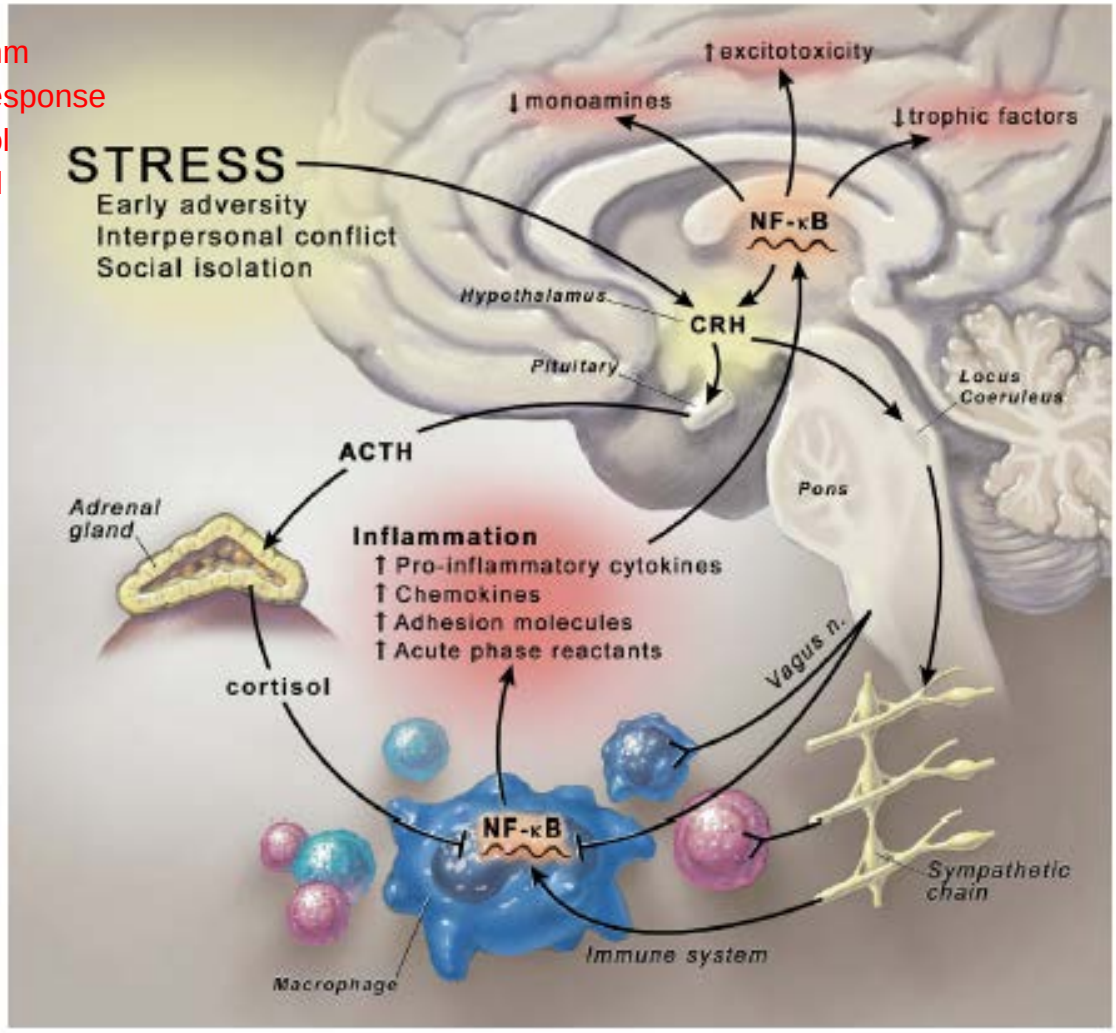
Spleen, Lymph nodes, Bone marrow



Rittirsch et al. (2008) Nature Reviews Immunology 8: 776

Stress-induced activation of the inflammatory response and CNS effects: Important roles for Noradrenaline and Nuclear Factor-κB

stress activates the sympathetic NS
we also have activation of HPA axis
short term stress: activate pro-inflamm response and ativate anti-inflamm response
long term stress: receptors of cortisol (there are two) become desensitized (internalized in the cell), we lose the anti-inflamm stress response, but pro-inflamm response remains.



NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells)

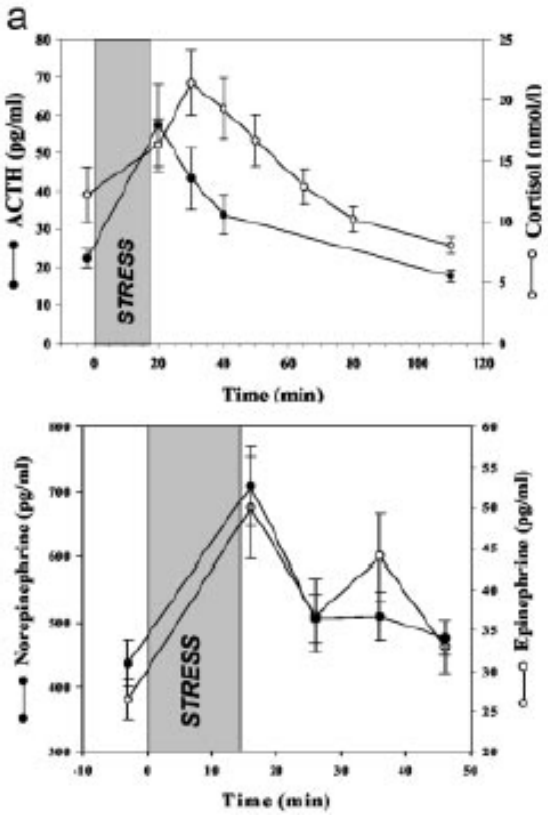
Miller et al. (2009) Biol Psychiatry 65: 732

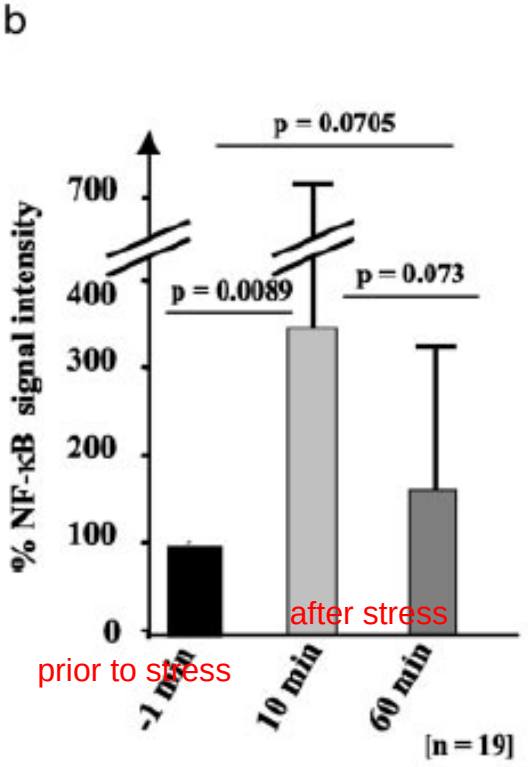
Psychosocial stress leads to increased NF-κB levels in peripheral blood mononuclear cells

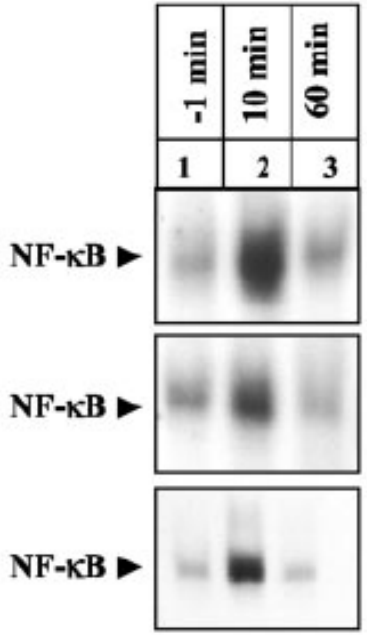
(as an example)

Trier Social Stress Test

Public speaking
Mental arithmetic



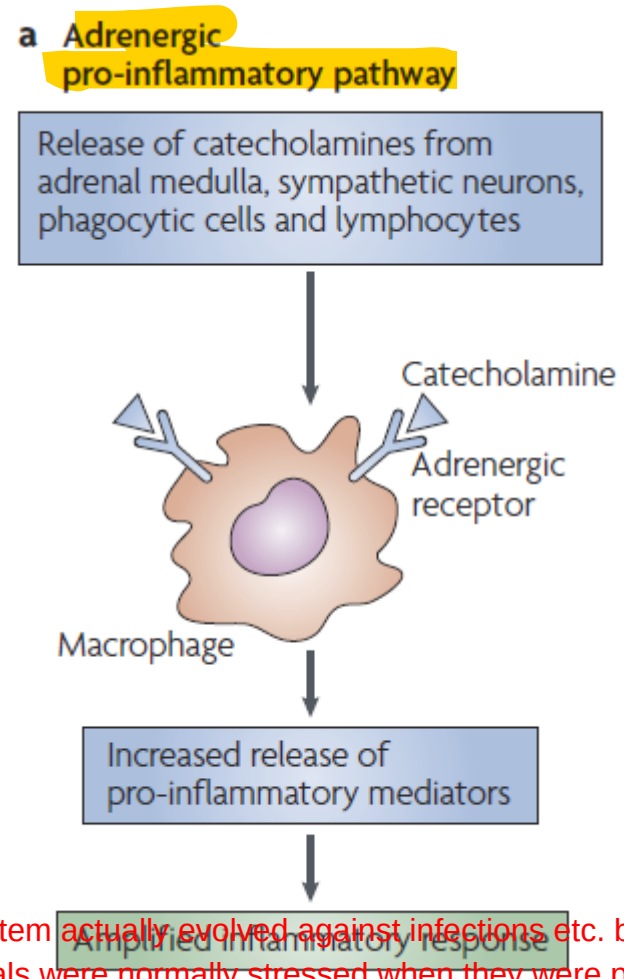


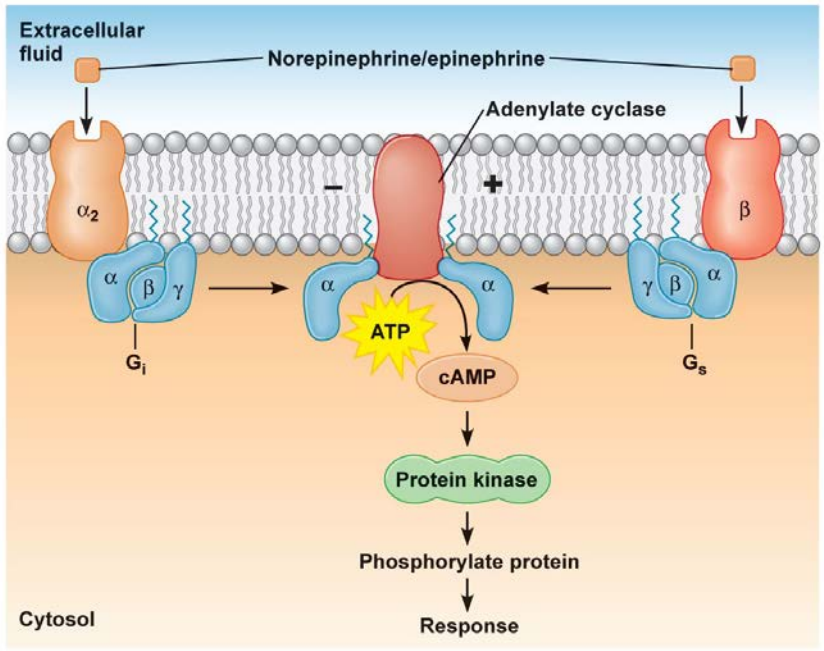


Bierhaus et al. (2003) PNAS 100: 1920

Stress-induced activation of the inflammatory response and CNS effects: Important roles for Noradrenaline and Nuclear Factor-κB

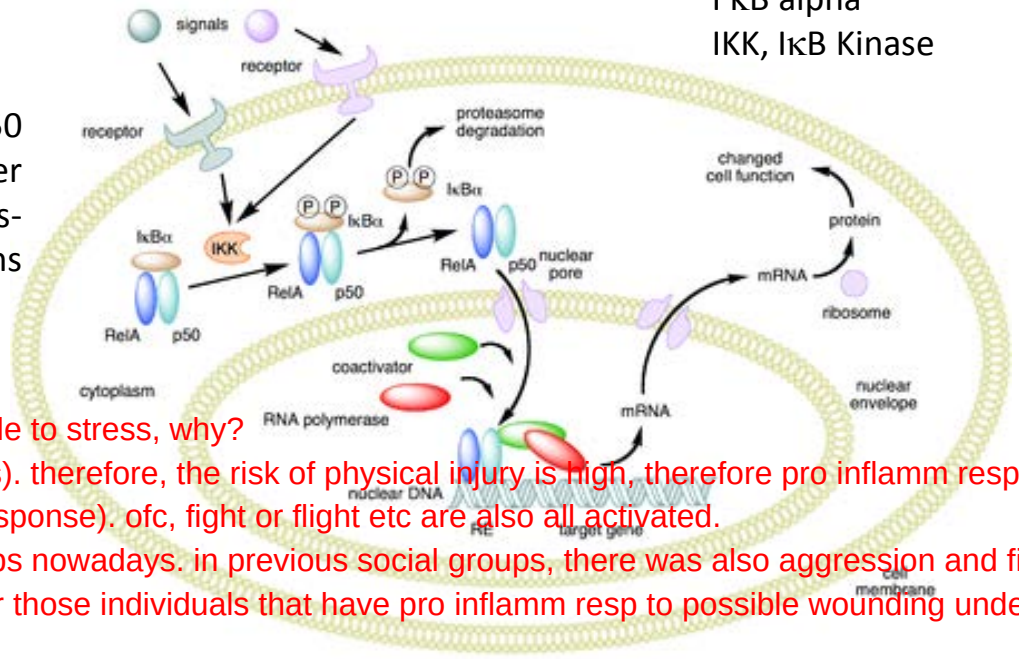
Spleen, Lymph nodes, Bone marrow





I κB alpha
IKK, IκB Kinase

NF-κB or p50 forms Dimer with Rel Trans-activation proteins



this system actually evolved against infections etc. but it is also very sensible to stress, why?
mammals were normally stressed when they were prey (species vs species). therefore, the risk of physical injury is high, therefore pro inflamm response already being active to a possible wounding is beneficial (higher survival response). ofc, fight or flight etc are also all activated.
it's in our case non-sensical that we have this activation too in social grouups nowadays. in previous social groups, there was also aggression and fights, so activation of pro inflamm response is also good there (selection selected for those individuals that have pro inflamm resp to possible wounding under social stress).

Pro-inflammatory Cytokine stimulation in Body and CNS is Noradrenaline dependent

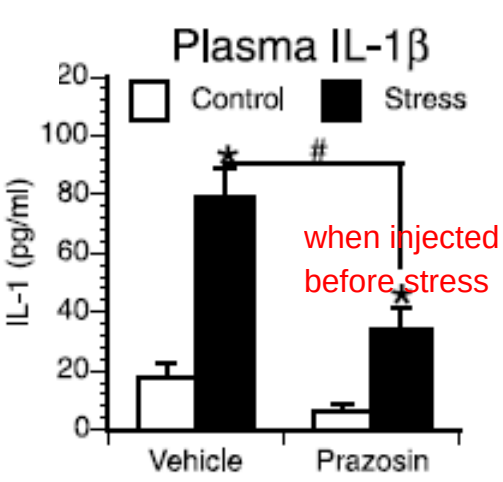
Stressor = Foot-Electroshock

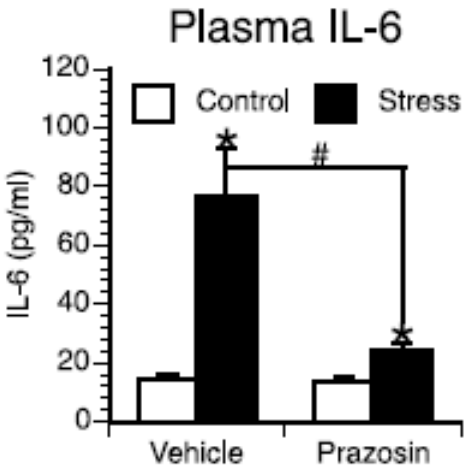
Interleukin-1β
Interleukin-6

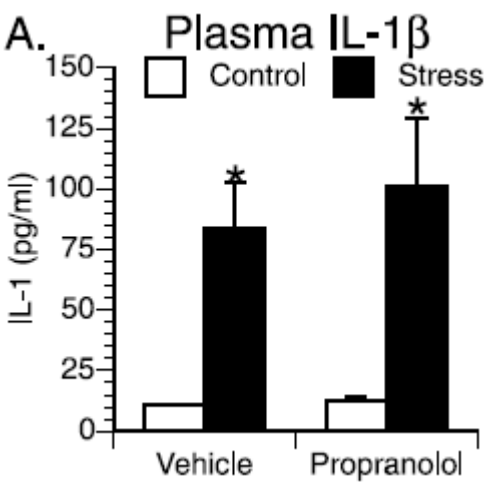
no involvement of beta-adrenoreceptor in stress response in the blood, but there was involved in hippocampus

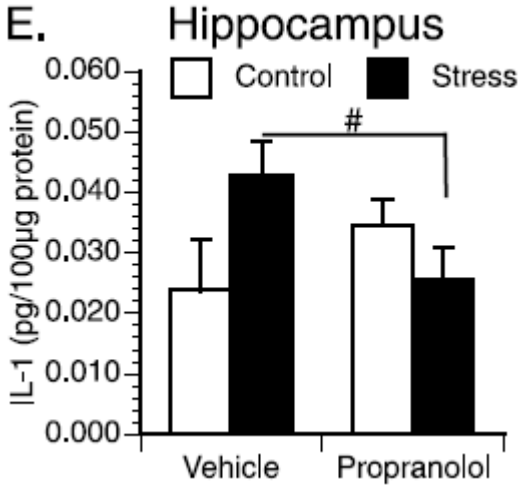
Prazosin, α1-adrenoreceptor antagonist

Propranolol, β-adrenoreceptor antagonist









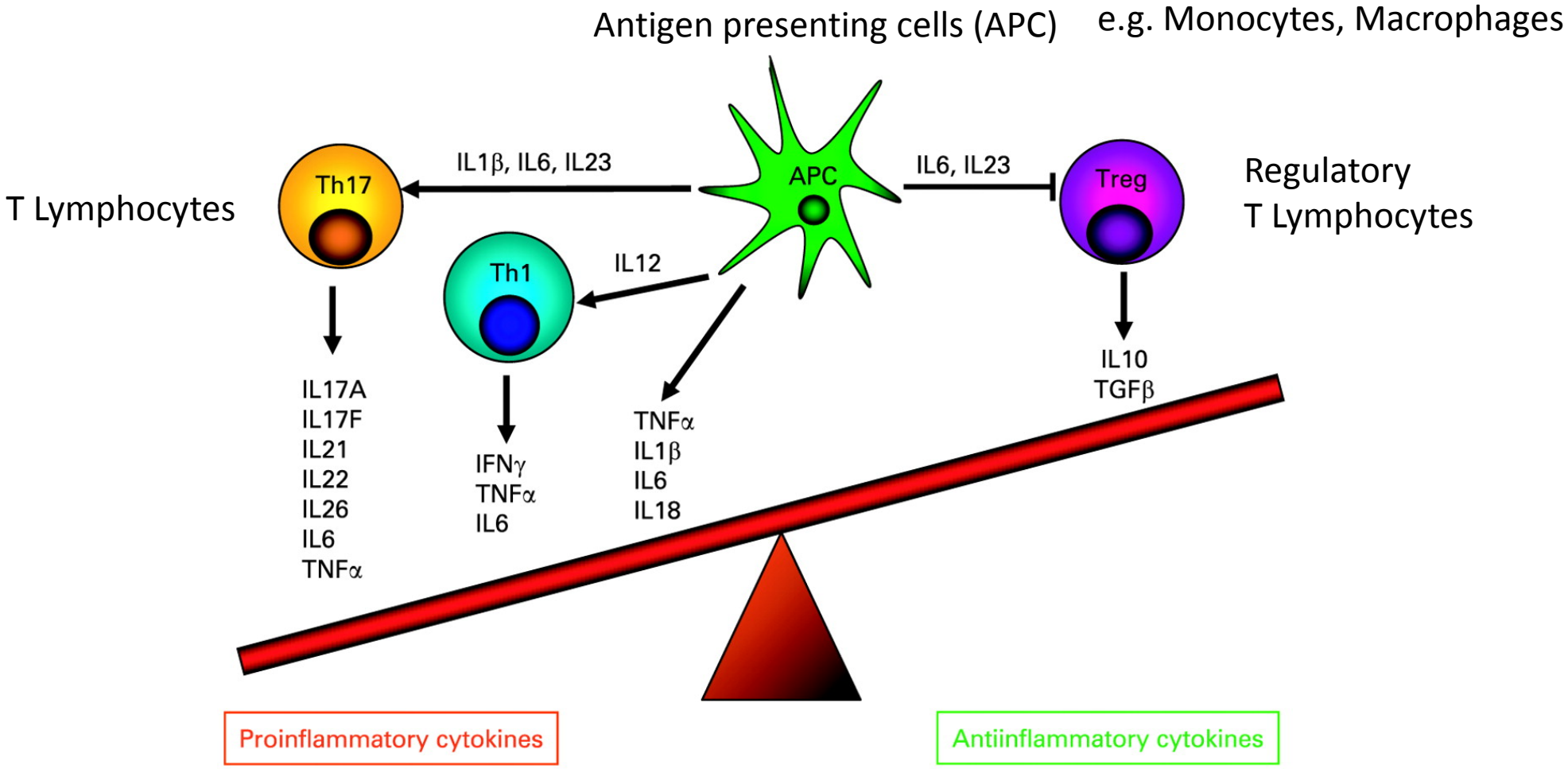
Pre-treatment with Prazosin reduced stress-induced plasma IL-1β and IL-6
Pre-treatment with Prazosin without effect on stress-induced brain IL-1β and IL-6

Pre-treatment with Propranol without effect on stress-induced plasma IL-1β
Pre-treatment with Propranol reduced brain 1L-1β

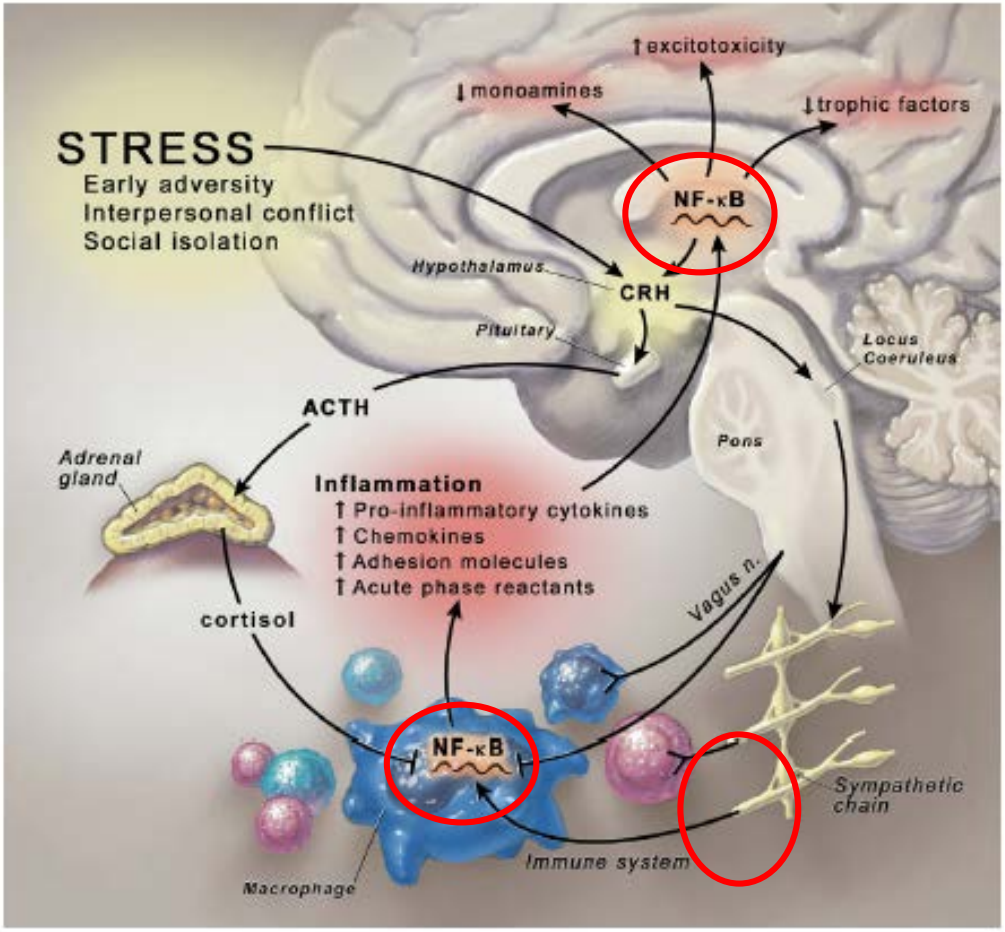
Johnson et al. (2005) Neuroscience 135: 1295

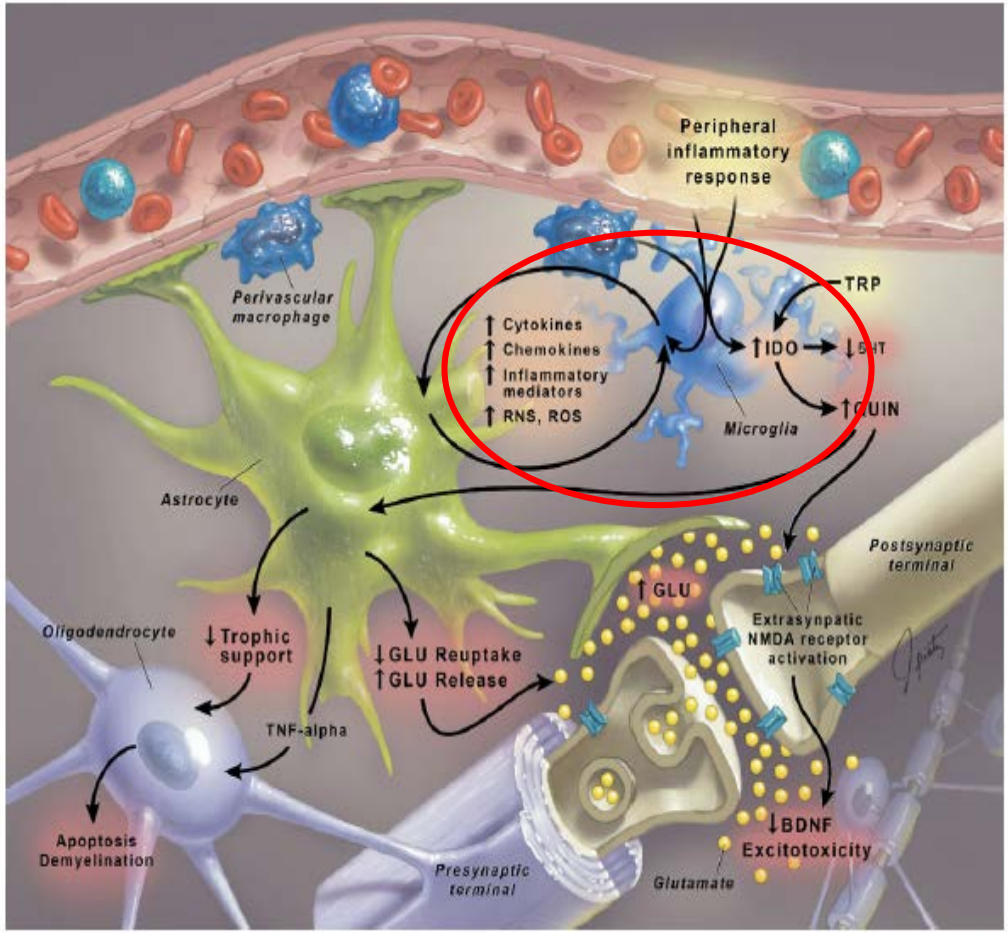
Cytokines: the messengers of the immune system

- Protein messengers produced and released by macrophages, T cells, B cells
- Communication between cells of the immune system
- Activation of immune system
- Development of blood cells



Summary: Stress-induced activation of the inflammatory response and CNS effects





Miller et al. (2009) Biol Psychiatry 65: 732

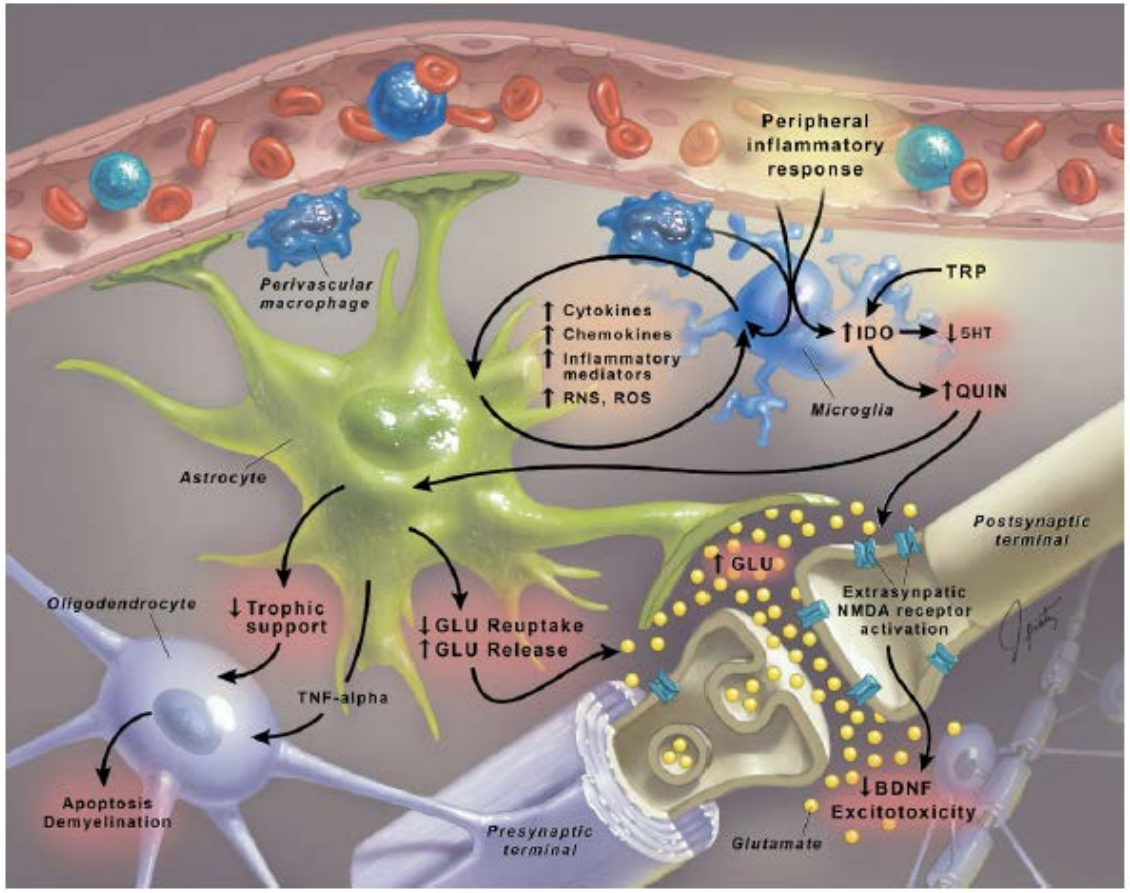
Cytokine activity in the central nervous system

Pathways of increased cytokine activity in the CNS

- Passage through blood-brain-barrier
- Active transport via saturable molecules
- Activation of cells (microglia) lining the cerebral vasculature
- Activation of cytokine receptors on peripheral nerves e.g. vagus nerve
- Activation of microglia by noradrenaline, cytokines

Cytokine effects in the CNS

- Reduced monoamine (5-HT, DA. NE) activity
- Reduced neurogenesis in hippocampus
- Oxidative stress
- Apoptosis in astrocytes and oligodendrocytes
- Dysregulation of astrocyte-neuron interactions
- Increased glutamate signalling



Miller et al. (2009) Biol Psychiatry 65: 732

Human evidence for an inflammation aetio-pathophysiology of depression

- **Candidate gene (SNP) case-control association studies:**

TNF	Tumor necrosis factor	Pro-inflammatory cytokine
DCNP1	Dendritic cell nuclear protein-1	Dendritic cells activate T cells and B cells
NPY	Neuropeptide Y	T helper cell differentiation

- **Increased post mortem CNS expression levels of pro-inflammatory cytokines:**

  E.g. Prefrontal cortex TNF receptor 1, IFN-γ receptor

- **Increased blood levels of:**

  Pro-inflammatory cytokines (TNF, IL-6)

  Cytokine-dependent monoamine-regulating enzymes and products (E.g. Indoleamine 2,3-dioxygenase)

- **Pro-inflammatory cytokines used to treat disease associated with high rates of depression:**

  E.g. IFN-α and Hepatitis C (around 60% of those treated with IFN-alpha against hepa C get also depression)

- **Depression and autoimmune disorders are highly co-morbid:** activawtion of immune system also partially responsible for increase in depression

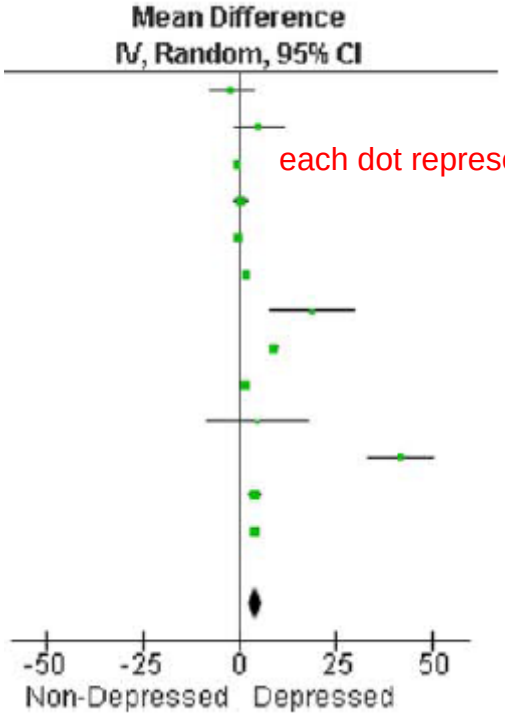
  E.g. Multiple sclerosis, Rheumatoid arthritis

- **Positive proof-of-concept data for anti-inflammatory biologics as anti-depressants:**

  E.g. TNF antibody Infliximab

Meta-analysis of proinflammatory cytokine blood levels in depression

Tumor necrosis factor-alpha (TNFα)



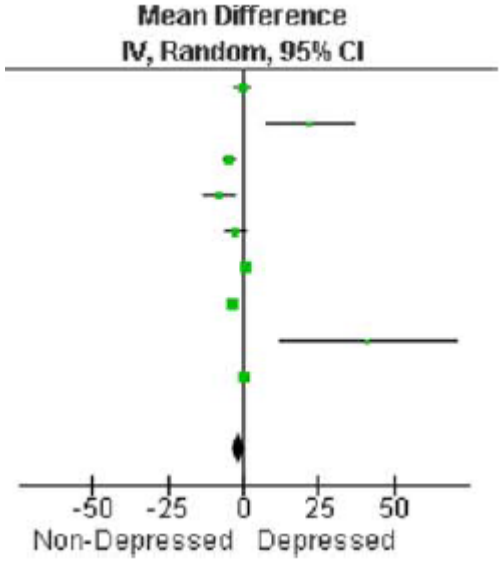
each dot represents one study

TNF cannot be used as a biomarker
but in overall, it is increased

Overall effect: p < 0.00001
Heterogeneity: p < 0.00001

heterogeniety: you cant predict what you get from one study to the next study

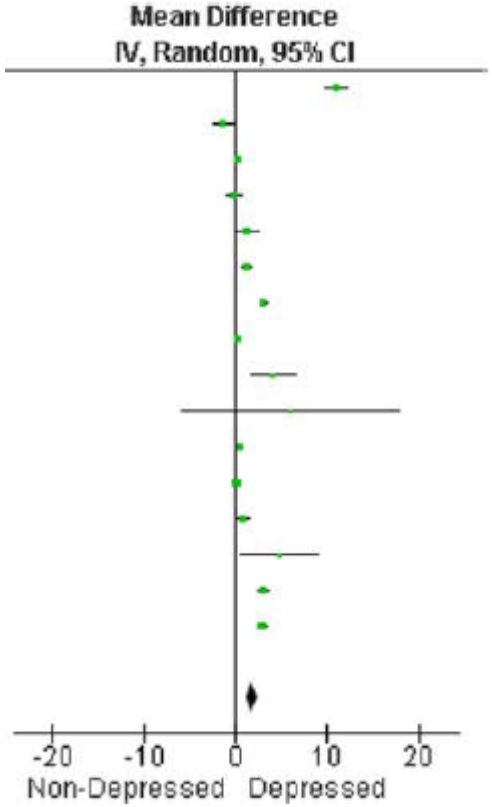
Interleukin 1beta (IL-1β)



no sign diff in IL-1beta

Overall effect: p < 0.12
Heterogeneity: p < 0.00001

Interleukin 6 (IL-6)

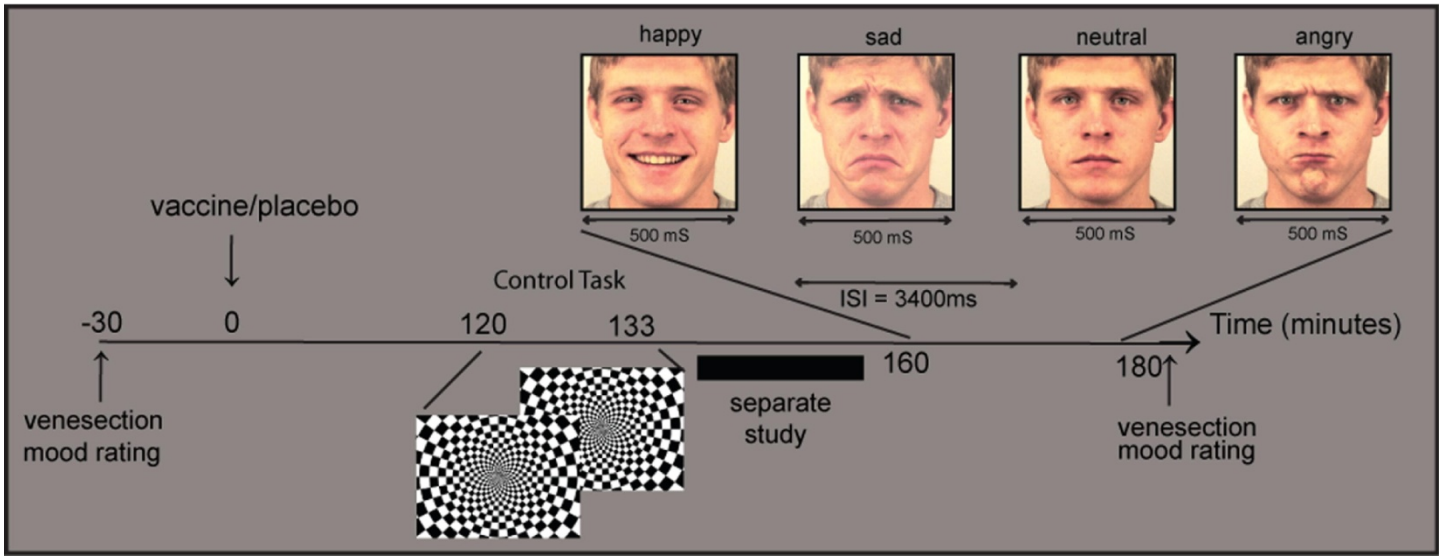


Overall effect: p < 0.00001
Heterogeneity: p < 0.00001

so here, TNFalpha and IL-6 are sign increased in depressed patients

Dowlati et al (2010) Biol Psychiatry 67: 446

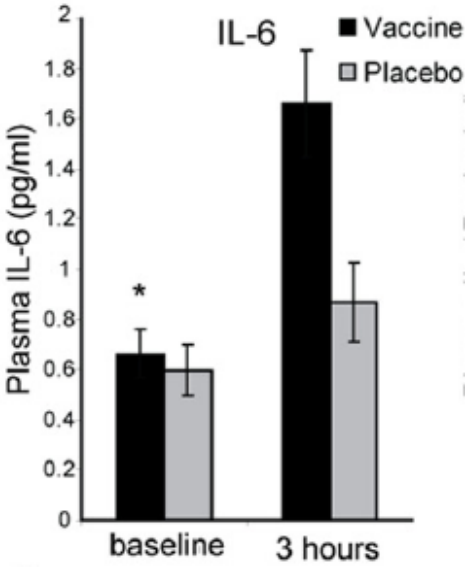
Salmonella typhi-induced inflammation increases Anterior Cingulate Cortex reactivity and lowers mood

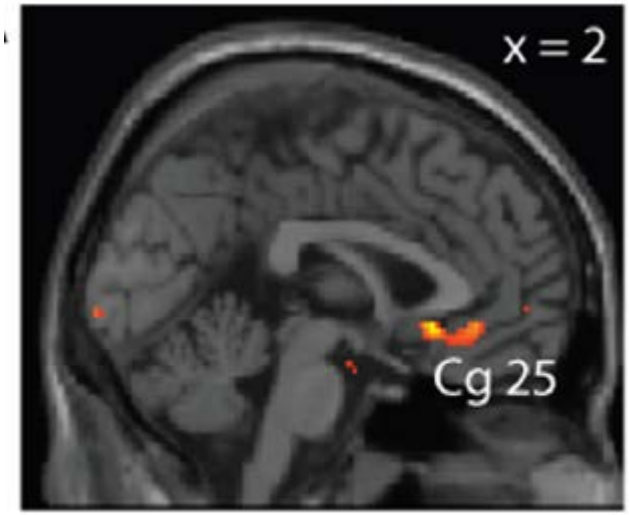


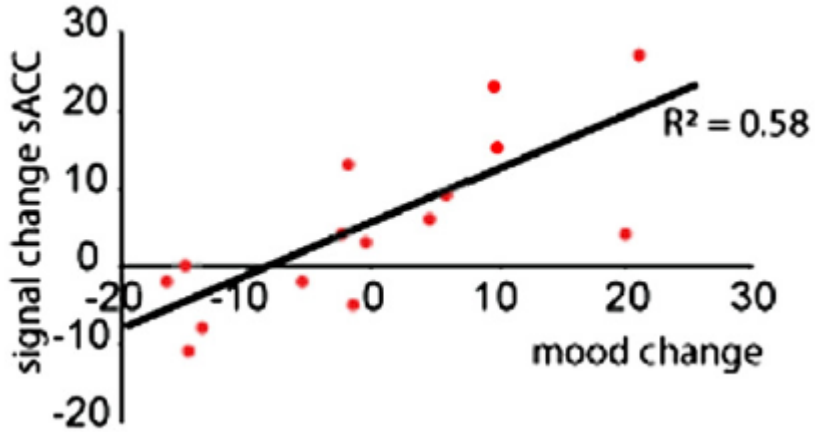
Vaccine group specifically:

Net response to [emotional - neutral] faces increased in subgenual ACC

Depression-like mood predicted by sg ACC net response [emotional - neutral] faces

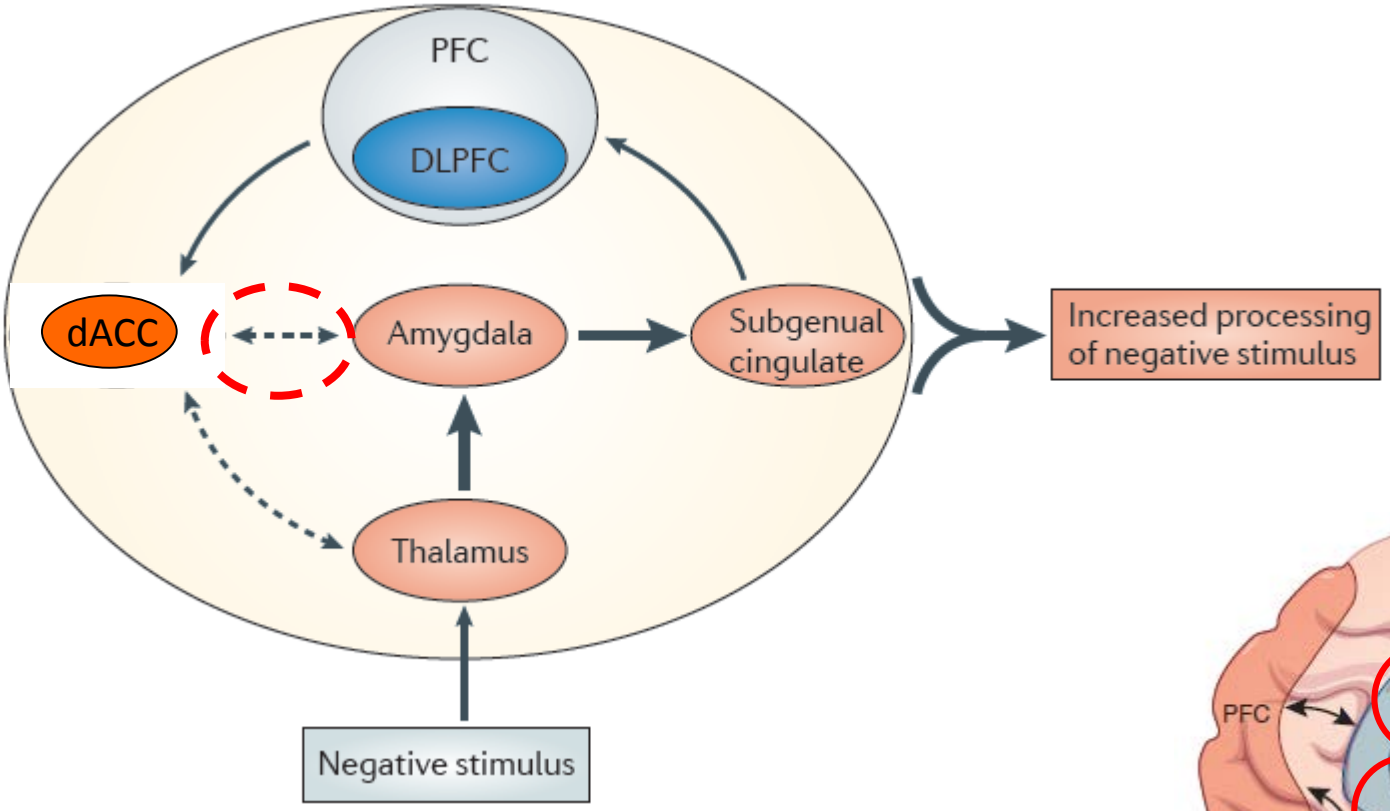




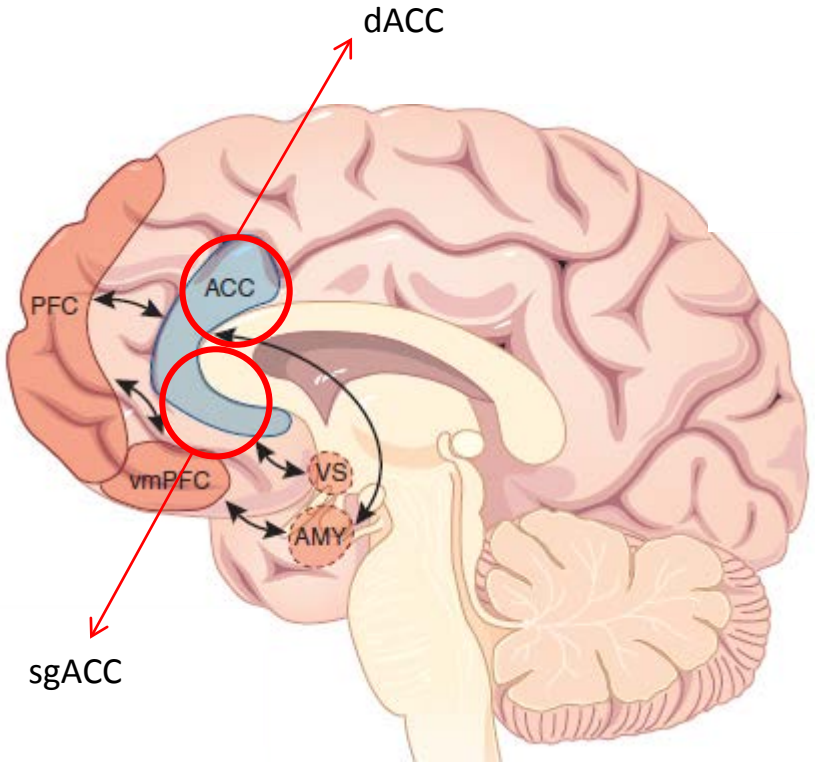


Harrison et al. (2009) Biol Psychiatry 66: 407, 415

Neurocircuitry model of processing aversive stimuli in Depression based on fMRI findings



ACC, Anterior cingulate cortex
dACC, dorsal ACC
sgACC, Subgenual ACC (Subgenual cingulate)
PFC, Prefrontal cortex
VS, ventral Striatum



Hyper-active region in MDD

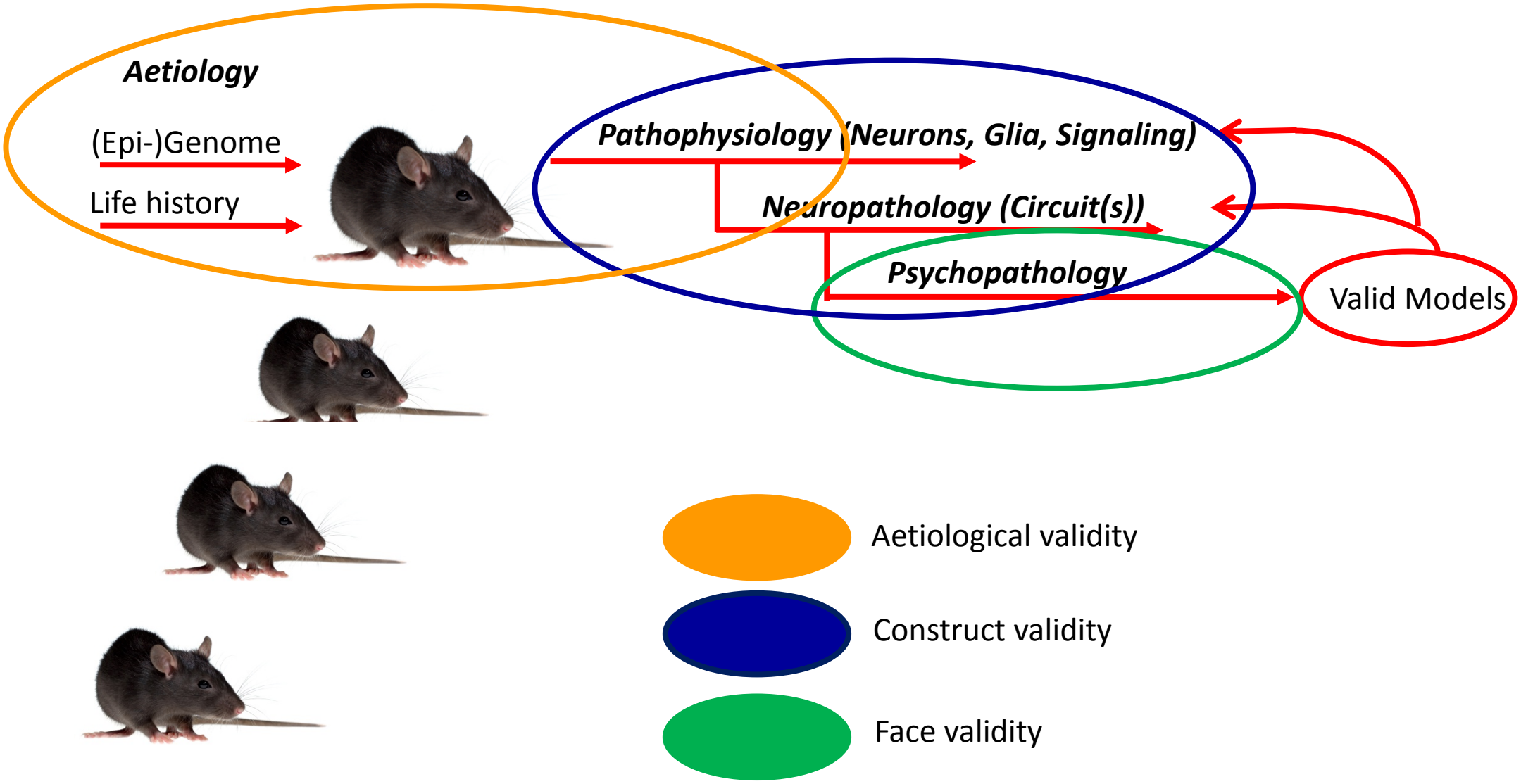
Hypo-active region in MDD

Intact connectivity

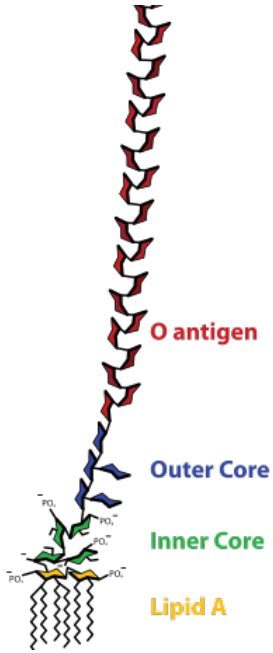
Reduced connectivity

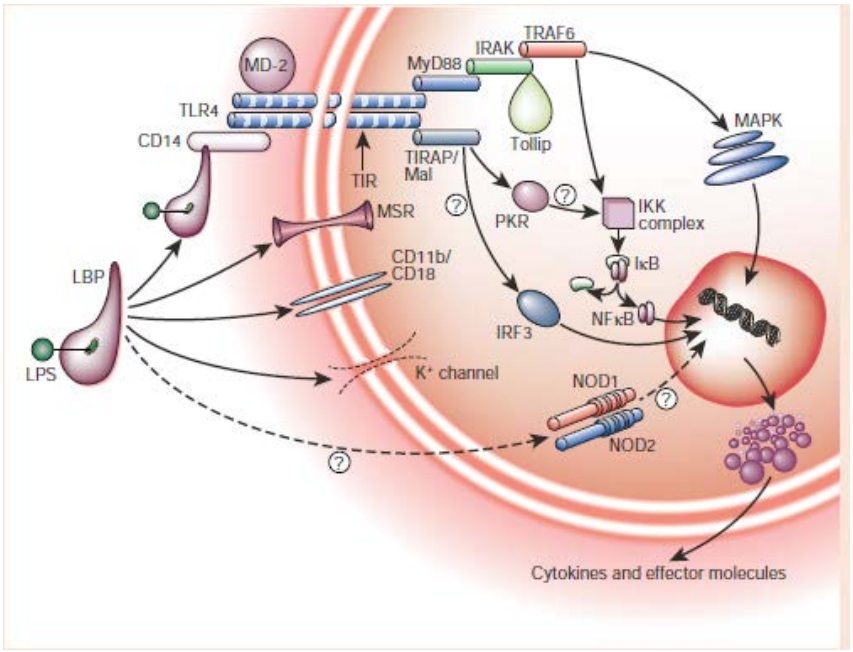
Disner et al (2011) Nature Rev Neurosci 12: 467

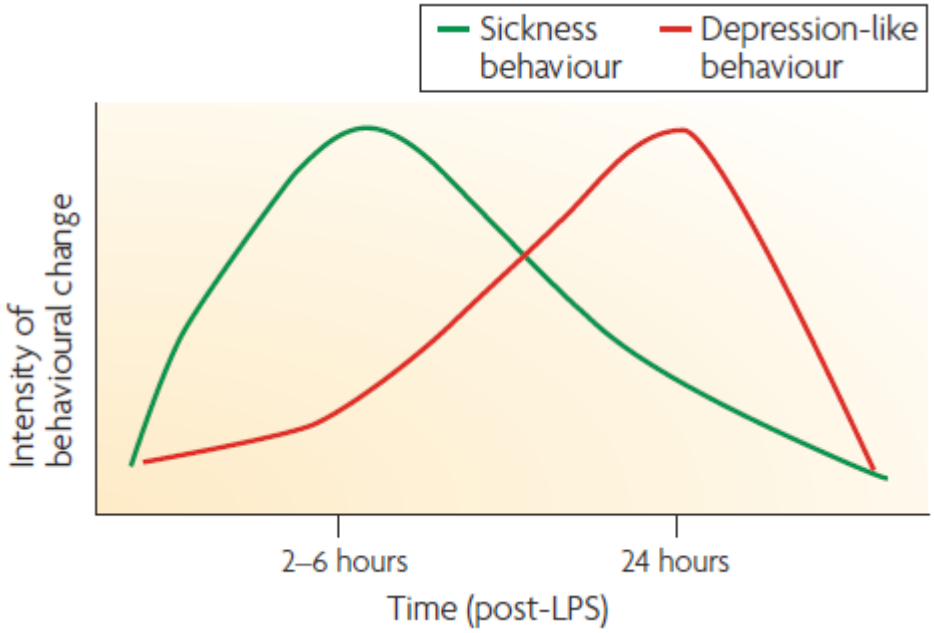
Animal models must have validity



Inflammation-induced sickness behaviour syndrome and depression-relevant behaviour: Lipopolysaccharide (Endotoxin)







Lipid+Polysaccharide
Outer membrane, Gram-negative bacteria
TLR4, Toll-like receptor 4

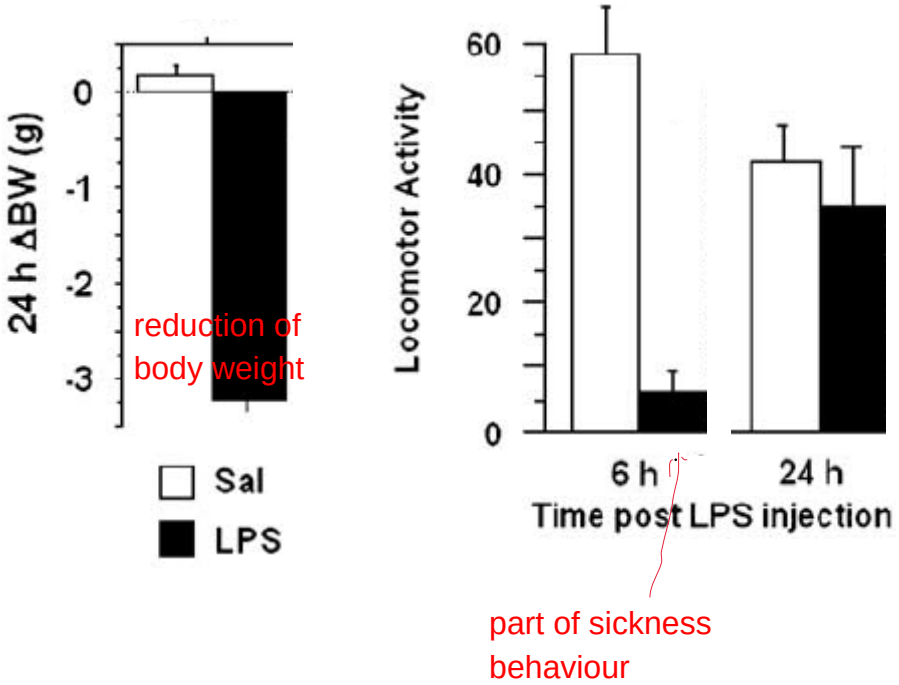
Lipopolysaccharide → ↑IL-1β, ↑TNF → **Sickness behaviour syndrome (SBS):**
Fever
Anorexia reduction in feeding and drinking
Increased sleep
Social withdrawal
Fatigue

Lipopolysaccharide → ↑IL-1β, ↑TNF → **Depression-relevant behaviour:**
Forced swim test floating
Sucrose preference
Operant behaviour for reward

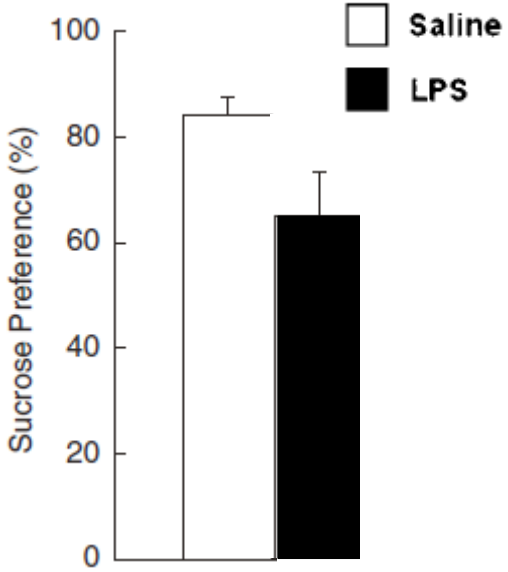
Dantzer et al. (2008) Nature Rev Neuroscience 9: 46

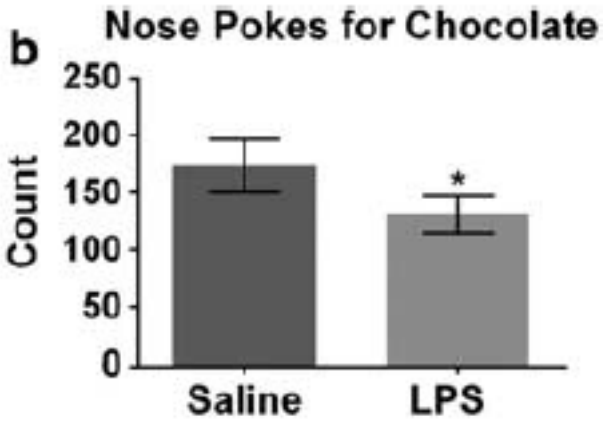
Inflammation-induced sickness behaviour syndrome and depression-relevant behaviour: Lipopolysaccharide

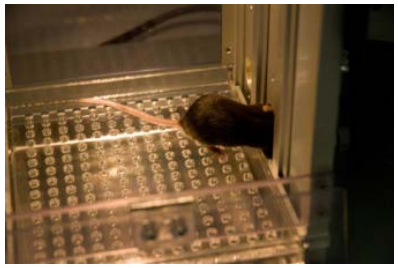
Sickness behaviour syndrome (SBS)



Depression-relevant behaviour

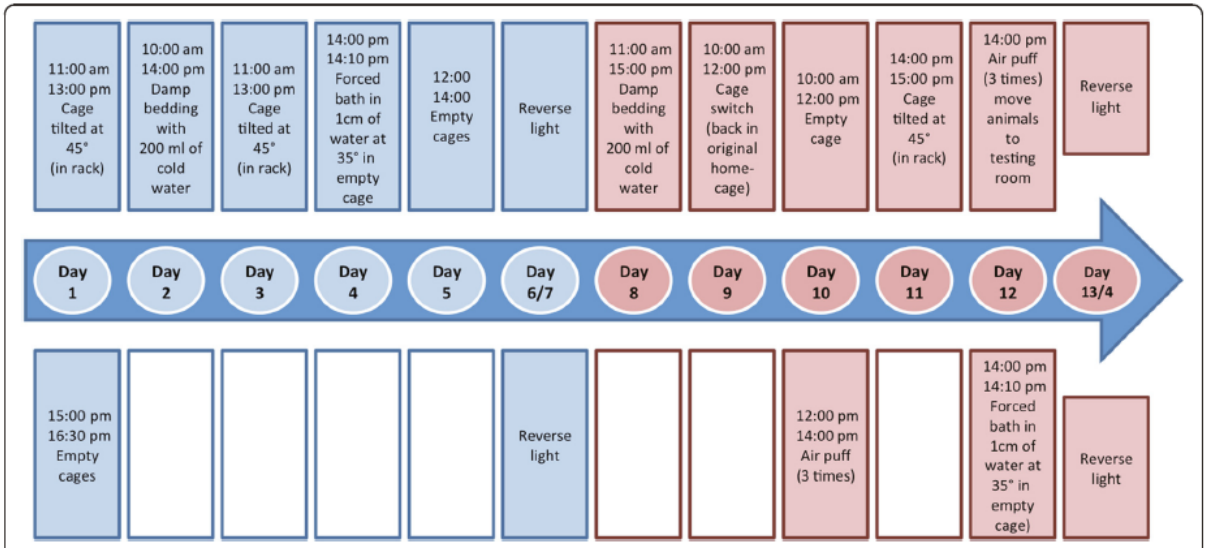






O'Connor et al. (2009) Mol Psychiatry 14: 511
Walker et al. (2013) Neuropsychopharmacol 38: 1609
Vichaya et al. (2014) Neuropsychopharmacol 39: 2884

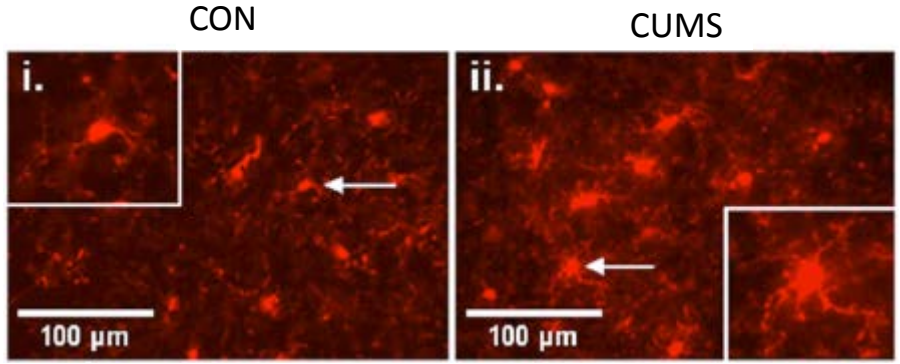
CUMS-induced Inflammation and depression-relevant behaviour: Cytokines and Microglia



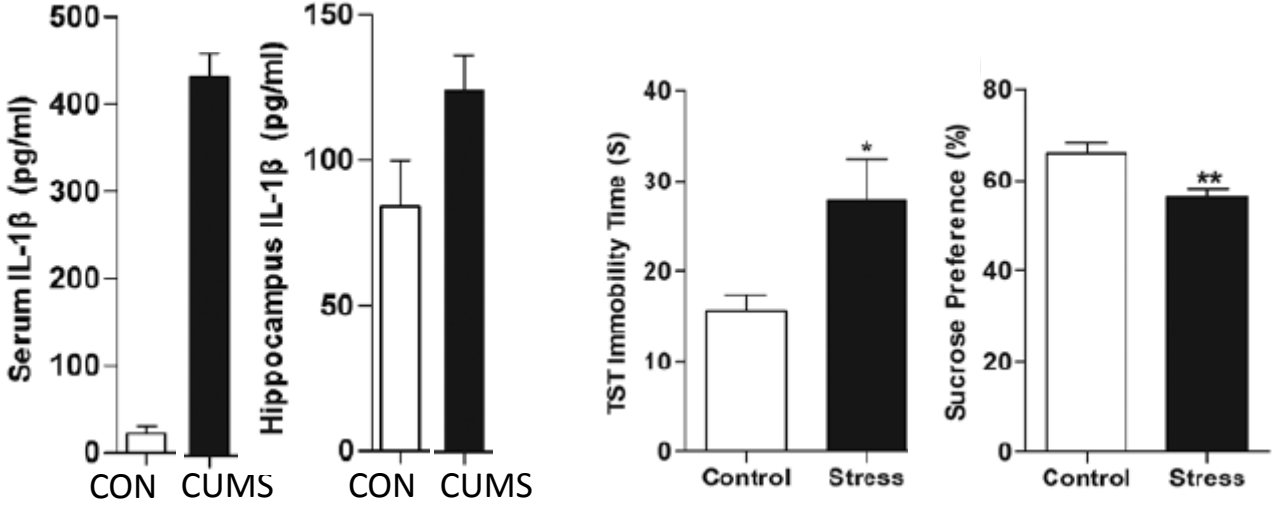
specific for microglia - gives and indication how active microglia are

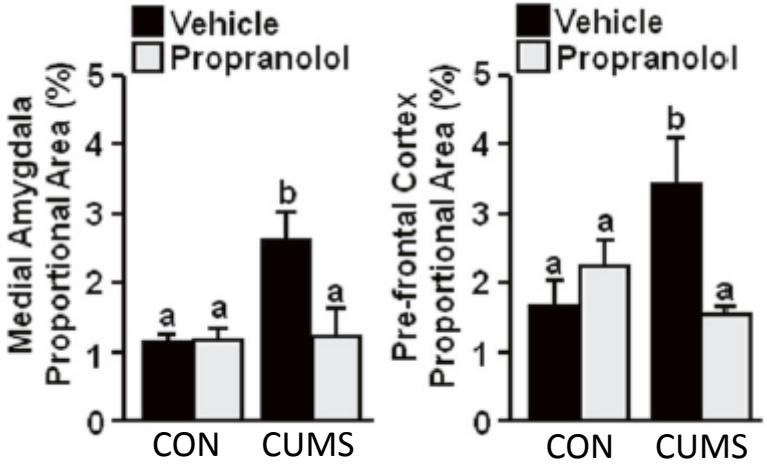
Microglia:

Ionized calcium-binding adapter molecule 1 (Iba1)



β1, β2 Adrenoreceptor Antagonist





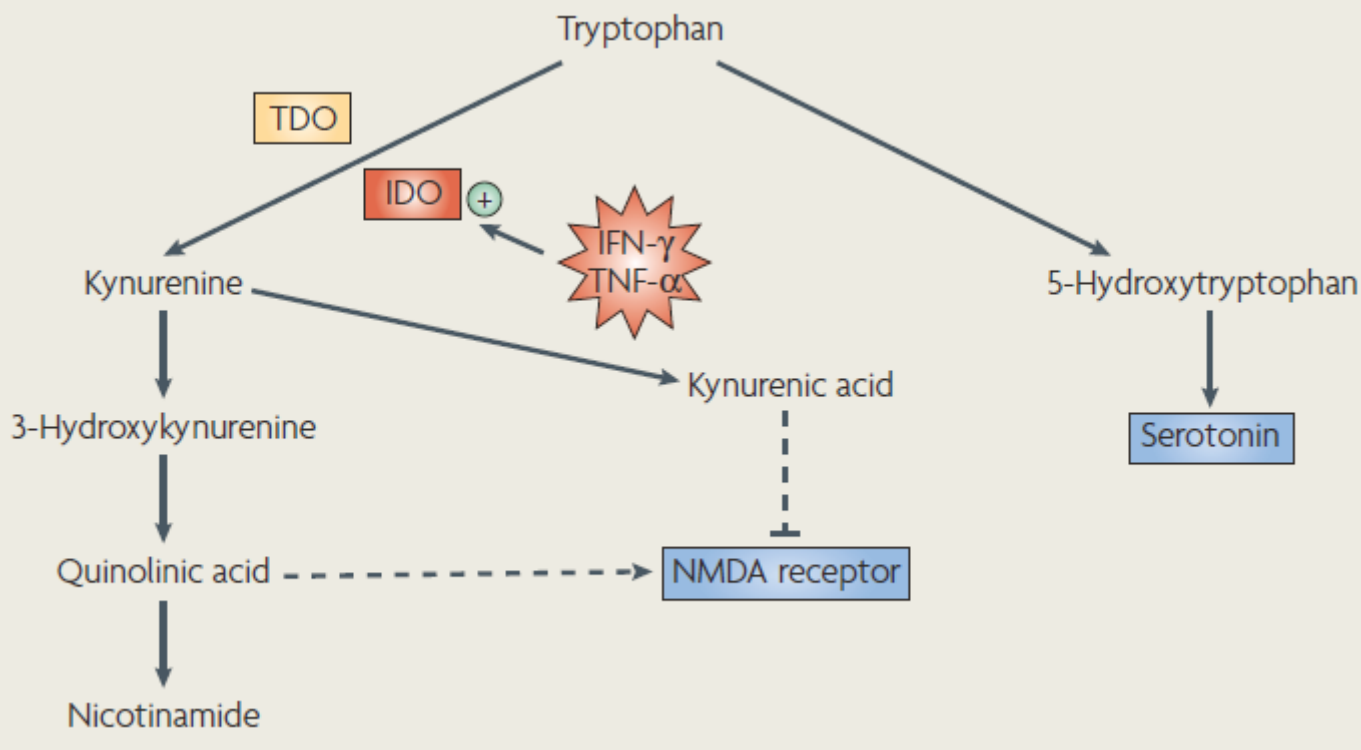
TST := tail suspension test - how long does the mouse struggle, when does it stop

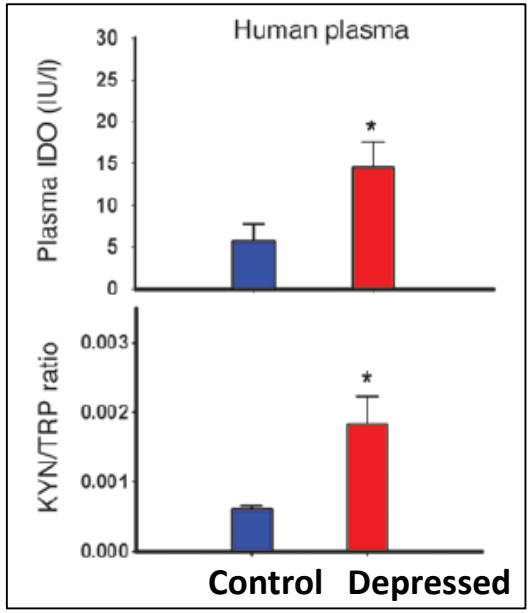
Zhang et al. (2015) Int J Neuropsychopharmacol

Wohleb et al. (2013) J Neuroscience 31: 6288

Stress – Cytokines - Kynurenine Pathway

in the presence of pro inflamm cytokines, tryptophan is eventually made into kynurenine





IDO = Indoleamine 2,3 dioxygenase

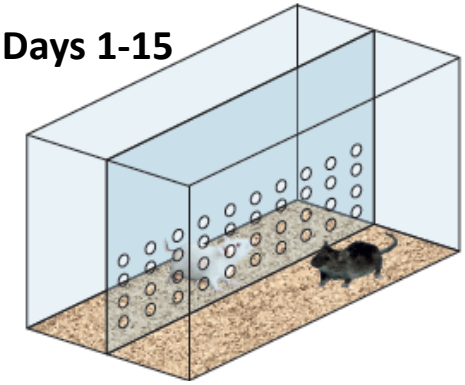
this pw is activated in depression

Dantzer et al. (2008) Nature Rev Neuroscience 9: 46
Kim et al. (2012) J Clin Invest 122: 2940

Mouse Chronic social defeat (CSD) and Depression-relevant Behaviour

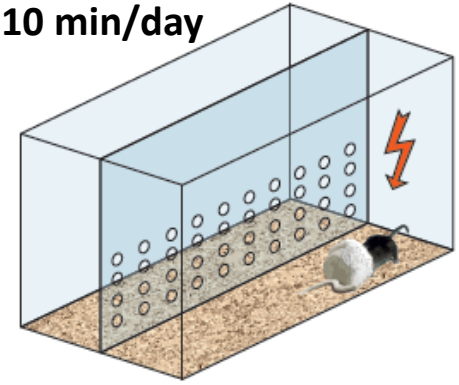
Chronic social defeat (CSD)

Days 1-15



Threat:
Visual
Olfactory
Auditory

10 min/day



Threat+Attack:
Physical
No wounds

Lack of social control
= Helplessness

Stress Systems:
Neuroendocrine
Autonomic
Neuro-immune

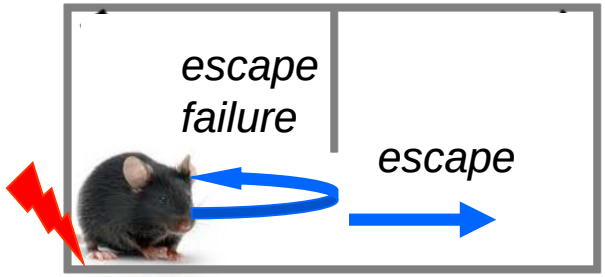
Aetio-Pathophysiology

Neurocircuit Pathology

Behaviour

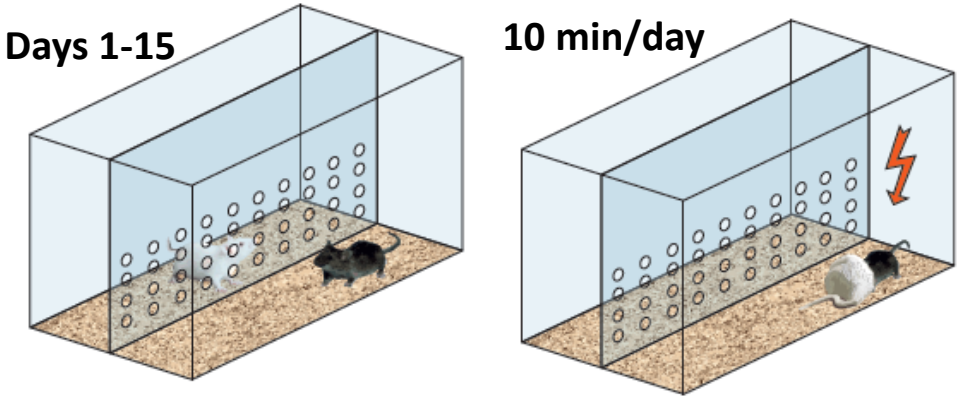
Fear Conditioning

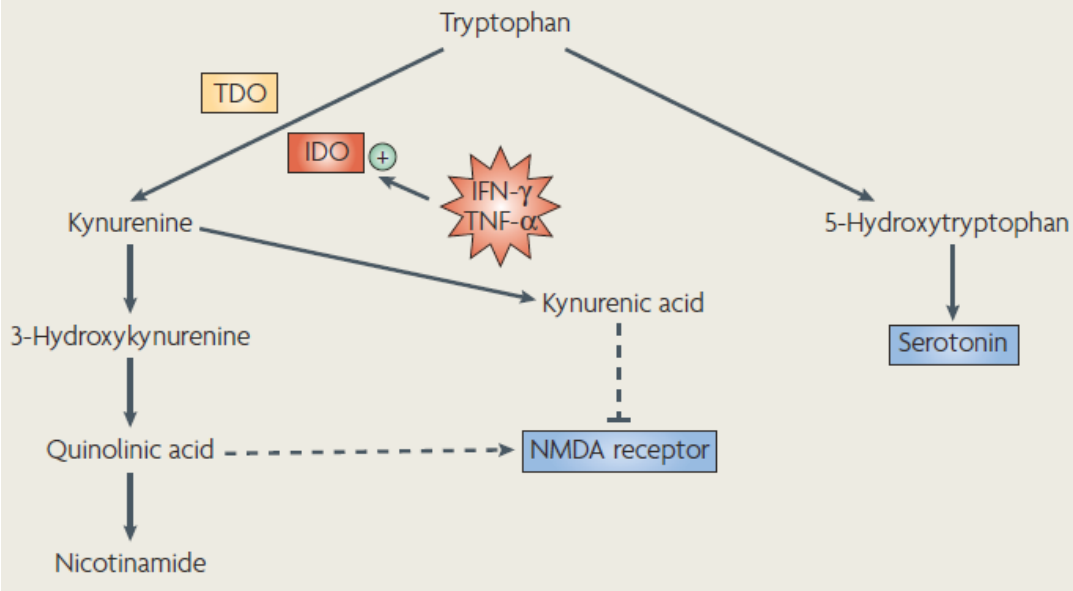
Helplessnesss



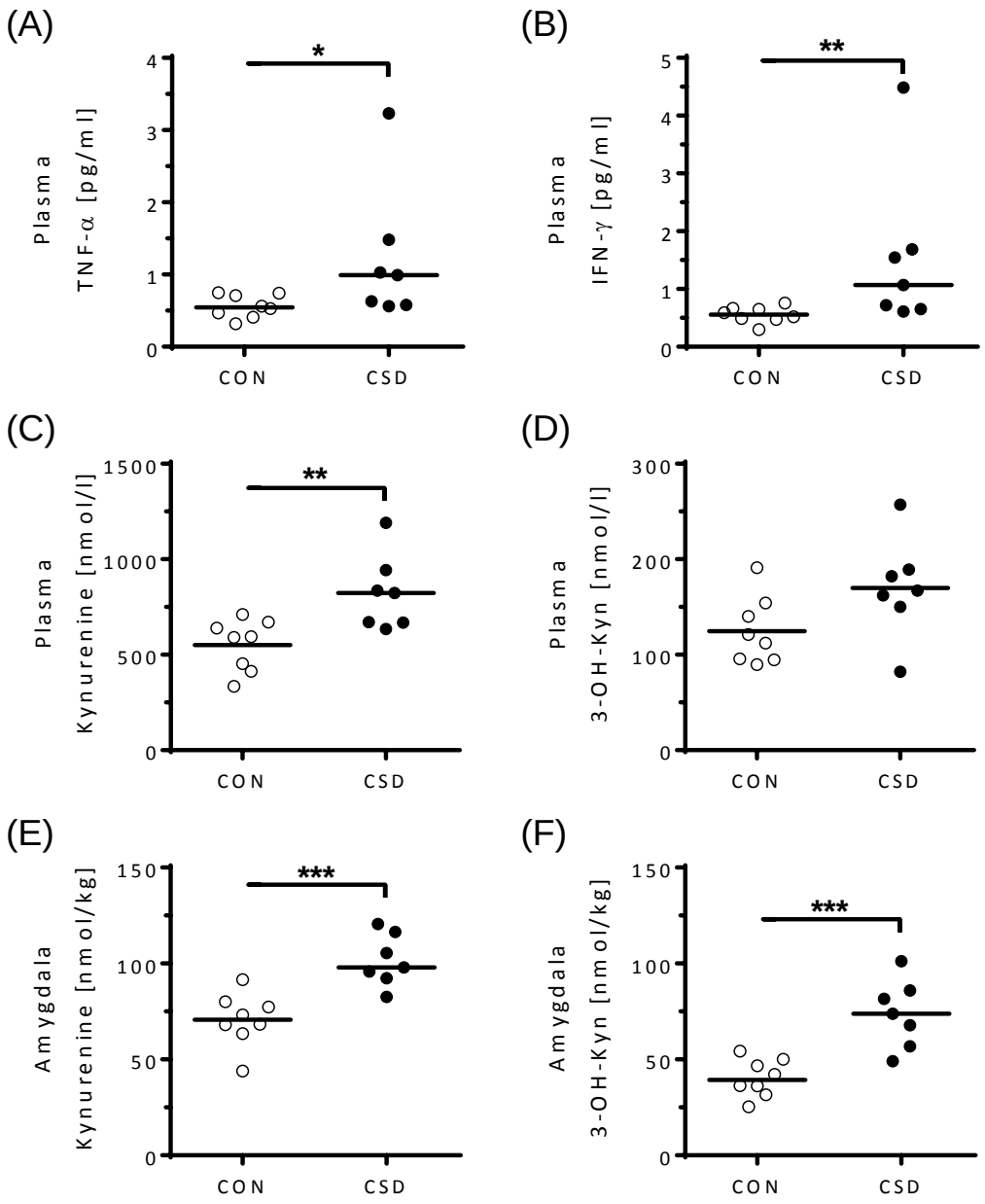
Mouse CSD and Immune-inflammation: Cytokines and Kynurenine Pathway

Chronic social defeat (CSD)





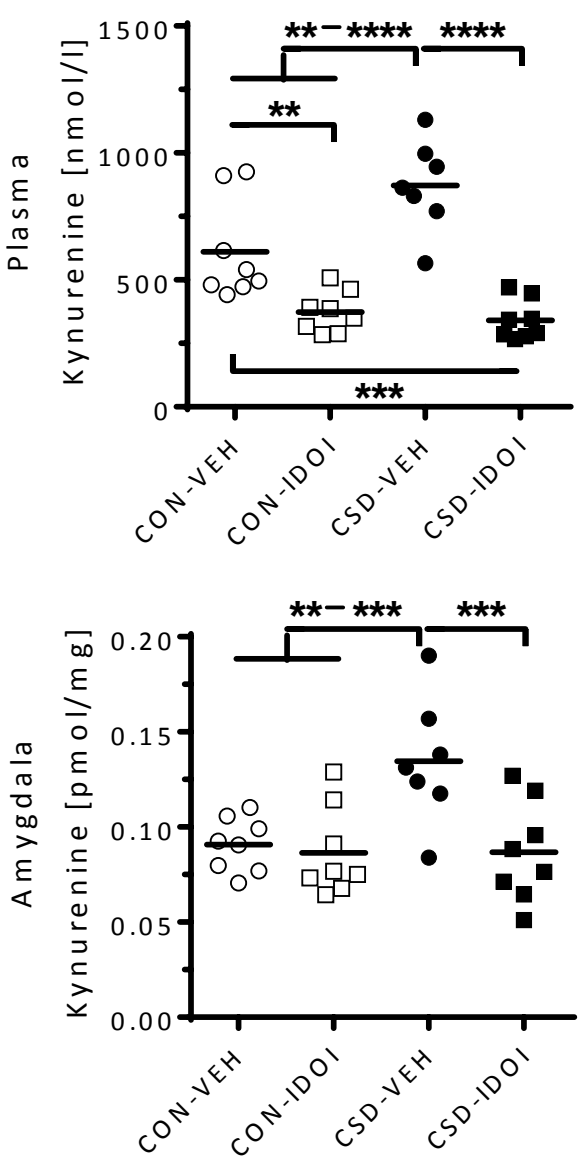
Inflammatory markers

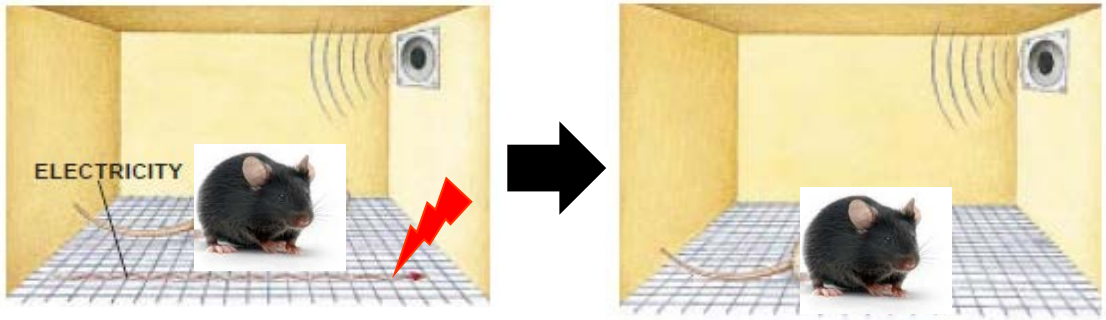


Fuertig et al (2016) Brain, Behavior, Immunity 54: 59

Kynurenine pathway contributes to CSD-induced Hyper-fear expression

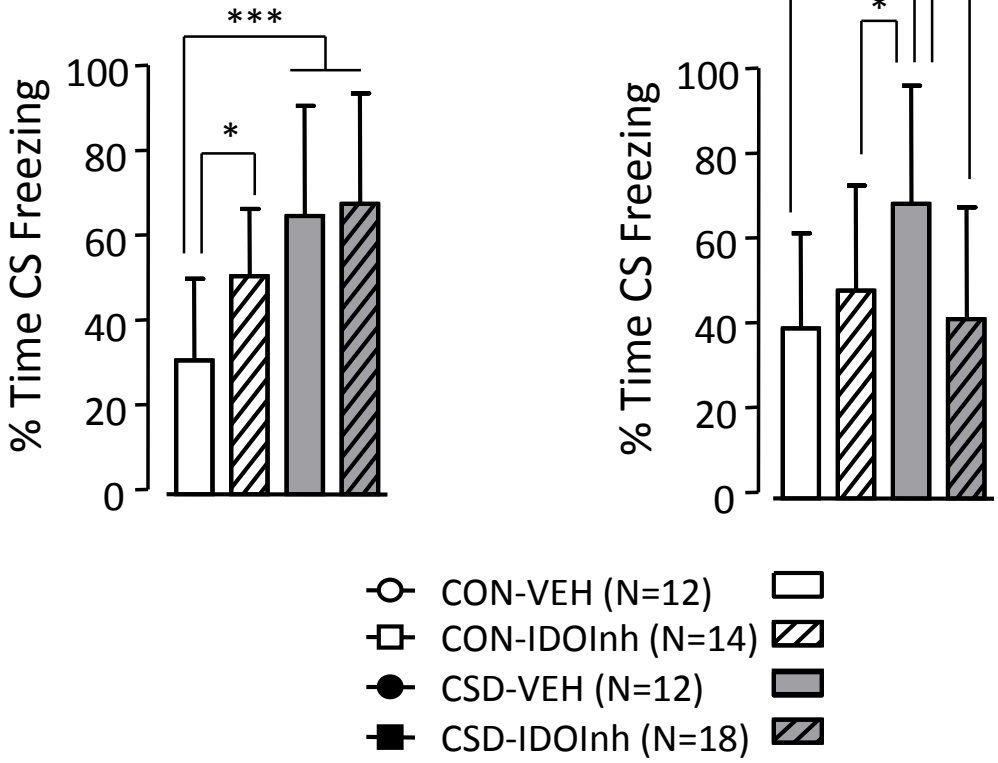
Pharmacological kynurenine-pathway inhibition restores normal fear





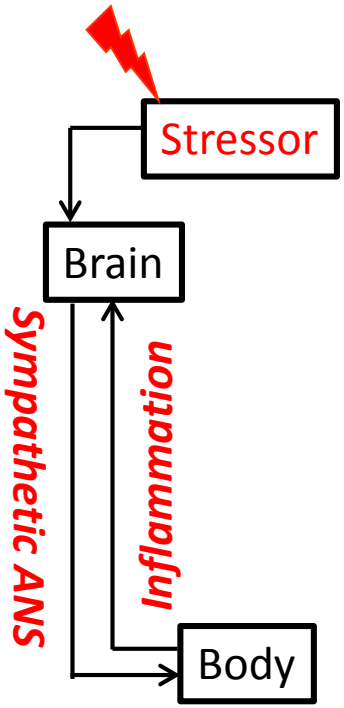
Day 16: Fear Conditioning

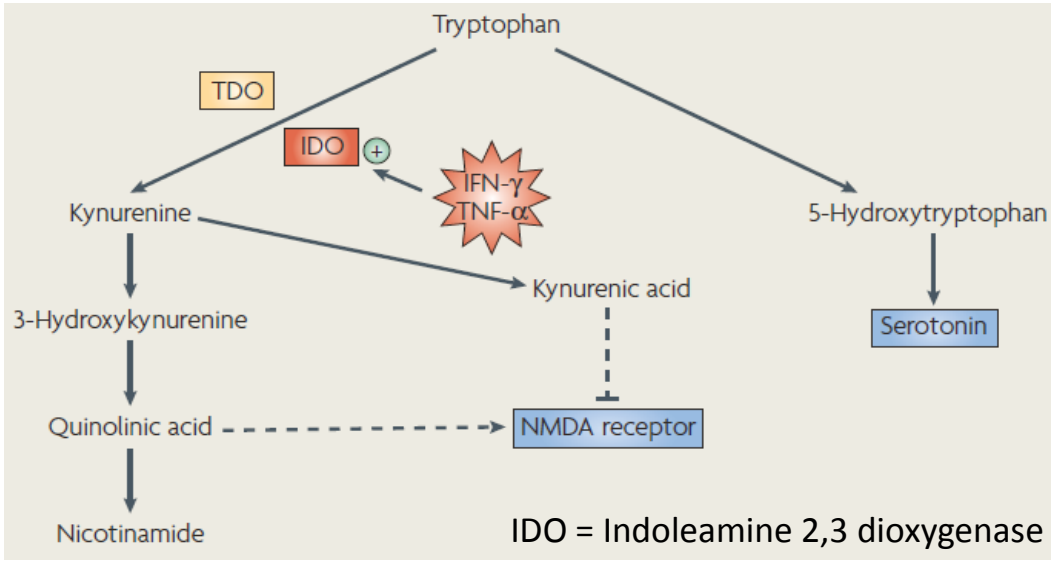
Day 17: Fear expression test



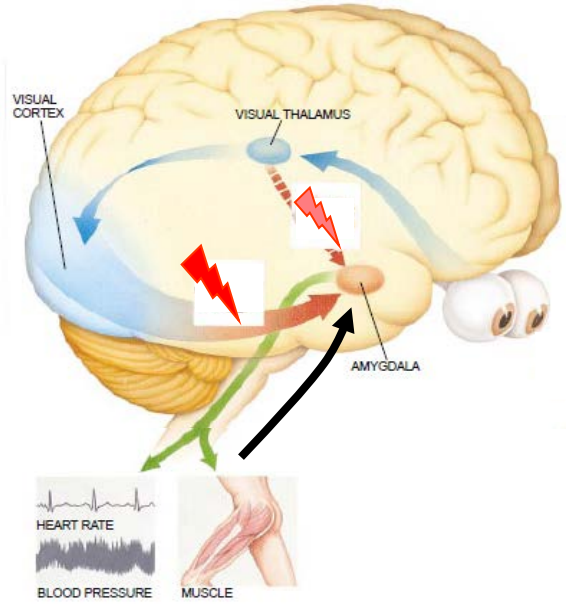
Fuertig et al (2016) Brain, Behavior, Immunity 54: 59

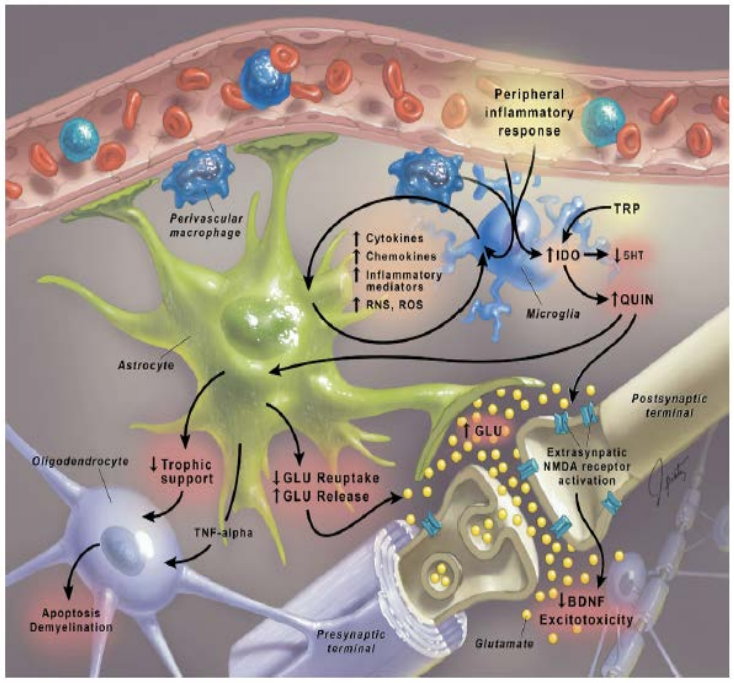
The stress-induced inflammatory response accesses the Brain: The Kynurenine Pathway





IDO = Indoleamine 2,3 dioxygenase



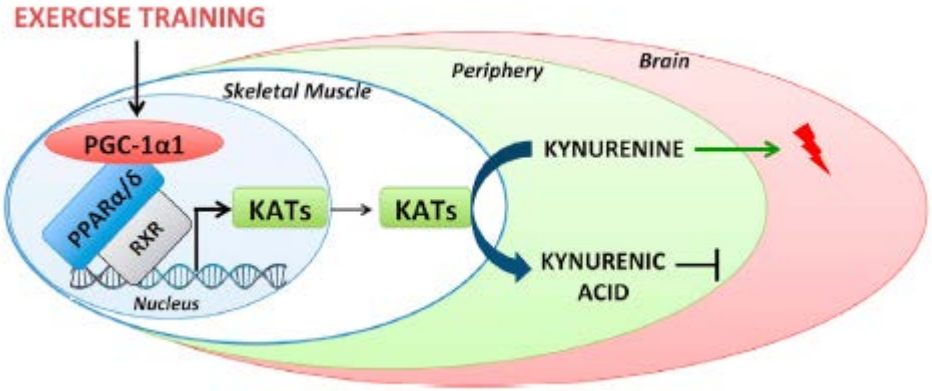


Miller et al. (2009) Biol Psychiatry 65: 732

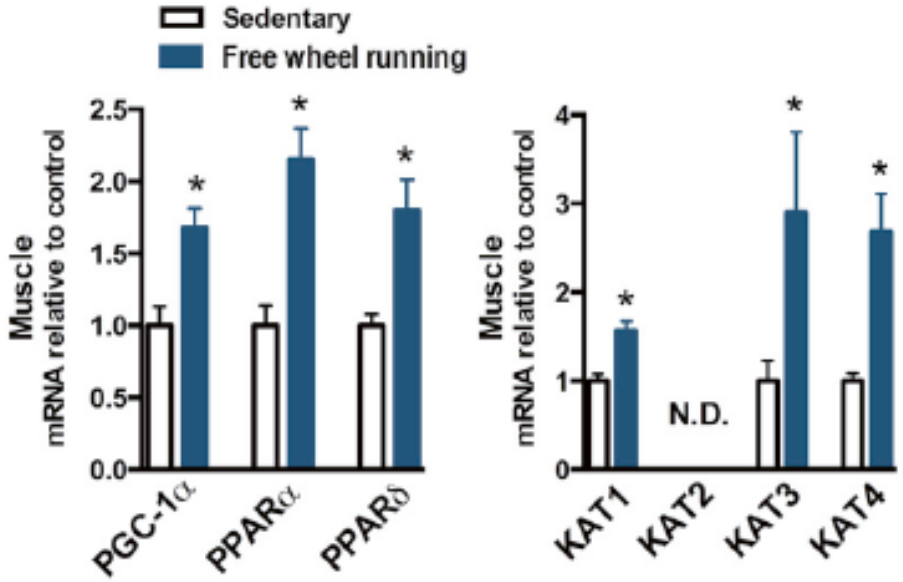
Dantzer et al (2008) Nature Rev Neuroscience 9: 46

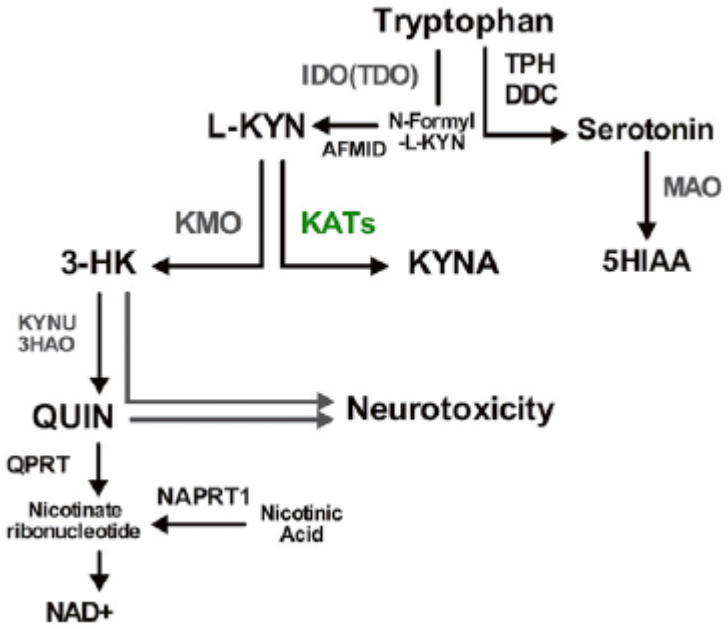
Skeletal muscle activation of kynurenine aminotransferases leads to shift in Kynurenine pathway

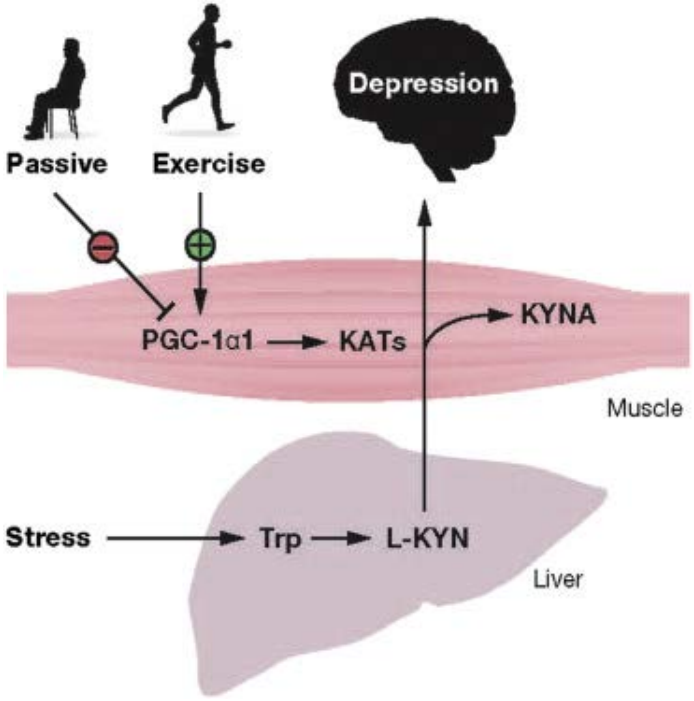
exercise makes kynuerine to kynueric acid which does not lead to increase in depression, so exercise protects

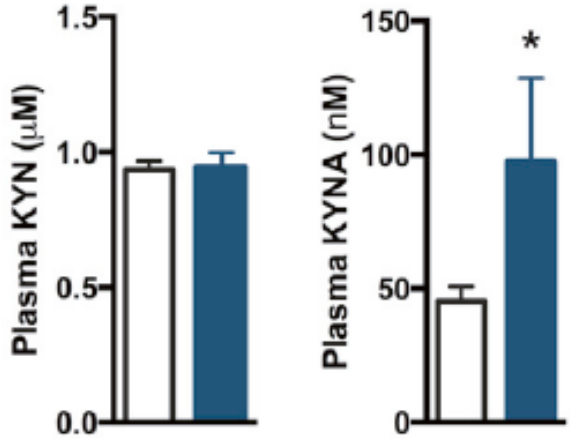


- PGC-1α1: Transcription co-activator
- Peroxisome proliferator-activated receptors (PPARα/δ): Transcription co-activator for genes involved in oxidative metabolism
- Retinoid X receptor (RXR): Transcription factor
- Kynurenine aminotransferases (KATS)



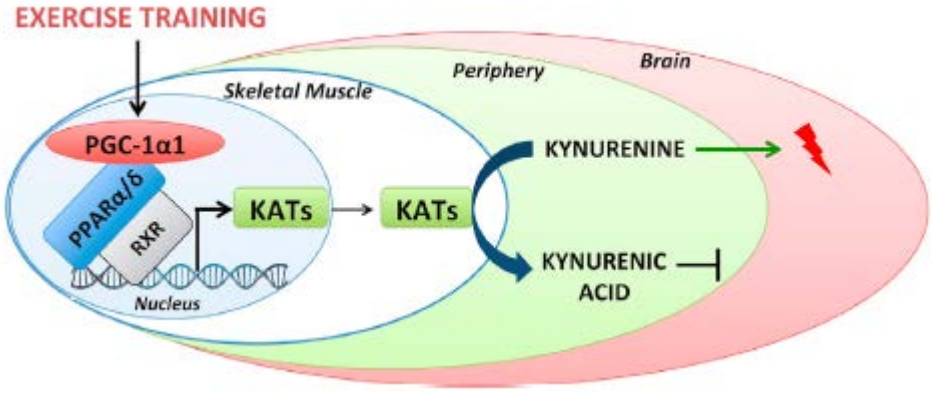


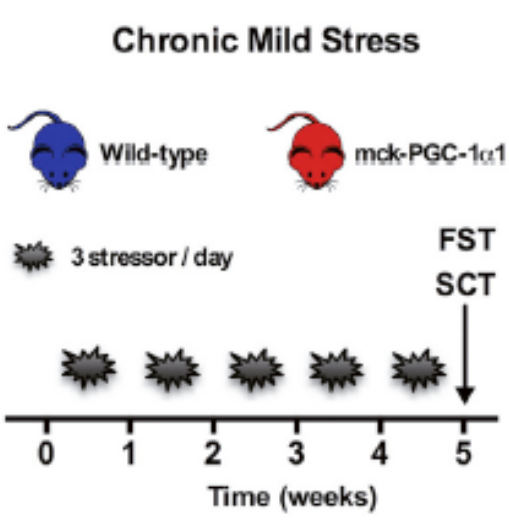


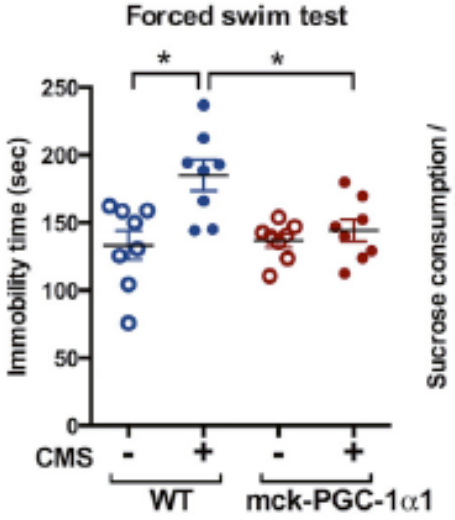


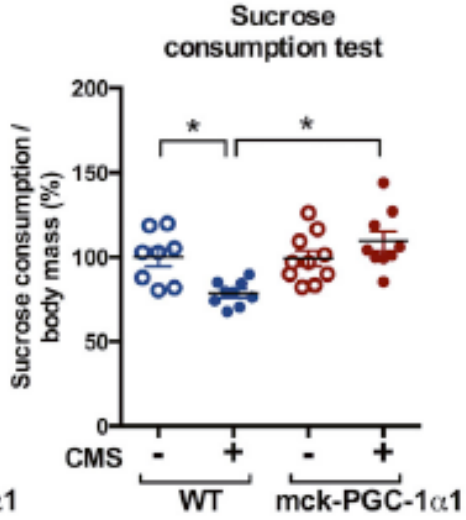
Agudelo et al. (2014) Cell 159: 33

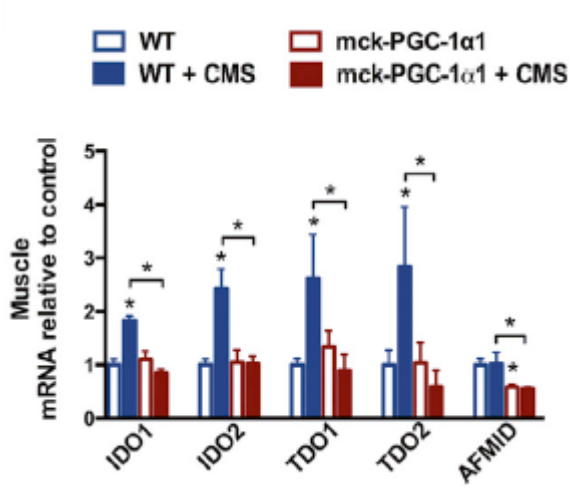
Mouse skeletal muscle-specific PGC-1α1 overexpression protects against CUMS effects on Kynurenine pathway AND Depression-relevant behaviour

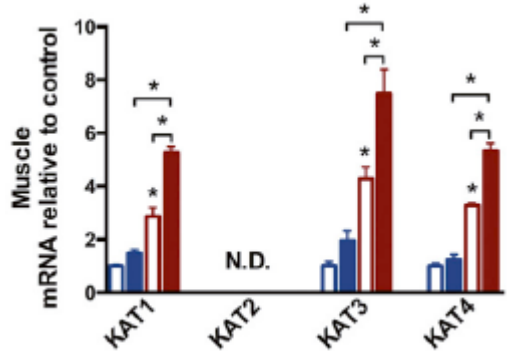


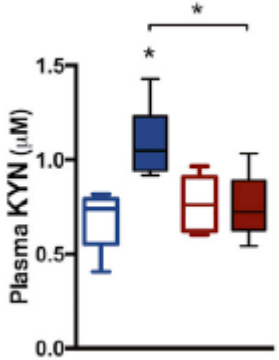


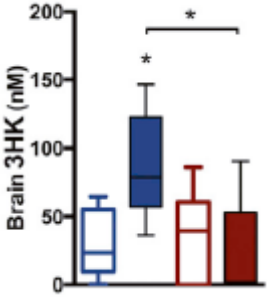






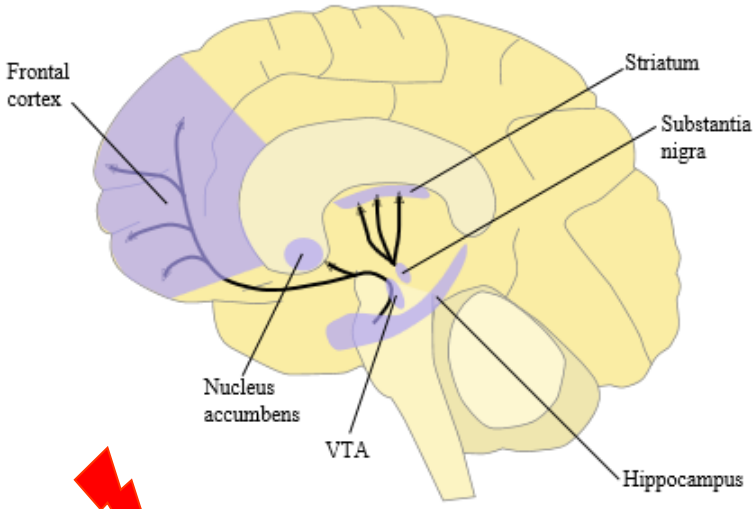


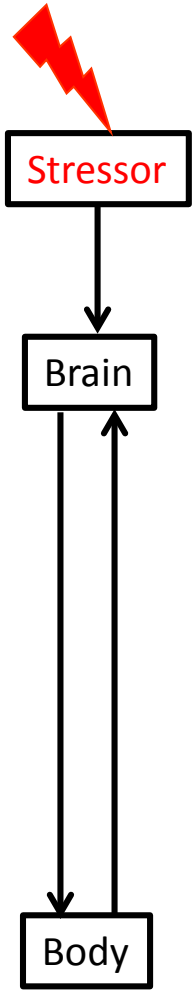


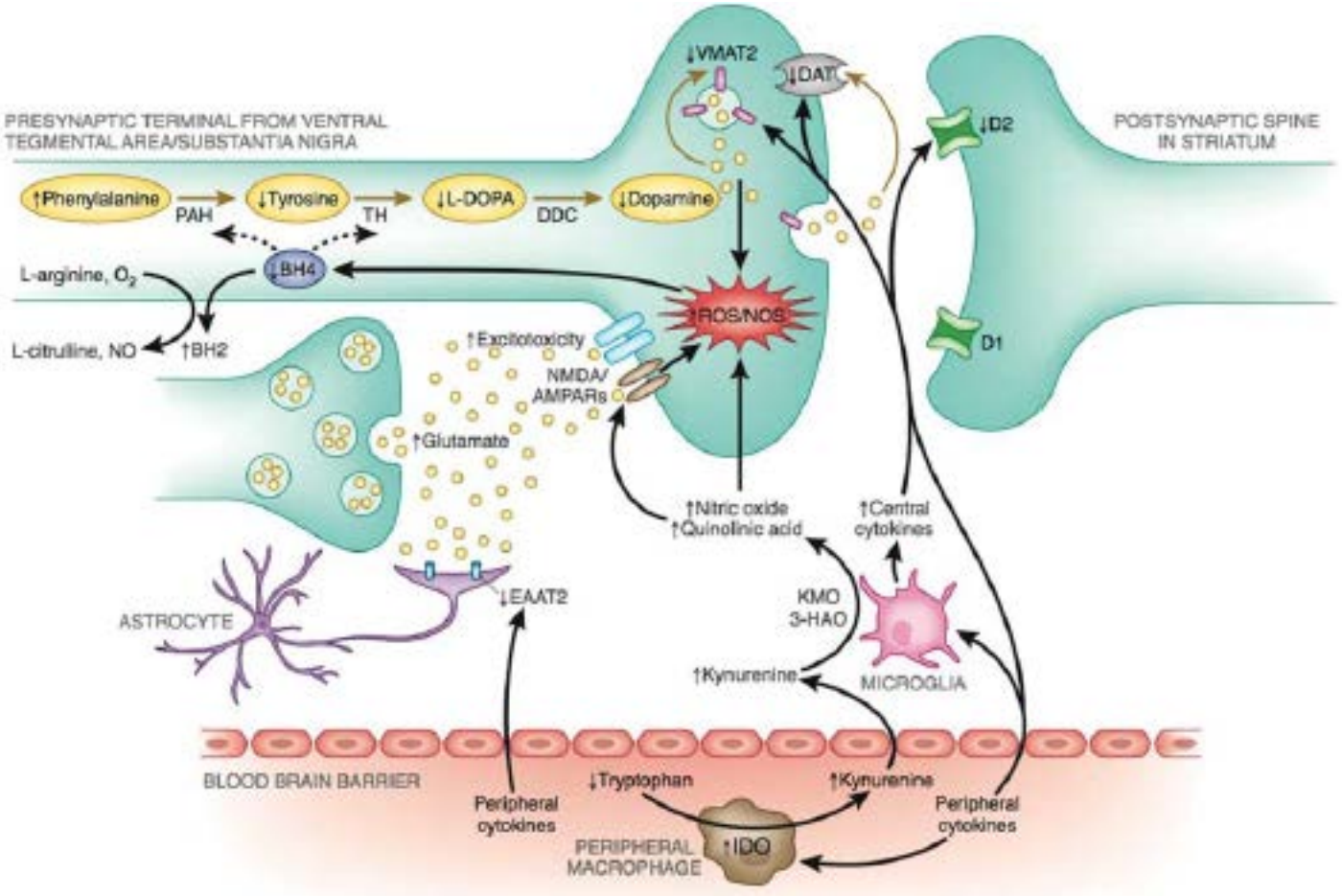


Agudelo et al. (2014) Cell 159: 33

Kynurenine Pathway inhibits Dopamine and Serotonin Neurotransmission







Felger & Treadway (2017) Neuropsychopharmacology 42: 216

Immune system and depression

- Stress processing by the CNS (NB. amygdala) can activate the immune-inflammation system in the body
- Sympathetic branch of the autonomic nervous system innervates important immune structures that express noradrenergic receptors on immune cells e.g. macrophages
- Nuclear factor κβ is a transcription factor for multiple pro-inflammatory cytokines and chemokines
- Cytokines are the messengers of the immune system
- Peripheral activation of inflammation stimulates inflammation pathways in the CNS
- Several lines of evidence that depression is associated with activation of the immune system
- Activation of inflammation stimulates depression-relevant mood states in healthy human subjects
- Inflammation induces sickness behaviour syndrome followed by depression-relevant behaviour in animals
- Activation of LPS signalling induces a short period of sickness and a longer period of anhedonia
- Rat/Mouse chronic unpredictable mild stress (CUMS) induces inflammation in periphery and brain
- Mouse chronic social defeat (CSD) induces inflammation in periphery and brain
- Stress-cytokine-kynurenine pathway is one pathway via which stress can activate inflammation processes in the CNS
- The products of the kynurenine pathway can inhibit synthesis and release of dopamine and serotonin