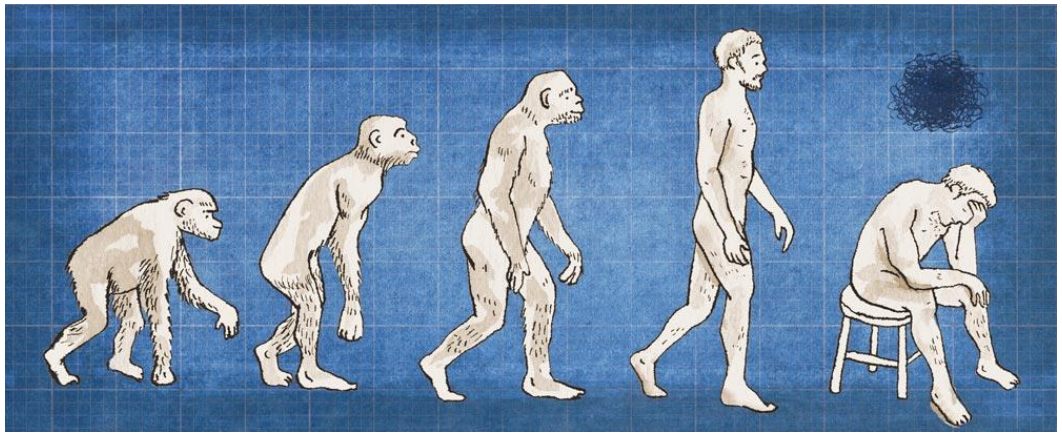
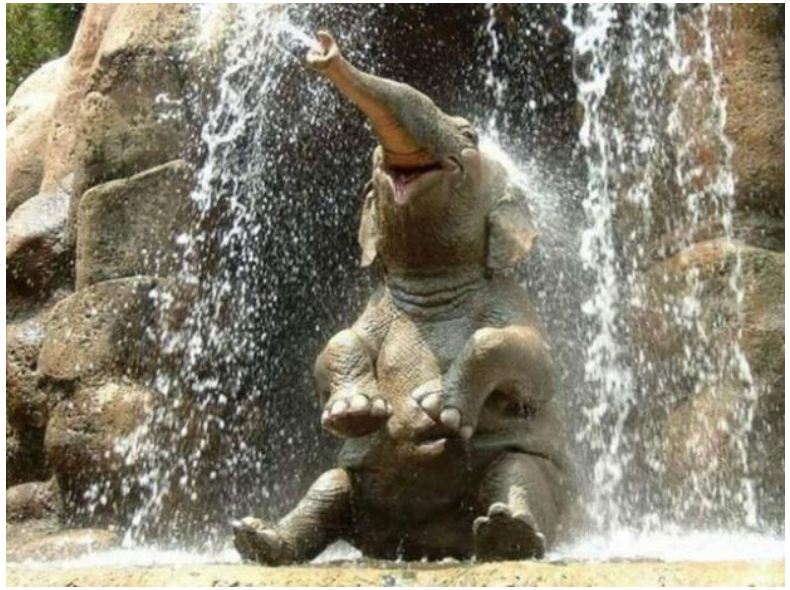
# An evolutionary model of depression

Markus J Rantala

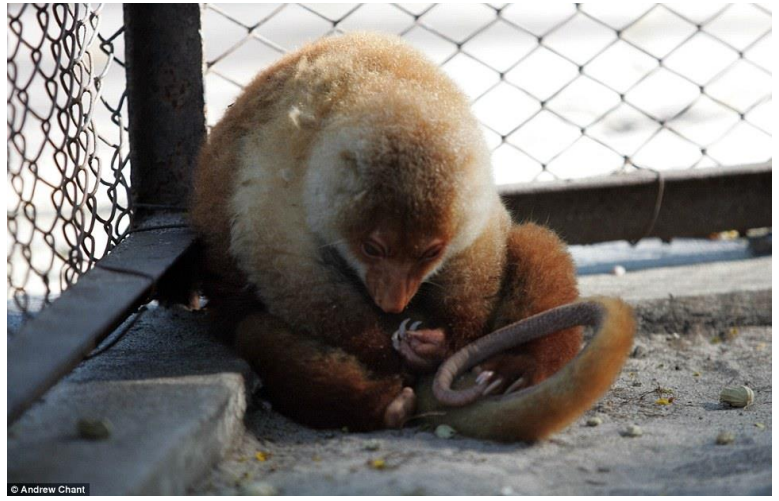
University of Turku



# Do animals get depressed?



# Depression is common in captivity




# Insects have emotions

- Unexpected rewards make bees optimistic
- Agitated honeybees become pessimistic.

Video:

http://www.cell.com/current-biology/abstract/S0960-9822%2811%2900544-6

COGNITION

**Unexpected rewards induce dopamine-dependent positive emotion–like state changes in bumblebees**

Clint J. Perry,* Luigi Baciadonna, Lars Chittka

Whether invertebrates exhibit positive emotion–like states and what mechanisms underlie such states remain poorly understood. We demonstrate that bumblebees exhibit dopamine-dependent positive emotion–like states across behavioral contexts. After training with one rewarding and one unrewarding cue, bees that received pretest sucrose responded in a positive manner toward ambiguous cues. In a second experiment, pretest consumption of sucrose solution resulted in a shorter time to reinitiate foraging after a simulated predator attack. These behavioral changes were abolished with topical application of the dopamine antagonist fluphenazine. Further experiments established that pretest sucrose does not simply cause bees to become more exploratory. Our findings present a new opportunity for understanding the fundamental neural elements of emotions and may alter the view of how emotion states affect decision-making in animals.

Science, 30 SEPTEMBER 2016 VOL 353 ISSUE 6307

Current Biology 21, 1070–1073, June 21, 2011 ©2011 Elsevier Ltd. Open access under CC BY license. DOI 10.1016/j.cub.2011.05.017

Report

**Agitated Honeybees Exhibit Pessimistic Cognitive Biases**

Melissa Bateson,[1] Suzanne Desire,[1] Sarah E. Gartside,[1] and Geraldine A. Wright[1,*]
[1]Centre for Behaviour and Evolution, Institute of Neuroscience, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK

a manipulation of state, the subjects' judgment is probed by testing their classification of novel stimuli with sensory properties intermediate between the two trained stimuli. A pessimistic cognitive bias is manifested in an increased tendency of subjects to classify stimuli as likely to predict punishment (or a reward of less value). We were able to use the same approach to test for cognitive biases in honeybees because

# Cockroaches developed depression (learned helplessness) when they were tortured with electric shocks.

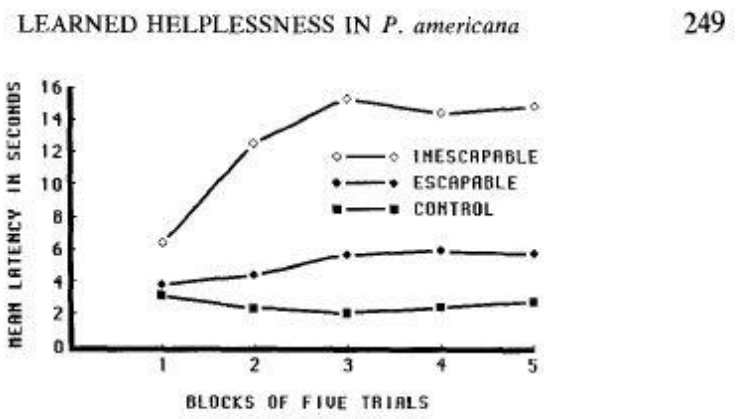
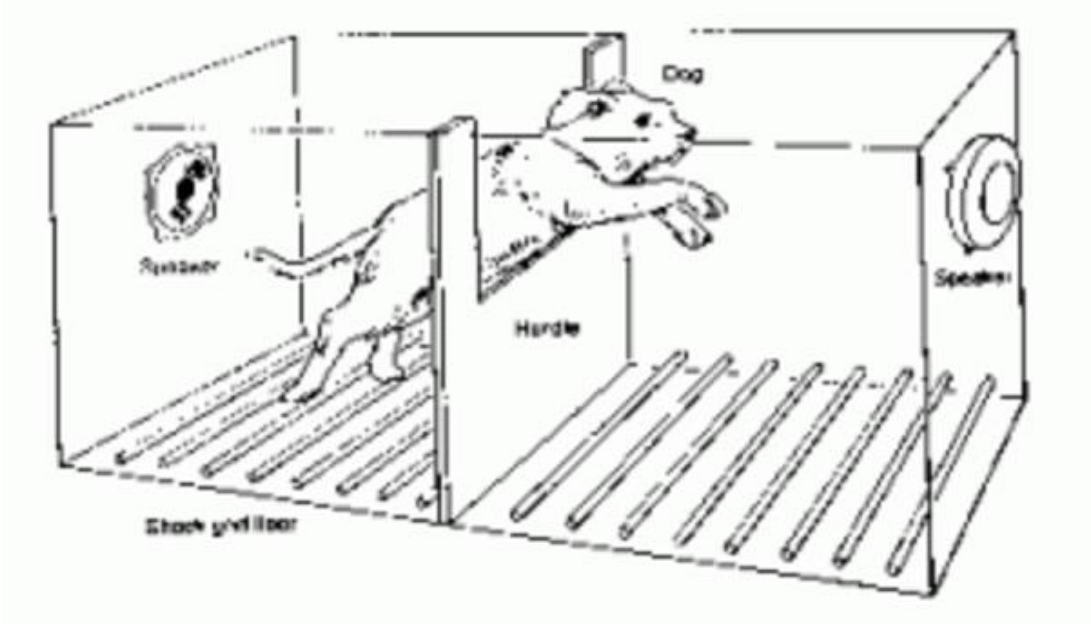



FIG. 1. Mean escape latencies for the escapable shock group, the inescapable shock group, and the control group.

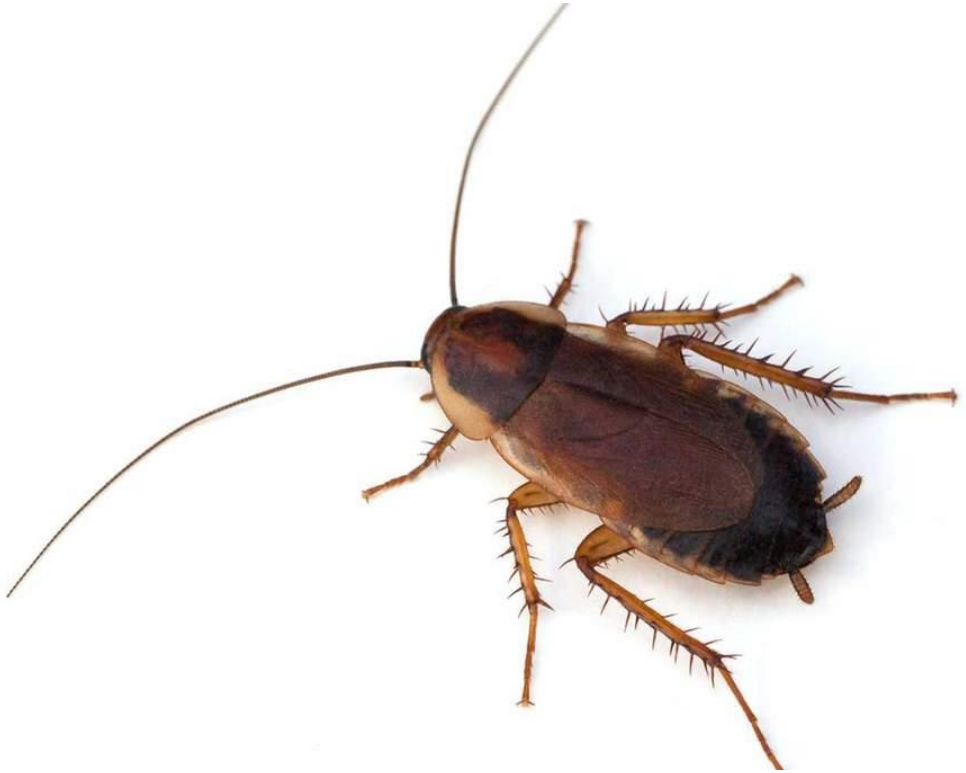
Brown & Stroup (1988). Learned helplessness in the cockroach (*Periplaneta americana*). *Behav. Neural. Biol*. 50(2):246-50.

# Shuttlebox



# Exercise alleviates depression in cockroaches

- For three consecutive days, adult female cockroaches received an inescapable shock.
- Next day half of females were exposed to ten minutes of forced exercise on a treadmill while the other half did not exercise.
- Both groups then performed a shuttle box escape task.
- The cockroaches exposed to forced exercise did not become helpless in the shuttlebox escape task.



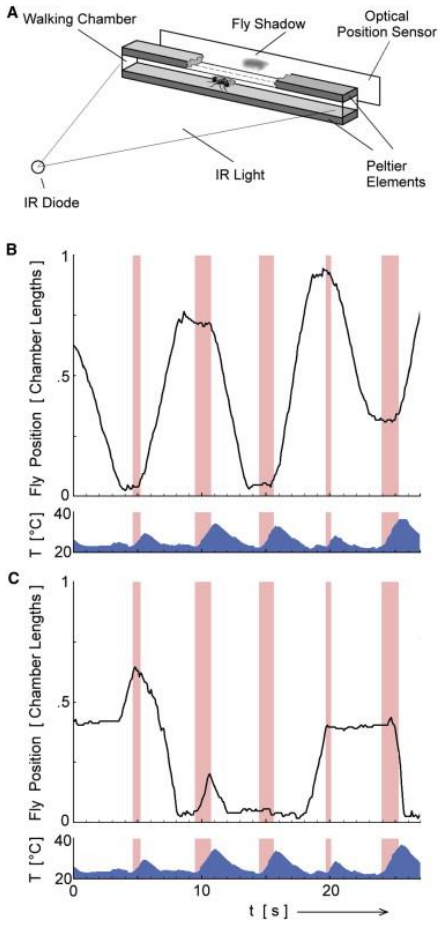
*Psychological Reports*, 1999, 84, 155-156 

FORCED EXERCISE BLOCKS LEARNED HELPLESSNESS IN THE COCKROACH (*PERIPLANETA AMERICANA*)[1]

GARY E. BROWN, ERIC DAVIS, AND AMANDA JOHNSON

*The University of Tennessee at Martin*

# In fruitflies, uncontrollable stress leads to depression (learned helplessness)




Yang et al. 2013. Flies Cope with Uncontrollable Stress by Learned Helplessness. *Current Biology* 23, 799–803.

nature COMMUNICATIONS

ARTICLE

Received 4 Aug 2016 | Accepted 25 Apr 2017 | Published 6 Jun 2017

DOI: 10.1038/ncomms15738 OPEN

Serotonin modulates a depression-like state in *Drosophila* responsive to lithium treatment

Ariane-Saskia Ries[1], Tim Hermanns[1], Burkhard Poeck[1] & Roland Strauss[1]

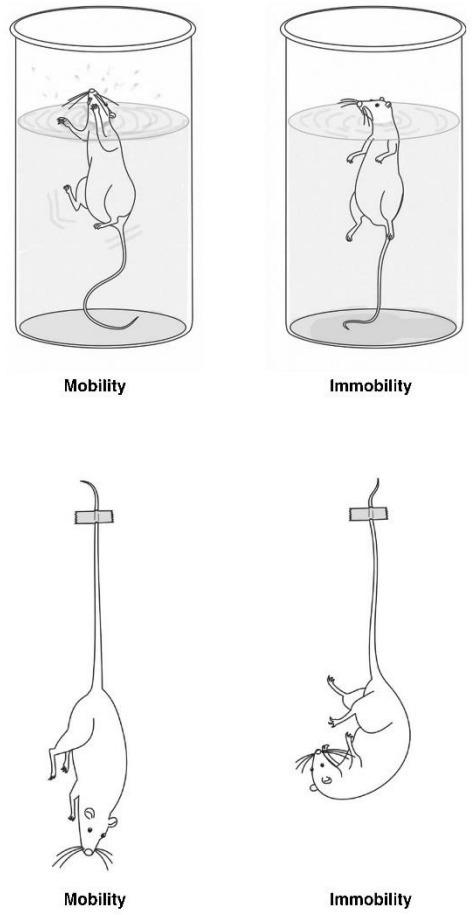
# Rejected flies turn to booze

- In the fruitfly study, researchers subjected male flies to four days of repeated rejection by pairing them with females who had already mated.
- The rejected males drank four times more alcohol than mated males


Shohat-Ophir et al. 2012. Sexual Deprivation Increases Ethanol Intake in *Drosophila. Science***.** 335, 1351-1355

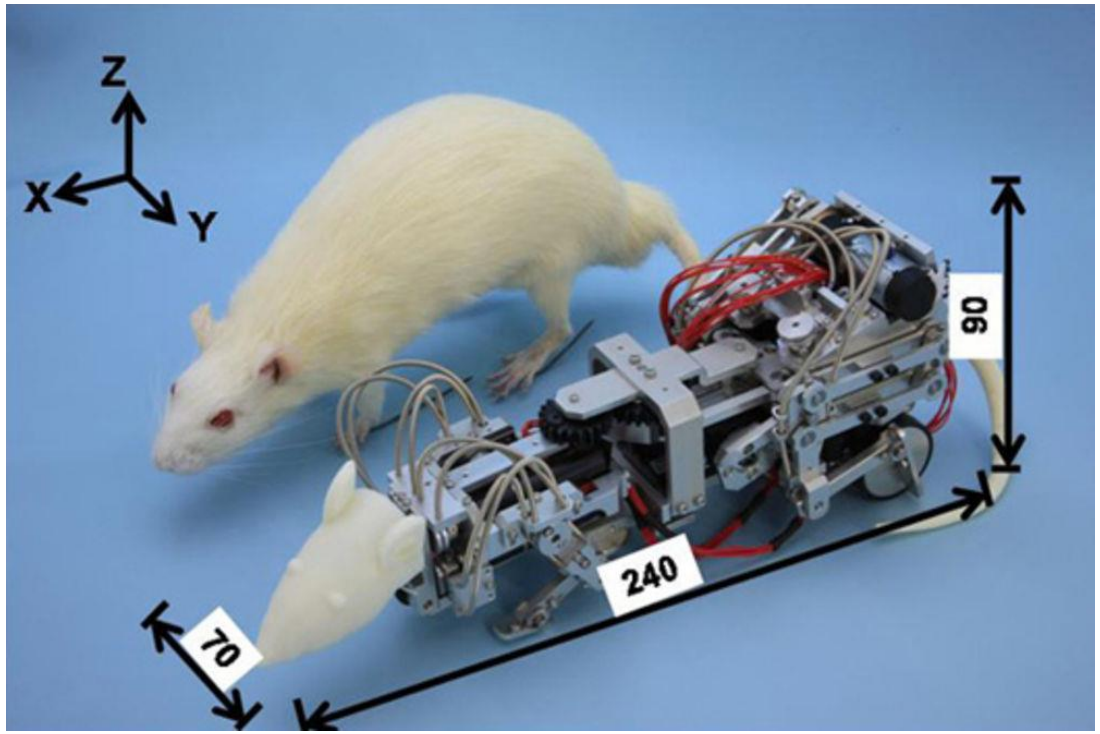
Video: https://www.youtube.com/watch?v=sH9Xjk28cZ0

# Rodents have been used for a long time as a model organism to study depression



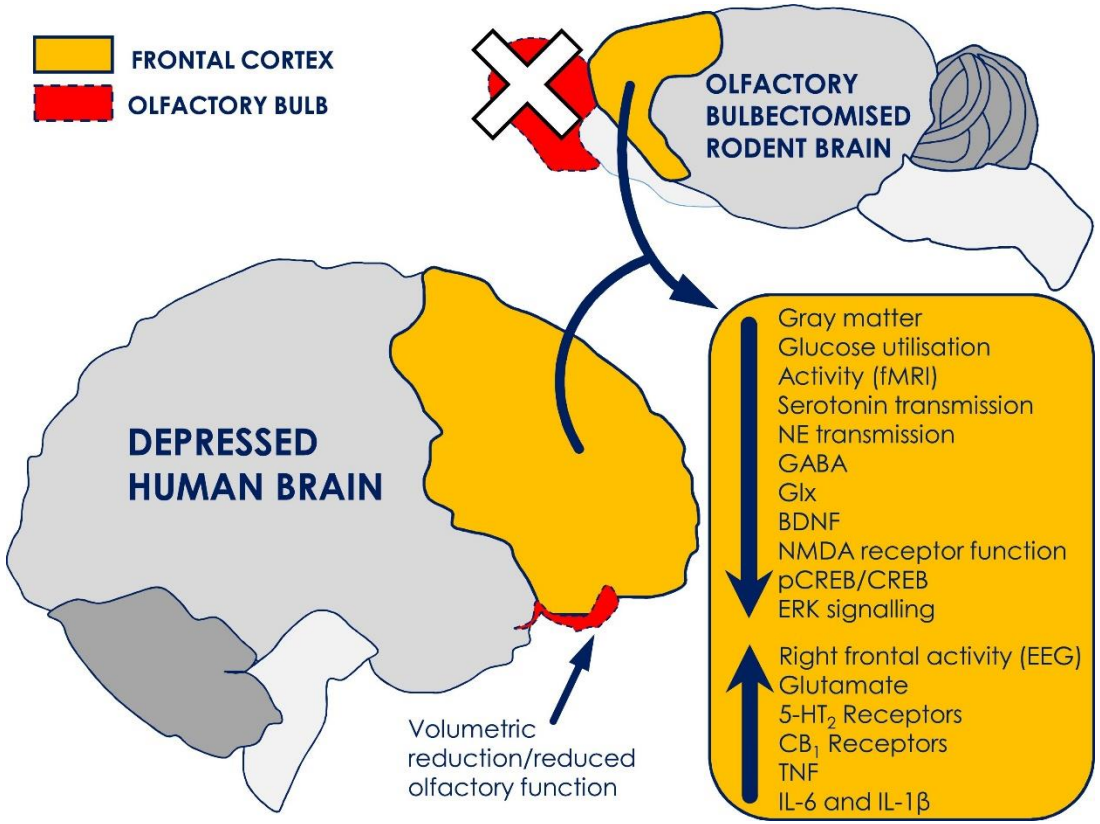

# How to make rodents depressed?

# Rats harassed with robots get depressed




Ishii et al. (2013). A novel method to develop an animal model of depression using a small mobile robot, *Advanced Robotics*, 27:1, 61-69,

# Olfactory bulbectomising causes depression in rats




Antidepressants reverse the effect!

ELSEVIER

Available online at www.sciencedirect.com
SCIENCE DIRECT®

Neuroscience and Biobehavioral Reviews 29 (2005) 627–647

NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS

www.elsevier.com/locate/neubiorev

Review

## The olfactory bulbectomised rat as a model of depression

Cai Song[a,*], Brian E. Leonard[b]

[a]*Department of Biomedical Science, AVC, University of Prince Edward Island and National Institute of Nutrisciences and Health, Charlottetown, Canada*
[b]*Department of Pharmacology, National University of Ireland, Galway and Department of Psychiatry and Neuropsychology, University of Maastricht, The Netherlands*

# Traumatic childhood experiences increase the risk of depression and anxiety in adulthood

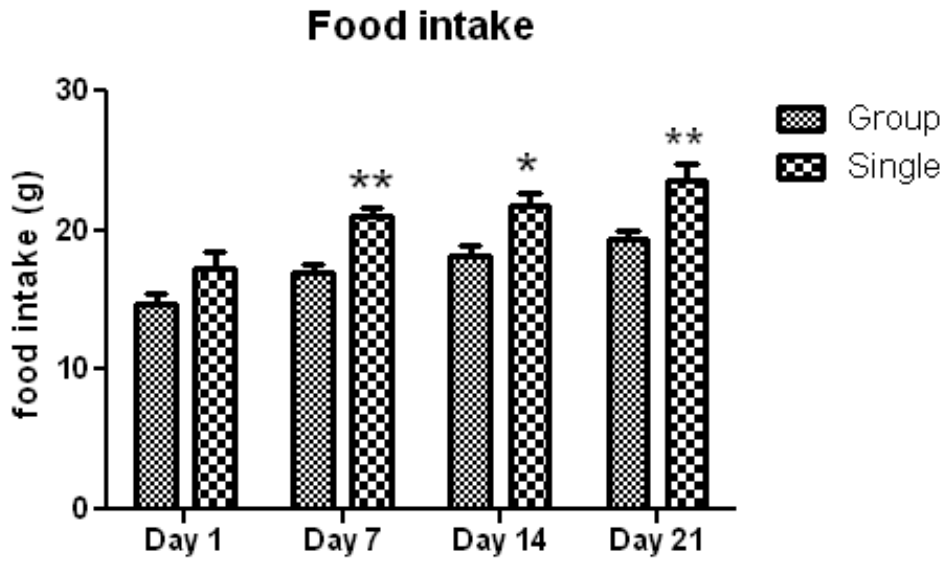
- Offspring are separated from their mother for 1-24 hours during the first two weeks of their lives.
- Maternal separation increases anxiety, depression and stress sensitivity in adulthood.

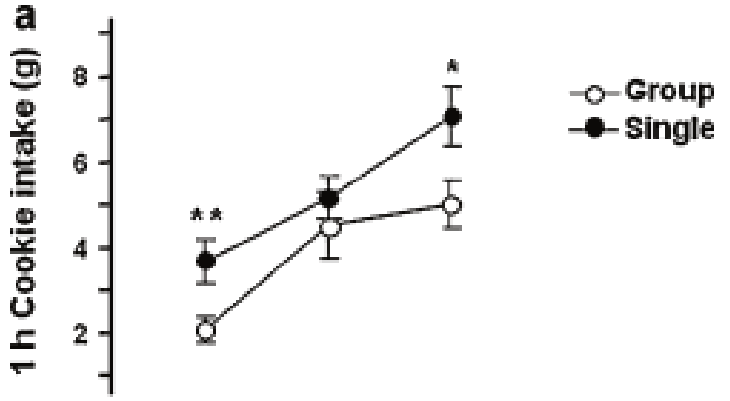
Meaney, M.J. (2001) Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annu. Rev.Neurosci. 24, 1161–1192

# Social isolation triggers depression in rats

- Jahng et al. "Hyperphagia and depression-like behavior by adolescence social isolation in female rats" international Journal of Developmental Neuroscience, 2011.
- Zanier-Gomes (2015). Depressive behavior induced by social isolation of predisposed female rats. Physiol Behav 151: 292-297.

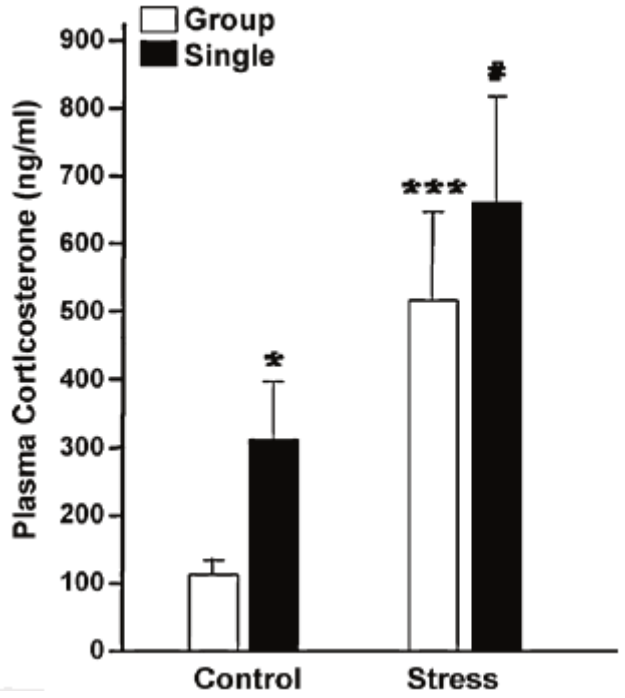
# Social isolation causes comfort eating in rats.

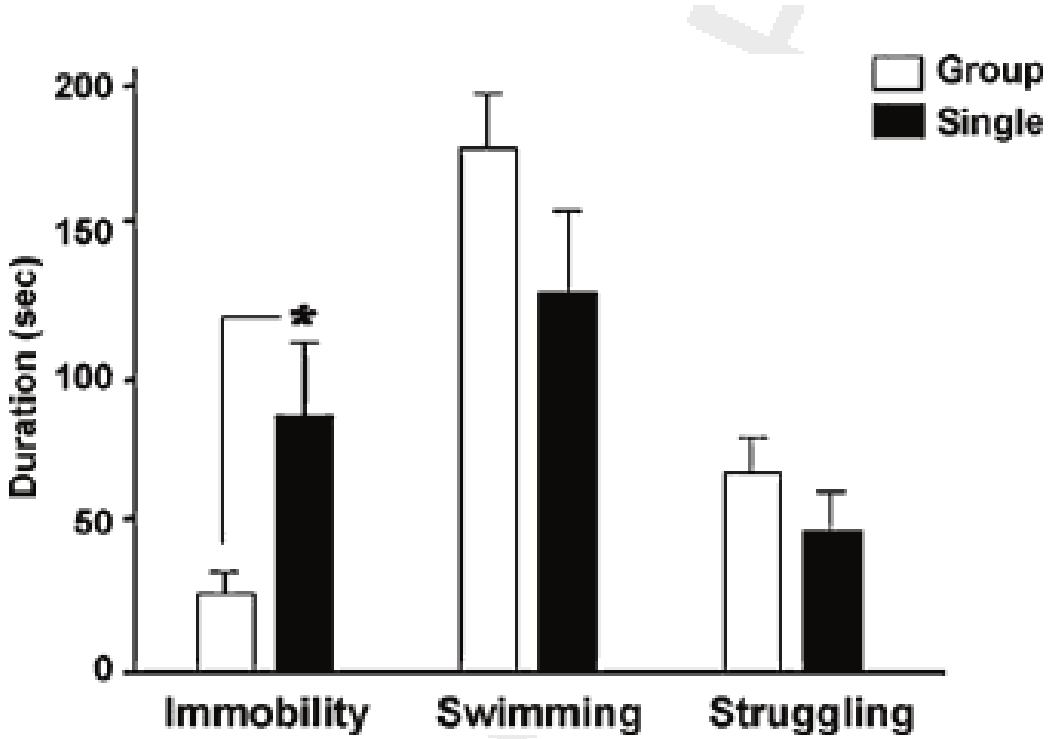



Jahng et al. "Hyperphagia and depression-like behavior by adolescence social isolation in female rats" international Journal of Developmental Neuroscience, 2011.

# Social isolation causes a  state of chronic stress



# Alcohol and certain drugs are able to trigger depression in rodents

O’Neil, M.F. and Moore, N.A. (2003) Animal models of depression: are there any? *Hum. Psychopharmacol*. *18*, 239–254

# Pollution is able to trigger depression in mice

- Mice were exposed to air pollution for six hours per day, five days per week for ten months.
- Air pollution caused depression and decreased memory and the ability to learn.


- Fonken *et al.* 2011. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. *Molecular Psychiatry* **16**, 987-995

# Losing a partner triggers depression in prairie voles

Bosch, O. J., Nair, H. P., Ahern, T. H., Neumann, I. D. & Young, L. J. The CRF System Mediates Increased Passive Stress-Coping Behavior Following the Loss of a Bonded Partner in a Monogamous Rodent. *Neuropsychopharmacology* **34**, 1406-1415

# Hierarchy conflict induces depression in chimpanzees

# Pimu, an alpha male chimp at Mahale Mountains National Park in Tanzania, being killed

# Serotonergic system interacts with dominance rank

*Brain Research*, 559 (1991) 181–190

*ADONIS* 0006899391169568

BRES 16956



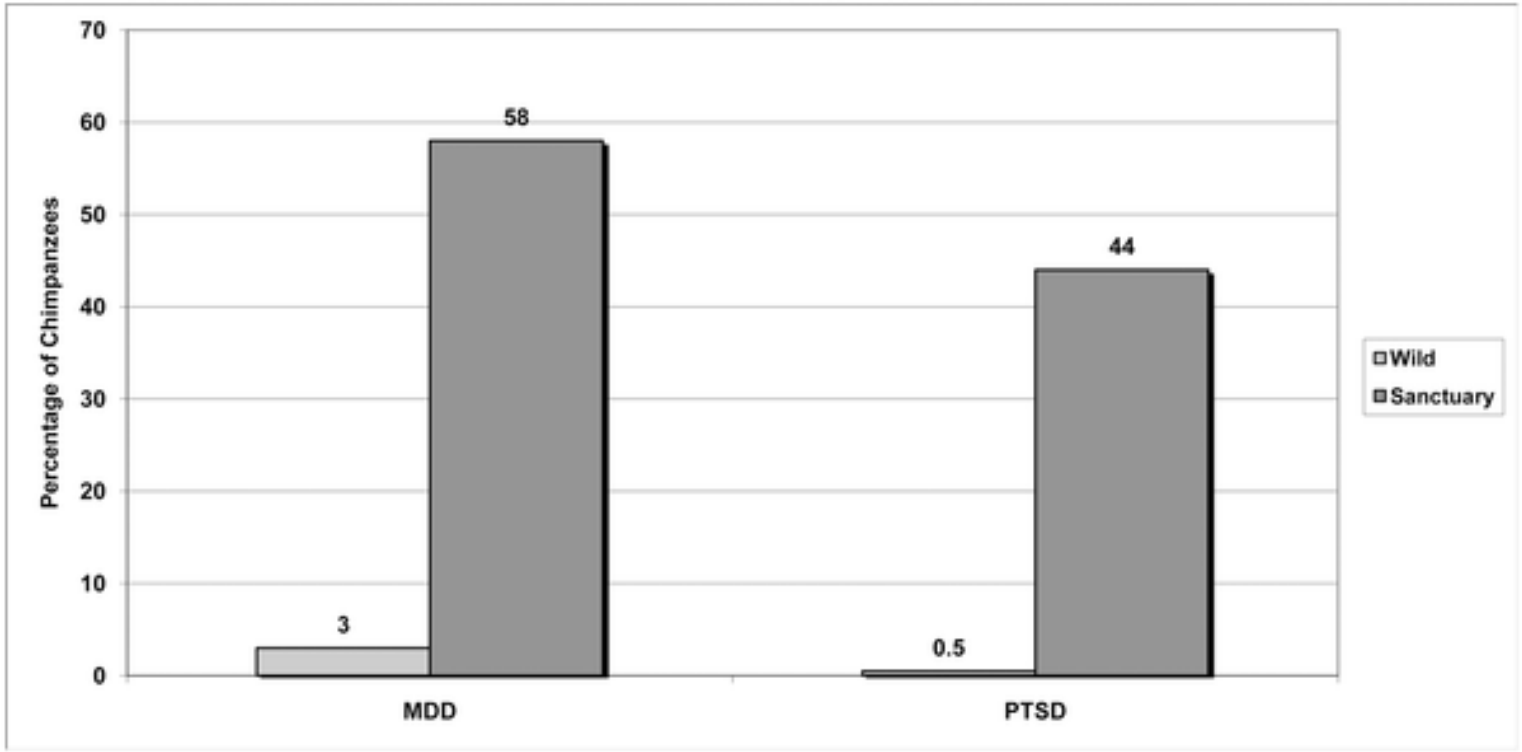
**Research Reports**

## Serotonergic mechanisms promote dominance acquisition in adult male vervet monkeys

Michael J. Raleigh[1,2,3,4], Michael T. McGuire[1,2,3,4], Gary L. Brammer[1,2,4], Deborah B. Pollack[1,2] and Arthur Yuwiler[1,3,4]

# Do chimpanzees meet the diagnostic criteria of major depressive disorder (DSM-IV)?

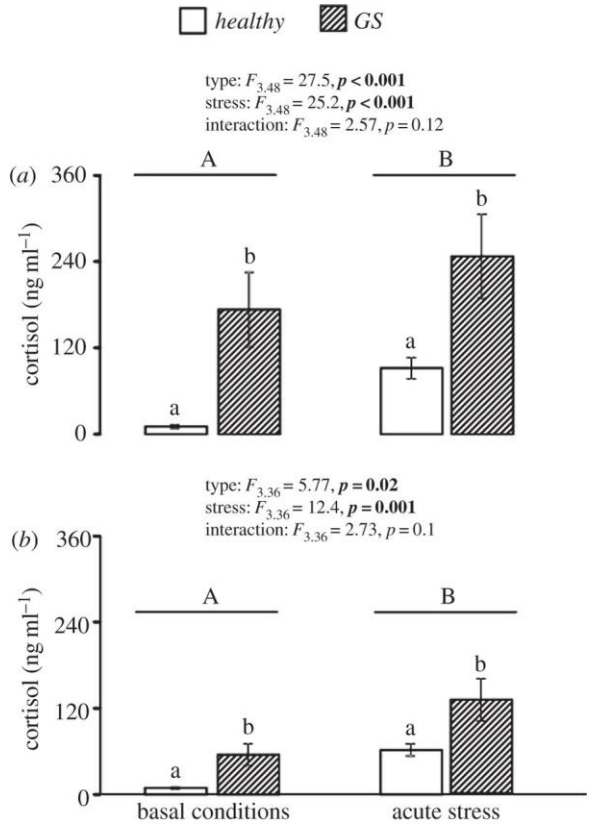
# Data collected from chimpanzees living in wild sites in Africa ($n = 196$) and chimpanzees living in sanctuaries ($n = 168$).




Ferdowsian HR, Durham DL, Kimwele C, Kranendonk G, Otali E, et al. (2011) Signs of Mood and Anxiety Disorders in Chimpanzees. PLOS ONE 6(6): e19855.
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0019855

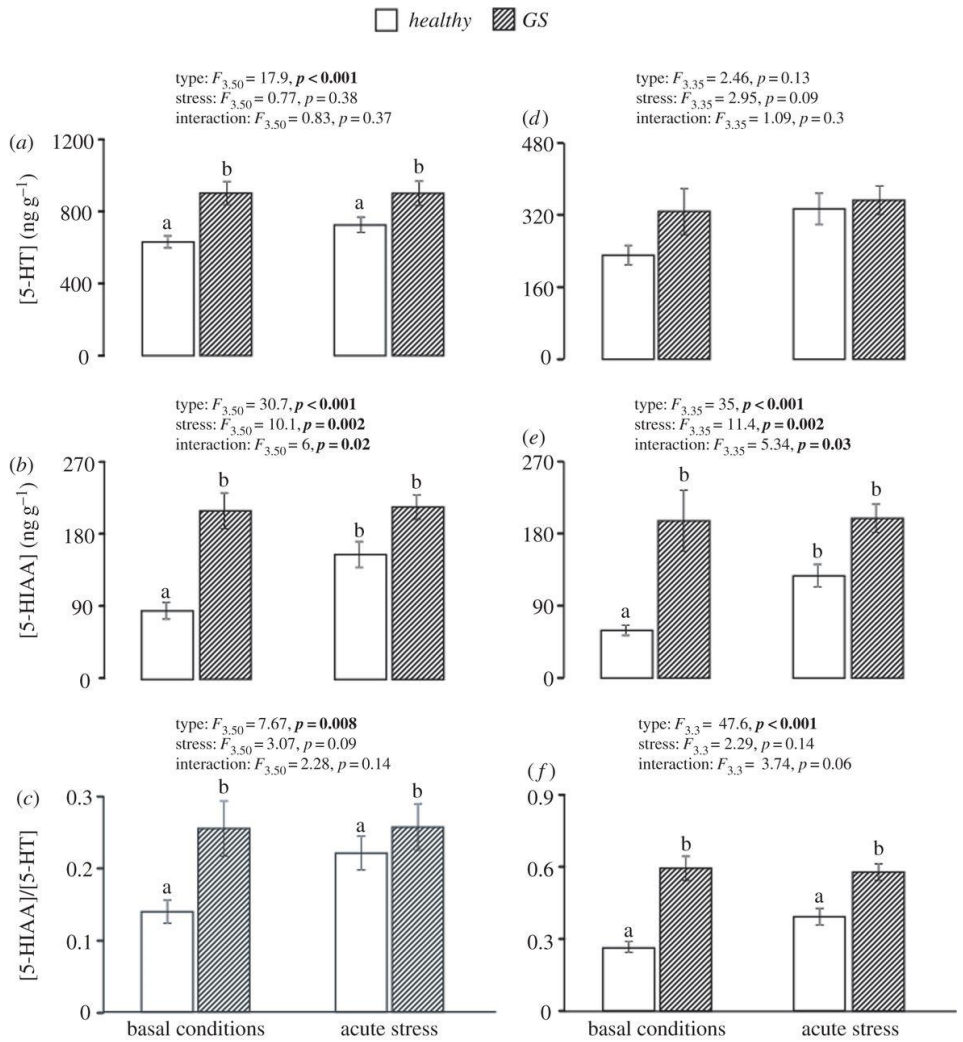
# Depression is common in fishes in fishfarms

# ¼ fishes in farms suffer depression


- Vindas et al. 2016. *R. Soc. Open Sci.* 3: 160030

# Depressed individuals have overactive serotonergic system and HPA-axis



# Stress upregulates serotonergic system in mice

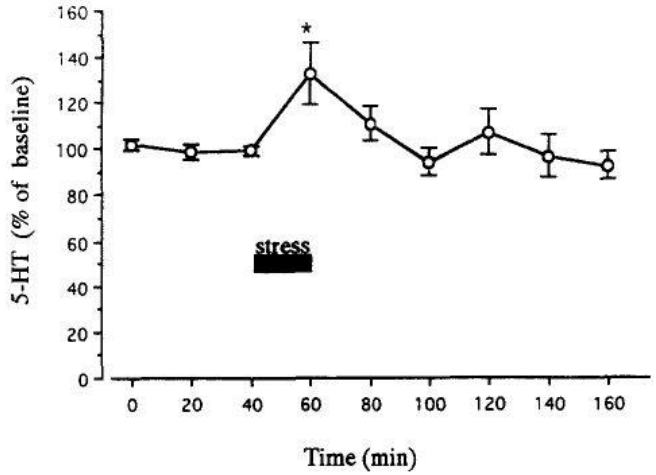



Fig. 1. Extracellular 5-HT recorded in the basolateral amygdaloid nucleus in response to psychological stress as percent of 3 baseline values. The value indicates the mean ± S.E.M. Statistical significance as compared to basal values. ★$P < 0.05$.

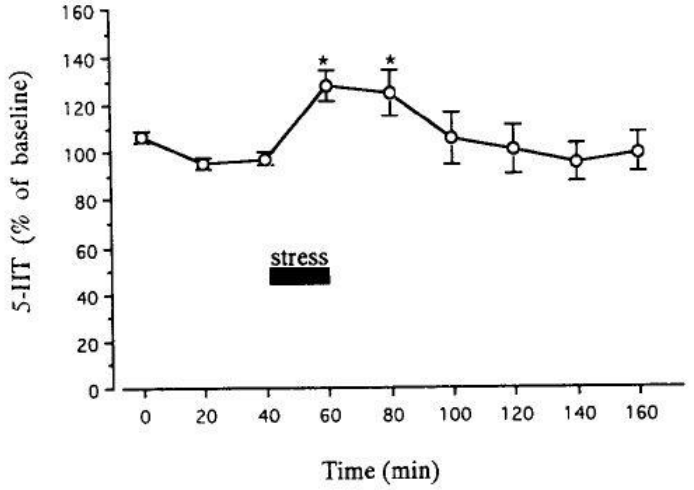



Fig. 2. Extracellular 5-HT recorded in the medial prefrontal cortex in response to psychological stress as percent of 3 baseline values. The value indicates the mean ± S.E.M. Statistical significance as compared to basal values. ★$P < 0.05$

Kawahara H, Yoshida M, Yokoo H, Nishi M, Tanaka M. Psychological stress increases serotonin release in the rat amygdala and prefrontal cortex assessed by in vivo microdialysis. Neurosci Lett. 1993;162:81–84.

# Studies in animals suggest that there are different subtypes of depression


# Empirical evidence in humans suggests that there are many different subtypes of depression

## Different adverse events lead to different patterns of depressive symptoms

Keller, M.C., Nesse, R.M., 2005. Is low mood an adaptation? Evidence for subtypes with symptoms that match precipitants. Journal of Affective Disorders 86, 27-35.

Keller, M.C., Nesse, R.M., 2006. The evolutionary significance of depressive symptoms: Different adverse situations lead to different depressive symptom patterns. Journal of Personality and Social Psychology 91, 316-330.

# Empirical evidence in humans suggests that there are many different subtypes of depression

Studies using functional magnetic resonance imaging (fMRI) found that depressed patients belong to at least four different neurophysiological subtypes, that is, clusters of individuals who have different symptom-linked brain features.

These clusters of individuals differed in responsiveness to transcranial magnetic stimulation therapy

Drysdale et al 2017. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nature Medicine* 23, 28-38.

# From the point of view evolutionary psychology, a depressive episode may be:

(1) an adaptation against the specific adaptive problem (adaptive mood change),

(2) a maladaptive state caused by an environmental mismatch as a result of modern lifestyle

(3) a byproduct of other adaptations

(4) a pathological state without any adaptive function

# 12 subtypes of depression based on evolutionary psychology

**1) Infection-induced depression**

**2) Depression induced by long-term stress**

**3) Depression induced by loneliness**

**4) Depression induced by grief**

**5) Depression induced by romantic rejection**

**6) Depression induced by traumatic events (PTSD-induced)**

**7) Depression induced by hierarchy conflict**

**8) Postpartum depression**

**9) Season-related depression**

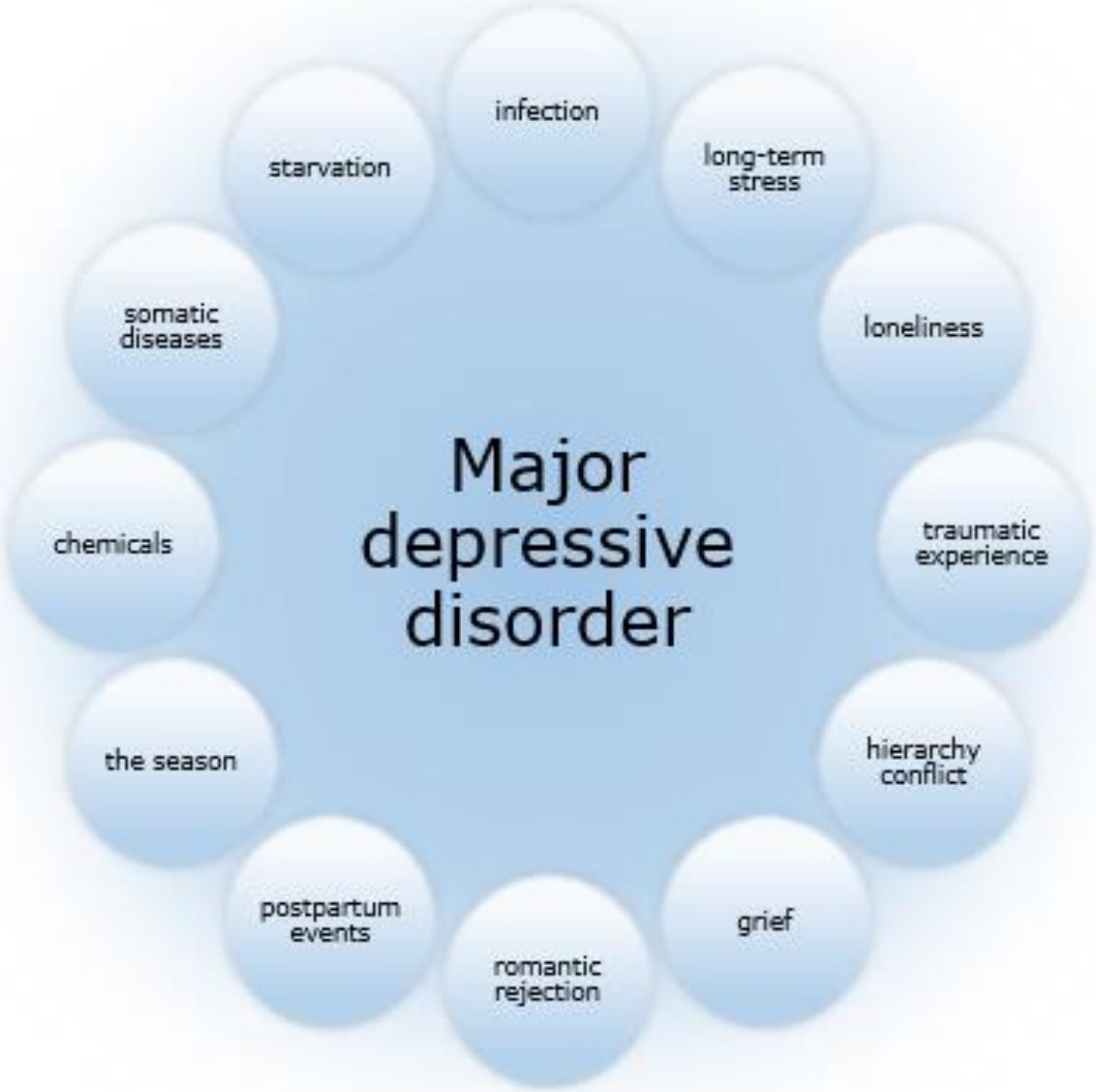
**10) Chemically induced depression**

**11) Depression induced by somatic diseases**

**12) Starvation-induced depression**

Rantala, MJ, Luoto, S., Krams I. & Karlsson H. (2018 )Depression subtyping based on evolutionary psychiatry: proximate mechanisms and ultimate functions. *Brain, Behavior, and Immunity*. 69: 603-617.

# 12 subtypes of depression based on evolutionary psychology

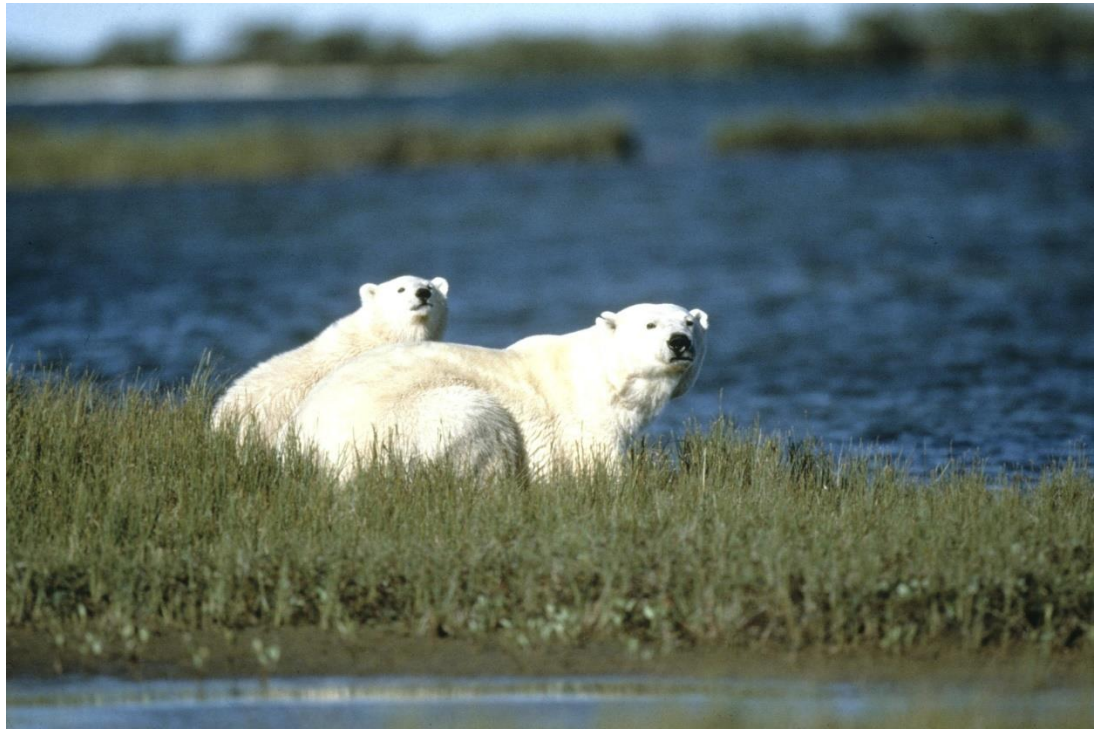



Rantala, MJ, Luoto, S., Krams I. & Karlsson H. (2018). Depression subtyping based on evolutionary psychiatry: proximate mechanisms and ultimate functions. *Brain, Behavior, and Immunity*. 69: 603-617.

Natural selection has produced responses such as anxiety, low mood, and pain, because they have helped our ancestors propagate their genes to the next generation (e.g. Nettle, 2011).

Cost of not having these emotions would have been huge.

# If the environment changes, a previously adaptive trait or behaviour may became maladaptive



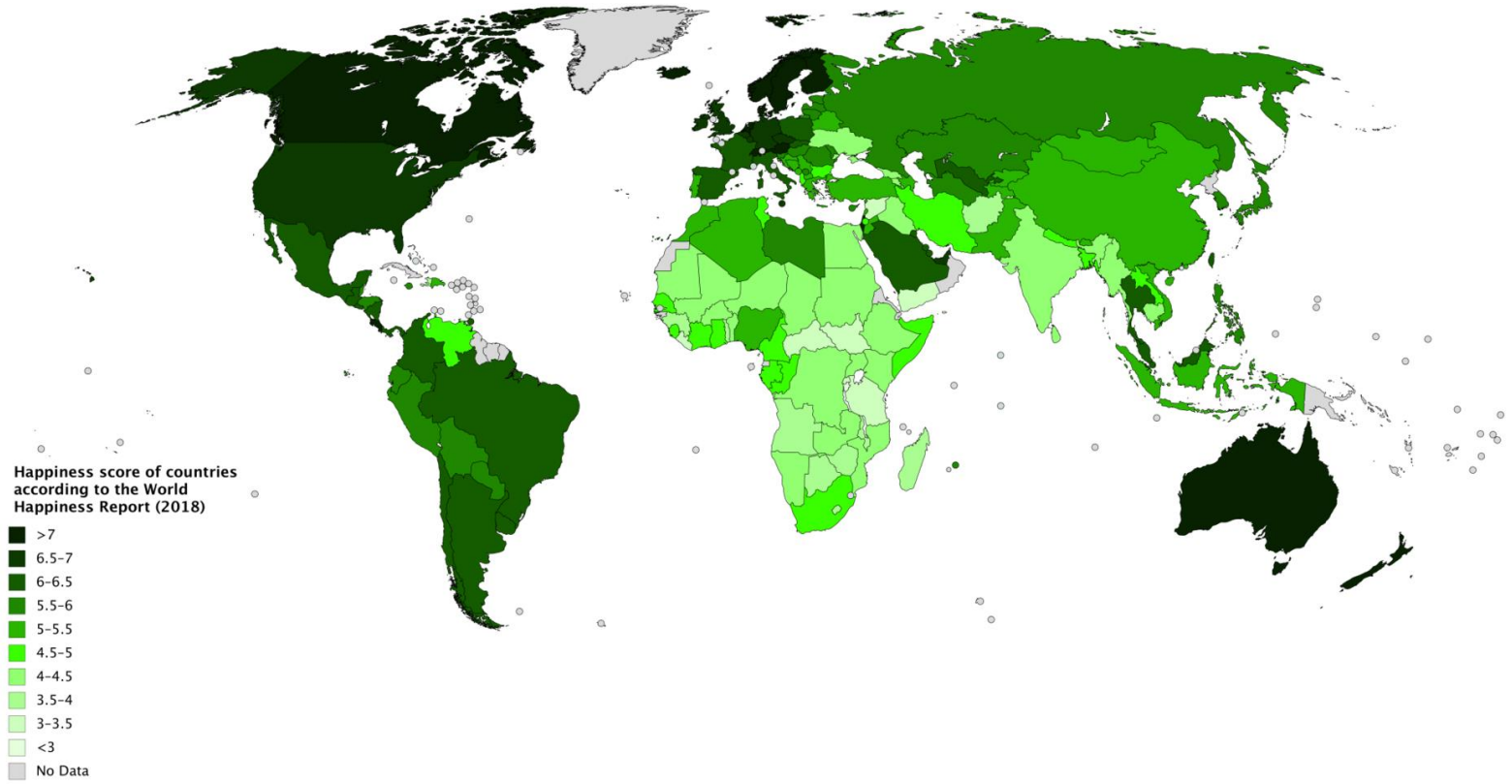
# Clinical depression is becoming more common

Prevalence of depression in Finland (FinTerveys 2017)

| | 2011 | 2017 |
|---|---|---|
| Men | 6% | 9% |
| Women | 9% | 13% |

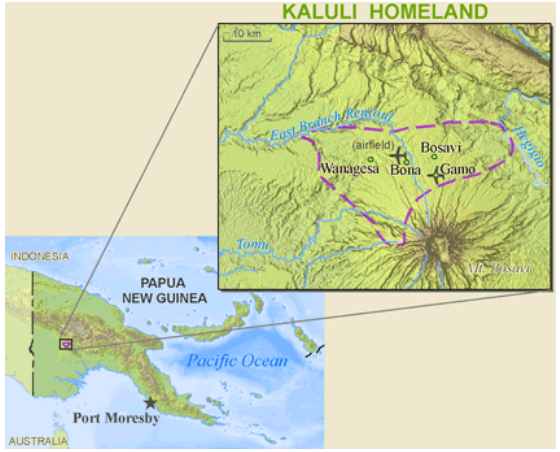
# The World Happiness Report

- 1. Finland
- 2. Danmark
- 3. Norway
- 4. Iceland
- 5. Nederland
- 6. Switcherland
- 7. Sweden
- 8. New Zealand
- 9. Canada
- 10. Austria



# The key to the mystery of increased depression prevalence may be with hunter-gatherers

- Prevalence of clinical depression was 1/2000 in Kaluli people. (The only diagnosed case was diagnosed as mild depression)





- Schieffelin EL. The cultural analysis of depressive affect: An example from New Guinea. In: Kleinman AM, Good B, editors. *Culture and depression: Studies in the anthropology and cross-cultural psychiatry of affect and disorder*. University of California Press; 1986. pp. 101–133.

# Hadza people do not suffer from clinical depression

(Apicella et al., unpublished, presented in a BBC documentary)

# Clinical depression is very rare among Toraja people

- Hollan, D. W. & Wellenkamp, J. C. *Contentment and suffering : culture and experience in Toraja*. (Columbia University Press, 1994).
- Hollan, D. W. & Wellenkamp, J. C. *The thread of life: Toraja reflections on the life cycle*. (University of Hawaii Press, 1996).

Chinese people born after 1966 are 22.4 times more likely to suffer from a depressive episode than Chinese people born before 1937



Published in final edited form as:
*Psychol Med*. 2007 January ; 37(1): 61–71.

**Lifetime Prevalence and Inter-cohort Variation in DSM-IV Disorders in Metropolitan China**

**Sing Lee, MB, BS, FRCPsych**,
*Department of Psychiatry, The Chinese University of Hong Kong, HKSAR, PRC*

**Adley Tsang, BSocSci**,
*Hong Kong Mood Disorders Center, The Chinese University of Hong Kong, HKSAR, PRC*

**Ming-Yuan Zhang, MD**,
*Shanghai Mental Health Center, PRC.*

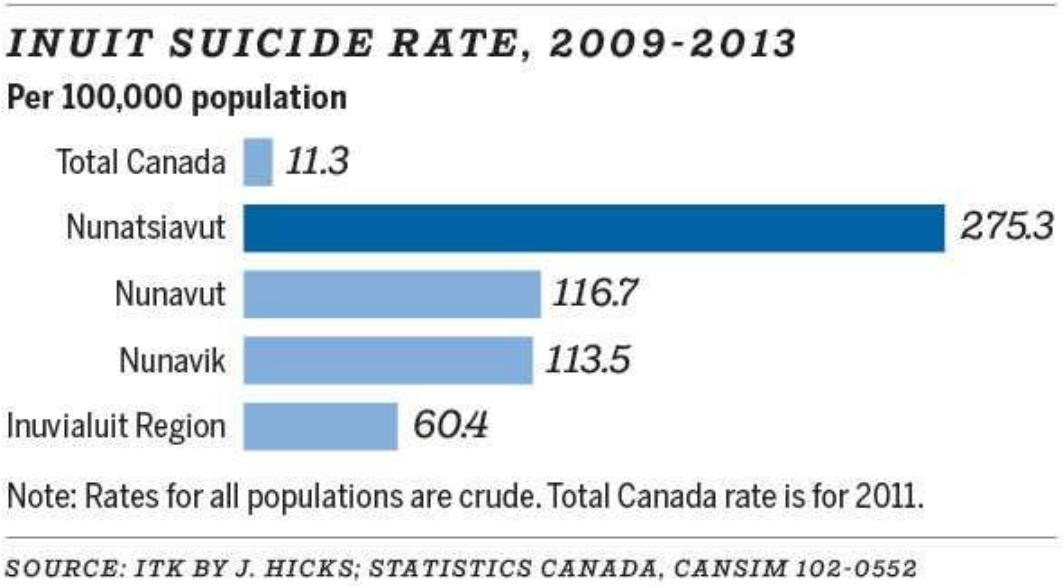
**Yue-Qin Huang, MD, MPH, PhD**,
*Peking University Institute of Mental Health, PRC.*

**Yan-Ling He, MD**,
*Shanghai Mental Health Center, PRC.*

**Zhao-Rui Liu, MD, MPH**,
*Peking University Institute of Mental Health, PRC.*

**Yu-cun Shen**, and **Ronald C. Kessler, PhD**
*Department of Health Care Policy, Harvard Medical School, MA, USA.*

# Indigenous people in the arctic areas that changed to a modern lifestyle experienced tripled suicide rates in a decade




Shephard & Rode, A., 2008. The health consequences of 'modernization' : evidence from circumpolar peoples, Reprint. ed. Cambridge University Press, Cambridge.

# The more “western” the lifestyle, the more common is depression



Published in final edited form as:
*J Affect Disord*. 2012 November ; 140(3): 205–214. doi:10.1016/j.jad.2011.12.036.

**Depression as a disease of modernity: explanations for increasing prevalence**

**Brandon H Hidaka, B.A. [MD/PhD Candidate]**
Department of Dietetics and Nutrition, University of Kansas Medical Center, 2116 W 47th Terr, Westwood, KS 66205, Phone: (913) 636-8095, Fax: (913) 945-6848

Brandon H Hidaka: bhidaka@kumc.edu

# Clinical depression is very rare among the old order amish

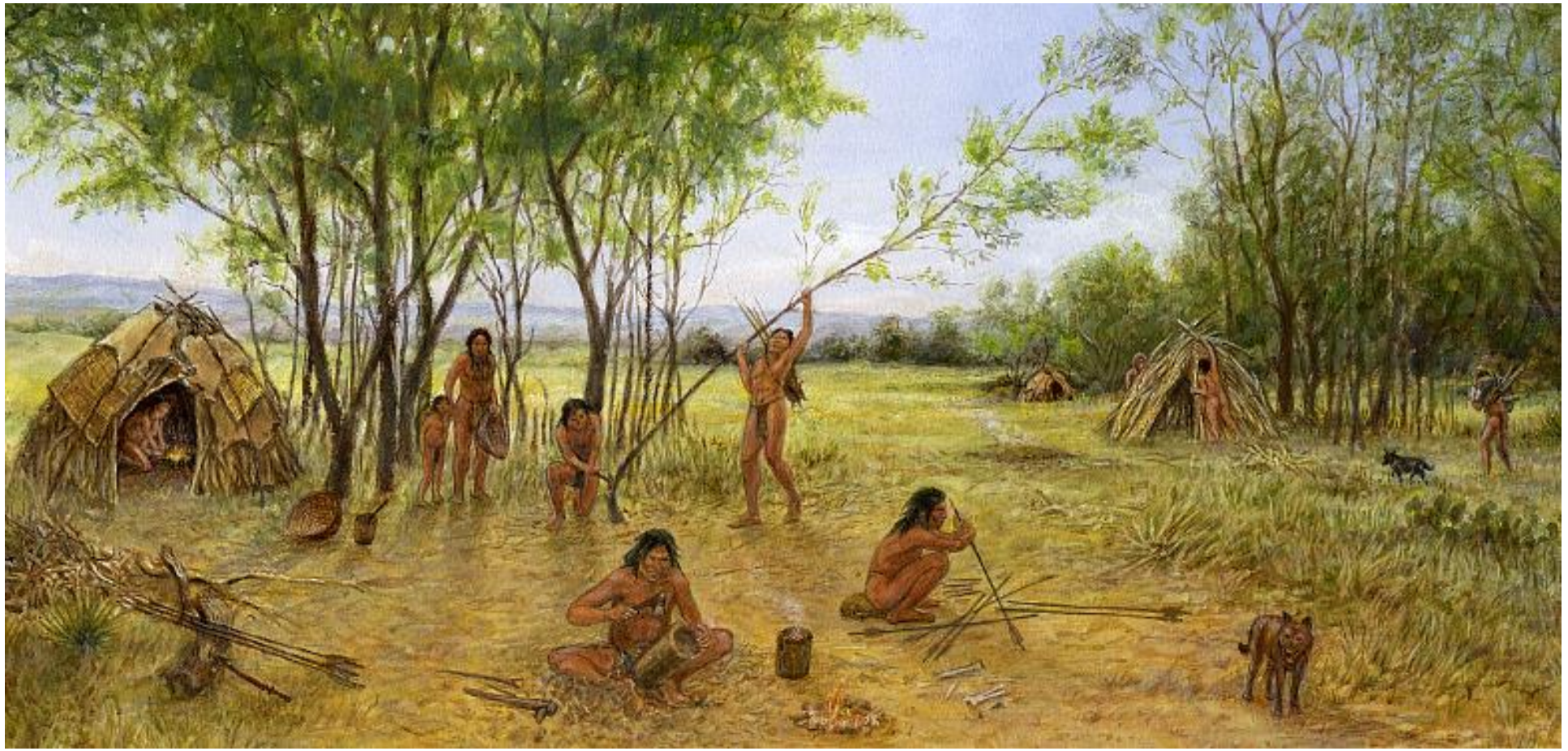
Prevalence of depression is 1%

Egeland & Hostetter (1983*). American Journal of Psychiatry* 140, 56-61

# The low prevalence of clinical depression does not mean that hunter-gatherers and Old Order Amishes do not have tragic events in their lives

- For some reason, however, in hunter-gatherers and Old Order Amishes the periods of low mood, sadness and grief after adverse events in life do not seem to transform to episodes of major depressive disorder that fulfil the diagnostic criteria of DSM-5 or ICD-10.

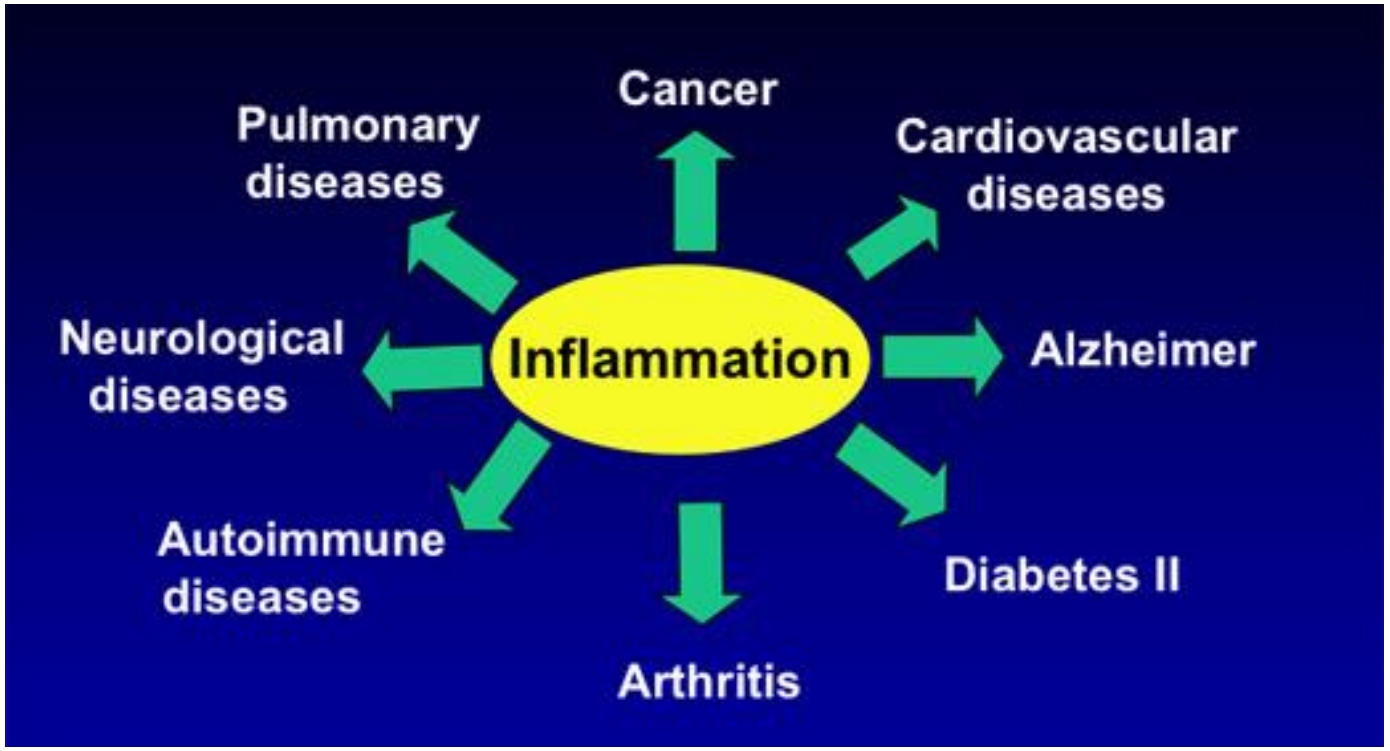
# Los Angeles in the 18th century




405 NORTH
Sacramento

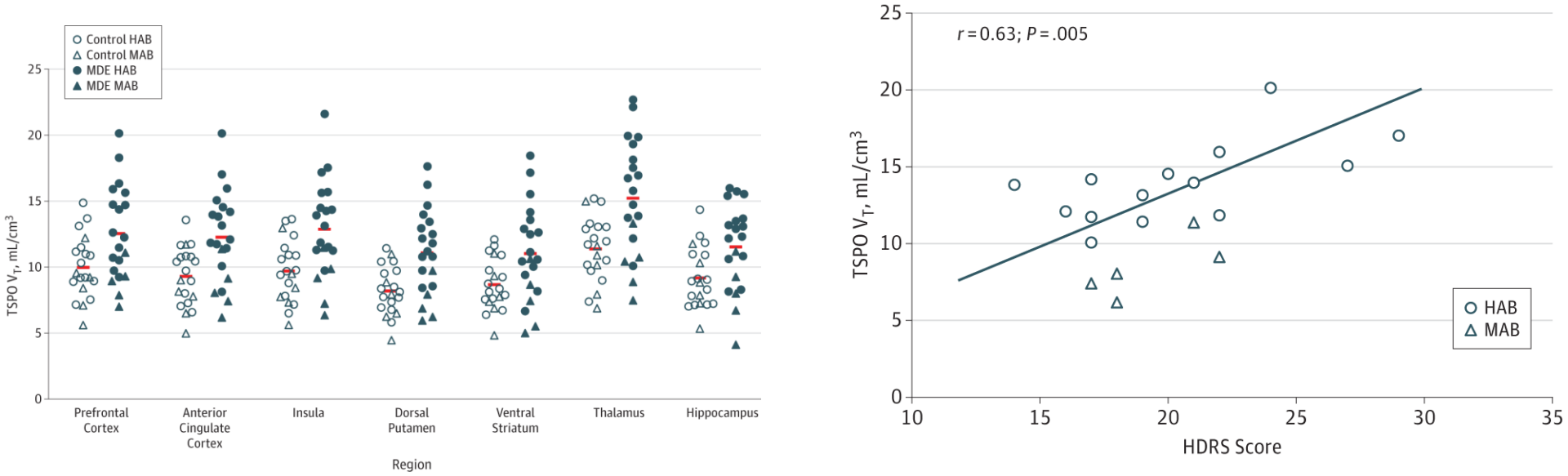
We are still equipped with similar brains and bodies as our ancestors who had hunter-gatherer lifestyles for millions of years

# Modern lifestyle brings “diseases of modernity”



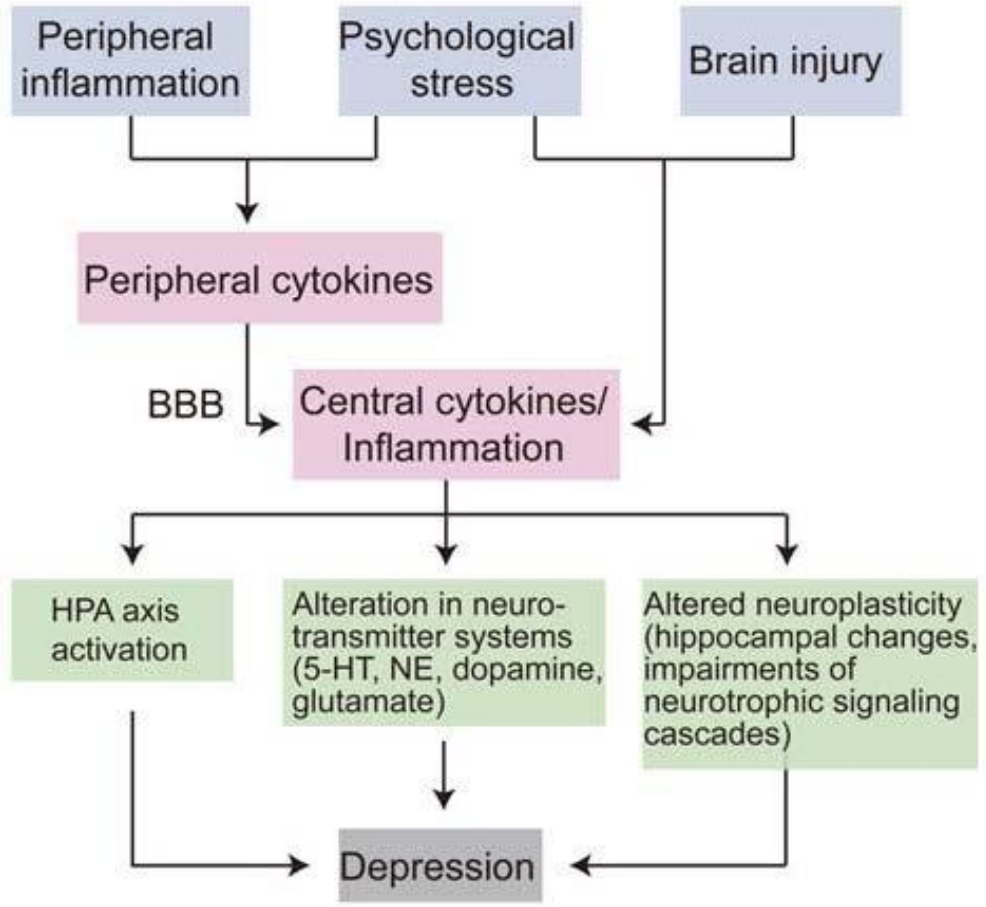

# Maybe clinical depression is a maladaptive byproduct of inflammation!

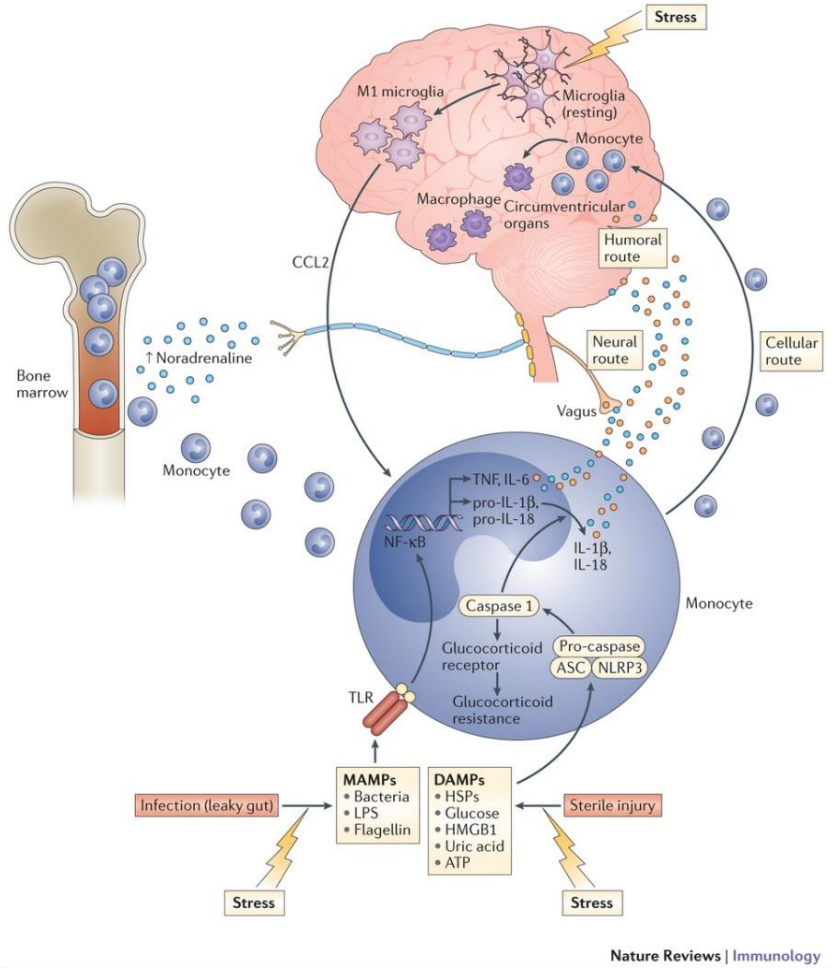
# Patients with clinical depression have neuroinflammation




Setiawa *et al.* (2015). Role of Translocator Protein Density, a Marker of Neuroinflammation, in the Brain During Major Depressive Episodes. *Jama Psychiatry* **72**, 268-275, doi:10.1001/jamapsychiatry.2014.2427 (2015).

# The role of inflammation in depression




REVIEWS

Nature Reviews Immunology 16, 22-34. (2016)

The role of inflammation in depression: from evolutionary imperative to modern treatment target

*Andrew H. Miller[1] and Charles L. Raison[2]*

# Experimental studies support the link between inflammation and clinical depression

- an experimental administration of proinflammatory cytokines or endotoxins causes symptoms of depression for otherwise healthy participants.

- vaccination against typhoid causes symptoms of depression for otherwise healthy persons

- cytokine antagonists and anti-inflammatory agents block the development of sickness behaviour / depression symptoms following immune activation

# Genes associated with higher vulnerability to clinical depression are associated with immune system function



**Table 2** Immune/host defense functions of single-nucleotide polymorphisms (SNPs) associated with major depression based on the largest meta-analysis of genome-wide association studies (GWASs) conducted to date for major depression (MDD)

| *Gene ID* | *Gene name* | *SNP with minimum P-value* | *Immune/host defense function of gene* |
|---|---|---|---|
| *SEL1L2* | *Sel-1 suppressor of lin-12-like 2* | rs17226852 | No specific immune or host defense functions identified for *SEL1L2*. However, the other member of the sel1 gene family, *SEL1L*, has been shown to be important for quality control of IgM,[100] and the infectious capacity of several viruses,[101] including human cytomegalovirus,[102] a microsatellite polymorphism of *SEL1L*, is associated with autoimmune thyroid diseases[103] |
| *ADCY3* | *Adenylate cyclase 3* | rs2384061 | *ADCY3* is integral to a rapid, NF-κB-independent, signaling cascade initiated by microbial stimulation of TLR4.[104] *ADCY3* also regulates crosstalk between FP prostanoid and prostaglandin E2 receptors.[105] This crosstalk regulates expression of *SAT1* gene, which has been reported to be underexpressed in prefrontal cortex of suicide completers.[106] |
| *UNC93A* | *Unc-93 homolog A* | rs2076008 | No specific immune or host defense functions identified for *UNC93A*, but a closely related homolog, UNC93B, plays a crucial role in antigen presentation and TLR functioning, and deficiency in its expression reduces TNF-α production and increases vulnerability to a number of infections.[107–109] Blockade of *UNC93B* may protect against autoimmunity.[110] |
| *TEX10* | *Testis expressed 10* | rs1930243 | No specific immune or host defense functions identified. |
| *TTLL2* | *Tubulin tyrosine ligase-like family, member 2* | | No specific immune or host defense functions identified for *TTLL2*; however, other TTLL family members have been shown to be essential for proper cilliary structure and function and with this ability to clear pathogens and other harmful substances from the airway.[111] |
| *GAL* | *Galanin* | rs2156464 | Signaling through either type 1 or type 2 receptors, *GAL* has numerous anti-inflammatory effects;[112–115] Consistent with PATHOS-D, multiple lines of evidence indicate *GAL* signaling is reduced in MDD;[116–118] GMAP, which is produced by cleavage of the same precursor as galanin, has direct antifungal activity[119] |
| *PDK4* | *Pyruvate dehydrogenase kinase, isozyme 4* | rs11531570 | *PDK4* gene expression is upregulated by IFN-α and by LPS and contributes to muscle glycogen breakdown and lactate accumulation;[120,121] conversely, *PDK4* is inhibited by TNF-α via p38 MAPK and NF-κB signaling, leading to increased glucose oxidation;[122] anti-inflammatory omega-3 fatty acids increase *PDK4* in immature dendritic cells via enhanced PPAR-γ signaling[123] |
| *NPM1* | *Nucleophosmin* | rs11134697 | Functions as an endogenous 'alarmin' that activates proinflammatory cytokines;[124–126] identified as a host virulence factor in viral infection;[127,128] may aid in HIV and HSV1 virus dispersal within cells;[129,130] complexes with, and inhibits, PKR, which has important antiviral properties[131] |
| *USP3* | *Ubiquitin-specific peptidase 3* | rs7183892 | Embedding of *USP* genes in the copy number variable β-defensin cluster on chromosome 8p23.1 suggests a close tie with innate immunity;[132] *USP3* is activated by IL-4 and IL-6 and has antiproliferative and apoptotic properties;[133] highly homologous *USP17* necessary for type I IFN production in response to virus infection;[134] |
| *ASB4* | *Ankyrin repeat and SOCS box-containing 4* | rs11531570 | No specific immune or host defense functions identified. |

Open

Molecular Psychiatry (2013) 18, 15–37

www.nature.com/mp

HYPOTHESIS

## The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D)

CL Raison[1,2] and AH Miller[3]

[1]*Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA;* [2]*John and Doris Norton School of Family and Consumer Sciences, University of Arizona, Tucson, AZ, USA and* [3]*Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA*

It seems that inflammation may cause the shift from a normal mood change into clinical depression!

# The hypothesis received empirical evidence

- Bereaved individuals with a higher grief severity had higher levels of the proinflammatory cytokines than those with less grief severity.

- Those who experienced higher levels of depression exhibited higher levels of proinflammatory cytokines than those who had lower levels of depression.

Psychoneuroendocrinology 100 (2019) 190–197

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Grief, depressive symptoms, and inflammation in the spousally bereaved

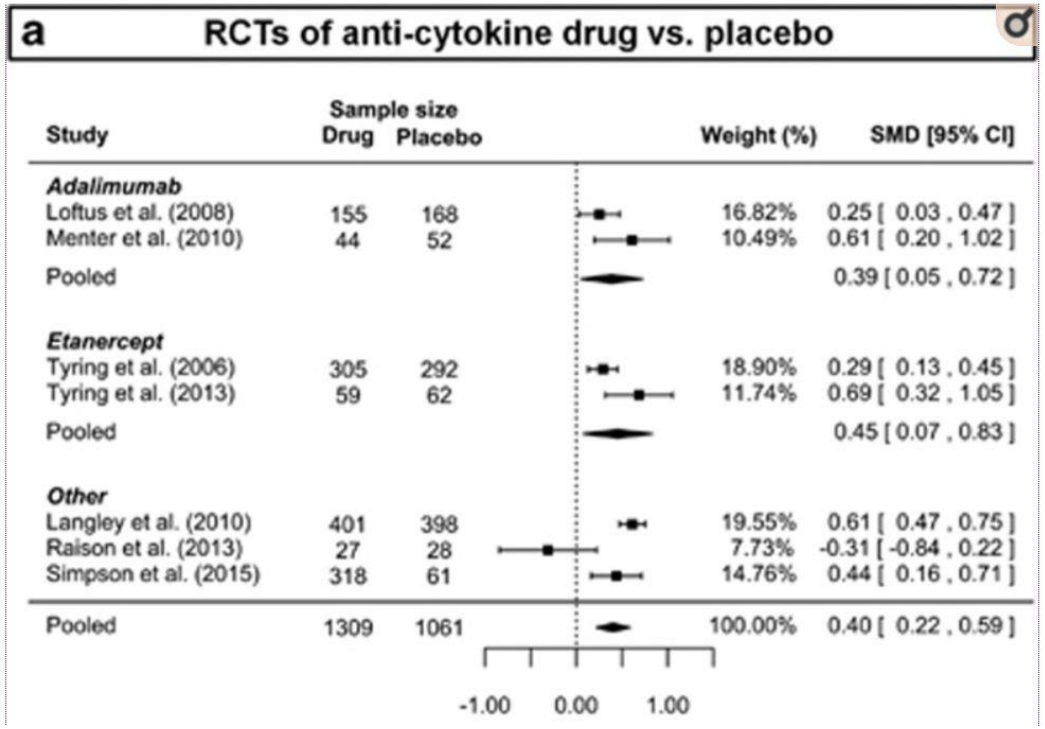
Christopher P. Fagundes[a,b,c,*], Ryan L. Brown[a], Michelle A. Chen[a], Kyle W. Murdock[d], Levi Saucedo[a], Angie LeRoy[a], E. Lydia Wu[a], Luz M. Garcini[a], Anoushka D. Shahane[a], Faiza Baameur[b], Cobi Heijnen[b,d]

# The inflammatory dysregulation common to modern lifestyle seems to increase the likelihood of developing clinical depression after adverse life events.

- This hypothesis is supported by the finding that the risk of major depression increases by 44% for each standard deviation increase in log c-reactive protein.

Pasco et al. 2010. Association of high-sensitivity C-reactive protein with de novo major depression. *British Journal of Psychiatry 197*, 372-377.

# Anti-cytokine treatment alleviates depression symptoms!




OPEN

Molecular Psychiatry (2016) 00, 1–9
www.nature.com/mp

ORIGINAL ARTICLE

## Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions

N Kappelmann[1], G Lewis[2], R Dantzer[3], PB Jones[1,4,5] and GM Khandaker[1,4,5]

Inflammatory cytokines are commonly elevated in acute depression and are associated with resistance to monoaminergic treatment. To examine the potential role of cytokines in the pathogenesis and treatment of depression, we carried out a systematic review and meta-analysis of antidepressant activity of anti-cytokine treatment using clinical trials of chronic inflammatory conditions where depressive symptoms were measured as a secondary outcome. Systematic search of the PubMed, EMBASE, PsycINFO and Cochrane databases, search of reference lists and conference abstracts, followed by study selection process yielded 20 clinical trials. Random effect meta-analysis of seven randomised controlled trials (RCTs) involving 2370 participants showed a significant antidepressant effect of anti-cytokine treatment compared with placebo (standardised mean difference (SMD) = 0.40, 95% confidence interval (CI), 0.22–0.59). Anti-tumour necrosis factor drugs were most commonly studied (five RCTs); SMD = 0.33 (95% CI; 0.06–0.60). Separate meta-analyses of two RCTs of adjunctive treatment with anti-cytokine therapy and eight non-randomised and/or non-placebo studies yielded similar small-to-medium effect estimates favouring anti-cytokine therapy; SMD = 0.19 (95% CI, 0.00–0.37) and 0.51 (95% CI, 0.34–0.67), respectively. Adalimumab, etanercept, infliximab and tocilizumab all showed statistically significant improvements in depressive symptoms. Meta-regression exploring predictors of response found that the antidepressant effect was associated with baseline symptom severity ($P = 0.018$) but not with improvement in primary physical illness, sex, age or study duration. The findings indicate a potentially causal role for cytokines in depression and that cytokine modulators may be novel drugs for depression in chronically inflamed subjects. The field now requires RCTs of cytokine modulators using depression as the primary outcome in subjects with high inflammation who are free of other physical illnesses.

*Molecular Psychiatry* advance online publication, 18 October 2016; doi:10.1038/mp.2016.167

# The effect of psychotherapies to alleviate depression may be based on their ability to reduce inflammation!

**Table 2**
Serum IL-6 and TNF- α levels and severity of depressive symptoms (BDI and OQ-45.2) at baseline and after psychodynamic psychotherapy.

| | Baseline | | Post-intervention | | p-value |
|---|---|---|---|---|---|
| | Median (Interquartile intervals) | Mean ± SD | Median (Interquartile intervals) | Mean ± SD | |
| BDI[a] | | 29.00 ± 10.24 | | 19.91 ± 14.63 | 0.000 |
| OQ-45.2[a] | | | | | |
| Total Score | | 82.20 ± 16.68 | | 72.09 ± 24.38 | 0.000 |
| SD score | | 45.15 ± 10.92 | | 38.70 ± 15.18 | 0.000 |
| IR score | | 20.64 ± 03.94 | | 19.38 ± 05.96 | 0.137 |
| SR score | | 15.47 ± 04.18 | | 12.71 ± 05.06 | 0.000 |
| IL-6 (pg/mL)[b] | 05.44 (02.58; 06.38) | | 02.82 (02.20; 04.42) | | 0.000 |
| TNF- α (pg/mL)[b] | 11.60 (07.61; 16.27) | | 05.47 (04.42; 07.95) | | 0.000 |

BDI = Beck Depression Inventory; OQ-45 = Outcome Questionnaire 45.2; SD = Symptom Distress; IR = Interpersonal Relationship; SR = Social Role; IL-6 = Interleukin-6; TNF-α = Tumor Necrosis Factor –α.
[a] Student's t test.
[b] Wilcoxon signed-ranked test.

Journal of Psychiatric Research 75 (2016) 57–64

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

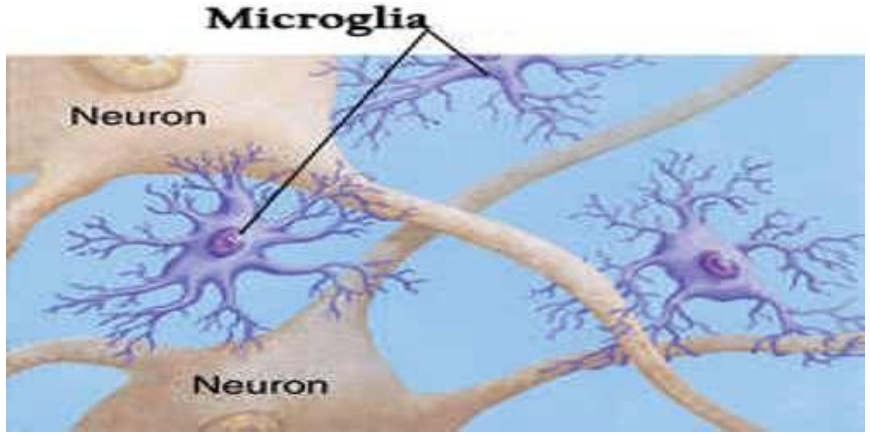
## Pro-inflammatory cytokines and psychotherapy in depression: Results from a randomized clinical trial

Giovanna Del Grande da Silva [a], Carolina David Wiener [a], Luana Porto Barbosa [a], Jaciana Marlova Gonçalves Araujo [a], Mariane Lopez Molina [a], Pedro San Martin [a], Jean Pierre Oses [a, b, c], Karen Jansen [a, b, c], Luciano Dias de Mattos Souza [a], Ricardo Azevedo da Silva [a, *]

[a] Translational Science on Brain Disorders, Department of Health and Behavior, Catholic University of Pelotas, Pelotas, RS, Brazil
[b] Translational Psychiatry Program, Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston (UTHealth) Medical School, Houston, TX, USA
[c] Center of Excellence on Mood Disorders, Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston (UTHealth) Medical School, Houston, TX, USA

# Why does inflammation cause mood changes that turn to a maladaptive state of clinical depression?

- Microglia cells in the brain are not able to recognize whether the source of proinflammatory cytokines that enter the brain are the result of health problems caused by a modern lifestyle or by an infection.




- If the amount of proinflammatory cytokines is high enough they trigger **sickness behaviour.**

# Sickness behaviour = Infection-induced depression

The behavioural patterns of sickness behaviour include:

- Loss of appetite,
- Psychomotor retardation
- Sleep disturbances
- Anergy
- Anhedonia
- Weakness
- Malaise
- Listlessness
- Hyperalgesia
- Impaired concentration
- Social isolation

These symptoms induced by sickness behaviour seem to be adaptations against infection, helping the immune system work more effectively.

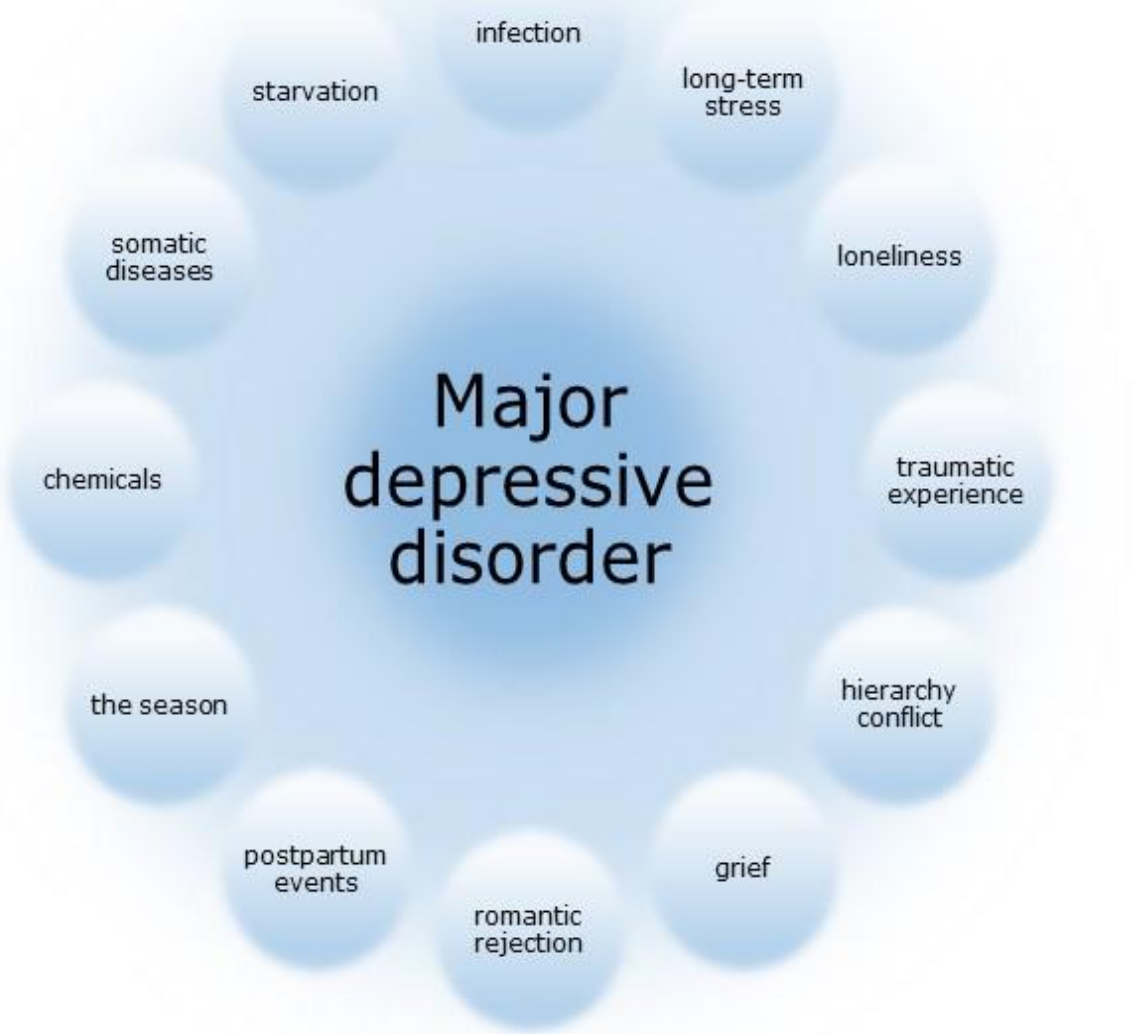
# When the symptoms of sickness behaviour are combined with an adaptive mood change, they may become maladaptive!

- Inflammation may enforce the symptoms and cause symptoms that do not help to resolve the adaptive problem that triggered the mood change.

# Treatment of depression should focus on treating the underlying causes of depression rather than treating the symptoms

It is also important to reduce the inflammation to reduce the risk of a new depressive episode!

# Intervention should be tailored individually based on the patient's subtype(s) of depression




Rantala, MJ, Luoto, S., Krams I. & Karlsson H. (2018 )Depression subtyping based on evolutionary psychiatry: proximate mechanisms and ultimate functions. *Brain, Behavior, and Immunity*. 69: 603-617.

# Inflammation can be reduced effectively by lifestyle interventions that mimic the life of hunter-gatherers

- Avoid chronic stress
- Exercise
- Eat a healthy, anti-inflammatory diet
- Avoid alcohol and drugs
- Spend time outdoors (in bright light)
- Sleep enough
- Be exposed to nature
- Reduce exposure to media
- Increase social life

# Thank you for your attention!