An evolutionary model of depression

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University of Turku
Do animals get depressed?
Depression is common in captivity
Insects have emotions

• Unexpected rewards make bees optimistic

• Agitated honeybees become pessimistic.
Cockroaches developed depression (learned helplessness) when they were tortured with electric shocks.

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 © Psychological Reports 1999

FORCED EXERCISE BLOCKS LEARNED HELPLESSNESS IN THE COCKROACH (*PERiplaneta americana*)

GARY E. BROWN, ERIC DAVIS, AND AMANDA JOHNSON

The University of Tennessee at Martin
In fruitflies, uncontrollable stress leads to depression (learned helplessness).

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


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

Olfactory bulbectomising causes depression in rats

Antidepressants reverse the effect!

Review
The olfactory bulbectomised rat as a model of depression

Cai Songa,b,*, Brian E. Leonardb

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bDepartment 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.

Social isolation triggers depression in rats

Social isolation causes comfort eating in rats.

Social isolation causes a state of chronic stress
Alcohol and certain drugs are able to trigger depression in rodents

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.

Losing a partner triggers depression in prairie voles

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
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 ($n = 168$). 


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

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.


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

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

12 subtypes of depression based on evolutionary psychology

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 become maladaptive
Clinical depression is becoming more common

Prevalence of depression in Finland (FinTerveys 2017)

<table>
<thead>
<tr>
<th></th>
<th>2011</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Women</td>
<td>9%</td>
<td>13%</td>
</tr>
</tbody>
</table>
The World Happiness Report

- 1. Finland
- 2. Danmark
- 3. Norway
- 4. Iceland
- 5. Nederland
- 6. Switchenland
- 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)

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


Chinese people born after 1966 are 22.4 times more likely to suffer from a depressive episode than Chinese people born before 1937.
Indigenous people in the arctic areas that changed to a modern lifestyle experienced tripled suicide rates in a decade.

The more “western” the lifestyle, the more common is depression.
Clinical depression is very rare among the old order amish

Prevalence of depression is 1%

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
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

The role of inflammation in depression

Nature Reviews Immunology 16, 22-34. (2016)
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 1: Immune host defense functions of single nucleotide polymorphisms (SNPs) associated with major depression based on the largest meta-analysis of genome-wide association studies (GWAS) conducted to date for major depression (MDE). (Continued)

<table>
<thead>
<tr>
<th>Gene ID</th>
<th>Gene name</th>
<th>SNP with minimum P-value</th>
<th>Immune host defense function of gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>SREFA</td>
<td>SRE family member 2</td>
<td>rs17220892</td>
<td>No specific immune or host defense functions identified for SREFA.</td>
</tr>
<tr>
<td>ALK1</td>
<td>Alkylidenic aldehyde dehydrogenase 1</td>
<td>rs2830808</td>
<td>ADGCR1 is involved in a rapid, NF-κB-dependent, signaling cascade initiated by microtubule stabilization of TLR4. ADGCR1 also regulates crosstalk between PI3K/Akt and proteoglycans in response to stimuli. This crosstalk regulates expression of SATI genes, which has been reported to be deregulated in preclinical models of autoimmune disorders.</td>
</tr>
<tr>
<td>UNC13A</td>
<td>Unc-13 homolog A</td>
<td>rs10207936</td>
<td>No specific immune or host defense functions identified for UNC13A, but a closely related homolog, UNC13A2, plays a crucial role in myelin processing and TLR7 functioning, and deficiency in its expression reduces TLR7 transcription and increases vulnerability to a number of infections.</td>
</tr>
<tr>
<td>TXN1</td>
<td>Tetrahydrobiopterin reductase 1</td>
<td>rs10605243</td>
<td>No specific immune or host defense functions identified.</td>
</tr>
<tr>
<td>TLR11</td>
<td>TLR11 homolog 1</td>
<td></td>
<td>No specific immune or host defense functions identified for TLR11; however, other TLR family members have been shown to be essential for proper immune function.</td>
</tr>
<tr>
<td>GAL</td>
<td>Galectin</td>
<td>rs10686984</td>
<td>Signaling through either type 1 or type 2 receptors, GAL has numerous cell-surface dependent effects. Consistent with PATHOS-D, multiple lines of evidence indicate GAL signaling is reduced in MDE. Reduced GMAP, which is produced by cleavage of the same precursor as galectin, has direct antiproliferative activity.</td>
</tr>
<tr>
<td>GOD</td>
<td>Glyoxalase</td>
<td>rs11683470</td>
<td>FYC gene expression is upregulated by TNP and by LPS and contributes to muscle glycogen breakdown and lactate accumulation. In mice, FYC is upregulated by TNP and MAPK and NF-κB signaling, leading to increased glucose utilization and diminished inflammatory cytokine release increases FYC in tumor-immune dendritic cells and enhanced TNP-induced signaling.</td>
</tr>
<tr>
<td>NPM1</td>
<td>Neutrophilic myeloperoxidase</td>
<td>rs11135899</td>
<td>Functions as an endogenous 'alarme' that activates proinflammatory cytokines (IL) and is identified as a host response factor in viral infections. It may aid in HIV and HCV virus dispersal within cells, and in the neutrophils, which has important survival properties.</td>
</tr>
<tr>
<td>USP4</td>
<td>Ubiquitin specific peptidase 3</td>
<td>rs1068302</td>
<td>Embedding of USP4 genes in the copy number variable δ-defensin cluster on chromosome 9p21 suggests a link with innate immunity. USP4 is activated by L- and L-pyroglutamic acid and is antiproliferative and apoptosis and proinflammatory properties.</td>
</tr>
</tbody>
</table>

HYPOTHESIS

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

CL Raison1,2 and AH Miller3

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.
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.

Anti-cytokine treatment alleviates depression symptoms!

**ORIGINAL ARTICLE**

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

N Kappelmans1, G Lewis2, R Darzi2, PB Jones1,4,5 and GM Khandaker1,4,5

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) = 0.46, 95% confidence interval (CI), 0.22–0.69). 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 ill 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.2016.107
The effect of psychotherapies to alleviate depression may be based on their ability to reduce inflammation!
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.

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!