COVID-19 and Immune Response Considerations from Co-morbid Psychiatric Diagnosis, Early Stress, Low Social Support, and Age

Presented by: Karen Lewicki, MD, JD for
White River VA Mental Health and Behavioral Sciences Grand Rounds
April 3, 2020
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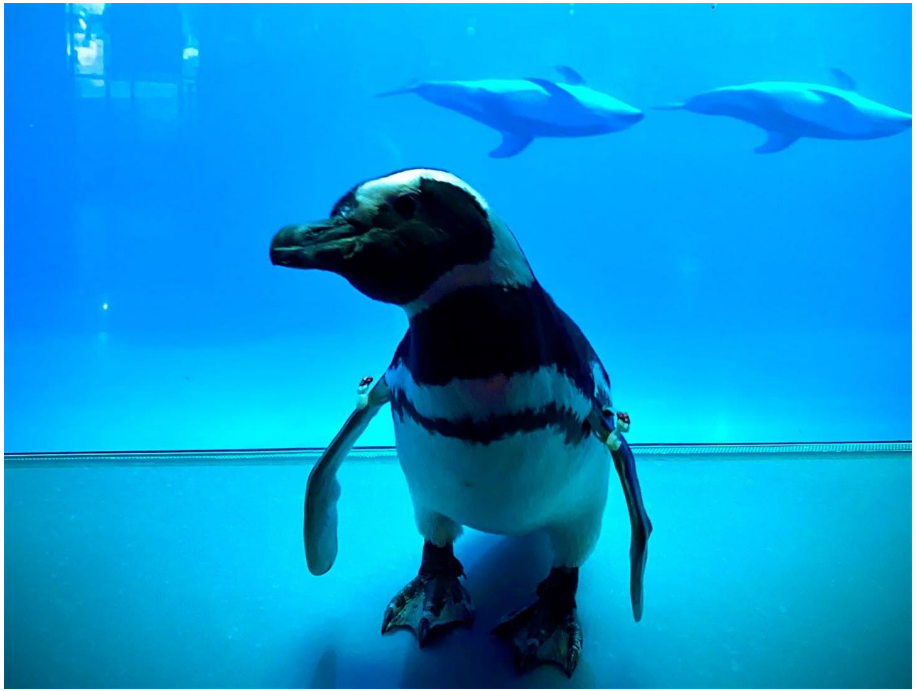
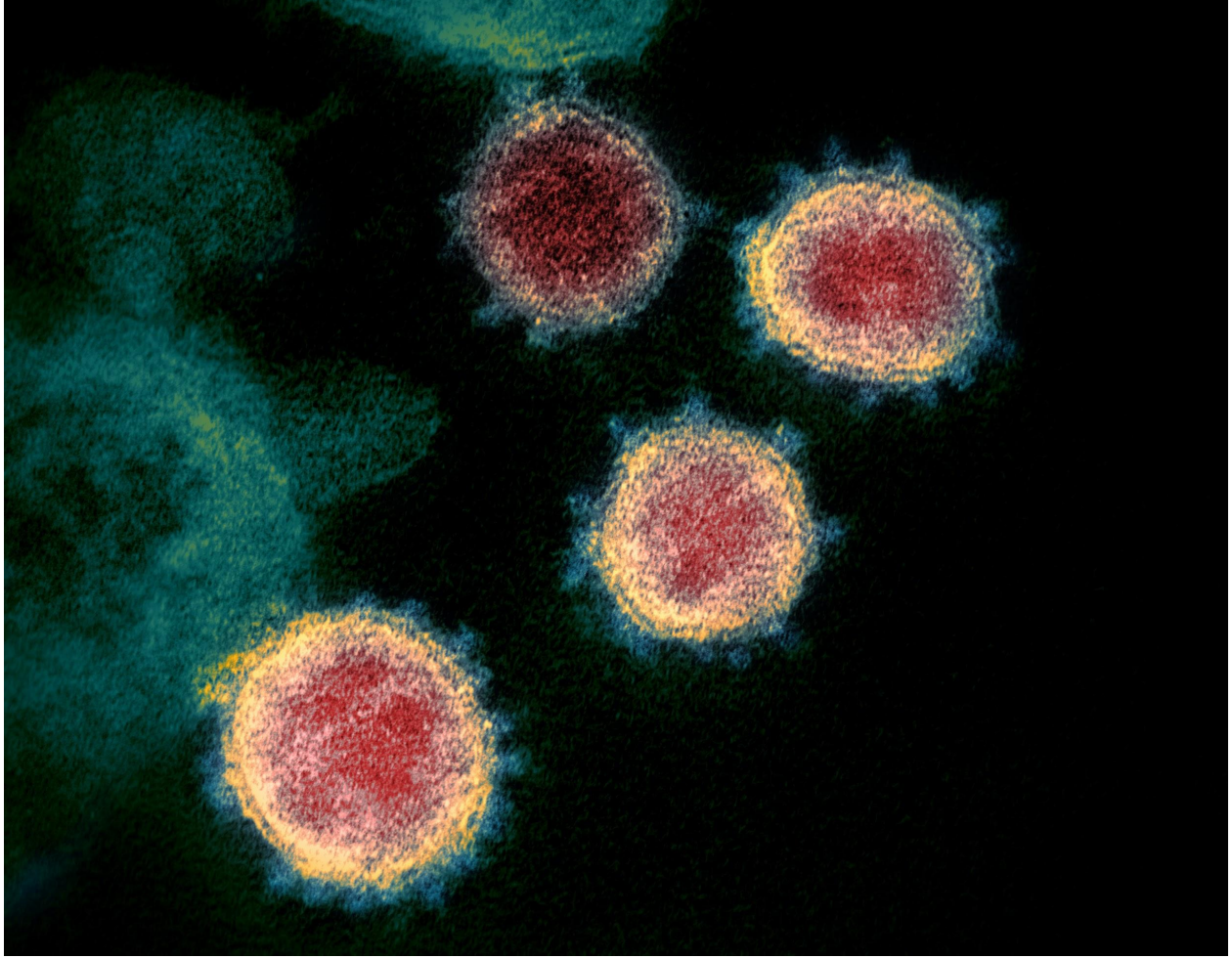
No conflicts to declare



Learning Objectives

1. Name several presentations of Covid-19 including digestive, cardiac, and neurological
2. Review the mechanisms of innate and adaptive immune responses to virus
3. Understand what is meant by the “Conserved Transcriptional Response to Adversity” whereby the central nervous and immune systems work together to anticipate pathogenic threats
4. Identify mechanisms through which inflammation becomes dysregulated in some identifiable patient groups
5. Name potential avenues of treatment focused on ameliorating dysregulated immune responses



Coronaviruses are positive-stranded RNA viruses in an envelope made of two proteins, M (membrane) and S (spike). There have been two previous zoonotic coronaviruses, SARS-CoV (11% fatality) and MERS-CoV (34% fatality). These viruses cause transient respiratory or GI illness, although SARS also had neurologic manifestations.

Commonly reported symptoms of COVID-19

Likelihood of symptoms[30]

Symptom	%
Fever	87.9
Dry cough	67.7
Fatigue	38.1
Sputum production	33.4
Shortness of breath	18.6
Muscle pain or joint pain	14.8
Sore throat	13.9
Headache	13.6
Chills	11.4
Nausea or vomiting	5.0
Nasal congestion	4.8
Diarrhea	3.7 to 31[31]
Haemoptysis	0.9
Conjunctival congestion	0.8

Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)(PDF) (Report). World Health Organization (WHO). 16–24 February 2020. Retrieved 21 March 2020.

Although respiratory symptoms continue to make the common and expected presentation of Covid-19, other presentations have been reported. In addition to anecdotal reports of coagulopathy, significant cardiac and neurologic symptoms and presentations have been recorded:

Tian-Yuan Xiong, Simon Redwood, Bernard Prendergast, Mao Chen, **Coronaviruses and the cardiovascular system: acute and long-term implications**, *European Heart Journal*, https://doi.org/10.1093/eurheartj/ehaa231

1. COVID-19 case reports suggest that there is increased myocardial injury (as evidenced by elevated high-sensitivity troponin I) in one study where 4 patients out of 41 required intensive care unit (ICU) care and another study (n = 138 patients) reported that 7.2% had acute cardiac injury, 8.7% had shock, and 16.7% had cardiac arrhythmias — most patients required ICU.

2. SARS virus is associated in one study (n = 121) with hypotension, bradycardia, tachycardia, cardiomegaly, and arrhythmia (mostly transient); cardiac arrest and death in another study (n = 15); and subclinical diastolic impairment with systolic involvement on echocardiography (reversible on clinical recovery) in a third report (n = 46).

3. Angiotensin-converting enzyme 2 (ACE2) is expressed in the heart and SARS-CoV-2 virus binds to cells expressing receptors, particularly ACE2.

COVID-19: Neurologists in Italy to Colleagues in US: Look for Poorly-Defined Neurologic Conditions in Patients with the Coronavirus

By Jamie Talan
March 27, 2020

The CDC has identified several conditions that put people at high risk for severe illness:

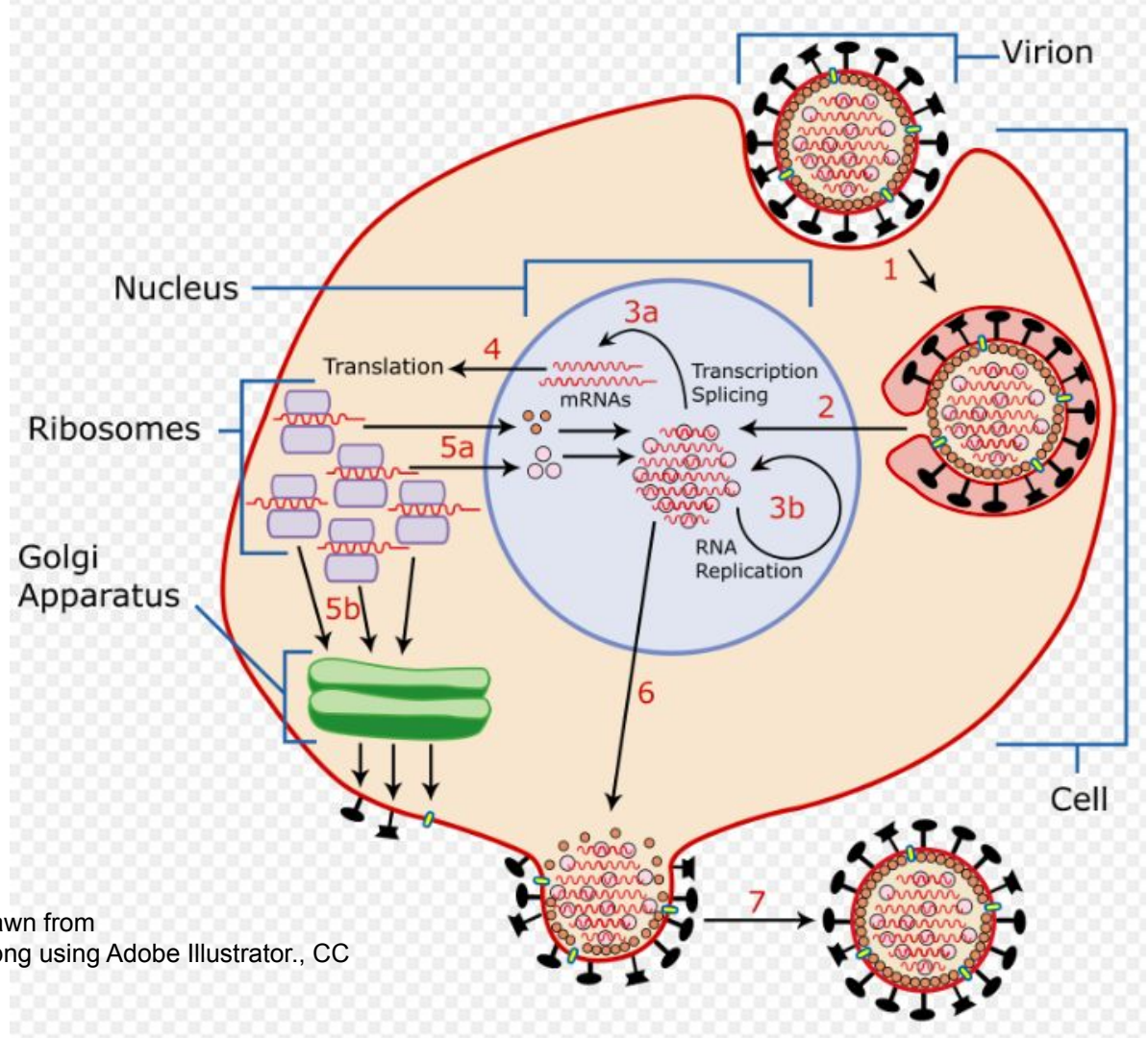
CDC.gov

Based upon available information to date, those at high-risk for severe illness from COVID-19 include:

- People aged 65 years and older
- People who live in a nursing home or long-term care facility
- Other high-risk conditions could include:
  - People with chronic lung disease or moderate to severe asthma
  - People who have serious heart conditions
  - People who are immunocompromised including cancer treatment
  - People of any age with severe obesity (body mass index [BMI] ≥40) or certain underlying medical conditions, particularly if not well controlled, such as those with diabetes, renal failure, or liver disease might also be at risk

This presentation will largely consider how a person's physical response to their social environment can increase their risk of contracting Covid-19 and experiencing a more severe course. In particular, we will be looking at the action of non-conscious, evolutionarily conserved responses, such as altered transcription of immune response genes, which has been the work of researchers including Steve Cole, Michael Irwin, and George Slavich.

First, however, we will review how viral infections work:



Anti-viral defense - a brief review

Toll-like receptors on macrophages and dendritic cells recognize viral patterns.

TLR4 - viral components on the infected cell surface

TLR3, 7, 8, 9 - viral nucleic acids on endosomal membranes

Ligand recognition leads to activation of Type 1 Interferons - so named because they interfere with viral replication

Interferon inducible genes go on to: induce maturation of dendritic cells, enhance antibody responses in B cells, and mediate induction of CD8+ T cell responses

Innate immune system action initiates action against pathogens, followed by action of the adaptive system

Natural Killer (NK) cells of the innate system recognize and destroy cells that are not displaying the normal volume of MHC I complexes.

Dendritic cells of the innate system activate “helper” T cells, which in turn release signalling molecules called cytokines which further activate both the innate and adaptive systems.

Is immune function or viral susceptibility altered in the context of psychiatric disease?

PTSD nearly doubles infection risk

Date: October 15, 2019

Source: Boston University School of Medicine

Summary: A new study is the first to examine the relationship between post-traumatic stress disorder (PTSD) and dozens of infection types in a nationwide cohort. Researchers found that PTSD affects infection risks for men and women differently, having, for example, more of an effect on a woman's risk of urinary tract infection and a man's risk of skin infection.

Tammy Jiang, Dóra Körmendiné Farkas, Thomas P. Ahern, Timothy L. Lash, Henrik T. Sørensen, Jaimie L. Gradus. **Posttraumatic Stress Disorder and Incident Infections**. *Epidemiology*, 2019; 30 (6): 911

However there has been a general awareness for decades that “stress” can alter immune function - this NEJM study is nearly 30 years old:

ORIGINAL ARTICLE

Psychological Stress and Susceptibility to the Common Cold

Sheldon Cohen, Ph.D., David A.J. Tyrrell, M.D., and Andrew P. Smith, Ph.D.

CONCLUSIONS.

Psychological stress was associated in a dose-response manner with an increased risk of acute infectious respiratory illness, and this risk was attributable to increased rates of infection rather than to an increased frequency of symptoms after infection. (N Engl J Med 1991; 325:606–12.)

The question has not been whether stress can make you sick, so much as what kind of stress, and how.

How stress influences disease: Study reveals inflammation as the culprit

Date: April 2, 2012

Source: Carnegie Mellon University

Summary: Stress wreaks havoc on the mind and body. Until now, it has not been clear exactly how stress influences disease and health. Now researchers have found that chronic psychological stress is associated with the body losing its ability to regulate the inflammatory response. The research shows for the first time that the effects of psychological stress on the body's ability to regulate inflammation can promote the development and progression of disease.

Sheldon Cohen, Denise Janicki-Deverts, William J. Doyle, Gregory E. Miller, Ellen Frank, Bruce S. Rabin, and Ronald B. Turner. **Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk**. *PNAS*, April 2, 2012

What kind of stress?

Social Safety Theory: A Biologically Based Evolutionary Perspective on Life Stress, Health, and Behavior

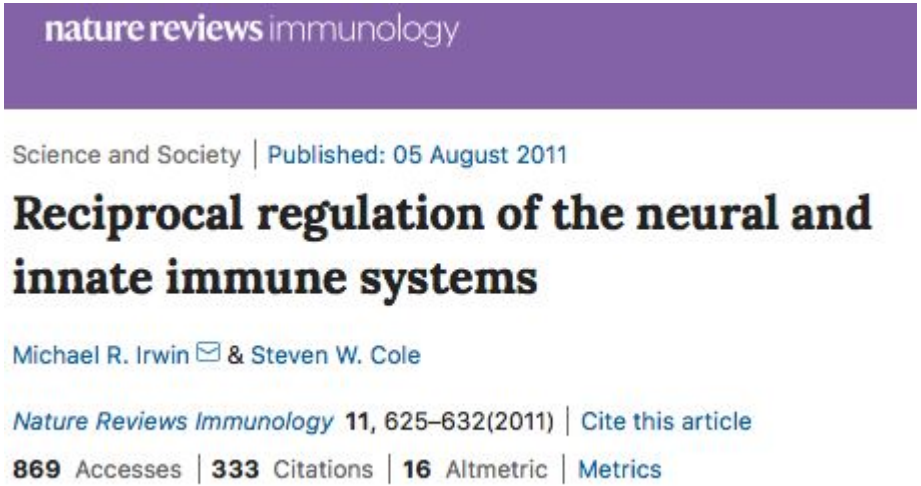
Annual Review of Clinical Psychology

Vol. 16:- (Volume publication date May 2020)
Review in Advance first posted online on March 6, 2020. (Changes may still occur before final publication.)
https://doi.org/10.1146/annurev-clinpsy-032816-045159

George M. Slavich

Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, California 90095-7076, USA; email: gslavich@mednet.ucla.edu

Multiple lines of research over the last two decades have indicated that across species of social mammals, the central nervous systems function cooperatively to track an individual's quality of social safety and connection



Connected and isolated social mammals face different risks and have different needs

Connected:

More likely to encounter viruses from nearby conspecifics, thus greater need of active anti-viral gene programs

Less anticipation of physical fighting, thus less active anti-coagulation

Able to rely on nearby others to sense danger, thus sleep more deeply

Isolated:

Lower virus exposure from conspecifics, thus less active anti-viral gene programs

As in many mammal groups a fight precedes expulsion more active coagulation factors

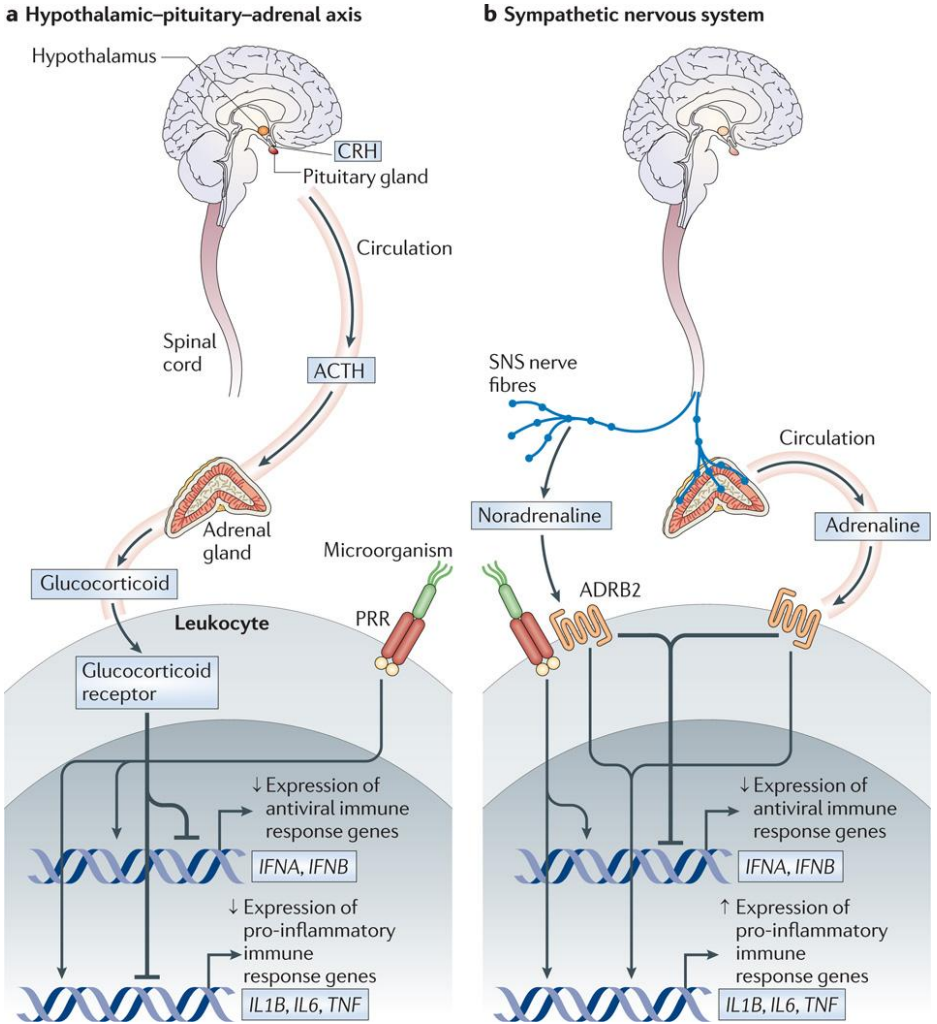
Lighter sleep

Overall increase of background inflammation

Figure from “Reciprocal regulation” detailing altered gene expression in the context of perceived social threat.

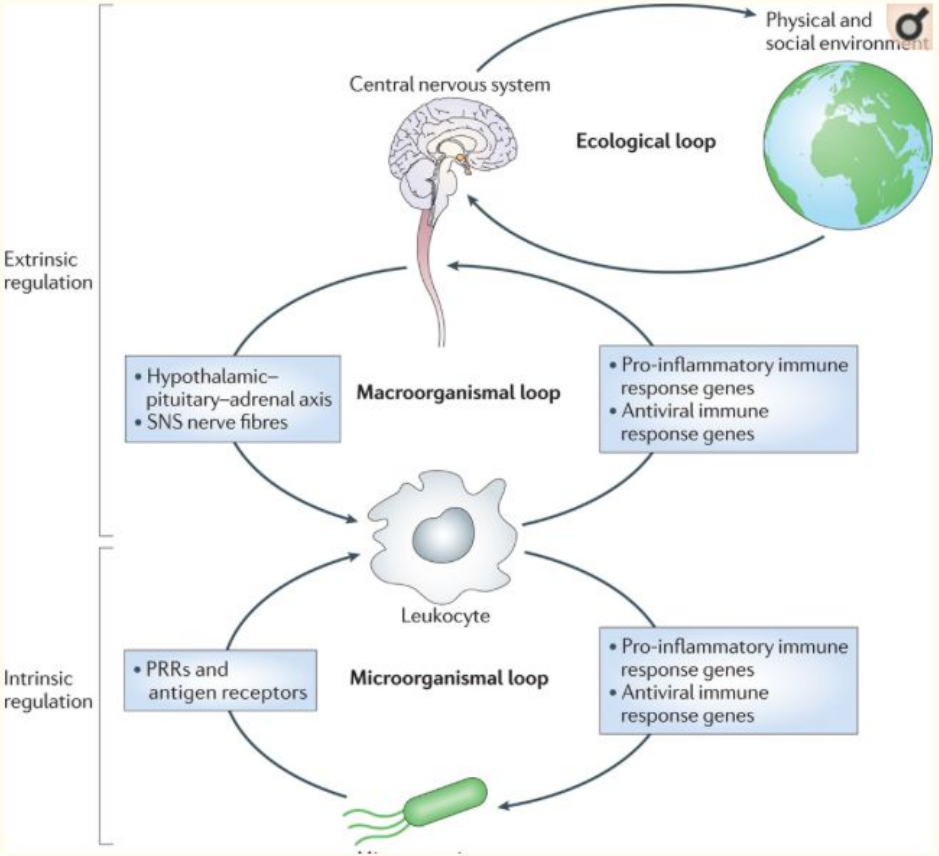
Although glucocorticoids act in the short term to decrease inflammatory signalling, over time receptor responsiveness decreases.

At the same time, sympathetic responses drive increased inflammatory gene activity



A second figure from this paper.

A key idea here is that transcriptional alterations are driven by **subjective perception** of social connection, as well as by immune system detection of damage and pathogen associated patterns



Open in a separate window

Figure 2

Multi-circuit control of the innate immune transcriptome

The work of Jos Brosschot on cardiovascular responses to social stress converges with Steven Cole’s concept of the CTRA, or Conserved Transcriptional Response to Adversity.

Eur J Psychotraumatol. 2017 Apr 10;8(1):1309934. doi: 10.1080/20008198.2017.1309934. eCollection 2017.

Ever at the ready for events that never happen.

Brosschot JF[1].

⊕ Author information

Abstract

Stress, whether daily stress, work stress or traumatic stress, is unhealthy. This lecture covers three recent theoretical approaches in explaining the mechanisms underlying the influence of psychological stress on somatic health. It is argued that stress research should focus less on stressors themselves and put more emphasis on prolonged stress responses. Three mechanisms are identified that cause this unhealthy prolonged stress response: first, the partly-proven mechanism of perseverative cognition; second, the mechanism of unconscious stress, which is currently being explored; and third, the notion of the stress response being a default response that is inhibited only when safety is perceived. All three mechanisms are deeply rooted in millions of years of our evolution. Although the dangers of the past have virtually disappeared, many of us remain ever at the ready for events that never happen.

KEYWORDS: Perseverative cognition; default stress response; generalized unsafety; loneliness; perceived safety; unconscious stress

Brosschot's acronym for his concept is GUTS

Int J Environ Res Public Health. 2018 Mar 7;15(3). pii: E464. doi: 10.3390/ijerph15030464.

Generalized Unsafety Theory of Stress: Unsafe Environments and Conditions, and the Default Stress Response.

Brosschot JF[1], Verkuil B[2], Thayer JF[3].

⊕ Author information

Abstract

Prolonged physiological stress responses form an important risk factor for disease. According to neurobiological and evolution-theoretical insights the stress response is a default response that is always "on" but inhibited by the prefrontal cortex when safety is perceived. Based on these insights the Generalized Unsafety Theory of Stress (GUTS) states that prolonged stress responses are due to generalized and largely unconsciously perceived unsafety rather than stressors. This novel perspective necessitates a reconstruction of current stress theory, which we address in this paper. We discuss a variety of very common situations without stressors but with prolonged stress responses, that are not, or not likely to be caused by stressors, including loneliness, low social status, adult life after prenatal or early life adversity, lack of a natural environment, and less fit bodily states such as obesity or fatigue. We argue that in these situations the default stress response may be chronically disinhibited due to unconsciously perceived generalized unsafety. Also, in chronic stress situations such as work stress, the prolonged stress response may be mainly caused by perceived unsafety in stressor-free contexts. Thus, GUTS identifies and explains far more stress-related physiological activity that is responsible for disease and mortality than current stress theories.

Decreased social connection, increased social isolation, and loneliness, are seen with many psychiatric disorders

Stigma of psychiatric diagnosis can drive perception of rejection

With some disorders, like depression, perception of social isolation, guilt and other feelings driving self-isolation, are parts of the disorder

With PTSD, lack of social support is a risk factor for and driver of symptoms

Increased risk of metabolic syndrome and diabetes seen in many psychiatric disorders is both a sign that CTRA/GUTS processes are at work and indicate patients are at increased risk of severe course of Covid-19 infection

Adverse Childhood Experiences are likely also to drive processes associated with CTRA/GUTS

The 10 questions of Dr. Felitti and Dr. Anda's ACE questionnaire speak to experiences in which a child has difficulty receiving social support - either because of active aggression or abuse (physical, emotional, sexual) - or because the parents are unable to provide social support due to absence, incarceration, drug use etc.

Adverse Childhood Experience (ACE) Questionnaire

Finding your ACE Score ra hbe 10 24 06

While you were growing up, during your first 18 years of life:

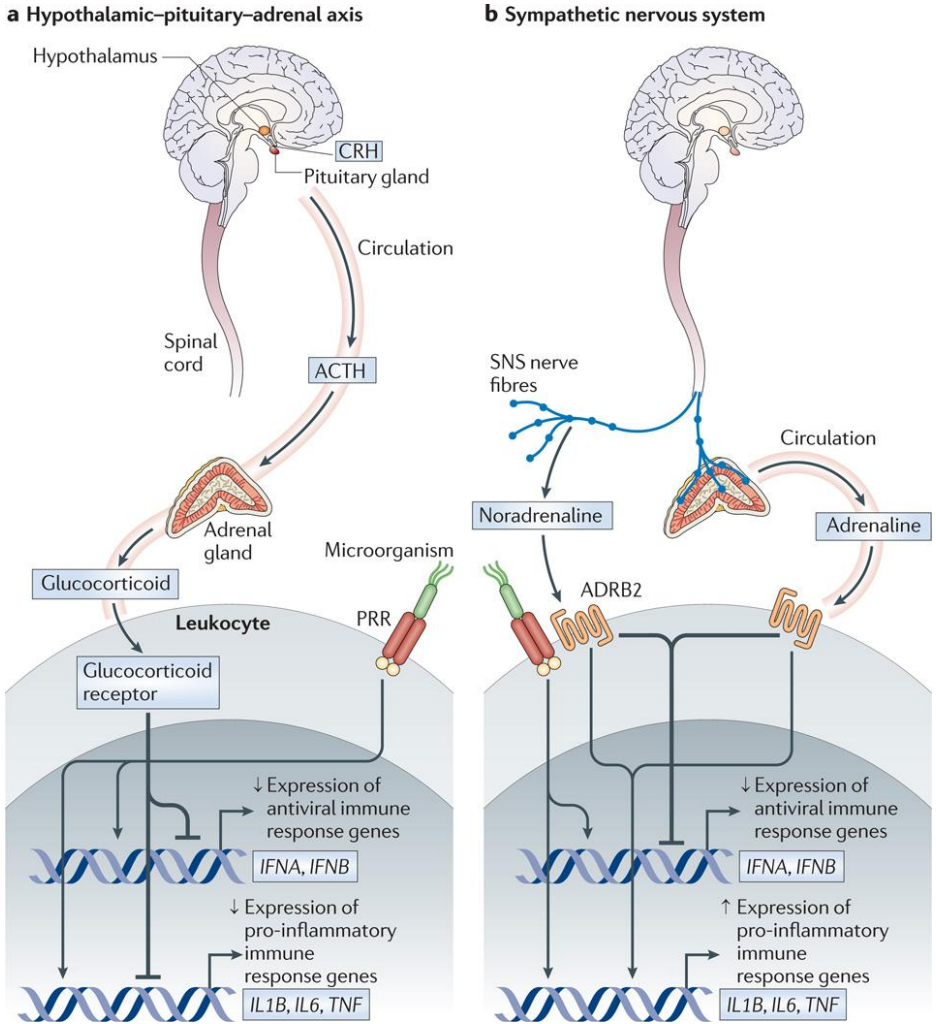
1. Did a parent or other adult in the household **often** …
   Swear at you, insult you, put you down, or humiliate you?
   or
   Act in a way that made you afraid that you might be physically hurt?
   Yes No If yes enter 1 _____

2. Did a parent or other adult in the household **often** …
   Push, grab, slap, or throw something at you?
   or
   Ever hit you so hard that you had marks or were injured?
   Yes No If yes enter 1 _____

3. Did an adult or person at least 5 years older than you **ever**…
   Touch or fondle you or have you touch their body in a sexual way?
   or
   Try to or actually have oral, anal, or vaginal sex with you?
   Yes No If yes enter 1 _____

4. Did you **often** feel that …
   No one in your family loved you or thought you were important or special?
   or
   Your family didn't look out for each other, feel close to each other, or support each other?
   Yes No If yes enter 1 _____

When frequent or significant social rejection is experienced during development, the formation of the nervous and immune systems is affected. Development in a socially hostile or neglectful environment can lead to more robust connection between the nervous and immune systems and overall increased inflammatory responses, which is a likely cause of the increased burden of both autoimmune and inflammatory disease seen in patients with high ACE scores (4 or greater).



Health risks associated with ACE scores:

At or over 2: Doubles risk of autoimmune disease

At or over 4: Increased risk for diabetes, stroke, COPD and emphysema

At or over 6: Premature mortality up to 20 years, not explained by health behaviors

At or over 7: Triple lifetime odds of lung cancer

3.5x odds of ischemic heart disease

Emotional responses and reaction styles also seem to have a direct connection to immune system function

Perspect Psychol Sci. 2017 Jul;12(4):588-612. doi: 10.1177/1745691616689091. Epub 2017 Jul 5.

Inflammation, Self-Regulation, and Health: An Immunologic Model of Self-Regulatory Failure.

Shields GS[1], Moons WG[2], Slavich GM[3].

Author information

1 1 Department of Psychology, University of California, Davis.

2 2 Moons Analytics, San Diego, CA.

3 3 Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles.

Abstract

Self-regulation is a fundamental human process that refers to multiple complex methods by which individuals pursue goals in the face of distractions. Whereas superior self-regulation predicts better academic achievement, relationship quality, financial and career success, and lifespan health, poor self-regulation increases a person's risk for negative outcomes in each of these domains and can ultimately presage early mortality. Given its centrality to understanding the human condition, a large body of research has examined cognitive, emotional, and behavioral aspects of self-regulation. In contrast, relatively little attention has been paid to specific biologic processes that may underlie self-regulation. We address this latter issue in the present review by examining the growing body of research showing that components of the immune system involved in inflammation can alter neural, cognitive, and motivational processes that lead to impaired self-regulation and poor health. Based on these findings, we propose an integrated, multilevel model that describes how inflammation may cause widespread biobehavioral alterations that promote self-regulatory failure. This immunologic model of self-regulatory failure has implications for understanding how biological and behavioral factors interact to influence self-regulation. The model also suggests new ways of reducing disease risk and enhancing human potential by targeting inflammatory processes that affect self-regulation.

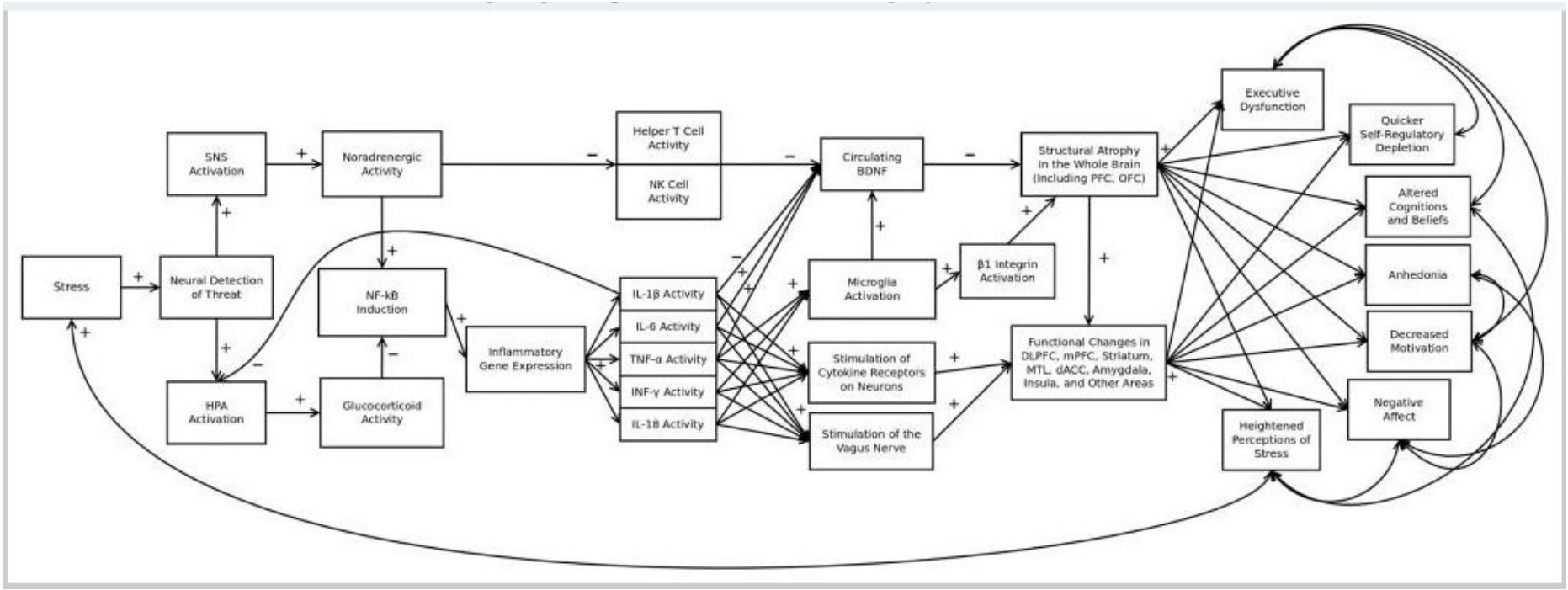
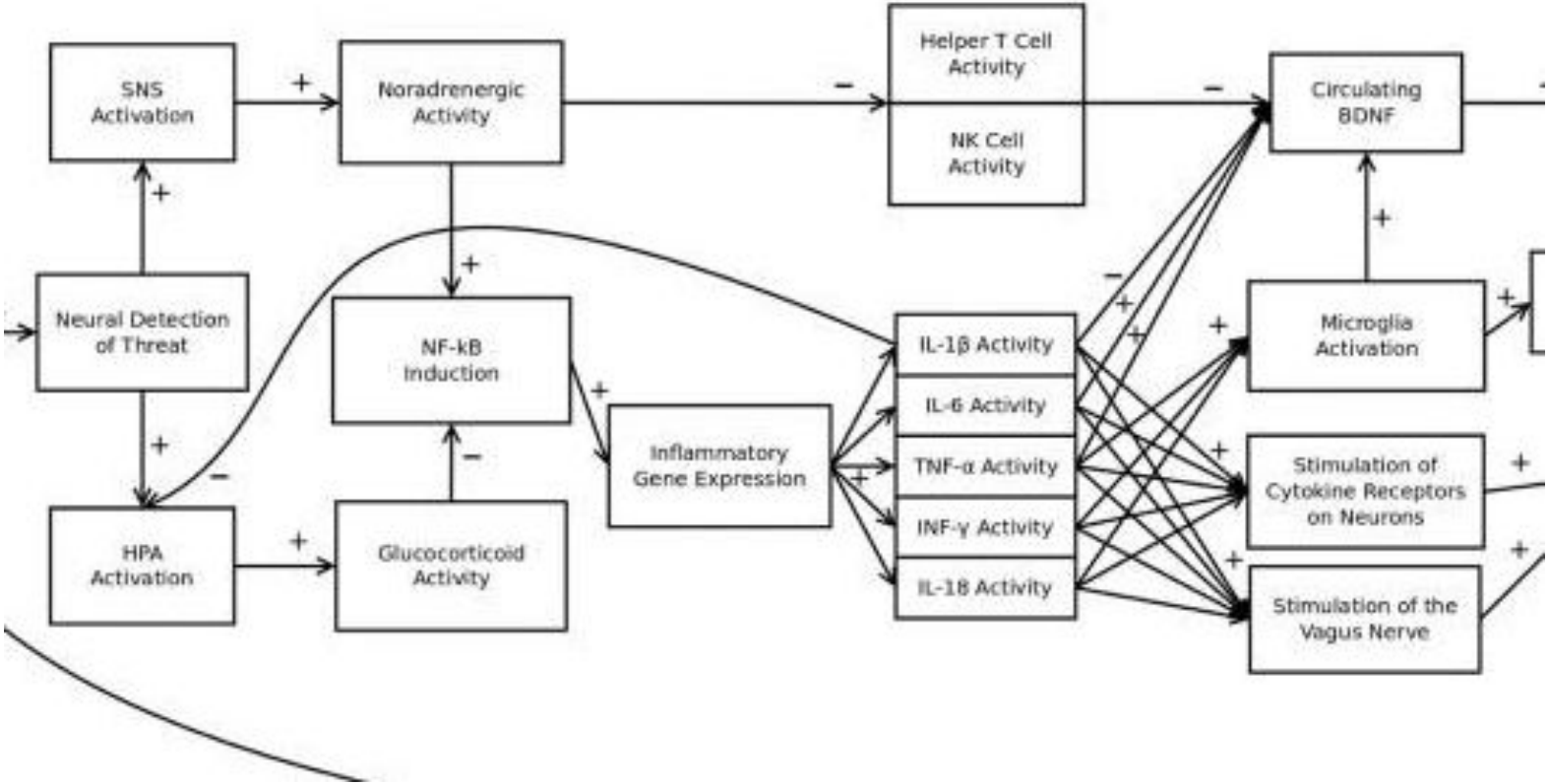
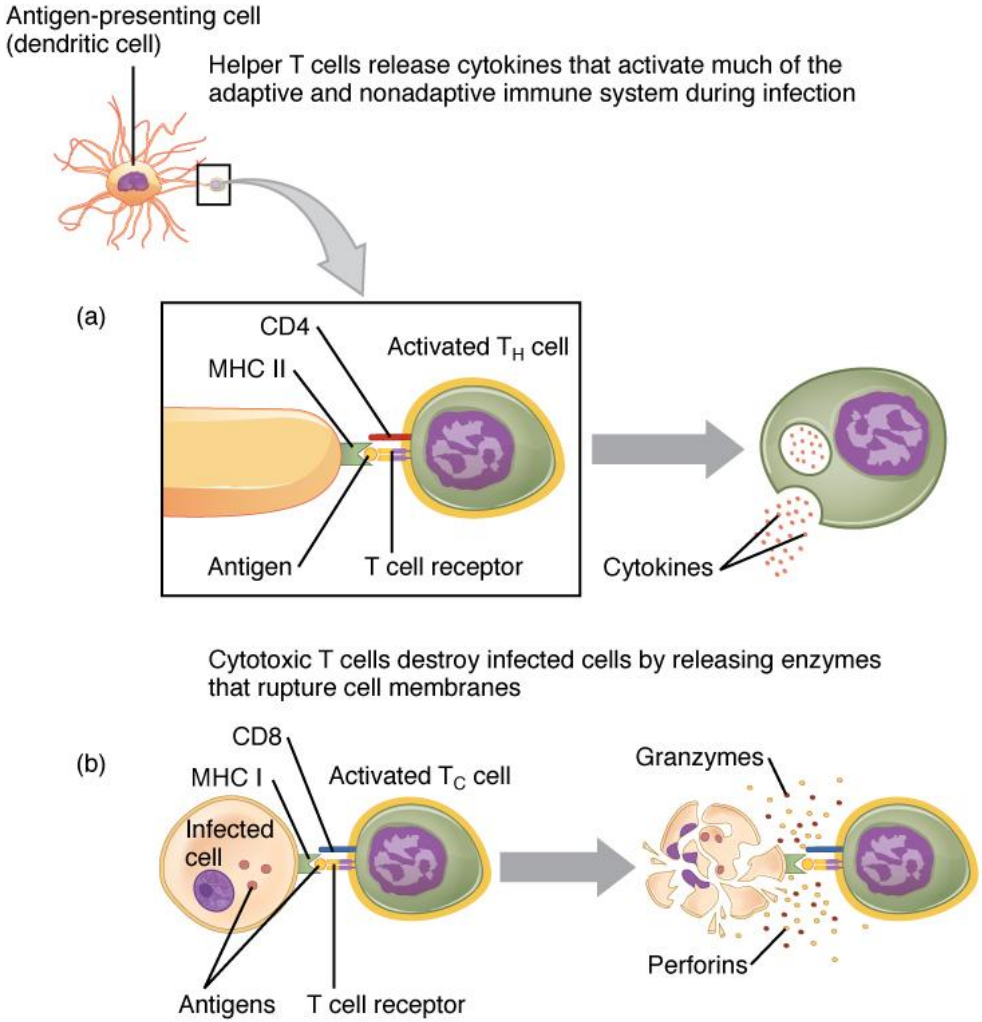


Figure from Inflammation, Self-regulation, and Health, previous

Reduced Helper T cell and Natural Killer cell activity is observed in the context of impaired self-regulation




Antigen-presenting cell
(dendritic cell)
Helper T cells release cytokines that activate much of the adaptive and nonadaptive immune system during infection
(a)
CD4
Activated T_H cell
MHC II
Antigen
T cell receptor
Cytokines
Cytotoxic T cells destroy infected cells by releasing enzymes that rupture cell membranes
(b)
CD8
MHC I
Activated T_C cell
Infected cell
Antigens
T cell receptor
Granzymes
Perforins

CDC guidelines for risk include moderate to severe asthma as a condition. It is worth being mindful of the role which subjective experiences of stress and early experiences contribute to this disease process

Curr Opin Allergy Clin Immunol. Author manuscript; available in PMC 2019 Apr 1.
Published in final edited form as:
Curr Opin Allergy Clin Immunol. 2018 Apr; 18(2): 148–158.
doi: 10.1097/ACI.0000000000000421

PMCID: PMC5835351
NIHMSID: NIHMS945528
PMID: 29369067

Evidence establishing a link between prenatal and early life stress and asthma development

Maria José Rosa, DrPH,[1] Alison Lee, MD, MS,[2] and Rosalind J. Wright, MD, MPH[1,3,4]

Why do older people appear to be at greater risk?

- Tissues and systems are more worn (cardiovascular)
- Immunosenescence

Notably, persistent social threat and loneliness appear to drive accelerated cellular aging and a more reactive, inflammatory-signal driven immune response

Thus although psychiatric patients are not identified by the CDC as belonging in a high risk category, it falls to us as clinicians who know our patient's histories - of early experience, of current social connection or disconnection - to estimate how the above characterized processes affect their risk

CDC.gov

Based upon available information to date, those at high-risk for severe illness from COVID-19 include:

- People aged 65 years and older
- People who live in a nursing home or long-term care facility
- Other high-risk conditions could include:
  - People with chronic lung disease or moderate to severe asthma
  - People who have serious heart conditions
  - People who are immunocompromised including cancer treatment *
  - People of any age with severe obesity (body mass index [BMI] ≥40) or certain underlying medical conditions, particularly if not well controlled, such as those with diabetes, renal failure, or liver disease might also be at risk

*or altered immune function due to CTRA-type transcriptional responses, especially if gauged by early developmental onset (ACE 4 or higher) or co-occurring inflammatory disorder

That was an exploration of factors potentially increasing Covid-19 infection risk or severity

Can understanding of how social connection impacts immune response point to ways to fight disease?

Ways to “boost” the immune system:

1. Limit alcohol

2. Exercise

   The signalling molecule IL-6 may be an inflammatory or anti-inflammatory messenger depending on context - exercise appears to promote its anti-inflammatory signalling action

As described here:

ELSEVIER

Brain, Behavior, and Immunity

Volume 73, October 2018, Pages 1-2

Viewpoint

Interleukin (IL)-6: A good kid hanging out with bad friends (and why sauna is good for health)

Charles L. Raison [a, b, c], Jennifer M. Knight [d], Carmine Pariante [e]

Show more

https://doi.org/10.1016/j.bbi.2018.06.008

Ways to “boost” the immune system:

1. Limit alcohol

2. Exercise

3. Sleep

Promotion of good sleep hygiene is always indicated, but melatonin has been investigated as a possible immune modulator in the context of viral infection, starting with Ebola

ELSEVIER

Life Sciences

Available online 23 March 2020, 117583

In Press, Journal Pre-proof

COVID-19: Melatonin as a potential adjuvant treatment

Rui Zhang [a], Xuebin Wang [a], Leng Ni [a], Xiao Di [a], Baitao Ma [a], Shuai Niu [a], Changwei Liu [a] ✉, Russel J. Reiter [b] ✉

⊞ Show more

https://doi.org/10.1016/j.lfs.2020.117583

Ways to “boost” the immune system:

1. Limit alcohol

2. Exercise

3. Sleep

4. **Social connection**

From Zoom to Netflix group watching apps, there are myriad ways for people to maintain social connection during the pandemic.

There are also ways for people to try to access the benefits of social connection during isolation, however, and these include the writing interventions pioneered by James Pennebaker, Expressive Writing

A common format of an expressive writing intervention is to direct a participant to identify a signal event they experienced, often a secret or a thing they have not talked about with others, and to direct them to write their “deepest thoughts and feelings” about it for a time-limited period of 30 minutes on 3 separate occasions. Participants are told their writing will be read. Immune system benefits have commonly been observed in research on this intervention. Notably discussion of the writing does not appear to be necessary for benefit; it seems necessary only that the writer knows that what they have written will be read.

Numerous studies have been done on the effects of Expressive Writing

Psychosom Med. 2004 Mar-Apr;66(2):272-5.

Effect of written emotional expression on immune function in patients with human immunodeficiency virus infection: a randomized trial.

Petrie KJ[1], Fontanilla I, Thomas MG, Booth RJ, Pennebaker JW.

⊕ Author information

Abstract

OBJECTIVES: To determine whether writing about emotional topics compared with writing about neutral topics could affect CD4+ lymphocyte count and human immunodeficiency virus (HIV) viral load among HIV-infected patients.

METHODS: Thirty-seven HIV-infected patients were randomly allocated to 2 writing conditions focusing on emotional or control topics. Participants wrote for 4 days, 30 minutes per day. The CD4+ lymphocyte count and HIV viral load were measured at baseline and at 2 weeks, 3 months, and 6 months after writing.

RESULTS: The emotional writing participants rated their essays as more personal, valuable, and emotional than those in the control condition. Relative to the drop in HIV viral load, CD4+ lymphocyte counts increased after the intervention for participants in the emotional writing condition compared with control writing participants.

CONCLUSIONS: The results are consistent with those of previous studies using emotional writing in other patient groups. Based on the self-reports of the value of writing and the preliminary laboratory findings, the results suggest that emotional writing may provide benefit for patients with HIV infection.

Immune benefits of other meditative practices also being explored

J Natl Cancer Inst Monogr. 2014 Nov; 2014(50): 295–301.
Published online 2014 Nov 4. doi: 10.1093/jncimonographs/lgu028
PMCID: PMC4411534
PMID: 25749595

Tai Chi, Cellular Inflammation, and Transcriptome Dynamics in Breast Cancer Survivors With Insomnia: A Randomized Controlled Trial

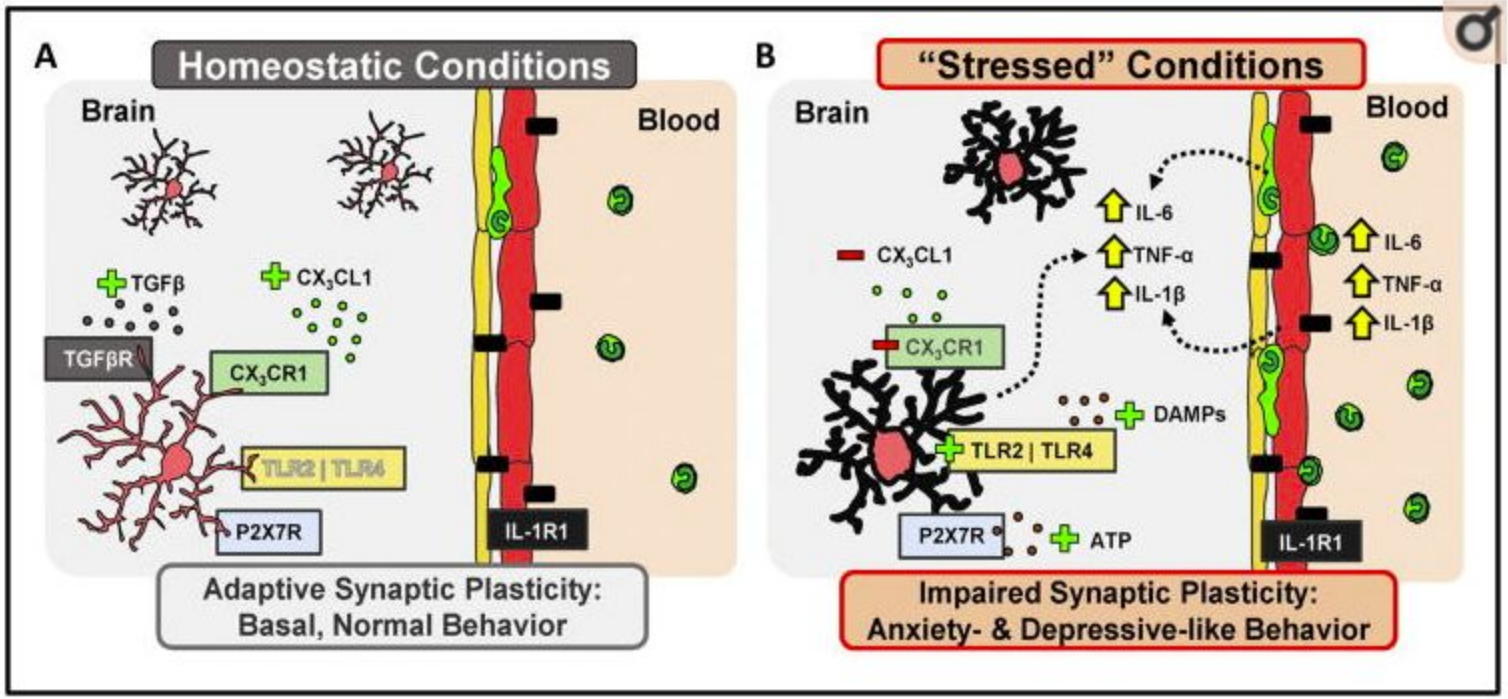
Michael R. Irwin,[✉] Richard Olmstead, Elizabeth C. Breen, Tuff Witarama, Carmen Carrillo, Nina Sadeghi, Jesusa M. G. Arevalo, Jeffrey Ma, Perry Nicassio, Patricia A. Ganz, Julienne E. Bower, and Steve Cole

Experimental trials:

- Melatonin

- Vitamin C

- Tociizumab, Baricitinib, Ruxolitinib, Fedratinib


A
Homeostatic Conditions
Brain
Blood
TGFβ
CX3CL1
TGFβR
CX3CR1
TLR2 | TLR4
P2X7R
IL-1R1
Adaptive Synaptic Plasticity:
Basal, Normal Behavior
B
"Stressed" Conditions
Brain
Blood
IL-6
TNF-α
IL-1β
CX3CL1
CX3CR1
DAMPs
TLR2 | TLR4
P2X7R
ATP
IL-1R1
Impaired Synaptic Plasticity:
Anxiety- & Depressive-like Behavior

Conclusion:

Converging lines of research show that social mammals have evolutionarily-driven biological responses to the perception of social disconnection.

These responses typically involve increases in systemic inflammation and immune response changes with overall poorer anti-viral responses.

When stress responses to social threat continue over time, the result can look like responses associated with greater age.

For these reasons, patients with early adversity and psychiatric histories may be at greater risk of contracting Covid-19, and experiencing a more severe course.

We can use our awareness of this biology to identify and protect vulnerable patients.

We can use it to aid everyone.

Thank you!