The Microbiome and Mental Health

Brain & Behavior Research Foundation Webinar
Tuesday, July 11, 2017 2:00 PM - 3:00 PM EDT

Illustration by Benjamin Arthur for NPR

Disclosures

• Presenter(s) has the following interest to disclose:
  • Member of Scientific Advisory Board (Immodulon Therapeutics, Ltd.)
Outline

• Prevention of mental health disorders
• The Hygiene Hypothesis and psychiatric disorders
• Psychiatric disorders as disorders with a failure of immunoregulation
• Restoration of immunoregulation prevents development of a stress-induced PTSD-like syndrome
• Future directions
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Mental health research

“In contrast to researchers in cancer and heart disease who have sought cures and preventions, biological psychiatrists in both academia and industry have set their sights on incremental and marketable advances, such as drugs with fewer adverse effects.”

Insel and Scolnick, 2006, Mol Psychiatry, 11, 11-17
Major depression is common and becoming more common.

**Rank Order of Disability-Adjusted Life-Years for the 15 Leading Causes**

<table>
<thead>
<tr>
<th>Rank by Year</th>
<th>Disease or Injury</th>
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<td>1990</td>
<td>2020</td>
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</table>

Mental health research

“Psychiatry will need to develop strategies for prevention for each of these disorders.”

[schizophrenia, mood disorders, and autism]

Thomas R. Insel, M.D.
NIMH Director

Dadu Shin, In, Should I tell my students I have depression?

Insel and Scolnick, 2006, Mol Psychiatry, 11, 11-17
Where should we start in search of prevention strategies for psychiatric disorders/optimizing resilience?

Risk factors for psychiatric disorders

- Genetic predisposition
- Environmental influences (ACE, microbial inputs)
- Failure of immunoregulation

↑ Inflammation

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↑ Inflammation

Proinflammatory microbial inputs \( \downarrow \) (+) (−) \( \downarrow \)
Immunoregulatory microbial inputs
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The hygiene hypothesis and psychiatric disorders

“…, some psychiatric disorders in developed countries might be attributable to failure of immunoregulatory circuits to terminate ongoing inflammatory responses.”

Rook and Lowry, 2008, Trends in Immunology, 29, 150-158
The hygiene hypothesis and psychiatric disorders

Depression
Multiple sclerosis
Type 1 diabetes
Crohn’s disease

↑IFN-γ
↑IL-4, IL-5, IL-13

Th1
Th2

Low ratio of regulatory to effector T cells

(adequate levels of IL-10 and TGF-β to terminate inappropriate inflammation)

↑IL-10, TGF-β

Normal ratio of regulatory to effector T cells

Rook and Lowry, 2008, Trends in Immunology, 29: 150-158

Image: New York Times, A Cure for the Allergy Epidemic?
By Moises Velasquez-Manoff
Published: November 9, 2013 http://nyti.ms/17V0rRe
The increasing incidence of immunoregulatory disorders

Serum C-reactive protein (CRP) concentrations are higher in urbanized countries

Median CRP concentrations in lowland Ecuador compared to the United States


Huaorani children in the remote Ecuadorian Amazon

McDade et al., 2012, Am J Hum Biol. 24: 675-681
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Reduced Treg in psychiatric disorders

1. Autism  
   Mostafa et al., 2010, J Child Neurology, 25: 328-335

2. Depression  
   Li et al., 2010, J Affect Disord, 124: 68-75

3. PTSD  
   Sommershof et al., 2009, Brain, Behav Immunity 23: 1117-1124
Evidence of inadequate immunoregulation in PTSD: increased risk of autoimmune disorders

O’Donovan et al., 2015, Biol Psychiatry 77: 365-374
Plasma CRP concentrations before deployment predict Clinician-Administered PTSD Scale (CAPS) scores ~3 and 6 months following deployment.

The Marine Resiliency Study, a prospective study of approximately 2600 war zone–deployed Marines

“Adjusting for the baseline CAPS score, trauma exposure, and other relevant covariates, we found baseline plasma CRP concentration to be a highly significant overall predictor of postdeployment CAPS scores ($p = 0.002$)”

Eraly et al., 2014, JAMA Psychiatr, 71(4): 423-431
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Strategies for prevention: “Old Friends” induce Treg proliferation, Treg activation, and anti-inflammatory cytokine production

Examples of the three overlapping categories of organism implicated in the “hygiene” or “Old Friends” hypothesis

1) Organisms that form part of the co-evolved human microbiota that are altered by modern diets, living conditions and antibiotics (e.g. *Bacteroides fragilis, Lactobacillus reuteri*, isolated from human maternal milk, *Akkermansia muciniphila*).

2) Infections commonly present in early man, usually harmless, transmitted by the fecal-oral route very early in life, that have been depleted since urbanization (e.g. helminths, hepatitis A virus, *Toxoplasma, Salmonella, Helicobacter pylori*).

3) Harmless environmental organisms in mud, untreated water and fermenting vegetable material (“pseudocommensals”: lactobacilli, environmental saprophytes, i.e., *Mycobacterium vaccae*) that are eliminated by the modern city lifestyle.

Co-evolved human microbiota:
The microbiome of uncontacted Yanomami Amerindians versus individuals in modern urban societies (USA)

Yanomami Amerindians in the remote Venezuelan Amazon: “Their diet consists of wild bananas, seasonal fruits, plantains, palm hearts, cassava, birds, small mammals, small fish, crabs, and frogs.”

Co-evolved human microbiota:

YOUR AMERICAN GUT SAMPLE

CHRISTOPHER LOWRY

What’s in your American Gut sample?

How do your gut microbes compare to others?

http://americangut.org/
Co-evolved human microbiota: Preliminary findings from the American Gut Project

1. The American Gut project has many more samples representing more groups of people than other studies, such as the Human Microbiome Project, Global Gut, or Personal Genome Project.

2. The microbiome changes as we grow! As you get older, your gut microbiome becomes more diverse.

3. Antibiotic usage also affects our microbiomes, by reducing diversity and thereby creating a less healthy gut environment.

4. The more different types of plants a person eats, the higher their gut microbiome diversity.

5. Alcohol consumption also affects microbiome diversity—those who had at least one drink per week had a more diverse microbiome than those who abstained from alcohol.

http://americangut.org/
Old Infections:

Case study: humans co-evolved with immunoregulatory *Helicobacter pylori*

- The most common bacterial infection worldwide
- Co-evolved with humans at least since humans migrated out of East Africa ~60,000 years ago
- Potent immunoregulatory effects (but a “difficult” Old Friend)

Photo by © Wim van den Heever

*H. pylori* induces immunoregulation and production of anti-inflammatory cytokines

1. Exposure to *H. pylori* induces semi-mature DCs with high expression of MHC class II and IL-18, TGFβ and IL-10

2. *H. pylori* experienced DCs induce conversion of naïve T-cells to FoxP3⁺ Tregs via IL-18, TGFβ, and possibly IL-10

3. *H. pylori* experienced DCs are poor inducers of Th17 and Th1 differentiation

H. pylori prevalence is lower in children from developed countries

Childhood H. pylori infection is common in developing countries

Childhood H. pylori infection is uncommon in developed countries

Environmental pseudocommensals: *Mycobacterium vaccae*, an immunoregulatory environmental saprophyte.
Review

Chronic subordinate colony housing paradigm: A mouse model for mechanisms of PTSD vulnerability, targeted prevention, and treatment—2016 Curt Richter Award Paper

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Reber et al. 2016 Psychoneuroendocrinology, 74, 221-230
Chronic subordinate colony housing model

Single housed controls (SHC)  Chronic subordinate colony (CSC) housing

Reber et al. 2016 PNAS, 113 (22), E3130-E3139
Chronic subordinate colony model

submissive behavior

absolute & relative adrenal weight

corticosterone response of adrenal cells (in vitro & in vivo)

GC sensitivity (splenocytes, lymph node cells, pituitary)

decreased GC signaling

anxiety related behavior (EPM, LDB, OF, OA exposure, SPAT)

histological damage score (spontaneous colitis)

risk for inflammation-related colon cancer

severity of chemically (DSS)-induced colitis

anxiety

somatic disorders


Christopher Lowry
Department of Integrative Physiology
University of Colorado Boulder, CO, USA
Immunization with *M. vaccae* induces a more proactive coping response to stress

Reber et al. 2016 PNAS, 113 (22), E3130-E3139
Stress decreases alpha diversity and increases beta diversity of gut microbial communities while *M. vaccae* stabilizes them.
Stress increases *Proteobacteria*, including *Helicobacter* spp., a known colitogenic species.

Reber et al. 2016 PNAS, 113 (22), E3130-E3139
*M. vaccae* prevents stress-induced colitis, without preventing stress-induced shifts in microbial communities

Reber et al. 2016 PNAS, 113 (22), E3130-E3139
M. vaccae immunization protects against CSC-exaggeration of chemically-induced colitis

Reber et al. 2016 PNAS, 113 (22), E3130-E3139
Pilot study of the gut microbiome of 18 PTSD subjects and 12 trauma-exposed controls in South Africa

Figure 1. Marginal plots of the predicted values the estimated probability of PTSD from the random forest versus the relative abundance of the three phyla identified as important for distinguishing PTSD status.

Hemmings, et al., 2017, Psychosomatic Medicine, in press
Relative abundance of Actinobacteria is inversely correlated with stress-induced gut permeability

51 km ski march

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Project Team Members

Noah Fierer (Project Lead; University of Colorado, CRES) and his lab will use molecular tools (picture a tiny, chemical decoder ring) to identify the microbes present in your shower head. Noah is an expert in soil bacteria but every so often finds himself lost in the wilderness indoors.

Rob Dunn (NC State Dept. of Applied Ecology) and his lab will coordinate sample processing in the U.S. Rob is an expert in the ecology of life on and around humans, from belly buttons to backyards.

Nate Sanders (Center for Macroecology, Evolution and Climato at the University of Copenhagen) and his lab will coordinate sample processing in Europe. Nate is an expert in global scale patterns of the diversity of life, be that the diversity of ants, trees, or, well, shower life.

Christopher Lowry (Dept. of Integrative Physiology at University of Colorado Boulder) will explore how novel Mycobacteria species/strains interact with our immune system, in hopes of understanding potential health benefits of Mycobacteria exposures. Christopher is expert in potential health benefits of Mycobacteria exposures, including increased stress resilience.

Jennifer R. Honda (Univ. of Colorado Anschutz Medical Campus & National Jewish Health) is an NTM microbiologist who knows the special sauce needed to grow and maintain NTM in the lab! She will also help to understand why some NTM are more likely to be found in showerhead biofilms than others and their impact on susceptible host populations.

Ed Chan (National Jewish Health) is a lung physician with special interests in infectious lung disease. He will help Dr. Honda culture the bacterial isolates and help relate what bacteria are found on shower heads to known human lung disease.

The Showerhead Microbiome Project

http://robdunlab.com/projects/showerheads/
Sealed, well-mixed and controlled chamber for environmental bacteria aerosol exposure studies

- Chamber Volume = 11 m³
- Temperature & humidity logger (T,RH)
- InstaScope Bioaerosol Monitor (Tracks aerosol concentration in real-time)
- HEPA Filter
- 12 mice/treatment
- M. vaccae aerosol generation (nebulization)
- Fans for complete air mixing
- Aerosol generator flow control
- Air
- Sequential bioaerosol capture for microscopy enumeration & bioaerosol viability (CFU)
Conclusions

• Exposure to immunoregulatory “Old Friends” has declined dramatically in developed countries in the last 50 years

• Psychiatric disorders are associated with decreased Treg, decreased immunoregulation, and increased inflammation

• Immunization with *M. vaccae* prevents stress-induced inflammation and anxiety/fear

• Microbiome-based interventions to increase anti-inflammatory/immunoregulatory signaling might be considered for prevention and treatment of psychiatric disorders