Putting the Brain Back in the Body:  
A call for integrating physical and mental health

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Disclosures

Raymond J. Kotwicki, MD, MPH

- Dr. Kotwicki has no relevant financial or research disclosures that bias or influence this discussion.
Learning Objectives

- Trace the mechanism of development of mental illnesses, using the stress-diathesis model
- Appreciate the complicated static/dynamic states of genetics, including the roles of genes, epigenes, RNA, and proteins
- Link inflammation with mental illnesses
- Be aware of the signs and symptoms of major mental illnesses such as depression and “sickness behaviors” that are associated with physical illnesses like infections
- Increase comfort in talking about mental health and seeking help when needed

Stress / Diathesis Model

- **Diathesis** = genetic predisposition
  - BPAD, Schizophrenia, Depression, OCD, Alcoholism, Suicide Completions
  - Not 100% heritable
  - Environmental impacts
- **Stressors**
  - Major losses, life transitions
  - Abuse, neglect
  - Early substance misuse
  - Bullying
  - Social determinants

The Stress-Diathesis Model

**Mental Illness known to have genetic predispositions**
- Bipolar illness (0.8 heritability)
- Schizophrenia
- Major depression
- Alcohol dependence
- OCD
- Completed suicides

**Genetics are not autosomal, dominant**
- Approximately 98 loci for schizophrenia
- Presence of genes does not guarantee development of symptoms, illness
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Biology of Psyche

- **Epigenes** (~ genes “behind genetics model”)
- **Proteins**
- **Anatomy**
- **Functionality**
- **Feelings**

- Transcription / Translation
- Cell growth, change, death
- Neurotransmitter modulation

Potential Points of Intervention

- Stabilize / Change epigenes (-CH₃ groups)
- Promote / Squelch genes (vectors)
- Interrupt transcription / Translation
- Change anatomy (DBS)
- Modulate symptoms; thinking, feelings, behaviors
- Modulate inflammation?

Sickness Behaviors

**SIGNS & SYMPTOMS OF INFECTION / GLOBAL INFLAMMATION**
- Fatigue
- Sleep disturbance
- Fever
- Anorexia
- Decreased libido
- Anhedonia
- Poor energy
- Poor concentration
- Psychomotor retardation

**SIGNS & SYMPTOMS OF DEPRESSION**
- Sadness / Suicide
- Interest loss
- Guilt / Worthlessness
- Energy problems
- Concentration difficulties
- Appetite change
- Psychomotor changes
- Sleep disturbance
### Sickness Behaviors

**SIGNS & SYMPTOMS OF infection / global inflammation**
- Fatigue
- Sleep disturbance
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**SIGNS & SYMPTOMS OF depression**
- Sadness / Suicide
- Interest loss
- Guilt / Worthlessness
- Energy problems
- Concentration difficulties
- Appetite change
- Psychomotor changes
- Sleep disturbance

### Sickness Behaviors, continued

- Goal is to conserve energy to mount immune response
- Evolutionarily advantageous

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**Local Effects**
- Increased vascular permeability
- Vasodilation
- Chemokine production
- Expression of adhesion molecules
- Pain

**Effects on Liver**
- Acute Phase Response
  - C-reactive protein
  - Albumin
  - Hyperglycemia
  - Alpha 1 antitrypsin

**Effects on Brain**
- Fatigue
- Anorexia
- Anhedonia
- Altered sleep

**Innate Immunity/Inflammation**

- **Acute Phase Response**
  - CRP
  - Serum amyloid A
  - Haptoglobin
  - Alpha 1 antitrypsin

- **Systemic Effects**
  - Tumor
  - Rubor
  - Calor
  - Dolor

**Conservation of energy resources to promote increased metabolic demands of fighting infection and mounting a fever**

**Source:** Miller AH 2013
Physical Changes in Depression

- Cohort comparisons between depressed patients, controls
  - Higher core body temperatures
  - Decreased heart rate variability
  - Abnormal concentrations of inflammatory mediators
  - Fat redistribution?
- Medically ill people have much higher rates of depression
  - Hep B, interferon
  - Pancreatic carcinoma
  - Hypothyroidism

Sources of Inflammation in Depression
(Non-resolving inflammation)

- **Adipose tissue** (macrophages)
- **Leaky gut** with entry of bacterial products into peripheral circulation – relative representation of bacterial species in the gut (diet and the microbiome)
- **Medical Illness** (e.g. cardiovascular disease, cancer, autoimmune disorders, infectious disease)
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### Sources of Inflammation in Depression
(Non-resolving inflammation)

- **Disruption in T cell regulation** of inflammation
  - Decreased anti-inflammatory T regulatory cells
  - Increased pro-inflammatory TH-1 and TH-17 cells
- **Psychosocial Stress**

### Top 10 Inflammatory Triggers

1. Sedentary lifestyle
2. Obesity
3. Smoking
4. Lack of resilience
5. Other sources of inflammation (gingivitis etc.)
6. Poor sleep
7. Poor diet (transgenerational effect)
8. Changes in gut permeability
9. Allergies
10. Vitamin D deficiency

### Treatment Implications

- Ongoing trials to determine if anti-inflammatory medications useful in treating mental illnesses
  - Infliximab (monoclonal Ab targeting TNF-alpha)
    - Miller, Raison, MolPsych, epub 2012
  - NSAIDS
    - Sommer et al. Journal of Clinical Psychiatry 2012
- Multi-vessel cardiac disease prophylactic treatment with SSRIs
  - Anti-platelet activities of SSRIs
  - Post-heart-attack depression triples mortality rates (Bush et al. 2005)
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Summary

- Mental illnesses are medical problems!!!!
- Inflammation appears to be a key factor in the linkage between physical and mental health
- The stress / diathesis model of mental illnesses can help one understand the interface between Nature and Nurture
- People with mental illnesses have aberrations in physical health indicators; people with certain physical illnesses are prone to comorbid mental disorders
- Integrated care is absolutely essential; get help for family members, friends, yourself when needed

Bibliography

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