Do Inflammation and Metabolic Disturbances Metastasize to the Brain? Implications for Disease Modeling and Novel Approaches in Psychiatry

Part 1 of 2
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Learning Objectives

• Describe the importance of cognitive symptoms as psychiatric targets
• Review immune and metabolic systems associated with cognitive deficits and mood disorders
• Discuss innovative approaches that may target these systems
Convergent Phenotypes
## Cognitive Dysfunction: A Transdiagnostic Psychopathologic Domain

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<th>MDD</th>
<th>BD</th>
<th>SCZ</th>
<th>ASD</th>
<th>ADHD</th>
<th>OCD</th>
<th>PTSD</th>
<th>Panic disorder</th>
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- ⚫, essentially absent; ⚫/[⚫], poorly documented, ambiguous, mild, and/or variable; ⚫, consistently present but not pronounced; ⚫[⚫], common, marked characteristic; ⚫[⚫], core, severe and virtually universal characteristic of the disorder; ⚫[⚫], increase. Brackets indicate an intermediate magnitude of deficit.

ADHD, attention-deficit/hyperactivity disorder; ALZ, Alzheimer’s disease; ASD, autism spectrum disorder; BD, bipolar disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PD, Parkinson’s disease; PTSD, posttraumatic stress disorder; SCZ, schizophrenia.

Cognitive Symptoms Are an Important Psychiatric Target

NIMH RDoC Classification of Mental Disorders

- Negative valence systems
- Positive valence systems
- Cognitive systems
- Systems for social processes
- Arousal/Regulatory processes

Perception, language, memory, and cognitive control

NIMH, National Institute of Mental Health; RDoC, research domain criteria.

Cognitive Dysfunction Is a Common Disturbance in Patients With Diabetes Mellitus


Cognitive Dysfunction in Control Participants (n=68) and Patients With Type 2 Diabetes (n=38)

Information-processing speed
- Nondiabetic control participants
- Patients with type 2 diabetes

Attention/executive functioning
- Nondiabetic control participants
- Patients with type 2 diabetes

Z-score, ± SE

Baseline Follow-up (4 years)

Psychiatric Disorder Plus Metabolic/Inflammatory Disorder Yields Greater Cognitive Dysfunction

BMI was negatively correlated with attention and psychomotor processing speed as measured by the Digit Symbol Substitution Test ($P<0.01$)

Patients with bipolar disorder who were overweight or obese demonstrated significantly lower scores on the Verbal Fluency Test when compared with patients of normal weight ($P<0.05$)

BMI, body mass index.

Association Between Metabolic and Neuropsychological Phenotypes

Phenotypic Expressions
- Obesity
- Metabolic syndrome
- Diabetes/Insulin resistance
- Major depressive disorder
- Bipolar disorder

Mediators/Moderators
- Brain energy metabolism
- Brain structure and function
- Brain-derived neurotrophic factor
- Inflammation
- Hypothalamic pituitary axis
- Adipocytes-derived hormones

Environmental Risk Factors
- Excessive/Inadequate food intake
- Sedentary lifestyle
- Childhood trauma

Genetics
- Obesity
- Mood Disorders


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Convergent Substrates
Adipose Tissue Contributes to Pro-Inflammation in Mood Disorders

- Inflammation markers were assessed in adults with depression* or with no history of psychiatric illness

- Patients with depression
  - Weighed significantly more
  - Demonstrated higher levels of CRP and IL-6

*Patients met the diagnostic criteria for a current major depressive disorder or minor depressive disorder.

BMI, body mass index; CRP, C-reactive protein; IL-6, interleukin-6.

Synergistic Relationship Between Depression and BMI

Patients with depression with BMI >30 demonstrated significantly higher levels of CRP and IL-6 compared with patients with depression with BMI <30

Discussion
Childhood Adversity is Associated With Metabolic Syndrome in Patients With Mood Disorders

- Association between childhood adversity and metabolic syndrome was assessed in patients with mood disorders*

- Childhood trauma† was associated with components of metabolic syndrome, including higher systolic blood pressure

*Systolic Blood Pressure in Patients With a Mood Disorder

<table>
<thead>
<tr>
<th>Systolic Blood Pressure, mmHg</th>
<th>No reported childhood trauma</th>
<th>Any reported childhood trauma</th>
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<tbody>
<tr>
<td>116</td>
<td>120</td>
<td>130</td>
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<td>118</td>
<td>122</td>
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<tr>
<td>122</td>
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</tbody>
</table>

*P < 0.05

*Mood disorders included major depressive disorder, bipolar I disorder, bipolar II disorder, mood disorder not otherwise specified, dysthymia, anxiety disorder, and other (eg, substance or alcohol abuse/dependence and psychotic disorder). †A total of 373 patients were assessed; 46.74% of patients reported any childhood trauma.

Discussion
Hippocampal Volume Changes in Diabetes Mellitus

Hippocampal Volumes, Measured by Brain MRI, in Subjects Without or Patients With Diabetes*

MRI, magnetic resonance imaging.
*Volumes adjusted for age and sex and normalized to average head size.

Prefrontal Lobe Network Functional Connectivity: Fasting Insulin Levels and Insulin Sensitivity in Lean and Obese Participants


OFC, orbitofrontal cortex.

*Adjusted for BMI. †Log scaled. *P<0.05, family-wise error corrected; color bar represents T values.

# Mechanism of Neuroinflammation

## Interplay Between Peripheral Immune Cells, the Blood-Brain Barrier, and Microglia-astrocytes Drives Neuroinflammation

<table>
<thead>
<tr>
<th>M1-type activation: Neuroinflammation</th>
<th>M2-type activation: Antiinflammatory response</th>
</tr>
</thead>
<tbody>
<tr>
<td>• DAMPS, PAMPs, TLR activation</td>
<td>• Phagocytosis, pruning, NFκB downregulation</td>
</tr>
<tr>
<td>• Chemokine-driven response, receptor activation, P2X7 ion channel activity</td>
<td>• Gliotransmitter and cytokine release: IL-4, IL-10, IL-13, BDNF, IGF-1, TGF-β</td>
</tr>
<tr>
<td>• Gliotransmitter and cytokine release: IL-1β, IL-6, TNF-α, CCL2, ROS, NO</td>
<td></td>
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<tr>
<td>• TSPO, COX-2 upregulation</td>
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</tbody>
</table>

BDNF, brain-derived neurotrophic factor; CCL2, chemokine; COX-2, cyclooxygenase 2; DAMPs, danger-associated molecular patterns; IGF-1, insulin-like growth factor 1; IL-1β, cytokine; IL-6, cytokine; IL-4, IL-10, IL-13, antiinflammatory interleukins; NFκB, nuclear factor; NO, nitric oxide; PAMP, pathogen-associated molecular patterns; ROS, reactive oxygen species; TGF-β, transforming growth factor beta; TLR, toll-like receptors; TNF-α, tumor necrosis factor alpha (cytokine); TSPO, translocator protein.

Depression Is Associated With Increased Inflammation

Significant positive relationships have been observed between depression and neuroinflammation markers (eg, CRP\textsuperscript{1}, IL-6\textsuperscript{1}, TNF-\alpha\textsuperscript{2}, and sIL-2R\textsuperscript{3})

In patients with MDD in a current major depressive episode, greater microglial activation was positively correlated with greater depression severity\textsuperscript{4}

CRP, C-reactive protein; IL-6, interleukin-6; MDD, major depressive disorder; sIL-2R, soluble interleukin-2 receptor; TNF-\alpha, tumor necrosis factor alpha.

Inflammatory and Fatigue Level Changes After an Immune Stimulus

**Change in Circulating Interleukin-6 (IL-6)**

- **Placebo**
  - Baseline (BL)
  - 4 h

- **Typhoid vaccine**
  - BL
  - 4 h

**Change in Fatigue**

- **Placebo**
  - BL
  - 4 h

- **Typhoid vaccine**
  - BL
  - 4 h

**IL-6 (mean ± SE), pmol/L**

- **Placebo**
  - BL: 1.0 ± 0.5
  - 4 h: 1.5 ± 1.0

- **Typhoid vaccine**
  - BL: 4.0 ± 0.5
  - 4 h: 5.0 ± 1.0

**Fatigue VAS (mean ± SE)**

- **Placebo**
  - BL: 20 ± 5
  - 4 h: 25 ± 5

- **Typhoid vaccine**
  - BL: 50 ± 10
  - 4 h: 55 ± 10

**P-values**

- **IL-6**
  - P = NS
  - P < 0.001

- **Fatigue**
  - P = 0.069
  - P < 0.001

**BL**, baseline; **NS**, not significant; **SE**, standard error; **VAS**, visual analog scale.

Association of Monoamine Metabolites with Neuroinflammation and Mood Burden

Significant positive correlations were observed between the proinflammatory cytokine IL-6 and increased serotonin and dopamine metabolites in patients who had attempted suicide\(^1\)

Concentration of MHPG, a monoamine metabolite, was positively associated with accumulated mood burden in patients with treatment-refractory unipolar and bipolar depression\(^2\)

IL-6, interleukin-6; MHPG, 3-methoxy-4-hydroxyphenylglycol.

Effect of Inflammatory Cytokines on Brain Circuitry

**Hypervigilance** (protection from attack)

- Anxiety
- Arousal, Alarm

**Withdrawal** (wound healing, infection fighting)

- Fatigue, Anhedonia, Motor Slowing
- Depression

Inflammatory Cytokines

- dACC
- Basal ganglia

**Cortical**

**Subcortical**

Patrick J. Lynch; illustrator; C. Carl Jaffe; MD; cardiologist Yale University Center for Advanced Instructional Media Medical Illustrations by Patrick Lynch, generated for multimedia teaching projects by the Yale University School of Medicine, Center for Advanced Instructional Media, 1987-2000.

dACC, dorsal anterior cingulate cortex.

Convergent Treatments
Treating Peripheral Metabolic Disturbance May Have a Positive Impact on Mental Health

- Patients with HLD had a significantly greater risk of depression vs patients without HLD
- Patients with HLD not treated with statins had a significantly greater risk of depression vs patients without HLD

HLD, hyperlipidemia.

In patients with mood disorders,* antidepressant effects of select agents

- Were significantly greater in patients treated with adjunctive antiinflammatory agents vs conventional therapy alone¹
- Trended toward an increase in patients with high baseline CRP²
- Were predicted by baseline adipokine adiponectin³ or inflammation markers,⁴ particularly in patients with BMI ≥30⁵

*Bipolar disorder or major depressive disorder.
BMI, body mass index; CRP, C-reactive protein.

Effect of Gut Microbiota on Mood-Related Behavior

- Effect of gut microbiota on psychobehavioral characteristics was assessed in germ-free and specific pathogen-free mice.

- Fecal microbiota transplantation from patients with MDD on GF mice resulted in depression-like behaviors compared with microbiota transplantation from healthy control individuals.

GF, germ free; MDD, major depressive disorder; SPF, specific pathogen free.

Discussion
Emerging Evidence for Increased Remission Rates With Add-On Exercise

Probability of Remission, as Measured by IDS-C₃₀, in Patients With Inadequate Response to SSRI, Who Received Add-On Exercise in the TREAD Study

IDS-C₃₀, Inventory of Depressive Symptomatology, Clinician-Rated; NNT, number needed to treat; SSRI, selective serotonin reuptake inhibitor; TREAD, Treatment with Exercise Augmentation for Depression study.

*NNT of 7.8 for high-exercise vs low-exercise group based on remission rate at week 12.

Summary and Key Points

Cognitive symptoms, which are prevalent in mood disorders and recognized as critical targets for treatment in psychiatry, may be associated with metabolic alteration.

Overlapping immune-related and metabolic systems may underlie cognitive deficits observed in mood disorders.

Emerging evidence from preclinical and clinical models suggest that targeting inflammation and metabolic disturbances may have a positive impact on mental health.
Questions
THANK YOU

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