MEDICAL COMORBIDITY IN MOOD DISORDERS: THE LINK WITH METABOLIC-INFLAMMATORY SYSTEMS
Learning Objective

• Explain the pathophysiological convergence of mood disorders and cardiometabolic illnesses
Presentation Outline

• Complex interactions between peripheral immune and metabolic changes, and altered brain function as these relate to the development and treatment of mental illness

• Immune-metabolic interactions may impact responses to currently available psychotropic agents and are beginning to support the development of novel interventions

• Studies in immune-stress interactions provide a rationale for recent findings that both anti-inflammatory and pro-inflammatory interventions may be of benefit in the treatment of mood disorders
There are two main types of immunity

Innate (Natural) Immunity
- Rapid response
- Cells – macrophages, neutrophils, natural killer cells, dendritic cells
- Memory – none
- Specificity – low
- Diversity – low (encoded in the germline)
- Proteins – complements and cytokines

Adaptive (Specific) Immunity
- Slower response
- Lymphocytes
  - B Lymphocytes
  - T Lymphocytes
- Memory – yes
- Specificity – high (human lymphocytes can distinguish between 10 billion antigens)
- Diversity – extremely high
- Proteins - antibiotics – (B Cells) and cytokines (helper T cells)

Innate Immunity – Let’s Meet the Various Members of the Immune System

**Neutrophils**
- Mean number per mL – 4400
- Humans produce $10^{11}$ neutrophils per day.
- Granules contain bacteria killing lysozymes.
- Life span is 1 to 2 days

**Monocyte**
- Mean number per mL – ~ 300

**Macrophage**
- Activation
- Tissue migration

**Activated macrophage**
- Cytokines
- Chemokines

Acquired Immunity – Lymphocytes: Their Role of B and T Lymphocytes

**Humoral Immunity**
- Bone marrow

**Cell Mediated Immunity**
- Thymus

**Lymphocytes**
- Mean number per mL – 2500
- 2% are in blood, 4% in the skin,
- 10% bone marrow, 15% mucosal lymphoid tissues, ~ 65% in spleen and lymph nodes
- Life span is days to years

**T Lymphocytes**
- Cytokines

**B Lymphocytes**
- Antibiotics

Macrophage – Microglia Interactions

Activated Macrophage (tissue presence - specially in adipose tissue)

Activated Microglia (psychosocial stressors)

Blood-brain barrier

IL-6
TNF-α
IL-1β

**Interplay Between Peripheral Immune Cells, Blood-Brain Barrier, and Microglia-Astrocytes Within the Brain to Drive Neuroinflammation**

DAMPs = danger-associated molecular patterns;
PAMPs = pathogen-associated molecular patterns;
TLR = toll like receptors;
ROS = reactive oxygen species;
NO = nitric oxide;
CCL2 = chemokine;
TSPO = translocator protein;
COX-2 = cyclooxygenase 2;
IL-1β, IL-6, TNF-α = cytokines.

NFKB = nuclear factor;
BDNF = brain-derived neurotrophic factor;
IGF-1 = insulin-like growth factor 1;
TGF-β = transforming growth factor beta;
IL-4, IL-10, IL-13 = anti-inflammatory interleukins.

First Things First –
Let’s Review Tryptophan Pathways

KYN = Kynurenine
KATs = Kynurenine Aminotransferases
KYNA = Kynurenic Acid
QUIN = Quinolinic Acid

Depression is associated with increased peripheral inflammation

IL-6 and depression

CRP and depression

Meta-analyses have also found depression is associated with increased TNF-α and soluble IL-2 receptors.1,2,3

A) Change in circulating IL-6 pre- and post-vaccine (V base and V 4Hrs) and placebo injection (P base and P 4Hrs). B) Change in fatigue pre- and post-typhoid vaccination and placebo saline injection.

Plasma IL-6 levels are correlated with cognitive performance in MDD.

Logical Memory Subtests of the Wechsler Memory Scale-Revised was administered to 30 patients with recurrent MDD. There was a statistically significant association between IL-6 levels and IVR ($B = -0.787$, $P = .000$) and DVR ($B = -0.695$, $P = .001$).

Impact of Inflammatory Cytokines on Brain Circuitry

Hypervigilance (protection from attack)

Withdrawal (wound healing, infection fighting)

Anxiety → Arousal, alarm

Fatigue, anhedonia, motor slowing → Depression

dACC = dorsal anterior cingulate cortex.

dACC = dorsal anterior cingulate cortex.

Inflammatory cytokines induce the death of astrocytes.

Astrocytes were stimulated across a 96-hour time course to assess the extent of cell loss following IL-1β and TNF-α treatment. Cell numbers were quantified by counting Hoechst stained nuclei.

*P < .05

CNS Inflammation and Pathophysiology of Psychiatric Disorders

M1 microglia

Prefrontal cortex

DLPFC

VLPFC

M2 microglia

Thalamus

Central/medial amygdala

Hippocampus

Major depressive disorder

DLPFC

Central amygdala

Hippocampus

Bipolar disorder

DLPFC

VLPFC

Medial amygdala

Central amygdala

Schizophrenia

DLPFC

VLPFC

Thalamus

Central/medial amygdala

Hippocampus

Possible initiating regions

Disruption of neural network

Elevation of inflammatory cytokines in CSF may alter 5-HT and dopamine metabolism.

- Inflammatory cytokines and monoamine metabolites were compared in 63 suicide attempters and 47 healthy controls.
- MADRS scores correlated significantly with CSF IL-6 levels.
- IL-6 and TNF-α correlated with CSF 5-HIAA and HVA.
- Higher cytokine levels were associated with increased suicidality.

5-HT = serotonin; HIAA = hydroxyindoleacetic acid; HVA = homovanillic acid; LN = natural log.

Increased Density of Microglial Cells in Brain Areas of Patients with MDD

Upregulation of Microglial QUIN in the Brains of Suicidal Patients


**QUIN + cell density (cells/mm³)**

- **sACC**
  - Control (n = 10)
  - Bipolar disorder (n = 5)
  - MDD (n = 7)

- **aMCC**
  - Control (n = 10)
  - Bipolar disorder (n = 5)
  - MDD (n = 7)

- **pACC**
  - Control (n = 10)
  - Bipolar disorder (n = 5)
  - MDD (n = 7)

Statistical significance:
- $P = 0.006**$
- $P = 0.042^*$
- $P = 0.028^*$
- $P = 0.015^*$
- $P = 0.003**$
- $P = 0.003**$
- $P = 0.023^*$
- $P = 0.023^*$
- $P = 0.006**$
Correlation between sgACC and PCC may be a marker of depressive rumination.

\[ y = 0.0068x - 0.0911 \]

\[ R^2 = 0.477, \quad P < 0.001 \]

*sgACC = subgenual anterior cingulate cortex*

DMN activity is associated with depressive symptoms.

Connection strength between the PCC and left amygdala predicted depressive symptoms on the HAM-D ($r = 0.65; P < .001$; cluster size, 503 voxels) in patients with dysthymia ($N = 41$).

Cognitive Decline: Patients with Type 2 Diabetes vs. Non-Diabetic Controls

Type 2 diabetes (n = 68) and matched non-diabetic control participants (n = 38), followed up for 4 years.

Insulin: A Critical Neuropeptide

AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
NMDA-R = N-methyl-D-aspartate receptor
PI3K = phosphoinositide 3-kinase
PKB = protein kinase B
BAD = BCL2-associated agonist of cell death
CNS = central nervous system.

Hippocampal and Amygdalar Volume Changes in Diabetes Mellitus

Hippocampal volumes and amygdalar volumes (+SE) on brain MRI in participants with diabetes (n = 41) and without diabetes (n = 465). Volumes are adjusted for age and sex and normalized to average head size.

MRI = magnetic resonance imaging

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

Sleep deprivation causes insulin resistance.

Diabetes impairs hippocampal neurogenesis via altered metabolic/inflammatory system.

Being overweight/obese has a negative effect on cognitive function in euthymic patients with bipolar disorder

BMI was negatively correlated with:

Attention and psychomotor processing speed as measured by the Digit Symbol Substitution Test ($P < .01$)

Overweight/obese patients with bipolar disorder had:

Significantly lower scores on the Verbal Fluency Test when compared with normal weight patients with bipolar disorder ($P < .05$)

BMI = body mass index

Adiposity, Inflammation, and Depression

• High caloric intake in the diet leads to increased accumulations of lipids in adipocytes

• Increased lipid content results in an increased release of MCP-1 (CCL2), a chemoattractant that increases the infiltration of macrophages into adipose tissue

• Both adipocytes and macrophages release inflammatory mediators, such as IL-6 and TNF-α, into the peripheral circulation

HDL = high-density lipoprotein; LDL = low-density lipoprotein; ROS = reactive oxygen species; mmLDL = minimally-modified low-density lipoproteins; MCP-1 = monocyte chemoattractant protein 1

MDD, Adiposity, and Inflammatory Markers

50 MDD patients compared with 50 healthy matched controls

IL-6 ± SEM (pg/mL)

P < .001

CRP ± SEM (mg/L)

P < .001

Relationship Between Neuroinflammation Marker and Severity of Depressive Symptoms

![Graph showing the relationship between TSPO $v_T$ and HAM-D score, with a linear regression line. The correlation coefficient is $r = .63$ and $P = .005$.]

- **HAB** = high affinity binders
- **MAB** = mixed affinity binders
- **HAM-D** = Hamilton Rating Scale for Depression
- **TSPO $v_T$** = translocator protein total distribution volume

Central Inflammation in Bipolar Disorder:
A \([11C]-(R)-PK11195\) PET Study


BD-I = bipolar I disorder
PET = positron emission tomography
Inflammation and Social Cognition

Performance on the Reading the Mind in the Eyes (RME) test at baseline and T2 (peak of inflammatory response for the endotoxin group). Error bars depict the standard error of the mean.

# Common Electrophysiological Markers Between DM and MDD

<table>
<thead>
<tr>
<th>EEG Parameter</th>
<th>T1DM</th>
<th>T2DM</th>
<th>MDD</th>
<th>Brain Region</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resting EEG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha band power</td>
<td>↓</td>
<td>↓</td>
<td>/</td>
<td>Posterior temporal</td>
</tr>
<tr>
<td>Beta band power</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>Temporal</td>
</tr>
<tr>
<td>Gamma band power</td>
<td>↓</td>
<td>/</td>
<td>↑</td>
<td>Posterior temporal</td>
</tr>
<tr>
<td>Theta band power</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Frontal and parieto-occipital; anterior cingulate cortex</td>
</tr>
<tr>
<td>Delta band power</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Frontal and parieto-occipital; anterior cingulate cortex</td>
</tr>
<tr>
<td><strong>Event Related Potentials</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P300 Latency</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Posterior</td>
</tr>
<tr>
<td>P300 Amplitude</td>
<td>↓</td>
<td>/</td>
<td>↓</td>
<td>Frontal and temporo-parietal</td>
</tr>
<tr>
<td>N100 Amplitude</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Central and posterior</td>
</tr>
</tbody>
</table>

EEG = electroencephalogram; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

SSRI therapy decreases incidence of cytokine-induced depression.

- **BAS = Brief Anxiety Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; SSRI = selective serotonin reuptake inhibitor.**

### Different Targets/Agents: Repurposing Opportunities

#### Metabolic:
- Glucagon-like peptide I (GLP-1)
  - Exenatide, liraglutide, taspoglutide, albiglutide, lixisenatide
- Dipeptidyl peptidase IV inhibitors (DPP-IV)
  - Alogliptin, anagliptin, gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, vildagliptin
- Insulin
- Others

#### Inflammatory:
- JAK-STAT
- Monoclonal antibodies (e.g., Infliximab)
- Disease-modifying antirheumatic drugs (DMARDs)
- Others (e.g., minocycline)
Intranasal insulin enhances executive function in bipolar disorder.

Intranasal Insulin: Efficacious in AD and MCI

AD = Alzheimer’s disease; MCI = mild cognitive impairment.

If bipolar disorder is progressive, can we prevent bipolar disorder onset?

OAA = oral antidiabetic agent

If bipolar disorder is progressive, can we prevent bipolar disorder onset?

GRPP = glicentin-related polypeptide; IP = intervening peptide; MPGF = major proglucagon fragment

The GLP-1 receptor is expressed in diverse CNS nuclei in the non-human primate.

<table>
<thead>
<tr>
<th>CNS Site</th>
<th>Monkey</th>
<th>Rodent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Forebrain</td>
<td>NAc</td>
<td>++</td>
</tr>
<tr>
<td>Striatum</td>
<td>AMGD</td>
<td>++++</td>
</tr>
<tr>
<td>Thalamus</td>
<td>PVN</td>
<td>+</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>ARc</td>
<td>++++</td>
</tr>
<tr>
<td>Midbrain</td>
<td>DTg</td>
<td>++++</td>
</tr>
<tr>
<td>Hindbrain</td>
<td>NTS/AP</td>
<td>++++</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>Dorsal Horn</td>
<td>++++</td>
</tr>
</tbody>
</table>

GLP-1RA Exert Neuroprotective Effects in a Diversity of Preclinical Models

**GLP-1R agonists:**
- ↑ neurite outgrowth
- ↑ neuronal differentiation
- ↑ synaptic plasticity (long-term potentiation, cognition within the hippocampus)
- ↑ associative and behavioral learning
- ↓ neuronal degeneration

**GLP-1R agonists in AD models:**
- liraglutide ↓ neuronal tau pathology in murine tauopathy model
- liraglutide ↑ neurotrophic, ↑ neuroprotective effects in amyloid-β (Aβ) toxicity models of AD
Liraglutide Prevents Degenerative Processes in Mouse Model of AD

Saline (8 weeks)

LIRA (8 weeks)

LIRA also improved indicators of memory function (e.g., object recognition, water maze performance) and synapse formation in AD models

Liraglutide improves memory retention and total hippocampal CA1 pyramidal neuron numbers in 10-month-old mice in an age-related sporadic AD (SAMP8) model.

Liraglutide preserved hippocampal CA1 pyramidal neuron numbers: Liraglutide (100 μg/kg/day) also significantly increased (14.3 ± 0.3%) total CA1 pyramidal neuron numbers (204,744 ± 5442, *P* < .01) as compared to age-matched vehicle-dosed SAMP8 control mice (*P* < .01).

Liraglutide Improves Cognitive Function In Adults With Mood Disorders

Standardized effect size (Cohen’s d) for neuropsychological tests.

*P < .05; **P < .01, ***P < .001.

DSST = Digit Symbol Substitution Test; RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test.

Unpublished data. ClinicalTrials.gov Identifier: NCT02423824.
Comparison between baseline and week 4 in dIPFC NAA/Cr Ratio

Pilot data. ClinicalTrials.gov Identifier: NCT02423824.
Correlation between Changes from baseline to endpoint in dIPFC NAA/Cr ratio and TMTB score

Pilot data. ClinicalTrials.gov Identifier: NCT02423824.
Decreased Fractional Anisotropy in Overweight/Obese Bipolar Patients vs. Normal Weight Bipolar Patients

Minocycline

• Second-generation, semi-synthetic tetracycline analog with antimicrobial properties

• Highly lipophilic, easily penetrates the blood-brain barrier in contrast to tetracycline

• Principal metabolite: 9-hydroxyminocycline (inactive)

Antidepressant-Like Effects of Minocycline Monotherapy on the Forced Swim Test

N = 7/group, systemic injection 23, 5, and 1 hour prior to Forced Swim Test

Adjunctive Minocycline Treatment for Bipolar Depression

Improvement: 20%Δ
Response: 50%Δ
Remission: score ≤ 10

Effect Size (full analysis set)=.325
Effect Size (responders)=.702

Forest Plot of Pooled Effect Sizes of Adjunctive Anti-Inflammatory Agents for Bipolar Depression

O3FA = omega-3 fatty acids
NSAIDs = nonsteroidal anti-inflammatory drug
NAC = N-acetylcysteine.
A Randomized Double-blind Placebo-Controlled Trial of Adjunctive Infliximab in the Treatment of Adults with Bipolar I/II Depression: Efficacy in Persons Reporting Childhood Trauma
Changes in MADRS Total Scores From Baseline to Week 12 in Infliximab- or Placebo-Treated Individuals With BD With No Versus Individuals With Clinically Significant History of Physical Abuse
Effect of Gut Microbiota on Mood-Related Behavior

GF = germ-free
SPF = specific-pathogen free

16S rRNA gene sequencing reveals changes to microbial diversity in MDD

Emerging Evidence: Increased Remission Rates With Add-On Exercise

TREAD: patients with inadequate response to SSRI received add-on exercise (low: 4 kcal/kg/week or high: 16 kcal/kg/week)

NNT = 7.8 for higher dose exercise group

IDS-C = Inventory of Depressive Symptomatology, Clinician-Rated; NNT = number needed to treat; KKW = kcal per kg per week.

Cytokine Antagonism as an Antidepressant Treatment

TRD Pts (N = 60) → Stratification Male vs Female CRP >2 vs CRP ≤2

Randomization

Clinician-administered psychiatric assessments (HAM-D, CGI)

adverse events evaluation

blood draw for inflammatory markers and safety labs

Adjusted mean HAM-D-17

Weeks

Baseline 1 2 3 4 6 8 10 12

Infliximab Placebo

Percent responders during study

Hs-CRP (tertiles)

Med + Low High

Pro-inflammatory state may predict short-term response to ketamine

In 108 patients with TRD receiving a single ketamine infusion, increased BMI predicted enhanced short-term antidepressant response. In 80 patients with TRD, lower levels of the anti-inflammatory adipokine adiponectin predicted improved antidepressant responses at 1-day post-treatment.

Increased Inflammation Associated With Enhanced Response to L-methylfolate

BMI = body mass index; hsCRP = high-sensitivity C-reactive protein; IL = interleukin; TNF-α = tumor necrosis factor α.

Cytokine Antagonism May Be Counterproductive for Many With MDD

Antidepressant Effects of Whole-Body Hyperthermia (WBH)


71% of sham-treated participants believed they had received WBH

Mean 17-item HAM-D score

Week

0 1 2 3 4 5 6

(16) (14) (12)

(15) (14) (12)

(11) (11)

(15) (15) (15)

(11) (11) (11)

d = 2.23 P < .001
d = 2.11 P = .001
d = 1.66 P = .02
d = 1.66 P = .02
Inflammation as a Treatment for Major Depression

In a small study of 7 severely depressed inpatients, the administration of LPS at 5 PM produced a significant reduction in depressive symptoms the next day ($P = .018$).

The improvement was maintained in 2 of the 7 patients, whereas the other 5 relapsed following a night of recovery sleep.

LPS increased IL-6 and TNF, and suppressed REM sleep.

Reductions in depressive symptoms were highly correlated with increased IL-6 after LPS administration ($rs = .95$, $P < .001$).

LPS = lipopolysaccharides

NSAID Use May Promote Antidepressant Resistance

Observational data from 1528 outpatients confirmed the observation in STAR*D trial that use of NSAIDs is associated with non-response to antidepressant medications.

Muscle as a “Peripheral” Anti-Inflammatory: Implications for “Central” Mental Health Issues

Muscle Biopsy from Quadriceps for mRNA levels for various enzymes. 30 mg of muscle tissue was extracted and analyzed for mRNA expression.

Exercise → Biopsy → Results

KAT = kynurenine aminotransferase (1, 2, 3, 4);
PGC-1α1 = peroxisome proliferator-activated receptor-gamma coactivator.

CTRL = Control Recreational Exerciser (8 subjects)
END = Endurance Athletes (9 subjects)

Mindfulness: An Anti-Inflammatory Agent

N = 49 community volunteers randomly assigned to either MBSR or HEP. TSST used to induce psychological stress and inflammation produced using topical application of capsaicin cream to forearm skin.

RESULTS: MBSR resulted in a significantly smaller post-stress inflammatory response compared to HEP, despite equivalent levels of stress hormones.

Conclusions

• Obesity and diabetes metastasize to the brain
• Inflammation and metabolic alteration critical mediators
• Targeting the metabolic and homeostatic network
• Capable of mitigating domains of psychopathology
• Implications for primary prevention and preemptive treatment