Get Ready for Your Future: Discoveries in Immune, Brain, and Metabolic Science That Will Change Your Treatment of Mental Illness

Understanding Disease Models and Treatment Opportunities: Lessons from Metabolism and Inflammation

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Outline

- Convergent Phenotypes
  - Cognition
- Convergent Substrates
  - The "CNN": Circuits, Nodes, and Networks
  - Inflammatory and metabolic targets
- Convergent "Repurposed" Treatments
  - Inflammatory and metabolic modulators

Mental Disorders are Developmental

<table>
<thead>
<tr>
<th>Age</th>
<th>Disease</th>
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<tr>
<td>&gt; 60 years</td>
<td>Alzheimer’s Disease</td>
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<td>15–20 years</td>
<td>Schizophrenia</td>
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<td>10–13 years</td>
<td>Social Phobias</td>
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<td>5–10 years</td>
<td>Panic Disorder</td>
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<td>Attention-Deficit/Hyperactivity Disorder</td>
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<td>Autism</td>
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Type 2 Diabetes vs Non-Diabetic Controls

Information Processing Speed

Attention and Executive Functioning

Type 2 diabetes (n = 68) and matched non-diabetic control participants (n = 38), followed up for 4 years. McGinniss RJ, et al. Lancet. 2012;379(9833):2291-2299.
Being Overweight / Obese Has a Negative Effect on Cognitive Function in Euthymic Patients with Bipolar Disorder

BMI = body mass index

**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 ($P < .05$)

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The Association between Childhood Adversity and Components of Metabolic Syndrome in Adults with Mood Disorders


**Systolic blood pressure in participants with a mood disorder and a reported history of childhood adversity:**

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Insulin: A Critical Neuropeptide


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Hippocampal and Amygdalar Volume Changes in Diabetes Mellitus

P = .042.

Hippocampal volumes and amygdalar volumes (±SE) on brain MRI in participants with diabetes ($n = 41$) and without diabetes ($n = 451$). Volumes are adjusted for age and sex and normalized to average head size. MRI = magnetic resonance imaging

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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

Interplay between Peripheral Immune Cells, Blood-Brain Barrier, and Microglia-Astrocytes within the Brain to Drive Neuroinflammation

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

Relationship between Neuroinflammation Marker and Severity of Depressive Symptoms

Crosstalk between Monoamines and Inflammation in Brain Disorders


- **Neuroinflammation**: Interplay between peripheral immune cells, blood-brain barrier, and microglia-astrocytes within the brain to drive neuroinflammation. (Bhattacharya A, et al. Psychopharmacology. 2016;233(9):1623-1636.)


Proposed Model of the Kynurenine Pathway in Anhedonia

- The kynurenine pathway metabolizes tryptophan (the primary amino acid precursor of serotonin) into kynurenine before its further metabolism into several neurotoxins.
- In adolescents with MDD (not receiving psychotropic medication), the ratio of tryptophan:kynurenine is positively correlated with anhedonia (Pearson correlation r = .42; P = .05).
- These neural effects may occur via activation of the kynurenine pathway neurotoxic branch, contributing to dopaminergic alterations within the neural reward circuitry.


Effect of Inflammation on Dopamine Metabolism

Obesity is Associated with Reduced White Matter Integrity in Otherwise Healthy Adults

Inflammation and Social Cognition

Common Electrophysiological Markers between DM and MDD

SSRI Therapy Decreases Incidence of Cytokine Induced Depression
Different Targets/Agents: Repurposing Opportunities

**Metabolic:**
- Glucagon-like peptide 1 (GLP-1)
  - Exenatide, Liraglutide, Taspoglutide, Albiglutide, Lixisenatide
- Dipeptidyl peptidase IV inhibitors (DPP-IV)
  - Alogliptin, Anagliptin, Gemigliptin, Linagliptin, Saxagliptin, Sitagliptin, Teneligliptin
- Insulin
- Others

**Inflammatory:**
- JAK-STAT
- Monoclonal antibodies (eg, Infliximab)
- Disease-modifying antirheumatic drugs (DMARDs)
  - Alogliptin, Anagliptin, Gemigliptin, Linagliptin, Saxagliptin, Sitagliptin, Teneligliptin
- Others (eg, Minocycline)

Intranasal Insulin Enhances Executive Function in Bipolar Disorder


Intranasal Insulin: Efficacious in AD and MCI

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

Glucagon-Like Peptide-1 is Synthesized and Secreted in the Intestine and in the CNS

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


If Bipolar Disorder is Progressive, Can We Prevent Bipolar Disorder Onset?

OAA = oral antidiabetic agent.

The GLP-1 Receptor is Expressed in Diverse CNS Nuclei in the Non-Human Primate

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

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: Recalibrating the Circuits Subserving Cognition in Mood Disorders

Liraglutide Improves Cognitive Function in Adults with Mood Disorders

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


Infliximab vs Placebo for the Treatment of Depressive and Cognitive Symptoms in Adults with Mood Disorders: Stratified Sample

University of Toronto (RS McIntyre)
Stanford University (T Suppes)
University of Paris (M Leboyer)

ClinicalTrials.gov Identifier: NCT02363738.

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

Minocycline

• Second-generation, semi-synthetic tetracycline analog with antimicrobial properties
• Highly lipophylic, easily penetrates the blood-brain barrier in contrast to tetracycline
• Principal metabolite: 9-hydroxyminocycline (inactive)


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


Adjunctive Minocycline Treatment for Bipolar Depression

ClinicalTrials.gov Identifier: NCT01483862.
Effect of Gut Microbiota on Mood-Related Behavior

GF = germ-free; SPF = specific-pathogen free.

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)

16-KKW group: fitted curve
4-KKW group: fitted curve
4-KKW group: percent
16-KKW group: percent

NNT = 7.8 for higher dose exercise group

Brain as the Target and Origin of Immune disturbances in Mood Disorders

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Neurobiology of Mood Disorders

Epigenetic Modification

DEVELOPMENT

IL-6 and Depression
IL-6 and Depression

CRP and Depression

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

CRP = C-reactive protein; TNF = tumor necrosis factor.
Inflammatory and Metabolic Derangement

Peripheral Inflammatory Response is Associated with Increased Insula Activity and Fatigue

Inflammatory and Metabolic Derangement May Influence the Course of Depression

Relationship between Peripheral IL-6 Levels and Depression Severity

Inflammatory and Fatigue Level Changes after an Immune Stimulus
Disturbance in IL-6 Circadian Rhythm in MDD


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, \( P = .001 \)).

Comparison of 9 MDD patients and 9 matched healthy controls.

Impact of Inflammatory Cytokines on Brain Circuitry


Interactions at the Glia–Synaptic Junction


TNF-α Amplifies Astrocytic Glutamate Release


In the normal brain, microglia are in the resting state and local TNF-α levels are low. In this condition, an astrocytic G protein-coupled receptor (GPCR) agonist such as the chemokine stromal-derived factor-1α (SDF1α/CXCL12), upon activating C-X-C chemokine receptor type 4 (CXCR4) receptors, induces a local Ca2+ increase in the astrocyte leading to moderate glutamate release, with a modulatory influence on synaptic activity. During brain inflammation, microglia are activated and release large amounts of TNF-α. By acting via astrocytic TNF receptor 1 (TNFR1) and downstream prostaglandin signaling, the cytokine amplifies the effects of SDF1α/CXCL12, promoting massive glutamate (Glu) release.
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.


Are Astrocytes GABAergic Cells?

In immunohistochemical studies of the adult human brain, astrocytes expressed GAD 67 and GABA-T at a comparable or greater intensity level to known GABAergic neurons.

GAD = glutamic acid decarboxylase; GFAP = glial fibrillary acidic protein; GABA-T = GABA transaminase; ST = stimulated.


Do Glial Cells Regulate Glu/GABA Balance?

Glu and GABA Pathways

GABAergic Neuron

GABAergic Neuron

Glutamatergic Neuron

Glutamatergic Neuron

Postsynaptic Neuron

Postsynaptic Neuron

Glu = glutamate; GABA = γ-aminobutyric acid; GLS = glutaminase; mGluR = metabotropic glutamate receptor; VGLUT = vesicles by the vesicular Glu transporters.


CNS Inflammation and Pathophysiology of Psychiatric Disorders

Impact of Inflammation on DAT Expression

DAT = dopamine transporter.


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; HAA = hydroxyindoleacetic acid; HVA = homovanillic acid; LN = natural log.

Lifetime Burden of Mood Episodes Impacts Norepinephrine Metabolite Levels in CSF

- Female, bipolar
- Female, unipolar
- Male, bipolar
- Male, unipolar

CSF MHPG levels were analyzed in 37 patients with severe treatment-refractory mood disorders and 27 healthy controls.

Lifetime Burden of Mood Episodes Impacts Norepinephrine Metabolite Levels in CSF

*Sum of each episode length multiplied by the episode depth.

MHPG = 3-methoxy-4-hydroxyphenylglycol.


"Ach = acetylcholine; AChE = acetylcholinesterase; AR = adrenergic receptor; NA = noradrenaline (norepinephrine); nAChR = nicotinic acetylcholinergic receptors.


"ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; LPS = Lipopolysaccharide; MAPK = mitogen-activated protein kinases; NE = norepinephrine; NFκB = nuclear factor.


The Role of Microglia in Synaptic Plasticity

Microglial processes are highly motile in surveillance mode and are instructed and directed by local neuronal activity to the most highly active neurons. Microglia interact with adjacent neurons through neuronally released signaling molecules, monitoring and directing their activity. Microglial processes (red) engage with the soma of highly active neurons (orange), after which there is a decrease in both spontaneous and evoked neuronal firing. Accumulation of C1q at targeted synapses leads to neuronal/CNS-microglial CNS signaling and subsequent synaptic engulfment of both pre- and postsynaptic structures (green) by microglia (red). Other appropriate synapses can be strengthened by a CX3CR1-dependent mechanism and subsequent maturation through postsynaptic NMDAR subunit changes and AMPAR insertion.


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

"aMCC = anterior midcingulate cortex; pACC = pregenual anterior cingulate cortex; sACC = subgenual anterior cingulate cortex.


"Major Depression = suicide attempt; AD-ns = nonsuicidal patients with affective disorder; AD-s = suicidal patients with affective disorder; Sz-ns = nonsuicidal individuals with schizophrenia; Sz-s = suicidal individuals with schizophrenia.

IL-1β in CSF of MDD Patients

CSF IL-1β levels in depressed patients and healthy controls. Means ± SD. CSF IL-1β levels are higher in depressed patients. ANOVA test: df = 1,20; F = 19.8; P < .0002.

Elevation of CSF IL-6 in MDD

Comparison of 32 patients with schizophrenia, 30 with MDD, and 35 healthy controls. (Schizophrenia: P = .0027; MDD: P = .012)

Circuits and Cytokines

Infection/Stress Activates Inflammation, Which Contributes to the Pathophysiology of MDD

Disturbed Microglia/Astroglia Balance May Precipitate Suicidality

QUIN and kynurenic acid in CSF of suicide attempters and healthy controls. The lines connect measures of CSF QUIN from the same patients, between the suicide attempt and at 6 months after the attempt.

Upregulation of Microglial QUIN in the Brains of Suicidal Patients

QUIN + Cell Density (cells/mm3)

P < .05

P < .01

P < .001

Inflammatory Cytokine/Glu Interaction May Contribute to Fatigue

- TNF-α, IL-1β, IL-6 interfere with Glu uptake
- Interfere with Glu transmission
- Decrease in signal-to-noise ratio
- Impair neuronal excitability
- Sensory acuity
- Astroglial swelling
- Increase in K+ uptake
- Decrease in Glu release
- Decrease in NE/5-HT
- Depression
- Attention
- Astroglial metabolism
- Increase in Glu transmission effective space
- Decrease in precision of information intake and processing

BBB = blood-brain barrier.

Course of MDD is Associated with Disturbance in Cortical Glu Transmission

- Decrease in Glu concentration
- Duration of illness (years)

A 3-Tesla MR facility was used to measure absolute Glu concentrations in vmPFC of 45 depressive patients (10 first-episode-MDD, 16 remitted-recurrent-MDD, and 19 chronic-MDD) and 15 healthy controls.

vmPFC = ventromedial prefrontal cortex.

Brain Areas Involved in Emotional Regulation

The dorsal anterior cingulate (dACC), insula, amygdala and periaqueductal grey (PAG) (shown in red) have been implicated in emotional reactivity. By contrast, the dorsolateral prefrontal cortex (dPFC), ventrolateral PFC (vPFC), supplementary motor area (SMA), pre-SMA and parietal cortex (shown in blue) have been implicated in “explicit” emotion regulation, and the ventral ACC (vACC), ventromedial PFC (vmPFC; also shown in blue) has been implicated in “implicit” emotion regulation.

Abnormal Implicit Regulation of Emotion in MDD

Reduced amygdala-rostral ACC/dorsal ACC/mPFC functional (and effective) connectivity to emotional stimuli; normalizes/increases with antidepressant treatment

Reduced amygdala-subgenual ACC/vmPFC functional (and effective) connectivity in response to emotional stimuli

Elevated subgenual ACC activity to emotional stimuli; normalizes/reduces with antidepressant treatment

Elevated amygdala activity to emotional stimuli; normalizes/reduces with antidepressant treatment


Neurobiology of Mood Disorders

Etiology
- Epigenetic Modulation
- Genetic
- Epistasis

Clinical Presentation
- Pathophysiology
- Neuroendocrine, autonomic, and immune dysregulation
- Systemic manifestations
- Neurocircuitry dysregulation
- Functional changes
- Structural changes

Development
- ELA
- Network level
- Dysregulation of neurocircuitry
- Structural changes

Etiology Clinical Presentation

Network Level: Dysregulation of Neural Circuitry
- Functional changes
- Structural changes

The 3 Network Theory of Mood Disorders

CEN = central executive network; PPC = posterior parietal cortex; DMN = default mode network; PCC = posterior cingulate cortex; AI = anterior insular; PI = posterior insular; SN = substantia nigra.


Deficits in self-referential mental activity (eg, excessive rumination, poor autobiographical memory)

DLPFC  CEN  PPC  vmPFC  DMN  PCC  PI  AI  SN

Weak salience mapping

Psychosocial poverty and impoverished goal-directed action

Top-Down

Sensory (eg, novel, deviant)

Limbic (eg, reward, motivation)

Self-Referential (eg, internal value, autobiographical memory)

Correlation between sgACC and PCC

May Be a Marker of Depressive Rumination

sgACC = subgenual anterior cingulate cortex.


y = .0068x – .0911

R^2 = .477, P < .001

Correlation of sgACC with PCC

Rumination and Depression

• There are significant associations between rumination, negative mood, and reduced subjective sleep quality
• Rumination is associated with greater depressive affect and reduced positive affect
• Rumination may be the principal symptom of depression that interferes with executive function and ability to shift attention
• Brooding rumination and perfectionism increase the risk of depression in stressful circumstances

sgACC–Amygdala Connectivity is Associated with Negative Affect and MDD

56 adolescents were part of a larger longitudinal study of adolescent development. They had no history of mental illness at the time of their baseline scan (mean age 16.5 years) and had a follow-up scan 2 years later (mean age 18.8 years). Amygdala–sgACC connectivity showed significant correlation with negative affectivity at both T3 and T4 time-points. 8 developed first-episode of depression.


Rumination and Depression (continued)

• Anger rumination mediates the association between MDD and anger
• Rumination remains elevated after remission from depression
  - It is associated with less treatment response
  - Rumination prospectively predicts the onset, severity, and duration of depression and level of anxiety symptoms
  - Suicidal rumination is strongly associated with the severity of depression


Rumination and Depression

Ruminations are a Part of Our Defensive Repertoire

Emotional Stressor

Stressor is immediate or imminent

Stressor requires extended effort

Social status is threatened

Physiological Outcomes

Associate Appraisals and Emotions

Surprise

Anticipation

Fear of loss of social approval

Self-conscious emotions

Stressor

Physiological changes to natural and specific immunity

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).


Depressed Patients Fail to Deactivate DMN during a Cognitive Task

Significantly decreased DMN deactivation (red) in rMDD patients compared to HC (A, C). Maximal effects are being found in the amPFC. Task activation (yellow) and deactivation (cyan) is presented as underlay of group comparison results in order to outline the DMN. Adolescent-onset rMDD patients exhibit significant and even more pronounced DMN deactivation decreases with punctum maximum in the amPFC and the PCC compared to HC (B, C).

HC = healthy controls; rMDD = full remission of MDD.


Aberrant DMN–DLPFC Connectivity Interferes with Working Memory

Differences in functional connectivity between adolescent-onset MDD patients (n = 42) and HC (n = 42). Significantly increased (red) coupling of the amPFC with the DLPFC and significantly decreased coupling (blue) with the mFG.

MFG = medial frontal gyrus.


Altered Reward Circuitry in MDD

Elevated mPFC/pregenual ACC activity to formerly rewarding stimuli during expectancy of monetary reward and during reward learning (reduced activity to reward)

Reduced ventral striatal activity to reward/reward learning; greater habituation of ventral striatal response to reward


Patients with Depression Had an Attenuated Ventral Striatal (Nucleus Accumbens) Response to Positive Stimuli

Mean (± SD) BOLD Response (%)

Left Ventral Striatum

Right Ventral Striatum

Valence

Negative

Neutral

Positive

Depressed Participants

Healthy Comparison Participants

Depressed Participants

Healthy Comparison Participants


Hypothetical Relationship between Hyperarousal and Anxiety

If tonic firing of the LC-NE system is low and not within the 1 to 3 Hz range during wakefulness, when phasic firing of the LC occurs, individuals appear inattentive and impulsive. If tonic firing of the LC-NE system is higher, when phasic firing of the LC occurs, individuals appear inattentive and display avoidant behaviors.

LC-NE = locus coeruleus norepinephrine.

Aberrant Evening Brain Activity in MDD Patients

Areas with greater relative glucose metabolism during evening wakefulness than morning wakefulness in the depressed sample only \( P < .05 \) at the corrected cluster level. The volumes of interest corresponding to left amygdala, ACC, and posterior hypothalamus are also presented.


MDD Patients Experience Elevated Arousal in the Evening

Areas where depressed patients significantly differed from healthy participants during evening relative to morning wakefulness projected onto glass brains. Volumes of interest corresponding to the midbrain reticular formation volume, left LC.

ARAS = ascending reticular activating system.


Elevated Diurnal Norepinephrine Levels in Melancholy Depression

Diurnal curves of CSF NE levels (mean ± SE) in 14 healthy volunteers and 10 patients with major depression, melancholic type. Curves result from the averaged measurement per time point across a group of subjects.


Key Take-Aways

- The brain is often both the target and the origin of immune perturbations in mood disorders
- Immune disturbances in the brain and body are associated with emotional, cognitive, and somatic symptoms of mood disorders
- Multiple changes in neurotransmission are related to excessive inflammatory signaling
- Medicines that modulate immune function may benefit some patients suffering from mood disorders

Hold the Aspirin: Recent Discoveries in Inflammation Point to Novel Immune-Based Therapeutic Strategies

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Mary Sue and Mike Shannon Chair for Healthy Minds, Children & Families
Professor, Human Development and Family Studies, School of Human Ecology
Professor, Department of Psychiatry, School of Medicine and Public Health
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Meta-Analysis Does Not Provide Strong Support for Cytokines Predicting Non-Response to Antidepressants

A meta-analysis of 35 studies examining the association of immune measures with treatment response and resistance found the following:
- IL-6, TNF, and CRP elevated in patients with major depression compared to non-depressed control participants
- No association was seen between pre-treatment plasma concentrations of IL-6, TNF, and CRP and subsequent response to antidepressant treatment
- A composite inflammatory factor showed trend level association with treatment non-response \( (P = .07) \)
- Reduction in TNF was associated with response to treatment. IL-6 reduced inflammatory measures, but no association seen between this reduction and clinical response. No effect of treatment on CRP

CRP = C-reactive protein; IL = interleukin; TNF = tumor necrosis factor.
On the Other Hand: Immune Gene Expression Biomarker Predicts Response and Non-Response

In an initial (GENDEP) and confirmatory patient population, absolute mRNA measures of Macrophage Migration Inhibitory Factor (MIF) and IL-1β predicted both response and non-response to treatment with either escitalopram or nortriptyline for major depressive disorder.


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 Predicts Response to Eicosapentaenoic Acid

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


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 as an Antidepressant Treatment

Infliximab Placebo

60 50 40 30 20 10 0 Med + Low High Percent Responders during Study

Hs-CRP (tertiles)

41 2 31 0 16 2 Baseline 8

Infliximab

Placebo

Randomization

Clinician-Administered Psychiatric Assessments (HAM-D, CGI)

Adverse Events Evaluation

Blood Draw for Inflammatory Markers and Safety Labs

Increased Inflammation May Be Counterproductive for Many with MDD

Whole Body Hyperthermia (WBH) as a Probe into Inflammation and Depression

Antidepressant Effects of WBH


Inflammatory Effects of WBH

IL-6 Response to WBH Associated with Macrophage Activation


Can Inflammation Sometimes Make People Feel Better?

Increased IL-6 Associated with Reduced Depression following WBH

PANAS = Positive and Negative Affect Schedule.

IDS-SR = Inventory of Depressive Symptomatology, Self-Report.
**Increased Neopterin Associated with Reduced Depression following WBH**

![Graph showing relationship between Delta Neopterin (nmol/L) and Delta IDS-SR Score (Baseline to Week 1), with lines for WBH and SHAM groups.](image)


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**Exercise Induces an Inflammatory Pattern Similar to the Pattern of WBH**

![Graphs comparing pro-inflammatory and anti-inflammatory responses](image)


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**THE OLD FRIENDS**

- Gut Flora
- Mycobacteria
- Helminth

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**Discovery of *Mycobacterium vaccae***

![Image of John Stanford and Graham Findlay, and a map showing the discovery of *Mycobacterium vaccae*.](image)


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**M vaccae Induces an Acute Antidepressant and Proinflammatory Response**

![Graphs and images showing the effects of *Mycobacterium vaccae*](image)


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**Testing the Stress-Relevant Effects of *M vaccae* in an Animal Model**

![Diagram showing stress testing in animal models](image)

**M vaccae Induces Behavioral Resilience and Blocks Inflammatory Response to Stress**

- Blocked the development of intestinal inflammation
- Prevented stress-induced increases in peripheral inflammatory cytokines
- Increased in proactive behavior, i.e., mice fought back more and because of this were left alone more by the “bully mouse”
- Prevented all measures of stress-induced increases in anxiety-like behavior
- Anti-anxiety and anti-inflammatory effects of *M vaccae* erased when regulatory T cells were blocked


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

LPS = lipopolysaccharide.

**Inflammation May Be Therapeutically Harnessed in Different Ways in Different Patients with Depression**

- **Therapeutic approach 1:** Block of chronic stress-induced monocyte/macrophage recruitment
- **Therapeutic approach 2:** Block of stress-induced monocyte/macrophage recruitment


**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.

NSAID = nonsteroidal anti-inflammatory drug; STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

**Above All Do No Harm**

- Approximately 107,000 patients are hospitalized each year from complications of NSAID use
- Close to 17,000 patients with rheumatoid arthritis alone die from GI complications from NSAIDs each year
- The addition of NSAIDs to SSRIs significantly increases bleeding risk
- Celecoxib increases the risk of myocardial infarction by 226%. All NSAIDs increase risk of vascular complications
- TNF-α antagonists increase the risk of tuberculosis and other infections and have been rarely associated with rare T-cell cancers

GI = gastrointestinal.

**Conclusion**

- Immune–brain interactions can produce a syndrome indistinguishable from MDD, which likely explains—at least in part—why populations of depressed patients have elevated peripheral inflammation
- Evidence increasingly suggest that only a sub-group of depressed patients—those with elevated inflammation—are likely to benefit from anti-inflammatory treatment modalities
- Pharmacological anti-inflammatory strategies—either in the periphery or CNS (i.e., microglia suppression)—may actually worsen depressive symptoms in some patients, whereas a little inflammatory stimulus might help some patients with depression, although the mechanism of this effect is currently unknown
Conclusion (continued)

The best anti-inflammatory approaches for enhancing emotional well-being don’t come in a pill….

Call to Action:

Converting Discoveries in Immune, Brain, and Metabolic Science to Change Our Treatment of Mental Illness

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Now that we know, based on the previous 3 presentations, that Immune, Brain, and Metabolic changes are hugely problematic –

What do we do?

How do we do it??

But first –

A Quick Primer on the Immune / Inflammatory System

There are 2 Main Types of Immunity

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<th>Innate (Natural) Immunity</th>
<th>Adaptive (Specific) Immunity</th>
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<tbody>
<tr>
<td>Rapid response</td>
<td>Slower response</td>
</tr>
<tr>
<td>Cells (Macrophages, Neutrophils, Natural Killer cells, Dendritic cells)</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Memory – None</td>
<td>B Lymphocytes</td>
</tr>
<tr>
<td>Specificity – Low</td>
<td>T Lymphocytes</td>
</tr>
<tr>
<td>Diversity – Low, Encoded in the germline</td>
<td>Memory – Yes</td>
</tr>
<tr>
<td>Proteins – Complements and cytokines</td>
<td>Specificity – High (human lymphocytes can distinguish between 10,000,000,000 antigens)</td>
</tr>
<tr>
<td></td>
<td>Diversity – Extremely high</td>
</tr>
<tr>
<td></td>
<td>Proteins - antibiotics – (B Cells) and Cytokines (helper T cells)</td>
</tr>
</tbody>
</table>


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 enzymes.
Life span is 1 to 2 days.

Monocyte
Mean number per mL — 300
Activation
Tissue migration
Macrophage
Activated Macrophage

Acquired Immunity – Lymphocytes

Their Role of B and T Lymphocytes

Cell Mediated Immunity

Humoral Immunity

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

B Lymphocytes

T Lymphocytes

Macrophage – Microglia Interactions

Activated Macrophage

(tissue presence – especially in adipose tissue)

Activated Microglia

(psychosocial stressors)

“Oh what a web we weave”

Immune–Metabolic–HPA and ANS Interactions

Caution: Before We Go Too Far Down the “Mental” Health Path

• We must, must, must screen patients for metabolic dysregulation. ADA/APA guidelines are very useful

• And if metabolic abnormalities are detected, we must, must, must treat, or make appropriate referrals

• There is emerging evidence that treating metabolic dysregulation in the body, positively impacts mental health

ADA Antipsychotic Medication Utilization Recommendations

Assessment(s) | Baseline | 4 weeks | 8 weeks | 12 weeks | Quarterly | Annually
--- | --- | --- | --- | --- | --- | ---
Personal/family history; physical exam | X | X | X | | |
Weight (BMI); Height | X | X | X | X | | X
Waist Circumference | X | X | X | | |
Blood Pressure | X | X | X | | |
Fasting Plasma Glucose/A1C | X | X | X | | |
Fasting Lipid Profile | X | X | X | | |

More frequent assessments may be warranted based on clinical status

Evidence: Treating “Peripheral” Metabolic Disturbance = ↑ + Mental Health Impact

Log rank test P = .0047

Risk of Depression Changes with Statin Treatment

Log rank test P = .0065

ADA = American Diabetes Association; APA = American Psychiatric Association.

It Appears There are 2 Key Fundamental Laws We Clinicians Must Follow

In order to minimize the impact of immune – brain – metabolic changes

1. Seek to drive psychiatric illnesses to remission
2. Seek to introduce Mental Wellness Concepts into the care of patients

Consider those Mental Wellness techniques that give you "two for the price of one" benefits – with positive Brain and Body outcomes

Which are These “Two for the Price of One” Wellness Techniques?
We have identified 5 such interventions. This is based on strength of scientific evidence, and our clinical experience

- Exercise
- Mindfulness
- Optimized Sleep
- Optimized Nutrition
- Optimized Socialization

Now Let’s Turn Our Attention to These 5 Tools

1) Exercise
2) Mindfulness
3) Optimized Sleep
4) Optimized Nutrition
5) Optimized Socialization

First, let's evaluate the scientific data supporting their utility
Second, let's examine the clinical studies
And finally, let's explore clinical application of these tools in our clinical practices

Potential Mechanisms Through Which Exercise Reduces Chronic Inflammation in Obesity

Acute Exercise: Effects on Skeletal Muscle and Systemic Inflammation

ROS = reactive oxygen species; TLR = toll-like receptor; RA = receptor antagonist.

Potential Mechanisms Through Which Exercise Reduces Chronic Inflammation in Obesity

Acute exercise stimulates skeletal muscle release of IL-6, which further inhibits actions of pro-inflammatory cytokines and increases levels of anti-inflammatory cytokines in other tissue/cells and systemically. Exercise training may increase angiogenesis, alleviate vasoconstriction and increase blood flow, thereby reducing hypoxia and the associated chronic inflammation in adipose tissue. Exercise also reduces adhesion molecule production by endothelial cells and stimulates the regeneration these cells, and lowers vascular wall inflammation. Exercise training may reduce the expression of toll-like receptors and production of pro-inflammatory cytokines in monocytes, lower the number of pro-inflammatory cells, and increase the number of regulatory T cells. All these mechanisms may contribute to the anti-inflammatory effects of exercise training. Adapted and updated from original text.

First Things First – Let’s Review Tryptophan Pathways

KYN = Kyurenine
KATs = Kyurenine Aminotransferases
KYNA = Kynurenic Acid
QUIN = Quinolic Acid

Exercise: How It Creates Its Antidepressant Effects

KYN = Kynurenine
PGC-1a1 = Peroxisome proliferator-activated receptor-gamma coactivator
AMPK = AMP-activated protein kinase
KAT = Kynurenine aminotransferase
KYNA = Kynurenic Acid

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

A Newly Emergent Brain–Body Link in Depression

Two Structures in the Human Body Contain KAT, the Enzyme that Clears Away the Neurotoxin Kynurenine

Astrocytes

Exercise

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.

Meditative Practice and Therapeutic Benefits in Chronic Inflammatory Conditions

37 MNP and 31 LTM. Psychological stress induced using the TSST. Cortisol and alpha-amylase, provided measures of magnitude of stress response (samples at baseline and before application of capsaicin cream). Subsequent samples were collected immediately after the end of the TSST plus every 10 minutes for the next 40 minutes (total 6 saliva samples).

RESULTS: LTM had lower TSST-evoked cortisol (P < .05) and perceived stress (P < .01), and smaller neurogenic inflammatory response (P < .05). LTM reported higher levels of psychological factors associated with well-being and resilience. Long-term meditation practice may reduce stress reactivity and be of therapeutic benefit in chronic inflammatory conditions characterized by neurogenic inflammation.
Sleep Disturbance and Systemic Inflammation

Systematic search of 72 primary research articles that characterized sleep disturbance and assessed inflammation by levels of circulating markers. Sleep disturbance: self-reported symptoms and questionnaires.

Sleep disturbance is associated with increases in markers of systemic inflammation.


Sleep–Metabolic–Oxidative Stress Connection


Restorative Sleep Results in Lower Inflammation

Observational study (N = 66) of US military personnel who presented for evaluation of sleep disturbance. Examined the relationship between reported sleep changes and concentrations of IL-6 and CRP in peripheral blood.

The restorative sleep group had significant reductions in CRP concentrations and depression symptoms, as well as reduced fatigue and improvements in emotional well-being, social functioning, and physical functioning at follow-up.


Why Care about Sleep? Sleep and Its Trophic/Metabolic/Immune Implications


Social Network Ties and Inflammation

Nationally representative sample of adults with a history of cancer (N = 1075) from the National Health and Nutrition Examination Survey III.

Lower SNI scores showed significantly greater inflammation marked by CRP and Fibrinogen.

SNI = Social Network Index.

Association between Childhood Social Isolation and Inflammation in Adulthood

Study used multiply-imputed data on 7462 participants of the National Child Development Study in Great Britain.

INCREASED ADULT INFLAMMATION

Socially isolated children had higher levels of C-reactive protein in mid-life.
Volunteering and Lower Inflammation

Representative survey of adults aged 57–85 from the National Social Life, Health, and Aging Project (N = 1790). Study investigates whether productive activities by older adults reduce bodily inflammation.

Productive activities—and frequent volunteering in particular—may protect individuals from inflammation.

CRP by frequency of volunteering, stratified by age groups (including adjustments for all control variables).


Mediterranean Diet and Inflammation

Pooled cross-sectional study of 50- to 74-year-old men and women in an elective outpatient colonoscopy population (N = 646).

Dietary patterns that are more Mediterranean-like may be associated with lower levels of systemic inflammation.


Food Choices Matter

Emerging Scientific Data on Nutrition and Health (Risks/Benefits)

Review of 304 studies examining the link between nutrition and chronic diseases (mental health, obesity, skeletal health, cardiovascular disease, cancers).

Radar plots for food groups and beverages vs number of references (percentages from 0%–100% shown on concentric circles) showing protective (solid green lines), neutral (dashed yellow lines), or deleterious effects towards all diet-related chronic diseases.


WILD 5 Wellness Program – 30-day Augmentation Program

1. Exercise 2. Mindfulness
5. Social Connectedness

The WILD 5 Program Philosophy

- All Equally Important
- "Do it all" approach – no picking and choosing
- Wellness/Immun/ Metabolic Interventions

Mindfulness

Exercise

Nutrition

Social Connection

Sleep
WILD 5 Wellness Program – The Psych Congress Attendee Participants

Exercise
Nutrition
Mindfulness
Social Connectedness
Sleep

WILD 5 Wellness Elements

PROGRAM EXPECTATIONS

- Exercise*: Exercise 30 minutes each day for 30 days, at least moderate intensity* (*FID Principles)
- Mindfulness: Practice mindfulness at least 8 minutes each day for 30 days
- Sleep: Implement at least 4 of the 6 pro-sleep hygiene practices each day for 30 days
- Social Connectedness: Text or call a family member or friend each day for 30 days
- Nutrition**: Log your daily meals/snacks/beverages/alcohol each day for 30 days** (MIND diet recommended

* If you’re unable to reach moderate intensity as you begin the program, that is fine. Do whatever you’re capable of doing. The goal is to increase your exercise at a level of moderate intensity or higher.
** We highly recommend you follow the MIND Diet during the program as it has shown pro-brain and pro-health benefits.

30-day WILD 5 Wellness Program Results in Mental Health, Chronic Pain, and Community Populations

MENTAL HEALTH (N = 82): Participants had a diagnosed Axis I condition
- CHRONIC PAIN (N = 51): Participants had a chronic pain condition of at least 6 months or longer duration
- COMMUNITY (N = 13): Participants did not report either a mental health or chronic pain condition

Impact of 30-day WILD 5 Wellness Program on Depressive Symptoms: PHQ-9 Changes

| Mental Health | N = 82 | Percentage Improvement = 43% | Mean: 11.4 | Mean: 6.4 | P = .0001
| Pain | N = 51 | Percentage Improvement = 43% | Mean: 11.9 | Mean: 6.7 | P = .0001
| Community | N = 13 | Percentage Improvement = 40% | Mean: 4.9 | Mean: 2.9 | P = .0000

PHQ-9 is a 9-item scale, scores range from 0 to 27. Lower score denotes improvement. ANOVA – comparison of means. PHQ-9 = Patient Health Questionnaire 9-item.

Jain R, Jain S. Poster presented at: 29th Annual US Psychiatric and Mental Health Congress; October 2016; San Antonio, TX.

Impact of 30-day WILD 5 Wellness Program on Anxiety: GAD-7 Changes

| Mental Health | N = 82 | Percentage Improvement = 40% | Mean: 9.9 | Mean: 5.9 | P = .0001
| Pain | N = 51 | Percentage Improvement = 39% | Mean: 10.3 | Mean: 6.2 | P = .0001
| Community | N = 12 | Percentage Improvement = 13% | Mean: 3.0 | Mean: 2.6 | P = .0001

GAD-7 is a 7-item scale, scores range from 0 to 21. Lower score denotes improvement. ANOVA – comparison of means. GAD-7 = Generalized Anxiety Disorder 7-item.

Jain R, Jain S. Poster presented at: 29th Annual US Psychiatric and Mental Health Congress; October 2016; San Antonio, TX.
Impact of 30-day WILD 5 Wellness Program on Sleep Quality: PSQI Changes

PSQI is a 9-item scale, scores range from 0 to 27. Lower score denotes improvement.

ANOVA – comparison of means. PSQI = The Pittsburgh Sleep Quality Index.

Jain R, Jain S. Poster presented at: 29th Annual US Psychiatric and Mental Health Congress; October 2016; San Antonio, TX.

<table>
<thead>
<tr>
<th>Mental Health</th>
<th>N = 62</th>
<th>Pain</th>
<th>N = 51</th>
<th>Community</th>
<th>N = 13</th>
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<tbody>
<tr>
<td><strong>Percentage Improvement</strong>&lt;br&gt;Pre</td>
<td>Post&lt;br&gt;Mean:</td>
<td>Mean:</td>
<td>Mean:</td>
<td>Mean:</td>
<td>Mean:</td>
</tr>
<tr>
<td>10.3</td>
<td>7.3</td>
<td>11.8</td>
<td>8.3</td>
<td>7.3</td>
<td>5.0</td>
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<tr>
<td><strong>P</strong>&lt;br&gt;P = .0001</td>
<td>P = .0001</td>
<td>P = .84</td>
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</table>

Impact of 30-day WILD 5 Wellness Program on Wellness: WHO-5 Changes

WHO-5 is a 5-item scale, scores range from 0 to 25. Higher score denotes improvement.


Jain R, Jain S. Poster presented at: 29th Annual US Psychiatric and Mental Health Congress; October 2016; San Antonio, TX.

<table>
<thead>
<tr>
<th>Mental Health</th>
<th>N = 62</th>
<th>Pain</th>
<th>N = 51</th>
<th>Community</th>
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</thead>
<tbody>
<tr>
<td><strong>Percentage Improvement</strong>&lt;br&gt;Pre</td>
<td>Post&lt;br&gt;Mean:</td>
<td>Mean:</td>
<td>Mean:</td>
<td>Mean:</td>
<td>Mean:</td>
</tr>
<tr>
<td>8.2</td>
<td>13.2</td>
<td>8.3</td>
<td>13.1</td>
<td>16.4</td>
<td>18.2</td>
</tr>
<tr>
<td><strong>P</strong>&lt;br&gt;P = .0001</td>
<td>P = .0001</td>
<td>P = .3</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

BPI: Scores in Chronic Pain Population

(Scale 0–10, lower number denotes improvement)

ANOVA – comparison of means. BPI = Brief Pain Inventory.

Jain R, Jain S. Poster presented at: 29th Annual US Psychiatric and Mental Health Congress; October 2016; San Antonio, TX.

<table>
<thead>
<tr>
<th>Item</th>
<th>Pre Score</th>
<th>Post Score</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>BPI – Worst Pain (last 24 hrs)</td>
<td>5.9</td>
<td>4.8</td>
<td>&lt; .0002</td>
</tr>
<tr>
<td>BPI – Least Pain (last 24 hrs)</td>
<td>2.8</td>
<td>2.2</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>BPI – Avg Pain (last 24 hrs)</td>
<td>4.4</td>
<td>3.6</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>BPI – Interference with General Activities</td>
<td>4.3</td>
<td>3.6</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>BPI – Pain Interference with Mood</td>
<td>4.5</td>
<td>3.6</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>BPI – Pain Interference with Relationships</td>
<td>3.6</td>
<td>2.6</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>BPI – Pain Interference with Sleep</td>
<td>4.3</td>
<td>3.2</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>BPI – Pain Interference with Enjoyment of Life</td>
<td>4.5</td>
<td>3.4</td>
<td>&lt; .0000</td>
</tr>
</tbody>
</table>

But, What about Improvement in the “Core” Wellness Elements?

WILD 5 Wellness “Core” Wellness Components are – Happiness, Enthusiasm, Optimism, and Resilience

N = 82

<table>
<thead>
<tr>
<th>Item</th>
<th>Pre</th>
<th>Post</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Happiness</td>
<td>Mean: 4.0</td>
<td>Mean: 5.2</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Enthusiasm</td>
<td>Mean: 3.3</td>
<td>Mean: 4.7</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Optimism</td>
<td>Mean: 3.3</td>
<td>Mean: 4.7</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Resilience</td>
<td>Mean: 3.3</td>
<td>Mean: 4.7</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

WILD 5 Wellness Program Implementation and Learnings

www.WILD5Resources.com
Password: wellnessmatters

WILD 5 Wellness Program Mindfulness Meditations

www.Wild5Resources.com
Password: wellnessmatters

CD OR DOWNLOAD

SHARE WITH YOUR PATIENTS
In Conclusion

- We are compelled to believe that there is a tight bond between Immune/ Metabolic/ Psychiatric issues
- These can adversely affect both short- and long-term mind–body outcomes for our patients
- Wise pharmacologic and non-pharmacologic treatment options are available to address these issues holistically
- Interventions should be designed with patient acceptability and acceptance in mind. Long-term interventions and lifestyle changes would be an ideal approach to improving patient care