The Brain / Body Connection: Inflammation and Microbiota
Learning Objectives

• Identify the relationship between inflammation and brain and body health
• Explain how gut microbiota are relevant to inflammatory milieu
• Identify novel and conventional multimodal treatments that may target inflammation
An increase in proinflammatory cytokines would be expected to lead to:

1. Decreased serotonin, increased norepinephrine and dopamine
2. Increased serotonin, norepinephrine, and dopamine
3. Decreased serotonin, norepinephrine, and dopamine
4. Increased serotonin, decreased norepinephrine and dopamine
NIH Prioritizes Cognition as a Critical Target for Treatment Discovery and Development in Psychiatry

"Develop, for research purposes, new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures"

Cognitive systems

- **Working memory**: dorsolateral PFC, other areas in PFC
- **Cognitive (effortful) control** (opposite pole – impulsivity, disinhibition, externalizing): anterior cingulate gyrus, various areas of medial and lateral PFC

Positive valence systems

- **Approach motivation** (opposite pole – anhedonia): mesolimbic dopamine pathway
- **Habit-based behavior** (including OCD spectrum): orbitofrontal cortex, thalamus, dorsal striatum

Negative valence systems

- **Fear** (opposite pole – fearlessness): amygdala, hippocampus, interactions with ventromedial PFC
- **Potential threat**: HPA, BNST, hippocampus, CRF, cortisol

Systems for social processes

- **Social dominance**: distributed cortical activity, mesolimbic dopamine systems, testosterone, serotonin
- **Facial expression recognition**: ventral visual stream, fusiform gyrus
- **Self-representational circuits**: dorsal and posterior ACC, insula

Arousal/regulatory processes

- **Stress regulation**: raphe nuclei circuits, serotonin
- **Facilitated stimulus processing**: locus coeruleus circuit, noradrenaline
- **Readiness for stimulus processing and responding**: brain resting state network


Development and Definitions of the RDoC Domains and Constructs.
Interplay between peripheral immune cells, the 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

NFκB, 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;

Bhattacharya et al. Psychopharmacology 2016
Molecular Effector Systems Relevant to Phenomenology

- Inflammation
- Excitatory–inhibitory
- Metabolic
- Cellular bioenergetics
- Monoamines

Rosenblatt and McIntyre 2015.
Results From Animal Studies

Inoculate with pro-inflammatory agent

"Sickness behavior"

Decreased:
- Locomotion
- Sex drive
- Appetite
- Motivation
- Socialization

The "happy" mouse

Neurotransmitter Changes

Inflammatory cytokines lead to decreased serotonin, norepinephrine, and dopamine centrally


Effect of Inflammation on Dopamine Metabolism


Sellgren et al. Mol Psychiatry 2015; doi:10.1038/mp.2015.186.
Inflammation Results in Anhedonia

- The kynurenine pathway metabolizes tryptophan (the primary amino acid precursor of serotonin) into kynurenine before it is metabolized into several neurotoxins

- In adolescents with MDD (not receiving psychotropic medication), the ratio of tryptophan to kynurenine is positively correlated with anhedonia (Pearson correlation $r=0.42$; $P=0.05$)

- These neural effects may occur via activation of the neurotoxic branch of the kynurenine pathway, contributing to dopaminergic alterations within the neural reward circuit

MDD: major depressive disorder. PFC: prefrontal cortex. NMDA: N-methyl-D-aspartate. QUIN: quinolinic acid. KA: kynurenic acid. 3-HK: 3-hydroxykynurenine. TRP: tryptophan. KYN: kynurenine. 3-HAA: 3-hydroxyanthranilic acid. IDO: indoleamine 2,3-dioxygenase.

Microbiome Links Together...

- Diet
- Stress
- Pain
- Infection
- Urbanicity

- HPA axis
- Inflammation
- Neurotransmitters
- Early life events
- Neurodevelopment
Gut Microbiome

- >100 trillion bacteria
- 10 times as many bacterial cells as human cells in the body
- 150 times as many genes as the human genome
Gut Microbiome

- >1,000 species, >7,000 strains
- 3 enterotypes (Bacteroides, Prevotella, Ruminococcus)
- Colonization is largely postnatal; depends on mode of delivery
- Composition of core microbiome is largely stable in adulthood but differs in the elderly
Change the Microbiome, Change the Behavior

Gregarious

Germ-free BALB/c mouse + NIH Swiss microbiome

Anxious

Germ-free NIH Swiss mouse + BALB/c microbiome

Bercik et al. Gastroenterology 2011;141:599.
• Maternal separation leads to elevated corticosterone and colonic acetylcholine release
• BUT maternal separation only leads to anxiety behaviors in specific pathogen-free (not germ-free) mice
• MICROBIOTA necessary for the development of anxiety behaviors

• Colonization of adult germ-free mice induces anxiety behaviors in maternal separation mice but not in controls

• MICROBIOTA works together with HOST FACTORS to produce anxiety phenotype

Is Inflammation the Link Between Mood Disorders and Metabolic Syndrome?

- **FFA**: Promotes foam cell formation
- **TNF-α**: Vascular inflammation, Promotes foam cell formation
- **CRP**: Predicts diabetes, Vascular inflammation
- **Oxidized LDL-C**: Promotes foam cell formation, Proinflammatory
- **Leptin**: Insulin-mediated glucose uptake, Mediates inflammation, immune responses
- **Sensitivity to angiotensin II**: Insulin resistance, Endothelial dysfunction

FFA: free fatty acid. TNF-α: tumor necrosis factor alpha. CRP: C-reactive protein. LDL-C: low-density lipoprotein cholesterol.

Excess Weight in Bipolar Disorder Is Associated With Proinflammatory Signature

Kynurenine and neopterin levels and the kynurenine:tryptophan ratio in patients with bipolar disorder or healthy controls

*B<0.025; †P<0.01 vs. patients with bipolar disorder who were of normal weight.

Investigation of the tryptophan/kynurenine metabolism pathway as a proxy of dysregulated inflammatory homeostasis in euthymic, overweight individuals with bipolar disorder (n=78) compared with healthy controls (n=156).

MDD and BD Are Independent Risk Factors for Heart Disease

Step 1: Risk stratification by disease process

Tier I: High Risk
- Diabetes mellitus, types 1 and 2
- Chronic kidney disease/end-stage renal disease/post kidney transplant
- Post heart transplant
- Kawasaki disease with current coronary artery aneurysms

Tier II: Moderate Risk
- Kawasaki disease with regressed coronary aneurysms
- Chronic inflammatory disease
- HIV
- Nephritic syndrome
- Major depressive disorder or bipolar disorder

Step 2: Access CV risk factors (≥2 risk factors → move to tier I)

CV Risk Factors/Comorbidities
- Family history of early CVD in expanded first-degree pedigree (male ≤55 y; female ≤65 y)
- Fasting lipid profile
- Smoking history
- BP, 3 separate occasions, interpreted for age/sex/height percentile
- FG
- Diet, physical activity/exercise history

MDD and BD Are Independent Risk Factors for Heart Disease

Tier I: High Risk
- BMI ≤85th percentile for age/sex
- BP ≤90th percentile for age/sex/height
- Lipids (mg/dL): LDL-C ≤100, TG <90, non-HDL <120
- FG <100 mg/dL, HbA1c <7%

Tier II: Moderate Risk
- BMI ≤90th percentile for age/sex
- BP ≤95th percentile for age/sex/height
- Lipids (mg/dL): LDL-C ≤130, TG <130, non-HDL-C <140
- FG <10 mg/dL, HbA1c <7%

Step 2: CV Risk Factors/Comorbidities
- Yes
- No

Step 3: Tier-specific cut points/treatment goals

Step 4: Lifestyle changes
- Intensive lifestyle management
- CHILD-1, activity Rx
- Weight loss as needed

Step 5: Drug therapy
- Condition specific management
- PLUS

If goals are not met, consider medication per risk-specific guideline recommendations

CHILD-1: Cardiovascular Health Integrated Lifestyle Diet
Treatment of Major Depressive Disorder: Florida Medicaid

The goals of acute treatment are safety, response to therapy, patient psychoeducation, and to begin the process of symptomatic, syndromal, and functional recovery.

Assess for:

- Prior history of hypomania/mania
- Psychiatric and medical comorbidities (e.g., substance use disorders, anxiety disorders, obesity, diabetes)
- Presence of specifiers, notably psychosis, mixed features, or suicidality
- Presence of cognitive dysfunction (e.g., memory complaints; difficulty concentrating, making decisions, or thinking clearly)

**Level 1** Initial Treatment:
- Discuss treatment options, including evidence-based psychotherapy (CBT, IPT), interpersonal psychotherapy (IPT)
- Monotherapy 4-8 week trial at adequate dose and evaluate:
  - Selective serotonin reuptake inhibitor (SSRI)*, serotonin-norepinephrine reuptake inhibitor (SNRI), or vortioxetine (if cognitive complaints)
  - Bupropion (if tolerability concerns) or mirtazapine (if insomnia a focus of clinical concern)
- If partial response at 4 weeks may continue for another 2-4 weeks or go to Level 2
- If no response at 4 weeks go to Level 2

*consider propensity for drug-drug interactions, differential risk for teratogenicity

**Level 2** If Level 1 is ineffective and/or not well tolerated:
- Evaluate adherence
- Dose optimization
- Switch to different monotherapy
  - Agent from different or same class (SSRI, SNRI, mirtazapine, bupropion)
- Combine existing monotherapy with:
  - Evidence-based psychotherapy (e.g. CBT, IPT)
  - Atypical antipsychotic FDA-approved for major depressive disorder (MDD) (i.e. aripiprazole, brexpiprazole)
  - An antidepressant (do not combine SSRI and SNRI)

www.medicaidmentalhealth.org
C-Reactive Protein (CRP) Alterations in Bipolar Disorder: A Meta-analysis


Figure 2. Meta-Analysis of C-Reactive Protein Levels in Bipolar Disorder

<table>
<thead>
<tr>
<th>Study</th>
<th>Bipolar Disorder</th>
<th>Control</th>
<th>SMD</th>
<th>95% CI</th>
<th>Weight</th>
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</table>

Overall effect

|          | 730 | 888 | 0.39 | 0.24 to 0.55 | 100% |

*P = .0001*

Heterogeneity: $I^2 = 47.6\%$, $\tau^2 = 0.0291$, $P = .0394$

Abbreviations: CI = confidence interval, SD = standard deviation, SMD = standardized mean difference.
Cytokine Studies for MDD

Strong association of TNF-α, IL-6, and CRP with MDD
Central Inflammation in Bipolar Disorder: A [11C]-(R)-PK11195 PET Study

Several studies found that cognitive dysfunction was associated with elevated levels of the proinflammatory markers YKL-40, IL-6, sCD40L, IL-1Ra, hsCRP, and TNF-α.

YKL-40: secreted glycoprotein YKL-40. IL-6: interleukin-6. sCD40L: soluble cluster of differentiation 40 ligand. IL-1Ra: interleukin-1 receptor antagonist. hsCRP: high-sensitivity C-reactive protein. TNF-α: tumor necrosis factor alpha.
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.

Association of Obesity and Treated Hypertension and Diabetes With Cognitive Ability in Bipolar Disorder and Schizophrenia

Global cognitive ability by body mass index (BMI) level clustered by diagnosis. Error bars are standard errors (SE). Group comparisons: bipolar disorder: \( F(2,338)=5.2, p=0.006 \) [adjusted for education, Positive and Negative Syndrome Scale negative score, atypical antipsychotic use, and residential status: \( F(2,320)=18.2, p=0.035 \)]; Tukey post hoc normal > obese; schizophrenia: \( F(2,413)=0.70, p=0.482 \). Effect size from lowest to highest BMI in bipolar disorder is Cohen's \( d=0.43 \) compared to \( d=0.16 \) for schizophrenia.

Partial regression plot of the relationship between 12-month homeostasis model of assessment for insulin resistance (HOMA-IR) and Switching of Attention–Letters (SOA–A). This plot depicts the nature of the relationship between 12-month HOMA-IR and 12-month SOA–A after accounting for baseline values of these variables, age, and education. Lower performance on SOA–A is better.

From: Effect of Anti-inflammatory Treatment on Depression, Depressive Symptoms, and Adverse Effects: A Systematic Review and Meta-analysis of Randomized Clinical Trials

Overall Results of Anti-inflammatory Intervention on Antidepressant Treatment: Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Cytokine Inhibitors

SMD: standard mean difference.

Omega-3 Fatty Acids

Figure 4. Forest plot of comparison: 1 n-3PUFAs vs placebo, outcome: 1.1 Depressive symptomology (continuous).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>n-3PUFAs</th>
<th>Placebo</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
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<td>14 6.9 12</td>
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<td>Carney 2009</td>
<td>9.7</td>
<td>6.5</td>
<td>62 9.1 67 60</td>
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<td>Coryell (1g/d)</td>
<td>17.8</td>
<td>8.3</td>
<td>3 16 3 2</td>
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<tr>
<td>Coryell (2g/d)</td>
<td>20.8</td>
<td>8.3</td>
<td>4 16 8.3 2</td>
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<td>Da Silva (AD) 2005</td>
<td>13.8</td>
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<td>Gertsik 2012</td>
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<td>Gharekhani 2014</td>
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<td>Su 2003</td>
<td>9.1</td>
<td>3.6</td>
<td>14 15.4 3 14</td>
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</table>

Total (95% CI) 727 646 100.0%

Heterogeneity: Tau² = 0.12; Chi² = 56.79, df = 24 (P = 0.0002); I² = 58%
Test for overall effect: Z = 3.18 (P = 0.001)

Omega-3 fatty acids for depression in adults (Review)
Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

n-3PUFA: omega-3 polyunsaturated fatty acid.
Inflammation Predicts Antidepressant Response to Exercise

IDS-C: Inventory of Depressive Symptomatology-Clinician.

CBT Is Anti-inflammatory

Cognitive Behavioral Therapy

Narrative Cognitive Therapy

A

B

C

D

ECT Is Anti-inflammatory

Change in depression scores and kynurenic acid across the study period. Graphs were truncated to save space. Hamilton Depression Rating Scale-17 items. KYNA: kynurenic acid (ng/ml).

### Results: Overall Antidepressant Effect of Adjunct Anti-inflammatories

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Adjunct Anti-inflammatory Mean</th>
<th>SD</th>
<th>Total</th>
<th>Adjunct Placebo Mean</th>
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<th>Weight</th>
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<td>-0.75 [-1.22, -0.28]</td>
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<td><strong>Subtotal (95% CI)</strong></td>
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<td>38</td>
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<td></td>
<td></td>
<td>21.8%</td>
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<td></td>
<td>21.8</td>
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<td>21.8%</td>
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<tr>
<td>Heterogeneity: Not applicable</td>
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<tr>
<td>Test for overall effect: Z = 3.15 (P = 0.002)</td>
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<tr>
<td><strong>1.1.4 Pioglitazone</strong></td>
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</tr>
<tr>
<td>Zeinoddini et al. 2015</td>
<td>-13.95</td>
<td>4.7</td>
<td>22</td>
<td>-11.68</td>
<td>3.6</td>
<td>22</td>
<td>14.6%</td>
<td>-0.53 [-1.13, 0.07]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>22</td>
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<tr>
<td></td>
<td></td>
<td>14.6%</td>
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<td></td>
<td>14.6</td>
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<td>14.6%</td>
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</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
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<tr>
<td>Test for overall effect: Z = 1.73 (P = 0.08)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>169</td>
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<tr>
<td></td>
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<td>100.0%</td>
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<td></td>
<td>100.0</td>
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<td>100.0%</td>
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</tr>
<tr>
<td>Heterogeneity: Tau² = 0.02; Chi² = 8.17, df = 7 (P = 0.32); I² = 14%</td>
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</tr>
<tr>
<td>Test for overall effect: Z = 3.08 (P = 0.002)</td>
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<tr>
<td>Test for subgroup differences: Chi² = 4.74, df = 3 (P = 0.19), I² = 36.7%</td>
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</tbody>
</table>

Celecoxib adjunctive therapy (400 mg/day) for acute bipolar mania: a randomized, double-blind, placebo-controlled trial

**Fig. 2.** Repeated measure for comparison of the effects of two treatments on the Young Mania Rating Scale (YMRS). Values represent mean ± standard deviation (SD) of the mean. The p-values demonstrate the result of the independent t-test for comparison of scores between the two treatment groups at each time point. NS = non-significant. *p < 0.05; **p < 0.01.
Minocycline

- Second-generation, semisynthetic tetracycline analog with antimicrobial properties
- Highly lipophylic; easily penetrates the BBB, in contrast to tetracycline
- Principal metabolite: 9-hydroxyminocycline (inactive)
Efficacy and Tolerability of Minocycline Augmentation Therapy in Schizophrenia: A Systematic Review and Meta-analysis of Randomized Controlled Trials

### a. Total scores

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaudhry 2012 Brazil</td>
<td>16.2%</td>
<td>-1.40 [-2.32, -0.49]</td>
<td></td>
</tr>
<tr>
<td>Chaudhry 2012 Pakistan</td>
<td>22.6%</td>
<td>-0.26 [-0.73, 0.21]</td>
<td></td>
</tr>
<tr>
<td>Khodae-Ardakani 2014</td>
<td>18.8%</td>
<td>-1.58 [-2.30, -0.88]</td>
<td></td>
</tr>
<tr>
<td>Levkovitz 2010</td>
<td>20.8%</td>
<td>0.27 [-0.30, 0.83]</td>
<td></td>
</tr>
<tr>
<td>Liu 2014</td>
<td>22.2%</td>
<td>-0.77 [-1.28, -0.31]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>-0.70 [-1.31, -0.08]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.39; Chi^2 = 21.53, df = 4 (P = 0.00002), I^2 = 81%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.23 (P = 0.03)</td>
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</tbody>
</table>

### b. Positive scores

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaudhry 2012 Brazil</td>
<td>9.2%</td>
<td>-1.20 [-2.05, -0.32]</td>
<td></td>
</tr>
<tr>
<td>Chaudhry 2012 Pakistan</td>
<td>25.9%</td>
<td>-0.22 [-1.09, 0.25]</td>
<td></td>
</tr>
<tr>
<td>Khodae-Ardakani 2014</td>
<td>18.9%</td>
<td>-0.25 [-0.87, 0.37]</td>
<td></td>
</tr>
<tr>
<td>Levkovitz 2010</td>
<td>19.6%</td>
<td>-0.15 [-0.72, 0.41]</td>
<td></td>
</tr>
<tr>
<td>Liu 2014</td>
<td>28.2%</td>
<td>-0.07 [-0.62, 0.37]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>-0.26 [-0.55, 0.02]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.02; Chi^2 = 5.18, df = 4 (P = 0.21); I^2 = 22%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.81 (P = 0.07)</td>
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</tr>
</tbody>
</table>

### c. Negative scores

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaudhry 2013 Brazil</td>
<td>15.3%</td>
<td>-0.16 [-1.49, 0.16]</td>
<td></td>
</tr>
<tr>
<td>Chaudhry 2012 Pakistan</td>
<td>23.4%</td>
<td>-0.40 [-1.59, 0.79]</td>
<td></td>
</tr>
<tr>
<td>Khodae-Ardakani 2014</td>
<td>17.1%</td>
<td>-1.74 [-2.46, -1.00]</td>
<td></td>
</tr>
<tr>
<td>Levkovitz 2010</td>
<td>20.9%</td>
<td>-0.52 [-1.09, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Liu 2014</td>
<td>23.3%</td>
<td>-1.12 [-1.59, -0.64]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>-0.86 [-1.32, -0.41]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.17; Chi^2 = 11.65, df = 4 (P = 0.02); I^2 = 89%</td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 3.73 (P = 0.0002)</td>
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</tbody>
</table>

### d. General scores

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaudhry 2012 Brazil</td>
<td>13.7%</td>
<td>-1.73 [-2.70, -0.76]</td>
<td></td>
</tr>
<tr>
<td>Chaudhry 2012 Pakistan</td>
<td>22.9%</td>
<td>-0.13 [-0.60, 0.34]</td>
<td></td>
</tr>
<tr>
<td>Khodae-Ardakani 2014</td>
<td>19.4%</td>
<td>-0.72 [-1.36, -0.08]</td>
<td></td>
</tr>
<tr>
<td>Levkovitz 2010</td>
<td>20.9%</td>
<td>0.19 [-0.38, 0.76]</td>
<td></td>
</tr>
<tr>
<td>Liu 2014</td>
<td>23.3%</td>
<td>-0.57 [-1.02, -0.12]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>-0.50 [-0.99, -0.01]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.22; Chi^2 = 14.23, df = 4 (P = 0.007); I^2 = 72%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.99 (P = 0.05)</td>
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</tbody>
</table>

A Randomized Controlled Trial of the Tumor Necrosis Factor Antagonist Infliximab for Treatment-Resistant Depression: The Role of Baseline Inflammatory Biomarkers

Percentage of Treatment Responders in Infliximab (5 mg/kg) vs. Placebo-Treated TRD Patients With a Baseline hs-CRP≤5mg/L or >5mg/L

hs-CRP: high-sensitivity C-reactive protein.
Glucagon-like Peptide Agonists Are Anti-inflammatory: Implications for Psychiatry

Effect of liraglutide on amyloid plaque count

Inflammation response (IBA-1 stain)

Holscher C. Vitam Horm 2010;84:331-54.
Glucagon-like Peptide-1 Administration Enhances Brain Connectivity Within the "CNN" of Mood Disorders

Obese male volunteers were given the GLP-1 receptor agonist exenatide. Differences were found by fMRI in hypothalamic connectivity in patients who lost weight after receiving exenatide (responders) and those who did not lose weight (non-responders).

Exenatide dosage: 0.12 pmol/kg body weight/min.

GLP-1: glucagon-like peptide-1. fMRI: functional magnetic resonance imaging.

Mental Health and the Gut-Brain Axis

• Healthy women assigned to receive fermented milk product with probiotic (n=12), non-fermented milk product (n=11), or no intervention (n=13) BID x 4 weeks
• Measured brain response to an emotional faces attention task

Tillisch K et al. Gastroenterology 2013;144(7):1394.
FMPP Resulted in Reduced Response to Emotional Faces Attention Task

A distributed network of brain regions showing decreases in the FMPP group during the emotional faces attention task is shown in the shaded regions. Three regions of interest selected from the network for study in the resting state are highlighted.

Fecal Microbiota Transplantation
Fecal Microbial Transplantation

• 70 patients with ulcerative colitis randomized to FMT or placebo
• 9 patients who received FMT (24%) and 2 who received placebo (5%) were in remission at 7 weeks (RD 17%, 95% CI 2-33%)
• 7 of 9 patients who achieved remission received a transplant from a single donor

Conclusion

• Inflammation is a critical effector system relevant to normal and abnormal brain and body health
• Inflammation activation is a cause, consequence, and comorbidity in brain illnesses
• Gut microbiota are relevant to inflammatory milieu
• Novel and conventional multimodal treatments may target inflammation