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Do Inflammation & Metabolic Disturbances Metastasize To The Brain? Implications For Disease Modeling & Novel Approaches In Psychiatry

Part 1 of 2

Otsuka Pharmaceutical Development & Commercialization, Inc.

Lundbeck, LLC

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Dr. McIntyre is a compensated contractor of OPDC

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Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) and Lundbeck, LLC. have entered into collaboration with *OPEN MINDS*, to explore new ways of bringing/increasing awareness around serious mental illness.

OPDC/Lundbeck's interaction with *OPEN MINDS* is through PsychU, an online, non-branded portal dedicated to providing information and resources on important disease state and care delivery topics related to mental illness. One of the methods employed for the sharing of information will be the hosting of virtual fora. Virtual fora conducted by OPDC/Lundbeck are based on the following parameters:

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- No continuing medical education (CME) credits are available for any PsychU program.
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Learning Objectives

- Describe the importance of cognitive symptoms as psychiatric targets
- Review immune and metabolic systems associated with cognitive deficits and mood disorders
- Discuss innovative approaches that may target these systems

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Convergent Phenotypes

Cognitive Dysfunction: A Transdiagnostic Psychopathologic Domain

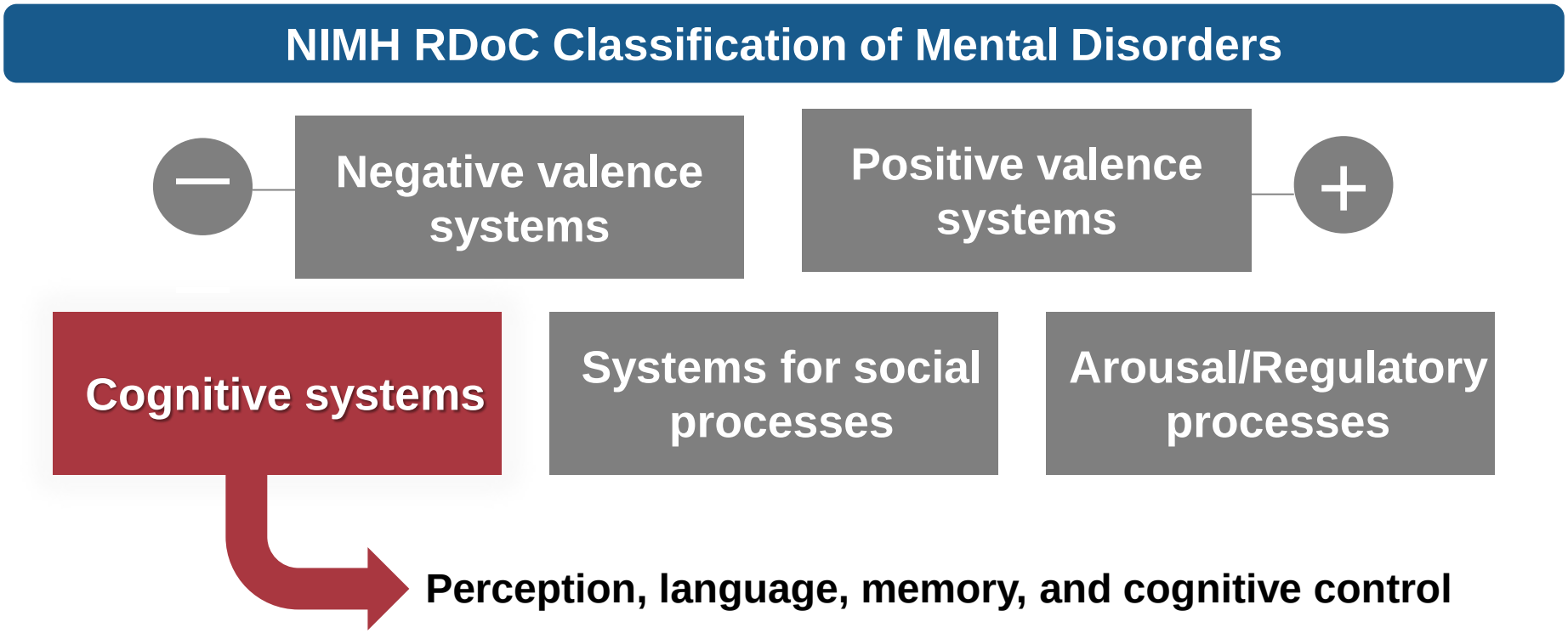
	MDD	BD	SCZ	ASD	ADHD	OCD	PTSD	Panic disorder	GAD	PD	ALZ
Attention and/or vigilance	◆[◆]	◆◆[◆]	◆◆◆	◆◆◆	◆◆◆	◆◆◆[🡅]	◆◆◆[🡅]	◆◆◆[🡅]	◆	◆◆	◆[◆]
Executive function	◆◆	◆◆	◆◆◆	◆◆◆	◆◆◆	◆◆	◆[◆]	○/◆	○	◆◆	◆[◆]
Memory											
Working	◆◆	◆◆	◆◆◆	◆	◆◆	◆[◆]	◆[◆]	◆	◆	◆◆[◆]	◆[◆]
Episodic	◆◆	◆◆	◆◆◆	◆◆	○/◆	◆	◆◆	◆	○	◆	◆◆◆
Semantic	◆	◆	◆◆	◆	◆	○/◆	◆	○/◆	◆	○/◆	◆◆◆
Visual	◆	◆	◆[◆]	◆	◆◆	◆	◆	○/◆	◆	◆	◆◆◆
Verbal	◆[◆]	◆◆	◆◆◆	◆[◆]	◆◆	○/◆	◆◆[◆]	◆	◆	◆	◆◆[◆]
Procedural	◆	○	◆	○/◆	◆	◆◆	○	○	○	◆◆◆	◆
Processing speed	◆	○	◆	○/◆	◆	◆◆	○	○	○	◆◆◆	◆

○, essentially absent; ○/◆, poorly documented, ambiguous, mild, and/or variable; ◆, consistently present but not pronounced; ◆◆, common, marked characteristic; ◆◆◆, core, severe and virtually universal characteristic of the disorder; 🡅, increase. Brackets indicate an intermediate magnitude of deficit.

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

Millan et al. *Nat Rev Drug Discov.* 2012;11:141-68.

Cognitive Symptoms Are an Important Psychiatric Target

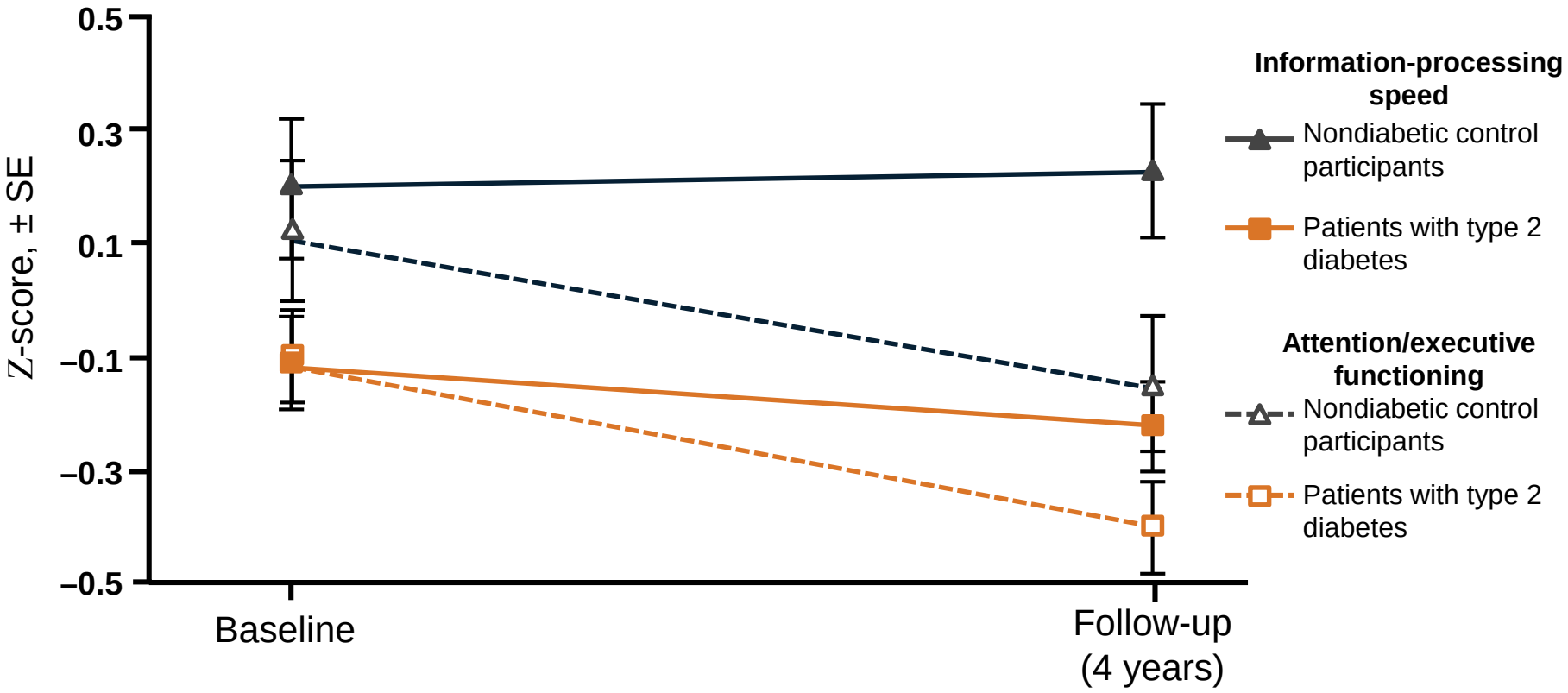


NIMH, National Institute of Mental Health; RDoC, research domain criteria.

RDoC Matrix. National Institute of Mental Health. http://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml. Accessed January 4, 2017.

Cognitive Dysfunction Is a Common Disturbance in Patients With Diabetes Mellitus

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



McCrimmon et al. *Lancet*. 2012;379:2291-2299.

Psychiatric Disorder Plus Metabolic/Inflammatory Disorder Yields Greater Cognitive Dysfunction

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

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

BMI, body mass index.

Yim et al. *Eur Psychiatry*. 2012;27:223-228.

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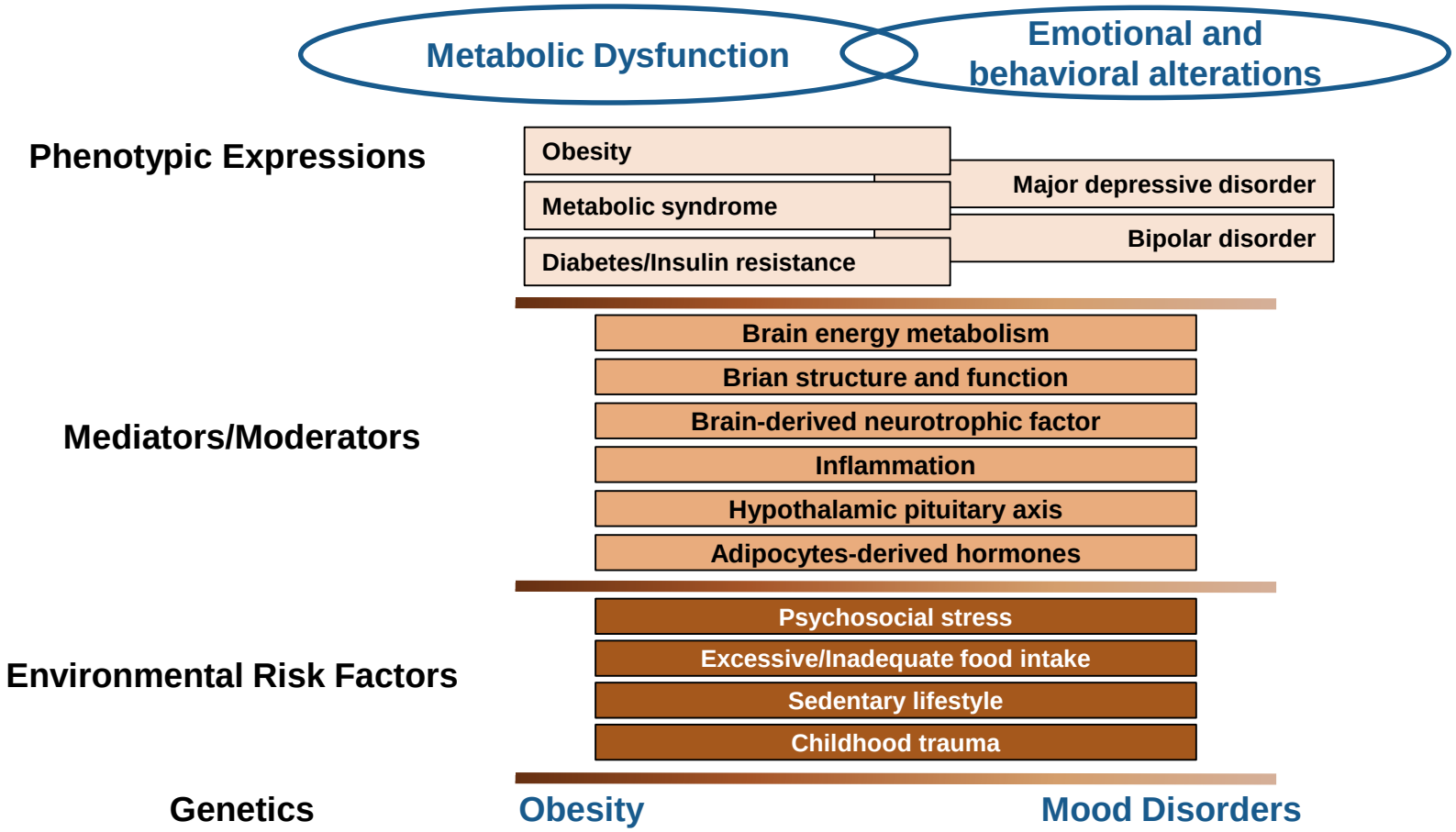
Discussion

Association Between Metabolic and Neuropsychological Phenotypes



Mansur et al. *Neurosci Biobehav Rev*. 2015;52:89-104.

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Convergent Substrates

Adipose Tissue Contributes to Pro-Inflammation in Mood Disorders

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

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

Synergistic Relationship Between Depression and BMI

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

*Patients met the diagnostic criteria for a current major depressive disorder or minor depressive disorder.
BMI, body mass index; CRP, C-reactive protein; IL-6, interleukin-6.

Miller et al. *Am J Cardiol*. 2002;90:1279-1283.

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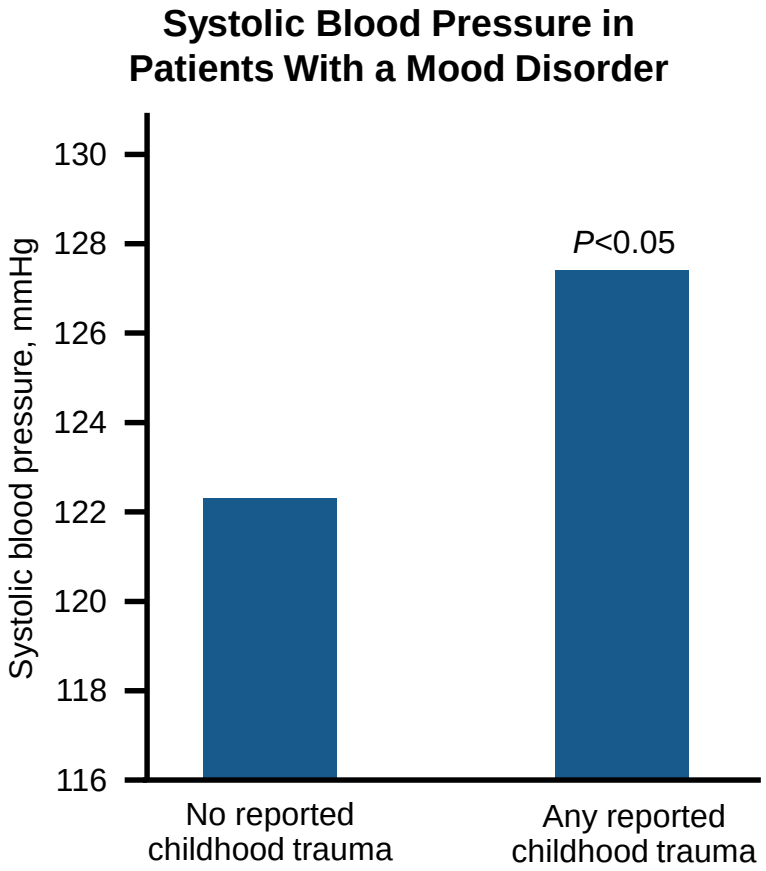
Childhood Adversity is Associated With Metabolic Syndrome in Patients With Mood Disorders

- Association between childhood adversity and metabolic syndrome was assessed in patients with mood disorders*
- Childhood trauma† was associated with components of metabolic syndrome, including higher systolic blood pressure



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

McIntyre et al. *Int J Psychiatry Med*. 2012;43:165-177.

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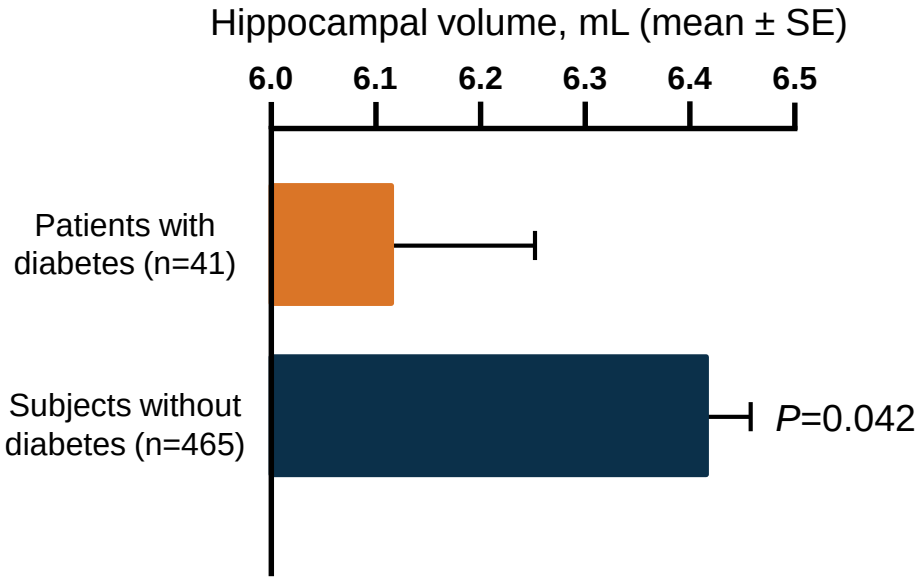
Hippocampal Volume Changes in Diabetes Mellitus

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

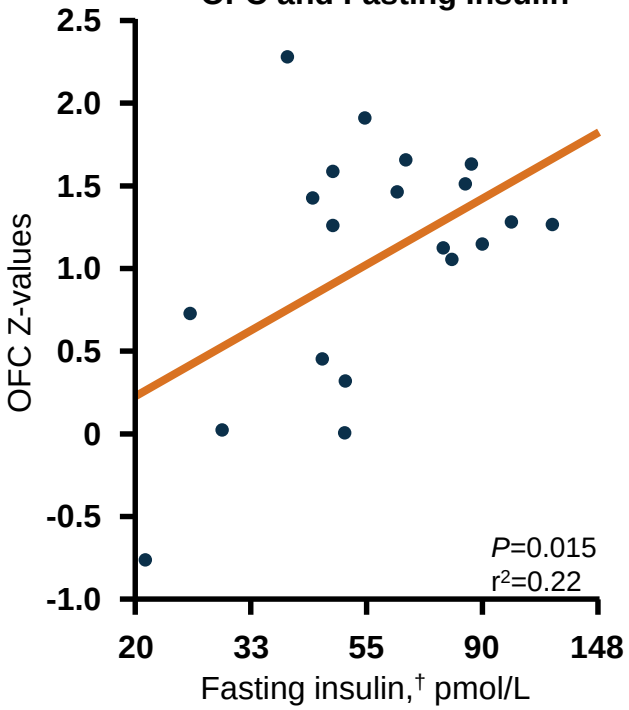


MRI, magnetic resonance imaging.
*Volumes adjusted for age and sex and normalized to average head size.

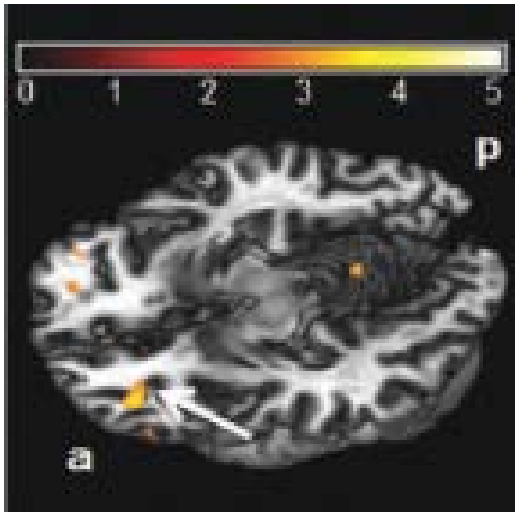
den Heijer et al. *Diabetologia*. 2003;46:1604-1610.

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

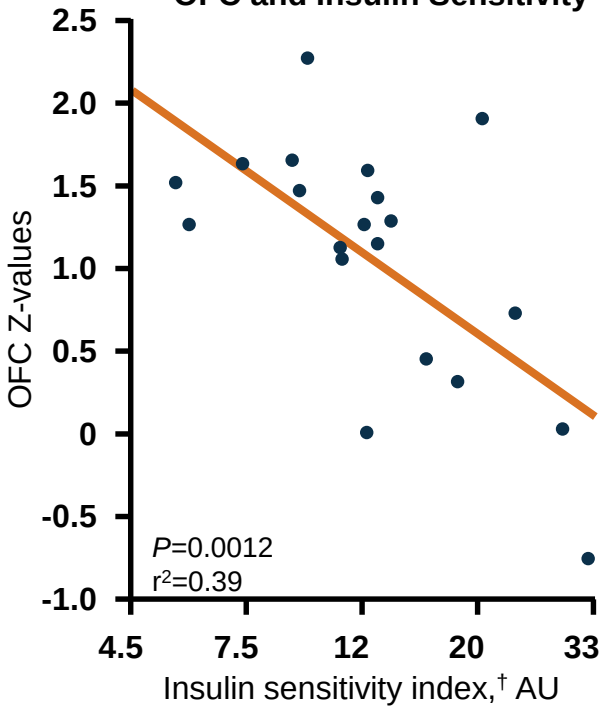
Positive Correlation Between Left OFC and Fasting Insulin*



Significant Voxels of Insulin-Associated Connectivity‡



Negative Correlation Between Left OFC and Insulin Sensitivity



Figures adapted from Kullman, S, Heni M, Veit R, et al. The obese brain: association of body mass index and insulin sensitivity with resting state network functional connectivity (pages 1052–1061). *Hum Brain Mapp*. 2012;33(5):1052-1061 with permission from John Wiley & Sons, Inc.

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

Kullmann et al. *Hum Brain Mapp*. 2012;33:1052-1061.

Mechanism of Neuroinflammation

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

M1-type activation: Neuroinflammation

- DAMPS, PAMPs, TLR activation
- Chemokine-driven response, receptor activation, P2X7 ion channel activity
- Gliotransmitter and cytokine release: IL-1β, IL-6, TNF-α, CCL2, ROS, NO
- TSPO, COX-2 upregulation

M2-type activation: Antiinflammatory response

- Phagocytosis, pruning, NFκB downregulation
- Gliotransmitter and cytokine release: IL-4, IL-10, IL-13, BDNF, IGF-1, TGF-β

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

Bhattacharya et al. *Psychopharmacology*. 2016;233:1623-1636.

Depression Is Associated With Increased Inflammation

Significant positive relationships have been observed between depression and neuroinflammation markers (eg, CRP[1], IL-6[1], TNF-α[2], and sIL-2R[3])

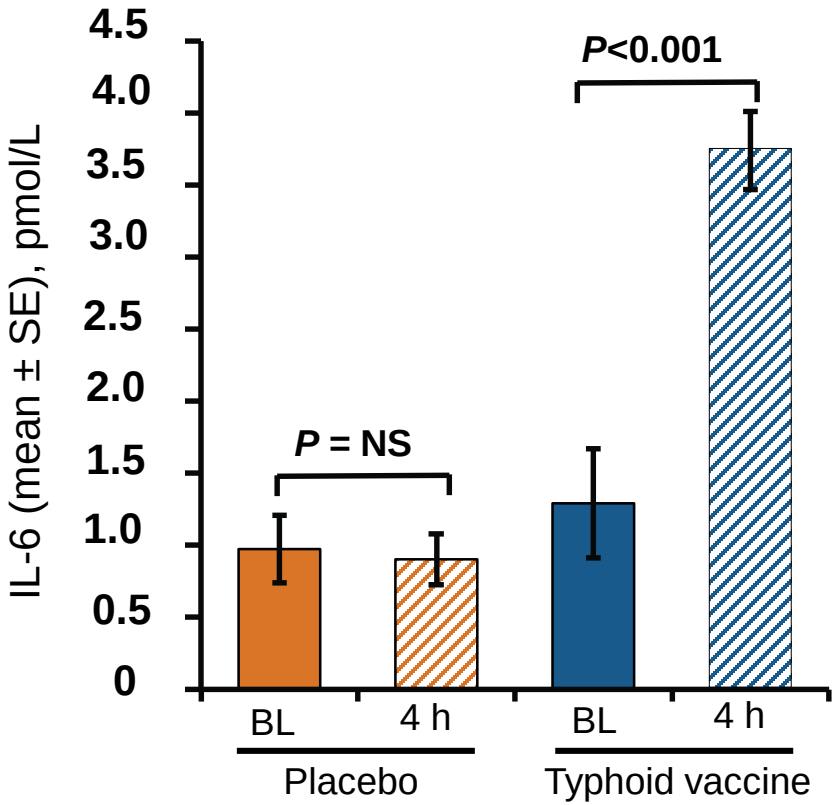
In patients with MDD in a current major depressive episode, greater microglial activation was positively correlated with greater depression severity[4]

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

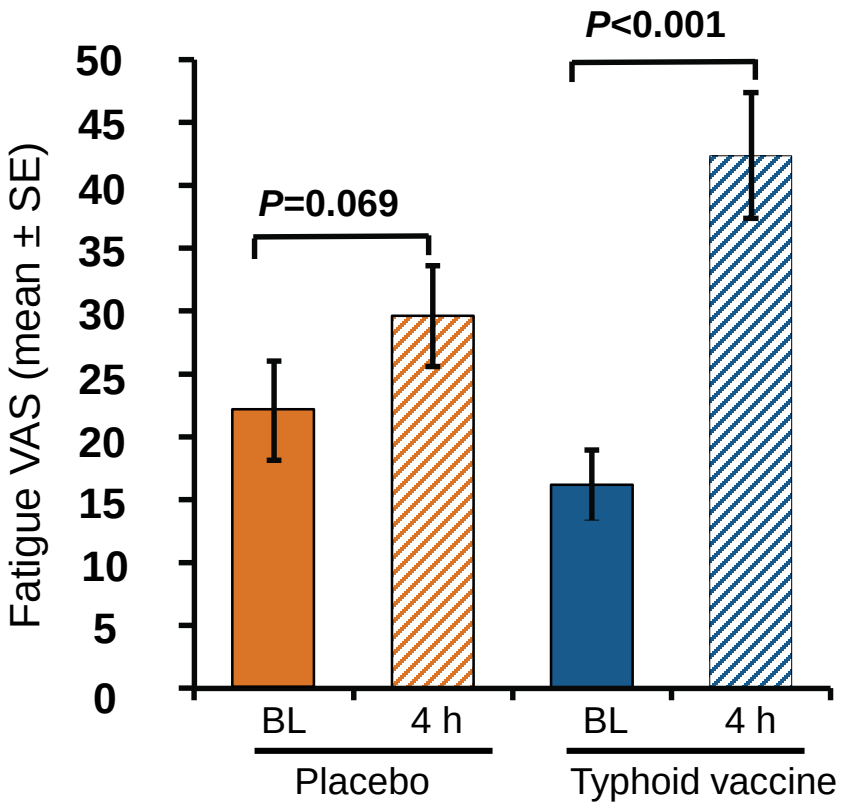
1. Howren et al. *Psychosom Med*. 2009;71:171-186. **2.** Dowlati et al. *Biol Psychiatry*. 2010;67:446-457. **3.** Liu et al. *J Affect Disord*. 2012;139:230-239. **4.** Setiawan et al. *JAMA Psychiatry*. 2015;72:268-275.

Inflammatory and Fatigue Level Changes After an Immune Stimulus

Change in Circulating Interleukin-6 (IL-6)



Change in Fatigue



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

Harrison et al. *Biol Psychiatry*. 2015;78:49-57.

Association of Monoamine Metabolites with Neuroinflammation and Mood Burden

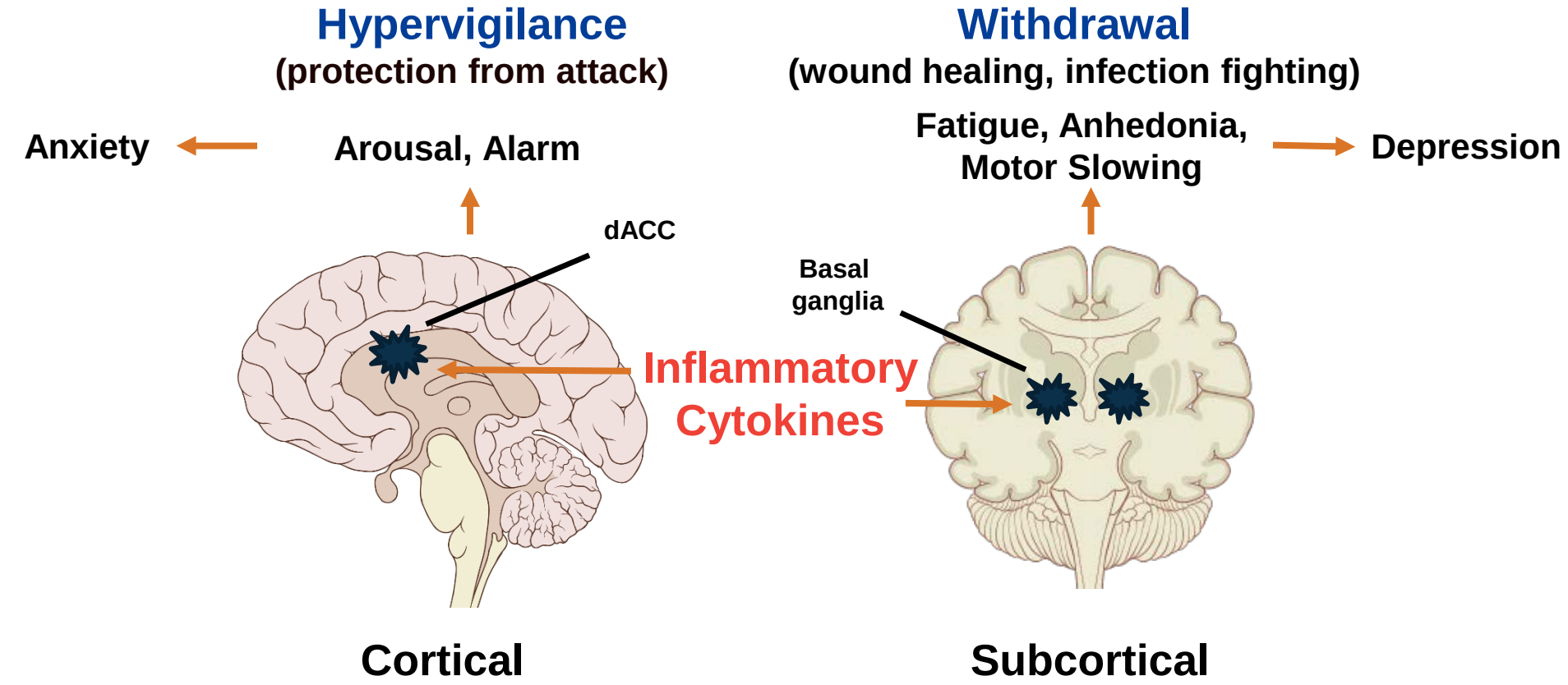
Significant positive correlations were observed between the proinflammatory cytokine IL-6 and increased serotonin and dopamine metabolites in patients who had attempted suicide[1]

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

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

1. Lindqvist et al. *Biol Psychiatry*. 2009;66:287-292. **2.** Ehnvall et al. *J Affect Disord.* 2003;74:185-189.

Effect of Inflammatory Cytokines on Brain Circuitry



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

dACC, dorsal anterior cingulate cortex.

Miller et al. *Depress Anxiety*. 2013;30:297-306.

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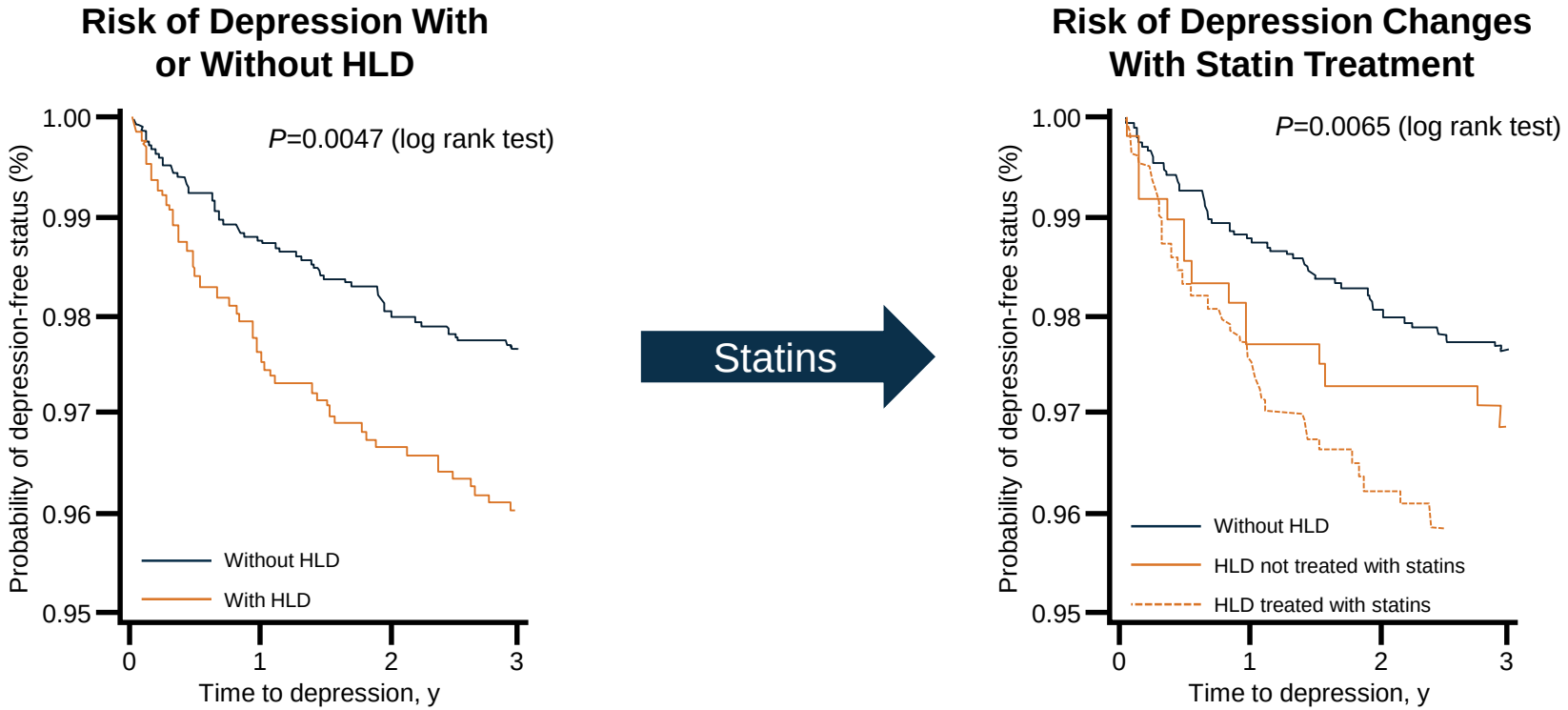
Convergent Treatments

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



Figures adapted from Wee HY, Ho CH, Liang FW, et al. Increased risk of new onset depression in patients with traumatic brain injury and hyperlipidemia: the important role of statin medications. *J Clin Psychiatry*. 2016;77(4):505-511 with permission from Physicians Postgraduate Press.

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

HLD, hyperlipidemia.

Wee et al. *J Clin Psychiatry*. 2016;77:505-511.

Baseline Inflammation May Predict Antidepressant Response to Multiple Agents

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

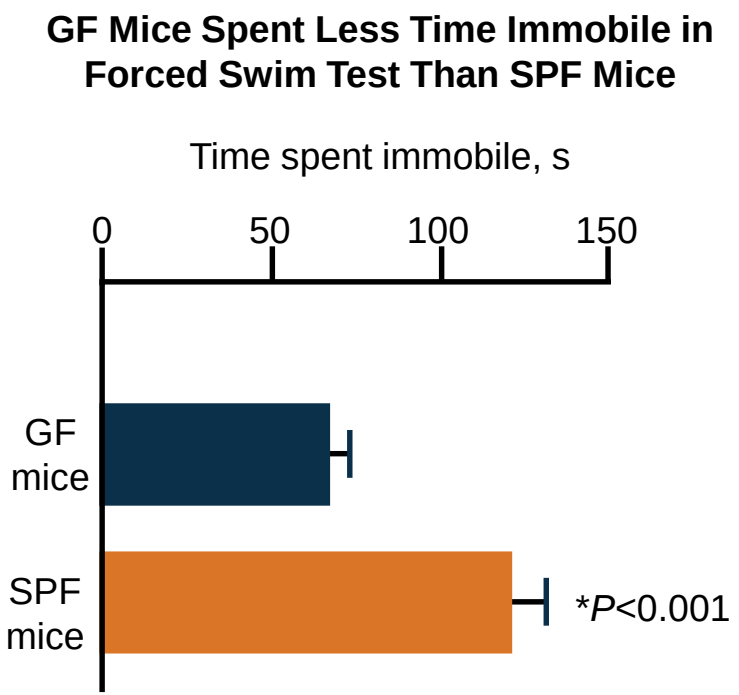
- Were significantly greater in patients treated with adjunctive antiinflammatory agents vs conventional therapy alone[1]
- Trended toward an increase in patients with high baseline CRP[2]
- Were predicted by baseline adipokine adiponectin[3] or inflammation markers,[4] particularly in patients with BMI ≥30[5]

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

1. Rosenblat et al. *Bipolar Disord*. 2016;18:89-101. **2.** Raison et al. *JAMA Psychiatry*. 2013;70:31-41. **3.** Machado-Vieira et al. *Mol Psychiatry*. 2017;22:127-133. **4.** Rapaport et al. *Mol Psychiatry*. 2016;21:71-79. **5.** Shelton et al. *J Clin Psychiatry.* 2015;76:1635-1641.

Effect of Gut Microbiota on Mood-Related Behavior

- Effect of gut microbiota on psychobehavioral characteristics was assessed in germ-free and specific pathogen-free mice
- Fecal microbiota transplantation from patients with MDD on GF mice resulted in depression-like behaviors compared with microbiota transplantation from healthy control individuals



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

Zheng et al. *Mol Psychiatry*. 2016;21:786-796.

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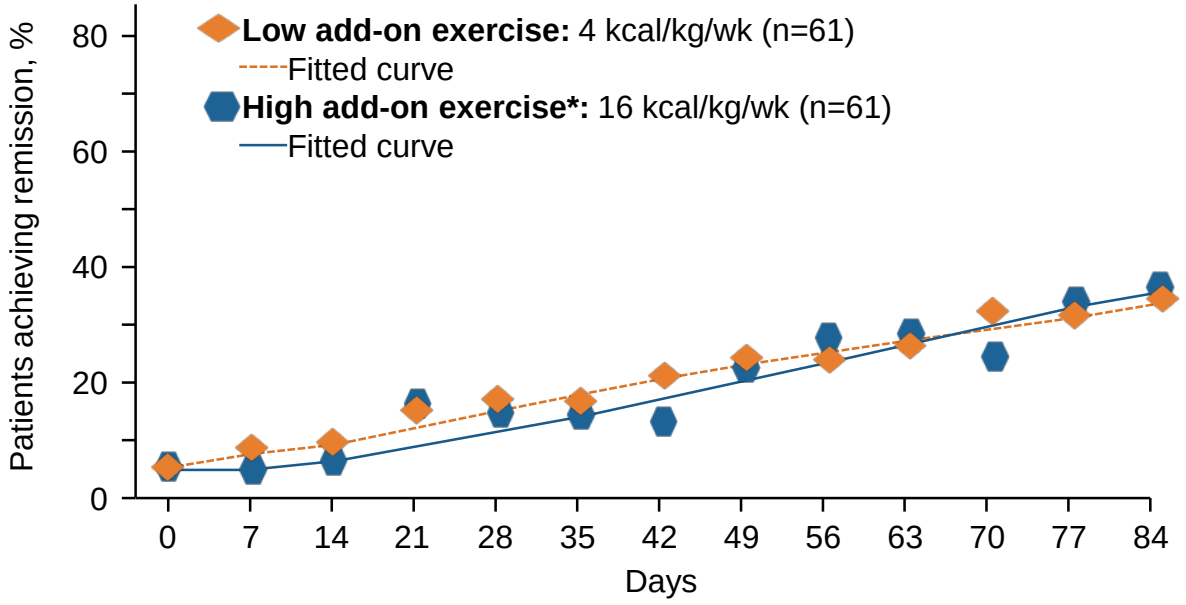
Emerging Evidence for Increased Remission Rates With Add-On Exercise

Probability of Remission, as Measured by IDS-C_{30}, in Patients With Inadequate Response to SSRI, Who Received Add-On Exercise in the TREAD Study



IDS-C_{30}, Inventory of Depressive Symptomatology, Clinician-Rated; NNT, number needed to treat; SSRI, selective serotonin reuptake inhibitor; TREAD, TReatment with Exercise Augmentation for Depression study.
*NNT of 7.8 for high-exercise vs low-exercise group based on remission rate at week 12.

Trivedi et al. *J Clin Psychiatry*. 2011;72:677-684.

Summary and Key Points

- Cognitive symptoms, which are prevalent in mood disorders and recognized as critical targets for treatment in psychiatry, may be associated with metabolic alteration
- Overlapping immune-related and metabolic systems may underlie cognitive deficits observed in mood disorders
- Emerging evidence from preclinical and clinical models suggest that targeting inflammation and metabolic disturbances may have a positive impact on mental health

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Questions

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Closing

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