The emerging role of the immune system in depression and other psychiatric disorders

Andrew H. Miller, M.D.
Professor of Psychiatry and Behavioral Sciences
Emory University School of Medicine
Atlanta, GA USA

Nothing to Disclose

Cytokines Sing the Blues

Depression: Scope and Consequences

Common

25 million adults in US

Fatal

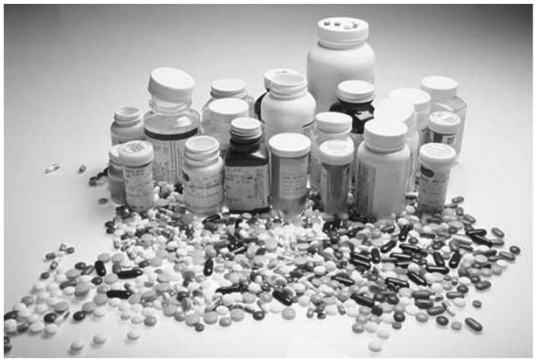
40,000 US adults
10th leading cause of death

Disabling

Leading cause of disability worldwide (years lived with disability)

Depression: Scope and Consequences

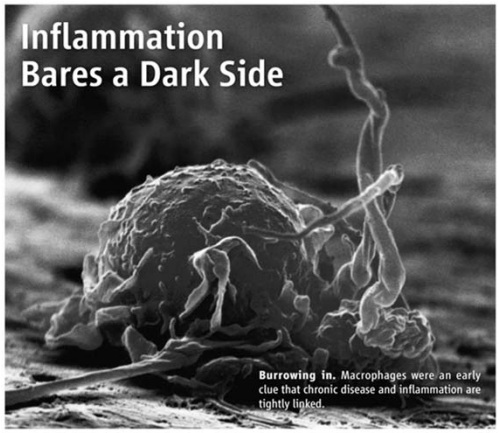
Treatment Resistance



1/3 of all depressed adults are non-responsive to conventional treatments

Need for new conceptual frameworks and targets to improve treatment outcome especially in patients with treatment resistance

Inflammation is the body's natural response to infection and wounding, but when chronic, inflammation can affect many parts of the body including the brain and behavior.



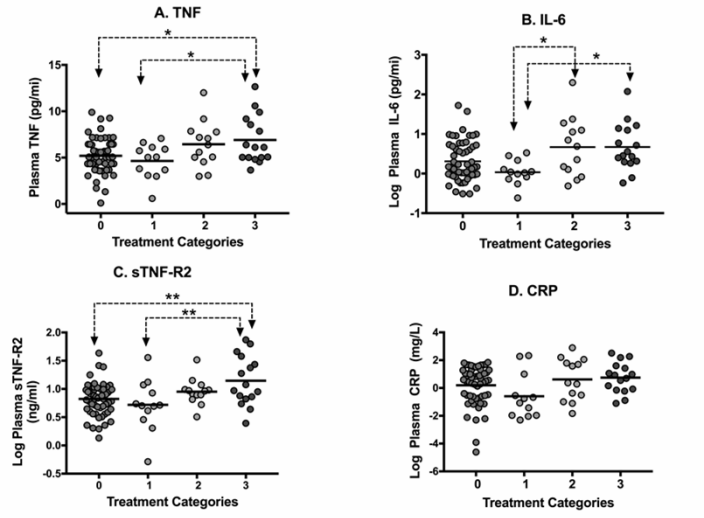
Inflammation: A Common Mechanism of Disease Insight of the Decade (*Science*, 2010)

Data that Indicates Inflammation Plays a Role in Depression

- **Patients with depression exhibit all the cardinal features of a chronic inflammatory response.**
  - **increased inflammatory cytokines (IL-6 and TNF-alpha most reliable)**
  - **increased acute phase reactants [C-reactive protein (CRP) most reliable]**
  - **increased chemokines and cellular adhesion molecules**
  - **increased inflammation in the brain**

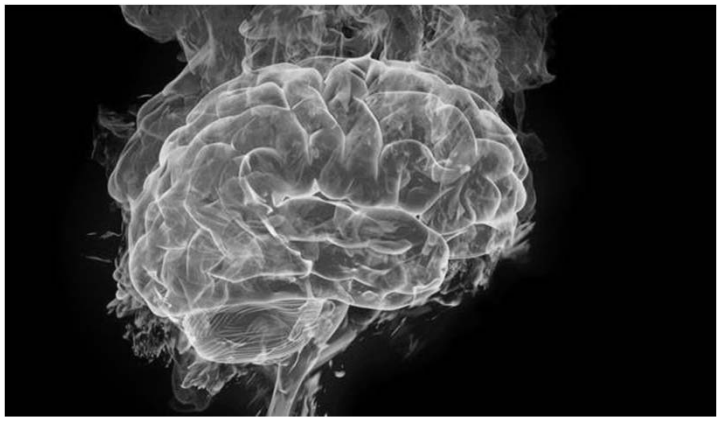
  Increased inflammatory markers are associated with treatment resistance and poor response to SSRIs and SNRIs
- **Administration of inflammatory cytokines/stimuli causes depressive symptoms.**
  - **neurotransmitters**
  - **neurocircuits**
- **Inhibition of inflammation reduces depressive symptoms.**
  - **autoimmune and inflammatory disorders**
  - **limited data demonstrating anti-inflammatory drugs treat depression in otherwise healthy individuals**

Number of Failed Treatment Trials and Inflammatory Markers in Patients with Major Depression

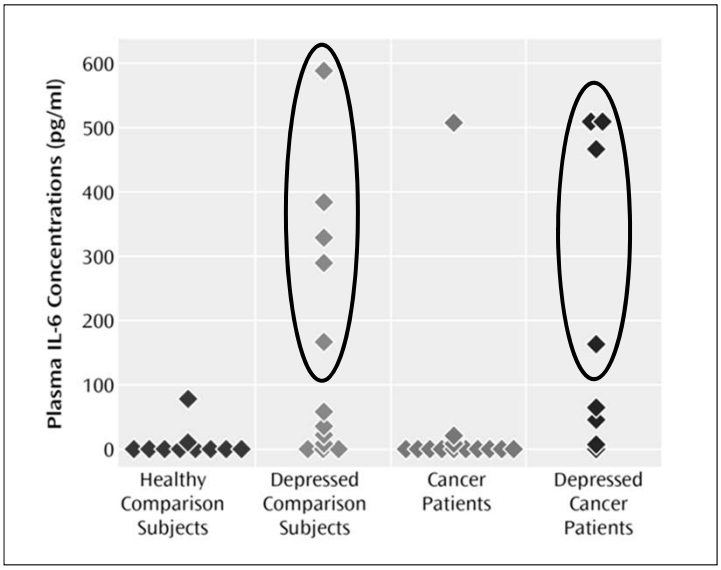


Haroon et al, *Psychoneuroendocrinology*, 95:43-49, 2018.al,

Depression is not an Inflammatory Disorder



Plasma IL-6 in Depressed Patients with and without Cancer



Musselman et al. *Am J Psychiatry*, 158:1252-1257, 2001.

1. **Inflammation is only increased in a subgroup of depressed patients.**

2. **Inflammation is also increased in multiple other disorders in association behavioral symptoms.**

- **Mood Disorders - Depression/Bipolar Disorder**
- **Anxiety Disorders - PTSD, GAD, OCD, Panic Disorder**
- **Schizophrenia**
- **Neurodegenerative Disorders - Alzheimer's Disease, Parkinson's Disease, HIV**
- **Medical Illnesses – Cancer, Autoimmune/ Inflammatory Disorders, Cardiovascular Disease**

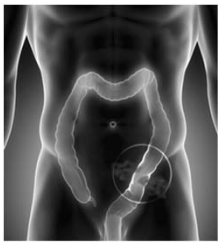
- **Inflammation effects on behavior are not about any specific disorder (transdiagnostic)**
- **Inflammation is about effects on specific neurotransmitter systems, neurocircuits and related symptoms across disorders**

Where Does Chronic Inflammation Come From?

Obesity

Chronic Stress

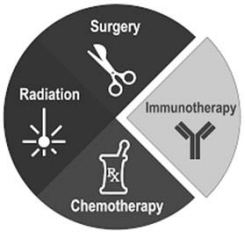
Dysbiosis



Chronic Illness

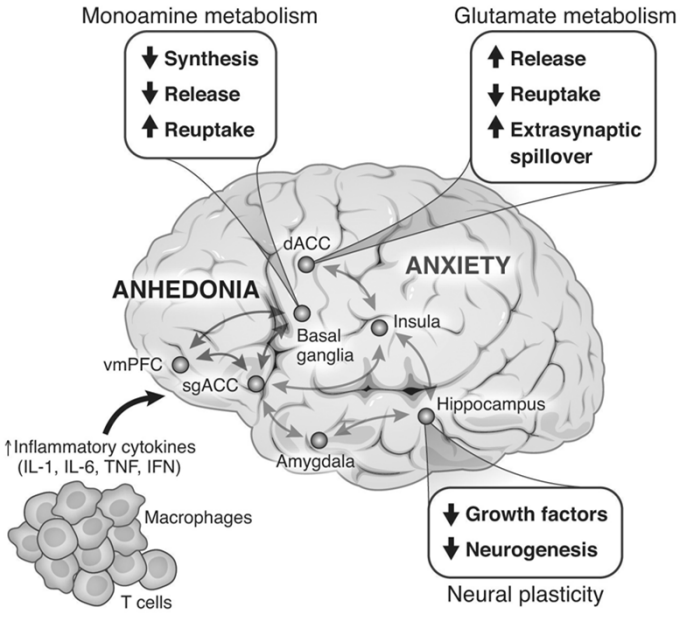
Chronic Infections

Medical Treatments



Mechanisms by which Inflammation Affects the Brain and Behavior

Inflammation Effects on the Brain



Raison & Miller, *Nat Rev Immunol*, 16:22-34, 2016.

Therapeutic Targets to Address Inflammation Effects on the Brain

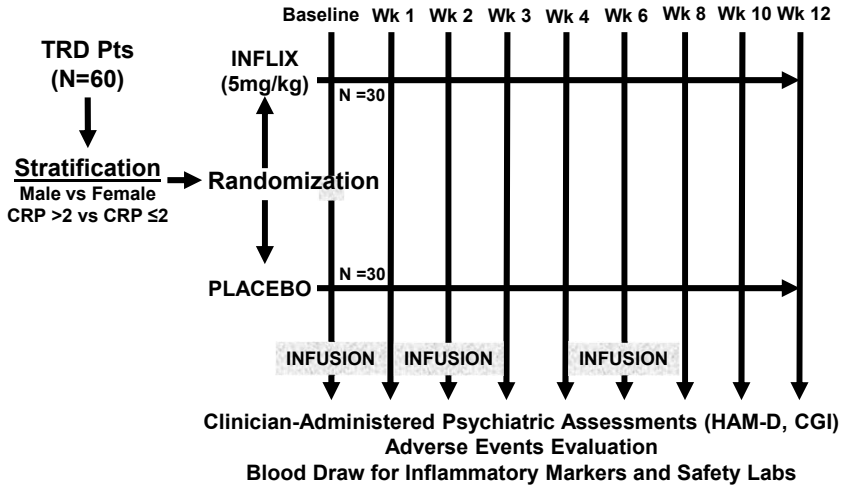
1. Inflammation
2. Downstream effects of inflammation on the brain (e.g. dopamine or glutamate)

Targeting Inflammation

TNF-alpha Blocker (Infliximab) to Treat Depressed Patients with Treatment Resistance

- **Biologics (monoclonal antibodies) are potent.**
- **Biologic anti-TNF drugs have no off-target effects and limited drug-drug interactions**
- **12 week randomized controlled trial in patients with treatment resistant depression (TRD)**

Double-Blind, Parallel-Group, Randomized Design



TRD - Treatment Resistant Depression INFLIX – infliximab - Remicade©

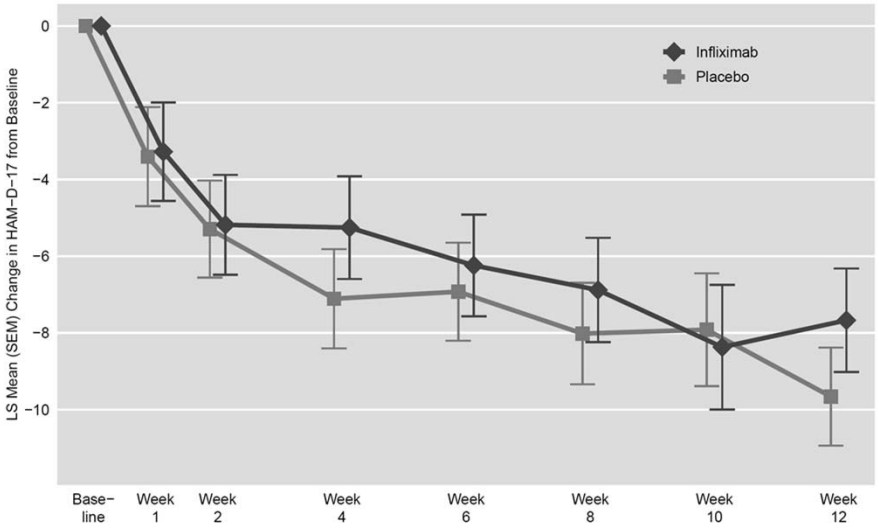
Clinical Characteristics of Study Sample

	Infliximab	Placebo
BMI (kg/m2) – mean (SD)	31.2 (6.9)	32.7 (8.0)
Baseline hs-CRP (mg/L) – mean (SD)	6.21 (9.1)	5.7 (8.1)
Baseline HAM-D 17 – mean (SD)	24.1 (4.0)	23.6 (3.8)
Baseline CGI-severity – mean (SD)	4.8 (0.59)	4.8 (0.81)

- **~50% of our TRD patients exhibited "high" inflammation according to CDC/AHA guidelines (CRP>3mg/L) - ~4.0 million depressed individuals in US**
- **~1.5 million individuals have RA in US, ~1.5 million have IBD**
-

Raison et al., *JAMA Psychiatry*, 70:31, 2013

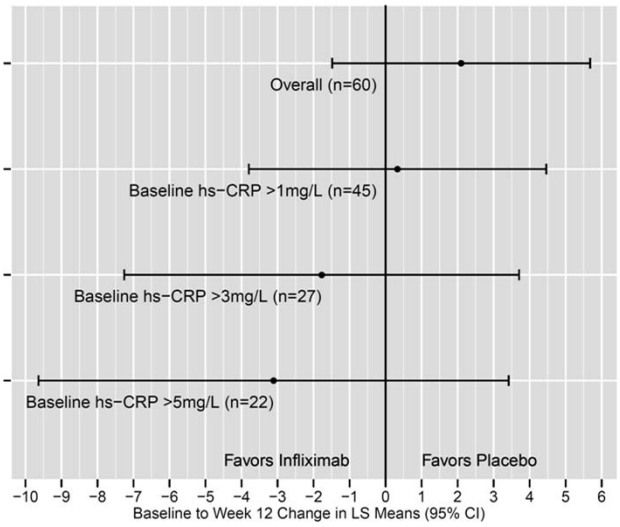
Change in HAM-D-17 in Infliximab- versus Placebo-Treated TRD Patients



Significant interaction among treatment, time and log hs-CRP (t=2.65, df=302, p=0.01)

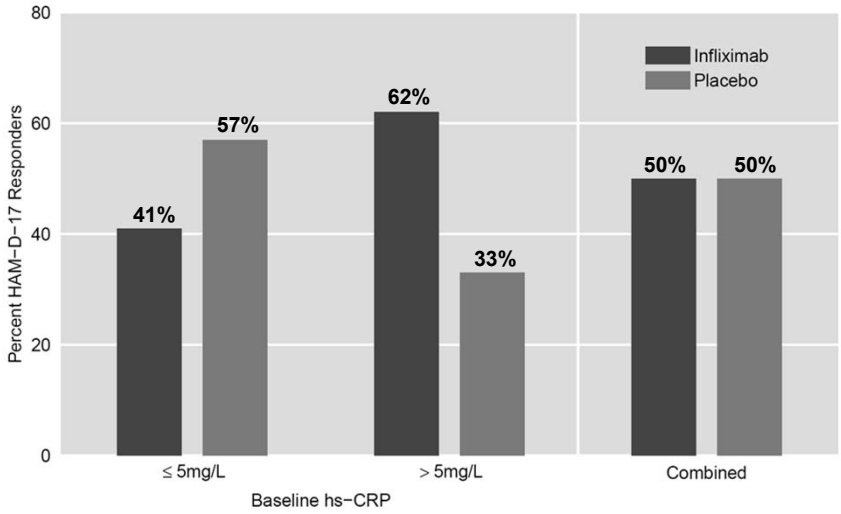
Raison et al., *JAMA Psychiatry*, 70:31, 2013.

Change in HAM-D-17 Score from Baseline to Week 12 (Infliximab-Placebo) in TRD Patients Subgrouped By Baseline Plasma CRP



Standardized Effect Size = 0.41 favoring infliximab at CRP>5mg/L

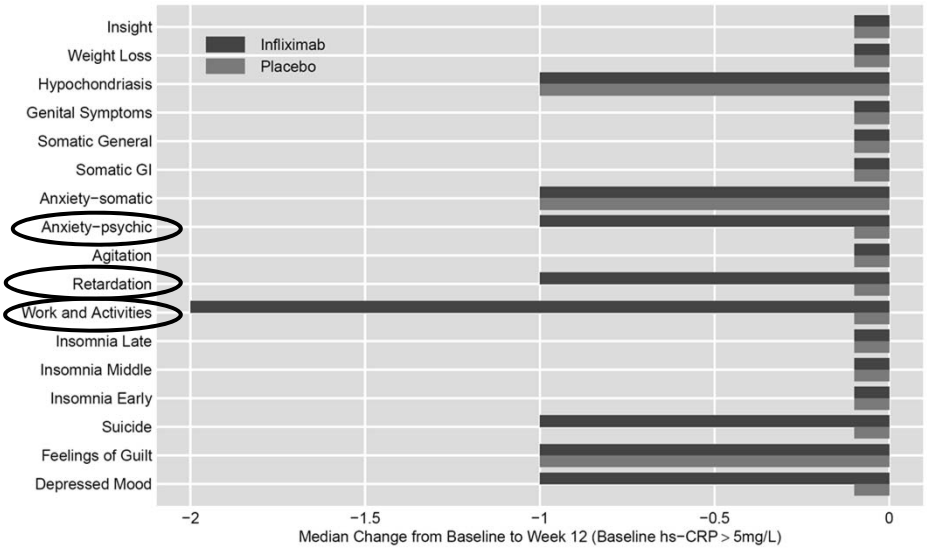
Percent Treatment Responders in Infliximab- Versus Placebo-Treated TRD Patients with a Baseline CRP≤5mg/L or >5mg/L



Treatment Response (≥50 reduction in HAM-D-17 at any point during treatment)

Raison et al., *JAMA Psychiatry*, 70:31, 2013.

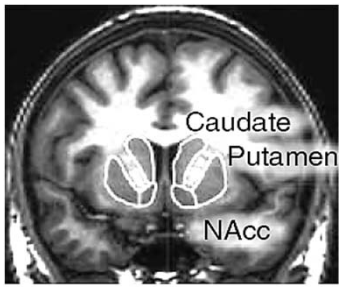
Symptoms Responsive to Infliximab and Placebo in TRD subjects with Baseline CRP>5



Raison et al., *JAMA Psychiatry*, 70:31, 2013.

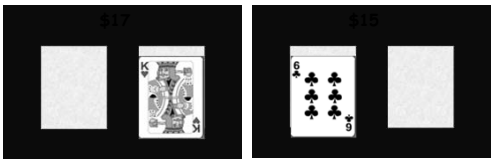
Targeting Downstream Effects of Inflammation on the Brain

Impact of IFN-alpha on Ventral Striatal Activation during a Hedonic Reward Task Using fMRI



Coronal View

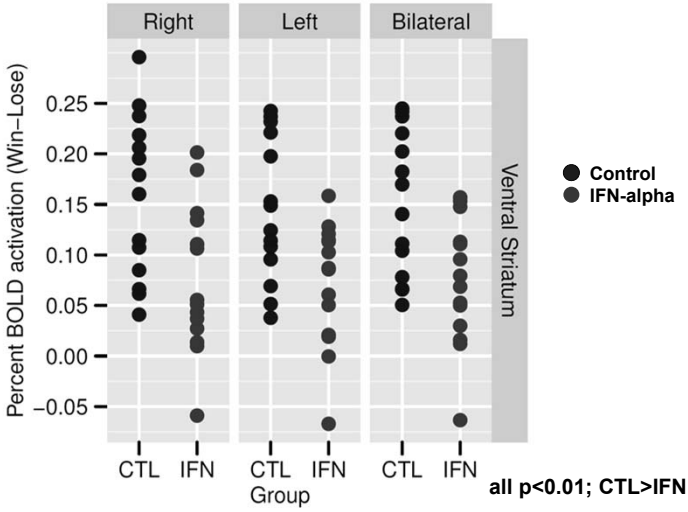
Gambling Task



Win Lose

Reuter et al. *Nat Neurosci.* 8(2):147-8, 2005

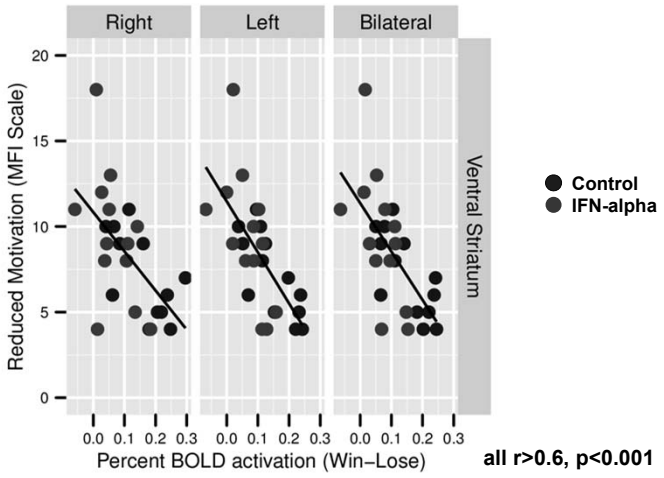
Impact of IFN-alpha on Ventral Striatal Activation during a Hedonic Reward Task Using fMRI



all p<0.01; CTL>IFN

Capuron et al. , *Arch Gen Psychiatry*, 69:1044, 2012

IFN-alpha-Induced Decrease in Ventral Striatal Activation is Associated with Reduced Motivation



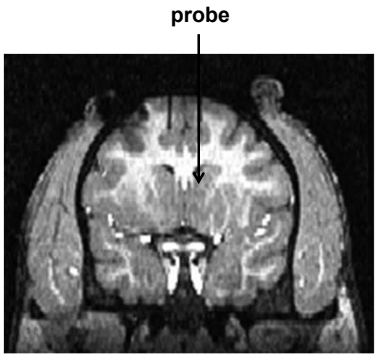
all r>0.6, p<0.001

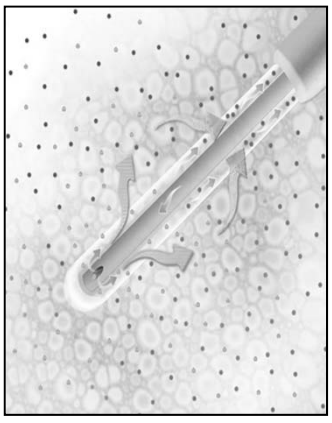
MFI–Multidimentional Fatigue Inventory

Capuron et al. , *Arch Gen Psychiatry*, 69:1044, 2012.

Similar Results with Endotoxin and Typhoid Vaccination
(Eisenberger et al. *Biol Psych*, 68:748, 2010, Harrison et al. *Biol Psych*, 80:73, 2016)

IFN-alpha and Dopamine Release in Striatum as measured by *In Vivo* Microdialysis in Rhesus Monkeys



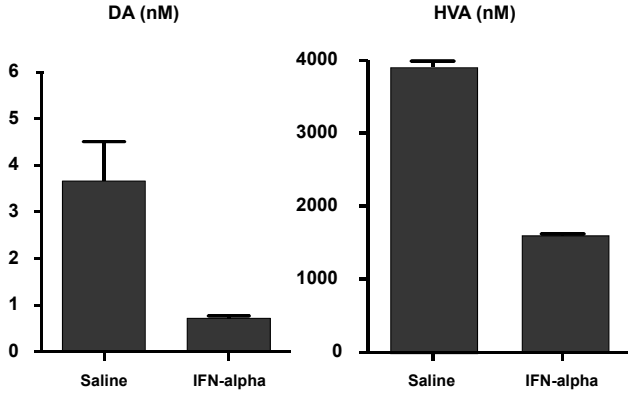


K+ - voltage dependent DA release

Amphetamine (Amph) - stimulated DA release and inhibited DA reuptake

IFN-alpha and Dopamine Release in Striatum as measured by *In Vivo* Microdialysis in Rhesus Monkeys

Baseline

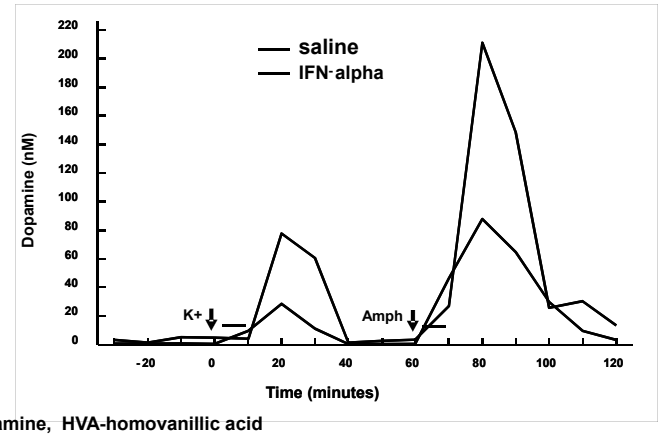


DA-dopamine, HVA-homovanillic acid

Felger et al. , *Neuropsychopharmacology*, 38:2179-87,2013.

IFN-alpha and Dopamine Release in Striatum as measured by *In Vivo* Microdialysis in Rhesus Monkeys

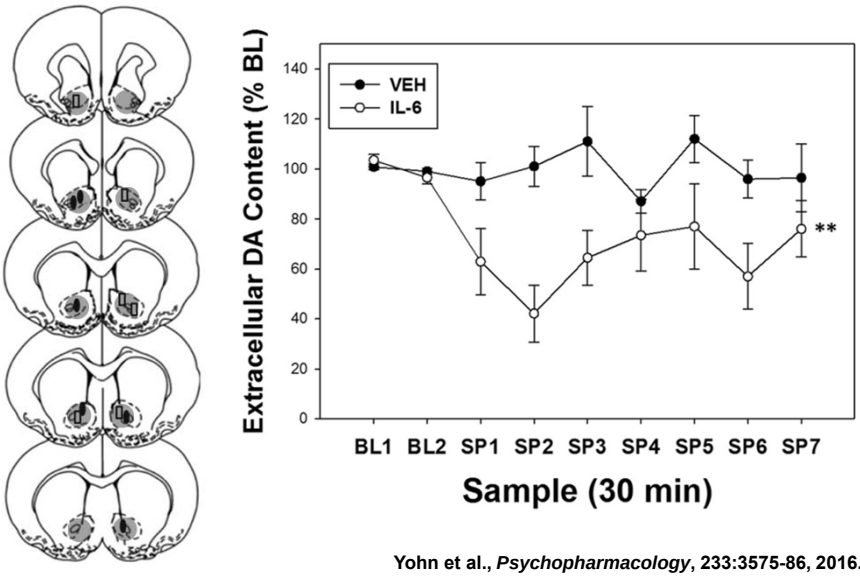
Stimulated via Reverse Microdialysis



DA-dopamine, HVA-homovanillic acid

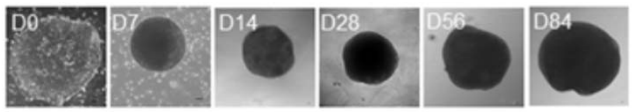
Felger et al. , *Neuropsychopharmacology*, 38:2179-87,2013.

IL-6 (ip) Leads to an Acute Reduction in Nucleus Accumbens Dopamine as Measured by *In Vivo* Microdialysis in Rats

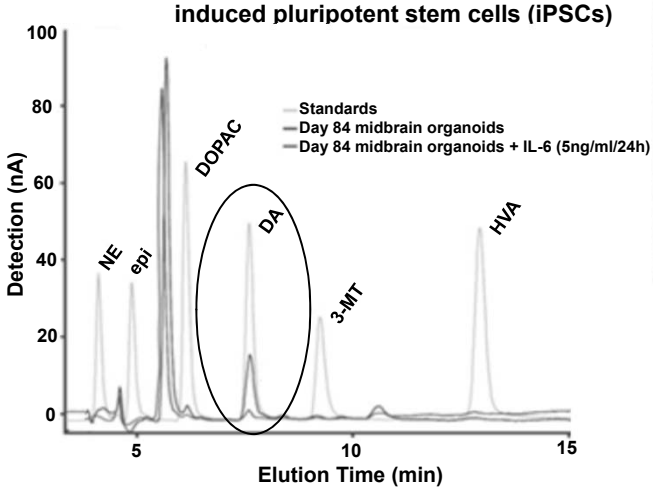


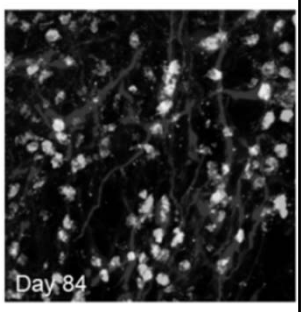
Yohn et al., *Psychopharmacology*, 233:3575-86, 2016.

IL-6 treatment decreases DA production in midbrain organoids



3D human brain organoids derived from induced pluripotent stem cells (iPSCs)



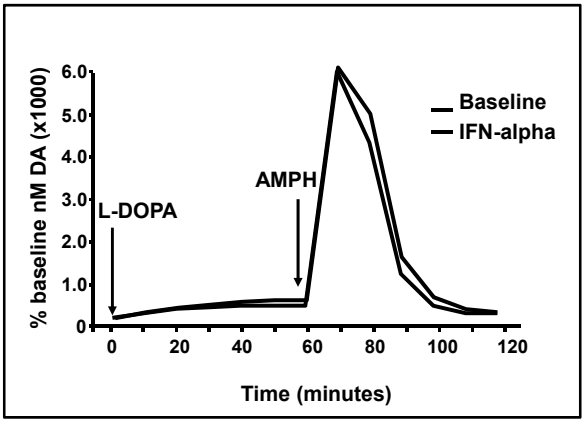


PITX3 (green): DA neurons
Tyrosine hydroxylase (red)

Wen, Treadway, unpublished.

L-DOPA Reverses IFN-alpha-Induced Decrease in Stimulated Dopamine Release

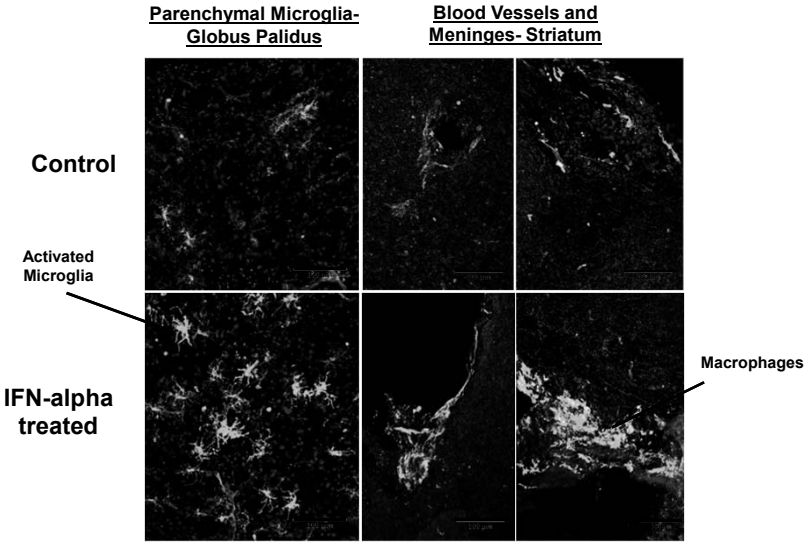
Stimulated DA Release



L-DOPA administered via reverse *in vivo* microdialysis
DOPAC - 3,4-Dihydroxyphenylacetic acid

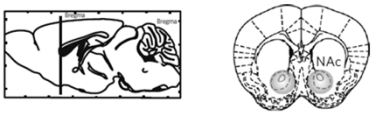
Felger et al., *Int J Neuropsychopharm*, 2014.

Microglial Activation and Monocyte Trafficking to Brain during Immune Stimulation with IFN-alpha

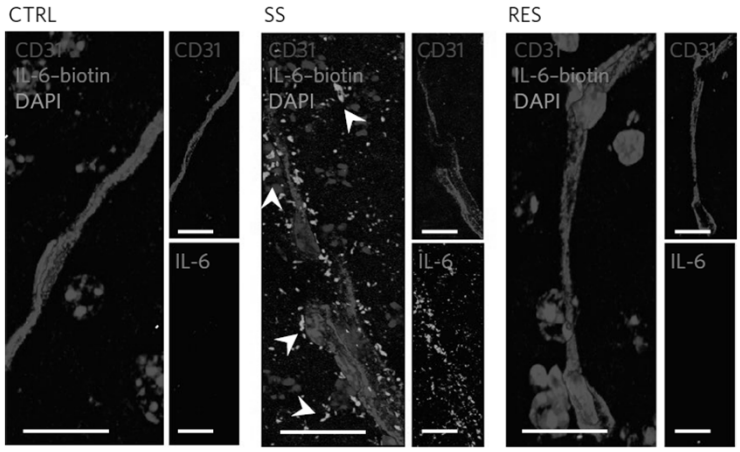


Felger et al., unpublished data.

Chronic Social Defeat Leads to Increased Permeability of the Blood Brain Barrier to IL-6 in Nucleus Accumbens



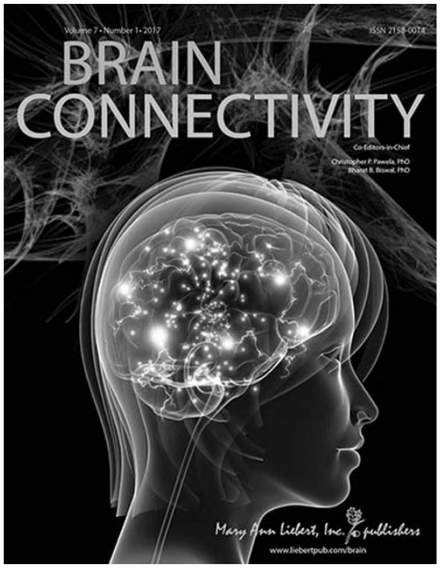
CTRL – control
SS – stress sensitive
RES – stress resilient



Menard et al., *Nat. Neurosci.*, 20: 1752–1760, 2017.

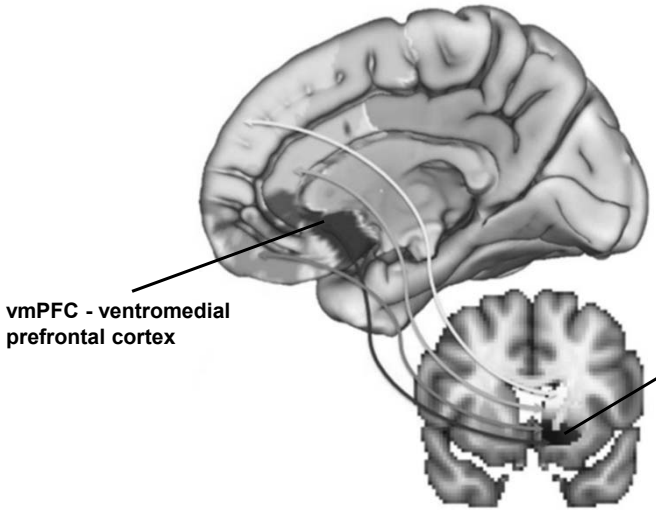
Do Inflammation Effects on Dopamine Affect Reward Circuitry in Patients with Major Depression?

Resting State Functional Connectivity



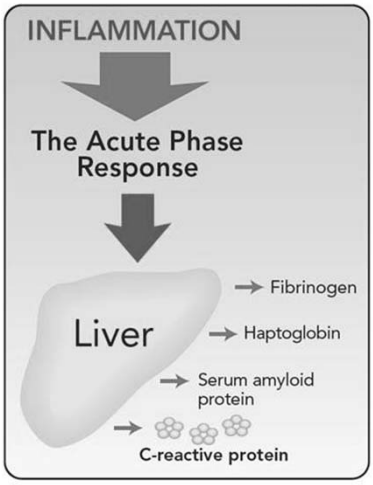
Does Inflammation Disrupt Connectivity in Dopamine-Related Reward Circuits in Depression?

Pathways of the Reward Circuit



Haber & Knutson, *Neuropsychopharm.*, 2010.

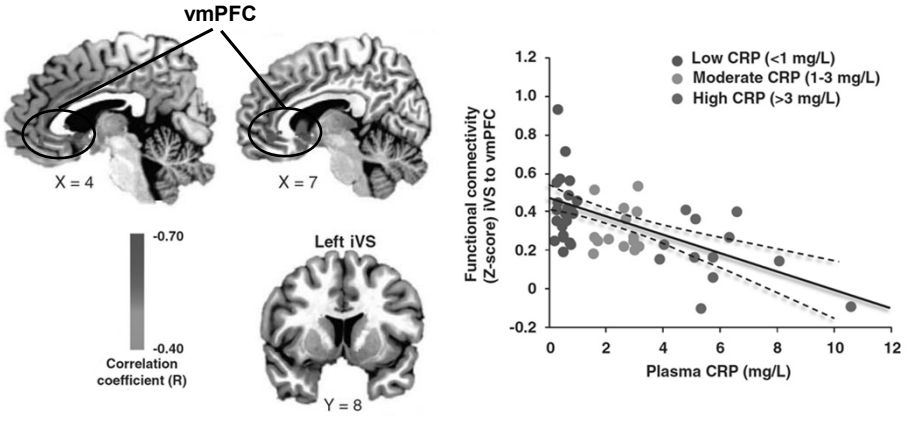
C-Reactive Protein (CRP) is a Marker of Endogenous Systemic Inflammation



hs-CRP Value	Inflammation*
< 1 mg/L	low
1-3 mg/L	average
> 3 mg/L	high

***American Heart Association/ Centers for Disease Prevention and Control (2003)**

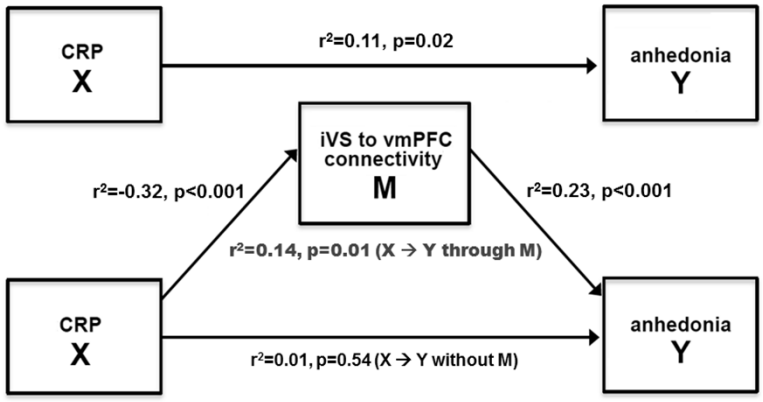
Inflammation Decreases Functional Connectivity in Reward Circuits during Resting State fMRI



iVS – inferior ventral striatum
vmPFC - ventromedial prefrontal cortex

Felger et al., *Molecular Psychiatry*, 21:1358, 2016.

Inflammation Affects Behavior (Anhedonia and Psychomotor Speed) in Depression by Decreasing Connectivity in Reward Circulits

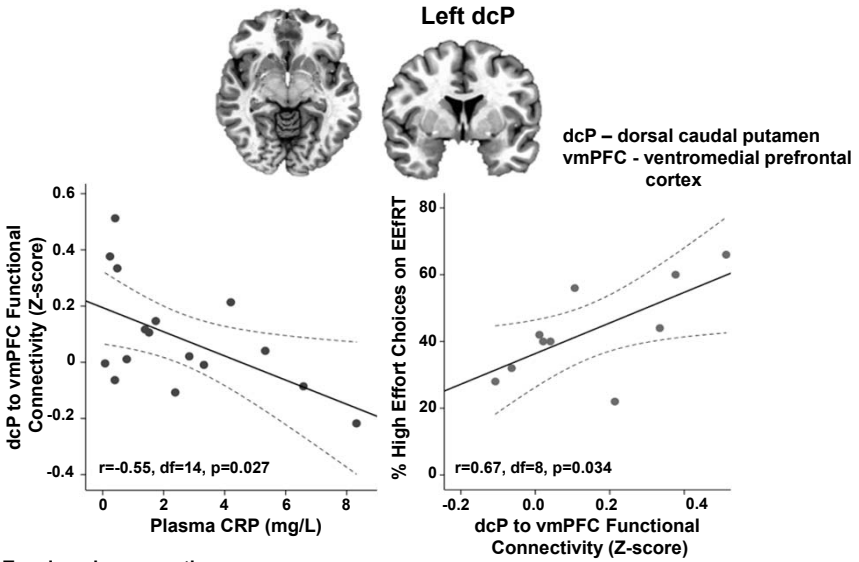


Similar findings with measures of psychomotor activity

iVS – inferior ventral striatum
vmPFC - ventromedial prefrontal cortex

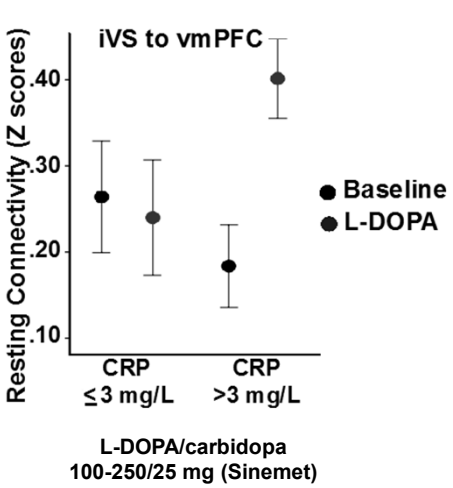
Felger et al., *Molecular Psychiatry*, 21:1358, 2016.

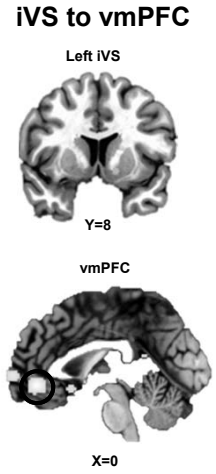
Inflammation is associated with decreased corticostriatal connectivity which is associated with Effort-Based motivation in women with breast cancer



Felger, Treadway in preparation.

Inflammation-Related Decreases in VS to vmPFC Connectivity Can be Reversed with L-DOPA





Felger et al., unpublished data.

iVS – inferior ventral striatum
vmPFC - ventromedial prefrontal cortex

Patients with high inflammation may preferentially respond to dopaminergic medications

Dopamine is a Target

Bupropion
Stimulants
Monoamine oxidase inhibitors
Dopamine agonists
- **pramipexole**
- **L-DOPA**
- **aripiprazole**

Summary

1. **Inflammation affects specific neurotransmitters and neurocircuits that can serve as targets of treatment, dopamine (and glutamate) as well as inflammation itself being especially attractive targets.**
2. **Patients with increased inflammation can readily be identified, allowing focused treatment and prevention on specific subgroups.**
3. **Precision medicine is possible for behavioral complications of inflammation.**

Acknowledgements

Clinical Studies:

Ebrahim Haroon, M.D.
Jennifer C. Felger, Ph.D.
Michael T. Treadway, Ph.D.
Canhua Xiao, Ph.D.
Mylin A. Torres, M.D.
Charles L. Raison, M.D.
Lucile Capuron, Ph.D.
Bobbi J. Woolwine, MSW
Charles B. Nemeroff, M.D., Ph.D.
Dominique L. Musselman, M.D.
Giuseppe Pagnoni, Ph.D.

Animal Studies:

Jennifer C. Felger, Ph.D.
Carla Hernandez
Mar Sanchez, Ph.D.
Amanda Freedman, Ph.D.
David B. Rye, M.D., Ph.D.

Laboratory Studies:

Evanthia Wommack
Thaddeus W.W. Pace, Ph.D.
Fang Hu, Ph.D.
Gerald Vogt, Ph.D.

Support- National Institutes of Health, NARSAD, CDC, American Cancer Foundation, and the DANA Foundation