Impact of Inflammation on the Brain: Significance for Chronic Illness

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

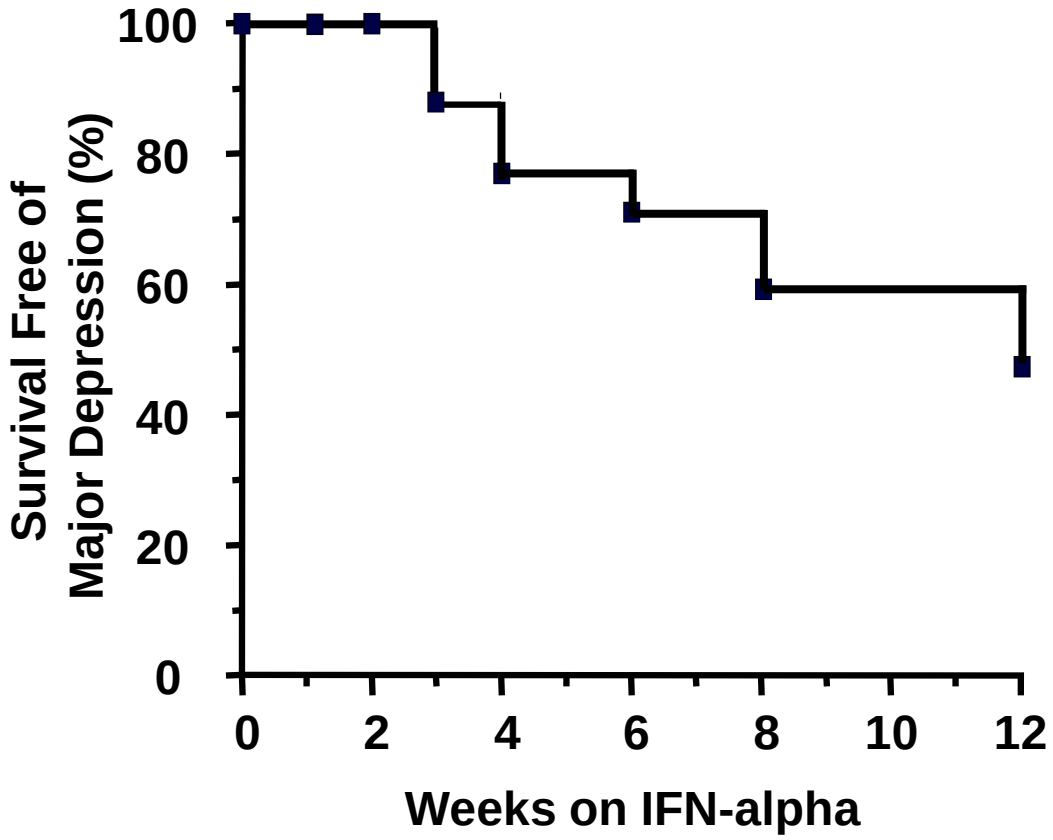
Disclosures:
Paid Consultant:
Cerevel Therapeutics
Sirtsei Pharmaceuticals, Inc.

Cytokines Sing the Blues

Behavioral Changes During the First 12 weeks of High Dose IFN-alpha for Malignant Melanoma

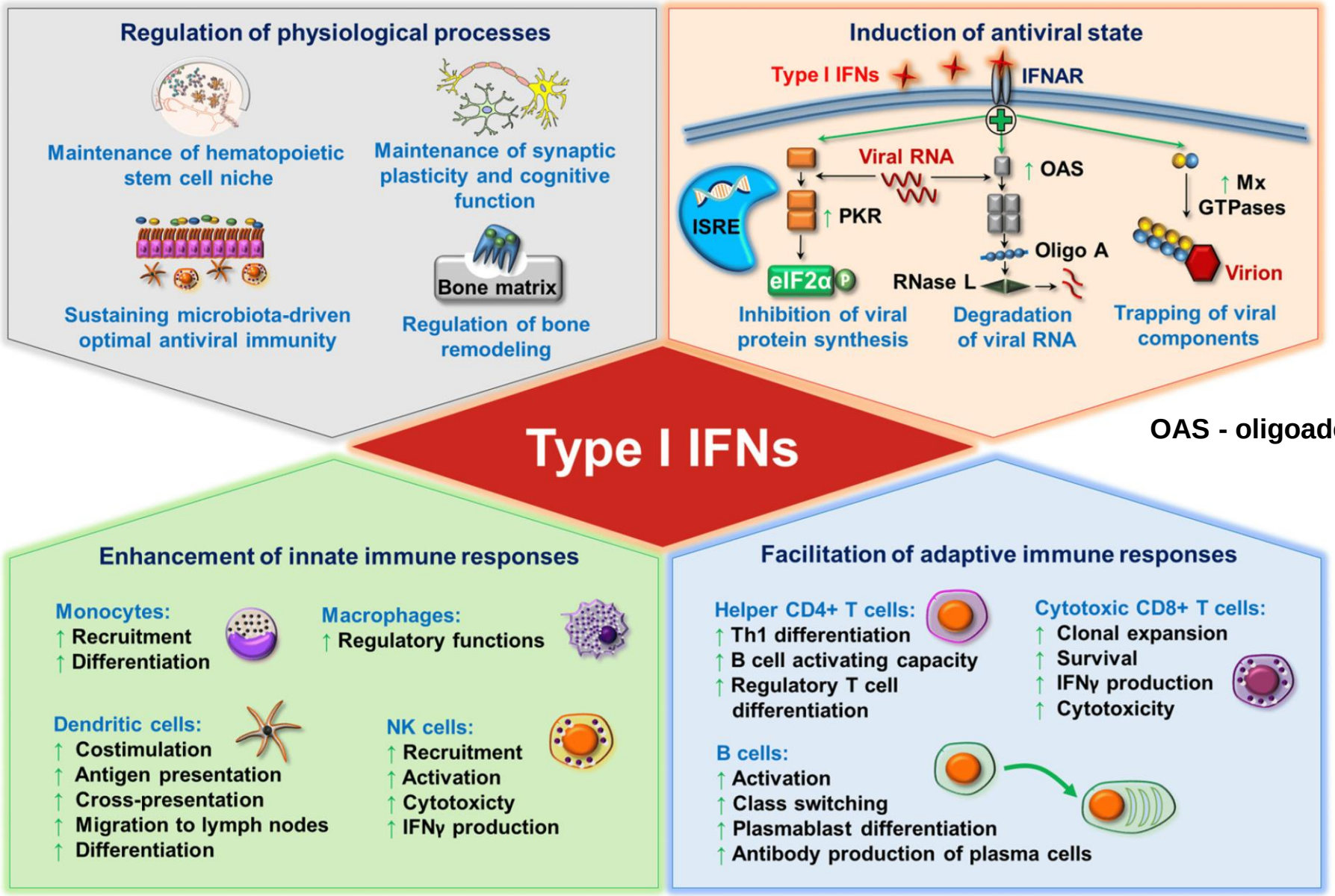
	Percent
Depressive Symptoms	
Depressed mood	60
Anhedonia	30
Suicidal Thoughts	10
Feelings of Guilt	5
Anxious Symptoms	
Tension/Irritability	50
Anxious Mood	45
Fear	15
Cognitive Symptoms	
Loss of Concentration	30
Memory Disturbances	15
Word-finding Problems	15
Episodes of Confusion	10
Indecisiveness	10
Neurovegetative Symptoms	
Fatigue/ Loss of Energy	80
Abnormal Sleep	45
Psychomotor Retardation	40
Abnormal Appetite	35
Somatic Symptoms	
Pain	55
Gastrointestinal Symptoms	50

Capuron et al., *Neuropsychopharmacology*, 26:643-652, 2002



Musselman et al., *NEJM,* 344:961-966, 2001.

IFN-alpha and Infectious Disease



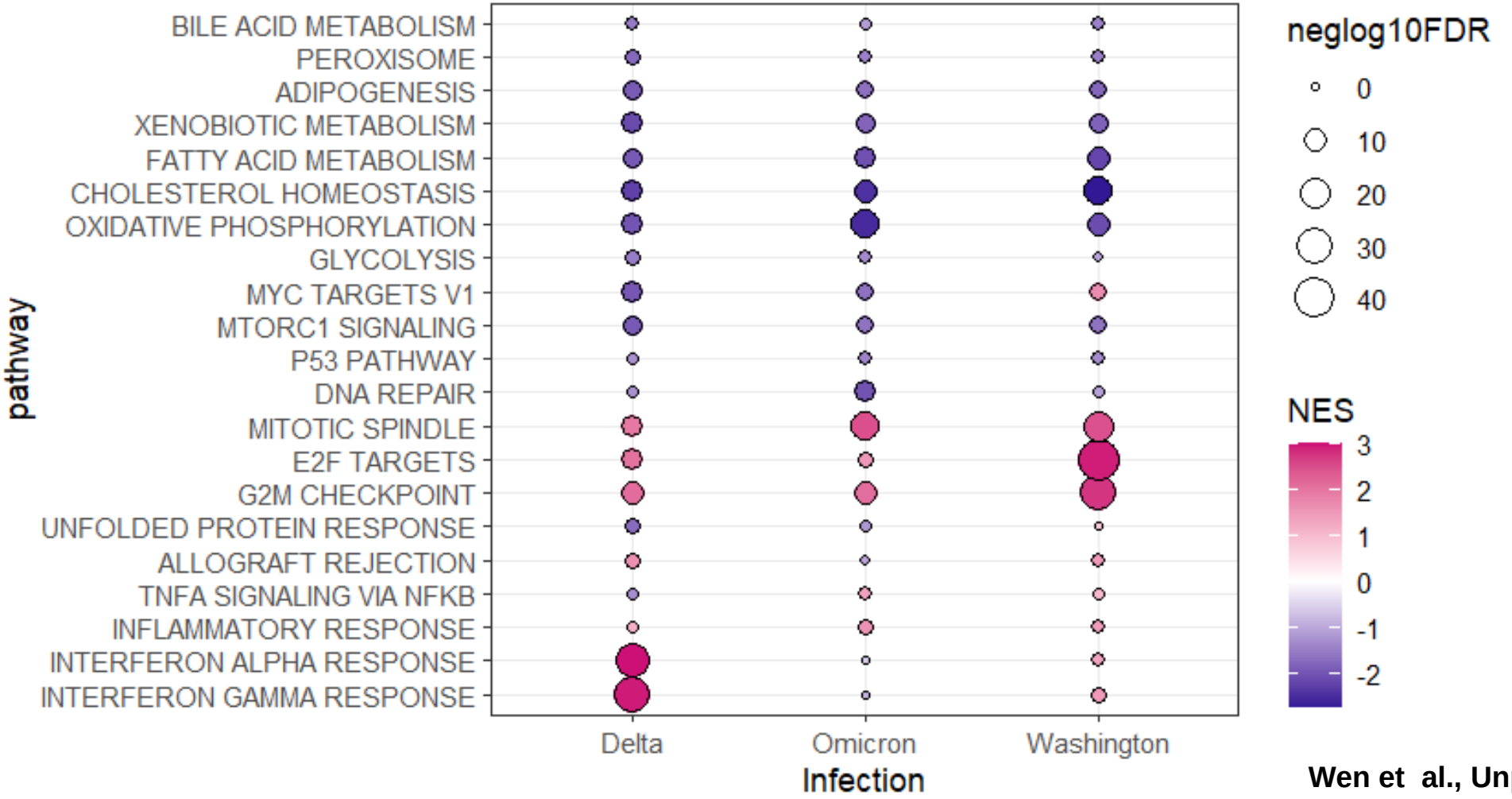
OAS - oligoadenylate synthetases

Bencze et al., *Int. J. Mol. Sci.*, 22:4190, 2021

IFN-alpha in Chronic Infection-Associated Illnesses

1. **IFN-alpha has been associated with ME/CFS as reflected by increased RNase L and OAS2 (Meirleir et al. *Am J Med*., 108:99, 2000; Vojdani et al., *J Clin Lab Immunol*., 50:1, 1998).**
2. **IFN-alpha is associated with behavioral changes in HIV infection including cognitive deficits (Anderson et al., *J Neurovirol*., 23:106, 2017).**
3. **Increased IFN-alpha activity has been associated with persistent symptoms of fatigue and cognitive deficits in Lyme's Disease (Jacek et al., *J. Neuroimmunol*, 255:85, 2013; Hernandez et al., *Emerg Infect Dis.*, 29:1091, 2023).**
4. **IFN-alpha and IL-6 play interdependent roles in innate immune, neuroinflammatory and sickness behavior responses to virus-like stimuli in laboratory animals (Murray et al., *Brain Behav Immun*., 48:274, 2015).**

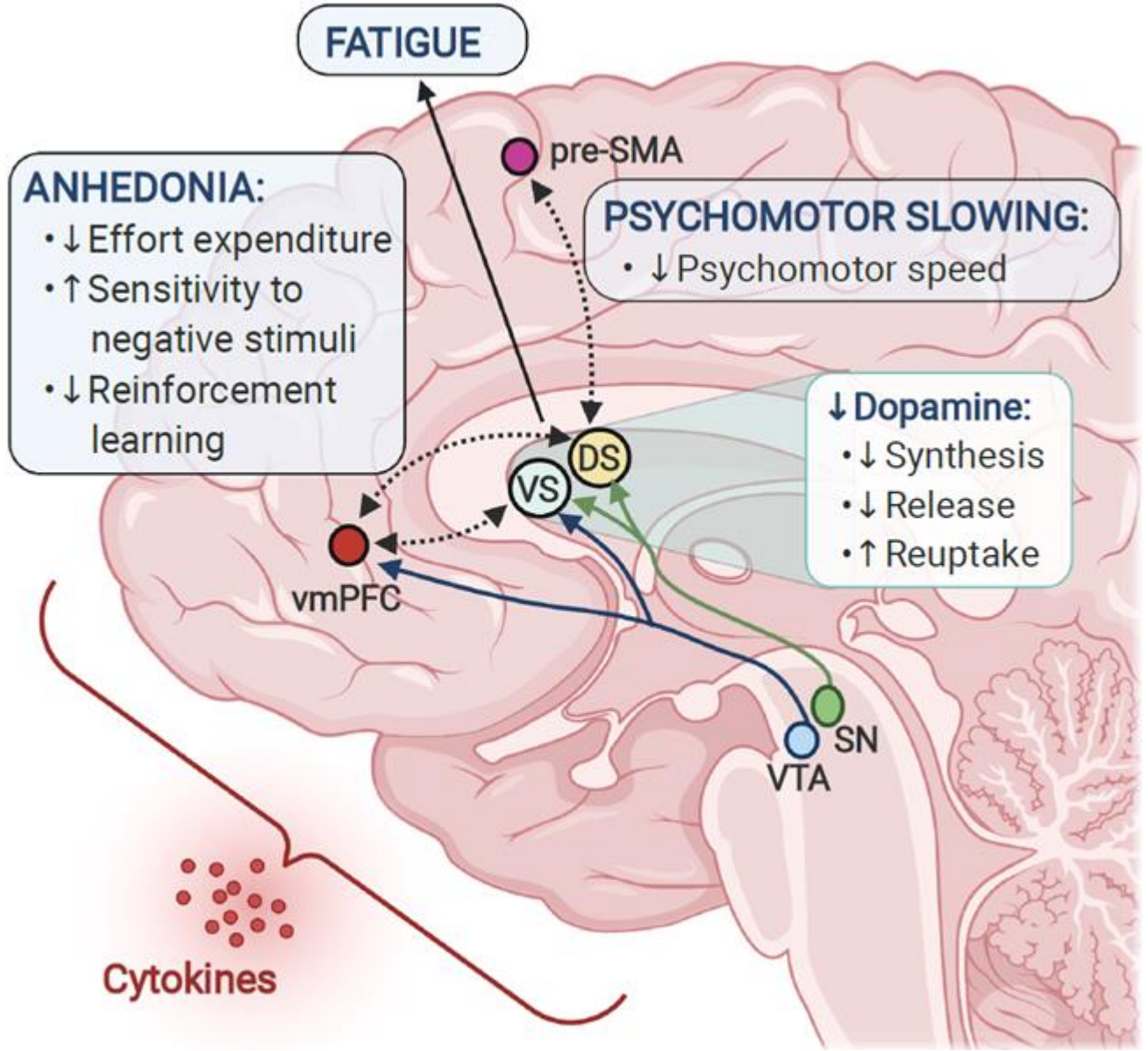
Strain Specific Human Microglial (iPSCs) Responses to SARS-CoV-2 infection: Increased IFN-alpha with Delta Strain



Wen et al., Unpublished Data

Antonelli et al. Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. *Lancet*, 399:2263, 2022.

Inflammation Effects on Neurotransmitters and Neurocircuits in the Brain Related to Behavior

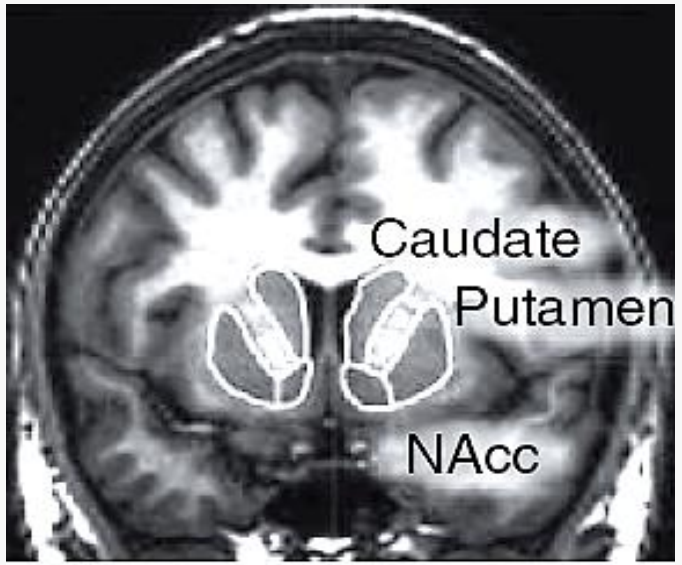


VS - ventral striatum
DS - dorsal striatum
vmPFC - ventromedial prefron

SMA - supplementary motor area
SN - substantia nigra
VTA - ventral tegmental area

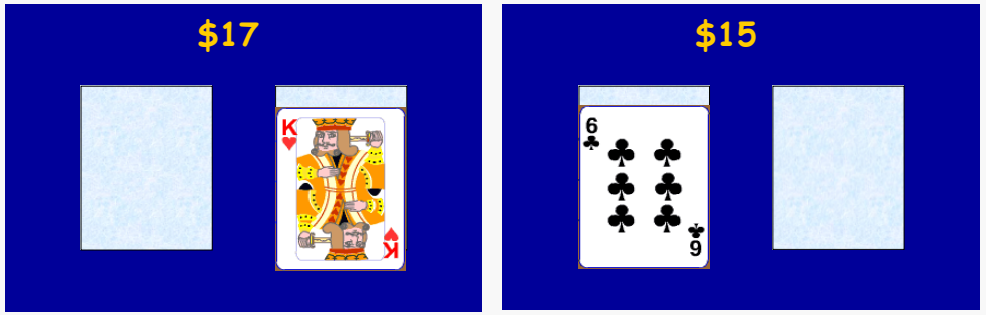
Lucido et al., *Pharm Rev,* 73:1084, 2021.

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



Coronal View

Gambling Task



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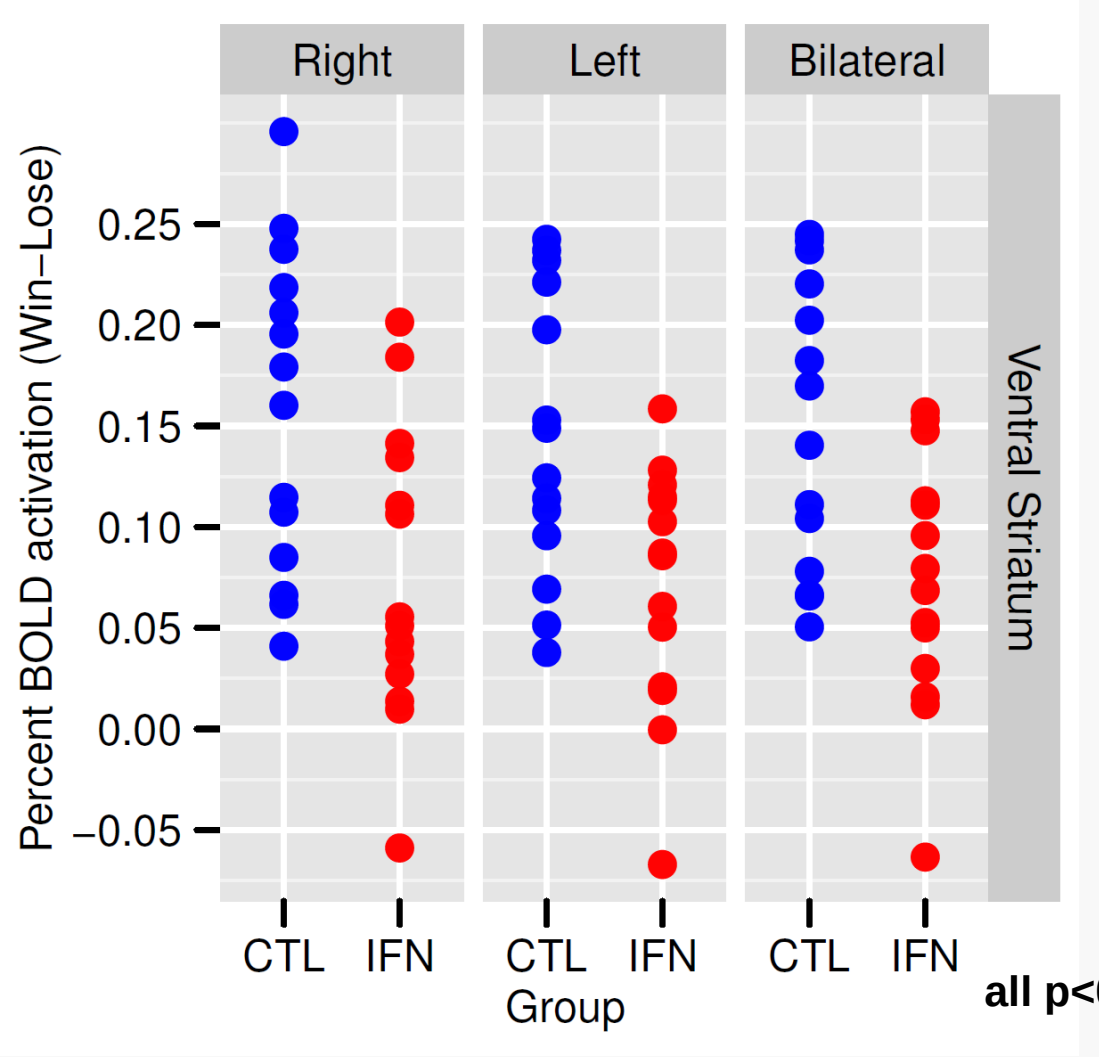
Reuter et al. *Nat Neurosci.* 8(2):147-8, 2005

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



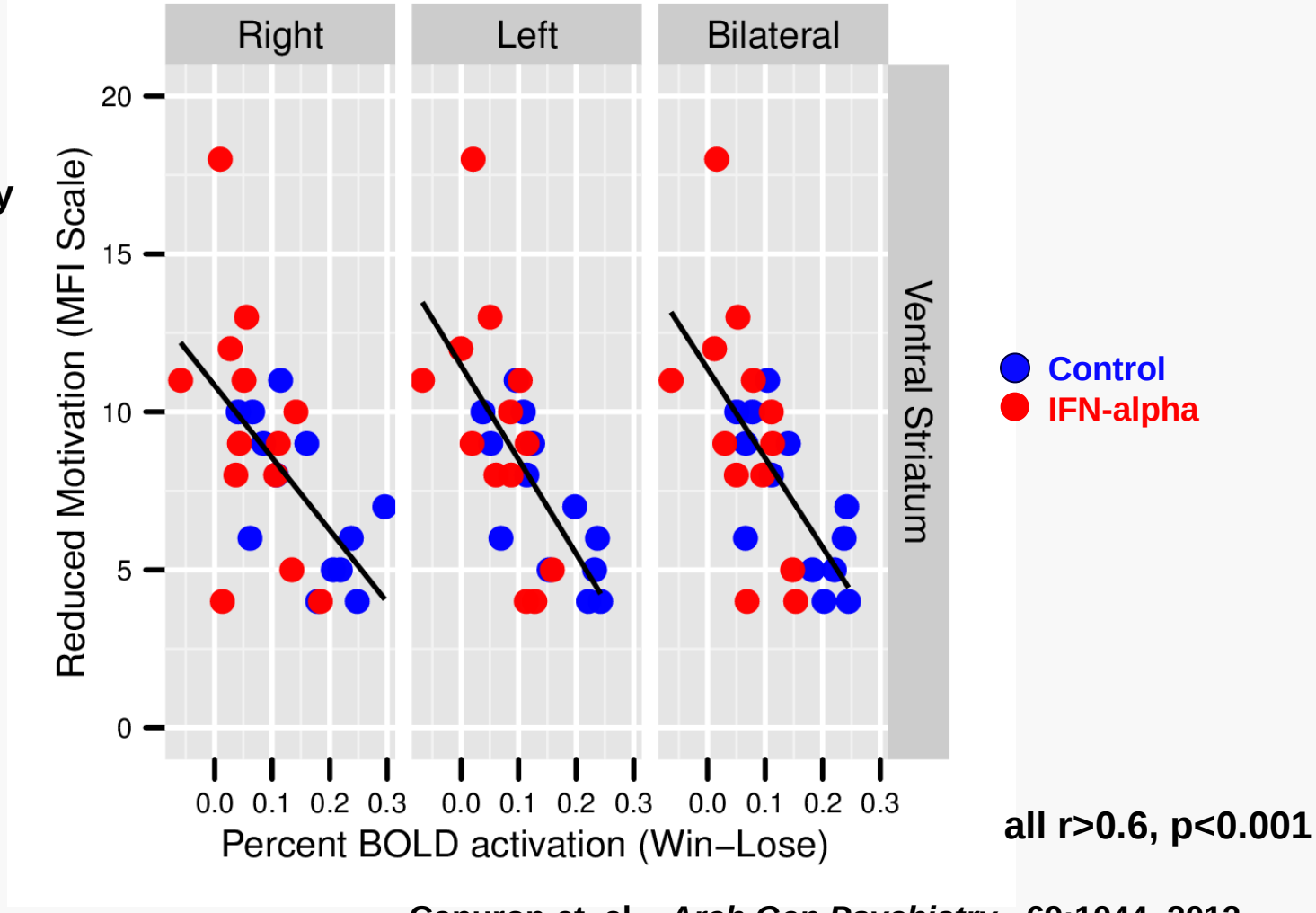
all p<0.01; CTL>IFN

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

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

MFI–Multidimensional Fatigue Inventory

RM: Reduced Motivation
GF: General Fatigue
PF: Physical Fatigue
RA: Reduced Activity
MF: Mental Fatigue

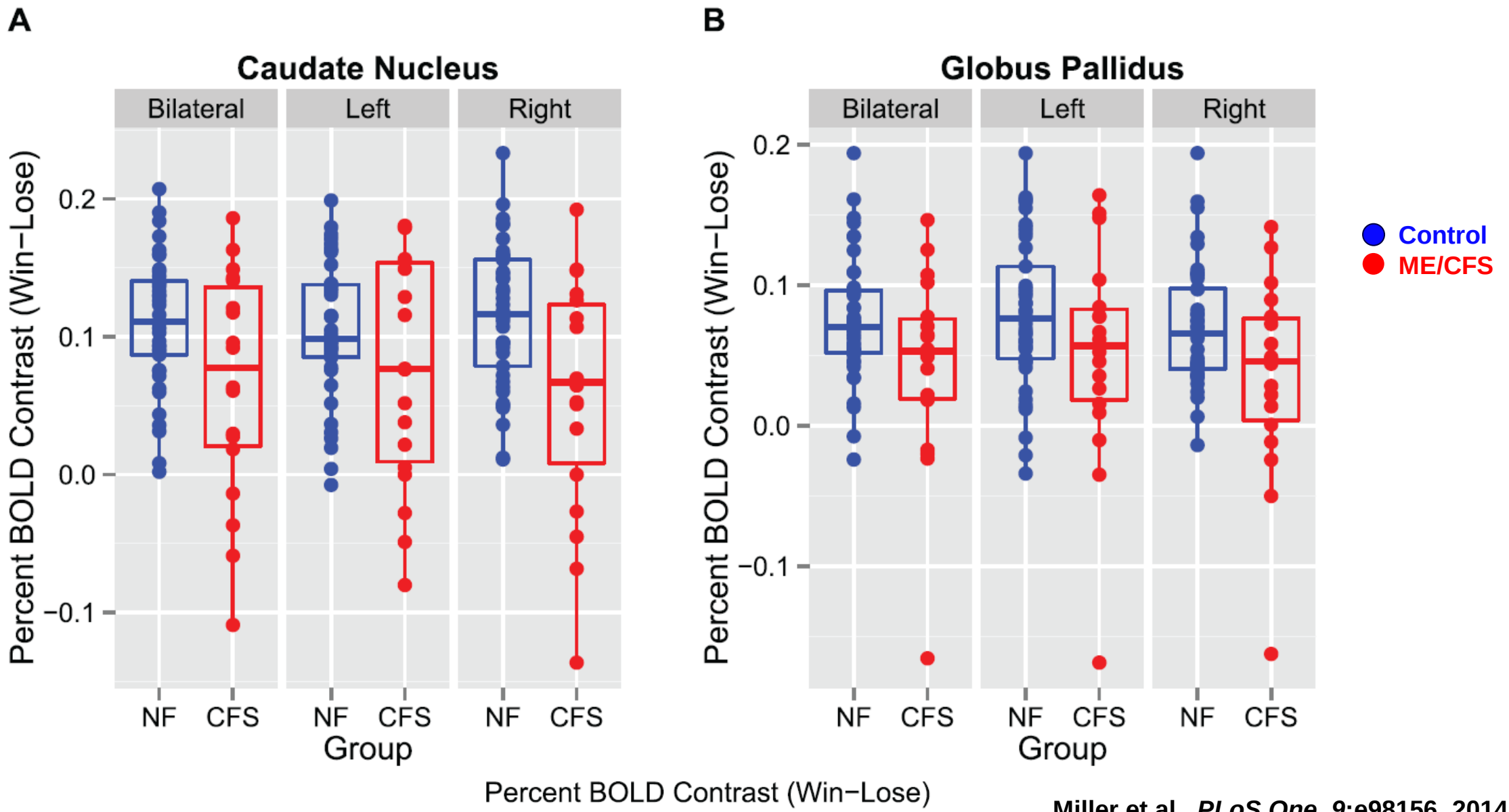


all r>0.6, p<0.001

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

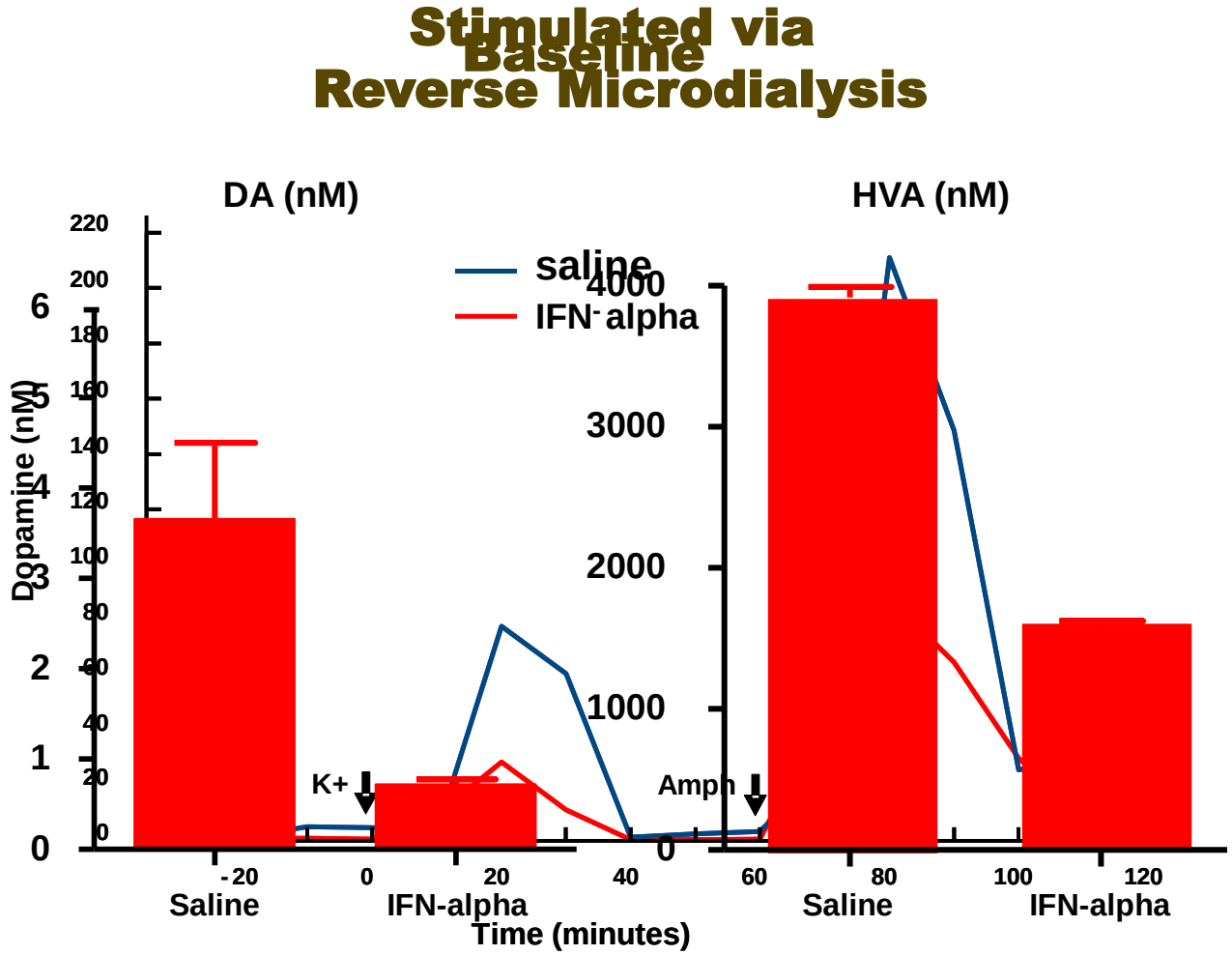
Similar Results with Endotoxin and Typhoid Vaccination
(Eisenberger et al. *Biol Psych*, 68:748, 2010, Harrison et al. *Biol Psych*, 80:73, 2016)

Neural Activation in the Basal Ganglia of Subjects with ME/CFS is Reduced and Correlates with Fatigue



Miller et al., *PLoS One, 9*:e98156, 2014.

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



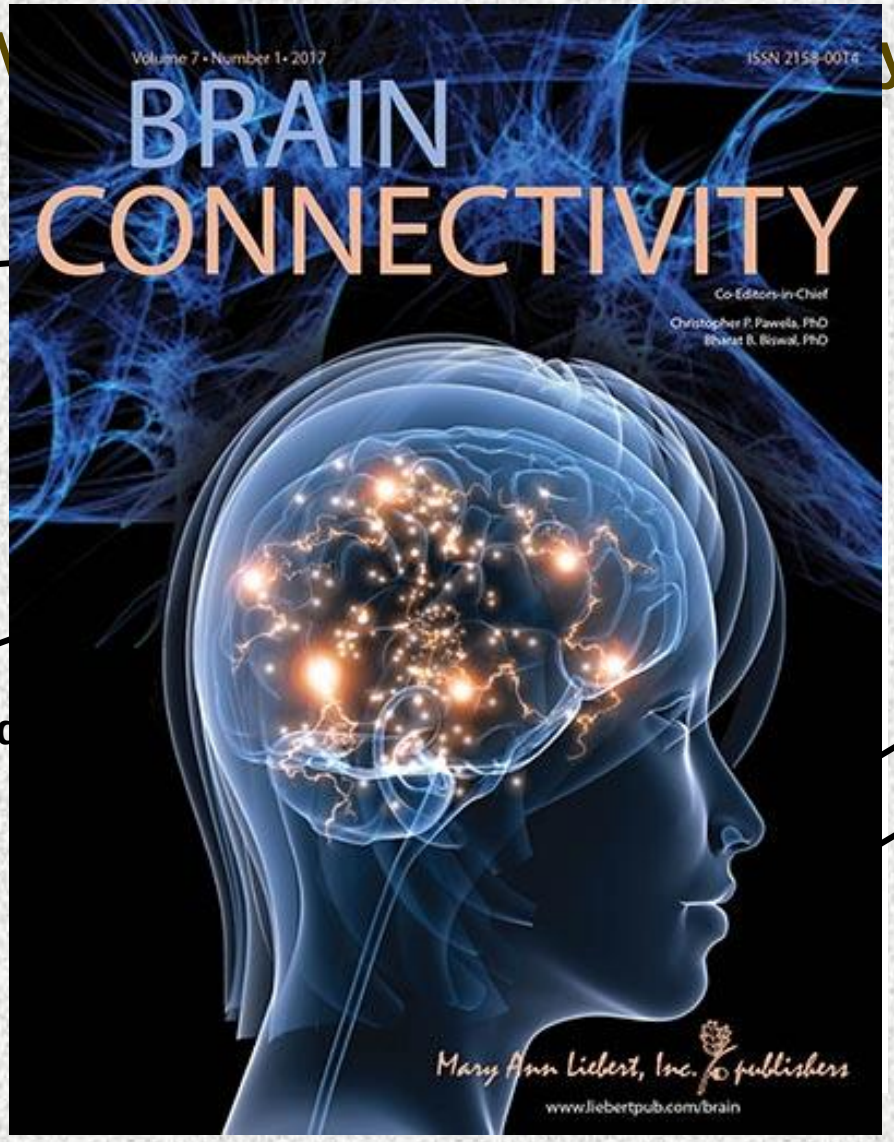
DA-dopamine, HVA-homovanillic acid

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

Does Endogenous Inflammation Disrupt Connectivity In Motivational and Motor Circuits (in Depression)?

SMA - supplementary motor area

vmPFC - ventromed prefrontal cortex

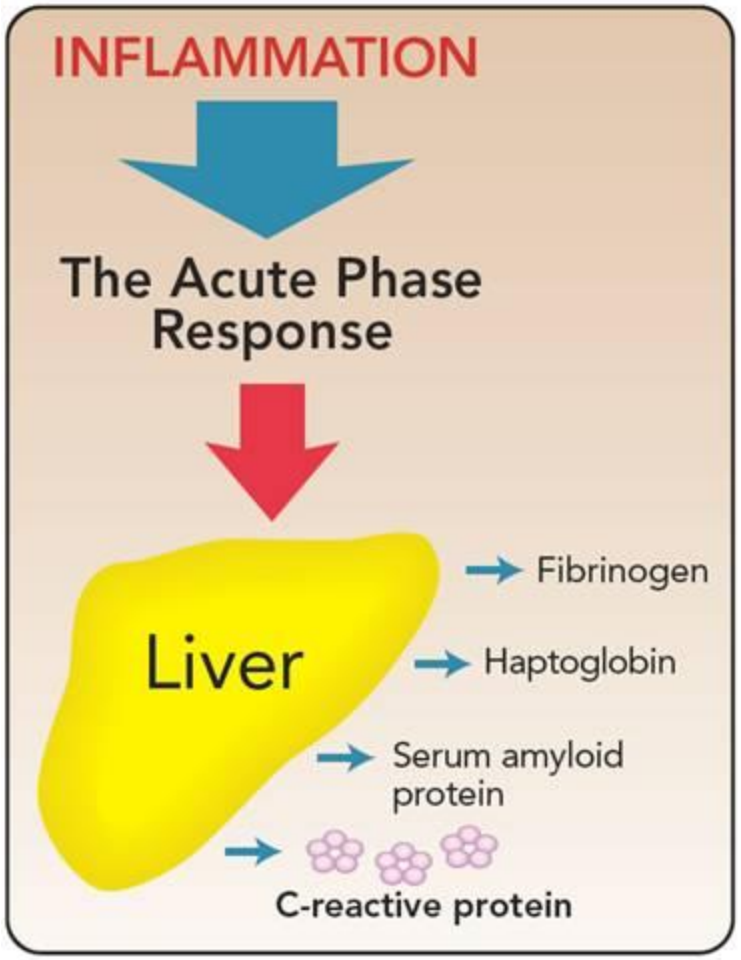


DS – dorsal striatum

VS – ventral striatum

Haber & Knutson, *Neuropsychopharm.*, 2010

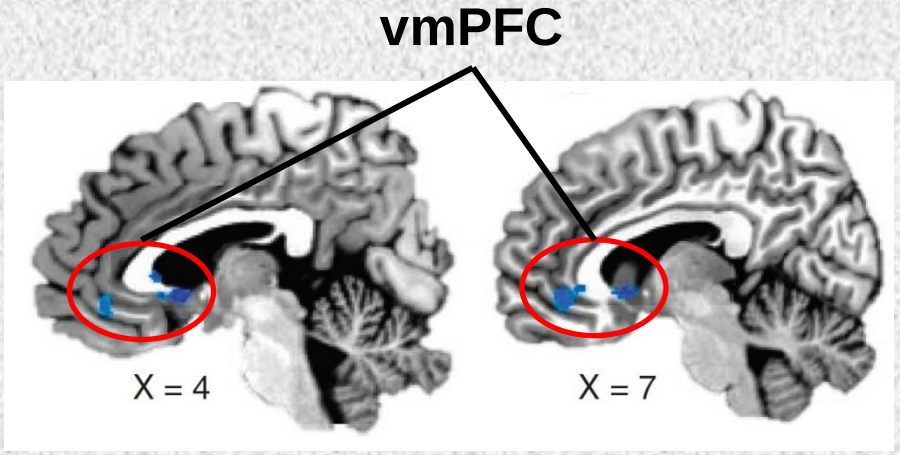
C-reactive protein (CRP) is a Marker of Endogenous Systemic Inflammation

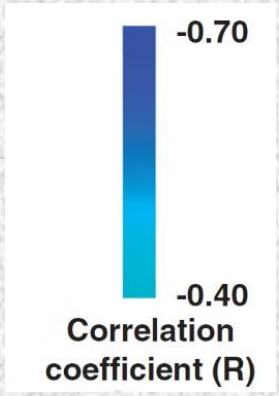


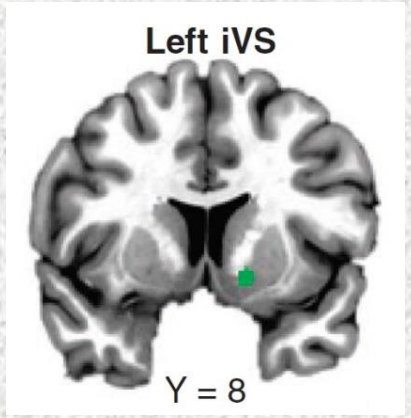
hs-CRP Value	Inflammation*
< 1 mg/L	low
1-3 mg/L	average
> 3 mg/L	high

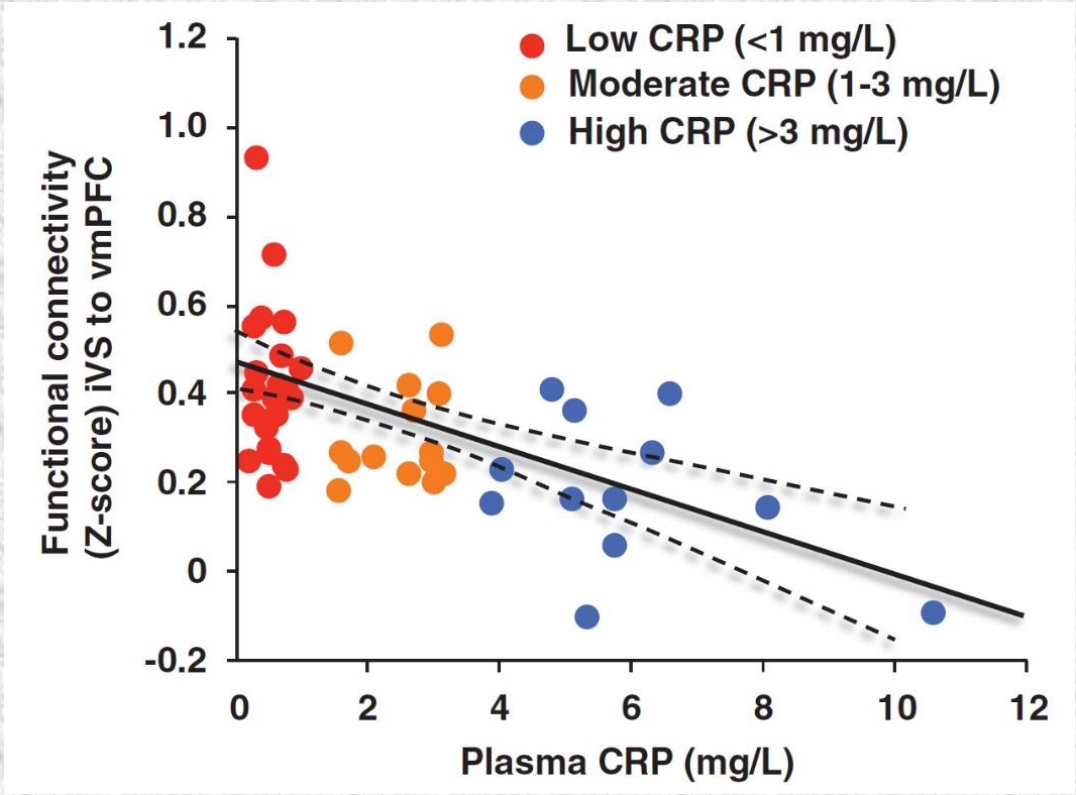
*American Heart Association/ Centers for Disease Prevention and Control (2003)

Inflammation Decreases Functional Connectivity in Motivational Circuits during Resting State fMRI







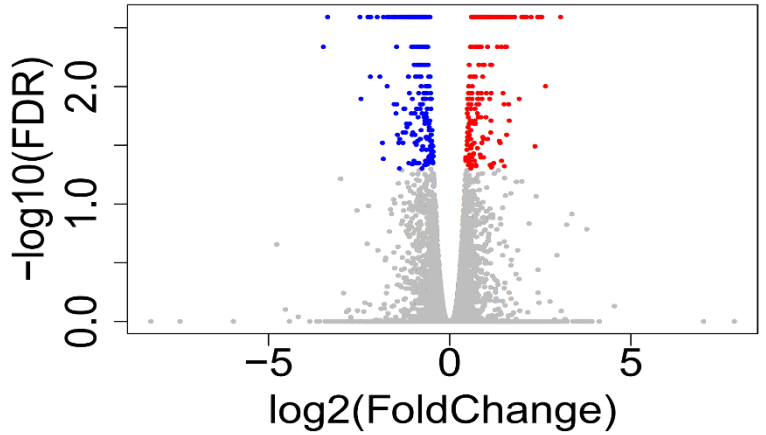


iVS – inferior ventral striatum
vmPFC - ventromedial prefrontal cortex

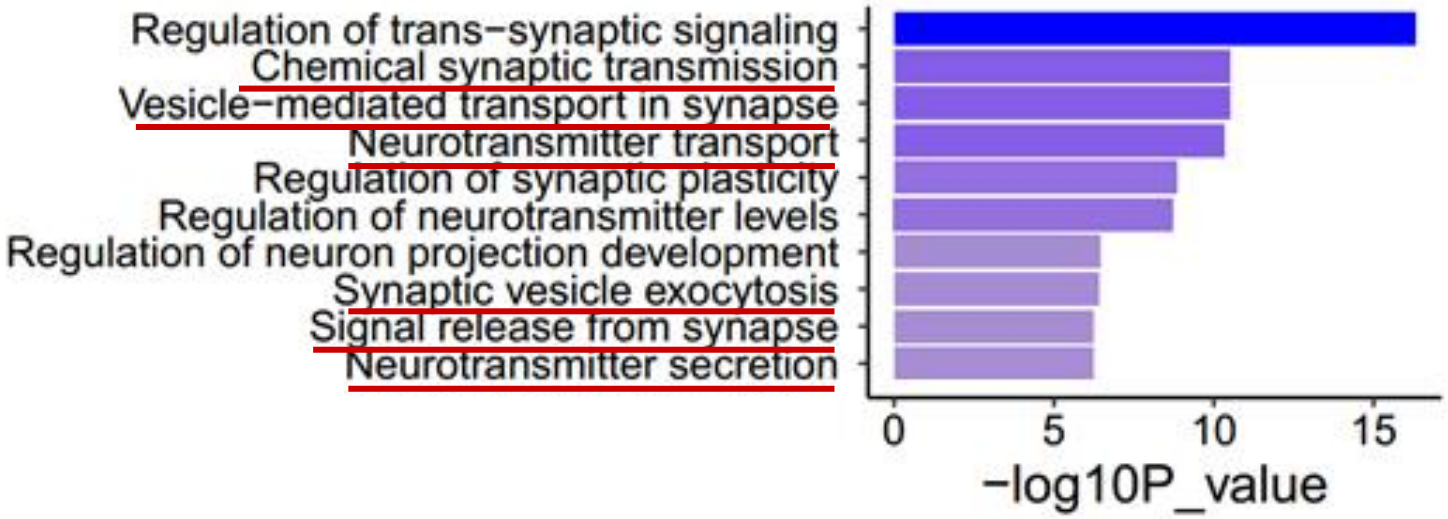
Felger et al., *Molecular Psychiatry*, 21:1358, 2016.

IL-6 decreases gene expression pathways associated with dopamine packaging and release

Gene Expression Pathways Downregulated in DA Neurons (iPSCs): IL-6 (100pg/ml/24h) vs Vehicle

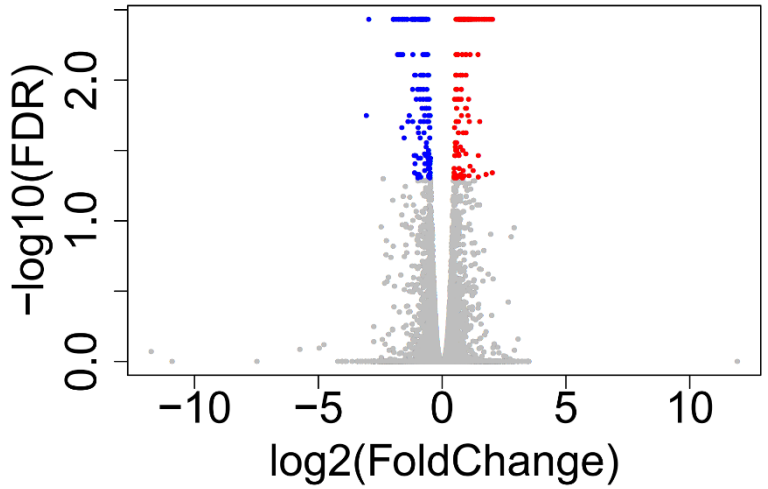


Upregulated: 247
Downregulated: 307

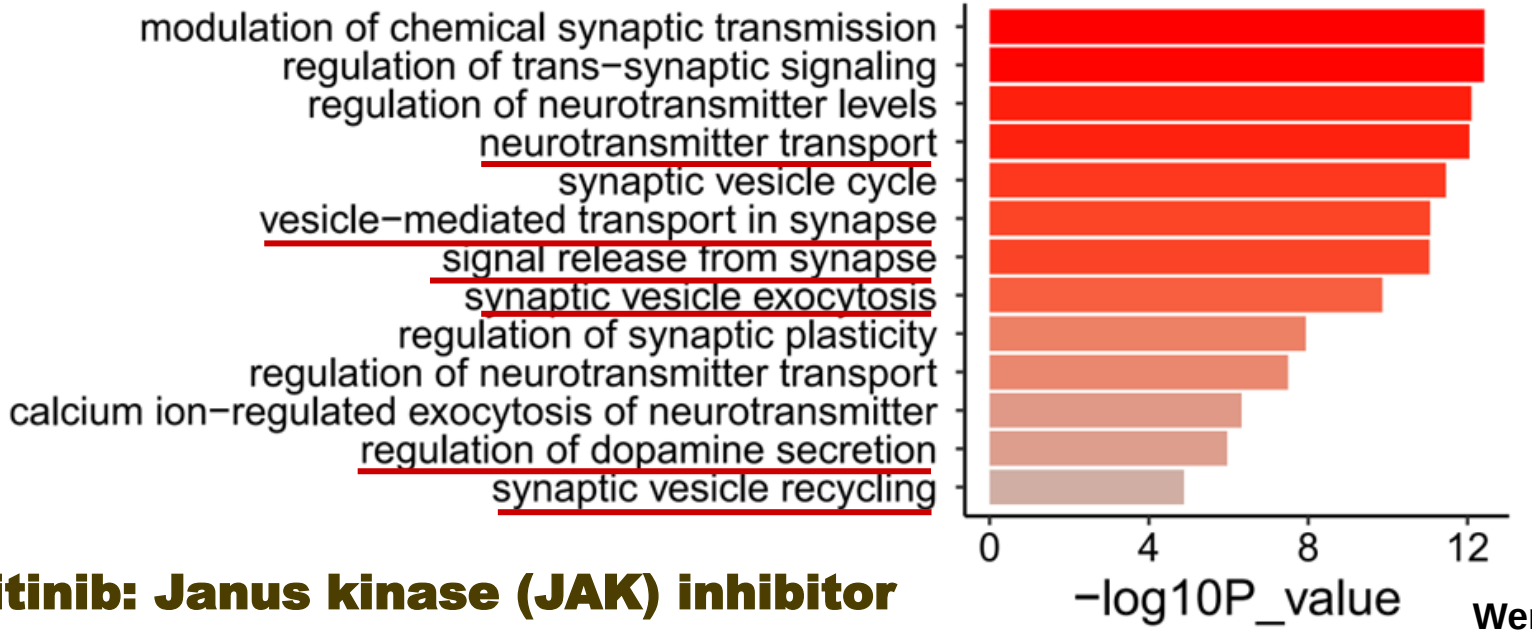


Wen et al., Unpublished Data

Gene Expression Pathways Upregulated in DA Neurons (iPSCs): IL-6 (100pg/ml/24h)+baricitinib (200nM) vs IL-6



Upregulated: 173
Downregulated: 199



baricitinib: Janus kinase (JAK) inhibitor

Wen et al., Unpublished Data

Highlights and Research Priorities

1. **Antiviral and inflammatory cytokines lead to chronic changes in neurocircuits and neurotransmitter systems that contribute to neurovegetative symptoms including anhedonia, fatigue, and cognitive dysfunction.**
2. **Research priorities include:**
    a) **Determination of common behaviors affected in infection-associated chronic illnesses.**
    b) **Determination of common CNS circuits affected in infection-associated chronic illnesses.**
    c) **Determination of effects of infection and infection-related immune changes on neuronal and microglial function with a focus on neurotransmitter metabolism.**
    d) **Test pharmacologic agents targeting antiviral and inflammatory cytokines and their signaling pathways as treatments for infection-associated chronic illnesses.**