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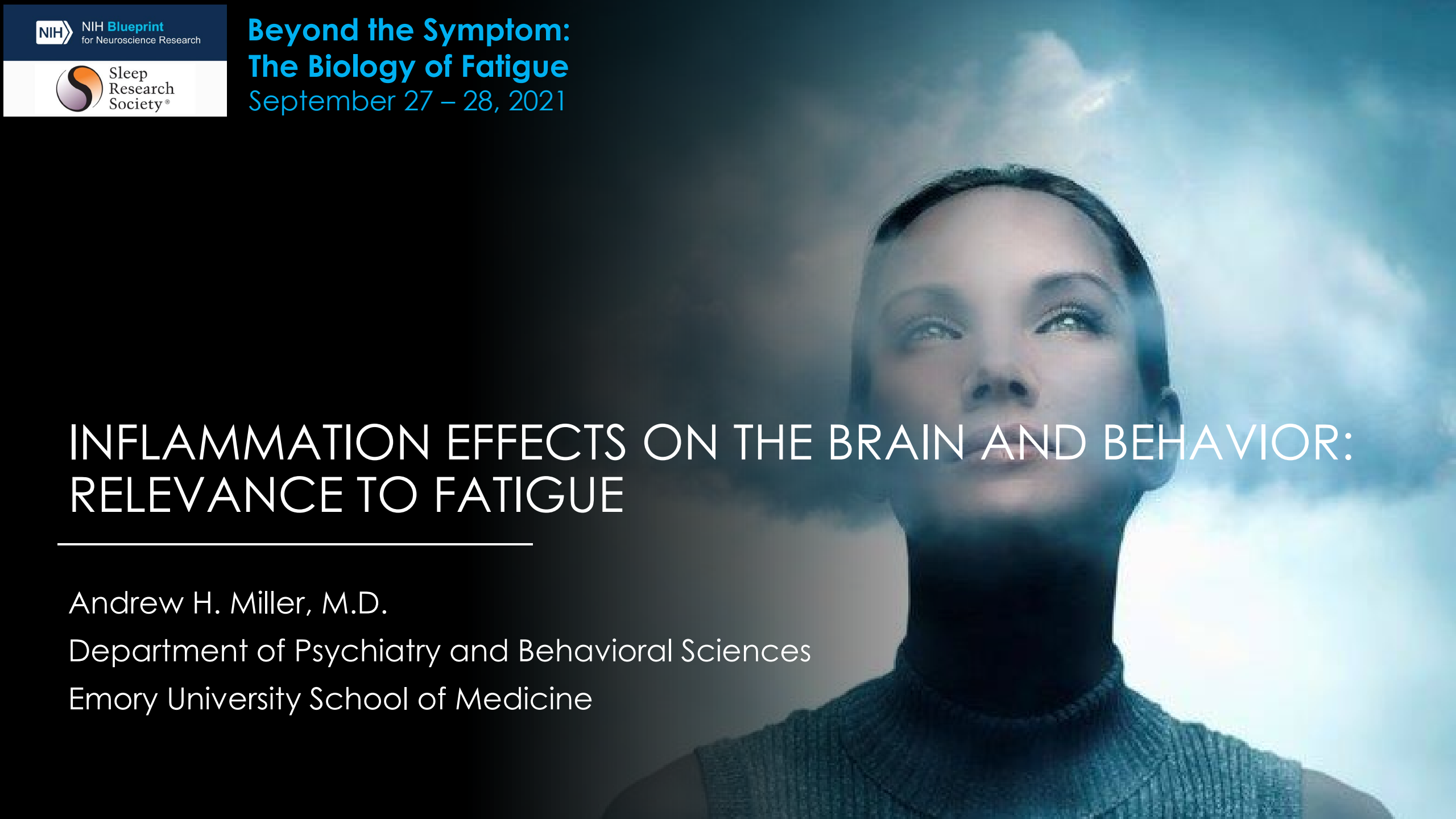
Beyond the Symptom: The Biology of Fatigue

September 27 – 28, 2021



INFLAMMATION EFFECTS ON THE BRAIN AND BEHAVIOR: RELEVANCE TO FATIGUE

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Disclaimer and Disclosures

Disclaimer
This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

Disclosure
I, Andrew H. Miller, serve as a paid consultant to Boehringer Ingelheim.

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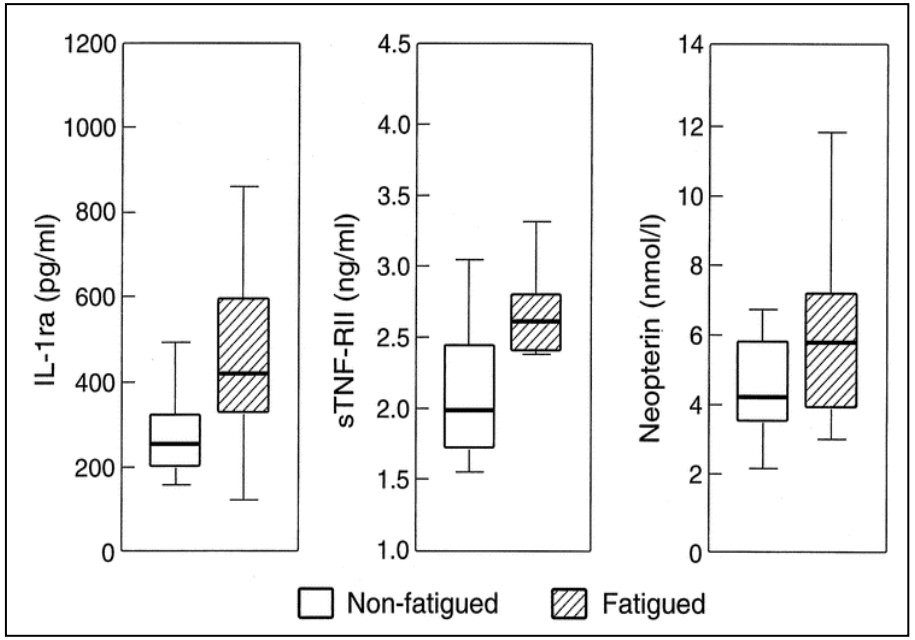
Inflammation is Associated with Fatigue

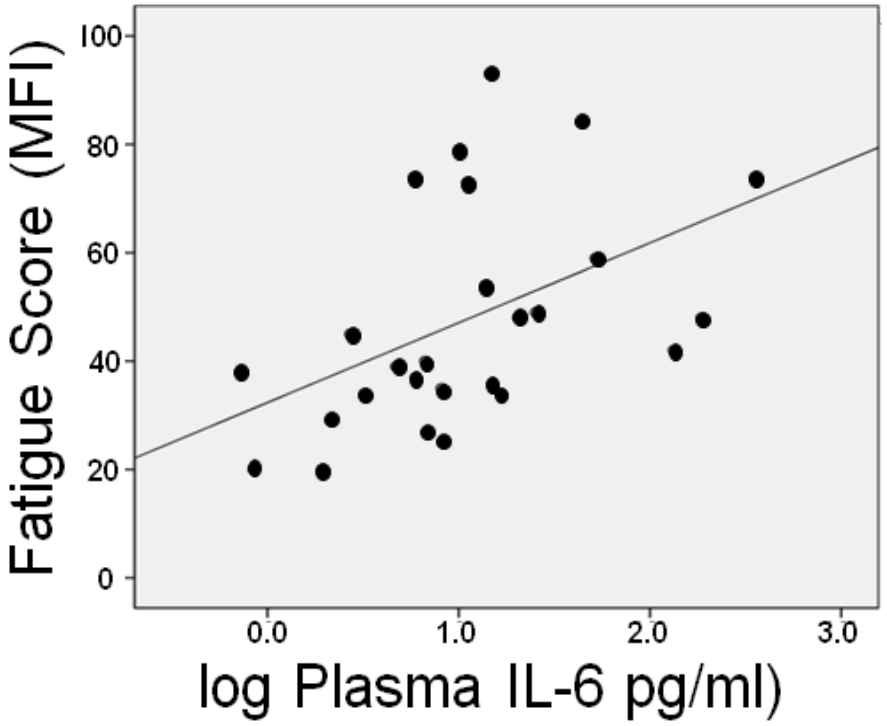
Fatigue and IL-1ra and sTNFR-II



Breast Cancer Survivors

Bower et al. *Psychosomatic Medicine,* 64(4):604-11, 2002

Fatigue and IL-6

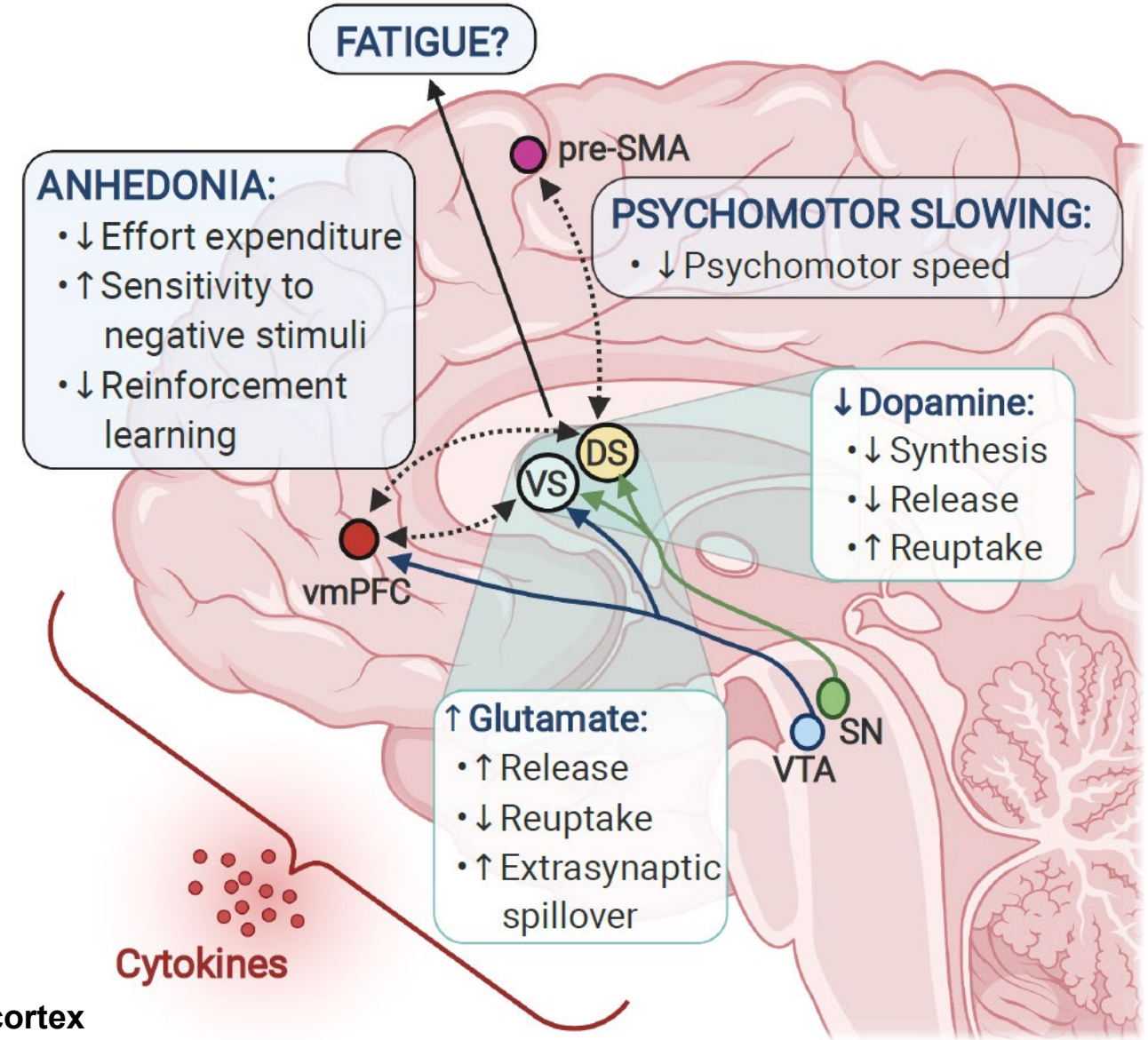


Breast Cancer During Treatment

Torres et al., *Cancer*, 119:1951, 2013

Also seen in multiple other patient populations

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



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

VS - ventral striatum
DS - dorsal striatum
vmPFC - ventromedial prefrontal cortex

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

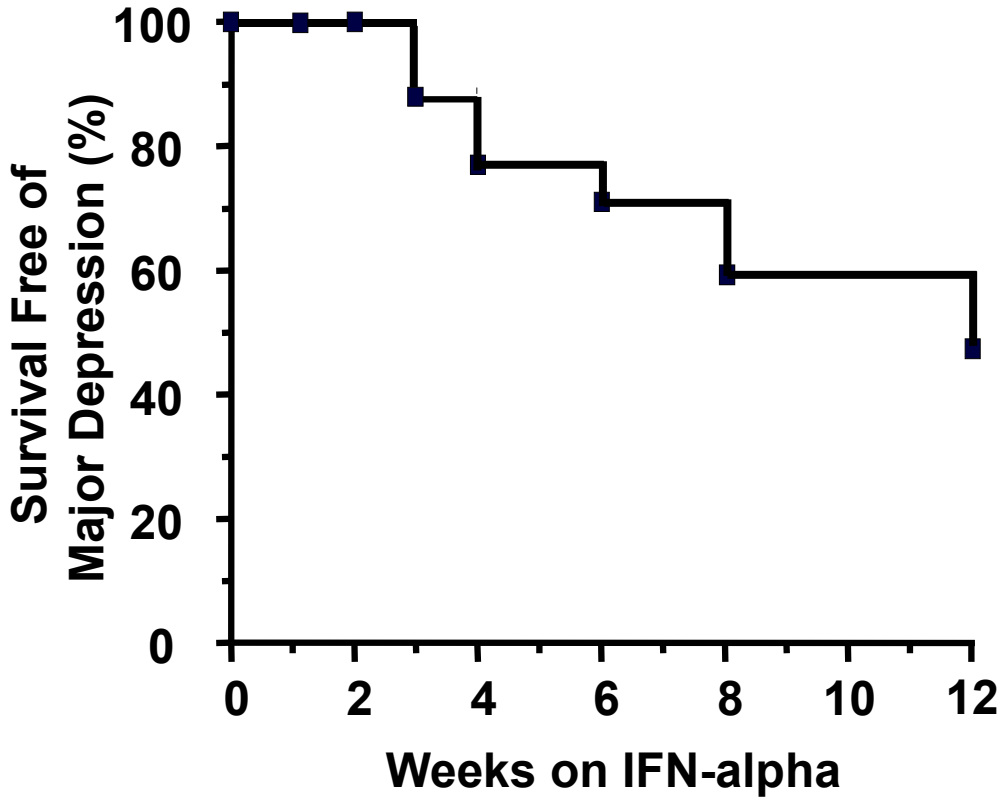
Overview of Talk

- **Regional Brain Activity**
  - IFN-alpha
  - ME/CFS
- **Dopamine Metabolism**
- **Functional Connectivity**
  - Depression
  - Breast Cancer
- **Immunometabolism**

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

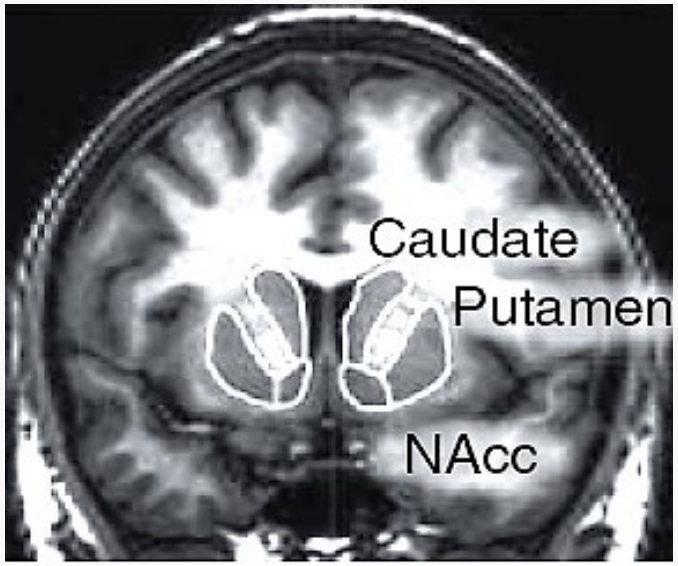
	Percent
Depressive Symptoms	
Depressed mood	60
Anhedonia	30
Suicidal Thoughts	10
Feelings of Guilt	5
Anxious Symptoms	
Tension/Irritability	50
Anxious Mood	45
Fear	15
Cognitive Symptoms	
Loss of Concentration	30
Memory Disturbances	15
Word-finding Problems	15
Episodes of Confusion	10
Indecisiveness	10
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



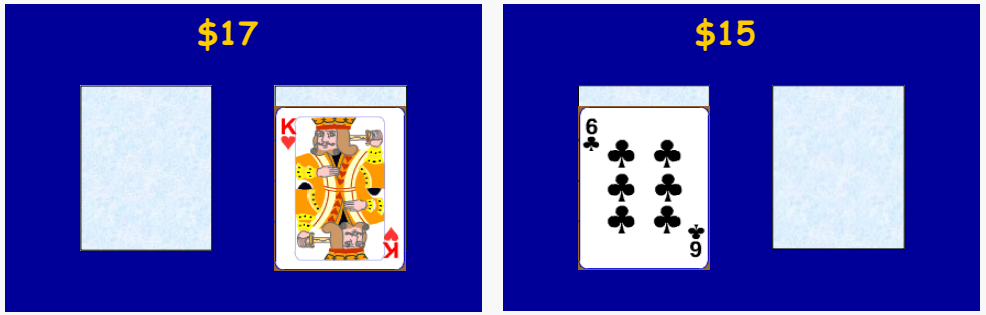
Musselman et al., *NEJM,* 344:961-966, 2001.

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



Coronal View

Gambling Task

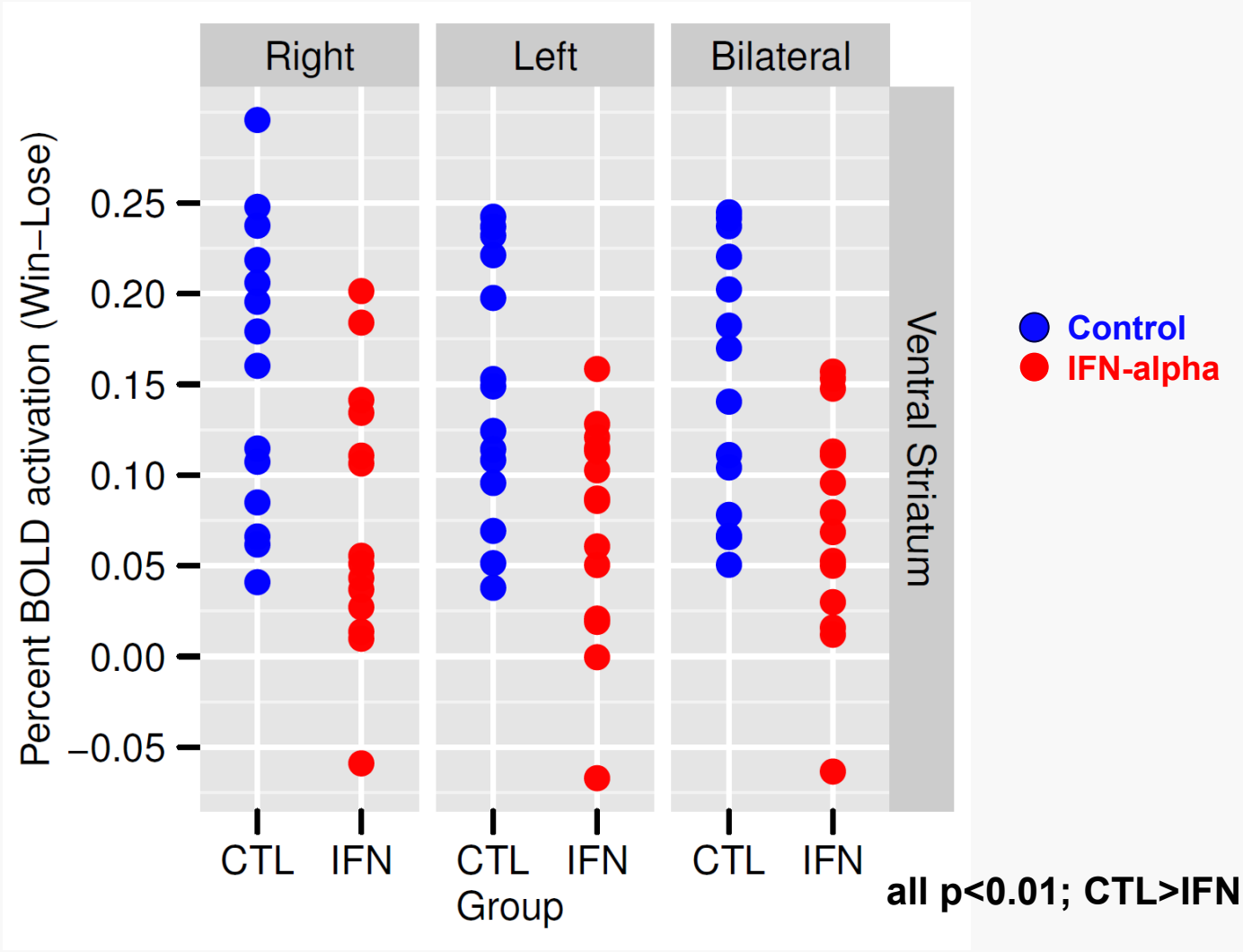


Win

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

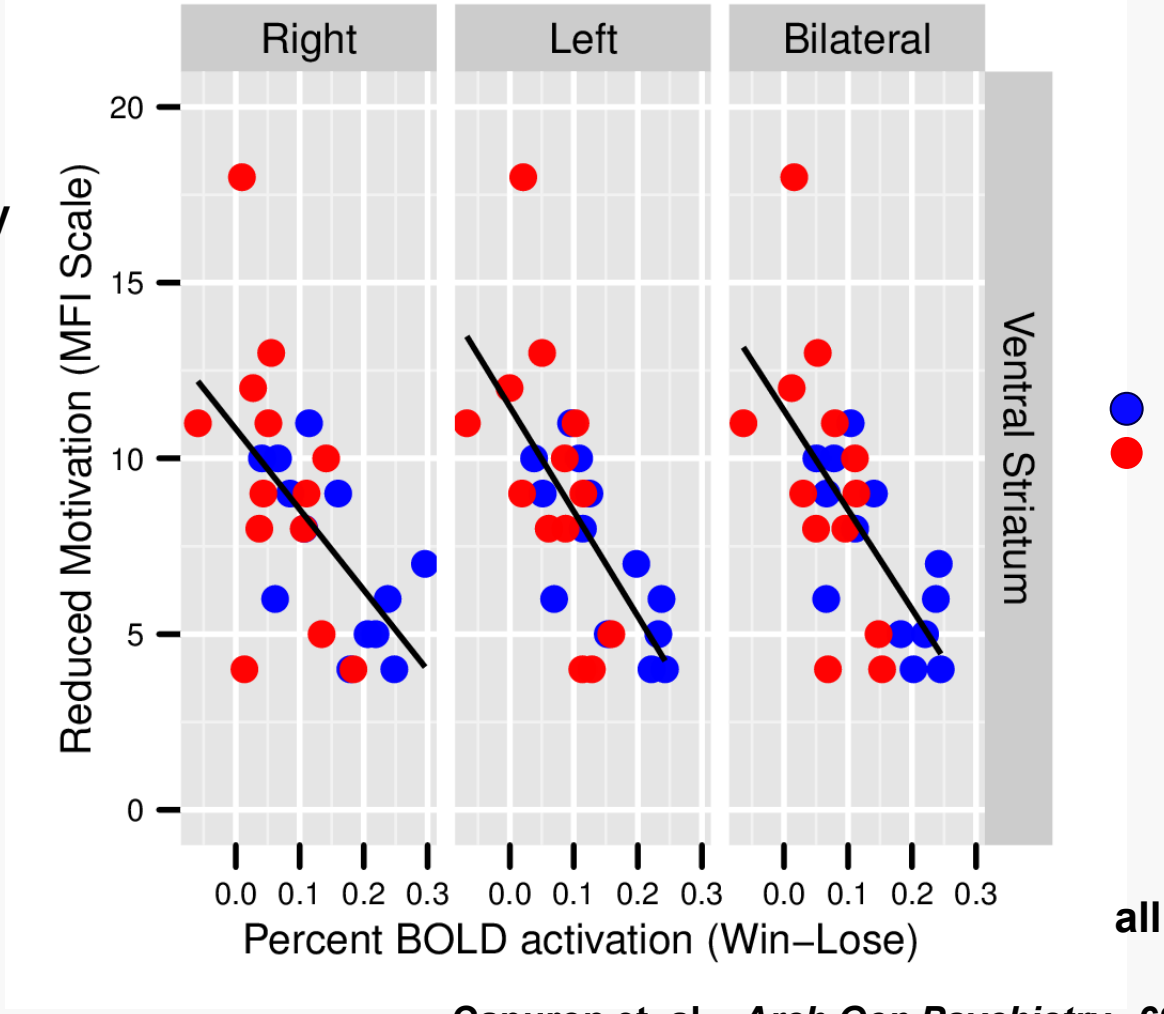


Capuron et al. , *Arch Gen Psychiatry*, 69:1044, 2012

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

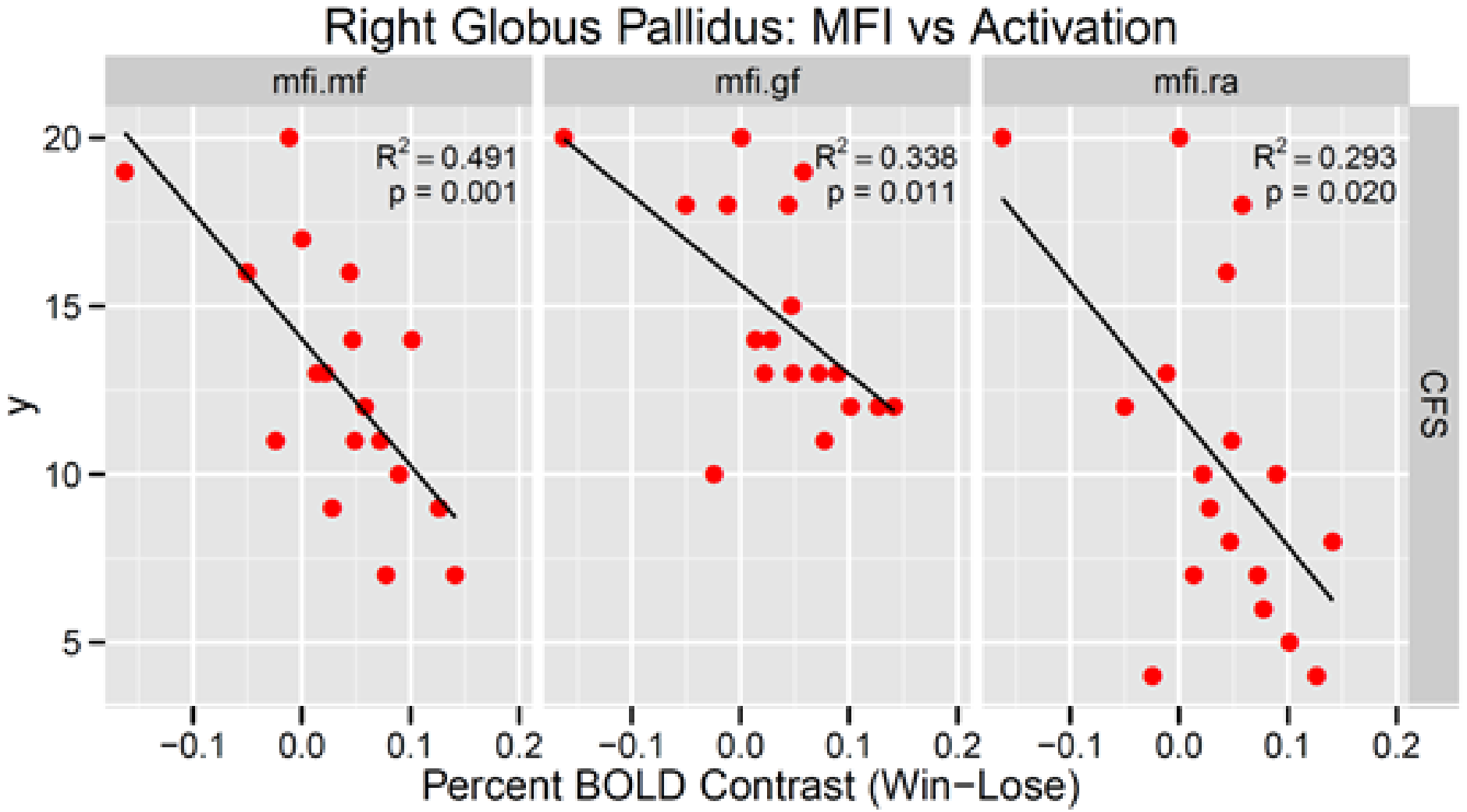


all r>0.6, p<0.001

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)

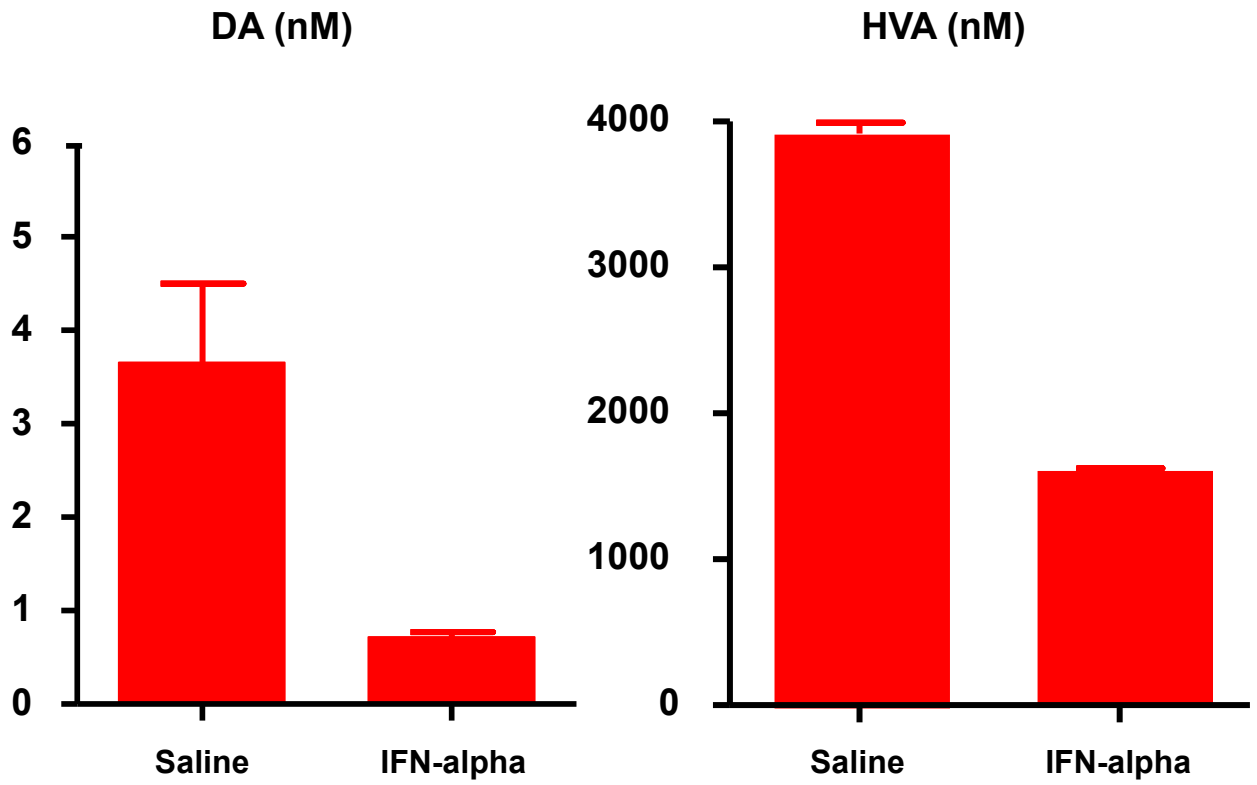
Neural Activation in the Globus Pallidus of Subjects with ME/CFS is Correlated with Symptoms of Fatigue



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

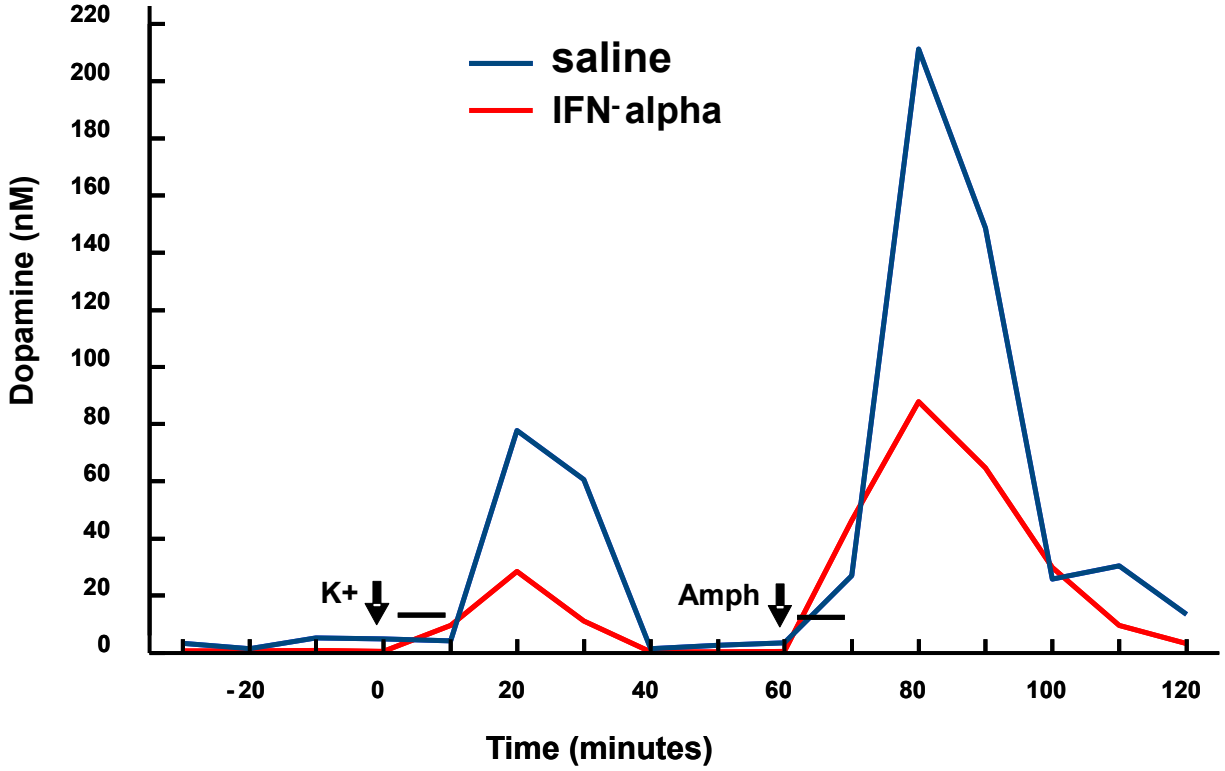
IFN-alpha and Dopamine Release in Striatum as Measured by *In Vivo* Microdialysis in Rhesus Monkeys

Baseline



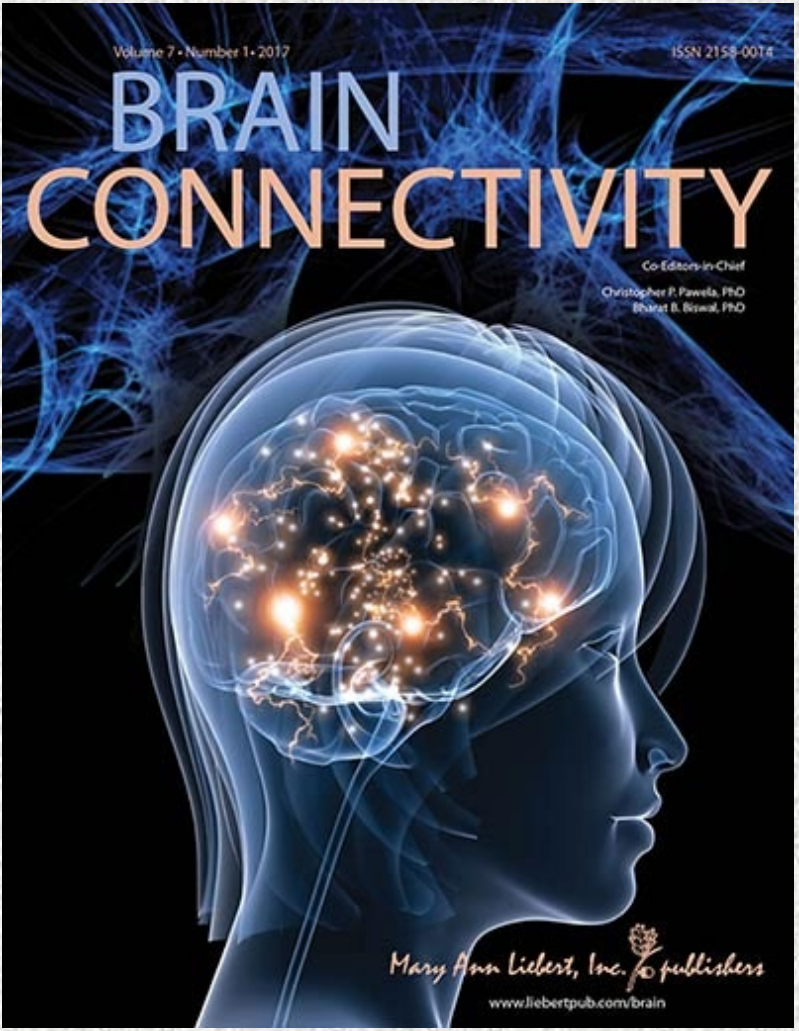
DA-dopamine, HVA-homovanillic acid

Stimulated via Reverse Microdialysis

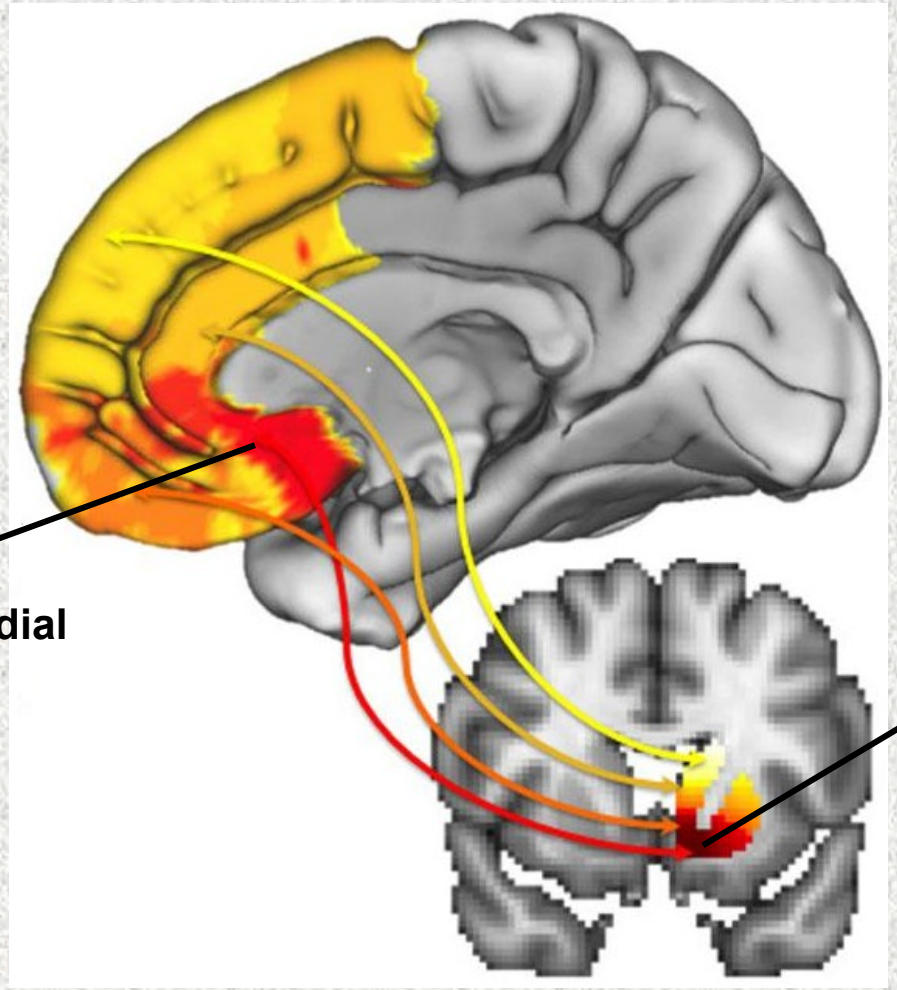


Felger et al. , *Neuropsychopharmacology*, 38:2179-87,2013.

Does Inflammation Disrupt Connectivity In Motivational Circuits in Depression?



Pathways of the Reward Circuit

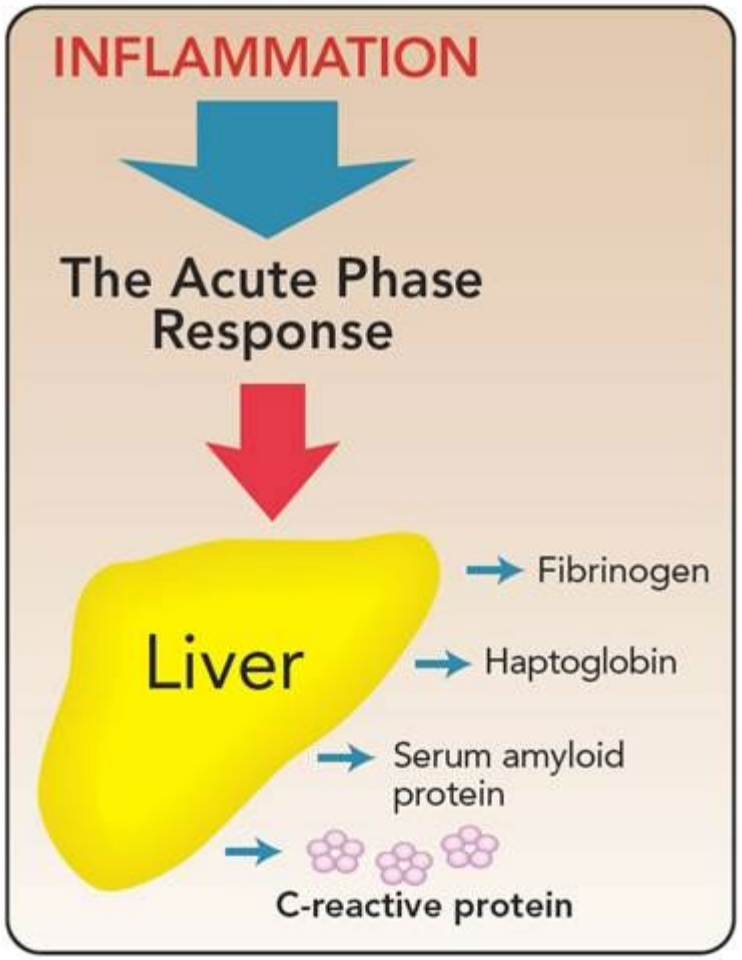


vmPFC - ventromedial prefrontal cortex

VS – ventral striatum

Haber & Knutson, *Neuropsychopharm.*, 2010

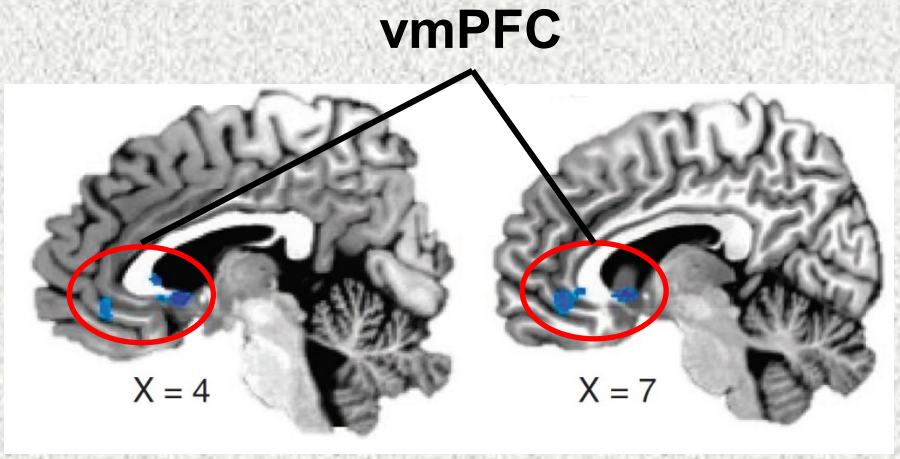
C-reactive protein (CRP) is a Marker of Endogenous Systemic Inflammation

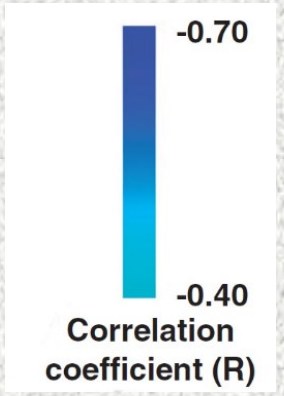


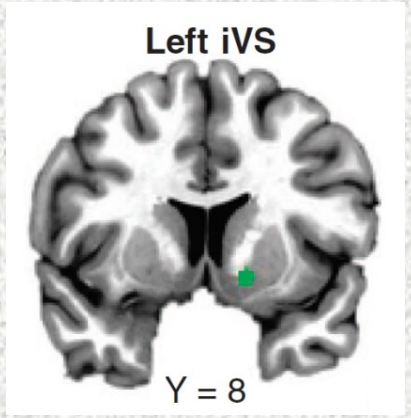
hs-CRP Value	Inflammation*
< 1 mg/L	low
1-3 mg/L	average
> 3 mg/L	high

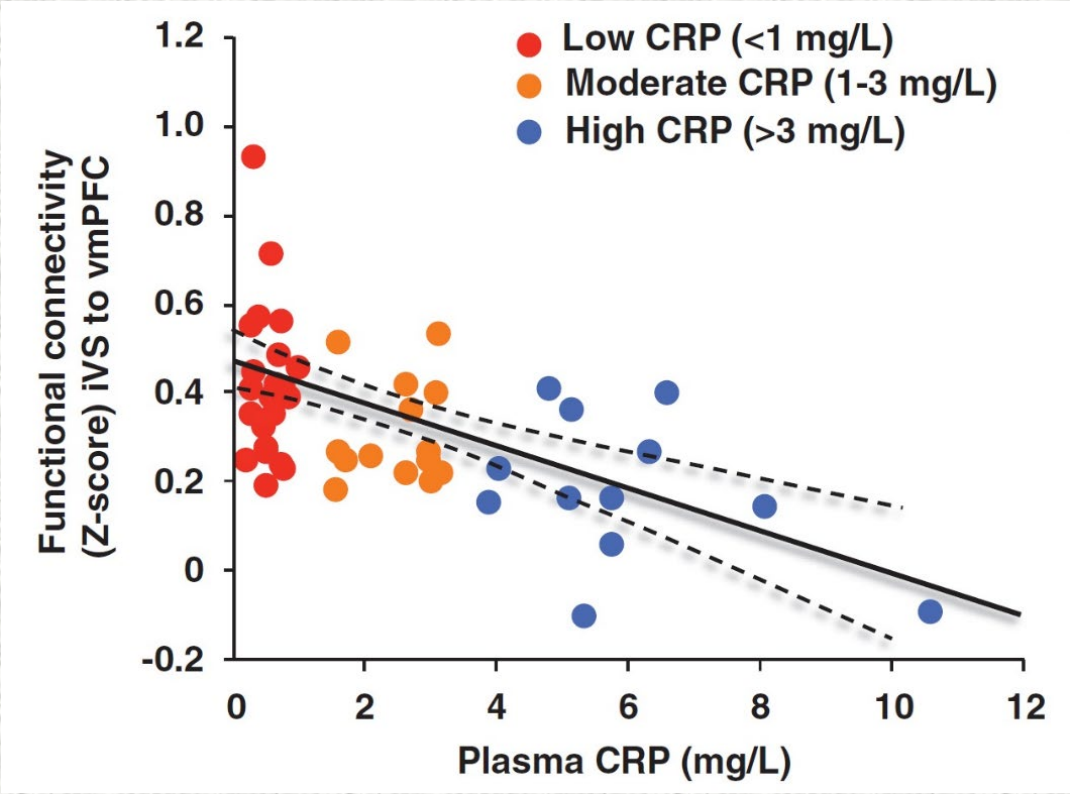
*American Heart Association/ Centers for Disease Prevention and Control (2003)

Inflammation Decreases Functional Connectivity in Reward Circuits during Resting State fMRI





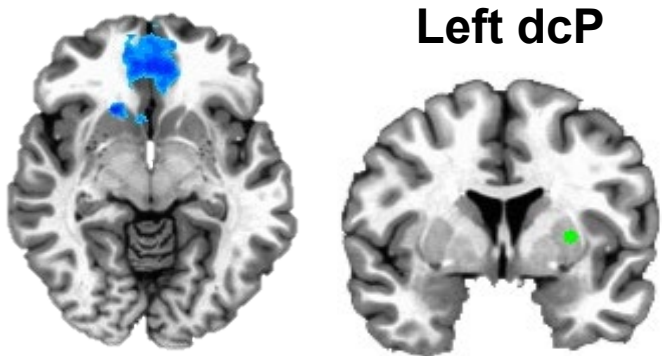




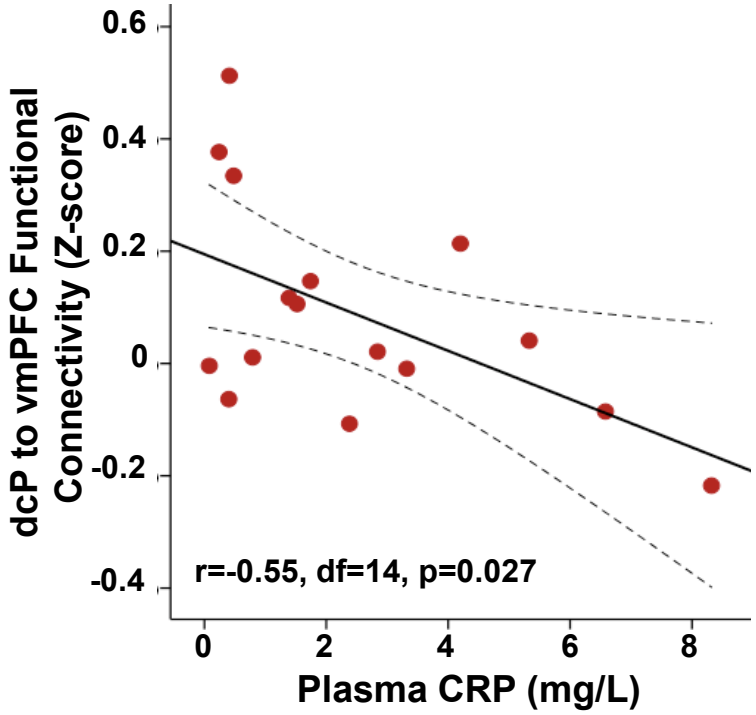
iVS – inferior ventral striatum
vmPFC - ventromedial prefrontal cortex

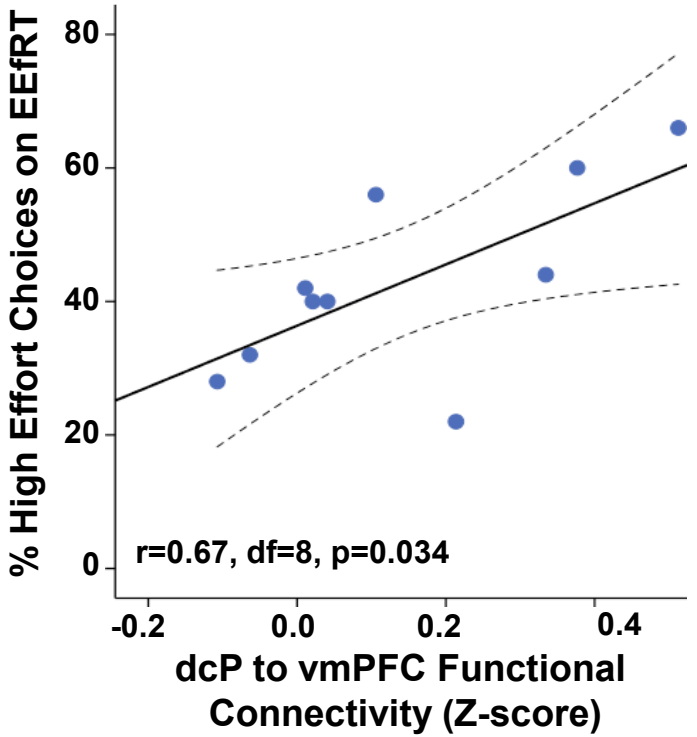
Felger et al., *Molecular Psychiatry*, 21:1358, 2016.

Inflammation is Associated with Decreased Corticostriatal Connectivity and Effort-Based Motivation in Women with Breast Cancer



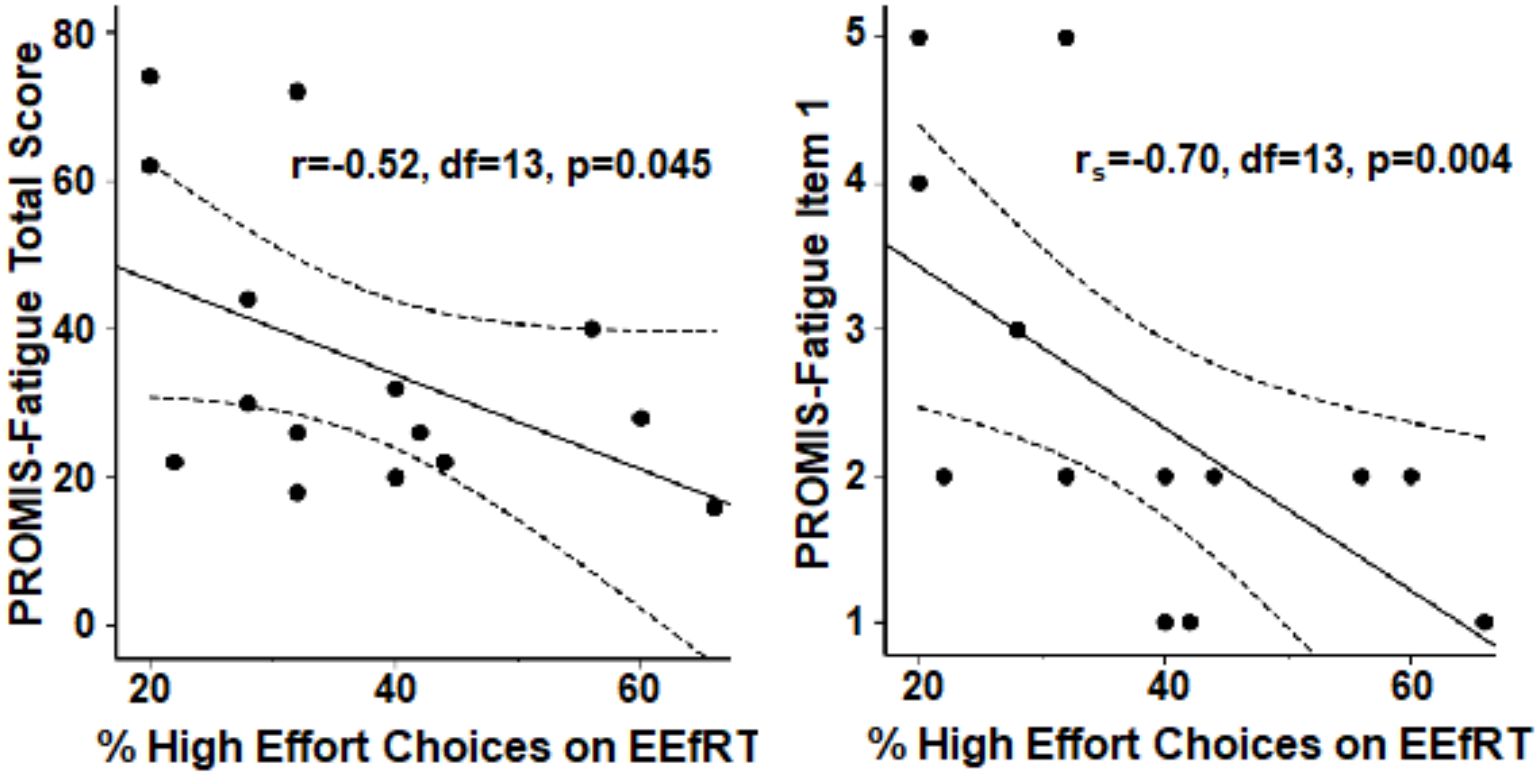
dcP – dorsal caudal putamen
vmPFC - ventromedial prefrontal cortex





EEfRT – Effort Expenditure for Reward Task

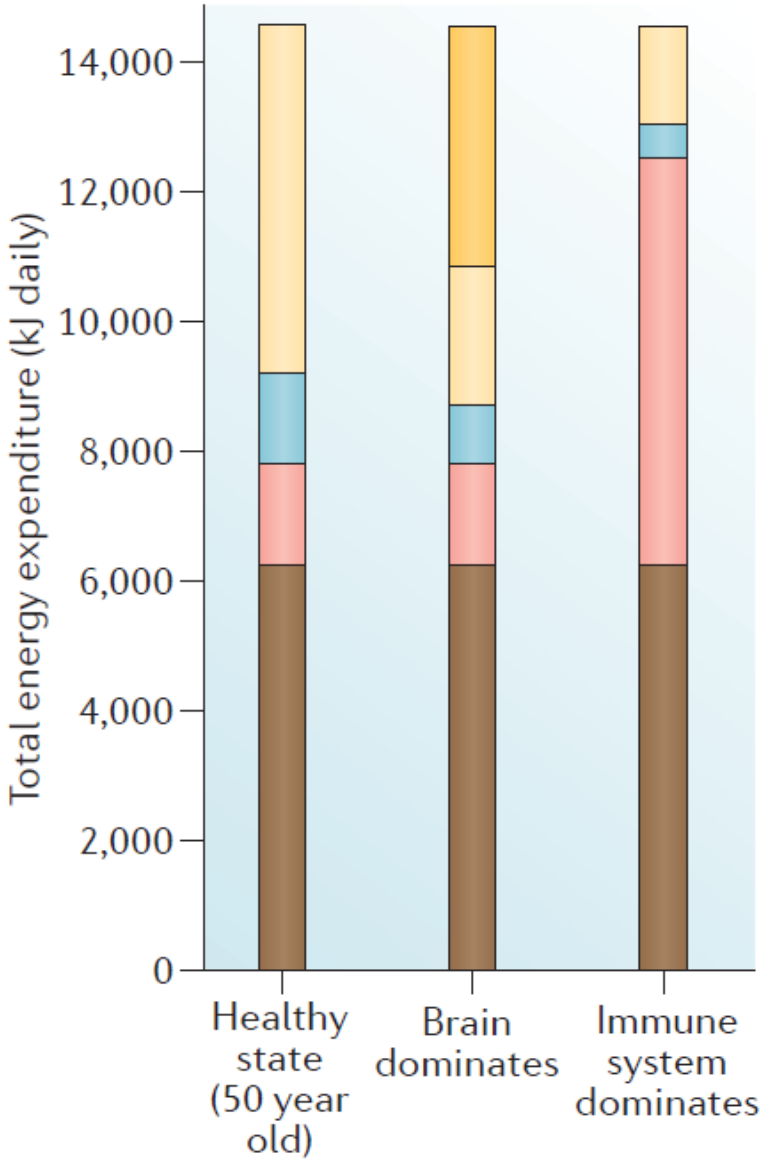
Effort-Based Motivation is Associated with Fatigue in Women with Breast Cancer



EEfRT – Effort Expenditure for Reward Task

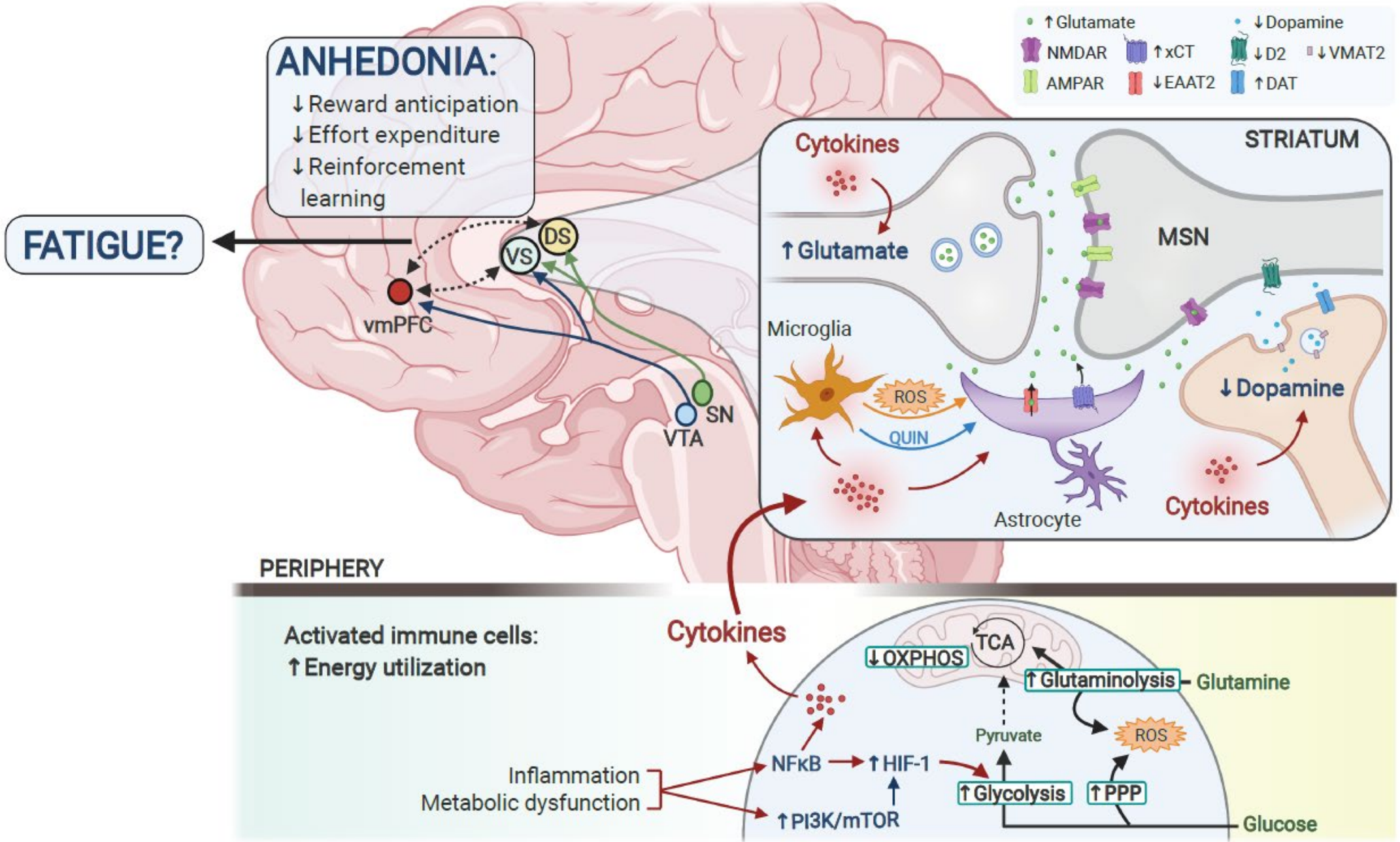
PROMIS-Fatigue Item 1 – “How often did you feel tired” (in the past 7 days)

Inflammation Costs Energy



- Resting metabolic rate
- Food-induced energy expenditure
- Volitional activity-induced energy expenditure
- Non-volitional activity-induced energy expenditure by the brain
- Energy expenditure by the immune system

Straub, Nat Rev Rheumatology, 13:743, 2017



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