INFLAMMATION EFFECTS ON THE BRAIN AND BEHAVIOR: RELEVANCE TO FATIGUE

Andrew H. Miller, M.D.
Department of Psychiatry and Behavioral Sciences
Emory University School of Medicine
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.
Inflammation is Associated with Fatigue

Fatigue and IL-1ra and sTNFR-II

Breast Cancer Survivors


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

FATIGUE?

ANHEDONIA:
- ↓ Effort expenditure
- ↑ Sensitivity to negative stimuli
- ↓ Reinforcement learning

pre-SMA

PSYCHOMOTOR SLOWING:
- ↓ Psychomotor speed

DS

↓ Dopamine:
- ↓ Synthesis
- ↓ Release
- ↑ Reuptake

DS

↑ Glutamate:
- ↑ Release
- ↓ Reuptake
- ↑ Extrasynaptic spillover

SN

VTA

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

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

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

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

Survival Free of Major Depression (%)

Weeks on IFN-alpha


Capuron et al., Neuropsychopharmacology, 26:643-652, 2002
Impact of IFN-alpha on Ventral Striatal Activation during a Hedonic Reward Task Using fMRI

Gambling Task

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

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

Similar Results with Endotoxin and Typhoid Vaccination
Neural Activation in the Globus Pallidus of Subjects with ME/CFS is Correlated with Symptoms of Fatigue

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

**Baseline**

<table>
<thead>
<tr>
<th>DA (nM)</th>
<th>HVA (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>3000</td>
</tr>
<tr>
<td>IFN-alpha</td>
<td>2000</td>
</tr>
</tbody>
</table>

**Stimulated via Reverse Microdialysis**

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

<table>
<thead>
<tr>
<th>hs-CRP Value</th>
<th>Inflammation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 mg/L</td>
<td>low</td>
</tr>
<tr>
<td>1-3 mg/L</td>
<td>average</td>
</tr>
<tr>
<td>&gt; 3 mg/L</td>
<td>high</td>
</tr>
</tbody>
</table>

Inflammation Decreases Functional Connectivity in Reward Circuits during Resting State fMRI

vmPFC

iVS – inferior ventral striatum
vmPFC - ventromedial prefrontal cortex

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

Left dcP

dcP – dorsal caudal putamen
vmPFC - ventromedial prefrontal cortex

\[ r = -0.55, \text{df} = 14, p = 0.027 \]

\[ r = 0.67, \text{df} = 8, p = 0.034 \]

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

Straub, Nat Rev Rheumatology, 13:743, 2017