Conflicts of Interest Disclosure

James N. Baraniuk, M.D.

Enterprises, etc. with which there is a COI relationship to be disclosed pertaining to the topic presentation:

(6) Funds for sponsored/joint research:
- Congressionally Directed Military Research Program, DoD
- National Institutes of Health
- Sergeant Sullivan Center for Post-Deployment Health at Georgetown University

Gulf War Disease
at Georgetown University

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Gulf War Disease

• Gulf War Disease affects the cohort of veterans from the 1990-1991 era

• The cohort had an unique exposure to a combination of agents:
  – Neurotoxic agents including acetylcholinesterase inhibitors such as nerve agents, pyridostigmine bromide and organophosphates ("pesticides"), strychnine (glycine neuron toxin)
  – Vaccines (Engler, 2015)
  – Inhaled and topical oil well fire combustion products
  – Unknown endemic viral and other infections (MERS?)

Patterns of Gulf War Disease

• Gulf War Disease has an acute onset pattern, followed by delayed onset and chronic progressive patterns

• The Gulf War Disease cohort has not had standard longitudinal neurotoxicological and epidemiological examinations for progressive cholinergic, myocardial, pulmonary, gastrointestinal, immune, neurocognitive and other dysfunction related to the most high probability exposures.

• Symptoms have been attributed to undefined (MUPS) somatoform (no medical explanation = psychological) causes

• Symptoms have not been examined as well recognized functional somatic syndromes
Issues Preventing Investigation of GWD

• Contrary to Congressional directives, medical records were either:
  – Destroyed in the Gulf (GulfLink), or
  – Burned in an Atlanta warehouse fire (rumor)

• Data presented to the Institute of Medicine focused on hospitalization rates, psychological illnesses, and does not include sufficiently detailed medical reports to make appropriate medical diagnoses

GWD: Cohort Effects

1980’s Cohort
Service in Persian Gulf regions during Iran-Iraq War with its heavy use of nerve and blistering agents

<table>
<thead>
<tr>
<th></th>
<th>Deployed</th>
<th>Not Deployed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>No Symptoms</td>
<td>?</td>
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</table>

First Gulf War Cohort
All Military personnel with 30 days service between August 1, 1990 to July 31, 1991
- Fukuda criteria Chronic Multisystem Illness

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<thead>
<tr>
<th></th>
<th>Deployed</th>
<th>Not Deployed</th>
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</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>25% to 30%</td>
<td>15%</td>
</tr>
<tr>
<td>No Symptoms</td>
<td>70% to 75%</td>
<td>85%</td>
</tr>
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</table>

Steele Kansas criteria, 2000
Excluded by Steele
Ignored, Lost to follow-up

August 1991 to 2002

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<tr>
<td>No Symptoms</td>
<td>?</td>
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</tr>
</tbody>
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2002 → OEF, OIF
- post-IED TBI
- Pneumonitis, dyspnea
- Burn pits
“It’s all in your head.”

- Chronic Multisymptom Illness (CMI)
- GWD: Gulf War Illness (GWI)
- Fibromyalgia (FM)
- Irritable Bowel Syndrome (IBS)
- Idiopathic Nonallergic Rhinopathy (iNAR)
- Chronic Fatigue Syndrome (CFS)
- Interstitial Cystitis (IC)
- Polymyalgia Rheumatica

- **Somato psycho illnesses?**

- Chronic Multisymptom Illness (CMI)
- GWD: Gulf War Illness (GWI)
- Irritable Bowel Syndrome (IBS)
- Fibromyalgia (FM) (*hyperalgesia, allodynia*)
- Idiopathic Nonallergic Rhinopathy (iNAR)
  - Autonomic neurological dysfunction
- Chronic Fatigue Syndrome (CFS)
  - 60% respond to rituximab → autoimmune?
- Interstitial Cystitis (IC) (↑mast cells on biopsy)
- Polymyalgia Rheumatica (↑sedimentation rate)

- “It’s all in your head, unless there is a biomarker.”
Research Studies of Somato Psycho Illnesses

- GWD: Gulf War Illness (GWI)
- Chronic Multisymptom Illness (CMI)
- Chronic Fatigue Syndrome (CFS)
- Fibromyalgia (FM)

- **AIM**: Define objective mechanisms, definitions, and treatments

- **OUTCOME**: Exercise – induced brain network dysfunction in these Brain System Disease(s)

---

Table 1. Overlap of SUBJECTIVE case designations

<table>
<thead>
<tr>
<th>condition</th>
<th>1990</th>
<th>wide spread pain</th>
<th>manual tenderness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromyalgia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systemic Hyperalgesia and Allodynia</td>
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</tbody>
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Nociceptive, Interoceptive and Fatiguing Illnesses (NIFTI)
Central Sensitization

**Chronic Nociceptive Stimulation** → Glutamate release → AMPA receptor activation

- Loss of Descending Aminergic Antinociceptive System NE, 5-HT

**Hyperalgesia**

**Allodynia**

“Parallel Pain”

Light touch → Burning Pain

Gut brain, Spinal Cord, Thalamus, Other Brain Pain Regulatory Centers

Abdominal pain, Photosensitivity, Phonosensitivity, MCS, Dyspnea
Table 1. Overlap of SUBJECTIVE case designations

<table>
<thead>
<tr>
<th>Fibromyalgia</th>
<th>1990</th>
<th>2010</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>□ fatigue</td>
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<td></td>
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<tr>
<td>□ waking unrefreshed</td>
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<td></td>
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<tr>
<td>□ cognitive symptoms</td>
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<tr>
<td>□ wide spread pain</td>
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<tr>
<td>□ wide spread pain index (WPI)</td>
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<tr>
<td>□ somatic symptoms</td>
<td></td>
<td></td>
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<tr>
<td>□ manual tenderness</td>
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<td></td>
</tr>
<tr>
<td>FM: A REAL DISEASE because there is a drug approved and advertised on TV</td>
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</tbody>
</table>

**Nociceptive, Interoceptive and Fatiguing Illnesses (NIFTI)**

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<td>□ waking unrefreshed</td>
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<td>□ cognitive symptoms</td>
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<tr>
<td>□ wide spread pain index (WPI)</td>
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<tr>
<td>□ somatic symptoms (GI)</td>
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<tr>
<td>□ manual tenderness</td>
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<tr>
<td>Depression</td>
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</tbody>
</table>

**Nociceptive, Interoceptive and Fatiguing Illnesses (NIFTI)**
### Table 1. Overlap of SUBJECTIVE case designations

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<td>□ fatigue</td>
<td>□ fatigue</td>
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<tr>
<td>□ waking</td>
<td>□ fatigue</td>
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<tr>
<td>□ refreshed</td>
<td>□ sleep disturbance</td>
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<tr>
<td>□ cognitive</td>
<td>□ memory or concentration</td>
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<tr>
<td>□ symptoms</td>
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<td>□ wide</td>
<td>□ myalgia</td>
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<td>□ spread</td>
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<td>□ pain</td>
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<td>□ index</td>
<td>□ sore throat</td>
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<td>□ WPI</td>
<td>□ lymph node</td>
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<td>□ somatic</td>
<td>□ headache</td>
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<tr>
<td>□ symptoms</td>
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<tr>
<td>□ GI</td>
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<tr>
<td>□ manual</td>
<td>□ exertional exhaustion</td>
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<tr>
<td>□ tenderness</td>
<td>□ exercise-induced dysfunction</td>
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<tr>
<td>□ depression</td>
<td>Extensive exclusion criteria</td>
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**Nociceptive, Interoceptive and FaTiguing Illnesses (NIFTI)**

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<table>
<thead>
<tr>
<th>Fibromyalgia</th>
<th>Systemic Exertion Intolerance Disease (SEID)</th>
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<tr>
<td>□ fatigue</td>
<td>□ fatigue</td>
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<tr>
<td>□ waking</td>
<td>□ fatigue</td>
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<td></td>
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<tr>
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<td>□ autonomic intolerance</td>
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</tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue + 4 / 8</td>
<td>“severe” in 2 or 3 categories;</td>
</tr>
<tr>
<td></td>
<td>Fukuda 1994</td>
<td>Fukuda 1998</td>
</tr>
</tbody>
</table>

- □ fatigue
- □ waking unrefreshed
- □ cognitive symptoms
- □ wide spread pain
- □ wide spread pain index (WPI)
- □ somatic symptoms
- □ manual tenderness
- □ exertional exhaustion
- □ exercise-induced dysfunction

Exposures of 1990-1991

- □ depression

Extensive exclusion criteria

Nociceptive, Interoceptive and Fatiguing Illnesses (NIFTI)
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<td>□ mood / cognition</td>
<td>□ attention networks</td>
</tr>
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<td>□ cognitive symptoms</td>
<td>□ memory or concentration</td>
<td>□ cognitive / anxiety</td>
<td>□ working memory</td>
</tr>
<tr>
<td>□ wide spread pain</td>
<td>□ myalgia</td>
<td>□ myalgia / arthralgia</td>
<td>□ sleep</td>
</tr>
<tr>
<td>□ manual tenderness</td>
<td>□ myalgia</td>
<td>□ arthralgia</td>
<td>□ depressive / moody</td>
</tr>
<tr>
<td>□ depression</td>
<td>□ myalgia / arthralgia</td>
<td>□ arthralgia</td>
<td>□ affect / anxiety</td>
</tr>
<tr>
<td></td>
<td>□ myalgia / arthralgia</td>
<td>□ arthralgia</td>
<td>□ noiceptive, interoceptive &amp; somatosensory central sensitization</td>
</tr>
<tr>
<td></td>
<td>□ myalgia / arthralgia</td>
<td>□ arthralgia</td>
<td>□ migraine</td>
</tr>
<tr>
<td></td>
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<td>□ arthralgia</td>
<td>□ exertional exhaustion exercise-induced dysfunction</td>
</tr>
<tr>
<td></td>
<td>□ systemic hyperalgesia</td>
<td>□ exertional exhaustion exercise-induced dysfunction</td>
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Nociceptive, Interoceptive and FaTiguing Illnesses (NIFTI)

Table 1. Overlap of SUBJECTIVE case designations → OBJECTIVE Mechanisms?

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Nociceptive, Interoceptive and FaTiguing Illnesses (NIFTI)
1. Cortical spreading depression (CSD) depolarizes cortical neurons and glia.
2. They release glutamate, K+, H+, metalloproteases and other agents that dilate cortical and pial vessels, and activate trigeminal nociceptive nerves.
3. The bifurcated neurons release calcitonin gene related peptide (CGRP) and other vasodilators near dural vessels by the axon response mechanism. Vascular wall stretching activates additional trigeminal nociceptive neurons (4.) that have their primary synapse (5.) in the upper cervical dorsal horn.
4. Ascending secondary afferents activate the thalamus.
5. Other afferents signal periaqueductal gray matter.
6. Descending relays to the magnus raphae nucleus activate descending serotonergic neurons to inhibit the primary trigeminal synapses (5. & 6.).
7. Thalamocortical projections stimulate the hypothalamus, somatosensory cortex, amygdala, Limbic system, and frontal cortex.
8. Pain, emotion, memory, frontal processing and other inputs converge on the anterior cingulate gyrus (ACC) and interfere with its executive decision making functions. Chronic CSD-like depolarization in GWI may promote central sensitization and progressive dysfunction of ACC and other neuroanatomical loci. “Neural plasticity” may reinforce conditioned memories and contribute to anxiety, fear, and posttraumatic stress disorder (PTSD); fatigue; pain, hyperalgesia and allodynia; autonomic, sleep, and cognitive dysfunction (“brain fog”). Neurovascular dysfunction may cause white matter (prevalence 16%-40%; OR=3.9, 95% CI 2.26-6.72) and grey matter abnormalities that accentuate the disabilities and promote illness chronicity.

Migraine Mechanisms

1. Cortical spreading depression (CSD) depolarizes cortical neurons and glia.
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GWI, CMI, CFS, SEID, ME, FM . . .

- Are these the same disease with overlapping symptom phenotypes?
- or
- Different pathophysiological processes leading to a similar final common pathway?
- or
- Are they somato-psycho delusional states?

Exercise in CFS & GWI Studies

**MITOCHONDRIAL DYSFUNCTION HYPOTHESIS:**

Submaximal exercise on DAY 1 → good muscle function

BUT Exercise on DAY 2 → bad muscle function
GWI and Healthy Veterans have identical responses to maximal exercise

**VO₂ vs HR**

**VCO₂ vs HR**

---

**Exercise in CFS & GWI Studies**

**MITOCHONDRIAL DYSFUNCTION HYPOTHESIS:**

Submaximal exercise on **DAY 1** → good muscle function

**BUT** Exercise on **DAY 2** → bad muscle function

Hypothesis Not Verified  
Exercise reproducible between **DAY 1** and **DAY 2**
Magnetic Resonance Imaging
Before and After Exercise

- Voxel based morphometry (VBM) for anatomy
- Molecular spectroscopy for [analytes]
- Diffusion tensor imaging (DTI) for white matter
- Blood oxygenation level dependent (BOLD) signal for regional blood flow
- Pulsed arterial spin labeling (pASL) for global blood flow

DTI: White matter dysfunction in rIFOF of GWI

- rMiddle Frontal Gyrus = VAN
  Ventral Attention Network
- rOrbitalfrontal cortex = Fatigue & Valuation of experiences
- Anterior Insula
  Perceptions of nociception, interoception and link to sympathetic nervous system
- Temporal Parietal Junction of VAN
  Ventral Attention Network
  sensory data integration → rIFOF → Anterior

Representative transverse slice of brain

SIGNIFICANCE as BIOMARKER?
Axial diffusivity distinguished GWI from controls
Two GWI Phenotypes Discriminated by Exercise Responses

After exercise → Orthostatic Tachycardia
Diastolic Hypertension

START (Stress Test Activated Reversible Tachycardia)
average ΔHR = 20.5 [18.3 to 22.7; 95%CI]

STOPP (Stress Test Originated Phantom Perception) plus Sedentary Control subjects →
average ΔHR = 11.7 [10.1 to 13.3]

Exercise – Induced Autonomic Dysfunction

Rayhan 2013: Brainstem volume loss in superior cerebellar peduncle, pons and medulla in GWI

GWI + CFS

MRI-Exercise-Exercise-MRI protocol

START: Stress Test Activated Reversible Tachycardia
- Postural tachycardia after exercise (none at rest)
- Brainstem atrophy
- Exercise-induced BOLD signal changes

STOPP: Stress Test Originated Phantom Perception
- Basal ganglia and insula activation
Introducing a New Major Concept in Brain Function

Mind the Gap
from past information

**Resting State Brain Networks**

- Specific regions of the brain work together to complete tasks and do the brain’s work
  - Visual system
  - Somatosensory and motor systems (pre- & post-central gyrus)

- → The brain is working in an organized fashion while you day dream (“mind wander”)

- Different regions of the brain communicate with each other while a person was resting
  - Like a “rehearsal” or “de-briefing”

- During a task, these same regions were activated to perform the task efficiently (BOLD signal)

- The correlation between regions that are activated at the same time or in synchrony is termed **Functional Connectivity**
Resting State Brain Networks & Functional Connectivity

Four functional networks
- **visual** (yellow) (occipital lobes),
- **sensory/motor** (orange) (pre-and post-central gyri),
- **basal ganglia** (red) (deep brain),
- **default mode network** (DMN) (maroon) (posterior cingulate, inferior parietal lobes, and medial frontal gyrus).

Regions within a network coordinate their electrical activity during tasks and at rest:

**Resting State Networks (RSN)**

BrainMap and ICA Statistical Networks

- Consortia have compiled atlases of resting state networks (RSNs).
- Regions in red/yellow act in concert to control and perform tasks.
  - ICN 1 (limbic and medial-temporal areas)
  - ICN 2 (subgenual ACC and OFC)
  - ICN 3 (bilateral BG and thalamus)
  - ICN 4 (bilateral anterior insula/frontal opercula, anterior body of the cingulate gyrus)
  - ICN 5 (midbrain)
  - ICN 6 (superior and middle frontal gyri)
  - ICN 7 (middle frontal gyri and superior parietal lobules)
  - ICN 8 (ventral precentral gyri, central sulci, postcentral gyri, superior and inferior cerebellum)
  - ICN 9 (superior parietal lobule)
  - ICN 10 (middle and inferior temporal gyri)
  - ICNs 11 and 12 (lateral and medial posterior occipital cortices)
  - ICN 13 (medial prefrontal and posterior cingulate/precuneus areas)
  - ICN 14 (cerebellum)
  - ICN 15 (right-lateralized fronto-parietal regions)
  - ICN 16 (transverse temporal gyrri)
  - ICN 17 (dorsal precentral gyrri, central sulci, postcentral gyrri, superior and inferior cerebellum)
  - ICN 18 (left-lateralized fronto-parietal regions)
  - ICN 19 & 20 (artifacts)

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BrainMap and Statistical Networks

- Published data is compiled (~1/3rd of the functional connectivity literature).
- Independent component analysis (ICA) and other methods are applied to the hundreds of thousands of individual datasets.
- The original 10 networks have been expanded to 70 here, and 300 in pioneering analysis.
- There is no standard set of RSNs so there are several in the literature. This makes comparisons of anatomical regions and specific functions difficult.
- Young healthy individuals are overrepresented.
- Networks from disease states are underrepresented.
- Identifying these components in your BOLD data is a statistical tour-de-force.
- Patterns of RSNs may be indicative of specific diseases.

3 Key Networks

• Salience Network
  – “What’s the buzz? Tell me what’s a’happening?”
  – External and internal (interoceptive) inputs via spinal cord, cranial nerves and brainstem through thalamus to association areas with conscious perception in the anterior insula

• Executive Control Network
  – Dorsolateral prefrontal cortex (DLPFC) ↔ Inferior Parietal Lobe
  – Working memory, focus on task completion
3 Key Networks

- Salience Network
- Executive Control Network
- Default Mode Network (DMN)
  - Midline anterior and posterior brain cortex
  - Activated when there are no active externally – oriented tasks
  - Activated for internally – oriented tasks such as introspection, planning, “mind wandering”
  - Turned off (“de-activated”) when external tasks are performed

N-Back Working Memory Task

- 0-back task
  - See a series of letters
  - Push a button as you see each letter
  - Stimulus – response task
  - Low cognitive load
- 2-back task
  - See a series of letters
  - Remember the letter seen 2 previously (2-back)
  - Push the button for the letter seen 2-back
  - High cognitive load
- Use BOLD to determine the brain regions activated in each task
Sedentary Control (SC)

0-back: stimulus matching

2-back: R&L DLPFC and Parietal lobes
GWI STOPP need more regions on DAY 1 for 0-back & 2-back

GWI STOPP need more regions on DAY 1 for 0-back & 2-back

GWI STOPP still need more regions on DAY 2 for 0-back & 2-back
What brain regions are “connected” or acting together?

**Functional Connectivity**

- Grey matter in region A ➔
- ➔ Axons in white matter ➔
- ➔ Activate grey matter in region B

- Neurons in region A activate astrocytes that cause vasodilation and increase the BOLD signal ➔
- ➔ Axons in white matter ➔
- ➔ Activate neurons in region B that activate astrocytes to cause vasodilation and increase the BOLD signal
Functional Connectivity

Functional parcellation of the brain into 90 regions of interest (ROIs) that cover the majority of cortical and subcortical gray matter.


Exercise Effects on Effective Connectivity Between Brain Regions During 2-back Task (high cognitive load)

Sedentary Controls
Exercise Decreases z-Score
D1>D2=0

These regions were connected on DAY 1 before exercise, but were no longer required on DAY 2 after exercise.
**Exercise Effects on Effective Connectivity Between Brain Regions During 2-back Task (high cognitive load)**

### Sedentary Controls
- Exercise Decreases z-Score
  - D1>D2=0
  - DMN4 Prec2
  - Sal1 ECN4

  These regions were connected on DAY 1 before exercise, but were no longer required on DAY 2 after exercise.

### STOPP
- Exercise Increases z (D2>D1)
  - DAN1 Sal6
  - DAN3 Sal7

  DAN and Salience

- Exercise Decreases z (D1>D2)
  - Sal6 BG2
  - Prec2 ECN2
  - Prec2 ECN6

  Cerebellum: decreased connectivity with DMN, Salience, Executive Control

### Exercise Effects on Effective Connectivity Between Brain Regions During 2-back Task (high cognitive load)

### Sedentary Controls
- Exercise Decreases z-Score
  - D1>D2=0
  - DMN4 Prec2
  - Sal1 ECN4

### STOPP
- Exercise Increases z (D2>D1)
  - DAN1 Sal6
  - DAN3 Sal7

  DAN and Salience

- Exercise Decreases z (D1>D2)
  - Sal6 BG2
  - Prec2 ECN2
  - Prec2 ECN6

  Cerebellum: decreased connectivity with DMN, Salience, Executive Control

### START
- Exercise Increases z-Scores (D2>D1)
  - Prec4 ECN1
  - DMN4 Prec2
  - Sal6 BG7

  Increased connections within Default Mode Network (DMN) / Precuneus, and with Salience and Executive Control

- Exercise Decreases z (D1>D2) for DAN, Salience, Basal Ganglia and Cerebellum
### OBJECTIVE Mechanisms

<table>
<thead>
<tr>
<th>GWI, CMI, CFS, SEID, FM Shared Features</th>
<th>Brain Network Interactions and Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ nociceptive, interoceptive &amp; somatosensory central sensitization</td>
<td><strong>Salience network</strong>: anterior insula (perception, consciousness) → dorsal anterior cingulate cortex (dACC, executive decision making) → thalamus (sensory transmission hub) → insula</td>
</tr>
<tr>
<td>□ systemic hyperalgesia □ migraine</td>
<td>Spinal cord dorsal horn and <strong>central sensitization</strong>, neural plasticity, glutamate-mediated</td>
</tr>
</tbody>
</table>
| □ attention networks □ working memory | **Dorsal attention network** (DAN) concentration on task  
**Frontoparietal control network**: dorsolateral prefrontal cortex for attention, inferior parietal to store working memory  
**Ventral attention network** (VAN) background surveillance  
**Salience network** |
| □ exertional exhaustion exercis-induced dysfunction | Complex interactions leading to cognitive and attentional dysfunction, autonomic dysfunction  
**Default mode network** (DMN) intrusions ("mind wandering", day dreaming, rehearsal) |
| □ fatigue □ affect / anxiety □ sleep | **Orbitofrontal cortex** for valuation, motivation, “fatigue”  
**Amygdala** (fear, avoidance, limbic system)  
Brainstem, **periaqueductal grey**, hypothalamus |

---

**Objective MRI measures as study outcomes**

**Depression involves dysfunction of amygdala – ventral prefrontal cortex connections (arrows)**

**Successful coping in Depression can be distinguished from Anxiety and Control status by MRI testing.**

![Correlation Between Postcongruent Incongruent Trial Minus Postcongruent Incongruent Trial Reaction Time Difference Scores and Brain Activation for the Same Contrast](image)

> *Brain activation is displayed with whole-brain correction for the false discovery rate (p<0.05). In panel A, positive correlations in the ventral cingulate and negative correlations in the amygdala (arrows) suggest a greater deficit in these regions when depressive-only patients show better reaction time adaptation. In panel B, negative correlations in the anterior lateral prefrontal cortex suggest regulation-related recruitment of this region with improved adaptation. For reaction time difference scores, more negative indicates more adaptation. Panel C (i.e. postcongruent incongruent trial vs. postcongruent incongruent trial) illustrates activity for the left anterior middle frontal gyrus cluster (arrows in panel B) extracted for the 0 vs. 1 contrast for each group, as well as separately for the 0 and 1 trials (see inset for the depression-only group). This cluster is activated only in the depression-only group, and this is driven by increased activity in 1 trials. The figure shows that engagement of compensatory activations in the anterior lateral prefrontal cortices in the depression-only group is associated with successful adaptation to emotional conflict in this group.*
Gulf War Disease I

- Gulf War Veterans had a neurotoxic exposure.
- The cohort has not been followed or compared to other cohorts in an appropriate fashion.
- “It’s all in your head” is not an appropriate diagnostic or treatment philosophy.
- Diagnostic criteria for allied conditions have evolved over time.
- GWD has stagnated for 25 years.
- Central sensitization, neural plasticity, and other mechanisms of disease can now explain facets of GWD, migraine, and co-morbid conditions.
- Submaximal exercise studies indicate reproducible effort on DAYS 1 and 2.
- Exercise causes distinct patterns of change in brain function in START and STOPP phenotypes.

Gulf War Disease II

- Exercise causes distinct patterns of change in brain function in START and STOPP phenotypes.
- STOPP have cognitive compensation by activating the basal ganglia and anterior insula of the salience network to perform the 2-back task.
- START have maximal cognitive compensation at rest and cannot recruit additional cognitive reserve regions when doing a task.
- Exercise causes significant changes in functional connectivity between brain regions in GWD.
- STOPP: Exercise increases connectivity between DAN and Salience, but decreases coordination of all systems by the cerebellum.
- START: Exercise activates the DMN (Default Mode Intrusion) but inactivates coordination of cerebellum, salience and executive control networks after exercise.
- MRI provides an objective measure of GWD dysfunction.
Now Recruiting to repeat this GWI Study

GW140064

IRB 2015-0579

baraniuklab@gmail.com
### CFS Severity Score

<table>
<thead>
<tr>
<th><strong>Fatigue plus 4 of 8:</strong></th>
<th><strong>Severity Scale</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Myalgia</td>
<td>• 0=absent</td>
</tr>
<tr>
<td>• Arthralgia</td>
<td>• 1=present</td>
</tr>
<tr>
<td>• Sore throat</td>
<td>• Fatigue + 4 of 8</td>
</tr>
<tr>
<td>• Lymph nodes</td>
<td></td>
</tr>
<tr>
<td>• Headache (migraine)</td>
<td></td>
</tr>
<tr>
<td>• Cognition (concentration and memory)</td>
<td></td>
</tr>
<tr>
<td>• Sleep</td>
<td></td>
</tr>
<tr>
<td>• Exertional exhaustion</td>
<td></td>
</tr>
</tbody>
</table>

### CFS Criteria with Fatigue

<table>
<thead>
<tr>
<th><strong>CFS Criteria with Fatigue</strong></th>
<th><strong>Severity Scale</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Myalgia</td>
<td>• 0=none</td>
</tr>
<tr>
<td>• Arthralgia</td>
<td>• 1=trivial</td>
</tr>
<tr>
<td>• Sore throat</td>
<td>• 2=mild</td>
</tr>
<tr>
<td>• Lymph nodes</td>
<td>• 3=moderate</td>
</tr>
<tr>
<td>• Headache (migraine)</td>
<td>• 4=severe</td>
</tr>
<tr>
<td>• Cognition (concentration and memory)</td>
<td></td>
</tr>
<tr>
<td>• Sleep</td>
<td></td>
</tr>
<tr>
<td>• Exertional exhaustion</td>
<td></td>
</tr>
<tr>
<td>• <strong>Sum of 8 ancillary symptoms</strong></td>
<td>• Sum_8 (Σ8) 0 to 32</td>
</tr>
</tbody>
</table>
CFS Severity Score: 4 Quadrants
Fatigue (3,4) vs. Sum of 8 (≥14)

% per group

Sum of 8
- Myalgia
- Arthralgia
- Sore throat
- Lymph nodes
- Headache (migraine)
- Cognition
- Sleep
- Exertional exhaustion

N ~ 300 CFS
N ~ 300 controls

Fatigue = 3,4 for CFS, CIF
CFS Severity Score: 4 Quadrants
Fatigue (3,4) vs. Sum of 8 (≥14)

% per group

Fatigue 3,4 for CFS,CIF

N ~ 300 CFS

N ~ 300 controls

CFS Severity Score: 4 Quadrants
Fatigue (3,4) vs. Sum of 8 (≥14)

% per group

Fatigue 3,4 for CFS,CIF

N ~ 300 CFS

N ~ 300 controls

Appendix A
Presentation 2 – James Baraniuk
CFS Severity Score: 4 Quadrants

Fatigue (3,4) vs. Sum of 8 (≥14)

% per group

Fatigue 3,4 for CFS, CIF

Control

N ~ 300 CFS

N ~ 300 controls

CIF=Chronic Idiopathic Fatigue

Fatigue = 3,4 for CFS, CIF

CFS Severity Score: 4 Quadrants

Fatigue (3,4) vs. Sum of 8 (≥14)

% per group

Fatigue 3,4 for CFS, CIF

Control

N ~ 300 CFS

N ~ 300 controls

CIF=Chronic Idiopathic Fatigue

Fatigue = 3,4 for CFS, CIF
CFS Severity Score: 4 Quadrants
Fatigue (3,4) vs. Sum of 8 (≥14)

GWI and CFS have the same patterns of scores
Proteomics of Cerebrospinal Fluid Clustered by CFS Q

A. Proteomics

Random Arrangement of Subjects

Appendix A
Presentation 2 – James Baraniuk
### Chronic Multisymptom Illness (CMI) ≥ 2 categories

#### “Kansas” GWI Definition

<table>
<thead>
<tr>
<th>Fatigue</th>
<th>Fatigue / Sleep</th>
<th>Fatigue</th>
<th>Fatigue or Loss of Energy</th>
<th>Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood / Cognition</td>
<td>Cognitive</td>
<td>Mood / Sleep</td>
<td>Cognitive Symptoms</td>
<td>Memory or Concentration</td>
</tr>
<tr>
<td>Mood / Cognition</td>
<td>Depressive</td>
<td>Mood / Sleep</td>
<td>Waking Unrefreshed</td>
<td></td>
</tr>
<tr>
<td>Mood / Cognition</td>
<td>Neurological / Mood</td>
<td>Mood / Sleep</td>
<td>Memory or Concentration</td>
<td>Memory &amp; Concentration</td>
</tr>
<tr>
<td>Myalgia / Arthralgia</td>
<td>Myalgia</td>
<td>Arthralgia</td>
<td>Widespread Pain Index (WPI)</td>
<td></td>
</tr>
<tr>
<td>Myalgia / Arthralgia</td>
<td>Myalgia</td>
<td>Arthralgia</td>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>Myalgia / Arthralgia</td>
<td>Myalgia</td>
<td>Arthralgia</td>
<td>Somatic Symptoms</td>
<td></td>
</tr>
<tr>
<td>Myalgia / Arthralgia</td>
<td>Myalgia</td>
<td>Arthralgia</td>
<td>Sore Throat</td>
<td></td>
</tr>
<tr>
<td>Myalgia / Arthralgia</td>
<td>Myalgia</td>
<td>Arthralgia</td>
<td>Lymph Node</td>
<td></td>
</tr>
<tr>
<td>Myalgia / Arthralgia</td>
<td>Myalgia</td>
<td>Arthralgia</td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Extensive Exclusion Criteria</td>
<td>Tenderness to Pressure</td>
<td>Systemic Hyperalgesia</td>
<td>Exertional Exhaustion</td>
<td>Exertional Exhaustion</td>
</tr>
</tbody>
</table>

#### Common Features

- Fatigue
- Fatigue / Sleep
- Fatigue or Loss of Energy
- Mood
- Myalgia / Arthralgia
- Pain
- Widespread Pain Index (WPI)
- Sore Throat
- Lymph Node
- Headache
- Systemic Hyperalgesia
- Exertional Exhaustion

#### Extensive Exclusion Criteria

- Pregnancy, depression, HIV, chronic viral, autoimmune, neoplastic or medical disease.
- * Significant loss of weight or appetite
- * Anhedonia
- * Psychomotor agitation or retardation
- * Feelings of worthlessness or excessive or inappropriate guilt
- * Recurrent thoughts of death

---

### Unsupervised Hierarchical Clustering of CFS Q Results

#### Severity Scores

- Fatigue
- Sleep
- HA
- Cog
- ExEx
- Myal
- Arth
- SThr
- LN

#### Severity Levels

- A<10
- B<10
- C<10
- A<10
- B<10
- C<10
- A<0.01
- B<0.01
- C<0.01

---

### Graphs

- Graph A: Severity scores for CFS Q results
- Graph B: Severity scores for HC-Q results

---

**Appendix A**

Presentation 2 – James Baraniuk
Working Memory Task

0 - back test

Do what the slide shows:

LEFT = Hold up your left hand,
RIGHT = Hold up your right hand, or,
CROSS = Cross your arms on your chest

Working Memory Task

0 - back test

Do what the slide shows:

LEFT
Working Memory Task

0 - back test

Do what the slide shows:

CROSS

Working Memory Task

0 - back test

Do what the slide shows:

LEFT
Working Memory Task

0 - back test

Do what the slide shows:

RIGHT

Working Memory Task

0 - back test

Do what the slide shows:

RIGHT
Working Memory Task

0 - back test

Do what the slide shows:

CROSS

Working Memory Task

2 - back test

Look at the slide
Remember what the slide says
Wait for the second slide to appear
Do what the slide said “2-back”, or 2 slides ago

LEFT = Hold up your left hand,
RIGHT = Hold up your right hand, or,
CROSS = Cross your arms on your chest
Working Memory Task

2 - back test

RIGHT

Working Memory Task

2 - back test

CROSS
Working Memory Task

2 - back test

CROSS

Working Memory Task

2 - back test

LEFT
Working Memory Task

2 - back test

RIGHT

Working Memory Task

2 - back test

CROSS
Working Memory Task

2 - back test

LEFT