

# Conflict of Interest Disclosure

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

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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

	Deployed	Not Deployed
Symptoms	?	?
No Symptoms	?	?

### First Gulf War Cohort

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

	Deployed	Not Deployed
Symptoms	25% to 30%	15%
No Symptoms	70% to 75%	85%

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

### August 1991 to 2002

	Deployed	Not Deployed
Symptoms	?	?
No Symptoms	?	?

### 2002 → OEF, OIF

-post-IED TBI  
 -Pneumonitis, dyspnea  
 -Burn pits

	Deployed	Not Deployed
Symptoms	?	?
No Symptoms	?	?

## “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?

## 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)

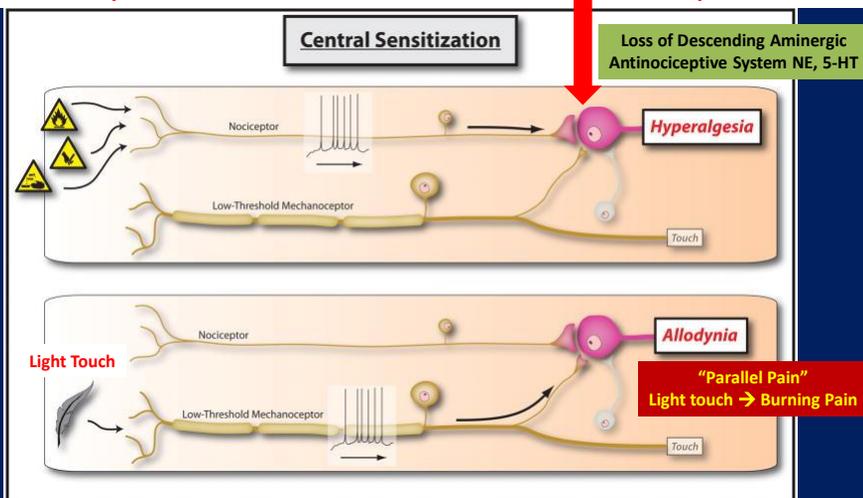
Table 1. Overlap of SUBJECTIVE case designations

<b>Fibromyalgia</b>					
1990					
<input type="checkbox"/> wide spread pain					
<input type="checkbox"/> manual tenderness					
<b>Systemic Hyperalgesia and Allodynia</b>					

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

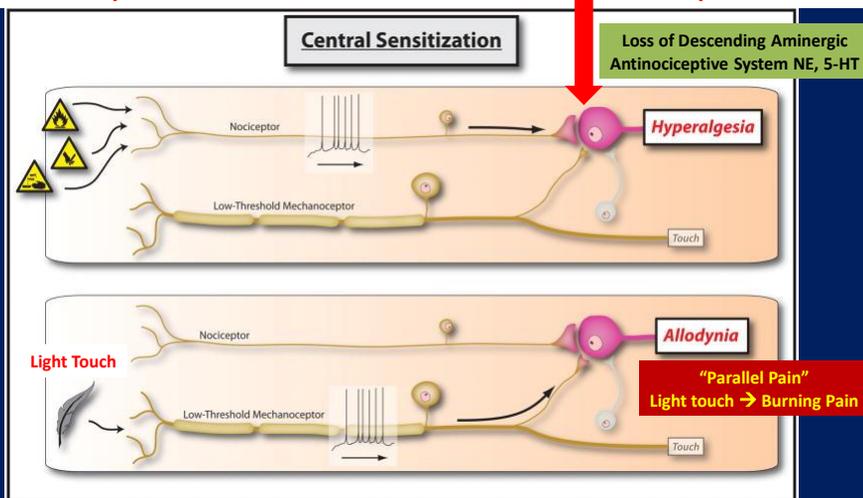
## Central Sensitization

Chronic Nociceptive Stimulation → Glutamate release → AMPA receptor activation



## Central Sensitization

Chronic Nociceptive Stimulation → Glutamate release → AMPA receptor activation



Gut brain, Spinal Cord, Thalamus, Other Brain Pain Regulatory Centers  
Abdominal pain, Photosensitivity, Phonosensitivity, MCS, Dyspnea

**Table 1. Overlap of SUBJECTIVE case designations**

Fibromyalgia					
1990	2010				
	<input type="checkbox"/> fatigue				
	<input type="checkbox"/> waking unrefreshed <input type="checkbox"/> cognitive symptoms				
<input type="checkbox"/> wide spread pain	<input type="checkbox"/> wide spread pain index (WPI)				
	<input type="checkbox"/> somatic symptoms				
<input type="checkbox"/> manual tenderness					
<b>FM: A REAL DISEASE because there is a drug approved and advertised on TV</b>					

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

**Table 1. Overlap of SUBJECTIVE case designations**

Fibromyalgia					
1990	2011				
	<input type="checkbox"/> fatigue				
	<input type="checkbox"/> waking unrefreshed <input type="checkbox"/> cognitive symptoms				
<input type="checkbox"/> wide spread pain	<input type="checkbox"/> wide spread pain index (WPI)				
	<input type="checkbox"/> somatic symptoms (GI)				
<input type="checkbox"/> manual tenderness					
	<b>Depression</b>				

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

**Table 1. Overlap of SUBJECTIVE case designations**

Fibromyalgia		Chronic Fatigue Syndrome (CFS)			
1990	<b>2011</b>	Fatigue + 4 / 8 (Fukuda 1994)			
	<input type="checkbox"/> fatigue	<input type="checkbox"/> fatigue			
	<input type="checkbox"/> waking unrefreshed <input type="checkbox"/> cognitive symptoms	<input type="checkbox"/> sleep disturbance <input type="checkbox"/> memory or concentration			
<input type="checkbox"/> wide spread pain	<input type="checkbox"/> wide spread pain index (WPI)	<input type="checkbox"/> myalgia <input type="checkbox"/> arthralgia			
	<input type="checkbox"/> somatic symptoms (GI)	<input type="checkbox"/> sore throat <input type="checkbox"/> lymph node <input type="checkbox"/> headache			
<input type="checkbox"/> manual tenderness					
		<input type="checkbox"/> exertional exhaustion <input type="checkbox"/> exercise-induced dysfunction			
	<b>depression</b>	Extensive exclusion criteria			

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

**Table 1. Overlap of SUBJECTIVE case designations**

Fibromyalgia		Systemic Exertion Intolerance Disease (SEID)			
1990	<b>2011</b>	IOM 2015			
	<input type="checkbox"/> fatigue	<input type="checkbox"/> <u>fatigue</u>			
	<input type="checkbox"/> waking unrefreshed <input type="checkbox"/> cognitive symptoms	<input type="checkbox"/> <u>sleep disturbance</u> <input type="checkbox"/> <u>memory or concentration</u>			
<input type="checkbox"/> wide spread pain	<input type="checkbox"/> wide spread pain index (WPI)	<input type="checkbox"/> myalgia <input type="checkbox"/> arthralgia			
	<input type="checkbox"/> somatic symptoms (GI)	<input type="checkbox"/> sore throat <input type="checkbox"/> lymph node <input type="checkbox"/> headache			
<input type="checkbox"/> manual tenderness		<input type="checkbox"/> <u>autonomic intolerance</u>			
		<input type="checkbox"/> <u>exertional exhaustion (PEM)</u>			
	<b>depression</b>	Extensive exclusion criteria			

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

**Table 1. Overlap of SUBJECTIVE case designations**

Fibromyalgia		Chronic Fatigue Syndrome (CFS)	Chronic Multisymptom Illness (CMI) (“GWI”)		
1990	<b>2011</b>	Fatigue + 4 / 8 Fukuda 1994	“severe” in 2 or 3 categories; Fukuda 1998		
	<input type="checkbox"/> fatigue	<input type="checkbox"/> fatigue	<input type="checkbox"/> fatigue		
	<input type="checkbox"/> waking unrefreshed <input type="checkbox"/> cognitive symptoms	<input type="checkbox"/> sleep disturbance <input type="checkbox"/> memory or concentration	<input type="checkbox"/> mood / cognition	<input type="checkbox"/> sleep <input type="checkbox"/> cognitive <input type="checkbox"/> anxiety <input type="checkbox"/> depressive <input type="checkbox"/> moody	
<input type="checkbox"/> wide spread pain	<input type="checkbox"/> wide spread pain index (WPI)	<input type="checkbox"/> myalgia <input type="checkbox"/> arthralgia	<input type="checkbox"/> myalgia / arthralgia	<input type="checkbox"/> arthralgia <input type="checkbox"/> stiffness <input type="checkbox"/> myalgia	
	<input type="checkbox"/> somatic symptoms	<input type="checkbox"/> sore throat <input type="checkbox"/> lymph node <input type="checkbox"/> headache			
<input type="checkbox"/> manual tenderness					
		<input type="checkbox"/> exertional exhaustion exercise-induced dysfunction	<b>Exposures of 1990-1991</b>		
	<input type="checkbox"/> depression	Extensive exclusion criteria			

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

**Table 1. Overlap of SUBJECTIVE case designations**

Fibromyalgia		Chronic Fatigue Syndrome (CFS)	Chronic Multisymptom Illness (CMI) (“GWI”)		<b>DEPRESSION</b> (DSM-IV-TR, 2000)
1990	<b>2011</b>	Fatigue + 4 / 8 Fukuda 1994	“severe” in 2 or 3 categories; Fukuda 1998		<b>40% to 60% of all chronic illnesses</b>
	<input type="checkbox"/> fatigue	<input type="checkbox"/> fatigue	<input type="checkbox"/> fatigue		<input type="checkbox"/> fatigue, energy loss
	<input type="checkbox"/> waking unrefreshed <input type="checkbox"/> cognitive symptoms	<input type="checkbox"/> sleep disturbance <input type="checkbox"/> memory or concentration	<input type="checkbox"/> mood / cognition	<input type="checkbox"/> sleep <input type="checkbox"/> cognitive <input type="checkbox"/> anxiety <input type="checkbox"/> depressive <input type="checkbox"/> moody	<input type="checkbox"/> diminished ability to think or concentrate, or indecisiveness <input type="checkbox"/> insomnia or hypersomnia <input type="checkbox"/> mood *
<input type="checkbox"/> wide spread pain	<input type="checkbox"/> wide spread pain index (WPI)	<input type="checkbox"/> myalgia <input type="checkbox"/> arthralgia	<input type="checkbox"/> myalgia / arthralgia	<input type="checkbox"/> arthralgia <input type="checkbox"/> stiffness <input type="checkbox"/> myalgia	<input type="checkbox"/> * significant loss of weight or appetite <input type="checkbox"/> * anhedonia <input type="checkbox"/> * psychomotor agitation or retardation
	<input type="checkbox"/> somatic symptoms	<input type="checkbox"/> sore throat <input type="checkbox"/> lymph node <input type="checkbox"/> headache			<input type="checkbox"/> * feelings of worthlessness or excessive or inappropriate guilt <input type="checkbox"/> * recurrent thoughts of death
<input type="checkbox"/> manual tenderness					
		<input type="checkbox"/> exertional exhaustion exercise-induced dysfunction	<b>Exposures of 1990-1991</b>		
	<input type="checkbox"/> depression	Extensive exclusion criteria (depression)			CBT, Exercise, Tai Chi

**Table 1. Overlap of SUBJECTIVE case designations**

Fibromyalgia		Chronic Fatigue Syndrome (CFS)	Chronic Multisymptom Illness (CMI) (“GWI”)		Shared Features Rayhan 2013
1990	<b>2011</b>	Fatigue + 4 / 8 Fukuda 1994	“severe” in 2 or 3 categories Fukuda 1998		
	<input type="checkbox"/> fatigue	<input type="checkbox"/> fatigue	<input type="checkbox"/> fatigue		<input type="checkbox"/> fatigue
	<input type="checkbox"/> waking unrefreshed <input type="checkbox"/> cognitive symptoms	<input type="checkbox"/> sleep disturbance <input type="checkbox"/> memory or concentration	<input type="checkbox"/> mood / cognition	<input type="checkbox"/> sleep <input type="checkbox"/> cognitive <input type="checkbox"/> anxiety <input type="checkbox"/> depressive <input type="checkbox"/> moody	<input type="checkbox"/> attention networks <input type="checkbox"/> working memory <input type="checkbox"/> sleep <input type="checkbox"/> affect / anxiety
<input type="checkbox"/> wide spread pain	<input type="checkbox"/> wide spread pain index (WPI)	<input type="checkbox"/> myalgia <input type="checkbox"/> arthralgia	<input type="checkbox"/> myalgia / arthralgia	<input type="checkbox"/> arthralgia <input type="checkbox"/> stiffness <input type="checkbox"/> myalgia	<input type="checkbox"/> nociceptive, interoceptive & somatosensory central sensitization <input type="checkbox"/> migraine
	<input type="checkbox"/> somatic symptoms	<input type="checkbox"/> sore throat <input type="checkbox"/> lymph node <input type="checkbox"/> headache			<input type="checkbox"/> systemic hyperalgesia
<input type="checkbox"/> manual tenderness					<input type="checkbox"/> exertional exhaustion exercise-induced dysfunction
	<input type="checkbox"/> depression	Extensive exclusion criteria			

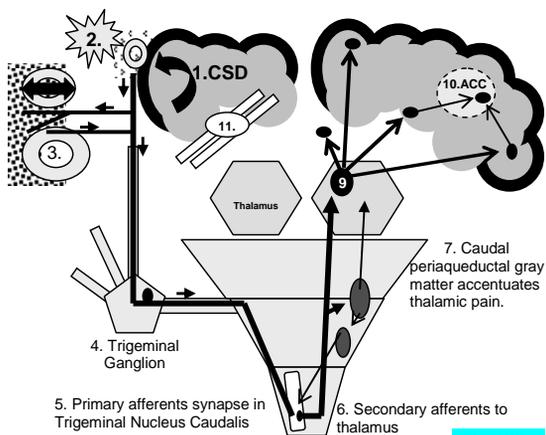
**Nociceptive, Interoceptive and FaTiguing Illnesses (**NIFTI**)**

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

Fibromyalgia		Chronic Fatigue Syndrome (CFS)	Chronic Multisymptom Illness (CMI)		Shared Features Rayhan 2013
1990	2010	Fatigue + 4 / 8 Fukuda 1994	“severe” in 2 or 3 categories Fukuda 1998		
	<input type="checkbox"/> fatigue	<input type="checkbox"/> fatigue	<input type="checkbox"/> fatigue		<input type="checkbox"/> fatigue
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	<input type="checkbox"/> somatic symptoms	<input type="checkbox"/> sore throat <input type="checkbox"/> lymph node <input type="checkbox"/> headache			<input type="checkbox"/> systemic hyperalgesia
<input type="checkbox"/> manual tenderness					<input type="checkbox"/> exertional exhaustion exercise-induced dysfunction
		Extensive exclusion criteria			

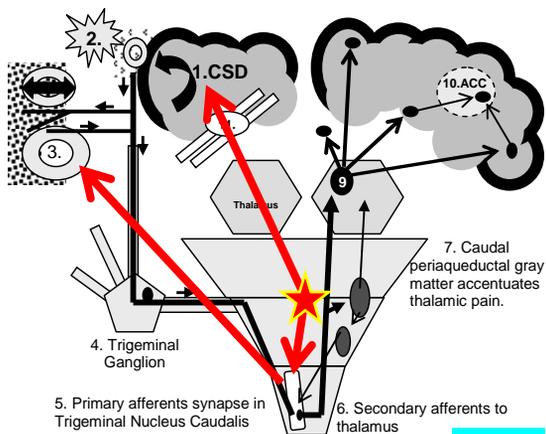
**Nociceptive, Interoceptive and FaTiguing Illnesses (**NIFTI**)**

## Migraine Mechanisms



1. Cortical spreading depression (CSD) depolarizes cortical neurons and glia.
2. They release glutamate, K<sup>+</sup>, H<sup>+</sup>, 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.
6. Ascending secondary afferents activate the thalamus.
7. Other afferents signal periaqueductal gray matter.
8. Descending relays to the magnus raphae nucleus activate descending serotonergic neurons to inhibit the primary trigeminal synapses (5. & 6.).
9. Thalamocortical projections stimulate the hypothalamus, somatosensory cortex, amygdala, limbic system, and frontal cortex.
10. 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



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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:

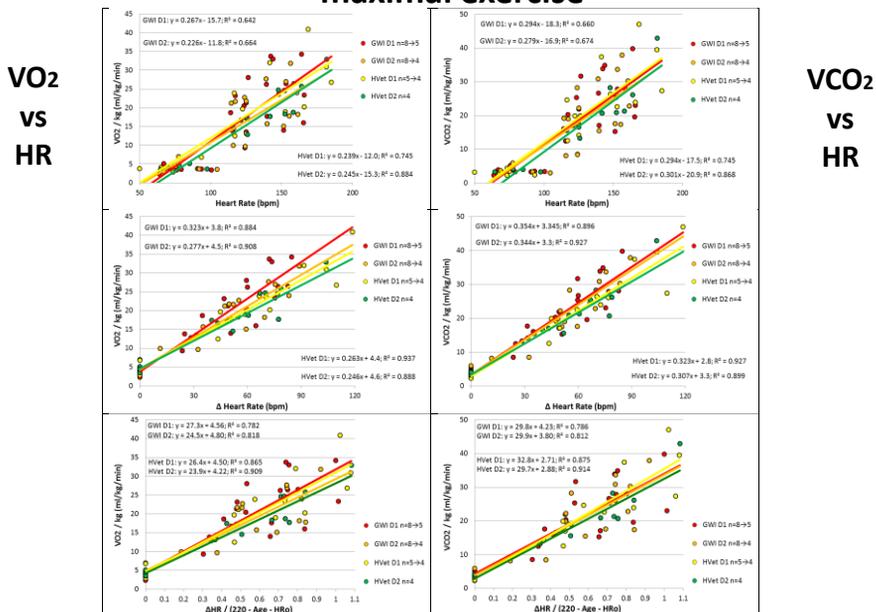
Submaximal exercise on DAY 1 → good muscle function



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



## GWI and Healthy Veterans have identical responses to maximal exercise



### Exercise in CFS & GWI Studies

MITOCHONDRIAL DYSFUNCTION HYPOTHESIS:

Submaximal exercise on DAY 1 → good muscle function

DAY 1 → DAY 2

*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

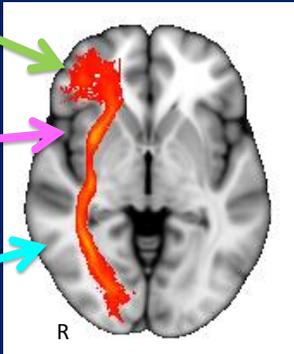
**DTI: White matter dysfunction in rIFOF of GWI**

rMiddle Frontal Gyrus = VAN  
Ventral Attention Network

rOrbitofrontal 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



R

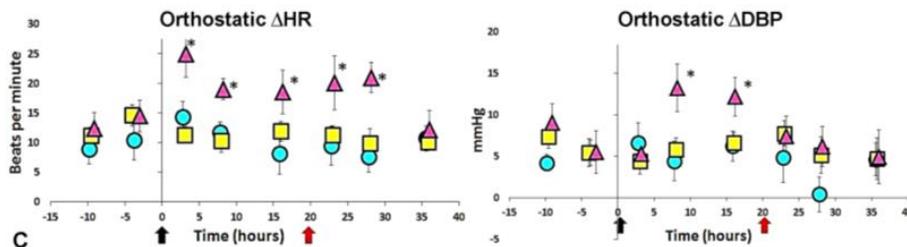
Representative transverse slice of brain

**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  $\Delta HR = 20.5$  [18.3 to 22.7; 95%CI]

### STOPP (Stress Test Originated Phantom Perception) plus Sedentary Control subjects →

average  $\Delta HR = 11.7$  [10.1 to 13.3]

**Exercise – Induced Autonomic Dysfunction**

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

### GW I + CFS

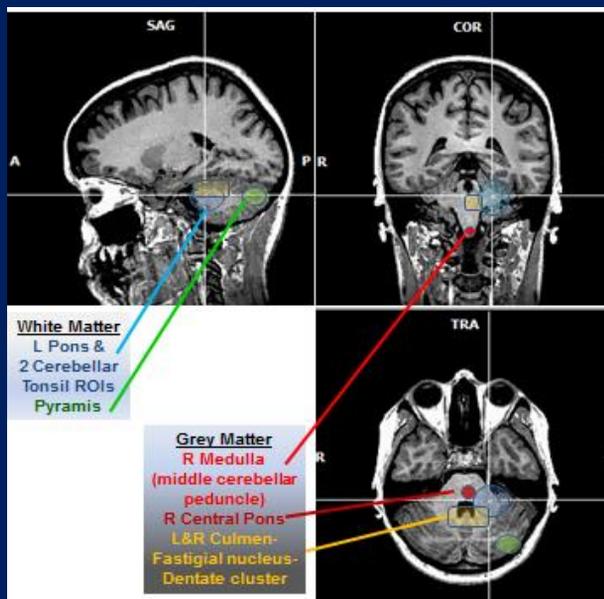
MRI-Exercise-Exercise-MRI protocol

### 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

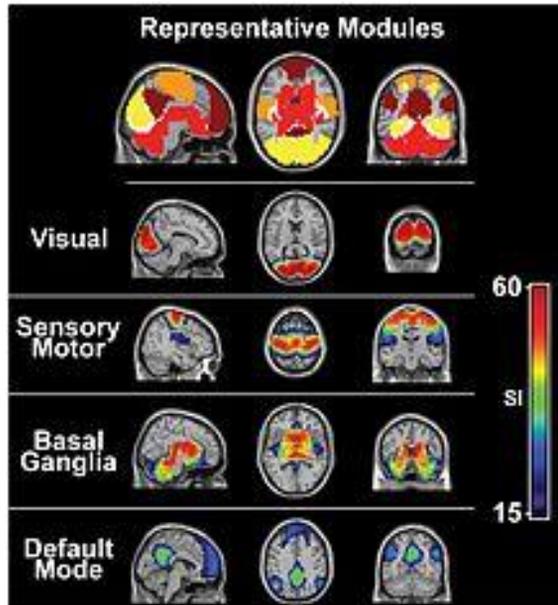
## Mind the Gap

### 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



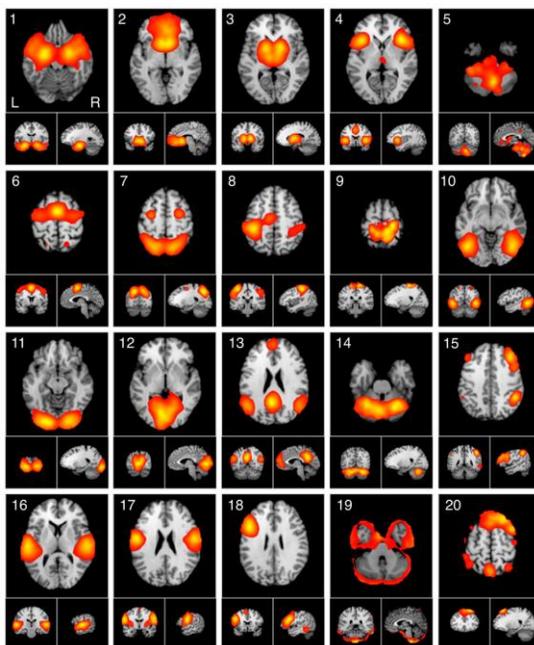
Four functional networks  
 -visual (yellow) (occipital lobes),  
 -sensory/motor (orange) (pre-and post-central gyri),  
 -basal ganglia (red) (deep brain),  
 -default mode network (DMN) (maroon) (posterior cingulate, inferior parietal lobes, and medial frontal gyrus).

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

### Resting State Networks (RSN)

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## BrainMap and ICA Statistical Networks

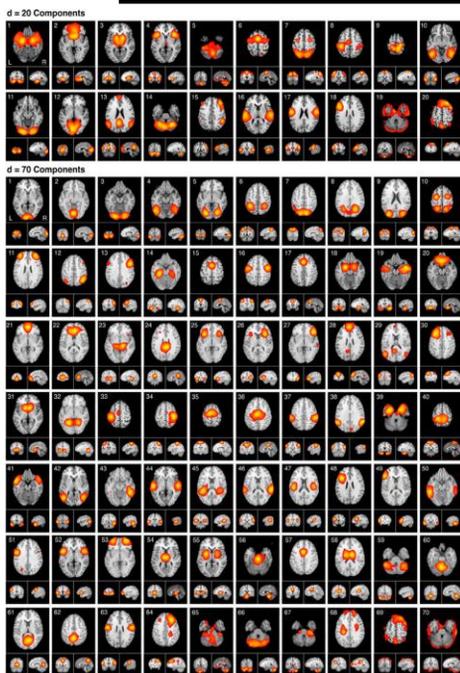


-Consortia have compiled atlases of resting state networks (RSNs).  
 -Regions in red/yellow act in concert to control and perform tasks.

- 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 gyri)
- ICN 17 (dorsal precentral gyri, central sulci, postcentral gyri, 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 (~1/3<sup>rd</sup> 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**

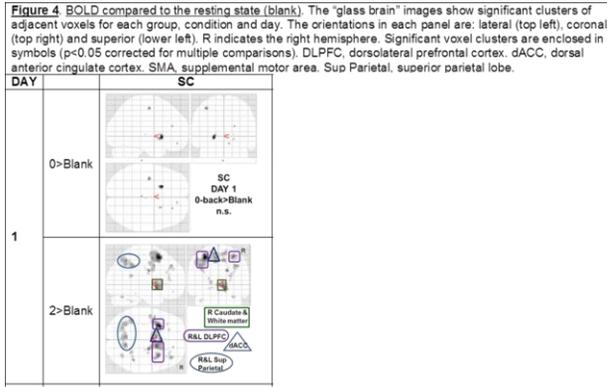
## N-Back Working Memory Task

- **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

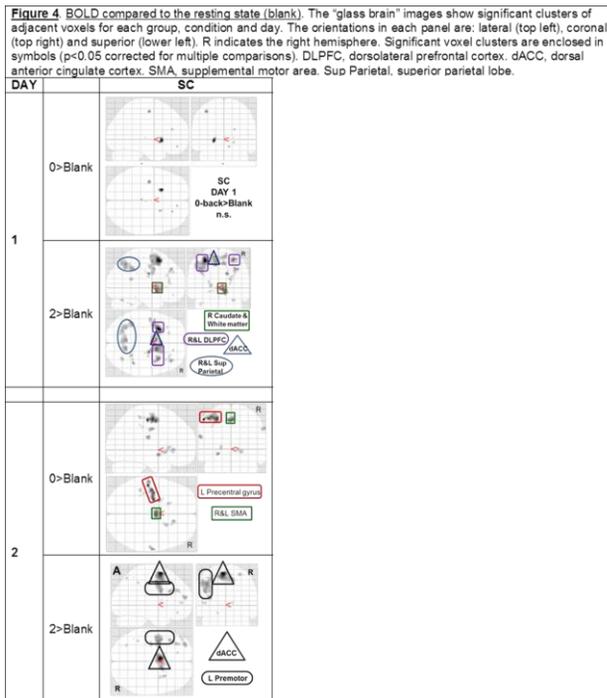
**Sedentary Control (SC)**

0-back:  
 stimulus  
 matching

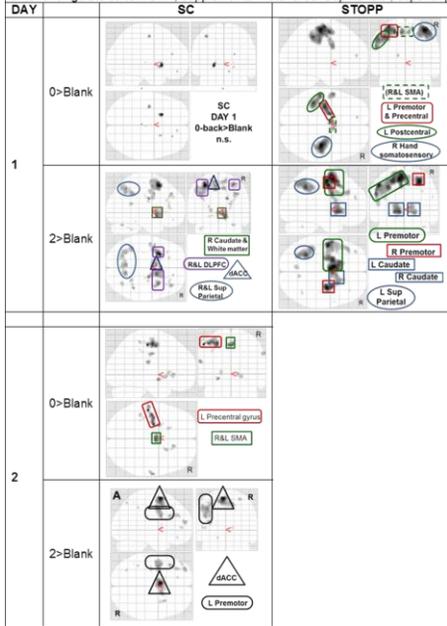
2-back:  
 R&L DLPFC  
 and Parietal lobes



**DAY 2 Learning**



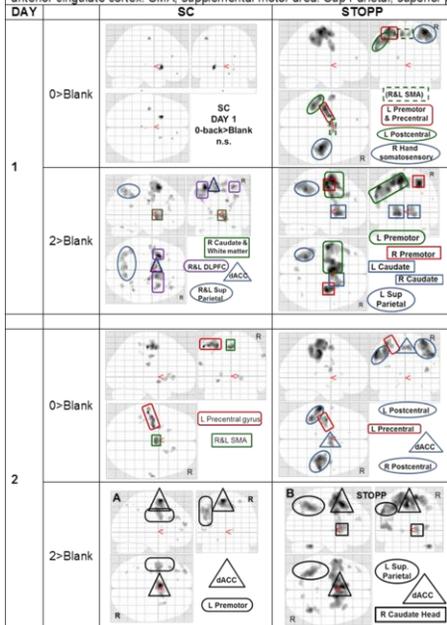
**Figure 4** BOLD compared to the resting state (blank). The "glass brain" images show significant clusters of adjacent voxels for each group, condition and day. The orientations in each panel are: lateral (top left), coronal (top right) and superior (lower left). R indicates the right hemisphere. Significant voxel clusters are enclosed in symbols ( $p < 0.05$  corrected for multiple comparisons). DLPFC, dorsolateral prefrontal cortex. dACC, dorsal anterior cingulate cortex. SMA, supplemental motor area. Sup Parietal, superior parietal lobe.



**DAY 2  
 Learning**

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

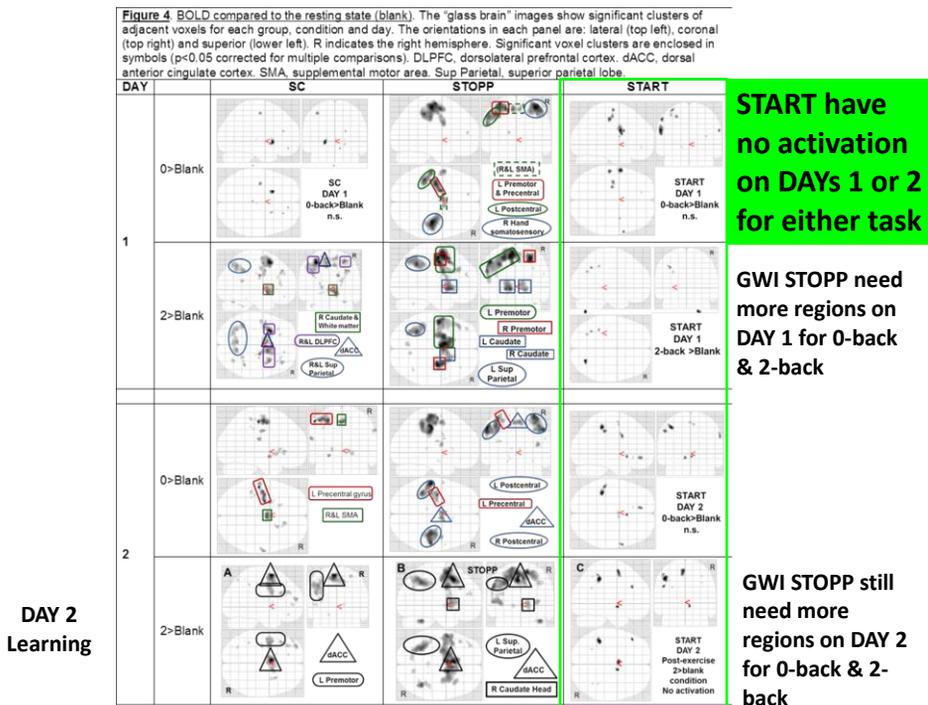
**Figure 4** BOLD compared to the resting state (blank). The "glass brain" images show significant clusters of adjacent voxels for each group, condition and day. The orientations in each panel are: lateral (top left), coronal (top right) and superior (lower left). R indicates the right hemisphere. Significant voxel clusters are enclosed in symbols ( $p < 0.05$  corrected for multiple comparisons). DLPFC, dorsolateral prefrontal cortex. dACC, dorsal anterior cingulate cortex. SMA, supplemental motor area. Sup Parietal, superior parietal lobe.



**DAY 2  
 Learning**

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

**GWV STOPP still  
 need more  
 regions on DAY 2  
 for 0-back & 2-  
 back**

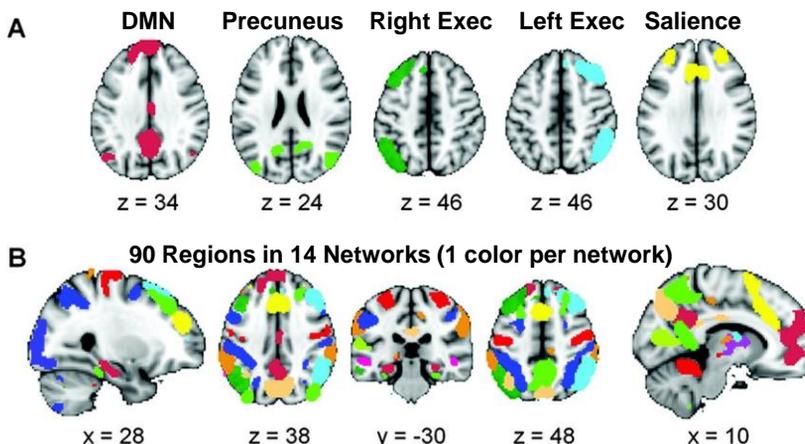


**What brain regions are “connected” or acting together?**  
**Functional Connectivity**

- 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.



W. R. Shirer et al. *Cereb. Cortex* 2012;22:158-165

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<sup>C</sup><sub>erebral</sub> <sup>D</sup><sub>orsal</sub> <sup>R</sup><sub>ight</sub> <sup>T</sup><sub>emporal</sub> <sup>X</sup><sub>enital</sub> **Cerebral CORTEX**

### 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

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**STOPP**

Exercise Increases z (D2>D1)

DAN1
Sal6

DAN3
Sal7

DAN and Salience

**STOPP**

Exercise Decreases z (D1>D2)

Sal6
BG2

Prec2
ECN2

Prec2
ECN6

DMN2	Cblm1	Cblm2	DMN2
		Cblm2	DMN3
		Cblm2	DMN4
Prec2	Cblm1	Cblm2	Prec2
Prec4	Cblm1		
		Cblm2	DAN4
		Cblm2	ECN3
		Cblm2	ECN4
		Cblm2	ECN7
		Cblm2	Sal6
		Cblm2	Sal7

Cerebellum: decreased connectivity with DMN, Salience, Executive Control

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DAN and Salience

**STOPP**

Exercise Decreases z (D1>D2)

Sal6
BG2

Prec2
ECN2

Prec2
ECN6

DMN2	Cblm1	Cblm2	DMN2
		Cblm2	DMN3
		Cblm2	DMN4
Prec2	Cblm1	Cblm2	Prec2
Prec4	Cblm1		
		Cblm2	DAN4
		Cblm2	ECN3
		Cblm2	ECN4
		Cblm2	ECN7
		Cblm2	Sal6
		Cblm2	Sal7

Cerebellum: decreased connectivity with DMN, Salience, Executive Control

**START**

Exercise Increases z-Scores (D2>D1)

			Prec4	ECN3	
			Prec3	ECN3	
			Prec3	Sal6	
		DMN2	Prec4	Sal7	
DAN2					ECN7
	DMN2				
	DMN2	DAN3	Sal7		
	DMN2	DAN3	DAN3		

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

**START**

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

Sal7	BG1				
BG1	DAN3	DAN3	BG2		
BG1	DAN4	DAN4	BG2		
BG1	DAN2				
DAN2	Sal3			Sal3	Cblm2
DAN1	Sal5			Prec1	Cblm1
DAN1	Sal2				Cblm1
	Sal2	DMN2			Aud1
	Sal2	Prec3	Prec1	DMN1	
ECN3	Sal2				
ECN2	Sal2				
ECN6	Sal1				

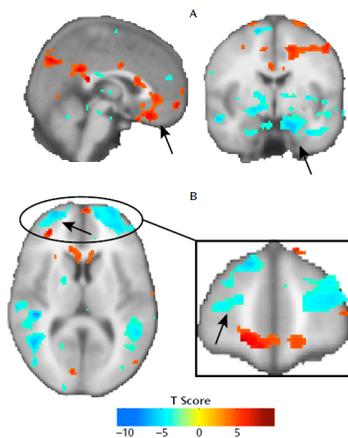
### OBJECTIVE Mechanisms

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

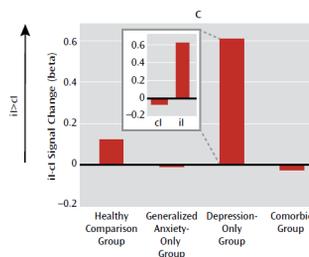
## Objective MRI measures as study outcomes

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

FIGURE 4. Correlation Between Postincongruent Incongruent Trial Minus Postcongruent Incongruent Trial Reaction Time Difference Scores and Brain Activation for the Same Contrast<sup>a</sup>



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



<sup>a</sup> Brain activation is displayed with whole-brain correction for the false discovery rate ( $q < 0.05$ ). In panel A, positive correlations in the ventral cingulate and negative correlations in the amygdala (arrows) suggest a greater deficit in these regions when depression-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 (il=postincongruent incongruent trial; cl=postcongruent incongruent trial) illustrates activity for the left anterior middle frontal gyrus cluster (arrows in panel B) extracted for the il-cl contrast for each group, as well as separately for the il and cl 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 il trials. The figure shows that engagement of compensatory activation 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 GWI.
- 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](mailto:baraniuklab@gmail.com)**

## CFS Severity Score

### Fatigue plus 4 of 8:

- Myalgia
- Arthralgia
- Sore throat
- Lymph nodes
- Headache (migraine)
- Cognition (concentration and memory)
- Sleep
- Exertional exhaustion

### Severity Scale

- 0=absent
- 1=present
- **Fatigue + 4 of 8**

## CFS Severity Score

### CFS Criteria with Fatigue

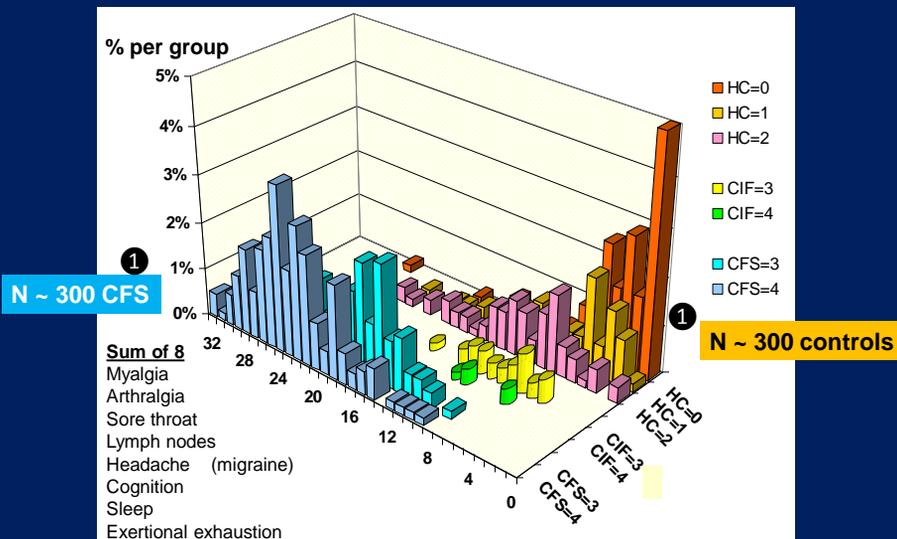
- Myalgia
- Arthralgia
- Sore throat
- Lymph nodes
- Headache (migraine)
- Cognition (concentration and memory)
- Sleep
- Exertional exhaustion

### Severity Scale

- 0=none
- 1=trivial
- 2=mild
- 3=moderate
- 4=severe
- **Sum of 8 ancillary symptoms**
- Sum\_8 ( $\Sigma 8$ ) 0 to 32

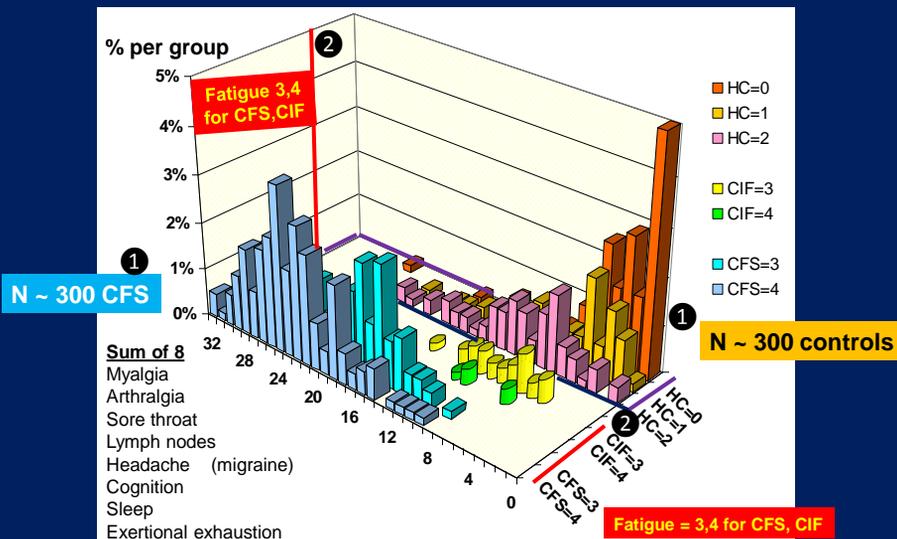
## CFS Severity Score: 4 Quadrants ①

Fatigue (3,4) vs. Sum of 8 ( $\geq 14$ )



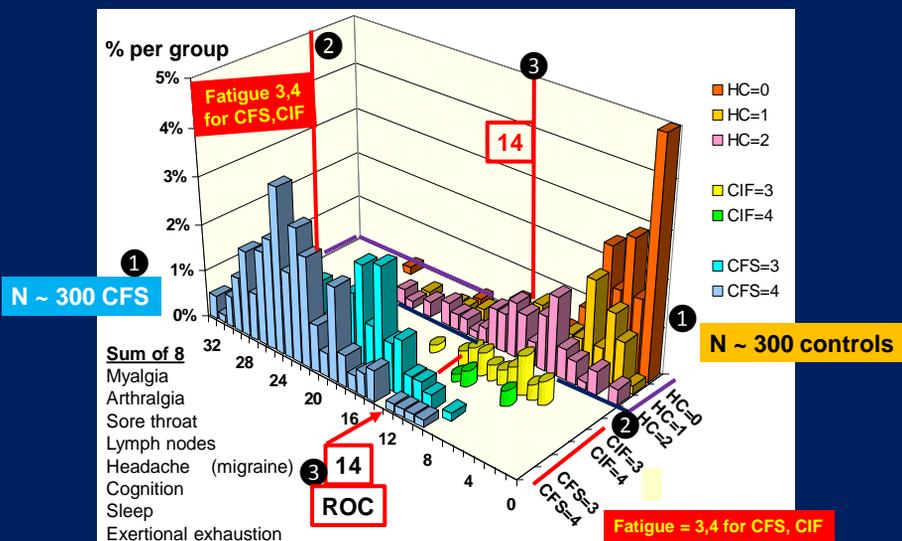
## CFS Severity Score: 4 Quadrants ②

Fatigue (3,4) vs. Sum of 8 ( $\geq 14$ )



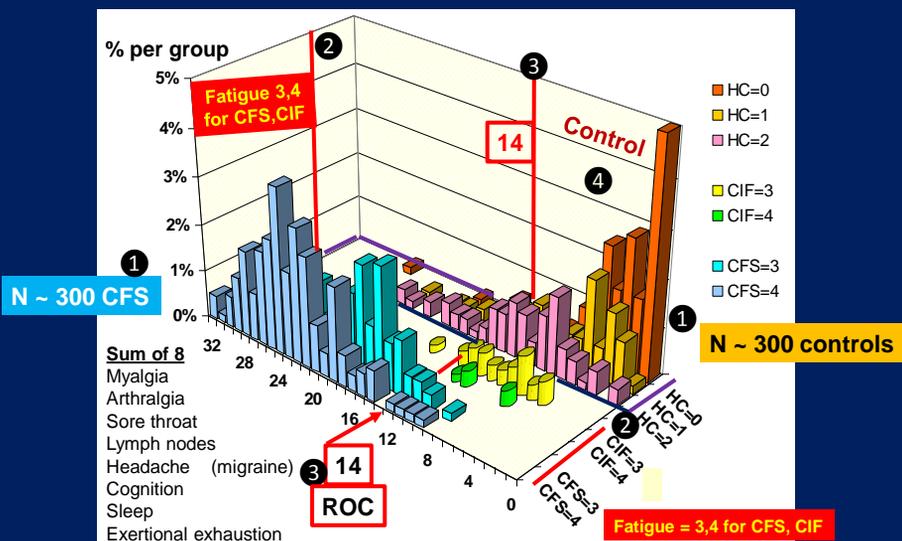
### CFS Severity Score: 4 Quadrants 3

Fatigue (3,4) vs. Sum of 8 ( $\geq 14$ )



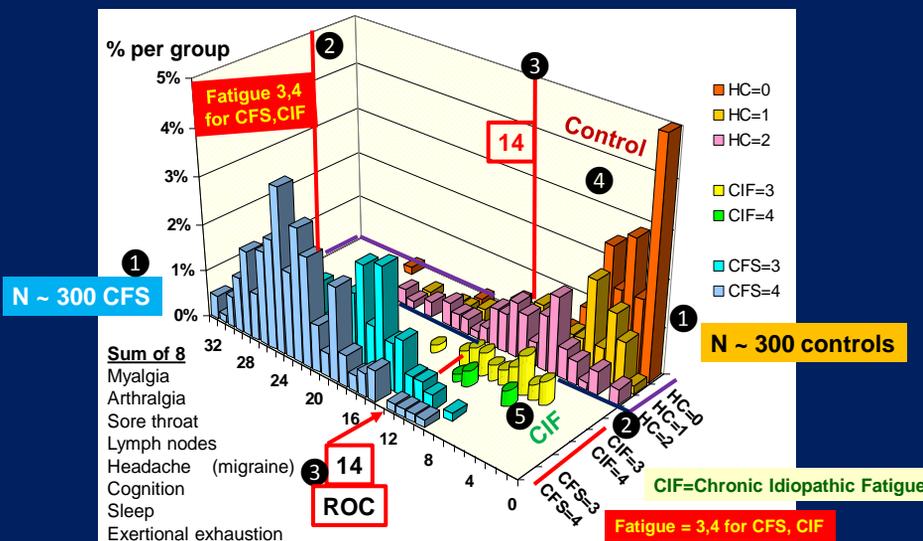
### CFS Severity Score: 4 Quadrants 4

Fatigue (3,4) vs. Sum of 8 ( $\geq 14$ )



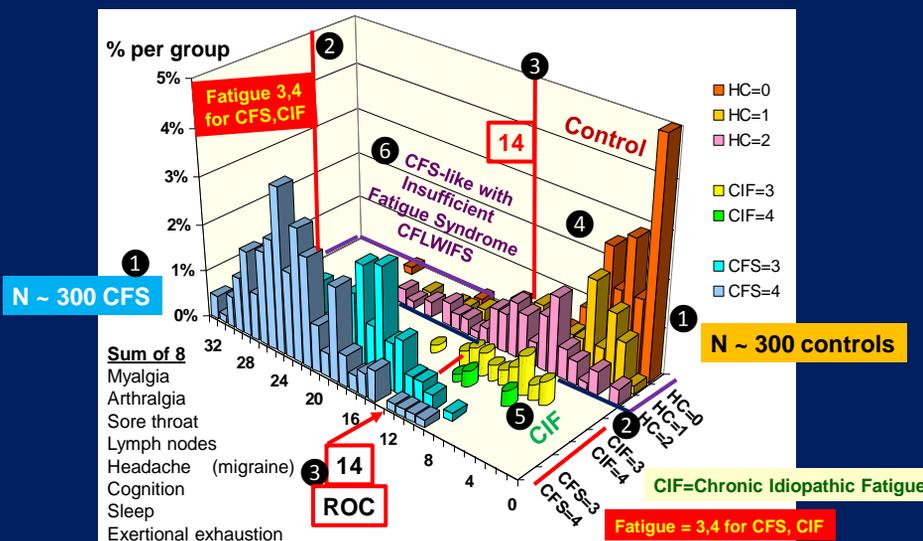
## CFS Severity Score: 4 Quadrants 5

### Fatigue (3,4) vs. Sum of 8 ( $\geq 14$ )



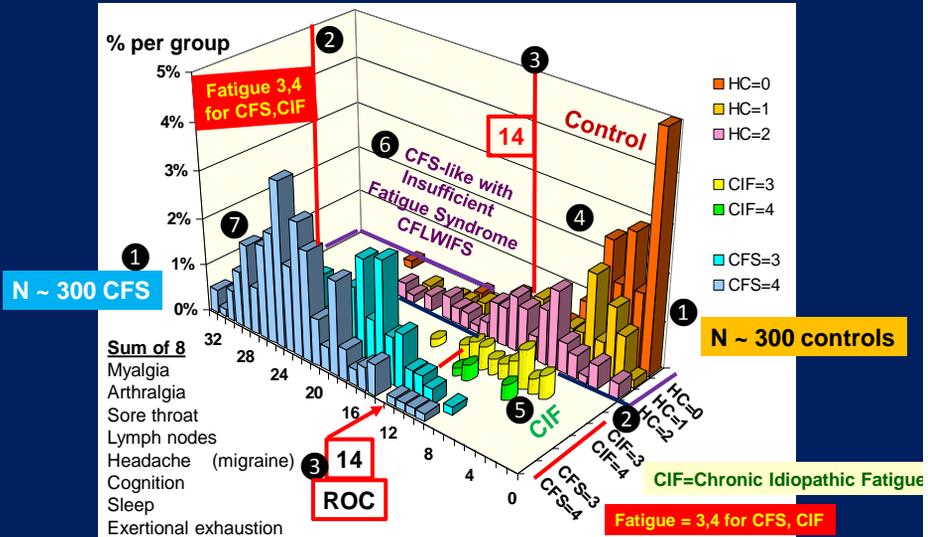
## CFS Severity Score: 4 Quadrants 6

### Fatigue (3,4) vs. Sum of 8 ( $\geq 14$ )



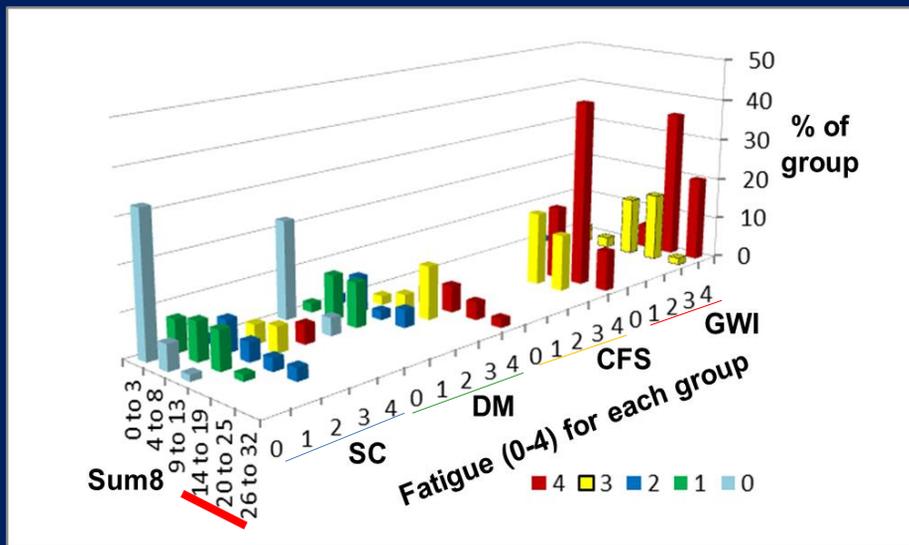
## CFS Severity Score: 4 Quadrants 7

Fatigue (3,4) vs. Sum of 8 ( $\geq 14$ )

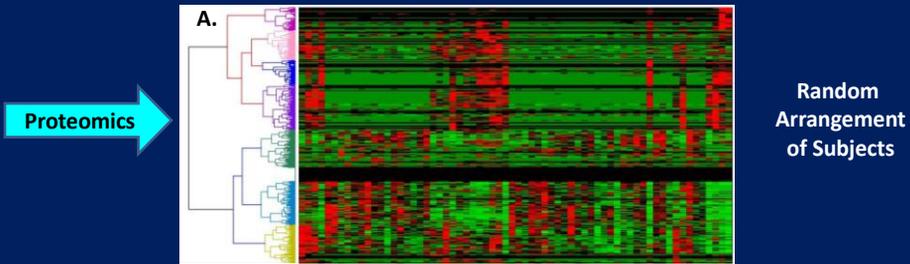


## CFS Severity Score

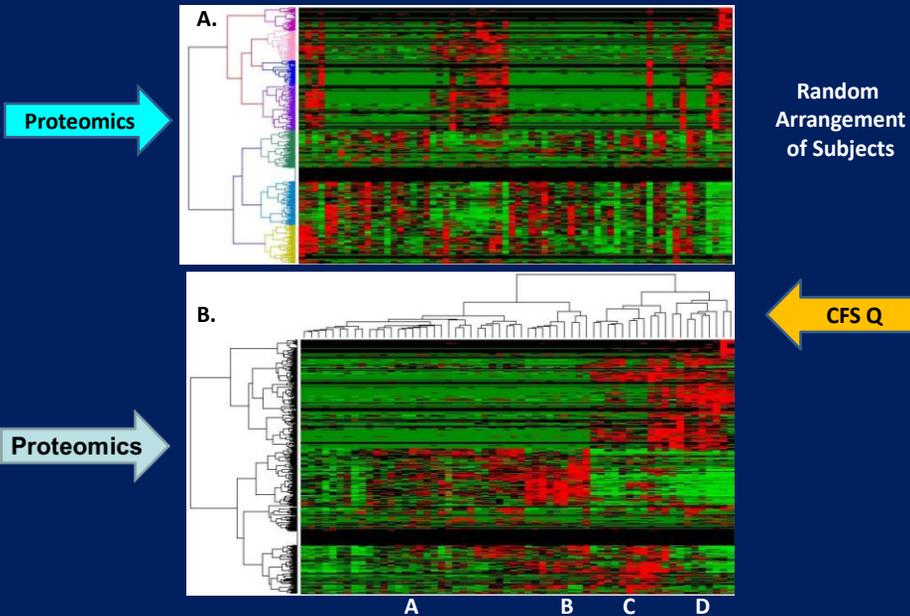
**GW** and CFS have the same patterns of scores



### Proteomics of Cerebrospinal Fluid Clustered by CFS Q

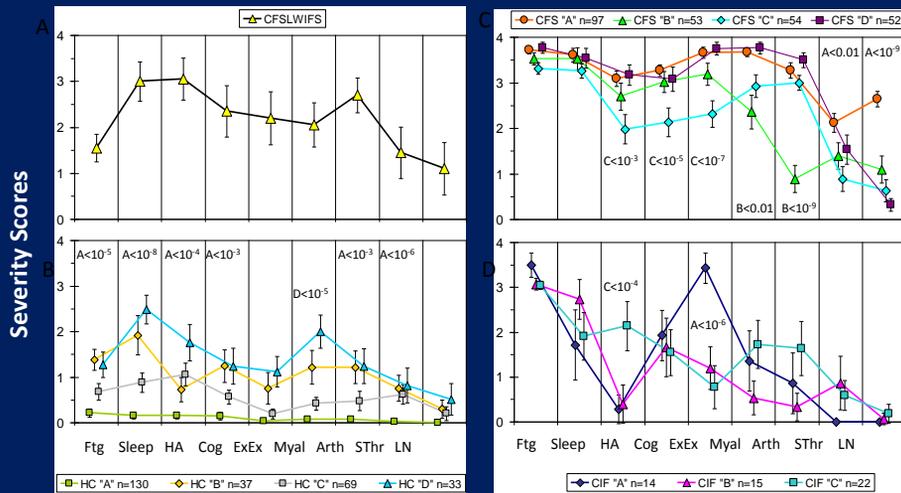


### Proteomics of Cerebrospinal Fluid Clustered by CFS Q



Chronic Multisymptom Illness (CMI) ≥ 2 categories	"Kansas" GWI Definition	Fibromyalgia 2010	Chronic Fatigue Syndrome	Depression (DSM-IV-TR, 2000)	Common Features
<input type="checkbox"/> fatigue	<input type="checkbox"/> fatigue / sleep	<input type="checkbox"/> fatigue	<input type="checkbox"/> fatigue	<input type="checkbox"/> fatigue or loss of energy	<input type="checkbox"/> fatigue
<input type="checkbox"/> mood / cognition	<input type="checkbox"/> cognitive <input type="checkbox"/> anxiety <input type="checkbox"/> depressive <input type="checkbox"/> moody <input type="checkbox"/> sleep	<input type="checkbox"/> cognitive symptoms <input type="checkbox"/> waking unrefreshed	<input type="checkbox"/> memory or concentration <input type="checkbox"/> sleep disturbance	<input type="checkbox"/> diminished ability to think or concentrate, or indecisiveness <input type="checkbox"/> insomnia or hypersomnia <input type="checkbox"/> mood *	<input type="checkbox"/> memory & concentration
<input type="checkbox"/> myalgia/arthralgia	<input type="checkbox"/> arthralgia <input type="checkbox"/> stiffness <input type="checkbox"/> myalgia	<input type="checkbox"/> widespread pain index (WPI)	<input type="checkbox"/> myalgia <input type="checkbox"/> arthralgia	<input type="checkbox"/> (somatization)	<input type="checkbox"/> pain
	<input type="checkbox"/> GI <input type="checkbox"/> airways <input type="checkbox"/> skin	<input type="checkbox"/> somatic symptoms	<input type="checkbox"/> sore throat <input type="checkbox"/> lymph node <input type="checkbox"/> headache		<input type="checkbox"/> systemic hyperalgesia
<b>Extensive exclusion criteria including pregnancy, depression, HIV, chronic viral, autoimmune, neoplastic or medical disease.</b>		<input type="checkbox"/> (tenderness to pressure)	<input type="checkbox"/> exertional exhaustion		<input type="checkbox"/> exertional exhaustion
				<input type="checkbox"/> * significant loss of weight or appetite <input type="checkbox"/> * anhedonia <input type="checkbox"/> * psychomotor agitation or retardation <input type="checkbox"/> * feelings of worthlessness or excessive or inappropriate guilt <input type="checkbox"/> * recurrent thoughts of death	

### Unsupervised Hierarchical Clustering of CFS Q Results



## 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**