CDMRP Work in Progress:

Study 229 "*Exercise in GWI*"

Pathophysiology of Exercise – Induced Cognitive Dysfunction in GWI Subjects with CFS

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Study 229 "*Exercise in GWI*" Protocol

DAY 0: Screening

-Arrival & orientation
-Informed consent
-**History & physical**

-Blood work
-Dolorimetry for systemic hyperalgesia
-Thumb nail pressure for hyperalgesia
-Isometric handgrip & acoustic rhinometry

DAY 1: 1st Exercise

-**fMRI; N-Back task**

-**Bicycle ergometry** to anaerobic threshold
-70% HR x 25 min then ~3-5 min until 85% HR and RQ>1

-Blood work
-Dolorimetry for systemic hyperalgesia
-Thumb nail pressure for hyperalgesia
-Isometric handgrip & acoustic rhinometry

DAY 2: 2nd Exercise

-Blood work
-Dolorimetry for systemic hyperalgesia
-Thumb nail pressure for hyperalgesia
-Isometric handgrip & acoustic rhinometry

-**Bicycle ergometry** to anaerobic threshold 70% HR x 25 min then ~3-5 min until 85% HR and RQ>1

-**fMRI; N-Back task**

-**Lumbar puncture**

DAY 3:

Migraine?

-Blood work
-Dolorimetry for systemic hyperalgesia
-Thumb nail pressure for hyperalgesia

Fatigue in GWI

- Healthy veterans
- GWI (which definition?)
- GWI + CFS

- How severe are the fatigue and fatigue – related symptoms?

CFS Severity Score (n=600 HC & CFS)

Score Severity of
-Fatigue

PLUS
8 Ancillary Criteria
- Concentration or memory problems
- Sleep disturbances
- Headache
- Sore throat
- Sore lymph nodes
- Muscle pain
- Joint pain
- Exertional exhaustion

Scale
0 = none
1 = trivial
2 = mild
3 = moderate
4 = severe

Sum of 8

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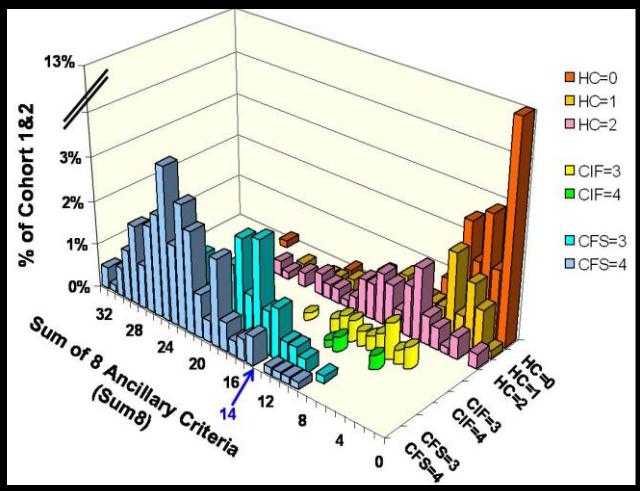


- Sum8 correlates with Fatigue.
- Fatigue scores of 3 or 4 *plus* the threshold of 14 distinguishes CFS from Chronic Idiopathic Fatigue (CIF), CFS-Like With Insufficient Fatigue Syndrome (CFSLWIFS) and HC.

Pain and Tenderness:

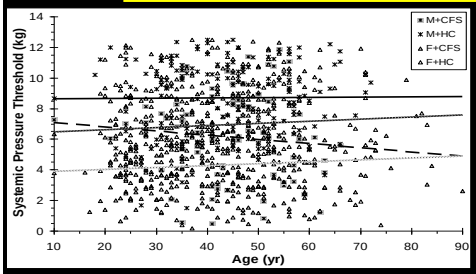
Nociception, Systemic Hyperalgesia and Allodynia

- Mechanisms of **central sensitization.**
- Dorsal horn of the spinal cord.
- Primary synapse between peripheral pain-carrying Type C neurons and ascending spinothalamic neurons.

- Long term loss of descending anti-nociceptive aminergic nerve function (decreased norepinephrine, serotonin and dopamine to dorsal horn) promotes more pain input.

- Loss of norepinephrine release that ascends from the brainstem locus coeruleus to the cortex:
  - This system regulates acute responses to stressors by altering analysis of sensory and interoceptive inputs, focus of attention, mood (fear) and “efferent” autonomic, neuroendocrine, and executive decision making processes. The neural connections are related to the “default mode pathway” that is active during rest.

Dolorimetry: Pressure-Induced Pain Thresholds



Dolorimetry

- Pressure was applied with a strain gauge over the 18 traditional American College of Rheumatology tender points.
- Averages were plotted against age for:
  - males with CFS (M+CFS, grey stars),
  - male controls (x M+HC),
  - female CFS (F+CFS, closed Δ) and
  - female controls (F+HC, open Δ)

(**n=893**).

- Explained variances were <8% indicating no effect of age on dolorimetry (***trait?***).

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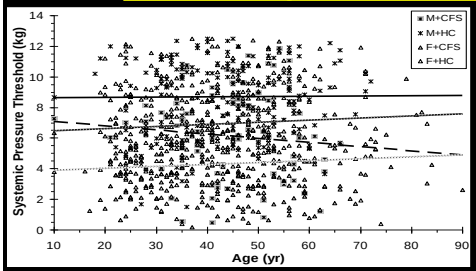

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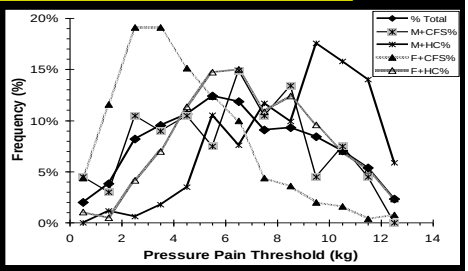
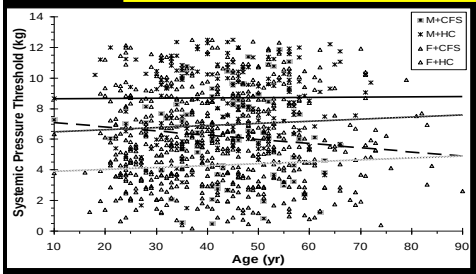
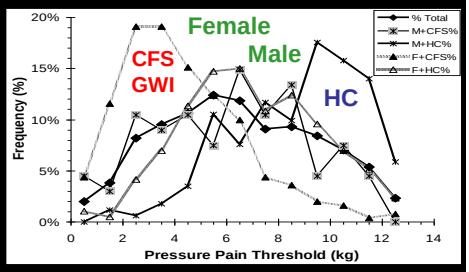


Frequency Analysis

- Pain thresholds were broadly distributed (Total; black diamonds).
- The M+CFS (grey stars) and F+HC (open triangles) phenotypes tracked the Total group.
- F+CFS was highly skewed to the left (low thresholds).
- M+HC was highly skewed to right (high thresholds).
- Distinct genotypes with some sexual dimorphism were anticipated (but not funded).

Dolorimetry: Pressure-Induced Pain Thresholds





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Digital Dolorimetry: Thumbsmashing to Test Exercise – Induced Changes in Spinal Cord Dorsal Horn Fuction and Central Sensitization

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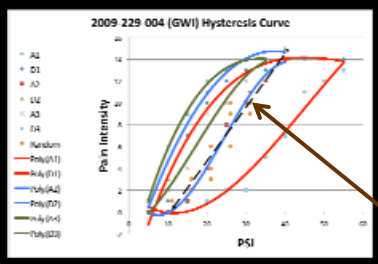
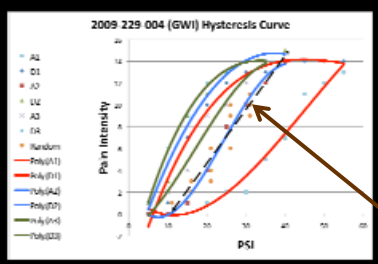


Apply random pressures and score pain level (20 point Gracely Box Score).

Measure the slope of the pain vs. pressure curve.

Digital Dolorimetry: Thumbsmashing to Test Exercise – Induced Changes in Spinal Cord Dorsal Horn Fuction and Central Sensitization



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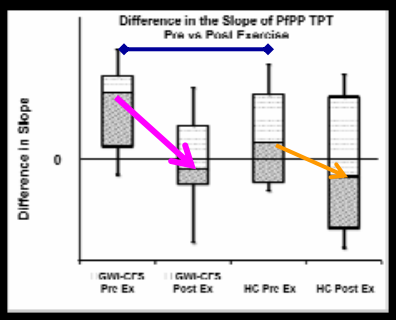


- The slopes of the pain vs. pressure curves (horizontal lines) before exercise were higher for GWI than HC (blue line; "more sensitive").
- Exercise normalized the responses in GWI (pink) and had no effect in HC (gold).

Digital Dolorimetry: Thumbsmashing to Test Exercise – Induced Changes in Spinal Cord Dorsal Horn Fuction and Central Sensitization

Data under evaluation

Cognition & Working Memory: N-Back Testing Paradigm

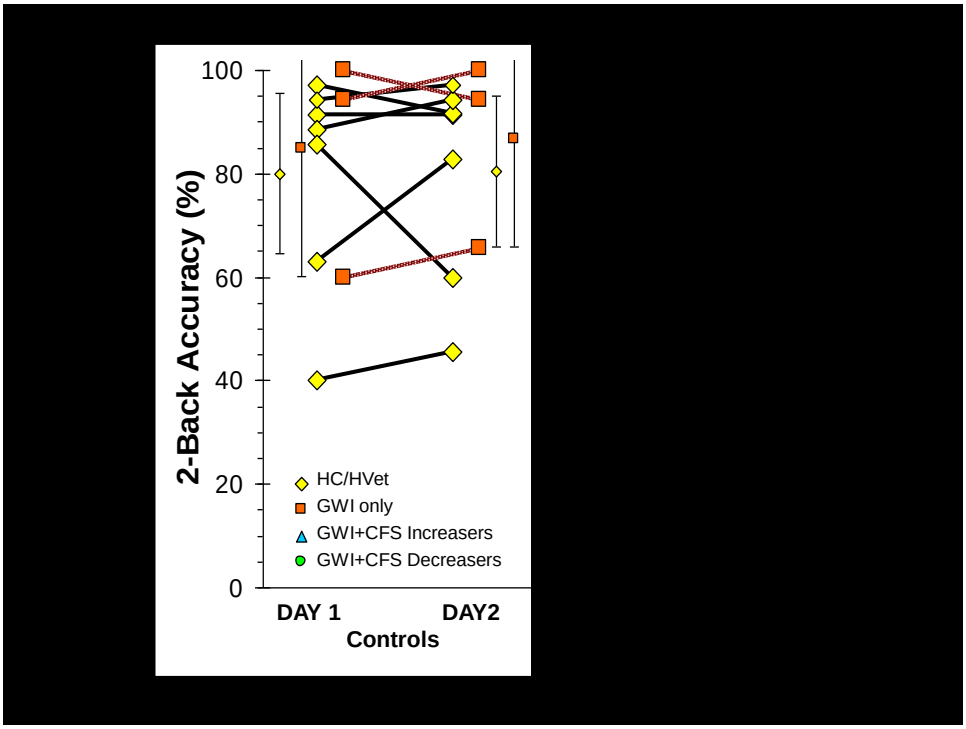
In the fMRI scanner,

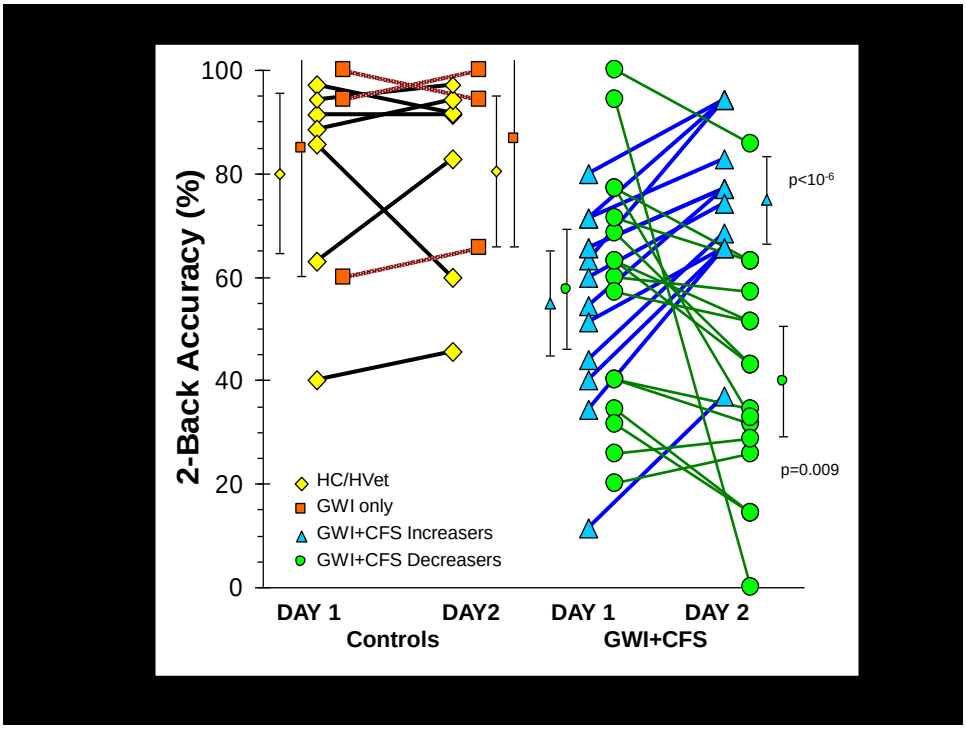
- focus on the screen,
- identify the letter,
- process the information,
- store the information in short term working memory (posterior parietal lobe), and
- plan the proper finger movements for the response (prefrontal and frontal executive decision making and motor regions).

Stimulus	Shown on Screen	**A**	D	C	C	**A**	B	D	B
Button Response	0-Back →	**A**	D	C	C	**A**	B	D	B
Button Response	2-Back →	-	-	**A**	D	C	C	**A**	B

Score test accuracy at % correct answers.

Compare DAY 1 (pre-exercise) to DAY 2 (post-exercise) % Accuracy.


2-Back Accuracy (%)
100
80
60
40
20
0
HC/HVet
GWI only
GWI+CFS Increasers
GWI+CFS Decreasers
DAY 1
DAY2
Controls


2-Back Accuracy (%)
100
80
60
40
20
0
HC/HVet
GWI only
GWI+CFS Increasers
GWI+CFS Decreasers
p<10-6
p=0.009
DAY 1
DAY2
Controls
DAY 1
DAY 2
GWI+CFS

Exercise – Induced Changes in Cognitive Function (2-Back % accuracy) in GWI/CFS

Group	N	Mean %Δ [95% C.I.]
HC/HVet/GWI	10	**3.0%** [-6.9% to 12.8%]
GWI+CFS Increasers	13	**52.3%** [21.5% to 83.1%] *
GWI+CFS Decreasers	16	**-25.8%** [-40.9% to -10.8%] * **

The percent changes in 2-back accuracy after the exercise protocol were calculated as ((DAY 2)-(DAY1))/(DAY 1).

* p = 0.015 vs. HC/HVet/GWI, and ** p=0.00006 between Increasers and Decreasers by 2-tailed unpaired Student's t-tests after significant ANOVA (p=0.00002).

fMRI of N-Back Task

Presentation terminated because of insufficient of time available before the end of the meeting.

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Collaborate with us:
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