Exercise, MRI, Lumbar Puncture and Other Studies on CFS and GWI at Georgetown University

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Amber Surian, MS
The Merry Minions (absent)

Exercise, MRI and Lumbar Puncture

- Exercise
  - Maximal vs. Submaximal
  - Guide to exercise tolerability
- Autonomic Orthostatic Intolerance
  - GWI START postural tachycardia subjects
  - Brain stem atrophy in START and CFS
- Brain fog and brain networks
- Metabolomics of cerebrospinal fluid
  - Biomarkers, insights into pathophysiology
- Rituximab
- SEID

Objective Evidence

Exertional Exhaustion

Pain and Tenderness

Fatigue

Cognition

Brain Magnetic Resonance Imaging (MRI) – Bicycle Exercise – Lumbar Puncture Study

DAY 1:	DAY 2:
Blood→MRI→Exercise→Blood	Exercise→MRI→ Lumbar Puncture (Spinal Tap)

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2 Day Exercise Studies in CFS

- Maximum effort: VO_{2MAX}
  - Severely increases fatigue after exercise
  - Reduces the amount of exercise that can be done on the 2^{nd} day
  - Decreased VO2max on DAY 2
  - Keller, VanNess, Klimas, Fluge & Mella

- Submaximal Test
  - Same effect on both days
  - No difference in VO2 at peak effort

Keller et al. Journal of Translational Medicine 2014, 12:104
http://www.translational-medicine.com/content/12/1/104

JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO_2peak indicates functional impairment

Betsy A Keller[1*], John Luke Pryor[2] and Ludovic Giloteaux[3]

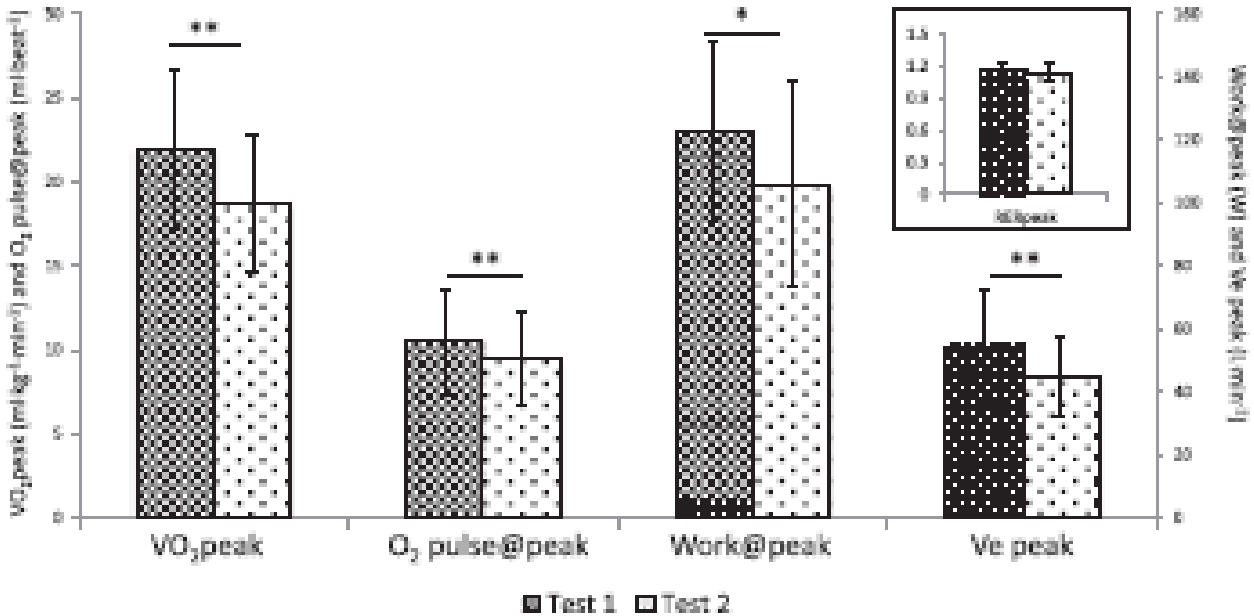


Figure 1 Changes in physiological and work variables from Test 1 to Test 2 at maximal intensity. Inset: Non-significant test differences for maximal respiratory exchange ratio showed that subjects achieved consistently high RER (>1.1) for Test 1 and Test 2, with maximum efforts on both tests (P = .157). Statistical significance is shown...

Table 2 Physiological and work variables for Tests 1 and 2 at peak and ventilatory threshold (VT) intensities, N = 22 (mean ± SD)

Peak exercise	Test 1	Test 2	%diff*	P
VO_2peak (ml kg^{-1} min^{-1})	21.9 (4.75)	18.6 (4.06)	−13.8%	.000¶
%predVO_2peak‡	77.1% (20.22)	65.2% (15.74)	—	.000¶
HRpeak (bpm)	159.4 (21.10)	150.0 (23.05)	−5.9%	.001¶
%predHRpeak†	91.0% (10.75)	85.2% (11.93)	—	.002¶
Work@peak (W)	122.7 (28.77)	105.7 (33.57)	−12.5%	.012∥
Ve peak (L min^{-1})	54.5 (17.56)	44.6 (12.63)	−14.7%	.003¶
VCO_2peak (L min^{-1})	1.91 (.477)	1.58 (.464)	−16.1%	.000¶
O_2 pulse@peak (ml beat^{-1})	10.48 (3.068)	9.46 (2.697)	−8.8%	.003¶
%predVO_2peak‡	77.1% (20.22)	65.2% (15.74)	—	.000¶
RERpeak	1.17 (0.079)	1.14 (0.081)	−1.9%	.157
Ventilatory threshold				
VO_2@VT (ml kg^{-1} min^{-1})	12.2 (3.68)	9.9 (2.89)	−15.8%	.003¶
HR@VT (bpm)	113.5 (21.78)	107.9 (20.61)	−4.9%	.086
Work@VT (W)	51.4 (24.97)	41.4 (28.8)	−21.3%	.030∥
Ve@VT (L min^{-1})	21.2 (6.07)	18.8 (4.86)	−7.4%	.035∥
VCO_2@VT (L min^{-1})	0.86 (.343)	0.72 (.265)	−11.3%	.014∥
O_2 pulse@VT (ml beat^{-1})	8.15 (2.603)	7.00 (2.323)	−12.6%	.003¶

*A negative %diff value indicates a decrease from Test 1 to Test 2.
†Percent of age-predicted maximum heart rate achieved.
‡% predicted VO_2peak for sedentary subjects from Bruce et al. [23].
∥Statistically significant difference between Test 1 and Test 2 at P < 0.05.
¶Statistically significant difference between Test 1 and Test 2 at P < 0.01.

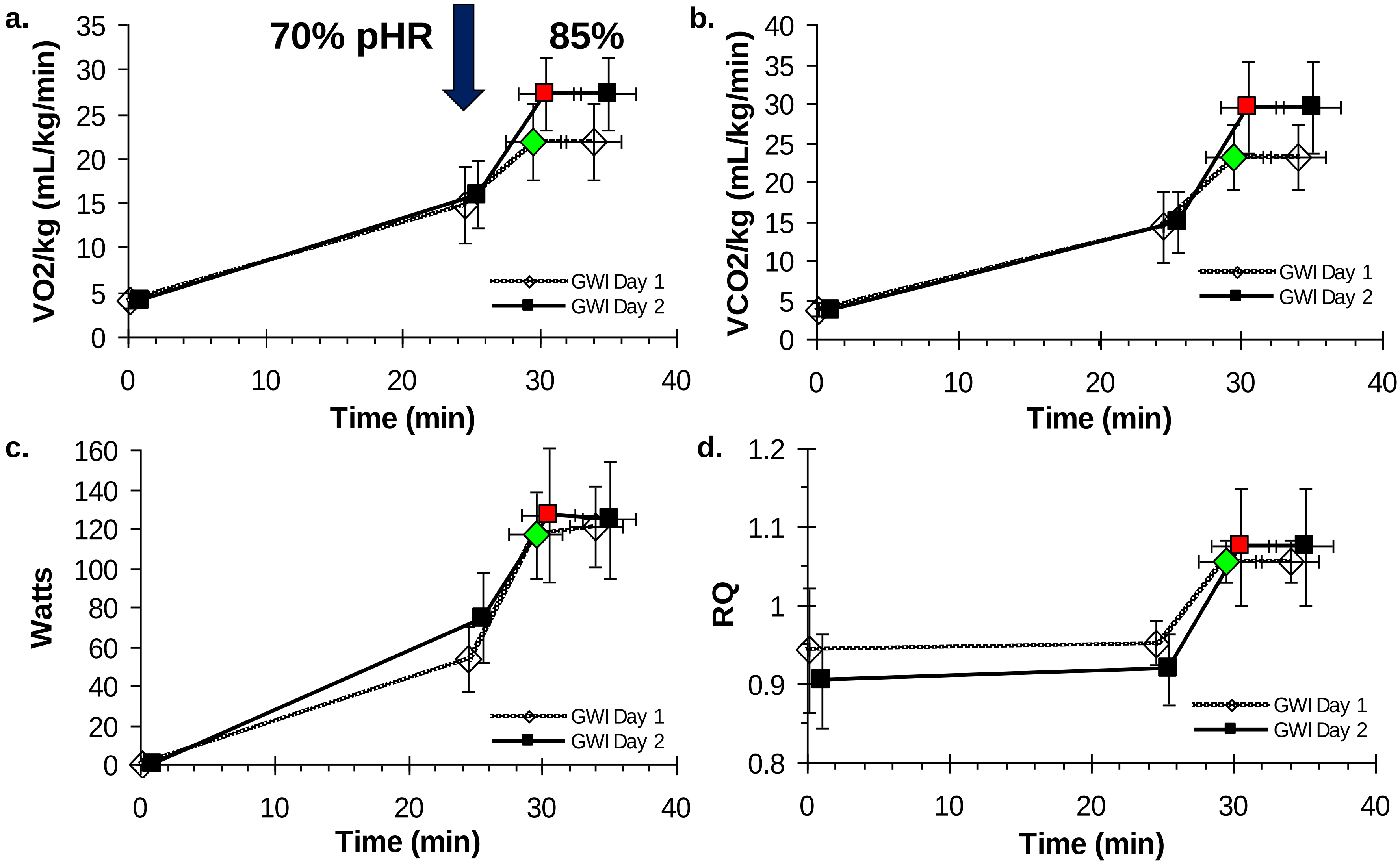
Max HR

Max HR on DAY 1=159 Drops to 150 on DAY 2

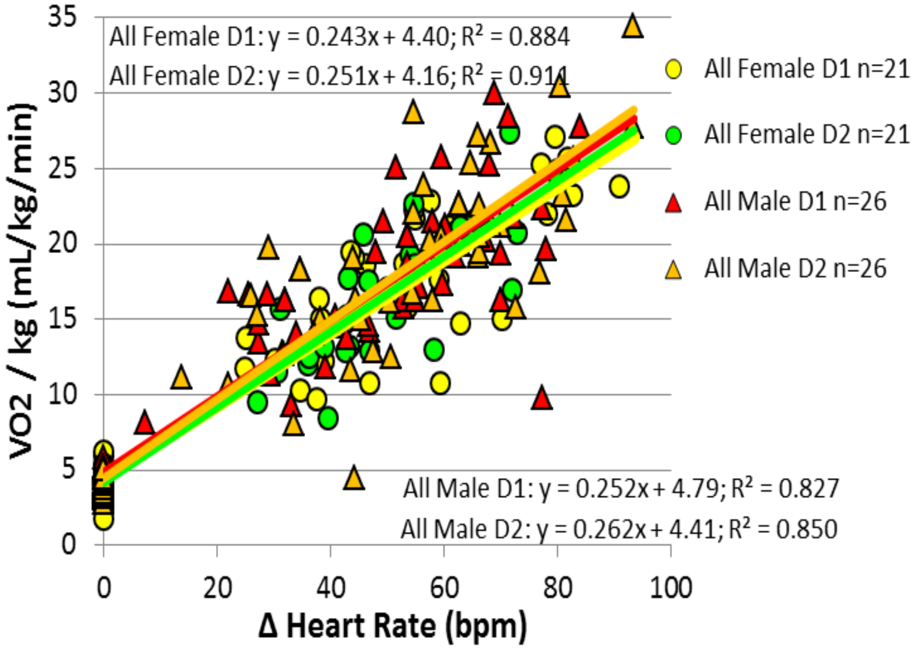
By definition, VO2 matches HR

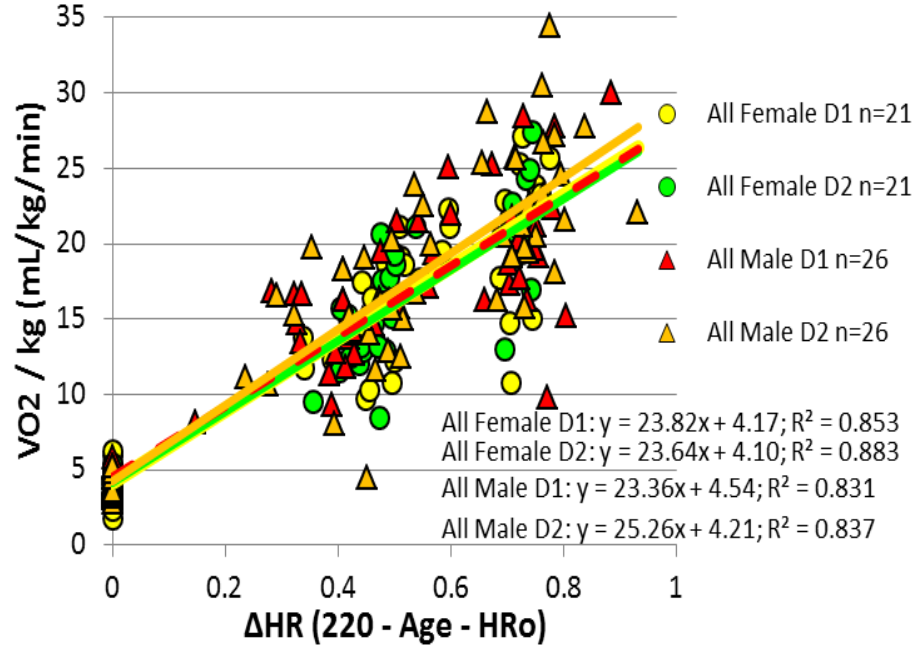
<u>Our Hypothesis:</u>
Dysregulation of brainstem heart rate is the cause of the DAY 2 drop in VO2max

Comparison of Exercise on DAY 1 and DAY 2



Linear Relationship Between VO2 and Heart Rate





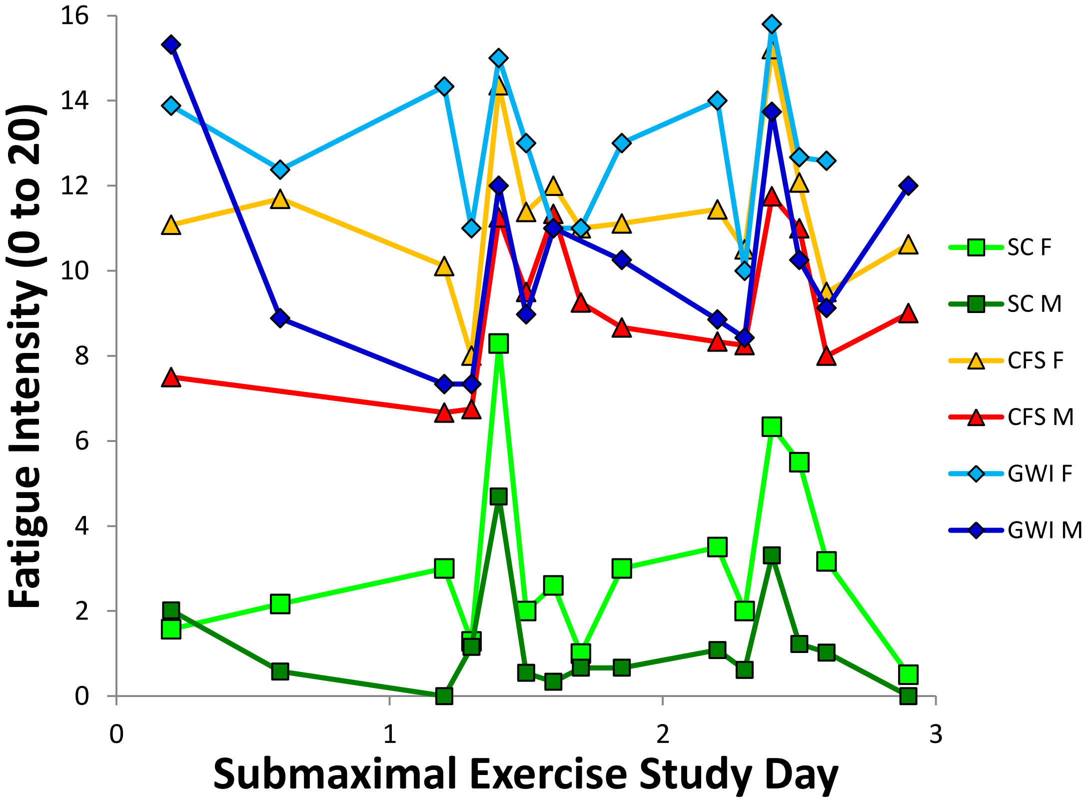
-The relationship between oxygen uptake by muscles and heart rate is linear when age and weight (gender) are accounted for.
-The maximal test on DAY 2 has decreased oxygen uptake and heart rate.
-The explanation is either “something magical happens between 85% and 100% HR or the brain puts the brakes on maximum heart rate on DAY 2 to limit use of energy.

SUBMAXIMAL Exercise and Fatigue

70% of predicted heart rate for 25 minutes

(Age – 220) x 0.7

Increase to 85% pHR (cardiac stress test; 5 min)



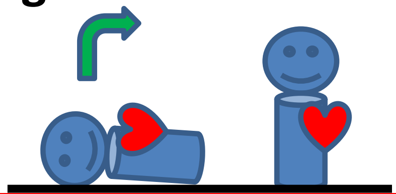
Fatigue increases with exercise in CFS and controls.

No overall change in fatigue because of the exercise

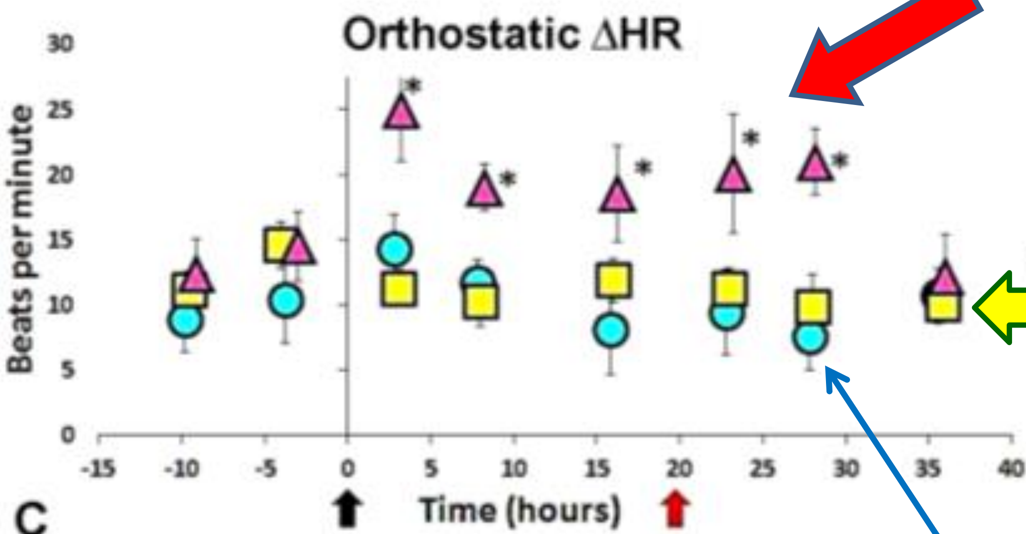
GWI: Objective Evidence

Exercise Separated 2 Groups of GWI Subjects

Heart rate Laying down → Standing up



Stress test activated reversible tachycardia = START group = 1/3rd of GWI



DAY 1 Exercise

DAY 2 Exercise

STOPP =
Stress test originated Phantom Perception
2/3rd of GWI
Activate brain regions as in phantom limb pain

Control Subjects

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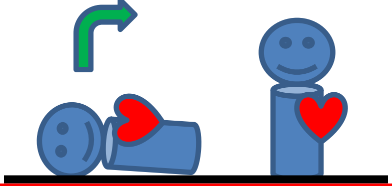
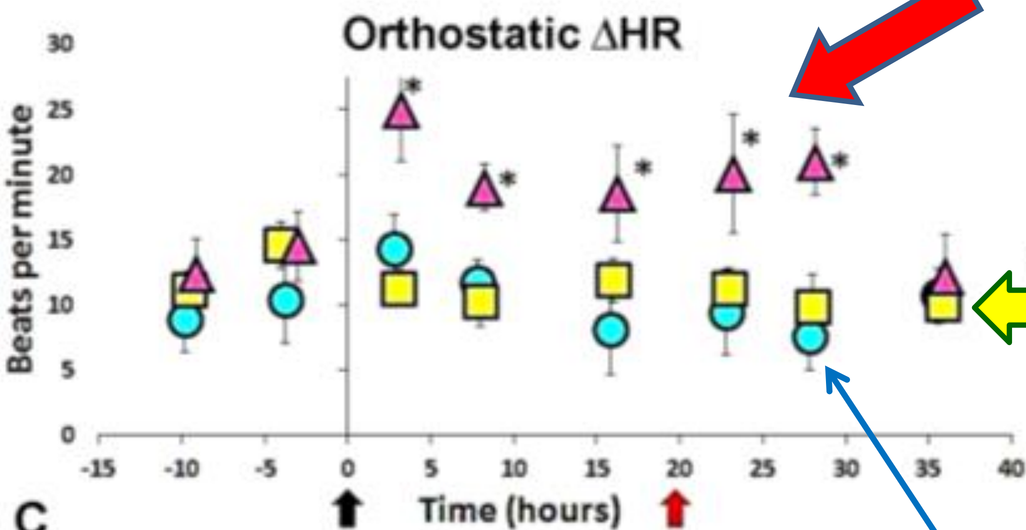


Stress test activated reversible tachycardia = START group = 1/3rd of GWI



DAY 1 Exercise

DAY 2 Exercise

STOPP =
Stress test originated Phantom Perception
2/3rd of GWI
Activate brain regions as in phantom limb pain

Control Subjects

Exercise – induced START subjects are also found in CFS

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Exercise

Add

Magnetic Resonance Imaging (MRI)

GWI: Objective Evidence

Exercise Separated 2 Groups of GWI Subjects

START only:
Loss of volume in the brain stem and cerebellum
Atrophy? Neurodegeneration?

MRI "slice" across the bottom of the brain through the pons and cerebellum

Colored regions are significantly shrunken compared to controls and STOPP group

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Loss of volume in the brain stem and cerebellum
Atrophy? Neurodegeneration?

MRI "slice" across the bottom of the brain through the pons and cerebellum

Colored regions are significantly shrunken compared to controls and STOPP group

Brain stem atrophy correlates with years of fatigue in CFS

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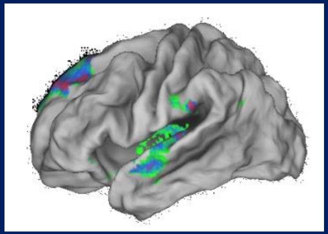
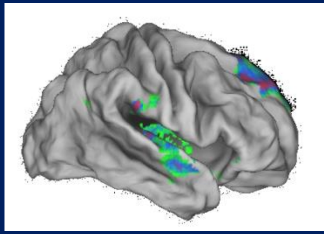
MRI - Exercise Study

HYPOTHESIS:

MRI before exercise on DAY 1 will show good brain function

MRI **DAY 1** → **DAY 2** **MRI**





→ Exercise on DAY 2 will show bad brain function

DAY		SC

CONTROL

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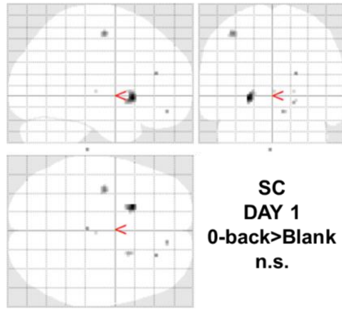
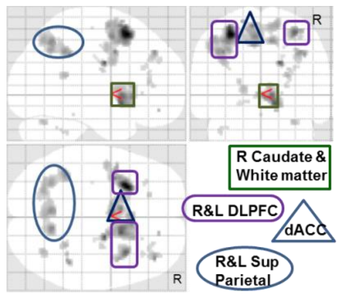


1

DAY 1:
Difficult task
Use cognitive reserve regions

2>Blank



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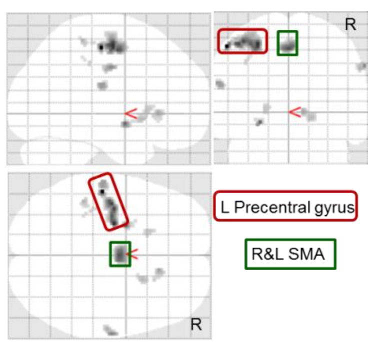
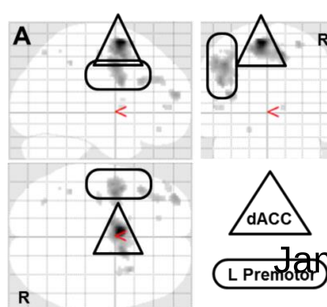


2

DAY 2:
Easier. Use fewer brain regions

2>Blank



DAY | SC | STOPP

0>Blank

CONTROL

1

DAY 1:
Difficult task
Use cognitive
reserve
regions

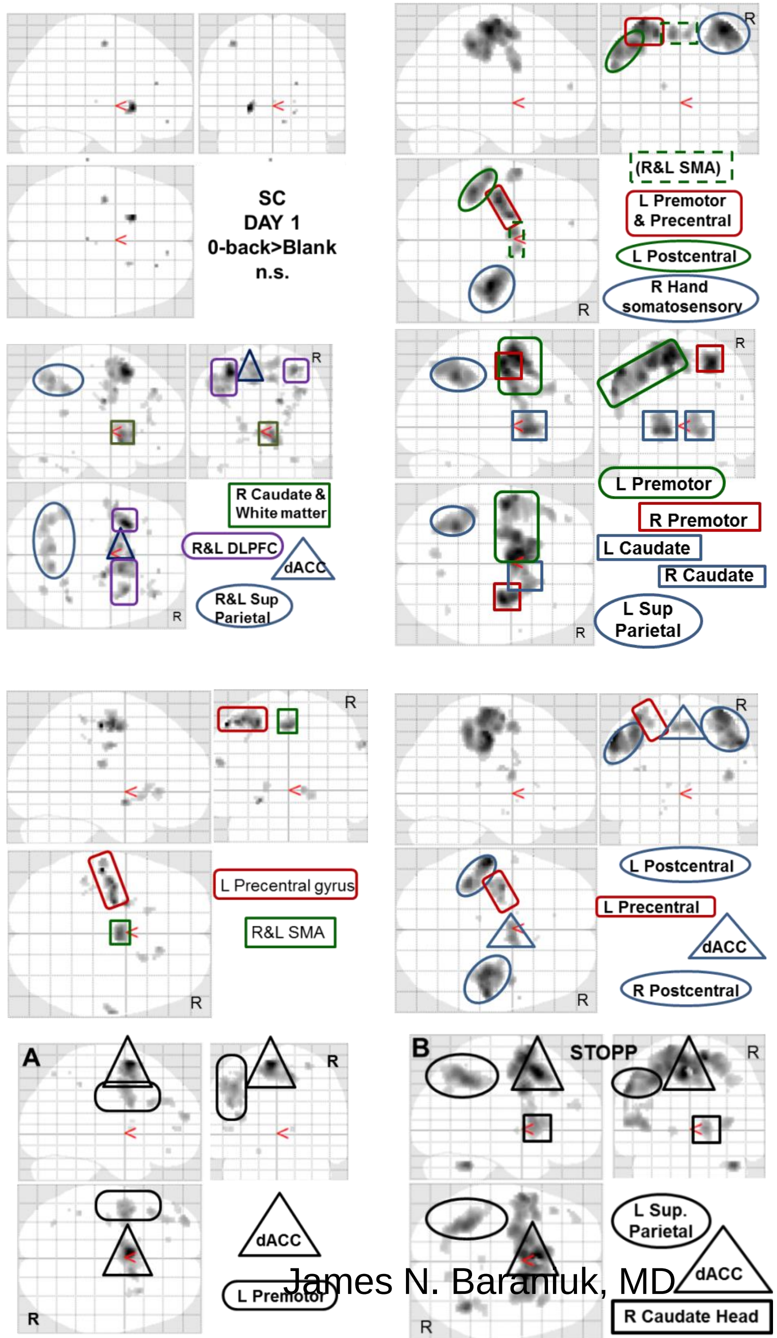
2>Blank

0>Blank

2

DAY 2:
Easier. Use
fewer brain
regions

2>Blank



STOPP

Phantom Perception

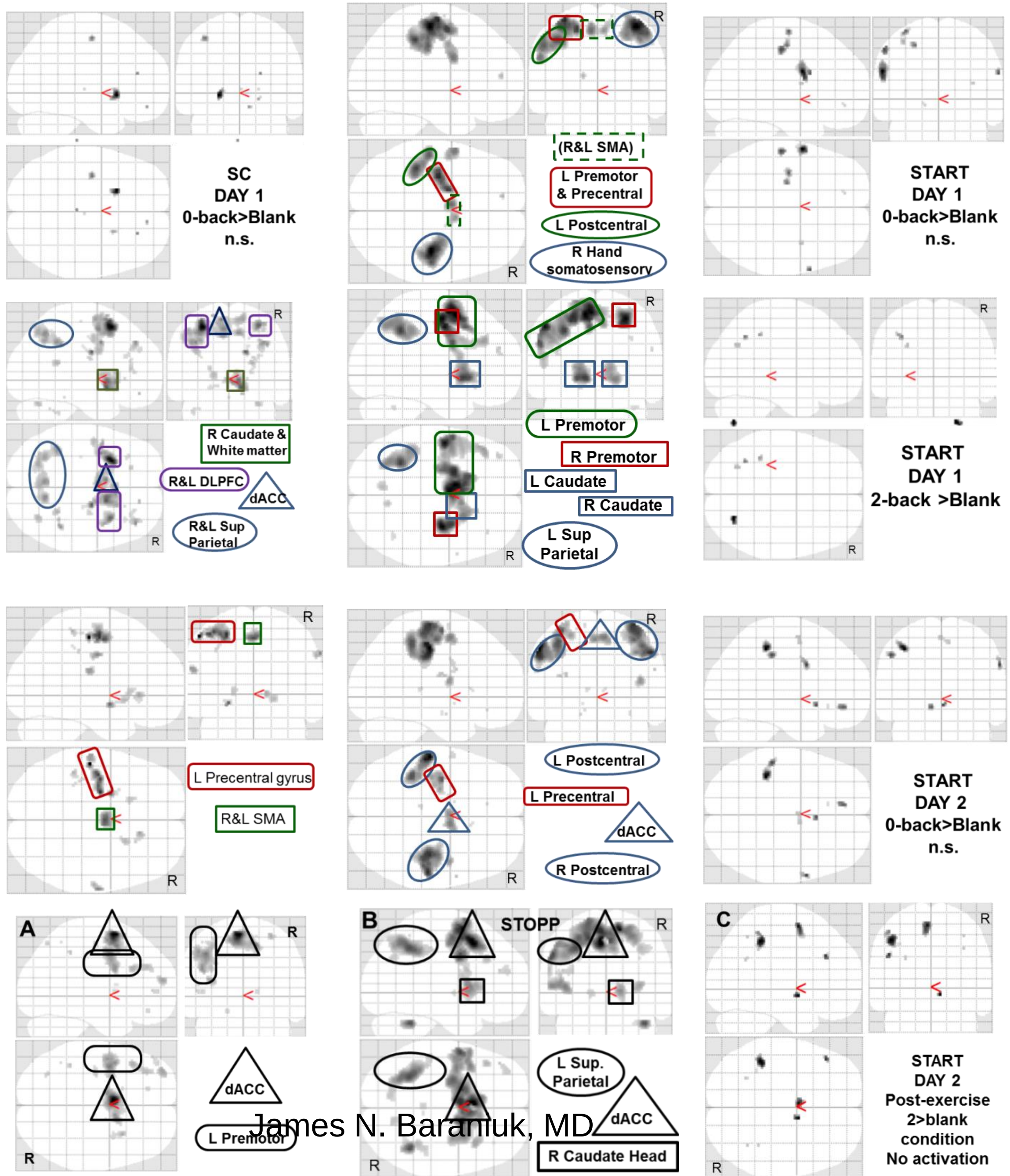
DAY 1:

Need to use lots of cognitive reserves

DAY 2:

Need even more cognitive reserve regions.

DAY		SC	STOPP	START
1	0>Blank			
	2>Blank			
2	0>Blank			
	2>Blank			



DAY 1:
Difficult task
Use cognitive reserve regions

DAY 2:
Easier. Use fewer brain regions

START

DAY 1:

Cannot start their brains.

DAY 2:

Cannot start their brains.

<u>Resting State Brain Networks</u>

- 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")

- <u>Different regions of the brain communicate with each other while a person was resting</u>
  - 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 **<u>Functional Connectivity</u>**

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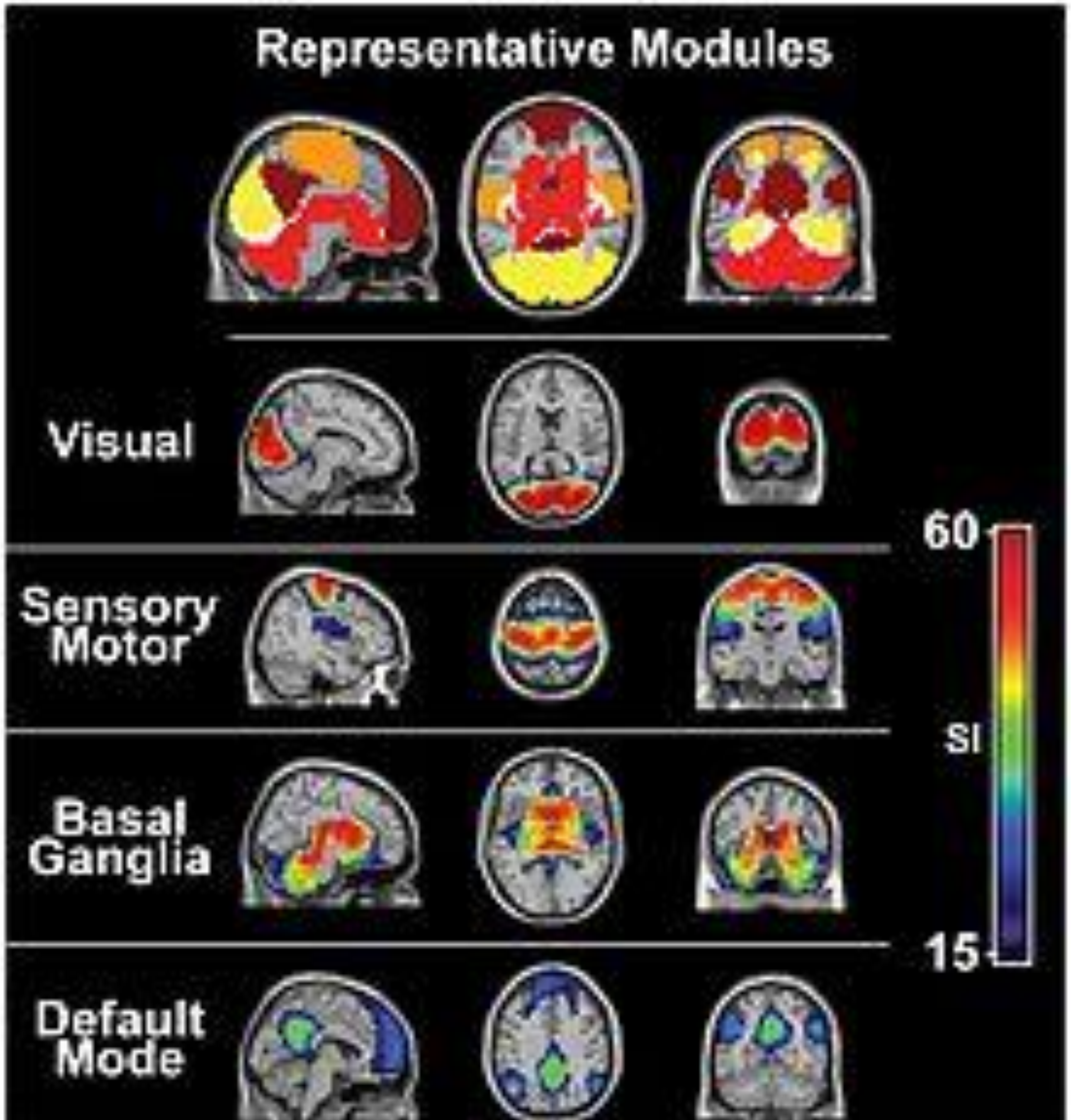
What brain regions are "connected" or acting together? Functional Connectivity

- 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

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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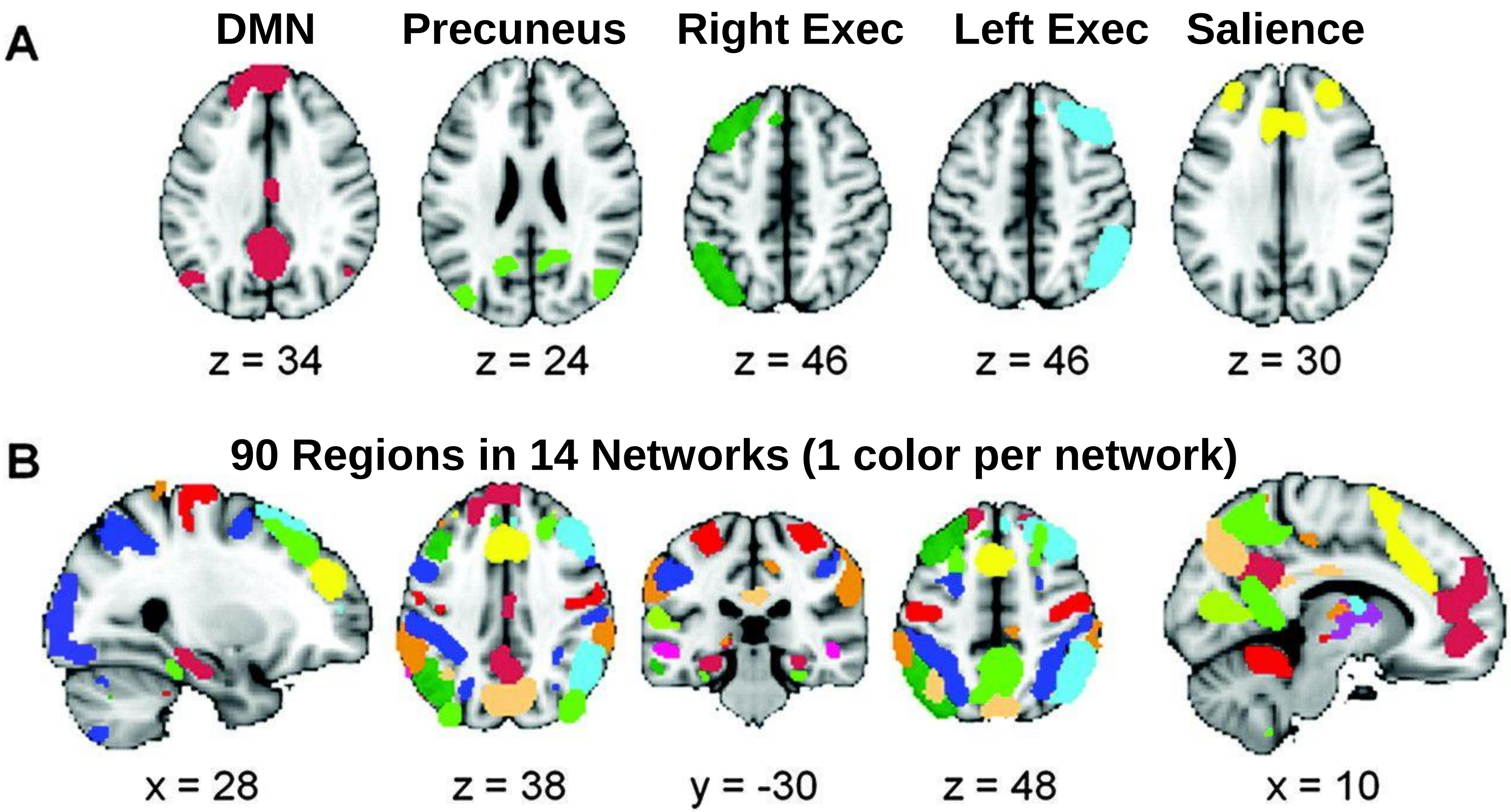
Functional Connectivity

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

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

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

STOPP

Exercise Decreases z (D1>D2)

Sal6	BG2

Prec2	ECN2
Prec2	ECN6

DMN2	Cbllm1	Cbllm2	DMN2
		Cbllm2	DMN3
		Cbllm2	DMN4
Prec2	Cbllm1	Cbllm2	Prec2
Prec4	Cbllm1		
		Cbllm2	DAN4
		Cbllm2	ECN3
		Cbllm2	ECN4
		Cbllm2	ECN7
		Cbllm2	Sal6
		Cbllm2	Sal7

Cerebellum: decreased connectivity with DMN, Salience, Executive Control

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

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DAN and Salience

STOPP

Exercise Decreases z (D1>D2)

Sal6	BG2

Prec2	ECN2
Prec2	ECN6

DMN2	Cbllm1	Cbllm2	DMN2
		Cbllm2	DMN3
		Cbllm2	DMN4
Prec2	Cbllm1	Cbllm2	Prec2
Prec4	Cbllm1		
		Cbllm2	DAN4
		Cbllm2	ECN3
		Cbllm2	ECN4
		Cbllm2	ECN7
		Cbllm2	Sal6
		Cbllm2	Sal7

Cerebellum: decreased connectivity with DMN, Salience, Executive Control

START

Exercise Increases z-Scores (D2>D1)

		Prec4	ECN3	
		Prec3	ECN3	
	Prec3	Prec3	Sal6	
	DMN2	Prec4	Sal7	
DAN2	DMN2		Sal7	ECN7
	DMN2	DAN3	Sal7	
	DMN3	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	Cbllm2	
		DAN1	Sal5		Prec1	Cbllm1	
		DAN1	Sal2			Cbllm1	Aud3
			Sal2	DMN2			
			Sal2	Prec3	Prec1	DMN1	
		ECN3	Sal2				
		ECN2	Sal2				
		ECN6	Sal1				

OBJECTIVE Mechanisms

CFS, SEID, GWI, CMI, FM Shared Features	Brain Network Interactions and Dysfunction
□ nociceptive, interoceptive & somatosensory central sensitization	**Salience network**: anterior Insula (perception, consciousness) → dorsal anterior cingulate cortex (dACC, executive decision making) → thalamus (sensory transmission hub) → insula
□ systemic hyperalgesia □ migraine	Spinal cord dorsal horn and **central sensitization**, neural plasticity, glutamate-mediated
□ 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 exercise-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

THE INNOVATION CENTER FOR BIOMEDICAL INFORMATICS

Chronic Fatigue Syndrome (CFS) and Gulf War Illness (GWI) Analysis in Cerebrospinal Fluid

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Shruti Rao

Dr. Amrita Cheema

Dr. James N. Baraniuk

Georgetown | Lombardi

Lumbar Puncture Patient Information:

Group	Description	Year of Protocol	# Patients	Males	Females
A	Healthy Before Exercise	2006	22	11	11
B	CFS Before Exercise	2006	43	9	34
C	GWI Before Exercise	2006	20	9	11
D	Healthy After Exercise	2009	7	7	0
E	GWI START After Exercise	2009	7	6	1
F	GWI STOPP After Exercise	2009	15	12	3

Spinal Headaches After 117 Lumbar Punctures

	LP-Induced Prolonged Headaches			No Prolonged Headaches	
	A. Strain-related spinal headache	B. Spinal headache	C. LP-Induced Migraine	D. No headache. Migraine history	E. No headache & no migraine history
N	6	12	20	35	44
LP-induced Photosensitivity	2 (33.3%)	7 (58.3%)	12 (60.0%)	0	0
LP-induced Migraine	2 (33.3%)	6 (50.0%)	17 (85.0%)	0	0

Intravenous fluids
Gatorade® (“Vitamin G”)
Aspirin
Clonazepam (anti-anxiety)
Sumitriptan (if atypical migraines, photophobia)
*** Pencil – tip spinal needles ***

<u>Avoid straining</u>
No lifting of luggage, weights
No back twisting or stretching
No long distance driving

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- Brain fog and brain networks
- Metabolomics of cerebrospinal fluid
  - Biomarkers, insights into pathophysiology
- Rituximab
- SEID

Rituximab in CFS

- Rituximab is a monoclonal anti-CD20 biological drug used to treat B-lymphocyte malignancies and autoimmune diseases
- Fluge and Mella observed that a CFS/ME subject with Hodgkin's lymphoma had remission of symptoms after rituximab.
- They recruited 2 other CFS/ME patients and again induced symptomatic remission.

Rituximab in CFS

- A randomized double blind placebo controlled study used 2 treatments with rituximab or saline in 30 CFS subjects.
- Fatigue improvement was “major” in 9/15 (60%) rituximab but only 1/15 (7%) placebo patients.
  - 1 rituximab subject was a non-responder
  - 2 placebo subjects improved spontaneously

Rituximab in CFS

- The recent open-label study examined the timing and frequency of treatment responses and relapse rates after rituximab was discontinued.
- Rituximab was given to 29 CFS patients using 2 infusions 2 weeks apart for induction, followed by maintenance infusions at 3, 6, 10 and 15 months. Follow-up was for 3 years.
- 21 subjects (72%) were rituximab responders
- Major responders (n=14) had an onset of action after 22 weeks that lasted 115 wk.
- Moderate responders (n=4) took 56 weeks to reach the "success" criterion with a 67 week duration of action.
- Marginal responders (n=3) had benefit at 86 weeks that lasted 25 weeks.
- 7 were nonresponders.

Rituximab in CFS

- Is CFS an autoimmune disease?
- When can we get a U.S. rituximab study?

Systemic Exertion Intolerance Disease (SEID)

- Post-exertional malaise / exertional exhaustion
- Sustained fatigue with impairment / disability
- Unrefreshing sleep
- Moderate to severe intensity
- Occur at least half of the time.
- And either cognitive or orthostatic alterations.
  - Cognitive impairment may be triggered by excessive effort of any kind, and manifest as “brain fog” with dysfunction of moment-to-moment, short-term working memory that is required for task completion and train-of-thought.
  - Orthostatic intolerance occurs as dizziness, lightheadedness, or malaise after standing up from a resting position. Postural changes in vital signs may not be evident.
- SEID criteria do not include pain symptoms because the strength of evidence is currently lacking.

Thank you for your patience and understanding.

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