Objective Findings in Gulf War Illness/Chronic Fatigue Syndrome
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Fatigue, widespread pain and tenderness, migraine, interoceptive and nociceptive somatic complaints are common subjective findings in chronic fatigue syndrome (CFS) and Gulf War Illness (GWI). Allergy, TH2, NK, and B cell dysfunction and autoimmunity have been suggested mechanisms.

One cardinal clinical feature of GWI/CFS is "exertional exhaustion". Exercise, cognitive or other stressors induce symptom relapse within 2 to 24 hr. To reproduce this finding, we developed a 2 day exercise provocation protocol. A bicycle exercise stress test on Day 1 was proposed to cause significantly worse performance when the same test was repeated on Day 2. Surprisingly, there was only a 20% worsening of symptoms of pain and fatigue. GWI subjects had significantly lower pain thresholds than controls indicating central sensitization and cerebral dysfunction leading to increased pain perception.

Magnetic resonance imaging (MRI) was performed before and after the exercise testing. "Static" tests measured of grey and white matter volumes, and white matter integrity by diffusion tensor imaging (DTI). White matter integrity was compromised in GWI subjects compared to sedentary controls. DTI may be useful to distinguish GWI from controls ("DIMENSION 1").

A cognitive test was performed to determine if exercise had any effects on working memory (accuracy on the 2-back test). "Dynamic" activation of different brain regions was assessed by blood oxygenation level dependent (BOLD) methods. The differences between the pre-exercise (Day 1) and post-exercise (Day 2) MRI scans revealed "kinetic" changes in BOLD patterns that were caused by exercise. This revealed mechanisms of exertional exhaustion.

Two patterns were found that divided GWI subjects into different phenotypes.

"DIMENSION 2": Half of the subjects had increased brain lactate levels (molecular spectroscopy) and accuracy on the 2-back test on Day 2 compared to Day 1 ("Increaser" phenotype). The other half had high lactate levels on both days and significantly worse accuracies on Day 2 ("Decreaser" phenotype). We propose dysfunction of the neuron-astrocyte lactate shuttle.

"DIMENSION 3": This set of findings was independent of DIMENSION 2. One third of GWI subjects developed postural tachycardia after the Day 1 exercise (START phenotype). This autonomic dysfunction has not been reported previously. START had brain stem atrophy by MRI, and BOLD activation of the midline cerebellum. After exercise, START maximized their brain blood flow on a simple task, so that they had no cognitive reserve to use on the difficult task.

The other 2/3rd of GWI had increased activation of the anterior insula as found in phantom limb pain ("Phantom Pain" = STOPP phenotype). They had no atrophy. After exercise, they showed a distinctly different BOLD pattern.

This study demonstrated objective evidence of brain grey and white matter dysfunction in GWI that was distinct from healthy controls, and that fit into 2 mutually exclusive DIMENSIONS. GWI is not a psychosomatic or allergic illness, but is a legitimate neurological disease.