

Treating Pain in Gulf War Illness (GWI)

Gulf War – Research Advisory Committee

J. Wesson Ashford, MD, PhD

Director, WRIISC-CA Site

Palo Alto VA Health Care System

wes.ashford@va.gov

War Related Illness & Injury Study Center (WRIISC)

www.warrelatedillness.va.gov

September 22, 2014

Approaching the Treatment of Pain

- The WRIISC experience
- Understanding Chronic Multi-symptom Illness???
- Tardive Sympathetic Dysautonomia (TDS)
- Symptoms Explained
- Pain Causation
- Management of Pain
 - Analgesics, Opioids
 - SNRIs (anti-depressants)
 - Sleep issues
 - rTMS
 - Exercise, YOGA
- Research – WRIISC projects



WRIISC

A national VA program established in 2001 to address post-deployment health issues.



Founding of the WRIISC

- Congressionally mandated
- Focus on epidemiologic research, Gulf War Registry, GW referral centers
- National Academy of Sciences Committee recommended Geriatric Research, Education, and Clinical Center (GRECC) model

WRIISC Mission

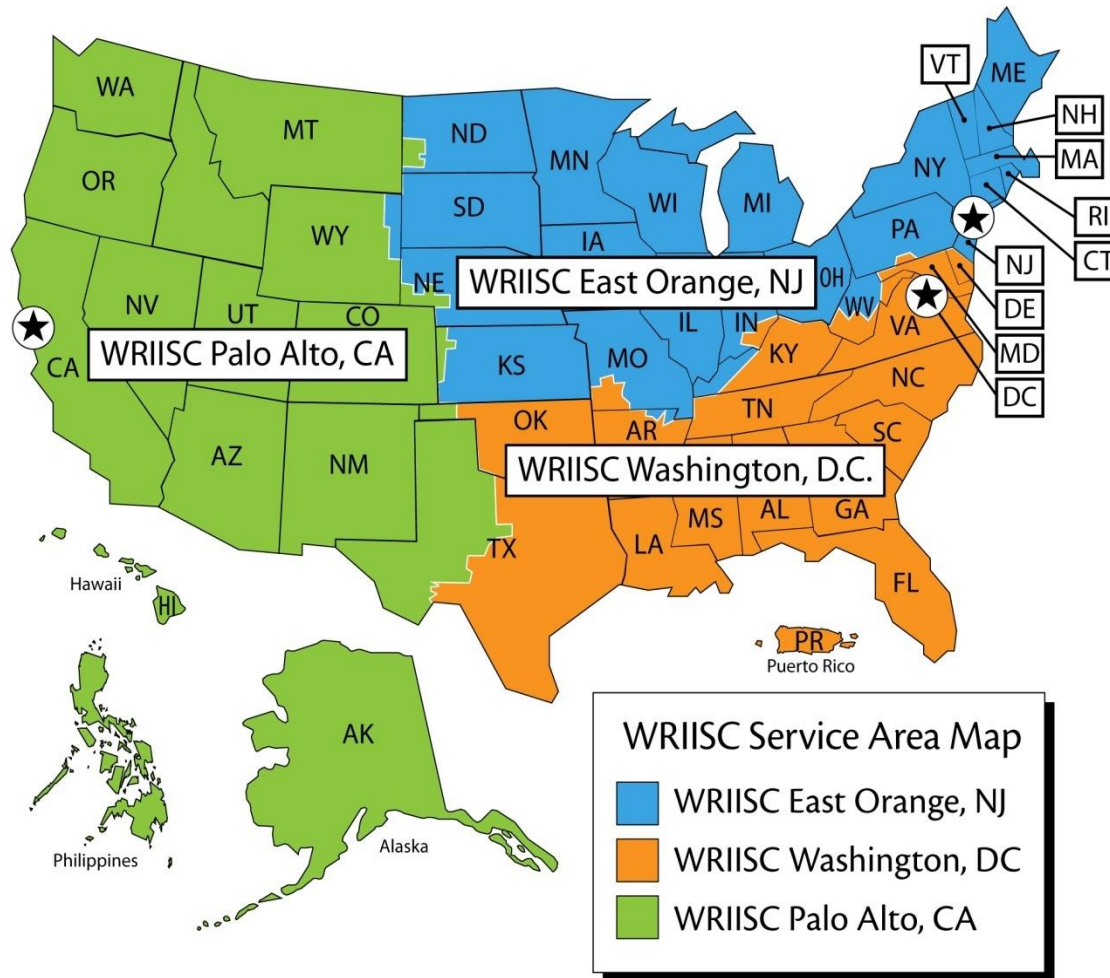
- To improve the health, quality of life and function of Veterans with *post deployment concerns* through clinical, research, education, and risk communication activities
- These include:
 - Chronic Multi-symptom Illness (CMI) (e.g., Gulf War Illness)
 - Occupational and environmental exposures
 - Complex and difficult-to-manage health conditions
 - Other conditions with unclear or controversial mechanism of disease (e.g., mild traumatic brain injury)

WRIISC Service Areas

CA WRIISC
1-888-482-4376
WRIISC.CA@va.gov
Dr. J. Wesson Ashford

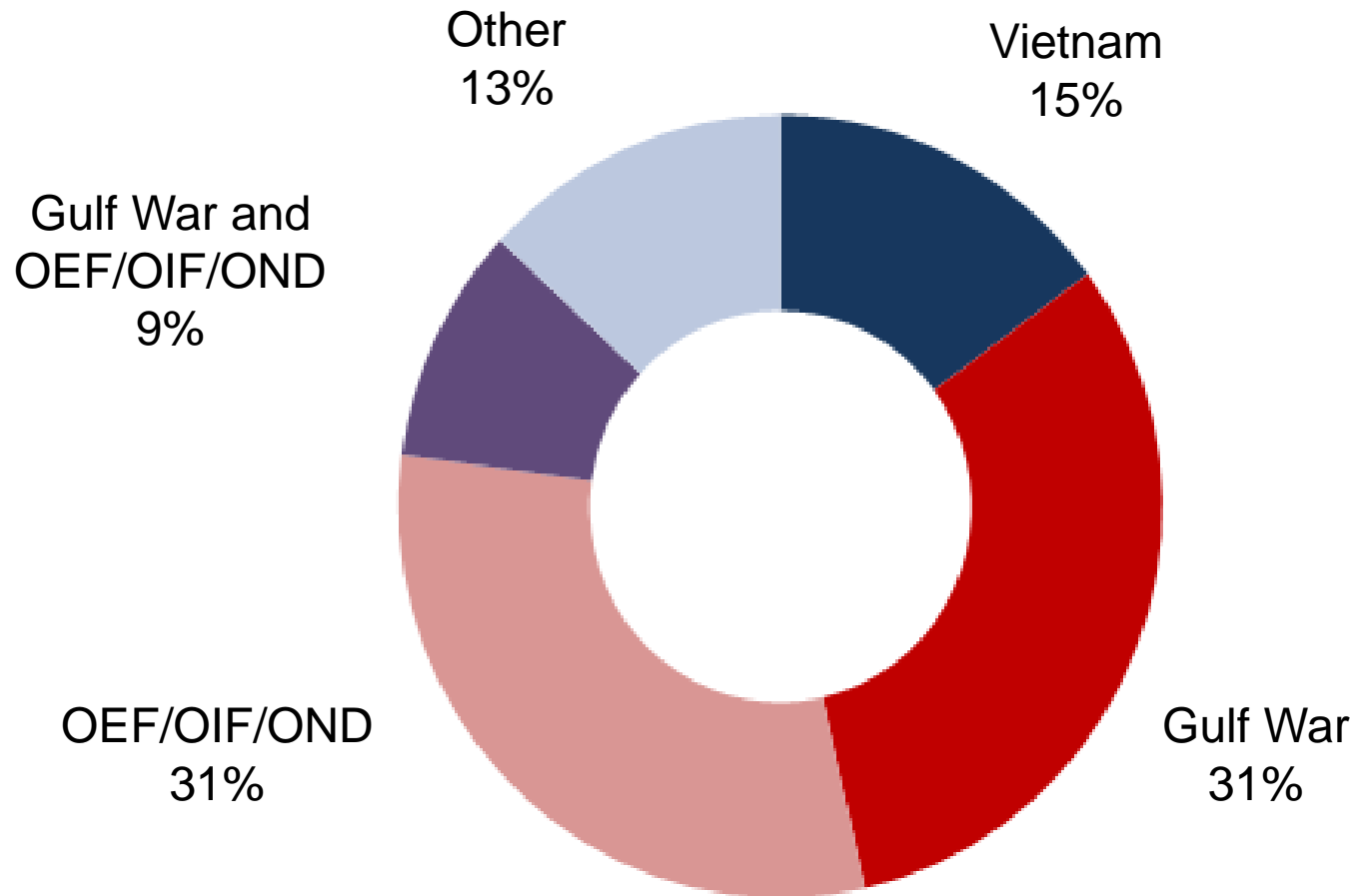
NJ WRIISC
1-800-248-8005
WRIISC.NJ@va.gov
Dr. Drew Helmer

DC WRIISC
1-800-722-8340
WRIISC.DC@va.gov
Dr. Matt Reinhard



The Veterans we serve

Most recent deployment for interfacility consults received in FY2013



Most Frequent Symptoms, Affected Systems of Veterans from Gulf War 1

Frequency of Symptoms of 53,835 Participants in VA Registry (1992–1997)

Symptoms

– Fatigue	20.5
– Skin rash	18.4
– Headache	18.0
– Muscle and joint pain	16.8
– Loss of memory	14.0
– Shortness of breath	7.9
– Sleep disturbances	5.9

Systems

– Musculoskeletal and connective tissue	25.4
– Mental disorders	14.7
– Respiratory system	14.0
– Skin and subcutaneous tissue	13.4
– Digestive system	11.1
– Chest pain	3.5

SOURCE: Murphy
et al., 1999

- Symptoms of fibromyalgia

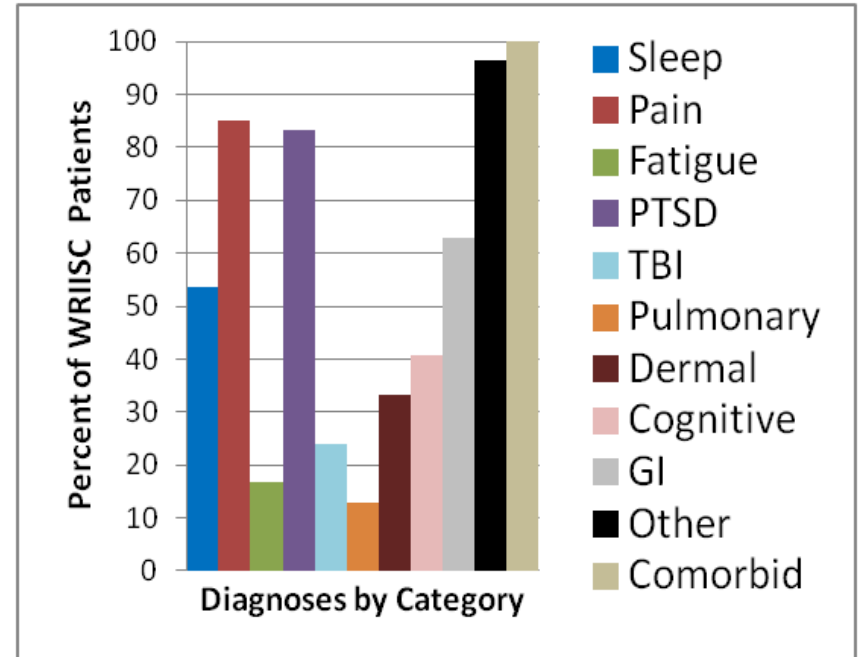
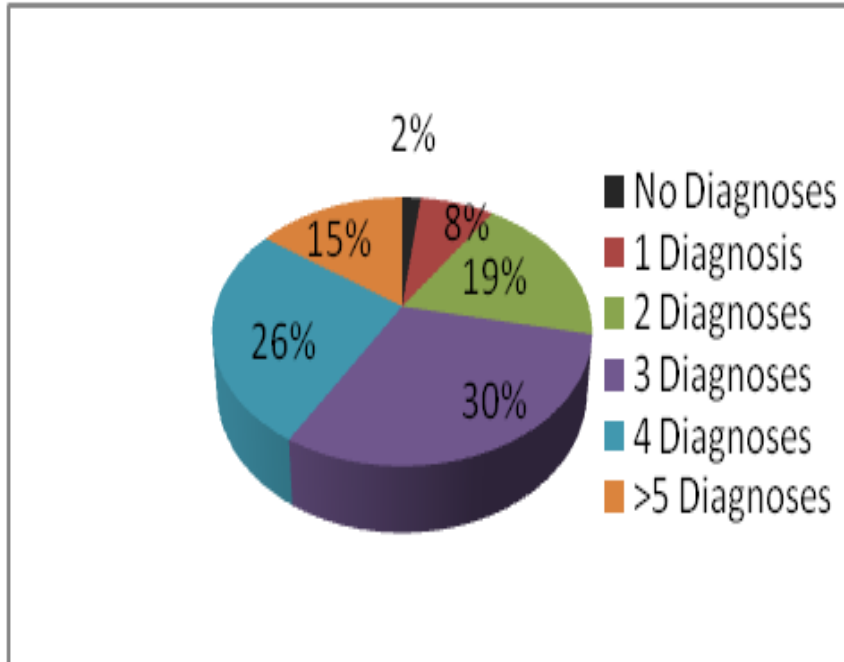
Results of Iowa Study – 3,695 Veterans:

Symptoms, % Prevalence

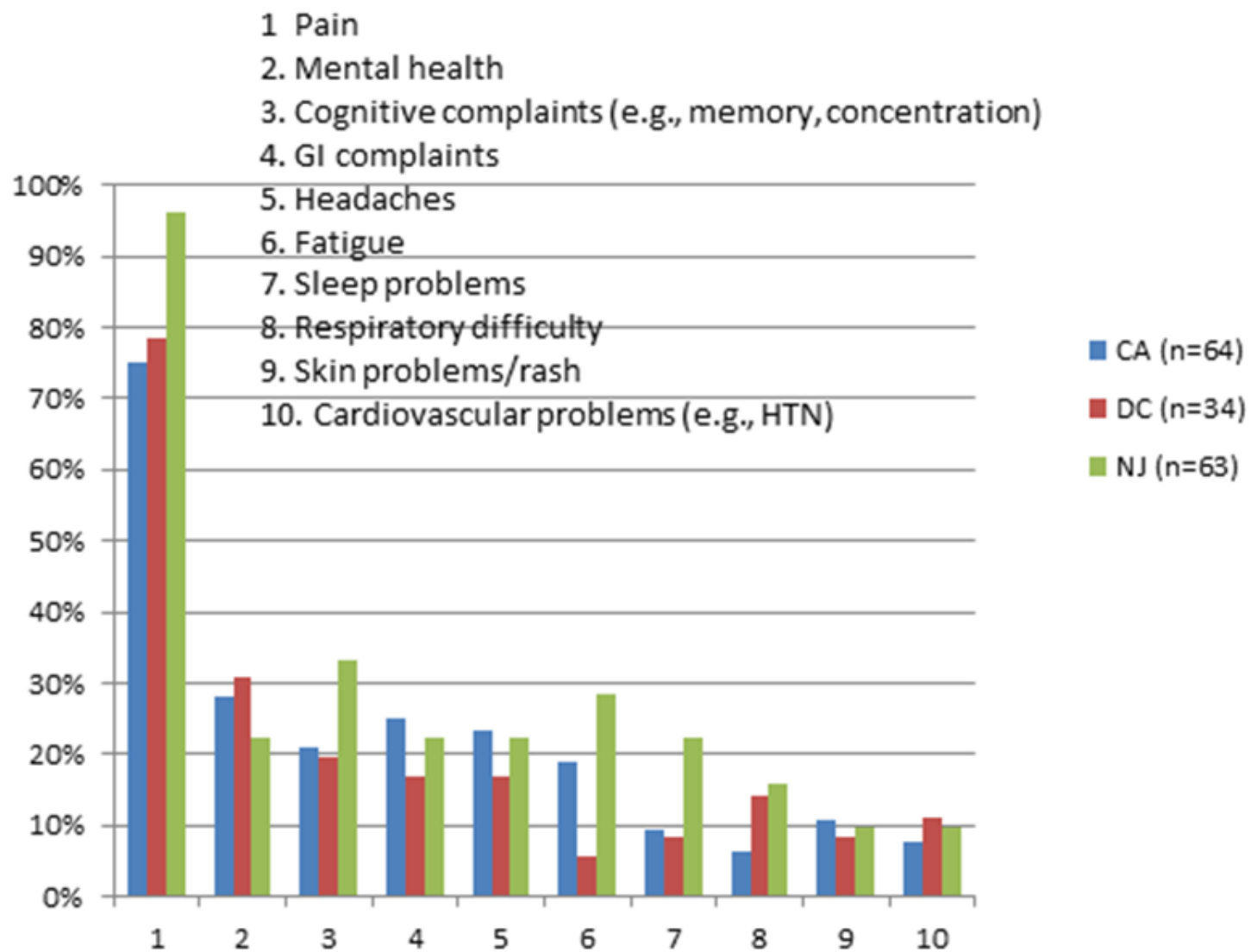
	GW Veterans	Non-GW Veterans
Fibromyalgia	19.2	9.6
Cognitive Dysfunction	18.7	7.6
Alcohol Abuse	17.4	12.6
Depression	17.0	10.9
Asthma	7.2	4.1
PTSD	1.9	0.8
Sexual Discomfort	1.5	1.1
Chronic fatigue	1.5	0.3

WRIISC-CA

- Since its creation in 2007, WRIISC-CA has evaluated over 200 complex referrals routed through Central Office from most States West of the Mississippi River (and all States West of the Rockies).
- Of these referrals, 42% have been Veterans of the First Gulf War.
- The largest single problem in the WRIISC referrals has been PAIN!!

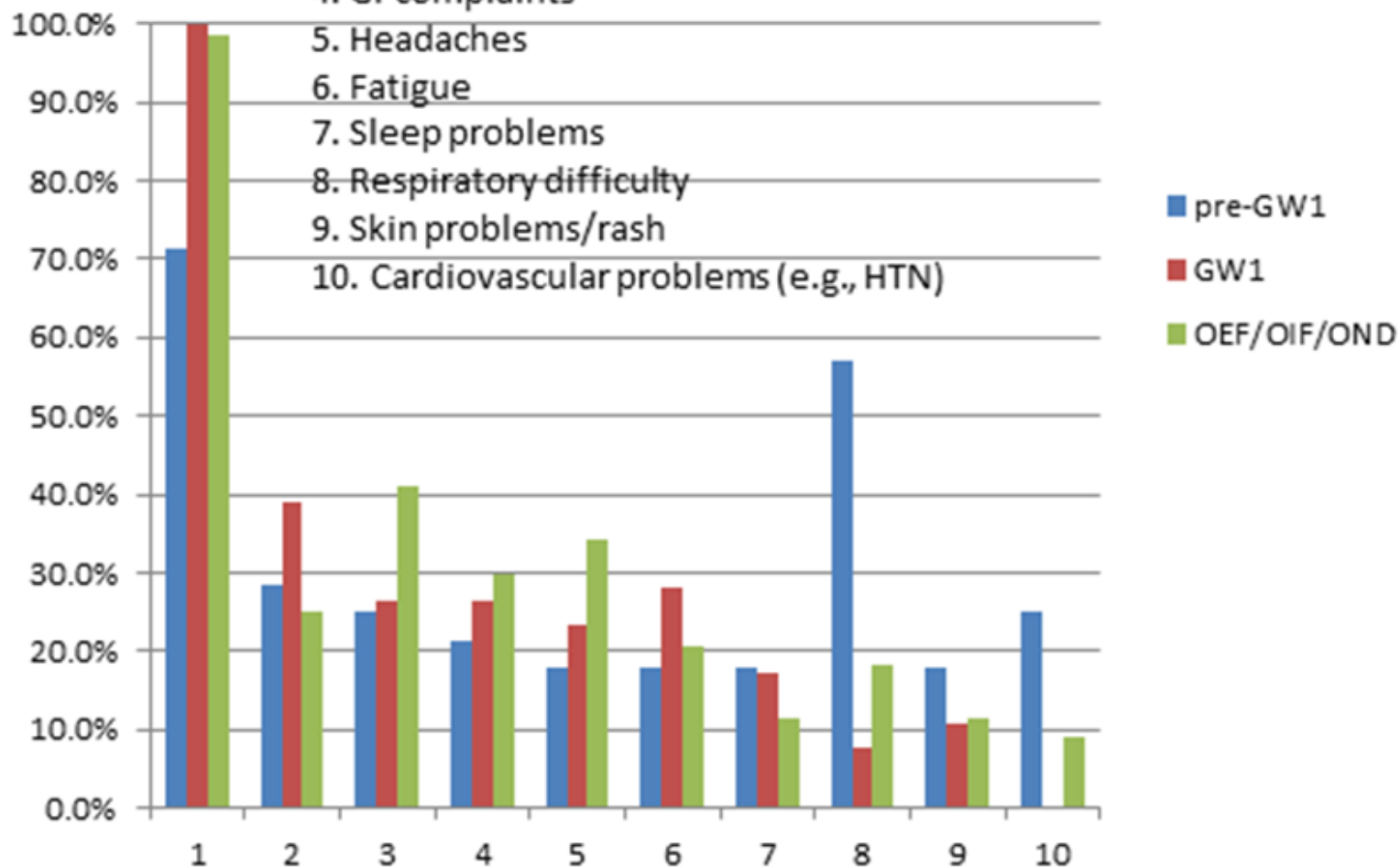


Top 3 Symptoms of Veterans Presenting to the WRIISC program - FY 2013

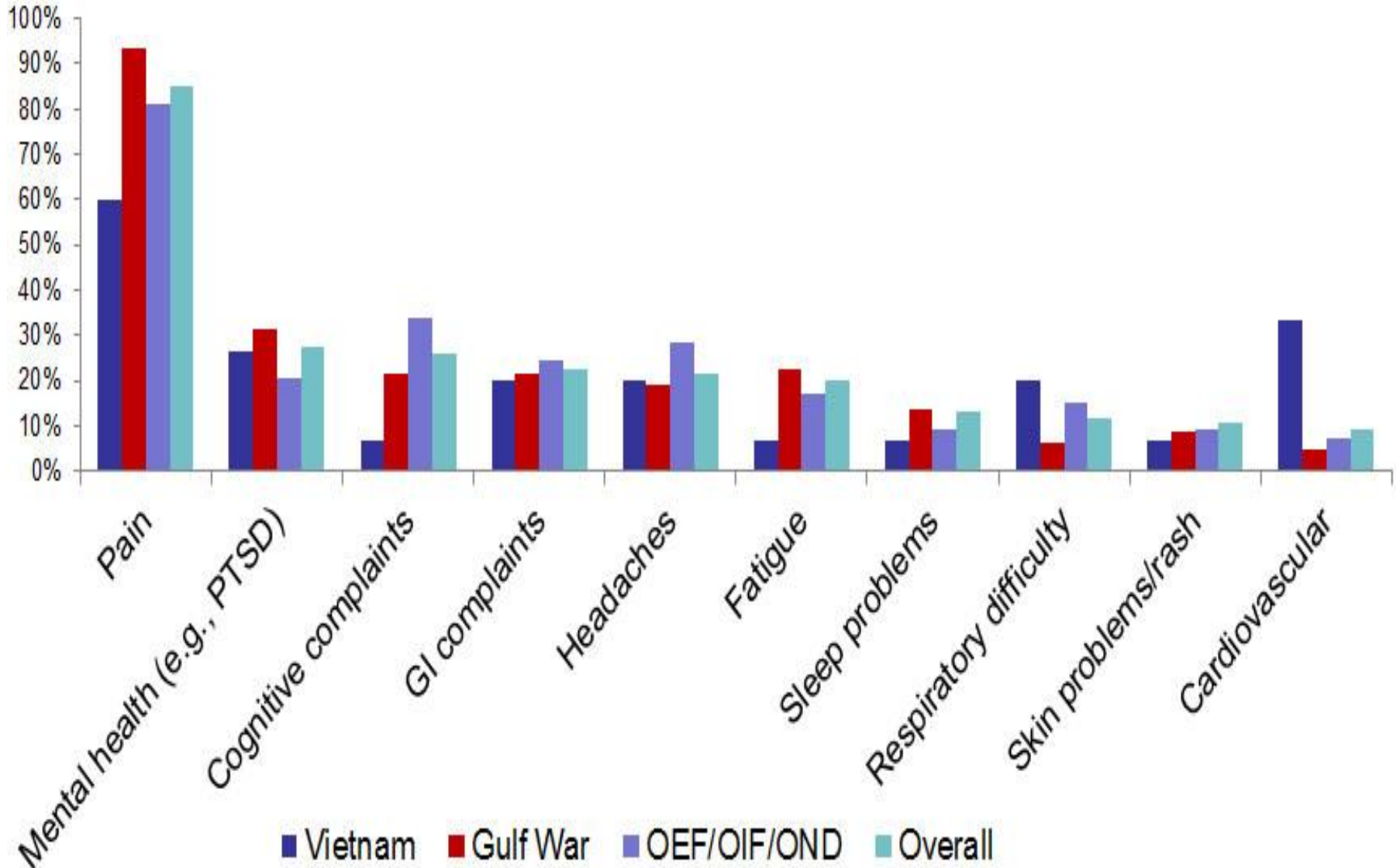


Top 3 Symptoms of Veterans Presenting to the WRIISC program - FY 2013

- 1 Pain
2. Mental health
3. Cognitive complaints (e.g., memory, concentration)
4. GI complaints
5. Headaches
6. Fatigue
7. Sleep problems
8. Respiratory difficulty
9. Skin problems/rash
10. Cardiovascular problems (e.g., HTN)



Veterans' Top Reported Symptoms



Gulf War Veterans Affected Systems

- Musculoskeletal
 - Gastrointestinal
 - Respiratory
 - Neurologic
 - Mood and Cognitive
 - Fatigue
 - Skin
-
- What do these systems have in common?

FUNDAMENTAL PROBLEMS

- There is no recognized “Gulf War Syndrome”
 - this was a transitional term
- “Gulf War Illness” is considered to exist
 - (Institute of Medicine, 2009)
 - But this term remains undefined
- “Chronic Multi-symptom Illness” provides no indication of the nature of the condition
- There have been many dozen explanations that have been considered, but none has yielded an acceptable explanation

Difficulties in Addressing Chronic Multisymptom Illness (CMI) in Gulf War Veterans

- Difficult to come up with a single case definition (diagnosis) for Gulf War Veterans Illnesses because of the many symptoms, some of which are not shared by all
- CMI is found in groups other than Gulf War Veterans
- There are no clinically validated tests or questionnaires for diagnosing CMI



Potential Operation Desert Shield/Desert Storm Exposure Concerns

- CARC Paint
- Chemical and Biological Weapons (Sarin, Soman)
- Depleted Uranium
- Harsh living conditions
- Incoming fire, explosive events
- Industrial solvents and chemicals
- Infections
- Injuries, musculoskeletal wear and tear
- Loud noises
- Oil Well Fires, Smoke, and Petroleum
- Pesticides
- Physical and Mental Stressors
- Pyridostigmine Bromide
- Sand, Dust, Airborne Particulate Matter
- Vaccinations

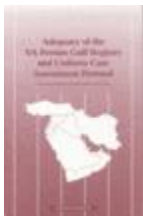
Numerous Institute of Medicine Studies/Reports on Gulf War Illness



January 1, 1995
Health Consequences of Service During the Persian Gulf War: Initial Findings and Recommendations for Immediate Action



January 1, 1996
Health Consequences of Service During the Persian Gulf War: Recommendations for Research and Information Systems



January 1, 1998
Adequacy of the VA Persian Gulf Registry and Uniform Case Assessment Protocols



January 1, 1998
Measuring the Health of Persian Gulf Veterans: Workshop Summary



August 1, 1999
Gulf War Veterans: Measuring Health



January 1, 2000
Gulf War and Health: Volume 1. Depleted Uranium, Sarin, Pyridostigmine Bromide, and Vaccines



July 26, 2001
Treating Symptoms and Syndromes



August 20, 2004
Gulf War and Health: Updated Literature Review of Sarin



September 12, 2006
Gulf War and Health: Volume 4. Health Effects of Serving in the Gulf War

At least 3 more from the IOM since 2006

Gulf War Illness Findings

No Identified Diagnostic Entity

- **Somatic Medical** - normal x-rays of joints
- **Neurological** -
 - peripheral electrophysiological abnormalities have been reported
 - normal MRI, PET scans
 - abnormal SPECT, MR spectroscopy, replication unclear
- **Psychiatric** –
 - depression
 - neuropsychological dysfunction – questionable vs hard to measure
- **Possible relation to other conditions**
 - chronic fatigue syndrome, fibromyalgia, IBS (irritable bowel syndromes), multiple chemical sensitivity, TBI (traumatic brain injury – especially from blasts)

Chronic Multi-symptom Illness Gulf War One Type

(see new definition from IOM 3/12/2014)

Complex Exposures Can Affect Large Groups and Lead to a Unique Variety of Conditions, Symptoms and Disorders.

Consider that there are many exposures and other factors that lead combat Veterans to have a higher incidence of a particular variety of symptoms. Those symptoms may result from a multitude of causes. Further, each conflict, having different exposures, may induce a different constellation of symptoms.

In all cases, treatments must address the symptoms of the Veterans, minimize their discomfort, and maximize their function.

Some of Possible Causes

- Cholinesterase inhibitors (including chemical weapons)
 - Pyridostigmine Bromide (PB tablets), Organophosphate Pesticides, other chemical pesticides, Sarin and Cyclosarin
- Other chemical exposures
 - CARC - Chemical Agent Resistant Coating, fuel, decontamination solution, oil fires
- Infectious Diseases
 - Leishmaniasis, travelers diarrhea, sandfly fever, malaria, and viscerotropic leishmaniasis found in 12 U.S. veterans
 - mycoplasma fermentans (cover of Popular Science, 1999)
 - Travelers diarrhea (foreign bacteria affecting gut, possible side-effects)
- Multiple vaccinations
 - Anthrax vaccine containing squalene as an adjuvant
- Depleted Uranium (as a heavy metal toxicity)
- Aspartame/Methanol Poisoning
 - At 85 °F, aspartame breaks down into methanol which then breaks down into formaldehyde

Idiopathic Small Fiber Neuropathy (an example of a possible explanation)

- Caused by diabetes, HIV, Erythromelalgia, postherpetic neuralgia, CRPS, alcoholism, and many other nerve pain conditions
- There are no known causes for most cases and most tests do not identify it
- This condition may provide a path to explaining the symptoms of the First Gulf War Veterans
- Autonomic Nervous System (peripheral, not somatic)
 - Parasympathetic nervous system – less relationship
 - Sympathetic nervous system – (relation to fibromyalgia, IBS, chronic fatigue)

Plausible biological explanations for small nerve fiber disorder in Gulf War I Veterans

- Anti-cholinesterase agents (insecticides, DEET, permethryn, flea collar stories, sarin exposure, combinations, PB predisposal).
- Spider Bites – toxin, not infectious agent, but a biological toxin that could damage small neurons
- Immunological response – chronic response to infectious agent attacking small neurons (like Guillan-Barre syndrome – auto-immune)
- Reaction of body to severe diarrhea or agent that caused severe diarrhea (local fruits, vegetables given to soldiers deployed early) or could be related to local bacteria (? virus) that has property of inducing irritation of peripheral neurons – anti-body, toxin

Anti-Cholinesterase Withdrawal Hypothesis

- Acetylcholinesterase inhibitor exposure is the factor most closely associated with “Gulf War Illness”
 - Golomb 2008 – (though disputed by Blazer et al., 2008)
- Anti-cholinesterase agent exposure was widespread, including:
 - Insecticides (DEET, permethryn, flea collar stories)
 - Sarin exposure (unlikely significance since no deaths)
 - Pyridostigmine Bromide (PB) – widely administered for months
 - Combinations
- The reported symptoms are not typical of anti-cholinesterase effects, and PB is commonly used long term with myasthenia gravis.
- A potential explanation is that withdrawal from the anti-cholinesterase agents, particularly PB, could have induced a diffuse anti-cholinergic state, with post-synaptic production of nerve-growth factor (NGF), leading to aberrant peripheral neuron sprouting (sympathetic predominant and all of the symptoms typically reported in First Gulf War Veterans, particularly chronic pain and GI irritability).
 - (Like tardive dyskinesia – see in withdrawal from dopamine antagonists)
- Alzheimer patients withdrawn from cholinesterase inhibitors often have rapid declines and unexplained early deaths

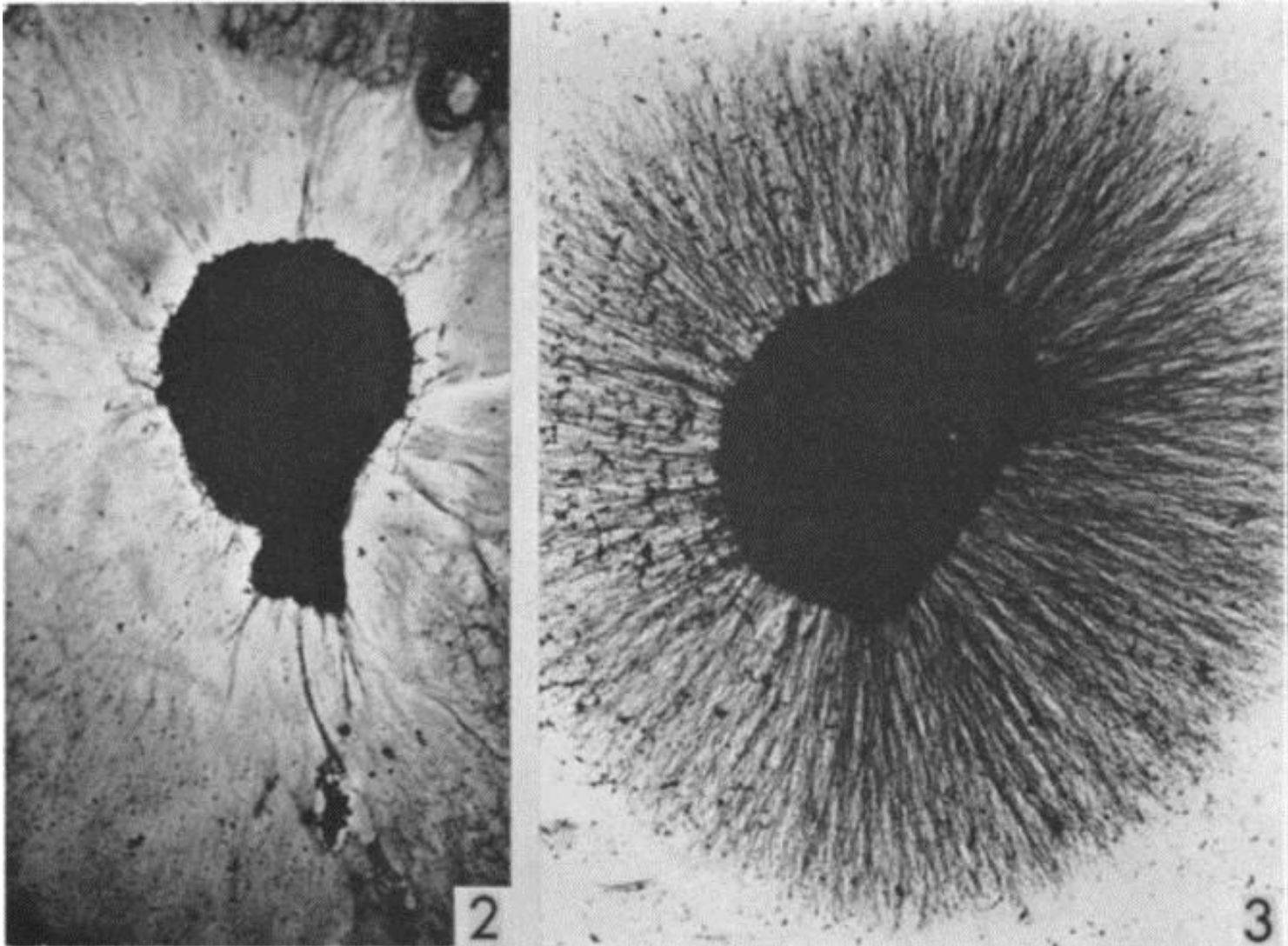
Tardive Sympathetic Dysautonomia (TSD)

- Sympathetic nervous system-predominant dysautonomia is common in fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome, raising the possibility that such dysautonomia could be their common clustering underlying pathogenesis. (Martínez-Martínez et al., "Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies.". J Clin Rheumatol, 2014)
- Occurs late in Gulf War Veterans, usually after return
 - (tardive; not a dystrophy – probably an excess of connections)
- The Gulf War Veterans have many symptoms
 - usually unexplained (most have possible autonomic relationship)
 - (cases with a clear cause get specific treatment recommendations)

NGF (nerve growth factor)

- NGF stimulates the outgrowth of sympathetic (norepinephrine) ganglion fibers
- NGF injections are related to chronic pain syndromes (seen Alzheimer's disease subjects)
- NGF genetic abnormalities are associated with a lack of pain sensation (Carvalho et al., 2014)
- Sympathetic neurons also moderate gut motility and blood flow everywhere, including the brain, and pathways to the pineal gland moderate sleep and energy levels,

Nerve Growth Factor (NGF) effect (Right) on sympathetic ganglion



Levi-Montalcini, Booker, PNAS, 1960

Levi-Montalcini won the Nobel prize for this image in 1986

Chronic Pain Syndromes

- **Chronic Regional Pain Syndrome (CRPS)**
 - (described as the most painful long-term condition)
 - **Type 1: Reflex Sympathetic Dystrophy (RSD)**
 - No demonstrable nerve lesions
 - **Type 2: Causalgia**
 - Related to specific nerve injury – presumable sympathetic nerve pathways
- **Chronic Pervasive Pain Syndrome (CPPS)**
 - **Tardive Sympathetic Dysautonomia (TSD)**
 - possibly NGF related – excess connections
 - Difficult to determine histopathologically

Possible Treatments for Pain and other Symptoms of Gulf War Illness

- Pharmacologic
 - Avoid narcotics, tranquilizers, central anti-cholinergics
 - May consider opioid blocking agent – naltrexone (note recent FDA action)
 - Consider anti-depressants with anti-pain effects
 - With anti-cholinergic effects: Nortriptyline, doxepin (stabilize GI symptoms)
 - Without anti-cholinergic effects: duloxetine, bupropion (note recent FDS action)
 - Anti-convulsant agents: gabapentin, pregabalin
 - Consider cholinergic agents (galantamine – short acting)
 - Numerous adrenergic agents – alpha, beta, etc.; melatonin
- Non-pharmacologic Approaches
 - Exercise – low-impact, non-exhausting, graded
 - 150 minutes/week
 - Swimming (need more use of Masters Swimming Programs – free to Vets: www.usms.org)
 - Aerobic exercises - elliptical exercise machines
 - Stretching and resistance routines
- New approaches needed for pain control
 - CAM: Yoga, Acupuncture
 - Noninvasive brain stimulation (rTMS)

Primary care, GWI and VA resources

- Without an “expert” GWI clinic, care is still accessible in the VA
 - WRIISC is developing SCAN-ECHO program
- PCP to manage endocrine, pain, sleep
- Sleep clinic to rule out apnea and assist in restorative sleep
 - Teach basic sleep hygiene principles
- Rehab/PT/chiropractic/acupuncture to help with pain management and develop rehab program. MOVE would need adaptation to the limits of the illness
- Cardiology for autonomic dysfunction if needed
- Pulmonary or Cardiology for shortness of breath
- GI Clinic for management of IBS (irritable bowel syndrome)
- Dermatology for management of skin problems
- Endocrine for complex endocrine management, metabolic disorders
- Comorbid conditions management as needed
 - Watch for PTSD and situational depression, suicide risk.



Treatment Recommendations from the 2001 IOM Report: Condition/Symptom Specific

Conditions	Recommendations
Chronic fatigue syndrome (CFS)	Cognitive behavioral therapy (CBT) and exercise therapies
Depression	Antidepressant medication (AD meds) and psychotherapy (CBT or interpersonal therapy)
Fibromyalgia	Do NOT use opioids or glucocorticoids Monitor results of studies on physical training, tricyclic antidepressants, and acupuncture
Headache	Medication mgmt of acute episodes, prophylactic medication for frequent headaches that disrupt functioning, behavioral and physical tx: relaxation training, EMG biofeedback, CBT, or behavioral therapy with drug therapy
Irritable bowel syndrome (IBS)	CBT, tricyclic antidepressants, smooth muscle relaxants
Panic disorder	Antidepressant and CBT
Posttraumatic stress disorder (PTSD)	Antidepressants (SSRIs, trazodone), prazosin, and CBT
Medically unexplained symptoms (MUS)	Develop explicit criteria for MUS, stepped intensity-of-care program, monitor studies of AD meds and CBT)



Treatment Recommendations from the 2013 IOM Report – Focus on CMI

Symptom	Treatment
Chronic Pain	NSAIDs (for acute use only), SNRIs & tricyclic med., pregabalin for central neuropathic pain, radio freq. ablation for LBP, acupuncture for LBP and headache
Fatigue	CBT, graded exercise (see handout), improve sleep patterns, CPAP when needed, reduce medication usage
Sleep Disorders	Prazosin, trazodone for PTSD-related nightmares, good sleep hygiene, exercise, acupuncture, mind-body approaches
Gastrointestinal Disorders	Tricyclic (doxepin) or SSRI medication, relaxation and stress mgmt along with CBT or interpersonal therapy
Depression	CBT, interpersonal therapy, exercise, acupuncture for mild, antidepressants for moderate, other med or tx for severe

The WRIISC-CA program has a major focus on the diagnosis and treatment development for GWI Veterans

Funded Studies:

rTMS (repetitive Transcranial Magnetic Stimulation) for the Treatment of Chronic Pain in GW1 Veterans

Wes Ashford, Ansgar Furst, Maheen Adamson, Valerie Darcy,

Allyson Rosen, David Clark, Janet Baldwin

Funded VA Merit Grant (10/1/2012 - 9/30/2016)

Motor Cortex Excitability after rTMS Therapy for Treatment of Chronic Pain: an fMRI and TMS Study (pilot)

Allyson Rosen, Gary Glover, JC Lamy, Wes Ashford

Funded by: France-Stanford Center for Interdisciplinary Studies

Yoga for Treatment of Chronic Pain in GWI

Peter Bayley, Louise Mahoney

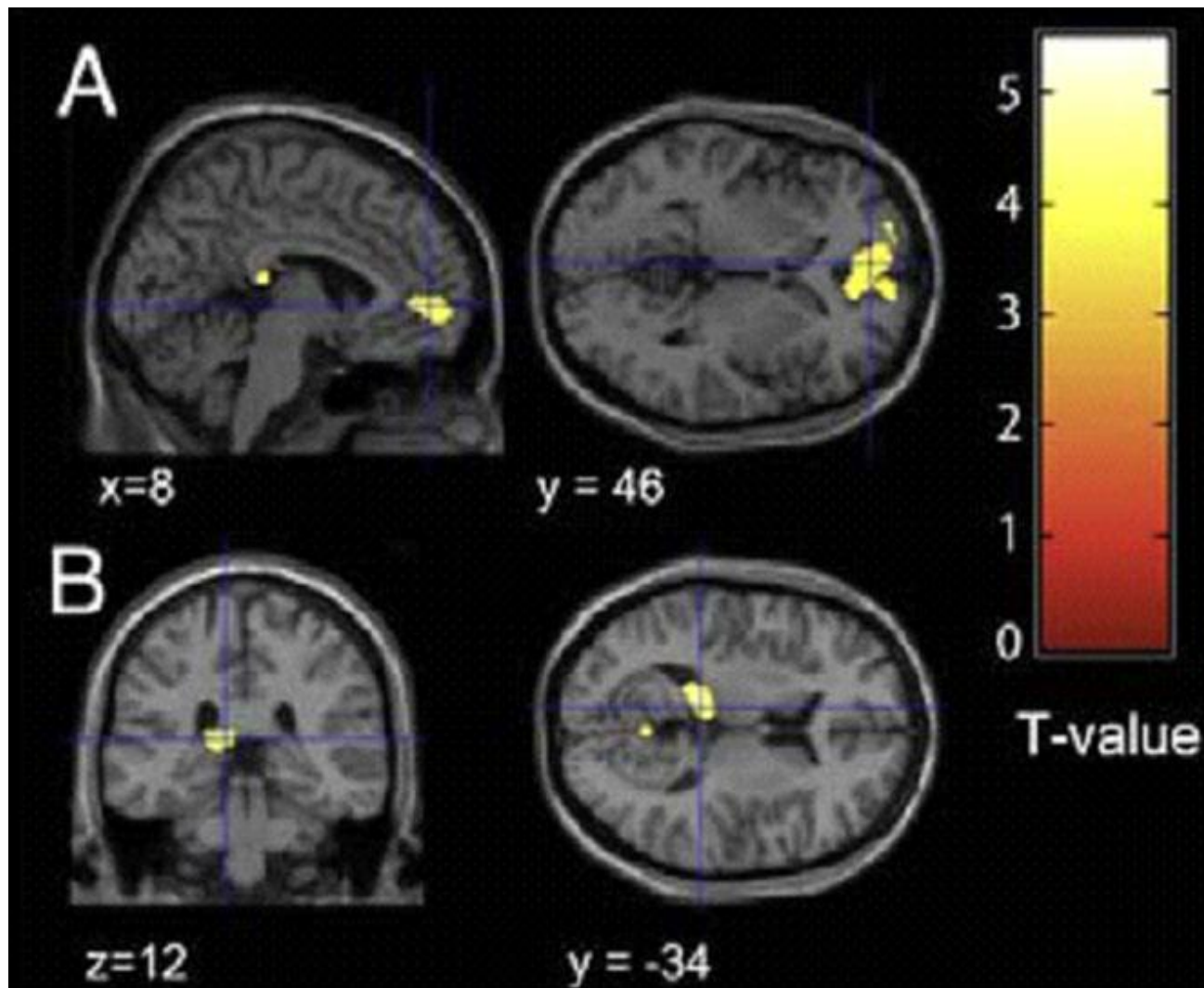
Proposed Studies

Location versus Symptom Severity in Veterans in Service August, 1990 to May, 1991, web/telephone screening, WRIISC-Evaluation

Joseph Cheng, Brian Yochim, Maheen Adamson, Wes Ashford

TMS (paired-pulse) and MRS of rTMS Pain Therapy Response

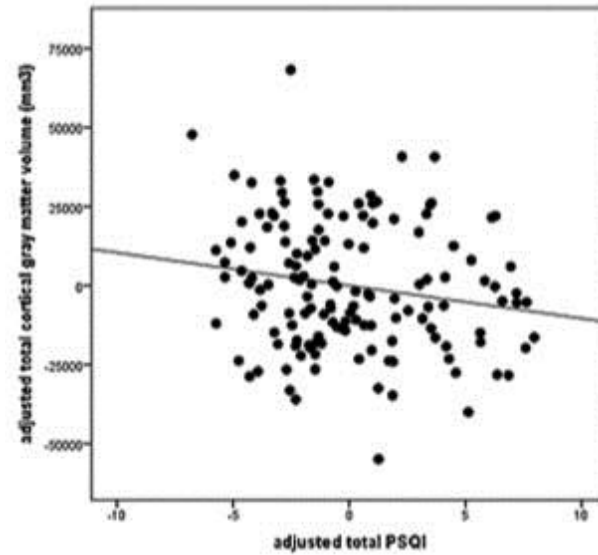
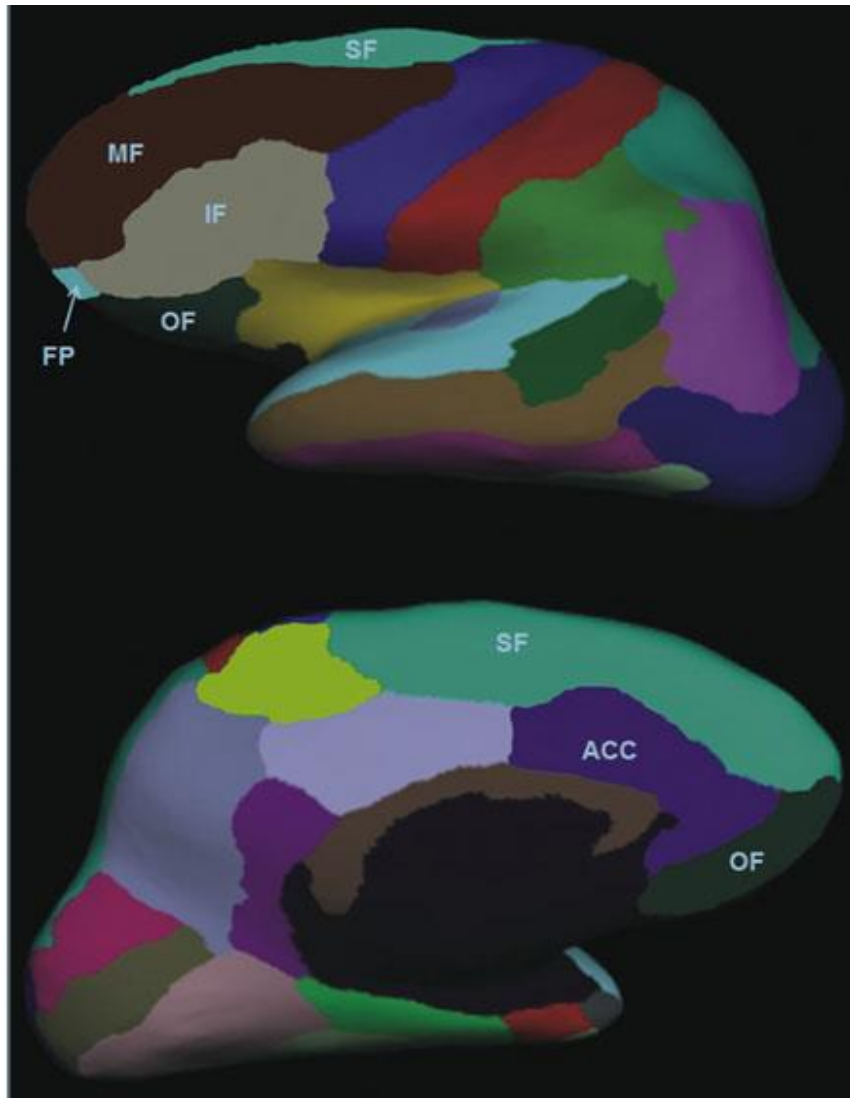
Allyson Rosen, Wes Ashford, Dan Spielman



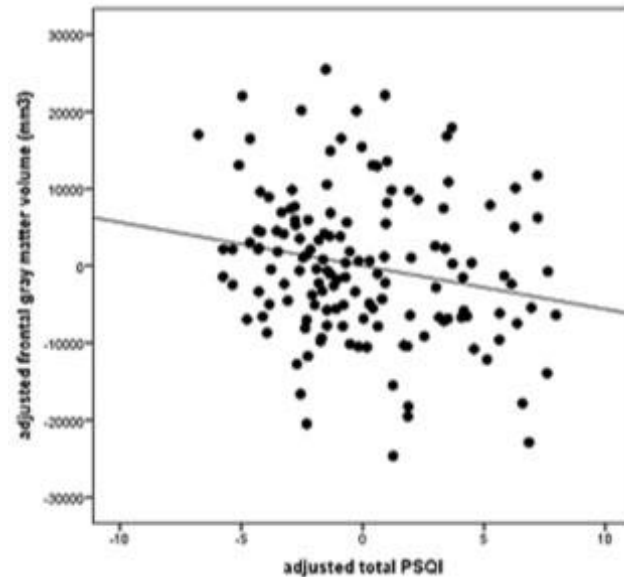
Regions of the brain where healthy controls have higher activity than Fibromyalgia Syndrome patients during subjectively calibrated painful stimulation minus sensory stimulation.

- Clusters corresponding to (A) the rACC, and (B) the pulvinar nucleus of thalamus.
- The exact locations (x,y,z) are given in MNI coordinates.

Gulf War Veterans' Pittsburgh Sleep Quality Index declines with gray matter loss



total



frontal

Freesurfer analysis

L.L. Chao; BS. Mohlenhoff; M.W. Weiner; T.C. Neylan, 2014

rTMS

(repetitive Transcranial Magnetic Stimulation)

for the Treatment of Chronic Pain in GW1 Veterans

Wes Ashford, Ansgar Furst, Maheen Adamson, Valerie Darcy,
Allyson Rosen, David Clark, Janet Baldwin, Kathy Kador

Funded VA Merit Grant (start 10/1/2012)

rTMS and Pain

- Chronic pain is present in more than 90% of Gulf War I Veterans referred to WRIISC
- rTMS identified as a possible treatment for chronic pain
- VA ORD funding to study rTMS in Gulf War Veterans with chronic pain
- Raised awareness of chronic pain and its management via a regional provider conference

rTMS for the Treatment of Chronic Pain

- What is Transcranial Magnetic Stimulation?
 - It is NOT a drug!
 - rTMS is a method of non-invasive brain stimulation that is done on an outpatient basis
 - The participant is awake and alert during treatments that last approximately 20 minutes
 - rTMS is an FDA-approved treatment for depression (focus – Right prefrontal cortex)

The rTMS System

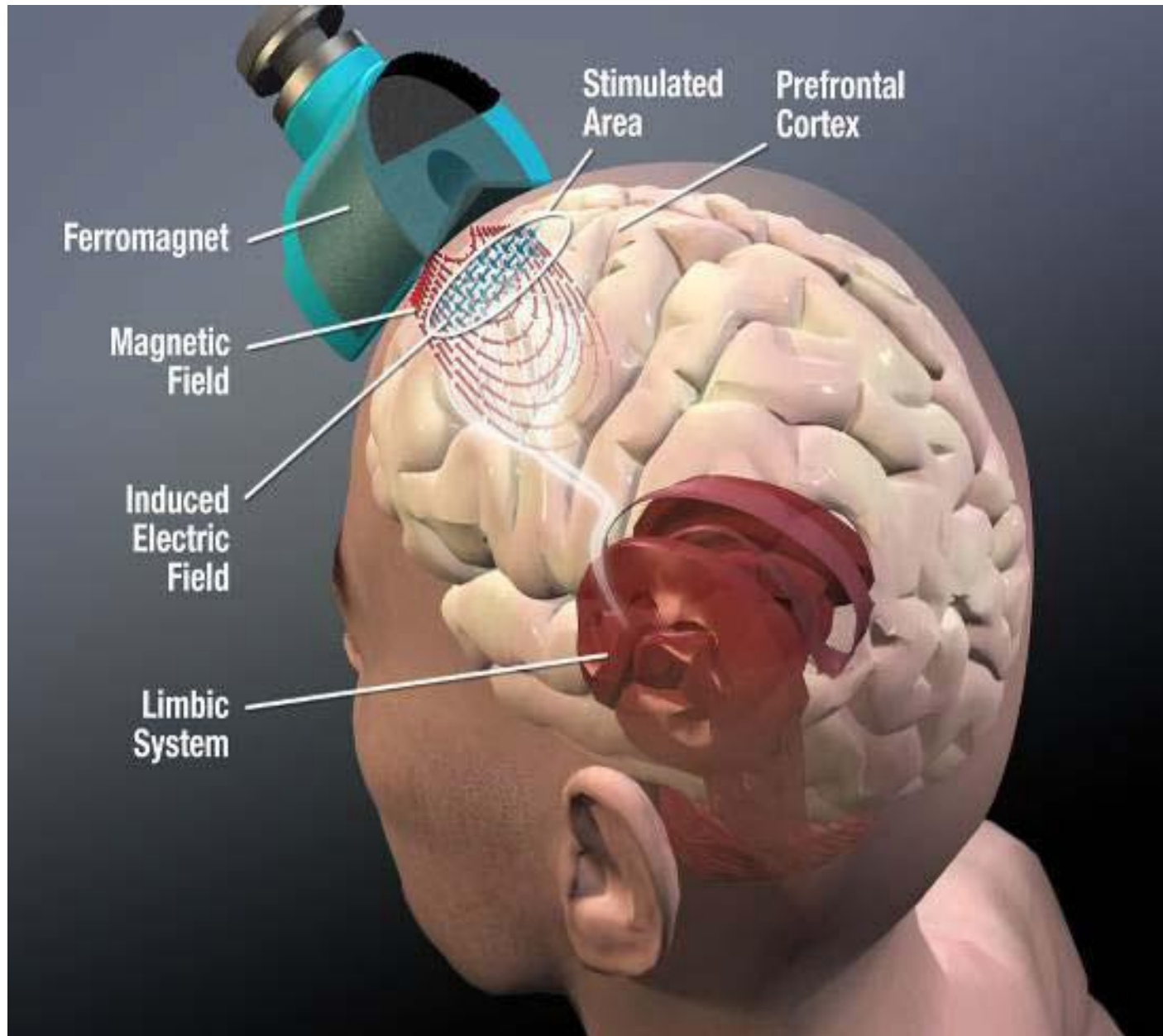


Transcranial Magnetic Stimulation (TMS)



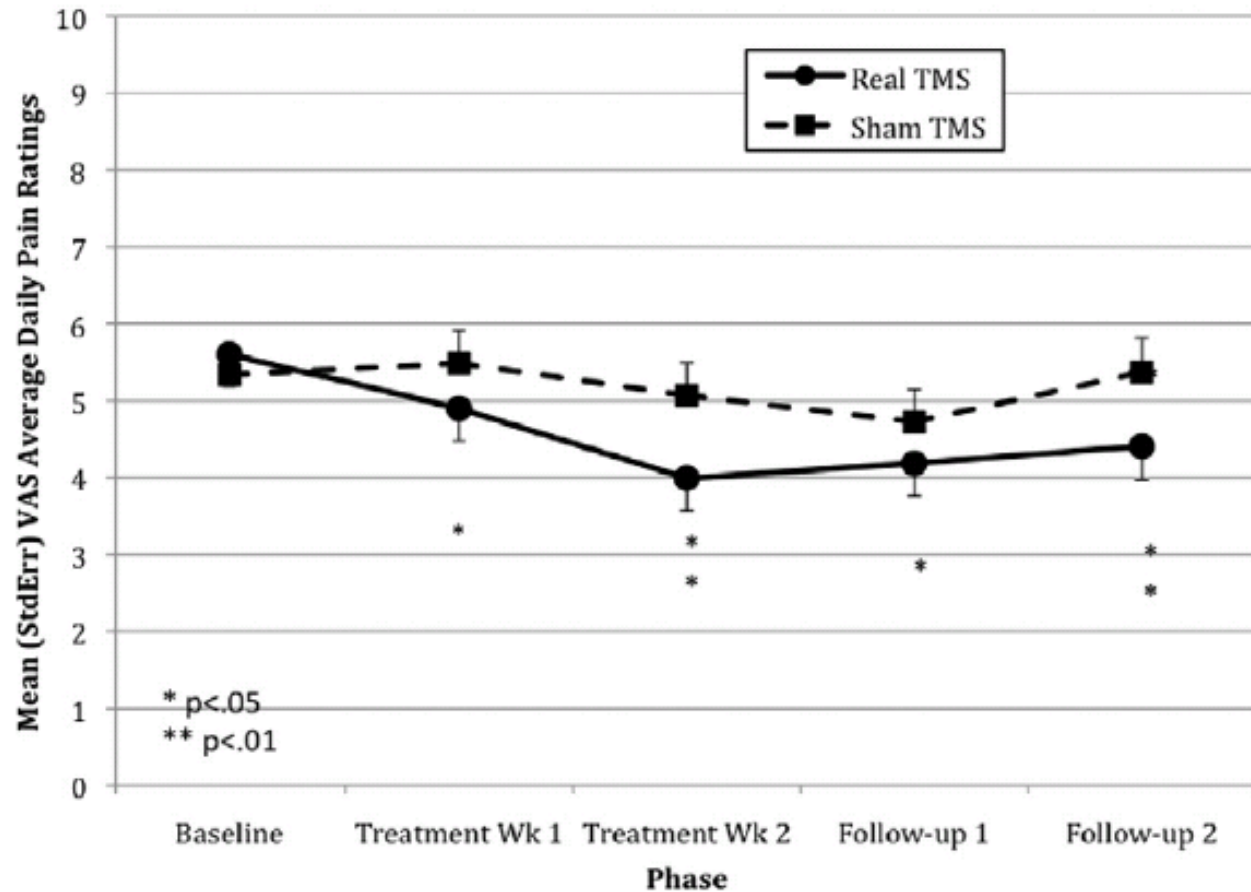
*Magventure

Diagram of simulated rTMS delivery



TMS Effect on Visual Analog Scale (VAS) in Fibromyalgia Patients

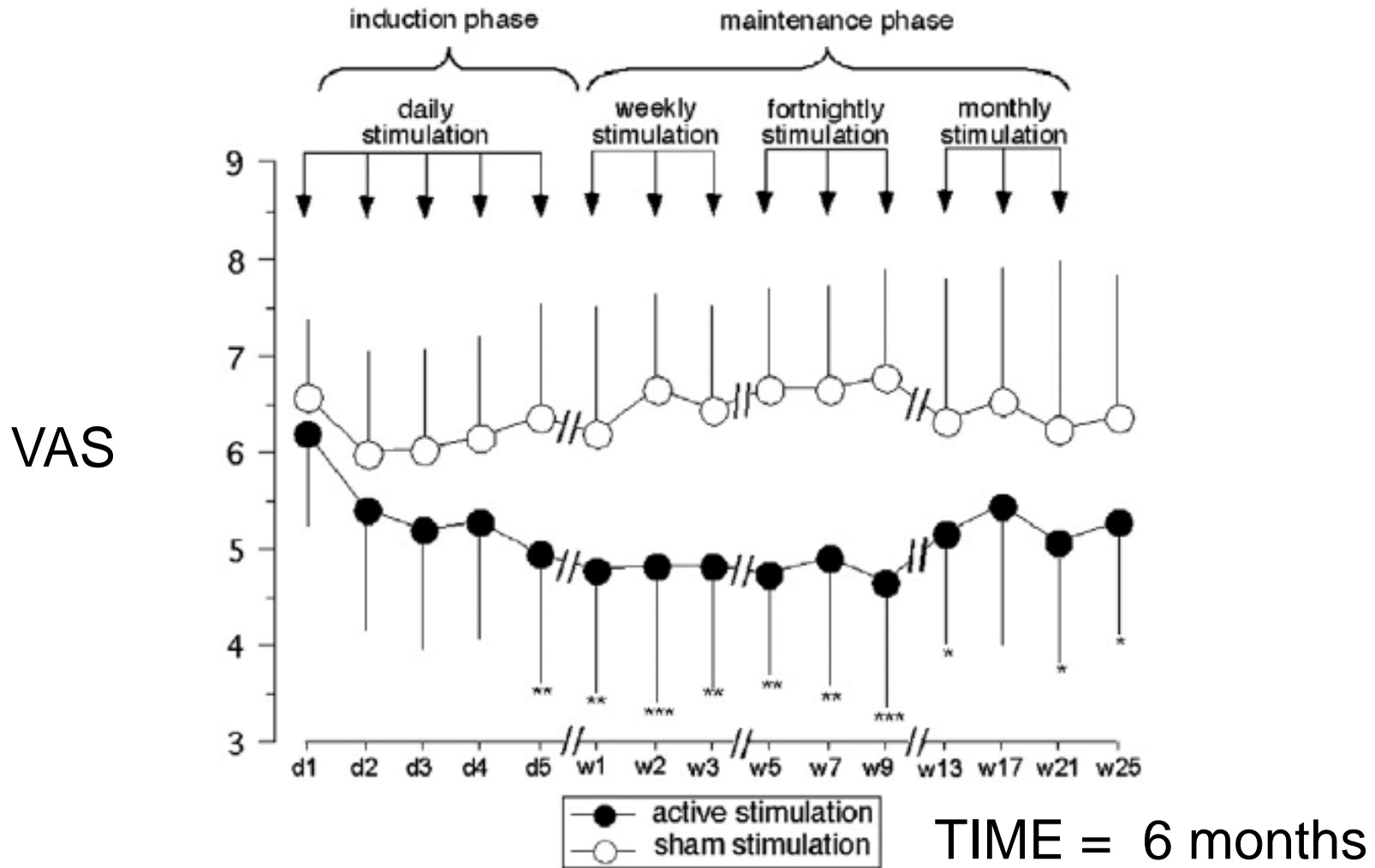
Worst pain



No pain

Left prefrontal rTMS reduces fibromyalgia pain (Short et al., Pain, 2011)

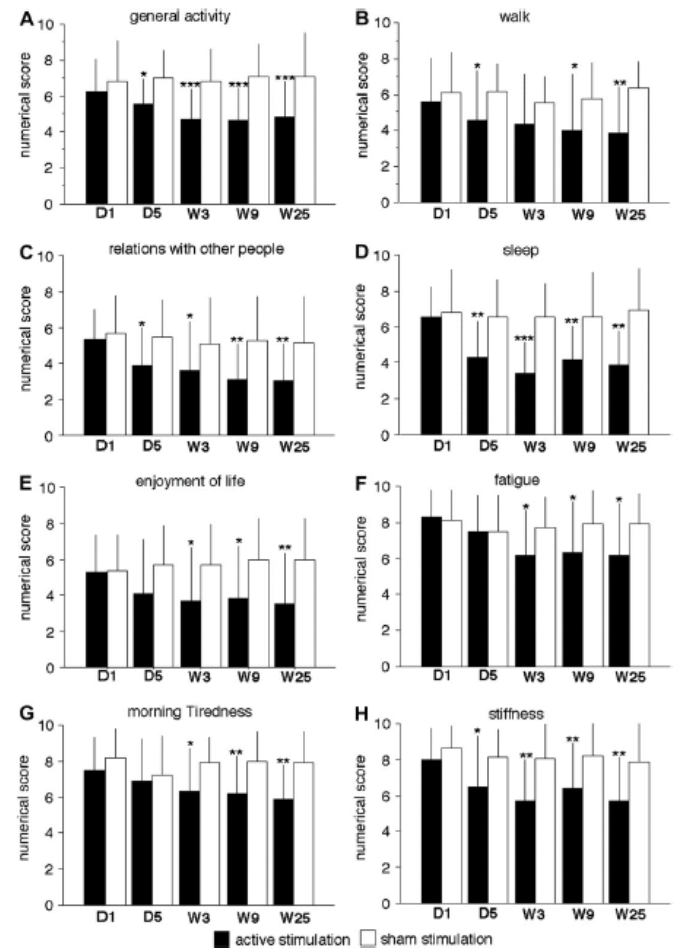
TMS Effect on Visual Analog Scale (VAS) in Fibromyalgia Patients



Long-term maintenance of rTMS analgesia in fibromyalgia (Mhalla et al., Pain, 2011)

Other significant symptomatic benefits of rTMS in fibromyalgia patients:

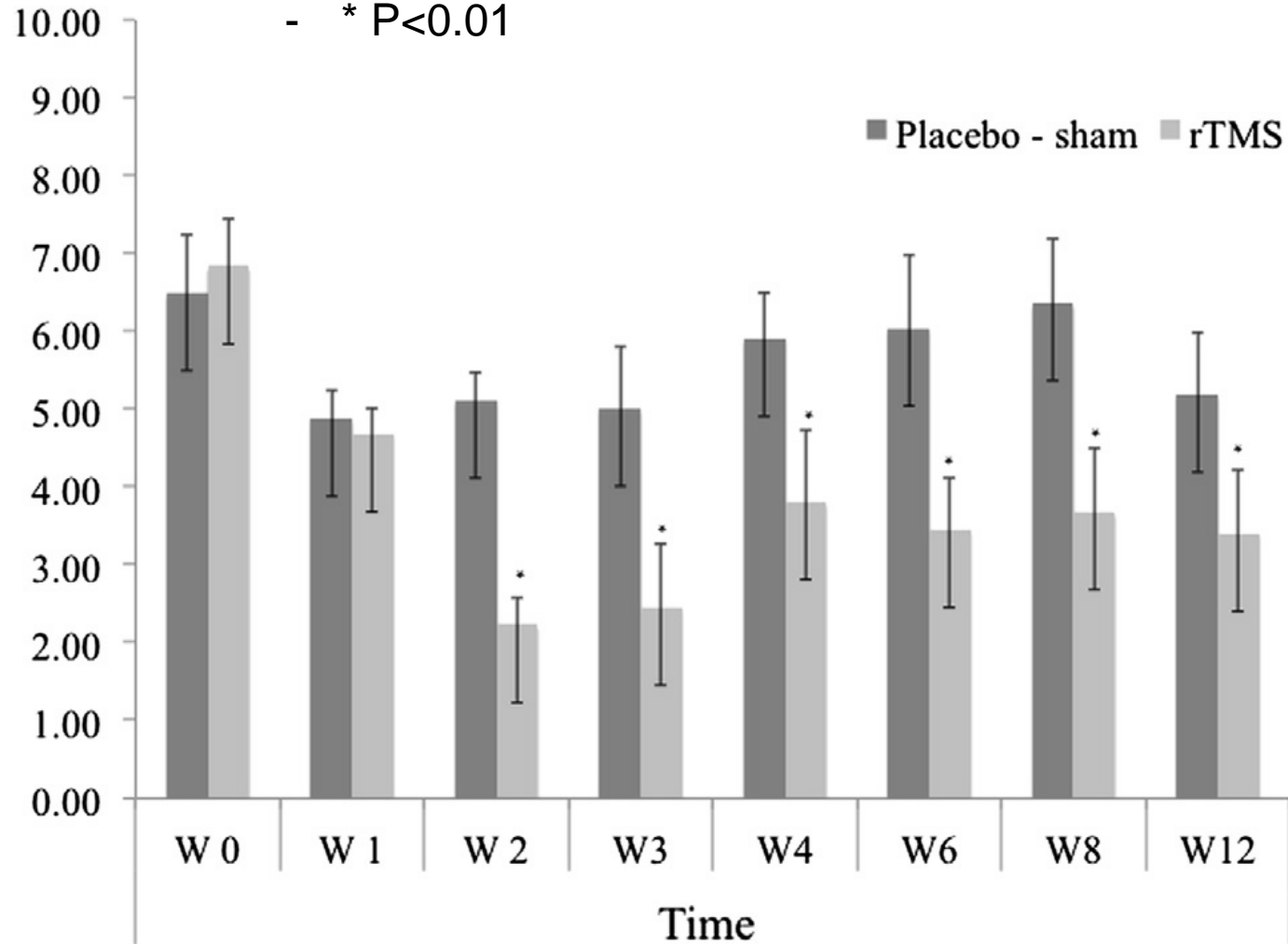
- General activity
- Relationships with other people
- Enjoyment of life
- Morning tiredness
- Sleep
- Fatigue
- Walking
- Stiffness



Long-term maintenance of rTMS analgesia in fibromyalgia (Mhalla et al., Pain, 2011)

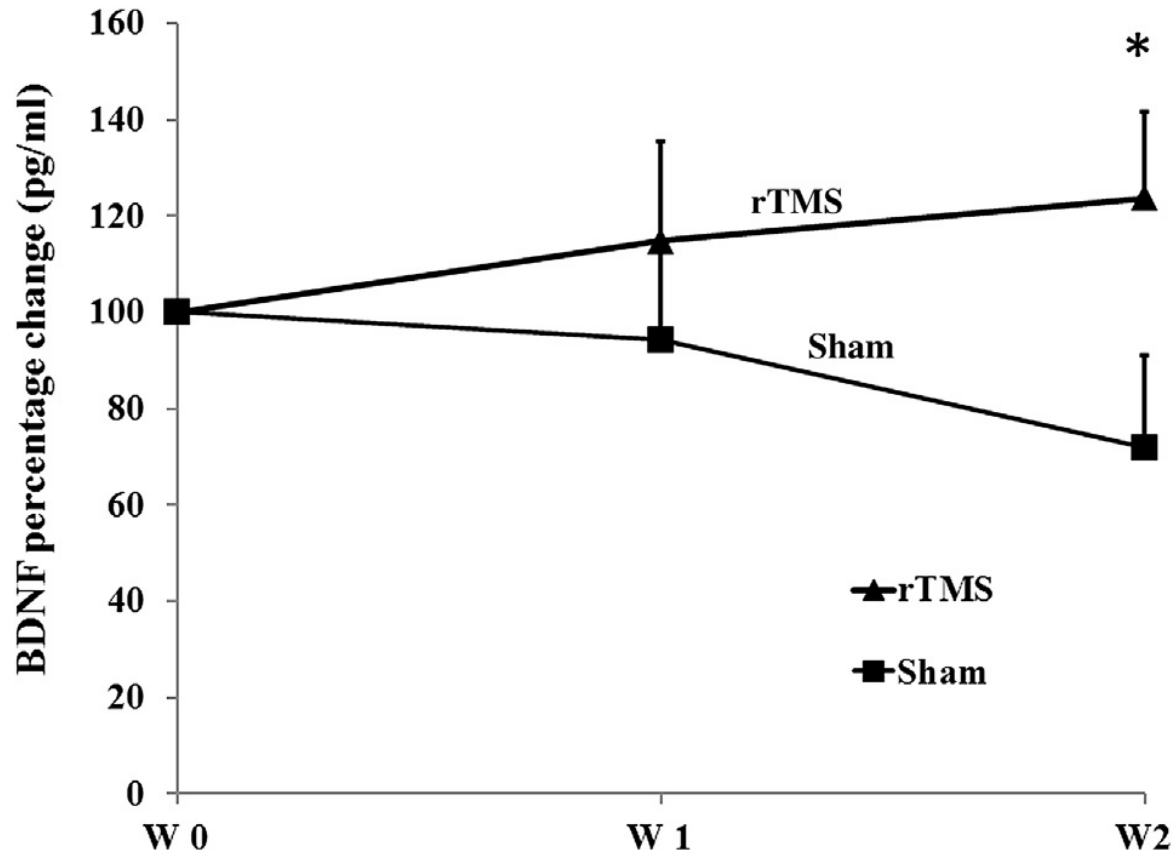
Weekly Pain Levels during rTMS treatment

- Visual Analog Scale 0-10
- Worst pain during prior 24 hours
- * $P < 0.01$



BDNF mean serum levels during rTMS treatment

- Visual Analog Scale 0-10
- Worst pain during prior 24 hours
- * $P < 0.05$



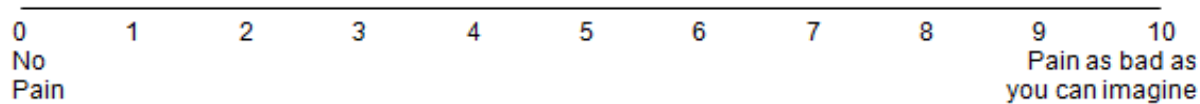
AIM of the STUDY

To determine whether repetitive Transcranial Magnetic Stimulation (rTMS) can benefit the symptoms of chronic pain of GWI Veterans

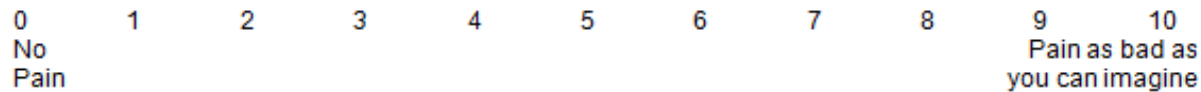
- This project will study 206 Veterans with Gulf War Illness (GWI) whose symptoms include chronic pain
- Veterans will be randomly assigned to treatment or sham (placebo) for the study.
- It is the intent of this study to determine if the newly FDA-approved treatment for depression, rTMS, may have some benefit to Veterans with GWI and chronic pain

Brief Pain Inventory

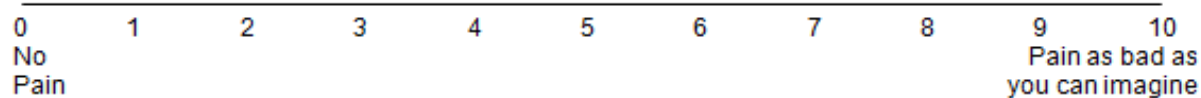
- 3) Please rate your pain by marking the one number that best describes your pain at its WORST in the past 24 hours.



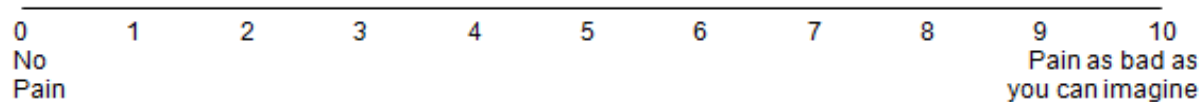
- 4) Please rate your pain by marking the one number that best describes your pain at its LEAST in the past 24 hours.



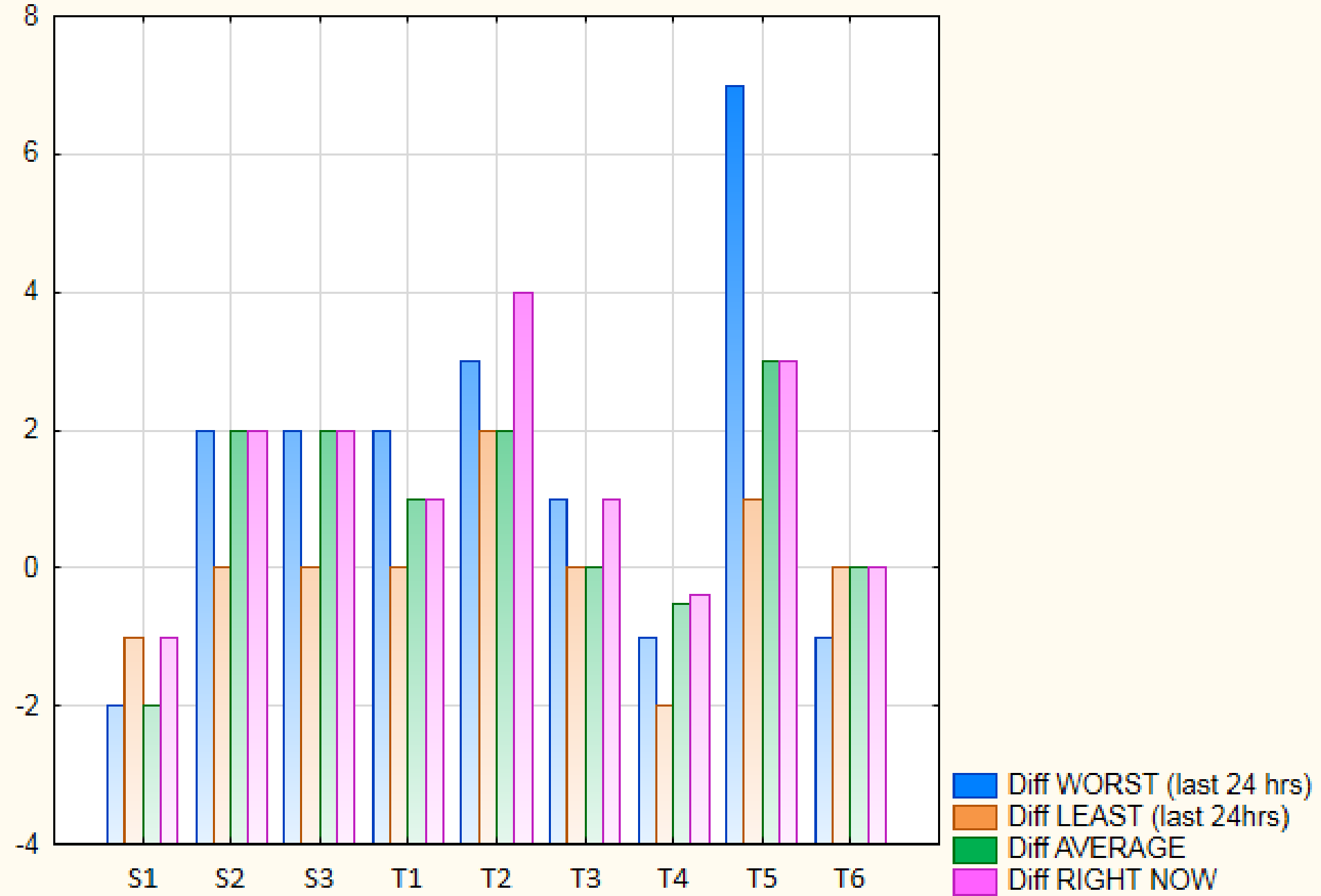
- 5) Please rate your pain by marking the one number that best describes your pain on the AVERAGE.



- 6) Please rate your pain by marking the one number that tells how much pain you have RIGHT NOW.

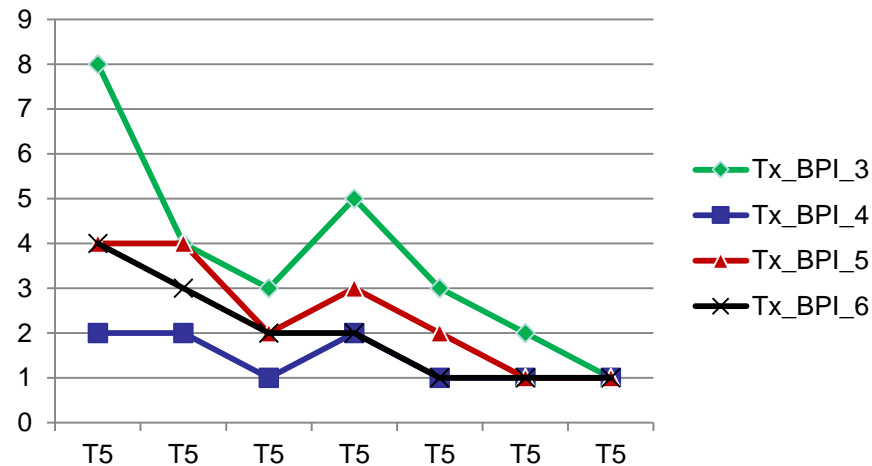
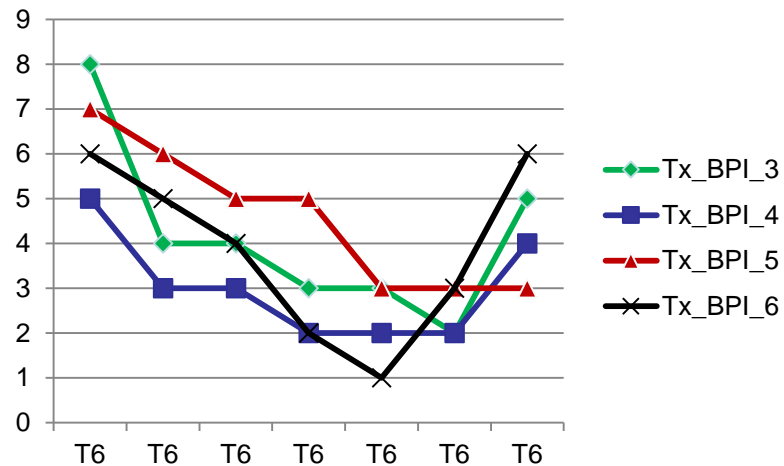


Brief Pain Inventory (BPI) item scores (3-6) for participants by treatment group (S1-3 = Sham; T1-6 = Treatment)

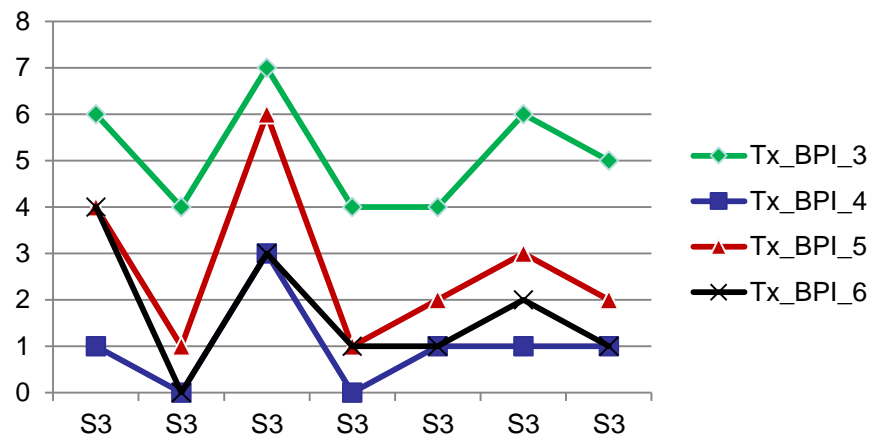
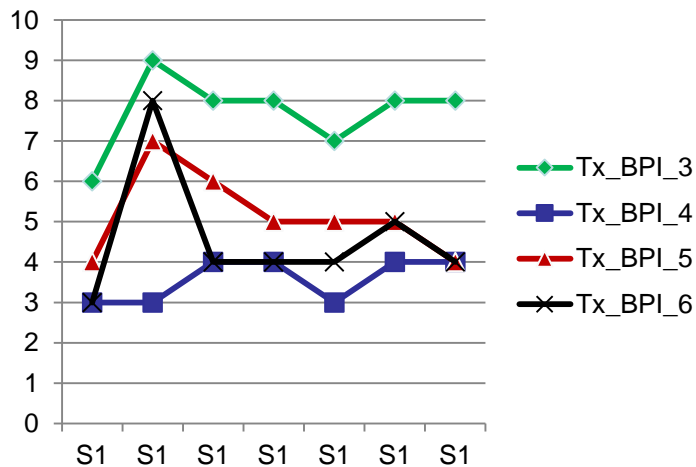


Treatment sessions for 4 participants

Treatment



Sham



BPI Average Pain Scores (change from baseline)

• Average	WORST	LEAST	AVERAGE	NOW
• Sham	0.67	-0.33	0.67	1.00
• STD	2.31	0.58	2.31	1.73
• Treatment	1.83	0.17	0.92	1.43
• STD	2.99	1.33	1.36	1.72
• Difference	1.17	0.50	0.25	0.43
• # Needed	21	15	215	64

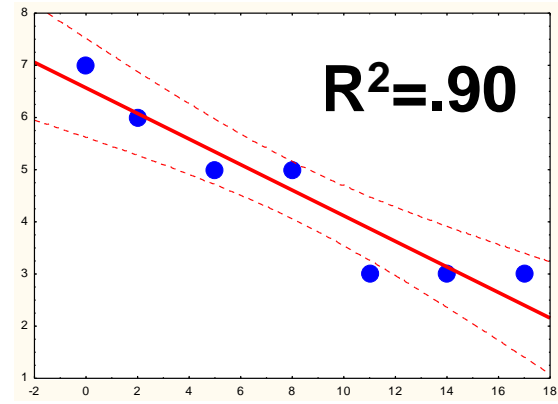
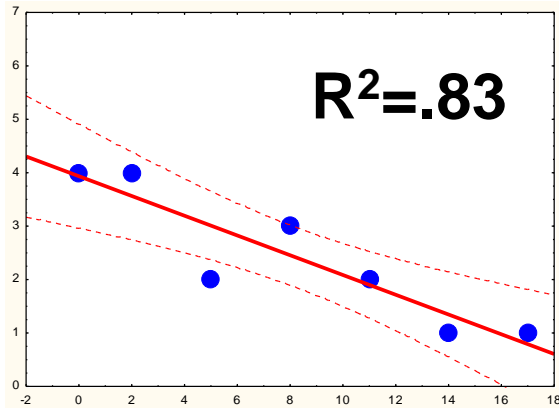
(number needed in each group to reach $p < 0.05$ given current trend)

(NOTE: all measures favor treatment at this point)

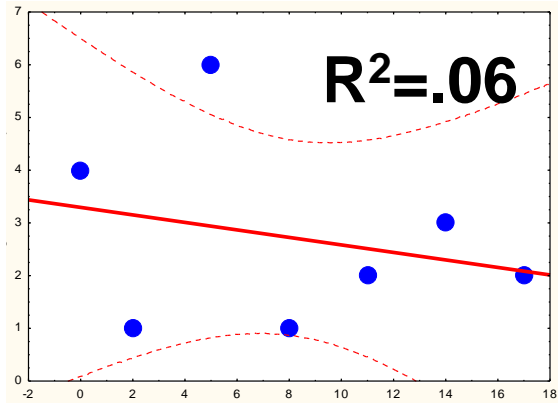
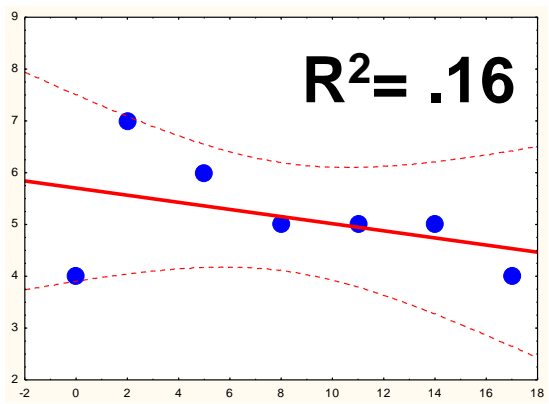
RTMS Subjects (2 Active, 2 Sham)

Active

Average Pain

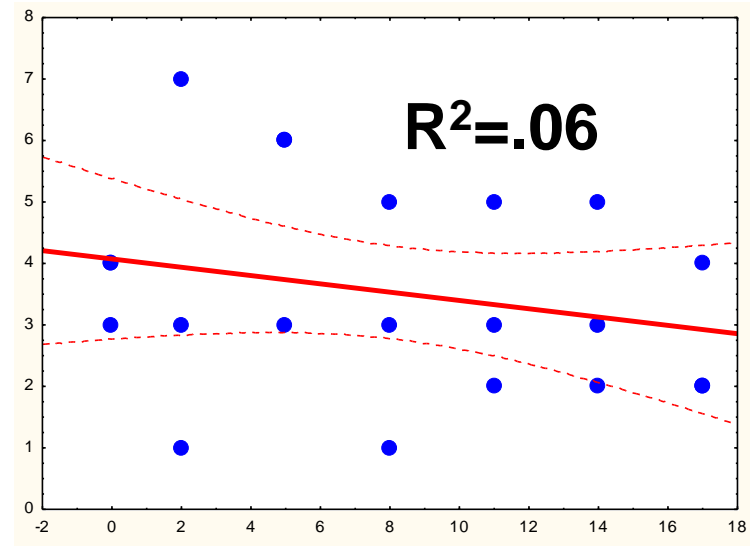
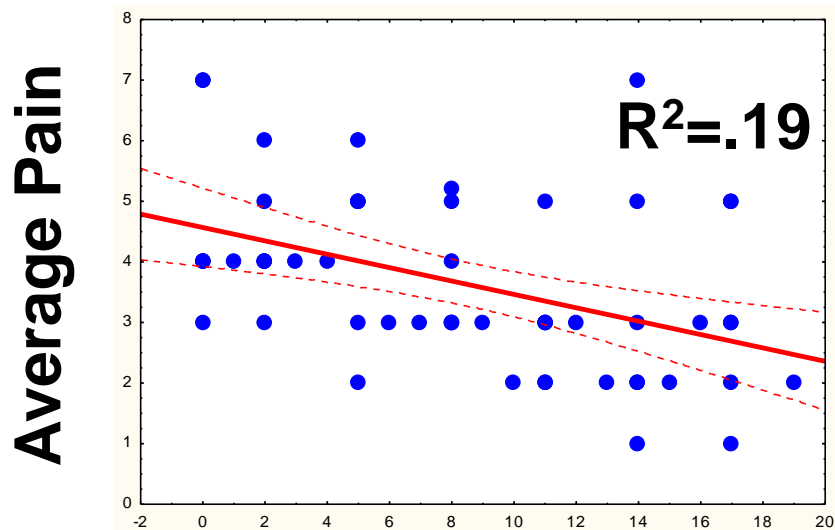


Sham



Number of Treatments

Effect of Treatment Sessions on Average Pain



Number of Treatments

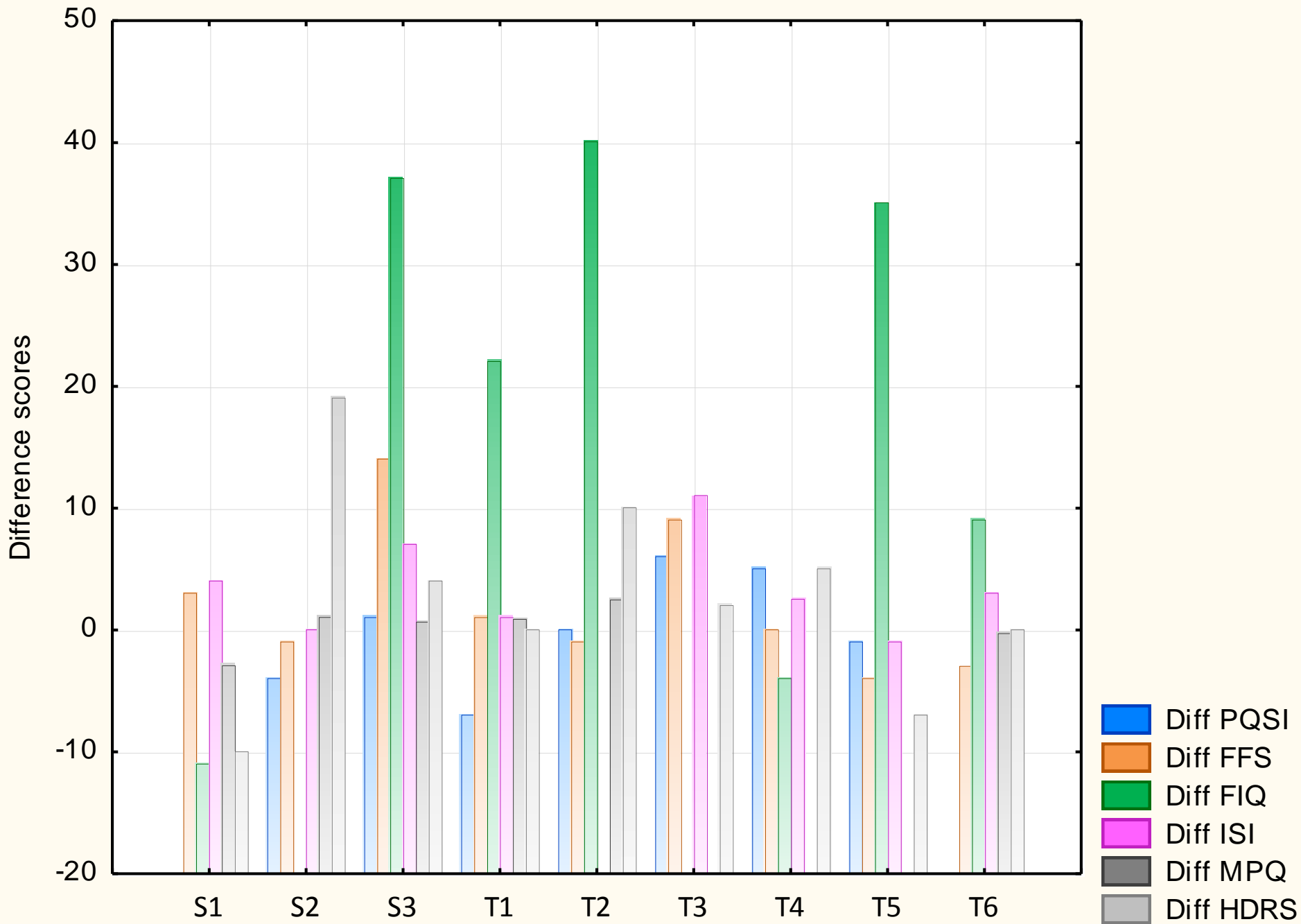
Active

Sham

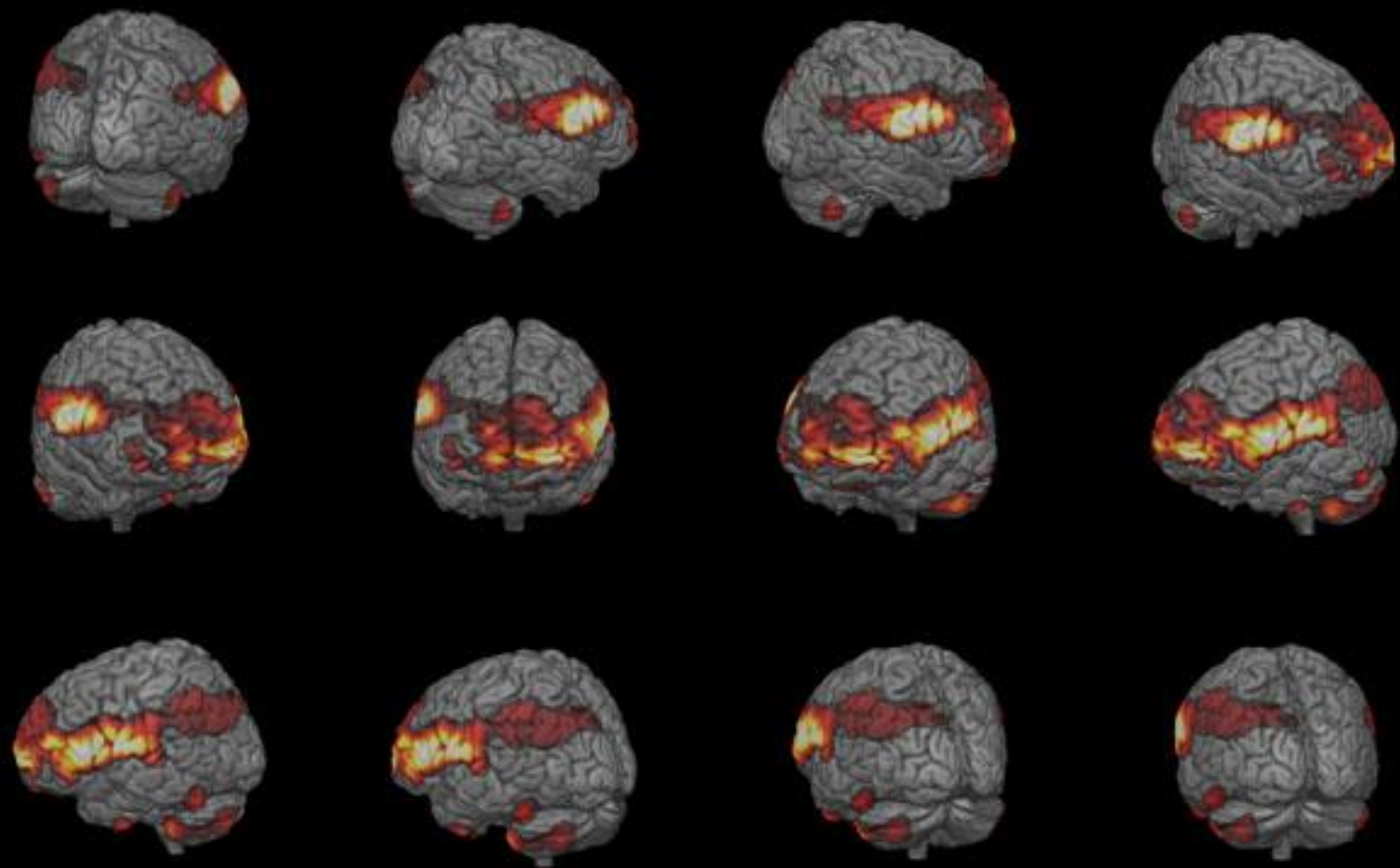
Other Outcome Measures

- PQSI: Pittsburgh Quality Sleep Index
- FFS: Flinders Fatigue Scale
- FIQ: Fibromyalgia Impact Questionnaire
- ISI: Insomnia Severity Index
- MPQ: McGill Pain Questionnaire
- HDRS: Hamilton Depression Rating Scale

Other outcome measure scores by treatment (S1-3 = Sham; T1-6 = Treatment)



Neuronal upregulation after rTMS in chronic pain



Percent increase of resting fMRI BOLD signal after treatment (one patient)

Please Help Us Find GW1 Veterans!

- We are looking for Veterans deployed to the Persian Gulf during Gulf War 1
- Who have chronic pain
- And who can come to the VA Palo Alto for 20 treatments (minimum 7 visits)
 - Plus visits for assessments before and after the treatments

(Dr. Ashford will travel to give pep-talks)

Introduction to YOGA Research Project

- Yoga is an increasingly popular form of complementary and alternative medicine.
- Current research, while limited in scope, suggests yoga is “probably efficacious” for treating chronic pain.
- No studies have examined the benefits of yoga for treating pain in Gulf War Illness.
- Evidence is needed to address questions in Gulf War Illness about yoga efficacy, safety, duration of effect, mechanisms of action.

A multimodal evaluation of the comparative efficacy of yoga vs. a patient centered support group for treating chronic pain in gulf war illness

Congressionally Directed Medical Research Programs, Department of Defense
(DoD) Gulf War Illness Research Program (GWIRP) Innovative Treatment
Evaluation Award.

Peter J. Bayley, Ph.D. (P.I.)

Associate Director of Cognitive Neuroscience

CA WRIISC, VA Palo Alto Health Care System

Assistant Professor (affiliated), Department of Psychiatry & Behavioral
Sciences, Stanford University

A study involving complementary medical treatments for chronic pain in Gulf War 1 Veterans

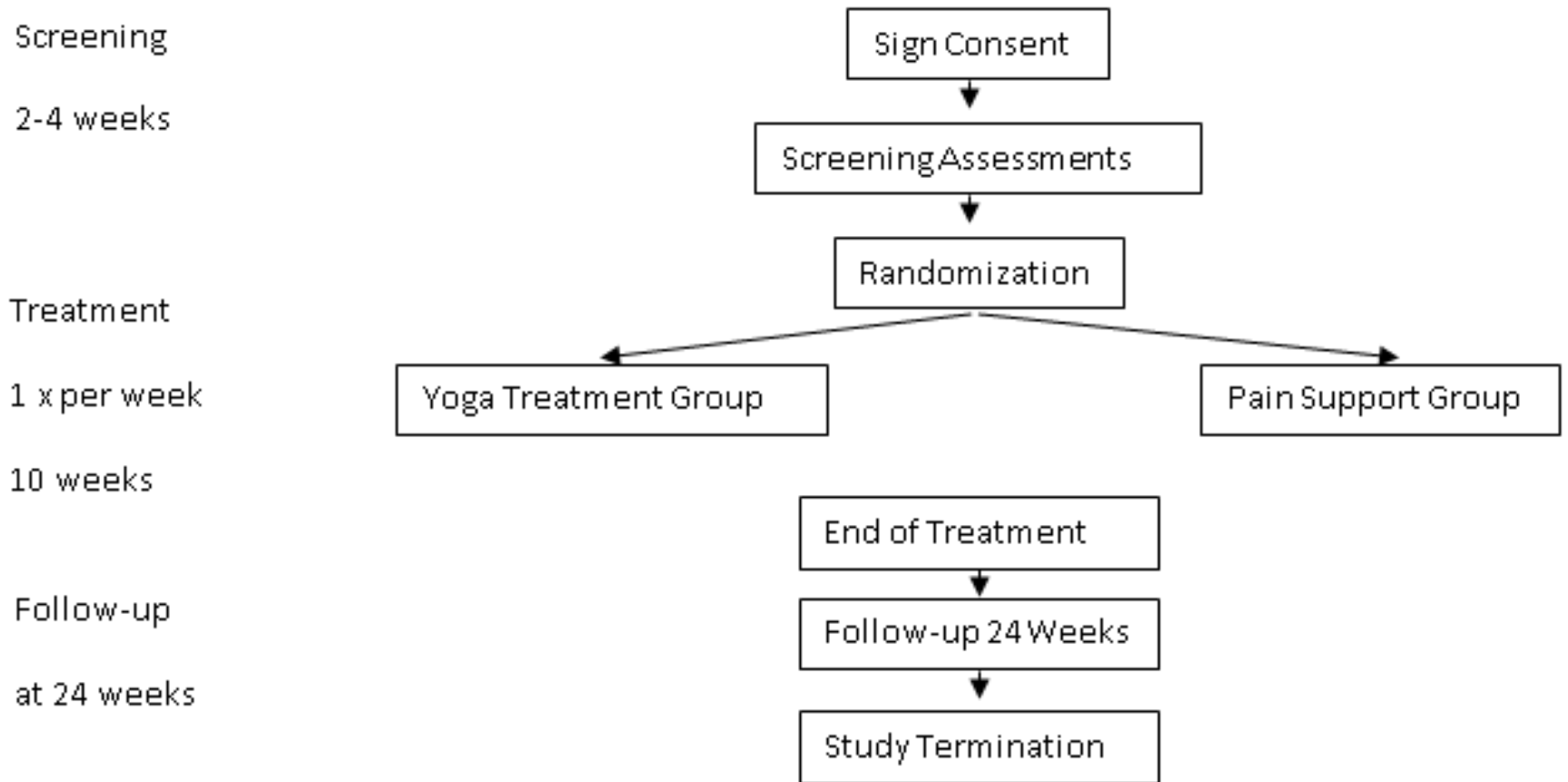
- Complementary medicine = non-mainstream therapies used in conjunction with conventional medical treatment.
- Strong evidence that yoga is effective for some types of chronic pain
- No studies have examined the benefits of yoga in Veterans from the first Gulf War
- The study will compare two types of treatment for pain
 - A yoga program designed specifically for Veterans
 - A “pain support group” (diet, exercise, coping strategies, etc.)

What is Yoga?

Office of Alternative Medicine, National Center for Complementary and Alternative Medicine (OAM/NCCAM) recognizes four CAM Domains:

- Mind-body medicine ← Yoga
- Biologically based medicine
- Energy medicine
- Manipulative and body-based medicine

Experimental design and procedures



N=100 (50 per group)

Outcome Measures

- Primary
 - Pain (Brief Pain Inventory)
- Secondary
 - Quality of life (SF-36)
 - Fatigue (6-minute walk test)
 - Medication use
 - Mood (Profile of Mood States)
 - Autonomic Nervous System Function
 - Heart Rate Variability (HRV) (24 hr monitoring)
 - Composite Autonomic Symptom Score (COMPASS)

Study Features

- **Frequency & Duration:**
 - 1 day / week for 10 weeks
 - Follow-up interviews at 18, 26, & 34 weeks

- **Study Locations:**
 - VA Palo Alto Health Care System
 - Palo Alto Division
 - Select Community Clinics

Possible Benefits

- Learn skills that can be used lifelong to promote health and well-being
- \$250 compensation for completing study

For more information please add your name to the signup sheet

For More Information

- rTMS Study Team direct phone line
 - 650-852-3233
- WRIISC Website
 - www.warrelatedillness.va.gov
 - Click on “Research”
- www.ClinicalTrials.gov
 - Search on “GW1 rTMS”

ACKNOWLEDGEMENTS

- rTMS Research Team
 - Maheen Adamson (Co-I)
 - Ansgar Furst (Co-I)
 - Allyson Rosen (Co-I)
 - David Clark (Co-I)
 - Valerie Darcy (coordinator)
 - Janet Baldwin (research associate)
 - Kathy Kador (research associate)
- WRIISC-CA Staff (VA Palo Alto -HCS)
 - Sandra Bell
 - Louise Mahoney
 - Stacy Moeder
 - Joseph Cheng
 - Steven Chao
 - Kaci Fairchild
 - Peter Bayley
 - Ahmad Salehi
 - Jerome Yesavage

References

- Murphy FM, Kang H, Dalager NA, et al.: The health status of Gulf War veterans: lessons learned from the Department of Veterans Affairs Health Registry. *Mil Med.* 164(5), 327-31 (1999).
- Iowa Persian Gulf Study Group: Self-reported illness and health status among Gulf War veterans. A population-based study. The Iowa Persian Gulf Study Group. *Jama.* 277(3), 238-45 (1997).
- Jensen KB, Kosek E, Petzke F, et al.: Evidence of dysfunctional pain inhibition in Fibromyalgia reflected in rACC during provoked pain. *Pain.* 144(1-2), 95-100 (2009).
- Chao LL, Mohlenhoff BS, Weiner MW, Neylan TC, Associations between Subjective Sleep Quality and Brain Volume in Gulf War Veterans. *Sleep.* 37(3):445-52 (2014).
- Carvalho et al. A novel NGF mutation clarifies the molecular mechanism and extends the phenotypic spectrum of the HSAN5 neuropathy. *J Med Genet.* 2011 Feb;48(2):131-5.
- Levi-Montalcini & Booker. Excessive growth of the sympathetic ganglia evoked by a protein isolated from mouse salivary gland. *Proc Natl Acad Sci U S A.* 1960; 46(3):373-84.
- Dall'Agnol et al. Repetitive transcranial magnetic stimulation increases the corticospinal inhibition and the brain-derived neurotrophic factor in chronic myofascial pain syndrome: an explanatory double-blinded, randomized, sham-controlled trial. *J Pain.* 2014; 15(8):845-55.

Final Points

- Health Care is the responsibility of all
- Weight, smoking, diet need control
- The most widely recommended treatment for everything is exercise – and chronic pain is no exception
- rTMS may artificially induce exercise effects in the brain
- YOGA involves exercise
- Consider swimming – www.usms.org