



UNITED STATES
DEPARTMENT OF VETERANS AFFAIRS

Diffusion Tensor Imaging in Gulf War Veterans with Chronic Musculoskeletal Pain

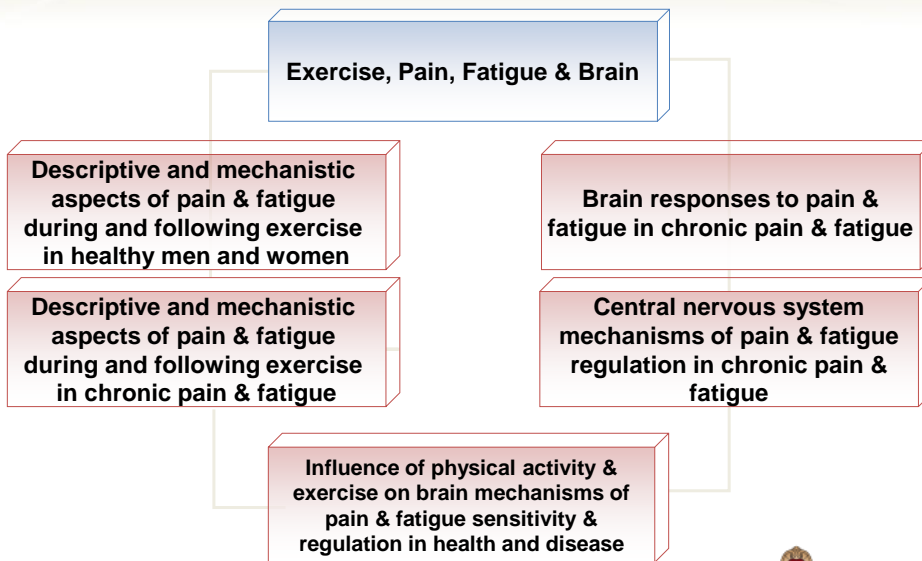
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Presentation Outline

- Summary and update of previous presentation to RAC on GWI
- Preliminary diffusion tensor imaging (DTI) data
- Brief update of Gulf War Veteran resistance exercise training trial



Chronic musculoskeletal pain in Gulf War Veterans

- 15% (100,000 of ~700,000) report chronic muscle pain symptoms (Kang et al., 2000)
- This number has grown considerably with ~200,000 veterans reporting symptoms consistent with Gulf War Illness (Research Advisory Committee on Gulf War Veterans' Illnesses (2004))
 - CMP - one of three major factors of Gulf War illness (Fukuda et al., 1997).
 - Reported twice as frequently (OR=3.06) in Gulf War Veterans (GVs) than non-GVs (Kang et al., 2000; Thomas et al., 2006)
 - Follow-up data indicate that symptoms have not resolved & that the health of GV's with GWI continues to worsen (Blanchard et al., 2006; Li et al., 2011; Ozakinci et al., 2006; Thomas et al., 2006)

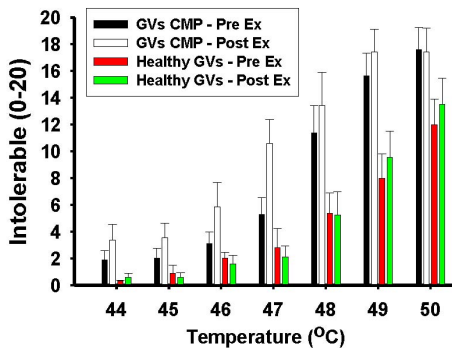


Can central nervous system dysregulation explain the persistent symptoms experienced by GVs with GWI?

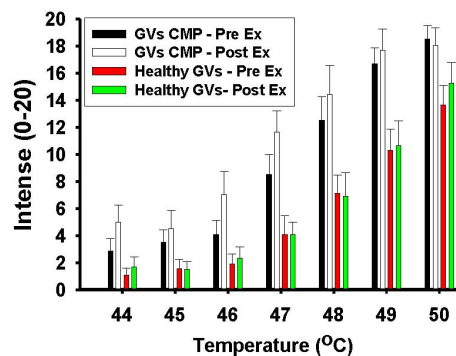
- Data in FM and emerging data in GVs with CMP/GWI suggest yes?
 - Enhanced sensitivity to & diminished inhibition of experimental pain stimuli (Cook et al., 2004; 2010; Kosek et al., 1996; Lautenbacher et al., 1994; Price et al., 2002; Staud et al., 2001)
 - Enhanced sensitivity post acute exercise (Exercise-Induced Hyperalgesia) (Cook et al., 2010; Kosek et al., 1996; Mengshoel et al., 1995; Vierck, Jr. et al., 2001)
 - Augmented neural responses to experimental pain stimuli (Cook et al., 2004; Gopinath et al., 2012; Gracely et al., 2002)
 - Altered connectivity among pain modulation brain regions (Cifre et al., 2012; Craggs et al., 2012; Napadow et al., 2010)



GVs w/ CMP are more sensitive to heat pain than healthy GVs and become more sensitive following acute exercise



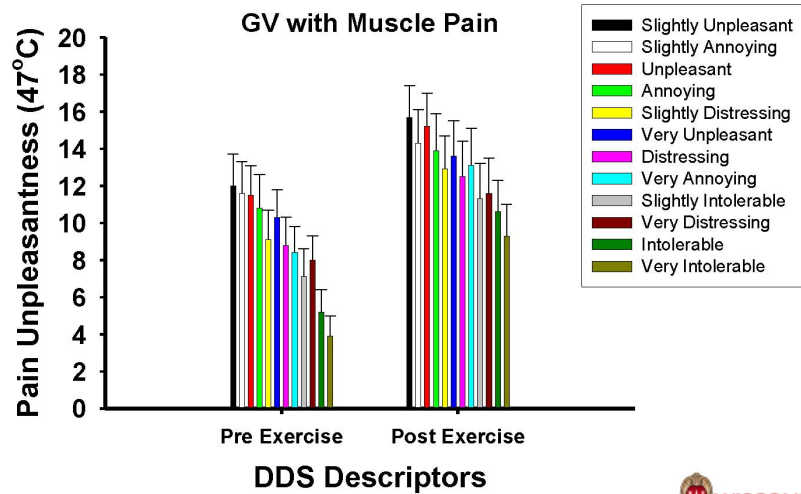
Group*Trials*Time: $F_{6,20}=2.7$, $p<0.05$



Group*Trials*Time: $F_{6,20}=5.9$, $p<0.01$



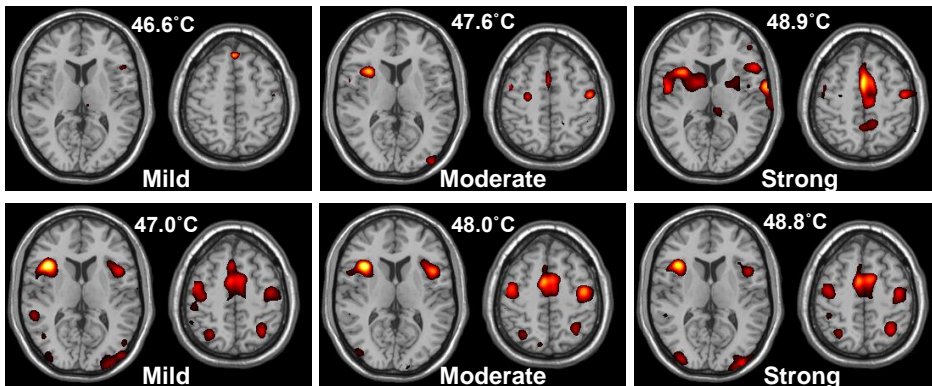
GVs with CMP demonstrated large increases in affective pain ratings from pre- to post-exercise



Cook et al., 2010



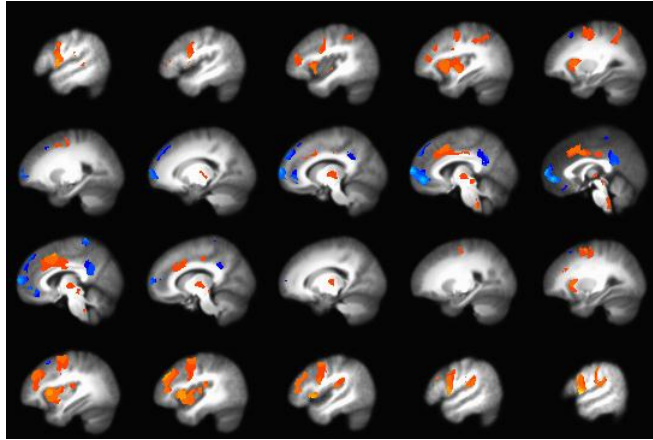
Functional MRI data demonstrating augmented brain responses to mild, moderate and strong pain stimuli in GVs with CMP



Stegner et al., In Preparation

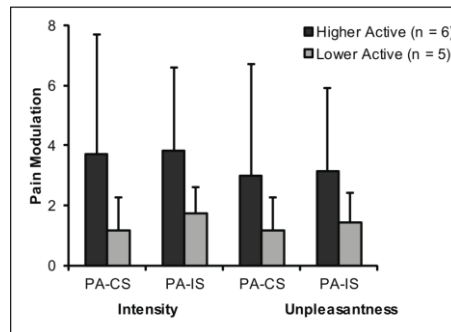
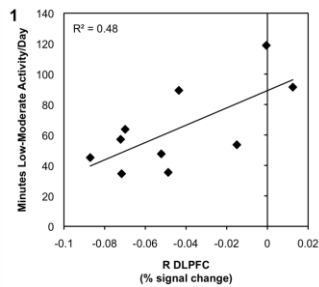
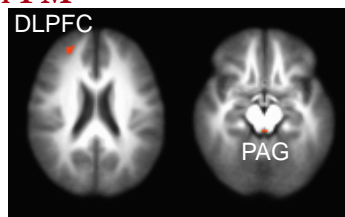


Relationships between physical activity and sedentary behaviors and pain processing



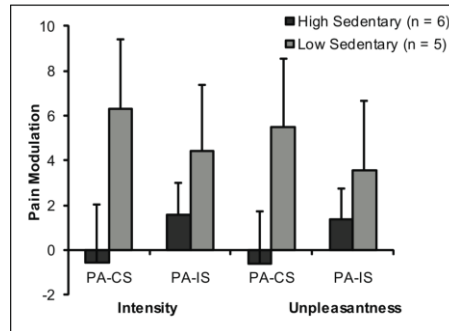
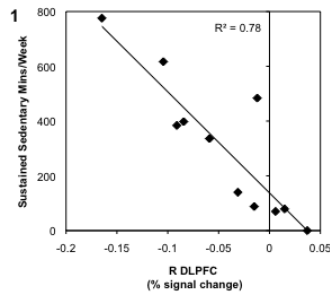
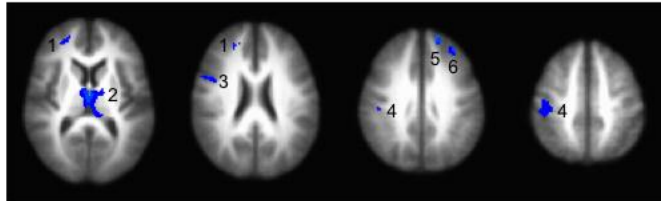
Using functional neuroimaging, we now have the opportunity to understand the mechanisms that underlie the effects of exercise on pain processing in humans.

Physical activity behaviors are positively associated with brain responses in regions involved in pain inhibition during pain modulation in FM



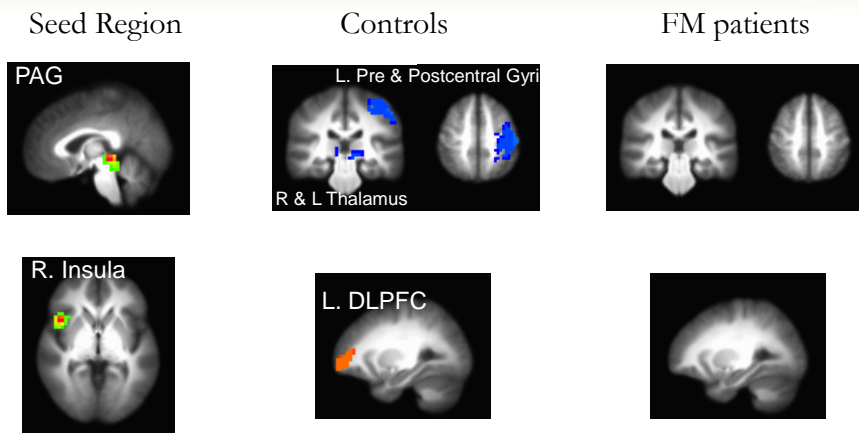
Ellingson et al., 2012

Sustained sedentary behaviors are negatively associated with brain responses during pain modulation



Ellingson et al., 2012

Functional Connectivity during Pain Stimuli



Healthy controls demonstrated functional connectivity between regions involved in pain modulation and pain processing. These relationships were absent in FM patients.

Shields et al., 2012

Take Home Points

- Patients with CMP are more sensitive to pain and are less efficient at regulating pain
- This may be in part due to poor communication between brain regions involved in descending pain control
- Augmented sensory processing and inefficient regulation may be one mechanism through which CMP/GWI may be maintained
- Diffusion Tensor Imaging is a method to measure the “integrity” of the neuronal connections (white matter tracts) between brain regions



Diffusion Tensor Imaging

- An imaging modality that provides information about the diffusion of water in biological tissues
 - When water movement is random (e.g. tank of water), the movement is isotropic
 - When water movement is constrained (e.g. in a tube), the movement is anisotropic
- Healthy brain white matter is highly anisotropic, moving parallel to axonal fibers
 - Reduced anisotropy is thus interpreted as less axonal integrity & is indexed by ‘fractional anisotropy’ (FA)
 - Mean diffusivity (MD) is the inverse measure of axonal membrane density and is sensitive to cell edema & necrosis



FA=0



FA=.8



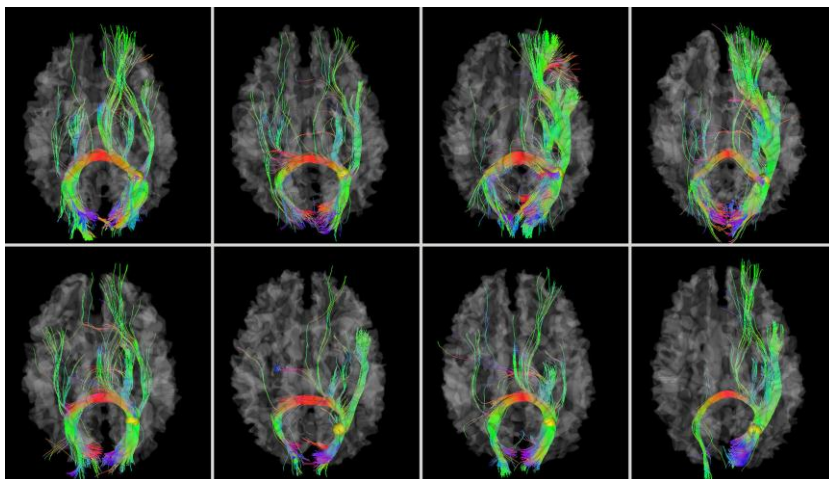
DTI and Microstructure

	FA	AD λ_1	RD $(\lambda_2 + \lambda_3)/2$	MD $(\lambda_1 + \lambda_2 + \lambda_3)/3$
Dense axonal packing	↑	–	↓	↓
High myelination	↑	↑	↓	↓
Large axonal diameter	↑	↑	↓	–
Axonal degeneration	↓	↓	↑	↑
Demyelination	↓	–	↑	↑

Sensitive to microstructural changes
 Sensitive to Cellularity, edema, necrosis



Tractography

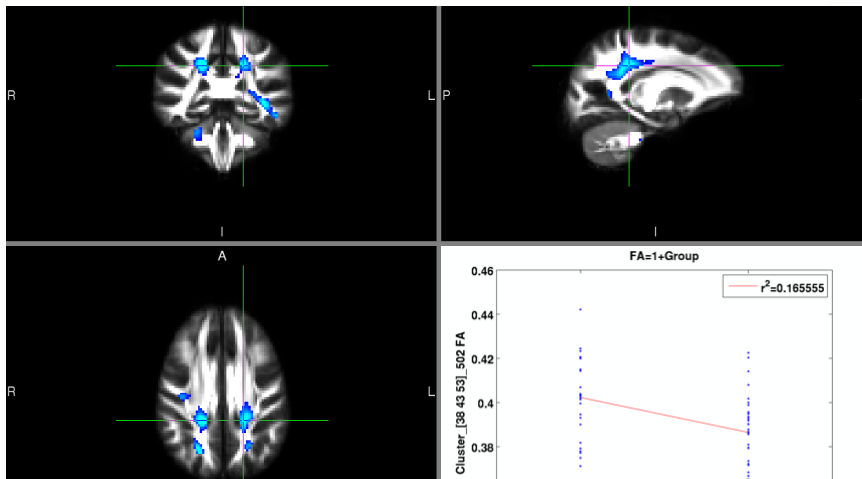




Preliminary descriptive DTI data demonstrating decreased fractional anisotropy and increased mean diffusivity in GV's with CMP



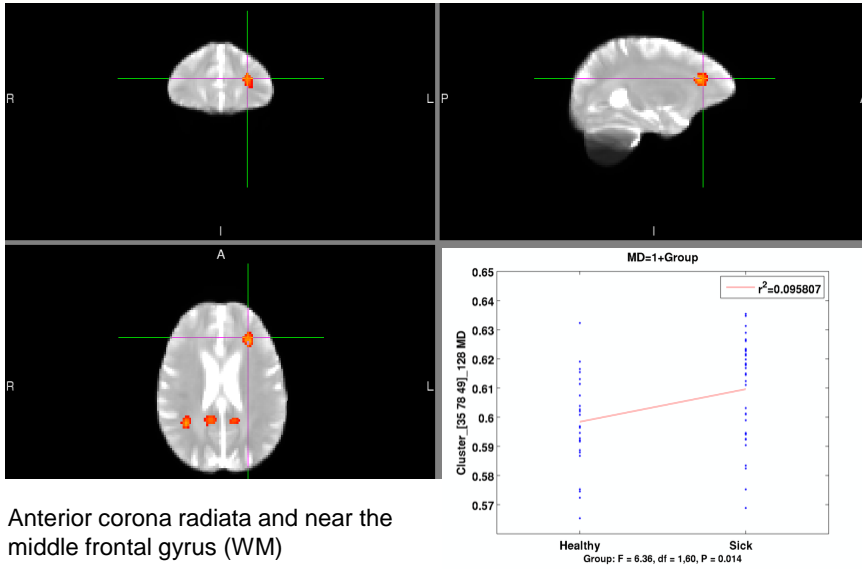
FA: GV's with CMP < Healthy GV's



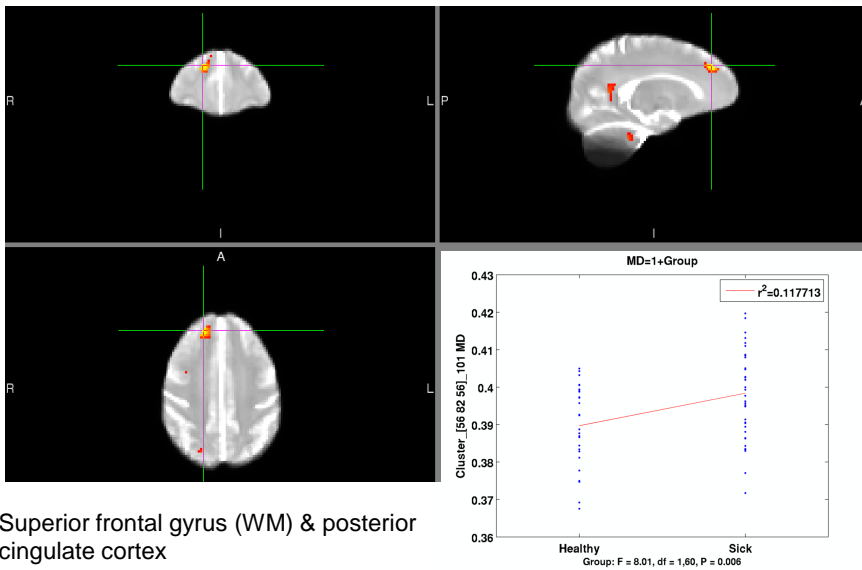
Cingulate gyrus (WM) and portions of the posterior corona radiata, postcentral gyrus and superior parietal lobule



MD: GVs with CMP > Healthy GVs



MD: GVs with CMP > Healthy GVs

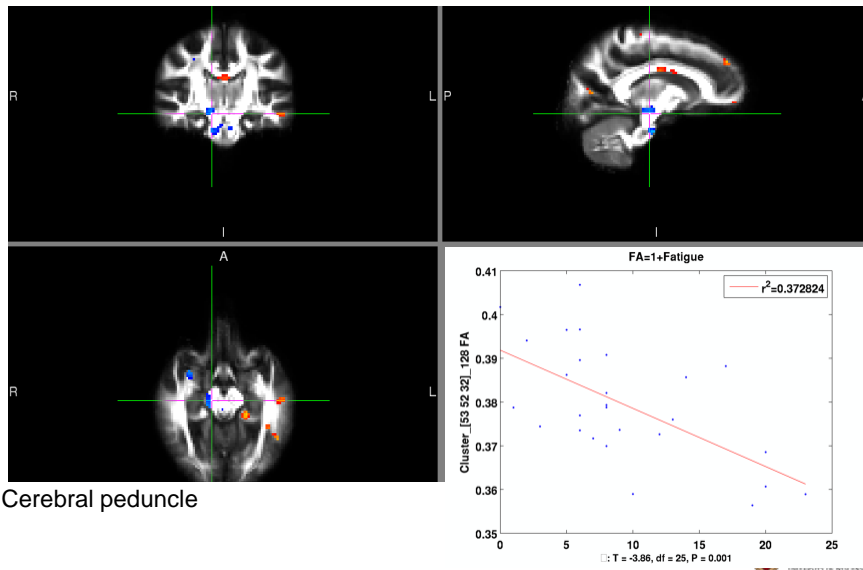


Relationship to behavior

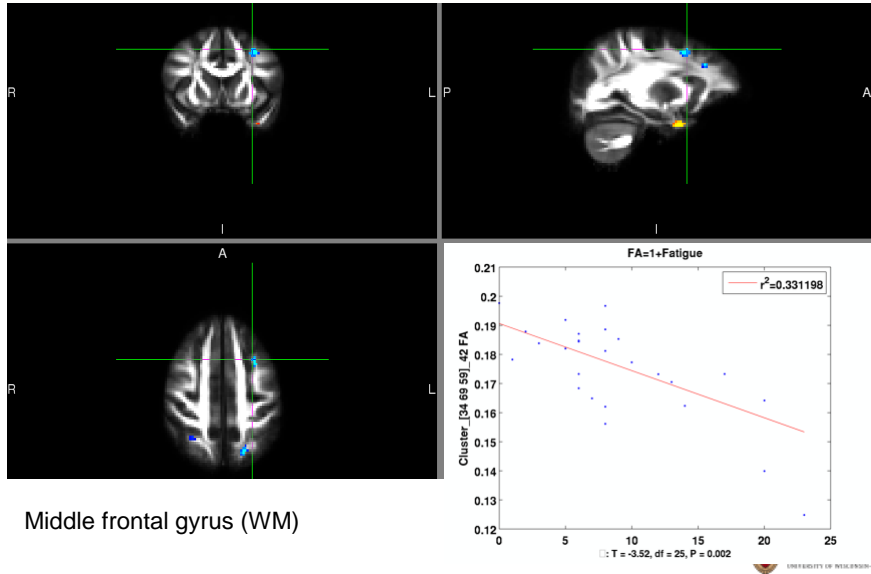
- Self-reported fatigue
- Pain sensitivity



Relationship between FA and fatigue: GV's with CMP

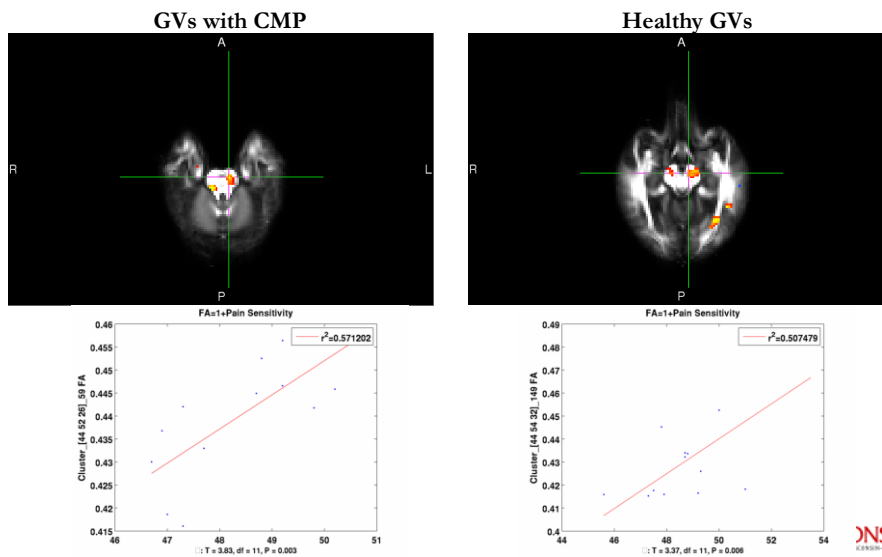


Relationship between FA and fatigue: GV's with CMP

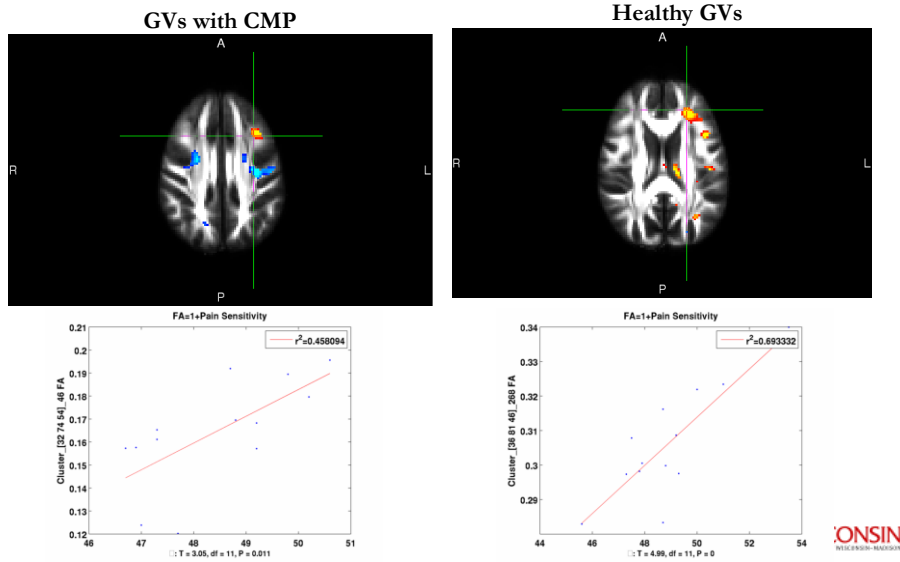


Middle frontal gyrus (WM)

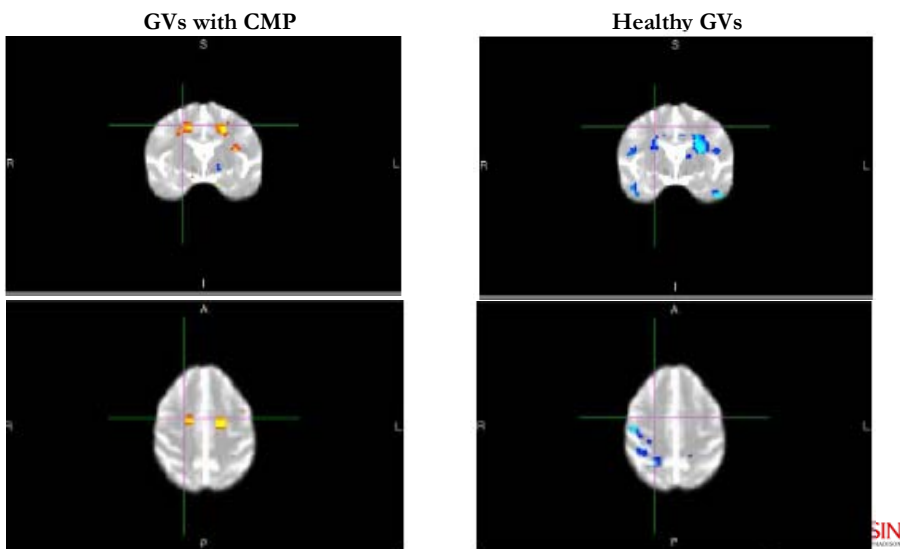
Relationship between FA and Pain Sensitivity: Corticospinal tract



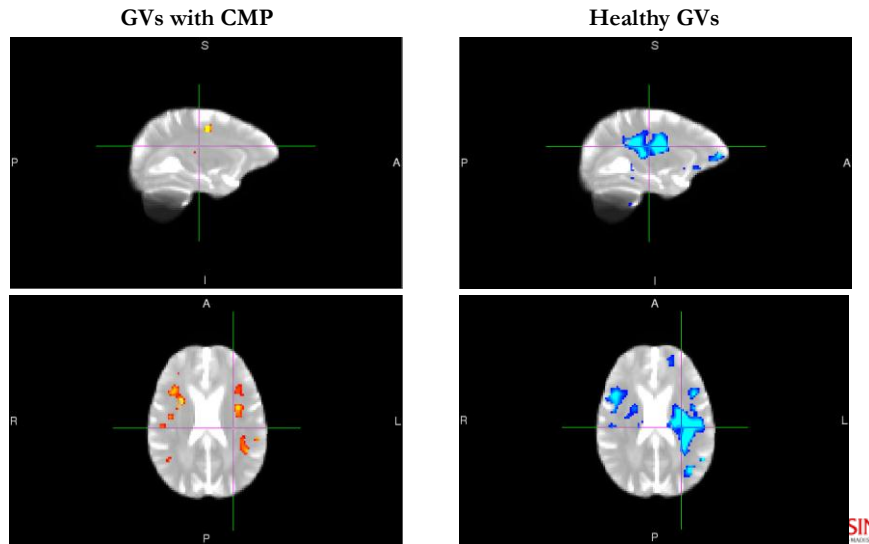
Relationship between FA and Pain Sensitivity: Middle frontal gyrus (WM)



Relationship between MD and Pain Sensitivity: Superior corona radiata



Relationship between MD and Pain Sensitivity: external & internal capsules, corona radiata, postcentral gyrus, precentral gyrus, longitudinal fasciculus



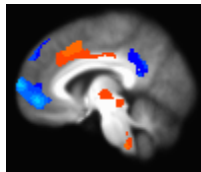
Initial interpretation of DTI data

- In general – GV with CMP show decreased white matter integrity (lower FA & higher MD) in several regions
- White matter density is associated fatigue and pain processing
- For MD there appears to be opposite relationships in GVs with CMP and healthy GVs suggestive of altered communication along spinal tracts that are involved in pain processing and modulation

A critical next step will be to determine whether potentially efficacious treatments of GWI influence brain structure and function and whether these changes predict illness improvement



The impact of resistance exercise training on pain and brain function in GV's with CMP



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