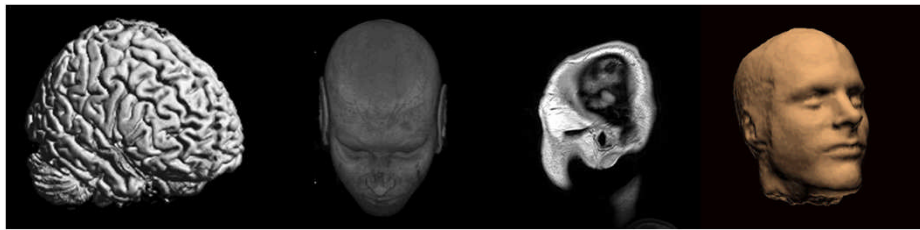


Fatigue in Gulf War Illness

Glenn Wylie, PhD



Disclaimer

The views expressed in this presentation are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government



Who's affected by fatigue?

- Democrats



- Republicans



Gulf War Illness and Fatigue

- 25%-35% of Gulf War Veterans (GVs) report chronic multi-symptom illness
 - Characterized by fatigue, pain and cognitive complaints
 - 175,000-250,000 individuals
- Prevalence of fatigue
 - At WRIISC
 - Of 224 GVs, 64% reported severe pain and fatigue
 - Online survey
 - Of 542 GVs with GWI, 94% reported significant fatigue



What does fatigue feel like?

Patient 10 years post severe TBI

- “The more distractions there are, the more cognitive energy that must be expended to filter out background noise, increasing the attentional demands on my brain to complete each task. Everything takes more cognitive energy after serious brain injury”

Howard (2004). *Brain Injury/professional*, 1, 28-31.



What is fatigue?

- Initially conceptualized as an illness
 - ‘Neurasthenia’ – George Beard (1869)
 - Symptoms:
 - general malaise
 - debility of all function
 - poor appetite
 - fugitive neuralgic pains
 - Hysteria
 - Insomnia
 - Hypochondriases
 - Disinclination for consecutive mental labor
 - Severe and weakening attacks of headaches



What is fatigue?

- Later conceptualized as a symptom
 - In the early to mid 1900's
 - Psychiatry shifted away from emphasizing diseases to symptoms
 - physiological to psychological explanations
 - Fatigue became a symptom rather than a disease
 - Fatigue narrowed to a symptom of 'tiredness'



What is fatigue?

- Fatigue has been conceptualized as
 - an "illness"
 - a "symptom"
- Plagues our understanding of fatigue to this day
- Other constructs which are both illnesses and symptoms
 - Depression
 - Anxiety
 - Sleep



Definition of Fatigue

- **MS Council for Clinical Practice Guidelines (1998) defined fatigue as:**
 - “A **subjective** lack of physical and/or mental energy that is **perceived** by the individual or caregiver to interfere with usual and desired activities”
 - Not too helpful...



Types of Fatigue

- Physical or motor fatigue:
 - Muscle weakness – ability to maintain motor output during
 - Sustained muscle contractions
 - Repetitive muscle contractions
 - Motor fatigue – loss of maximal capacity to generate force during exercise
 - Not of interest today



Types of Fatigue

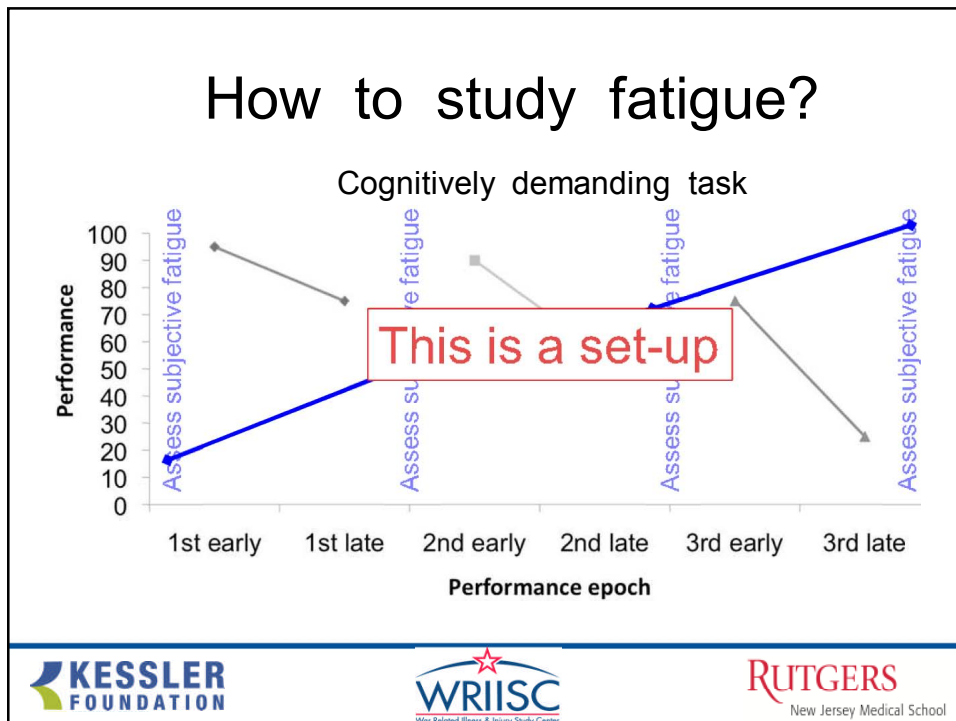
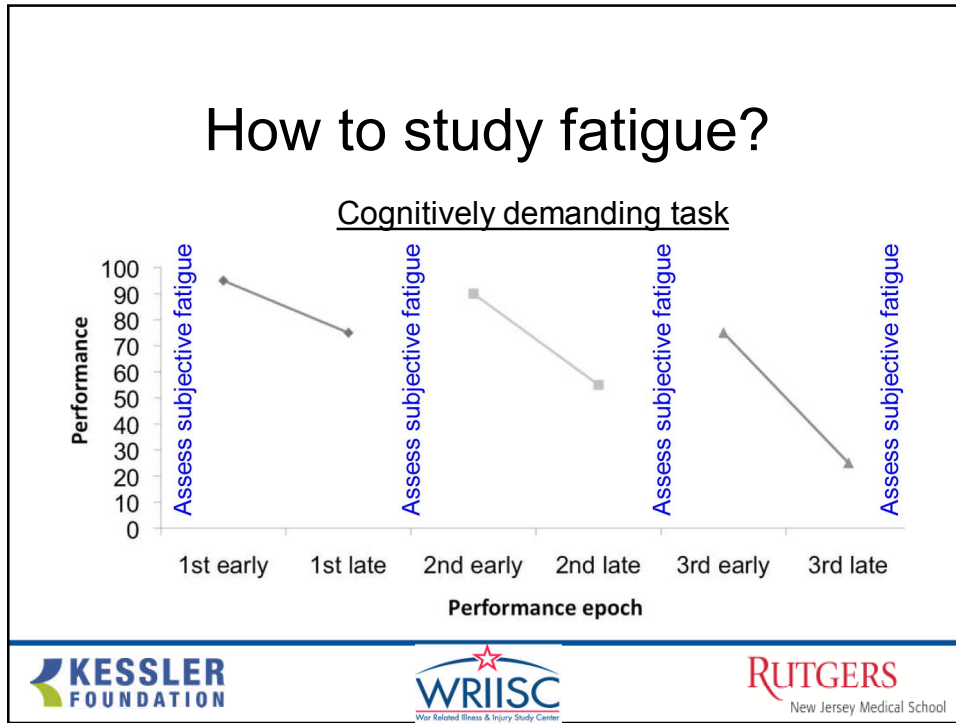
- Cognitive fatigue
 - Feeling mentally drained
 - Perceived difficulty in maintaining attention
 - Studied in two ways
 - Over a period of time
 - During the course of the workday
 - Sustained mental effort
 - During the performance of a demanding task



How to study fatigue?

Shoveling Snow





How to study fatigue?

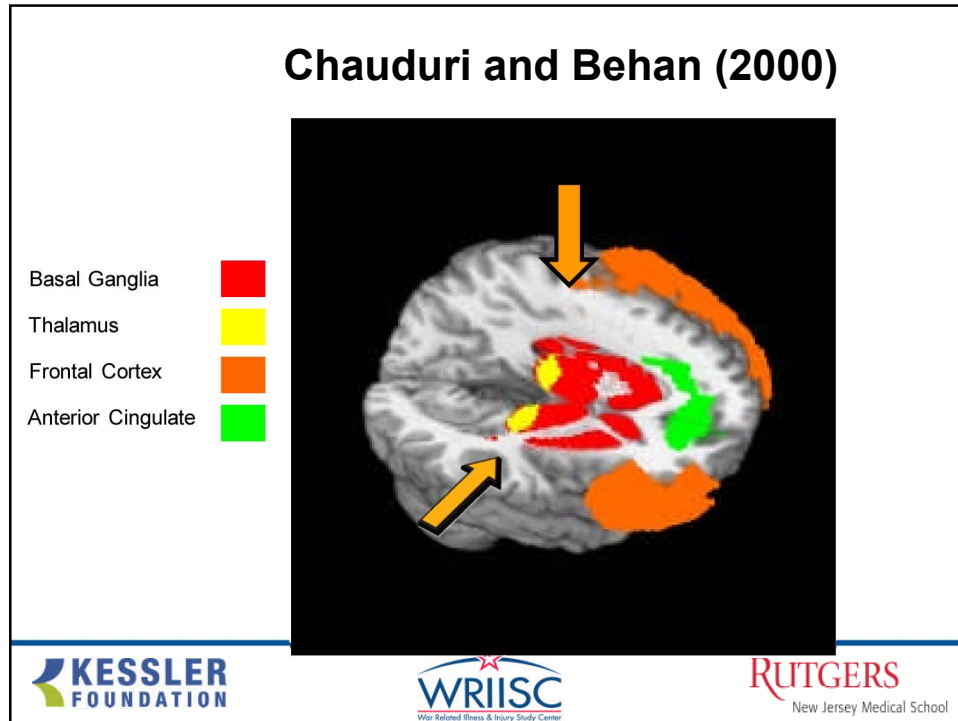
- It would be nice if performance suffered as fatigue increased
- But there is no such relationship
 - Over 100 years of research has shown this
 - There is no known relationship between subjective feelings of fatigue and objective measures of performance



Towards an objective measure of fatigue

- Subjective reports and objective measures of performance do not correlate
- But we believe that all psychological states are based on activity in the brain
 - (We are materialists, after all)
 - Even subjective reports of fatigue
 - So, perhaps brain activity can be used as an objective measure of fatigue





Fatigue in GWI

- A working memory paradigm was used to induce fatigue in
 - 21 individuals with GWI
 - 9 matched healthy controls (HCs)
- fMRI was acquired while they performed
 - 4 blocks of 0-back (less fatiguing)
 - 4 blocks of 2-back (more fatiguing)
 - Counterbalanced
- Subjective reports of fatigue were collected before and after each block

Paradigm to elicit fatigue

- The N-Back task
 - A matching task
 - Two levels
 - 0-back: match against an item in memory (e.g., K)
 - N ... R ... S ... K ... Q ... B ...
 - 2-back: match against an item “2-back” in the list
 - N ... R ... Q ... K ... Q ... B ...



Subjective Reports

- Subjects were asked to rate:
 - Cognitive fatigue
 - Happiness
 - Sadness
 - Anger
 - Pain
 - Tension



Method

How **mentally fatigued** do you feel right now, at this moment?

Sample

	GWI (n =21)	GWC (n =9)	p
Age	49.5 ± 5.7	50.3 ± 8.0	ns
Education	14.4 ± 2.0	15.5 ± 2.4	ns
% Male	89%	90%	ns

Kohl et al. (2009), *Brain Inj.* 23:420-432

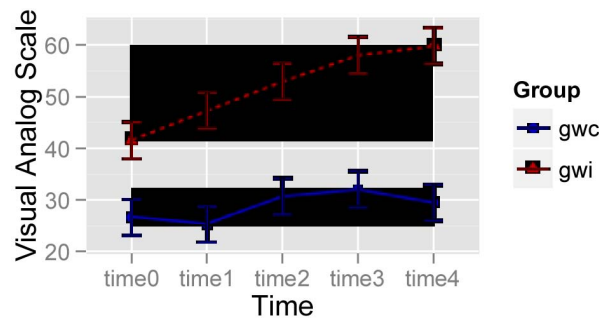
Response time



- Main effect of Task: $F(1,23)=35.07$, $p<0.0001$
- Interaction of Task X Block: $F(3,21)=4.09$, $p=0.02$



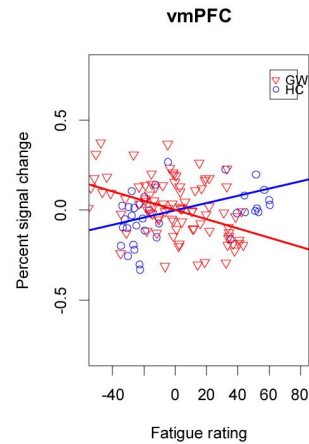
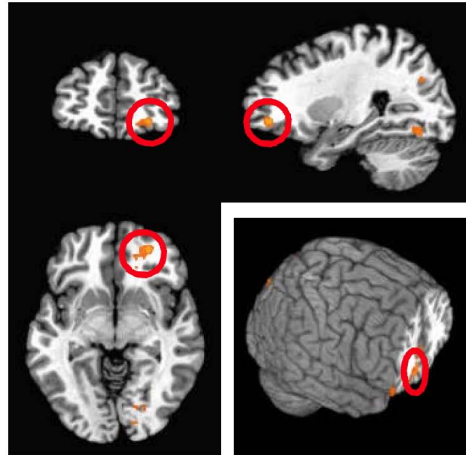
Fatigue ratings



- Main effect of Group: $F(1,29)=4.25$, $p<0.05$
- Main effect of Observation: $F(4,116)=11.73$, $p<0.001$
- (Interaction of Group X Obs: $F(4,116)=2.15$, $p=0.07$)

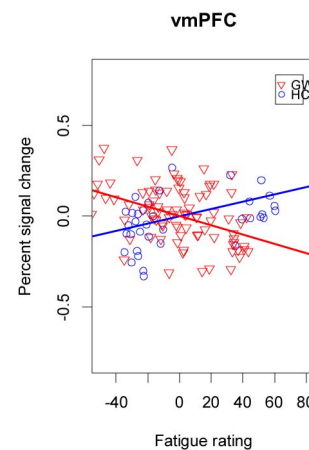


Neuroimaging Results

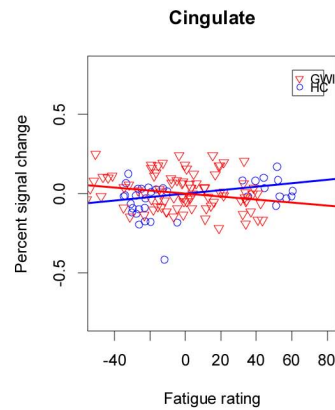
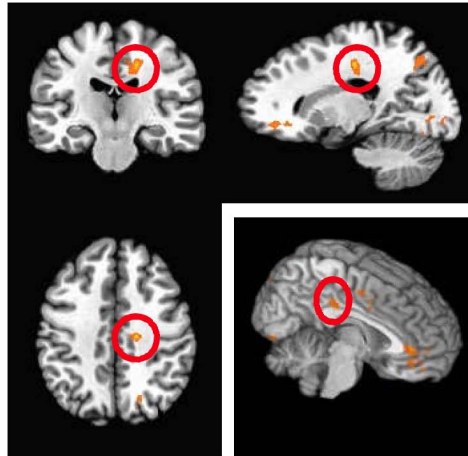


vmPFC

- For GWI (red) as activity increases, fatigue decreases
 - Correlation: $r = -0.42$, $p < 0.0001$
- For GWC (blue) as activity increases, fatigue increases
 - Correlation: $r = 0.49$, $p = 0.002$

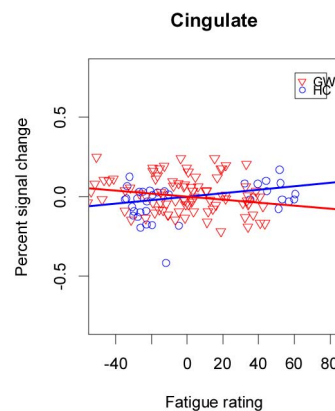


Cingulate

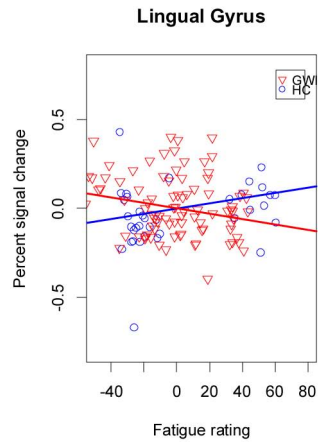
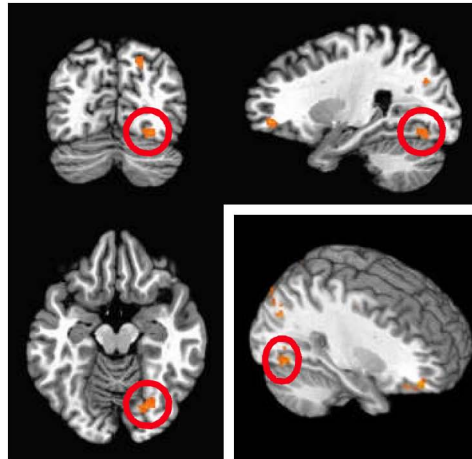


Cingulate

- For GWI (red) as activity increases, fatigue decreases
 - Correlation: $r = -0.22$, $p < 0.04$
- For GWC (blue) as activity increases, fatigue increases
 - Correlation: $r = 0.33$, $p < 0.05$

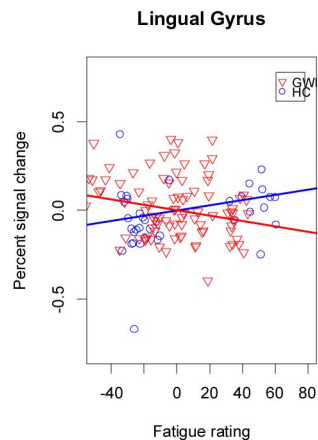


Lingual gyrus

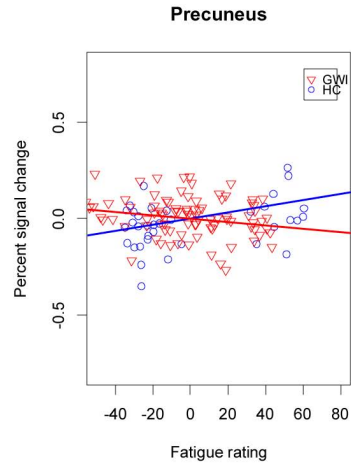
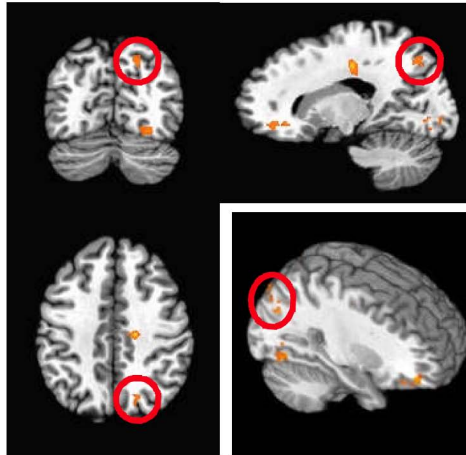


Lingual gyrus

- For GWI (red) as activity increases, fatigue decreases
 - Correlation: $r = -0.23$, $p=0.03$
- For GWC (blue) as activity increases, fatigue increases
 - Correlation: $r = 0.28$, $p=0.09$

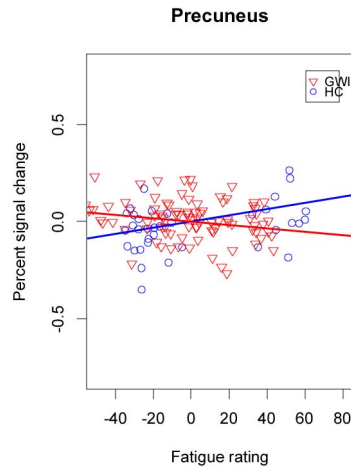


Precuneus



Precuneus

- For GWI (red) as activity increases, fatigue decreases
 - Correlation: $r = -0.23$, $p=0.03$
- For GWC (blue) as activity increases, fatigue increases
 - Correlation: $r = 0.46$, $p=0.005$



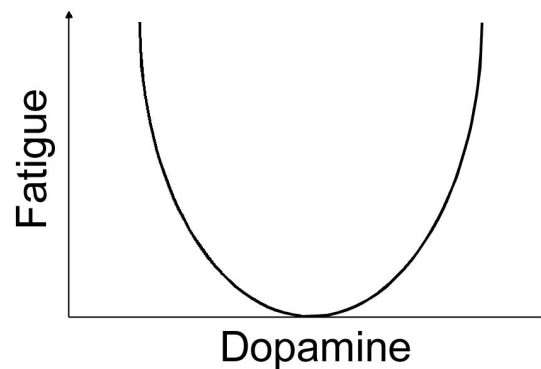
Conclusions

- We are able to measure changes in the brain associated with fatigue
- We find fatigue related activation changes in areas implicated in other populations
 - vmPFC and parietal areas
- In all cases, as activity increases, fatigue decreases
 - Activation seems to combat fatigue



Speculative interpretation

- Dopamine imbalance hypothesis



Future directions

- Using a home-based, individually calibrated exercise intervention to alleviate fatigue in GWI
 - CDMRP
- Investigating the interaction of physical and cognitive fatigue in GWI
 - Piloting now



Thanks to

- WRIISC
 - Drew Helmer, MD
 - Jorge Serrador, PhD
 - Mike Falvo, PhD
 - Amanda Acosta, BA
- VA, Madison WI
 - Dane Cook, PhD
- Kessler Foundation
 - John DeLuca, PhD
 - Helen Genova, PhD
 - Nancy Chiaravalloti, PhD
 - Aerielle Belk, BA
 - Liz Santana, MA



This material is based upon work supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, CSR&D (5I01CX000893)



Finis

