

# Diagnosis, Mechanism and Management of Fatigue in Mild Traumatic Brain Injury

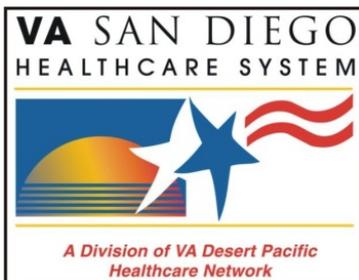
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# Disclaimer

- Dawn Schiehser, Ph.D., has no relevant relationship to disclose with any entity associated with this presentation.
- Her research is supported by the Veterans Administration CDA grant program
- Her opinions and assertions provided in this presentation are her own and do not necessarily reflect the opinion of the Veterans Administration or the University of California.

# Poll Question #1

- What is your primary role in the VA?
  - Student, Trainee, or Fellow
  - Clinician
  - Researcher
  - Manager or Policy-maker
  - Other

# Presentation Overview

- Overview of Traumatic Brain Injury (TBI) and Postconcussive Symptoms (PCS)
- Defining Fatigue in TBI
- Epidemiology and Correlates of Post-TBI Fatigue
- Assessment and Diagnosis of Fatigue in TBI
- Mechanism of Post-TBI Fatigue
- Management and Treatment of Fatigue in TBI

# Traumatic Brain Injury (TBI)

- *VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury (2009):*
  - A traumatically induced structural injury and/or physiologic disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least *one* of the following:
    - (1) any period of loss of consciousness (LOC)
    - (2) any loss of memory for events immediately before or after the accident (Post-traumatic amnesia; PTA)
    - (3) any alteration in mental state at the time of the accident (Alteration of Consciousness; AOC)
    - (4) neurological deficits that may or may not be transient

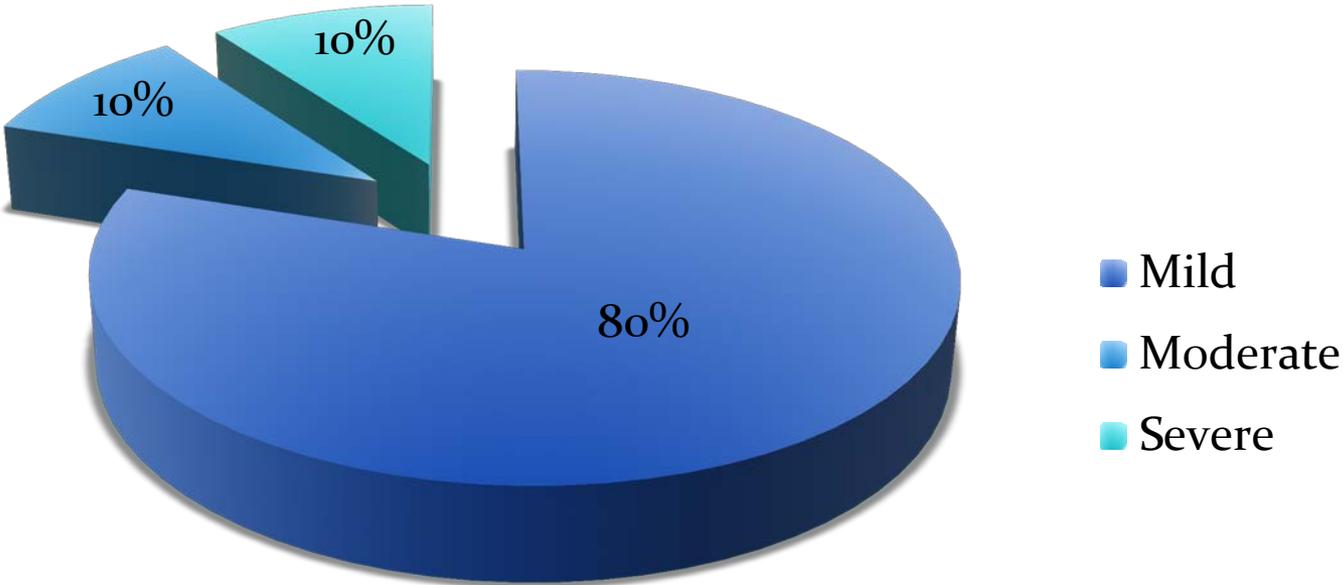
# Traumatic Brain Injury (TBI)

## VA/DoD TBI Severity Stratification Criteria

Criteria	Mild	Moderate	Severe
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of Consciousness (LOC)	0–30 min	> 30 min and < 24 hrs	> 24 hrs
Alteration of consciousness/mental state (AOC) *	a moment up to 24 hrs	> 24 hours. Severity based on other criteria	
Post-traumatic amnesia (PTA)	0–1 day	> 1 and < 7 days	> 7 days
Glascow Coma Scale (best available score in first 24 hours)	13-15	9-12	< 9

\* Alteration of mental status must be immediately related to the trauma to the head. Typical symptoms would be: looking and feeling dazed and uncertain of what is happening, confusion, difficulty thinking clearly or responding appropriately to mental status questions, and being unable to describe events immediately before or after the trauma event.

# TBI Severity



# Postconcussive Symptoms (PCS)

- Physical
  - **Fatigue**, Headaches, Nausea, Dizziness, Vision problems, Sleep disturbance, Noise/Light Sensitivity, Balance problems
- Cognitive
  - Problems in Attention/Concentration, Memory, Processing Speed, Executive function
- Behavioral/Emotional
  - Depression, Anxiety, Agitation, Irritability, Impulsivity, Aggression

# Postconcussive Symptoms (PCS)

- Approximately 85-90% of individuals experience resolution in symptoms within weeks to 3 months following mild TBI
- For 10-15%, symptoms become chronic (persisting longer than 3 months\*)
  - \*Definitions of chronic vary from 4 weeks to 6 months or longer

# Postconcussional Disorder: DSM-IV-TR

- A. A history of head trauma that has caused significant cerebral concussion.
- B. Evidence from neuropsychological testing or quantified cognitive assessment of difficulty in attention or memory.
- C. Three (or more) of the following occur shortly after the trauma and last at least 3 months\*:
  - Becoming fatigued easily 
  - Disordered sleep
  - Headache
  - Vertigo or dizziness
  - Irritability or aggression with little or no provocation
  - Anxiety, depression, or affective lability
  - Changes in personality (eg, social or sexual inappropriateness)
  - Apathy or lack of spontaneity

\*Onset following head trauma; significant impairment in function

# Postconcussional Syndrome: ICD-10

- History of head trauma with loss of consciousness preceding the onset of symptoms by a period of up to four weeks
- At least three of the following:
  - Complaints of unpleasant sensations and pains, such as headache, dizziness, general malaise and **excessive fatigue** or noise intolerance 
  - Emotional changes
  - Subjective complaints of difficulty in concentration and in performing mental tasks, and of memory complaints, without clear objective evidence (e.g., psychological tests)
  - Insomnia
  - Reduced tolerance to alcohol
  - Preoccupation with above symptoms and fear of brain damage with hypochondriacal over-valued ideas / adoption of sick role



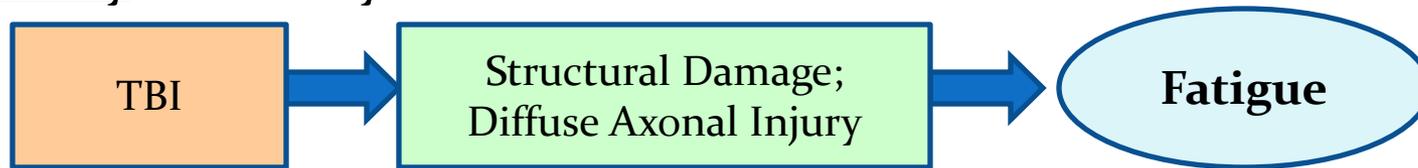
# **Defining Fatigue in TBI**

# What is Fatigue?

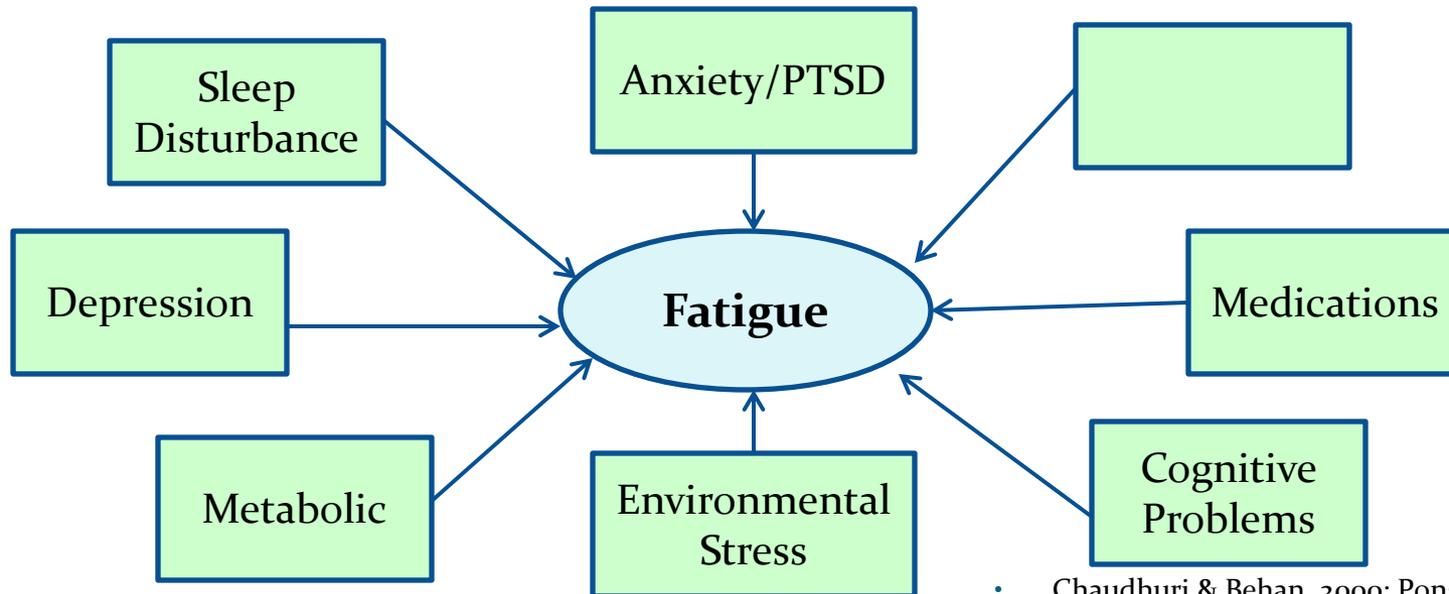
- There is no universally accepted definition of fatigue
- Surprisingly, little is known about fatigue...
  - What exactly is it?
  - What is its function?
  - What causes it?
- Terminology overlap
  - tiredness, exhaustion, lethargy, listlessness, “worn out”, “petered out”, lack of energy, sleepy...
- What fatigue is not:
  - *Sleepiness*: feeling of being tired, needing or desiring sleep, and which is alleviated by sleep

# Defining Fatigue: Primary vs. Secondary

- Primary: caused by a disease or disorder



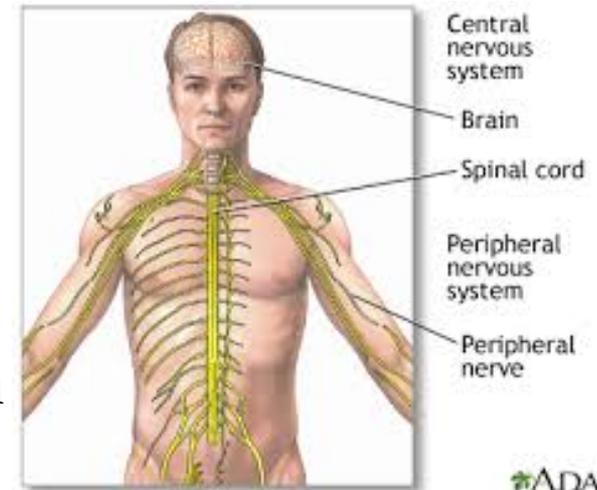
- Secondary: results from or exacerbated by a secondary cause (e.g., pain, sleep disturbance, psychological distress)



• Chaudhuri & Behan, 2000; Ponsford et al., 2012

# Defining Fatigue: Peripheral vs. Central

- Peripheral
  - **Physical**, metabolic or muscular origin
- Central
  - **Cognitive/Mental**
  - Arises from Central Nervous System (CNS)
  - “The failure to initiate and/or sustain attentional (cognitive/mental) tasks and physical activities requiring self-motivation” (Chaudhuri & Behan, 2000)



# Defining Fatigue: Subtypes

- Central Fatigue Subtypes
  - Mental/Cognitive
  - Physical
  - Others: Emotional/Psychological, Psychosocial
- State vs. Trait
  - State: situational; at a particular point in time
  - Trait: over time; more stable symptom
- Acute vs. Chronic
  - Acute: transient, immediately following injury
  - Chronic: persisting, longer-term post-injury

# Defining Fatigue in TBI

- Post-traumatic Fatigue (PTF) / Post-TBI Fatigue (PTBIF)
  - Central/Cognitive Fatigue
  - Primary
  - Acute (days or weeks) / Chronic (>3 months)
  - Definitions vary, making epidemiology difficult to describe



# **Epidemiology and Correlates of Post-TBI Fatigue**

# Post-TBI Fatigue: Epidemiology

- Fatigue is ubiquitous
- Problematic fatigue occurs in 10-20% of the general population
- For those with TBI, fatigue is significantly higher (21%-77%)
- One of the most common symptoms in TBI
- While post-TBI fatigue may improve, some studies suggest that fatigue remains problematic or becomes worse over time

# Post-TBI Fatigue: Epidemiology

- Veterans a positive or negative VA TBI screen (Scholten et al., 2012)

Table 111. Moderate-to-very severe neurobehavioural symptoms by TBI evaluation results.

Variable	TBI		No TBI		TBI vs No TBI	
	(n = 30 267)		(n = 20 934)		Odds ratio <sup>a</sup>	95% CI
	n	%	n	%		
<u>Moderate-to-very severe symptoms in last 30 days</u>						
Irritability, easily annoyed	25 846	85	16 284	78	1.64	1.57, 1.72
Sleep disturbance	25 562	84	16 180	77	1.62	1.55, 1.70
Forgetfulness	24 972	83	14 306	68	2.21	2.12, 2.30
Anxious or tense	24 273	80	14 946	71	1.62	1.56, 1.70
Headaches	23 553	78	13 352	64	2.05	1.97, 2.13
Poor concentration	23 021	76	12 948	62	1.98	1.90, 2.06
Poor frustration tolerance, easily overwhelmed	22 697	75	13 692	65	1.62	1.55, 1.68
Fatigue	20 816	69	12 472	60	1.58	1.52, 1.64
Hearing difficulty	19 845	66	11 288	54	1.62	1.56, 1.68
Slowed thinking, difficulty organizing, difficulty finishing things	19 377	64	10 487	50	1.84	1.77, 1.90
Depressed or sad	18 936	63	11 805	56	1.35	1.30, 1.40
Sensitivity to noise	17 709	59	10 111	48	1.59	1.53, 1.65
Sensitivity to light	16 770	55	9 132	44	1.67	1.61, 1.73
Difficulty making decisions	16 738	55	9 055	43	1.69	1.63, 1.75
Numbness of tingling in parts of body	15 181	50	8 854	42	1.49	1.44, 1.55
Change in appetite	14 321	47	8 123	39	1.45	1.40, 1.50
Vision problems, blurring, trouble seeing	13 327	44	7 384	35	1.57	1.51, 1.63
Feeling dizzy	12 356	41	6 099	29	1.80	1.73, 1.87
Poor co-ordination	12 280	41	5 768	28	1.88	1.81, 1.95
Loss of balance	11 749	39	5 736	27	1.81	1.74, 1.88
Nausea	9 015	30	4 496	21	1.63	1.56, 1.70
Change in taste or smell	6 377	21	3 091	15	1.70	1.62, 1.78
Moderate-to-very severe symptom interference in last 30 days <sup>b</sup>	21 160	74	12 371	65	2.10	2.00, 2.19

<sup>a</sup>Logistic regression models were used to compute odds ratios, adjusting for age, gender, race and ethnicity.

<sup>b</sup>No of individuals with symptom interference information was 28 514 for TBI and 19 009 for no TBI cases.

# Post-TBI Fatigue: Epidemiology

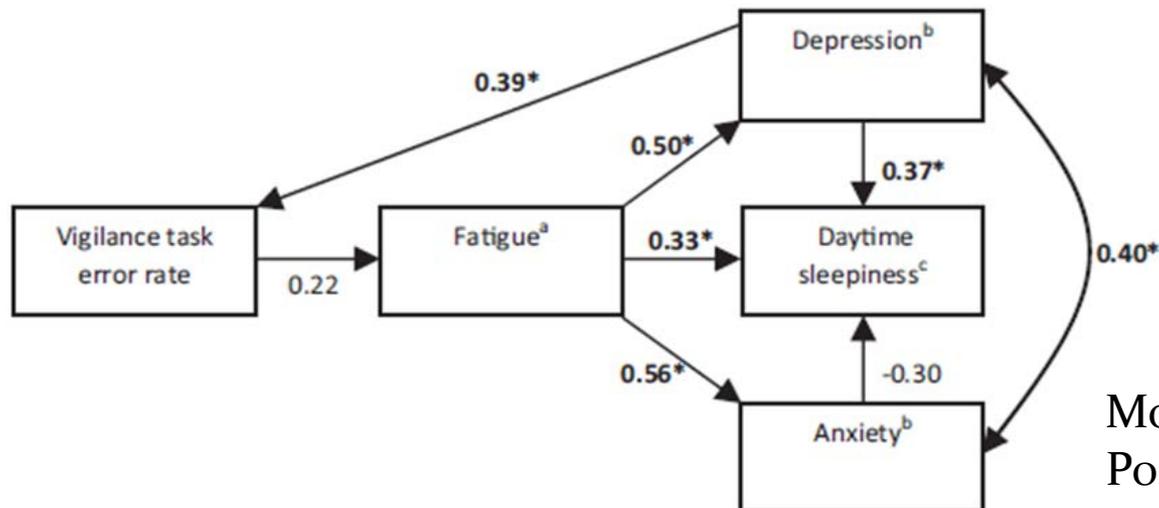
- Mixed TBI sample at 2 years (n=254) and 5 years (n= 103) post-injury (Olver et al., 1996)

Table 4. Proportion of patients reporting cognitive, behavioural and emotional problems at 2 and 5 years post-injury

Problems with	2 years %	5 years %
Forgetfulness	69	71
Slower thinking	64	69
Concentration	63	60
Fatigue	68	73
Planning	43	48
Irritability	68	66
Impulsiveness	43	44
Inappropriate social behaviour	31	36
Needs prompting	47	46
Self-centred	36	36
Anxiety	51	53
Depression	54	56

# Post-TBI Fatigue and PCS Associations

- PTF not typically associated with age, gender, education, TBI severity, or years since injury
- PTF is associated with other PCS (depression, sleep disturbance, anxiety, pain)
- Is fatigue the chicken or the egg?



Model adapted from Ponsford et al., 2014

# Post-TBI Fatigue and Quality of Life

- Fatigue is one of the most critical PCS (out of 22) associated with decreased QoL in Veterans with chronic mild TBI (Schiehser et al., 2014).

**TABLE 3** Multiple linear regression results for the final models of the 4 WHOQOL-BREF domains<sup>a</sup>

WHOQOL-BREF domains	R <sup>2</sup>	F	P	B	SEB	β	P
Physical	0.278	11.17	<b>.000</b>				
Sleep Difficulty (NSI)				- 3.50	1.14	- .379	<b>.003</b>
Depression (NSI)				- 2.40	1.23	- .241	<i>.055</i>
Psychological	0.266	10.51	<b>.000</b>				
Depression (NSI)				- 4.00	1.59	- .330	<b>.015</b>
Fatigue (NSI)				- 3.27	1.66	- .260	<i>.054</i>
Social	0.366	16.71	<b>.000</b>				
Fatigue (NSI)				- 9.47	2.78	- .418	<b>.001</b>
Depression (NSI)				- 5.84	2.66	- .269	<b>.032</b>
Environmental	0.279	11.23	<b>.000</b>				
Depression (NSI)				- 5.37	2.06	- .341	<b>.012</b>
Fatigue (NSI)				- 4.31	2.15	- .263	<b>.049</b>

Abbreviations: β, standardized coefficient; B, estimated coefficient; NSI, Neurobehavioral Symptom Inventory; SEB, estimated standard error of coefficient B.

<sup>a</sup>Bolded numbers represent significance at a corrected P value less than .05; italicized numbers represent trend significant at P value less than .10.



# **Assessment and Diagnosis of Fatigue in TBI**

# Assessment/Diagnosis of Fatigue

- No “gold standard” measure of fatigue
- Subjective Assessment
  - Interview
  - Self-reports
- Objective Assessment
  - Performance decline over time
  - Physiological measures
  - Imaging

# Assessment of Fatigue: Interview

- Questions to ask during the Interview:
  - When did the symptoms of post-TBI fatigue start?
  - Did the onset of fatigue symptoms correlate with any other event such as starting a new medicine or getting depressed?
  - What helps make the fatigue go away, or decrease?
  - What aggravates it?
  - What triggers it?
  - In what ways are you fatigued physically, and when?
  - In what ways are you fatigued mentally, and when?
  - How is your sleep?
  - How is your mood?
  - Do you suffer from significant chronic pain?

# Assessment of Post-TBI Fatigue: Rule-Outs

- Rule-outs for PTF
  - Seizure-related fatigue
  - Hormonal abnormalities, like hypothyroidism
  - Nutritional deficiencies such as low B<sub>12</sub>, anemia, or blood cancers (i.e., leukemia)
  - Renal failure
  - Hepatitis
  - Substance use/abuse
- Medications that can cause fatigue
  - Muscle relaxers
  - Pain medication
  - Blood pressure medications
  - Benzodiazepines (Xanax, Valium)
  - Antihistamines
  - Antidepressants
  - Antibiotics

# Assessment of Fatigue: Self-Report Measures

- A fatigue measure by any other name... is not the same
  - State (Situational) vs. Trait (Chronic)
    - State: At that specific point in time
      - Visual Analogue Scale-Fatigue (VAS-F): “...how you are feeling RIGHT NOW.”
    - Trait: Longer term (over weeks or months)
      - Modified Fatigue Impact Scale (MFIS): “how often fatigue has affected you...**during the past four weeks.**”
  - Unidimensional vs. Multidimensional
    - Unidimensional: general or overall fatigue
      - Fatigue Severity Scale (FSS): Total score derived from 9 items
    - Multidimensional: Cognitive/Mental, Physical, other Subtypes
      - MFIS: Cognitive & Physical subscales

# Assessment of Fatigue: Self-Report Measures

- Fatigue impact vs. “fatigue” quantification
  - Fatigue Impact (e.g., MFIS)

Name: \_\_\_\_\_ Date: \_\_\_\_\_

Because of my fatigue during the past 4 weeks I have...

		Never	Rarely	Sometimes	Often	Almost Always
1	been less alert	0	1	2	3	4
2	had difficulty paying attention for long periods of time	0	1	2	3	4

- Fatigue Quantification (e.g., Multidimensional Fatigue Symptom Inventory-Short Form; MFSI-SF)

	Not at all	A little	Moderately	Quite a bit	Extremely
1. I have trouble remembering things.....	0	1	2	3	4
2. My muscles ache.....	0	1	2	3	4
3. I feel upset.....	0	1	2	3	4
4. My legs feel weak.....	0	1	2	3	4
5. I feel cheerful.....	0	1	2	3	4

# Assessment of Fatigue: Self-Report cont.

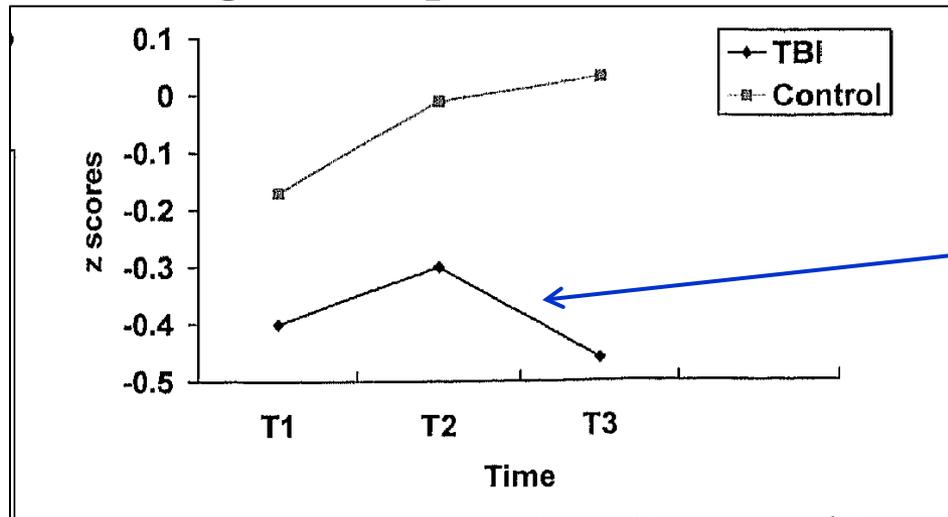
- Psychometric properties and use of cut-off scores
  - Is it valid and reliable in TBI?
    - MFIS validated in mild-moderate TBI (Schiehser et al., 2014)
- Advantages of self-report measures
  - Assessment of subjective fatigue as an internal state
- Limitations of self-report measures
  - Measurement overlap (depression, sleep disturbance)
  - Biases

## Poll Question #2

- Do you use self-report measures of fatigue with your patients or research subjects?
  - Yes
  - No

# Assessment of Fatigue: Objective Measurement

- Decline of (cognitive) performance over time



Mental  
Fatigue

CANTAB accuracy scores at double baseline (T1 & T2) and after 2 hours of questionnaires (T3) – Ashman et al., 2008

- Accuracy & Reaction Time
- Objective is not always associated with subjective fatigue
- Fatigued individuals may achieve adequate performance

# Assessment of Fatigue: Objective Measurement

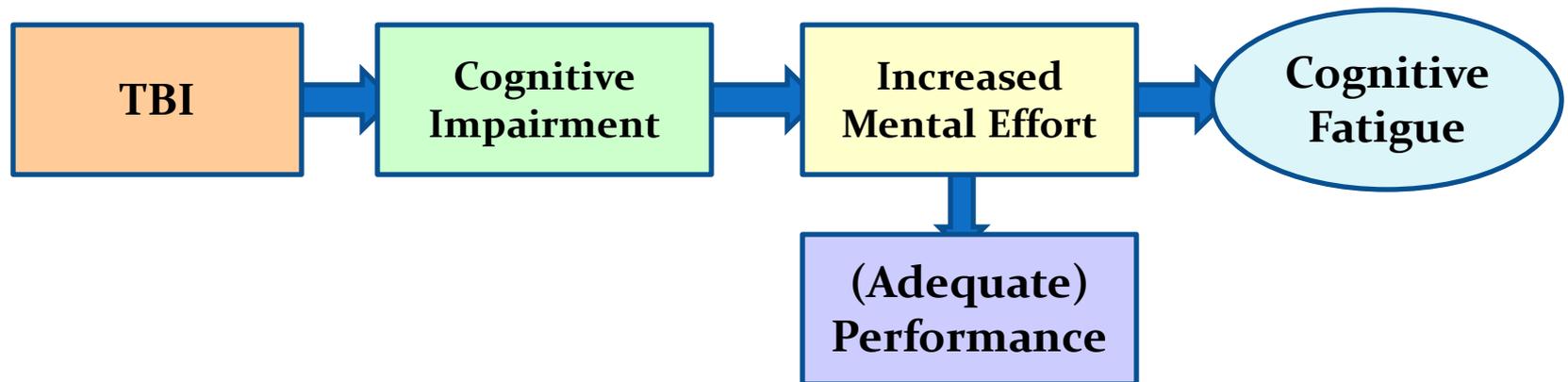
- Compensation: The role of effort
  - $\uparrow$  Effort to maintain adequate performance =  $\uparrow$  fatigue
- Measuring Effort as a proxy for fatigue
  - Physiological measures (blood pressure)
    - TBI and controls performed task adequately, while TBI had increased blood pressure (greater effort), which was associated with subjective fatigue (Ziino & Ponsford, 2006)
  - Neuroimaging (fMRI)
    - $\uparrow$  Cortical activation =  $\uparrow$  effort =  $\uparrow$  fatigue



# **Mechanism of Post-TBI Fatigue**

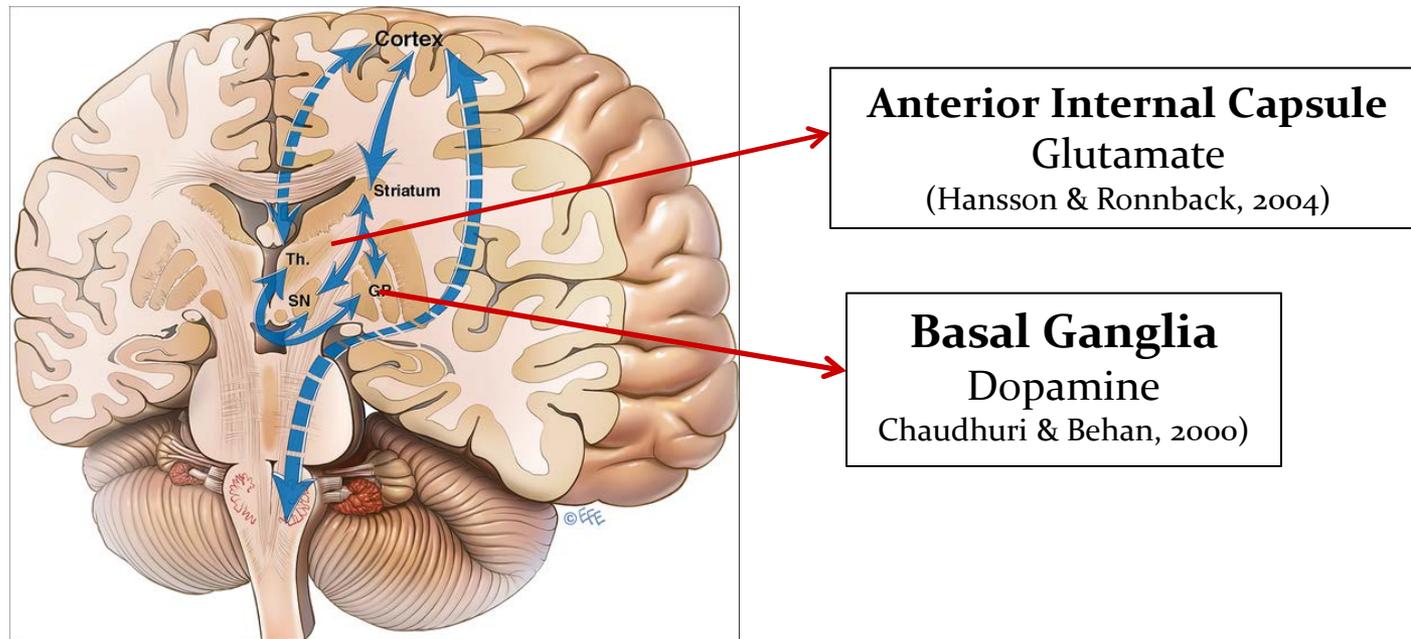
# Mechanism of Post-TBI Fatigue

- Theoretical Model of Cognitive Fatigue in TBI
  - “Coping Hypothesis” (van Zomeren et al., 1984)
    - Cognitive fatigue is due to the constant (mental) effort individuals with TBI need to exert to compensate for cognitive impairments (attentional problems and slowed processing) in order to maintain adequate task performance.



# Mechanism of Central Fatigue

- Chaudhuri & Behan (2000, 2004) theoretical mechanistic model of fatigue
  - Striatal-thalamic-frontal cortical system (“loop”) disruption
  - Basal Ganglia and prefrontal cortex-thalamus connection



**Prototypical frontal cortico-striatal circuit.** Bidirectional arrows: pathways with both afferent and efferent connections. Dotted lines: notional connections. Solid lines: literal connections. Th: Thalamus. SN: Substantia nigra. GP: Globus pallidus. Striatum: caudate nucleus and putamen . Model adapted from Hayhow et al., 2013

# Mechanism of Post-TBI (Central) Fatigue

The neural correlates of cognitive fatigue in traumatic brain injury using functional MRI

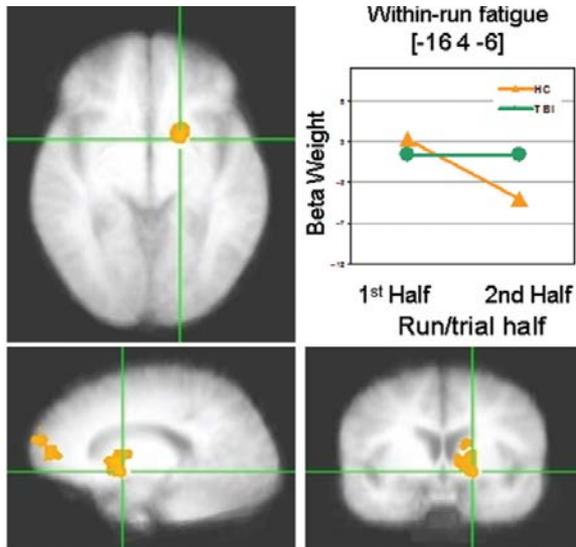
A. D. KOHL<sup>1,2</sup>, G. R. WYLIE<sup>2,3</sup>, H. M. GENOVA<sup>2,3</sup>, F. G. HILLARY<sup>4</sup>, & J. DELUCA<sup>2,3</sup>

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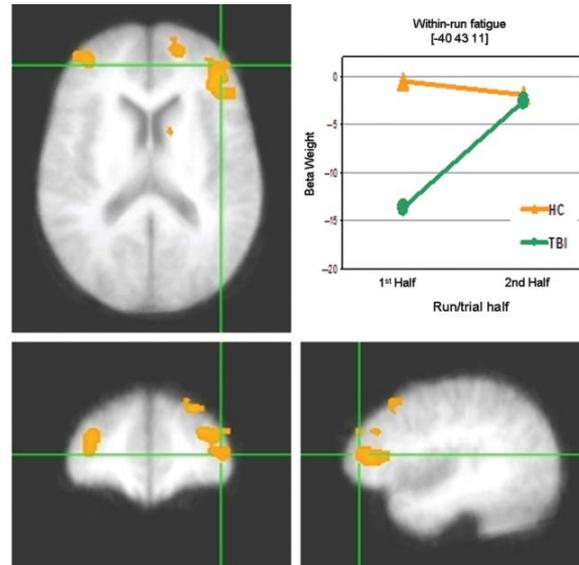
## Study Overview

- 11 moderate to severe TBI v. 11 HC
- fMRI attentional task (mSDMT)
- No differences in performance between TBI and HC

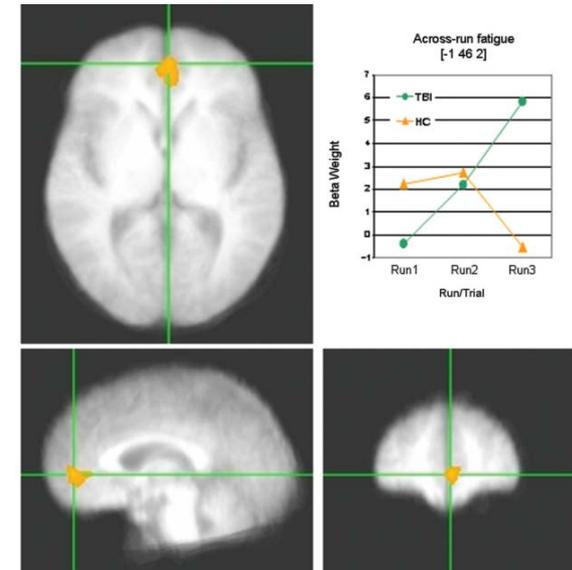
### Left Basal Ganglia



### Middle Frontal Gyrus



### Anterior Cingulate



# Mechanism of Post-TBI Fatigue

- Research is still needed
  - Neural correlates of subjective & objective cognitive fatigue
  - Mild TBI
  - Correlates with injury (blast v. blunt) and comorbid symptoms (sleep, depression)
- What we're doing ...
  - Neural correlates of cognitive fatigue in OEF/OIF Veterans
  - Functional MRI (fMRI), Diffusion Tensor Imaging (DTI)

# Mechanism of Fatigue in mTBI: DTI

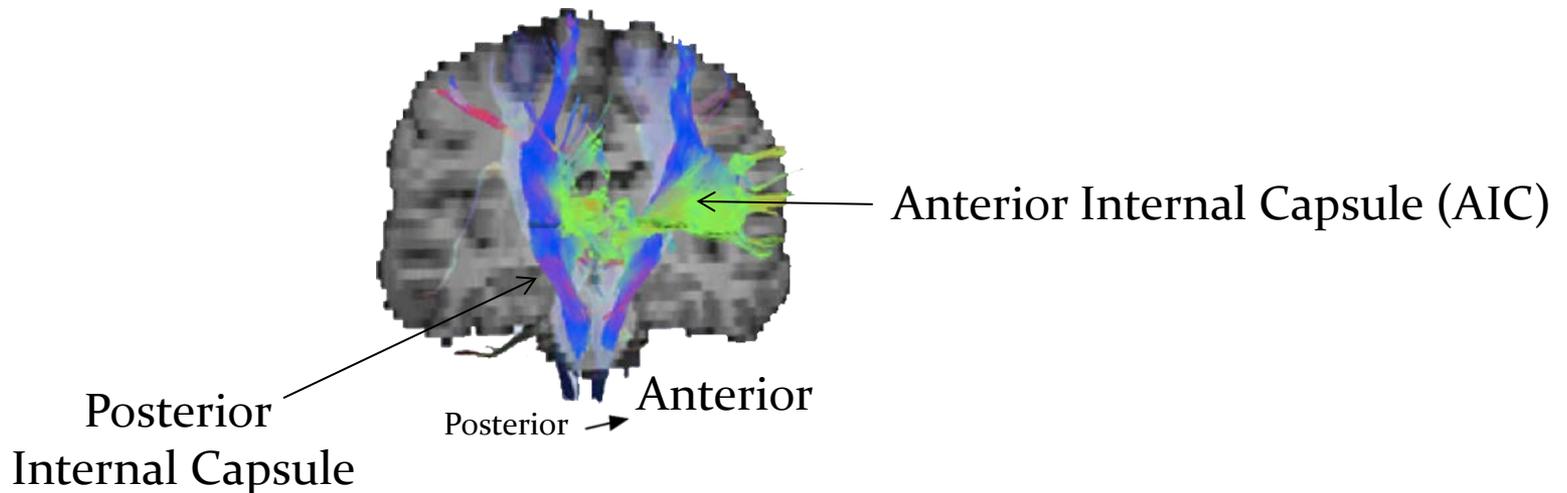
- 38 Veterans with mild TBI

<b>Demographics</b>	<b>Mean (SD)</b>
Age (years)	32.9 (7.1)
Gender (m:f)	34:4
Education (years)	14.4 (1.6)
Number of TBIs	2.3 (1.1)
% Reporting any LOC	68%
“Worst” TBI LOC duration in minutes	4.68 (9.47)
Months Since Last TBI	59.28 (33.96)

- Measure of Fatigue: MFIS (Total, Cognitive, Physical)
- Measure of white matter integrity: Diffusion Tensor Imaging (DTI) / FA
  - Schiehser et al., in preparation

# Mechanism of Fatigue in mTBI: DTI

- Fatigue (cognitive, but not physical) was associated with decreased white matter integrity (FA) in the AIC



- AIC has connections through the caudate and thalamus
- Results support the role of the striatal-thalamic-frontal system in fatigue



# **Management and Treatment of Fatigue in TBI**

## Poll Question #3

- Do you treat patients with fatigue?
  - Yes, it is a primary symptom I treat
  - Yes, but it is a secondary symptom of other disorders/diseases that I treat (e.g., depression, sleep problems)
  - No, I do not treat fatigue in my patients
  - No, I am not involved in treatment work

# Management and Treatment of Fatigue

- To treat or not to treat?
  - Adaptive theory: Fatigue as a warning signal
  - Rest
- Dysfunctional fatigue
  - Interferes with activities of daily living
- No empirically supported treatments for PTF
- Two main approaches:
  - Pharmacological
  - Behavioral

# Pharmacological Treatment of Fatigue

- What should you treat first?
- Primary vs. Secondary Fatigue?
  - Depression
    - Antidepressants: Prozac, Wellbutrin, Effexor, Tricyclics (Vivactil)
  - Sleep Disorder
  - Medication effects (e.g., for pain)

# Pharmacological Treatment of Fatigue cont.

- Primary (TBI) Fatigue
  - Little research support for medications to treat PTF
  - Commonly (off-label) used medications
    - Neurostimulants (Ritalin, Dexedrine, Cylert)
    - Dopaminergic medications (Symmetrel)
    - Herbal (St. John's Wart, Ginko biloba, Ginseng); Caffeine
  - Modafinil: 2 double blind, placebo-controlled studies in TBI (Jha et al., 2008; Kaiser et al., 2010): No clinical benefits over placebo for fatigue
  - **Ritalin**: double blind, cross-over study: decreased mental fatigue in 29 mild TBI subjects (Johansson et al., 2014)

# Behavioral Treatment of Fatigue

- Psychoeducation
  - sleep hygiene, nutrition, self pacing (breaks, rest)
- Cognitive Behavioral Therapy (CBT)
  - CBT improves fatigue in other populations (MS, CFS)
  - 8 weeks of CBT for post-TBI insomnia improved fatigue in 11 (mild-severe) TBI patients (Oullet & Morin, 2007)
- Mindfulness-based Stress Reduction (MBSR)
  - Randomized controlled trial of 8 weeks of MBSR in TBI/stroke patients; fatigue improved (Johansson et al., 2012)
- Physical Exercise
  - Shown to reduce fatigue in other populations (e.g., MS)
  - 12-weeks (30 minutes; 3x/week) of aerobic exercise on treadmill reduced subjective fatigue (FSS) in 10 TBI (50% mild) patients (Chin et al., 2014)

# Summary and Conclusions

- Fatigue is one of the most common and persistent symptoms of TBI and is associated with poor QoL.
- Post-TBI fatigue is most often defined as central/ cognitive/ mental fatigue.
- There is no gold standard measure of PTF; however, it can be assessed with self-reports, interviews and objective-based methods.
- PTF appears to involve a disruption in the striatal-thalamic-frontal cortical system.
- There are no empirically-supported treatments for PTF; however, behavioral (CBT, MBSR, Exercise) and some pharmacological (Ritalin) treatments appear promising.
- More research is needed to better ascertain the mechanisms, trajectory, treatment, and management of Post-TBI fatigue.

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Thank you