Sequelae of Blast-related mTBI: Hypopituitarism

Kathleen Pagulayan, PhD
Clinical Neuropsychologist,
VA Puget Sound Health Care System
Assistant Professor
University of Washington
Department of Psychiatry

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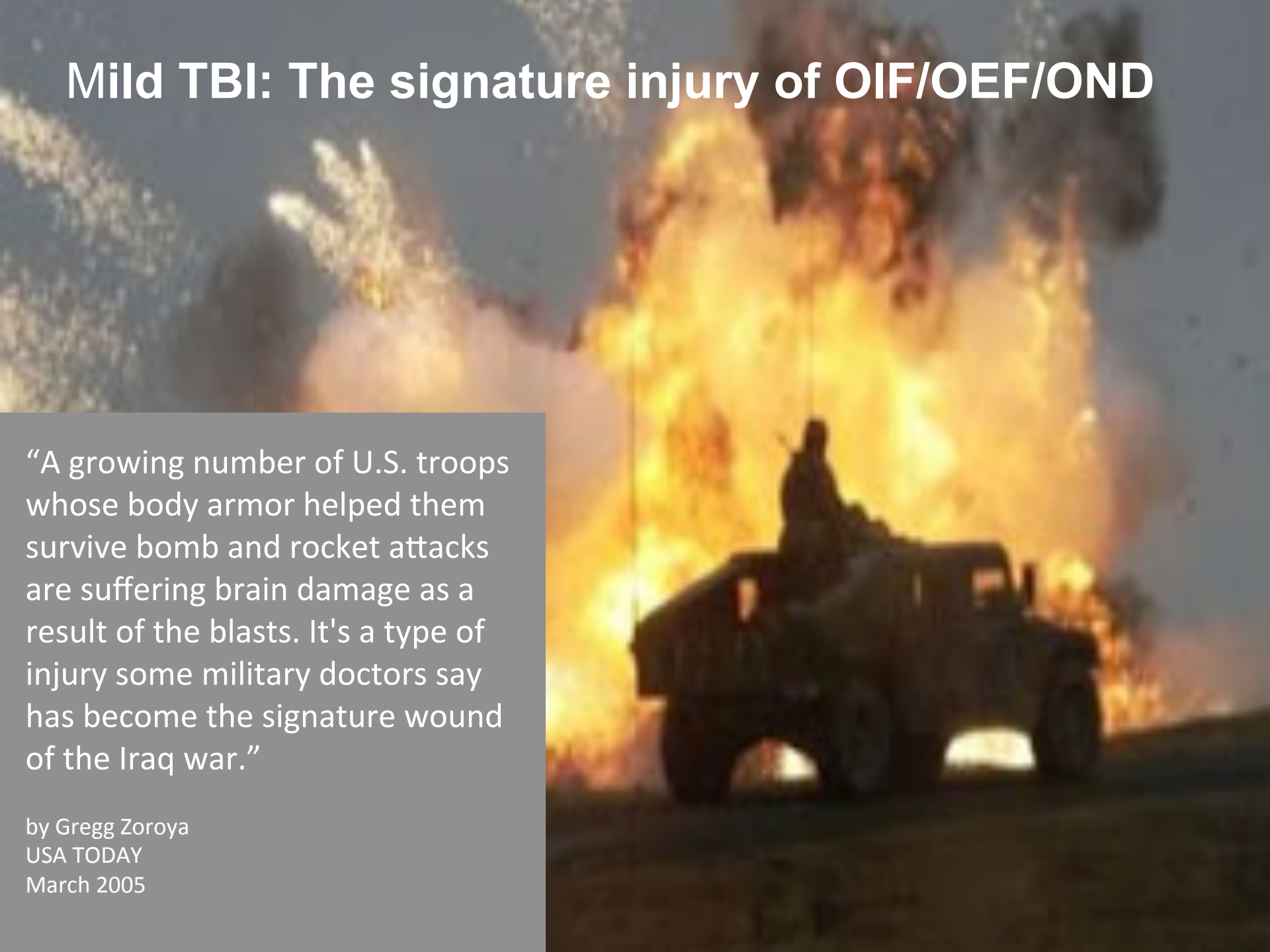
Mild TBI: The signature injury of OIF/OEF/OND



"A growing number of U.S. troops whose body armor helped them survive bomb and rocket attacks are suffering brain damage as a result of the blasts. It's a type of injury some military doctors say has become the signature wound of the Iraq war."

by Gregg Zoroya
USA TODAY
March 2005

MILD TRAUMATIC BRAIN INJURY: DIAGNOSTIC CRITERIA

Traumatically induced physiologic disruption of brain function, indicated by at least one of the following:

- Any period of loss of consciousness
- Any loss of memory for events immediately before or after the accident
- Any alteration in mental state at the time of the accident
- Focal neurologic deficits that may or may not be transient

Severity of injury does not exceed:

- Loss of consciousness of 30 minutes
- GCS score of 13-15 after 30 minutes
- Posttraumatic amnesia of 24 hours

- **Majority of combat-related TBI are mTBI**

BLAST-RELATED MTBI

- Even in times of peace, the military has a higher rate of TBI than civilians. The incidence increases with war.
- Over 2 million U.S. service members have been deployed to Iraq and Afghanistan as of 12/10; nearly 800,000 more than once. Approximately 20% of those Veterans sustained at least one TBI.
- Improvised explosive devices (IEDs) are the weapons of choice of insurgents. 2/3 of war zone evacuations and 88% of injuries treated were due to blast injury.

Controlled IED detonation in Khan Bani Sa'ad, Iraq

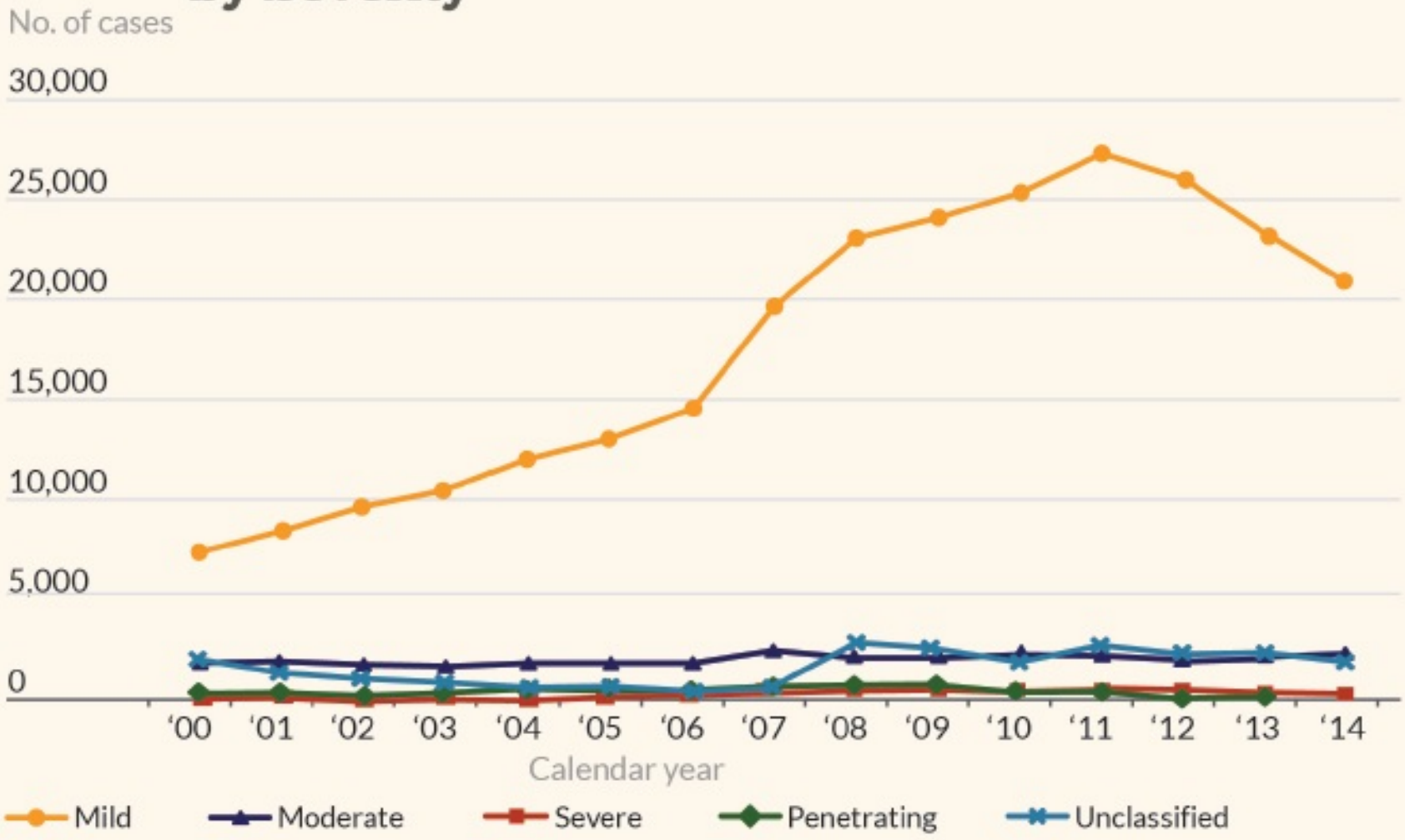
An Example:

One Stryker Brigade operating in Iraq over a 12 month period in 2004-2005

experienced 3056 enemy attacks, 1336 IEDs, 84 suicide vehicle-borne IEDs, 1513 direct fire attacks, and 631 indirect fire attacks.

DoD Numbers for Traumatic Brain Injury Worldwide

Number of Service Members Diagnosed by Severity



Source: Defense Medical Surveillance System (DMSS), Theater Medical Data Store (TMDS)

Prepared by the Defense and Veterans Brain Injury Center (DVBIC)

2000-2014, as of Dec 8, 2015

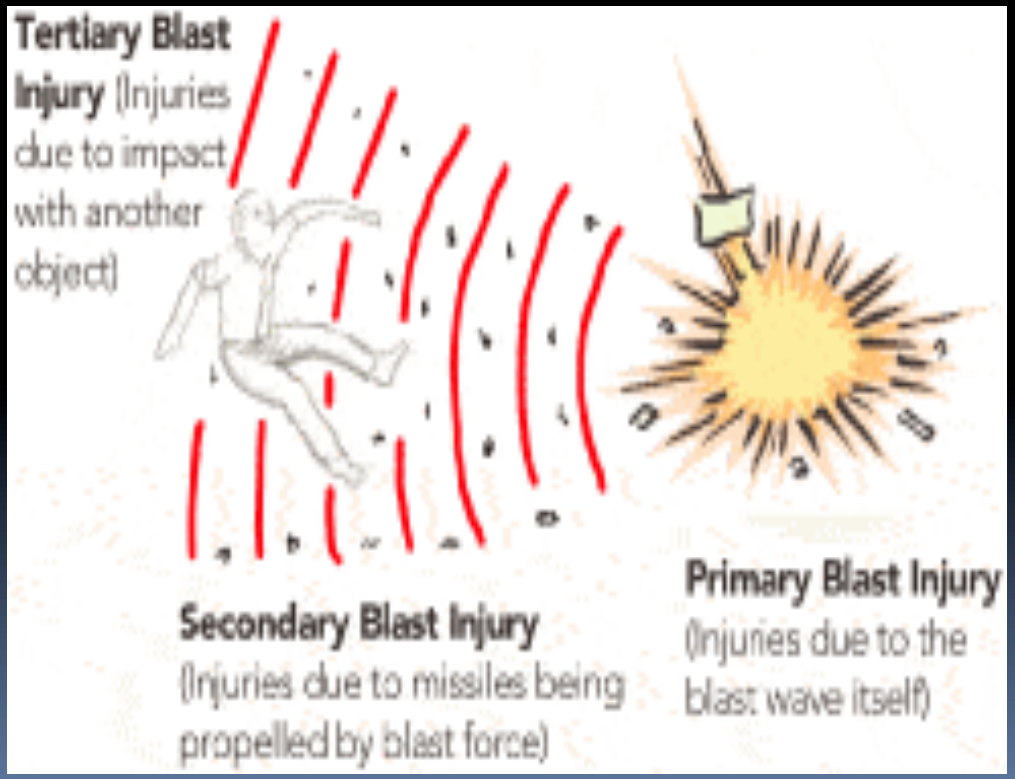
Blast Injuries

Primary: Injury from over-pressurization force (blast wave) impacting the body surface

Secondary: Injury from projectiles (bomb fragments, flying debris)

Tertiary: Injuries from displacement of victim by the blast wind, and impact with other objects

Quaternary: All other injuries from the blast



For further information see www.bt.cdc.gov/masscasualties

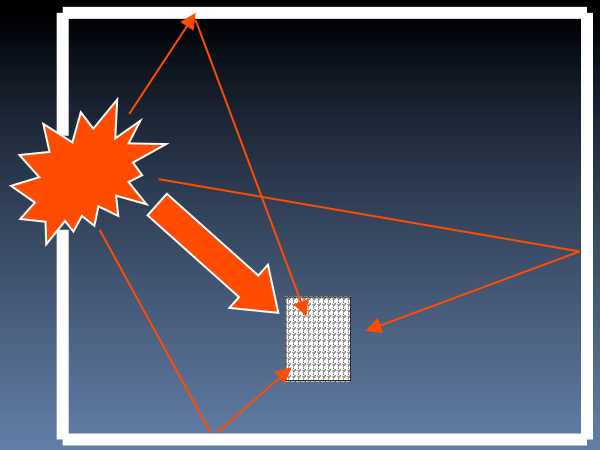
Blast exposures

Bombs and explosions can cause a unique patterns of injury seldom seen outside of combat

Explosions in confined spaces (buildings, large vehicles) and/or structural collapse are associated with greater morbidity and mortality.

Primary blast waves can cause concussions or mild traumatic brain injury (MTBI) without a direct blow to the head.

Strength of blast affected by multiple factors including composition and amount of explosive materials, distance from blast, and presence (or absence) of protective barrier.



http://www.cdc.gov/masstrauma/preparedness/primer.pdf

Outcome differences between blast-related and blunt force TBI

- Current research does not suggest significant difference in neuropsychological outcomes (e.g., Belanger et al., 2009).

- **But** research has found more negative personality changes (Mendez et al., 2013) and higher endorsement of post-concussive symptoms (average 5.7) among those with blast-related mTBI than those with blunt force trauma (average 3.8 symptoms) (Lew et al., 2006).

WHAT HAVE OIF/OEF VETERANS EXPERIENCED?

- 98% experienced hostile incoming small arms fire
- 95% participated in support convoy
- 91% combat patrols/ missions
- 55% witnessed American/ allies being seriously wounded or killed
- 61% witnessed enemy combatants being seriously wounded or killed
- 49% participated in daily combat missions
- 98% saw people begging for food
- 77% witnessed villages or homes destroyed
- 63% saw Americans/allies after being severely wounded or disfigured in combat

TBI AND PTSD

- Soldiers who report mild TBI were more likely to:
  - have high combat intensity
  - be injured in a blast
  - have multiple blast exposures
  - be hospitalized during deployment

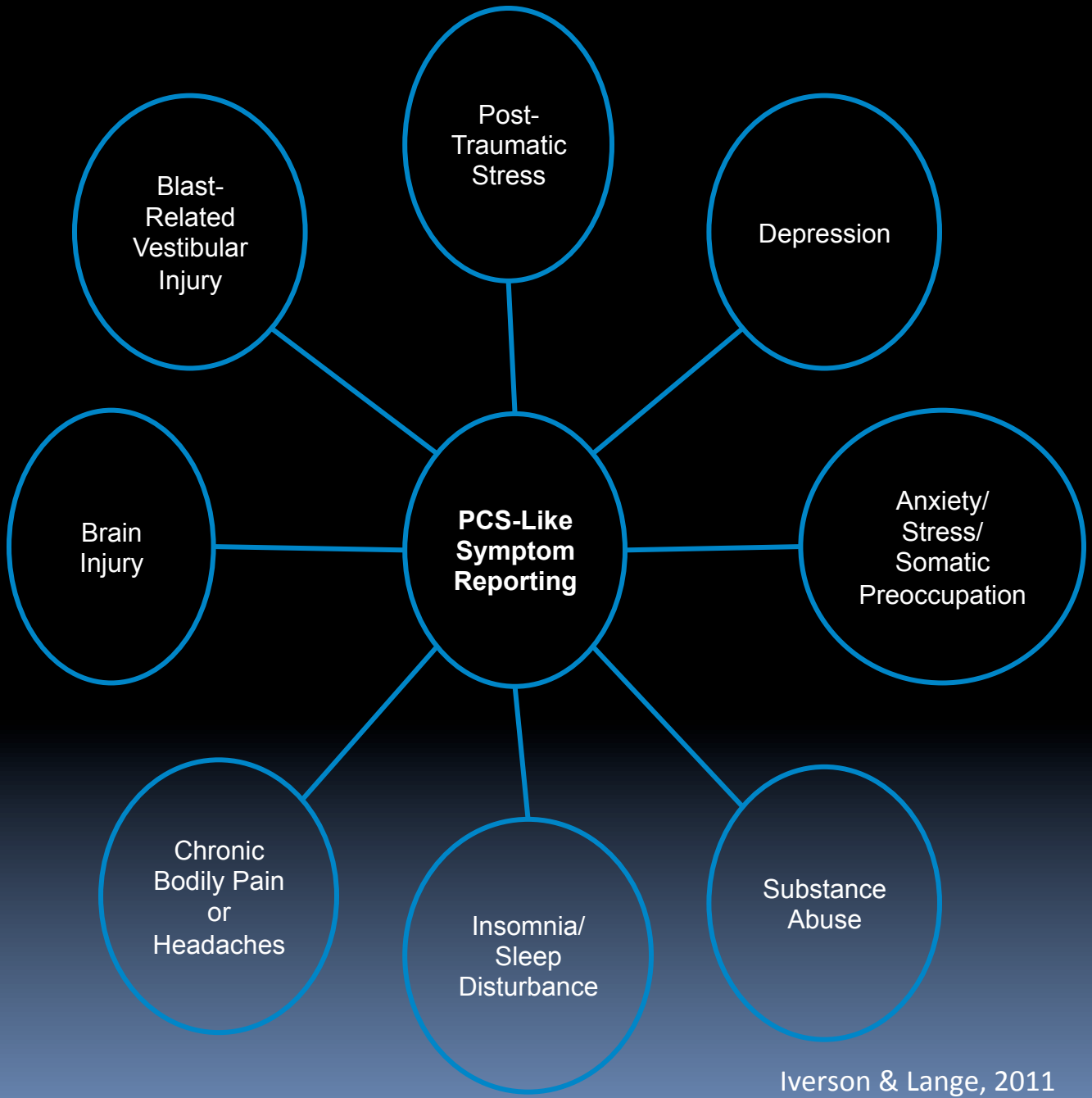
  Hoge et al., NEJM, 2008

- Of those reporting a deployment-related mTBI, approximately 34% also screened positive for PTSD (Tanielian & Jaycox, 2008)

COMMON SYMPTOMS AMONG OIF/OEF VETERANS SEEN FOR POSSIBLE TBI

- Poor sleep (2-4 hours per night)
- Chronic headache and back pain
- Memory/attention/concentration/speed of processing difficulties
- Increased anger/irritability
- Conflict at home
- Reduced performance at work or school

Clinical conditions that influence post-concussion like symptom reporting in Veterans and soldiers after mTBI



Iverson & Lange, 2011

STATEMENT OF THE PROBLEM

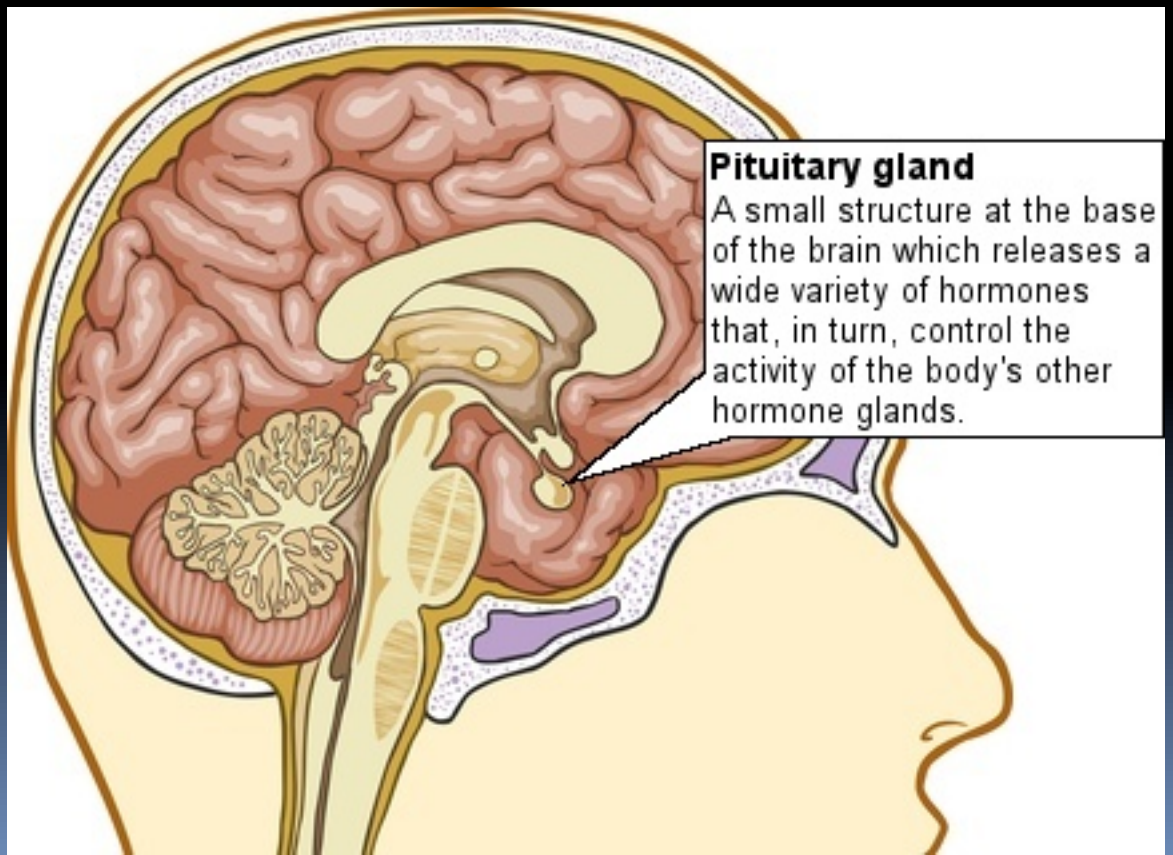
- Many Veterans with combat-related mTBI return from deployment with a range of post-concussive (somatic, cognitive, and behavioral) symptoms.
- These symptoms often persist in Veterans for months to years post injury, but are not specific to or diagnostic of mTBI.
- There is significant debate over the etiology of these symptoms, with PTSD and depression receiving considerable attention.
- However, the impact of blast waves on brain structure and function is not yet understood. Could the persisting symptoms represent changes in brain functioning such as post-traumatic hypopituitarism?

Post-traumatic hypopituitarism

Post traumatic hypopituitarism (PTHP)

Definition of PTHP: diminished production of one or more pituitary hormones due to traumatic brain injury

PTHP is considered chronic if it lasts beyond acute injury phase, typically defined as greater than 6-12 months post injury



GROWING AWARENESS OF PTHP

- PTHP from TBI was first reported in 1918, but considered very rare until approximately 15 years ago.

- Recent studies, since 2000, have demonstrated high prevalence of pituitary hormone deficiency among survivors of TBI.

- Symptoms can be subtle and may be overlooked due to significant overlap with comorbid conditions.

- Direct anatomical evidence of hypopituitarism is very difficult to detect with conventional neuroimaging.

PREVALENCE OF PTHP

- Reported prevalence of chronic TBI-related hypopituitarism has ranged from 5-90%

- Meta-analysis of more than 1000 patients with TBI 3 months- 7 years post injury found prevalence rate of 27.5% (Schneider et al., 2006) …which is approximately 500 times the normal frequency of pituitary dysfunction.
  - At 5+ months post injury, GH and gonadotropin deficiencies were most prevalent.

- Preliminary data on blast-related mTBI suggest approximately 1/4 – 1/3 of individuals had PTHP (Baxter et al., 2013; Stokes & Gallagher, 2011)

- PTHP usually presents as an isolated deficiency, complete pituitary failure more rare

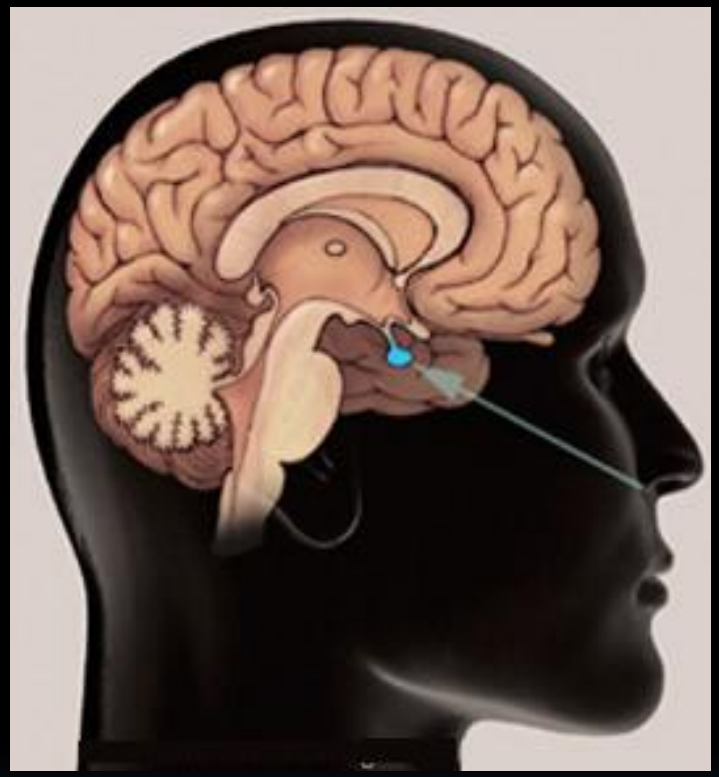
PTHP: Relationship with Injury Severity

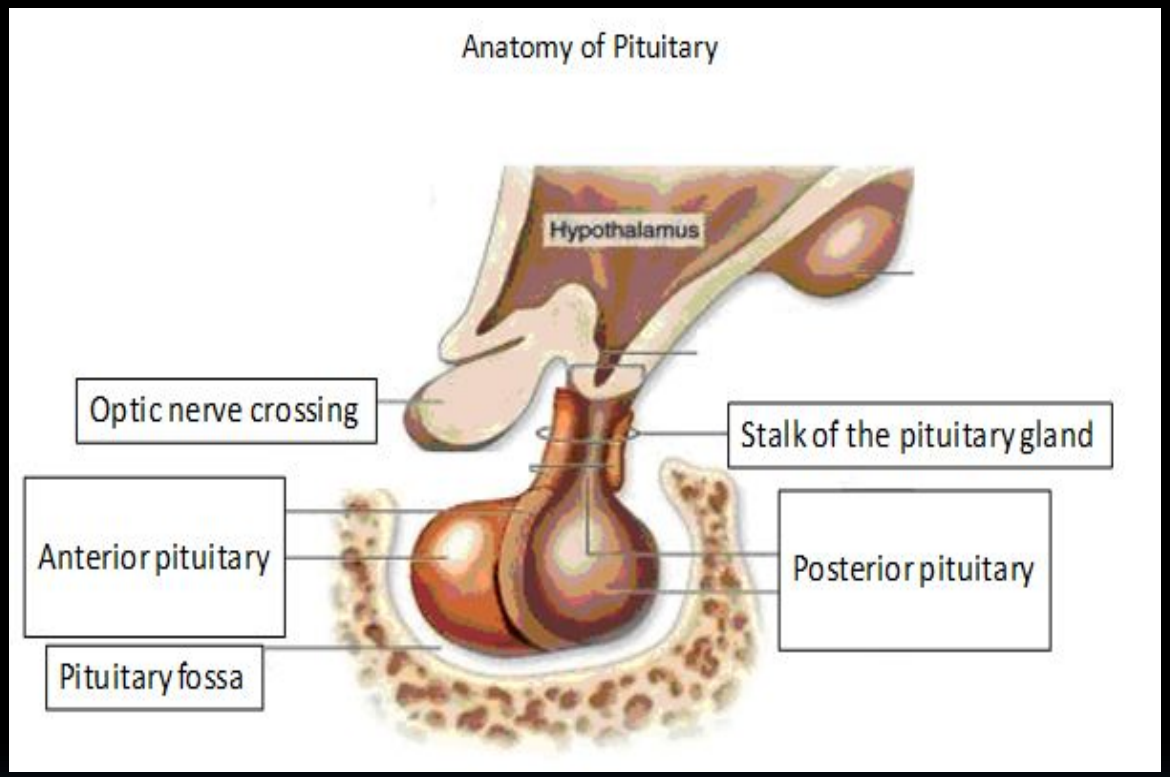
- PTHP has been reported after mild, moderate and severe TBI
- Occurrence of pituitary hormone abnormalities has not consistently been found to be related to severity of injury
- Predictors of pituitary dysfunction among civilians include diffuse axonal injury, basal skull fracture, post-traumatic seizures, intracranial hemorrhages, and focal cortical contusions (Schneider et al., 2006; Silva et al., 2015)

Mild TBI and PTHP-evidence from sports

- 6 studies of anterior pituitary dysfunction after mTBI have reported prevalence of 18-45%
  - 45% of professional boxers with history of repetitive head trauma had growth hormone deficiency (Kelestimur et al., 2004)
  - 27.3% of amateur kick boxers had GH and/or adrenocorticotropin (ACTH) deficiencies (Tanriverdi et al., 2007)
  - 23.5% of retired NFL players with an average of 3 prior concussions had hormone deficiencies, including 19% with GHD (Kelly et al., 2014)

Pituitary Vulnerability to TBI

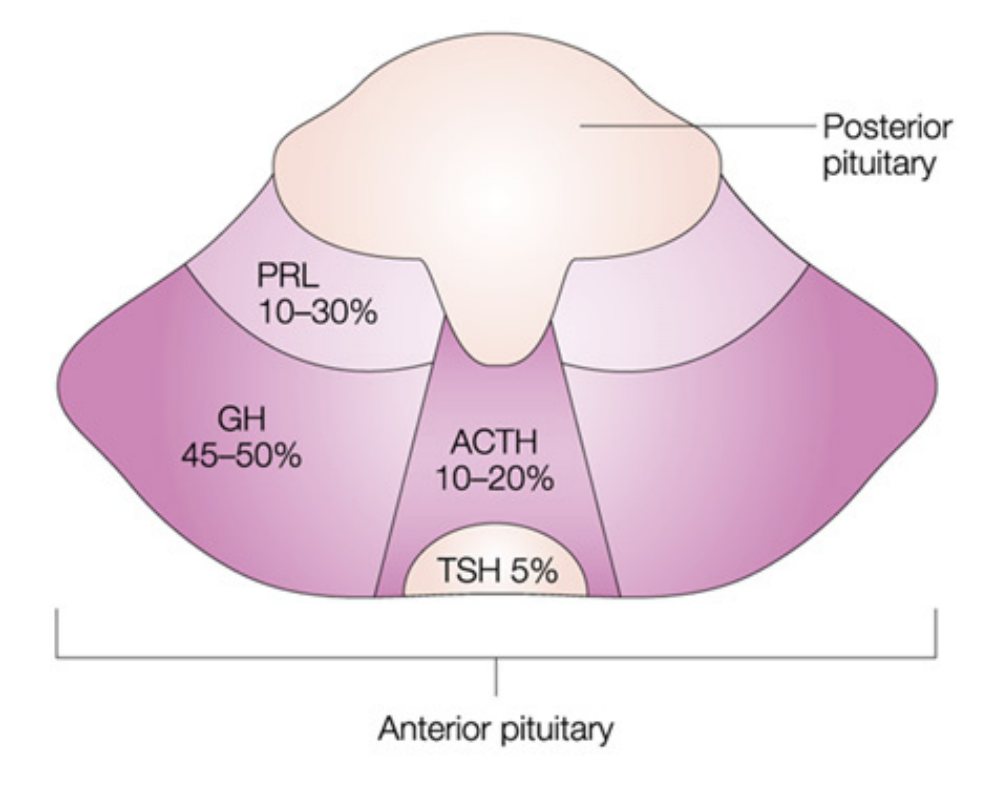




- Damage can occur due to:
  - Compression
  - Torsional and rotational forces from rapid acceleration/deceleration of the brain can affect pituitary stalk (2-3 mm in diameter)
  - Pressure surges through pituitary vasculature

ANATOMICAL VULNERABILITY OF THE ANTERIOR PITUITARY

- Anterior pituitary dysfunction more common than posterior lobe dysfunction.
- Growth hormone (GH) and gonadotropic hormones (FSH and LH) are located in the lateral wings of the pituitary and are particularly vulnerable to injury



Key: PRL= prolactin; GH= growth hormone; ACTH= adrenocorticotropic hormone; TSH= thyroid stimulating hormone; FSH= follicle stimulating hormone; LH= luteinizing hormone

Acute pituitary response in TBI

Adrenocorticotropin (ACTH)

Prolactin

Growth Hormone (GH)

- Multiple transient endocrine abnormalities in the initial (~ 3-month) period following TBI
- Some problems resolve in the first six months (Agha et al., 2005).

- Smaller proportion of new dysfunctions may emerge during the same period
- After 6-12 months, posttraumatic hypopituitarism (PTHP) is considered permanent.

Luteininzing hormone (LH)
Follicle stimulating hormone
Thyrotropin (TSH)

Consequences of PTHP for Psychological Health

- Pituitary abnormalities have been associated with behavioral and cognitive deficits, reductions in quality of life (QoL), and increased mortality
- The symptoms are similar in many respects to those of postconcussive syndrome and PTSD
- PTHP is generally responsive to treatment with replacement hormones
- Failure to screen for PTHP may result in inappropriate and ineffective treatment of these symptoms

Symptoms suggestive of possible PTHP

Behavioral, Cognitive, Emotional and Sleep Symptoms	Reproductive Function	Somatic Symptoms
Depression	Loss of libido	Loss of muscle mass
Emotional lability	Infertility	Increased body fat around waist
Anxiety	Amenorrhea	Low blood pressure
Fatigue		Reduced heart rate
Poor memory		Hair loss
Poor concentration		Anemia
		Constipation
		Cold Intolerance
		Dry Skin

Many symptoms non-specific. Clinical manifestations depend on specific hormone deficiency and degree of deficiency

Growth Hormone Deficiency Symptoms

Physical/Cognitive/Emotional Symptoms
Loss of lean muscle mass and strength
Increased body fat around the waist
Weight gain
Reduced heart rate
Low blood pressure
Constipation
Poor memory
Reduced concentration
Depression
Anxiety
Fatigue
Decreased sex drive

Adult GH deficiency is now recognized as a significant clinical entity with deleterious effects on QOL as well as metabolism, body composition and cardiovascular functioning.

https://dvbic.dcoe.mil/material/indications-and-conditions-neuroendocrine-dysfunction-screening-post-mtbi-recommendations

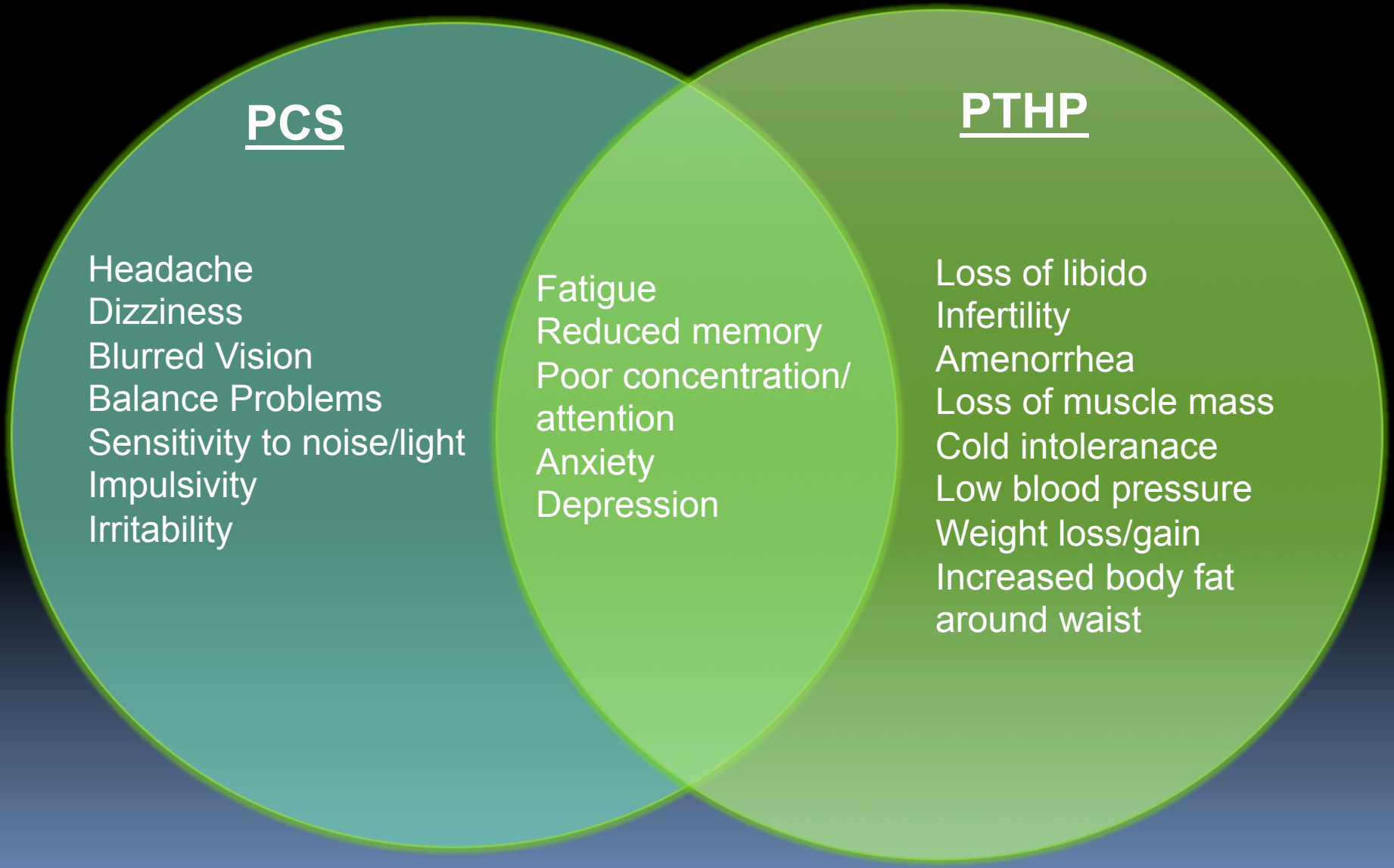
Symptoms of Gonadotropin (LH/FSH/ Testosterone/Estradiol) Deficiency

Physical and Emotional Symptoms (males)
Decreased libido, erectile dysfunction, infertility
Testicular atrophy
Anemia
Hair Loss
Decreased muscle mass and strength
Decreased energy
Dysthymia

Symptoms (females)
Amenorrhea
Sexual dysfunction
Breast atrophy

https://dvbic.dcoe.mil/material/indications-and-conditions-neuroendocrine-dysfunction-screening-post-mtbi-recommendations

Overlap of PCS and PTHP



Referral Recommendations
Defense Centers of Excellence (DCoE 2012 Clinical Recommendations)

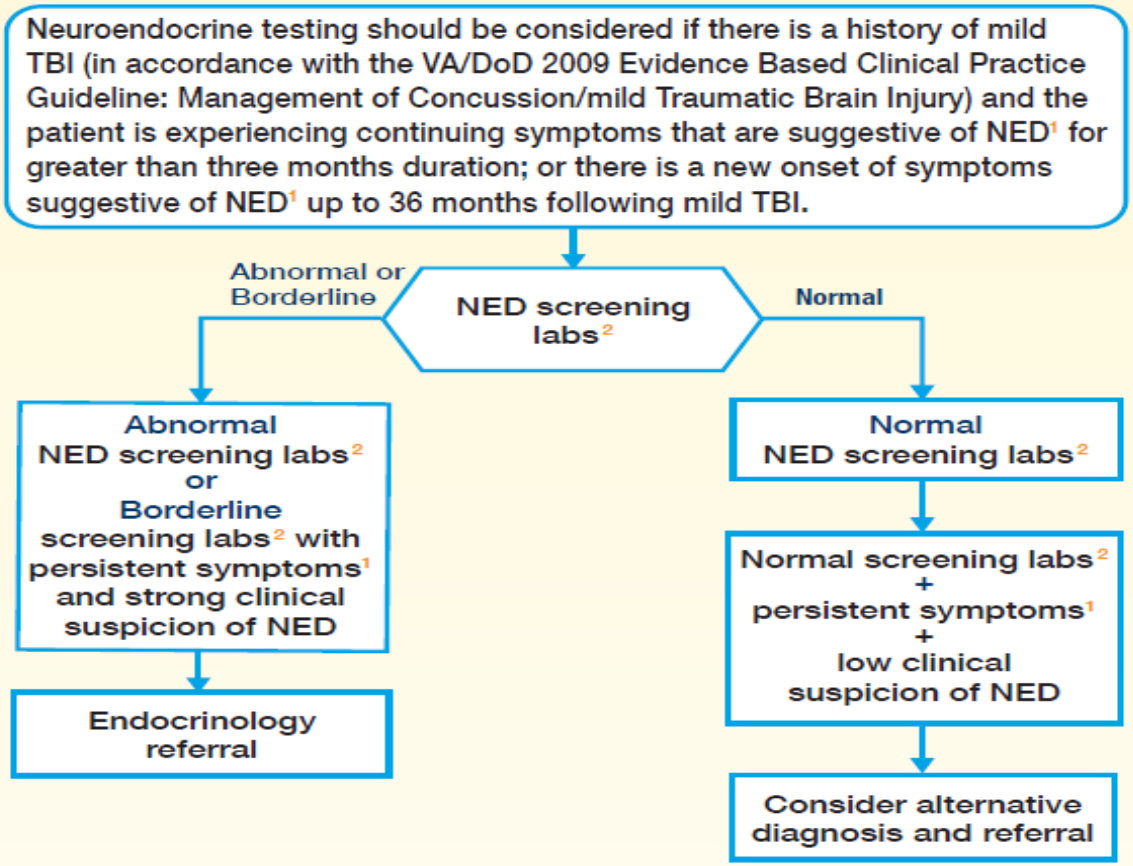
Consider further evaluation of pituitary functioning if:

- Confirmed diagnosis of mTBI
- Service member/Veteran remains symptomatic for more than 3 months or becomes symptomatic up to 36 months post injury.
- Refer to endocrinology if lab results suggest neuroendocrine dysfunction or if strong clinical suspicion remains

https://dvbic.dcoe.mil/material/indications-and-conditions-neuroendocrine-dysfunction-screening-post-mtbi-recommendations

VA /DOD 2009 Management of Concussion/mTBI Guidelines

Neuroendocrine Dysfunction Screening Post Mild TBI



Referral Recommendations

Defense Centers of Excellence (DCoE 2012 Clinical Recommendations)

Recommended labs
Cortisol levels (0800)
Thyroid Stimulating Hormone (TSH)
Luteinizing Hormone
Follicle Stimulating Hormone
Prolactin
Insulin Growth Factor
Free Thyroxine
Testosterone (males)
Estradiol (females)

https://dvbic.dcoe.mil/material/indications-and-conditions-neuroendocrine-dysfunction-screening-post-mtbi-recommendations

Case Study

Veteran with a history of 1 blast-related mTBI with no loss of consciousness while deployed to Iraq.

In theatre post-injury symptoms	New symptoms 3 weeks post injury	3 months post injury (post deployment)
Headache	Anxiety	Increased anxiety and mood swings
Sensitivity to light	Difficulty sleeping	Difficulty sleeping
Dizziness	Lack of concentration	Reduced concentration
Ringing in ears	Mild but transient headaches	Poor appetite but 50 pound weight gain
		Decreased interest in sexual activity

Diagnostic considerations: post-concussive syndrome, PTSD, depression, PTHP

Case Study Part 2

PCP orders labwork, which reveals:

- Low insulin-like growth factor-1
- Borderline testosterone deficiency
- Low LH

- These results suggest probable growth hormone deficiency and hypogonadism.
- The lab results, combined with persisting symptoms, suggested PTHP and referral to endocrinologist was initiated.

Treatment of GHD

- Many symptoms of GHD can be ameliorated with GH replacement therapy. Studies have shown:
  - Improved cognitive abilities (processing speed, memory, executive functioning) (High et al., 2010; Maric et al., 2010; Reimunde et al., 2011)
  - Reduced depression (Maric et al., 2010)
  - Improved QOL (Svensson et al., 2007; Kreitschmann-Andermahr et al., 2008)
- Patients who stopped growth hormone therapy experienced return of psychiatric and cognitive symptoms

Prevalence of PTHP in Veterans with blast-related mTBI: A Seattle VA Study

PI: Charles Wilkinson, PhD

Investigators: Kati Pagulayan, PhD
Elaine Peskind, MD

Study Rationale & Questions

- Effect of blast-related mTBI on pituitary function remains unclear
- Lack of routine hormonal screening after TBI
- Considerable overlap in symptoms between PTHP, post-concussive symptoms and PTSD

Study Aims:

1. Does blast mTBI result in rates of PTHP comparable to those seen after TBI from other causes?
2. What pituitary hormone axes are most frequently affected?

EXPERIMENTAL DESIGN

- Acquisition of blood samples from two groups of Veterans of deployment to Iraq/Afghanistan
  - Veterans diagnosed with blast mTBI
  - Deployed Veterans not blast exposed
- Establishment of normal hormone reference ranges using samples from age-matched community controls
- Measurement of basal levels of hormones
- Determination of prevalence of abnormalities in each pituitary hormone axis in each group

Inclusion Criteria	Exclusion Criteria
All Participants	**All participants**
Age 21-40 years	Penetrating head wound
Body Mass Index between 18 and 36	Moderate/severe TBI
	Seizure disorder
mTBI Group	Insulin-dependent diabetes
Documented hazardous duty in Iraq/ Afghanistan	Current DSM-IV diagnosis of alcohol/substance abuse
Meets ACRM criteria for mTBI	DSM-IV diagnosis of schizophrenia or other psychotic disorder, bipolar disorder, or dementia
Greater than 12 mos. since last blast exposure	Medications likely to affect cognitive performance (e.g., opiates, benzodiazepines)

DEMOGRAPHIC CHARACTERISTICS

	Deployed Controls (N=18)	mTBI (N=29)	mTBI+PTHP (N=10)
Age	31.7	32.5	35.5
Years of Education	13.7	14.3	14.1
Race			
% Caucasian	78%	76%	60%
% Asian/Pacific Islander	17%	10%	10%
% African-American	0%	7%	0%
% Other	6%	7%	30%

BLAST CHARACTERISTICS

	mTBI (N=29)	mTBI+PTHP (N=10)
# Blast exposures during Iraq deployment(s)	10.0 ± 15.1	35. 8± 37.9**
Range of # of blast exposures	1-71	4-100
# Blast exposures with LOC during Iraq deployment	0.7 ± 0.7	0.9 ± 1.3

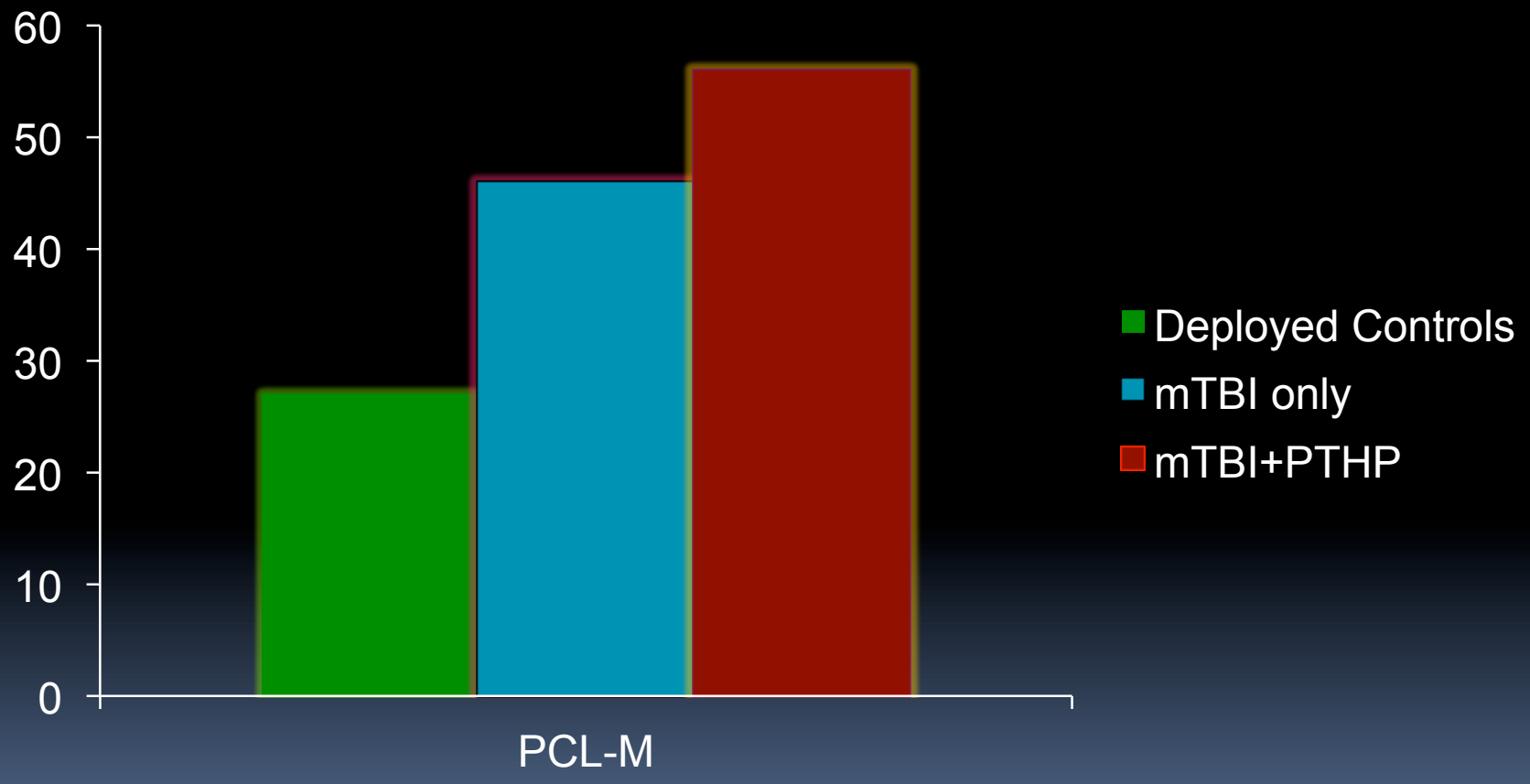
Results

10 of 39 (26%) mTBI participants had anterior PTHP

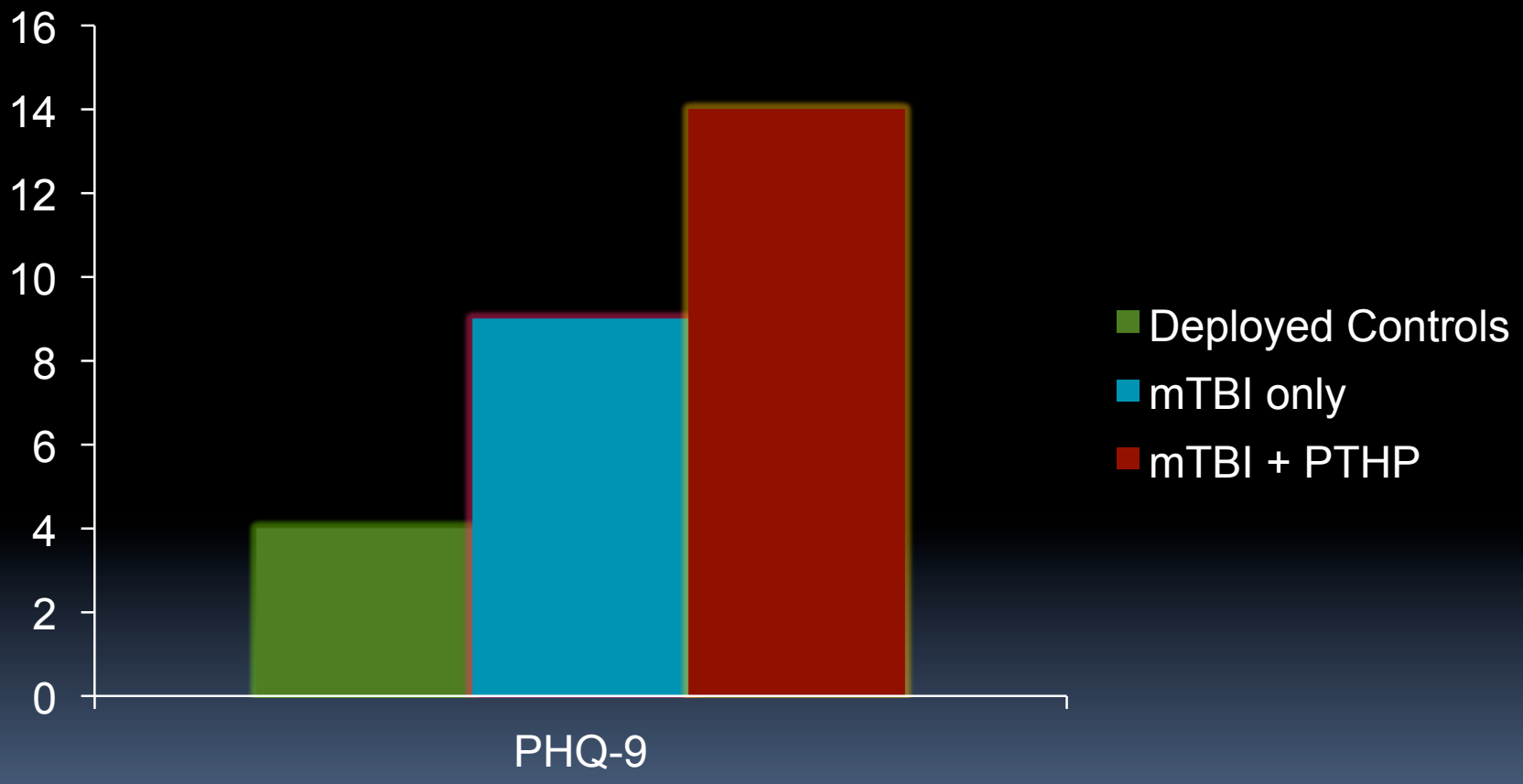
- 5 with growth hormone deficiency
- 2 hypergonadal
- 2 with thyroid hormone deficiency
- 1 with multiple deficiencies

2 of 20 deployed controls (10%) also had pituitary hormone abnormalities

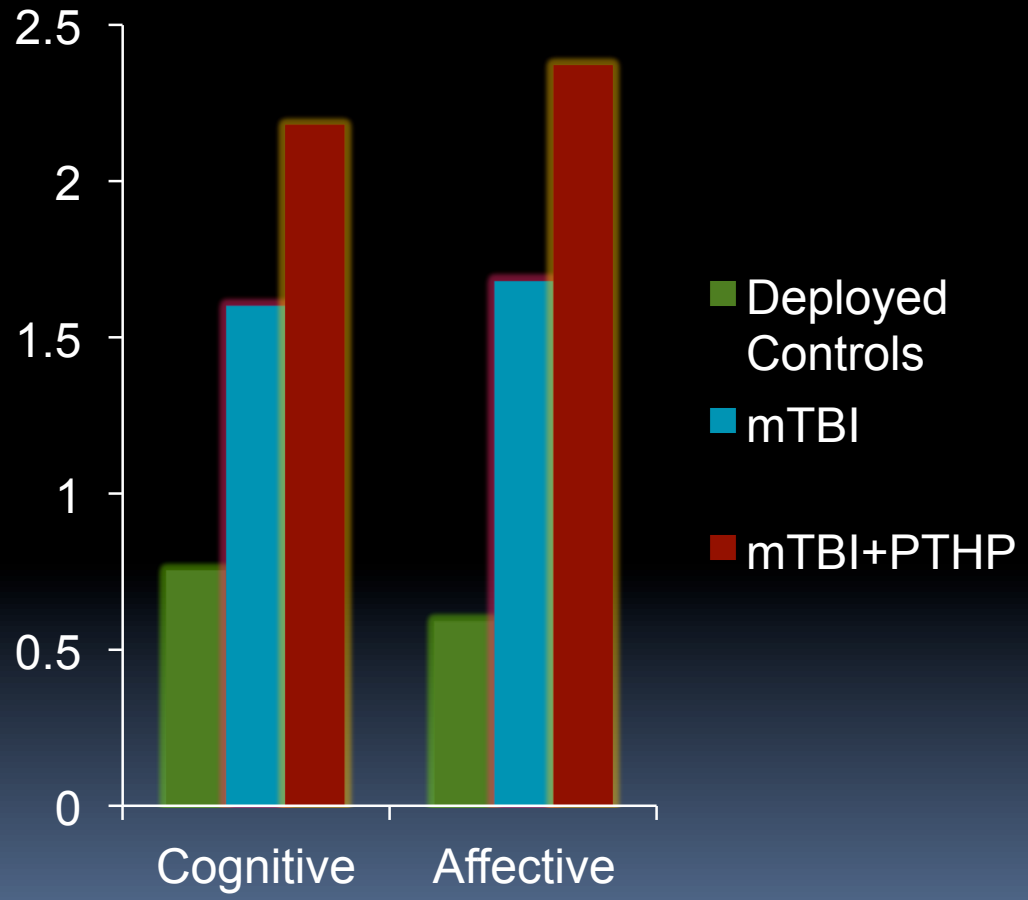
PTSD Symptoms Across Groups



Depression symptoms across groups



NSI Cognitive and Affective Symptoms (Self-Report)



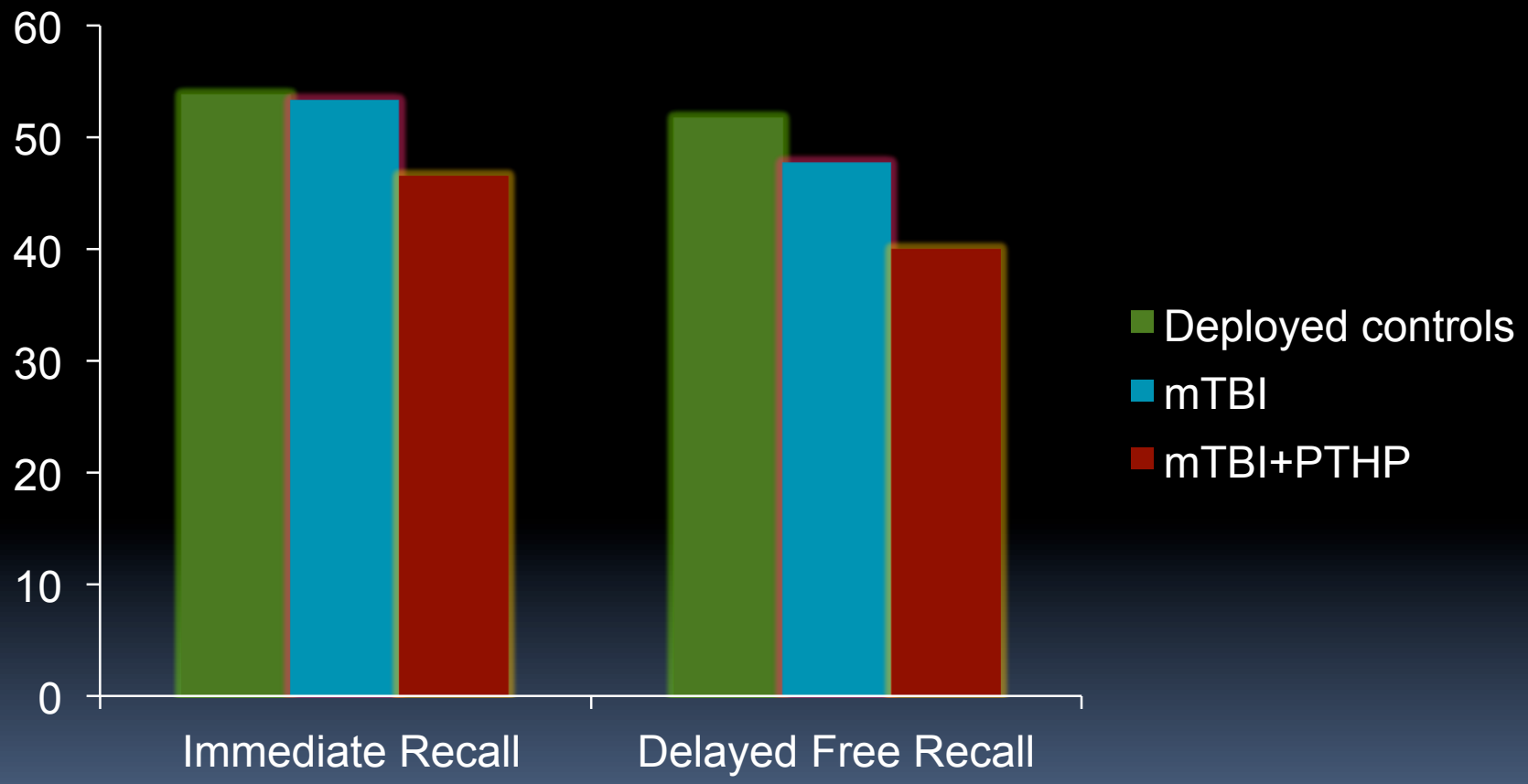
Cognitive Items

- Poor concentration
- Forgetfulness
- Difficulty making decisions
- Slowed thinking

Affective Items

- Fatigue, loss of energy
- Difficulty falling/staying asleep
- Feeling anxious or tense
- Feeling depressed or sad
- Irritability/easily annoyed
- Poor frustration tolerance

CVLT-II performance



NEUROBEHAVIORAL SYMPTOM INVENTORY ITEM FREQUENCY (%) RATED SEVERE OR VERY SEVERE ACROSS GROUPS

	MTBI+ PTHP (N=10)	MTBI (N=29)	Control (N=18)
Forgetfulness	50%	34%	11%
Poor concentration/attention	40%	28%	6%
Slowed thinking	40%	21%	6%
Irritability	60%	21%	0%
Feeling anxious or tense	50%	24%	0%
Sadness	50%	24%	0%
Difficulty falling or staying asleep	50%	38%	6%
Reduced energy/fatigue	40%	21%	11%

Summary and Conclusions

- In this preliminary study, 26% of participants with blast mTBI were found to have hormonal abnormalities
- Consistent with earlier studies of TBI from all causes, GH deficiencies were most frequent
- PTHP was associated with a constellation of psychiatric and cognitive symptoms
- Suggests that blast-related mTBI carries a high risk for hypopituitarism.

Seattle VA Study #2 (Wilkinson, PI)

- Evaluates GH and adrenal insufficiencies with more rigorous method called provocative testing (Glucagon stimulation test).
- Glucagon is a pancreatic hormone that is a powerful stimulant to pituitary secretion of ACTH and GH.
- GST consists of the injection of glucagon in study participants followed by collection of blood samples at 30-minute intervals over 3-1/2 hours.
- Determinations of the concentrations at the peak of ACTH, cortisol, and GH responses provide indices of adrenal insufficiency and GH deficiency.

GOALS OF STUDY

- Continue measurement of basal hormone levels in blast mTBI and deployment control groups
- Use provocative testing to provide a benchmark for assessment of pituitary disorders
- Investigate the association of other variables – neuropsychological and behavioral test scores, body composition, blood measures – with PTSP
- Determine if these additional measures can be combined to approximate the diagnostic accuracy of provocative testing and to lessen the need for it

PRELIMINARY FINDINGS

- Pituitary hormone deficiencies in 8/16 Veterans with a history of blast related mTBI (50%) and in 0 of 13 deployed controls
  - Growth hormone deficiency again the most common (4/8)
  - Adrenal insufficiency, hypogonadism, and thyroid hormone deficiency were also present in some Veterans

Pituitary Dysfunction Conclusions

- There is a high prevalence of PTHP in Veterans with history of blast-related mTBI.
- If symptoms characteristic of PTHP, PTSD, and post-concussive syndrome can be linked to pituitary dysfunction, they may be amenable to treatment with hormone replacement.
- Screening for hormone deficiencies after concussions shows promise for appropriately directing diagnostic and therapeutic decisions

THIS WORK WAS MADE POSSIBLE BY:

- **Collaborators**
  - Charles Wilkinson, PhD
  - Elaine Peskind, MD
  - Elizabeth Colasurdo
  - Jane Shofer, MS

- **Research Staff**
  - Carl Sikkema
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