DEFENSE CENTERS OF EXCELLENCE

For Psychological Health & Traumatic Brain Injury

Why Does Concussion Affect Men Differently Than Women?

June 12, 2014, 1-2:30 p.m. (EDT)

Presenters

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DVBIC Defense and Veterans Brain Injury Center

DHCC Deployment Health Clinical Center

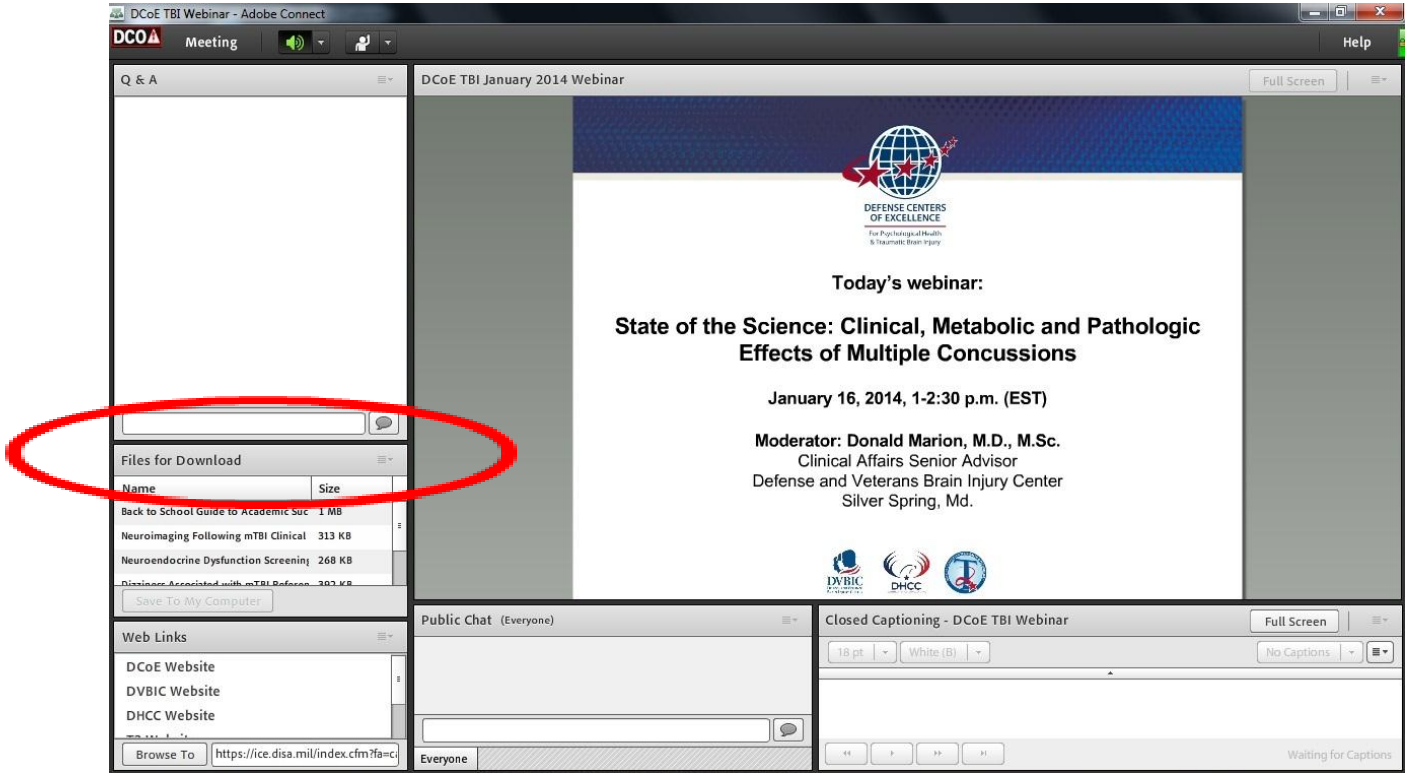
National Center for Telehealth & Technology

Webinar Details

- Live closed captioning is available through Federal Relay Conference Captioning (see the “Closed Captioning” box)
- Webinar audio is **not** provided through Adobe Connect or Defense Connect Online
  - Dial: CONUS **888-877-0398**; International **210-234-5878**
  - Use participant pass code: **3938468**
- Question-and-answer (Q&A) session
  - Submit questions via the Q&A box

Resources Available for Download

- Today's presentation and resources are available for download in the "Files" box on the screen, or visit **dvbic.dcoe.mil/online-education**



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- All who registered **prior** to the deadline on **Thursday, June 12, 2014,** at 3 p.m. (EDT) and meet eligibility requirements stated above, are eligible to receive a certificate of attendance or CE credit.

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Continuing Education Details (continued)

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  - 1.5 AMA PRA Category 1 Credit(s)
- Additional Credit Designation includes:
  - 1.5 ANCC nursing contact hours
  - 0.15 IACET continuing education credit
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National Association of Social Workers
Approval Year
2014

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- Throughout the webinar, you are welcome to submit technical or content-related questions via the Q&A pod located on the screen. **Please do not submit technical or content-related questions via the chat pod**.
- The Q&A pod is monitored during the webinar; questions will be forwarded to presenters for response during the Q&A session.
- Participants may chat with one another during the webinar using the chat pod.
- The chat function will remain open 10 minutes after the conclusion of the webinar.

Webinar Overview

- Increasing concern in the military and sports medicine communities that concussive events may have different effects on men compared with women
- Controversy exists regarding the risk and prevalence of hypogonadism following concussion or more severe traumatic brain injury (TBI), possible neuroprotective effects of sex hormones and the potential benefits of treating men with TBI with the female sex hormones progesterone or estrogen
- Webinar will address the pathophysiologic and neuroendocrine responses to concussion and more severe brain injuries, recovery patterns for men and the clinical evidence regarding hormone therapy after TBI
- At the webinar's conclusion, participants will be able to:
  - Describe the different effects of TBI on long-term quality of life depending on gender
  - Articulate the importance of post-traumatic multidisciplinary rehabilitation that is sensitive to gender issues
  - Discuss the prevalence of hypogonadism after TBI
  - Relate the clinical evidence regarding the use of hormone therapy after TBI

Presenter: Amy K. Wagner, M.D.

Amy K. Wagner, M.D.

- Associate professor and Endowed Research Chair in the Department of Physical Medicine and Rehabilitation at the University of Pittsburgh
- Associate Director for Rehabilitation Research at the Safar Center for Resuscitation Research
- Leading investigator in the use of biomarkers in developing and optimizing individualized treatment outcomes
- Research focus on the neurobiology of neuroplasticity and recovery after TBI and how commonly used therapeutic agents impact neurobiological and neurobehavioral processes associated with neuroplasticity and recovery
- Published more than 50 original research manuscripts and has more than a dozen review articles on her work

Sex, Hormone Physiology and Hypogonadism After Traumatic Brain Injury (TBI)

Amy K. Wagner, M.D.

Disclosures

- The views expressed in this presentation are those of the presenter and do not reflect the official policy of the Defense Department or the U.S. Government.

- The presenter does not intend to discuss the off-label/investigative (unapproved) use of commercial products or devices.

Background

- Funding sources and research findings presented
  - Data Modeling Approaches for Biomarkers in Clinical Traumatic Brain Injury. Principal Investigator (PI): Amy Wagner DODW91XWH-08-1-0237
  - Evaluating the Impact of Neuroendocrine Hormones on Pathophysiology and Outcomes after Traumatic Brain Injury. Study PI: Amy Wagner; Center PI, Hank Weiss
    CDC #R49/CCR323155
  - Biomarkers: Evaluating and Treating Acute and Chronic TBI. Study PI: Amy Wagner. DODW81XWH-071-0701

Graphs, charts and tables not referenced in this presentation are associated with research study results.

Sex and TBI Epidemiology

- Overall incidence: 200 per 100,000 persons per year
  - Males under 25: 700 per 100,000 per year
- Men have a higher incidence of TBI than women at all ages with reported incidence ratios ranging from 2.0:1 to 2.8:1 and mortality ratios of 3.5:1
- The increased incidence in men may be secondary to greater prevalence of men involved in higher risk activities and occupations
  - Contact sports
  - Military

Increasing interest in hormone physiology and hormones as treatments for TBI

TBI: ¿Sex ≠ Hormone Effects? Separating Myth From Fact

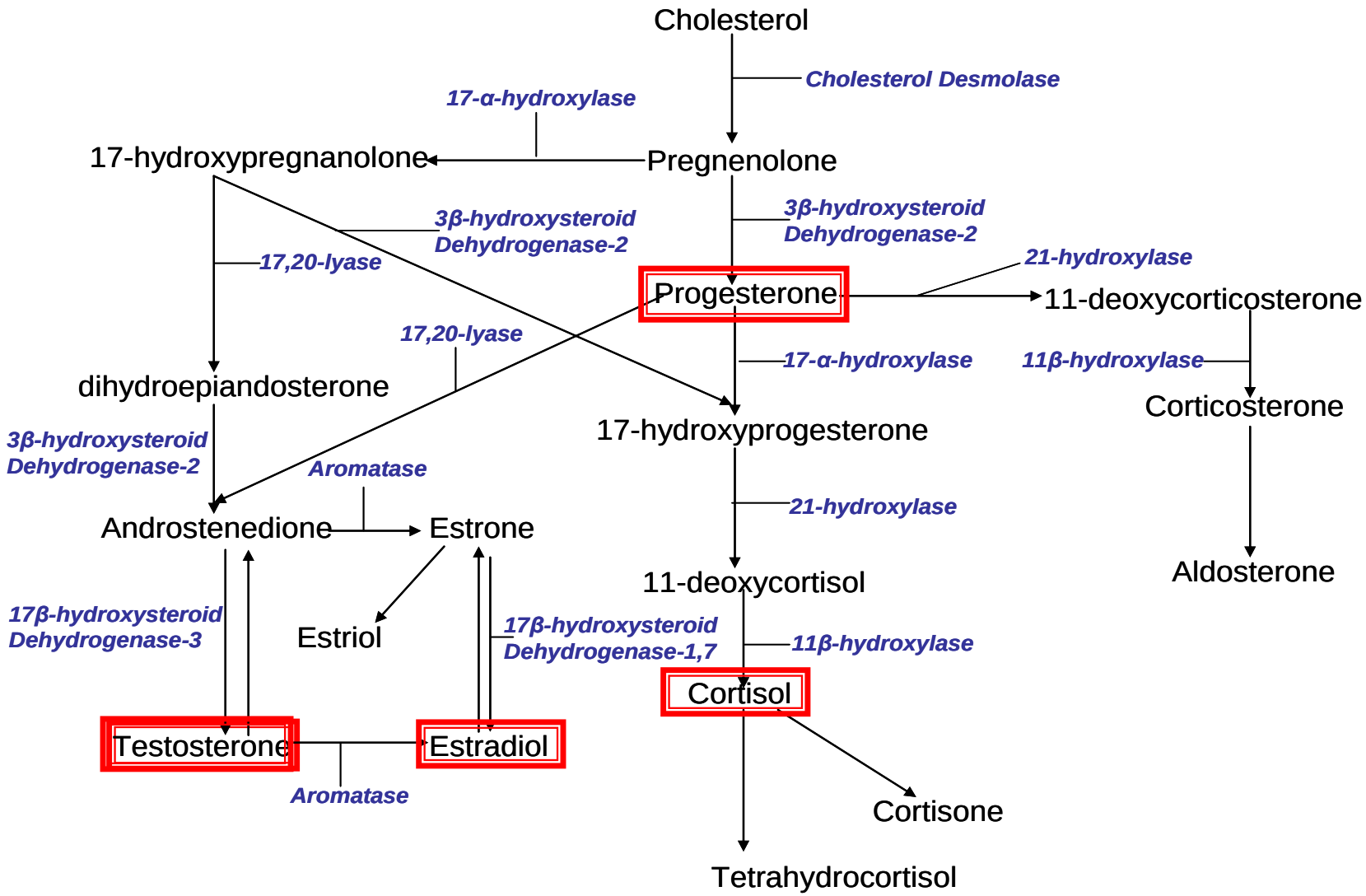
- **<u>Myth vs. Fact 1</u>:** Ovarian hormones are neuroprotective so women should be neuroprotected and have better outcomes than men.
- **<u>Myth vs. Fact 2</u>**: Women would not benefit from hormone therapy after TBI since they already have protective hormones as a part of their natural physiology.
- **<u>Myth vs. Fact 3</u>**: Endogenous estradiol for men and testosterone for women are not relevant to hormone physiology after TBI.
- **<u>Myth vs. Fact 4</u>**: Serum hormone physiology is a likely reflection of central nervous system (CNS) physiology after TBI.
- **<u>Myth vs. Fact 5</u>**: Hypogonadism is a transient syndrome and probably does not influence outcome.

What are the research questions and literature that inform whether these statements are myths or fact?

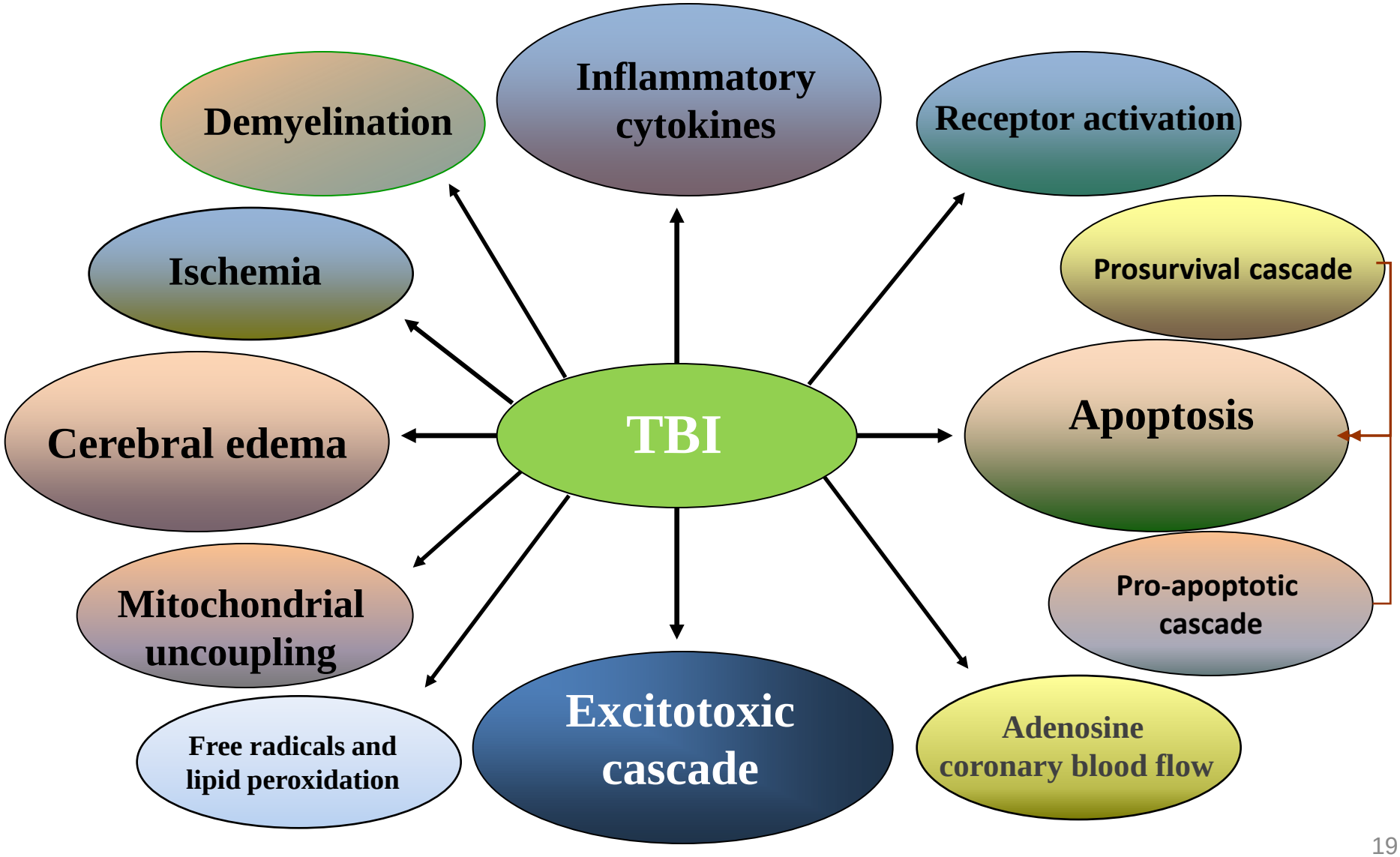
What Are the Research Questions?

- How are hormones interrelated?
- What mechanisms of injury can hormones target?
  - Generated from the experimental literature

Hormone Synthesis and Metabolism



Secondary Injury Cascades



Neuroprotective Mechanisms of Sex Hormones After TBI

- Estradiol
  - Maintains cerebral blood flow
  - Prevents apoptosis
  - Facilitates growth factor production
  - In the presence of toxic levels of glutamate, estrogens attenuate N-methyl-D-aspartate-mediated calcium^{++} activity
  - Scavenging of glutamate-driven free radical formation
  - Reactive maintenance of lactate production and neuronal lactate utilization as an energy source
  - Known to increase with stress of critical illness and trauma
    - Adrenal synthesis and/or peripheral aromatization (adipose tissue)
    - Likely cause due to inflammatory surge associated with trauma or critical illness

Neuroprotective Mechanisms (continued)

- Testosterone – Double-edged sword
  - Exacerbates cerebral ischemia-reperfusion injury
  - Testosterone reduction decreases lesion volume in middle cerebral artery occlusion model
  - Aromatization in cortical astrocytes is associated with cell survival and may be important for neuroprotection
- Progesterone
  - Decreases cerebral edema
  - Influences brain aquaporin levels
  - Decreases lipid peroxidation
  - Attenuates blood-brain barrier disruption
  - Decreases neuroinflammation
  - Improves behavioral outcome in male rats after acute injury

Neuroprotective Mechanisms (continued)

- Cortisol – Double-edged sword
  - Progesterone is the primary substrate for adrenal cortisol synthesis
  - Cortisol may impair the ability of astrocytes to remove damaging glutamate from the synapse
  - Cortisol perpetuates inflammation in the CNS
  - Adrenal insufficiency noted in a significant portion of people with severe TBI

Do We Have the Answers?

- How are hormones interrelated?
  - Steroidogenesis pathways include the major reproductive hormones and can be generated in the gonad, the adrenal and in peripheral sites like adipose tissue
- What mechanisms of injury can hormones target?
  - Generated from the experimental literature
  - Estrogen and progesterone can be neuroprotective when manipulated or administered as pharmacotherapeutics
    - Hormones like progesterone and estrogen are pleiotropic compounds that can target many of the same targets implicated in secondary injury
    - Testosterone and cortisol have a mix of potentially protective vs. deleterious effects that are situationally dependent
- Most animal studies look at hormones as treatments and do not evaluate innate physiology

What Are the Research Questions?

- What happens to endogenous hormone levels after TBI?
  - Can early endogenous hormone levels be linked to outcome?
  - How does aging influence hormone physiology?

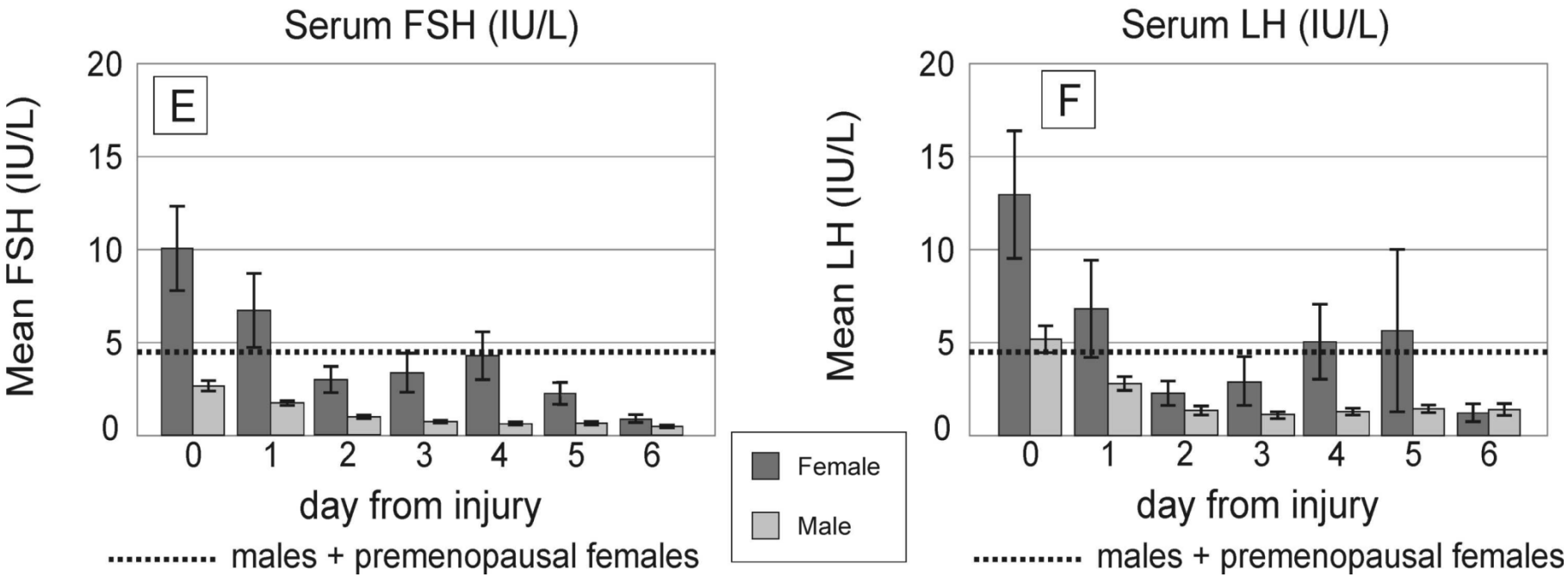
Hypogonadism in TBI

- Acute hypogonadism
  - Can occur with mild TBI
  - Measurements median 12 days (range 7-20 days) post injury in moderate/severe TBI (Agha et al., 2004)
    - Hypogonadism in 80% of males and 90% females
    - Low gonadotrophins in concert with low estradiol/testosterone

Acute Serum Hormone Studies

- Temporal characterization of hormones over an acute time course post-TBI (Wagner et al., 2011)
  - Identify potential sources of endogenous hormone production after severe TBI
  - 117 men and women with severe TBI
  - Daily serum samples for one week post injury
  - Determine if serum hormone profiles can be linked at all to later outcome
  - Hormone levels in healthy control group for comparison

Pituitary Hormones and TBI

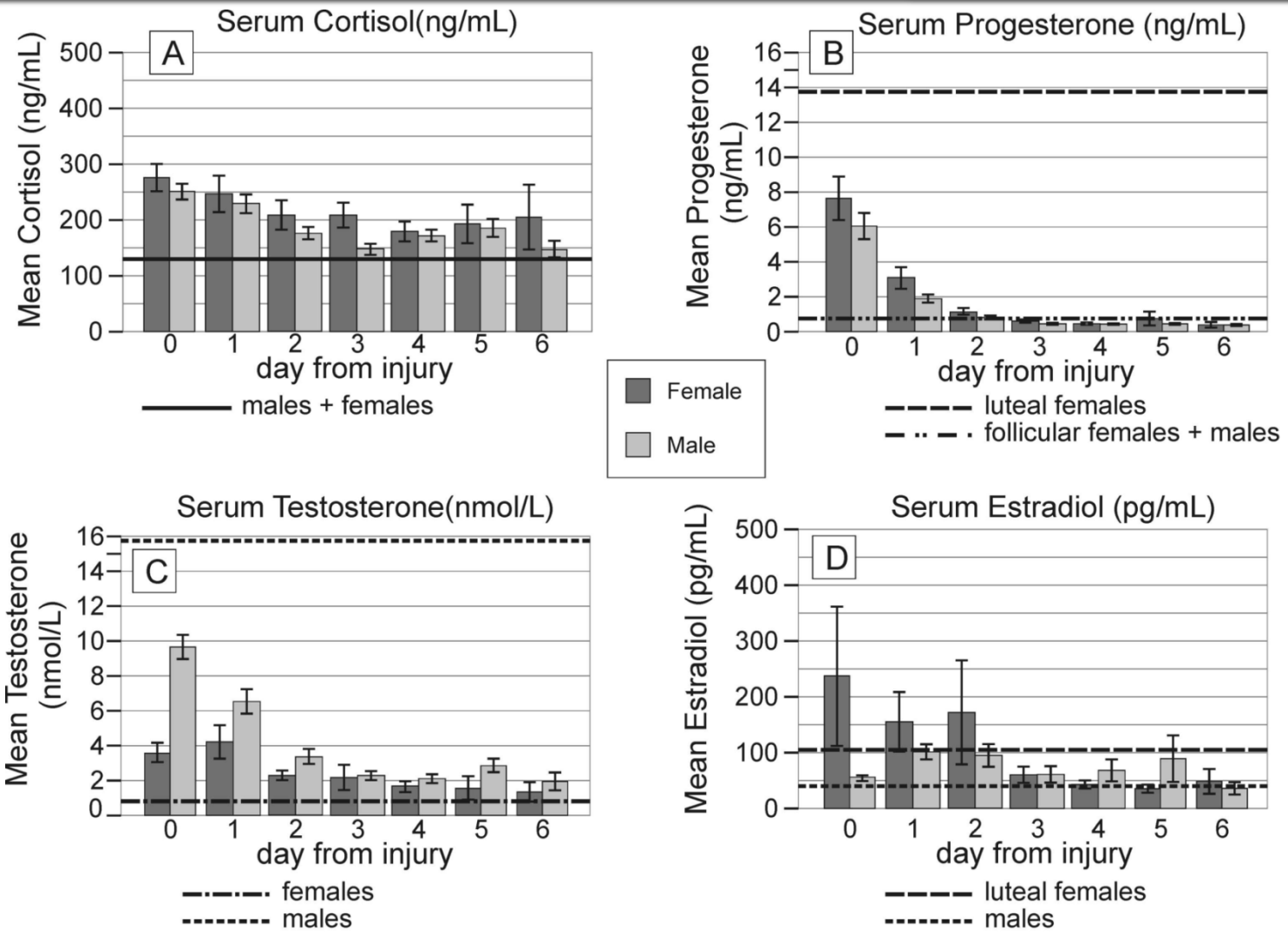


Post-menopausal 51.6IU/L

Post-menopausal 26.2IU/L

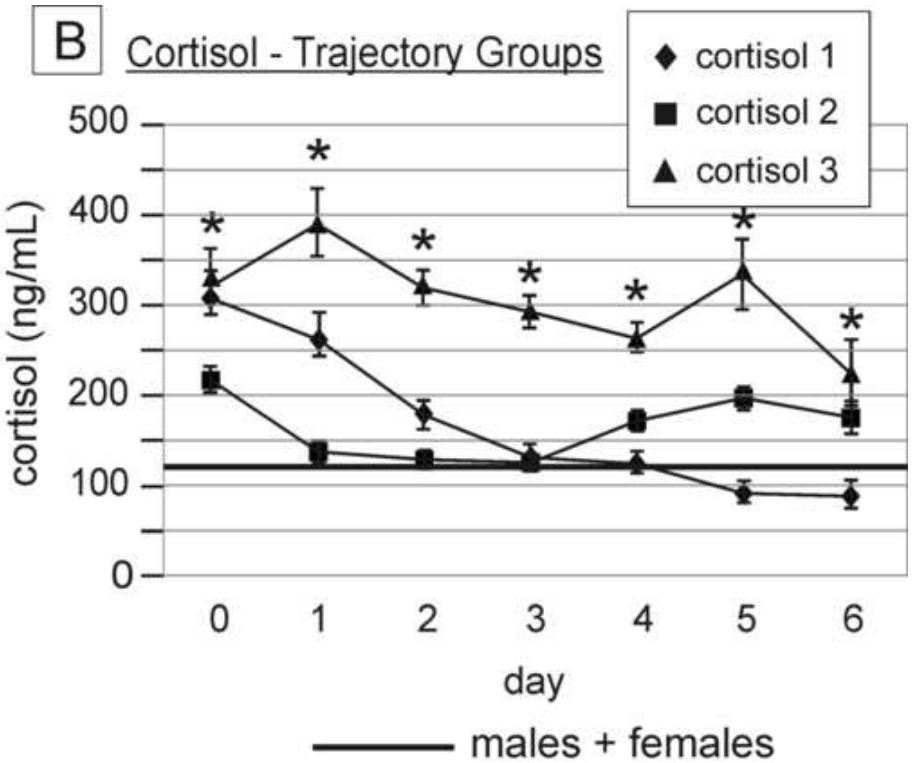
Pituitary gonadotropins plummet quickly after severe TBI

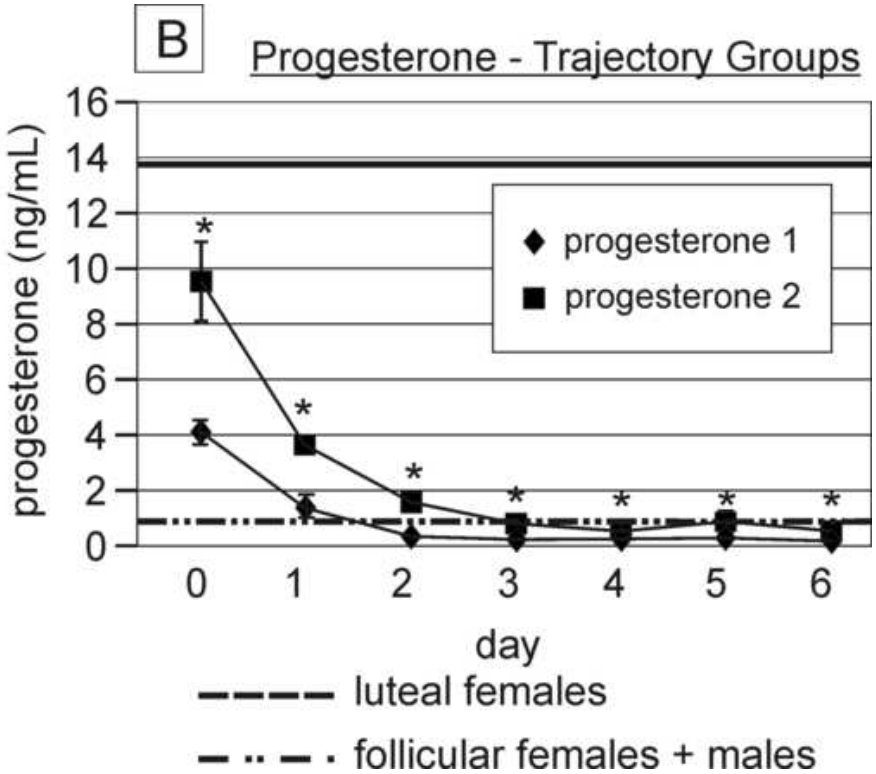
Serum Hormones and TBI



Adrenal and peripheral hormone synthesis drive serum hormone levels

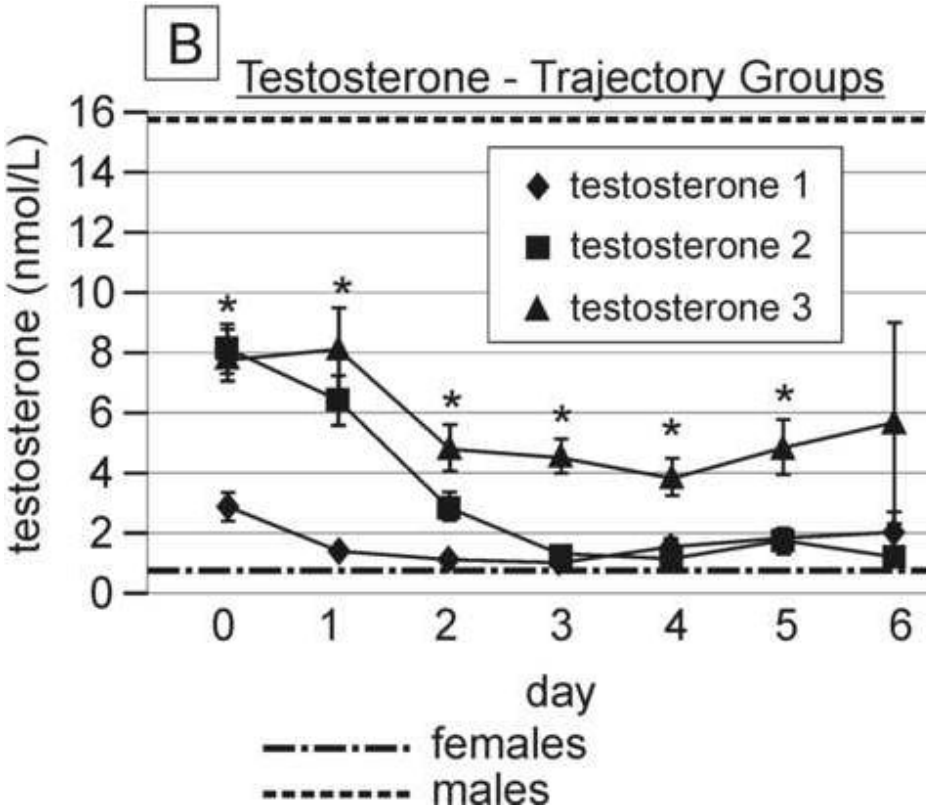
Serum Hormones by TRAJECTORY Group Membership

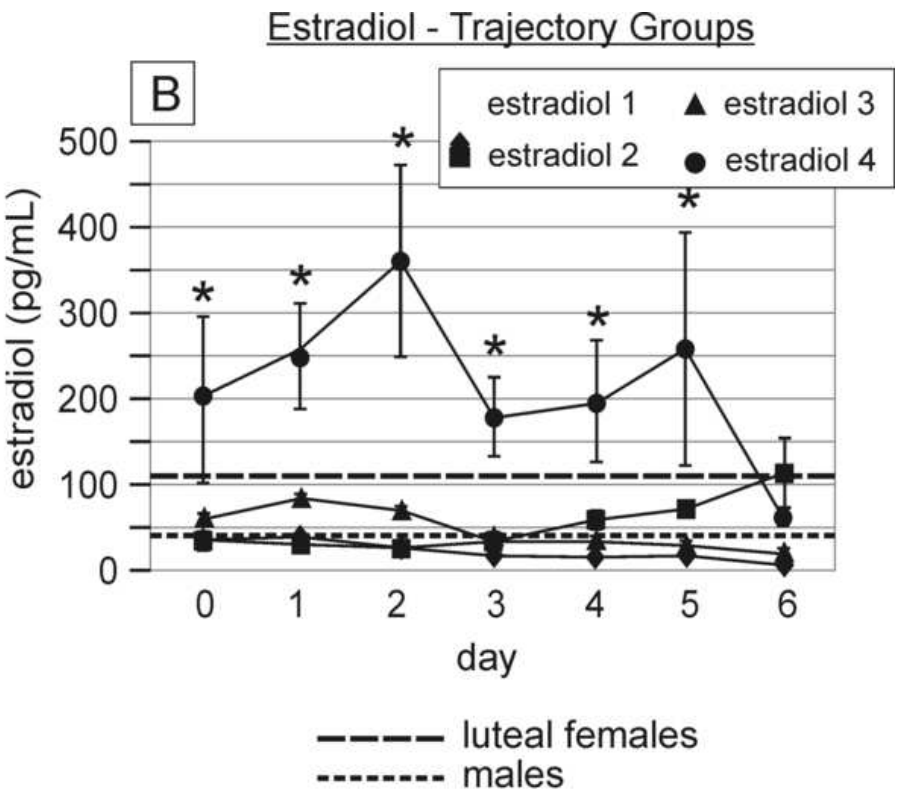




- 75% of females in higher progesterone trajectory (*p = 0.01)
- Progesterone elevated early on for men
- No gender exclusive groups; age a better determinant of hormone profiles
- 2 of 3 cortisol groups are elevated above controls
- High progesterone group associated with acute mortality
- Cortisol group membership NOT associated with outcome

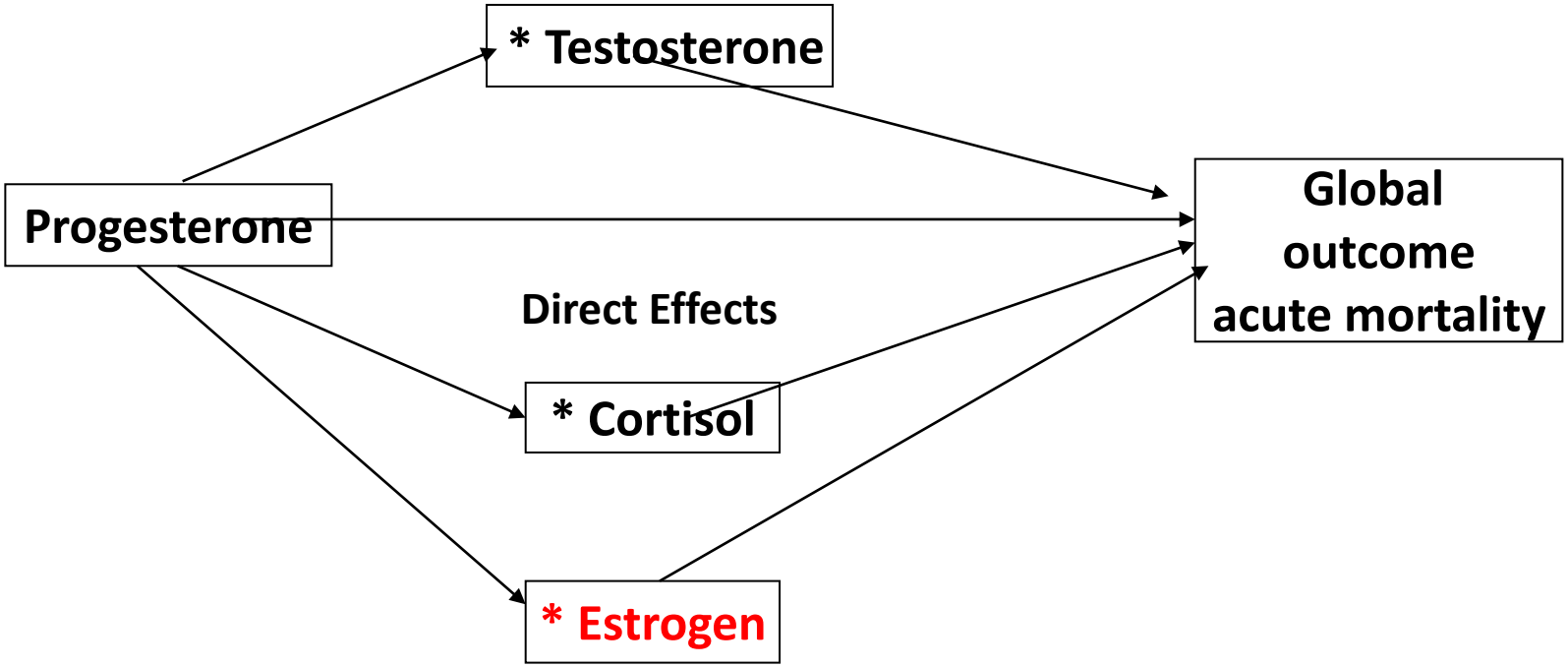
Serum Hormones by TRAJECTORY Group Membership





- Older subjects in trajectory groups with higher hormone levels
- No gender exclusive groups
- Older men in high estradiol group and older women in high testosterone group
- High estradiol and testosterone groups at increased risk for acute mortality and poor long term outcome

Acute Serum Hormone Prognostic Model



Structural equation model:

- Endogenous progesterone effects on outcome are mediated by its role as a synthetic precursor for estradiol levels wherein high levels are associated with bad outcome
- Independent effects of increased testosterone on bad outcome despite being the synthetic precursor for estradiol

Do We Have the Answers?

- What happens to endogenous hormones after TBI and are they neuroprotective?
  - Endogenous pituitary gonadotrophins plummet over first few days post-TBI
  - Unique temporal profiles for gonadal/adrenal hormones
  - Peripheral aromatization and/or adrenal synthesis is responsible for residual testosterone and estradiol levels in response to stress for both men and women
  - Elevated estradiol and testosterone associated with **WORSE** outcomes
    - Estradiol is the strongest predictor of acute mortality and poor global outcome
    - Progesterone is the adrenal metabolic precursor to other hormones associated with outcome
    - Although considered neuroprotective as a treatment, progesterone associations with outcome mediated through relationship with other hormone synthesis
    - Serum hormone profiles do not reflect CNS protective effects from experimental literature
    - Aging (rather than sex) is a primary effector of peripheral hormone physiology

What Are the Research Questions?

- How are chronic hormone levels affected by injury?
- Are chronic hormones and hypogonadism related to TBI outcomes?
- When should we test for hypogonadism after TBI?

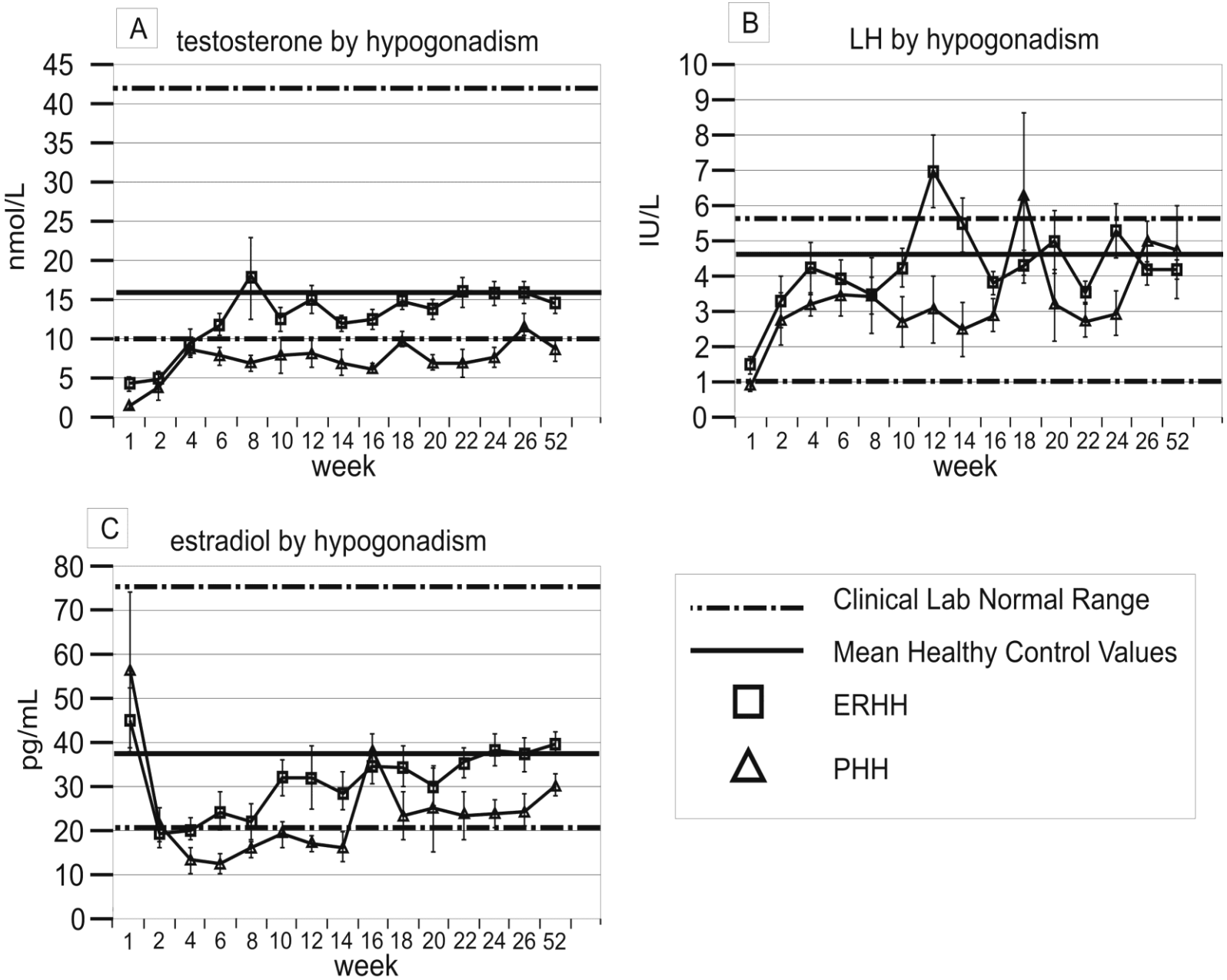
Chronic Hypogonadism

- Affects 21-32% of patients 3-12 months after TBI
  - Hypogonadism is largely secondary to pituitary dysfunction
  - Can have a negative impact on outcome
- Menstrual cycle function can be impaired for women up to several months after severe TBI (Ripley et al., 2008)
- Relevant complication after blast-induced concussion (Wilkinson et al., 2012)

Chronic Hypogonadism: Male Survivors

Brain Injury (Wagner et al., 2012)

- 38 males with severe TBI who survived their injuries
  - Week 1 averaged
  - Every two weeks sampling
  - Luteinizing hormone (LH) levels examined in the setting of estrogen and testosterone
  - Early resolving hypogonadotropic hypogonadism (ERHH) vs. persistent hypogonadotropic hypogonadism (PHH)
    - PHH >50% time point with hormone levels meeting clinical criteria for hypogonadotropic hypogonadism
  - 6 and 12 month outcomes
  - FIM-COG – Functional Cognition
  - Cognitive Composite – Cognitive Function
  - GOS – Global Outcome
  - DRS – Disability Measurement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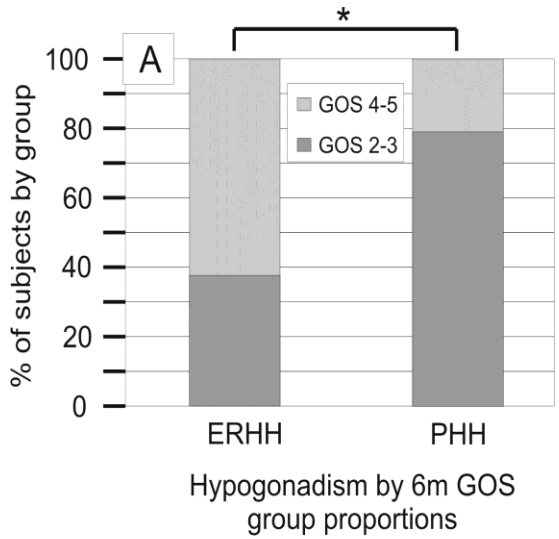
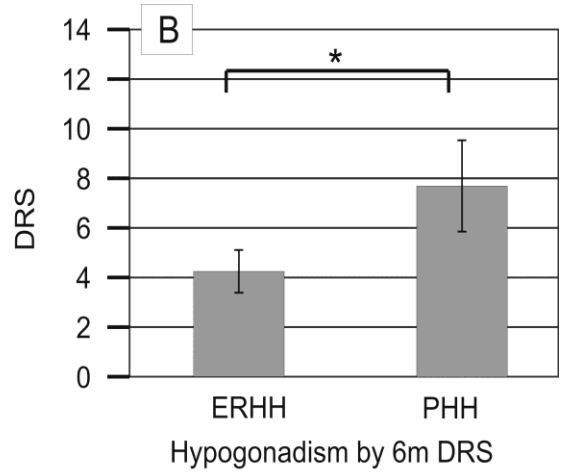
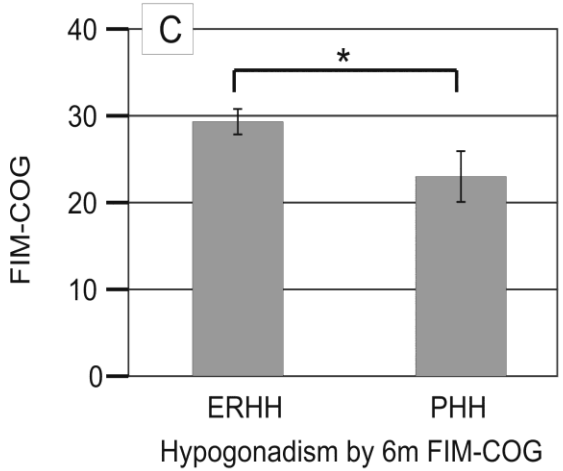
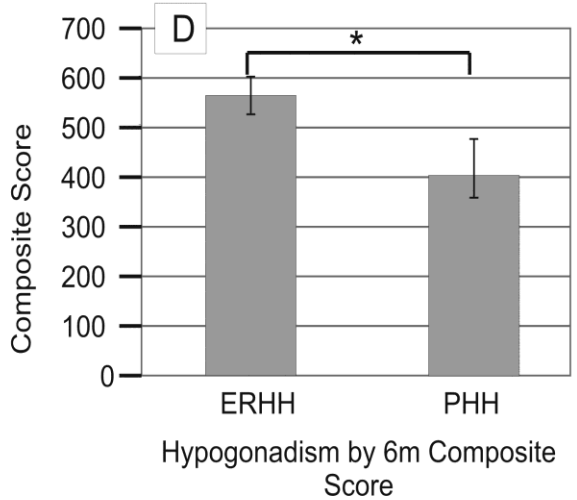
Six Month Outcomes

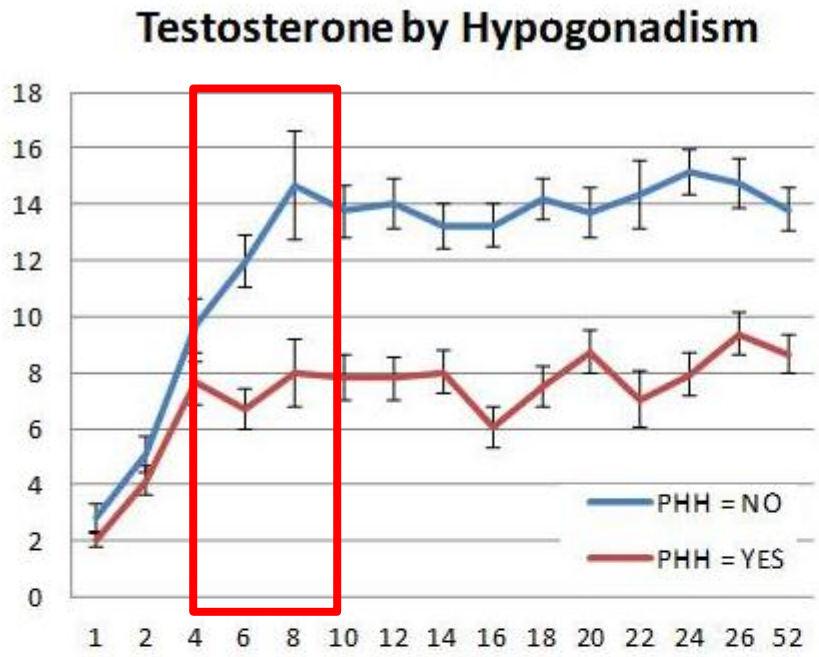


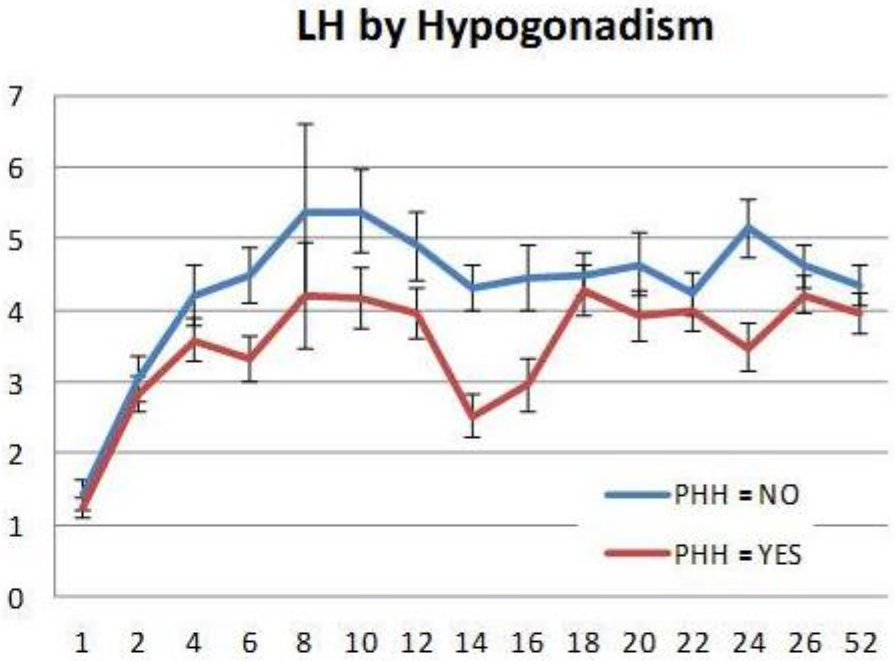


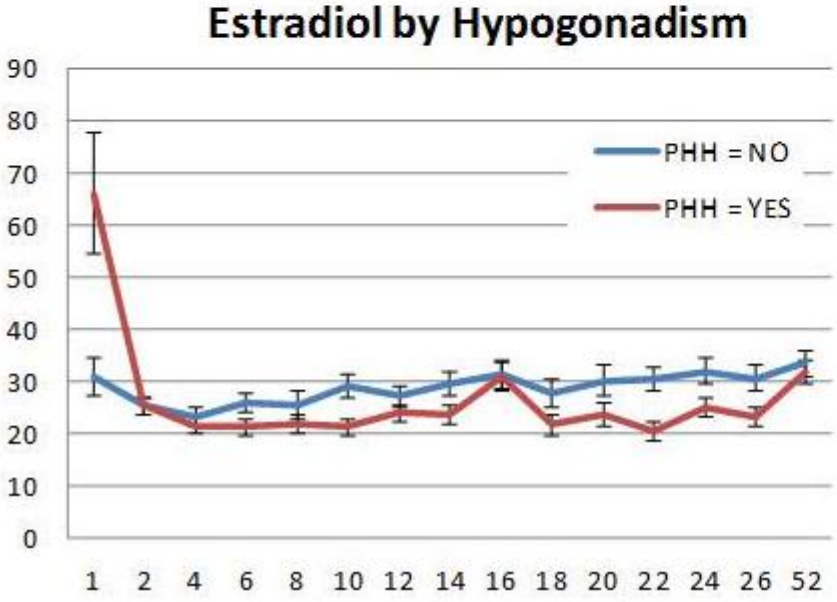




- **Persistent hypogonadism**
- Worse global outcome
- Higher disability burden
- Lower functional cognition metrics
- Lower performance with cognitive testing







Chronic Hypogonadism Combined Cohort

- N = 78 men survivors severe TBI
- Healthy control cohort
- Hormone assessments weeks 1, 2-26, 52

- Neuroendocrine testing 6-8 weeks after TBI
- Developing sensitivity/specificity cut points
- Mechanisms for PHH and longitudinal tracking with aging

Do We Have the Answers?

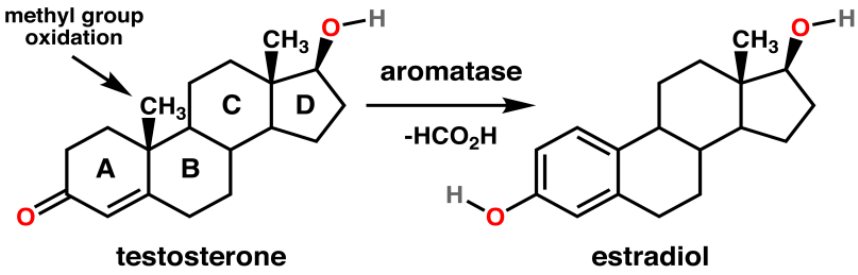
- What happens to chronic endogenous hormones after TBI and how do they relate to TBI outcomes?
  - Testosterone profiles for male survivors show that over the long term are associated with persistent hypogonadism are also associated with poor outcome
  - Low estradiol levels noted for PHH group
    - May have implications for plasticity and recovery
  - Hypogonadism can be considered a chronic condition for some and may be linked to persistent TBI pathology
    - More work looking at profile and outcomes beyond one year is needed
    - More work on chronic hormone profiles for females is needed
    - Mechanisms of hypogonadism need to be explored
    - Screening and treatment algorithms need to be researched and developed

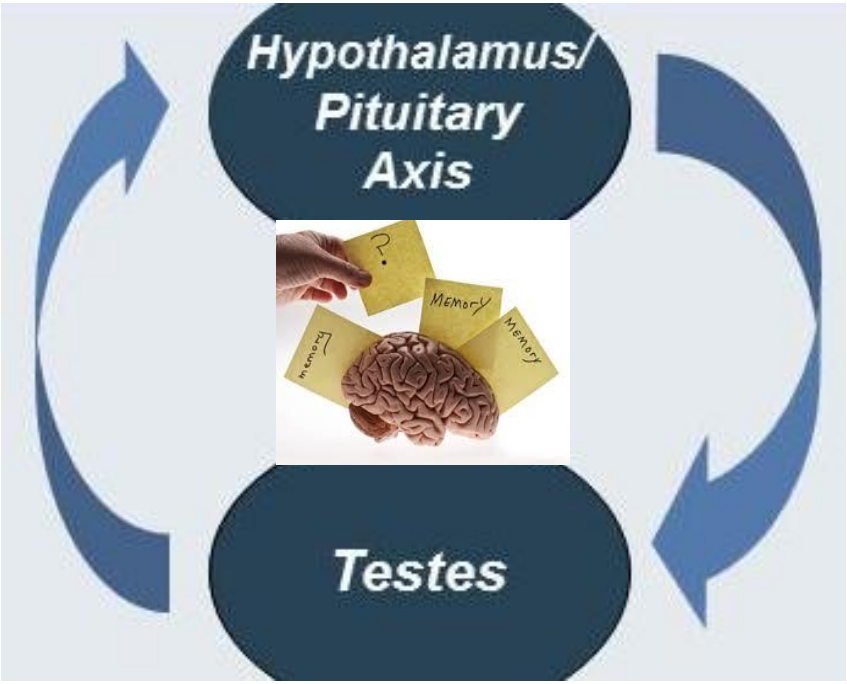
What Are the Research Questions?

- Can hormones be used as pharmacotherapies for neuroprotection or to enhance recovery after TBI?

Biomarker-based Implications for Chronic Hormone Treatment and Management

- **Consensus: Duration, dose and treatment endpoints for testosterone therapy not worked out**
- **Symptom profiles**
  - Fatigue
  - Cognitive dysfunction
  - Low androgen state
- **Neuroendocrine testing 4-6 weeks after TBI**
  - Persistent dysfunction
  - Interval testing
- **Full neuroendocrine panel**
  - Thyroid/adrenal axis
  - Growth hormone
- **Multi-faceted treatment approach**
  - Correct multiple hormone abnormalities prior to androgen therapy
  - Interval testing





Estradiol as a Therapeutic Prescription

- **Estrogen Therapy**
  - University of Texas Southwestern RESCUE – TBI Single dose IV Premarin – Phase II clinical trial (U.S. NIH)
  - http://clinicaltrials.gov/show/NCT00973674
  - Study plan to have concluded 2013
  - Premarin is NOT the same as natural E2 (estrogen)
    - Women's Health Initiative: Premarin detrimental to cardiovascular outcomes
  - Serum estradiol linked with increased mortality (Wagner et al., 2011)
  - Preliminary data: Increases in serum tumor necrosis factor associated with higher serum estrogen and estrogen/testosterone ratios
    - Serum inflammatory load after injury impacts secondary TBI
  - Estradiol in the CNS – can it be neuroprotective?
    - Cerebrospinal fluid studies suggest impaired aromatization in the CNS but those with normal estrogen/testosterone ratios likely to have better outcome (Garringer et al., 2013)

Hormones as Therapies

- **Progesterone Therapy**
  - ProTECT (Progesterone for the Treatment of Traumatic Brain Injury) Phase II clinical trial: Safe and potentially neuroprotective (Wright et al., 2007)
  - Large Phase II – Protective in severe TBI (Xiao, Wei, Yan, Wang, & Lu, 2008)
- **Glucocorticoids**
  - CRASH (Corticosteroid Randomisation After Significant Head Injury) trial: Acute methylprednisolone increases risk of death after TBI (Roberts et al., 2004)
- Since progesterone is a precursor to other hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal hormones, can pharmacological supplementation have a "downside" to these profiles?
  - Serum cortisol not related to outcome but many patients with adrenal insufficiency (AI)
- What is the CNS exposure to progesterone and cortisol after TBI?
  - CNS glucocorticoid exposure via endogenous transport of serum cortisol is up to 10x control values and associated with <u>worse</u> outcomes (Santarsieri et al., 2014)
  - Progesterone levels in the CNS elevated and track with CNS cortisol

Hormones as Therapies: Do We Have the Answers?

- Supplemental testosterone use should be pursued in a systematic away, along with exploration and management of other neuroendocrinopathies
  - Initial testing 4-6 weeks post injury
  - Interval follow-up
- No clinical studies to support estradiol use
  - Premarin not an adequate surrogate
- CNS glucocorticoids elevated after severe injury
  - Impact of AI treatments needs to be considered
- Definitive study results from ProTECT pending
- Bio-ProTECT: Studies pending
  - Progesterone effects on steroidogenesis
  - Progesterone and hormone associations with other biomarkers

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  - Gender differences in post-acquired brain injury/TBI
  - Data elements, outcomes measurement

Hormones and TBI

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Disclosures

- The views expressed in this presentation are those of the presenter and do not reflect the official policy of the Defense Department or the U.S. Government.
- The presenter does not intend to discuss the off-label/ investigative (unapproved) use of commercial products or devices.
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Overview

- Background and significance
- Literature on post-traumatic brain injury (TBI) gender differences
- Review of three studies exploring gender differences, possible hormonal factors in these differences and cognitive correlates of differences
- Impact of TBI on the life and health of women
- Targeting needs of women after TBI

Hormones and TBI: Background and Significance

Gender Differences in the TBI Literature

- Mixed findings in outcomes after TBI
  - Females with TBI are:
    - More likely than males to have better outcomes following multidisciplinary rehabilitation (Goranson, Graves, Allison, & La Freniere, 2003)
    - Rate their quality of life more highly than men as much as 8-24 years following injury (Gerhart, Mellick, & Weintraub, 2003; Steadman-Pare, Colantonio, Ratcliff, Chase, & Vernich, 2001)
    - Have better predicted outcomes related to work capacity evaluations (Groswasser, Cohen, & Keren, 1998)

Gender Differences in the TBI Literature (continued)

- Mediated by perceived social support, depressive symptoms, post-traumatic headache (Jensen and Thulstrup, 2001; McCauley, Boake, Levin, Contant, & Song, 2001)
  - Males with TBI are:
    - More likely to receive vocational rehabilitation services
    - More likely to be successfully employed
    - Less likely to have vocational services prematurely terminated than women (Bounds, Schopp, Johnstone, Unger, & Goldman, 2003)
- The reasons for these differences and findings are not clear

Gender Differences in the TBI Literature (continued)

- Cognition and neuropsychological test performance
  - After TBI, as compared to men, women:
    - Outperform men in verbal memory (Bengtson et al., 2000)
    - Outperform males on tests of executive function (Barr, 2003; Bounds, Schopp, Johnstone, & Unger, & Goldman, 2003; Putukian, Echemendia, & Mackin, 2000; Schopp, Shigaki, Johnstone, & Kirkpatrick, 2001)
    - (High school athletes) obtain better scores on intelligence tests – Wechsler Adult Intelligence Scale (WAIS-R) Verbal and Full Scale IQ as well as on attention and memory subtests (Johnstone et al., 2001)

Mixed Findings – Post-TBI Gender Differences

Outcome Variable	Who Recovers Better from TBI?		
	Men	Women	No Differences
Memory	Liossi et al., 2009	Ratcliff et al. 2007 Niemeier et al., 2007 Moore et al., 2010 Niemeier et al., 2013	
Visual analysis	Ratcliff et al., 2007		
Written language		Bounds et al., 2003	
Rehabilitation Outcomes	Farace et al., 2000	Goranson et al., 2003 Slewa-Younan et al., 2008	Leitgeb et al., 2012
Community Integration/ vocation success	Bounds et al., 2003 Corrigan et al. 2007 Parks et al. 2010	Doninger et al., 2003 Groswasser et al., 1998 McMordie et al., 1990	
Survival	Kraus et al., 2000 Ponsford et al., 2008	Berry et al., 2009 Ley et al., 2013	Leitgeb et al., 2011 Davis et al., 2006 Yeung et al., 2011
Executive Functions		Niemeier et al., 2007, 2013	
Bilateral strength/motor speed	Bounds et al., 2003	Cutler et al., 2007	
LOS			Avesani et al., 2012

Gender Differences in Executive Functions Following TBI

- TBI often results in disruptions of the so-called ***executive functions*** of planning, initiation, problem solving, self-awareness, control of cognition (Lezak, 2004)
- Neurologic region of interest in the frontal lobes (Denckla, 1994; Perecman, 1987), particularly prefrontal tracts (Pettit, Bastin, Smith, Bak, Gillingwater, & Abrahams, 2013)
    - Decreased ability to monitor and regulate one's own behavior is associated with frontal lobe injury (Perecman,1987)
    - More frontotemporal lesions in agitated (81% vs. 39%) than in behaviorally appropriate patients (van der Naalt, van Zomeren, Sluiter, & Minderhoud, 2000)
    - Difficulty with establishment of mental set in subjects with orbitofrontal system damage (Gansler, Covall, McGrath, & Oscar-Berman et al.,1996)

Executive Deficits and Recovery

- Deficits
  - Ability to monitor and regulate one's behavior appropriately in response to daily life demands
  - Self-awareness
  - Problem solving
  - Planning, consistent focus of attention
- Executive functions impairments are negative prognostic sign for successful community reintegration and post-injury adjustment as well as caregiver burden (Bogdanova & Verfaellie, 2012; Prigatano, Borgaro, Baker, & Wethe, 2005)

Gender Differences in Executive Functions Following TBI

- Prior research suggests association between gender differences following TBI and preponderance of males who sustain frontal lobe injury and sequelae
- After TBI males are more likely than females to:
  - Have acquired their injury violently
  - Develop post-injury neurobehavioral problems when Glasgow Coma Scale (GCS) is low (Geraldina et al., 2003)
  - Develop adjustment difficulties after TBI (Geraldina et al., 2003; Gerhart, Mellick, & Weintraub, 2003)
- However, gender differences not observed in frequency, duration or extent of post-traumatic agitation (Kadyan, Mysiw, Bogner, Corrigan, Fugate, & Clinchot, 2004)

Post-TBI Neuropsychological Testing

- One of the uses of post-injury neuropsychological evaluations is to develop individualized profiles of neurobehavioral and cognitive strengths and weaknesses
- Clinicians can utilize test findings to characterize their patient's frontal lobe deficits and pave the way for targeted interventions that will improve coping (Lezak, 2004)

Wisconsin Card Sort Test (WCST)

- Measure of executive function which has been well validated, well studied and had no prior reports of gender effects
- Linked to early investigations of abstraction ability in humans and animals (Weigl, 1941)
- Formally devised by Grant and Berg (1948) to assess abstraction as well as ability to shift cognitive strategies in response to changing environmental contingencies
- Generally accepted as one of the best measures of frontal lobe/executive functions deficits (Barcelo & Santome-Calleja, 2000; Crockett, Bilsker, Hurwitz, & Kozak, 1986)
- Considered a measure of executive function in that it requires:
    - Strategic planning
    - Organized searching
    - Ability to use environmental feedback to shift cognitive sets
    - Goal-oriented behavior
    - Ability to modulate impulsive responding (Heaton, Chelune, Talley, Kay, & Curtiss, 1993)
- Two WCST subscales (Categories Completed and Perseverative Errors) hone in on executive deficits above

Gender Differences in Executive Functions Following TBI

- Need to study further due to impact on long-term outcomes:
  - Effect of gender on presentation of executive dysfunction following TBI
  - Variables that might impact the course and degree of recovery
    - Retrospective analysis of TBI Model Systems database
    - Compared performance of men and women on WCST

(Niemeier, Marwitz, Lesher, Walker, & Bushnik, 2007)

Study Sample

- 1,331 males and females with moderate to severe TBI; 73% males
- Mean GCS score on emergency room admission was 8.7 (standard deviation = 4.2)
- 67% white, 33% minorities
- 73% high school education
- 73% employed at the time of injury
- Cause of injury
  - Vehicular crash (65%)
  - Violence (14%)
  - Falls (10%)
  - Pedestrian injury (7%)
  - Sports (2%)
  - Other etiology (2%)

(Niemeier, Marwitz, Lesher, Walker, & Bushnik, 2007)

Results

- Independent effect of gender
  - Female subjects performed significantly better on the WCST than male subjects as shown by analyses of variance
    - Scores of 1,331 patients for Categories Completed (means for females = 4.09, males = 3.67, p = .003)
    - Perseverative Responses (means for females = 32.17, males = 36.42, p = .003).
- Outperformance by females related to
  - Interaction of education and gender and ethnicity and gender in relation to Categories Achieved (p = .01)
  - Ethnicity and gender in relation to Perseverative Responses (p = .01)

(Niemeier, Marwitz, Lesher, Walker, & Bushnik, 2007)

Conclusions

- Are men possibly more at risk for post-TBI executive functions deficits and all negative effects on outcomes that go along with these impairments?
- Research needed on possible hormonal associations with findings
- Brain injury researchers beginning to study TBI and hormones connection with animal model and in humans (Pettus, Wright, Stein, & Hoffman, 2005; Ponsford et al., 2008; Stein, Wright, & Kellermann, 2008; Wagner, 2004)

Are There Cognitive and Neurobehavioral Correlates of Hormonal Neuroprotection for Women after TBI?

- **Aim:** Examine possible cognitive correlates of hormonal neuroprotection after TBI
- **Hypothesis:** Based on literature related to progesterone, oldest group (55-64 years) of women will perform more poorly on neurpsychological tests than other groups of women and oldest group of men

(Niemeier et al., 2013)

Are There Cognitive and Neurobehavioral Correlates of Hormonal Neuroprotection for Women after TBI? (continued)

- Mixed model comparison of neuropsychological test performance of men and women with moderate to severe TBI in matched age groups
- Ages 18-24, 25-34, 35-44, 45-54, 55-64
- Groupings based on Stages of Reproductive Aging Workshop (STRAW) system (Soules, 2005; Soules et al., 2001) and presumed age of onset of menopause
  - Age related to how much progesterone and estradiol on board

(Niemeier et al., 2013)

Are There Cognitive and Neurobehavioral Correlates of Hormonal Neuroprotection for Women after TBI? (continued)

- Age 16 and above
- Patients in 17 TBI Model System sites
- Received acute inpatient TBI rehabilitation
- Completed neuropsychological testing while inpatient
- Consent

(Niemeier et al., 2013)

Are There Cognitive and Neurobehavioral Correlates of Hormonal Neuroprotection for Women after TBI? (continued)

- Study sample
  - 1,563 men and women with moderate to severe TBI, enrolled 1989-2002 in TBI Model System sites
- Measures
  - Motor speed (Grooved Pegboard)
  - Word Fluency (Controlled Oral Word Association Test - COWA)
  - Verbal Learning (Rey Auditory Verbal Learning Test - RAVLT)
  - Attention (Symbol Digit Modalities Test - written and oral, Trail Making Test A)
  - Mental Flexibility (Trail Making Test B)
  - Executive Functions (WCST)

(Niemeier et al., 2013)

Results

- Verbal memory (RAVLT) significant age * gender
  - Oldest males performed worse than females in all age groups
  - Oldest women performed worse than youngest women
- Oldest women outperformed oldest men in mental flexibility

(Niemeier et al., 2013)

Conclusions

- May be that older women retain mental flexibility despite changes in levels of endogenous hormones over time
- Need further research into underlying contributions to these differences
  - Limitation: Cohort likely to have taken hormone replacement therapy (HRT) as doctors did not advise otherwise during time of rehabilitation for sample
  - No measure of hormones prior to study

(Niemeier et al., 2013)

Progesterone

- Study of role of reproductive hormones as possible treatment for TBI
  - High doses given after experimental TBI facilitated functional recovery (Asbury, Fritts, Horton, & Isaac, 1998; Djebaili, Hoffman, & Stein, 2004)
  - Reduces edema, inflammation
  - Improves functional outcomes up to six months in men and women with severe TBI (Xiao, Wei, Yan, Wang, & Lu, 2008)
  - Progesterone for the Treatment of Traumatic Brain Injury (ProTECT) and Study of Progesterone in Severe TBI (SyNAPSe) trials testing on men and women with TBI

But Should We Give All People with TBI Progesterone?

- Will everyone respond the same way?
- Not clear what additional underlying mechanisms could affect responses?
- **Are we oversimplifying?**
- **Some investigators show negative impact of progesterone** (Wunderle, Hoeger, Wasserman, & Bazarian, 2013)

Basic Science Increasingly Important

- Mixed findings in post-TBI gender difference research
- Increased understanding of TBI and search for a "cure" may lie in cross-field collaboration
- A variety of biomarkers of TBI have been studied (Jeter, Hergenroeder, Hylin, Redell, Moore, & Dash, 2013)
  - Examples: UCH-L1, C-tau, S100B, glial fibrillary acidic protein (GFAP) promising
  - ***No biomarker associated with progesterone or estrogen activities has been yet identified***

A Carolinas Research Team Assembled to Study Hormonal Neuroprotection

- Each member added something to our understanding
- Development of our study grew out of synergistic discussion
- We educated each other about our fields
  - Dr. Bradley Hurst – obstetrics/gynecology, fertility specialist
  - Dr. Lori Grafton – M.D., brain injury attending physician
  - Dr. Jean-Luc Mougeot, Ph.D. – amyotrophic lateral sclerosis, basic scientist and hormone researcher

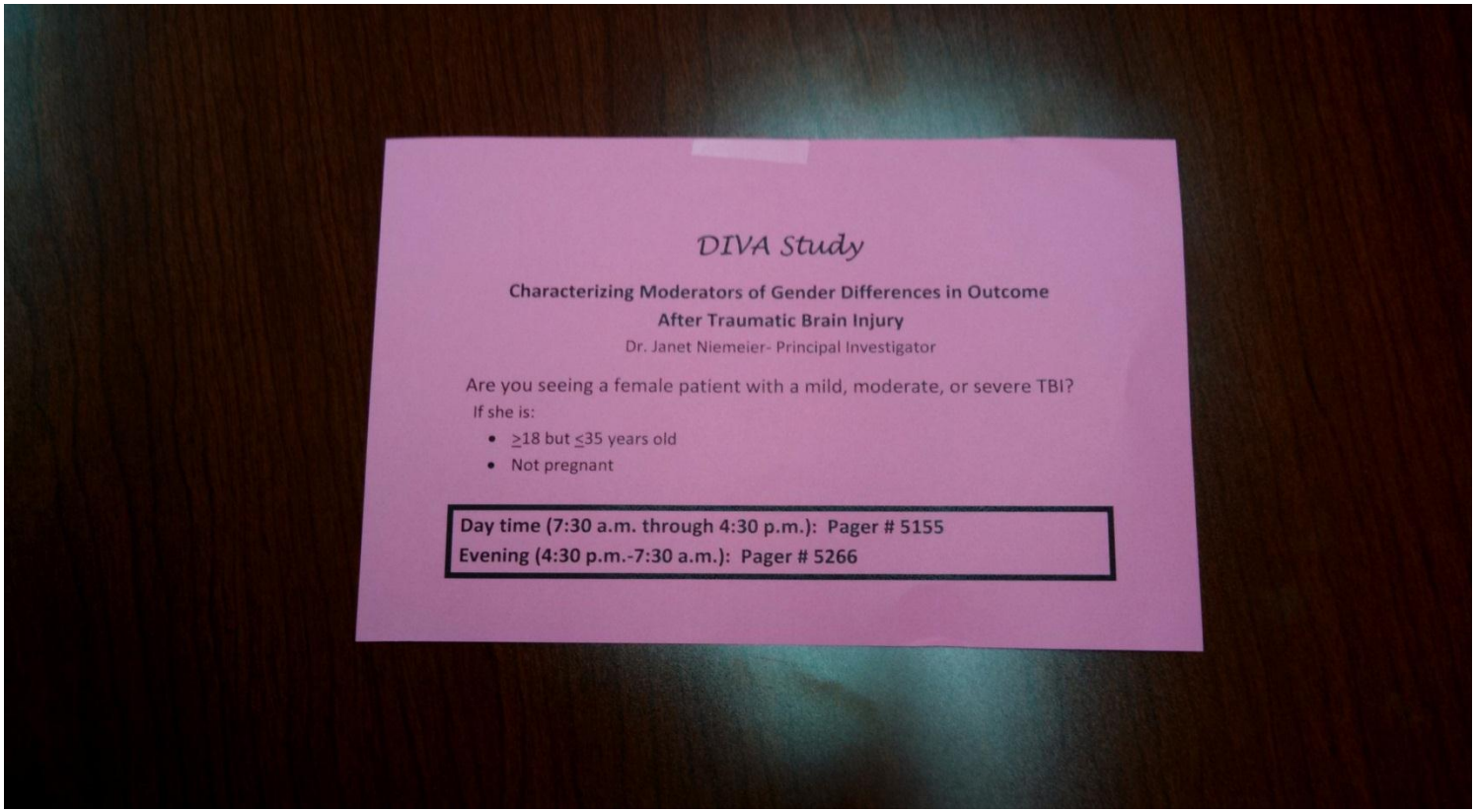
Hormonal Study Carolinas Health System

Pilot, Proof-of-Concept study

- **Design:** Nested case control, repeated measures
- **Subjects:** 21 women, ages 18-35 (relative stability in menstrual cycle) with TBI and 10 healthy controls matched for age with mild to severe TBI
- **Procedure:** Two blood draws; one within 24 hours of injury, one two days later
- Controls, two blood draws, one two days after first
- Assays of all blood samples for hormone levels, RNA; also measuring mental status, demographics and health history (including menstrual and reproductive history); outcomes, community reintegration (three month follow up)

Flyer for Emergency Department and Trauma Doctors

DIVA flyer



Impact of Hormones on Behavior and Cognition

- Progesterone is a neurosteroid
  - Precursor to allopregnanolone, a potent neurosteroid
- Affects synaptic function
- Neuroprotective
- Affects myelination

Premenstrual Syndrome (PMS) and Menopausal Symptoms

Mood

- Anxiety/tension
- Depression
- Fatigue
- Irritability
- Mood swings

Physical Symptoms

- Abdominal cramps
- Acne
- Bloating
- Breast soreness
- Headache
- Leg pain
- Nausea
- Swelling/edema
- Vomiting
- Weakness
- Weight gain

All symptoms can be worsened after TBI but few studies

(Colantonio et al., 2010)

Impact of TBI on Reproductive Hormones

- Stress suppresses follicle-stimulating hormone and luteinizing hormone
- Impairs follicular development
- Cycle is disrupted for months, especially with severe TBI
- Impact on PMS, menopause symptoms for women?

Targeting Treatments for Women After TBI

- At risk for cycle disruption before menopause
- At risk for early onset menopause
- HRT and increase in symptoms of TBI
- Osteoporosis and fracture risk, deep vein thrombosis risk increase due to ankle foot orthosis, weightbearing
- Interventions to minimize discomfort due to reproductive life phases such as menopause, possible early onset
  - Complementary alternative medicine
  - Assess for mood disorder (Amara, Iverson, Krengel, Pogoda, & Hendricks, 2014)
  - Nutrition
  - Sleep regulation, exercise

Targeting Treatments for Women After TBI (continued)

- Rehabilitation therapies can build on female strengths in executive functions
- Monitor mood and coping
- Assess and treat for both mood and cognitive symptoms, especially with increased likelihood of combat exposure for women (Amara, Iverson, Krengel, Pogoda, & Hendricks, 2014)
- Monitor and prevent occurrence of intimate partner violence

How to Improve Our Understanding of Hormones and TBI

- Cross-field collaborative team ideal for addressing complexities of TBI and gender differences
  - Underpinnings of gender differences in outcomes after TBI may be more complex than first thought
    - Olfactory receptors may be gateways to hormonal neuroprotection after TBI
    - We may need to titrate doses of hormones when using as a treatment of TBI depending on levels at time of injury
- Rewards of this kind of collaboration are worth any challenges
- Further research necessary

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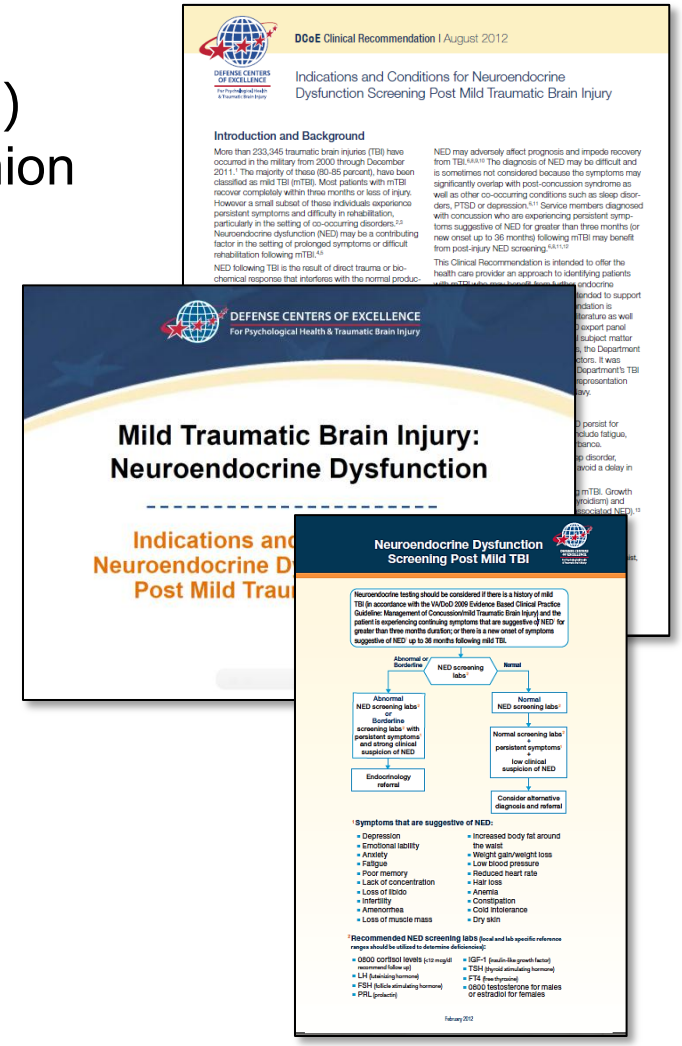

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