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TBI Rehabilomics Research: Conceptualizing a Humoral Triad for Designing Effective Rehabilitation Interventions

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Abstract

Most areas of medicine use biomarkers in some capacity to aid in understanding how personal biology informs clinical care. This article draws upon the Rehabilomics Research model as a translational framework for programs of precision rehabilitation and intervention research focused on linking personal biology to treatment response using biopsychosocial constructs that broadly represent function that can be applied to many clinical populations with disability. The summary applies the Rehabilomics research framework to the population with traumatic brain injury (TBI) and emphasizes a broad vision for biomarker inclusion, beyond typical brain-derived biomarkers, to capture and/or reflect important neurological and non-neurological pathology associated with TBI as a chronic condition. Humoral signaling molecules are explored as important signaling and regulatory drivers of these chronic conditions and their impact on function. Importantly, secondary injury cascades involved in the humoral triad are influenced by the systemic response to TBI and the development of non-neurological organ dysfunction (NNOD). Biomarkers have been successfully leveraged in other medical fields to inform pre-randomization patient selection for clinical trials, however, this practice largely has not been utilized in TBI research. As such, the applicability of the Rehabilomics research model to contemporary clinical trials and comparative effectiveness research designs for neurological and rehabilitation populations is emphasized. Potential points of intervention to modify inflammation, hormonal, or neurotrophic support through rehabilitation interventions are discussed.

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Keywords

Personal Biology; Inflammation; Neurotrophins; Glucocorticoids; Traumatic Brain Injury; humoral triad; precision medicine; intervention

1.0 The Epidemiology and Impact of Chronic Conditions after TBI:

Each year, the Centers for Disease Control (CDC) estimates that 2.5 million Americans sustain a Traumatic Brain Injury (TBI) that results in either an emergency department (ED) visit, acute hospitalization, or death (“Report to congress on traumatic brain injury in the United States,” 2014). A subset of these individuals require care in a specialized brain injury rehabilitation program, wherein practitioners typically have a resource-limited time frame in which to lay in place a foundation to support recovery and minimize secondary conditions and complications after TBI. Most individuals with moderate to severe TBI take months to years to recover, and a majority of individuals never fully return to pre-injury functioning and live with chronic disability (Corrigan et al., 2010; Wilson et al., 2017). The cost of TBI care and associated disability is considerable, particularly when considering acute medical care costs associated with the incident injury and the chronic care costs for conditions that evolve over time and increase disability burden. The costs associated with prolonged disability are largely tied to the loss of productivity; individuals with moderate to severe TBI often are unable to return to work or school.

Disability after TBI arises from impairments that accompany both the acute injury complex as well as a plethora of long term chronic conditions including depression, behavioral dysfunction (impulsivity, apathy, and complex decision-making), cognitive dysfunction, headaches, neuroendocrine dysfunction, fatigue, sleep dysfunction, and epilepsy among others. Given these late effects of TBI, many of which increase disability burden, the field has largely come together to characterize and consider TBI as a chronic condition (Masel and DeWitt, 2010). The World Health Organization (WHO) defines a chronic condition as having one or more of the following characteristics: it is permanent, caused by a non-reversible pathological alteration, requires special training of the patient through rehabilitation, and/or may require a long period of observation, supervision, or care (Epping-Jordan et al., 2004). A majority of individuals with moderate to severe TBI possess all or most of these characteristics. The reality is that TBI is a complex chronic disease process that leads to significant homeostatic disruption and a great deal of heterogeneity with regard to recovery course and multidimensional outcome. These functional domains align well with the WHO’s International Classification of Functioning, Disability and Health (WHO-ICF) (ICF Organization, 2001) framework, which defines functioning and disability in terms of “body functions and structures, activities, participation, and environmental factors.”

2.0 WHO-ICF: Rehabilitation, Recovery, and Rehabilomics Research

With rehabilitation care and outcomes, phenotypes capturing the complexities of TBI recovery should be anchored across multiple WHO-ICF domains of functioning and disability, as this framework guides clinical care as well as rehabilitation-focused outcomes and interventions research. The WHO-ICF framework (Pistarini et al., 2011; Ptyushkin et al.,

2010) builds upon the biomedical model and represents important biopsychosocial elements of function that are typically assessed in the context of daily activities and participation. Notably, personal factors and environmental exposures impact function. When considering the WHO-ICF model within the context of the neurological impact on functioning after TBI, it demonstrates how regional brain damage, along with medical complications, result in impairments affecting cognitive, behavioral, mood, language, sensory, or neuromuscular functions. These impairments lead to limitations and restrictions, including loss of independence with daily activities, difficulty resuming pre-injury life roles, and reduced community integration.

The Rehabilomics Research model builds on the WHO-ICF as a conceptual framework from which to investigate diverse outcomes by examining the complex interplay between personal, biological, psychosocial, and environmental factors to provide a foundation for evidence-based personalized clinical care and management (Wagner, 2010). For many neurological populations, including TBI, research is needed to support rehabilitation relevant prognostic marker discovery and utilization and to develop biomarker guided clinical decision algorithms. In addition, this work may generate appropriate biosusceptibility tools for screening and prevention of secondary conditions and complications arising among disability populations (Wagner, 2017, 2014). Importantly, these biomarkers may be useful for pre-randomization patient selection within rehabilitation focused interventional studies and also as a biological readout for treatment effects (Wagner, 2011; Wagner and Sowa, 2014). We developed the Rehabilomics Research model to represent a translational path for programs of rehabilitation research focused on linking personal biology, and physiological responses to environmental exposures/states to the biopsychosocial constructs that constitute the WHO-ICF model. Although there is a significant need for platform development and clinical translation (Berger et al., 2011; Kobeissy et al., 2011), research products and deliverables generated from a focused Rehabilomics research program can serve as companion tools for comparative effectiveness, as well as stratified or adaptive clinical trial designs, needed to develop biologically grounded, personalized approaches to rehabilitation (Wagner, 2011; Wagner and Sowa, 2014). Our work in TBI-Rehabilomics provides some exemplars that are focused on achieving these goals.

3.0 A targeted Overview of Chronic Conditions after Severe TBI

Post-traumatic depression (PTD) is a common complication after TBI, with prevalence rates ranging between 13–53.1% in the first year after TBI, a nearly 8-fold increased rate compared to the general population (Bombardier et al., 2010; Jorge RE et al., 2004; Rapoport et al., 2005; Sigurdardottir et al., 2013; Whelan-Goodinson et al., 2009). Individuals with PTD more often endorse chronic functional impairment and psychosocial difficulties when compared to individuals without PTD (Hibbard et al., 2004; Pagulayan et al., 2008). Individuals with TBI often suffer from behavioral problems (e.g. impulsivity, apathy, and personality changes) that create psychosocial difficulties (Kim et al., 1999; Rao et al., 2009) and are barriers in assuming pre-injury life roles (Benedictus et al., 2010). Further, our work suggests that behavioral dysfunction leads to depression for many with TBI (Juengst et al., 2017a). Cognitive deficits after TBI are among the most common symptoms reported, with ~70% of severely injured patients experiencing substantial

cognitive deficits across multiple domains (Tate et al., 1991), including attention, information processing, reaction time, memory and learning, verbal fluency, and mental flexibility (Lannoo et al., 1998). The functional consequences of cognitive deficits may be further amplified by depression to adversely impact of cognitive deficits on downstream ICF domains (Failla et al., 2016c). Cognitive impairments among those with TBI are important treatment targets for clinicians, as they have implications for rehabilitation planning (Dikmen et al., 2009) and are the primary indicator of the ability to return to work (Benedictus et al., 2010). Yet, large-scale clinical trials are sparse with regard to using cognitive performance and mental health as primary treatment outcome metrics, leaving most treatment guidelines subject primarily to expert opinion (Cicerone et al., 2011; Neurobehavioral Guidelines Working Group et al., 2006; Scholten et al., 2017). However, recent work has identified multiple genetic variants that may, if validated, further inform treatment for cognitive impairment (Failla et al., 2015b; Markos et al., 2017; Myrka et al., 2016).

Individuals with moderate to severe TBI are at high risk for developing hypothalamic-pituitary deficiencies including persistent hypogonadotropic hypogonadism (PHH) (Fernandez-Rodriguez et al., 2011). These deficiencies may result in more frequent self-reporting of fatigue, greater disability, and poor neurological outcomes within the first year post-injury when compared to those without PHH (Barton et al., 2016; Wagner et al., 2012). While current guidelines indicate waiting to treat hypogonadism until after 1 year (Ghigo et al., 2005), many with PHH experience poor health, function, and quality of life during their first year post-TBI.

Post-traumatic epilepsy (PTE) accounts for 20% of those with symptomatic seizures and 5% of those with any seizure in the general population (Englander et al., 2003). Further, PTE is also associated with greater mental health burden (Juengst et al., 2017b). Despite these numbers, few have attempted to develop risk models for PTE (Ritter et al., 2016b). Further, there are no accepted biomarkers reflective of epileptogenesis or PTE risk (Pitkänen and Immonen, 2014), and there are no definitive preventative agents or restorative treatments for PTE (Szaflarski et al., 2014). Though, recent work suggests that inflammatory genes (Diamond et al., 2014) as well genetic variation within multiple neurotransmitter pathways (Darrach et al., 2013; Diamond et al., 2015; Ritter et al., 2016a; Wagner et al., 2010), may have utility in estimating PTE risk and informing therapeutic development and management with PTE.

4.0 TBI Rehabilomics: Defining and Characterizing the Humoral Triad Among Individuals with TBI

To date, pharmacological treatments for TBI have failed to show efficacy due to the high degree of heterogeneity and complicated pathophysiology that accompanies the injury. The reason why individuals with similar mechanisms of injury and clinical management can have vastly different recovery trajectories is likely multifaceted. For example, intrinsic factors like age and sex, which play a large role in most conditions, must be considered. Also, genetic variation as well as gene*environment interactions and epigenetic

considerations may affect an individual's response to treatment as well as risk for TBI-related complications (Adams et al., 2017).

There are plethora of brain-specific biomarkers characterized in TBI and other acquired neurological injuries (Kobeissy et al., 2011; Kochanek et al., 2015, 2008; Papa et al., 2008; Svetlov et al., 2009; Wagner, 2011). In addition to structural brain damage, the components of the secondary injury response to TBI include mediators of cascades involved in secondary injury or repair. These biomarkers may be potentially informative with regard to chronic conditions associated with TBI which can be considered in the context of a *humoral triad*. Traditionally speaking, humoral signaling represents a collection of hormones and other fluid based markers (e.g. cytokines, trophins) capable of exerting regulatory signaling at remote targets. In the context of this review, we have grouped several biomarkers under the umbrella of a **humoral triad** (figure 1), which involve a triune of neurotrophic, endocrine, and immunological signaling cascades. Each of these cascades have independent functions, but they also possess the regulatory capacity for cross-talk across central nervous system (CNS) signaling systems and the periphery that contribute to their homeostatic regulation. Emerging evidence suggests that the non-neurological systemic components of these pathways may impact TBI physiology and outcome (Kemp et al., 2008; Lund et al., 2016; Schirmer-Mikalsen et al., 2007; Zygun et al., 2005). Acute dysfunction in the humoral triad may eventually lead to chronic pathology involving these humoral signaling networks, which may in part contribute to the late effects of TBI and accelerated biological aging (Di Benedetto et al., 2017; Gubbels Bupp, 2015; Liang et al., 2017). Accelerated aging can lead to brain atrophy, (Cole et al., 2015) premature neurodegenerative disease (Norden et al., 2015), as well as increased risk for chronic health conditions often observed after TBI, such as depression and suicide, cognitive and behavioral dysfunction, epilepsy, and neuroendocrine dysfunction (Wagner and Zitelli, 2013).

Inflammation, hormone, and neurotrophin biomarkers reflective of the humoral triad may provide valuable information regarding the heterogeneous biology of TBI as a complex chronic disease. The components of the secondary injury response to brain injury associated with **humoral triad** associated signaling and regulation each have independent functions, but also possess the capacity for cross-talk via multiple signaling pathways that contributes to homeostatic regulation. For clinical providers, biomarker signaling reflective of the humoral triad may represent a permissive plastic versus a dysfunctional homeostatic state, either of which may have prognostic value regarding outcome and/or risk for secondary conditions. Perhaps more importantly, these humoral markers may also provide needed information before randomization of individuals into clinical trials and aid as dynamic markers of treatment response.

Existing literature has examined how variability of acute biomarkers involving the humoral triad are associated with recovery from injury across multidimensional outcomes (Woodcock and Morganti-Kossmann, 2013). Fewer studies, however, have integrated multiple humoral signaling and regulatory systems into their assessment to understand if/how these are connected. While not exhaustive, the discussion below summarizes important clinical studies, and highlights our own work, involving the humoral triad and associations with outcomes.

4.1 Neurotrophins:

Neurotrophins comprise one component of the humoral triad that promotes survival, development, maintenance and function of neurons. Following TBI, an extensively studied biomarker in the neurotrophic family is brain-derived neurotrophic factor (BDNF), the systemic levels of which are initially reduced in the periphery, but modestly increased in the brain after moderate to severe TBI (Failla et al., 2016a). Clinical studies demonstrate BDNF genetics and levels are associated with mortality, with nuanced effect modification observed across the lifespan of patients; the biological actions of BDNF in older adults differs compared to their younger counterparts, wherein traditional protective effects of this neurotrophin are limited to younger individuals with TBI (Failla et al., 2016a, 2015a). The hippocampus is a brain region that is particularly vulnerable to the effects of TBI, with focal depression of BDNF expression at post-acute time points (Chen et al., 2005), and genetic variation in the BDNF gene is associated with hippocampal volume after TBI (Hayes et al., 2018). Our recent work suggests that low serum BDNF levels have an adverse impact on depression and functional cognition after moderate to severe TBI (Failla et al., 2016b). Yet more work is needed to determine if/how age and BDNF interact to impact survivor based outcomes.

4.2 Hormones:

A second component of the humoral triad is the endocrine system. In the setting of TBI, pituitary dysfunction may result in several clinical conditions, known as neuroendocrine dysfunction (Agha et al., 2004; Barton et al., 2016; Lieberman et al., 2001; Schneider et al., 2006; Wagner et al., 2012). Signaling abnormalities may be due to direct or indirect damage to the hypothalamus or pituitary, which impacts functioning of the hypothalamus-pituitary-adrenal (HPA) or hypothalamus-pituitary-gonadal axis (HPG) axes. In addition to direct/indirect damage, TBI induces an acute stress response that increases endogenous cortisol production (Woolf, 1992). The beneficial and detrimental effects of cortisol elevations provide a robust exemplar of the existence of regulatory cross-talk within the humoral triad, is a significant mediator of dysfunction in both neuroinflammation (Santarsieri et al., 2015) and BDNF expression (Munoz et al., 2017). Also, in pre-menopausal women, chronically elevated cortisol may contribute to amenorrhea and menstrual cycle dysfunction (Ranganathan et al., 2016), and acute increases in cortisol are associated with long-term cognitive impairments (Barton et al., 2016).

Endocrine dysfunction after TBI extends beyond early elevations in cortisol, and include concurrent factors such as obesity (Karelina et al., 2016). Medications including many psychotropic and anticonvulsant agents as well as steroids and anti-hypertensives commonly used post-TBI (such as β -blockers), can impact obesity and/or neuroendocrine function. Men experience a period of hypogonadotropic hypogonadism (low testosterone and low luteinizing hormone) that for some resolve after 8–12 weeks post-TBI, but for others, may extend for several months after injury and lead to poorer functional outcomes (Barton et al., 2016). Clinical observational studies, also show that steroidogenesis via typical pathways is acutely disrupted following TBI, with acute post-injury steroidogenesis primarily occurring in extra-gonadal regions, [e.g. adrenals and adipose tissue (Wagner et al., 2011)] that may work, via reciprocal relationships with systemic inflammatory pathways, to drive the

evolution of critical illness and non-neurological organ dysfunction (Santarsieri et al., 2015). The downstream consequence of acute HPG axis disruption is also homeostatic dysregulation in sex hormone production leading to secondary hypogonadism (Barton et al., 2016; Wagner et al., 2011, 2012).

4.3 Inflammation:

The third component of the humoral triad is inflammation. Acute inflammation after TBI is characterized by an aggressive *innate immune response*, the body's "first-line" defense response to injury (Schmidt et al., 2005). The neuroimmune response is largely mediated by resident microglia that rapidly change from a resting to an activated state upon surveillance and detection of CNS damage, like that which occurs with TBI (Loane and Byrnes, 2010; Loane and Kumar, 2016). Activated microglia facilitate inflammation by recruiting pro-inflammatory cytokines, chemokines, and cell-adhesion molecules to injury sites to clear debris and dead neural tissues and cells (Jeong et al., 2013). The negative consequences of excessive neuroinflammation on complicating conditions and multidimensional outcomes following TBI are becoming increasingly apparent from several recent clinical studies from our group. We recently demonstrated variable longitudinal IL-6 profiles acutely after TBI. Individuals in the high IL-6 trajectory were more likely to have unfavorable outcomes over the first year post-TBI, and they also had elevated levels of other pro- and anti-inflammatory cytokines as well as cell-surface markers (Kumar et al., 2015). Another study found that acute interleukin-1 β levels and genetic variability in the interleukin-1 β gene influences both IL-1 β levels increases risk for seizures after TBI (Diamond et al., 2014). Other studies have determined that acute inflammatory markers in the cerebrospinal fluid are associated with depression risk (Juengst et al., 2014) as well as risk for suicidal ideation and impulsive behavior (Juengst et al., 2014). Further, serum tumor necrosis factor-alpha (TNF α) levels are a relevant biomarker for mortality risk after severe TBI (Kumar et al., 2014).

Infection often co-occurs with TBI; acute infection rates vary from ~30–60% (Esnault et al., 2017; Kourbeti et al., 2012; Schirmer-Mikalsen et al., 2013). The underlying causes of infection after TBI are not well understood, yet research suggests prolonged ventilation, surgical procedures, immunodeficiency, prolonged hospitalization, CNS damage, cerebrospinal fluid (CSF) leak may contribute to infection after TBI. Acute immunosuppression is the result of sympathetic nervous system (SNS) activation and an initial innate immune response, which, when prolonged, can lead to lymphocyte depletion and increased lymphocyte apoptosis. This suggest that the immune response following TBI results in perturbations to both the innate and adaptive immune system. Specifically, Kasten (Kasten et al., 2010) suggest that early innate and adaptive responses to trauma are concurrent and divergent. The innate arm is hyper-inflammatory, and the adaptive arm is hypo-inflammatory. Over the acute and chronic phase of experimental TBI, the innate immune response is activated and dysfunctional, while the adaptive immune response remains suppressed (Ritzel et al., 2018). Clinically, we show recent data suggesting lymphopenia up to three weeks post-injury in humans that impacts recovery as well as health resource utilization (Calcagno et al., 2018). Other previous clinical TBI studies suggest there is a lack of T cell proliferation in patients with head injuries, leading to an increased risk of developing an infection (Hoyt et al., 1990; Quattrocchi et al., 1991). Also,

polymorphonuclear leukocyte function was unaffected after TBI, again suggesting disruption of the adaptive immune system (Hoyt et al., 1990).

The innate inflammatory cascade is considered a crucial component in the healing process; however, persistent inflammation over long time periods can have deleterious effects (Woodcock and Morganti-Kossmann, 2013). Excessive acute inflammation may predispose individuals to chronic inflammation. Generally, the beneficial effects of inflammation are derived when these processes are under tight physiological control, as unregulated inflammation may be counterproductive to TBI recovery (Boison and Masino, 2015). Recent observational studies have examined chronic immunological disturbances after severe TBI. A landmark study (Ramlackhansingh et al., 2011) determined that individuals with TBI can still have microglial activation in subcortical brain regions up to 17 years after injury. Increased microglial activation also has been documented 60 days out from injury (Acosta et al., 2013). Our previous work shows a chronic systemic inflammatory state present in the first year after TBI, and increased inflammatory load in the first three months is associated with poorer global outcomes at 6 and 12 months after injury (Kumar et al., 2015).

5.0 Humoral Triad Interactions: Exemplars in TBI

5.1 Clinical Exemplars of Humoral Cross Talk

5.11 HPA regulation of Immunity: It is well established in other disease states that endogenous glucocorticoids are modulators of the body's immune system, and there is a reciprocal relationship between neuroendocrine and immune systems (Chen and Miller, 2007; Nijm and Jonasson, 2009). Under certain conditions, glucocorticoids can have neuroprotective, anti-inflammatory, and anticonvulsive after neurological injury, as the end product of the stress-activated HPA axis (McEwan, 1999; Jeanneteau et al., 2008; Joëls, 2008). However, this cross-talk was previously not established in the setting of TBI, until our recent study demonstrated that endogenous CSF cortisol is a significant regulator of acute neuroinflammation and its impact on global outcomes after severe TBI (Santarsieri et al., 2015). These findings were seminal in that we observed three physiological states that suggest neuroendocrine-immune cross-talk occurs after TBI: 1) physiological, 2) sub-physiological, and 3) pathological connections. Individuals with a sub-physiological and pathological inflammatory response to injury were most likely to have unfavorable global outcomes. For some, increased cortisol levels in the CNS facilitates a permissive inflammatory response, with very high levels of CSF cortisol associated with an adverse pro-inflammatory response. Conversely, some individuals had relatively modest inflammatory responses (i.e. immunoparalysis) that were further diminished at higher CSF cortisol concentrations.

Another example of complex signaling effects associated with cortisol and post-acute inflammation can be gleaned from interleukin-6, a cytokine which can undergo either classical signaling or trans-signaling depending on the binding patterns of interleukin-6 to its membrane-bound receptor (classical) or soluble receptor (trans). Classical signaling promotes an anti-inflammatory environment, while trans-signaling, perpetuates chronic inflammatory state (Rose-John, 2012; Rose-John et al., 2006). Our preliminary work suggests higher IL-6 soluble receptor signaling during the subacute phase after TBI does

have a negative impact on global outcome (Ranganathan et al., 2017). Also, its negative effects on outcome are mediated substantially by post-acute cortisol levels (Schuster et al., 2017).

Another of our previous studies identified two clusters of individuals with distinct neuroinflammation patterns acutely after severe TBI (Kumar et al., 2016). Here, inflammatory cluster can be conceptualized as a molecular phenotype of the innate immune response among individuals with severe TBI (Simon et al., 2017). Interestingly, individuals in the pro-inflammatory cluster were on average 15 years older than individuals in the average-low inflammatory cluster; however, inflammatory clusters predicted poor GOS outcomes at 6 months even after adjustment for age in a multivariate model, suggesting multi-factorial contributions of age on pro-inflammatory biomarker patterns as well as age related comorbidities contributing to global outcome. Furthermore, individuals in the pro-inflammatory cluster had significantly higher levels of CSF hormones (cortisol, progesterone, E2, testosterone) and CSF BDNF, in addition to serum cortisol and BDNF, further supporting potential points of a coordinated central-systemic response to injury for these biomarkers.

5.12 HPA regulation of Neurotrophin Injury Response: BDNF and cortisol regulation are interconnected via multiple mechanisms involving the stress response (Rothman and Mattson, 2013), which are relevant in the context of TBI, a major pathophysiological stressor. The specific pathways by which cortisol and BDNF interact are not well elucidated, although research shows glucocorticoid response elements located in the *BDNF* gene promoter region, suggesting transcriptional control over BDNF (Rothman and Mattson, 2013). Other indirect mechanisms have been proposed for glucocorticoid regulation of BDNF through CREB, MAPK/ERK, or Shp2 (Alboni et al., 2011; Kumamaru et al., 2011, 2008). BDNF, through synaptic modulation involving the nucleus of the solitary tract (Clark et al., 2011) and hypothalamus (Tapia-Arancibia et al., 2004), may also regulate HPA-axis reactivity (Jeanneteau et al., 2012).

We previously explored relationships between CNS neurotrophins and hormones in the setting of severe TBI (Munoz et al., 2017). We determined that cortisol acts as a substantive mediator of CSF BDNF effects on mortality. We also showed an interaction between BDNF gene and levels in younger, but not older adults, which is consistent with previous reports that BDNF genetics and age are important variables that mediate BDNF concentrations and moderate mortality risk after TBI (Failla et al., 2016a, 2015a). The regulatory role of cortisol in the setting of neurotrophins, in addition to its regulatory role in neuroinflammation (Santarsieri et al., 2015), provides evidence of the central role of cortisol in the humoral triad signaling and regulation.

5.2 Experimental Exemplars of Humoral Cross-Talk:

Evidence from experimental TBI studies suggests a disrupted humoral triad after injury. However, less is known about how cortisol might regulate BDNF and/or inflammation and associations between BDNF and inflammation post-TBI. The immune response to TBI in the CNS are mediated by microglia, the immune cells of the brain. In response to injury,

microglia are activated and could be expressed as two polarized phenotypes M1 or M2. The M1 phenotype is primarily pro-inflammatory. The M2 phenotype, however, promotes CNS repair and regeneration. Opposing actions of M1 vs. M2 phenotypes may impact neurogenesis. That is, evidence from animal studies shows that the M2-phenotype may increase neurotrophic factor expression, while the M1-phenotype suppresses neurogenesis and synaptic plasticity (Loane and Kumar, 2016).

Some reports show that hippocampal BDNF is chronically decreased (Chen et al., 2005). Hippocampal BDNF plays a critical role in synaptogenesis and maintenance via long-term potentiation (Kovalchuk et al., 2002) storage as well as with long-term memory (Bekinschtein et al., 2008a, 2008b). Increased BDNF levels also can inhibit neuronal degeneration and apoptotic cell death (Itoh et al., 2011). However, BDNF signals through both the pro-survival tyrosine-related kinase-B (TrkB) receptor, as well as the pro-apoptotic p75^{NTR} receptor, activating antagonistic signaling cascades that are dependent on receptor milieu. Studies suggest that dynamic expression changes in these receptors occur following experimental TBI (Rostami et al., 2013) and that BDNF's role in TBI recovery may be dependent on the relative balance of these target receptors.

Other experimental TBI studies show important relationships between stress, behavior and BDNF following TBI. One study shows that both stressed and injured rats showed increased levels of CORT up to 2 months following blast TBI that was related to altered anxiety-like behaviors (Kwon et al., 2011). Other experimental TBI work shows that corticosterone and adrenocorticotrophic hormone are upregulated in response to injury through an activation of the HPA-axis (Griesbach et al., 2011). A follow-up study determined that stress decreases neuronal plasticity in the hippocampus by decreasing the precursor form of BDNF (Griesbach et al., 2012, 2004). Importantly, the benefits of exercise in experimental TBI also seem to be dependent on recovery of the stress response prior to induction of exercise (Griesbach et al., 2014) and impact neurotrophin production (Griesbach et al., 2012).

6.0 Brain and Body Contributors to the Humoral Triad: crosstalk, regulation, signaling

When considered together, the literature outlined above regarding the humoral triad and its roles in regulation and signaling provides evidence of brain-body-brain interconnectivity in the context of TBI through signaling pathways that comprise the humoral triad (Figure 2). Emerging evidence suggests that chronic post-injury derangements occur as a part of the brain-body-brain communication. These data show that a research and clinical translation focus based only on brain-derived biomarkers may be incomplete when considering long-term pathology as well as the potency of rehabilitation relevant interventions. As such, a Rehabilomics focused perspective on the extracerebral trauma complex, as well as non-neurological phenomenon that occur in the context of TBI, warrants more attention and research when considering rehabilitation focused intervention and pre-randomization screening approaches for likely treatment responders to these interventions.

6.1 The Extracerebral Trauma Complex:

Despite TBI being primarily an injury to the brain, inflammatory processes, HPA activation, and neurotrophin physiology are not confined to the CNS. After injury, inflammatory cells from the periphery cross a damaged blood brain barrier to aid in brain tissue repair (Schmidt et al., 2005). Among individuals that sustain polytrauma, or concurrent traumatic injuries to regions of the body, peripheral immune markers are recruited to aid in repair of these other bodily injuries (Kumar et al., 2015). Under normal conditions, the brain and the peripheral immune system communicate via the sympathetic nervous system (SNS) (Elenkov et al., 2000; Kenney and Ganta, 2014). In response to an acute injury like TBI, two main “stress” pathways are activated: the SNS and the HPA axis (Elenkov et al., 2000). SNS activation follows a release of sympathetic neurotransmitters, including norepinephrine (NE), which has direct effects as a neuromodulator in lymphoid organs that supports cytokine production (Elenkov et al., 2000; Kenney and Ganta, 2014). The SNS also facilitates an acute phase hepatic response, producing pro-inflammatory cytokines like tumor necrosis factor- α (TNF α) (Baumann and Gauldie, 1994; Dinarello, 1984; Heinrich et al., 1990; Kossmann et al., 1995).

TNF α also potentiates aromatization within the steroidogenesis pathway to produce injury associated increases in estradiol, a hormone with reciprocal effects on systemic inflammation by reducing norepinephrine reuptake for SNS innervated lymphoid tissue. Specifically, TNF α in the adipose tissue is a transcription factor for the expression of the aromatase gene, located in promotor region I.4 (Irahara et al., 2006; Simpson, 2004; Zhao et al., 1996). The result of aromatase expression at this site is an increase in extra-gonadal production of E2. Specifically, E2 acts as a potent vasodilator through promoting nitric oxide and hydrogen sulfide pathways (Egami et al., 2005; Garbán et al., 2004; Tep-areenan et al., 2003; Zhou et al., 2013). These data suggest that vasodilation, mediated by E2 and TNF α , may contribute to NNOD, and our work shows that amplified conversion of androgen to estrogen ultimately carries an increased risk for mortality (Wagner et al., 2011).

Peripheral contributors to the acute immune response associated with TBI are further highlighted by TNF α , an extensively studied inflammatory proteins in the field of immunology (Probert, 2015; Shohami et al., 1999; Strieter et al., 1993). Experimental TBI studies using TNF α gene knockout mice show a neuro-protective role for TNF α (Scherbel et al., 1999), which may be mediated by the potent pro-inflammatory capacity of TNF α to signal other cytokine production as well as chemokines, and cell-surface markers to aid in tissue repair (Probert, 2015). Other studies suggest, TNF α contributes to brain edema and cell death (Ziebell and Morganti-Kossmann, 2010). TNF α and its receptor (TNF-R1) also initiate a phenomenon known as necroptosis, or programmed cell death of inflammatory cells (You et al., 2008). This may be one reason why elevated TNF α levels have been associated with poor outcomes in several clinical observational studies of TBI (Juengst et al., 2014; Kumar et al., 2014; Kumar et al., 2015; Santarsieri et al., 2015).

6.2 Infection, Inflammation and Non-neurological Organ Dysfunction:

Systemic Infection commonly co-occurs with TBI which can propagate systemic inflammation and perpetuate NNOD. Patients with TBI are particularly at risk for

pulmonary infections stemming from prolonged mechanical ventilation and long hospital and intensive care unit lengths of stays. Injury induced suppression in lymphocyte production decreases capacity to fight new pathogens and an increases risk for opportunistic infections. Several studies from polytrauma populations have explored the harmful effects of lymphopenia (Heffernan et al., 2012; Kasten et al., 2010; Kopp et al., 2013; Lucin et al., 2009; Stirling and Yong, 2008), including one study where persistent lymphopenia after the first four days of trauma had a 2.5 times increased risk of death compared to those with normal lymphocyte levels (Heffernan et al., 2012).

The concept of NNOD is commonly observed with critical illness (Kemp et al., 2008; Zygun et al., 2005). Zygun and colleagues (Zygun et al., 2005) determined that, in a cohort of severe TBI, roughly 1 in 3 patients develop some form of non-brain organ failure during their hospital stay. Respiratory failure occurred in nearly 1 in 4 patients, and cardiovascular failure occurred in nearly 1 in 5 patients (Zygun et al., 2005). The same study determined that individuals with the NNOD had a 63% increase in their odds for mortality and 53% increase in odds of poor Glasgow Outcome Scale (GOS) scores during their hospitalization, compared to their counterparts without NNOD (Zygun et al., 2005). Similarly, another study (Kemp et al., 2008) determined that NNOD accounts for 2/3 of all deaths after severe TBI.

Acute kidney injury (Moore et al., 2010), platelet dysfunction (Davis et al., 2013; Sillesen et al., 2013), acute phase liver response (Liu et al., 2008), acute lung and cardiac injury (Rincon et al., 2012) as well as permeability of tight junctions within the gut (Katzenberger et al., 2015b) have been documented in the setting of acute TBI, and these conditions have also been associated with high mortality rates in clinical studies as well as experimental model systems (Anthony et al., 2012; Katzenberger et al., 2015a; Moore et al., 2010). These and other attributes of NNOD remain under-appreciated, though reports do document increased mortality associated with these conditions after TBI (Lim and Smith, 2007). Systemic inflammation, reduced BDNF levels, prolonged HPA axis activation, and injury induced steroidogenesis (aromatization) likely contribute to mortality (Failla et al., 2016a, 2015a; Garringer et al., 2013; Kumar et al., 2016; Lim and Smith, 2007; Munoz et al., 2017; Wagner et al., 2011); these systemic effects are likely contributors to ongoing secondary brain injury and should be considered when conducting TBI interventional trials and pre-randomization assessments of likely treatment responders.

7.0 Exercise as an Exemplar of Rehabilitation Intervention Impact on the Humoral Triad and Recovery

Exercise is a core rehabilitative intervention that may be used alone or in conjunction with other cognitive, occupational, and pharmaceutical interventions to facilitate neurological recovery (Archer et al., 2012). Physical activity (exercise) enhances mood and cognitive function in both healthy and neurologically impaired populations (Hillman et al., 2008). Previous clinical research in general and aging populations suggests exercise can increase hippocampal volumes (Erickson et al., 2011), grey matter volumes (Erickson et al., 2014), and white matter integrity (Voss et al., 2013b), as well as improve cognition (Bherer et al.,

2013; Voss et al., 2013b), reduce depression (Erickson et al., 2012), promote brain plasticity (Voss et al., 2013a) and reduce neurodegenerative diseases (Barnard et al., 2014).

Animal studies report show that exercise can yield quantifiable improvements in cognition while inhibiting neuronal degeneration and apoptotic cell death and restoring homeostatic regulation (Hillman et al., 2008). Exercise increases BDNF expression and secretion, which in turn can elevate learning, memory, and mood (Erickson et al., 2011). An immediate increase in BDNF protein can occur even with a single exercise session; the duration and amount of exercise also positively correlate to hippocampal increases in BDNF levels (Oliff et al., 1998). Modifications in monoaminergic function and inflammatory cytokines (e.g. IL-6) are also instrumental in explaining the positive effects of exercise on brain health. Importantly, animal studies suggest exercise may reduce the adverse effects of inflammation through increased BDNF levels (Wu et al., 2007).

Griesbach's work shows that voluntary exercise can improve recovery from injury through by upregulating endogenous BDNF, enhancing synaptic plasticity (Griesbach et al., 2004). Further, maximal benefits of exercise are observed after experimental TBI when delayed by two weeks post injury (Griesbach et al., 2004), which corresponds to recovery of the homeostatic stress response post-injury (Griesbach et al., 2014). Consistent with these reports, other work suggests that delayed exercise (up to 5 weeks after injury) can have beneficial effects on neuroinflammation and TBI recovery (Piao et al., 2013), shedding new light on potentially therapeutic time windows for facilitating neurological repair and recovery through multiple arms of the humoral triad. Importantly, activity based interventions thought to increase brain BDNF expression, like environmental enrichment (Chen et al., 2005; Wagner et al., 2002), show translational value as rehabilitation relevant therapies supporting cognitive recovery post-TBI.

8.0 Rehabilitation and Rehabilomics Relevant Biologic and Pharmacological Approaches to Homeostatic Function addressing the Humoral Triad.

In addition to exercise, other pharmacotherapeutics can impact the humoral triad and may be beneficial in the setting of TBI and during what are considered to be the traditional rehabilitation phases of recovery. Interestingly some literature suggests that in addition to progesterone, the corticosteroid, dexamethasone, can reduce neuroinflammation after experimental TBI.(Xu et al., 2014). Other work suggests that Lithium has wide spread protective effects in brain after experimental TBI, including upregulation of neurotrophins and other growth factors as well as reduction in inflammation (Leeds et al., 2014).

However, immunotherapies are increasingly used for conditions, such as cancer, arthritis, and autoimmune disease, may be of value. For example, the TNF-alpha inhibitor, Etanercept, reportedly is neuroprotective when given early after experimental stroke(Clausen et al., 2014), TBI (Chio et al., 2010; Ekici et al., 2014), and other acute CNS injury (Bae et al., 2016; Roh et al., 2012) and may be worth additional study. Other experimental data suggest this drug may address anxiety (Bayramgürler et al., 2013) and depression (Krügel et

al., 2013). Clinical studies are now corroborating findings in experimental models (Butchart et al., 2015; Kekow et al., 2011; Krishnan et al., 2007) including stroke and TBI (Ignatowski et al., 2014; Tobinick et al., 2012). Others have suggested that recombinant human IL-1 receptor antagonist (rhIL-1ra) treatment, in combination with SSRI therapy, can more effectively treat depression in an experimental model (Andrade, 2014; Pineda et al., 2012). Interestingly, rhIL-1ra is being studied in the clinical trial pipeline for acute neuroprotection after TBI (Helmy et al., 2014) and early treatment has shown some cognitive benefits and also reduced seizure tendency in an experimental models of TBI (Semple et al., 2017). Also, both propranolol (Ley et al., 2012) and levetiracetam (Zou et al., 2013) reportedly reduce IL- β expression in the acute and post-acute settings respectively.

Importantly, beta-blockade with propranolol also has a substantial beneficial effect on acute care mortality, based on a recent multi-site study (Ley et al., 2018). In the rehabilitation setting, propranolol reduces symptoms of hyperadrenergia associated with paroxysmal sympathetic hyperactivity more chronically (Baguley et al., 2014). These results suggest the importance of the SNS in the context of NNOD and the extra-cerebral trauma complex in the systemic response to TBI both during the acute and rehabilitation phases after TBI.

Dietary supplementation, particularly for those who cannot participate in exercise programs due to physical impairment, may be beneficial with regard to depression and cognition (Gomez-Pinilla and Tyagi, 2013; Levant, 2013). For example, omega fatty acids can support BDNF expression after TBI (Wu et al., 2004). Further, some omega fatty acids can quell the adverse effects of inflammation by modulating microglial activation (Chen et al., 2018) and other inflammatory signaling cascades (Chen et al., 2017; Lin et al., 2017).

9.0 Rehabilomics in Action: Future Directions for Developing Companion Tools for Rehabilitative Intervention.

The effects of TBI are heterogeneous compared to other clinical diseases. In this review we have introduced the Rehabilomics research model, which considers an “-omics” approach (proteomics, genomics, metabolomics) to characterize TBI heterogeneity in pathophysiology. Further, we discuss the applicability of Rehabilomics framework as a rubric by which current and future research can be conducted and contextualized for *future work* specifically focused on developing a biomarker-based tool kit for examining and treating neurologic and non-neurological conditions arising over the acute/post-acute continuum that impact function and rehabilitation outcomes. We discuss timing and chronicity of treatments, as well as overview intrinsic factors like genetics, age, and sex that can influence personal biology in response to TBI and rehabilitation focused care. To improve neurorehabilitation and recovery, we must examine the diverse sequelae post-TBI within a framework that considers these factors. A focus on the humoral triad, and its links to ongoing signaling and regulatory effects on pathology through HPA and SNS dysfunction, may be fruitful when examining the substrates underlying chronic conditions, including neurodegenerative disorders, which occur after TBI. Moving forward, the development of a Rehabilomics tool kit to help characterize pathology and stratify risk for treatment and outcome assessment will be a useful aid when assessing rehabilitation relevant treatments

and interventions that decrease secondary injury burden, reduce disability and address function. Additionally, the Rehabilomics model is more than just a framework from which to study disease, but also emphasizes the importance of infrastructure building. Among individuals with moderate-to-severe TBI, we have been able to accrue an expansive biobank of CSF, serum, and saliva samples at acute and chronic timepoints following injury. Importantly, matching participant biosamples with extensive phenotypic characterization across multiple TBI impairments can be leveraged by TBI researchers for impactful proteomic and genomic studies aimed at increasing our understanding of recovery and function, particularly in the context of rehabilitation relevant treatments.

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Highlights:

- This review overviews Rehabilomics as a conceptual framework that can guide rehabilitation intervention studies, including rehabilitation relevant TBI interventions.
- This review uses the Rehabilomics framework to summarize the impact of inflammation, neurotrophins, and glucocorticoids as relevant biomarkers after TBI.
- The humoral triad is introduced in relation to inflammation, neurotrophins and glucocorticoids in the context of TBI.
- Exercise as well as pharmacotherapies and biologics are reviewed as rehabilitation relevant therapies that can influence the humoral triad and impact outcome.

Humoral Triad in TBI

Figure 1:

The Humoral Triad of TBI focuses on three biomarker families (Neurotrophins, Inflammation, and Glucocorticoids) that correspond to three inter-related systems affected after injury. Converging results in studies with brain derived neurotrophic factor (BDNF), cortisol, and inflammation show that cortisol is mediator (regulator) of mortality risk and unfavorable outcomes after moderate-severe TBI. Sympathetic nervous system (SNS) and Hypothalamic-Pituitary-Adrenal (HPA) axis stimulation are fundamental physiological responses to trauma; these systems also support signaling mechanisms between BDNF, cortisol, and inflammation. This TBI Humoral Triad has inter-individual variability that is influenced by several personal factors, including race, age, sex, and genetics.

Humoral Triad Conceptual Model

Figure 2:

TBI induces a cascade of central nervous system (CNS) and systemic responses. The neurobiological response to TBI is complex, and involves perturbations within inflammatory, glucocorticoid, and neurotrophin signaling pathways. The neuroinflammatory response to TBI is mediated by the immune cells of the CNS, the microglia, which produce pro-inflammatory mediators, like tumor necrosis factor- α (TNF α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β). Other elements of brain injury pathology represented include activating the Hypothalamus-Pituitary-Adrenal (HPA) axis, for which glucocorticoids impact recovery regulate neuroinflammation. TBI also results in elevations in elevated Brain Derived Neurotrophic Factor (BDNF); two BDNF target receptors, TrkB-R and p75-R, have differing roles of neuronal proliferation and facilitation of cell death pathways, respectively. Blood brain barrier (BBB) disruption acutely after injury provides one source of communication between the brain and periphery. The nuanced effects of TBI on peripheral body systems and their contribution to the humoral triad is portrayed. Peripheral sources of TNF α production early after TBI are initially liver derived through a sympathetic nervous system (SNS) initiated acute phase response, which triggers activation of cellular immunity and inflammatory signaling pathways. TNF α importantly aids in extra-gonadal production of E2 in adipose tissue. The negative effects of excessive E2 and TNF α is vasodilation of systemic vasculature, which may contribute to non-neurological organ dysfunction (NNOD) and mortality. The primary source of BDNF production after TBI is via platelet activation in the periphery. HPA-axis activation after TBI results in the adrenal production of cortisol. TBI may also results in a trauma-induced state of immunosuppression, known as lymphopenia, which may increase risk for infections, like pneumonia. Acute pneumonia

after TBI contributes to a chronic inflammatory state that increases risk for poor long-term outcomes.

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