

Neurocognitive Perspectives on PTSD, mTBI and Suicide in the Military

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Summary of Report:

- **It is well-established that either traumatic psychological stress or mild traumatic brain injury (mTBI), alone, can produce long-lasting adverse effects on brain functioning**
- **The emotional and physical toll of PTSD can interact with mTBI to exacerbate brain pathology which may contribute to increased suicidal tendencies in traumatized veterans**
- **We have described a novel research program which is based on the integration of a rodent model of PTSD with brain trauma**
- **Our preliminary findings provide evidence of a greater extent of brain injury and memory deficits in mice exposed to psychosocial stress in conjunction with physical trauma**
- **Our animal model of mTBI-PTSD interactions is an important strategy for developing pharmacological treatments which can rapidly ameliorate the pathological effects of physical and emotional trauma on the brain**

Introduction: The Story of a Fallen Warrior

The issue of how psychological stress interacts with mild traumatic brain injury (mTBI) to increase risk for suicide has been discussed extensively in stories on how our veterans have been affected by wartime combat. All too often combat-related trauma experienced by our warriors has resulted in difficulty for them to adjust to civilian life. An illustration of how military service resulted in personal tragedy is described in a 2012 New York Times article written by Nicholas Kristof¹ based on a publication in the medical journal *Neurosurgical Focus*. The subject was a 27-year-old former Marine who was struggling to adjust to civilian life after two tours in Iraq.

During his first deployment this man witnessed marines killed and wounded when a vehicle in his patrol was blown up. In another incident, he witnessed a school bus full of Iraqi citizens, many of whom were children, blown up by an IED. In addition to the psychological trauma of combat, he was also exposed to repeated mortar blasts and improvised explosive device (IED) blasts less than 50 yards away from him. Following his second deployment he developed a progressive history of cognitive impairment, impaired memory, mood disorders and alcohol abuse. Once an A student, he found himself unable to remember conversations, dates and routine bits of daily life. He became irritable, snapped at his children and withdrew from his family. He was diagnosed with a form of PTSD that included hyperarousal (irritability and insomnia) and emotional numbing. In 2011 he committed suicide by hanging himself with a belt, approximately 8 months after his honorable discharge from the USMC.

An autopsy of this man's brain revealed evidence of degenerative effects that may shed light on why there is an epidemic of suicides and emotional struggles among soldiers following combat. In a landmark study published in *Neurosurgical Focus*, lead author Bennet Omalu, M.D., reported that this man's brain developed a disease called chronic traumatic encephalopathy (CTE). Normally, CTE is diagnosed as a degenerative condition typically affecting athletes who experience repeated blows to the head, such as boxers and football players. In this case, the subject had experienced intense emotional stress in conjunction with physical trauma to his brain, which produced his emotional instability and cognitive impairments. Dr. Omalu's assessment of this subject emphasized that this was a sentinel case which should stimulate new lines of thought and research in how PTSD interacts with mTBI to produce physical degeneration of the brain.²

Scope of the Problem

Since 2001, over 2,000,000 Americans have served in the Iraq/Afghanistan war.³ There is a growing awareness of the adverse consequences of combat in this vast population of veterans, including a doubling in the rate of suicides by military personnel since 2001. The Department of Veterans Affairs has diagnosed at least 200,000 of these war veterans with PTSD. A study by the RAND Corp., which was confirmed by the VA's National Center for PTSD, suggested that at least 14 percent of all veterans in the past decade suffer from the headaches, sleeplessness, irritability, depression, rage and other symptoms of PTSD.³ mTBI is caused by external impact to the head or by a pressurized wave blast injury, resulting in a rapid rotational acceleration/deceleration of the brain in the closed skull of restrained occupants. Conservative

estimates indicate 18% of returning veterans have been diagnosed with mTBI, primarily due to exposures to combat related blast injuries from improvised explosive devices (Hoge et al., 2008).

Veterans of combat with mTBI can develop neurological symptoms such as chronic headaches, dizziness, vertigo, memory-executive dysfunction and impaired concentration. Neuropsychological symptoms can also arise due to the trauma surrounding the injury and involve insomnia, depression, irritability, impulsiveness, anxiety, apathy and aggression, resembling a cluster of PTSD-like symptoms. The most concerning of these features of mTBI is PTSD, which has been shown to be the strongest risk factor associated with persistent post-mTBI/concussion symptoms. Hoge et al, (2008) found that 44% of Iraq war returnees who experienced a loss of consciousness as a result of brain trauma also met the criteria for PTSD 3-4 months after deployment, compared to 9% with no injury. Combat related mTBI has been demonstrated to approximately double the risk for PTSD (Bazarian et al., 2013).

Finally, in the most extensive study of veteran suicides ever conducted, a recent report by the VA examined suicide data from 1999 to 2010.^{4,5} This study revealed that almost once per hour a military veteran commits suicide, for an average of 22 veteran suicides per day. This sobering statistic includes a substantial number of young veterans who were in the prime of their life. Two retired Army generals, Peter W. Chiarelli and Dennis J. Reimer, have spoken out about the urgency of reversing the trend of increasing rates of suicide among veterans. "One of the things we learned during our careers," they wrote in *The Washington Post*, "is that stress, guns and alcohol constitute a dangerous mixture. In the wrong proportions, they tend to blow out the lamp of the mind and cause irrational acts." ⁴

Neurobiological Perspective on mTBI, PTSD and Suicide

Researchers over the last few decades have documented the types of brain damage associated with mTBI and PTSD. The mechanisms implicated in mTBI largely involve white matter (axonal/cytoskeletal) damage primarily to frontal and temporal lobe structures, and is also associated with neuroinflammation and blood brain barrier (BBB) dysfunction. The neurobiological background of PTSD is more complex, involving an aberrant regulation of the sympathetic nervous system and the hypothalamus-pituitary-adrenal (HPA) axis, low grade inflammation and excessive activation of the amygdala (Zoladz and Diamond, 2013).

It is a challenge to understand mTBI and PTSD, alone and in conjunction. To further understand how these neuropathological triggers can lead to suicides is a great challenge to neuropsychiatric research. There is evidence that the activity of three neurobiological systems has a role in the pathophysiology of suicidal behavior. This includes hyperactivity of the hypothalamic-pituitary-adrenal axis, dysfunction of the serotonergic system, and excessive activity of the noradrenergic system. While the first and the last system appear to be involved in the response to stressful events, dysfunction of the serotonergic system is thought to be trait-dependent and associated with disturbances in the regulation of anxiety, impulsivity, and aggression. It can be hypothesized that neurobiological dysfunctions mediate the occurrence of suicidal behavior through the disturbed modulation of basic neuropsychological functions.

Taken together, to understand mTBI, PTSD and suicidal behavior, we need to focus on neurochemical abnormalities, such as abnormal hormonal levels produced by intense stress, as well as increased brain inflammatory processes, which underlie brain pathology. In theory, the impairment of inhibition over behaviors which are common in mTBI and PTSD include a range of behaviors such as alcohol and drug abuse, as well as acting on suicidal thoughts. One of the most important of all brain structures is the ventrolateral prefrontal cortex. Functional imaging studies have demonstrated abnormal neurochemistry in this brain region of patients who attempted suicide, particularly in violent attempters.

Animal Research on the Neurobiology of mTBI-Stress Interactions

The complexity of pathological outcomes of mTBI and PTSD, individually and in conjunction, illustrates the importance of developing rapid and effective treatment strategies for brain trauma. Optimal strategies for attaining this goal requires the strategic benefits of animal research, with its efficient testing of novel candidate compounds and improved understanding of the pathophysiological mechanisms involved in mTBI and PTSD. Finally, animal research provides effective models for assessing how stress interacts with physical injury to exacerbate the development of brain pathology.

In a research program on PTSD-mTBI interactions, we have developed a mouse model of concussive injury, which has been extensively characterized from 24 hours to 24 months post injury (Mouzon et al., 2014;Ojo et al., 2013). Mice exposed to concussion show evidence of memory dysfunction with repetitive mTBI, axonal injury, demyelination, white matter (corpus callosum) thinning and glial activation. In our recent work this concussive injury model was combined with a novel PTSD paradigm involving predator odor exposure (fox urine) with the mice under restraint, in conjunction with a conditioned footshock stimulus which was paired with mTBI. We found distinct and overlapping outcomes in neurobehavioral, neuropathological and biochemical changes (in brain and plasma) in this newly developed model of mTBI-PTSD. Specifically, we have reported a powerful increase in brain measures of inflammation which were present in greater magnitude in the mice that experienced both PTSD and mTBI (Ojo et al., 2014).

In cognitive testing our research has revealed an important aspect of memory which may be highly relevant to abnormal cognitive processing in soldiers that experience emotional trauma in conjunction with mTBI. Under control conditions, mice are administered a fear-provoking stimulus (pawshock) in a unique place (a fear conditioning chamber). In addition, training involves a cue (a tone) which is delivered in the shock chamber. Under normal conditions, when the mouse is returned to the chamber it exhibits fear (freezing) in response to the chamber, as well as to the sound of the tone. This type of training can help to identify the functioning of different brain memory systems. Specifically, memory for the place in which shock occurred is dependent on the hippocampus and memory for the sound associated with the shock is dependent on the amygdala. It is therefore highly relevant to human stress-mTBI interactions that we found impaired hippocampal memory for the context in which the shock occurred in the combined PTSD-mTBI group, but their memory of the specific cue present

during trauma remained intact. This finding is consistent with the disturbing “fragmented” and abnormal memories of trauma routinely reported in soldiers with PTSD in which impaired processing of the hippocampus appears to contribute to abnormal memories in people who experience physical and emotional trauma.

The significance of a relevant rodent model is that the consequences of mTBI, stress exposure, and their interactions, can be evaluated at the molecular level to fully understand the brain’s response at a level that is not possible in human subjects. Our animal research includes analyses of brain neurochemistry using state-of-the-art biotechnology to reveal proteins and lipids that are disrupted in response to mTBI and stress, which can then reveal specific targets for therapeutic intervention. Moreover, these molecular level processes can be examined over the time course of development of brain damage, enabling creation of a temporal profile of pathology, from the acute aftermath of trauma exposure to chronic time points. Ultimately, animal research provides the opportunity to maximize intervention strategies for developing therapeutic approaches in translational studies from rodents to human applications.

In summary, there is great value in a rodent model of trauma-stress interactions. The fundamental neurochemical and physiological processes which are disturbed with stress and physical trauma are quite similar in humans and rodents. Our approach, therefore, can identify how emotional trauma interacts with physical trauma to exacerbate brain damage and to produce cognitive abnormalities with relevance to clinical outcomes. The approach, as well, will enable us to identify rapid treatment approaches which will improve the outcomes of combat-related trauma.

Relevant links:

1. http://www.nytimes.com/2012/04/26/opinion/kristof-veterans-and-brain-disease.html?_r=0
2. <http://www.stripes.com/news/doctors-study-link-between-combat-and-brain-disease-1.98394>
- 3 - <http://www.rand.org/multi/military/veterans.html>
- 4 - <http://www.military.com/daily-news/2013/01/14/2012-military-suicides-hit-record-high-of-349.html>
- 5 - http://www.va.gov/opa/speeches/2012/06_20_2012.asp

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Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA (2008) Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med* 358: 453-463.

Mouzon BC, Bachmeier C, Ferro A, Ojo JO, Crynen G, Acker CM, Davies P, Mullan M, Stewart W, Crawford F (2014) Chronic neuropathological and neurobehavioral changes in a repetitive mild traumatic brain injury model. *Ann Neurol* 75: 241-254.

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