

EDITORIALS



Disentangling Mild Traumatic Brain Injury and Stress Reactions

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The study by Hoge and colleagues in this issue of the *Journal* provides an important profile of the sequelae of mild traumatic brain injury in military personnel after combat.¹ The findings demonstrate that mild traumatic brain injury results in increased rates of psychological, health, and functional problems. Although the study provides strong evidence for impairments in military personnel serving in Iraq and Afghanistan, it also raises a number of critical questions concerning the impairments that may be attributed to mild traumatic brain injury.

One striking finding from this study is that although mild traumatic brain injury predicted a range of health problems, its effects became nonsignificant after post-traumatic stress disorder (PTSD) and depression were considered. This pattern is in accordance with other studies² and points out that one must use caution when attributing health problems to mild traumatic brain injury, because associated PTSD and depression may be the primary problem. This is an important point because mild traumatic brain injury typically occurs in the context of a traumatic event, and psychological stress will probably be influential in many cases of mild traumatic brain injury.

If Hoge and colleagues had not assessed for PTSD and depression, the possible conclusion from this study would have been that mild traumatic brain injury is the causative agent for the impairment observed in many soldiers. This mistaken conclusion often has been made in clinical settings, and impairment observed in the aftermath of mild traumatic brain injury has been attributed incorrectly to neurologic insult, rather than psychological distress.

One of the classic features of mild traumatic brain injury, and the presumed cause of impair-

ment after mild traumatic brain injury, is postconcussive symptoms. These symptoms can include problems with memory, balance, and concentration, as well as ringing in the ears, sensitivity to light or sound, and irritability. There has been a long-standing debate about the extent to which postconcussive symptoms are a result of organic or psychological factors, or an interaction between the two.³ Incontrovertible evidence now shows that psychological factors play a significant role in postconcussive symptoms; one recent study showed that postconcussive symptoms occur at similar rates in persons with mild traumatic brain injury and in those with no traumatic brain injury.² Misattributing postconcussive symptoms to brain injury may have unfortunate implications, because it may be concluded that recovery depends on neurologic factors. The evidence suggests that participation in educational programs that normalize the reactions can alleviate postconcussive symptoms.⁴ The evidence from Hoge and colleagues, as well as from other studies,⁵ that psychological factors account for many postconcussive symptoms suggests that more effective interventions may involve augmenting educational programs with strategies that aim to reduce PTSD and depression.

The finding that mild traumatic brain injury is associated with an increased incidence of PTSD raises interesting possibilities about how mild traumatic brain injury may compound PTSD. Biologic models posit that a fundamental mechanism underpinning PTSD involves an exaggerated response of the amygdala, resulting in impaired regulation by the medial prefrontal cortex.⁶ The amygdala is central to the development and expression of conditioned fear reactions, and studies in humans and animals have shown that learning to inhibit these fear reactions involves

inhibition by the medial prefrontal cortex. Consistent with this model, patients with PTSD have diminished activation of the medial prefrontal cortex during the processing of fear.⁷ Mild traumatic brain injury often involves damage to the prefrontal cortex due to shearing forces of the frontal regions against the skull. It is possible that a person's capacity to regulate the fear reaction may be impaired after mild traumatic brain injury because the neural networks involved in the regulation of anxiety may be damaged as a result of the mild traumatic brain injury.⁸

Cognitive models propose that PTSD is maintained when trauma survivors have inadequate cognitive resources to manage their trauma memories and to engage adaptive cognitive strategies to manage the traumatic experience (e.g., they are unable to appraise a distressing state as temporary and, therefore, have heightened anxiety).⁹ Mild traumatic brain injury can impair cognitive resources¹⁰ and may compromise the capacity to engage in cognitive strategies to manage the aftermath of a psychological trauma. There is overwhelming evidence that maladaptive cognitive strategies (e.g., ruminating that one will never recover from the traumatic experience) after trauma are a major predictor of PTSD.⁹ Therefore, it is possible that people with mild traumatic brain injury have insufficient cognitive resources to engage appropriate cognitive strategies, which results in a greater incidence of PTSD.

The current study also highlights the need for clear operational definitions of mild traumatic brain injury. The study retrospectively assessed for mild traumatic brain injury by inquiring about having a loss of consciousness, being dazed, or not remembering the injury. Each of these reactions can be attributed to acute stress responses.¹¹ There are no reliable means to differentiate between symptoms involving impaired awareness that are caused by severe stress or mild traumatic brain injury,³ so differential diagnosis is problematic. This problem is highlighted by retrospective accounts of injury, because during recall of trauma reactions, people with severe psychological disturbance overestimate the symptoms that they had in the acute phase¹² and also their exposure to harm.¹³ It is preferable to use validated measures of post-traumatic amnesia in the immediate aftermath of the suspected mild traumatic brain injury to determine the extent of impaired awareness.

There are two very important outcomes of the study by Hoge and colleagues. First, soldiers who have mild traumatic brain injury are at greater risk for health-related problems. Second, soldiers should not be led to believe that they have a brain injury that will result in permanent change. Previous military conflicts have led to syndromes that have involved specific constellations of symptoms that are ascribed to some cause. After the first Gulf War, many soldiers had unexplained somatic symptoms — the so-called Gulf War syndrome — which many commentators ascribed to concern about chemical agents, even though exhaustive tests failed to determine a neurologic basis for the symptoms.¹⁴ If troops currently serving in Iraq or Afghanistan are informed about a postconcussive syndrome and persistent problems emerging from mild traumatic brain injury, a new syndrome could arise from the current conflict in which soldiers attribute a range of common stress reactions to the effects of brain injury. This could be damaging to morale and to the person's future mental health, because it could lead to the expectation of poor recovery. In contrast, the normalization of many of these reactions and the recognition that stress-related conditions can be managed with evidence-based strategies may minimize the unnecessary attribution of common stress reactions to pathology and facilitate resilience after mild traumatic brain injury.

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Molecular Origins of Cancer

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Over the past decade, insights into the origins and behavior of human cancers have reshaped our understanding of these diseases and have generated advances in clinical care. The seminal feature of this research is the focus on human cancers. By using ideas and technologies originally derived from basic science laboratories, investigators have shifted the forefront of cancer research from *in vitro* models of tumor growth to the characterization and treatment of cancers in humans.

This issue of the *Journal* launches a series of reviews on the molecular origins of cancer. The goal of this series is to highlight advances in the biology of cancer and their relevance to clinical practice. The topics relate to three broad areas of tumor biology.

The first area concerns genetic changes in the cancer cell — inborn and acquired — that give rise to the transformed phenotype. Chromosomal abnormalities and alterations in oncogene expression are widely documented in all cancers and often serve as the calling card for unique tumor subtypes and as targets for new kinds of treatment. Other acquired epigenetic changes that alter the structure and expression of genes contribute to tumor progression and may also serve as treatment targets. Molecular methods have defined many hereditary cancer syndromes, each driving unique abnormalities in cell function, and each with distinct clinical features. The development of genetic testing has allowed patients and family members to make better-informed assessments of personal cancer risk and to weigh prophylactic and surveillance options.

The second area centers on the interactions between the tumor and the patient — the modern expression of the “seed and soil” hypothesis. In contrast with most laboratory tumor models, cancers in humans arise and spread through multi-

ple and specific physiological niches. Cancers interact with surrounding tissue stroma and micro-environments both at the original cancer site and at sites of metastasis, and they are disseminated through lymphatic and vascular channels. “Host” responses include changes in vascularity and immune responses to tumors. Advances in the fields of tumor angiogenesis and tumor immunology are leading to novel treatments for many cancers, alongside therapies that seek to alter the biology of metastasis and of the microenvironment.

The third category concerns the tools that can characterize common tumors in humans, such as breast, lung, colorectal, and prostate cancers, at the level of the gene. Genomic analysis increasingly serves as a valuable complement to traditional pathology, capturing a degree of tumor-to-tumor variation that can refine the classification of tumors into clinically relevant subsets, thereby also refining prognosis and treatment selection.

Two lessons emerge from studies of the molecular origins of cancer: the remarkable biologic heterogeneity of cancers in humans and the intimate relationship between that variation and clinical results in oncology. Much of the heterogeneity in treatment outcomes for patients with cancer stems directly from the underlying variation in tumor biology, which dictates the likelihood and pace of tumor dissemination and the tumor’s sensitivity to both traditional and novel cancer treatments. The corollary is that the better our appreciation for the unique biologic features of each tumor, the better will be our ability to tailor treatment to each patient, bringing the right type and the right amount of therapy to bear on the cancer.

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