An Update on the Complexity and Importance of Accurately Diagnosing Post-Traumatic Stress Disorder and Comorbid Traumatic Brain Injury

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ABSTRACT: As awareness for diagnosing and screening patients for trauma has grown, more effective evidence-based treatments are available to treat post-traumatic stress disorder (PTSD). Despite these gains, several patients are non-responsive to care and research has shifted to determining barriers for cure or improvement. With the advent of modern warfare, the combination of intermittent explosive devices and more robust armor has resulted in service members surviving blasts that historically would have been lethal, resulting in a rise in traumatic brain injuries (TBIs). Post-traumatic stress disorder and TBI are often comorbid and can serve as the aforementioned barriers for cure or improvement for each other if one goes unrecognized. This mini-review will discuss the importance of diagnosing both entities, especially when they are comorbid, by examining how misdiagnosis may interfere with treatment outcomes. Several recent advances in methods to successfully distinguish between the two disorders will be reviewed.

KEYWORDS: Traumatic brain injury, post-traumatic stress disorder, diagnostic challenges, diagnostic accuracy, diagnostic uncertainty, diagnostic difficulty

Introduction

Since 1980 when post-traumatic stress disorder (PTSD) was first recognized as a formal diagnostic entity (see Table 1), more astute awareness exists of the disorder. Estimated prevalence rates are 6.8% in the civilian population and 5% to 20% for Veterans from Iraq and Afghanistan. Despite the growing awareness, PTSD symptoms often mimic other psychiatric disorders and without careful screening it is not uncommon to have multiple psychiatric diagnoses prior to being accurately diagnosed. Symptom overlap with major psychiatric diagnoses includes but is not limited to borderline personality disorder, attention deficit/hyperactivity disorder (ADHD), bipolar disorder, depression, generalized anxiety disorder/social anxiety/panic disorder, and psychotic disorders (see Table 2). To complicate matters further, any of the above-listed diagnoses can be comorbid with PTSD, and some of these disorders can also occur as a response to a trauma.

The last decade has also seen considerable progress made in evidence-based treatments for PTSD, one of the most effective being cognitive processing therapy (CPT) with an estimated 53% of treatment completers no longer meeting criteria for PTSD. But what of the 47% who do not respond? Undiagnosed mild to moderate traumatic brain injury (TBI) may be contributory and is being increasingly studied, in part due to the rise in TBI among Veterans. In this review, undiagnosed refers to either a patient’s inability to recognize or report symptoms or a clinician’s inability to identify a presentation as TBI. The world-wide numbers for TBI since 2000 to the first quarter of 2018 reached 383,947 as reported by the Department of Defense. This review focuses on mild traumatic brain injury (mTBI) with instances of moderate TBI, which represents most head injuries. In Veterans, similar to civilians, approximately 80% of all TBIs are categorized as mild. Two other reasons for concentrating on the mild and moderate TBI population are that many mild TBIs go undiagnosed and untreated. Corrigan and Bogner acknowledge that mild and older TBIs are the most difficult to diagnose. Similar to PTSD, persistent, post-concussive symptoms of mild TBI (see Table 3) are often vague, non-specific and can mimic many psychiatric disorders. When the symptoms of PTSD and TBI overlap and/or co-occur, diagnosis can be made more difficult and treatment can be ineffective if only one disorder is identified.

This article will summarize difficulties that contribute to accurately distinguishing between PTSD and mild to moderate TBI and methods to better recognize when the two co-occur. This mini-review is written from the standpoint of psychiatrists with the goal of examining the extent to which undiagnosed TBI may be responsible for a significant subset of non-responders to evidence-based treatments for PTSD. This article will discuss ways in which treatment for one may negatively impact the other. New methods being studied to elucidate the difference between the two will be discussed.

In this review, the term traumatic event refers to the psychological trauma that was experienced by a patient, excluding a TBI. The term TBI alone will be used to refer to any physical brain injury. Mild TBI will be indicated by mTBI, whereas TBI will indicate mild and moderate TBIs. Studies selected
were chosen based on their breadth, depth, or innovation, particularly in their contribution in distinguishing between PTSD, TBI, and co-occurring PTSD and TBI.

**Methods**

For this mini-review, a search of PubMed was performed with the following search terms: “traumatic brain injury(s),” “post-traumatic stress disorder,” “diagnostic challenges,” “diagnostic accuracy,” “diagnostic uncertainty,” and “diagnostic difficulty.” More recent articles were targeted, in particular those that addressed PTSD, mTBI, and comorbid occurrence. These articles were used to find links to other relevant studies.

**The Importance of Proper Diagnosis of PTSD Comorbid With TBI**

It is paramount to accurately diagnose PTSD with comorbid TBI as effective treatments are available that can significantly improve functional impairment in PTSD. Un-diagnosed comorbid PTSD and TBI may hinder a patient’s ability to engage in trauma work due to difficulty with emotion regulation, impulse control, or pain, in addition to cognitive limitations. If recognized, first-line treatment modalities for PTSD can be modified for patients with comorbid TBI or cognitive impairments. Two trauma-focused psychotherapies noted to have a robust evidence base for PTSD are CPT and prolonged exposure (PE). Cognitive processing therapy (CPT) has modified worksheets if cognitive impairment is present. Chard et al demonstrated that CPT was effective in reducing PTSD symptoms in Veterans with mild to moderate TBI in a residential program. Jak et al found components of compensatory cognitive training from Cognitive Symptom Management and Rehabilitation Therapy (CogSMART) combined with cognitive processing therapy (SMART-CPT) demonstrated clinically significant reductions in post-concussive symptoms and PTSD symptoms similar to that of CPT alone in Veterans from Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) eras with comorbid PTSD and mild to moderate TBI. The combined approach showed additional improvements in attention/working memory, verbal learning, and novel problem solving over CPT alone. Wolf et al demonstrated a significant reduction in PTSD symptoms in Veterans with mild to moderate TBI treated with PE. Minimal modifications were made including using behavioral memory enhancers such as calendars and smartphones, increased structure, and increased session time for cognitive deficits. Ragsdale and Voss Horrell reported that TBI in a population of Veterans with PTSD did not prevent positive treatment outcomes for PTSD using PE or CPT. This discrepancy may be due to differing severities of TBIs in these studies. We argue that it is still imperative to recognize comorbid TBI and PTSD to ensure that, even if PTSD is resolved, residual TBI symptoms are treated optimally. These studies where modifications to PTSD treatments show enhanced benefits for patients with PTSD and comorbid TBI further strengthen the argument for the importance of proper identification of both disorders.

Undiagnosed PTSD may add to a TBI patient’s avoidance of treatment. The inability to feel calm, fear responses to

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**Table 1. Summary of DSM-5 diagnostic criteria for PTSD for adults.**

| Criterion A | Exposure to threatened death, serious injury, or sexual violence either directly, witnessing the event happening to others, hearing that a traumatic event happened to close friends or family, or working in a profession where one is continuously exposed to trauma |
|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Criterion B | Intrusive symptoms such as distressing memories, nightmares, flashbacks, psychological reactions to trauma cues or reminders, or dissociative responses |
| Criterion C | Avoidance of trauma stimuli with efforts to avoid any reminders, thoughts, or feelings related to the trauma |
| Criterion D | Negative changes in mood/cognitions related to the trauma such as lapses in memory, reduced interest in activities, detachment from others, negative mood with inability to have positive emotions, distorted cognitions, and negative beliefs about oneself and others |
| Criterion E | Arousal and reactivity related to trauma such as hypervigilance, increased startle response, anger and irritability, poor sleep and concentration, and self-destructive behavior |
| Criteria F, G, and H | Duration longer than 1 month; clinically significant distress or impairment; and symptoms are not attributable to a substance or other medical condition |

Source: Adapted from American Psychiatric Association. Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders (5th ed.); PTSD, post-traumatic stress disorder.
trauma triggers, or substance use to numb symptoms may preclude the ability to effectively engage in cognitive rehabilitation. If recognized and treated, PTSD would no longer serve as a barrier to effective TBI treatment.

Regarding medications, selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are often used to treat both conditions and are deemed to be helpful in both.24,25 However, TBI patients are at an increased risk of seizure,26 have sensory processing limitations,27 and trouble with gait and/or balance.28 Many psychotropic medications increase the risk of seizures,29 can cause balance issues due to sedation, and anticholinergic side effects can worsen existing cognitive impairments.30 In TBI, stimulants are often used to aid with concentration but can worsen
Table 4. Shared and differentiated symptoms of PTSD and TBI.

| SYMPTOMS SPECIFIC TO PTSD | COMMON IN BOTH PTSD AND MILD TO MODERATE TBI | SYMPTOMS SPECIFIC TO MILD TO MODERATE TBI |
|---------------------------|----------------------------------------------|------------------------------------------|
| Re-experiencing (nightmares and flashbacks) | Depression | Headaches |
| Shame | Anxiety | Sensitivity to light and sound |
| Guilt | Emotional numbing | Tinnitus |
| Self-blame | Fatigue | Changes in taste or smell |
| Alterations in how one sees the world (ie, changes in how one trusts self or other) | Difficulty with concentration/focus | Dizziness |
| | Insomnia | Blurry vision, dilated pupils |
| | Fatigue | Nausea |
| | | | |

Source: Adapted from a figure from Stein and McAllister.41
Abbreviations: PTSD, post-traumatic stress disorder; TBI, traumatic brain injury.

Risk of PTSD After TBI

Yurgil et al34 looked at Marines and determined that deployment-related TBIs nearly doubled the likelihood of post-deployment PTSD for those who reported minimal to no symptoms pre-deployment. The probability of post-deployment PTSD was greatest for participants reporting prior psychiatric symptoms and deployment-related TBI. Stein et al,35 in a prospective cohort study of 4645 Veterans deployed to Afghanistan, demonstrated that deployment-acquired TBI was associated with substantially increased risk for PTSD at three and nine months post-deployment. Often a mild TBI damages the prefrontal cortex, the area responsible for regulating a fear reaction and assessing situations for danger. This deficit reduces capacity to assess a danger risk after trauma, negatively impacting fear extinction, and thereby increasing the risk of developing PTSD.36,37

Risk of TBI After PTSD

Shucard et al38 studied Vietnam Veterans with PTSD and found hyperarousal led to slowed central processing and impaired ability to screen irrelevant information. Twamley et al39 found that more severe dissociative symptoms from PTSD were associated with poorer reasoning performance. They concluded cognitive slowing from PTSD may be due to reduced attention as mental resources are shifted to deal with psychological distress. A patient with PTSD may feel psychologically damaged post-trauma and may then put themselves in dangerous situations as they feel they are not worthy of protection: (1) they may feel any attachment is positive, even if dangerous, (2) they may use substances to numb and not be as aware of their surroundings, or (3) they may desire the rush and adrenalin of danger to numb their pain. With any of these scenarios, a soldier may be placed in a dangerous situation where quick processing speed and reasoning is needed; one can postulate, if impaired in these areas, that they are at risk for many negative circumstances, including a TBI.

Barriers to Recovery With Comorbid PTSD and TBI

For those exposed to a traumatic event, up to 80% recover on their own after three months, and the 20% who go on to meet full criteria for PTSD may be conceptualized as having barriers in place that prevented natural recovery.40 Mild TBI can also be conceptualized as a problem of non-recovery. Most recover fully within weeks to months, but a minority, approximately 15% of those with mild TBI, experience post-concussive syndrome, where symptoms persist for more than a year.41

Post-traumatic stress disorder and TBI may serve as barriers to recovery for each other, especially if the second entity is comorbid and undiagnosed.41 These two disorders are increasingly found to be comorbid. Illustrating this point, Taylor et al42 discovered in a group of 327,388 OEF/OIF Veterans, of those with mTBI seeking care, 73% had comorbid PTSD.

Diagnostic challenges abound in this space. The symptom overlap is remarkably similar (see Table 4). Often in clinical practice, diagnosis of PTSD relies on self-disclosure of trauma...
which can be elusive due to avoidance. Coping strategies to avoid experiencing negative emotions contribute greatly to PTSD.\textsuperscript{43,44} A study looking at treatment-seeking barriers for Veterans with PTSD from conflicts in Iraq and Afghanistan found that greater than one third reported not being emotionally ready for treatment connected to avoiding wanting to talk about their trauma for fear of worsening symptoms.\textsuperscript{45} Similarly, a study by Hundt et al\textsuperscript{46} investigating why Veterans decline evidence-based treatments for PTSD reported that the most common emotional barrier was avoidance due to fears of not being ready to address their trauma and of what would happen in treatment. For PTSD, avoidance of thinking about the trauma is a required criterion for the diagnosis itself. If one is avoiding thinking about their trauma, it follows that they would avoid seeking treatment altogether. Regarding TBI, a patient may not be aware that they have a TBI, making self-reporting impossible. The current research cannot accurately report that mTBI is a reason for non-response to PTSD treatments if patients in the studies have undiagnosed, comorbid TBI.

As discussed, when comorbidity is known, monitoring responses to medications and treatment is warranted because one can negatively impact the other. As PTSD and TBI can impede recovery of the other if undiagnosed, it is paramount to establish more effective means to diagnose both when they are comorbid. What follows is a brief review of some methods that have been studied over the past 7 years to distinguish between TBI, PTSD, and TBI + PTSD. A search of recent studies was limited to studies attempting to specifically delineate between these disease states.

New Approaches to Differentiate PTSD and TBI

In the American Journal of Psychiatry, Stein and McAllister\textsuperscript{47} highlighted the importance of attending to both disorders when they are comorbid. In the 10 years since this article, research has significantly progressed in differentiating between these two disorders, from self-report measures to advanced radiological imaging techniques such as diffusion tensor imaging.

Self-Report Scales

Betthauser et al\textsuperscript{48} observed that the use of clinical interviews remained the “gold standard” for differentiating between mTBI and PTSD, which remains true today. They determined that no self-report measure reliably assessed for comorbid PTSD and TBI. Using a self-report measure was shown to hinder the subject’s ability to give detailed symptomology necessary to make the distinction between the two accurately. In contrast, the Clinical Administered PTSD Scale (CAPS)\textsuperscript{48} and Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID),\textsuperscript{49} structured clinical interviews, elicited this information and aided in assessing whether an individual’s description accurately reflected disease criteria.

Visual deficits

The potential to use visual function characteristics as a diagnostic tool was detailed by Goodrich et al.\textsuperscript{50} In reviewing the medical records of 100 patients with a history of TBI, noting those with and without PTSD diagnoses, high rates of oculo-motor/binocular vision deficits suggesting internal, organic damage were found in patients diagnosed with TBI, but not in patients with PTSD. Patients with PTSD were more likely to self-report general visual symptoms of light sensitivity, diplopia, and reading difficulties which were hypothesized to be associated with PTSD-associated hypersensitivity and hyperarousal.\textsuperscript{50}

Neuropsychological testing

A study reviewing 251 OIF and OEF Veterans, found a variety of distinguishable results between groups of Veterans with mTBI versus PTSD versus mTBI + PTSD versus a group of control Veterans using a battery of standard neuropsychological evaluations. It was expected that the PTSD group would perform more poorly than the mTBI and control groups; however, there were few significant deficits on any variable other than immediate verbal recall compared with controls and verbal memory compared with mTBI. The mTBI group performed worse than PTSD in flexibility of thinking and visual–motor coordination. The mTBI + PTSD performed worse than PTSD in visual scanning. The mTBI + PTSD group reported greater depression and PTSD than all other groups and greater anxiety and insomnia than controls and mTBI. The overall trend of severity for every psychiatric measure was mTBI + PTSD > PTSD > mTBI > controls.\textsuperscript{51}

Biomarkers

Biomarkers from blood samples have been used to successfully discern mTBI from PTSD from mTBI + PTSD. Apolipoprotein E genotyping and phospholipid profiles were distinctly different in these three groups of 120 active duty US soldiers studied by Emmerich et al,\textsuperscript{52} although levels varied depending on severity. Lipidome analysis is an emerging biomedical research tool which is a comprehensive and quantitative description of lipids present in an organism.\textsuperscript{53} Emmerich et al\textsuperscript{52} proposed that combining lipidome analysis with genotyping could lead to a standard blood biomarker that will distinguish between PTSD, mTBI, and comorbid cases.

Single-photon emission computerized tomography (SPECT) is a type of nuclear imaging that acquires 2-dimensional (2D) images from multiple angles and then reconstructs these into a 3-dimensional (3D) data set.\textsuperscript{54} Amen et al\textsuperscript{55} using SPECT, performed at rest and on task, separated out patients with TBI and PTSD. Post-traumatic stress disorder showed increased perfusion in the limbic structures, cingulum, basal ganglia, insula, thalamus, prefrontal cortex, and temporal lobes.
Traumatic brain injury showed hypoperfusion in the orbitofrontal cortex, temporal poles, and anterior cingulum.

Magnetoencephalogram (MEG) is a non-invasive functional imaging technique that measures magnetic signals outside the brain generated by neuronal activation in gray matter with high temporal resolution and spatial localization accuracy. Magnetoencephalogram demonstrates sensitivity to abnormal neuronal signals from axonal injuries and has been used to identify a distinct signature for mTBI more accurately than electroencephalogram (EEG) or conventional magnetic resonance imaging (MRI). Huang et al used MEG identification to propose a distinctive pattern for PTSD: hyperactivity in the amygdala/anterior hippocampus and hypoactivity of the ventromedial prefrontal cortex. They proposed a potential MEG signature for comorbid mTBI + PTSD.

Diffusion tensor magnetic resonance imaging (DTI) is another non-invasive imaging technique that is a variant of conventional MRI based on water diffusion rate within the tissues of the brain. It indirectly measures anisotropy and structural orientation allowing visualization of white matter architecture. A 2018 study used DTI metrics combined with neuropsychological testing results to successfully evince distinct abnormal signatures for mTBI, mTBI + PTSD, and controls. Given the growing evidence of TBI and PTSD as risk factors for developing Alzheimer disease, an increasing number of studies are using positron emission tomography (PET) to measure and monitor the accumulation and distribution of amyloid-beta plaque and phosphorylated tau protein that are considered hallmarks of this disease. Positron emission tomography is another type of nuclear imaging similar to SPECT. Mohamed et al re-investigated imaging obtained during a Department of Defense and Alzheimer’s Disease Neuroimaging Initiative to see if focal alterations in amyloid-beta depositions could be found in PTSD survivors. This information distinguished PTSD from TBI, TBI + PTSD, and controls. Reviewing previously obtained neuropsychological assessments, cerebrospinal fluid (CSF) samples, MRI, and amyloid PET imaging of 164 subjects, they established a rank order of amyloid tracer uptake of PTSD > TBI + PTSD > TBI > controls. The distribution of uptake demonstrated that, for PTSD versus TBI + PTSD, different pathways of amyloid-beta accumulation exist.

In a separate study that used the same database of information, Mohamed et al looked for differences in tau accumulation between the same four groups (PTSD, TBI, TBI + PTSD, controls [80 subjects]) using in vivo tau PET. Post-traumatic stress disorder and TBI + PTSD showed similar tau profiles to that seen in Alzheimer disease patients with elevated levels of tau and associated cognitive impairment. The same pattern was not present in the TBI or healthy control groups. The elevated tau and other associated patterns typically seen in Alzheimer disease were only seen in PTSD subjects.

These are but a few of the study modalities investigating ways to further define, and ultimately distinguish between, TBI and PTSD. Advancements in tools and techniques are taking place in omics-based metrics, functional imaging, and machine learning algorithms applied to data sets. The breadth and complexity of the current research in its totality goes beyond the limitations of this mini-review.

Conclusions
Distinguishing between PTSD and TBI is difficult due to (1) vague and overlapping symptoms between these entities and other mental health disorders, (2) patients’ inability to recognize TBI symptoms, (3) a reliance on self-report measures, and (4) avoidance of disclosure of trauma. Diagnostic inaccuracy in distinguishing between TBI and PTSD leads to poor patient outcomes due to treatment-interfering symptoms of the undiagnosed entity, resulting in suboptimal and potentially inaccurate treatment. When TBI is comorbid with PTSD, the literature is rich with modifications in evidence-based PTSD treatments, highlighting the importance of delineating when they co-occur. Rates of comorbidity are high as having PTSD puts one at risk for TBI and having TBI similarly increases one’s risk of developing PTSD.

Limitations of this mini-review include looking at a focused portion of the literature to briefly summarize and underscore that more research is needed in this area to increase the number of successful outcomes in treating PTSD and TBI. Further review and research should include a focus on how the severity of TBI influences outcomes and diagnostic certainty and looking at results in populations other than Veterans.

This mini-review aimed to shed light on the importance of developing more effective methods to diagnose comorbid PTSD and TBI, as having undiagnosed TBI may be a variable stratifying responders from non-responders of evidence-based treatment for PTSD. To become a mainstay for PTSD and TBI evaluations, these modalities must be translated into convenient and affordable measures that can quickly and accurately be used in diagnosis. This will assist in assuring that the most effective treatment is used and aid in developing new, more effective treatments for PTSD and TBI.

Author Contributions
Each of the authors contributed equally to this manuscript. Review of articles and background research was conducted by VR and GA.

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