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Relationship between transdiagnostic dimensions of psychopathology and traumatic brain injury (TBI): A TRACK-TBI study

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Abstract

Neuropsychiatric symptoms are common, comorbid, and often disabling for patients with traumatic brain injury (TBI). Identifying transdiagnostic symptom dimensions post-TBI may help overcome limitations of traditional psychiatric diagnoses and advance treatment development. We characterized the dimensional structure of neuropsychiatric symptoms at 2-weeks post-injury in *n*=1,732 TBI patients and *n*=238 orthopedic-injured trauma controls (OTC) from the Translating Research and Clinical Knowledge in TBI (TRACK-TBI) study. Symptoms were reported on the Brief Symptom Inventory-18, Patient Health Questionnaire-9 Depression checklist, PTSD Checklist for DSM-5, PROMIS Pain Intensity, and Insomnia Severity Index. We established a novel factor model of neuropsychiatric symptoms and evaluated how three TBI severity strata and OTC patients differed in symptom severity. The final factor model had 6 first-order factors subsumed by 2 second-order factors: Internalizing (encompassing Depression, Anxiety, and Fear) and Somatic symptoms (Sleep, Physical, Pain). Somatic symptoms fit better as a correlated factor of (vs. a lower-order factor within) Internalizing. All symptom dimensions except for Pain were more severe in one or more TBI subgroups, as compared to the OTC group. Milder brain injury was generally associated with more severe symptoms, whereas more general injury severity (higher level of care, e.g., emergency department, intensive care unit) was associated with more pain. The findings indicate a broad factor resembling the internalizing factor of general psychopathology in traumatically injured patients, alongside a distinct somatic symptom factor. Brain injury, especially milder brain injury, may exacerbate liabilities toward these symptoms. These neuropsychiatric dimensions may help advance more precision medicine research for TBI.

General Scientific Summary:

Psychiatric symptoms are extremely common after traumatic brain injury but are poorly understood. This study identifies 6 distinct dimensions of psychiatric symptoms relevant to patients with recent traumatic brain injuries and reveals unique patterns of association between the symptom dimensions and injury severity characteristics.

Keywords

neurobehavioral symptoms; psychopathology; clinical outcomes; traumatic brain injury; factor analysis; orthopedic injury; clinical phenotypes

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A majority of hospital-treated TBI patients have new or worsened neuropsychiatric symptoms—such as depression, anxiety, and somatic symptoms—that persist for months to years after their injuries (Bryant et al., 2010; Dikmen et al., 2017; Hesdorffer et al., 2009; McAllister, 2008; Nelson et al., 2017; Stein et al., 2019). As compared with other clinical sequelae of TBI (e.g., cognitive deficits) these symptoms are more enduring (Dikmen et al., 2017; Nelson et al., 2019) and more strongly implicated in functional impairments faced by the TBI population (Bryant et al., 2010; Zahniser et al., 2019). Despite their

central importance to patients with TBI, there is limited understanding of the mechanisms underlying neuropsychiatric symptomatology following brain injury and limited data to guide efforts to prevent and mitigate persisting symptoms (Lee et al., 2003).

Most research on the neurobehavioral sequelae of TBI has relied on traditional categorical mental health diagnoses—e.g., major depression, generalized anxiety, posttraumatic stress disorder (Stein et al., 2019)—or symptom severity estimates from broad screening tools such as the Rivermead Post-Concussion Symptoms Questionnaire (RPQ; King et al., 1995). Traditional psychiatric diagnostic categories, developed through expert consensus, are increasingly recognized as problematic for advancing mechanistic and treatment research due to limitations in their reliability and validity (Insel et al., 2010; Kotov et al., 2017). For example, categorical psychiatric diagnoses are phenotypically and neurobiologically complex (contributing to high rates of comorbidity) and do not account for subclinical, albeit disabling, symptoms that are common in the TBI population (McAllister, 2008). Consequently, there is increasing momentum to identify and use core, transdiagnostic dimensions of psychopathology that appear more reliable, informative, and etiologically precise. In particular, structural modeling work in community and psychiatric samples has revealed replicable dimensions of psychopathology (e.g., a higher-order internalizing spectrum, encompassing fear and distress disorders) that reflect common genetic vulnerabilities and show stronger associations with neurobiological abnormalities and functional impairments than do traditional diagnostic categories (Hyman, 2010; Nelson et al., 2015; Vaidyanathan et al., 2012). Identifying analogous dimensions underlying the diverse symptoms evident in TBI samples may provide stronger targets for translational research on the neurobiology of neuropsychiatric sequelae of TBI and also help to reveal important patterns of heterogeneity needed to conduct more targeted, successful intervention studies.

Our objective was to characterize the dimensional structure of neuropsychiatric symptoms in patients with recent traumatic injuries – including both brain-injured (TBI) patients and orthopedic trauma controls (OTC) – and examine how observed symptom dimensions relate to TBI. The study leveraged data from the prospective, multicenter Translating Research and Clinical Knowledge in TBI (TRACK-TBI) study, which enrolled patients with diverse injury severity levels within 24 hours of injury and assessed them longitudinally with self-report symptom inventories recommended by the National Institutes of Health (NIH) TBI Common Data Elements (CDE; Thurmond et al., 2010; Wilde et al., 2010). In accordance with the primary TBI CDE symptom inventories and the most prevalent types of symptoms in TBI patients (Bryant et al., 2010; Nelson et al., 2019), assessment emphasized subdomains of internalizing (i.e., major depression, anxiety, and posttraumatic stress disorder symptoms) and diverse somatic/neurobehavioral symptoms (i.e., physical, cognitive, and sleep symptoms).

Major study aims were to (a) characterize the dimensional structure of diverse neuropsychiatric symptoms collected within the CDE-compliant assessment battery at 2 weeks post-injury, and (b) compare three TBI severity subgroups and the OTC group on the identified symptom dimensions. The TBI sample was subdivided into three injury severity groups to inform understanding of the relevance of the neuropsychiatric symptom

dimensions from milder to more severe TBI subpopulations and allow us to examine group differences in symptom severity. Secondary analyses explored the relationship between highest level of acute clinical care on symptoms, to evaluate the impact of general injury severity on symptoms and ensure appropriate interpretation of injury group differences. An early (2-week) assessment point was selected because symptoms typically emerge or worsen soon after injury and because we sought to identify distinct clinical phenotypes of TBI that could inform patient selection for early intervention studies (Saatman et al., 2008). The TBI group was stratified into three subgroups differing in classic acute markers of brain injury severity. We expected that the because of the focus on internalizing and somatic symptoms, which have been most closely linked to mild TBI, the factors identified might be most severe in the more mildly brain-injured patients (Belanger et al., 2010; Gordon et al., 2000).

Method

Sample

The TRACK-TBI U01 study enrolled 2,997 trauma patients (2,698 TBI, 299 OTC) at 18 level 1 trauma centers from 2014–2019. Inclusion criteria for the TBI group were having a head trauma with altered mental status (i.e., unconsciousness, peritraumatic amnesia, or other signs of altered consciousness), having a head computed tomography (CT) scan ordered by the treating emergency department (ED) physician, and enrollment within 24 hours of injury. Inclusion criteria for the OTC group included sustaining a traumatic injury to the body with no signs of altered mental status, amnesia, or physical signs of head trauma, as well as no head CT ordered for suspicion of brain injury by the treating physician. Exclusion criteria for all participants were being pregnant, in police custody, having non-survivable trauma, non-English- and non-Spanish-speaking, and history of debilitating neurological or mental disorders. The online Supplemental Material depicts the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) diagram of the sample through the 2-week follow-up assessment included in this paper. Of the enrolled participants, n=116 withdrew and n=97 died before completing the 2-week follow-up. N=451 were ineligible to complete the measures of interest due to age < 17 years old (n=143) or being deemed too impaired to complete the assessments (n=308). In total, N = 1,970 participants (1,732 TBI, 238 OTC) had follow-up data necessary for inclusion in the current study analyses.

Analyses of TBI severity stratified the TBI group into 3 subgroups based on traditional markers of brain injury severity: the presence (+) versus absence (−) of clinical neuroimaging (computed tomography, CT) findings indicative of acute intracranial injury and the admission Glasgow Coma Scale (GCS) score (Teasdale et al., 2014). GCS scores reflect a patient's level of consciousness and responsiveness upon hospital admission and are scaled from 3 (totally unconscious and unresponsive) to 15 (conscious and responsive to basic questioning). Following conventions for defining TBI severity, while also considering the relatively small number of participants with moderate and severe TBI who completed the 2-week clinical assessment, we defined three TBI severity strata: uncomplicated mild TBI (u-mTBI; i.e., GCS 13–15 CT-; n = 1,011), complicated mild TBI (c-mTBI; i.e., GCS 13–15 CT+; n = 502), and moderate-severe TBI (i.e., GCS 3–8; n = 126).[1]

Primary Outcome (Neuropsychiatric Symptom) Measures

Primary outcomes were derived from item responses at 2 weeks post-injury to the following CDE-compliant self-report inventories of neurobehavioral symptoms: the 18-item Brief Symptom Inventory (BSI-18; 5-point scale; Derogatis, 2001), Patient Health Questionnaire-9 Depression checklist (PHQ-9; 9 items; 4-point scale; Kroenke et al., 2001), PTSD Checklist for DSM-5 (PCL-5; 20 items; 5-point scale; Weathers et al., 2013), PROMIS Pain Intensity scale (3 items; 4-point scale; Cella et al., 2007), and the Insomnia Severity Index (ISI; 7 items; 5-point scale; Bastien et al., 2001).

Statistical Analysis

Factor and measurement invariance analyses were performed in *Mplus* (version 8.3; Muthén & Muthén, 1998–2019); other analyses were performed in IBM SPSS Statistics (version 24; Armonk, NY) or R (R Core Team, 2018). Sample characteristics were compared between groups using Mann-Whitney U tests or Fisher's exact tests ($\alpha = .05$). The 57 items of the primary inventories were subjected to exploratory factor analysis (EFA) in one randomly-selected half of the combined TBI+OTC dataset, followed by confirmatory factor analysis (CFA) in the second half. Given the ordinal nature of the items, models used mean- and variance-adjusted weighted least squares (WLSMV) estimation. Because of the strong evidence that subfactors of psychopathology are correlated (Kotov et al., 2017), EFA analyses emphasized correlated-factor models (using Geomin rotation), although bifactor models (specifying a general factor along with orthogonal specific factors) were also considered. CFA models were developed from the EFA results, placing each item on 1 factor based on a combination of its loading pattern, prior findings for a given instrument, and theoretical considerations.

Model fit was considered excellent if root mean squared error of approximation (RMSEA) < .05 and comparative fit index (CFI) and Tucker Lewis index (TLI) were > .95; fit was considered acceptable if RMSEA < .08 and CFI/TLI > .90 (Hu & Bentler, 1999; MacCallum et al., 1996). Chi-square fit statistics were not considered in model selection given their oversensitivity to minor model misfit in large samples (Bentler & Bonett, 1980)., After identifying the best model, measurement invariance analyses were performed in the full sample to compare the structural parameters and latent factor means by group (Chen et al., 2005; Meredith, 1993). Following conventional methods (Meredith, 1993). invariance of lower-order factors was evaluated across increasing levels—configural, weak, strong, phi, and strict—reflecting equivalence of item-factor placement, loadings, thresholds, factor correlations, and residual variances, respectively, across groups. Invariance of the second-order model was tested using an established 7-step procedure (Chen et al., 2005). The fit of each invariance model was compared to the next model, and higher invariance was inferred when imposing its constraints resulted in ≤ .015 increase in RMSEA or ≤ .01 reduction in CFI (Chen, 2007; Cheung & Resnvold, 2002). The online Supplemental Material provides additional details about group invariance modeling.

[1]Due to missingness in acute injury characteristics, 93 participants with TBI could not be classified in terms of TBI severity. These participants were included in preliminary factor analytic modeling but not in group measurement invariance analyses.

After establishing sufficient invariance to compare group means on the symptom dimensions, general linear models were used to examine group differences in factor scores (estimated in *Mplus*) with and without covarying for group differences in demographic variables, as well as to examine the influence of brain injury severity and general injury severity (operationalized as highest level of care; i.e., emergency department, inpatient floor, intensive care unit [ICU]) on symptomology. Post-hoc pairwise comparisons are discussed as significant only when they remained significant after adjustment for multiple comparisons using the false discovery rate (FDR) control method (Benjamini, 1995), although *p*-values are reported before FDR adjustment.

Results

Participant Characteristics

Table 1 displays demographic, history, and injury characteristics by group. The 2-week assessment sample had a *M* age of 39.9 (*SD* = 16.7) years and was 67.2% male, 77% White, and 78.8% non-Hispanic. The groups were not significantly different in psychiatric or TBI history but showed significant differences in age, sex, race, and education. These variables were incorporated into relevant analyses as covariates as described below. The causes of injury differed significantly between groups (e.g., motor vehicle/traffic crashes were least common in the OTC group and most common in the u-mTBI group). Highest level of care was different between groups, with a higher percentage of c-mTBI and moderate-severe TBI participants admitted to the hospital floor or ICU but similar admission rates for the u-mTBI and OTC groups.

Model Selection

Exploratory Factor Analyses—EFA and CFA analyses were run on different random halves of the sample (*n* = 982 and 988, respectively) that did not differ significantly on any of the demographic, history, or injury variables listed in Table 1. EFAs extracted 1–12 factors with use of an oblique (Geomin) rotation. Based on 1) an increase in CFI, 2) theoretical considerations about the item loading patterns, and 3) visual inspection of scree plot eigenvalues, the 6-factor solution was judged to have the best balance of increased fit (compared to extracting fewer factors), parsimony (compared to extracting more factors), and theoretical positioning of items onto their respective factors. Item loadings for the 6-factor EFA model are available in eTable 1 of the online Supplement. The fit of the 6-factor EFA was very good, $\chi^2(1269) = 3143.40$, $p < .001$, CFI = .97, TLI = .96, RMSEA = .04. Based on the content of the items loading highly and selectively onto each factor, the six factors resembled, in order of largest to smallest eigenvalues: depressivity (14 items), sleep problems (9 items), fear (13 items), physical complaints (10 items), anxiety (7 items), and general physical pain (4 items). Of note, all factors included items from multiple parent inventories, such that they likely reflect a coherence of thematic content rather than method-related variance.

Confirmatory Factor Analyses—Next, CFA models were run based on the EFA results. The CFA analyses emphasized first-order (correlated-factor) models, for which fit statistics can be found in Table 2. First, a correlated 6-factor model was specified according to the

EFA results. Item placement and loadings of the 6-factor model are shown in the online Supplemental Material (eTable 2). The Depression scale comprised 14 questions from the BSI-18, PHQ-9, and PCL-5 pertaining to anhedonia/low positive emotions, feeling down/worthless, and suicidal ideation; the Anxiety factor comprised 7 PCL-5 items referring to avoidance of reminders of the trauma, strong negative feelings, and irritability; the Fear factor encompassed 13 items from the BSI-18 and PCL-5 pertaining to feeling afraid/fearful, tense, re-experiencing the trauma, and physiological arousal to reminders of the trauma. The Sleep factor comprised 9 items from the ISI, PHQ-9, and PCL-5 related to disruption in or dissatisfaction with sleep. The Physical factor comprised 10 items from the BSI-18, PHQ-9, and PCL-5 spanning diverse physical symptoms (e.g., dizziness, nausea, numbness/tingling, fatigue, psychomotor retardation/agitation, appetite changes) and concentration difficulties. The Pain factor comprised 4 items pertaining to chest pain (BSI-18 item) and general physical pain (PROMIS Pain Intensity scale). The correlated 6-factor model fit well, $\chi^2(1524) = 6{,}295.42$, $p < .001$, CFI = .93, TLI = .93, RMSEA = .06. Furthermore, the factor reliabilities of these factors were good (ω = .89 - .97) and the loadings of items onto their respective factors were very high overall (mean λ = .79). Factor intercorrelations ranged from modest (ψ = .38 [Pain and Anxiety]) to very high (ψ = .88 [Fear and Anxiety]).

Competing confirmatory models were also specified (see Table 2), including alternative correlated first-order factor models (1, 4, and 5 factors) and second-order models (1 second-order, 6 lower-order). An alternative 5-factor model fit similarly well but was less interpretable and appeared less valid than the 6-factor or higher-order model (i.e., the 5-factor model combined anxiety and fear symptoms together, whereas neurophysiological evidence (e.g., Davis, 1998; Grillon et al., 2006; Vaidyanathan et al., 2012) supports characterizing them separately. Because of strong inter-factor correlations, we then explored different second-order model configurations, including one in which all factors loaded onto a common factor and another in which the factors were subsumed by 2 correlated second-order factors of Internalizing (Depression, Anxiety, Fear) and Somatic (Sleep, Physical, Pain) symptoms. The latter model fit very well, $\chi^2(1532) = 6{,}563.88$, $p < .001$, CFI = .93, TLI = .92, RMSEA = .06. Loadings of first-order onto second-order factors were robust and significant, and second-order factor reliabilities very good (Internalizing ω = .93; Somatic ω = .86; (see Table 2 and Figure 1). Given the strong fit of this higher-order model and its conceptual appeal, it was selected for further analyses.

Bifactor models were also considered (see eTable 3). One bifactor model, comprising two general and six specific factors, fit better than our second-order model presented above. However, given the high fit propensity of bifactor models (Bonifay et al., 2017; Greene et al., 2019; Rodriguez et al., 2016), we also considered the relative specific factor stability through examination of the factor reliability (ω). These specific factors appeared highly unstable (mean ω = .48, range = .07 – .78), consistent with some of the challenges to interpreting superior fit of bifactor models rather than substantive theory in guidance of model selection (Bonifay et al., 2017; Greene et al., 2019; Watts et al., 2019). Furthermore, from a statistical standpoint, unmodeled complexity of bifactor models not represented in higher-order models renders model comparisons solely based on model fit ineffective for adjudicating model selection (Gignac, 2016; Murray & Johnson, 2013). Lastly, recent work on the hierarchical structure of psychopathology suggests better validity for higher-order

factors from correlated-factor models compared to general factors from bifactor models (Hyland et al., 2020). Given the coherence between the observed factor analytic results here and structural models of psychopathology reported in previous work, we selected the higher-order model (Figure 1) as the preferred latent representation of internalizing and somatic problems.

Invariance of Factor Model Across TBI Severity Strata and OTC Groups

Fit statistics for measurement invariance models appear in the online Supplemental Material (eTable 4). Invariance analyses (run on the full sample) supported conclusions of the highest level of invariance by injury group for the 6-factor first-order and the second-order model, indicating that observed item-level differences across the groups can be interpreted as reflecting group differences in the models' latent dimensions. As invariance analysis results can be sensitive to differences in group sizes (Yoon & Lai, 2018), we fit invariance models in random subsamples more closely matched in group sample size. These analyses (summarized in Supplemental eTable 5) also supported conclusions regarding the level of group invariance achieved.

Differences Between Groups in Severity of Neuropsychiatric Symptoms

Standardized factor mean differences (and 95% CIs) between each TBI subgroup and the OTC group, adjusted for age, sex, race, and education, are depicted in Figure 2. Counterpart analyses performed without adjustment for demographic covariates produced highly similar results. All pairwise comparisons are available in Table 3. As compared to the OTC group, the u-mTBI group reported significantly higher symptom severity on all factors apart from the Pain factor, with group differences largest for Physical (standardized *M* difference [M_{diff}] = 0.99) and Anxiety (M_{diff} = 0.58) dimensions. The c-mTBI group reported weaker symptom severity than the u-mTBI group, but remained above OTC group levels on 5 of the 6 factors: Internalizing, Anxiety, Fear, Somatic, and Physical. The moderate-severe TBI group also exhibited weaker symptom severity than the u-mTBI group, with symptoms elevated above the OTC group on only three dimensions: Anxiety, Somatic, and Physical.

Next, we examined how general injury severity (operationalized as highest level of care) was associated with symptomatology. First, we added Level of Care to the aforementioned general linear models, excluding the moderate-severe TBI group due to this group's limited variability in Level of Care (most were treated in an ICU). The Internalizing factor and its subfactors (Depression, Anxiety, Fear) all maintained significant main effects of Injury Group (u-mTBI, c-mTBI, OTC, ps ≤ .002), but main effects of Level of Care were nonsignificant (ps ≥ .621), as were Injury Group × Level of Care interactions (ps ≥ .346). In contrast, the Somatic factor and its subfactors (Sleep, Physical, Pain) all showed significant main effects of both Injury Group (ps < .001) and Level of Care (ps ≤ 0.032), with no 2-way interactions (ps ≥ .343). In contrast to TBI severity, where milder brain injury was associated with more severe symptoms, having a higher level of care was associated with more severe pain/physical symptoms. This finding was further supported by analyses testing for effects of Level of Care, adjusted for age, sex, race, and education, on the somatic/physical symptom dimensions within each group of u-mTBI, c-mTBI, and OTC. All three models yielded significantly more severe Pain for subjects within each group at higher

levels of care (Pain main effect p ≥ .006), whereas other symptom dimensions showed no significant effects of Level of Care within these injury groups. The main effect of Level of Care on Pain from the 3-Injury Group model (OTC, u-mTBI, and c-mTBI) is depicted in Figure 3A.

Finally, given the robust impact of Level of Care on the Pain symptomatology, we compared all four injury groups in the subset of the sample that was treated in an ICU. Factor-score means for the four Injury Groups (ICU cohort) are depicted in Figure 3B. A significant main effect of Injury Group was present, $F(3,516) = 10.34$, $p < .001$. Post-hoc pairwise comparisons indicated that the c-mTBI-ICU and moderate-severe TBI-ICU groups both reported significantly less Pain than the OTC-ICU and u-mTBI-ICU groups ($p \leq .013$). The c-mTBI-ICU and moderate-severe TBI-ICU were not significantly different from each other in Pain scores, $p = .464$, nor were the OTC-ICU and u-mTBI-ICU groups, $p = .665$.

Discussion

In the current large, prospective sample of nearly 3,000 level 1 trauma center patients, we found that the neuropsychiatric symptoms reported by individuals with recent traumatic injuries (>90% in the GCS 13–15 range) at 2 weeks post-injury can be conceptualized as reflecting 6 underlying dimensions: depression, anxiety, fear, sleep problems, physical symptoms, and pain. These dimensions coalesced around second-order Internalizing and Somatic factors. That we replicated the widely documented Internalizing dimension and closely mirrored prior findings of its sub-facets suggests that these dimensions, which have been primarily documented from structural models of categorical psychiatric diagnoses (Higa-McMillan et al., 2008; Kotov et al., 2017; Krueger, 1999; Wright et al., 2013), generalize to a traumatic injury population and appear assessable with brief, TBI-CDE-recommended self-report inventories administered during the acute/subacute post-injury period (Thurmond et al., 2010). Additionally, our findings support the existence of a Somatic spectrum that is distinct from, but highly correlated with, the Internalizing spectrum. The finding that Somatic symptoms are not merely a subfacet of Internalizing supports tentative proposals from others based on limited empirical data (Kotov et al., 2017).

Importantly, items from many of our study inventories loaded across multiple factors, consistent with the notion that the classic psychiatric diagnoses they assess (e.g., major depression, PTSD) are phenotypically heterogeneous, and highlights the distinct vantage point offered by empirically- versus rationally-derived neuropsychiatric constructs. For the BSI-18 and PCL-5, these findings also support prior factor analytic findings that these instruments are multidimensional (Armour et al., 2016; Petkus et al., 2010; Recklitis et al., 2006). Although the factors uncovered in this study should be further validated, to the degree that they reflect previously recognized subdivisions of the internalizing spectrum, researchers may be able to apply increasing knowledge about the distinct neurobiological underpinnings of those constructs to advance more precision medicine approaches to care for TBI patients. For example, fear and anxious-depressive subdivisions of internalizing show highly distinct patterns of association with baseline and stress-induced brain response variables (Nelson et al., 2015; Vaidyanathan et al., 2012), supporting their distinction and potential to serve as more informative targets for treatment research than the heterogenous

psychiatric diagnoses that conflate the phenotypic features of these dimensions. Further, there appear to be distinct neurochemical pathways that contribute particularly strongly to anhedonia, the core feature of depression (Clark & Watson, 1991; Parrott et al., 2016; Singh et al., 2016; Tellegen, 1985; Walker et al., 2013). Taken together, these emerging findings support distinguishing between depression, anxiety, and fear subfactors of internalizing. It may be valuable to investigate to what degree these factors could be used to discern distinct clinical phenotypes relevant to TBI, such as traditional major depression (i.e., anhedonia combined with negative affect) versus more pure apathy (amotivation with low negative affect; Rao & Lyketsos, 2000).

The neuropsychiatric-symptom model showed strict invariance across three TBI subgroups (differing in brain injury severity) and OTC groups, demonstrating that these groups differed quantitively but not qualitatively in the broad array of symptoms assessed. Given similar rates of pre-injury psychiatric disorders across groups and higher mean levels of most neuropsychiatric symptom dimensions in the TBI groups as compared to the OTC group, these findings may imply that head trauma exacerbates underlying vulnerabilities to aspects of internalizing and somatic symptomatology (as opposed to giving rise to categorically distinctive patterns of TBI-specific sequelae in the psychopathology domain).

Although findings supported the presence of the same neuropsychiatric symptom dimensions across TBI subgroups differing in brain injury severity, we observed important distinctions between the severity of symptoms across subgroups varying in brain injury severity and general injury severity. Interestingly, the severity of symptoms tended to be inversely associated with brain injury severity, with the most mildly brain-injured group (u-mTBI) reporting the most severe symptoms. In contrast, patients with more severe brain injuries tended to report less severe symptoms relative to other TBI subgroups, although all TBI subgroups reported more severe symptoms on some dimensions than orthopedically-injured controls (with TBI vs. OTC group differences being largest for the Physical and Anxiety factors). That Internalizing and its subfactors were unrelated to Level of Care demonstrates that the reported Injury Group differences were robust and related more to the presence and type of TBI than to general injury severity. In contrast, lower-order somatic factors, and Pain in particular, were influenced by both brain and general injury severity, but in opposing directions. Although treatment in a higher-level unit (i.e., ICU vs. inpatient floor vs. ED) was associated with greater pain symptomatology, within the same level of care (ICU) the more severely brain-injured groups (c-mTBI, moderate-severe TBI reported less pain than other groups (OTC, u-mTBI). The distinct effect of Level of Care on Internalizing versus Somatic symptom dimensions supports the separation of these dimensions and the potential utility of this factor model to discern distinct neuropsychiatric phenotypes of TBI.

Although the finding that patients with milder brain injuries tended to reported more symptoms than those with more severe injuries is counterintuitive at first glance, this result has been reported by others and may be explained in different ways (Belanger et al., 2010; Gordon et al., 2000). One possibility is that patients with more severe brain injuries may experience less emotional distress because of cognitive impairment, which may limit self-awareness and has been associated with the apathy syndrome experienced by a subset of the severe TBI population (Bivona et al., 2019; McAllister, 2008). Alternatively,

it is conceivable that the more intensive supportive care and rehabilitation offered to many patients with recent, more severe TBIs diminishes emotional distress. Yet another possibility is that physical discomfort could be diminished by the use of stronger medications to manage pain in individuals with more severe brain injury. However, the finding of greater reported pain in individuals with more severe general injury severity (i.e., injuries resulting in ICU stays) does not support this hypothesis. Considering patients with milder TBIs on the other hand, especially those treated and released from emergency departments, the lack of clinical follow-up for their injuries (Seabury et al., 2018) could theoretically amplify reports of emotional distress. Finally, there is evidence that having acute injury characteristics suggestive of milder brain injury (including better memory of the traumatic injury event) increases risk for posttraumatic stress symptoms (Bryant et al., 2009; Jamora et al., 2012), which would be expected to enhance reporting of distress (Belanger et al., 2010).

The presence of a familiar internalizing psychopathology dimension in the TBI population provides encouragement that existing treatments for this spectrum of disorders may prove be effective for TBI patients with such problems. Thus, in the absence of specific evidence contraindicating traditional psychiatric treatments in TBI populations, clinicians should consider routine screening and intervention for TBI patients with these symptoms (Lee et al., 2003). However, given the limited evidence-base for many treatments in TBI patients specifically, and the unique features of this population, there remains a serious need to improve the evidence-base for these treatments in TBI through larger, randomized controlled trials (Lee et al., 2003).

Limitations

Limitations of the current study include its focus on level 1 trauma center patients, which precludes generalization of findings to other traumatic injury populations such as those who pursue lower levels of (or no) clinical care. Additionally, the sample predominantly comprised patients with relatively mild injury characteristics (i.e., GCS 13–15), along with a subset of more severely injured patients who were sufficiently recovered to complete self-report assessments at two weeks post-injury. Given this, it is unclear to what degree the findings might generalize to all severities of TBI, or to the later subacute and chronic recovery periods. The study also did not thoroughly assess for externalizing or thought disorders, relevant to some (particularly more severely injured) TBI patients (Hesdorffer et al., 2009; McAllister, 2008). On the other hand, the injury characteristics of the sample (i.e., > 90% “mild” TBI) is representative of the level 1 trauma center population, groups were reasonably matched on key demographic variables (with any differences accounted for in analyses), and participants completed a relatively comprehensive assessment of internalizing and somatic symptoms, including broader representation of somatic/neurobehavioral symptoms than much of the prior work on the structure of psychopathology. Finally, it is premature to definitively conclude that the neuropsychiatric dimensions uncovered in this study fully align with those previously established in the general community.

Conclusions

In this large prospective sample of level 1 trauma center patients with recent traumatic injuries, neuropsychiatric symptoms coalesced around 6 lower-order dimensions

(depression, anxiety, fear, sleep, physical symptoms, and pain) subsumed by 2 correlated second-order factors of internalizing and somatic symptoms. These findings address calls to move away from traditional categorical mental health diagnoses toward dimensional, empirically-derived neuropsychiatric constructs with greater phenotypic and etiologic specificity (Insel et al., 2010; Kotov et al., 2017; Moore et al., 2006). They closely mirror findings from previous research on the structure of internalizing disorders in general clinic and community samples based on other assessment approaches and extends prior work by providing insight into the placement of somatic symptoms within the construct network of psychopathology.

Current findings also indicate that neuropsychiatric problems in TBI patients vary in meaningful ways by brain injury severity and, in the case of somatic symptoms such as general pain, with overall injury severity (level of care). Findings of distinct relationships between the symptom dimensions and these variables support the potential utility of the proposed model, although further research is needed to determine contexts in which it is more informative to focus on the model's lower-level dimensions (e.g., depression, anxiety, fear) versus its higher-order dimensions (e.g., internalizing). These transdiagnostic symptom dimensions may help explain contradictory findings about the relationship between TBI and traditional mental health disorders (Moore et al., 2006) and may be better suited to advance more precision medicine translational and treatment research for the many TBI patients with problematic neuropsychiatric symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Armour C, Mullerova J, & Elhai JD (2016). A systematic literature review of PTSD's latent structure in the Diagnostic and Statistical Manual of Mental Disorders: DSM-IV to DSM-5. Clinical Psychology Review, 44, 60–74. 10.1016/j.cpr.2015.12.003 [PubMed: 26761151]

Bastien CH, Vallieres A, & Morin CM (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med, 2(4), 297–307. http://www.ncbi.nlm.nih.gov/pubmed/11438246 [PubMed: 11438246]

Belanger HG, Kretzmer T, Vanderploeg RD, & French LM (2010). Symptom complaints following combat-related traumatic brain injury: Relationship to traumatic brain injury severity and posttraumatic stress disorder. Journal of the International Neuropsychological Society, 16(1), 194–199. 10.1017/S1355617709990841 [PubMed: 19758488]

Benjamini Y, Hochberg Y (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. Journal of the Royal Statistical Society. Series B (Methodological), 57(1), 289–300.

Bentler PM, & Bonett DG (1980). Significance tests and goodness of fit in the analysis of covariance structures. Psychological Bulletin, 88, 588–606.

Bivona U, Costa A, Contrada M, Silvestro D, Azicnuda E, Aloisi M, Catania G, Ciurli P, Guariglia C, Caltagirone C, Formisano R, & Prigatano GP (2019). Depression, apathy and impaired self-awareness following severe traumatic brain injury: A preliminary investigation. Brain Injury, 33(9), 1245–1256. 10.1080/02699052.2019.1641225 [PubMed: 31304792]

Bonifay W, Lane SP, & Reise SP (2017). Three concerns with applying a bifactor model as a structure of psychopathology. Clinical Psychological Science, 5(1), 184–186. 10.1177/2167702616657069

Bryant RA, Creamer M, O'Donnell M, Silove D, Clark CR, & McFarlane AC (2009). Post-traumatic amnesia and the nature of post-traumatic stress disorder after mild traumatic brain injury. Journal of the International Neuropsychological Society, 15(6), 862–867. 10.1017/S1355617709990671 [PubMed: 19703323]

Bryant RA, O'Donnell ML, Creamer M, McFarlane AC, Clark CR, & Silove D (2010). The psychiatric sequelae of traumatic injury. American Journal of Psychiatry, 167(3), 312–320. 10.1176/appi.ajp.2009.09050617

Cella D, Yount S, Rothrock N, Gershon R, Cook K, Reeve B, Ader D, Fries JF, Bruce B, Rose M, & Group PC (2007). The Patient-Reported Outcomes Measurement Information System (PROMIS): Progress of an NIH Roadmap cooperative group during its first two years. Medical Care, 45(5 Suppl 1), S3–S11. 10.1097/01.mlr.0000258615.42478.55

Chen FF (2007). Sensitivity of goodness of fit indexes to lack of measurement invariance. Structural Equation Modeling, 9, 233–255.

Chen FF, Sousa KH, & West SG (2005). Testing measurement invariance of second-order factor models. Structural Equation Modeling, 12, 471–492.

Cheung GW, & Resnvold RB (2002). Evaluating goodness-of-fit indexes for testing measurement invariance. Structural Equation Modeling, 9(2), 233–255.

Clark LA, & Watson D (1991). Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. Journal of Abnormal Psychology, 100(3), 316–336. http://www.ncbi.nlm.nih.gov/pubmed/1918611 [PubMed: 1918611]

Davis M (1998). Are different parts of the extended amygdala involved in fear versus anxiety? Biological Psychiatry, 44(12), 1239–1247. 10.1016/s0006-3223(98)00288-1 [PubMed: 9861467]

Derogatis LR (2001). Brief Symptom Inventory 18 (BSI-18): administration, scoring, and procedures manual. Pearson.

Dikmen S, Machamer J, & Temkin N (2017). Mild traumatic brain injury: Longitudinal study of cognition, functional status, and post-traumatic symptoms. Journal of Neurotrauma, 34(8), 1524–1530. 10.1089/neu.2016.4618 [PubMed: 27785968]

Gignac GE (2016). The higher-order model imposes a proportionality constraint: That is why the bifactor model tends to fit better. Intelligence, 55, 57–68. 10.1016/j.intell.2016.01.006

Gordon WA, Haddad L, Brown M, Hibbard MR, & Sliwinski M (2000). The sensitivity and specificity of self-reported symptoms in individuals with traumatic brain injury. Brain Injury, 14(1), 21–33. 10.1080/026990500120907 [PubMed: 10670659]

Greene AL, Eaton NR, Li KQ, Forbes MK, Krueger RF, Markon KE, Waldman ID, Cicero DC, Conway CC, Docherty AR, Fried EI, Ivanova MY, Jonas KG, Latzman RD, Patrick CJ, Reininghaus U, Tackett JL, Wright AGC, & Kotov R (2019). Are fit indices used to test psychopathology structure biased? A simulation study. Journal of Abnormal Psychology, 128(7), 740–764. 10.1037/abn0000434 [PubMed: 31318246]

Grillon C, Baas JM, Pine DS, Lissek S, Lawley M, Ellis V, & Levine J (2006). The benzodiazepine alprazolam dissociates contextual fear from cued fear in humans as assessed by fear-potentiated startle. Biological Psychiatry, 60(7), 760–766. 10.1016/j.biopsych.2005.11.027 [PubMed: 16631127]

Hesdorffer DC, Rauch SL, & Tamminga CA (2009). Long-term psychiatric outcomes following traumatic brain injury: A review of the literature. Journal of Head Trauma Rehabilitation, 24(6), 452–459. 10.1097/HTR.0b013e3181c133fd

Higa-McMillan CK, Smith RL, Chorpita BF, & Hayashi K (2008). Common and unique factors associated with DSM-IV-TR internalizing disorders in children. Journal of Abnormal Child Psychology, 36(8), 1279–1288. 10.1007/s10802-008-9250-8 [PubMed: 18607718]

Hu L, & Bentler PM (1999). Cutoff criteria for fit indices in covariance structure analysis: Conventional crtieria versus new alternatives. Structural Equation Modeling, 6, 1–55.

Hyland P, Murphy J, Shevlin M, Bentall RP, Karatzias T, Ho GWK, Boduszek D, & McElroy E (2020). On top or underneath: where does the general factor of psychopathology fit within a dimensional model of psychopathology? Psychological Medicine, 1–11. 10.1017/S003329172000104X

Hyman SE (2010). The diagnosis of mental disorders: The problem of reification. Annual Review of Clinical Psychology, 6, 155–179. 10.1146/annurev.clinpsy.3.022806.091532

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, & Wang P (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. American Journal of Psychiatry, 167(7), 748–751. 10.1176/appi.ajp.2010.09091379

Jamora CW, Young A, & Ruff RM (2012). Comparison of subjective cognitive complaints with neuropsychological tests in individuals with mild vs more severe traumatic brain injuries. Brain Injury, 26(1), 36–47. 10.3109/02699052.2011.635352 [PubMed: 22149443]

King N, Crawford S, Wenden F, Moss N, & Wade D (1995). The Rivermead Post Concussion Symptoms Questionnaire: A measure of symptoms commonly experienced after head injury and its reliability. Journal of Neurology, 242, 587–592. [PubMed: 8551320]

Kotov R, Krueger RF, Watson D, Achenbach TM, Althoff RR, Bagby RM, Brown TA, Carpenter WT, Caspi A, Clark LA, Eaton NR, Forbes MK, Forbush KT, Goldberg D, Hasin D, Hyman SE, Ivanova MY, Lynam DR, Markon K, Miller JD, Moffitt TE, Morey LC, Mullins-Sweatt SN, Ormel J, Patrick CJ, Regier DA, Rescorla L, Ruggero CJ, Samuel DB, Sellbom M, Simms LJ, Skodol AE, Slade T, South SC, Tackett JL, Waldman ID, Waszczuk MA, Widiger TA, Wright AGC, & Zimmerman M (2017). The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. Journal of Abnormal Psychology, 126(4), 454–477. 10.1037/abn0000258 [PubMed: 28333488]

Kroenke K, Spitzer RL, & Williams JB (2001). The PHQ-9: Validity of a brief depression severity measure. Journal of General Internal Medicine, 16(9), 606–613. http://www.ncbi.nlm.nih.gov/pubmed/11556941 [PubMed: 11556941]

Krueger RF (1999). The structure of common mental disorders. Archives of General Psychiatry, 56(10), 921–926. http://www.ncbi.nlm.nih.gov/pubmed/10530634 [PubMed: 10530634]

Lee HB, Lyketsos CG, & Rao V (2003). Pharmacologic management of the psychiatric aspects of traumatic brain injury. International Review of Psychiatry, 15, 359–370. [PubMed: 15276957]

MacCallum RC, Browne MW, & Sugawara HM (1996). Power analysis and determination of sample size for covariance structure modeling. Psychological Methods, 1, 130–149.

McAllister TW (2008). Neurobehavioral sequelae of traumatic brain injury: Evaluation and management. World Psychiatry, 7(1), 3–10. 10.1002/j.2051-5545.2008.tb00139.x [PubMed: 18458777]

Meredith W (1993). Measurement invariance, factor analysis and factorial invariance. Psychometrika, 58, 525–543.

Moore EL, Terryberry-Spohr L, & Hope DA (2006). Mild traumatic brain injury and anxiety sequelae: A review of the literature. Brain Injury, 20(2), 117–132. 10.1080/02699050500443558 [PubMed: 16421060]

Murray AL, & Johnson W (2013). The limitations of model fit in comparing the bi-factor versus higher-order models of human cognitive ability structure. Intelligence, 41(5), 407–422. 10.1016/j.intell.2013.06.004

Nelson BD, Perlman G, Hajcak G, Klein DN, & Kotov R (2015). Familial risk for distress and fear disorders and emotional reactivity in adolescence: An event-related potential investigation. Psychological Medicine, 45(12), 2545–2556. 10.1017/S0033291715000471 [PubMed: 25851615]

Nelson LD, Ranson J, Ferguson AR, Giacino J, Okonkwo DO, Valadka AB, Manley GT, McCrea MA, & the TRACK-TBI Investigators. (2017). Validating multidimensional outcome assessment

using the TBI Common Data Elements: An analysis of the TRACK-TBI Pilot sample. Journal of Neurotrauma, 34, 3158–3172. 10.1089/neu.2017.5139

Nelson LD, Temkin NR, Dikmen S, Barber J, Giacino JT, Yuh E, Levin HS, McCrea MA, Stein MB, Mukherjee P, Okonkwo DO, Diaz-Arrastia R, Manley GT, & the TRACK-TBI Investigators. (2019). Recovery After mild traumatic brain injury in patients presenting to US level I trauma centers: A Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study. JAMA Neurol, 76, 1049–1059. 10.1001/jamaneurol.2019.1313 [PubMed: 31157856]

Parrott JM, Redus L, Santana-Coelho D, Morales J, Gao X, & O'Connor JC (2016). Neurotoxic kynurenine metabolism is increased in the dorsal hippocampus and drives distinct depressive behaviors during inflammation. Translational Psychiatry, 6(10), e918. 10.1038/tp.2016.200 [PubMed: 27754481]

Petkus AJ, Gum AM, Small B, Malcarne VL, Stein MB, & Wetherell JL (2010). Evaluation of the factor structure and psychometric properties of the Brief Symptom Inventory-18 with homebound older adults. International Journal of Geriatric Psychiatry, 25(6), 578–587. 10.1002/gps.2377 [PubMed: 20013879]

R Core Team. (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Rao V, & Lyketsos C (2000). Neuropsychiatric sequelae of traumatic brain injury. Psychosomatics, 41(2), 95–103. 10.1176/appi.psy.41.2.95 [PubMed: 10749946]

Recklitis CJ, Parsons SK, Shih MC, Mertens A, Robison LL, & Zeltzer L (2006). Factor structure of the brief symptom inventory--18 in adult survivors of childhood cancer: Results from the childhood cancer survivor study. Psychological Assessment, 18(1), 22–32. 10.1037/1040-3590.18.1.22 [PubMed: 16594809]

Rodriguez A, Reise SP, & Haviland MG (2016). Evaluating bifactor models: Calculating and interpreting statistical indices. Psychological Methods, 21(2), 137–150. 10.1037/met0000045 [PubMed: 26523435]

Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT, Workshop Scientific T, & Advisory Panel M (2008). Classification of traumatic brain injury for targeted therapies. Journal of Neurotrauma, 25(7), 719–738. 10.1089/neu.2008.0586 [PubMed: 18627252]

Seabury SA, Gaudette E, Goldman DP, Markowitz AJ, Brooks J, McCrea MA, Okonkwo DO, Manley GT, & the TRACK-TBI Investigators. (2018). Assessment and follow-up care after emergency department presentation for mild traumatic brain injury and concussion: Results from the TRACK-TBI study. JAMA Network Open, 1(e180210), 1–13. 10.1001/jamanetworkopen.2018.0210

Singh R, Savitz J, Teague TK, Polanski DW, Mayer AR, Bellgowan PS, & Meier TB (2016). Mood symptoms correlate with kynurenine pathway metabolites following sports-related concussion. Journal of Neurology, Neurosurgery and Psychiatry, 87(6), 670–675. 10.1136/jnnp-2015-311369

Stein MB, Jain S, Giacino JT, Levin H, Dikmen S, Nelson LD, Vassar MJ, Okonkwo DO, Diaz-Arrastia R, Robertson CS, Mukherjee P, McCrea M, Mac Donald CL, Yue JK, Yuh E, Sun X, Campbell-Sills L, Temkin N, Manley GT, & the TRACK-TBI Investigators. (2019). Risk of posttraumatic stress disorder and major depression in civilian patients after mild traumatic brain injury: A TRACK-TBI study. JAMA Psychiatry, 76(3), 249–258. 10.1001/jamapsychiatry.2018.4288 [PubMed: 30698636]

Teasdale G, Maas A, Lecky F, Manley G, Stocchetti N, & Murray G (2014). The Glasgow Coma Scale at 40 years: Standing the test of time. Lancet Neurology, 13(8), 844–854. 10.1016/S1474-4422(14)70120-6 [PubMed: 25030516]

Tellegen A (1985). Structures of mood and personality and their relevance to assessing anxiety, with an emphasis on self-report. In Maser AHTJD (Ed.), Anxiety and the anxiety disorders (pp. 681–706). Erlbaum.

Thurmond VA, Hicks R, Gleason T, Miller AC, Szuflita N, Orman J, & Schwab K (2010). Advancing integrated research in psychological health and traumatic brain injury: Common data elements. Archives of Physical Medicine and Rehabilitation, 91(11), 1633–1636. 10.1016/j.apmr.2010.06.034 [PubMed: 21044705]

Vaidyanathan U, Nelson LD, & Patrick CJ (2012). Clarifying domains of internalizing psychopathology using neurophysiology. Psychological Medicine, 42(3), 447–459. 10.1017/S0033291711001528 [PubMed: 21854683]

Walker AK, Budac DP, Bisulco S, Lee AW, Smith RA, Beenders B, Kelley KW, & Dantzer R (2013). NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. Neuropsychopharmacology, 38(9), 1609–1616. 10.1038/npp.2013.71 [PubMed: 23511700]

Watts AL, Poore HE, & Waldman ID (2019). Riskier tests of the validity of the bifactor model of psychopathology. Clinical Psychological Science, 7(6), 1285–1303. doi: 10.1177/2167702619855035

Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, & Schnurr PP (2013). The PTSD Checklist for DSM-5 (PCL-5). www.ptsd.va.gov

Wilde EA, Whiteneck GG, Bogner J, Bushnik T, Cifu DX, Dikmen S, French L, Giacino JT, Hart T, Tulsky DS, Vanderploeg RD, & von Steinbuechel N (2010). Recmmendations for the use of common outcome measures in traumatic brain injury research. Archives of Physical Medicine and Rehabilitation, 1650–1660.e1616. [PubMed: 21044708]

Wright AG, Krueger RF, Hobbs MJ, Markon KE, Eaton NR, & Slade T (2013). The structure of psychopathology: Toward an expanded quantitative empirical model. Journal of Abnormal Psychology, 122(1), 281–294. 10.1037/a0030133 [PubMed: 23067258]

Yoon M, & Lai MHC (2018). Testing factorial invariance with unbalanced samples. Structural Equation Modeling, 25(2), 201–213.

Zahniser E, Temkin NR, Machamer J, Barber J, Manley GT, Markowitz AJ, Dikmen SS, & the TRACK-TBI Investigators. (2019). The Functional Status Examination in mild traumatic brain injury: A TRACK-TBI sub-study. Archives of Clinical Neuropsychology, 34, 1165–1174. 10.1093/arclin/acy103 [PubMed: 30608522]

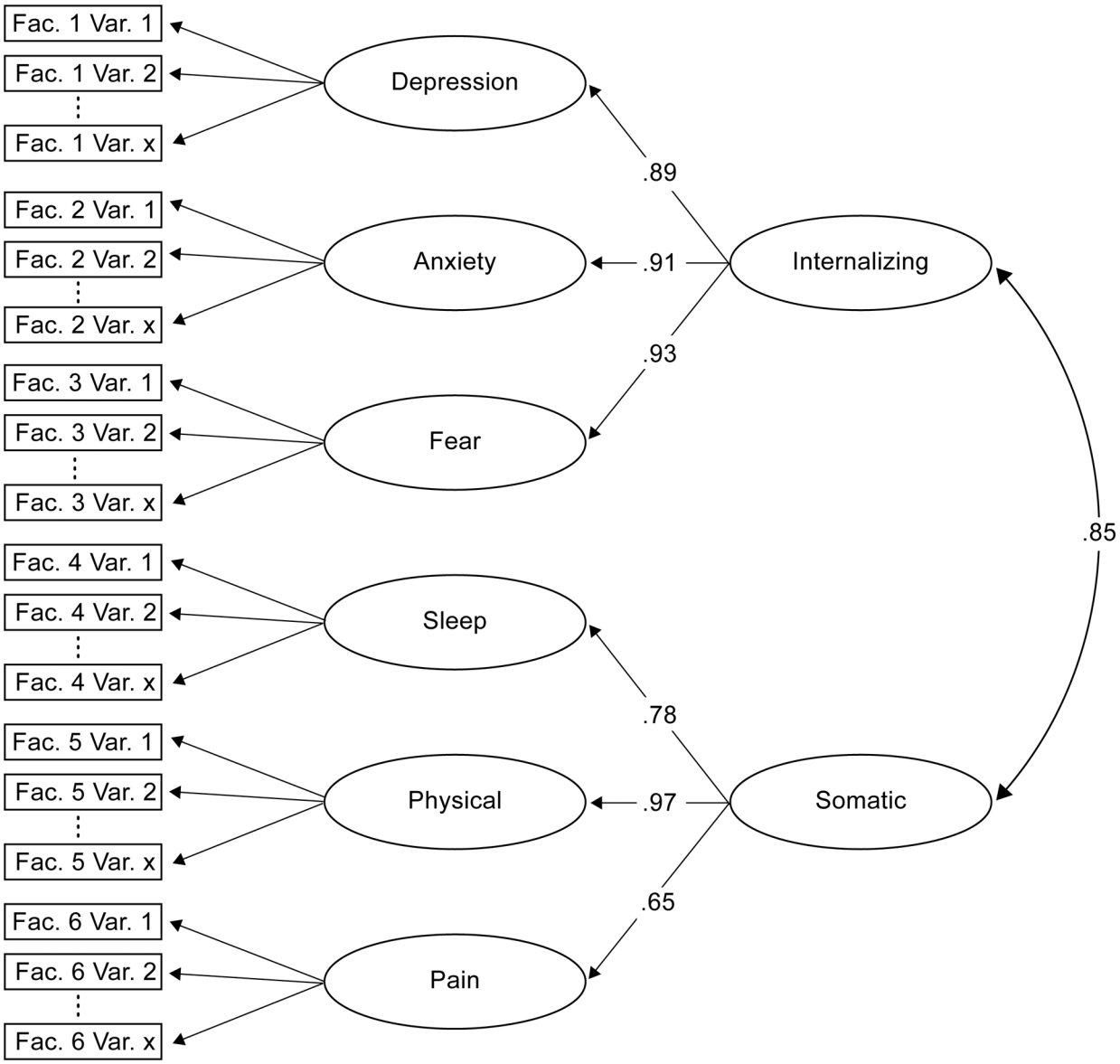

Figure 1. Higher-Order Model of Psychiatric Symptoms at 2 Weeks Post-Traumatic Brain Injury and Orthopedic Injury

Note. List of items and item loadings are in the online Supplemental Material

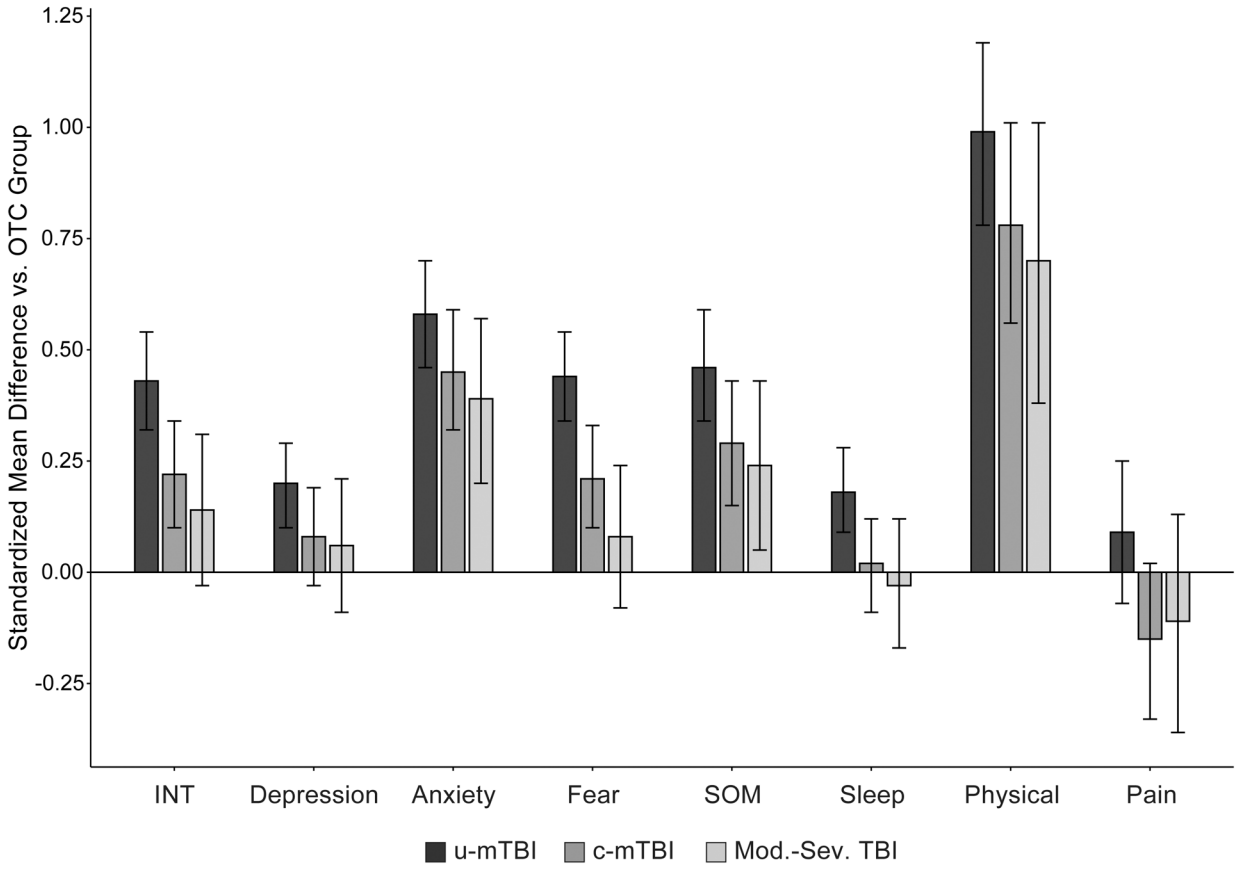

Figure 2. Standardized Mean Difference Between Traumatic Brain Injury Subgroups and Orthopedic Trauma Controls in Neuropsychiatric Symptom Factors.

Note. Bars represent the factor mean difference (M_{diff} ± 95% CI) between the traumatic brain injury (TBI) subgroup—denoted u-mTBI (uncomplicated mild TBI), c-mTBI (complicated mTBI), and Mod.-Sev. (moderate-severe TBI)—and the orthopedic trauma control (OTC) group, adjusting for age, sex, race, and education. With the exception of the Pain factor, the u-mTBI group reported significantly greater severity than the OTC group on all other symptom dimensions, M_{diff} range 0.18 (Sleep) – 0.99 (Physical). The c-mTBI group reported significantly higher Internalizing (M_{diff} = 0.22), Anxiety (M_{diff} = 0.45), Fear (M_{diff} = 0.21), Somatic (M_{diff} = 0.29), and Physical symptoms (M_{diff} = 0.78, p < .001) than the OTC group. The moderate-severe TBI group reported significantly higher Anxiety (M_{diff} = 0.39), Somatic (M_{diff} = 0.24), and Physical symptoms (M_{diff} = 0.70) than the OTC group.

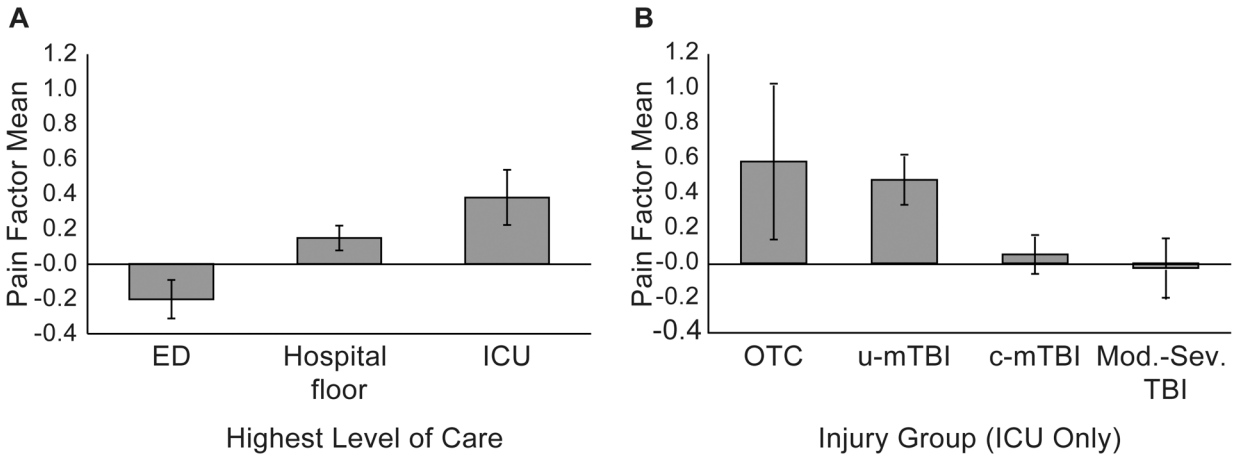

Figure 3. Pain Factor Means (95% CIs) Stratified by Overall Injury Severity (A; Level of Care) and Brain Injury Severity (B; within the ICU Level of Care).

Note. Figure 3A: Level of Care, evaluated on the Injury Groups with sufficient variance on this factor (orthopedic trauma controls [OTC], uncomplicated mild traumatic brain injury [u-mTBI, complicated mild traumatic brain injury [c-mTBI]), demonstrated a significant main effect, $F(2, 1714) = 21.14$, $p < .001$. Post-hoc comparisons indicated more pain in ICU- than hospital floor- than Emergency Department-treated patients. Figure 3B: Within the ICU Level of Care, Injury Group showed a significant main effect, $F(3,516) = 10.34$, $p < .001$, due to significantly more Pain in the OTC-ICU and u-mTBI-ICU participants as compared to the c-mTBI-ICU and Moderate-Severe TBI-ICU participants.

Table 1

Sample Demographics and Injury Characteristics (N = 1,877)

	u-mTBI (*n* = 1,011) No. (%) or M (SD)	c-mTBI (*n* = 502) No. (%) or M (SD)	Mod-Sev TBI (*n* = 126)[3] No. (%) or M (SD)	OTC (*n* = 238) No. (%) or M (SD)	*p*-value[2]
Demographics					
Age, y	37.5 (15.6)	45.7 (18.3)	33.0 (13.5)	39.8 (15.0)	<.001
Sex (male)	642 (63.5%)	356 (70.9%)	100 (79.4%)	154 (64.7%)	<.001
Race					<.001
White	742 (73.4%)	426 (84.9%)	95 (75.4%)	183 (76.9%)	
Black	203 (20.1%)	44 (8.8%)	22 (17.5%)	38 (16.0%)	
Other/unknown	66 (6.5%)	32 (6.4%)	9 (7.1%)	17 (7.1%)	
Hispanic ethnicity	201 (19.9%)	109 (21.7%)	23 (18.3%)	55 (23.1%)	.623
Education, y	13.5 (2.7)	13.8 (3.2)	13.0 (2.5)	13.9 (2.9)	.001
Psychiatric history[1]	243 (24.1%)	94 (18.7%)	27 (21.4%)	59 (24.8%)	.096
TBI history	139 (16.2%)	52 (11.8%)	13 (12.3%)	23 (10.8%)	.065
Injury characteristics					
Cause of injury					<.001
Motor vehicle/traffic crash	669 (66.2%)	222 (44.2%)	72 (57.1%)	87 (36.6%)	
Fall	203 (20.1%)	180 (35.9%)	30 (23.8%)	82 (34.5%)	
Assault/violence	47 (4.6%)	51 (10.2%)	12 (9.5%)	2 (0.8%)	
Other/unknown	92 (9.1%)	49 (9.8%)	12 (9.5%)	67 (28.2%)	
Highest level of care					<.001
Emergency department	390 (38.6%)	44 (4.8%)	4 (3.2%)	93 (39.1%)	
Inpatient floor	471 (46.6%)	199 (39.6%)	9 (7.1%)	129 (54.2%)	
Intensive care unit	150 (14.8%)	259 (51.6%)	113 (89.7%)	16 (6.7%)	
Loss of consciousness[2]	846 (83.7%)	405 (80.7%)	112 (88.9%)	0 (0.0%)	<.001
Post-traumatic amnesia[2]	710 (70.2%)	396 (78.9%)	97 (77.0%)	0 (0.0%)	<.001

Note. CT, computed tomography; GCS, admission Glasgow Coma Scale score; MCC, motorcycle crash; mTBI, mild traumatic brain injury; MVC, motor vehicle crash; OTC, orthopedic trauma control; TBI, traumatic brain injury

[1] Psychiatric history reflected any self-reported pre-injury history of treatment for a psychiatric condition.

[2] Yes and Suspected categories collapsed

[3] *n* = 50 TBI patients had GCS 9–12; *n* = 76 had GCS 3–8

Table 2

Fit Statistics for Confirmatory Factor Models of 2-Week Self-Report Outcomes

Model	χ^2	df	RMSEA	RMSEA 90% CI	CFI	TLI
First-order factors						
1-factor	14,743.97	1539	.09	.09 – .10	.80	.80
4-factor	7,677.23	1533	.06	.06 – .07	.91	.90
5-factor	6,489.94	1529	.06	.06 – .06	.93	.92
6-factor	6,295.42	1524	.06	.06 – .06	.93	.93
Second-order models						
7-factor (1SO, 6FO)	7,348.66	1533	.06	.06 – .06	.91	.91
8-factor (2SO, 6FO)	6,563.88	1532	.06	.06 – .06	.93	.92

Note: CFA models were run on a second independent half of the dataset from those used in exploratory factor models. χ^2 = chi-square statistic; *df* = degrees of freedom; CFI = comparative fit index; FO = first-order factor; RMSEA = root mean square error of approximation statistic; SO = second-order factor; TLI = Tucker-Lewis index

Table 3

Standardized Mean Differences (and 95% Confidence Intervals) Between Groups in Neuropsychiatric Dimensions

	u-mTBI vs. OTC	c-mTBI vs. OTC	Mod-Sev TBI vs. OTC	u-mTBI vs. c-mTBI	u-mTBI vs. Mod-Sev TBI	c-mTBI vs. Mod-Sev TBI
INTERNALIZING	**0.43 (0.32, 0.54)**	**0.22 (0.10, 0.34)**	0.14 (−0.03, 0.31)	**0.21 (0.12, 0.30)**	**0.29 (0.14, 0.44)**	0.08 (−0.08, 0.24)
Depression	**0.20 (0.10, 0.29)**	0.08 (−0.03, 0.19)	0.06 (−0.09, 0.21)	**0.12 (0.04, 0.20)**	0.19 (0.03, 0.35)	0.07 (−0.10, 0.24)
Anxiety	**0.58 (0.46, 0.70)**	**0.45 (0.32, 0.59)**	**0.39 (0.20, 0.57)**	**0.12 (0.03, 0.22)**	**0.12 (0.03, 0.22)**	−0.07 (−0.24, 0.10)
Fear	**0.44 (0.34, 0.54)**	**0.21 (0.10, 0.33)**	0.08 (−0.08, 0.24)	**0.23 (0.15, 0.31)**	**0.36 (0.22, 0.50)**	0.13 (−0.02, 0.28)
SOMATIC	**0.46 (0.34, 0.59)**	**0.29 (0.15, 0.43)**	**0.24 (0.05, 0.43)**	**0.17 (0.08, 0.27)**	**0.22 (0.06, 0.39)**	0.05 (−0.13, 0.23)
Sleep	**0.18 (0.09, 0.28)**	0.02 (−0.09, 0.12)	−0.03 (−0.17, 0.12)	**0.16 (0.09, 0.24)**	**0.21 (0.08, 0.33)**	0.04 (−0.09, 0.18)
Physical	**0.99 (0.78, 1.19)**	**0.78 (0.56, 1.01)**	**0.70 (0.38, 1.01)**	**0.20 (0.04, 0.36)**	**0.29 (0.02, 0.56)**	0.09 (−0.20, 0.38)
Pain	0.09 (−0.07, 0.25)	−0.15 (−0.33, 0.02)	−0.11 (−0.36, 0.13)	**0.24 (0.12, 0.37)**	0.21 (−0.01, 0.42)	−0.04 (−0.26, 0.19)

Note. Factor scores estimated from the 6 first-order, 2 second-order correlated-factor model of 2-week neuropsychiatric symptoms. Group comparisons adjusted for age, sex, race, and education. Effect sizes (and 95% CIs) bolded where significant after FDR correction within each dependent variable. Abbreviations: u-mTBI, uncomplicated mild traumatic brain injury ([TBI]; i.e., Glasgow Coma Scale [GCS] score 13–15, negative for objective evidence of structural brain injury on clinical neuroimaging); c-mTBI, complicated mild traumatic brain injury (i.e., Glasgow Coma Scale [GCS] score 13–15, positive objective evidence of structural brain injury on clinical neuroimaging); Mod-Sev TBI, moderate-to-severe TBI; OTC, orthopedic trauma control.