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CLINICAL RESEARCH ARTICLE

Preliminary study examining the mediational link between mild traumatic brain injury, acute stress, and post-traumatic stress symptoms following trauma

Chia-Hao Shih[a,*], Palguna R. Thalla[a,*], Jon D. Elhai[a,b], Jeremy Mathews[a], Kristopher R. Brickman[c], Roberta E. Redfern [d], Hong Xie[e] and Xin Wang[a,e]

[a]Department of Psychiatry, University of Toledo, Toledo, OH, USA; [b]Department of Psychology, University of Toledo, Toledo, OH, USA; [c]Department of Emergency Medicine, University of Toledo, Toledo, OH, USA; [d]Research Department, ProMedica Toledo Hospital, Toledo, OH, USA; [e]Department of Neurosciences, University of Toledo, Toledo, OH, USA

ABSTRACT

Background: The presence of mild traumatic brain injury (mTBI) increases post-traumatic stress disorder (PTSD) symptoms in the months following injury. However, factors that link mTBI and PTSD development are still unclear. Acute stress responses after trauma have been associated with PTSD development. mTBI may impair cognitive functions and increase anxiety immediately after trauma.

Objective: This research aimed to test the possibility that mTBI increases acute stress symptoms rapidly, which in turn results in PTSD development in the subsequent months.

Method: Fifty-nine patients were recruited from the emergency rooms of local hospitals. Post-mTBI, acute stress, and PTSD symptom severity were measured using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ), Acute Stress Disorder Scale (ASDS), and PTSD Checklist for DSM-5 (PCL-5), respectively.

Results: Moderated mediation analysis indicated that ASDS, at 2 weeks post-trauma, mediated the relationship between RPQ scores at 2 weeks and PCL-5 scores at 3 months post-trauma, only for patients who met mTBI diagnostic criteria.

Conclusions: These findings present preliminary evidence suggesting that acute stress disorder symptoms may be one of the mechanisms involved in the development of PTSD among trauma survivors who have experienced mTBI, which provides a theoretical basis for early intervention of PTSD prevention after mTBI.

Estudio preliminar que examina la relación de mediación entre las lesiones traumáticas cerebrales leves, el estrés agudo y los síntomas post-traumáticos, luego de un trauma.

Antecedentes: La presencia de lesiones cerebrales traumáticas leves (mTBI, por su sigla en inglés) aumenta los síntomas del trastorno de estrés postraumático (TEPT) en los meses posteriores al daño. Sin embargo, los factores que relacionan mTBI y el desarrollo del TEPT no están claros aún. Es posible que mTBI induzca una respuesta aguda al estrés inmediatamente después del trauma, que a su vez, se asocie al desarrollo posterior de TEPT.

Objetivo: Este estudio buscó probar la hipótesis de si la asociación de mediación entre mTBI, estrés agudo y severidad de los síntomas de TEPT depende del estado de mTBI.

Métodos: Se reclutó a cincuenta y nueve pacientes de las salas de emergencia de hospitales locales. Se midió la severidad de los síntomas post-mTBI y de estrés agudo dentro de las 2 semanas posteriores al trauma utilizando el cuestionario de síntomas post-concusión de Rivermead (RPQ, por su sigla en inglés) y la Escala para el Trastorno de Estrés Agudo (ASDS, por su sigla en inglés), respectivamente. Se midió la severidad de los síntomas de TEPT 3 meses después del trauma utilizando la Lista de Chequeo para TEPT del DSM-5 (PCL-5, por su sigla en inglés).

Resultados: Los análisis de mediación moderada indicaron que los puntajes de ASDS, a las 2 semanas post-trauma, mediaban la relación entre los puntajes de RPQ a las 2 semanas y los puntajes de la PCL-5 a los 3 meses post-trauma, sólo para pacientes que cumplían los criterios diagnósticos para mTBI.

Conclusiones: Estos hallazgos presentan evidencia preliminar que sugiere que los síntomas del trastorno de estrés agudo pueden ser uno de los mecanismos involucrados en el desarrollo del TEPT entre los sobrevivientes de trauma con un diagnóstico de mTBI, lo cual provee una base teórica para la intervención temprana de TEPT después de mTBI.

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KEYWORDS
Traumatic event; mTBI; ASD; PTSD; moderated mediation analysis

PALABRAS CLAVE
evento traumático; mTBI; ASD; TEPT; análisis de mediación moderada

关键词
创伤事件; mTBI; ASD; PTSD; 有调节的中介分析

HIGHLIGHTS

- Mild traumatic brain injury (mTBI) linked to post-traumatic stress disorder (PTSD) symptoms.
- mTBI also associated with acute stress disorder (ASD) symptoms.
- mTBI and PTSD symptom severity association is mediated by ASD symptoms only for trauma survivors who met mTBI diagnosis.

CONTACT Chia-Hao Shih ChiaHao.Shih@utoledo.edu Department of Psychiatry, University of Toledo, Toledo, OH 436140, USA
*These authors contributed equally to this work.

考查轻度创伤性脑损伤 急性应激和创伤后应激症状之间的中介关联的初步研究

背景: 受伤后几个月内, 轻度创伤性脑损伤 (mTBI) 的出现会加强创伤后应激障碍 (PTSD) 症状。但是, 尚不清楚将 mTBI 和 PTSD 的发展联系在一起的因素。 mTBI 有可能在创伤后立即引起急性应激反应, 进而与 PTSD 的发展相关联。
目的: 本研究旨在验证以下假设 :mTBI, 急性应激和 PTSD 症状严重程度之间的中介联系是否取决于 mTBI 的状态。
方法: 从当地医院的急诊室招募了 59 名患者。在创伤后两周内分别使用瑞弗米德脑震荡后症状问卷 (RPQ) 和急性应激障碍量表 (ASDS) 来测量 mTBI 后和急性应激症状的严重程度。创伤后 3 个月, 使用 DSM-5 的 PTSD 检查表 (PCL-5) 测量 PTSD 症状的严重程度。
结果: 有调节的中介分析表明, 仅在符合 mTBI 诊断标准的患者中, 创伤后 2 周的 ASDS 评分对创伤后 2 周的 RPQ 评分与创伤后 3 个月的 PCL-5 评分之间的关系有中介作用。
结论:这些发现为急性应激障碍症状可能是符合 mTBI 诊断的创伤幸存者中 PTSD 的发展机制之一提供了初步证据, 为 mTBI 后预防 PTSD 的早期干预提供了理论依据。

1. Introduction

Traumatic brain injury (TBI), irrespective of severity, often coexists with post-traumatic stress disorder (PTSD) after trauma exposure. TBI involves brain damage caused by sudden head trauma, which leads to physical, cognitive, emotional, and sleep-related symptoms (Menon, Schwab, Wright, & Maas, 2010). TBI affects 12% of the general population (Frost, Farrer, Primosch, & Hedges, 2013) and the rate is much higher in the emergency room population (Boswell, McErlean, & Verdile, 2002). On the other hand, PTSD is a trauma- and stress-related disorder caused by exposure to psychological traumatic events, where symptoms can be categorized into domains such as intrusive memories, avoidance behaviours, negative changes in thinking and mood, as well as alterations in physical and emotional reactions (Sareen, 2014). Although population-based studies indicate that more than 50% of people have been exposed to traumatic events, less than 10% of these trauma survivors developed PTSD (Kilpatrick et al., 2013; Terhakopian, Sinaii, Engel, Schnurr, & Hoge, 2008). Still, PTSD is a major health concern which produces negative impacts on both the individual and societal level (Cohen et al., 2009; Sareen, 2014). Despite research efforts on comorbidity between TBI and PTSD, less explored are the underlying mechanisms between these two conditions, particularly with appropriate statistical methodologies, which is the focus of the present study.

PTSD is a multifaceted and multidetermined, trauma- and anxiety-related disorder. Some risk and protective factors for PTSD have been identified (Brewin, Andrews, & Valentine, 2000; Carlson et al., 2016). Studies have revealed that mild TBI (mTBI) increases risk for PTSD. Bryant et al. (2010) tracked more than 1,000 patients who were admitted to hospitals and investigated how traumatic brain injury influenced development of psychiatric disorders. The authors reported that patients who sustained mTBI had nearly a two-fold risk for developing PTSD at 12-month follow-up, as compared to patients who did not have mTBI. Another study with a comparable sample size also showed consistent findings where patients with mTBI history were nearly three times more likely to develop a psychiatric disorder 3 years later compared to patients who did not have mTBI (Fann et al., 2004). Similar patterns have been reported in the military population. In a study where 2525 soldiers were surveyed, 44% of soldiers who had mTBI met PTSD criteria, as compared to 27%, 16%, and 9% of the soldiers who reported altered mental status, other injuries, and no injury, respectively (Hoge et al., 2008). The extent to which mTBI increases risk of PTSD is not fully understood but some proposed explanations include neural damage to brain regions that involve emotional regulation and depletion of cognitive resources (Bryant, 2008, 2011).

Related to PTSD, acute stress disorder (ASD) was introduced to fill the nosological gap between traumatic events and PTSD. ASD shares common symptoms with PTSD but emphasizes dissociative symptoms such as emotional numbing, reduced awareness of one's surroundings, derealization, depersonalization, and dissociative amnesia (Harvey & Bryant, 2002). It is not surprising that research has consistently reported a strong relationship between ASD and PTSD in trauma survivors, irrespective of the types of traumatic events. Brewin, Andrews, Rose, and Kirk (1999) reported that among victims of interpersonal violence, an ASD diagnosis was predictive of subsequent PTSD at 6-month post-trauma. Similar predictive characteristics of ASD to PTSD were also found for motor vehicle accident survivors (Bryant, Harvey, Guthrie, & Moulds, 2000). In addition, approximately 80% of motor vehicle accident survivors who had been diagnosed with ASD would develop PTSD 6 months after trauma (Bryant & Harvey, 1998; Harvey & Bryant, 1998b). The rate dropped with a longer time frame, yet, nearly half of the trauma survivors with ASD were still

diagnosed with PTSD 2 years after the traumatic event (Bryant, Harvey, Guthrie, & Moulds, 2003).

Altogether, acute and chronic stress reactions to trauma and mild traumatic brain injury are common in trauma survivors. Research generally suggests that both mild traumatic brain injury and acute stress disorder increase the risk of developing PTSD (Brewin et al., 1999; Bryant & Harvey, 1998; Bryant et al., 2000, 2003, 2010, 2010; Harvey & Bryant, 1998b). To our knowledge, no studies have tied these constructs together and tested whether acute stress mediates the association between mTBI and PTSD symptom severity, which is the focus of the present study. We hypothesized that acute stress mediates the relationship between a) mTBI symptom severity at an early stage post-trauma and b) PTSD symptom severity at several months later post-trauma. We also expected that the mediation effect would be stronger in trauma survivors with an mTBI diagnosis. The strong associations among mTBI, ASD, and PTSD, as well as the temporal relationships among these constructs, make the statistical framework of mediation a suitable candidate to depict relationships among these constructs.

2. Methods

2.1. Participants

The current study is a part of a U.S. federally sponsored, ongoing longitudinal study examining neural mechanisms that contribute to development of PTSD in trauma survivors. Individuals who visited emergency rooms in local hospitals in Northwest Ohio after experiencing a traumatic event (e.g. motor vehicle accidents and interpersonal violence) were contacted to assess if they were willing and eligible to participate in the study. Patients were excluded if they (a) had presence of major injury with severity greater than 2 on the Abbreviated Injury Scale; (b) had moderate to severe traumatic brain injury as defined by the diagnostic criteria of the American Congress of Rehabilitation Medicine (ACRM) (Mild Traumatic Brain Injury Committee, A. C. o. R. M., Head Injury Interdisciplinary Special Interest Group, 1993); (c) had major medical problems affecting general health; (d) had a history of chronic PTSD diagnosis; (e) were under the influence of alcohol or recreational drugs at the time of trauma; or (f) had other conditions that prohibited inclusion in the ongoing longitudinal study (e.g. contraindications to magnetic resonance imaging scans). Initially, 80 patients were eligible and consented to participate in the study. Participants completed self-report and interviewer-administered surveys within 2 weeks and at 3-month post-trauma. Additionally, medical records were reviewed to determine if they met criteria for mTBI diagnosis based on the ACRM guidelines (Mild Traumatic Brain Injury Committee, A. C. o. R. M., Head Injury Interdisciplinary Special Interest Group, 1993) and 21 did not have sufficient data for mTBI diagnosis. Therefore, analyses in the current study were based on 59 patients (i.e. 14 mTBI and 45 non-mTBI).

2.2. Symptom assessment

2.2.1. Mild traumatic brain injury symptom severity

The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) (N. S. King, Crawford, Wenden, Moss, & Wade, 1995) was completed by participants within 2 weeks post-trauma as a proxy for mTBI symptom severity. The RPQ includes questions regarding somatic, cognitive, and emotional symptoms and scores range from 0 to 220, with higher scores indicating more severe symptomatology. The RPQ has shown appropriate psychometric properties (Eyres, Carey, Gilworth, Neumann, & Tennant, 2005; King et al., 1995).

2.3. Acute stress symptoms

Participants' acute stress symptoms were assessed by the Acute Stress Disorder Scale (ASDS) (Bryant, Moulds, & Guthrie, 2000) within 2 weeks post-trauma. ASDS is a 19-item self-administered measure for acute stress. The score range is from 19 to 95, with higher scores reflecting higher degrees of acute stress. The ASDS has shown strong reliability, good sensitivity, and specificity for acute stress disorder, and predicts development of chronic PTSD (MacDonald et al., 2015).

2.4. Post-traumatic stress disorder symptoms severity

The Post-traumatic Stress Disorder Checklist for DSM-5 (PCL-5) (Blevins et al., 2015) was used to assess participants' PTSD symptom severity at 3 months after the traumatic event. The PCL-5 is a self-report measure of PTSD symptoms and scores ranges from 0 to 80, where higher scores indicate more severe PTSD symptoms. The PCL-5 has shown good psychometric properties across countries and different trauma-exposed populations (Ashbaugh, Houle-Johnson, Herbert, El-Hage, & Brunet, 2016; Bovin et al., 2016; Krüger-Gottschalk et al., 2017; Wortmann et al., 2016).

2.5. Statistical analysis

We examined whether the association between mTBI and PTSD symptom severity is mediated by acute

stress for mTBI and non-mTBI groups by fitting a moderated mediation model. In this model, RPQ scores represented the independent variable, ASDS scores represented the mediator, PCL-5 scores represented the dependent variable, and mTBI status represented the moderator of the relationship between the ASDS and PCL-5 scores. Independent samples t-tests and chi-square tests were used to test differences between mTBI and non-mTBI groups on age, gender, and other variables of interest (i.e. RPQ, ASDS, and PCL-5). Pearson and Point-Biserial correlations were used to evaluate linear relationships between demographic and other variables of interest. Ordinary least squares regression was used to test the proposed moderated mediation model. For this moderated mediation model, significance of the direct, and conditional indirect (i.e. moderated mediation) effects were tested with 95% confidence intervals (CI), which were established by utilizing non-parametric bootstrapping with 5,000 samples. These effects were considered statistically significant if 0 was not included in the 95% CI. All statistical analyses were performed using SPSS version 23 (IBM Corporation, Armonk, NY) and the 'PROCESS' macro for SPSS (Hayes, 2017). Statistical significance level was set at α =.05, two-tailed.

3. Results

Descriptive statistics of participants' demographic information and symptoms are presented in Table 1. Independent samples t-tests showed a significant difference on RPQ scores between mTBI and non-mTBI groups, $t(57) = 3.08$, $p < .01$, Cohen's $d = .96$. In addition, there was a significant relationship between mTBI status and sex, χ^2 (1) = 5.58, $p = .03$, $\varphi = .73$. No other differences reached statistical significance. Bivariate correlations between the above-mentioned variables are presented in Table 2. Correlation analyses revealed that RPQ scores, ASDS scores, and PCL-5 scores were all significantly correlated with each other (all p values < .001). No other correlation reached statistical significance (all p values > .05).

We then tested whether the association between mTBI and PTSD symptom severity was mediated by acute stress, and whether this mediation is contingent by mTBI status using a moderated mediation model (Figure 1(a)). Model estimation is summarized in Table 3, and 95% CIs for direct and indirect effects are presented in Figure 1(b). The direct effect between mTBI and PTSD symptom severity was statistically significant ($\beta_{c'}$ = .1401, SE = .0586, 95% CI [.0226, .2577]). Importantly, the indirect effect of acute stress in the association between mTBI and PTSD symptom severity was contingent upon the mTBI status as hypothesized. Specifically, the indirect effect only reached statistical significance for trauma survivors who met mTBI diagnostic criteria (β_{ab_mTBI} = .1434, SE = .0733, 95% CI [.0066, .2753]) but not for trauma survivors who did not meet mTBI diagnostic criteria ($\beta_{ab\_non\text{-}mTBI}$ = .0692, SE = .0437, 95% CI [−.0202, .1565]).

Table 1. Demographic information and symptoms of interest.

	mTBI (n = 14)	non-mTBI (n = 45)	p
Age (yrs)	34.64 (10.77)	33.69 (11.12)	.78[+]
Gender (F/M)	4/10	29/16	.03[#]
RPQ	137.36 (46.61)	94.18 (43.07)	.01[+]
ASDS	76.29 (16.07)	67.73 (14.08)	.06[+]
PCL-5	41.79 (19.68)	35.16 (18.37)	.25[+]

[+]Independent sample t-test; [#]Chi-square test; RPQ = Rivermead Post-Concussion Symptoms Questionnaire; ASDS = Acute Stress Disorder Scale; PCL-5 = Post-traumatic Stress Disorder Checklist for DSM-5.

Table 2. Bivariate correlation for demographic information and variables of interest.

	Age	Gender	RPQ	ASDS
Age	-			
Gender	.032	-		
RPQ	.185	−.225	-	
ASDS	.128	−.027	.657***	-
PCL-5	.149	−.235	.554***	.560***

***p <.001; RPQ = Rivermead Post-Concussion Symptoms Questionnaire; ASDS = Acute Stress Disorder Scale; PCL-5 = Post-traumatic Stress Disorder Checklist for DSM-5.

4. Discussion

The current study examined the extent to which acute stress mediates the association between mTBI and PTSD symptom severity in trauma survivors with and without mTBI. Results showed that the mTBI group had more severe mTBI symptoms as compared to the non-mTBI group, but no group differences reached statistical significance on measures of acute stress and PTSD symptom severity. In addition, findings from correlation analyses were consistent with previous studies, showing bivariate correlations between mTBI symptom severity, levels of acute stress symptoms, and PTSD symptom severity (Brewin et al., 1999; Broomhall et al., 2009; Bryant & Harvey, 1998, 1999; Bryant et al., 2003, 2010; Fann et al., 2004; Harvey & Bryant, 1998b). Importantly, as hypothesized, the moderated mediation analysis revealed that acute stress indeed mediates the association between mTBI and PTSD symptom severity for mTBI group only, but not for non-mTBI group. Thus, for patients who met mTBI diagnostic criteria, more severe mTBI symptom is associated with higher levels of acute stress, which in turn, is prospectively associated with worse PTSD symptom severity.

Our finding of a strong association between mTBI symptom severity and level of acute stress is consistent with previous studies (Broomhall et al., 2009; Harvey & Bryant, 1998a). Yet, mechanisms of how mTBI increases ASD are not fully understood. It is possible

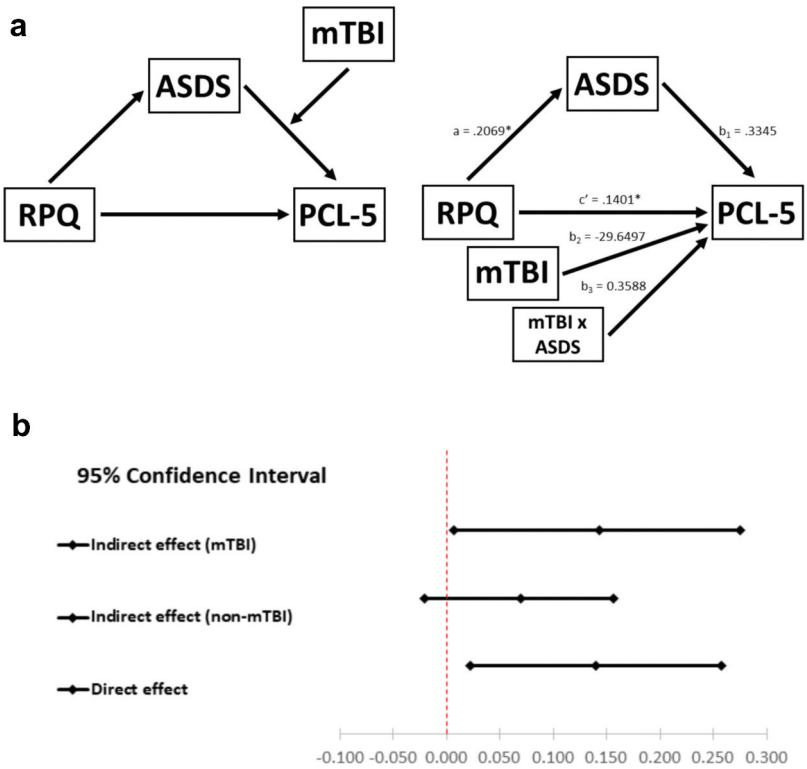

Figure 1. (a) Conceptual (left) and Statistical (right) diagrams of moderated mediation model and (b) Bootstrapped 95% confidence intervals for direct and indirect effects.

Table 3. Moderated mediation model coefficient estimation.

		Consequent						
		M(ASDS)				Y(PCL-5)		
Antecedent	path	Coeff.	SE	*p*	path	Coeff.	SE	*p*
X (RPQ)	a	.2069	.0314	<.001	c′	.1401	.0586	.0204
M(ASDS)	-	-	-	-	b_1	.3345	.1953	.0926
W (mTBI)					b_2	−29.6497	23.2011	.2067
M x W					b_3	.3588	.3069	.2475
constant	i_M	48.1562	3.5988	<.001	i_Y	−0.6943	11.3450	.9514
			R^2 =.4318				R^2 =.3944	
			F(1,57) = 43.3166, *p* <.001				F(4,54) = 8.7903, *p* <.001	

Coeff. = unstandardized model coefficient; RPQ = Rivermead Post-Concussion Symptoms Questionnaire; ASDS = Acute Stress Disorder Scale; mTBI = mild traumatic brain injury status; PCL-5 = Posttraumatic Stress Disorder Checklist for DSM-5.

RPQ = Rivermead Post-Concussion Symptoms Questionnaire; ASDS = Acute Stress Disorder Scale; mTBI = mild traumatic brain injury status; PCL-5 = Posttraumatic Stress Disorder Checklist for DSM-5.

that psychological trauma exposure induces early brain alternations, particularly in emotion processing regions, which leads to ASD development (Wang et al., 2016). In the current study, we further demonstrated that acute stress mediates the association between mTBI and PTSD symptom severity in patients with mTBI only. Studies have suggested that higher levels of behavioural avoidance and especially subjective distress, two ASD symptoms often observed in patients with mTBI, may provide an explanation (Broomhall et al., 2009; Meares et al., 2006). Specifically, high levels of avoidance may prevent emotional processing of the traumatic event whereas high levels of distress may indicate misinterpretation of symptoms or serous pathology, which in turn, lead to later PTSD development. Alternatively, it is possible that trauma can cause neural damage sustained in brain regions pertinent to fear conditioning. Therefore, trauma-induced fear and the traumatic event were conditioned in which reminders of the trauma later trigger inappropriate reactions to the trauma reminders.

Indeed, human neuroimaging studies provide supportive evidence for this hypothesis, where patients with PTSD showed exaggerated amygdala responses and impaired medial prefrontal cortex functioning in fear-associated learning tasks, as compared to trauma-exposed patients who did not develop PTSD (Fullana et al., 2016; Garfinkel et al., 2014; Harnett et al., 2018; Rauch, Shin, & Phelps, 2006). There are also other explanations speculating that the depletion of cognitive resources may contribute to the increased risk of PTSD. Specifically, it is stipulated that managing trauma-related and other ongoing stressors in the environment require adequate

cognitive resources, and cognitive resource deficits attributed to mTBI limits optimal management of these stressors (Bryant & Harvey, 1995; King, King, Foy, Keane, & Fairbank, 1999; Landre, Poppe, Davis, Schmaus, & Hobbs, 2006). It should be noted that these two possible explanations are not mutually exclusive and findings from the current study could be attributed to either or both possibilities. PTSD is a complex phenomenon involving multiple causal factors that may interact with mTBI to increase the risk of PTSD development. Therefore, future research is warranted to elucidate the intricate and dynamic relations among these variables.

Although the current study provides preliminary evidence showing acute stress symptoms mediate the association between mTBI and PTSD symptom severity, some limitations should be noted. First, although the measures used provide temporal relationships, the nature of our observational study prevents us from drawing causal conclusions. More rigorous study designs with adequate statistical analyses should be employed in future studies, where more direct conclusions could be made. Second, despite the RPQ showing appropriate psychometric properties and given the overlap between mTBI and post-concussive symptoms, the RPQ is not specifically designed to assess mTBI severity. However, to our knowledge, there is no instrument assessing mTBI severity and we believe the RPQ is an appropriate proxy. Future research validating the RPQ to assess mTBI severity is desired. Last, as mentioned above, the relationship between mTBI and PTSD is complex. The current study only elucidates parts of the whole picture. Future studies considering other relevant demographic, psychological, social, and environmental factors are warranted to provide a more comprehensive understanding of mTBI and PTSD relationship.

Despite some limitations inherent in the current study, our findings provide clinically relevant preliminary findings where acute stress may play a critical role in PTSD development among trauma survivors, especially for trauma-exposed patients who with mTBI diagnosis. These findings could suggest that appropriate treatment and management of mTBI may reduce ASD, which in turn, prevent PTSD development.

In summary, we demonstrated that acute stress mediates the association between mTBI and PTSD symptom severity in trauma survivors with an mTBI diagnosis. These preliminary findings suggest that mTBI may increase ASD symptom severity, and that may contribute to chronic PTSD development. Limitations noted in the current study need to be addressed so more direct conclusions can be made, and future research should incorporate more relevant factors to provide a comprehensive picture of the mTBI and PTSD relationship.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data Availability

To protect the confidentiality of patient information, the University of Toledo IRB will not allow the authors to make data publicly available. Data are available upon request from Carol Brikmanis at the Departmental Research Committee of Department of Psychiatry at the University of Toledo, for researchers who meet the criteria for access to confidential data.

ORCID

Roberta E. Redfern http://orcid.org/0000-0001-9883-2910

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