Original Investigation

A Multisite Analysis of the Fluctuating Course of Posttraumatic Stress Disorder

Richard A. Bryant, PhD; Meaghan L. O'Donnell, PhD; Mark Creamer, PhD; Alexander C. McFarlane, MD; Derrick Silove, MD

IMPORTANCE Delayed-onset posttraumatic stress disorder (PTSD) accounts for approximately 25% of PTSD cases. Current models do not adequately explain the delayed increases in PTSD symptoms after trauma exposure.

OBJECTIVE To test the roles of initial psychiatric reactions, mild traumatic brain injury (MTBI), and ongoing stressors on delayed-onset PTSD.

DESIGN, SETTING, AND PARTICIPANTS In this prospective cohort study, patients were selected from recent admissions to 4 major trauma hospitals across Australia. A total of 1084 traumatically injured patients were assessed during hospital admission from April 1, 2004, through February 28, 2006, and 785 (72.4%) were followed up at 3, 12, and 24 months after injury.

MAIN OUTCOME AND MEASURE Severity of PTSD was determined at each assessment with the Clinician-Administered PTSD Scale.

RESULTS Of those who met PTSD criteria at 24 months, 44.1% reported no PTSD at 3 months and 55.9% had subsyndromal or full PTSD. In those who displayed subsyndromal or full PTSD at 3 months, PTSD severity at 24 months was predicted by prior psychiatric disorder, initial PTSD symptom severity, and type of injury. In those who displayed no PTSD at 3 months, PTSD severity at 24 months was predicted by initial PTSD symptom severity, MTBI, length of hospitalization, and the number of stressful events experienced between 3 and 24 months.

CONCLUSIONS AND RELEVANCE These data highlight the complex trajectories of PTSD symptoms over time. This study also points to the roles of ongoing stress and MTBI in delayed cases of PTSD and suggests the potential of ongoing stress to compound initial stress reactions and lead to a delayed increase in PTSD symptom severity. This study also provides initial evidence that MTBI increases the risk of delayed PTSD symptoms, particularly in those with no acute symptoms.

JAMA Psychiatry. 2013;70(8):839-846. doi:10.1001/jamapsychiatry.2013.1137
Published online June 19, 2013.

Author Affiliations: School of Psychology, University of New South Wales, New South Wales, Australia (Bryant); Brain Dynamics Centre, University of Sydney and Westmead Millennium Institute, Sydney, Australia (Bryant); Australian Centre for Posttraumatic Mental Health, Department of Psychiatry, University of Melbourne, National Trauma Research Institute, Melbourne, Australia (O'Donnell); Australian Centre for Posttraumatic Mental Health, Department of Psychiatry, University of Melbourne, Melbourne, Australia (Creamer); Centre for Military and Veteran Health, Queensland, Australia (McFarlane); School of Psychiatry, University of New South Wales, New South Wales, Australia (Silove).

Corresponding Author: Richard A. Bryant, PhD, School of Psychology, University of New South Wales, Sydney, New South Wales, Australia 2052 (r.bryant@unsw.edu.au).

One of the most poorly understood presentations of posttraumatic stress disorder (PTSD) is delayed-onset PTSD, which is defined as the onset of symptoms at least 6 months after trauma exposure.[1] Meta-analyses estimated that delayed-onset PTSD occurs in approximately 25% of cases of PTSD.[2,3] Delayed-onset PTSD is more likely after a period of subsyndromal PTSD (usually defined as meeting at least 2 of the 3 symptom clusters) in the acute symptom period.[3-7] In addition, however, meta-analyses indicate that PTSD can develop after a protracted symptom-free period.[2,3] Hence, questions remain about the sequencing of symptom development over time in the pathway to delayed-onset PTSD.

Data concerning the mechanisms of delayed-onset PTSD are scant. In terms of acute predictors, delayed-onset cases have been associated with stronger PTSD reactions in the period immediately after trauma exposure,[4,8] as well as elevated heart rate after trauma[4] (relative to asymptomatic people in the acute phase). Cumulative stressors in the aftermath of trauma are greater in those who develop delayed-onset PTSD relative to those who maintain their symptom-free status over time,[9-13] although not all studies have observed this pattern.[14] These findings suggest that delayed reactions after a period of apparent absence of symptoms may be fueled by acute fear reactions that are subsequently compounded by stressors in the subsequent period. The evidence is limited, however, by the cross-

Table 1. Participant Characteristics of Those Completing 24-Month Assessment

Characteristic	No. (%) of Participants	
	PTSD (n = 100)	No PTSD (n = 730)
Sex		
Male	69 (69.9)	538 (73.7)
Female	31 (31.0)	192 (26.3)
Age, y		
18-24	18 (18.0)	138 (18.8)
25-34	28 (28.0)	151 (20.7)
35-44	24 (24.0)	182 (25.0)
45-54	23 (23.0)	153 (21.0)
55-64	7 (7.0)	87 (11.9)
≥65	0	19 (2.6)
Previous disorder		
Prior disorder	31 (31.0)	394 (54.0)
No prior disorder	69 (69.0)	336 (46.0)
Type of injury		
Transport	74 (74.0)	474 (65.0)
Assault	9 (9.0)	40 (5.5)
Fall	11 (11.0)	123 (16.9)
Work injury	1 (1.0)	43 (5.9)
Other Injury	5 (5.0)	50 (6.7)
Length of hospital stay, d		
2-4	15 (15.0)	131 (17.9)
5-10	41 (41.0)	331 (45.3)
11-15	15 (16.0)	112 (15.3)
16-20	7 (7.0)	68 (9.3)
≥21	21 (21.0)	88 (12.1)
Injury severity score		
Minimum	38 (38.0)	408 (55.9)
Moderate	32 (32.0)	176 (24.1)
Severe	21 (21.0)	97 (13.3)
Serious or critical	9 (9.0)	49 (6.7)
MTBI		
MTBI	58 (58.0)	299 (40.9)
No MTBI	42 (42.0)	431 (59.1)
Ethnic status		
White	87 (87.0)	631 (86.5)
Other	13 (13.0)	99 (13.5)
Marital status		
Married/de facto	40 (40.0)	382 (52.2)
Single	60 (60.0)	348 (47.5)
Employment status		
Employed	83 (83.0)	675 (92.5)
Unemployed	17 (17.0)	55 (7.5)
Education		
Trade/higher degree	62 (62.0)	449 (61.5)
High school	38 (38.0)	281 (38.5)

Abbreviations: MTBI, mild traumatic brain injury; PTSD, posttraumatic stress disorder.

sectional design of studies that rely on retrospective recall of symptoms, small sample sizes, and/or abbreviated or self-reported measurement of PTSD symptoms.

The aims of this study were to examine longitudinally the trajectory of PTSD symptoms and to identify the factors associated with delayed-onset PTSD symptoms. The current study describes a multisite, longitudinal investigation of trauma injury survivors who were assessed for PTSD symptoms during hospitalization and again at 3, 12, and 24 months after the trauma. To evaluate delayed-onset posttraumatic stress to the initial trauma, we ensured that PTSD symptoms (particularly reexperiencing and avoidance) were indexed in relation to the initiating traumatic event.

Methods

Participants

Randomized patients admitted on a weekday to 4 level I trauma centers across 3 states in Australia were recruited into the study from April 1, 2004, through February 28, 2006. The study was approved by the Human Research Ethics Committee at each hospital. Individuals who met entry criteria were randomly selected using an automated, random assignment procedure and stratified by length of stay. This approach was adopted to ensure that patients who had longer hospital stays were not differentially recruited because they may have been more accessible. Inclusion criteria included hospital admission of greater than 24 hours after traumatic injury, age between 16 and 70 years, and the ability to understand and speak English proficiently. Individuals were excluded if they had moderate or severe brain injury, were currently psychotic or suicidal, were non-Australian visitors, or were under police guard.

There were 1590 trauma patients who met inclusion criteria, and 1084 (68.2%) agreed to participate and completed the initial assessment. Four hundred thirty-seven (40.3%) experienced a mild traumatic brain injury (MTBI); MTBI was defined by the *International Classification of Diseases, Ninth Revision (ICD-9),* requirement of documented injury to the head, loss of consciousness for less than 30 minutes, no focal neurologic deficit or intracranial complications, and normal computed tomography findings.[15] Individuals who refused to participate in the current study did not differ from participants in terms of sex ($\chi^2_1 = 0.80$, $P = .23$), length of hospital admission ($t_{1082} = 0.03$, $P = .88$), injury severity score ($t_{1419} = 1.1$, $P = .16$), or age ($t_{1475} = 1.6$, $P = .14$).

At the 3-month follow-up assessment, 152 patients could not be contacted or declined to participate; 987 were interviewed by telephone (91.1% of the initial sample). Of these patients, 838 participants (77.3%) completed the 12-month assessment, and 785 participants (72.4%) completed the 24-month assessment. Of these 785 patients who completed the 24-month assessment, 620 completed a measure of stressful life events at 12 and 24 months. Patients at the 24-month follow-up interview did not differ from those who did not participate in terms of sex ($\chi^2_1 = 0.87$, $P = .35$), length of hospital admission ($t_{1080} = 1.03$, $P = .30$), or injury severity score ($t_{1080} = 1.49$, $P = .14$). Those who were lost to follow-up were younger (mean [SD], 35.65 [13.58] years vs 39.17 [13.37] years) ($t_{1088} = 4.30$, $P = .001$) than those who participated (see **Table 1** for full participant characteristics).

Outcome Measures

Posttraumatic stress disorder was assessed using the Clinician-Administered PTSD Scale IV (CAPS).[16] CAPS is a structured clinical interview that possesses good sensitivity (0.84) and specificity (0.95) relative to the Structured Clinical Interview for *DSM-IV* PTSD diagnosis and also possesses sound test-retest reliability (0.90). CAPS was administered during hospitalization and again at 3, 12, and 24 months. Importantly, each administration of CAPS was indexed to the traumatic injury that led to the initial hospitalization; for example, endorsement of questions concerning intrusive memories were restricted to memories about the traumatic injury.

The Mini-International Neuropsychiatric Interview (version 5.5; MINI)[17] was used to assess lifetime psychiatric disorder. MINI is a short, structured diagnostic interview based on the *DSM-IV* and the *International Statistical Classification of Diseases, 10th Revision (ICD-10),* classification of mental illness. We administered MINI at the baseline assessment in the hospital to identify lifetime history of major depressive episode, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, generalized anxiety disorder, alcohol abuse and dependence, and marijuana abuse and dependence.

Subsequent aversive events were assessed by an adaptation of the Recent Life Events Questionnaire, which indexes the occurrence of 20 common stressful life events that encompass both traumatic (eg, assaults) and aversive (eg, losing one's job) events.[18] Each item was dichotomously scored if each event occurred in the prior 9 months at the 12-month assessment and in the prior 12 months at the 24-month assessment.

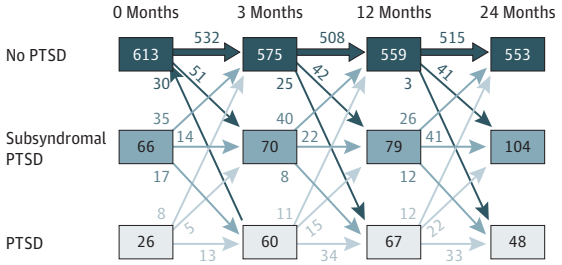
Procedure

After written informed consent was obtained, participants were assessed before discharge from each trauma center a mean (SD) of 7.2 (9.6) days after injury. Information regarding demographic, hospital admission, and injury-related factors were obtained from medical records. At 3, 12, and 24 months after injury, participants were contacted by telephone and completed CAPS to assess current prevalence of PTSD related to the original traumatic injury. Self-report questionnaire booklets containing the Recent Life Events Questionnaire were sent to participants to complete. All assessments were conducted by psychology honors graduates who were trained in CAPS administration (M.L.O.D. and R.A.B.) for 1 month before commencing assessments. All assessments were audio recorded to ensure ongoing adherence to the protocol. Five percent of all CAPS interviews were rescored while masked to the original scoring to test interrater reliability. Overall, the interrater reliability was strong for both PTSD diagnostic consistency and symptom severity at 3 months (1.00 and 0.84, respectively), 12 months (0.98 and 0.85, respectively), and 24 months (0.96 and 0.82, respectively).

Statistical Analysis

We calculated the proportion of participants who met full, subsyndromal, or no PTSD at baseline and 3, 12, and 24 months after injury according to participants' diagnostic (or subsyndromal) status at earlier time points. To determine the influence of predictor variables on subsequent PTSD, we created 2 groups of participants with delayed-onset PTSD. The delayed-onset group contained participants who had no PTSD at 3 months (defined as those not meeting criteria for more than one PTSD symptom cluster [B, C, or D] at the 3-month assessment on CAPS) and then developed PTSD at 24 months. The subsyndromal group contained those who at 3 months met criteria for at least 2 symptom clusters on the CAPS and developed PTSD at 24 months. The *DSM-IV* stipulates that 3 months is the demarcation between acute and chronic PTSD, at which point many trauma survivors are expected to experience remission.[19] To determine the effect of predictor variables on subsequent posttraumatic stress levels, we conducted 2 hierarchical linear regressions to predict PTSD severity (CAPS total score) at 24 months: one with the minimal symptom group of participants with delayed-onset PTSD and one with the subsyndromal group of participants. The following variables were used to predict 24-month PTSD within these groups: sex at step 1, prior psychiatric diagnosis at step 2, baseline heart rate at step 3, MTBI at step 4, type of injury (motor vehicle collision vs other type of injury) at step 5, baseline PTSD severity (CAPS total score) at step 6, days in hospital at step 7, and number of adverse life events at step 8. Heart rate was included because of evidence that is associated with delayed-onset PTSD,[4] MTBI because of recent reports that it is associated with higher rates of PTSD,[20,21] and days in hospital because of the possibility that preoccupation with immediate needs may contribute to delayed-onset stress response. To determine the symptoms most responsible for delayed onset, we compared patients who had no PTSD at 3 months and who did and did not subsequently develop at least subsyndromal levels of PTSD at 24 months on increases of reexperiencing, active avoidance, passive avoidance, and arousal clusters.

Figure. Posttraumatic Stress Disorder



Diagnoses of full-blown, subsyndromal, and no posttraumatic stress disorder and changing diagnoses during the first 2 years after trauma exposure. Size within diagram and arrow reflect proportion of participants in each grouping and changing course from one grouping to another.

Results

Trajectories of Full and Subsyndromal PTSD

The **Figure** presents the PTSD status of participants at each assessment and the number of participants who changed from each diagnostic grouping to another over time based on only those participants who completed every assessment (n = 705).

Table 2. Summary of Hierarchical Regression Models for Predicting 24-Month PTSD Severity for 620 Patients With at Least Subsyndromal PTSD at 3 Months[a]

Step	*B* (SE)	β	*P* Value
1: Sex	3.05 (5.00)	.06	.54
2: Prior disorder	8.24 (5.54)	.15	.40
3: Heart rate	0 (0.03)	0	.95
4: MTBI	5.80 (4.78)	.11	.23
5: Type of injury	−10.32 (5.06)	−.20	.04
6: Baseline CAPS score	0.31 (0.13)	.25	.02
7: Days in hospital	0.23 (0.16)	.13	.15
8: Adverse events	0.86 (0.46)	.18	.08

Abbreviations: CAPS, Clinician-Administered PTSD scale; MTBI, mild traumatic brain injury; PTSD, posttraumatic stress disorder.

[a] Step 1: $R^2 = 0.02$, $\Delta R^2 = 0.03$; step 2: $R^2 = 0.09$, $\Delta R^2 = 0.09$; step 3: $R^2 = 0.09$, $\Delta R^2 = 0.01$; step 4: $R^2 = 0.11$, $\Delta R^2 = 0.02$; step 5: $R^2 = 0.14$, $\Delta R^2 = 0.04$; step 6: $R^2 = 0.21$, $\Delta R^2 = 0.08$; step 7: $R^2 = 0.22$, $\Delta R^2 = 0.01$; and step 8: $R^2 = 0.24$, $\Delta R^2 = 0.03$.

Table 3. Summary of Hierarchical Regression Models for Predicting 24-Month PTSD Severity for 620 Patients With No PTSD at 3 Months[a]

Step	*B* (SE)	β	*P* Value
1: Sex	0.60 (1.51)	.02	.66
2: Prior disorder	2.16 (1.36)	.07	.11
3: Heart rate	0 (0.03)	.00	.95
4: MTBI	4.15 (1.40)	.13	<.001
5: Type of injury	−0.41 (1.41)	−.01	.77
6: Baseline CAPS score	0.25 (0.06)	.18	<.001
7: Days in hospital	0.13 (0.06)	.06	.05
8: Adverse events	1.55 (0.21)	.32	<.001

Abbreviations: CAPS, Clinician-Administered PTSD scale; MTBI, mild traumatic brain injury; PTSD, posttraumatic stress disorder.

[a] Step 1: $R^2 = 0$, $\Delta R^2 = 0$; step 2: $R^2 = 0.02$, $\Delta R^2 = 0.03$; step 3: $R^2 = 0.03$, $\Delta R^2 = 0$; step 4: $R^2 = 0.06$, $\Delta R^2 = 0.03$; step 5: $R^2 = 0.06$, $\Delta R^2 = 0$; step 6: $R^2 = 0.10$, $\Delta R^2 = 0.05$; step 7: $R^2 = 0.11$, $\Delta R^2 = 0.01$; and step 8: $R^2 = 0.20$, $\Delta R^2 = 0.09$.

The incidence of PTSD at 3, 12, and 24 months was 8.5%, 9.5%, and 6.8%, respectively.

The Figure demonstrates that most participants had no PTSD within days of the trauma, and this status remained constant for at least 80% of these participants at each assessment throughout the following 2 years. In contrast, a significant proportion of participants with subsyndromal or full PTSD (minus the duration criterion) at baseline had variable trajectories in the ensuing 2 years. Of the 26 participants with PTSD at baseline, only 42.3% had PTSD 2 years later. Reflecting a similar pattern, half of the participants with subsyndromal PTSD at baseline had no PTSD at 24 months. Approximately, half of patients with PTSD at 3 (44.2%), 12 (45.4%), and 24 (50.0%) months had no PTSD at baseline. Whereas the rates of subsyndromal and full PTSD remained fairly consistent across time, the membership in each category changed by approximately half of cases at each assessment: 54.8% of cases at 12 months and 60.3% of cases at 24 months were cases at 3 months, and 61.5% of cases at 24 months were cases at 12 months.

We calculated rates of delayed-onset PTSD by dividing the number of participants with PTSD at a subsequent assessment who did not meet criteria for PTSD at 3 months (including no PTSD and subsyndromal PTSD) by the total number who had PTSD at the follow-up assessment. Delayed-onset PTSD was reported by 49.3% at 12 months and by 18.8% at 24 months. When we defined delayed onset as having less than subsyndromal PTSD at 3 months (labeled as no PTSD) and meeting PTSD criteria at the subsequent assessment, 37.3% and 8.3% reported delayed-onset PTSD at 12 and 24 months, respectively. In terms of later delayed development of PTSD, only 6.2% of patients with PTSD at 24 months had no PTSD at 12 months and 31.2% had no or subsyndromal PTSD at 12 months.

Frequency of Posttraumatic Adverse Events

Most participants reported adverse life events in the period between 3 and 24 months after traumatic injury, with a mean (SD) of 4.49 (3.96) events. Participants reported being injured again (23.3%), family or close friends being seriously injured (50.4%), death of family or close friends (42.6%), separation from partner (14.6%), serious problem with friend or relative (22.5%), subject to attack or discrimination (14.6%), unemployment (32.4%), financial difficulties (32.4%), legal difficulties (26.7%), participant or family member mugged (8.0%), gave birth (5.8%), miscarriage (3.6%), moved residence (29.8%), and housing difficulties (12.7%).

Predictors of PTSD Severity at 24 Months

In terms of those who reported at least subsyndromal PTSD at 3 months, the summary model of the hierarchical linear regression predicting PTSD severity at 24 months is presented in **Table 2**. The significant predictors were type of injury (ie, motor vehicle collision, accounting for 4% of the variance) and PTSD severity during hospitalization (accounting for 8% of the variance).

In terms of those who reported minimal PTSD at 3 months, the summary model of the hierarchical linear regression predicting PTSD severity at 24 months is presented in **Table 3**. Comparable with the category of participants with subsyndromal PTSD, later PTSD severity was predicted by PTSD severity during hospitalization (accounting for 5% of the variance). In the minimal PTSD group, however, PTSD severity at

24 months was predicted by the presence of MTBI (accounting for 3% of the variance), the number of days spent in hospital (accounting for 1% of the variance), and the number of adverse life events after the 3-month assessment (accounting for 9% of the variance).

A further comparison was made between those with no PTSD at 3 months who did or did not develop PTSD at 24 months. **Table 4** presents the changes in symptom cluster scores (subtracting CAPS severity scores of reexperiencing, active avoidance, and passive avoidance at 3 months from scores at 24 months). Participants with no PTSD at 3 months who presented with delayed-onset symptoms had greater increases in reexperiencing ($t_{1,642}$ = 14.92, P <.001) and active avoidance ($t_{1,642}$ = 17.08, P <.001) symptoms than those who did not develop increased symptoms.

Table 4. Changes in PTSD Cluster Scores From 3 to 24 Months for 785 Patients With No PTSD at 3 Months[a]

PTSD Status at 24 mo	Subsyndromal or Full PTSD	No PTSD
Reexperiencing	6.75 (8.10)	−0.37 (3.13)
Active avoidance	7.27 (5.26)	1.39 (2.47)
Passive avoidance	−1.09 (3.38)	−0.69 (2.04)
Arousal	−5.1 (4.85)	−4.10 (4.70)

Abbreviation: PTSD, posttraumatic stress disorder.

[a] Change score calculated by subtracting Clinician-Administered PTSD Scale IV severity score for cluster at 3 months from total at 24 months.

Discussion

Although there was consistency in rates of full and subsyndromal PTSD at each assessment, there was marked fluctuation insofar as the membership in each diagnostic grouping that changed at each assessment. Chronic PTSD can be unstable and fluctuate over time[22]; however, there is little evidence of multiple surveillance of chronic PTSD. The finding that approximately half of participants with subsyndromal or full PTSD at any assessment shifted membership at the subsequent assessment highlights the fluctuating levels of PTSD severity in those with some level of symptoms. The profile of both worsening and improving state across the 4 assessments illustrates a complex course of posttraumatic adjustment that challenges proposals that the trajectory of posttraumatic stress is linear.

Focusing on the relationship of baseline reactions and subsequent PTSD responses indicates a complex pattern. Only half of those who met PTSD criteria at any subsequent time point displayed full or subsyndromal PTSD at baseline. Attempts to predict subsequent PTSD from baseline reactions, including reliance on initial posttraumatic stress severity,[23] acute stress disorder,[24] heart rate,[25] respiration rate,[26] cortisol levels,[27] and cognitive style,[28] have resulted in only modest prediction. The current finding highlights that there is not a linear relationship between acute response and later PTSD and that it may not be possible to accurately predict long-term PTSD on the basis of acute reactions.

We found that 37.3% of patients who had PTSD at 12 months did not have PTSD at 3 months; this rate is generally higher than the 25% rate of delayed-onset PTSD reported in most studies,[3] although it is comparable to a number of studies.[29,30] The observation that only 6.2% of patients with PTSD at 24 months had no PTSD at 12 months suggests that it is less common for people to develop PTSD at a chronic phase after a lengthy period of being symptom free, although in some studies[3] more than 2 assessments have found new cases of PTSD at the third assessment. One implication of the current finding is that there is less fluctuation in the course of PTSD reactions as time elapses after the traumatic event, although longer-term assessments would be needed to clarify this proposal.

In terms of those who reported PTSD symptoms at 3 months (the subsyndromal group), PTSD severity at 24 months was predicted by the severity of PTSD symptoms shortly after the trauma. This pattern is consistent with previous research that found the severity of the initial stress reaction after trauma to be linked to subsequent adaptation.[19] In terms of people who reported no PTSD at 3 months, 24-month PTSD severity was predicted by initial PTSD severity, MTBI, length of hospitalization, and frequency of stressful life events after the initial 3 months. The finding of elevated initial posttraumatic stress responses predicting subsequent PTSD severity is consistent with previously reported evidence of an association between acute stress severity and delayed-onset PTSD.[4,31,32] The combination of an increased acute stress response and subsequent posttraumatic stressors predicting delayed PTSD severity, a consistent finding in the literature,[33,34] suggests a number of possible interpretations in relation to the mechanisms involved.

Fear conditioning models posit that a traumatic event leads to a fear reaction, which becomes conditioned to stimuli associated with the traumatic event.[35] This model conceptualizes recovery from trauma as a form of extinction learning, whereby the survivor is repeatedly exposed to trauma reminders that do not result in adverse outcomes, which in turn results in new learning that inhibits the original conditioning.[36] Fear reinstatement involves the return of fear after exposure to a previously extinguished response because there has been reexposure to the initial unconditioned stimulus conditions.[37,38] Although fear reinstatement has been proposed as a mechanism that explains symptom return in anxiety disorders,[38] the present results provide evidence that this mechanism may underlie the return of initial PTSD symptoms after exposure to subsequent adverse events. The current findings support the hypothesis that fear associations established in the course of a traumatic experience are not necessarily erased during extinction learning and that exposure to repeated stresses and traumas after the remission of symptoms can reinstate initial fearful associations. Fear reinstatement involves reexposure to stimuli that are comparable to the stimuli in which initial conditioning occurred[39,40]; however, we did not index the details of each initial and subsequent traumatic event sufficiently to assess the effect of context specificity on reinstatement. Further, we did not have a sufficient sample size to conduct analyses matching types of initial and subsequent traumatic events; this would be an important avenue for further research.

The current findings are also consistent with a sensitization model, which posits that the predisposition to an excessive response to less severe stressful stimuli occurs because neural circuitry is sensitized after an initial traumatic experience.[41] Sensitization to subsequent stressors has been demonstrated in animals and humans who have been exposed to an initial aversive event.[42,43] This model is supported by evidence that previous traumatic events are associated with more reactive responses to subsequent stressors[44,45] and evidence that trauma survivors who subsequently develop PTSD do not display elevated startle responses immediately after the traumatic event but do so in the following months.[46,47] The influence of both the extent of the initial stress reaction and the dosage of subsequent stressors accords with the model that delayed-onset stress response may, at least in part, be a result of heightened reactivity to subsequent stressful but not necessarily traumatic experiences.[41]

We note that PTSD involves more than fear reactions, potentially including alterations in a range of mood states, cognitive ability, social interactions, and appraisals. Accordingly, a comprehensive understanding of the contribution of ongoing stressors to delayed-onset PTSD may require models that extend beyond those centering on fear-related mechanisms. For example, the increase in PTSD severity may occur as a consequence of diminishment of resources that result from accumulating stressors. Resource models posit that one's capacity to manage stress responses is dependent on the resources that one can bring to bear on the trauma reactions, as well as the ongoing stressors.[48] Consistent with this model, a recent study[49] found that rates of PTSD increased between 6 and 18 months after Hurricane Katrina, possibly because people had dimished available as the ongoing demands of the postdisaster drained coping capacity.

Alternately, cognitive models propose that subsequent stressors may trigger different appraisals of the original traumatic event, thereby resulting in delayed PTSD responses to the trauma.[50,51] Exposure to subsequent aversive life events in the current patient sample may have resulted in more distressing appraisals of the traumatic injury—possibly to the level of threat they initially experienced—or a diminished capacity to cope with the sequelae of the injury; these different attributions of the injury may have led to highten PTSD symptoms as time progressed. We note that we did not index appraisals over time, which precludes inferences concerning the applicability of cognitive models to our pattern of findings.

The finding that MTBI predicted delayed PTSD severity accords with mounting evidence that MTBI is associated with increased rates of PTSD.[20,21,52] It has been suggested that the increased risk of PTSD after MTBI may be attributed to impaired emotion regulation because damage to the medial prefrontal cortex, which is pivotal to regulatory processes, may limit one's capacity to manage posttraumatic stressors or may limit cognitive coping strategies as a result of mild cognitive impairment.[53] In addition, many patients with MTBI will initially be amnesic of their traumatic experience but subsequently reconstruct the trauma experience.[54] It is possible that MTBI contributes to delayed posttraumatic stress because people reconstruct their trauma memories over time, which then leads to elevated levels of PTSD. This finding is relevant to evidence of higher rates of delayed-onset PTSD in military rather than civilian samples[2] because it is possible that exposure to bomb blasts and other causes of MTBI may result in a greater likelihood of delayed-onset PTSD.

The observation that length of hospitalization contributed to delayed-onset PTSD symptoms accords with proposals that delayed-onset PTSD may occur because a patient is initially preoccupied with more immediate needs (eg, pain or surgery) that distract attention from one's symptoms.[55] This proposition is consistent with suggestions that delayed-onset PTSD in military samples may be attributed to the tendency to focus on issues and protocols that are predominant immediately after deployment, which delays the experience or reporting of symptoms that are increasingly apparent as these postdeployment matters abate.[56,57] In addition, length of hospitalization may reflect severity of injury, which could also contribute to subsequent stress levels.

The observation that patients who developed at least subsyndromal PTSD after reporting no PTSD at 3 months had increased reexperiencing and active avoidance symptoms at 24 months relative to their counterparts who did not develop delayed symptoms suggests that exacerbation of trauma memories and the associated avoidance play a role in delayed onset. Interestingly, passive avoidance and arousal symptoms did not display a similar increase. Reexperiencing is regarded as a core component of PTSD insofar as it reflects ongoing conditioned response that triggers secondary reactions.[58] It may be argued that the passive avoidance and arousal are secondary responses, and the current findings reflect the mechanism of a persistent conditioned response that is driving the surge in PTSD response over time. This interpretation is consistent with fear reinstatement and sensitization models insofar as it indicates that delayed responses were characterized by symptoms that involve renewed focus on trauma memories.[38] This finding also supports the use of exposure therapy in the acute phase after trauma as a means of secondary prevention to limit the development of subsequent PTSD.[59]

We recognize several methodologic limitations to this study. First, we did not assess for PTSD to the subsequent traumatic events that participants experienced because the focus of interest was on the effects of the initial traumatic injury. Consequently, we were not able to determine the relationship between initial trauma and subsequent PTSD in response to the more recent event; further, we did not index current PTSD to prior traumatic events. Second, we did not closely assess the contextual factors associated with the initial traumatic event and any subsequent traumas or stresses. As noted above, experimental studies[60] robustly find fear reinstatement in cases when the subsequent unconditioned stimulus is presented in the same context as the initial learning. Although difficult to achieve outside experimental settings, future studies should aim to achieve sufficient sample sizes and to analyze traumatic experiences sufficiently to permit comparison of contextual similarities between initial and subsequent traumatic experiences to evaluate the role that contextual overlap plays in delayed-onset PTSD. Third, our sample was restricted to injury (mostly from motor vehicle collisions) survivors and those

requiring hospital admission; the observed trajectories may not generalize to other trauma populations. Fourth, we did not index delayed-onset PTSD according to *DSM-IV* criteria (ie, 6-month delay after trauma exposure). Fifth, only 72.4% of the initial sample was retained 2 years later, which may bias the final results; for example, the younger age of those who dropped out of the study may have influenced the outcomes. Sixth, we note that assessing stressful events by self-report may not be as accurate as through interview,[61] and assessing PTSD by telephone may limit observational data.

There is increasing attention on the trajectories of PTSD. The present study demonstrates longitudinally that there is not a linear relationship between acute trauma response and long-term PTSD and highlights that PTSD levels fluctuate markedly in the initial years after trauma exposure. This pattern can explain the modest predictive capacity of acute markers to identify subsequent PTSD status. The complexity of these trajectories is further indicated by the delayed occurrence of PTSD responses, which appears to result from a combination of the immediate stress response and cumulative stress in the aftermath of the trauma. Identifying the factors that contribute to these fluctuations at different points during adaptation will facilitate attempts at prevention, treatment, and relapse prevention.

ARTICLE INFORMATION

Submitted for Publication: June 30, 2012; final revision received August 29, 2012; accepted November 20, 2012.

Published Online: June 19, 2013. doi:10.1001/jamapsychiatry.2013.1137.

Author Contributions: *Study concept and design:* All authors.
Acquisition of data: O'Donnell and McFarlane.
Analysis and interpretation of data: Bryant, Creamer, McFarlane, and Silove.
Drafting of the manuscript: Bryant, McFarlane, and Silove.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Bryant.
Obtained funding: Bryant, Creamer, McFarlane, and Silove.
Administrative, technical, and material support: Bryant, O'Donnell, and Creamer. *Study supervision:* All authors.

Conflict of Interest Disclosures: None reported.

Funding/Support: This research was supported by grant 568970 from the National Health and Medical Research Council Program (Drs Byrant, Silove, McFarlane, and Creamer), Victorian Trauma Foundation grant V-11 (Drs Creamer and O'Donnell), and National Health and Medical Research Council Australian Clinical Research Fellowship grant 359284 (Drs Creamer and O'Donnell).

Role of the Sponsor: The study sponsors had no role in the design or conduct of the study or in the collection, analysis, or interpretation of the data.

Correction: This article was corrected online July 10, 2013, for the corresponding author's address.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.

2. Andrews B, Brewin CR, Philpott R, Stewart L. Delayed-onset posttraumatic stress disorder: a systematic review of the evidence. *Am J Psychiatry*. 2007;164(9):1319-1326.

3. Smid GE, Mooren TT, van der Mast RC, Gersons BP, Kleber RJ. Delayed posttraumatic stress disorder: systematic review, meta-analysis, and meta-regression analysis of prospective studies. *J Clin Psychiatry*. 2009;70(11):1572-1582.

4. Bryant RA, Harvey AG. Delayed-onset posttraumatic stress disorder: a prospective evaluation. *Aust N Z J Psychiatry*. 2002;36(2):205-209.

5. Carty J, O'Donnell ML, Creamer M. Delayed-onset PTSD: a prospective study of injury survivors. *J Affect Disord*. 2006;90(2-3):257-261.

6. Blanchard EB, Hickling EJ, Barton KA, Taylor AE, Loos WR, Jones-Alexander J. One-year prospective follow-up of motor vehicle accident victims. *Behav Res Ther*. 1996;34(10):775-786.

7. Green MM, McFarlane AC, Hunter CE, Griggs WM. Undiagnosed post-traumatic stress disorder following motor vehicle accidents. *Med J Aust*. 1993;159(8):529-534.

8. Solomon Z, Mikulincer M, Waysman M. Delayed and immediate onset posttraumatic stress disorder: the role of life events and social resources. *J Community Psychol*. 1991;19(3):231-236.

9. Boscarino JA, Adams RE. PTSD onset and course following the World Trade Center disaster: findings and implications for future research. *Soc Psychiatry Psychiatr Epidemiol*. 2009;44(10):887-898.

10. Smid GE, van der Velden PG, Lensvelt-Mulders GJ, Knipscheer JW, Gersons BP, Kleber RJ. Stress sensitization following a disaster: a prospective study. *Psychol Med*. 2012;42(8):1675-1686.

11. Tsai KY, Chou P, Chou FH, et al. Three-year follow-up study of the relationship between posttraumatic stress symptoms and quality of life among earthquake survivors in Yu-Chi, Taiwan. *J Psychiatr Res*. 2007;41(1-2):90-96.

12. Ruzich MJ, Looi JC, Robertson MD. Delayed onset of posttraumatic stress disorder among male combat veterans: a case series. *Am J Geriatr Psychiatry*. 2005;13(5):424-427.

13. Horesh D, Solomon Z, Zerach G, Ein-Dor T. Delayed-onset PTSD among war veterans: the role of life events throughout the life cycle. *Soc Psychiatry Psychiatr Epidemiol*. 2011;46(9):863-870.

14. Buckley TC, Blanchard EB, Hickling EJ. A prospective examination of delayed onset PTSD secondary to motor vehicle accidents. *J Abnorm Psychol*. 1996;105(4):617-625.

15. Carroll LJ, Cassidy JD, Peloso PM, et al; WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J Rehabil Med*. 2004;43(suppl):84-105. .

16. Blake DD, Weathers FW, Nagy LM, et al. The development of a Clinician Administered PTSD Scale. *J Trauma Stress*. 1995;8(1):75-90.

17. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22-57.

18. Brugha T, Bebbington P, Tennant C, Hurry J. The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychol Med*. 1985;15(1):189-194.

19. Bryant RA. Early predictors of posttraumatic stress disorder. *Biol Psychiatry*. 2003;53(9):789-795.

20. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. *N Engl J Med*. 2008;358(5):453-463.

21. Bryant RA, O'Donnell ML, Creamer M, McFarlane AC, Clark CR, Silove D. The psychiatric sequelae of traumatic injury. *Am J Psychiatry*. 2010;167(3):312-320.

22. Shalev AY. Measuring outcome in posttraumatic stress disorder. *J Clin Psychiatry*. 2000;61(suppl 5):33-42.

23. Freedman SA, Brandes D, Peri T, Shalev A. Predictors of chronic post-traumatic stress disorder: a prospective study. *Br J Psychiatry*. 1999;174:353-359.

24. Bryant RA. Acute stress disorder as a predictor of posttraumatic stress disorder: a systematic review. *J Clin Psychiatry*. 2011;72(2):233-239.

25. Shalev AY, Sahar T, Freedman S, et al. A prospective study of heart rate response following trauma and the subsequent development of posttraumatic stress disorder. *Arch Gen Psychiatry*. 1998;55(6):553-559.

26. Bryant RA, Creamer M, O'Donnell M, Silove D, McFarlane AC. A multisite study of initial respiration rate and heart rate as predictors of posttraumatic stress disorder. *J Clin Psychiatry*. 2008;69(11):1694-1701.

27. Yehuda R, McFarlane AC, Shalev AY. Predicting the development of posttraumatic stress disorder from the acute response to a traumatic event. *Biol Psychiatry*. 1998;44(12):1305-1313.

28. Ehlers A, Mayou RA, Bryant B. Psychological predictors of chronic posttraumatic stress disorder after motor vehicle accidents. *J Abnorm Psychol*. 1998;107(3):508-519.

29. Mayou RA, Tyndel S, Bryant B. Long-term outcome of motor vehicle accident injury. *Psychosom Med*. 1997;59(6):578-584.

30. Gillies ML, Barton J, Di Gallo A. Follow-up of young road accident victims. *J Trauma Stress*. 2003;16(5):523-526.

31. Solomon Z, Kotler M, Shalev A, Lin R. Delayed onset PTSD among Israeli veterans of the 1982 Lebanon War. *Psychiatry*. 1989;52(4):428-436.

32. Berninger A, Webber MP, Niles JK, et al. Longitudinal study of probable post-traumatic stress disorder in firefighters exposed to the World Trade Center disaster. *Am J Ind Med*. 2010;53(12):1177-1185.

33. Horesh D, Solomon Z, Zerach G, Ein-Dor T. Delayed-onset PTSD among war veterans: the role of life events throughout the life cycle. *Soc Psychiatry Psychiatr Epidemiol*. 2011;46(9):863-870.

34. Andrews B, Brewin CR, Stewart L, Philpott R, Hejdenberg J. Comparison of immediate-onset and delayed-onset posttraumatic stress disorder in military veterans. *J Abnorm Psychol*. 2009;118(4):767-777.

35. Milad MR, Rauch SL, Pitman RK, Quirk GJ. Fear extinction in rats: implications for human brain imaging and anxiety disorders. *Biol Psychol*. 2006;73(1):61-71.

36. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. *Biol Psychiatry*. 2006;60(4):376-382.

37. Hermans D, Dirikx T, Vansteenwegen D, Baeyens F, Van den Bergh O, Eelen P. Reinstatement of fear responses in human aversive conditioning. *Behav Res Ther*. 2005;43(4):533-551.

38. Norrholm SD, Jovanovic T, Vervliet B, et al. Conditioned fear extinction and reinstatement in a human fear-potentiated startle paradigm. *Learn Mem*. 2006;13(6):681-685.

39. Bouton ME. Context and behavioral processes in extinction. *Learn Mem*. 2004;11(5):485-494.

40. LaBar KS, Phelps EA. Reinstatement of conditioned fear in humans is context dependent and impaired in amnesia. *Behav Neurosci*. 2005;119(3):677-686.

41. McFarlane AC. The long-term costs of traumatic stress: intertwined physical and psychological consequences. *World Psychiatry*. 2010;9(1):3-10.

42. Stam R. PTSD and stress sensitisation: a tale of brain and body, part 1: human studies. *Neurosci Biobehav Rev*. 2007;31(4):530-557.

43. Stam R. PTSD and stress sensitisation: a tale of brain and body, part 2: animal models. *Neurosci Biobehav Rev*. 2007;31(4):558-584.

44. Breslau N, Davis GC, Andreski P. Risk factors for PTSD-related traumatic events: a prospective analysis. *Am J Psychiatry*. 1995;152(4):529-535.

45. King DW, King LA, Foy DW, Gudanowski DM. Prewar factors in combat-related posttraumatic stress disorder: structural equation modeling with a national sample of female and male Vietnam veterans. *J Consult Clin Psychol*. 1996;64(3):520-531.

46. Griffin MG. A prospective assessment of auditory startle alterations in rape and physical assault survivors. *J Trauma Stress*. 2008;21(1):91-99.

47. Shalev AY, Peri T, Brandes D, Freedman S, Orr SP, Pitman RK. Auditory startle response in trauma survivors with posttraumatic stress disorder: a prospective study. *Am J Psychiatry*. 2000;157(2):255-261.

48. Hobfoll SE, Tracy M, Galea S. The impact of resource loss and traumatic growth on probable PTSD and depression following terrorist attacks. *J Trauma Stress*. 2006;19(6):867-878.

49. Kessler RC, Galea S, Gruber MJ, Sampson NA, Ursano RJ, Wessely S. Trends in mental illness and suicidality after Hurricane Katrina. *Mol Psychiatry*. 2008;13(4):374-384.

50. Clohessy S, Ehlers A. PTSD symptoms, response to intrusive memories and coping in ambulance service workers. *Br J Clin Psychol*. 1999;38(pt 3):251-265.

51. Ehlers A, Clark DM. A cognitive model of posttraumatic stress disorder. *Behav Res Ther*. 2000;38(4):319-345.

52. Schneiderman AI, Braver ER, Kang HK. Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: persistent postconcussive symptoms and posttraumatic stress disorder. *Am J Epidemiol*. 2008;167(12):1446-1452.

53. Bryant RA. Disentangling mild traumatic brain injury and stress reactions. *N Engl J Med*. 2008;358(5):525-527.

54. Harvey AG, Bryant RA. Reconstructing trauma memories: a prospective study of "amnesic" trauma survivors. *J Trauma Stress*. 2001;14(2):277-282.

55. Andreasen NC. Acute and delayed posttraumatic stress disorders: a history and some issues. *Am J Psychiatry*. 2004;161(8):1321-1323.

56. Gray MJ, Bolton EE, Litz BT. A longitudinal analysis of PTSD symptom course: delayed-onset PTSD in Somalia peacekeepers. *J Consult Clin Psychol*. 2004;72(5):909-913.

57. Wolfe J, Erickson DJ, Sharkansky EJ, King DW, King LA. Course and predictors of posttraumatic stress disorder among Gulf War veterans: a prospective analysis. *J Consult Clin Psychol*. 1999;67(4):520-528.

58. Brewin CR, Gregory JD, Lipton M, Burgess N. Intrusive images in psychological disorders: characteristics, neural mechanisms, and treatment implications. *Psychol Rev*. 2010;117(1):210-232.

59. Bryant RA, Mastrodomenico J, Felmingham KL, et al. Treatment of acute stress disorder: a randomized controlled trial. *Arch Gen Psychiatry*. 2008;65(6):659-667.

60. Bouton ME. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. *Biol Psychiatry*. 2002;52(10):976-986.

61. Monroe SM. Modern approaches to conceptualizing and measuring human life stress. *Annu Rev Clin Psychol*. 2008;4:33-52.