Psychological Medicine

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Distinct trajectories of neuropsychiatric symptoms in the 12 months following traumatic brain injury (TBI): a TRACK-TBI study

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Original Article

Cite this article: Martinez KA *et al* (2024). Distinct trajectories of neuropsychiatric symptoms in the 12 months following traumatic brain injury (TBI): a TRACK-TBI study. *Psychological Medicine* **54**, 3089–3098. https://doi.org/10.1017/S0033291724001211

Received: 17 November 2023
Revised: 14 April 2024
Accepted: 26 April 2024
First published online: 4 September 2024

Keywords:
Growth mixture modeling; mental health; orthopedic injury; psychological health; resilience; symptoms; traumatic brain injury

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Abstract

Background. Neuropsychiatric symptoms are common after traumatic brain injury (TBI) and often resolve within 3 months post-injury. However, the degree to which individual patients follow this course is unknown. We characterized trajectories of neuropsychiatric symptoms over 12 months post-TBI. We hypothesized that a substantial proportion of individuals would display trajectories distinct from the group-average course, with some exhibiting less favorable courses.

Methods. Participants were level 1 trauma center patients with TBI ($n = 1943$), orthopedic trauma controls ($n = 257$), and non-injured friend controls ($n = 300$). Trajectories of six symptom dimensions (Depression, Anxiety, Fear, Sleep, Physical, and Pain) were identified using growth mixture modeling from 2 weeks to 12 months post-injury.

Results. Depression, Anxiety, Fear, and Physical symptoms displayed three trajectories: Stable-Low (86.2–88.6%), Worsening (5.6–10.9%), and Improving (2.6–6.4%). Among symptomatic trajectories (Worsening, Improving), lower-severity TBI was associated with higher prevalence of elevated symptoms at 2 weeks that steadily resolved over 12 months compared to all other groups, whereas higher-severity TBI was associated with higher prevalence of symptoms that gradually worsened from 3–12 months. Sleep and Pain displayed more variable recovery courses, and the most common trajectory entailed an average level of problems that remained stable over time (Stable-Average; 46.7–82.6%). Symptomatic Sleep and Pain trajectories (Stable-Average, Improving) were more common in traumatically injured groups.

Conclusions. Findings illustrate the nature and rates of distinct neuropsychiatric symptom trajectories and their relationship to traumatic injuries. Providers may use these results as a referent for gauging typical *v.* atypical recovery in the first 12 months post-injury.

Introduction

Most research on the clinical outcomes of traumatic brain injury (TBI) has emphasized group-averaged longitudinal studies. Consequently, it is well understood that symptoms commonly experienced after TBI are, on average, maximal soon after injury and rapidly improve within 3 months (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Carroll et al., 2004; Rohling et al., 2011). However, group comparisons do not illuminate patterns of heterogeneity in TBI outcomes, which can inform clinical practice. The limited studies examining individual patient trajectories have found a concerning percentage of patients who display symptom courses that depart from group-averaged data. For example, studies examining depression (Bombardier, Hoekstra, Dikmen, & Fann, 2016; Gomez, Skilbeck, Thomas, & Slatyer, 2017), anxiety (Ren et al., 2017), and sleep (Wickwire et al., 2022) have identified subsets of patients with delayed or persistent problems 1 year post-TBI. This is noteworthy given that treatment for TBI is typically time-limited and focused on the time period during which persons exhibit, on average, the most problems (National Academies of Sciences, Engineering, and Medicine, 2022). Documenting the prevalence of differing trajectories of clinical symptoms will inform improvements in systems of TBI care. These could inform prognostic projections, facilitate early discussions with patients about recovery after injury, and ensure that follow-up is not prematurely terminated in those at risk of prolonged or worsening problems.

Neuropsychiatric symptoms are among the most common and disabling symptoms experienced in persons with TBI (Howlett, Nelson, & Stein, 2022; Nelson et al., 2019; Polinder et al.,

2018; Wickwire et al., 2022; Zahniser et al., 2019). These include emotional symptoms, such as irritability, depression, anxiety, and sleep difficulties, and somatic symptoms, such as headaches, nausea, dizziness, fatigue, blurred vision, and pain (Polinder et al., 2018). Heterogeneity of symptom presentation is common (Brett et al., 2021), and traditional categorical psychiatric diagnoses limit providers' ability to reliably capture this heterogeneity (Kotov et al., 2017, 2021). Thus, to advance more precise treatment, Nelson and colleagues (2021) proposed a novel transdiagnostic 6-dimensional factor model of neuropsychiatric symptoms derived from self-report symptom questionnaires endorsed by the National Institutes of Health (NIH) TBI Common Data Elements (CDE; Thurmond et al., 2010). This model, which parallels the structure of psychopathology identified in non-TBI samples (Kotov et al., 2017, 2021), identifies 6 first-order factors reflecting components of Internalizing and Somatic symptoms: Depression, Anxiety, Fear, Sleep, Physical, and Pain. For example, the Anxiety factor reflects trauma avoidance, strong negative feelings, and irritability, whereas the Fear factor encompasses feeling tense, afraid/fearful, reexperiencing trauma, and physiological arousal to reminders of trauma (see Nelson et al., 2021 for additional details). These dimensions, which were modeled at 2 weeks post-injury, displayed differing relationships with TBI severity and general injury severity level, supporting the utility of the model for delineating distinct symptom patterns.

Our primary objective was to extend this prior work by characterizing the prevalence of distinct trajectories of the 6 neuropsychiatric symptom dimensions post-TBI from 2 weeks to 12 months post-injury. Using data from the prospective, multicenter Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study of level 1 trauma center patients, we performed growth mixture modeling (GMM) analyses to characterize variations in the trajectories of the 6 symptom dimensions identified by Nelson et al. (2021). In addition, we evaluated subgroups of TBI severity, along with orthopedic trauma controls (OTC) and non-injured friend controls (FC), to clarify the degree to which symptom trajectories are associated with TBI and general trauma exposure. We hypothesized that a substantial proportion of the sample would display symptom courses distinct from the gradually improving course evident in group-averaged studies, and that TBI would be associated with more unfavorable symptom trajectories.

Method

Sample

The TRACK-TBI study enrolled 2697 patients with TBI and 299 OTC between 2014 and 2019 from 18 Level 1 trauma centers, as well as 300 FC. Inclusion criteria for the TBI group were head injury accompanied by altered mental status (using American Congress of Rehabilitation Medicine criteria; Kay et al., 1993), clinically indicated head computed tomography (CT) scan ordered by the emergency department (ED) physician, and enrollment within 24 h of injury. Inclusion criteria for the OTC group were traumatic injury to the body within 24 h of enrollment, no physical signs of a head injury, and no altered mental status or amnesia. FC included friends or family of TBI participants that did not have a traumatic injury within the year prior to enrollment. Exclusion criteria for all participants included having nonsurvivable trauma; being in police custody, on a psychiatric hold, non-English or non-Spanish speaking, or pregnant; and having a history of debilitating mental or neurologic disorders.

For the GMMs, we included participants who had at least 1 symptom factor score (see statistical analysis below) across 4 assessments (2 weeks and 3, 6, and 12 months; $N = 2585$). Eighty-five participants with TBI were excluded from TBI group comparison analyses because of missing data needed to classify their TBI severity. Following widely-used conventions to classify the TBI group by admission Glasgow Coma Scale (GCS) score and the presence (CT+) or absence (CT−) of acute intracranial findings, and given the relatively small subsample with more severe TBI, we defined 3 TBI subgroups: uncomplicated mild TBI (u-mTBI; i.e. GCS 13–15, CT−; $n = 1077$), complicated mild TBI (c-mTBI; i.e. GCS 13–15, CT+; $n = 596$), and moderate-severe TBI (i.e. GCS 3–12; $n = 270$). In total, analyses of subgroups included 1943 TBI, 257 OTC, and 300 FC participants. Table 1 displays demographic and injury characteristics (e.g. admission GCS score, loss of consciousness, posttraumatic amnesia) by group. The sample was 67.4% male, 76.9% White, and 79.5% non-Hispanic. The mean age was 39.7 (S.D. = 16.7) years with 13.6 (S.D. = 2.8) years of education.

Measures

As described in Nelson et al (2021), the 6-factor model of neuropsychiatric symptoms was developed in TBI and OTC participants at 2 weeks post-injury from the following self-report questionnaires endorsed by the NIH TBI CDE (Thurmond et al., 2010): Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer, & Williams, 2001), Brief Symptom Inventory-18 (BSI-18; Derogatis, 2001), Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5; Weathers et al., 2013), Insomnia Severity Index (ISI; Bastien, 2001), and PROMIS Pain Intensity Scale (Cella et al., 2007). We extended this model through 12 months post-injury and to the FC group, who completed assessments at the same four timepoints as the injured groups.

Statistical analyses

Confirmatory factor analysis was performed to extend the 6-factor model of neuropsychiatric symptoms across the four timepoints (Nelson et al., 2021). The 6-factor model fit well at each timepoint when tested cross-sectionally. Longitudinal factor modeling was used to establish factorial invariance across time so that the factor scores are comparable across time. After testing the configural invariance model, weak (invariance in factor loadings) and strong (invariance in factor loadings and thresholds) invariance models were tested (see online Supplementary eTable 1 for fit statistics). The strong invariance model fit the data well. Factor scores (interpretable relative to mean = 0 and variance = 1 at 2 weeks) were saved from this model for use in the growth mixture analyses.

Before conducting growth mixture analysis, we tested three forms of change over time to establish the baseline growth model. The baseline growth model served as a starting point (1-class model) based on which unobserved groups were explored. Linear, piecewise linear, and quadratic growth models were examined. For the linear growth model, the growth intercept (I) was set at 2 weeks, the growth slope (S) represented the change per month, and I and S were allowed to covary. For the piecewise model, I was also set at 2 weeks, the first and second slope parameters ($S1$ and $S2$) represented, respectively, the change

https://doi.org/10.1017/S0033291724001211 Published online by Cambridge University Press

Table 1. Sample demographics and injury characteristics

Demographic/injury characteristic	Total sample[a] (*n* = 2585) *n* (%) or *M* (S.D.)	u-mTBI (*n* = 1077) *n* (%) or *M* (S.D.)	c-mTBI (*n* = 596) *n* (%) or *M* (S.D.)	Mod-Sev TBI (*n* = 270) *n* (%) or *M* (S.D.)	OTC (*n* = 257) *n* (%) or *M* (S.D.)	FC (*n* = 300) *n* (%) or *M* (S.D.)	*p* value[b]
Demographics							
Age, years	39.72 (16.65)	37.52 (15.63)	46.20 (18.12)	35.07 (14.80)	40.07 (15.22)	37.59 (15.30)	<0.001
Sex (male)	1741 (67.4%)	680 (63.1%)	420 (70.5%)	215 (79.6%)	169 (65.8%)	191 (63.7%)	<0.001
Race							<0.001
White	1988 (76.9%)	789 (73.7%)	498 (83.6%)	210 (78.1%)	196 (77.5%)	227 (76.2%)	
Black	420 (16.2%)	217 (20.3%)	60 (10.1%)	40 (14.9%)	43 (17.0%)	45 (15.1%)	
Other/unknown	177 (6.8%)	64 (6.0%)	38 (6.4%)	19 (7.1%)	14 (5.5%)	26 (8.7%)	
Hispanic ethnicity	530 (20.5%)	208 (19.4%)	128 (21.5%)	50 (18.7%)	64 (25.2%)	53 (17.8%)	0.167
Education, years	13.57 (2.84)	13.53 (2.72)	13.66 (3.18)	12.93 (2.49)	13.80 (2.95)	14.12 (2.51)	<0.001
Psychiatric history[c]	582 (22.5%)	261 (24.3%)	119 (20.0%)	55 (20.4%)	62 (24.1%)	66 (22.0%)	0.261
TBI history	479 (18.5%)	253 (25.0%)	94 (16.8%)	35 (14.3%)	39 (16.0%)	46 (16.3%)	<0.001
Health insurance							0.018
Medicaid/uninsured	804 (31.1%)	347 (32.6%)	163 (27.7%)	103 (39.3%)	78 (30.7%)	93 (31.2%)	
Other	1706 (66.0%)	709 (66.6%)	416 (70.6%)	157 (59.9%)	170 (66.9%)	199 (66.8%)	
Unknown	41 (1.6%)	8 (0.8%)	10 (1.7%)	2 (0.8%)	6 (2.4%)	6 (2.0%)	
Injury characteristics							
Admission GCS score	13.74 (3.00)	14.79 (0.46)	14.61 (0.63)	6.34 (3.23)	14.98 (0.14)	–	<0.001
Cause of injury							<0.001[d]
Motor vehicle/traffic crash	1247 (48.2%)	706 (65.7%)	265 (44.7%)	155 (58.1%)	89 (35.9%)	–	
Fall	619 (23.9%)	217 (20.2%)	219 (36.9%)	59 (22.1%)	90 (36.3%)	–	
Assault/violence	143 (5.5%)	52 (4.8%)	56 (9.4%)	24 (9.0%)	2 (0.8%)	–	
Other/unknown	576 (22.3%)	100 (9.3%)	53 (8.9%)	29 (10.9%)	67 (27.0%)	–	
Highest level of care							<0.001[d]
Emergency department	864 (33.4%)	406 (37.7%)	47 (7.9%)	3 (1.1%)	97 (37.7%)	–	
Inpatient floor	911 (35.2%)	510 (47.4%)	221 (37.1%)	12 (4.4%)	142 (55.3%)	–	
Intensive care unit	810 (31.3%)	161 (14.9%)	328 (55.0%)	255 (94.4%)	18 (7.0%)	–	
Loss of consciousness[e]	1697 (65.6%)	899 (86.6%)	478 (86.0%)	249 (97.6%)	–	–	<0.001[f]
Posttraumatic amnesia[e]	1477 (57.1%)	758 (76.1%)	464 (83.9%)	188 (95.9%)	–	–	<0.001[f]

Note. GCS, Glasgow Coma Scale; u-mTBI, uncomplicated, mild traumatic brain injury; c-mTBI, complicated, mild traumatic brain injury; TBI, traumatic brain injury; OTC, orthopedic trauma control; FC, friend control.
[a]Total sample (*n* = 2585) that contributed to the factor model.
[b]*F* test was used to compare the means of age, education, and admission GSC score. χ^2 test was used for all other characteristics. The total sample was not included in these analyses.
[c]Psychiatric history reflected any self-reported preinjury history of treatment for a psychiatric condition.
[d]The χ^2 test was computed with FC group excluded.
[e]Yes and suspected categories collapsed.
[f]The χ^2 test was computed with FC and OTC groups excluded.

per month from 2 weeks to 3 months, and the change per month from 3 months through 12 months. Two different covariance structures were explored for the growth parameters. Piecewise model 1 constrained the covariance between *S1* and *S2* to zero. Piecewise model 2 did not allow individual difference for *S2*. Quadratic growth models included one with a fixed quadratic growth parameter and one that allowed for variance.

In the GMMs, each dimension was analyzed separately, with each latent class allowed to have its own mean, variance, and covariance of the growth parameters. The residual variances were assumed to be equal in all classes. All GMMs were estimated using Mplus (version 8.7) with the MLR estimator. GMMs were tested with 2, 3, 4, 5, and 6 (for Pain only) latent classes. The following information criteria and likelihood ratio (LR) tests were used to compare models: Akaike's information criterion (AIC), Bayesian information criterion (BIC), sample size-adjusted BIC (aBIC), Bootstrapped LR test (BTLR; TECH14 in Mplus), Vuong-Lo-Mendell-Rubin LR test (VLMR; TECH11), and Lo-Mendell-Rubin adjusted LR test (LMR; TECH11; Asparouhov & Muthen, 2012; Lo, Mendell, & Rubin, 2001; McLachlan and

https://doi.org/10.1017/S0033291724001211 Published online by Cambridge University Press

Peel, 2000; Nylund, Asparouhov, & Muthén, 2007). We also considered entropy, the proportion of individuals in each latent class, and interpretability of the estimated trajectories in selecting the best model for each symptom dimension. Smaller information criteria, LR test (significant ($p < 0.05$) results prefer more classes), higher entropy, and solutions that did not include one or more classes with extremely small proportions indicated a better model.

Percentages of agreement (i.e. the degree to which individuals exhibited similar patterns of change) between pairs of symptom dimensions were calculated. χ^2 tests and F tests were used to compare demographic and injury characteristics between injury groups (Table 1), with FC and OTC groups excluded from analyses when appropriate (e.g. loss of consciousness, posttraumatic amnesia). χ^2 tests of independence were used to test the association between trajectory class and injury group. We then ran a sensitivity analysis that used multinomial logistic regressions to compare injury groups by trajectory groups while covarying for demographic variables that were significantly different between groups.

Results

Baseline growth model

Based on the overall model fit statistics, the mean residuals (online Supplementary eTable 2), and the plots, the piecewise models were preferred over the linear growth model. The overall fit statistics for Piecewise model 1 were slightly better than those for piecewise model 2, though model 1 had a small variance of *S2*. The statistics for model 2 indicated good fit and mean residuals were no worse than those for model 1. Considering the small variability of *S2* in piecewise model 1, model parsimony, and the computational burden for GMMs when the base model has an additional variance parameter close to the boundary (and possibly a covariance as well), piecewise model 2 with a fixed second slope was selected as the base model for the mixture analysis. Compared to piecewise linear growth model 2, the quadratic growth models resulted in similar or worse model fit statistics, fewer degrees of freedom for four of the symptoms, and larger mean residuals. See the online Supplemental eMethods for additional information.

GMMs of neuropsychiatric trajectories

For Depression, Anxiety, Fear, Sleep, and Physical symptoms, the 3-class model was selected as the best solution based on fit statistics, entropy, and interpretability (see Table 2). For Pain, the 5-class model was preferred over the 4-class and 6-class models based on fit statistics, entropy, classification proportions (e.g. the 6-class model resulted in a class membership with a small proportion [0.01]), and interpretability. See the online Supplemental eMethods for additional information regarding the selection of each model.

Overall course and prevalence of symptom trajectories

Trajectories followed multiple distinct courses. Figure 1 displays the course and prevalence of each trajectory in the full sample of TBI, OTC, and FC participants. Trajectories were named based on features that distinguished the course and/or endpoint of symptoms across classes within a dimension. There was sufficient similarity in the trajectories that we applied a common naming convention across most dimensions:

- *Stable-Low trajectory*: Relatively low symptom burden at 2 weeks through 12 months. Prevalence rates ranged from 86.2% to 88.6% for Depression, Anxiety, Fear, and Physical; and 7.6%–11.9% for Pain and Sleep.
- *Worsening trajectory*: Relatively low symptom burden at 2 weeks and an increasing course from 3 to 12 months. Prevalence rates ranged from 5.6% to 13.9% for all dimensions except for Sleep, which did not show a Worsening trajectory.
- *Improving trajectory*: Relatively high symptom burden at 2 weeks, with a progressive decline to the levels of the Stable-Low group by 12 months. Prevalence rates for all dimensions except Pain ranged from 2.6% to 6.4%. For Pain, the Improving trajectory manifested as two classes: an Improving-Gradually (14.0%) class, with a steady rate of gradual improvement over time that approached symptom resolution near the levels of the Stable-Low group by 12 months, and an Improving-Rapidly (19.5%) class, that showed rapid improvement in symptoms from 2 weeks through 3 months and then plateaued after 3 months.
- *Stable-Average trajectory* (Sleep [82.6%] and Pain [46.7%] dimensions only): Moderate symptom burden at 2 weeks that showed mild improvement in the first 3 months and then plateaued, with symptoms exceeding the Stable-Low and Improving groups at 12 months.

To aid clinical interpretation, online Supplementary eTable 3 presents the severity of the mean factor score for each class represented by the percentile of the corresponding score within the FC group at 2 weeks and 12 months. For reference, the 25th–75th normative percentile is commonly considered average, whereas ⩾91st percentile is commonly considered clinically elevated (i.e. above high average range; Guilmette et al., 2020). Notably, the Improving trajectories exhibited marked symptoms (80–99th percentile) across all dimensions at 2 weeks that declined to average levels (21–47th percentile) at 12 months. Worsening trajectories showed greater variability in symptom levels at 2 weeks across dimensions (47–77th percentile), with increases to the 86–94th percentile at 12 months.

Relationships among neuropsychiatric trajectory groups

A heatmap displaying the percentage of agreement when comparing two dimensions is provided in Fig. 2. The percentage of agreement among Depression, Anxiety, Fear, and Physical dimensions ranged from 86% to 92%. These high percentages indicate that more individuals displayed similar symptom courses for each of the two-dimensional comparisons (e.g. having Stable-Low symptoms in both Depression and Anxiety). Notably, the high degree of agreement amongst these four dimensions was primarily driven by the prevalence rates of individuals in the Stable-Low trajectory for these dimensions, with lower agreement in the Improving and Worsening trajectories for each two-dimensional comparison (31–52%). Due to variability in trajectories for Sleep and Pain, the two Improving trajectories for Pain (Improving-Rapidly, Improving-Gradually) were combined into a single Improving class for these computations. The Stable-Average trajectory for Sleep was considered concordant with Worsening trajectories, given that both displayed the highest symptoms at 12 months. Similarly, the Stable-Average and Worsening trajectories for Pain were combined and considered concordant with the Stable-Average trajectory for Sleep and the Worsening trajectories for all other dimensions. Despite this lenient definition of agreement, Sleep (18–21%) and Pain (14–16%) displayed relatively low

https://doi.org/10.1017/S0033291724001211 Published online by Cambridge University Press

Table 2. Model fit statistics from growth mixture models with 1–5 or 6 latent classes

NClass	Nparm	AIC	BIC	aBIC	Entropy	Δdf	BTLR	VLMR	LMR
Depression (*N* = 2584)									
1	9	57 449.61	57 502.33	57 473.73					
2	16	57 260.20	57 353.91	57 303.07	0.651	7	203.415***	203.415*	199.782*
3	23	57 167.32	57 302.03	57 228.95	0.636	7	106.879***	106.879**	104.970**
4[a]	30	57 083.34	57 259.05	57 163.74	0.535	7	97.978***	97.978	96.228
5[b]	35	57 070.00	57 275.00	57 163.79	0.592	5	86.207[c]	86.207**	84.667**
Anxiety (*N* = 2572)									
1	9	56 303.12	56 355.79	56 327.20					
2	16	56 212.38	56 306.02	56 255.18	0.619	7	104.737***	104.737	102.866
3	23	56 091.82	56 226.43	56 153.35	0.629	7	134.564***	134.564***	132.159***
4[a]	30	56 056.67	56 232.25	56 136.03	0.490	7	49.146	49.146	48.267
5[b]	37	56 029.83	56 246.37	56 128.81	0.489	7	40.843	40.843	40.113
Fear (*N* = 2584)									
1	9	55 776.55	55 829.26	55 800.67					
2	16	55 626.07	55 719.78	55 668.95	0.661	7	164.480***	164.480**	161.543**
3	23	55 515.00	55 649.71	55 576.64	0.656	7	125.071***	125.071***	122.837***
4[a]	30	55 491.81	55 667.53	55 572.21	0.644	7	37.187	37.187	36.523
5[b]	37	55 456.92	55 673.63	55 556.07	0.539	7	48.892[c]	48.892*	48.019*
Sleep (*N* = 2584)									
1	9	58 116.73	58 169.45	58 140.85					
2	16	58 002.96	58 096.67	58 045.83	0.647	7	127.776***	127.776*	125.494*
3	23	57 925.46	58 060.17	57 987.10	0.670	7	91.497***	91.497	89.863
4[a]	30	57 862.65	58 038.37	57 943.05	0.582	7	76.806***	76.806**	75.434**
5[b]	37	57 813.03	58 029.75	57 912.19	0.626	7	63.621[c]	63.621*	62.485*
Physical (*N* = 2584)									
1	9	55 236.83	55 289.54	55 260.94					
2	16	55 113.99	55 207.70	55 156.86	0.566	7	136.840***	136.840**	136.396**
3	23	55 063.19	55 197.91	55 124.83	0.605	7	64.792***	64.792	63.635
4[a]	30	55 005.63	55 181.35	55 086.03	0.603	7	71.562[c]	71.562	70.284
5[b]	35	54 981.78	55 186.78	55 075.58	0.682	5	54.772[c]	54.772**	53.794**
Pain (*N* = 2584)									
1	9	59 311.97	59 364.68	59 336.08					
2	16	58 929.35	59 023.07	58 972.23	0.893	7	396.613***	396.613***	389.530***
3	23	58 804.72	58 939.44	58 866.36	0.643	7	138.629***	138.629	136.153
4	28	58 666.88	58 830.88	58 741.92	0.656	5	147.845***	147.845*	144.175*
5	35	58 424.57	58 629.57	58 518.36	0.677	7	256.312***	256.312*	251.735*
6[d]	42	58 305.87	58 551.87	58 418.42	0.718	7	132.697[d]	132.697**	130.328**

Note. NClass, number of latent classes; Nparm, Number of parameters; AIC, Akaike information criterion; BIC, Bayesian information criterion; aBIC, sample size adjusted BIC; Δdf, degrees of freedom for BT LR, VLMR LR, and LMR adjusted LR; BTLR, Bootstrapped LR test computed by TECH14 option in Mplus; VLMR, Vuong-Lo-Mendell-Rubin likelihood ratio test computed by TECH 11 option in Mplus; LMR, Lo-Mendell-Rubin adjusted likelihood ratio test computed by TECH11 option in Mplus. All LR tests compare each model to the previous model with one fewer classes (e.g. 3-class model to 2-class model). In the 5-class model for Depression, the variance of S1 was fixed to zero in one of the classes. In the 4-class model for Pain, the variance of S1 was fixed to zero in one of the classes.

[a]The 4-class models resulted in a class membership with small proportions: 0.019 for Depression, 0.021 for Anxiety, 0.014 for Fear, 0.021 for Sleep, and 0.008 for Physical.

[b]The 5-class models resulted in a class membership with extremely small proportions: 0.001 for Depression, 0.006 for Anxiety, 0.010 for Fear, 0.033 for Sleep, and 0.002 for Physical.

[c]A trustworthy *p* value was not obtained because some of the bootstrap draws did not converge even with a large number of random starts.

[d]The 6-class model for Pain resulted in a class membership with a small proportion 0.011. Smaller information criteria, LR test (significant [$p < 0.05$] results prefer more classes), higher entropy, and solutions that did not include one or more classes with extremely small proportions indicated a better model. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

https://doi.org/10.1017/S0033291724001211 Published online by Cambridge University Press

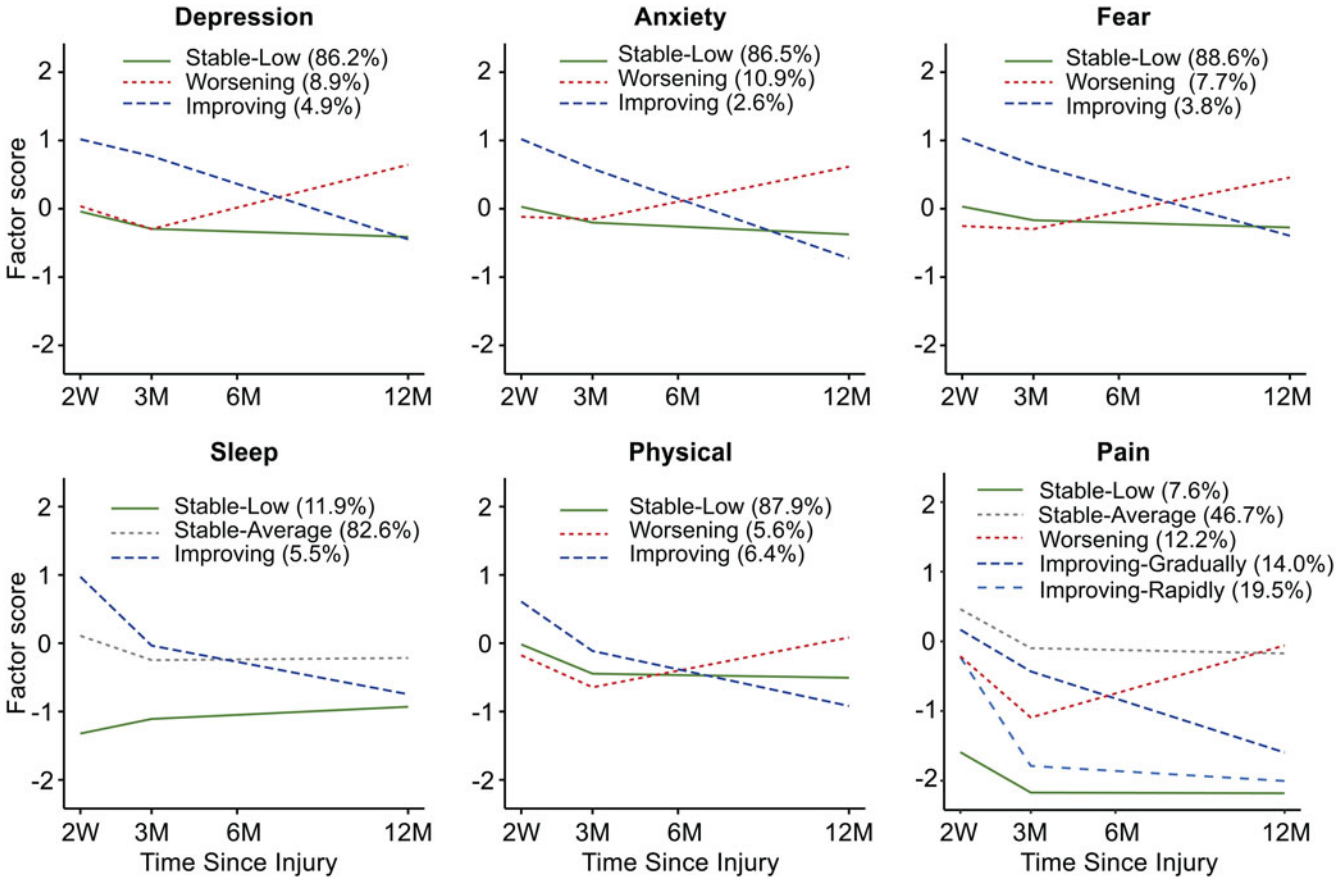

Figure 1. Course and prevalence of each symptom trajectory from 2 weeks to 12 months post-injury.
Note. The factor scores are interpretable relative to mean = 0 and variance = 1 at 2 weeks.

	Depression	Anxiety	Fear	Sleep	Physical	Pain
Depression	100%	89%	90%	20%	90%	16%
Anxiety	89%	100%	92%	21%	87%	16%
Fear	90%	92%	100%	18%	90%	14%
Sleep	20%	21%	18%	100%	19%	59%
Physical	90%	87%	90%	19%	100%	16%
Pain	16%	16%	14%	59%	16%	100%

Figure 2. Percentage agreement in trajectory group across the six neuropsychiatric symptom dimensions.
Note. Agreement based on the percentage of participants that were in both the Stable-Low, Worsening, or Improving class across dimensions ($N = 2584$). The denominator was lower for percentage agreement with the Anxiety dimension ($n = 2572$) because of less completed data for this dimension. The Improving-Gradually and Improving-Rapidly trajectories were combined into one Improving trajectory for these computations. The Stable-Average trajectory for Sleep was considered to be concordant with Worsening trajectories. The Stable-Average and Worsening trajectories for Pain were combined and considered to be concordant with the Stable-Average trajectory for Sleep and the Worsening trajectories for all other dimensions.

agreement with the other dimensions, though they displayed moderate agreement with each other (59%).

Association between injury group and neuropsychiatric trajectory group

There was a significant association between injury group and neuropsychiatric trajectory group membership for all symptom dimensions ($p < 0.001$; see Fig. 3). Significant post hoc comparisons ($p < 0.05$) are identified in online Supplementary eFigs 1–6. Comparisons described below remained significant (online Supplementary eTable 4) even when controlling for identified demographic covariates (Table 1).

There was a significantly higher proportion of u-mTBI individuals (5.8–9.6% *v.* 0.8–5.4%) with Improving trajectories compared to all other groups in the following dimensions: Depression, Fear, Sleep, and Physical. Individuals with u-mTBI also had significantly higher proportions (3.8% *v.* 0.8–2.0%) in the Improving trajectory for Anxiety compared with all other groups except moderate-severe TBI. For the Physical dimension, all TBI groups had higher prevalences of Improving trajectory (5.2–9.6%) than FC (1.7%).

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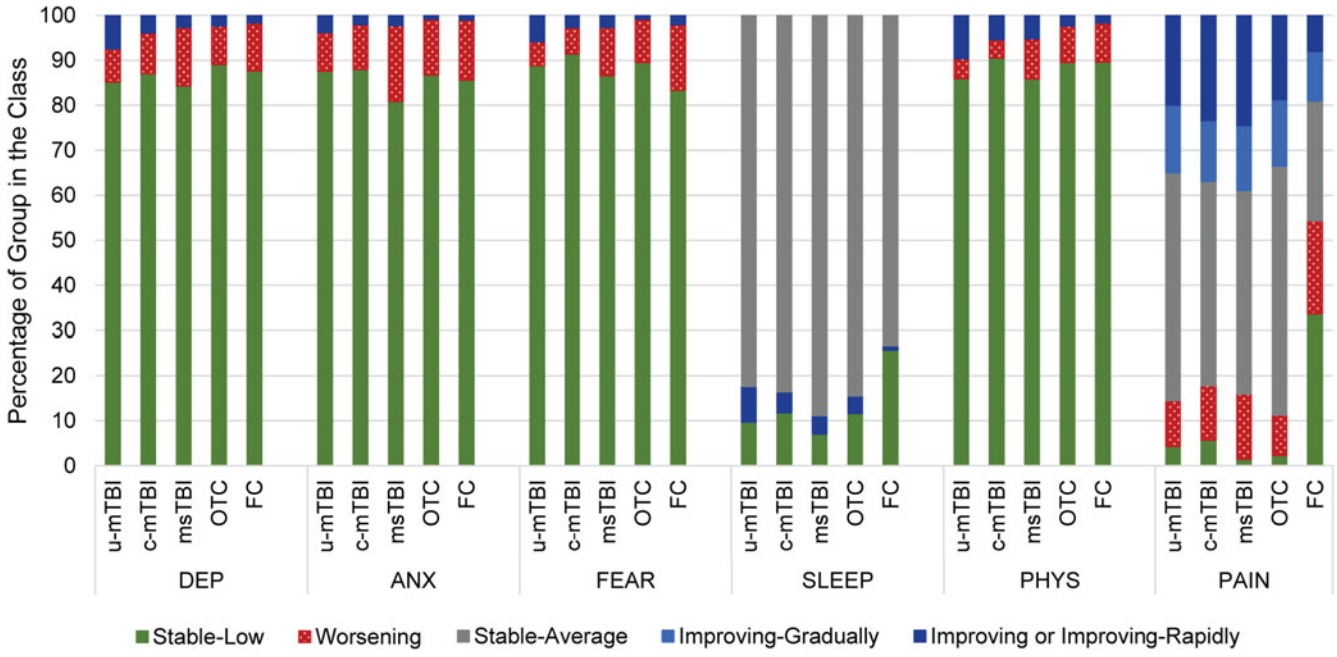

Figure 3. Association between injury group and neuropsychiatric trajectory group.
Note. ANX, anxiety; c-mTBI, complicated mild traumatic brain injury; DEP, depression; FC, friend controls; msTBI, moderate-severe TBI; PHYS, physical; OTC, orthopedic controls; u-mTBI, uncomplicated mild traumatic brain injury.

The moderate-severe TBI group had significantly higher proportions in the Worsening trajectories compared to u-mTBI for Depression (13.0% *v.* 7.3%) and Pain (14.4% *v.* 10.2%) and for Anxiety compared to both mTBI groups (16.9% *v.* 8.6–10%). Moderate-severe TBI also had higher proportions in Stable-Average Sleep compared to FC (73.3%) and both mTBI groups (88.8% *v.* 82.4–83.6%).

FC had a significantly higher proportion of Stable-Low Pain (33.7% *v.* 1.5%–5.7%) and Sleep (25.7% *v.* 7.1–11.7%) compared with all other groups. All TBI groups as well as OTC evidenced a significantly higher proportion of Stable-Average Pain compared to FC (45.2–55.3% *v.* 26.7%). However, FC had a higher proportion of Worsening Pain compared with all other groups except moderate-severe TBI (20.7% *v.* 8.9–12.1%). Additionally, within Pain, TBI groups and OTC evidenced significantly higher proportions of Improving-Rapidly trajectories (18.7–24.4%) compared with FC (8.0%). There were no differences among the groups within the Improving-Gradually Pain trajectory.

Discussion

In this large U.S.-based sample that included individuals treated at level 1 trauma centers for traumatic injuries (TBI, OTC), we found diverse longitudinal trajectories of neuropsychiatric symptoms over 12 months that markedly diverged from the well-documented course of symptom recovery evinced from group-averaged data. Group-averaged data of samples with traumatic injuries display, on average, marked symptoms following injury that gradually improve within the first 3 months, followed by slow or minimal improvement thereafter (Belanger et al., 2005; Carroll et al., 2004; Rohling et al., 2011). However, for the present study, only a minority of individuals fell into a trajectory group that paralleled this average symptom course. For internalizing symptom dimensions (Depression, Anxiety, Fear) and the Physical dimension, none of the identified trajectories displayed the prototypical average-level symptom course. Instead, across the 12 months of follow-up, participants most often displayed resilience in these domains manifested in consistently low symptoms (Stable-Low; 86.2–88.6%). Participants with TBI who displayed elevated symptoms in these domains, showed varied courses, including high levels of initial symptoms that steadily improved (i.e. Improving; 2.6–4.9%; most likely in persons with less severe TBI) or lower symptoms that worsened to clinically elevated levels (Worsening; 7.7–10.9%; more likely in persons with more severe TBI). In contrast, Sleep and Pain symptoms displayed more distinct rates across trajectory groups, with most individuals displaying an average level of symptoms that remained stable over time (Stable-Average; 46.7–82.6%). One Pain trajectory (Improving-Rapidly; 19.5%) closely resembled the group-average findings, with injured participants displaying an average level of early symptoms that resolved quickly over the first 3 months.

These findings provide an important referent for gauging typical *v.* atypical recovery and can help inform clinical discussions with patients about what to expect in their recovery over the first 12 months post-injury. That a substantial minority of participants displayed stable or mildly improving symptoms over the first 3 months followed by worsening symptoms from 3 to 12 months (5.6–13.9% across symptom dimensions) further emphasizes the heterogeneity of neuropsychiatric symptom recovery following TBI that has been emerging in the broader TBI literature in recent years (Brett et al., 2021; Carmichael, Hicks, Gould, Ponsford, & Spitz, 2023). The heterogeneity in recovery trajectories also highlights the value of using transdiagnostic approaches to more precisely detect these symptoms, as the use of traditional psychiatric diagnoses results in high rates of subclinical and comorbid diagnoses (Alway, Gould, Johnston, McKenzie, & Ponsford, 2016).

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Depression, anxiety, fear, and physical trajectories

Investigation of the relations between injury group and Depression, Anxiety, Fear, and Physical dimensions revealed several important findings. First, our finding that Stable-Low Depression comprised the most common trajectory group is consistent with prior studies (Bombardier et al., 2016; Gomez et al., 2017). In contrast, we did not find a persistent depressive group in our sample, with possible reasons including methodological differences in how depression was measured (transdiagnostically *v.* a single self-report measure), the inclusion of OTC and FC populations in our sample, or alternatively, that our sample did not include a significant proportion of individuals with persistent depressive symptoms. Second, the similar pattern of trajectories between the Physical dimension and the three Internalizing dimensions was notable and may reflect common co-occurrence of physical symptoms (e.g. dizziness, fatigue, psychomotor retardation/agitation, appetite changes) with internalizing symptoms. Third, persons with less severe TBI (u-mTBI) more often fell into the Improving class, with elevated early symptoms that resolved to low levels by 12 months. This is promising, as it indicates that despite u-mTBI being associated with higher symptom severity at 2 weeks than more severe TBI (Belanger, Kretzmer, Vanderploeg, & French, 2010; Nelson et al., 2021), these symptoms typically improve markedly or completely over time. Fourth, persons with moderate-severe TBI were more likely to display less favorable trajectory outcomes for all dimensions compared with the u-mTBI groups. While it is unclear why moderate-severe TBI was more often associated with Worsening trajectories, we offer several hypotheses to explore in future work. First, these less favorable trajectories could reflect initial limited insight into TBI-related deficits and symptoms, followed by increasing awareness of these cognitive and functional changes. Another possibility is that emotional distress increases as persons with moderate-severe TBI exhaust treatment and rehabilitation opportunities and/or come to the realization that injury sequelae may be persistent. Finally, Worsening symptoms may have occurred for reasons other than TBI. Nevertheless, the group comparisons in Worsening trajectories might counter the clinical narrative that experiencing worsening symptoms after TBI is related to factors such as motivation for secondary gain (Belanger et al., 2005; Mooney, Speed, & Sheppard, 2005). Research to clarify factors associated with distinct outcomes will be important for identifying ways to promote resilience following TBI.

Sleep and pain trajectories

The forms and occurrence rates of symptom recovery were more distinct for Sleep and Pain. Across all groups, most participants showed a stable trajectory of sleep problems across time, reporting either a consistently average level (Stable-Average; 82.6%) or a consistently low level of such problems (11.9%). A Stable-Average trajectory was more evident in all traumatically injured groups than in the FC group. This aligns with other work reporting a high prevalence of persistent, low levels of insomnia in persons with TBI (Wickwire et al., 2022). Interestingly, our results did not reveal a worsening trajectory for sleep as was found by Wickwire et al. (2022), and in all other symptom dimensions in this study. The stability of the dominant sleep trajectories might indicate that sleep problems were commonly pre-existing, which raises the possibility that sleep dysfunction could be a risk factor for sustaining traumatic injuries (Tham et al., 2012). On the other hand, if sleep symptoms were attributed to injuries, their stability would imply that sleep was not adequately addressed by participants' medical care. However, these alternative explanations are speculative and similarly plausible, and additional research is needed to clarify the causal factors contributing to sleep disturbance in persons with traumatic injuries.

The course and injury correlates of Pain symptoms were also distinct from other symptom dimensions. Whereas displaying consistently low symptoms was most common for internalizing and physical symptoms, only a minority of the injury groups (1.5–5.7%) showed this trajectory for Pain. Instead, similar to Sleep, it was most common for persons with traumatic injuries to report a stable, average level of symptoms across time (Stable-Average; 45.2–55.3%). The next most common trajectories for those in the injury groups included having elevated 2-week symptoms followed by rapid (Improving-Rapidly; 18.7–24.4%) or gradual (Improving-Gradually; 13.4–15.0%) improvement. Persons with moderate-severe TBI were more likely to display a Worsening Pain trajectory relative to u-mTBI, consistent with the other symptom dimensions. Interestingly, while the FC group generally displayed more favorable Pain trajectories than the injured groups (e.g. higher proportion [33.7%] in the Stable-Low trajectory, lower proportion [26.7%] in the Stable-Average trajectory), there was a surprisingly high proportion (20.7%) with Worsening pain over time. This finding highlights that the diverse symptoms associated with TBI are commonly reported by purportedly healthy individuals (Asken et al., 2017; Garden & Sullivan, 2010; Iverson & Lange, 2003). This finding can also be seen in other symptom dimensions, where the FC group contributed cases to the symptomatic groups. It should also be noted that the FC group included individuals with a psychiatric history as well as a history of TBI (though not in the last year), and thus ongoing psychiatric symptoms and/or long-term symptoms related to prior TBIs may have contributed to these findings.

Limitations

One limitation of this study is its focus on novel symptom dimensions identified via factor analysis of multiple measures, which precluded our ability to apply established clinical cutoffs to well-known neuropsychiatric symptoms scales. However, our use of empirically derived, transdiagnostic symptom dimensions may have advantages, as they may reflect more precise, homogeneous constructs than traditional heterogenous psychiatric diagnostic categories (Cuthbert & Insel, 2013; Insel et al., 2010; Kotov et al., 2017, 2021). This increased precision may lead to a better understanding of the neurobiological underpinnings of TBI sequelae and/or more precise treatment approaches. Additionally, we overcame the lack of clinical cutoffs by using the non-injured FC group as a point of normative comparison to interpret factor scores (online Supplementary eTable 3). Second, due to the limited number of timepoints available, our use of piecewise modeling may not have captured more symptom fluctuations which could be informative for treatment. Another limitation is that the multifaceted descriptive results precluded a thorough examination of the factors that predict different symptom trajectories. For example, certain causes of injury (i.e. assault/violence) have been associated with greater emotional symptoms (Bown et al., 2019; Mathias, Harman-Smith, Bowden, Rosenfeld, & Bigler, 2014) and social determinants such as type of health insurance has been associated with worse outcomes

https://doi.org/10.1017/S0033291724001211 Published online by Cambridge University Press

following TBI (Yue et al., 2024). Further research is needed to explore the role of factors such as these on symptom trajectories. Finally, this study sample predominately included individuals with mTBI, with a smaller portion of individuals with moderate-to-severe TBI. Of this latter group, there was even a smaller number of individuals with more severe TBI, requiring us to combine persons with admission GCS scores of 3–12 into a single broad group. Given greater severity, it is also quite possible that individuals with more severe TBI may have had limited engagement in the 2-week post-injury assessment.

Conclusions

This study employed a 6-dimensional model of neuropsychiatric symptoms (i.e. Depression, Anxiety, Fear, Sleep, Physical, Pain) previously derived from participants at 2 weeks post-injury to characterize individual trajectories of symptoms over 12 months. Its findings counter the prevailing clinical notion that TBI-related symptoms are typically maximal right after injury and then gradually resolve within 3 months. Instead, a substantial portion of individuals with milder and more severe TBI displayed either continuously low symptoms, steady improvement beyond 3 months, or worsening symptoms from 3 to 12 months post-injury. Long-term symptom improvement was more common following u-mTBI, whereas less favorable trajectories were more common after moderate-severe TBI. These findings can inform discussions with patients about the degree to which their experiences of recovery are typical. They also highlight the value of using transdiagnostic approaches and longer-term clinical follow-up for TBI to detect and provide early intervention for worsening symptoms that occur in a non-trivial minority of patients. Future research examining additional characteristics beyond TBI severity is needed to understand the factors that contribute to better long-term neuropsychiatric outcomes and help identify patients who would benefit from long-term monitoring and interventions to target persistent disabling symptoms.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724001211

Acknowledgement. None.

Funding statement. This secondary data analysis project was supported by the U.S. National Institute for Neurological Disorders and Stroke (NINDS; LN, grant number R01 NS110856). The TRACK-TBI study was funded by NINDS (GM, grant number U01 NS1365885), One Mind, and Neurotrauma Sciences LLC. The manuscript's contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health and are not necessarily endorsed by the other study sponsors.

Ethical standards. The study was approved by the institutional review board of each enrolling institution. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Competing interests. The authors have none to declare.

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