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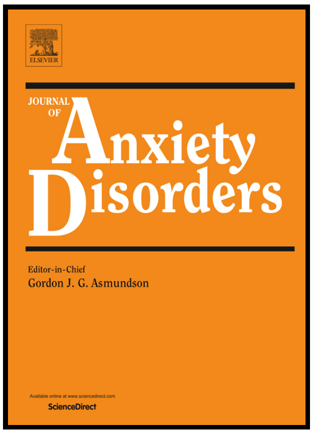

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Acute Stress and PTSD Among Trauma-Exposed Children and Adolescents: Computational Prediction and Interpretation

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Abstract

Background: Youth receiving medical care for injury are at risk of PTSD. Therefore, accurate prediction of chronic PTSD at an early stage is needed. Machine learning (ML) offers a promising approach to precise prediction and interpretation.

Aims: The study proposes a clinically useful predictive model for PTSD 6-12 months after injury, analyzing the relationship among predictors, and between predictors and outcomes.

Methods: A ML approach was utilized to train models based on 1,167 children and adolescents of nine perspective studies. Demographics, trauma characteristics and acute traumatic stress (ASD) symptoms were used as initial predictors. PTSD diagnosis at six months was derived using DSM-IV PTSD diagnostic criteria. Models were validated on external datasets. Shapley value and partial dependency plot (PDP) were applied to interpret the final model.

Results: A random forest model with 13 predictors (age, ethnicity, trauma type, intrusive memories, nightmares, reliving, distress, dissociation, cognitive avoidance, sleep, irritability, hypervigilance and startle) yielded F-scores of .973, .902 and .961 with training and two external datasets. Shapley values were calculated for individual and grouped predictors. A cumulative effect for intrusion symptoms was observed. PDP showed a non-linear relationship between age and PTSD, and between ASD symptom severity and PTSD. A 43% difference in the risk between non-minority and minority ethnic groups was detected.

Conclusions: A ML model demonstrated excellent classification performance and good potential for clinical utility, using a few easily obtainable variables. Model interpretation gave a comprehensive quantitative analysis on the operations among predictors, in particular ASD symptoms.

Keywords

PTSD, acute stress, machine learning, prediction, computational interpretation

Introduction

Injury is a major health problem for children and adolescents (Branche, Ozanne-Smith, Oyebite & Hyder, 2008). A large longitudinal study in Canada showed that given any year of the investigated 9 years, 21% of participants had at least one injury and repeat injuries were common (73%) (Spady, Saunders, Schopflocher & Svenson, 2004). The causes of injury vary from unintentional accidents such as motor vehicle crashes, sports, fires, falls, to interpersonal assaults, violence or abuse. Besides potential consequences such as death and disability, 13-22.5% of injury-exposed youth are susceptible to PTSD regardless of the cause (Aaron, Zaglul & Emery, 1999; de Vries et al., 1999; Marsac, Kassam-Adams, Delahanty, Widaman, & Barakat, 2014; Olofsson, Bunketorp & Andersson, 2009, van Meijel et al., 2019). As youth are moving through pivotal developmental stages, trauma exposure and PTSD at a young age not only confer risks for other mental health issues such as anxiety and depression (Marshall, 2016) but also double the chance of having depression and PTSD in adulthood compared to peers with the same trauma exposure but occurring at later in life (Dunn, Nishimi, Powers, & Bradley, 2017).

It is therefore very important to develop precise prediction tools to identify PTSD at an early stage and design interventions to minimize the enduring effect of pediatric PTSD. To date, the field mainly relies on two approaches to estimate risks – risk analysis using general regression modeling (i.e. general linear modelling [GLM]) and PTSD screening measures. Although both approaches provide directional prediction for trauma-exposed groups, neither is currently sufficient to quantitively forecast PTSD in an individual with accuracy in a way that is useful in the clinical setting. Saxe et al. (2017) argue that although risk identified by GLM analysis may help clinicians to roughly evaluate the risks, the method is not able to incorporate the complexity involved in making predictions in an individual case. In regard to the utility of PTSD screening tools, these measures are typically designed to assess exposure and PTSD symptoms rather than to provide a prognosis. Moreover, a systematic review study that examined 18 measures for children and adolescents (Eklund, Rossen, Koriakin, Chafouleas, & Resnick, 2018) reported that only six of them had more than one study examining their psychometric properties. They also reported general lack of sensitivity or specificity such that one could have confidence in avoiding too many false positives or negatives.

The prediction problem may be addressed with the introduction of rapidly growing machine learning theories and technologies. Machine learning (ML) refers to the field of study that gives computers the ability to learn without being explicitly programmed (Samuel, 1959) and it has changed medical research profoundly (Rajkomar, Dean & Kohane, 2019). Among 49 PTSD studies that utilized ML techniques, 33 (67%) were prognostic studies and all of them yielded fair to good performance (Ramos-Lima et al., 2020). In particular, a proof-of-concept study (Saxe et al., 2017) compared five ML classification methods (Support vector machine, i.e., SVM, linear, SVM poly, SVM RBF, Random Forest, Lasso) to two conventional methods (logistic regression, stepwise logistic regression) in children and adolescents hospitalized with injuries. All five ML algorithms outperformed regressions in terms of AUC (area under curve, a common metric indexes classification accuracy), where regression models performed no better than chance level. The encouraging results suggested that ML held great potential in determining predictive PTSD classification models. Thus, one of the aims of this study is to develop a PTSD prognostic model that can be efficiently deployed in clinical practice.

ML applications are not free from caveats, however. First, it is consistently observed that although ML models function well in testing data, they often exhibit unexpectedly poor behavior when they are deployed with unseen data and real-world domains; this is referred to as the credibility challenge (D'Amour et al., 2020). Secondly, while the prediction model may generate perfect outputs, it will provide limited information as to how exactly the inputs are related to the outputs or how the features work together to produce the results. This issue is referred to as "the black box problem" (Castelvecchi, 2016).

Luckily, the credibility challenges can be mitigated by external validation (Schultebraucks & Galatzer - Levy, 2019), while interpretable machine learning (IML) is a feasible solution for the black box problem. IML, in a nutshell, deciphers the relationship by decomposing the models (Molnar, 2020). A few model-agnostic theories have been developed to understand a feature's influence over the outcome. Common methods include PDP (Partial Dependence Plots) (Friedman, 2001), permutation feature importance (Fisher, Rudin & Dominici, 2019), Shapley values (Shapley, 1997) and SHAP (SHapley Additive exPlanations) (Lundberg & Lee, 2017).

Schultebraucks et al. (2020) demonstrated a good example of how to address these validation as well as interpretation issues. In their study, set out to build a predictive formula for non-remitting PTSD 12 months after discharge from the emergency department, Schultebraucks and colleagues trained and tested a model using 70 variables extracted from longitudinal cohort data collected at one site. They externally validated the model against another prospective cohort from the second site. Thus, the algorithm was proved to be reproducible across independent samples. Moreover, they also reported SHAP values for each predictive feature to determine their importance in predicting.

Following a similar approach, we aimed to develop a predictive ML function for children and adolescents after exposure to single-incident trauma. The two objectives of the research were 1) to fit a model that is precise, robust, and succinct that withstands thorough external validation; and 2) to use IML techniques to deconstruct the model and to look at feature importance for a better understanding of the operations of the PTSD risks.

Material and Methods

ML workflow and key concepts

Details of a ML task can be technically complex. In their proof-of-concept study, Saxe et al. (2017) gave an in-depth description on the key concepts pertinent to supervised classification task for PTSD prediction. A diagram summarizing the ML method is available in the supplementary material (Appendix I: Overview diagram of supervised machine learning). To summarize, there are usually a diverse selection of methods to accomplish a task. For example, a classification task can be done using GLM, SVM, random forest (RF), classification and regression tree (CART) and so on, with plenty of variants within each group. Hence, it becomes important to use cross-method metrics to evaluate the performance of each option. Notably, there is also a circumstantial aspect playing in the modeling decision making, as sometimes a method is chosen merely because of its availability (e.g. access to the software). This contingent element should not be overlooked as feature importance is conditional on methods. That is, a feature found to be highly influential in one model may not necessarily be predictive in another. In particular, since the study examined the clinical implications of the risks and their relationships, it is helpful to fit the model with different methods to optimize the outcomes.

Dataset and study inclusion criteria

We utilized the PACT/R data archive as the data source (https://www.childtraumadata.org/datasets-pactr-archive). PACT/R is an international depository of prospective PTSD studies tracking symptoms and recovery following acute trauma among children and adolescents (Kassam-Adams et al., 2020). In order to fulfill the aim of the study, we decided on the following inclusion criteria, where a study must

- have PTS assessment within one-month posttrauma;
- have PTS assessment at 6-12 months, where the measures are compatible with DSM-IV PTSD diagnostic criteria; and
- have good retention rates (i.e., missing data rate < 40% at any sampling point).

After applying the screening criteria, nine studies comprising 1,167 records were included.

Predictive variables

Although a ML design is data-driven and what is fed into the model is flexible, overarching principles are needed to ensure the analysis is effective and meaningful. Regarding the predictor variables, previous studies have suggested that integrating multiple post-traumatic stress (PTS) risk variables improves accuracy (Galatzer-Levy, Karstoft, Statnikov, & Shalev, 2014; Karstoft, Galatzer-Levy, Statnikov, Li, & Shalev, 2015; Saxe et al., 2017; Schultebraucks et al., 2020). We therefore sought in the present study to make use of a broad range of dimensions, including acute stress disorder (ASD) symptoms, trauma characteristics, biological samples, demographic data and pre-trauma indices. However, some variables, especially from pre-trauma and the biological domain, were reported by too few studies to be considered, leaving our choice of predictors to largely consist of demographic, trauma characteristics and ASD symptoms.

To note, unlike other variables that can be retrieved directly from PACT/R, ASD symptoms are compound constructs measured by multiple items depending on the instruments each study employed. To ensure cross-study compatibility, we mapped the measure items into the 14 symptoms described in the DSM-5 ASD criterion B (see details in data harmonization).

Outcome variable

In respect of outcome variables, a binary label of meeting the PTSD diagnosis or not at six months onwards would be used, as it is unlikely that a child would lose a PTSD diagnosis without intervention beyond six months (Hiller et al., 2016).

Measures

The cross-study dataset presented diverse PTS measures from self-report questionnaires to structured clinical interviews, most of which are compatible with the DSM-IV PTSD or ASD diagnostic scheme (see supplementary appendix A: PTS measures for the details of the measures).

Post-hoc model interpretation

PTSD incorporates a broad range of symptoms that are usually categorized into clusters (i.e., intrusion, dissociation, negative mood, avoidance and arousal); since a significant part of the predictors in this study were ASD symptoms, it is of clinical interest to discern how these clusters as a whole influence the outcome. Therefore, we not only examined how each feature contributed to the prediction in the final model but also examined groups of features.

Two methods were utilized: feature importance and grouped feature importance, based on Shapley values (Shapley, 1953) from local model-agnostic approaches and PDP from global model-agnostic approaches.

Shapley feature importance. Shapley value was first proposed to explain the contribution of a feature value to the difference between the actual prediction and the mean prediction. Casalicchio, Molnar and Bischl (2018) extended the concept to the model's performance (rather than its outcome) and used it as a way to compare relative importance among features. More importantly, Au, Herbinger, Stachl, Bischl, and Casalicchio (2021) recently developed grouped Shapley importance (GSI), an algorithm that measures the importance of a group of features by the expected loss when these features are perturbed in a permutation approach or removed in a refitting approach. The complete R code can be found at: https://github.com/JuliaHerbinger/grouped_feat_imp_and_effects. Of note, GSI is not equivalent to the sum of Shapley importance of each individual features in the group. GSI scores account for feature interactions as they measure the average contribution of a given group to all possible combinations of groups and fairly distribute the importance value caused by interaction values among all groups. In other words, the larger the gap between GSI and sum of individual Shapley value, the higher level of interaction within the group.

PDP is a global model-agnostic method that focuses on the average behavior of a model. The plot describes the predicted values based on the distribution of the data when all other features are marginalized out. The advantage is that it displays the relationship between the target and a feature (e.g., linear, monotonic). We used the R package "iml" (https://cran.r-project.org/web/packages/iml/index.html) to run the PDP analysis.

Calculation

Data harmonization and missing data

There are a marked number of PTS measures across studies. To combine them in a comparable view requires an extra step called data harmonization. We adopted two different harmonizing strategies for the measures to be used as *outcome* variables and the measures to be used as *predictive* variables. Missing data were handled at two levels: during and after data harmonization (see supplementary Appendix K: Data harmonization and missing data handling, for details).

Predictor correlation checking

It is routine to check the correlation among predictor features and the strongly correlated features will be reduced to one to represent the group. No strong linear associations were found within the 23 candidate predictors (see supplementary Appendix F: List of candidate predictive features and correlation matrix). The tentative predictive variables are age, gender, ethnicity, trauma type, if it is a direct exposure, trauma history, if it involves multiple injuries, days of hospitalization, pulse at hospital admission, and 14 symptoms in DSM-5 ASD cluster B.

Model fitting

We chose "caret" R package (https://cran.r-project.org/web/packages/caret/caret.pdf) to fit the models because of its versatile ML functions and extensive community support. Importantly, we picked four commonly used ML classification families (GLM, CART, RF and SVM; see Appendix J: Brief introduction of 4 classification machine learning algorithms) to minimize the chance effect of method selection, and each of them were applied in the same procedure.

Metrics for model evaluation.

The PTSD outcome (positive) was about 5% in our sample; therefore, the dataset was highly imbalanced. With imbalanced data, accuracy is no longer a reliable way to evaluate classification performance (Metz, 1978). Because this study was mostly concerned with the positive class (i.e., cases diagnosed with PTSD), false positive (i.e., wrong diagnosis) and false negative (i.e., missing the diagnosis), we used F-score, also called F-measure, as the primary matric (Sun, Wong, & Kamel, 2009). The formula illustrates the calculation of the F-score:

Precision = True Positives / (True Positives + False Positives),

Recall = True Positives / (True Positives + False Negatives),

F-score = (2 * Precision * Recall) / (Precision + Recall),

where precision describes the true positive rate, recall describes the positive predictive value, and F-score is the harmonic mean of the two. A high F-score ensures that both precision and recall are reasonably high. We reported Precision, Recall and F-score values to compare the model performance. In addition, we included the conventional AUC for extra reference.

External validation and second external validation

We planned to use a PACT/R study (PACT/R studyID = 1036 and 1008; N=221) not included in the original dataset to serve as the external dataset. The two studies met all inclusion criteria except the PTSD outcome measure was assessed at 3-6 months rather than 6 months onwards. We hope the similarity as well as the variation make them a good source for external validations.

Model diagnostic and finalizing

We aimed to identify one final winner model based on F-scores despite not being the only consideration. In case of close performance, we would favor a model with fewer predictors for more generalization potential. As GLM is a parametric method, post-hoc model diagnostics would be required. We accepted or rejected the model according to the assumption diagnostic results.

Results

Dataset description

Nine studies comprising a total of 1,167 participants were included in the final dataset. Besides the apparent heterogeneity in PTS measures, the dataset contained a large degree of homogeneity in other characteristics. Participants were recruited either via EDs or hospitals. All studies almost covered a whole school age range, except one study investigating injury in young children (5-7 years old). In terms of trauma type, the prevalence of interpersonal trauma in most of the studies is quite low except for one that has interpersonal assault cases in more than half of its samples. Overall, the distribution of trauma types was: Injury: 49.87%, Interpersonal: 10.63%, Medical: 1.20%, and RTA: 35.65%, where "RTA" refers to road traffic accidents, "Interpersonal" refers to intentional injuries, "Injury" refers to other accidental injuries, and "Medical" refers to health related incidents. In addition, the external validation study (1036) exhibited much higher PTSD rates in non-interpersonal traumas, which is distinct from the studies in the main dataset. Detailed study characteristics are summarized in **Table 1**.

Models

We tried several methods from the four method families and picked one final option for each. The shortlisted R methods were: glm, treebag, rf and svmLinear2 (see "A List of Available Models in train" in the caret documentation). We initially entered 23 features into the candidate models, 14 of which were harmonized DSM-5 acute symptom variables. We trained the models with main configurations of 70% as training set, 10 times * 5 repeats repeatedCV, sampling = up (see supplementary Appendix G: R scripts of model training and testing for details).

Table 2 lists the final predictive features and the performance metrics. All four trained models yielded good to excellent values in precision, recall and F-score values with the testing dataset, while yielded disparate results in external validation. The RF model reported stable excellent F-scores (.973). Notably, we experimented with alternative models using only the ASD symptoms that were listed in the four candidate models. All methods returned slightly reduced scores compared to the original model.

Final model

Weighing all the metrics, Fandom Forest was the final winner model given its consistently high F-scores in the model internal testing, ASD feature only prediction and external validation. In addition, the RF model again reported excellent results (precision: .925, recall: 1 and F-score .961) in the secondary external validation. The final model utilized a total of 13 features including age, ethnic minority status, type of trauma, intrusive memories, having nightmares, reliving emotional or physiological distress, altered sense of reality, avoiding thoughts and feelings, sleep disturbance, irritability, hypervigilance and exaggerated startle.

Model interpretation

Individual and grouped feature importance. We first organized the total 13 features into four groups: age, ethnicity, trauma type and ASD symptom group, comprised of ten ASD symptom items (Figure 1a). Their Shapley values were .016, .019, .039, and .328 respectively. We then broke the ASD group into four clusters: intrusion, dissociation, avoidance and arousal. Figure 1b illustrates the Shapley importance on the cluster level (left) on the feature level (right). The Shapley values of the four clusters in order were: .110, .023, .071, and .145. Last, we listed the Shapley values for all the features in Figure 1c. The numbers read: .016, .019, .039, .013, 0, .007, .007, .015, .071, .009, .040, .047, .075.

PDP displays the probability of positive PTSD given different values of the feature (s). We sorted the 13 features into three groups: age, categorical predictors (trauma type, minor ethnic group) and ASD symptom predictors. Figure 2a illustrates that the risk does not change by age between 5 and 16 while there is a 50% increase around age 16, leaping from .096 CI [.0871, .106] to .157 CI [.148, .166]. Figure 2b shows the risk by each ethnicity and trauma type category in order. Being exposed to interpersonal trauma or belonging to a minority ethnic group imposes greater risk than a having medical, injury, RTA or other trauma. There is a 43% difference in the risk between non-minority and minority groups (.085 CI[.076, .094] and .122 CI[.112,.132]) whereas the increment can be as high as 55% between the lowest risk group and the highest (.072 CI[.064, .079], .122 CI[.112,.132]).

Figure 2c shows the influence of individual ASD symptoms in a comparative view. Regardless of the fluctuation, a higher level of ASD symptoms in general predicts a higher chance of six months PTSD with irritability having the relatively strongest influence. It is also notable that the risk rises significantly once the severity of an ASD symptom reaches 75% of the full scale.

Discussions

With the aim of developing a robust PTSD prognosis tool using ML, we built a model using harmonized data pooled from nine prospective studies. In spite of the heterogeneity in PTS measures and study characteristics, the random forest model yielded excellent discriminatory accuracy, both internally and externally, using two demographics, one trauma type and ten ASD symptom variables as predictors. While it is often believed that structured clinical interviews are the gold-standard for PTS symptom assessment, many ASD symptoms in this study were collected by self-report questionnaires. Since the model used harmonized variables in both predictive features and PTSD outcome, it is compatible to any PTS measures as long as they properly assess DSM-5 acute symptoms and follow the diagnostic framework. The flexibility and easily obtainable predictor of the model suggest that it is highly apt to clinical administration.

Regarding the specific predictors, the three non-ASD features: age, ethnic minority, trauma type were the common intensively studied factors. Younger age, ethnic minority and interpersonal trauma in general are considered to be associated with greater risk of having PTSD (Alisic et al., 2014; Trickey et al., 2012). ASD symptoms made up the majority (10 out of 13) of the final predictors and the ASD-symptom-only models, although slightly less potent, were still adept. Although the final model incorporates other factors (e.g., trauma type, ethnicity, age), we infer that acute phase symptoms are essential predictors of PTSD.

Predicting PTSD from acute phase symptoms is not new to the literature while what makes the best selection of predictors has been a long-term research interest. An early study seeking symptom-based screening instrument for adults found that endorsing a random combination of minimum six intrusion or arousal symptoms produced the best efficiency in non-interpersonal accident and violent crime samples (Brewin et al., 2002). Kassam-Adams and Winston (2004) reported that, among injured children, full-blown ASD had much lower predictive power in comparison to meeting any one of the four symptom cluster criteria (especially arousal and dissociation). It is therefore not surprising that the ASD features in the model did not cover the entire set of ASD symptoms, mainly encompassing the symptoms of intrusion and arousal.

The inclusion of cognitive avoidance into the model was only to be expected. According to the cognitive model of PTSD (Ehlers & Clark, 2000), cognitive processes relating to the memory of the traumatic experience is central to the development and maintenance of chronic PTSD. It is also consistent with the findings where aspects of emotion regulation, in particular thought suppression and experiential avoidance (i.e., cognitive avoidance), demonstrated the strongest association with PTSD (Seligowski, Lee, Bardeen & Orcutt, 2015). In children and adolescents, a meta-analysis found that thought suppression and distraction, forms of cognitive avoidance had the largest and the fourth largest effect sizes (.70 [.51, .88] and .47 [.12 , .83] respectively) among the 25 PTSD risks (Trickey et al., 2012).

While all 13 predictors appear to be "conventional", we would like to stress that the merit of utilizing ML is its ability to engineer novel algorithms that outperform traditional models, even using the same predictors. To demonstrate the point, a conventional logistic regression model using the same predictor variables and the same training set was trained. Prediction performance was evaluated on the same testing set and one of the external dataset (studyId = 1036). The model made no correct prediction for positive cases, making scores of precision, recall, and f-score all zero. It is not surprising as conventional model barely functions for individual case prediction when positive rate is low (5% in the current study, see details in Appendix L: Prediction by logistic regression and performance evaluation). This is a perfect example that how ML outperforms conventional models even when the predictors are the same.

The more important contribution of the study came from our model interpretation analysis. Doshi-Velez and Kim (2017) have argued that the need for interpretability arises from an incompleteness in problem formalization. Correct prediction only partially solves the problem: a model must also explain how it came to the prediction. Practically, IML is crucial to detect algorithmic biases and in the case of the present study where predictors were core PTSD symptoms, it should offer an informative source to examining the underlying mechanism in terms of how acute symptoms evolve into chronic PTSD.

The Shapley importance analysis gave a comprehensive view on the impact of the predictors and their potential interactions. On an individual feature level, it is clear that trauma type, cognitive avoidance, irritability, hypervigilance and startle had two to four times greater importance than the remaining variables (Figure 1c). At the cluster level, the intrusion and arousal clusters were unquestionably the most influential (Figure 1b). Because GSI incorporates the impact from feature/group interaction, we were able to quantify the interaction level by the gap between GSI and the sum of the Shapley values of group member. When no higher-order interactions are present, the sum should add up to GSI and the larger gap suggests a higher level of interaction among group members. As per this logic, it can be deducted that interaction was low within the four arousal symptoms (.171 vs .145) and between the four ASD clusters (.349 vs .328). What was striking is that the Shapley values were fairly low for the individual intrusion symptoms (.013, 0, .007, .007) but its GSI value as a group was four times the sum of member importance (.110), suggesting a significant level of interaction. A cumulative effect might be a way to interpret such a phenomenon. Cumulative effect refers to the result of multiple factors whose individual direct impacts may be relatively minor but in combination are significant. In the case of the intrusion cluster, while one single symptom may not be of concern, there could be a disproportionate increase in the likelihood of PTSD when all intrusion symptoms are present.

The PDP analysis strived to answer an intuitive question which is: what is the probability of having PTSD 6-month post trauma given a value of a predictor? The figures of continuous variables (age and ASD symptoms) saw consistent non-linear patterns in the relation between the predictors and PTSD outcome. Specifically, the age plot depicted a flat, no change of risk line before age 16, followed by a surge at age 16. Likewise, Figure 2c showed that mild to moderate ASD symptoms did not predict PTSD until it became severe (3/4 of the full scale). These patterns partially explain why non-linear algorithms such as RF and CART performed better.

The spike of PTSD at age 16 is worth mentioning given that the influence of the developmental factor in this age group has long been of interest (Salmon & Bryant, 2002). A previous study looked at the age difference in PTSD symptom structure and found that symptoms can be measured more precisely in adolescents than in younger children as adolescents reported greater symptom severity for reliving, numbing and arousal (Contractor et al., 2013). The advanced developmental stages in adolescents may explain the phenomenon. A study looking at brain development suggests that critical brain regions undergo significant change in childhood and that developmental differences may be affected by traumatic stress. (Weems, Russell, Neill, & McCurdy, 2019). However, what exactly underlines the particular age-16 spike is unclear.

The categorical PDP of trauma type and ethnic minority displayed a finding of concern, namely that being in an ethnic minority group imposes the equivalent level of risk as interpersonal trauma. It is well known that interpersonal trauma is an exacerbating factor to developing PTSD across all ages (Alisic et al., 2014; Santiago et al., 2013) whereas the effect of ethnicity on youth PTSD is less studied. Trickey et al. (2012) reported a very small magnitude (.08 [.04, .12]) based on six studies. Since PDP describes an overall effect, there could be confounding elements involved, for instance, interpersonal trauma and gender were found to interact (Alisic et al., 2014) and children belonging to ethnic minority groups might be exposed to more interpersonal violence. However, these risks were not correlated in the dataset where the model was trained (see supplementary appendix F), which suggests that the culprit might reside in a more complex nexus. Considering attending medical care for injury is one of the most common potential traumatic experiences for children and adolescents, it is paramount to look further at what gives rise to this ethnic disparity.

Clinical implications and future research

Three findings from our model interpretation are highly pertinent to clinicians when assessing PTSD risk. First, a cumulative effect in the intrusion cluster was evident, suggesting that the number of the presenting symptoms matters. Second, simply belonging to an ethnic minority increases by 43% the chance of having PTSD after 6 months. Last, change in the probability of chronic PTSD and the ASD symptom severity were not linearly correlated; mild symptoms had a marginal effect while symptoms at high scale (75%) drastically pushed up the risk.

We speculate that the combination of ASD-symptom predictors together with their Shapley importance, albeit not causal, to some extent reflect their role in the etiology of PTSD. The fact that cognitive avoidance rather than behavioral avoidance was chosen and was one of the most influential factors, in part support the eminence of the cognitive model, which gives an extensive account of the role of maladaptive cognitions in PTSD. In contrast, the association between hyperarousal and PTSD is well known (Armour et al., 2020) and our model clearly confirms its significance while comprehensive theories addressing the potential mechanism are limited. A preliminary investigation suggests that prolonged negative mood states are a result of deficits in executive attention (Bardeen & Read, 2010). Future research should consider addressing this gap by focusing on the physiobiological side of the condition.

In respect of model building, the ML models as the final product that can be stored, duplicated and retrieved independently. This separation means that our model can be easily deployed for public access. Indeed, the next phase will be to build a web-based PTSD prognosis tool that is similar to clinical calculators widely used in hospital medicine (e.g., http://mdanderson.org/for-physicians/clinical-tools-resources/clinical-calculators.html).

Although the model holds potential, considerable barriers need to be worked out as PTSD screenings are not routinely implemented in hospitals. For example, in a study implementing a PTSD screening protocol in pediatric EDs (Ward-Begnoche et al., 2006), nurses reported that they felt uncomfortable asking children about subjective life threat ("did you think you might die"). Ultimately, its success will depend on how well the algorithm is deployed and how it integrates with the care system. Translational research shall follow up and monitor the feedback to continuously evaluate and improve its utility.

Limitations

The model is trained and tested on mainly unintentional, one-off trauma data from high income countries; therefore, its ability to generalize to other contexts such as multiple trauma or disaster or low- and middle-income countries needs to be tested. In addition, due to the availability of the data, the two datasets used as external validation presented PTSD outcomes at 3-6 months which did not fit the aim of the model precisely. Additional validation with 6-months PTSD outcomes would be desirable.

As PTSD is a function of time, trajectory profiling is considered to be a more comprehensive method than diagnosis at a single time point to classify outcomes. Schultebraucks et al. (2020) used latent growth mixture modeling to label the participants into “resilient”, “non-remitting”, “recovery” and “worsening” groups and then trained the model based on the non-remitting versus the resilient trajectory. However, in our dataset, PTS sampling time points differed across studies and therefore, trajectory modeling was not applicable. Furthermore, the outcome variable was derived from various PTS measures; it remains unknown how it would be consistent to the outcome if standard structure interview were applied.

The majority of the studies in the model training dataset utilized measures corresponding to DSM-IV whereas DSM-5 has become a common standard for PTSD in clinical practice and research since its release in 2013. The study mapped predictive symptoms to DSM-5, but the PTSD outcome variables still followed DSM-IV criteria due to the complexity involved in transferring DSM-IV measures into DSM-5 diagnosis. Although the estimated prevalence of PTSD using DSM-IV and DSM-5 is in general consistent (Kilpatrick et al., 2013) and predictive symptoms of the final model are compatible with

DSM-IV clusters, the differences between DSM-IV and DSM-5 are undeniable. Whether the model performs at the same level on DSM-5 data is unknown; it can be expected that more testing and tuning will be required to ensure a wider application of the model.

Conclusions

The study produced a machine learning (ML) algorithm to predict PTSD 6-months posttrauma for children and adolescents who had received medical care for injury. The model was trained by large international longitudinal data and has excellent classification performance. The model was proven to be highly robust by two external validations. The succinct model requires only 13 easily obtainable features (demographics and early symptoms) and therefore, has potential for clinical utility. Further model interpretation examined the importance ranking for each predictor and grouped features (ASD symptom clusters). Intrusion, arousal and cognitive avoidance are most influential in critical to chronic PTSD and a cumulative effect was detected within the intrusion cluster. PDP analysis revealed non-linear relations between age, ASD severity and probability of having PTSD. A disparity was found that belonging to ethnic minority groups increases the chance of having PTSD by 43% compared to non-minority groups.

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Figure 1a: overall importance

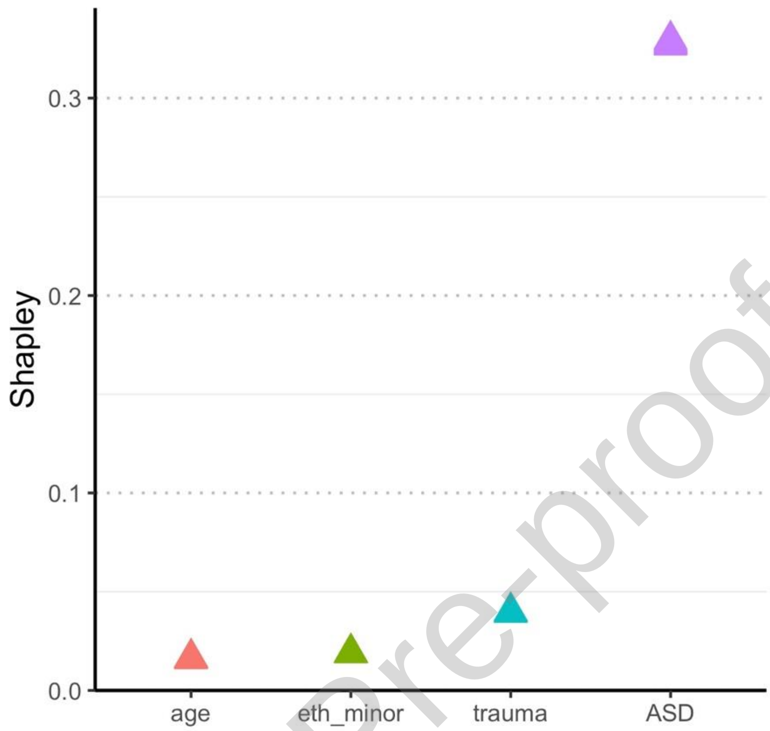
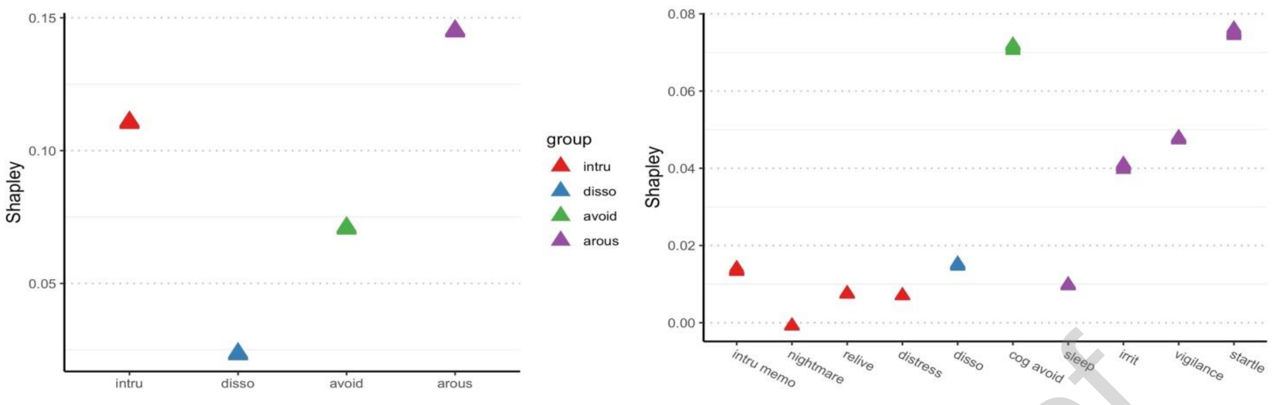


Figure 1b: Shapley importance on ASD clusters (left) and on ASD symptom level (right)



intru: intrusion cluster; **disso**: dissociation cluster; **avoid**: avoidance cluster; **arous**: arousal cluster; **intru memo**: recurrent, involuntary, and intrusive distressing memories; **nightmare**: recurrent distressing dreams; **relive**: dissociative reactions; distress: intense or prolonged psychological or physiological distress; **disso**: altered sense of the reality of one's surroundings or oneself; **cog avoid**: efforts to avoid trauma related memories, thoughts, or feelings; sleep: sleep disturbance; **irrit**: irritable behavior and angry outbursts; **vigilance**: hypervigilance; **startle**: exaggerated startle response

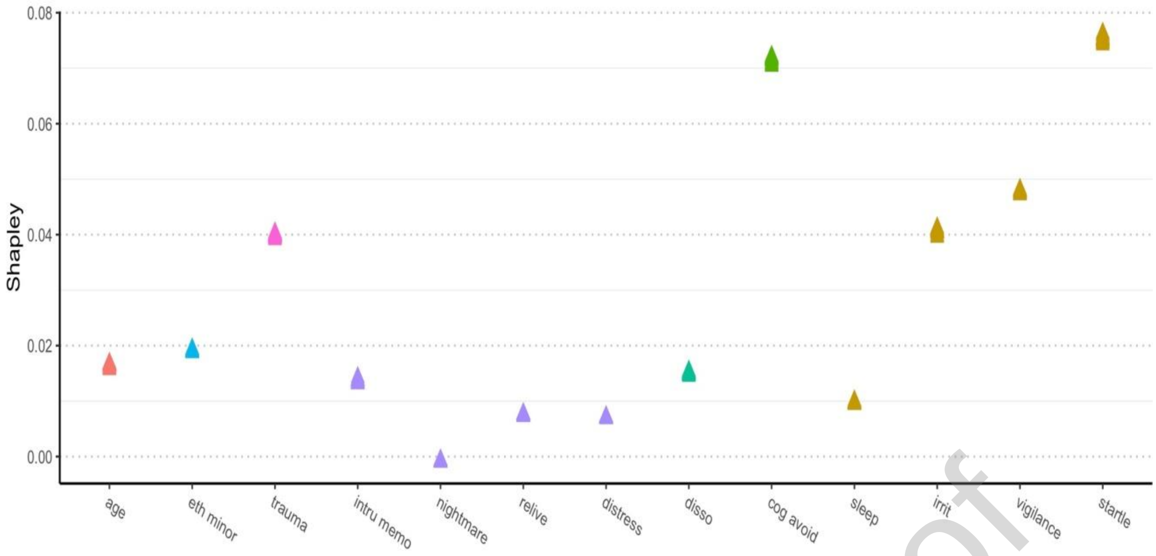


Figure 1c: Shapley importance on each predictive feature

eth minor: ethnic minority; **trauma**: trauma type; **intru memo**: recurrent, involuntary, and intrusive distressing memories; **nightmare**: recurrent distressing dreams; **relive**: dissociative reactions; distress: intense or prolonged psychological or physiological distress; **disso**: altered sense of the reality of one's surroundings or oneself; **cog avoid**: efforts to avoid trauma related memories, thoughts, or feelings; sleep: sleep disturbance; **irrit**: irritable behavior and angry outbursts; **vigilance**: hypervigilance; **startle**: exaggerated startle response

Figure 2a: PDP by age

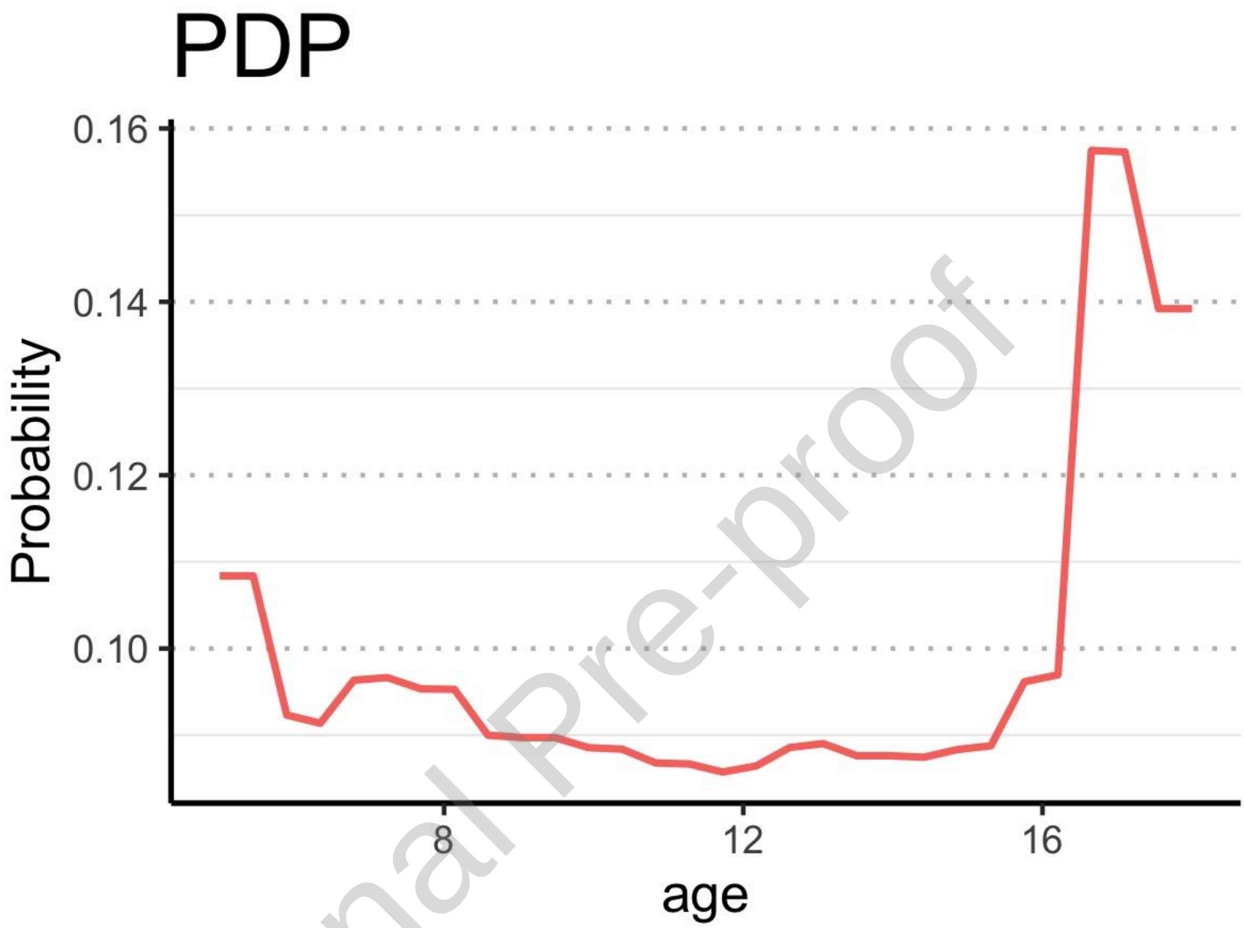
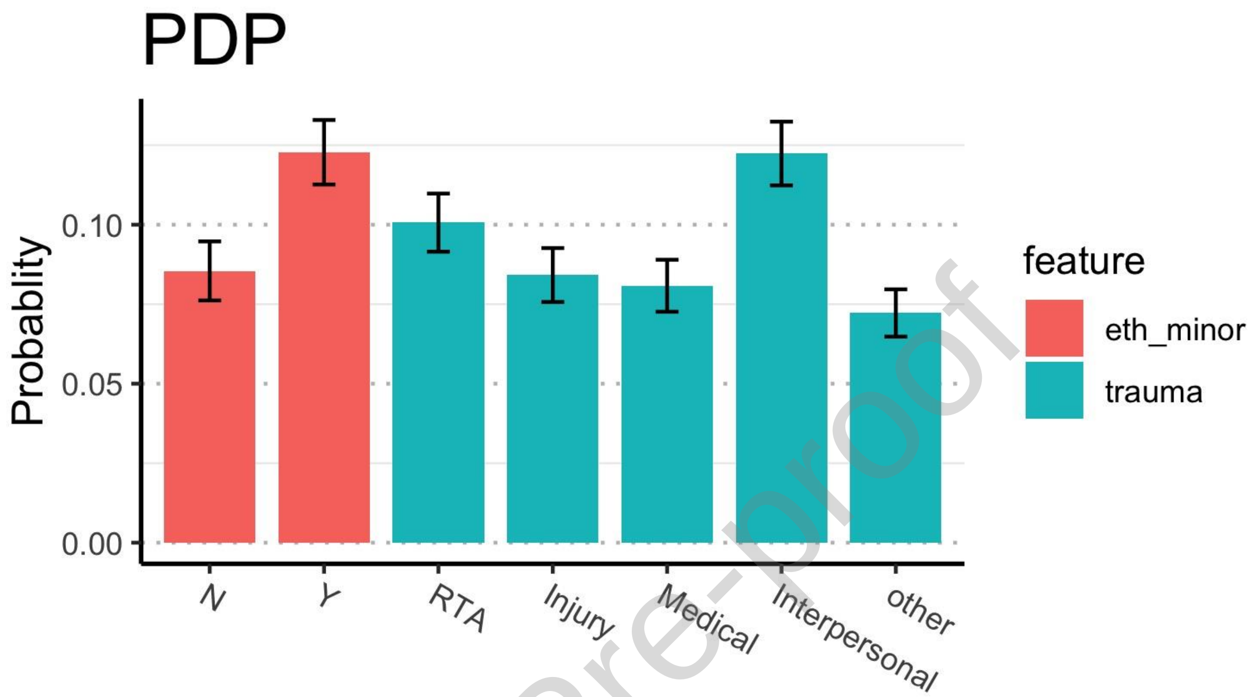
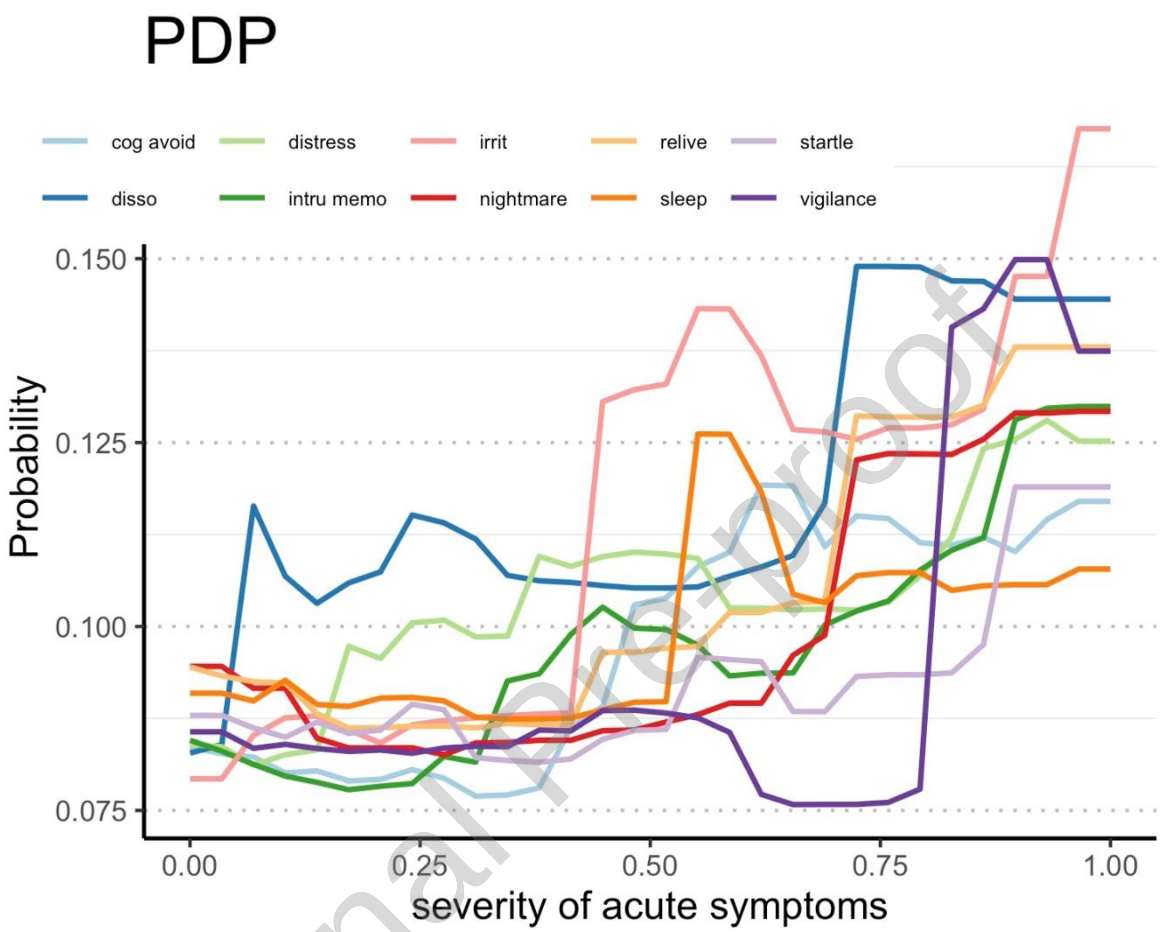


Figure 2b: PDP by trauma type and ethnic minority



N: not ethnic minority; **Y**: ethnic minority; **RTA**: road and traffic accident; **Injury**: unintentional injury trauma; **Medical**: acute medical event (non-injury) trauma; **Interpersonal**: interpersonal violence; **other**: other trauma type

Figure 2c: PDP by ASD features



intru memo: recurrent, involuntary, and intrusive distressing memories; **nightmare**: recurrent distressing dreams; **relive**: dissociative reactions; distress: intense or prolonged psychological or physiological distress; **disso**: altered sense of the reality of one's surroundings or oneself; **cog avoid**: efforts to avoid trauma related memories, thoughts, or feelings; sleep: sleep disturbance; **irrit**: irritable behavior and angry outbursts; **vigilance**: hypervigilance; **startle**: exaggerated startle response

Table1: Data summary

PACT/R StudyID	N	age	ethnic minor (%)	trauma types (%)	< 1m PTS measure	6 m+ PTS measure	6 m+ PTSD (%)	6 m+ missing rate (%)
1002	122	M = 6.18 Min = 5 Max = 7 SD = .78	59.02	Injury: 100	CASQ at T3	PTSIC at T7	4.10	41.80
1007	131	M = 12.42 Min = 8 Max = 17 SD = 2.48	44.27	Injury: 100	CPSS at T2	CPSS at T7	2.29	19.85
1020	104	M = 13.95 Min = 10 Max = 17 SD = 1.96	65.38	Interpersonal: 56.73 RTA: 43.27	CRIES at T3	CADIS at T7	24.04	34.62
1022	135	M = 12.14 Min = 7 Max = 17 SD = 2.71	5.19	Injury: 51.11 Interpersonal: 6.67 Medical: 2.96 RTA: 33.33 Other: 5.93	CPSS at T3	CAPS at T7	2.22	33.33

1023	50	M = 11.36 Min = 7 Max = 16 SD = 2.79	32.00	RTA: 100	CAPS at T2	CAPS at T7	0	0
1025	108	M = 15.88 Min = 12 Max = 18 SD = 1.89	24.07	Injury: 89.81 Interpersonal: 10.19	CUCLA-IV at T2	CUCLA-IV at T9	3.70	17.59
1032	130	M = 10.73 Min = 7 Max = 15 SD = 2.52	35.38	Injury: 28.46 RTA: 71.54	CUCLA-5 at T2	CUCLA-5 at T7	4.62	12.31
1037	260	M = 13.40 Min = 8 Max = 17 SD = 2.96	6.92	Injury: 31.54 Interpersonal: 16.54 Medical: .77 RTA: 45.38 Other: 5.77	CPSS at T3	CPSS at T8	1.54	38.85
1038	127	M = 9.82 Min = 6 Max = 13	7.09	Injury: 34.65 Interpersonal: 1.57	CUCLA-IV at T3	CUCLA-IV at T7	3.94	7.09

		SD = 1.96		Medical: 6.30 RTA: 51.18 Other: 6.30				
Pooled	1,167	M = 11.89 Min = 5 Max = 18 SD = 3.48	27.42	Injury: 49.87 Interpersonal: 10.63 Medical: 1.20 RTA: 35.65 Other: 2.66	-	-	4.71	25.96
1036*	101	M = 10.86 Min = 8 Max = 17 SD = 2.02	48.51	Injury: 81.19 Interpersonal: 1.98 RTA: 16.83	CPSS at T2	CPSS at T6	17.82	22.77
1008*	120	M = 11.90 Min = 8 Max = 17 SD = 2.75	42.5	Injury: 100	ASC at T3	CPSS at T6	7.50	28.33

*for external validation

T2: 24 hours to < 2 weeks; T3: 2 weeks to < 1 month; T6: 3 months to < 6 months; T7: 6 months to < 9 months; T8: 9 months to < 12 months; T9: 12 months to < 15 months; ASC: Acute Stress Checklist (ASC-Kids); CASQ: Child Acute Stress Questionnaire; CAPS: Clinician-Administered PTSD Scale; CRIES: Children's Impact of Event Scale; CPSS: Child PTSD Symptom Scale; PTSIC:

Post Traumatic Symptom Inventory for Children; CUCLA-IV: UCLA PTSD Reaction Index for DSM-IV; CUCLA-5: UCLA PTSD Reaction Index for DSM-5

Table 2: Performance of candidate models

Method	**N. of features**	**Features**	**Precision**	**Recall**	**F-score**	**AUC**
Internal validation						
GLM	7	eth_minor, trauma, ASDB6, ASDB8, ASDB10, ASDB11, ASDB14	.982	.837	.904	.836
CART	12	age, trauma, hosp_days, ASDB1, ASDB2, ASDB4, ASDB6, ASDB8, ASDB10, ASDB11, ASDB12, ASDB14	.961	.971	.971	.701
RF	13	age, eth_minor, trauma, ASDB1, ASDB2, ASDB3, ASDB4, ASDB6, ASDB8, ASDB10, ASDB11, ASDB12, ASDB14	.961	.987	.973	.830
SVM	13	age, eth_minor, trauma, ASDB1, ASDB2, ASDB3, ASDB4, ASDB6, ASDB8, ASDB10, ASDB11, ASDB12, ASDB14	.977	.798	.879	.754
ASD features only						
GLM		ASDB1, ASDB2, ASDB3,	.970	.798	.876	.752
CART	10	ASDB4, ASDB6, ASDB8,	.955	.969	.962	.764
RF		ASDB10, ASDB11, ASDB12,	.959	.984	.973	.760

SVM	ASDB13, ASDB14	.980	.765	.860	.768
External validation					
GLM	same as internal validation	.880	.795	.835	.646
CART		.816	.963	.883	.570
RF		.821	1.00	.902	.715
SVM		.893	.710	.791	.643
External validation (arousal + avoidance model)					
GLM		.867	.710	.781	-
CART		.833	.963	.893	-
RF		.824	.963	.888	-
SVM		.839	.566	.676	-
Second external validation					
RF	same as internal validation	.925	1.00	.961	.603

eth_minor: ethnical minority; trauma: trauma type; hosp_days: length of time in hospital (in days) with day of admit; ASDB1: recurrent, involuntary, and intrusive distressing memories; ASDB2: recurrent distressing dreams; ASDB3: flashbacks; ASDB4: intense or prolonged psychological or physiological distress; ASDB5: persistent inability to experience positive emotions; ASDB6: altered sense of the reality of one's surroundings or oneself; ASDB7: Inability to remember an important aspect of the traumatic event(s); ASDB8: efforts to avoid trauma related memories, thoughts, or feelings; ASDB9: efforts to avoid external reminders that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s); ASDB10: sleep disturbance; ASDB11: irritable behavior and angry outbursts; ASDB12: hypervigilance; ASDB13: problems with concentration; ASDB14: exaggerated startle response

Highlights

- a machine learning model trained by large international longitudinal data and has excellent classification performance.
- model proved to be highly robust by two external validations. The succinct model requires only 13 easily obtainable features, has potential for clinical utility.
- unique model interpretation examined the importance ranking for each predictor and grouped features, in particular, ASD clusters.
- a cumulative effect was detected within the intrusion cluster.
- belonging to ethnic minority groups increases by 43% the chance of having PTSD compared to non-minority groups.