A Computational Approach to Understanding Early Trauma and Paediatric PTSD

Yi Zhang

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Name of candidate: Yi Zhang

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Abstract

Research on post-traumatic stress disorder (PTSD) has developed successful theories to understand the condition and to inform intervention. However, it faces challenges regarding efficiently explaining individual differences, comorbidity and certain treatments. The computational movement in mental health research not only opens up new methods to study the phenomena in PTSD but provides new prospects to looking at PTSD.

The computational approach is a data-centred research method. Using complex mathematical modelling, the approach seeks new ways to describe and record phenomena in mental functioning (i.e., phenotyping). With big data, the approach aims to discover more robust patterns (i.e., data mining), and ultimately, to build models (i.e., computational modelling) that improve explanatory power and predictive accuracy. Although the computational approach has potential, its application in clinical psychology lacks systematic understanding and theoretical guidance.

The thesis aims to explore the computational approach in child and adolescent PTSD research. Four empirical studies were conducted to: investigate symptomatic trajectory and PTSD-depression comorbidity; trauma memory and appraisal; chronic PTSD prediction and risk interpretation; and the long-term impact of early stress on panic disorder. Importantly, all the studies utilized unconventional computational methods, including trajectory modelling, natural language processing, supervised machine learning modelling, interpretable machine learning techniques, and robust variance estimation.

The four studies serve as successful implementations of computational methodologies. The advantages of these methods are explained in the context of the necessity for computational phenotyping and the benefits of data mining. The findings address PTSD-specific research questions, concluding that negative trauma appraisals, memory coherence, cognitive avoidance and physiological reactions are critical factors to PTSD symptom development, comorbidity

and individual differences. A review of those findings provides the basis for an in-depth discussion of acute stress symptoms, pre-trauma factors, long-term impact and the omission of physiological aspect in the cognitive-behavioural model of PTSD. The thesis concludes by proposing a preliminary computational model of PTSD.

Acknowledgement

"Beyond the East the sunrise, beyond the West the sea, and East and West the wanderlust that will not let me be."

- *Gerald Gould*

As I write up the very last piece of this thesis, I remember the chilly air one early September morning a few years ago when my children and I arrived at Gatwick airport. My two daughters, Julie and Joann, wanted to visit Hogwarts. I wanted to be a clinical psychologist and to research PTSD. Four and half years later, Hogwarts has become a childhood fantasy for the girls, and I know I will not practice as a clinical psychologist, but I will make a good PTSD researcher.

Having reached the stage of completing my PhD, I owe a tremendous debt of gratitude to a lot of people. First, I would like to thank my supervisor Richard Meiser-Stedman. He is someone I can always trust, despite disagreements and arguments. Both Richard and Saber Sami, another member of my supervisory team, have demonstrated great patience and tolerance, giving me the space to learn and to make mistakes. I am very grateful to them for timely discussions, comments and feedback. I thank Nancy Kassan-Adams and the PACT/R team, Sarah Halligan and Rachel Hiller from Bath University for generous data sharing, support and advice; Tim Dalgleish from MRC for his comments and sponsoring the publication of one of the studies; Irene Valero Sanchez from Leicester NHS trust and Ian Smith from Papworth hospital for their cooperation on the sleep study (although it did not find a home in my thesis).

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and encouragement, especially Dave, Franzi, Harvey, Jennifer, Linda, Peony, Tara and Vanessa.

Table of Contents

Glossary and Terminology

1. All confidence intervals in the thesis are 95% confidence intervals.
2. An online version is available online for all big tables and figures for clearer view.
3. All implemented codes, original outputs of the analysis and other supporting materials are available in supplemental materials included in a separate document.
4. ACE: adverse childhood experience
5. AIP: adaptive information processing model
6. ASD: acute stress disorder
7. CBT: cognitive behaviour therapy
8. CI: confidence interval
9. DRT: dual representation theory
10. DSM: diagnostic and statistical manual of mental disorders
11. EMDR: eye movement desensitization and reprocessing.
12. EPT: emotional process theory
13. FEP: free energy principle
14. GSI: grouped Shapley importance
15. IML: interpretable machine learning
16. Markov blanket: the minimal set of variables in a Bayesian network required to infer a variable
17. ML: machine learning
18. NLP: natural language processing
19. PDP: partial dependency plot
20. Phenotype: a measurable trait of an organism that is subject to natural selection
21. Phenotyping: a method to describe a phenotype
22. PD: panic disorder

23. PTSD: post-traumatic stress disorder

24. PTSS: post-traumatic stress symptom

25. RL: reinforcement learning

26. TF-CBT: trauma-focused cognitive behavioural therapy

27. RVE: robust variance estimation.

28. SAM: situationally accessible memory

29. Shapley importance: a value that indexes the influence of a feature in a model

30. VAM: verbally accessible memory

1. Chapter 1: Introduction

"for you know only / a heap of broken images"

- *T.S. Eliot, The Waste Land*

1.1. Three Questions

Since the official designation of Post-traumatic Stress Disorder (PTSD) in DSM-III (Diagnostic and Statistical Manual of Mental Disorders [DSM], 3rd edition; American Psychological Association, 1980), the modern era of PTSD research has seen four decades of great progress in understanding as well as treating the condition. Various theoretical models have been proposed and the effectiveness of front-line treatments of different modalities have been encouraging. However, our knowledge remains limited with regards to a few critical questions. First, although going through stressful or traumatic events is a ubiquitous human experience, vast individual differences have been observed in terms of responding to adversity in almost all types of trauma exposures. For many, the experience leaves minimum impact to their well-being (resilience), some undergo elevated distress but eventually recover (recovery) while some endure prolonged disruption (chronicity). There are also cases where subthreshold symptoms at early stage deteriorate over time (delayed onset) (Galatzer-Levy, Huang & Bonanno, 2018). The field has begun to look at genetic predispositions, pre-trauma history, peri-event factors and post-trauma experiences to account for the variance, but findings are limited at present.

Second, mental disorders are highly comorbid. A network analysis using 201 distinct mental disorders and 522 diagnostic criteria in DSM-IV found not only that half of the symptoms are connected but that the connections form a highly clustered "small world" architecture (Borsboom, Cramer, Schmittmann, Epskamp, & Waldorp, 2011). In PTSD, comorbidity of depression, anxiety and substance abuse is commonplace. Depression, for

instance, is estimated to be as high as 52%, CI[48, 56] in adults with PTSD (Rytwinski, Scur, Feeny & Youngstrom, 2013), and 24.2%, CI[20.6-28.0] in trauma-exposed children and adolescents (Vibhakar, Allen, Gee, & Meiser-Stedman, 2019). A 20-year longitudinal study involving veterans reported that triple comorbidity (PTSD, depression and anxiety) was more prevalent (26.7–30.1%) than PTSD alone (9.3–11.1%) or PTSD-depression comorbidity (1.2–4.5%) (Ginzburg, Ein-Dor, & Solomon, 2010). Rather than seeing comorbidity as an artefact of the classification approach, Borsboom et al. (2011) believe the individual symptoms should be treated in their own right and it is likely that they have autonomous causal relevance to the rise of the co-occurrence. However, to date, research on how symptoms develop and interact after trauma exposure is limited and there is a need for a theoretical framework to enable a systematic account of the potential mechanisms.

Third, there is an explanatory gap as to why some treatments work. The National Institute for Health and Care Excellence (NICE, 2018) has recommended two evidence-based psychological interventions for PTSD: Trauma-focused Cognitive Behavioural Therapy (TF-CBT) and Eye Movement Desensitization and Reprocessing (EMDR). Unlike TF-CBT, which is closely designed according to behavioural and cognitive theories (Ehlers & Clark, 2000; Foa & Kozak, 1986), the discovery of EMDR was somewhat "accidental". As the phenomenon is beyond the explanation by any existing theories, the Adaptive Information Processing (AIP) model, the theoretical underpinning for EMDR, was proposed afterwards to vindicate the treatment (Hill, 2020). Appealing as the hypotheses about physiologically based information processing system and bilateral stimulation procedures are, they are mostly untested. The implication of identifying this gap, however, is not to refute EMDR as an effective treatment; on the contrary, this gap suggests that there is at least one pathway involving trauma-related memory, emotion and cognition that has yet to be investigated. Addressing this gap may cast

a very different light on the understanding of PTSD and the brain functions, particularly in memory formation, retention and post hoc changes.

The challenges the field faces are certainly not limited to the aforementioned three questions while they represent issues that arise from important areas of symptomology, etiology and intervention in PTSD. Given that mental condition is the product of brain, the most complicated biological organ, and the environment, which is equally complicated for humans, the conventional theory-driven approach that focuses on the study of local effect is unlikely to suffice; a new perspective to conceptualize mental function and dysfunction is needed.

1.2. Aims and Structures

The thesis addresses why and how the computational approach offers a potential paradigm shift in clinical psychology research of PTSD. It also demonstrates efforts made by the author to apply the computational approach via four empirical studies.

The thesis begins with an introduction to the core ideas in computational psychiatry, followed by the discussions about their implications for clinical psychology and PTSD. The introduction also summarizes theories of PTSD in the current literature. Chapters 2-5 cover the four studies that investigated specific research questions regarding post-trauma symptomatic trajectory, trauma memory and appraisal, PTSD prediction and risk interpretation and the long-term impact of early adversity. Chapter 6 synthesizes the methods and findings from the studies and discusses them in the overarching context of the computational approach and current PTSD literature. Lastly, since the computational approach in characterizing mental dysfunction is in its infancy, elaboration on the limitations of the approach and future directions are given in Chapter 7.

1.3. A Computational Approach to Psychopathology

"Computational" has recently become a prevalent word in mental health research. With fields such as computational psychiatry, computational psychology emerging, questions with regard to the definition of the term arise. That is, what does "computational" exactly betoken? What kind of study is "computational"? How does computational research differ from non-computational research? More importantly, what will this approach bring to clinical psychology? For, understanding of these critical questions remains fragmented: it is "data-driven", it uses "machine learning" or it does "computational modelling", and so on. There does not appear to be a systematic and in-depth discussion about the concept, particularly in the field of clinical psychology. Before attending to the applications of the computational approach in PTSD, therefore, this chapter begins with a review of the concept and its use in the field. This review also provides a framework for further discussion of the empirical studies in the thesis.

The idea of using computational approach in mental health was introduced as computational psychiatry (Montague, Dolan, Friston, & Dayan, 2012). The drive behind this movement was the lack of intermediate levels bridging the findings at the neurobiological level with clinical terms. That is, despite substantial advances in neuroscience and biological psychiatry, for instance, the discovery of the critical role of neuromodulatory system (e.g., dopamine, serotonin), little is known about how their dysregulation gives rise to high level mental phenomena such as schizophrenia, depression and anxiety. While the researchers identify the importance of neurobiophysical models, the account that such models have of mental function is not the same as a computational account.

The computational account of cognitive function assumes that the brain solves problems in a computational fashion and indeed, that the biology of the brain has evolved to support it. For example, when animals are repeatedly exposed to adversities beyond their

control, they do not explore or try to escape to a new environment. The phenomenon is called learned helplessness (Maier & Seligman, 1976). Human are also found to be susceptible to learned helplessness and it has been used to explain depression and anxiety (Miller & Seligman, 1975). The computational account of learned helplessness can be viewed through Bayesian or reinforcement learning (RL) modelling. During the exposure, the animal or human forms a prior probability distribution over the current and the possible future environments, which is that their behaviour has little influence over outcomes. Because exploration is only worthwhile when good outcomes are likely to be achieved, this prior belief will subsequently discourage exploration or escape to a new environment where the subject's estimation of the likelihood of controllability is low. The advantage of this computational interpretation of learned helplessness is its ability to incorporate rich priors that provide a new way to understand the role of environments in etiology.

1.4. Psychological Formulation

Taking prior personal beliefs and environmental factors into considerations for psychopathology is not novel in clinical psychology. In fact, it has been a core practice of clinical psychology called formulation. In CBT, a client's beliefs about the world, other people and themselves developed throughout their past experience are an important component of the formulation. In systematic therapy, the wider socio-cultural context is often included in the formulation from a social constructionist perspective. It can therefore be easy to confuse the computational approach with formulation.

Psychological formulation is not a computational approach. The two processes hold distinct goals and methods. Psychological formulation has been described as "the summation and integration of the knowledge that is acquired by the assessment process that may involve psychological, biological and systemic factors and procedures. The formulation will draw on psychological theory and research to provide a framework for describing a client's problems

or needs, how it developed and is being maintained" (Johnstone & Dallos, 2013). In other words, formulation applies existing models and theories to conceptualize individual cases and is therefore deductive whereas the computational approach seeks general patterns based on data of instances and hence, is inductive. Moreover, the computational approach is inherently quantitative while formulation is mostly qualitative.

1.5. The Computational Approach in Clinical Psychology

The example of learned helplessness given in the previous section demonstrates how a cognitive phenomenon can be constructed by a computational model. However, the scope of the computational approach to mental function/dysfunction is much broader than that. Montague et al. (2012) summarize the four basic components in computational psychiatry as data mining, biophysical modelling, computational modelling and computational phenotyping. Specifically, the aims are: to identify new genetic, molecular, cellular and neural dynamics; to enable large-scale data-sharing; to explore biomarkers for healthy and damaged cognition; and to provide computational assessments of therapies.

Compared to psychiatry, clinical psychology is less concerned with brain functions at the neurobiophysical level. Instead, the field strives to understand psychopathology by looking at high level brain functions including cognitions, emotions, motivations and behaviors, along with elements of physiology and environment. Nevertheless, these components are still highly pertinent. In the following sections, these are addressed one by one in detail, with the emphasis on the new perspectives these approaches bring.

1.5.1. Computational phenotyping

Phenotyping is the process that conceptualizes and describes phenotypes of interest. It is the first task when researchers wish to understand a phenomenon. A phenotype is a measurable trait of an organism that is subject to natural selection. Montague et al. (2012)

define a computational phenotype as "a measurable behavioural or neural type defined in terms of some computational model". To better fit into the scope of clinical psychology, for the purposes of this research, the definition is revised as "a measurable cognitive or behavioural pattern defined in terms of some computational model" where "cognitive or behavioural" refers to the generalized human brain function, including cognitions, emotions, motivations, relations, behaviors.

An example of computational phenotyping is using games to phenotype autism spectrum disorder. One of the traits in autism is the social communication deficits that are caused by the lack of theory of mind, that is, the capacity to understand others' mental states (e.g., emotions and intentions). To measure the degree of theory of mind (or lack of it), computational phenotyping uses two-player economic games where it is beneficial if a player can make accurate inferences about their partner's intentions (Yoshida, Dolan, & Friston, 2008). These inferences are recursive, i.e., my model of you incorporates my model of your model of me, and so on. The depth of recursion reflects the player's sophistication level in theory of mind and is estimated via their gaming strategy. A computational model is then built upon the behavioral data. Results showed that autism participants were more likely (78% probability) to adopt a fixed-strategy (low sophistication) while there was a higher probability for non-autism participants to opt for a theory-of-mind strategy (high sophistication).

The study made two critical points. First, the model parameterized a complex cognition (use of depth of recursion to measure theory of mind) by utilizing a standardized prober (gaming). Second, it collected normative data that described a full spectrum of possible responses from healthy and autism samples. It thereby provides a way to formalize cognitive components in computational terms.

Its implications for clinical psychology are profound. At present, a descriptive culture prevails in areas of clinical psychology from assessing presentations, measuring symptoms to

delivering psychotherapy. The field relies heavily on verbal description (written or oral) to communicate symptoms, cognitions, emotions and physical feelings. Although effective when used well, words can be vague and contentious, making it difficult to formalize. That is not to say that computational phenotyping should replace the current descriptive approach; rather, it offers an alternative lexicon for communication. More importantly, this new lexicon is likely to foster opportunities for large-scale data sharing and collaboration because of its quantitative and principled nature.

The normative nature of computational phenotyping is equally important. In mental disorder research, there have been debates regarding a fundamental question, which is: What is normal and what is not? Which mental conditions should be classified as pathological and which as normal suffering? Wakefield (1992) constituted the concept of harmful dysfunction wherein harmful is determined by socio-cultural norms and dysfunction refers to the failure of performing a mental function designed by evolution. However, the author did not give any operational definition regarding how such failure is discerned. Clinical psychology views a mental function / dysfunction on a spectrum, but it is not immune to the similar issue arising from the lack of precise description of the spectrum. Using computational phenotyping with normative data that account for both clinical and non-clinical populations, computational dimensions can be built to characterize a mental condition. This more comprehensive view may improve diagnosis and clinical judgement.

1.5.2. **Data mining**

Data mining is a process of extracting and discovering patterns in large data sets. With the expansion of digital devices and storage capacity, human have officially entered the era of zettabytes [1]. The amount of data created, captured, copied and consumed globally surpassed 2

[1] Zettabyte is a digital unit of measurement. One zettabyte is equal to 10^{21} (1,000,000,000,000,000,000,000) bytes.

zettabytes in 2010 and was forecast to reach 64.2 zettabytes by 2020 (Holst, 2021). Since all knowledges are fundamentally derived from information (data), data of this unprecedented scale provide a rich source for new knowledges, whereas they also require new methods that are capable of processing and making sense of them.

This method turns out to be machine learning (ML). ML is a field of study in computer science that gives computers the ability to learn without being explicitly programmed (Samuel, 1959). In a nutshell, ML searches patterns from examples (supervised learning) or explores patterns on directed algorithms (unsupervised learning). Powered by mathematical theories and computing technologies, ML is able to process highly dimensional data in all formats: structured data, free texts, images, sounds and mixed data forms.

Owing to ML, data mining is changing the practice of science. For example, in biology neuroscience, data mining is widely used to identify genetic, biological markers of phenotypes or to discover pathways in brain functioning (Bracher-Smith, Crawford & Escott-Price, 2021). In clinical medicine, improved accuracy in classification and prediction has given birth to a new field called precision medicine, where clinical care and treatment are customized to a subgroup of patients, instead of a one-drug-fits-all model. Customization is guided by models yielded from large data that inform clinical decisions from diagnosis, prognosis, to treatment selection (Ashley, 2016).

Similar applications are also apt in clinical psychology. For example, a study developed a targeted prescription algorithm to identify subgroups of patients who respond differentially to CBT and counseling (Delgadillo & Gonzalez Salas Duhne, 2020). Overall, during the ML booms in clinical psychology, most studies fall into the domain of data mining. Extensive reviews on its impact are available in almost all areas including depression and bipolar (Librenza-Garcia et al., 2017), PTSD (Ramos-Lima, Waikamp, Antonelli-Salgado, Passos, &

Freitas, 2020), psychosis (Benoit, Onyeaka, Keshavan, & Torous, 2020) and psychotherapy (Aafjes-van Doorn, Kamsteeg, Bate, & Aafjes, 2021).

1.5.3. **Psychophysiology modelling**

This component corresponds to biophysical modelling in computational psychiatry. As mentioned above, clinical psychology is less biologically oriented, but it would be a mistake to assume that it sidesteps physiology. On the contrary, clinical psychology deals closely with physiological symptoms and in a multitude of ways. From pain, panic and fatigue to sleep disturbance, physiological factors are a significant facet of the onset, development and maintenance of mental disorders. In a small world study, Borsboom et al. (2011) noticed that many symptoms in DSM-IV relate to basic homeostatic brain functions such as eating, sex, sleeping and mood regulation. They argued that it was essential to investigate their precise role in the network of comorbidity. A recent study reviewing the association between insomnia and major psychiatric disorders (i.e., schizophrenia, depression and PTSD) found that the successful treatment of sleep problems tends to alleviate all types of mental disorders, suggesting that sleep is likely to be a causal factor in the occurrence of most mental health conditions (Freeman, Sheaves, Waite, Harvey, & Harrison, 2020).

These observations in a way corroborate the traditional mind and body theory (Littrell, 2008) which is that physiological activities can alter state of mind and vice versa. Although the idea is unsurprising, the underlying mechanisms are currently under studied. For instance, breathing techniques are effective in reducing stress (Perciavalle et al., 2017) and are used as a regular treatment component in many psychological interventions but why it works remains unclear. Considering the example of EMDR again, the entire treatment is tied to a hypothetical physiological information processing system and researchers are still perplexed about how to devise a feasible strategy to test it. Hence, we propose psychophysiology modelling as a method to investigate the reciprocal relationship between physiology and mental status.

1.5.4. **Computational modelling**

The term "computational modelling" should not be understood as using a computer to build models. It has a much more specific meaning here. A computational model refers to mathematical models that "express concepts important to brain function, and the relationships between these concepts" (Huys, Moutoussis, & Williams, 2011). The idea of a computational model was briefly touched on in the example of the RL model for learned helplessness. Along with the RL model, there is a diverse collection of computational models, including optimal inference models, game theory models, connectionist models and so on. Some of them (e.g., RL, optimal) take a Bayesian stance, that is, a mental function operates under the principles of statistical inference. In psychology and neuroscience, there is a school of Bayesian theories that posits the further claim that the brain itself is a Bayesian machine. While this view has provoked many debates (Bowers & Davis, 2012; Colombo & Seriès, 2020), it is not the concern of this thesis.

The value of computational modelling in mental health and clinical psychology, for the purpose of this research, is two-fold. First, it offers a new theoretical perspective through which to look at mental dysfunction. In a theoretical analysis, Huys, Daw and Dayan (2015) employed Bayesian decision theory (BDT) and provided a decision-theoretical account of depression. The heart of their argument is that a series of missteps in decision making gives rise to key symptoms of depression such as anergia or anhedonia. Specifically, it is the aberrant prior estimation and flawed Bayesian model-based evaluations that lead to these missteps. What makes the theory attractive is its prospect of unifying many core cognitive and emotional processing deficits (e.g., depressive schemas about self, negative appraisal, rumination, biased selective attention, etc) into a single account.

Second, computational modelling is a method that promotes rigorous empiricism. Those who are sceptical about computation models may question whether a model that is so

versatile does not run the risk of becoming unfalsifiable. They should be reassured that because many of these models not only make quantitative predictions but also provide algorithmic mechanisms and parameters that allow simulation, they are intrinsically accommodating to validation and falsification. Moreover, computational models are built directly upon empirical data and are therefore less prone to biases in comparison to hypothesis-driven models.

1.6. Aims and Scopes of Computational Clinical Psychology

The four components of the computation approach within psychiatry have been only briefly introduced. In reality, a short review like this cannot do justice to the many subdomains and complicated issues that each component encompasses. However, it is necessary to outline them in a broad and simplified overview because to date no definition of the computational approach has been proposed under the principles of clinical psychology. To summarize, the aims and scopes can be stated as:

By computational phenotyping, data mining, psychophysiology modelling and computational modelling, computational clinical psychology aims to describe patterns in healthy and pathological mental functions in order to: identify risk markers; discover new dynamics linking cognitive, behavioural, physiological and environmental factors to explain psychopathology; enable large-scale data sharing; and to inform and assess interventions.

1.7. Methodological Implications of the Computational Approach

It is clear that a computational approach differs from conventional approaches at many levels, of which methodological difference is probably the most pronounced. Because data play a central role, computational clinical psychology is more data-driven compared to hypothesis-driven research. Hypothesis-driven research forms hypothesis/hypotheses around certain research questions and then uses data to prove/disprove them, while data-driven does not make assumptions. Instead it relies on results derived from data to generate hypothesis/hypotheses.

In short, data-driven research operates stochastically while hypothesis-driven research operates deterministically. One critique of hypothesis-driven research is that setting a premise in advance of an experiment constrains reasoning so as to match that premise; one advantage of data-driven research is that it can avoid such pitfall, leading to less biases and more serendipitous connections.

A variant of a hypothesis-driven approach is a theory-driven approach, in which models adopt an existing theoretical algorithm about a phenomenon but do not explicitly state any hypothesis. It can be tremendously useful when the prior theory is sufficiently accurate that it allows theory-driven methods to massively reduce the dimensionality of the data. When such enabling factors are present, some preliminary studies suggest that the combined use of theory-driven and data-driven approaches can be advantageous (Huys, Maia & Frank, 2016).

Last, it is worth mentioning that in the computational approach, all methods, whether data-driven or theory-driven, are inevitably dependent on mathematical and/or probabilistic solutions to a great extent (Huys et al., 2016). Such exigency could appear to be a stumbling block to many clinical researchers who are not intensively trained in mathematics. A common practice in computational research nowadays is that research usually collaborates with statisticians and data scientists who are specialized in the technical part. High level programming tools (e.g., R, Python) and a panoply of well-encapsulated function packages are also useful to ease the modelling processes, so that researchers only need to heed meanings and logics, while being spared the technical details.

1.8. Symptomatic Definition of PTSD

We now turn to PTSD. The latest description of the core PTSD symptoms is given by DSM-5 (APA, 2013) and ICD-11 (World Health Organization, 2018). In DSM-5, PTSD symptoms are organized into intrusion, avoidance, altered mood and cognitions and arousal clusters. Intrusion symptoms include involuntary, intrusive memories of the traumatic event,

flashbacks or nightmares, as if the event were recurring, and marked emotional/physiological distresses reacting to the cues of the event. Avoidance can occur at behaivoural level where the person goes to great lengths to stay away from external reminders like places, people and objects. It can also occur at the cognitive level where one makes efforts to avoid memories, thoughts and feelings associated with the experience. Altered mood and cognitions refer to a series of changes in mood such as numbing, anhedonia, or persistent negative emotional state (e.g., fear, anger, guilt, shame). Mood change is often accompanied by negative beliefs about self (e.g., "my life is ruined"), others (e.g., "others cannot be trusted") and the world (e.g., "the world is full of danger"). Another type of cognitive change is amnesia. It is the inability to recall important aspects of the traumatic event without the influence of drug or alcohol. The hyperarousal cluster includes irritability, sleep disturbance, hypervigilance, exaggerated startles, difficulty in concentration and self-destructive behaviors.

ICD-11 defines PTSD symptoms in three categories: re-experiencing that matches the intrusion cluster; avoidance which is identical to the DSM-5 avoidance cluster; and perception of heightened current threat that corresponds to the hyperarousal cluster. It does not take into account the mood/cognition change or the dissociative subtype extended by DSM-5. At the same time, ICD-11 introduced a new diagnosis called complex PTSD (CPTSD). The ICD-11 diagnosis of CPTSD consists of the three PTSD criteria and three self-organisation symptoms, which are negative self-concept, emotional dysregulation and interpersonal difficulties. The application of CPTSD often involves prolonged, repeated trauma exposure, but single trauma exposure is not excluded. As all the empirical studies in this thesis did not investigate research questions concerning CPTSD, the DSM-5 definition of PTSD symptoms is used throughout the thesis for simplicity and consistency.

1.9. PTSD as Function of Time and Environment

Symptoms only do not suffice to conceptualize PTSD. To make sense of the disorder, one needs a context in which PTSD is narrated in a neutral way that allows space for speculation while at the same time being independent from explanations (i.e., theoretical theories or models). Hence PTSD is proposed as a function of time and environment (Figure 1-1) as the basic framework for further discussion.

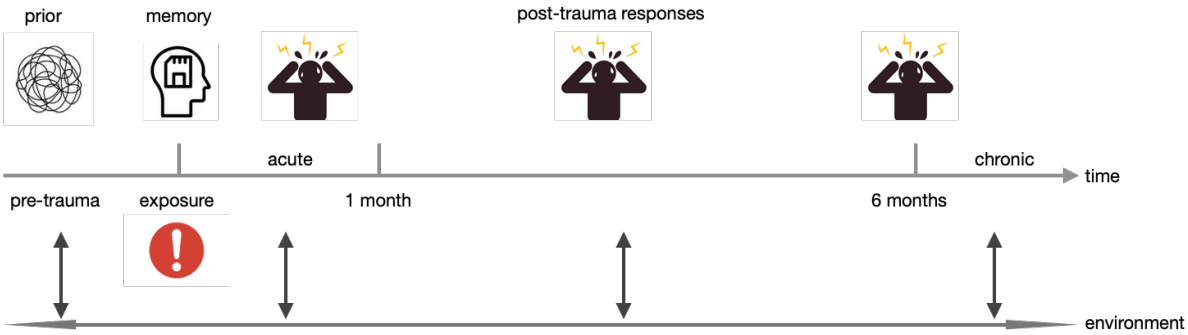


Figure 1-1: PTSD as function of time and environment

Figure 1-2: PTSD as function of time and environment

The concept of PTSD closely incorporates the idea of time. An explicit exposure needs to occur before the onset of the stress symptoms, and it is considered to be the original cause of all the downstream reactions. The diagnosis of PTSD requires a minimum period of one month after the trauma exposure because the consensus assumption is that acute post-traumatic distress is normal and should be given time to "play out"; only prolonged distresses are atypical, and therefore pathological (NICE, 2018) (Marshall, Spitzer and Liebowitz, 1999). Systematic investigation often organizes PTSD elements by their temporal relation to the event as such time is divided into pre-trauma, exposure, acute phase and chronic phase (Ozer et al., 2012). Likewise, on the time axis illustrated in Figure 1-1, key elements to PTSD phenomena are arranged by the four phases. Specifically, prior is the sum of the personal experience/states before the exposure; trauma memory is the autobiographical memory formed during the

exposure; post-trauma responses refer to part of the cognitive, behavioral, physiological activities after the exposure that presumably are linked to the exposure. Depending on temporal distance to exposure, post-trauma responses can be further split into acute phase, chronic or in between. Conventionally, one month marks the end point of the acute phase whereas there is no definite cutoff for the chronic phase. Although six months in Figure 1-1 is arbitrary, evidence suggests that, without intervention, PTSD prevalence and symptom severity are unlikely to change after six months in children and adolescent populations (Hiller et al., 2016).

The axis that is parallel to the time axis denotes the external environment across all times wherein the person is, has influence over and is also influenced by.

1.10. Current Theories of PTSD

Among the constellation of PTSD symptoms, clinicians and researchers have noticed that trauma-related memory and heightened physiological reactivities associated with fear are the two elements which distinguish PTSD from other mental disorders. Without exception, existing PTSD theories and models have focused on one or both of them when trying to provide a way of explaining PTSD. In this part, we review major PTSD models and theories in chronological order. The selection is based on criteria that they either have influenced the development of PTSD literature or have become the theories underpinning current psychological interventions for PTSD.

1.10.1. Emotional processing theory (EPT)

Emotional processing theory was developed from behavioral exposure therapy for fear reduction. Unlike behavioral theories that see behaviors and emotions as stimuli-response (S-R), Foa and Kozak (1986) proposed the “fear structure” or “structure of fear memory”. It is a network incorporating feared stimuli, physiological and behavioral responses, and meaning of the stimuli and responses. They believe that two conditions are required in order to reduce fear.

First, the fear memory must be activated; next, information conflicting with the fear memory should be provided. It is through the presence of both conditions that new memory can be formed. This process of reconstructing the memory around the feared stimuli is called "emotional processing" and prolonged exposure (PE) therapy is established based on this principle (Foa et al., Rothbaum, Riggs, & Murdock, 1991).

PE has now been highly manualized and is being used as a standardized component in TF-CBT. A meta-analytic review of PE for PTSD showed a large effect for PE versus waiting lists or psychological placebos. The study reported Hedges's g = 1.08 and Hedges's g = .77 in primary and secondary outcome measures and Hedges's g = .68 and Hedges's g = .41 in follow-up assessments (Powers et al., Halpern, Ferenschak, Gillihan, & Foa, 2010).

An important contribution of EPT is its integration of the meaning of feared stimuli and its perceived consequences into the theory of fear. In doing so, EPT made a progressive move from pure behavioral approach towards a cognitive-behavioral approach.

1.10.2. **Dual representation theory (DRT)**

Dual representation theory turns the spotlight on trauma-related memory. Traumatic memory is characterized with a few unique features, one of which is reliving it or flashbacks. A flashback is a vivid experience in which the person relives some aspects of the event or feels as if it was happening right now. Flashbacks often consist of rich sensory inputs (e.g., touch, taste, sound, vision, movement, and smell) and are highly emotional. This kind of memory is given the name SAM, i.e., situationally accessible memories, because it cannot be induced voluntarily. As opposed to SAM, the part of the traumatic memory that can be voluntarily retrieved is named VAM (verbally accessible memories). SAM is believed to be more selective compared to episodic memories of non-traumatic events.

According to Brewin, Dalgleish and Joseph (1996), EPT falls short of explaining the distinction between SAM and VAM. They put forward a dual representation theory that VAM

follows the same structure as the fear memory suggested by EPT, whereas SAM is the outcome of the more extensive nonconscious processing of the trauma. In DRT, the emotional processing of trauma is a conscious process that comprises of two parts. One, referred to as the information-process account, involves the activation of SAMs in order to aid cognitive reconstruction by supplying trauma-related sensory and physiological information. As can be seen, this is essentially the same as the emotional process described by EPT. The other part, referred to as the social-cognitive account, involves the attempt to assimilate new information acquired from the traumatic experience with prior knowledges of the world.

DRT predicts three possible outcomes of emotional processing: completion, chronic processing or premature inhibition of processing. Failure of emotional processing, i.e., chronic or inhibition, is expected to cause various mental, behavioral and physical dysfunctions, including depression, panic, anxiety, substance abuse, memory impairment, dissociation and somatization.

In relation to EPT, DRT addresses physiological reactivity and its change in a similar way, while it accounts for two phenomena that EPT does not. Although preliminarily, the social-cognitive part of the emotional processing provides a framework to explain secondary emotions in PTSD (e.g., shame, guilt). Moreover, DRT also ascribes comorbidities to the two potential unsuccessful outcomes of the emotional processing.

1.10.3. **Cognitive model of PTSD**

By the time EPT was developed, the evidence that perceived threat predicts PTSD better than actual threat had already emerged. Both EPT and DRT accommodated meaning making in their theory but did not provide details in terms of how it participates in the development and maintenance of PTSD. The cognitive model was timely in filling the gap (Ehlers & Clark, 2000).

The cognitive model suggests that the nature of trauma and pre-trauma beliefs/experiences influence a person's responses during trauma, which set the basic tone of the initial trauma memory and trauma-related appraisal. The memories and appraisals, together with coping strategies then form a dynamic that determines post-trauma presentations and their developmental courses. This dynamic can turn into a vicious cycle where the serious sense of current threat, i.e., PTSD, is maintained. The model gives a detailed account of the factors that could trigger a negative cycle. First, the intrusive, "here and now" quality of reliving accompanied by strong physiological feelings, serve as a direct cause to perceived threat. Negative appraisals about the event, the sequalae of the event, and the responses to the event, are all able to fuel the ongoing sense of threat, with catastrophic beliefs such as "nowhere is safe", "I will be homeless", "I am going mad". Lastly, maladaptive coping behaviors (e.g., avoidance) and cognitive strategies (e.g., thought suppression) may release stress in the short term but in the long-term perpetuate other maintenance factors of PTSD.

Accordingly, the model prescribes three areas for treatment consideration. First, the trauma memory needs to be elaborated in order to reduce intrusive reexperiencing. Second, problematic appraisals need to be modified. Third, maladaptive behavioral and cognitive strategies that prevent memory elaboration or reassessment of trauma appraisals, need to be dropped.

The cognitive model has been very successful. It manages to explain a broad set of clinical phenomena, and many predictions it has made have been supported by empirical data. Most importantly, a first line treatment, TF-CBT, governed by the three strategies recommended by the model, has proved to be very efficient (Watts et al., 2013). It is the most tested and first choice of psychological treatment for PTSD across all age groups and various types of trauma.

1.10.4. **Adaptive information-processing model (AIP)**

As mentioned in the beginning, the adaptive information-process model was built to unravel why EMDR works. The model has been updated a few times since its establishment, Hill (2020) gives the latest summary.

The AIP model makes a few assumptions about information processing and memory. Information is processed by two independent systems: the prefrontal cortex which is responsible for logical processing, and the limbic system which handles emotional processing. The logical processing is conscious, deliberate and slow whereas emotional processing is unconscious, primitive and fast. The two systems generate representations of the information, then store them in a connected neural network as long-term memories. The theory further states that, unlike emotional processing, logical processing will be compromised or impaired when a stressful event occurs, and the impairment consequently produces maladaptively stored memory. Trauma symptoms including intense, overwhelming emotions and feelings of being "stuck" or of reexperiencing are all believed to originate from such memories.

These assumptions do not fall far from the neuroscience findings of explicit/inexplicit memories (Kandel, Dudai & Mayford, 2014), nor from the three theories discussed so far. The defining feature of AIP, however, is the bilateral stimulation procedures (e.g., eye movements, auditory and tactile stimulations) that EMDR follows to assist reconsolidating trauma memory. AIP posits that the brain's typical functioning is capable of restoring trauma memories. The role of the bilateral procedure is to facilitate communications among regions, structures and two hemispheres of the brain when trauma memory is activated and being reprocessed. A successful reconsolidation unites all the pieces of memory representations, including those that had been maladaptively stored, and trauma memory is eventually processed in the same way as non-traumatic memories.

As we have seen, EPT, DRT and the cognitive model all acknowledge the unconscious part in trauma responses, while they emphasize the conscious part to explain and treat psychopathology. API, in contrast, relies largely on the unconscious processes whose mechanisms are thus far unknown. While more evidence is needed to verify the assumptions as well as the hypotheses made by AIP, EDMR enjoys the same level of treatment efficacy as PE, TF-CBT in treating PTSD for adults and children. Therefore, instead of dismissing it as an unorthodox myth, this author views AIP as the "Kelvin's clouds" in PTSD – deciphering the phenomenon can broaden our understanding of PTSD, memory and learning.

1.10.5. **Other Theories**

Apart from the four theories/models reviewed, there are other PTSD theories and models in the literature that have certainly contributed to the ongoing discussion of how to understand PTSD. However, they either address a focused set of issues in PTSD or there is insufficient empirical data to support the hypotheses; their significance is yet to be tested. Again, the list is not exhaustive.

Psychobiological model. Based on the neuroimaging data of trauma memory recall tasks in healthy and PTSD individuals, Frewen and Lanius (2006) proposed that reliving or hyperarousal could be regarded as the result of a failed inhibitory control over fear-induced arousal whereas dissociative symptoms could be regarded as the consequence of an enhanced suppression of fear-induced arousal. In essence, intrusion, arousal and dissociation are the two ends of the arousal dysregulation spectrum. This model is supported by neurobiological evidence that lower activation of medial prefrontal regions is associated with reexperiencing /hyperarousal while increased activation of medial prefrontal structures in dissociative subtype (Lanius et al., 2010).

Mnemonic model. The model is generally in line with the cognitive model except it pushes the role of trauma memory to the centre of PTSD. Rubin, Berntsen and Bohni (2008)

have argued that the effect of a trauma event is mediated by trauma memory. In other words, the availability of memory increases the chance of having PTSD and the severity of the symptoms. In contrast to the usual assumption that amnesia is positively linked to PTSD, Rubin and colleagues claimed that amnesia should protect a person from PTSD. They further hypothesize that the impact of the trauma experience depends on the extent to which a traumatic memory forms a central component of personal identity, a turning point in the life story and a reference point for everyday inferences. Centrality of Event Scale, designed to measure the construct, is reported to have positive correlations with PTSD.

1.11. Summary

The current literature of PTSD needs to close gaps in explaining individual differences responding to trauma, comorbidity and the physiological aspects of PTSD. A data-driven computational movement originated from psychiatry is believed to have a significant implications for mental health research, including clinical psychology principles. In particular, the four components, i.e., computational phenotyping, data mining, psychophysiological modelling, and computational modelling, offer unconventional methods and new perspectives to address those gaps. As research using computational approach in clinical psychology is currently limited, this thesis is to explore applications within the domains of computational phenotyping, data mining and computational modelling to answer questions regarding comorbidity, trauma-related memory, risks and long-term impact. More precisely, the thesis plans 1) to phenotype post-traumatic symptoms by trajectory modelling, then examine PTSD-depression comorbidity via developmental courses and risks; 2) to phenotype trauma-related appraisal and memory coherence by natural language processing, then check their relations with PTSD symptom levels; 3) to identify risks associated with PTSD outcomes from a large dataset by data mining machine learning modelling and interpretation; 4) to pool correlation magnitudes between different types of early adversities and panic disorder using robust

variance estimation, and 5) to propose a preliminary model that incorporates both cognitive and physiological dimensions and enables computational simulation.

2. Chapter 2: Post-trauma Symptomatic Trajectory[2]

"Time is like the wind; it lifts the light and leaves the heavy."

- *Doménico Cieri Estrada*

Highlights

- Trajectory is a comprehensive method to describe post-traumatic responses and its development.
- High depression symptom group did not recover after 9 months post-trauma.
- PTSD symptom development is highly in accordance with development of depression symptoms.
- Negative trauma appraisal is the shared risk to both PTSD and depression high symptom group.

From this chapter to chapter 5, we will focus on empirical questions in paediatric PTSD and early trauma. These studies are not constructed specifically under the computational framework. Nevertheless, they do in fact either grapple with a computational component or pave groundwork towards such goals. Their relevance to the computational approach will be addressed in detail in chapter 6.

2.1. Introduction

The co-occurrence of PTSD and depression has been widely observed. Rytwinski, Scur, Feeny, and Youngstrom (2013) reported that the prevalence of PTSD and major depression disorder comorbidity was 52% (CI [48, 56]) in adults. Another meta-analysis estimated the

[2] The study is published as Zhang, J., Meiser-Stedman, R., Jones, B., Smith, P., Dalgleish, T., Boyle, A., ... & McKinnon, A. (2022). Trajectory of post-traumatic stress and depression among children and adolescents following single-incident trauma. European journal of psychotraumatology, 13(1), 2037906.

prevalence of depression to be 24.2% (CI [20.6–28.0]) in trauma-exposed children and adolescents, and the odds ratio of having a depression diagnosis to be 2.6 (CI [2.0, 3.3]) for those exposed to trauma, compared with no or only mild trauma exposure (Vibhakar et al., 2019). The high rates of co-occurrence across age groups suggest this is an issue of some clinical and theoretical importance.

PTSD-depression comorbidity is known for being associated with more severe impairments in various domains (Cook et al., 2017) and the key question with regard to their relationship has been 'is depression part of the PTSD symptoms or are they two independent trauma responses?' Prior studies investigated the question mainly by looking into hazard ratio, prevalence, risk factors and vulnerabilities (Breslau, Davis, Peterson, & Schultz, 2000; Shalev et al., 1998; Spinhoven, Penninx, van Hemert, de Rooij, & Elzinga, 2014). The consensus is that while the two evidently share common risk factors and vulnerabilities, they are viewed as independent diagnoses because post-traumatic depression is beyond a mere sharing of common symptoms (Jovanovic et al., 2010; Stander, Thomsen, & Highfill-Mcroy, 2014).

Although these early studies helped to understand how PTSD and depression may relate, Stander et al. (2014) pointed out that most of these studies were limited to examination of associations between PTSD and depression at the macro level. They therefore suggested that future research should consider identifying the time-sensitive mechanisms that facilitate and mediate comorbidity. This point of view echoed Bonanno's (2004) argument that interpretation of post-traumatic responses would only be meaningful when symptoms were considered in their temporal context. This argument was based on the observations that there are a wide range of individual differences in responding to a potentially traumatic event over time. Bonanno further proposed four prototypical trajectory patterns (Bonanno, 2004), namely: resilient, recovery, delayed and chronic trajectories. In PTSD, these patterns are frequently observed despite diversity in the nature of the traumas (Galatzer-Levy, Huang, & Bonanno, 2018). These

trajectories are also found in the youth population. Several children studies have reported that a majority of trauma-exposed children and teenagers may experience elevated distress during the acute phase, but many recover (recovery) while some present persistently low (resilient) or high symptoms (chronic) over time (Hong et al., 2014; La Greca et al., 2013; Lauterbach & Armour, 2016; Punamäki, 2 J. ZHANG ET AL. Palosaari, Diab, Peltonen, & Qouta, 2015). Late onset (delayed) is relatively less reported (Bonde et al., 2021), however, a comprehensive review of the evidence is only available for adult data.

The implication of recognizing individual differences in trajectories is pivotal. If we are able to describe the developmental patterns of symptoms and to explain what causes the large discrepancies between trajectories after similar trauma exposure, we will have a better understanding of post-trauma psychopathology. With the application of trajectory modelling, a technique specially devised to identify latent longitudinal clusters, more studies exploring PTSD and depression trajectories have emerged. For example, deRoon-Cassini, Mancini, Rusch, and Bonanno (2010) conducted a latent class growth analysis (LCGA) study in adult traumatic injury. They reported four PTSD symptom trajectories (low symptom 59%, chronic 22%, delayed 6% and recovering 13%) and four similar depression groups. Overall, 69.7% of participants were in accordance with the assigned PTSD group (e.g. low PTSD and low depression). Further, they found that individuals in the chronic PTSD and depression group were more likely to have been assaulted, had higher levels of anger and less coping self-efficacy.

Taking the same approach, the present study first aims to look at the natural trajectories of posttraumatic stress symptoms (PTSS) and depression symptoms in children and adolescents by utilizing group-based trajectory modelling (GBTM). GBTM, equivalent to LCGA, has evinced reliable performance in identifying latent developmental clusters in clinical research (Nagin & Odgers, 2010; Twisk & Hoekstra, 2012). The modelling algorithm analyses the overarching symptom changes over multiple time points and classifies each participant into

one particular profile group according to probability. Secondly, we are interested to know whether PTSS and depression symptoms develop in synchrony. The examination was carried out using joint trajectory modelling that returns conditional probabilities linking trajectory groups across two respective outcomes (Jones & Nagin, 2007). The results report the probability of being assigned to a group in PTSS and the chance they would be categorized in the same (or a different) group in their depression trajectory.

Following Hong and colleagues' study (Hong et al., 2014), which also comprised children and adolescents who had been exposed to single incident (mainly non-interpersonal injury), we hypothesized that the trajectory modelling for both PTSS and depression would result in a majority falling into either the low symptoms or recovery groups, and only a small group who would be chronically distressed/depressed. Importantly, in addition to classifying trajectory profiles, we also sought to identify the potential risk factors associated with the high symptom group in comparison to the low symptom group. By evaluating the risks predicting PTSS with those predicting depression, the study aims to reveal shared processes involved in comorbidity.

The putative risk factors chosen in this study are based on the findings from a risk factor meta-analysis for PTSS in children and adolescents (Trickey, Siddaway, Meiser-Stedman, Serpell, & Field, 2012). Their study examined 25 types of risk that included demographic, trauma characteristics, and post-trauma environmental and psychological factors. They conclude that subjective peri-trauma factors and post-event factors, primarily cognitive processes (e.g. thought suppression, blaming others, perceived threat) are likely to have a major role in the onset of PTSD.

Naturally, the following question would be how much these risks are involved in depression. We hypothesize that the role of age and gender in PTSS might differ from depression. Gender and age are not significant risks for PTSD as per the previous study

(Meiser-Stedman et al., 2019), whereas depression tends to be more prevalent in older female adolescents among school-age population (Allgood-Merten, Lewinsohn, & Hops, 1990; Saluja et al., 2004; Thapar, Collishaw, Pine, & Thapar, 2012).

We also predict that cognitive processes could be the common risks for PTSD and depression posttrauma. Maladaptive appraisal and cognitive coping (e.g. rumination, thought suppression) have been found to be robust in maintaining PTSD symptoms (Ehlers & Clark, 2000; Lavi & Solomon, 2005; Meiser- Stedman, Dalgleish, Smith, Yule, & Glucksman, 2007; Stallard & Smith, 2007). Negative cognitive style (e.g. rumination, self- blaming) is also predictive of depression (Alloy et al., 2000, 2006).

In summary, we hypothesize that PTSS and posttrauma depression are two reactions to trauma which follow matching developmental courses and share certain risks. To examine the elements of the relationship, the study uses a trajectory modelling approach, where the differences and similarities are compared in three ways: 1) symptom changes in time (trajectories); 2) the synchronicity of the trajectories: and 3) their predictors.

2.2. Methods

2.2.1. **Participants**

The study used longitudinal data collected by the Acute Stress Programme for Children and Teenagers (ASPECTS), a project set up to study acute PTSD among children and adolescents. Two previous studies have focused on the acute time frame at 2 weeks and 2 months (Meiser-Stedman et al., 2017, 2019); these studies used the extended data collected at 9 months. Two hundred and seventeen participants were consenting child and adolescent attendees (8–17 years) at four emergency departments (EDs) in the East of England following single event trauma between 3 September 2010 and 30 April 2013. The potentially traumatic events included assault, road traffic accident (RTA) and accidental injury. Participants who did

not complete the questionnaires at 2 weeks were not included in the present study. Ten cases with high PTSS measurement scores were referred for treatment after T2, and were therefore excluded from T3 data in the study.

2.2.2. **Symptom measures**

All symptom and predictors measures used in the study were child-report. The two key variables of the study were the severity of PTSS and depression symptoms after trauma. These were measured using the Child PTSD Symptom Scale (CPSS; Foa, Johnson, Feeny, & Treadwell, 2001) and the Short Mood and Feelings Questionnaire (SMFQ; Angold, Costello, Messer, & Pickles, 1995).

The CPSS is a self-report questionnaire developed to assess PTSS for school-aged children. It is comprised of 24 items that can be divided into two parts. The first 17 items measure the type and frequency of PTSS (mapping directly on to DSM-IV criteria for PTSD), while the other seven items measure the degree of impairment in functioning. It has shown high reliability and validity across various types of trauma (Foa et al., 2001; Gillihan, Aderka, Conklin, Capaldi, & Foa, 2013; Nixon et al., 2013). A score of 16 was considered a clinical cut-off (Nixon et al., 2013).

The SMFQ is a short version (13 items) of the Mood and Feelings Questionnaire, an inventory that measures depressive symptoms in children and adolescents. Each item is rated on a 3-point scale: ‘true’, ‘sometimes true’, and ‘not true’ with respect to their mood and feelings in the past 2 weeks. It has been shown to be an efficient discriminative tool for school age children (Cheng, Cao, & Su, 2009; Thabrew, Stasiak, Bavin, Frampton, & Merry, 2018) through to late adolescents (Turner, Joinson, Peters, Wiles, & Lewis, 2014). A total score of eight or higher signifies clinical levels of depression (Angold et al., 1995).

2.2.3. **Predictor measures**

We considered eight main factors comprised of three domains controlled at the baseline: demographic (age, gender), peri-event panic, and post-trauma cognitive processes (appraisal, adaptive processing, thought suppression, rumination and self-blame). In addition, anxiety is believed to have a bidirectional relation with depression (Jacobson & Newman, 2017), therefore, post-trauma anxiety was added to our set of putative predictor measures. Last, it is prudent to have pre-trauma emotional wellbeing controlled as the baseline in the model to eliminate the chance of the observed PTSS and depression symptoms being the result of pre-existing mental health difficulties.

The scores of the ten independent variables were mostly derived from measures developed in previous studies (Meiser-Stedman et al., 2019). Pre-trauma emotional well-being was assessed using the adapted 10 items from the Post-traumatic Adjustment Scale (CPAS) (O'Donnell et al., 2008; $\alpha = 0.81$) that indexes anxiety, low mood and anger. Peri-event panic (CPP) was assessed using a 10-item questionnaire addressing the symptoms associated with a panic disorder diagnosis (Meiser-Stedman et al., 2019; $\alpha = .72$). Post-trauma anxiety was assessed using the Spence Children's Anxiety Scale (SCAS; Spence, 1998; $\alpha = 0.91$). Negative trauma-related appraisals were assessed using the Child Post-Traumatic Cognitions Inventory (CPTCI; Meiser-Stedman et al., 2009; $\alpha = .92$), a 25-item self-report designed to assess dysfunctional trauma-related cognitions. Thought suppression (Children's Thought Suppression Questionnaire, CTSQ) and rumination were assessed using five and three questionnaire items from a previous study that examined thought control strategies and rumination in youths with acute stress disorder (Meiser-Stedman et al., 2014; $\alpha = .85$). Adaptive processing, referring to deliberate efforts to mentally clarify what happened in the traumatic event, was assessed using a five-item measure (Children's Adaptive Processing Questionnaire, CAPQ; Meiser- Stedman et al., 2019; $\alpha = .73$). Self-blame, referring to a cognitive process in

which a person attributes the stress event to oneself, was assessed using a two-item measure (i.e. 'I made the event happen', 'it was my fault the event happened'; Meiser-Stedman et al., 2019; $\alpha = .90$).

2.2.4. **Procedure**

The study was approved by the UK National Research Ethics Service, Cambridgeshire 1 Research Ethics Committee (10/H0304/11). Parents provided informed consent on behalf of their children, and the child or young person's assent was also required for study entry.

ED research nurses reviewed and screened cases of children attending ED. The parents/caregivers of eligible children were initially contacted by letter 2– 4 days post-ED attendance. The nurses excluded cases of chronic trauma exposure, intellectual disability, organic brain damage, significant self-harm and not being a fluent English speaker based on clinical records and parents' report at the initial contact. After T2 (the screening phase), participants with elevated symptoms were referred for intervention. At T3 follow- up, those who sought/received counselling or treatment were documented while the data were collected as usual. As the current study focused on natural trajectory, we decided to exclude data of participants ($n = 10$) who received multiple sessions of an active psychological intervention for PTSD following T2. Children who had other forms of psychological input, such as one session counselling or treatment for other reasons, were still included.

Consenting participants completed self-report questionnaires at 2 weeks (T1), 2 months (T2) and 9 months (T3) via the telephone or online survey. The survey at T1 and T2 comprised the PTSS and depression measures previously described and the 10 risk variables. The 9-month follow-up only included the PTSS and depression measures. Demographic information, nature of the incident, injury severity and medical treatment were obtained from the ED. PTSS and depression symptoms (assessed by the CPSS and SMFQ, respectively) at T1, T2 and T3 were used for trajectory modelling. Predictive variables were all from T1.

2.2.5. **Statistical analysis**

The data analysis followed several steps. First, the distributions of CPSS and SMFQ were checked in order to determine the distribution choice for trajectory modelling. We then used the GBTM program 'Proc Traj' to run modelling for CPSS and SMFQ separately to estimate their candidate models. These candidate models were assessed by their Bayesian Information Criterion (BIC) values along with other interpretive criteria so that we could choose a best fit model for each of the two measures. Next, a joint trajectory model was carried out based on the chosen individual models with a dropout option that compensated for missing data. The joint trajectory returned fine-tuned trajectory probability groups as final results, together with the conditional probability that indexed the connection between the CPSS and SMFQ trajectory groups. Finally, we utilized logistic regression analysis to investigate the link between the predictors and the high symptom groups. Details of each step are as follows.

Data analysis software – Proc Traj

Proc Traj is a SAS/STATA procedure developed by Jones, Nagin, and Roeder (2001). It uses a specialized application of finite mixture modelling to estimate trajectories and does not assume a one size-fits-all model for characterizing symptom onset and progression. Beside the basic modelling function, the package has been extended with functions such as dual trajectory modelling (Jones & Nagin, 2007). Detailed documentation of the Traj procedure can be found at https://www.andrew.cmu.edu/user/bjones/.

Distribution estimation

Estimating the distribution of CPSS and SMFQ variables became necessary so that an appropriate modelling option (CNORM vs. Zero-inflated Poisson, ZIP) could be chosen. An R package, 'fitdistrplus' (https://cran.r-project.org/ web/packages/fitdistrplus/index.html) was employed to ascertain the distribution of the scores of CPSS and SMFQ at T1. Negative exponential distribution was then considered the best fit for both variables across the three time

points (see supplemental material S2-B). Therefore, ZIP distribution was chosen for the trajectory modelling.

Single modelling

Given the exploratory nature of modelling, there was no guarantee the procedure would find a successful fit and so determining starting values becomes critical (Jones et al., 2001). Single modelling was used to approximate the parameters of the CPSS and SMFQ trajectories separately before embarking on the joint modelling. Based on previous findings in the literature, potential models with three and four groups were tested. A model of two groups was included as baseline for comparison. For ZIP distribution, Proc Traj's statistical modelling assumes

$$\ln(\lambda_{it}^{j}) = \beta_0^j + \beta_1^j Time_{it} + \beta_2^j Time_{it}^2 + \beta_3^j Time_{it}^3 + \beta_4^j Time_{it}^4$$

where $\lambda_{it}^{j}$is the event of interest i at time t, given membership in group j, and $Time_{it}$ is the sampling time point at time t lapsed since the event. The model's coefficients — $\beta_0^j, \beta_1^j, \beta_2^j, \beta_3^j and\ \beta_4^j$ determine the shape of the trajectory. Since Proc Traj allows up to four degrees, our strategy was to probe the possible combinations of a group's polynomial order and to find their highest significant ($p < .05$) degree.

Model selection

Once the single modelling was completed, a best-fit model was selected for each of the outcome measures. Although Jones et al. (2001) recommended an algorithm using two times the change of the BIC values of the adjacent models as the criterion, we argued that it is equally important to realize that depending solely on a statistical figure might fail to identify a model that is clinically meaningful and succinct.

Joint modelling

This was the second step of the modelling analysis. It was undertaken to refine the trajectories and to calculate the conditional probability of group membership based on Bayesian theorem, in order to make immediate linkage between the trajectory groups of PTSS

and depression. The configurations of the two selected models produced by the previous steps were entered into the joint modelling function. False convergence warning was given after the first iteration, therefore a fine-tuning was needed. We used the option 'detail' to obtain the parameters returned from the first iteration. We removed insignificant parameters ($p > .05$) and entered the rest into a second iteration as starting values (see complete STATA script in supplemental material S2-C). The program adjusted well and the model was finalized.

Dropout analysis

Attrition has been a challenge for longitudinal studies and where data is missing careful handling is required or there will be a high risk of bias in the results yielded. Strategies for handling missing data may depend on whether the data are missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). In practice, the difference between MCAR, MAR and MNAR is often too elusive to ascertain (Graham, 2009).

There was an attrition rate of approximately one third at nine months in our study and the randomness of the missing data was hard to estimate. Fortunately, Haviland, Jones, and Nagin (2011) have extended the Proc Traj package with a dropout option. They demonstrated that non-random attrition, in which the dropout rate is uneven across the latent groups, has a consequential impact on modelling the group size. In an extreme case, a group might completely diminish. They further illustrated that the dropout extension was successfully able to optimize the model by taking account of different dropout rates. Thus, we adopted the dropout option in modelling to estimate a better model and offer informative judgement on the missing data. Specifically, if dropout rate is not randomly distributed across symptom groups in the dataset, the dropout analysis will identify the patterns, for example, participants with more severer symptoms might be more likely to withdraw from the follow ups. The correct identification will help to make adjustment accordingly when trajectory groups are estimated.

Predictive factor analysis

After the joint modelling, each case was categorized into one PTSS group and one depression group according to the course of their symptoms over the 9 months. Membership profiles were labelled as low, medium or high. A multinomial logistic regression analysis was then deployed to calculate the relative risk ratio of falling into the high symptom trajectory group compared to the low symptom trajectory group according to predictor variables of age and gender, measures of pre-trauma emotional wellbeing (CPAS), peri-trauma panic (CPP), post-trauma anxiety (SCAS), appraisal (CPTCI), rumination, thought suppression and adaptive-processing and self-blaming. Trauma severity, a common factor that may influence the post-trauma response, was not included in the modelling. The previous study using the same sample revealed that objective indices of trauma severity (number of injuries, sustaining a fracture, being seen in resuscitation, sustaining an injury with permanent loss of function) were not significantly related to PTSS (Meiser-Stedman et al., 2019). That study suggested, however, that the cognitive processes (peritraumatic panic, post-traumatic rumination, negative appraisals and adaptive processing) played an important role in the onset and maintenance of PTSS; thus, the present study focused on examining the impact of the cognitive elements. Regression analysis also confirmed that trauma severity was not associated with depression (SMFQ) scores; model outputs are listed in supplemental material S2-Table 3.

2.3. Results

2.3.1. Descriptive statistics

The data analysis included 217 participants, of whom 124 were males and 93 were females. Participants were aged between 8.01 and 17.97 years (M = 14.09, SD = 2.96). The traumatic events that participants had been exposed to were RTA (n = 98), accidental injury (n = 71), assault (n = 35), dog attacks (n = 11) and other acute medical emergencies (n = 2). At

T2, there were 13 participants missing CPSS scores and 14 cases missing SMFQ scores. At T3, 58 cases missed both CPSS and SMFQ scores.

2.3.2. **Model selection**

As illustrated in supplementary S2-Table 1, for the PTSS (CPSS) trajectories, the BIC criterion favoured models comprising four groups; for depression symptoms (SMFQ) there was no significant difference between the three and four group options (i.e. the BIC difference was less than 10). Figure 2-1 presents the two proposed models: three groups vs four groups (see Figure 1a for CPSS and Figure 1b for SMFQ). The two models (3-group model vs. 4-group model) were similar in some key regards – they both encompassed a consistently low score group and high score group with broadly equivalent group size (29.3% vs. 26.1% for the low score group and 21.1% vs. 17.1% for the high score group in PTSS; 19.6% vs. 17.6% for the high score group in depression).

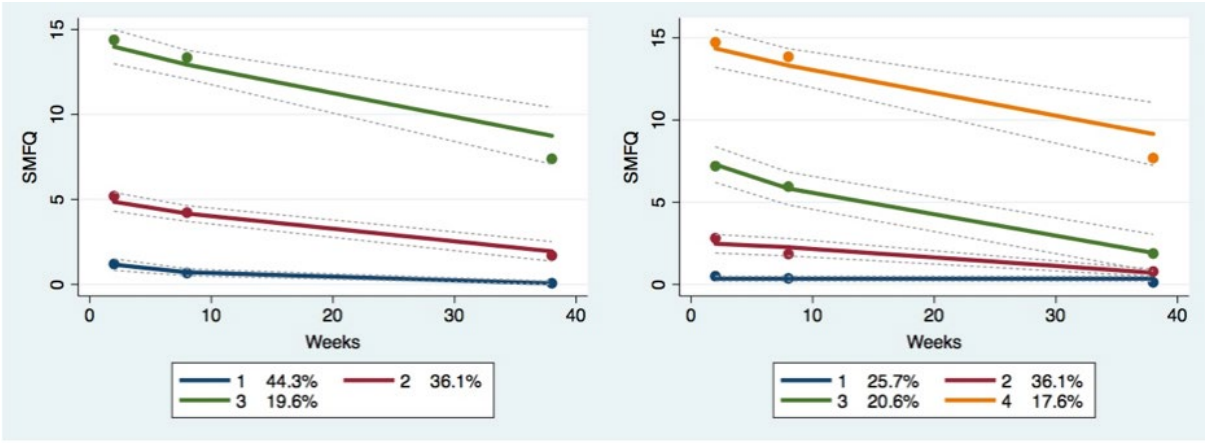


Figure 2-12: A): Candidate models of CPSS

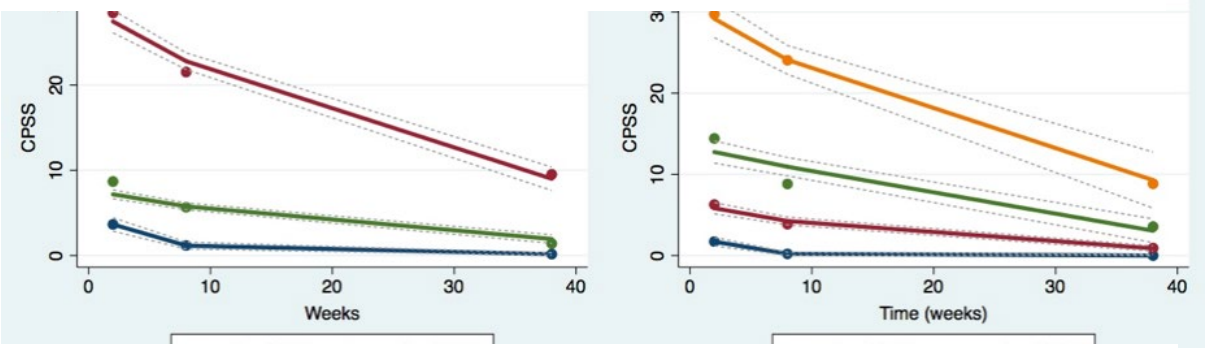


Figure 2-10: B): Candidate models of SMFQ

The main difference between the three- and four-group models concerned the medium groups. The three-groups model recommended one medium severity group, whereas two separate groups were proposed by the four-group models. We favoured the more succinct three-group model for several reasons. First, in those two groups, the starting point at T1 of one group is higher than the other and almost reaches the cut-offs for each outcome (16 for CPSS and eight for SMFQ). Although subthreshold symptoms can be of a potential concern, treatment usually will only be considered when symptoms last more than 1 month. Since both symptoms dropped further at T2, it will make no material difference between the two middle groups in terms of clinical management. Second, the four-group models also had larger confidence intervals (CI: areas between the dashed lines). Third, the more parsimonious models would be beneficial when it came to joint modelling because, when linking the outcomes of the two trajectories, the proliferation of probability matrices could easily become unmanageable. Specifically, the four PTSS and four depression groups produce 16 combinations while the three-group option only produces nine. Those seven extra combinations are the hybrids from the medium groups, which can be expected to be almost identical.

2.3.3. **CPSS & SMFQ joint modelling**

The shape of the trajectory of each group is determined by a vector of coefficients ($\beta_0^j, \beta_1^j, \beta_2^j, \beta_3^j \; and \; \beta_4^j$). Our model attained significant ($p < .00001$) coefficients for all trajectory groups and drop out polynomials (see complete output in supplemental material S2-Table 2). Conditional as well as joint membership probabilities have been reported.

2.3.4. **PTSS trajectory**

The final joint model (Figure 2-2) yielded three distinct PTSS trajectory probability groups including a low symptom group (42.4% of the sample size) with persistently low CPSS scores, a group (35.6%) with marginally significant CPSS score at week 2 which dropped

below the clinical cut-off at 2 months, and a high symptom group (21.9%) presenting marked distress at 2 weeks and 2 months At 9 months, the scores of the three groups were all in the non- clinical range.

2.3.5. **Depression trajectory**

Similarly, the joint model produced three depression trajectory groups (low, medium and high) comprising 45.9%, 34.0% and 20.1% of the participants, respectively. In contrast to the low and medium groups, whose depression level remained persistently low, the SMFQ score of the high depression group at nine months (M = 7.96, 95% CI [7.32, 11.17]) was still around the clinical cut-off.

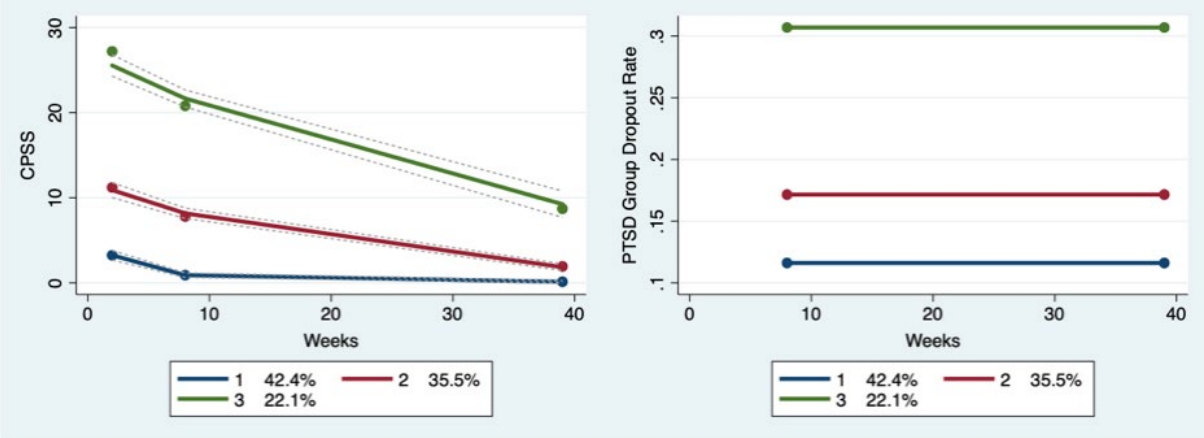


Figure 2-14: A) Final trajectory and dropout model of CPSS.

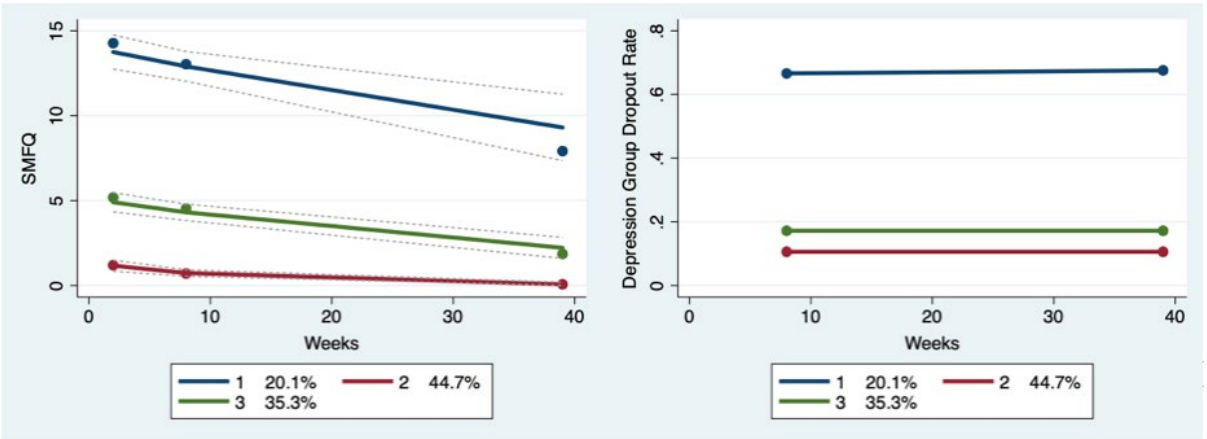
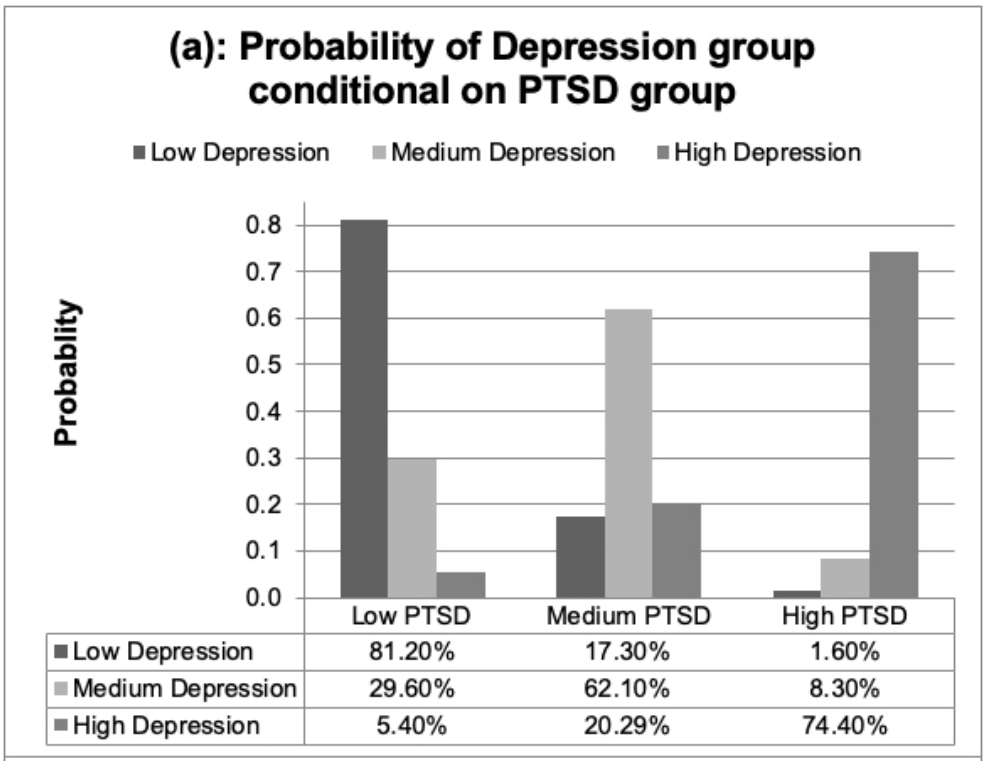


Figure 2-15: B) Final trajectory and dropout model of SMFQ.

2.3.6. **Conditional group membership**

In probability theory, conditional probability is a measure of the probability of an event occurring given that another event has occurred. If we knew a case was categorized as high PTSS, the probability of its belonging to the low, medium and high depression symptom trajectory groups would be 1.6%, 8.3% and 74.4%, respectively. Conversely, the probability of belonging to the low, medium and high PTSS groups conditional on membership of a high depression group would be 2.5%, 13.1% and 81.8%, respectively.

Figure 2-3 lists the conditional probabilities of all the possible combinations. In addition, the model also reported the joint probability of belonging to the PTSS group and the depression group (Table 2-1c).



	Low PTSD	Medium PTSD	High PTSD
Low Depression	81.20%	17.30%	1.60%
Medium Depression	29.60%	62.10%	8.30%
High Depression	5.40%	20.29%	74.40%

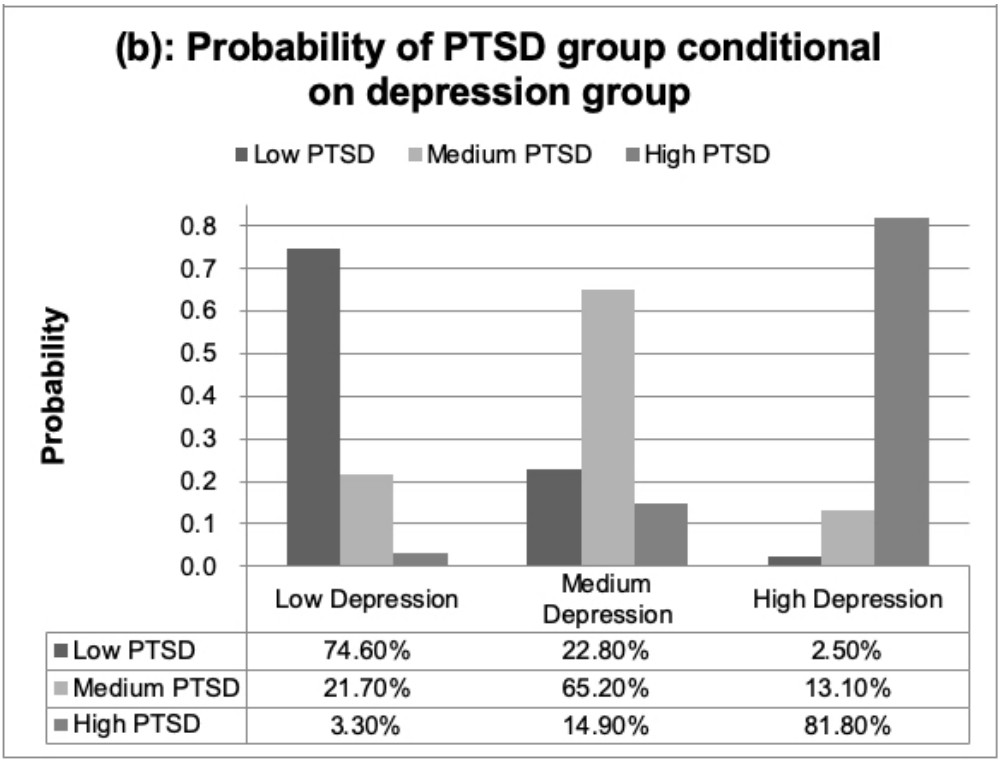


Figure 2-16: A) Conditional probability of depression if PTSD is known. B) Conditional probability of PTSD if depression is known.

Table 2-1: Parameters of trajectory groups and joint probability

2-1a: PTSD trajectory groups					
	Group	**Mean**	**Est. Mean**	**95%CI**	**Dropout%**
2 weeks	Low	3.243	3.238	[2.703, 3.773]	-
	Medium	11.125	10.873	[9.987, 11.759]	-
	High	27.582	25.789	[24.529, 27.048]	-
8 weeks	Low	.879	.875	[.607, 1.142]	14.1%
	Medium	7.780	8.096	[7.498, 8.695]	15.5%
	High	20.824	21.746	[20.742, 22.750]	30.2%
9 months	Low	.127	.127	[0, .258]	14.1%
	Medium	1.921	1.854	[1.467, 2.241]	15.5%
	High	8.709	9.271	[7.718, 10.825]	30.2%
2-1b: Depression trajectory groups					
	Group	**Mean**	**Est. Mean**	**95%CI**	**Dropout%**

	Low	1.230	1.231	[.9152, 1.546]	-
2 weeks	Medium	5.220	4.998	[4.438, 5.559]	-
	High	14.351	13.831	[12.762, 14.899]	-
	Low	.702	.753	[.5677, .938]	16.3%
8 weeks	Medium	4.599	4.375	[3.898, 4.852]	11.9%
	High	12.936	12.933	[12.021, 13.845]	65.1%
	Low	.068	.0645	[0, .185]	16.3%
9 months	Medium	1.848	2.248	[1.625, 2.871]	11.9%
	High	7.960	9.246	[7.321, 11.171]	65.1%

2-1c: Joint probability of combined membership

		Depression Group		
		Low	**Medium**	**High**
	Low	34.5%	7.3%	0.7%
PTSD Group	**Medium**	10.5%	22.1%	3.0%
	High	1.2%	4.4%	16.3%

2.3.7. **Dropout model**

Dropout model explains the heterogeneity in the dropout pattern within each trajectory group. It also describes the change of attrition rate across the time using the sample size at T1 as baseline. A flat linear model was proposed suggesting an equal rate of attrition at T2 and T3. Estimated dropout rates for the low, medium and high PTSS groups were 14.1%, 15.5%, 30.2%, respectively. Likewise, estimation for the depression groups were 16.3%, 11.9% and 65.1%, respectively. The models indicated that the higher symptoms a child had, either in PTSS or depression, more likely they would dropout.

For the record, the actual dropout rates at T2 were: 3.16%, 3.47% and 6.77% for PTSS groups, and 3.93%, 2.87% and 15.7% for depression groups. At T3, the rates were: 14.9%, 16.2%, 36.7% for PTSS groups, and 11.3%, 10.9% and 67.8% for depression groups.

2.3.8. **Predictive factors**

Using low symptom groups as the referent, gender, age, pre-trauma emotional wellbeing, peri-event panic, post-trauma anxiety, trauma-related appraisal, rumination, thought suppression, adaptive processing and self-blaming were entered as independent variables into two multinomial logistic regressions (see STATA scripts in supplemental material S2-D) to predict the PTSS and depression trajectory outcome, in particular for high symptom groups. The relative risk ratio in the model estimates that for one unit increase in each of the predictive factors the change in the probability of falling into the high symptom group rather than the low symptom group, given that the other variables in the model are held constant.

The statistically significant predictors ($p < .05$), ordered from strongest to weakest, for the high PTSS trajectory group were: peri-event panic (RR = 2.09, 95% CI [1.38, 3.19]), rumination (RR = 1.60, 95% CI [1.07, 2.39]), thought suppression (RR = 1.27, 95% CI [1.04, 1.56]) and negative appraisals (RR = 1.26, 95% CI [1.12, 1.42]). The statistically significant predictors for the high depression trajectory group (also from strongest to weakest) were: negative appraisals (RR = 1.31, 95% CI [1.15, 1.48]), pre-trauma emotional wellbeing (RR = 1.24, 95%CI [1.03, 1.49]), and post-trauma anxiety (RR = 1.20, 95% CI [1.09, 1.34]). Gender and age did not predict PTSS or depression (Table 2-2).

Table 2-2: Multinomial logistic regression analysis

2-2a: Predictors of high PTSD group using low PTSD symptom group as referent

Log likelihood = - 112. 91091			# of obs: 214 LR chi2(20) = 228.84 Prob > chi2 = 0.000 Psudo R2 = 0.5033		
	`RRR	**Std. Err.**	**Z**	**P > |Z|**	**[95% Conf. Interval]**
Age	1.66	1.31	0.64	0.520	[.36, 7.73]

Gender	1.05	.14	0.38	0.704	[.81, 1.37]
Pre-trauma emotional wellbeing	.92	.09	- 0.93	0.354	[.76, 1.10]
Peri-trauma panic*	2.09	.45	3.47	0.001	[1.38, 3.19]
Post-trauma anxiety	1.07	.05	1.33	0.182	[.97, 1.17]
Cognitive apprasial*	1.26	.08	3.86	0.000	[1.12, 1.42]
Rumination*	1.61	.33	2.32	0.020	[1.08, 2.39]
Thought suppression*	1.27	.13	2.35	0.019	[1.04, 1.56]
Adaptive processing	.85	.09	-1.47	0.140	[.68, 1.06]
Self blame	.68	.14	- 1.83	0.068	[.45, 1.03]
_cons	6.34e-09	2.42e-08	- 4.94	0.000	[3.54e-12, .0000114]

2-2b: Predictors of high depression group using low depression symptom group as referent

Log likelihood = -110.86479			# of obs: 214 LR chi2(20) = 225.83 Prob > chi2 = 0.000 Psudo R2 = 0.5046		
	`RRR	**Std. Err.**	**Z**	**P > |Z|**	**[95% Conf. Interval]**
Gender	.95	.74	0.07	0.947	[.21, 4.34]

Age	1.30	.18	1.89	0.059	[.99, 1.71]
Pre-trauma emotional wellbeing*	1.24	.12	2.24	0.025	[1.03, 1.49]
Peri-trauma panic	.98	.18	-0.09	0.930	[.68, 1.42]
Post-trauma anxiety*	1.21	.06	3.62	0.000	[1.09, 1.34]
Cognitive apprasial*	1.31	.08	4.22	0.000	[1.15, 1.48]
Rumination	1.28	.24	1.30	0.194	[.88, 1.86]
Thought suppression	1.06	.12	0.61	0.542	[.87, 1.30]
Adaptive processing	.87	.09	-1.20	0.229	[.70, 1.09]
Self blame	1.34	.25	1.54	0.123	[.92, 1.93]
_cons	2.30e-13	1.05e-12	-6.38	0.000	[3.03e-17 1.75e-09]

RRR: relative risk ratio

Note: _cons estimates baseline relative risk for each outcome

2.4. Discussion

The study investigated the natural recovery trajectories of PTSS and depression symptoms for the 9 months period following a single event trauma. Overall, our model suggested that PTSS reduced to non-clinical level for all participants by 9-months. The PTSS trajectories finding was consonant with the typical trauma response pattern proposed in 2004 (Bonanno, 2004), although no delayed onset cluster was detected in our sample. The majority

(80%) were observed to be consistently displaying low symptoms or able to recover within two months. About one-fifth of participants experienced high levels of PTSS but managed to reach the recovery range within 9 months. Unlike the other non-interpersonal one-time trauma studies in youth (Hong et al., 2014; La Greca et al., 2013; Punamäki et al., 2015), there was no chronic/ increase group.

Another possible reason for the absent chronic group could be that participants with elevated PTSS were referred to intervention and were excluded from the study. It is difficult to be certain how different the PTSS trajectory groups would be if the data of children who received treatment had been included into the modelling. Since their PTSD symptoms were expected to drop at T2 and T3 after treatment, they would likely be merged into the high symptom trajectory group. Meanwhile, we also postulate that in the less ethical counterfactual situation where no intervention is offered, the 10 cases would form a fourth group with a PTSS level higher than the current high symptom group at T1 and possibly with symptoms continuing to deteriorate over T2 and T3. This hypothesis is based on the shared characteristics of the chronic/increase group reported by two similar injury studies (Hong et al., 2014; Punamäki et al., 2015). The shared characteristics were: that the group made up a very small portion (1.8% and 12%); that the initial symptom level at the acute phase was the highest among all groups; and that there was no natural recovery even after periods as long as 30 (Hong et al., 2014) and 11 months (Punamäki et al., 2015). Alternatively, these cases may have increased the predicted depression score of the high symptom group at the T3 assessment.

The depression trajectories were quite different. The three trajectories all described a steady decline but the divergence between the high depression group (20%) and the rest was such that the high depression trajectory group were more likely to have persistently high depression symptoms for nine months, during which time the other two groups demonstrated

only mild symptoms. Such a dichotomous pattern has not been apparent in previous trajectory studies in paediatric populations.

In respect of the relationship between the PTSS and depression trajectories, the conditional membership analysis reported high synchronicity: low PTSS participants were highly likely to be classified in the low depression group, while a participant who experienced high PTSS was anticipated to be in the highly depressed group. Similarly, being in the high depression group predicted being in the more severe PTSS group. The finding is consistent with previous studies in injured adults (deRoon-Cassini et al., 2010) and children (Hong et al., 2014). Given that PTSD- depression comorbidity is well established, this finding is not surprising. However, trajectory is a temporal concept and it addresses the dynamic of symptom change. The synchrony between the two trajectories following the same stressor has more profound cations than a simple indication of symptoms lapping at some time point. It is reasonable to hypothesize that if PTSS and depression evolve in similar patterns, there should be either a common mechanism underlying their development, or there is/are shared factor(s) driving the mechanisms that determine the symptoms.

The high PTSS and depression trajectory groups shared few predictive factors. Rumination in general is considered a transdiagnostic feature associated with depression and PTSD, and it was strongly related to PTSS in this study although it did not predict depression in our model. This phenomenon suggests that a certain subtype(s) of rumination may maintain PTSD but not depression. Birrer and Michael (2011) conducted a study examining the characteristics of rumination such as duration and content in PTSD and depression; they found that rumination served as a powerful internal trigger for intrusive memories in PTSD, but not in depression. Constructions of various types of rumination (e.g. depressive rumination, stress-reactive rumination) have been suggested and their clinical impact needs further investigation.

In line with the literature, peri-trauma panic (perceived threat), thought suppression and negative appraisal were linked with high PTSS, while only negative appraisal was a factor that was associated with both high symptom groups. This finding confirms that negative appraisal plays a role in maintaining broader post-trauma psychopathology (Hiller et al., 2019). Hamilton et al. (2012) integrated findings from a large body of neuroimaging research and pro-posed that depression is sustained by the increased salience of negative information leading to biased appraisal. Combined with the heightened sense of threat (e.g. intrusive memory, hypervigilance) in PTSD, which serves as an ongoing source of negative information, appraisal may be central to understanding PTSD-depression comorbidity. The negative appraisals that are proposed to play a major role in the maintenance of PTSD (Ehlers & Clark, 2000) also help to maintain depression.

In summarizing the PTSS-depression relationship observed in the study, we concluded that PTSS and depression are two distinct, but overlapping, responses to a traumatic stressor, and that they are maintained by different processes. This conclusion is based on 1) the high synchronicity in their trajectories, and 2) few mutual predictors. Negative appraisals appeared to play a critical role bridging their mechanisms. Anxiety manifested as the second strongest predictor of depression trajectories. This may be a by-product of the overlapping presentations of physiological arousal and avoidance in both anxiety disorders and PTSD.

Lastly, our study is the first to examine trajectory and attrition rate in the field and found that the more severe symptoms a participant has, the more likely they will drop out from the study. We hypothesize that this may hold universally in longitudinal research and clinical trials, and the consequences can be serious. The immediate consequence is that, without correction, the averages of the examined measures will be lower than their real means, and other prime parameters of the sampled distribution, such as standard deviation, will be altered. This may make inferred statistical interpretation less accurate. Therefore, this conclusion supports

handling missing data with great caution and, if possible, applying appropriate statistical methods (e.g. dropout modelling or imputation) to minimize the impact.

2.4.1. **Clinical implication**

In the case of acute post-traumatic psychopathology, depression may be a more lasting condition than PTSD symptoms. In our sample, PTSS tended to diminish over time, whereas depression often persisted. This supports the routine screening of trauma- exposed children and adolescents for depression. Similarly, depression should be included in any consideration of core post-traumatic symptoms when making clinical decisions such as active monitoring or offering an intervention.

There was a clear correlation between high PTSS and high depression symptoms. Although this study was limited to the non-clinic-referred group (i.e. participants receiving multiple-session interventions were excluded), this relationship is likely to hold in the clinical population given the findings from other dies. This means that patients seeking treatment for PTSD are prone to high levels of depression. Effective intervention should incorporate components sing both PTSD and depression.

Most importantly, negative appraisal was the only predictor for both high PTSS as well as high depression symptom trajectories; this suggests a possible effective treatment approach, addressing PTSS and depression holistically by focusing on negative appraisal.

2.4.2. **Limitations**

The study had several discernible limitations. First of all, the data were limited to children and adolescents, mainly following a one-off, mostly non-interpersonal trauma. Thus, the interpretation of the results may not apply to interpersonal or multiple traumas. Second, for ethical reasons, the dataset was only able to track the natural course of participants with relatively mild symptoms. Ten cases with high PTSS measurement scores were referred for

treatment and were therefore excluded from the study. The trajectories that emerged in this study may, therefore, not represent the clinical population. Third, the drop out model predicted equal dropout rates at T2 and T3, which did not fit the actual data perfectly (the missing rate at T2 was much lower (13/14 cases) than at T3 (58 cases). Consequently, the estimated means at T2 could be higher than their true values as the joint modelling compensates for the missing data by applying the high score, high dropout formulation.

2.5. Conclusion

Within children and adolescents exposed to single event trauma resulting in minor physical injury, the majority were able to recover without intervention over the following months, although about one-fifth presented with symptoms of lasting depression at 9-month follow-up. PTSS trajectory groups are in high accordance with depression trajectory groups. By examining predictors of high symptom groups, negative appraisals appeared to be a shared risk factor to PTSS and depression.

3. Chapter 3: Trauma Memory and Appraisal[3]

"...the memory of a particular image is but regret for a particular moment."

- *Marcel Proust, In Search of Lost Time.*

Highlights

- Memory coherence and trauma appraisal are crucial elements in PTSD.
- NLP techniques are reliable and valid methods to measure memory coherence and trauma appraisal by analysing trauma narratives.
- Poorer memory coherence and more negative trauma appraisals predict higher PTSD symptoms level.
- With NLP, trauma narrative is a valuable source to extract data of post-traumatic cognitions and emotions.

3.1. Introduction

Memory is proposed to play a key role in the etiology of PTSD. Interventions of recognized efficacy (e.g., TF-CBT, EMDR) all put trauma memory at the centre of treatment. The cognitive model of PTSD holds that one of the main problems in persistent PTSD is the poor integration into the autobiographical memory base, and there is a reciprocal relation between trauma memory and negative trauma appraisals, another component that maintains PTSD (Ehlers & Clark, 2000). In the mnemonic model, Rubin et al. (2008) elaborated this point of view to the extent that PTSD in essence is a disorder of memory. They argue that the current content and quality of memory of the trauma are central to the development and the maintenance of PTSD.

[3] This study has been submitted to Journal of Psychopathology and Clinical Science.

Narrative accounts of traumatic events have frequently been used to capture key elements of trauma memories. To date, studies have explored the content, the structure and the linguistic characteristics of the trauma narrative in search of empirical evidence to evaluate the PTSD theories and models. A review of 22 studies (Crespo & Fernández-Lansac, 2016) reported that 1) fragmented/disorganized narrative is associated with more severe PTSD symptoms; 2) a greater number of sensory/perceptual words and fewer cognitive words are found in trauma than non-trauma narratives; 3) the tone of the trauma narrative is in general more emotional and greater expression of negative emotions in particular is associated with PTSD; 4) use of present tense in describing the event is more prevalent in participants with PTSD; and 5) a small number of studies looked at self-defining expressions or subjective perspective but data were insufficient to draw conclusions. More recent studies also found that 6) the relation between narrative coherence and depression and PTSD symptoms was mediated by rumination (Vanderveren, Bijttebier, & Hermans, 2020); and 7) veterans with PTSD generated equivalent number of memories as non-PTSD controls, albeit with more non-episodic details (Memel, Lynch, Lafleche, & Verfaellie, 2021).

Although the majority of the findings are in line with cognitive theories that highlight the roles of memory and appraisals in the etiology of PTSD, there are also marked limitations of the extant literature. First, important terms such as fragmentation, disorganization, coherence or reference to self are not defined either conceptually or operationally (Crespo & Fernández-Lansac, 2016; O'Kearney & Perrott, 2006). Instead, researchers are left to their own devices to construct and to measure these terms. For example, disorganization was assessed based on three sub-domain scores at the "chunk" (i.e., smallest unit of meaning) level, whereas coherence was used as a globe index of disorganization at the whole narrative level (Halligan, Michael, Clark, & Ehlers, 2003). In another study, Rubin (2011) used the rater's comprehension of the text and Narrative Coherence Coding Scheme, i.e., NACCS (Reese et

al., 2011) to calculate coherence. Secondly, apart from simple properties like narrative length, tense or counts of certain types of words, the measurements have been obtained mostly by subjective ratings, which are inevitably prone to errors and biases. Thirdly, there has been poor validation of the rating methods used, including limited validation of coding reliability (e.g., by using multiple coders) and limited attempts to validate resultant scores against other memory measures.

We propose that Natural Language Processing (NLP) could be a valuable approach for the study of trauma narratives. NLP is a field of artificial intelligence (AI) that uses computational algorithms to understand human natural language data in text or speech. NLP can be used to perform objective, large-scale data analysis (Zhou, Duan, Liu, & Shum, 2020), and the applications of NLP in medical and clinic settings have shown its potential to improve research and quality of care (Le Glaz et al., 2021; Li et al., 2021; Vaci et al., 2020; Wang et al., 2020). NLP potentially has considerable advantages for the study of PTSD and trauma narratives. As text preprocessing and analysis are run by automated NLP programs, errors and biases should be significantly reduced. In addition, the availability of different computational models can provide information about reliability, and the performance of different methods can be compared quantitatively.

In the present study, we aim to investigate whether NLP can be a reliable method to assess two important features of trauma narratives: negative appraisals of the trauma and narrative coherence, each of which are key elements of cognitive models of PTSD. In NLP coding terms, *polarity* refers to how positive or negative the narrator's attitude is towards the experience (Nasukawa & Yi, 2003), and in the context of trauma narratives it provides an index of trauma appraisals; *coherence* is an overall score that marks the degree to which the story makes sense. As NLP tasks (e.g., calculating the coherence score) can be achieved via different methods, one way to verify reliability is to cross check the scores yielded by different

algorithms. Accordingly, two algorithms were implemented for each coding domain and consistency between scores used to index reliability. In addition, with NLP, validity is usually determined by comparing the machine results to another independent measurement of the same outcome. Here, to ascertain validity, subjective self-report of memory quality was used (i.e., participant's self-report on the characteristics of their memory of the event) and trauma-related appraisals.

In addition to assessing reliability and validity of the NLP-derived indices of coherence and appraisal, key hypotheses deriving from cognitive models of PTSD were tested. Specifically, whether:

H1: narrative length is positively linked to the level of PTSS;

H2: poorer coherence predicts higher PTSS severity;

H3: more negative appraisal predicts more PTSS;

H4: coherence and appraisal scores change over time. Narrative will become less negative and more coherent with the lapse of time from the trauma event.

Hypothesis 1 is based on the mnemonic model whereby the availability of trauma memory should increase PTSD (Rubin et al., 2008). If narrative word count operates as a crude index of the degree of trauma memory availability, then shorter length should predict less PTSD. This is only partially supported by some of the comparison studies between trauma narratives versus non-trauma narratives (Crespo & Fernández-Lansac, 2016; Fernández-Lansac & Crespo, 2015). Findings of a direct link between PTSD and narrative length have been contradictory (Beaudreau, 2007; Foa, Molnar & Cashman, 1995). Shorter narratives might also could indicate avoidance so the relationship among narrative length, PTSD severity and avoidance symptom are worth reexamining.

H2-4 address core aspects of cognitive models of PTSD that have been considered previously and are broadly endorsed – though not universally – by the current literature (Crespo

& Fernández-Lansac, 2016; O'Kearney & Perrott, 2006). The purpose of replication is to confirm that NLP produces consistent outcomes, as studies utilized conventional methods and therefore shall be trusted in future research.

3.2. Methods

3.2.1. Data characteristics

The study made use of existing data from PROTECT (Parental Responses to Child Experiences of Trauma) project. Children between ages 6 and 13 (n = 132) who had attended hospital due to injury were recruited and invited to complete assessments at 1 month (T1) and 6 months (T3[4]) posttrauma, during which post-traumatic stress symptoms (PTSS) were measured and trauma narratives were collected. The types of trauma were mainly non-interpersonal, from motor vehicle accidents (52%), accidental injury (27%, e.g., sports injury, fall) to acute medical episodes (8%) or other events such as attack by dog (8%); only 2% were assault. 34 (26%) met criteria for PTSD at T1 and 12 (10%) at T3 (Hiller et al., 2018).

3.2.2. Trauma narratives

At T1 and T3, participants were asked to talk about the event in their own way, beginning just before the event and were encouraged to give details of their experiences, thoughts and feelings, by using prompts such as “Is there anything else you want to add?”, “How were you feeling then?” and “Were there any particular thoughts going through your head at that time?” The narratives were recorded and then transcribed verbatim in the form of conversations. the lines from the interviewer(s) and other notations regarding the child’s nonverbal responses were removed to warrant only pertinent data to be analyzed. Narratives were missing for one child at T1 and for 17 at T3.

[4] The PROTECT study collected data at three times: 1 month (T1), 3 months (T2) and 6 months (T3) (Hiller et al., 2018). Although the current study only included data of 1 month and 6 months, we used the same label T1 and T3 instead of T1 and T2 to be consistent with original dataset.

3.2.3. **PTSS measures**

PTS symptoms were measured by the adapted version of UCLA PTSD Reaction Index (UCLA-CA; Steinberg, Brymer, Decker, & Pynoos, 2004), a self-report questionnaire to screen trauma exposure and to measure PTSD symptoms in school-age (6-18) children and adolescents. The instrument assesses the frequency as well as the intensity of occurrence of PTSD symptoms during the past month on a scale of zero (none of the time) to four (most of the time). The items map directly onto DSM-IV intrusion, avoidance, and arousal criteria.

3.2.4. **Memory quality self-report**

The Adapted Trauma Memory Quality Questionnaire (ATMQQ; Hiller et al., 2019) was admitted at T1. ATMQQ is an 18-item self-report adapted from TMQQ (Meiser-Stedman, Smith, Yule, & Dalgleish, 2007). It measures the nowness (e.g., "When I remember the frightening event, I feel like it is happening right now") and disorganization (e.g., "I get mixed up about what order things happened in during the frightening event") of the trauma memory as well as how much the memory is sensory-based (e.g., "My memories of the frightening event are mostly pictures or images") or poorly verbalized (e.g., "I can't seem to put the frightening event into words"); the full survey can be found in supplementary material C: Adapted Trauma Memory Quality Questionnaire.

3.2.5. **Trauma-related appraisal self-report**

Participants completed the Child Post-Traumatic Cognitions Inventory (CPTCI) at T1. CPTCI is a 25-item self-report questionnaire that measures maladaptive cognitions in trauma-exposed children and adolescents aged 6-18 (Meiser‐Stedman et al., 2009); see full questionnaire in supplemental material S3-G.

3.2.6. **Narrative NLP tasks**

Calculating appraisal and coherence were the two NLP tasks of the present study. Like any NLP task, they share a workflow consisting of text cleaning, preprocessing and feature acquisition, whereas the implementation of the core functions can differ drastically depending on the task. The algorithms are highlighted in this section while peripheral information is provided in the supplemental material S3-A: Brief Introduction of NLP, Sentiment Analysis and Topic Modeling.

Appraisal. As a part of sentiment analysis, appraisal detects opinions in texts, which can then be broadly classified as positive, neutral or negative. Various algorithms have been developed for this purpose (Medhat, Hassan & Korashy, 2014). Two popular pre-trained Python libraries were used, Vader (http://www.nltk.org/howto/sentiment.html) and Flair (https://github.com/flairNLP/flair), to assess appraisal. Using lexicon and grammatical rules, Vader looks up predefined positive/negative terms in the text, adjusts the direction and intensity according to grammar rules (e.g., negations, modifiers) then sums up the scores and returns the normalized final score between -1 (most negative) and 1 (most positive) (Hutto & Gilbert, 2014). Flair, on the other hand, adopts a character level embedding approach in order to take context into account when predicting sentiments (Akbik, Blythe, & Vollgraf, 2018). Similarly, it returns a label of "POSITIVE" or "NEGATIVE" along with a real number between 0 and 1 indicating the magnitude of the classification.

Coherence. One way to measure coherence of a discourse is by topic modelling and topic coherence evaluation. Topic modeling assumes that any text (i.e., discourse, document or corpus) is a mixture of a set of finite topics. The modeling process extracts topics from a document and the topic coherence score describes the degree of semantic similarity between high frequency words within the topics generated by the modelling. For every piece of trauma narrative, two topic models were built utilizing two distinct methods: Latent Semantic Analysis

(LSA) and Latent Dirichlet Allocation (LDA); the C_v score of each model was then computed as the final coherence indices.

LSA treats a document as a bag-of-words and creates a matrix to represent the relation between words/terms and documents. Its key technique is to reduce the dimensions of the matrix by combining terms of similar meanings (Dumais, 2004). LDA produces a hierarchical Bayesian model of probabilities of the underlying topics to characterize the document. The generating process is based on a prior (Dirichlet) distribution approximated by empirical Bayes parameter estimation (Blei, Ng, & Jordan, 2003). C_v in essential is the score reflecting the level of similarities shared by high frequency words, and it is commonly used to index coherence level (Röder, Both, & Hinneburg, 2015). This study employed the genism library (https://radimrehurek.com/gensim/) to implement the LSA and LDA modeling. Codes of both tasks can be found in supplementary material B: Python Code for NLP Tasks.

3.2.7. **Statistical analysis**

The statistical analysis encompassed reliability/validity checking and hypothesis testing. NLP reliability was tested by linear regression between the scores of different algorithms. Likewise, NLP validity was tested against subjective self-reports (i.e., ATMQQ and CPCTI). Correlations between all collected variables, including memory quality, independent variables for hypothesis testing (word count, avoidance symptom, coherence and appraisal), control variables (age at T1 and days of hospitalization), and the dependent variables (PTSS), were also routinely checked by Spearman's regression method to give a basic view of their relations. As for hypothesis testing, a generalized linear model (GLM) with Poisson transformation was chosen as more suitable for H1 – H3, as the dependent variables were positively skewed. ANCOVA was used for H4, group difference analysis between T1 and T3.

3.2.8. **Hypothesis testing control variables**

Two potential confounding variables need to be controlled when testing the proposed hypotheses.

Age. It is well established that language is pivotal to autobiographical memories, not only because it is the medium through which the experience is expressed but also because language provides structure to organize memory. Children were found to be unable to verbally retrieve information that was not part of their productive vocabulary at the time of encoding (Simcock & Hayne, 2002), and the emergence of autobiographical memory is paced with the development of language of past, self and others (Fivush & Nelson, 2004). As a result, *developmental level* influences narrative report. Because the age range (6 to 13) of the participants in the current study crossed different developmental stages, we included age at T1 in the analysis to control the impact of developmental stage.

Number of days of hospitalization. Although objective injury severity does not predict PTSD (Delahanty et al., 2003; Gabert-Quillen, Fallon, & Delahanty, 2011), head injury is reportedly associated with narratives of less cohesion among children and adults (Chapman et al., 1992; Coelho, 2002; Hartley & Jensen, 1991). Since head injury information was not available in the dataset, we instead used the number of days of hospitalization as an indirect control.

3.3. Results

3.3.1. **Descriptive data**

Table 3-1 listed descriptive data for all variables introduced in the methods section.

Table 3-1: Descriptive data summary

	T1				T3			
	n	Mean	CIL	CIU	n	Mean	CIL	CIU

Age	132	9.76	9.42	10.10			-	
Hospital days	120	2.64	1.77	3.51			-	
UCLA	131	18.49	16.17	20.80	122	12.85	10.72	14.98
UCLA-avoid	129	6.18	5.30	7.06	121	4.04	3.27	4.82
ATMQQ	130	37.50	35.71	39.29			-	
CPTCI	120	40.20	37.76	42.63				
Wordcount	131	447.87	397.35	498.40	115	463.66	401.39	525.92
Coherence-LSA	131	0.508	0.494	0.532	115	0.571	0.553	0.589
Coherence-LDA	131	0.549	0.532	0.565	115	0.618	0.599	0.637
Appraisal-Vader	131	0.051	0.037	0.064	115	0.061	0.053	0.081
Appraisal - Flair	131	-0.287	-0.323	-0.250	115	-0.241	-0.276	-0.207
Coherence	131	0.528	0.514	0.542	115	0.595	0.577	0.612
Appraisal	131	-0.112	-0.136	-0.089	115	-0.095	-0.115	-0.075

n: number of non-missing data points

CIL: 95% confidence interval lower bound

CIL: 95% confidence interval upper bound

Coherence = (LSA+LDA) / 2

Appraisal = (Vader + Flair) / 2

3.3.2. **NLP reliability test**

Two scatter plots in Figure 3-1 illustrate the relation between the scores computed by two NLP algorithms for coherence (panel a) and appraisal (panel b) at T1 and T3. Scores were first transformed into z scores to standardize the scales. Correlations were all significant:

coherence: $r = .65$, $p < .001$ at T1 and $r = .88$, $p < .001$ for T3; appraisal: $r = .68$, $p < .001$ at T1, and $r = .61$, $p = .009$ at T3 (see full report in supplemental material E: Original Outputs of General Linear Regression Analysis). As scores were fairly consistent across algorithms, pooled values (mean) were used as the final scores for coherence and appraisal in further analysis, to counterbalance the errors introduced by different methods.

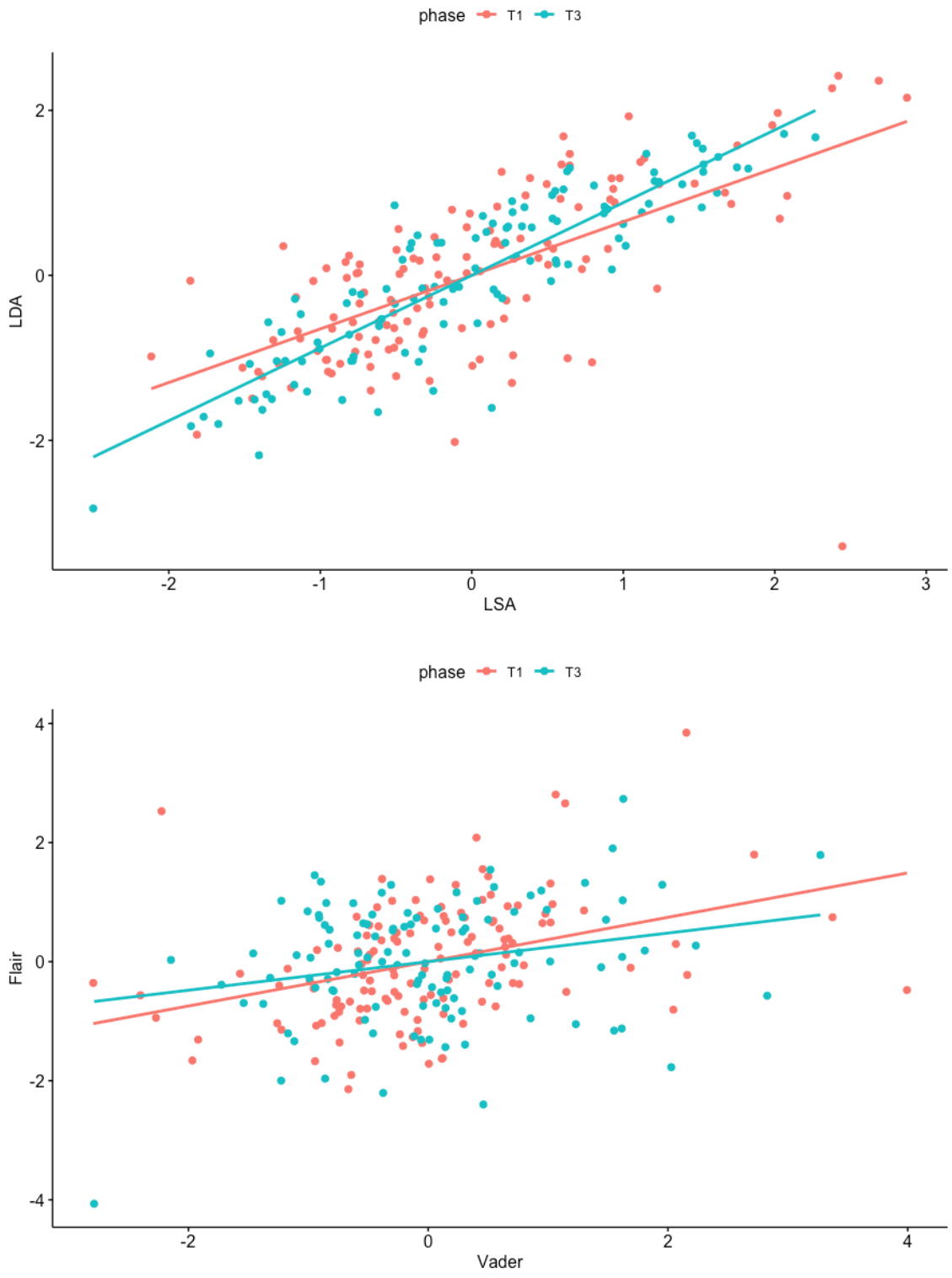


Figure 3-1: Reliability of coherence and appraisal scores

3.3.3. **NLP validity test**

The general linear regression analysis reported significant correlations between coherence and ATMQQ at T1, r = -0.61, p = .002; appraisal and CPTCI at T1, r = -0.45, p = .001 (see full report in Supplementary Material E: Original Outputs of Linear Regression Analysis).

3.3.4. **Hypothesis testing**

Table 3-2 summarizes the results from the regression models for H1 to H3. Narrative length (wordcount) was positively linked to PTSS, even when controlled by avoidance level. Coherence and appraisal predicted PTS symptoms at T1 and T3 and both coherence and appraisal scored higher at T3 compared to T1. For H4, ANCOVA test results were: F(1,219) = 40.31, p < .0001, η_g^2 = .16; and F(1,220) = 2.78, p = .037, η_g^2 = .01 respectively. Note: variance test was controlled by wordcount, age at T1 and days of hospitalization for coherence; and controlled by age at T1 and days of hospitalization for appraisal.

Table 3-2: GLM results for H1-H3. Online version: https://osf.io/a6frp/

	T1			
	Estimate	**Std. Err**	**z**	**Pr(>|z|)**
H1a: PTSS ~ wordcount	0.00036	0.00007	5.46500	<0.001 ***
H1b: PTSS ~ wordcount + avoidance	0.00032	0.00007	4.65700	<0.001 ***
H2: PTSS ~ coherence	-1.03889	0.28307	-3.670	<0.001 ***
H3: PTSS ~ appraisal	-0.81344	0.15949	-5.1000	<0.001 ***
	T3			

H1a: PTSS ~ wordcount	0.00020	0.00007	2.738	0.00618 **
H1b: PTSS ~ wordcount + avoidance	0.000324	0.00008	4.041	<0.001 ***
H2: PTSS ~ coherence	-1.34645	0.29543	-4.558	<0.001 ***
H3: PTSS ~ appraisal	-0.97149	0.24407	-3.980	<0.001 ***

Note: models were all controlled by age and days of hospitalization

H1b: PTSS avoidance as controlled variable

T1: 1 month posttrauma; T3: 6 months posttrauma

numbers were rounded to 5 decimals

Signif. codes: '***' 0.00; '**' 0.01; '*' 0.05

3.4. Discussion

This study explored the feasibility of using NLP to analyze features in trauma narrative and used the outcomes to test a set of critical hypotheses concerning the relationship between trauma narrative and posttraumatic symptoms. Two features were computed, coherence and appraisal, and their reliability assessed by cross-checking between NLP algorithms. Large correlation coefficients were observed between NLP methods for both features at both times. Although the degree of consistency was not completely optimal and there is still room for improvement, the NLP approach used demonstrated adequate reliability.

The validity of the NLP-generated coherence scores was examined by comparing them with the memory quality self-rating at T1 and the tests reported medium magnitude. Strictly speaking, ATMQQ does not explicitly measure memory itself nor does it directly describe

narrative coherence; thus the validation was only indirect. Nevertheless, the nowness, non-verbal, disorganized and fragmented quality in episodic memory that ATMQQ does measure are closely interwoven with trauma narrative. Episodic memory is fundamental to narrative abilities (i.e., comprehension and generation) (Anderson, 2015) and people with episodic memory deficits (but with normal IQ and linguistic skills) generated less cohesive narrative discourses when recalling personal past events (Seixas-Lima et al., 2020). In the same way, higher scores on the ATMQQ entails more disturbed episodic memory regarding the traumatic event, so predicting a lower coherence score; findings were congruent with this speculation.

Likewise, NLP appraisal scores were validated by CPTCI scores and the level of the agreement was medium. Upon reflection, one concern was that NLP might not be able to differentiate negative appraisal from negative content, given that sentiment analysis is only able to incorporate context to a very limited level. For example, according to the algorithms described in Vader and Flair, a negative score could be generated simply based on the word "hospital" without the presence of appraisal processes. To look at this issue, all the narrative texts were merged, and two large corpora formed for T1 and T3, topic modeling was conducted to extract the topics visualized in two interactive charts. It can be observed that with regard to the overall salient terms, apart from the words related to injury and hospital, sensemaking words (e.g., "think", "remember", "feel", "know", "happen", "tell") took up a moderately large proportion on both occasions (see supplemental material S3-D: Narrative Theme Extraction). Therefore, this author is confident that cognitive processes were present in the narrative texts and that the appraisal score should be at least partially derived from cognitive processes. Furthermore, although this method was not the same as the usual questionnaire-based measures and far from ideal, it could be argued that the appraisal calculation is likely to be statistically valid because the data satisfied two important constraints which were stated as hypothesis 3 and 4.

It is worth mentioning that a study utilizing the same dataset to investigate similar research questions (McGuire et al., 2021) reported disparate results. The study coded fragmentation and global coherence by methods established in prior works but found that these narrative features did not relate to memory quality or PTSS. One possible explanation is that the protocols designed for manual coding differed significantly from NLP algorithms and as a result, they produced inconsistent outcomes.

The statistical analysis supported hypotheses H1-4 and the implication is consequential. First, H1 confirmed that cognitive or behavioral avoidance was not linked to narrative length, and that longer narrative was correlated to more PTS symptoms. As introduced earlier, the heart of the mnemonic model of PTSD is the claim that effects of a potentially traumatic event are mediated by memory; in other words, a person without recollections of the experience, regardless of how negative it is, would be PTSS free. This piece of evidence corroborates the mnemonic prediction. It is also reassuring that people exhibiting avoidant symptoms do not produce fewer VAMs, making trauma narrative a dependable source of data for PTSD research.

H2-4 functioned as constraints to further test the validity of the NLP method, in particular for appraisal scores derived from trauma narratives. As expected, narrative coherence and appraisal improved with time and the scores predicted PTSS. The successful verification first suggests the NLP methods were valid; second and more importantly, it shows that trauma narrative is not a mere representation of trauma memory; it is also the media carrying multilayers of latent but critical trauma-related processes that might be used to better understand PTSD.

3.4.1. **Clinical implications**

Trauma narrative has been proven to be useful to PTSD research while it has been considered less practical in clinical settings, given the considerable effort required to collect, store and analyze such data. However, in the light of easy access to recording devices,

automated transcription and most importantly, progress in NLP and ML, it is time to reconsider its utility in the clinical setting.

There indeed have been successful applications of NLP narrative analytics in domains from assessment to treatment. An automated screening tool for PTSD was built on patients' self-narratives using NLP and text-mining (He, Veldkamp, Glas, & de Vries, 2017); dropout rate in cognitive therapy for PTSD has been a difficult clinical issue to tackle, and a study used trauma narratives written in early sessions to predict drop out (Alpert, Hayes, Barnes, & Sloan, 2020); Norman et al. (2020) employed NLP in narrative writings to evaluate posttraumatic growth that was not captured by self-report symptom measures for veterans taking an online PTSD intervention.

Such examples suggest that narrative analysis not only offers alternative solutions to common tasks (e.g., assessment), but forges new areas where conventional methods (e.g., self-report questionnaires) are unsuitable or ineffective; it is unlikely to be long before clinical practices can benefit from efficient and economical applications utilizing narratives.

3.4.2. **Limitations**

In general, the children in the study presented with relatively mild PTSS and the majority did not reach the clinical threshold for PTSD.

The study relied on the pre-trained NLP libraries entirely to compute coherence and appraisal, without any additional modeling. Despite how powerful NLP tools have become, their performance can by no means compete with human judgement at the current stage. The particular libraries utilized in this study are trained on internet content such as social media or Wikipedia and thus are not specialized in narrative analysis. For the same reason, other potentially important features were excluded such as centrality of event. More work combining NLP and ML to build in-depth narrative analysis models would be desirable.

3.5. Conclusion

Combining all the findings, the study concludes that 1) the NLP approach to trauma narrative analysis is reliable and valid; 2) the mnemonic model prediction that availability of trauma memory increases PTSD was confirmed; 3) the cognitive model prediction of PTSD being associated with less coherent memories and negative trauma-related appraisals were supported by the data.; and 4) trauma narrative is a media containing essential trauma-related emotional and cognitive processes and should be better utilized for future research and practice.

4. Chapter 4: Prediction and Interpretation[5]

"The future is already here – it's just not evenly distributed."

- *William Gibson*

Highlights

- Machine learning offers powerful method to build predictive models.
- Interpretable machine learning (IML) explains how models work to provide more clinical insights.
- A random forest model of 13 features demonstrated excellent performance in predicting PTSD 6-15 months post-trauma.
- IML suggested arousal symptom cluster and cognitive avoidance were mostly influential in predicting PTSD.
- IML revealed non-linear relations between age and PTSD, acute symptoms and PTSD.

4.1. Introduction

Injury (intentional and unintentional) 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, 21% of the participates had at least one injury, and repeat injury was common (73%) (Spady, Saunders, Schopflocher, & Svenson, 2004). Besides the consequence such as death and disability, 13-22.5% of this population are susceptible to PTSD (Aaron, Zaglul, & Emery, 1999; de Vries et al., 1999; Marsac, Kassam-Adams, Delahanty, Widaman, & Barakat, 2014; Olofsson, Bunketorp, & Andersson, 2009). As the youth are moving through pivotal developmental stages, trauma exposure and PTSD at young age not

[5] This study is under review by Journal of Anxiety Disorder.

only confer risk 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 same trauma exposure but occurred at later time in life (Dunn, Nishimi, Powers, & Bradley, 2017).

It is therefore very important to develop tools to identify PTSD at early stage 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. Sadly, neither of them is adequate to quantitively forecast PTSD with sufficient accuracy to be useful in the clinical setting. Although risk identified by GLM analysis may help clinicians to roughly evaluate the risks, Saxe, Ma, Ren, and Aliferis (2017) thoroughly considered in their study how the method is not able to incorporate the complexity involved in predicting for an individual case. With 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 examined their psychometric properties, and there was a general lack of sensitivity or specificity data such that one could have the confidence in avoiding too many false positives or false negatives.

The prediction problem may be addressed by 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). It has changed the medicine research profoundly (Rajkomar, Dean, & Kohane, 2019). According to a review, among the 49 PTSD studies that utilized ML techniques, 33 (67%) are prognostic studies and all of them yielded fair to good performance (Ramos-Lima, Waikamp, Antonelli-Salgado, Passos, & Freitas, 2020). Moreover, a proof-of-concept study (Saxe et al.,

2017) compared the prediction performance of five ML classification methods (Support vector machine, i.e., SVM, linear, SVM poly, SVM RBF, Random Forest, Lasso) to the two conventional methods (logistic regression, stepwise logistic regression) using data of children and adolescents hospitalized from injuries. All five ML algorithms outperformed regressions in terms of AUC (area under curve, a common metric indexes classification accuracy), whereas the regression models performed no better than chance level. The encouraging results suggest that ML holds potential in building predictive PTSD classification models. Thus, one of the aims of this study is to develop a PTSD prognostic model that can be efficiently deployed to a clinical practice.

ML applications are not free from caveats, however. First, it is constantly observed that the ML models function well in testing data often exhibit unexpectedly poor behavior when they are deployed to unseen data or real-world domains; this is referred to as "the credibility challenge" (D'Amour et al., 2020). Secondly, while a model may generate perfect outputs, it will provide limited information as to how exactly the inputs are related to the outputs, or how the independent variables work together to produce the results. This issue is referred 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 relationships by decomposing models (Molnar, 2020). A few model-agnostic theories have been developed to understand a feature's influence over the outcome. Common methods include Partial Dependence Plots (PDP; Friedman, 2001), permutation feature importance (Fisher, Rudin, & Dominici, 2019), Shapley values (Shapley, 2016) and SHAP (SHapley Additive exPlanations) (Lundberg & Lee, 2017).

Schultebraucks et al. (2020) demonstrated a good example of how to address the validation and interpretation issues. They conducted a study which set out to build a predictive formula for non-remitting PTSD 12 months after discharge from the emergency department (ED). Schultebraucks and colleagues trained and tested a model using 70 variables extracted from longitudinal cohort data collected at one site. They then validated the model against another prospective cohort data collected at 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 the similar approach, we aim to develop a predictive ML model for children and adolescents after exposure to a single-incident trauma. The two objectives of the study are 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 for a better understanding of the operations of the PTSD risks.

4.2. Methods

4.2.1. ML workflow and key concepts

Details of a ML task can be technically complex. In the proof-of-concept study, Saxe et al. (2017) have given a detailed description on the key concepts pertinent to supervised classification task for PTSD prediction. A diagram summarizing the ML method is available in the supplemental material (S4-I: Overview diagram of supervised machine learning). To summarize, there usually are 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 method. Hence, it becomes important that cross-method metrics are used 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 their 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 this study is looking to examine the clinical implications of the risks and their relationships, it is therefore helpful to fit the model with different methods to optimize the outcomes.

4.2.2. **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.

4.2.3. **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 integrating multiple PTSS 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, biologic samples, demographic data and pre-trauma indices. However, some variables, especially the ones in pre-trauma and biological domain, were reported by too few studies to be considered, leaving the choice of predictors largely to 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 14 symptoms described in the DSM-5 ASD criterion B (see details in data harmonization).

4.2.4. **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 supplemental material S4-A: PTS measures for the details of the measures).

4.2.5. **Outcome variable**

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

4.2.6. **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 are ASD symptoms, it is of clinical interest to discern how these clusters as a whole influence the outcome. Therefore, we examined how much each of the feature and how much each group of features contributed to the prediction in the final model.

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. 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 gap between the GSI and the sum of individual Shapley value indicates the higher level of interaction within the group.

PDP is a global model-agnostic method that is interested in 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.

4.2.7. 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 for *outcome* variables and the measures to be used for *predictive* variables. Meanwhile, missing data were handled at two levels: during and after data harmonization (see supplemental material S4-K: Data harmonization and missing data handling for details).

4.2.8. **Predictor correlation checking**

It is routine to check the correlation among the predictor features and the strongly correlated features will be reduced to one to represent the group. No strong linear association were found within the 23 candidate predictors (see supplemental material S4-F: List of candidate predictive features and the correlation matrix).

4.2.9. **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 supplemental material S4-J: Brief introduction of 4 classification machine learning algorithms) to minimize the chance effect of method selection, and each of them were applied the same procedure.

4.2.10. **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 the classification performance (Metz, 1978). Because this study was mostly concerned with the positive class (i.e., cases diagnosed with PTSD) 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 caculation 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 true positive rate, recall describes positive predictive value, and F-score is the harmonic mean of 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.

4.2.11. **External validation**

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

4.2.12. **Model diagnostic and finalizing**

We aimed to identify one final winner model based on F-scores while they are not the only considerations. In case of close performance, we would favor a model with fewer predictors for better generalization. GLM is a parametric method therefore post-hoc model diagnostics would be required. We accepted or reject the model according to the assumption diagnostic results.

4.3. Results

4.3.1. **Dataset description**

Nine studies comprising total 1,167 participants were included into 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 investigated injury in young children (5-7 years old). In terms of trauma type, one has interpersonal assault cases in more than half of its samples while the prevalence of interpersonal trauma in other studies is quite low. In addition, the external validation study (1036) exhibited much higher PTSD rate in non-interpersonal traumas, which is distinct from the studies in the main dataset. Detailed study characteristics are summarized in Table 4-1.

Table 4-1: Data summary. Online version: https://osf.io/yuxj4/

Study ID	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	5.19	Injury: 51.11 Interpersonal: 6.67	CPSS at T3	CAPS at T7	2.22	33.33

		Max = 17 SD = 2.71		Medical: 2.96 RTA: 33.33 Other: 5.93				
Study ID	**N**	**age**	**ethnic minor (%)**	**trauma types (%)**	**< 1m PTS measure**	**6 m+ PTS measure**	**6 m+ PTSD (%)**	**6 m+ missing rate (%)**
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

Study ID	N	age	ethnic minor (%)	trauma types (%)	< 1m PTS measure	6 m+ PTS measure	6 m+ PTSD (%)	6 m+ missing rate (%)
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 SD = 1.96	7.09	Injury: 34.65 Interpersonal: 1.57 Medical: 6.30 RTA: 51.18 Other: 6.30	CUCLA-IV at T3	CUCLA-IV at T7	3.94	7.09
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

Study ID	N	age	ethnic minor (%)	trauma types (%)	< 1m PTS measure	6 m+ PTS measure	6 m+ PTSD (%)	6 m+ missing rate (%)
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

4.3.2. **Models**

We tried several methods from the four method families and screened various configuration options. 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 models, 14 of which were harmonized DSM-5 acute symptom variables. The models were trained main configurations of 70% as training set, 10 times * 5 repeats repeatedCV, sampling = up (see supplemental material S4-G: R scripts of model training and testing for details).

Table 4-2 lists the predictive features and the performance metrics for each model. All four trained models yielded good to excellent values in precision, recall and F-score with the testing dataset whereas saw disparate results in external validations. The RF model reported stable excellent F-scores (.973). Notably, we experimented alternative models using only the ASD symptoms that were listed in the four candidate models. All methods returned slightly reduced scores compared to its original model.

Table 4-2: Performance of candidate models

Method	N. of features	Features	Precision	Recall	F-score
Internal validation					
GLM	7	eth_minor, trauma, ASDB6, ASDB8, ASDB10, ASDB11, ASDB14	.982	.837	.904
CART	12	age, trauma, hosp_days, ASDB1, ASDB2, ASDB4, ASDB6, ASDB8, ASDB10, ASDB11, ASDB12, ASDB14	.961	.971	.971

RF	13	age, eth_minor, trauma, ASDB1, ASDB2, ASDB3, ASDB4, ASDB6, ASDB8, ASDB10, ASDB11, ASDB12, ASDB14	.961	.987	.973
SVM	13	age, eth_minor, trauma, ASDB1, ASDB2, ASDB3, ASDB4, ASDB6, ASDB8, ASDB10, ASDB11, ASDB12, ASDB14	.977	.798	.879
ASD features only					
GLM	10	ASDB1, ASDB2, ASDB3, ASDB4, ASDB6, ASDB8, ASDB10, ASDB11, ASDB12, ASDB13, ASDB14	.970	.798	.876
CART			.955	.969	.962
RF			.959	.984	.973
SVM			.980	.765	.860
External validation					
GLM		same as internal validation	.880	.795	.835
CART			.816	.963	.883
RF			.821	1.00	.902
SVM			.893	.710	.791
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

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

4.3.3. **Final model**

Weighing all the metrics, random 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

4.3.4. **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 4-1a). 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 4-1b 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 4-1c. The numbers read: .016, .019, .039, .013, 0, .007, .007, .015, .071, .009, .040, .047, .075.

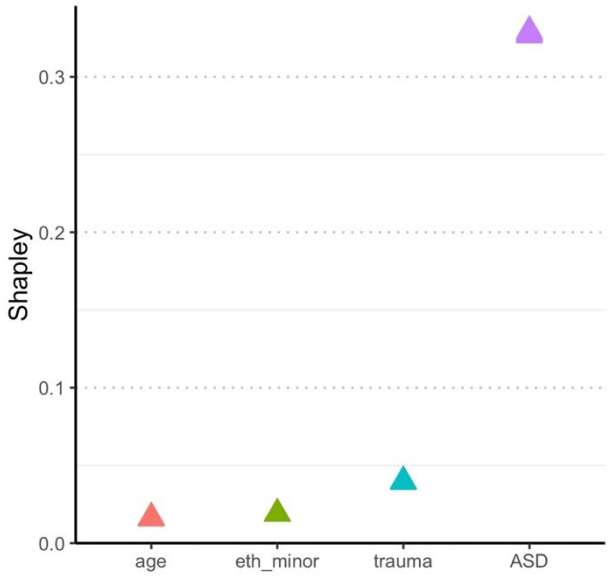


Figure 4-1: a: overall importance;

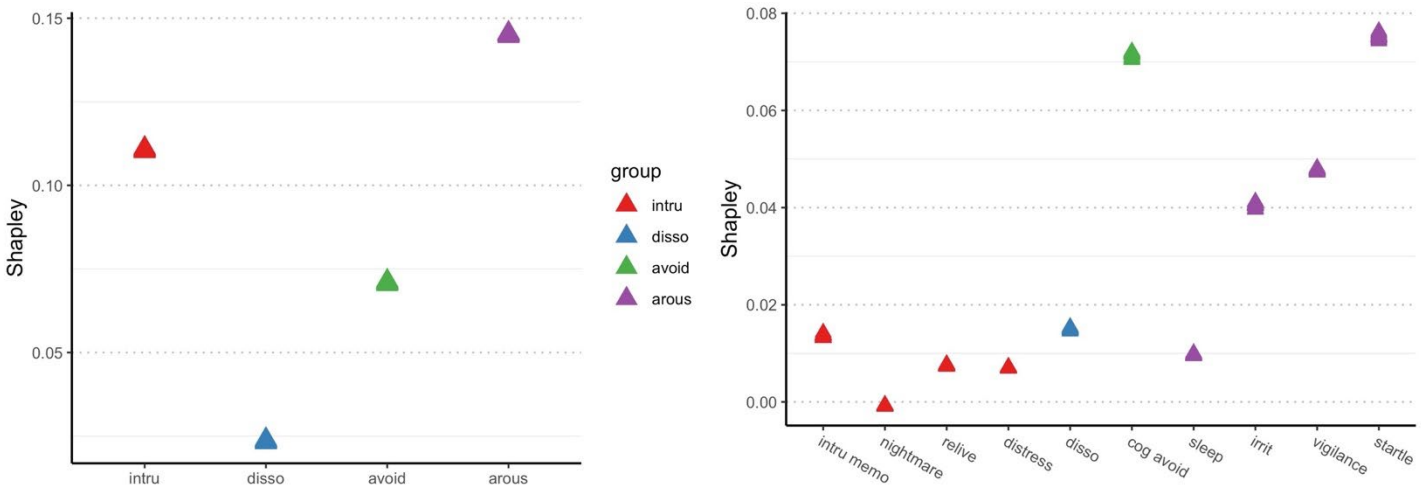


Figure 4-2: b: Shapley importance on ASD clusters (left) and on ASD symptom level (right);

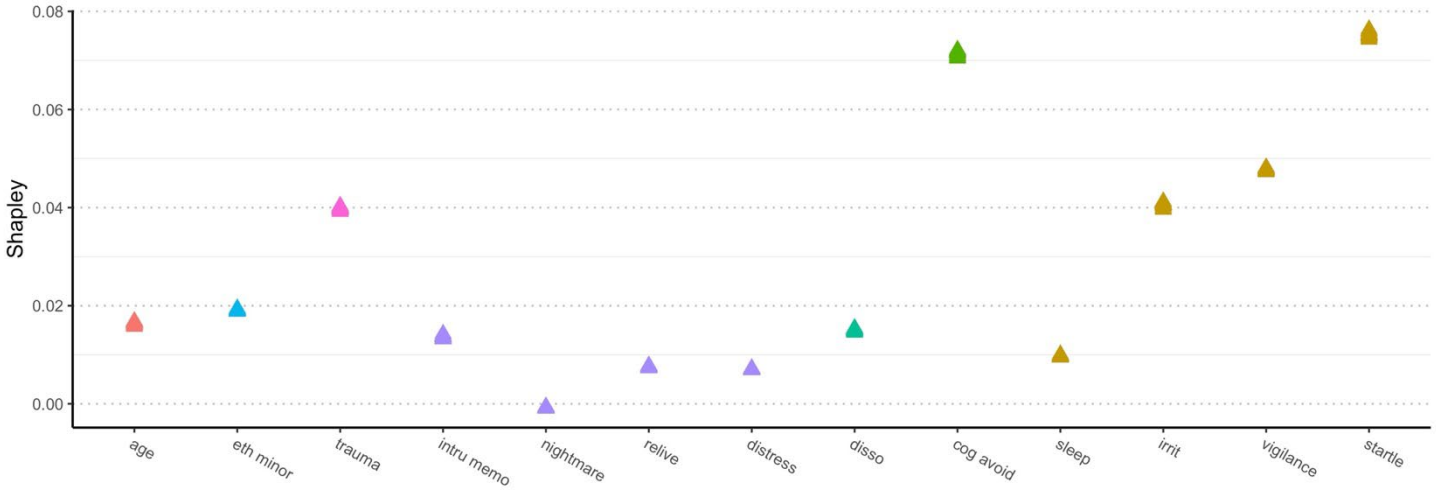


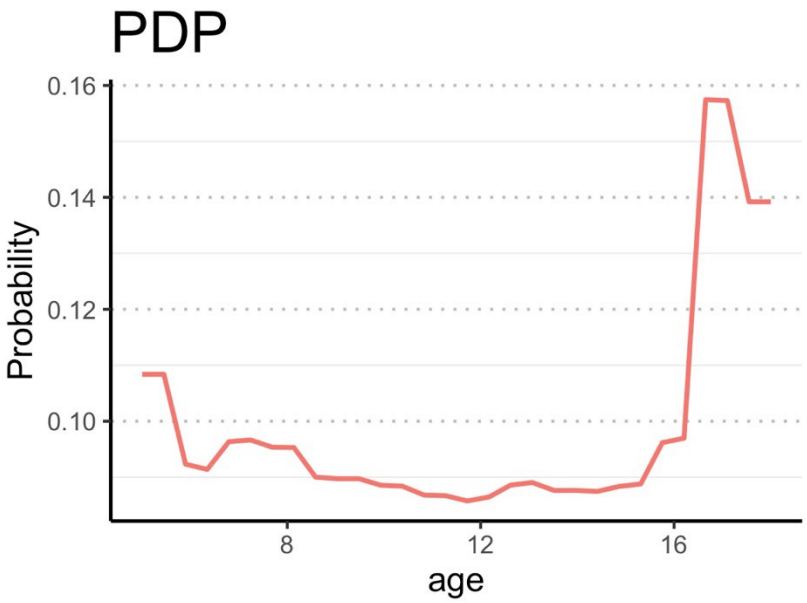
Figure 4-3: c: Shapley importance on each predictive feature. Online version: panel b: https://osf.io/fbtqp/ panel c: https://osf.io/jzfbv/

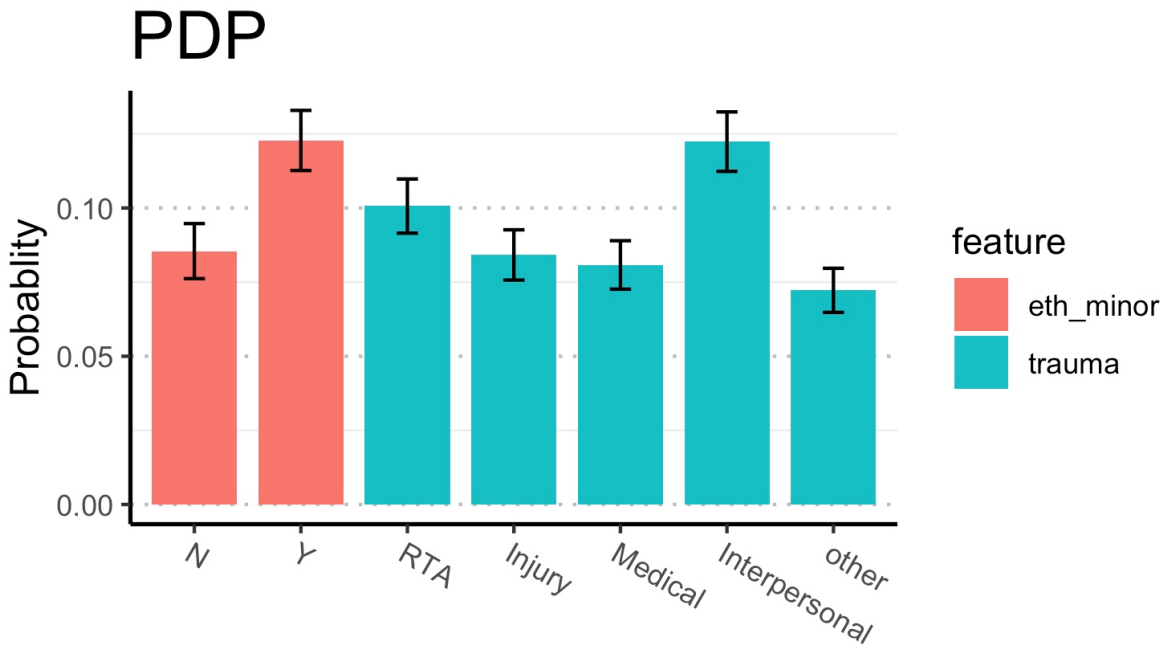
eth minor: ethnic minority; **trauma**: trauma type; **intru memo**: recurrent, involuntary, and intrusive distressing memories; **nightmare**: recurrent distressing dreams; **relive**: dissociative reactions; distress: intense or prolonged psychological or physiological distress; **disso**: altered 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.

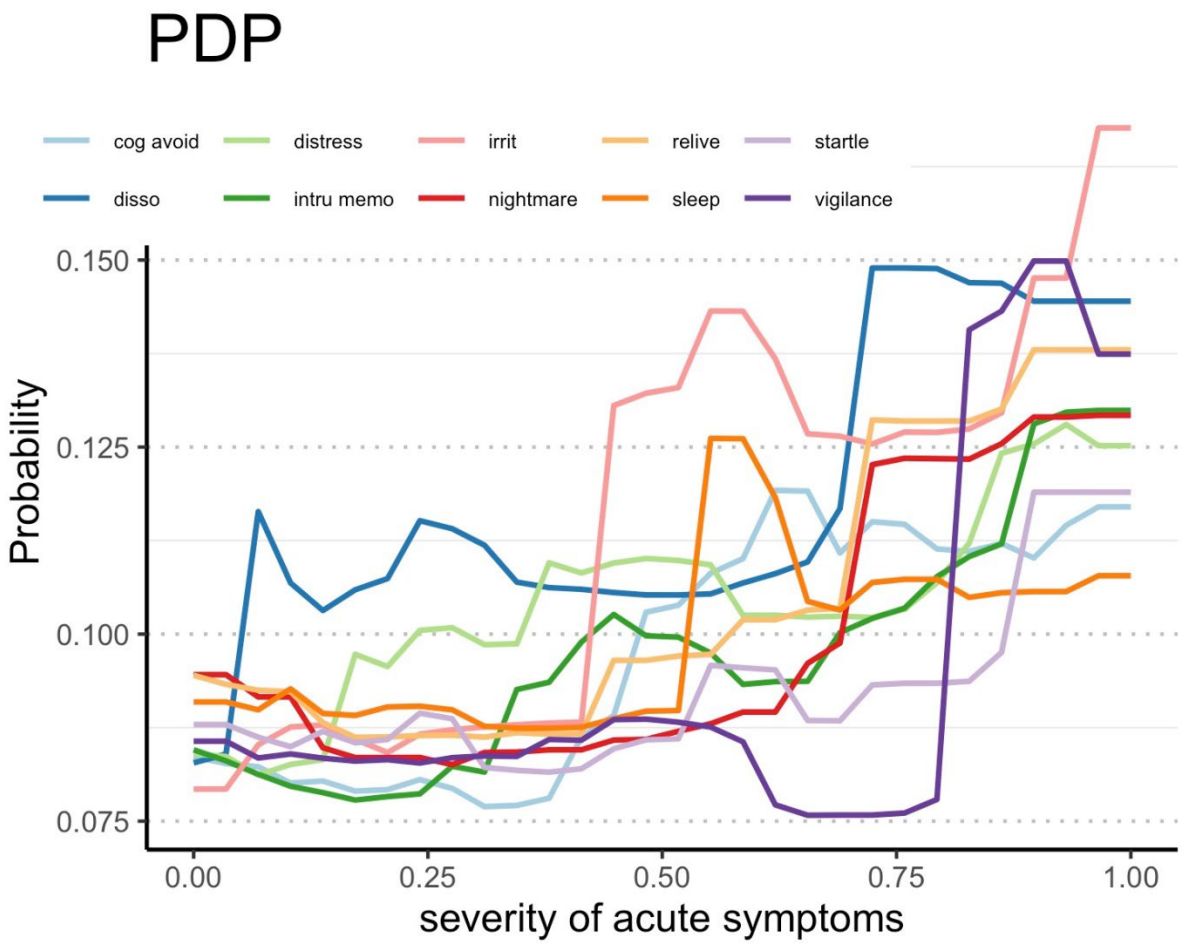
PDP displays the probability of positive PTSD given different values of the feature (s). We sorted the 13 features into three groups: age, categorical predictors (trauma type, minor ethnic group) and ASD symptom predictors. Figure 4-2a illustrates that the risk does not change by age between 5 and 16 while there is a 50% increase around age 16 leaping from .096 CI [.0871, .106] to .157 CI [.148, .166]. Figure 4-2b shows the risk by each ethnicity and trauma type category in order. Being exposed to interpersonal trauma or belonging to minority ethnical group imposes greater risk than having medical, injury, RTA or other trauma. There is a 43% difference in the risk between non-minority and minority group (.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 4-2c shows the influence of individual ASD symptoms in a comparative view. Regardless of the fluctuation, a higher level of ASD symptoms in general predicts higher chance of six months PTSD with irritability having the relatively strongest influence. It is also visible that the risk rises significantly once the severity of an ASD symptom reaches 75% of the full scale.


PDP
0.16
0.14
0.12
0.10
Probability
8
12
16
age


PDP
0.10
0.05
0.00
Probability
N
Y
RTA
Injury
Medical
Interpersonal
other
feature
eth_minor
trauma



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 4-4: a: PDP by age; b: PDP by trauma type and ethnic minority; c: PDP by ASD features

4.4. Discussion

With the aim of developing a robust PTSD prognosis tool using ML, we built a model based on 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 internally and externally using two demographic, one trauma type and

ten ASD symptom variables as predictors. While it is often believed that the structured clinical interviews are the gold-standard for PTS symptom assessment, many ASD symptoms in this study were collected via 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 the economic qualities 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 factors that have been intensively studied. 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, Siddaway, Meiser-Stedman, Serpell, & Field, 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. Thus, we infer that acute phase symptoms are essential and efficient predictors to 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, a 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, and it mainly encompassed 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, one of the most successful PTSD theories, cognitive processes relating to the memory of the traumatic experience is central to the development and maintenance of chronic PTSD (Ehlers & Clark, 2000). A meta-analysis found that thought suppression and distraction, which are 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 in children and adolescents (Trickey et al., 2012).

While all the 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. Moreover, the consistency with prior studies in a way warrants the reliability of the model.

A more important contribution of the study came from our model interpretation analysis. Doshi-Velez and Kim (2017) believe 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; in the case of the present study where predictors are core PTSD symptoms, it should offer an informative source to examine the underlying mechanism how acute symptoms evolve into chronic PTSD.

The Shapley importance analysis gave a comprehensive view on the impact of the predictors and their interactions. On the individual feature level, it is clear that trauma type, cognitive avoidance, irritability, hypervigilance and startle have the importance level two to four times greater than the remaining variables (Figure 4-1c). At the cluster level, the intrusion and arousal clusters are the most influential (Figure 4-1b). Because GSI incorporates the impact from feature/group interaction, it enables us 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 higher level of interaction among the 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 is striking is that the Shapley values are fairly low for the individual intrusion symptoms (.013, 0, .007, .007) but its GSI value as a group are four times of 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 answers an intuitive question: 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) see 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 become severe (3/4 of the full scale). These patterns partially explain why the non-linear algorithms such as RF and CART performed better.

The categorical PDP of trauma type and ethnic minority displayed a concerning figure 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 supplemental material S4-F), which suggests the culprit might reside in a more complex fashion. 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 what gives rise to this ethnic disparity.

4.4.1. **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 is evident, suggesting that the number of the presenting symptoms matters. Second, simply being minority ethnically increases 43% of the chance having PTSD after 6 months. Last, change in the probability of chronic PTSD and the ASD symptom severity are not linearly correlated; mild symptoms have marginal effect while symptoms at high scale (75%) drastically push up risks.

We investigated the combination of ASD-symptom predictors and their Shapley importance. Although not causal, the Shapley importance values to some extend reflects the role of a symptom in the etiology of PTSD. The fact that cognitive avoidance rather than behavioral avoidance was chosen, and it is one of the most influential factors in part supported the eminence of the cognitive model, which gives an extensive account of the role of maladaptive cognitions in PTSD. In contrast, although the association between hyperarousal and PTSD is well known and our model clearly confirmed its significance, comprehensive theories addressing the potential mechanism are absent. Future research shall consider fill the gap with studies focusing on the physiobiological side of the condition.

In respect of model building, the ML models as the final product can be stored, duplicated and retrieved independently. This separation from training data entails 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 the 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 screening is not routinely implemented in most 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 feedbacks to continuously evaluate and improve its utility.

4.4.2. **Limitations**

The model was trained and tested on mainly non-interpersonal one-off trauma data from high income counties, its ability to generalize to other context such as multiple trauma or disaster or low- and middle-income counties 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 are not exactly the same as the aim of the model (6 months onwards). Additional validation with 6-months PTSD outcome would be desirable.

As PTSD is a function of time, trajectory profile 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 before training the model on non-remitting versus resilient. However, in our dataset, PTS sampling time points differed across studies therefore trajectory modeling was not applicable. Furthermore, the outcome variable was derived from various PTS measures, it was unknown that how it would be consistent to the outcome if standard structure interview were applied.

4.5. Conclusion

The study produced a machine learning algorithm to predict PTSD 6-months posttrauma for children and adolescents received medical care for injury. The model was trained by large international longitudinal data and has excellent classification performance. The model is proved to be highly robust by two external validations. The succinct model requires only 13 easily obtainable features (demographics and early symptoms) 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 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 detected that belonging to ethnic minority groups increases by 43% the chance of having PTSD compared to non-minority groups.

5. Chapter 5: Long-term Impact of Early Adversity[6]

"It's a poor sort of memory that only works backwards."

- *Lewis Carroll, Alice in Wonderland.*

Highlights

- Adverse childhood experiences (ACEs) are associated with many mental and physical conditions in adults.
- Robust variance estimation enables pooling effect size from studies that report multiple results.
- Heterogeneous mild to medium magnitude of association are found in various types of ACEs and panic disorder.
- No between-group difference is found by either sociolegal classification or threat-deprivation dimensions.

5.1. Introduction

Panic disorder (PD) is a debilitating condition affecting 2–5% (Guo et al., 2016; Kessler et al., 2006) of the general population over lifetime. Among them, 80.4% reportedly have comorbid conditions of other anxiety, mood, or substance abuse disorder (De Jonge et al., 2016) and its impact is stronger than many chronical physical illnesses (Investigators et al., 2004a, b). Pharmacotherapy and cognitive behavioural therapy are the two options for first-line treatment. Both of them are effective albeit with limited effect size (Bighelli et al., 2018; Carpenter et al., 2018), therefore further research into its etiology is necessary for future interventions. A promising area of enquiry that may shed new light on PD pathology is adverse childhood experiences (ACEs).

[6] This study is published as Zhang, J., Wiecaszek, P., Sami, S., & Meiser-Stedman, R. (2021). Association between panic disorder and childhood adversities: a systematic review and meta-analysis. Psychological medicine, 1-11.

ACEs refer to a broad range of stressful experiences that infants, children, and adolescents can be exposed to whilst growing up (Bernstein et al., 2003; Bifulco, Brown, & Harris, 1994). A large body of evidence has shown that ACE-exposed adults are at higher risk of various psychiatric and physical disorders (Edwards, Holden, Felitti, & Anda, 2003; Heim & Nemeroff, 2001; Takizawa, Maughan, & Arseneault, 2014; Walker et al., 1999); it might be anticipated that there should be a significant relationship between ACEs and PD. However, an estimate of the magnitude of this relation is absent from the current literature. The present study aimed to conduct a meta-analysis to estimate the overall odds ratio (OR) of having PD in adults who had ACEs compared to those who did not experience ACEs.

The present review, in addition to obtaining an estimate of the relationship between ACEs and PD in adulthood, also sought to consider the relative importance of different ACE types. 'ACEs' is a broad term encompassing experiences from malnutrition, poverty to physical abuse, parental mental health, lack of positive nurturance, and so on (Smith & Pollak, 2021). It is therefore reasonable to question if ACEs can be treated as one homogeneous group and be assumed to have similar neurobiobehavioral effects that in turn give rise to PD. Naturally, to explore the potential mechanisms, it would be beneficial to examine the specific ORs associated with different types of ACEs.

This task however is challenged by the lack of consensus among the literature over how to best conceptualize ACEs (Afifi et al., 2020; Guyon-Harris, Humphreys, & Zeanah, 2021; Karatekin & Hill, 2019; McLaughlin, Sheridan, & Lambert, 2014; Pollak, Vardi, Putzer Bechner, & Curtin, 2005). Originally ACEs were classified into three main forms: abuse, neglect, and household dysfunction (Edwards et al., 2003; Felitti et al., 1998). A later deprivation-threat/trauma dimensional framework was proposed (McLaughlin et al., 2014; Zeanah & Sonuga-Barke, 2016). Synthesizing the progress in neuroscience, Smith and Pollak (2021) pointed out that the conventional sociolegal categories (i.e. abuse, neglect, household

dysfunction) are not likely to map onto human biology. Moreover, it has been argued that it is very difficult to classify an experience on a definite deprivation-threat dimension as ACEs tend to be highly interrelated (Dong et al., 2004). For example, deprivation is often accompanied by perceived threat and chronic threat may also commonly co-occur with deprivation. The same authors further objected to the assumption that a specific type of ACEs is associated with a corresponding specific effect. They subsequently hypothesized that the form of an adversity has little effect on its impact, and that the ultimate neurobiological outcome depends on more lucid elements such as the developmental period, the intensity of the event(s), the child's environment, social context, and perception of the experience.

As a result, we believed that it would be premature to limit the ACE subgrouping approach to being either categorical or dimensional. We instead opted to test out multiple approaches. To be specific, we investigated whether the effect of ACEs on PD varies among groups divided by (1) categories such as abuse, neglect and dysfunction; (2) by spectrums of high or low in deprivation/threat and (3) by other means such as number of exposures (intensity) and time of the exposure (developmental period).

As there is no conclusive list of ACEs, we felt it was preferable to include as many types of ACEs as possible in the meta-analysis and thereby produce a richer understanding. In addition to the 10 items in the early ACE studies (Felitti et al., 1998), we applied the extended list (physical abuse, sexual abuse, emotional abuse, emotional neglect, physical neglect, exposure to domestic violence, household substance abuse, household mental health problems, parental separation or divorce, parental problems with police, spanking, peer victimization, household gambling problems, foster care placement or child protection agency contact, poverty, and neighbourhood safety) suggested by a recent factor analysis study based on data from 1000 children and 1001 parents (Afifi et al., 2020) when screening citations.

In summary, we sought to (i) obtain an estimate of the relationship between ACEs and PD in adulthood and (ii) consider how different ACEs subtypes may be related to PD by taking multiple classification approaches (i.e. sociolegal, dimensional, cumulative effect, and developmental period of the exposure).

5.2. Methods

5.2.1. Search strategy and selection

The study was pre-registered at PROSPERO (ID: CRD42018111506). We searched for English articles in PsycINFO, MEDLINE, EMBASE and PILOTS using the following keywords: (child* OR adolescent*) AND (trauma OR abuse OR neglect OR maltreatment* OR adversity* OR separation* OR loss*) AND panic. The last search was run in June 2021. Inclusion criteria were studies that recruited: adults with diagnosis of PD (panic group); adults with no PD or PA (nonclinical control group) and assessed ACEs in both groups. Exclusion criteria were studies with participants who were under 18 years old or adults who reported traumatic events that had happened when they were over 18 years old. A total of 2,967 citations were returned: 987 were duplicated, 1,980 were then screened by their titles and abstracts. In total, 1,921 were found to be irrelevant, leaving 59 for further assessment. Of these, 25 more citations were removed due to: nonrepresentative control group (11), missing ORs/missing critical data to calculate the ORs (9), non-listed ACEs (4), and identical dataset used by two separate studies (1). There were, therefore, 34 studies eligible for final analysis (see supplemental material S5-A: PRISMA flowchart).

5.2.2. Data extraction

The study design, nature of the participants, ACE types, and ACE measures were summarized by YZ. YZ and PW graded the quality of the studies independently following the STROBE checklist for cohort, case-control, and cross-sectional studies (https://www. strobe-

statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf) (Vandenbroucke et al., 2014). Scores based on a scale of one to five, with five being best quality, were given to each of the 22 items, then the standardized total score (maximum 100) was converted to high (above 90), medium, and low (below 75). Missing ORs and their 95% confidence intervals were derived from the number of incidences of the four conditions (panic without ACE, panic with ACE, control with ACE, and control without ACE). Missing standard errors were estimated from confidence intervals utilizing the algorithm recommended by the Cochrane handbook:

$$SE = (LOG(CI\ Upper)-LOG(CI\ Low))/3.92$$

https://training.cochrane.org/handbook/current/chapter-06#section-6-3-2. Taking the advantage of the robust variance estimation (RVE) model (discussed in the next section), we created one record for each point estimation. Multiple records were generated for studies that reported multiple ORs, either of various ACE types or of different populations.

5.2.3. **Effect size analysis**

Conventionally two models, fixed effects or random effects, are routinely used in meta-analysis. Compared to fixed-effect models, random-effects model relaxes the implausible assumption that all studies have exactly the same effect size. The relaxation allows the model to incorporate between-study errors. Nevertheless, both models share another assumption that effect sizes from different studies are independent, where there is generally no reason to presume such an assertion. It is obviously violated when a study produces several estimates based on the same individuals or when there are clusters of studies that are not independent (e.g. carried out by the same investigator or share the same dataset). Such violations are even more exigent in the current study when we tried to extract multiple indices of ACEs from one study. Therefore, we used RVE, a meta-analytic method for dealing with dependent effect sizes without knowing their covariance structure (Hedges, Tipton, & Johnson, 2010; Tipton, 2015).

The R package robumeta (https://cran.r-project.org/web/ packages/robumeta/index.html) was chosen to run the analysis. However, RVE retains the advantage of being able to account for between-study variance as in random-effects model.

5.2.4. **Effect size interpretation**

To interpret the strength of the OR in epidemiological studies, Chen, Cohen, and Chen (2010) provided a calculation that maps OR to Cohen's d. They suggested that at a 5% disease rate in the non-exposed group, OR 1.52, 2.74, and 4.72 are equivalent to Cohen's d = 0.2 (small), 0.5 (medium), and 0.8 (large), respectively.

5.2.5. **Subgroup difference analysis**

We used the robumeta package (https://cran.r-project.org/package= robumeta) in R to run meta-regression supporting RVE and Wald tests to ascertain whether the effect sizes of subgroups are statistically different. Wald tests are hypothesis tests that involve multiple constraints on the regression coefficients (Gourieroux, Holly, & Monfort, 1982). In other words, it determines if the predictive variable(s) in a linear model is significant.

5.2.6. **Heterogeneity and moderator analysis**

Heterogeneity was estimated using I^2 statistics (Higgins, Thompson, Deeks, & Altman, 2003). The heterogeneity was expected to be high given the diversity of ACEs and study designs. In order to identify possible sources of heterogeneity, we used the R package 'metacart' (https://cran.r-project.org/web/packages/ metacart/index.html) to assess the impact of potential moderators such as study quality, study design, sampling, and assessment methods. The package uses classification and regression trees (CART) model to identify multiple moderators and their interactions simultaneously (Li, Dusseldorp, Su, & Meulman, 2020). The reasons that we selected CART instead of the regular meta-regression model are threefold. First, the linear assumption of the relation between moderators and effect size is not always warranted. Second,

when the number of included studies is small, meta-regression suffers from low statistical power (Tanner-Smith & Grant, 2018). Third, since behavioral and medical research are susceptible to multiple confounding factors, the number of moderators can be too large to fit into one meta-regression model. Conversely, the tree model is good at dealing with non-linear situation with many predictor variables that may interact, and produce easy-to-interpret results (Dusseldorp, van Genugten, van Buuren, Verheijden, & van Empelen, 2014). In brief, tree-based models split the data multiple times according to certain cut-off values in the predictor variables. A CART output forms a tree where each fork is a split in a predictor variable and each end (leaf) node presents a final prediction for the outcome variable.

5.2.7. **Publication bias analysis**

Determining the level of publication bias is problematic as the conventional approach such as the funnel plot or Egger's test cannot be applied to clustered multiple point estimates where the assumption of independence would be violated. Mathur and VanderWeele (2020) introduced an advanced method which relaxes the distributional and asymptotic assumptions. Accordingly, the R package PublicationBias (https://cran.r-project.org/web/packages/PublicationBias/index.html) was used to return the S-values and significant funnel plot.

The S-value, defined as the severity of publication bias, is the ratio by which affirmative studies (i.e. studies whose findings support the research questions) are more likely to be published than non-affirmative studies that would be required to shift the pooled point estimate (or the upper limit of the confidence interval) to the null hypothesis value. In other words, it is the minimum number of unpublished studies with a mean point estimate of zero (or another fixed value) that would need to be included in the meta-analysis to reduce the pooled estimate to 'statistical nonsignificance' (Rosenthal, 1979). A bigger S-value implies greater robustness to publication bias. Although there is no clear cut-off defined for S-value as it is a newly

developed method, we referred to a previous study (Frederick & VanderWeele, 2020) and concluded that the results were unlikely to be sensitive to publication bias as both values were bigger than 10.

5.3. Results

5.3.1. Study summary

We identified 34 studies between 1985 and 2018 with a total of 192 ,182 participants (Table 5-1: study summary for study characteristics). Nine of these are case-control studies (5, 7, 8, 16, 30, 36, 45, 47, 50), while the rest are cross-sectional including one cohort study (13). The number of participants varied from 61 to 43,093. Fourteen studies assessed more than one type of ACE (1, 3, 5, 7, 13, 14, 21, 30, 31, 41, 42, 44, 45, 48); three studies examined one ACE but reported separate ORs for males and females or for different age groups (15, 28, 39); two studies evaluated a set of ACEs in each gender (44, 45); and four studies recruited participants in one gender only (40, 41, 49, 103). The majority of the studies used recognized clinical criteria to assess PD (DSM-III, DSM-IV, and ICD-10) but saw diverse methods of ACE assessment. Ten studies adopted standardized questionnaires (1, 3, 5, 6, 16, 30, 34, 42, 45, 46), and the remaining 24 studies developed their own methods or relied on screening criteria based on the characteristics of the samples.

The studies can be classified as ACE studies which explored the influence of a specific ACE (6, 13, 14, 15, 27, 28, 40, 41, 46, 49, 101, 102, 103) or a collection of ACEs (1, 3, 5, 30, 31, 42, 44, 48, 53), and panic studies which were interested in early experiences within the PD population (7, 21, 45, 47). There were seven comorbidity studies (16, 21, 40, 42, 45, 47, 48, 49) that recruited participants with other psychiatric conditions (PTSD, bipolar, major depression, and substance use). Whereas the panic studies focused on PD only, the ACE studies dealt with a range of psychiatric disorders. In addition to the association between PD and ACEs,

two studies inquired into gender differences (44, 45), and one study compared the impact of trauma in childhood and adulthood (53). It is noteworthy that the majority of the studies relied on retrospective reporting to sample the prevalence of ACEs; only four studies utilized prospective sampling (6, 8, 13, 22).

In respect of ACE types, most studies included physical, sexual, and emotional abuse/neglect, which are the conventionally representative ACEs, fewer studies included covert parental and familial conditions. Altogether, five looked at parental alcoholism (8, 16, 34, 36, 39), four family mental illness (7, 22, 29, 50), and eight studied parental loss/separation (28, 41, 44, 47, 101, 102, 103). Regarding the more recently recognized ACEs, one studied bullying (13), one studied daily hassle (6), one studied economic deprivation (44), and one studied involvement with child protection agencies (44). We organized the 20 ACEs by two approaches, the sociolegal and threat-deprivation perspectives (see Table 2). The left part of Table 5-2 shows four groups: abuse, neglect, household dysfunction, and peer victimization (i.e. the sociolegal classification), while the right side enumerates three groups: high on threat, high on deprivation, and mixed, based on the dimensional model. These subgroups are inevitably arbitrary due to the yet to come objective measures for ACE classification.

Table 5-1: Study summary. Online version: https://osf.io/279ky/

ID	Study	Country	Design	N	Participants	ACE	Analysis Method	Study Quality	ACE Measure	PD Measure
1	Afifi (2014)	Canada	CS	23395	adults in general population	PA, SA, DV, ANY AB	RGS	2	CEVQ	DSM-IV
3	Asselmann (2018)	Germany	CS	2263	adult in general population	PA, SA, EA, PN, EN	RGS	1	CTQ	ICD-10, DSM-IV
5	Asselmann (2018)	Germany	CC	286 + 286	adult in general population	PA, SA, EA, PN, EN, ANY AB, ANY NG	RGS	2	CTQ	ICD-10, DSM-IV
6	Asselmann (2017)	Germany	CS/PRS	2797	young people (14-17) / 10 years daily hassles	HSSL	RGS	1	DHS	ICD-10, DSM-IV
7	Bandelow (2002)	Germany	CC	115 + 124	adults with PD + control	STE, FAD	RGS	2	QwR	DSM-IV

8	Bidaut-Russell (1994)	USA	CC/PRS	74 + 978	offspring of alcoholic mother	PAL	RGS	2	QbS	DSM-III-R

ID	**Study**	**Country**	**Design**	**N**	**Participants**	**ACE**	**Analysis Method**	**Study Quality**	**ACE Measure**	**PD Measure**
13	Copeland (2013)	USA	CH/PRS	1420	young adults	BLVM, BLPP, ANY BL	RGS	2	QwR	DSM-IV
14	Copeland (2010)	USA	CS	4140	adults in general population	PA, SA	RGS	2	QwR	DSM-IV
15	Dinwiddie (2000)	AUS	CS	5995	twins in general population	SA	RGS	3	QwR	DSM-III-R
16	El-Guebaly et al. (1991)	Canada	CC	80 + 170	patient with anxiety/substance abuse	PAL	CONT	2	CAST	DSM-III
21	Goodwin (2005)	USA	CS	1150	young adults (21 yrs)	PA, SA, DV	RGS	1	QwR	DSM-IV
22	Goodwin (2005)	USA	CS/PRS	940	young adults	FAD	RGS	1	QbS	DSM-IV

ID	Study	Country	Design	N	Participants	ACE	Analysis Method	Study Quality	ACE Measure	PD Measure
27	Jonas (2010)	UK	CS	7403	adults in general population	SA	RGS	2	QwR	CIS-R
28	Keyes (2014)	USA	CS	27534	adults in general population	LOSS	RGS	1	QwR	DSM-IV
29	Leen-Feldner et al. (2011)	USA	CS	3931	offspring of parents with PTSD	PPD	CONT	3	QbS	DSM-IV
30	Kraan et al. (2018)	EU	CC	259 + 48	adults with child maltreatment	PA, SA, EA, PN, EN, ANY ML	RGS	2	CTQ	DSM-IV
31	Libby et al. (2005)	USA	CS	3084	American Indian	PA, SA	RGS	2	QwR	DSM-IV
34	MacPherson et al. (2001)	Canada	CS	213	university students	PAL	RGS	3	CAST	PAQ-R
36	Mathew et al. (1993)	USA	CC	408 + 1477	adults with alcoholic parents and control	PAL	RGS	2	QwR	DSM-III
39	Morgan et al. (2010)	USA	CS	40374	adult in general population	PAL	RGS	2	QwR	DSM-IV

ID	Study	Country	Design	N	Participants	ACE	Analysis Method	Study Quality	ACE Measure	PD Measure
40	Murrey et al. (1993)	USA	CS	185	adult females with depression and anxiety	SA	CONT	2	QwR	DSM-III-R
41	Otowa et al. (2014)	USA	CS	2605	male twins	LOSS, SPT	RGS	1	QwR	DSM-III-R
42	Pavlova et al. (2016)	Canada	CS	174	patients with bipolar	PA, SA, EA, PN, EN	RGS	1	CTQ	DSM-IV-TR
44	Sareen et al. (2013)	Canada	CS	8340	military population	SPT, ED, PAL, CP, PA, DV, SA	RGS	1	QwR	DSM-IV
45	Seganfredo et al. (2009)	Brazil	CC	123 + 123	patients with anxiety	PA, SA, EA, PN, EN	RGS	1	CTQ	DSM-IV
46	Sugaya et al. (2012)	USA	CS	43093	adults in general population	PA	RGS	1	CTQ	DSM-IV
47	Torgersen et al. (1986)	Norway	CC	29 + 32	twins with PD or GAD	SPT	CONT	3	QwR	DSM-III

ID	Study	Country	Design	N	Participants	ACE	Analysis Method	Study Quality	ACE Measure	PD Measure
48	Vitriol et al. (2016)	Chile	CS	394	patients with MDD	PA, SA, SPT, PAL, EF	CONT	2	QwR	ICD-10
49	Walker et al. (1992)	USA	CS	100	women scheduled for diagnostic laparoscopy (50 for chronic pain, 50 for tubal ligation or infertility evaluation)	SA	RGS	3	QwR	DSM-III
50	Weissman et al. (2006)	USA	CC	101 + 50	offspring of parents with depression	PPD	RGS	1	QbS	DSM-IV
53	Zlotnick et al. (2008)	Chile	CS	1338	adults in general population	STE	CONT	2	QwR	DSM-III-R
101	Tweed et al. (1989)	USA	CS	3803	adults in general population	SPT	CONT	1	QwR	DSM-III
102	Ogliari et al. (2009)	Norway	CS	712	twins in general population	SPT	CONT	1	QwR	DSM-IV

ID	Study	Country	Design	N	Participants	ACE	Analysis Method	Study Quality	ACE Measure	PD Measure
103	Kendler et al. (1992)	USA	CS	2036	female twins in general population	LOSS	RGS	1	QwR	DSM-III-R

Note:

CS: cross sectional; CC: case control; CH: cohort; PRS: prospective; ANY AB: any abuse; SA: sexual abuse; PA: physical abuse; EA: emotional abuse; ANY NG: any neglect; PN: physical neglect; EN: emotion neglect; PAL: parental alcoholism; PPD: parental mental illness; FAD: family anxiety disorder; SPT: family separation; LOSS: loss of loved ones; CP: child protection; HSSL: daily hassles; DV: domestic violence; ED: economic deprivation; BLPP: bully perpetrator; BLVM: bully victim; ANY BL: any bullying; STE: other traumatic event; ANY ML: any maltreatment; QbS: characteristics of participants; QwR: questions design by the study; CTQ: childhood trauma questionnaire; THQ: trauma history questionnaire ; CAST: children of alcoholics screening test; CEVQ: childhood experiences of violence questionnaire; DHS: daily hassles scale; RGS: regression modelling; CONT: incident counts; 1: high; 2: medium; 3: poor

Table 5-2: ACE summary. Online version: https://osf.io/wvq9t/

Group	Adversity	k	
By sociolegal categories			
Abuse	any abuse	3	43
	sexual abuse	19	
	physical abuse	15	
	emotional abuse	6	
Neglect	any neglect	1	13
	physical neglect	6	
	emotion neglect	6	
Household dysfunction	parental mental illness	2	35
	family anxiety disorder	2	
	parental alcoholism	9	
	family separation	7	
	parental loss	5	
	child protection	2	
	daily hassles	1	
	domestic violence	5	
	economic deprivation	2	
Peer victimization	bully perpetrator	1	3
	bully victim	1	
	any bullying	1	
	other traumatic event	2	2
By deprivation-threat dimensions			
High on threat	any abuse	3	54
	sexual abuse	19	
	physical abuse	15	

	emotional abuse	6	
	child protection	2	
	daily hassles	1	
	domestic violence	5	
	bully perpetrator	1	
	bully victim	1	
	any bullying	1	
Mixed	parental mental illness	2	29
	family anxiety disorder	2	
	parental alcoholism	9	
	family separation	7	
	parental loss	5	
	economic deprivation	2	
	other traumatic event	2	
High on deprivation	any neglect	1	13
	physical neglect	6	
	emotion neglect	6	

K: number of extracted data entries, not number of studies

5.3.2. **Overall and subgroup effect size estimates**

Ninety-six effect sizes extracted from 34 studies were entered into our main analysis (see supplemental material S5-Table 1; or https:// osf.io/m3dsy/ for csv file). Although the data were extracted from 34 studies, several studies published point estimates of identical ACEs obtained from different samples. Therefore, the R program recognized 40 clusters. Subsequently, we marked these subgroups as separate studies in the results (see Figure 5-1).

The forest plot (Figure 5-1) displays the distribution of the point estimates. The RVE model yielded an overall OR of 2.85, 95% CI (2.03–3.66). Three studies stood out for their large effect size. Copeland, Wolke, Angold, & Costello (2013) reported 14.5, CI (5.7–36.6) on

bullying (both perpetrator and victim), Walker et al. (1992) reported 15.6, CI (1.43–170.12) on sexual abuse and Zlotnick et al. (2008) reported 11.1, CI (3.2–38.2) with other trauma. Analysis was not feasible for several individual ACE types (physical neglect, parental mental illness, family separation, parental loss, child protection, daily hassles, domestic violence, economic deprivation, peer victimization, other traumatic event, and neglect group), either because the sample sizes were too small, or the degree of freedom was insufficient (smaller than four). A post-hoc decision was paid to pool family separation and parental loss effects together as a 'parental separation/loss'. Pooled results for single ACE types and subgroups are presented in Table 5-3. These ranged from 1.53, 95% CI (0.756–2.31) for emotional neglect, to 2.51, 95% CI (1.23–3.8) for sexual abuse. All abuse types increased the odds of having a PD with the exception of emotional abuse and emotional neglect.

With respect to groups (either sociolegal, or deprivation-threat dimensions) the mixed group yielded the largest OR [2.91, 95% CI (1.87–3.94)]; this remaining the case even after outliers were removed. All groups significantly increased the odds of having PD.

Heterogeneity was moderate for physical abuse, emotional abuse, and parental alcoholism, while considerably greater for all other ACE subtypes and groups. Heterogeneity was substantially reduced after excluding the outliers; adjusted ORs were therefore used as final results for discussion.

Table 5-3:Pooled OR estimates

Estimations of individual ACEs										
ACE	**k**	**Cluster**	**I^2**	**τ^2**	**Estimate**	**StdErr**	**t-value**	**Dfs`**	**95 % CI**	
Sexual abuse	19	19	92.755	2.298	2.51	.611	4.12	17.7	1.23	-
Sexual abuse (no outlier)	18	18	80.905	.725	1.92	.258	7.45	16	3.80 1.37 2.46	-

Physical abuse	15	15	44.113	.140	1.71	.154	11.1	11.2	1.37 - 2.05	
Emotional abuse	6	6	58.860	.218	1.61	.273	5.9	4.22	.868 - 2.35	
Emotion neglect	6	6	63.648	.225	1.53	.283	5.4	4.16	.756 - 2.31	
Parental alcoholism	9	9	54.125	.275	1.83	0.25	7.34	7.04	1.24 - 2.43	
Parental separation/loss	13	12	64.946	.616	1.82	.305	5.97	10.1	1.14 - 2.50	
Overall	96	40	93.462	3.372	2.85	.403	7.07	38.6	2.03 - 3.66	
Overall (no outlier)	93	38	81.810	1.022	2.20	.187	11.7	35.4	1.82 - 2.58	
Estimations of groups by sociolegal categories										
Abuse	43	20	91.972	2.166	2.52	562	4.48	18.7	1.34 - 3.69	
Abuse (no outlier)	42	19	77.280	.615	1.95	.225	8.63	16.9	1.47 - 2.42	
Neglect	13	-	-	.-	-	-	-	-	-	
Household dysfunction	35	23	83.059	1.496	2.37	.276	8.6	21.4	1.80 - 2.94	
Estimations of groups by deprivation-threat dimensions										
High on threat	54	22	93.980	3.038	2.66	.57	4.66	20.8	1.47 - 3.84	
High on threat (no outlier)	52	21	74.555	.547	1.91	.201	9.46	18.7	1.48 - 2.33	

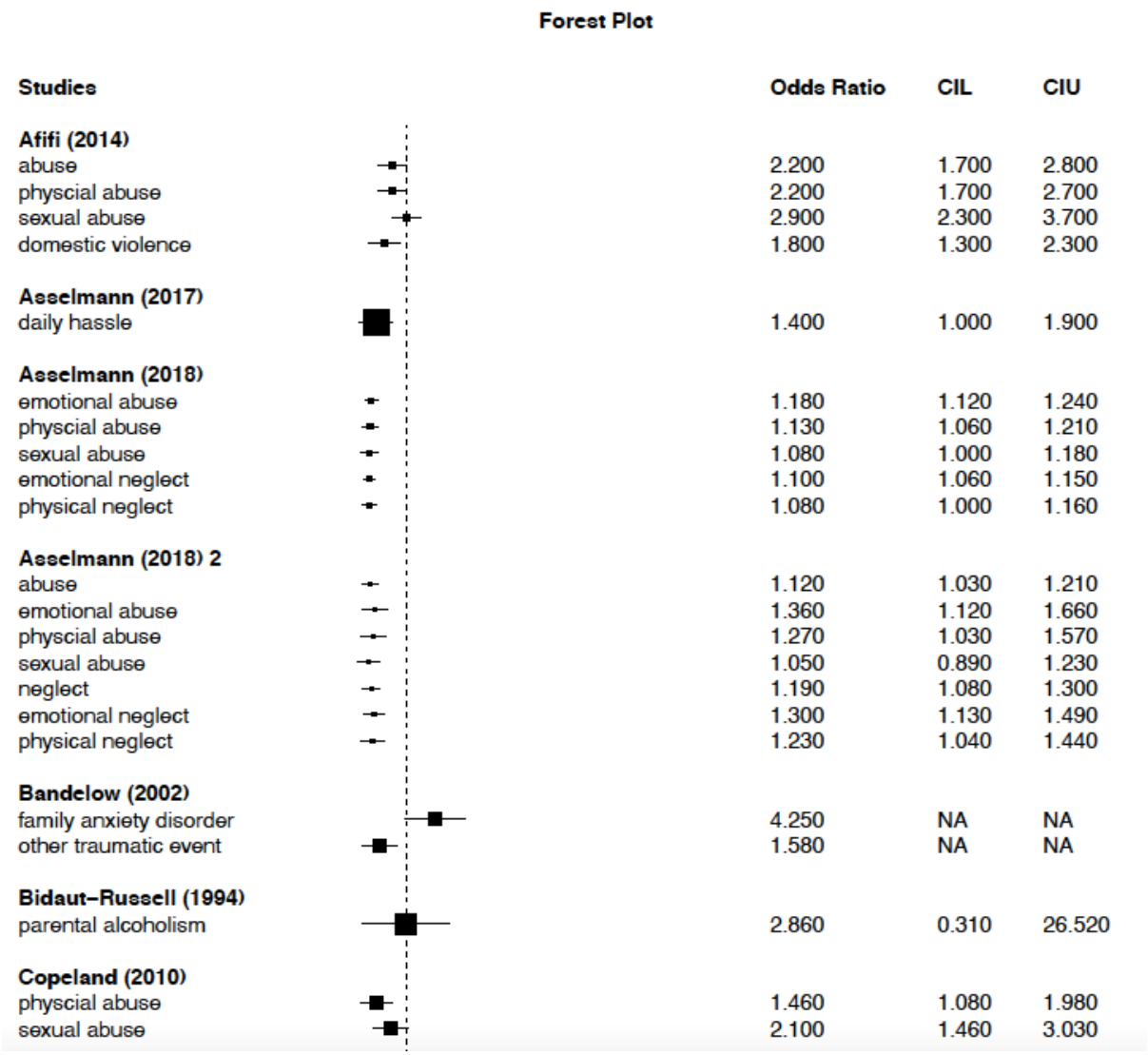
Mixed	29	22	92.194	3.766	2.91	.497	5.85	20.8	1.87 – 3.94	
Mixed (no outlier)	28	21	86.483	1.993	2.5	.338	7.41	19.6	1.80 - 3.21	
High on deprivation	13	-	-	-	-	-	-	-	-	

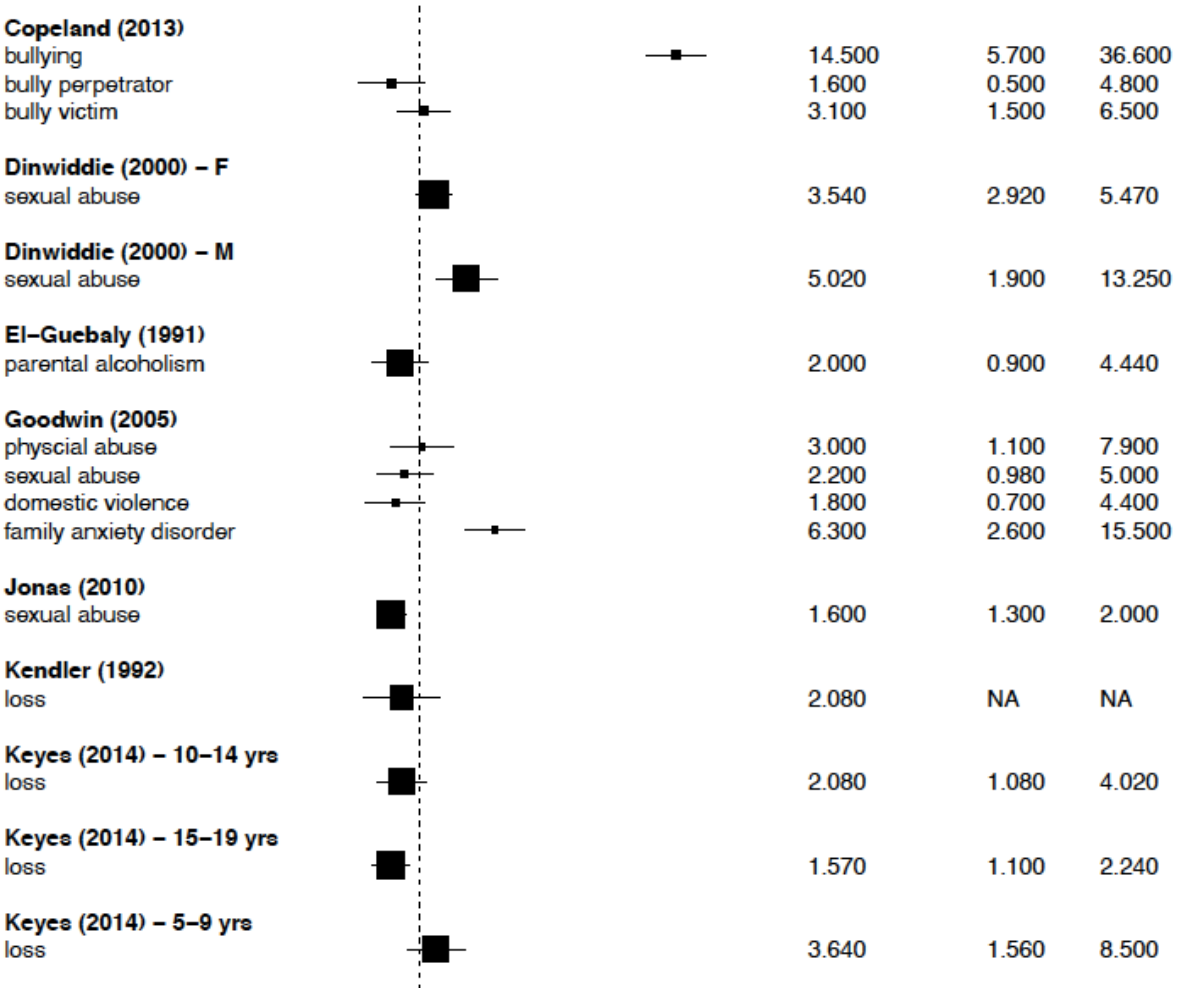
Note:

-: df < 4, pooling not applicable

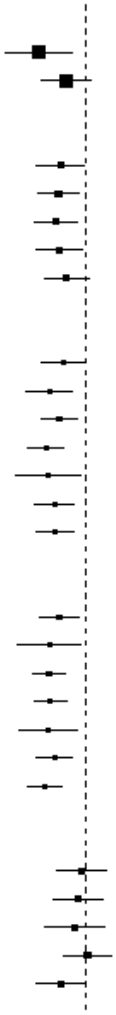
k: number of point estimates

Cluster: number of clustered groups




Copeland (2013)
bullying 14.500 5.700 36.600
bully perpetrator 1.600 0.500 4.800
bully victim 3.100 1.500 6.500
Dinwiddie (2000) – F
sexual abuse 3.540 2.920 5.470
Dinwiddie (2000) – M
sexual abuse 5.020 1.900 13.250
El–Guebaly (1991)
parental alcoholism 2.000 0.900 4.440
Goodwin (2005)
physcial abuse 3.000 1.100 7.900
sexual abuse 2.200 0.980 5.000
domestic violence 1.800 0.700 4.400
family anxiety disorder 6.300 2.600 15.500
Jonas (2010)
sexual abuse 1.600 1.300 2.000
Kendler (1992)
loss 2.080 NA NA
Keyes (2014) – 10–14 yrs
loss 2.080 1.080 4.020
Keyes (2014) – 15–19 yrs
loss 1.570 1.100 2.240
Keyes (2014) – 5–9 yrs
loss 3.640 1.560 8.500

Kraan (2018)			
emotional abuse	0.810	0.400	1.650
physcial abuse	2.000	1.000	3.990
sexual abuse	0.850	0.460	1.580
abuse	0.640	0.350	1.190
emotional neglect	0.670	0.300	1.490
physical neglect	1.310	0.690	2.460
Leen−Feldner (2011)			
parental mental illness	5.300	3.740	7.520
Libby (2005) – N			
physcial abuse	2.880	NA	NA
sexual abuse	1.400	NA	NA
Libby (2005) – S			
physcial abuse	3.350	NA	NA
sexual abuse	4.410	NA	NA
MacPherson (2001)			
parental alcoholism	2.500	NA	NA
Mathew (1993)			
parental alcoholism	4.060	NA	NA
Morgan (2010) – F			
parental alcoholism	1.730	NA	NA
Morgan (2010) – M			
parental alcoholism	1.610	NA	NA
Murrey (1993)			
sexual abuse	1.100	0.370	3.290
Ogliari (2009)			
seperation	1.560	0.750	3.250



Otowa (2014)			
loss	0.780	0.240	2.520
seperation	2.010	1.090	3.720
Pavlova (2016)			
emotional abuse	1.750	0.990	3.120
physcial abuse	1.660	1.070	2.560
sexual abuse	1.520	0.960	2.420
emotional neglect	1.680	0.960	2.920
physical neglect	2.020	1.200	3.400
Sareen (2013) – F			
physcial abuse	1.890	1.130	3.170
sexual abuse	1.250	0.730	2.120
parental alcoholism	1.700	1.230	2.340
seperation	1.100	0.790	1.530
child protection	1.190	0.410	3.470
domestic violence	1.490	1.010	2.190
economic deprivation	1.490	1.050	2.130
Sareen (2013) – M			
physcial abuse	1.700	1.140	2.540
sexual abuse	1.250	0.440	3.550
parental alcoholism	1.230	0.940	1.610
seperation	1.300	1.000	1.700
child protection	1.180	0.490	2.790
domestic violence	1.480	1.070	2.040
economic deprivation	1.060	0.780	1.440
Seganfredo (2009) – F			
emotional abuse	2.660	1.420	4.970
physcial abuse	2.520	1.320	4.780
sexual abuse	2.400	0.980	5.900
emotional neglect	2.960	1.600	5.490
physical neglect	1.770	0.960	3.240

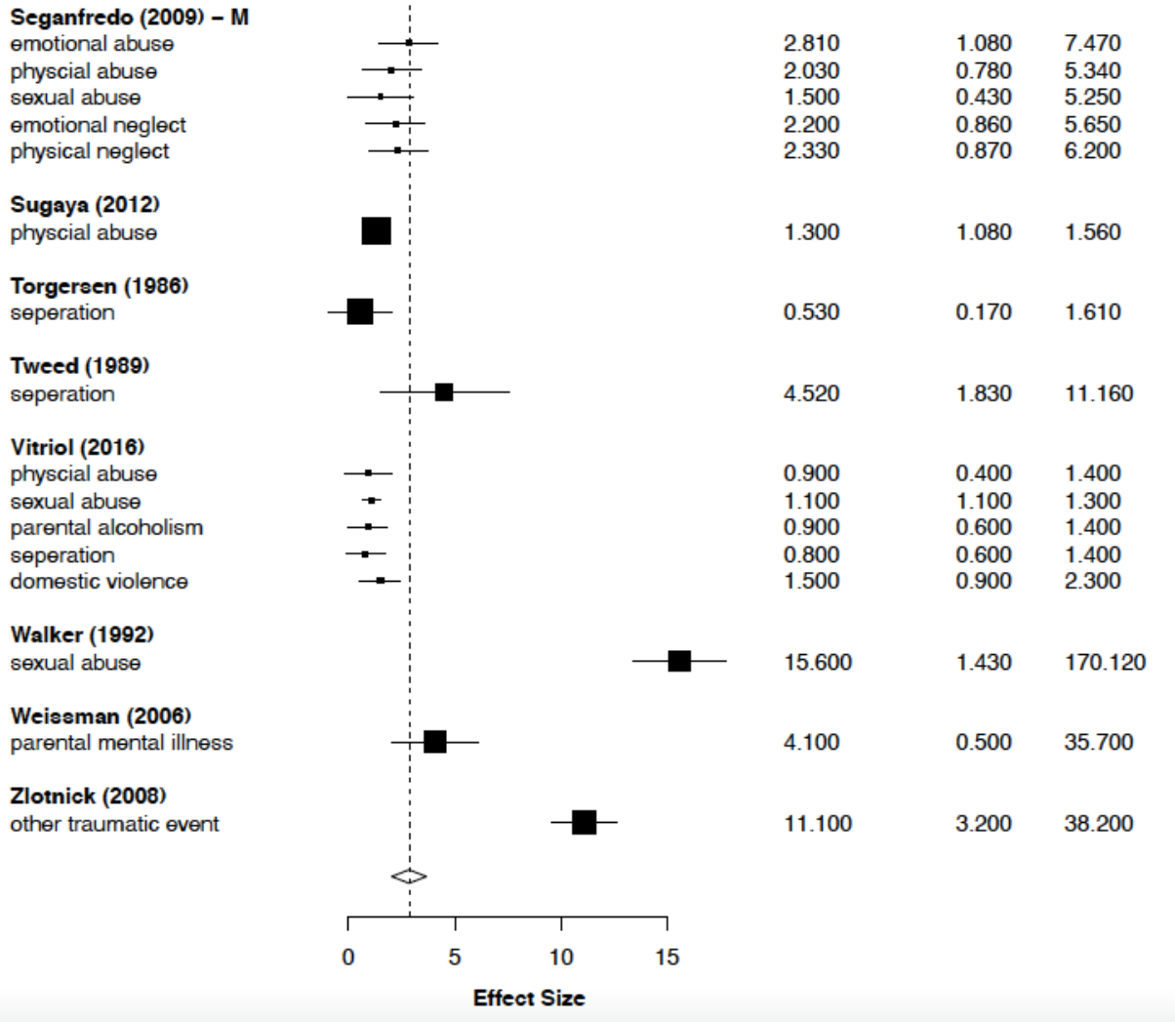


Figure 5-1: Forest plot. Online version: https://osf.io/msp4k/

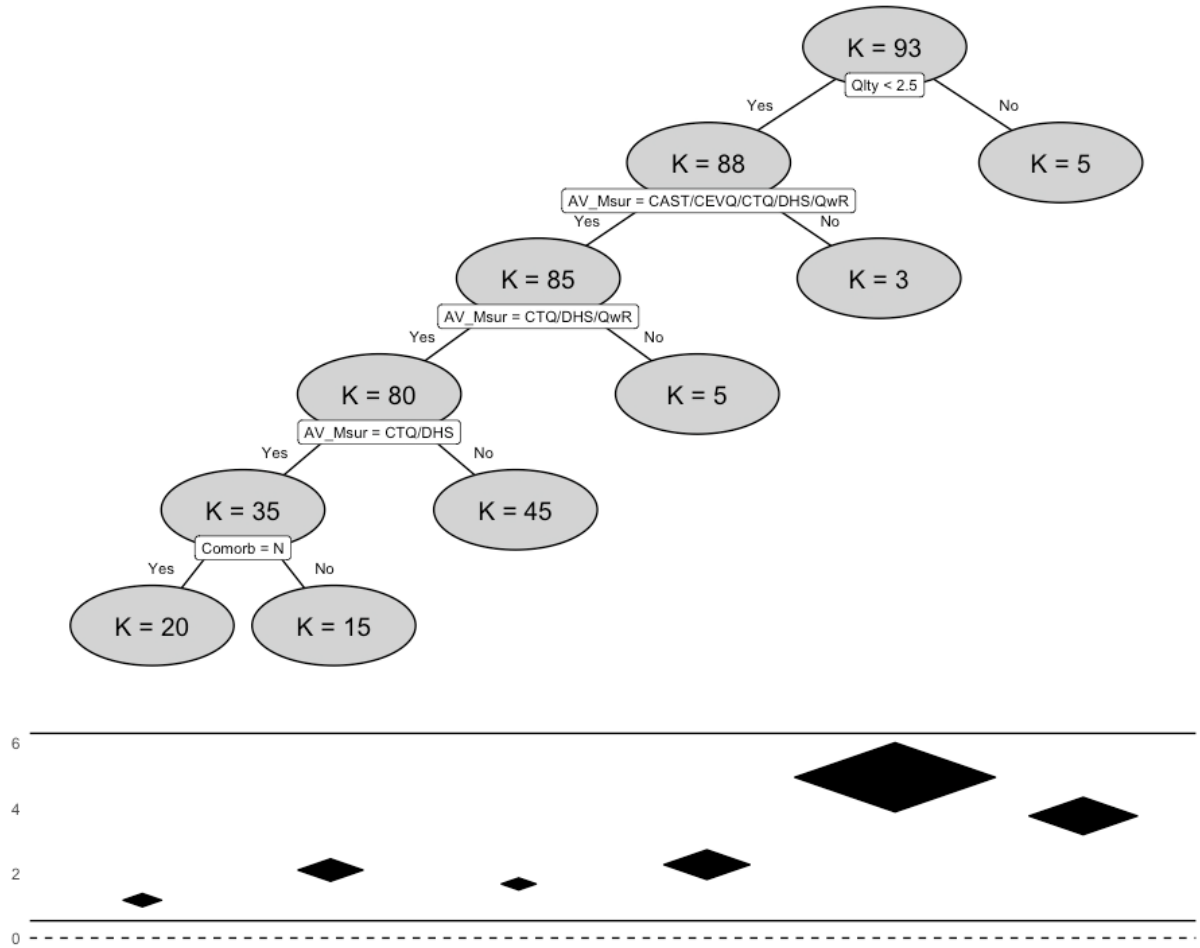
5.3.3. **Subgroup difference**

There was no significant difference detected among the effect size of subgroups either by sociolegal categories ($p = 0.261$) or threat-deprivation dimensions ($p = 0.145$; see supplemental material S5-C: original R outputs of subgroup difference analysis). This pattern of results remained even when excluding outliers (ps = 0.350 and 0.341, respectively).

5.3.4. **Moderators**

Study design, OR calculation method, quality of study, participants with comorbid psychiatric disorders, and adversity assessment method were entered into the multiple

moderator analysis. Only study quality, comorbidity, and ACE assessment method were identified as influential moderators (see the original R output in supplemental material S5-B). Figure 5-2 illustrates the splitting process and six more homogeneous subgroups identified by the CART model. Studies measuring ACEs based on the characteristics of the sample without further assessment (AV_Msur ≠ CAST/CEVQ/CTQ/DHS/QwR, k = 3) reported the highest pooled OR [4.9, 95% CI (3.8−6.0)], followed by the group of lower study quality [Qlty > 2.5, k = 5, OR = 3.7, 95% CI (3.1−4.3)]. The remaining 85 entries formed four similar groups where the type of ACE measure mainly accounted for heterogeneity. It is worth noting that the comorbidity group (Comorb ≠ N, k = 15) reported significantly higher mean OR 2.0, CI (1.7−2.4) than the noncomorbid group [Comorb = N, k = 20, 1.1, CI (0.9–1.3)].



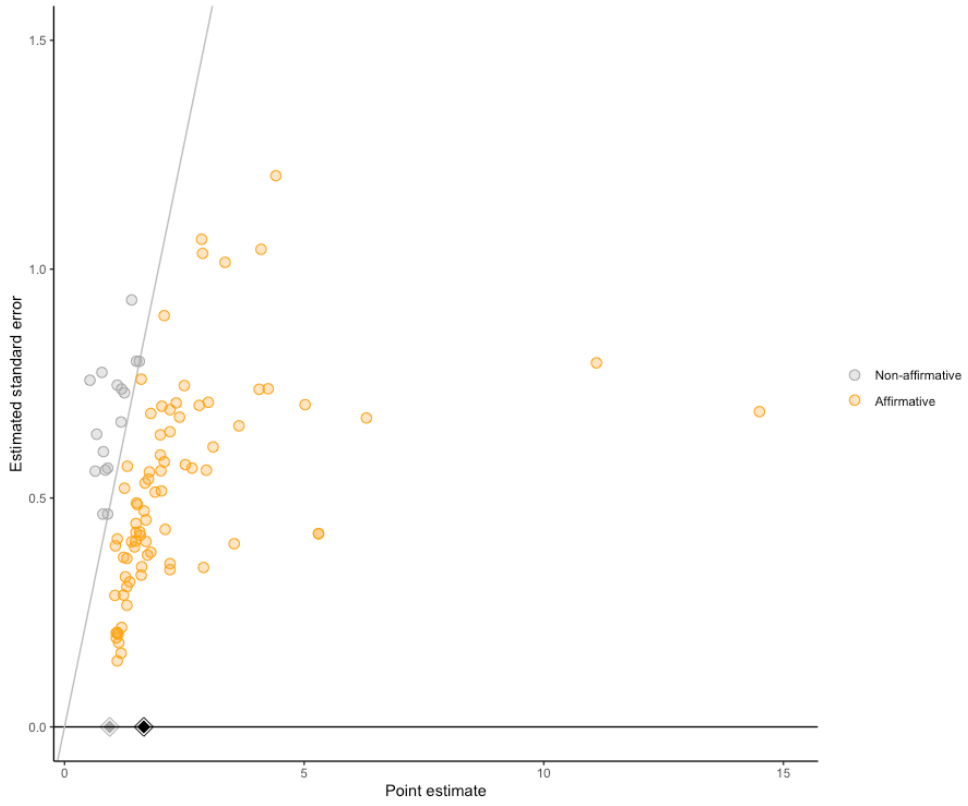
Note: k denotes the number of entries instead of number of studies. Qlty: study quality (1: high; 2: medium; 3: poor); AV_Msur: adversity measure; Comorb: if participants had other psychiatric comorbidity (N: no); QbS: characteristics of participants; QwR: questions design by the study; CTQ: childhood trauma questionnaire; THQ: trauma history questionnaire ; CAST: children of alcoholics screening test; CEVQ: childhood experiences of violence questionnaire; DHS: daily hassles scale; diamond: pooled OR of the group; height of diamond: confident interval; width of diamond: standard error

Figure 5-2: Moderator tree

5.3.5. **Publication bias and sensitivity test**

The significant funnel plot (Figure 5-3) demonstrates an unconventional funnel plot. The effect size distribution is skewed toward affirmative studies, and there is a tendency to a positive correlation between effect size and standard error, which suggests publication bias.

We conducted sensitivity testing by measuring the S-values of null hypothesis (OR = 1), and a value close to 1 (OR = 1.1); the results are presented in Table 5-4. Based on the robust model which took account of the dependent clusters, it appeared that it would be almost impossible to shift the estimated magnitude from the pooled effect size estimate suggested in the present study to the null hypothesis, since it would require the number of non-affirmative studies to be more than 200 times of the number of affirmative ones. Likewise, the ratio between non-affirmative and affirmative studies would need to be as high as 72 in order to shift the OR to 1.1.



The grey dots are non-affirmative point estimates, and orange ones are affirmative. Studies lying on the diagonal line have exactly p = .05. The black diamond is the robust independent

point estimate within all studies; the grey diamond is the robust independent point estimate within only the non-affirmative studies. The smaller the distance between the two diamonds, the less severe the publication bias.

Figure 5-3: Significant funnel plot

Table 5-4: Publication bias sensitivity test

Model	S($\dot{\hat{\mu}}'$, 1)	S($\hat{\mu}^{lb\prime}$, 1)	S($\dot{\hat{\mu}}'$, 1.1)	S($\hat{\mu}^{lb\prime}$, 1.1)
Fixed (common-effect)	170	26	54	17
Robust (clustered)	>200	10	73	7

Note: severity of publication bias (S) required to attenuate $\dot{\hat{\mu}}'$ (effect size) or $\hat{\mu}^{lb\prime}$ (the upper limit of the CI) to null (q = 1) or q' = 1.1 on the odds ratio. Values are conservatively rounded down to the nearest integer.

5.4. Discussion

With the assistance of an RVE model, we overcame the issue of clustered point estimates and conducted a meta-analysis assessing the magnitude of the association between childhood adversity and PD. Our analysis returned a mild to medium strength association between ACEs and PD. We should note that although the overall magnitude is stronger than some of the individual ACEs, it should be interpreted with great caution due to high heterogeneity. Based on their medium levels of heterogeneity and small variance, we are inclined to conclude that pooled results within individual types of ACEs are more robust.

Moderator analysis revealed that, apart from common methodological factors such as study design, quality, and measurement issues, comorbidity was the only clinical factor that influenced the effect size and ACEs were more prevalent in the comorbid population (Figure

5-2). It is estimated that the majority (80%) of the PD population present comorbidities (De Jonge et al., 2016) while there were only seven citations in this review that were comorbidity studies, it is unclear whether other studies excluded comorbidity cases for better controlled data or they neglected to report the condition. Thorough investigation on this subject with qualitative magnitude will be valuable information. If stronger link was found in ACEs and PD with comorbidity than PD only, it would suggest early-life stress could be a global risk to mental illnesses.

Looking for specificity between types of ACE and PD was another goal of the study. If we classify the results into significant or non-significant based on whether the confidence intervals contain the null hypothesis value, sexual abuse, physical abuse, parental alcoholism, and separation/loss are significant risks for PD, whereas emotional abuse and neglect are not. However, considering the number of entries ($k = 6$) and the degrees of freedom ($df < 5$) were much lower than those eligible for pooling, we are uncertain if they are an artefact of insufficient data. Moreover, from the continuous point of view, the effect sizes of emotional abuse and emotional neglect are somewhat homogeneous with regard to the pooled estimates and their confidence intervals overlapped with others, it is more likely that the mean ORs are not statistically different from the other ACEs.

The study also explored the specificity by exploring two systems for conceptualizing ACEs. One divided the ACEs from a sociolegal point of view and the other dissected them against threat-deprivation dimensions. No difference was found among the ORs of these subgroups by either grouping method; on the contrary, we observed consistent pooled estimations. ACEs are one of many factors that may predispose people to developing PD; other factors such as genetic disposition and life events could have attenuated the between-ACE variations. Nevertheless, the non-conclusive results could also imply that the current ACEs constructions (abuse, neglect, dysfunction, threat, deprivation, etc.) might not be able to

successfully account for the neurobiobehavioral impacts of ACEs that lead to PD. This may be consistent with Smith and Pollak's hypothesis that other elements such as perception and attachment are the real drivers to specificity.

These findings add to the concerns raised about the measurement of ACEs, as these domains are not often integrated in ACEs studies. Although the neuroscience in ACEs research has progressed beyond the traditional sociolegal categorical models, there is a lag in the clinical studies. In the 34 reviewed studies, despite many of them examining multiple types of ACEs, none of them reported the cumulative data that are sufficient to allow the calculation of the ORs of PD and varied number of ACEs. The developmental period in which the child experienced the adversity is even less studied. Only one out of the 34 studies compared the impact of ACEs that occurred at different age groups and no study at all was concerned with the other dimensions (environment, social context, and attachment).

5.4.1. **Clinical implications**

The mild, albeit consistent, link between ACEs and PD should not be overlooked in delivering PD treatment. The learning prospective of PD and ACEs has provided ample evidence that hyper(re) activity to stressors formed at an early age remains deep-seated in the complex human stress-response system (Dempster, O'Leary, MacNeil, Hodges, & Wade, 2020; Shonkoff et al., 2012), and that these chronic patterns create extra obstacles to extinction learning and to behavioral change (Soltani & Izquierdo, 2019). A study that investigated the role of childhood trauma in CBT outcomes for PD with agoraphobia found that ACEs predicted greater psychopathology at pretreatment, poorer treatment response, and higher relapse rates (Michelson, June, Vives, Testa, & Marchione, 1998). It may be that assessment protocols for PD should include ACEs history. To improve treatment efficacy, clinicians may also consider adapting the number of sessions, treatment modalities, treatment components, and case management for PD patients with history of ACEs.

5.4.2. **Limitations and future research**

We sought to be as inclusive as possible in order to evaluate the impact of ACEs on PD as extensively as possible. However, there was an absence of eligible studies that would allow us to address the planned list. Even when we obtained a few point estimations for family mental illness, bullying and other trauma, the data were not sufficient to approximate a pooled effect size. Family mental illness, in particular anxiety disorders, provides a unique perspective to examine the combined effect of genetic and environmental risks. Bullying (e.g. bullying at school, cyberbullying) is a growing concern for school-age children and adolescents. Our understanding of its pernicious effect on PD could have been advanced if data were available; more research is needed.

For the same reason, our analysis did not take account of the other dimensions (e.g. intensity, developmental period, cumulative effect) that might be more neurobiologically meaningful. Whether these newly proposed dimensions are more pertinent to the PD etiology and whether they foster a more sophisticated ACE construct need to be tested. Besides the absence of a concrete ACE definition at the conceptual as well as at operational level, the moderator analysis suggested the major source of heterogeneity resides within the ACE measures. We speculate that developing reliable and meaningful new ACE measures will be a continuous endeavour to the field. PD presents a broad set of presentations in terms of symptoms, severities, and comorbidities, and assessing the relationship between ACEs and these PD characteristics may bear more fruitful findings.

5.5. Conclusion

Our literature search returned 34 studies with a total of 192 182 participants. Ninety-six estimations of 20 types of ACEs were extracted. An RVE model, supporting meta-analysis for clustered estimations, returned mild to medium overall OR and significant but small ORs across sexual abuse, physical abuse, parental alcoholism, and parental separation/loss.

Homogeneous mean effect sizes were yielded across subgroups. No between-group difference was identified by either sociolegal classification (abuse, neglect, household dysfunction) or threat-deprivation dimensions (high on threat, high on deprivation, and mixed). The non-conclusive results either suggest the effects of ACEs on PD are truly comparative, or it raised the question whether the categorical or dimensional constructs of ACEs are the definitive ways to conceptualize the impact of ACEs on later mental health.

6. Chapter 6: Discussion

"How can the events in space and time which take place within the spatial boundary of a living organism be accounted for by physics and chemistry?"

- *Erwin Schrödinger*

In this chapter, the methods and findings from the four studies are brought together and discussed from three angles: methodology, understanding of PTSD and a theoretical framework of PTSD using a computational approach. For simplicity, the studies are referred to as the trajectory study, the NLP study, the ML study and the MA study, respectively. Methodology is undoubtedly one of the marked areas where a computational approach is distinctive compared to other approaches. The methodological deliberation will focus on how other methodologies relate to the computational approach and what differences they made in investigating PTSD. Next, the findings regarding the facets on the time axis illustrated in Figure 1-1 are reviewed, including acute responses, trauma memory, prior trauma factors and long-term impact. Together with studies in the broader literature, the discussion aims to evaluate current understanding of PTSD. In conclusion, a preliminary computational model of PTSD is outlined and discussed as providing a theoretical guideline towards developing a computational approach to researching PTSD.

6.1. Overview of the Studies

The four studies include three secondary data studies and one meta-analysis study exploring: PTSD-depression comorbidity (trajectory study); trauma memory and appraisal (NPL study); prediction of PTSD (ML study); and long-term association with panic disorder (MA study).

6.1.1. **Trajectory study**

The trajectory study investigated PTSD-depression comorbidity. The design of the study involved placing PTSD and post-trauma depression symptoms on a time axis and comparing the courses of the symptoms. Using longitudinal data collected at two weeks, two months and nine months, the study identified three distinct groups in the course of PTSS and depression symptom development. In the PTSS trajectories, we observed a group (42%) with consistent low symptoms, a group (36%) whose symptoms recovered within two months, and a high symptom group (22%) whose symptoms only recovered at nine months post-trauma. On the other hand, the depression groups saw two mild symptom groups (46%, 34%) and a chronic group (20%) where individuals did not recover at nine months, suggesting post-trauma depression was more persistent than PTSS in the sampled population. More importantly, a dependent probability analysis revealed high synchronicity between PTSS and depression groups. In other words, PTSS and depression symptoms develop at the same pace; if a person has high PTSS level, then they are very likely (74%) to present high depression levels as well.

Furthermore, a risk analysis examined 10 factors, mainly trauma-related cognitive processes (e.g., appraisals, rumination, self-blaming). It found that cognitive appraisal was the shared risk factor to high symptom groups for both PTSS and depression.

6.1.2. **NLP study**

The NLP study explored the feasibility of using natural language processing techniques to extract measurements of memory coherence and negative trauma appraisal from trauma narratives. To validate the reliability of the techniques, two NLP topic modeling algorithms (LSA and LDA) and two NLP sentiment analysis methods (Vader and Flair) were applied to compute narrative coherence and trauma appraisal. Memory coherence scores were also cross checked with self-report trauma memory quality scores. The reliability test reported significant ($p < .001$) and strong correlations between the two coherence methods, with $r = 0.65$ and 0.88

at T1 and T3; and between the two appraisal methods, with r = 0.68 and 0.61, indicating that those NLP techniques were reliable. Scores yielded by NLP were validated by self-report measures. The results found a significant and medium correlation between NLP coherence and self-reported memory quality at T1, r = -0.61, between NLP appraisal and cognitions inventory (CPTCI) at T1, r = -0.45.

After the measurement calculation, scores were used to test four hypotheses: i) narrative length is positively linked to the level of PTSS; ii) poorer coherence predicts higher PTSS severity; iii) more negative appraisal predicts more PTSS; and iv) coherence and appraisal scores change over time, where narratives become less negative and more coherent with the lapse of time from the trauma event. The results concluded that all hypotheses were supported by the data. The availability of trauma memory increases PTSD, and PTSD is associated with less coherent memories and negative trauma-related appraisals. Trauma narrative is a media containing essential trauma-related emotional and cognitive processes and may be utilized for future research and practice.

6.1.3. **ML study**

The ML study examined how machine learning could be utilized to build a clinically useful model to predict PTSD 6-15 months after injury in child populations. A random forest model was built based on pooled data of 1,167 records from an international data depository (PACT/R). The final model encompasses 13 predictors (age, ethnicity, trauma type, intrusive memories, nightmares, reliving distress, dissociation, cognitive avoidance, sleep, irritability, hypervigilance and startle). It yielded F-scores of .973, .902 and .961 with training and two external datasets, demonstrating excellent classification performance. The model also has good potential for clinical utility as it uses a few easily obtainable variables.

The study further applied interpretable machine learning (IML) to evaluate the operations among predictors, in particular ASD symptoms. Shapley importance values

revealed that the arousal symptom cluster was the most influential group, and cognitive avoidance and arousal symptoms were the most influential individual symptoms in predicting PTSD. Moreover, it observed a cumulative effect for intrusion symptoms. That is, although the Shapley values of each intrusion symptoms were low, the importance value as a group was much higher than the sum of each symptom.

Another IML technique, partial dependency plot (PDP), was used to depict relations between predictor variables and the outcome variable, i.e., the marginal effect each predictive feature has on chronic PTSD. PDP showed a non-linear relationship between age and PTSD, and between individual ASD symptom severity and PTSD. A 43% difference in the risk between non-minority and minority ethnic groups was detected.

6.1.4. **MA study**

The MA study turned to the impact of childhood adversities on adult panic disorder. The rationale of including the study into the PTSD literature is that it offers a way of evaluating the long-term effect of childhood stress, which is highly pertinent to pediatric PTSD. Its implications for PTSD are discussed in section 6.5.2, “pre-trauma factors and long-term impact”.

The aim of the study was to estimate the overall, as well as subgroups odds ratio of having PD in adults who report ACEs, compared to adults who do not. It shall be highlighted that instead of the usual choice for MA analysis, i.e., fixed-effects or random-effects model, the study employed robust variance estimation (RVE). The advantage of RVE is that it allows clustered estimations where one study reports multiple estimations. The literature search and screening returned 34 final studies, comprising 192,182 participants. Ninety-six estimations of 20 types of ACEs were extracted. The results showed mild to medium strength between overall ACEs and PD, as well as individual ACEs. Specifically, pooled ORs are: overall 2.2 CI[1.82, 2.58]; sexual abuse 1.92 CI[1.37, 2.46]; physical abuse 1.71 CI[1.37, 2.05]; emotional abuse

1.61 CI[.868, 2.35]; emotional neglect 1.53 CI[.756, 2.31]; parental alcoholism 1.83 CI[1.24, 2.43]; and parental separation/loss 1.82 CI[1.14, 2.50].

The study explored another important question, which is: what the best way is to categorize various types of ACEs? Traditionally, ACEs are grouped by sociolegal classification (abuse, neglect, household dysfunction), and a recent theory has proposed threat-deprivation dimensions (high on threat, high on deprivation and mixed). We compared the pooled estimations between those groups and found no between-group differences by either sociolegal classification or threat-deprivation dimensions. The homogeneous effect sizes across ACEs either suggests that the effects of ACEs on PD are comparable, or it raises the question as to whether the categorical or dimensional approaches to classifying ACEs are the definitive ways to conceptualize the impact of ACEs on later mental health.

6.1.5. **Summary**

Besides the broad range of research questions covered by the four studies, a distinctive feature shared by the studies is that all of them adopted unconventional methods. Conventionally, symptom change (i.e., trajectory) can be described by scores at different times; memory coherence is indexed by manual processing; trauma-related appraisals are often measured by questionnaires; a predictive model of PTSD cannot incorporate too many predictors, not to mention the decomposition of a model; and MA is conducted via either a fixed- or random-effects model. Nevertheless, the four studies expanded to endorse diverse computational methods. The advantages are discussed in the following three sections (6.2-6.4).

6.2. Necessity for the Computational Phenotyping of Trauma-related Phenomena

As stated in the introduction to computational phenotyping (section 1.5.1), a phenotype is a trait or a phenomenon that researchers are interested in studying. Phenotyping in short is the method or procedure that describes a phenotype. Methods of phenotyping a same

phenomenon can be various. For example, trauma appraisal, i.e., a person's opinion regarding their experience of trauma, is an important phenotype in PTSD research and devising a self-report questionnaire to measure trauma appraisal is phenotyping. Theoretically, trauma appraisal can also be described by the speech of a person talking about the traumatic experience.

In essence, methods of phenotyping are the lenses that shape how we look at a phenomenon. When the lenses are taken for granted, it can be difficult to distance ourselves from them and see a phenomenon differently. Although classical methodologies are valid means (e.g., self-report questionnaires), they are not necessarily the most optimized options. The trajectory study is a good example. Whereas symptoms can be described by scores at times, trajectory modelling integrates time more compressively. Given the ongoing AI revolution that is consistently pushing methodological boundaries, it is important to re-examine the key concepts in PTSD and see whether new methods could offer new perspectives to look at the crucial phenotypes such as post-traumatic symptoms, trauma memories and trauma-related cognitions. In this section (6.2), we elaborate why new methods of phenotyping are necessary. In the next section (6.3), we explain what the studies in the thesis did, and why they provide solutions to those requirements.

6.2.1. **Symptomatic course and individual differences**

Precise descriptions of symptoms are important as the first step to understanding a condition. In chapter 1, we proposed PTSD as a function of time and the environment. It can be simplified to PTSD as the function of time when the interest is to record the presentations manifested in persons rather than to explain them. In chapter 2, we elaborated why a snapshot of symptoms would not be sufficient to reflect the concept of PTSD, and that any legitimate solution should combine the dimensions of symptoms as well as the dimension of time.

This principle should hold for individual differences too. The ability to give an account of the differences in trauma responses would ultimately solve a large piece of the puzzle of

PTSD etiology, but its success depends on the correct identification of differences. If PTSD is a function of time, constructs of individual differences will also constitute time accordingly. Furthermore, the term "difference" suggests relativity and the definition of what is normal or healthy functioning serves as a critical baseline or reference in pathology research. Hence, being able to give a normative account of trauma responses is another condition that new methods need to meet.

6.2.2. **Trauma memory**

From "structure of fear memory" in EPT, "SAM" and "VAM" in DRT, to the "nature of trauma memory" in the cognitive model, "maladaptively stored memory" in AIP, and the mnemonic model, trauma memory is clearly a core component to PTSD. A growing body of research focusing on the relationship between acute stress and episodic memory found that stress prior to or during encoding impairs memory, and stress prior to or during retrieval also impairs memory. These effects are larger for emotional materials than neutral materials (Shields, Sazma, McCullough, & Yonelinas, 2017). Moreover, exposure to a significant psychological stressor preserves or even enhances memory for the emotional aspects of the event, and simultaneously disrupts memory for non-emotional aspects of the same event (Payne et al., 2006). These findings are consonant with the key characteristics of trauma memories that are thought to be highly emotionally valanced, selective and less coherent. Thereby, we can deduce that trauma memory is impaired episodic memory, and that the level of memory impairment should predict severity of PTSD.

However, unlike research conducted in the laboratory, where memory impairment is measured by the accuracy of recall or recognition tasks, it is practically impossible to measure memory impairment in the same way for a real-life event, as there are no objective records to compare with. Moreover, episodic memories, once reactivated, are subject to behavioral and physiological inference. Memory will go through another round of consolidation that integrates

new information presented after reactivation, via behaviors and psychological states. In other words, memory is labile and susceptible to influences from later physical and mental conditions (Nader, Schafe, & LeDoux, 2000; Scully, Napper, & Hupbach, 2017). Therefore, due to the retrospective sampling method typically used in PTSD research, memories about the traumatic event can only be treated as a reflection of a person's present mental states rather than an accurate record of the past event. Thus, a way, and the only way, left to bypass the impasse is that research needs to study trauma memory in its own right.

Previous studies on the subject of memory deficit in PTSD populations, already found evidence for characteristics like compromised verbal memory, lack of specificity, and disorganized, fragmented autobiographical memory recall (Brewin, 2007, 2011). These findings offer promising directions to advance the investigation of characteristics in trauma memories whereas they require sophisticated interpretations and analytical techniques. At present, research in this area suffers from the lack of reliable and efficient methods in order to extract complex constructs from unstructured data like memory narratives on a large scale; however, once the methods become available, trauma memory may conceivably be directly used to index the severity of PTSS.

6.2.3. **Trauma-related cognitive processes**

Two studies, the trajectory study and the NLP study, examined the role of cognitive appraisal. The trajectory study found negative appraisal of trauma during the acute phase was the only risk factor shared between high PTSS and depression trajectory groups, and in the NLP study, the correlation between appraisal and PTSS not only occurred in the early phase but persisted at six months post-trauma. Besides appraisals, trauma-relative appraisals and other cognitive processes explain PTSD presentations as well as secondary emotions such as anger, guilt and shame (Lee, Scragg, & Turner, 2001). According to the cognitive model of depression, cognitive biases like selective attention to negative stimuli, greater perception for

negative information, are accountable for depression (Disner, Beevers, Haigh, & Beck, 2011). The findings of the trajectory study indeed suggest that negative appraisal might also be behind PTSD-depression comorbidity.

Despite the significance, measuring cognitive appraisal processes appears to be an arduous task. Questionnaire administration is currently the primary way to measure cognitive appraisal processes; because there are many distinctive cognitions (e.g., appraisal of the event, appraisal of the responses, rumination, thought suppression, self-blaming, adaptive thinking etc.), each of which require their own specific measures, immense effort will be spent to developing, validating and evaluating questionnaire-based measurements. Inevitably, this causes lags between the processes researchers want to investigate and the measures at hand. Such impediments can be noticed in the trajectory study where a few cognitive appraisal measures (e.g., self-blaming, thought suppression, rumination) did not have validated psychometric properties. The discrepancy hinders research on the roles of cognition in PTSD and raises the question whether there are other methods to measure trauma-related cognitions besides self-report questionnaires.

6.3. Solutions to Computational Phenotyping Trauma-related Phenomena

The previous section outlined the need for methodologies that are able to either support the conceptualization of PTSD or to provide normative measures for trauma-related phenomena. Two empirical studies (trajectory study and NLP study) utilized advanced methods to consider these issues. We now discuss them from the computational approach perspective and their implications for research of developmental courses, individual differences, trauma memory traits and trauma-related cognitive processes.

6.3.1. **Trajectory modelling**

The trajectory study demonstrated that trajectory modeling on PTSD symptoms was able to solve the time dimension problem competently. The notion of trajectory intrinsically integrates the passage of time, making it an ideal option to phenotype the developmental course of PTSD symptoms. Because of the time-sensitive nature of PTSD, PTSD studies are mostly prospective and inspecting trajectories is common, but the conventional approach does not necessarily involve computational modeling (Santiago et al., 2013; Solomon & Mikulincer, 2006). The benefit using a computational technique that integrates multiple points mathematically, is that trajectory modeling identifies latent heterogeneous groups that would be otherwise too complex to detect. Moreover, when Bonanno (2004) proposed the four prototypical trajectories of disruption in normal functioning across time, following potentially traumatic events (PTEs), he stressed that the reason why symptoms should not be isolated from time is because what is typical or atypical in trauma responses can only be decided by symptomatic courses. He predicted that the majority of PTE exposed populations fall into resilience and recovery groups (Figure 6-1) which should be considered as normal, and a review on trauma trajectories studies supports the prediction (Galatzer-Levy et al., 2018).

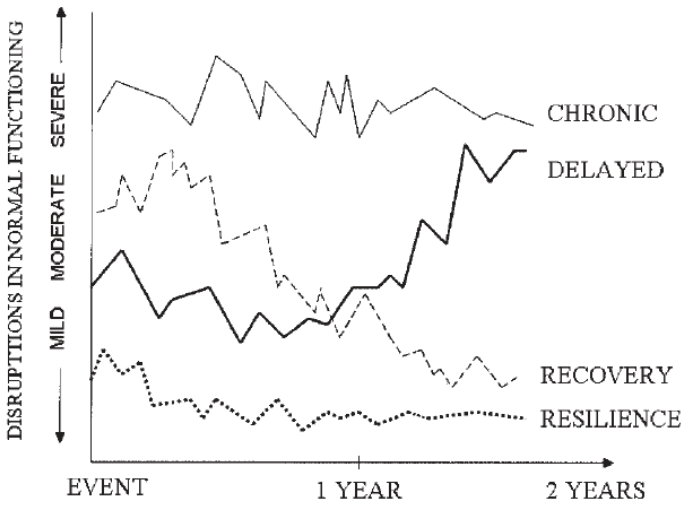


Figure 6-1: prototypical patterns of disruption in normal functioning across time following personal loss or PTEs (Bonanno, 2004)

From its establishment, the concept of trauma trajectory (Bonanno, 2004) originated from the motivation to address normal as well as pathological reactions; therefore, trajectories in essence portray normative individual differences. More importantly, trajectory modelling is not limited to PTSD symptoms: practically, it can be applied to any trauma-related features. For example, various post-traumatic reactions such as trauma narrative coherence or cognitive appraisals, can be built into models. Their trajectories will capture individual differences in trauma reactions of different aspects and their relation to symptom trajectories might reveal underpinning processes responsible for PTSD development and maintenance.

6.3.2. **Nature language processing**

In a previous section on trauma memory (6.2.2), the argument was made that studying features of trauma memory is critical, as PTSD is fundamentally a disorder of impaired memory. In the NLP study, computational methods (nature language processing in this case) demonstrated the powerful capacity of phenotyping two key elements of PTSD: narrative coherence that indexes memory impairment and cognitive appraisals that have been demonstrated to maintain PTSD, and possibly other post-traumatic psychopathology. Notably, the two phenotypes are derived from trauma narratives that act as a probe task through which data are collected. When expounding the necessity for computational phenotyping, we highlighted the difficulties in measuring cognitive processes by questionnaires (6.2.3). As stated in chapter 3, trauma narratives (i.e., relating personal experiences regarding the trauma event) are probably the most accessible way to preserve firsthand trauma memories. Unlike highly structured questionnaires that are designed to measure specific construct(s), trauma narratives are the products of high level cognitive/emotional processes working together in a relatively natural setting. As long as methodologies permit, narratives are sources of rich data, offering opportunities for all sorts of trauma-related phenotyping. Their merit cannot be overemphasized.

In respect of the specific benefits of NLP methodology, we use the example of the trajectory study and the NLP study. Both studies examined trauma appraisals but using quite different methodologies. Appraisal in the trajectory study was measured by the self-report questionnaire the CPTCI, which comprises two themes, “permanent and disturbing change” and “fragile person in a scary world”. In comparison, the nature language process method applied in the NLP study is much less explicit or structured. Essentially, NLP depends on the statistics of words/phrases and their associations with negativity in opinions. The associations are extracted from a large human knowledge base such as Wikipedia or movie review database, and there are no discrete distinctions in assessing trauma narratives from other experiences (e.g., watching a movie). The vagueness in this approach, however, should not lead to the view that NLP method is less effective; on the contrary, fuzzy algorithms can better approximate sets of relative or subjective constructs such as "large", "bad" or "beautiful". They attempt to mimic the way humans analyze real-world problems in a heuristic way that relies on vague or imprecise values rather than specific dimensions of absolute of truth or falsehood (Zadeh, 1988). Because fuzzy logic requires large data to inform the analysis, it is only with the rise of machine learning that fuzzy algorithms have become widely implemented, especially in decision making (Korenevskiy, 2015). The NLP study is an experiment that tested whether a similar method can be applied to evaluate cognitive appraisal based on trauma narratives, and the results prove its potential utility.

6.4. Data Mining and Interpretable Machine Learning

Data mining is another important domain of the computational approach that this thesis explored. As mentioned in the introduction (section 1.5.2), the great development in the ability to search for patterns has particularly benefitted areas like genetic and environmental research that inherently deals with large data. The ML study explored the application of machine

learning in the study of PTSD. When data size is not as great, the utility of ML resides in feature screening and model interpretation rather than the speed of handling large numbers of records.

The term "data mining" suggests a non-discriminative inclusion of independent variables in the early stage and multiple layers of filtering in search of a model. In the end, the smaller the number of independent variables (i.e., dimensions) a model composites, the more potential it has for generalization; therefore, this selection procedure is crucial. The variable screening process is conventionally done by human judgment; in a hypothesis-driven approach, stating that a hypothesis can be seen as the same procedure of dimension reducing. However, heuristic discernment is vulnerable to bias and cannot compete with the efficiency of algorithm-directed computing that is capable of incorporating unlimited dimensions. The ML study managed to reduce the number of predictive variables from the original 23 to 13. While it may not seem impressive by the standard of ML, it has far exceeded the number of variables that a conventional model in the field is able to examine or take in.

The goal of building a model is usually two-fold. From the *utility* perspective, a model is often used to predict outcome(s) of unknown information that is already known. From the *understanding* perspective, a model is used to investigate relations between independent and dependent variables. As demonstrated by the ML study, IML is particularly helpful for this purpose. IML techniques like PDP depict predictor-outcome relations, and the Shapley importance allows the comparison of predictor variables, both of which provides highly informative methods to how a model should be interpreted. Using the example of the ML study, PDP revealed interesting non-linear connections between predictors (e.g. age, acute symptoms) and the risk of PTSD. The finding first explains why the RF model improved prediction performance considerably, even the predictors that do not differ much from conventional models. Second, it reminds us that linear approximation is useful and that non-linear association is probably a more common relationship than linear correlation between any two

given variables. If the linear assumption gives descriptive, crude and directional results, dropping the linear assumption is necessary in order to enhance accuracy.

6.5. Understanding of PTSD

Since each study has thoroughly explored the theoretical and clinical implications with respect to the specific research questions, this extended discussion will look at all the findings from the empirical studies to address one of the questions raised at the very beginning of the thesis: individual differences in stress symptoms as responses to trauma. Individual differences can be further broken down into two questions: Q-1) why and how do individuals develop different responses to trauma exposure in the first place? and Q-2) why and how can someone recover from the initial stress while someone else's symptoms continue or even deteriorate?

6.5.1. Acute stress symptoms

Acute responses are a commonly studied component of PTSD. The ML study is a typical data mining application that searches patterns in big data. Despite the initial inclusion of diverse predictors, the final predictive variables concentrated on acute stress symptoms. It is therefore worthwhile to consider acute stress symptoms again.

Recalling the first individual difference question ("why and how do individuals develop different responses to trauma exposure in the first place?"), the question actually implies that there could be a group of people who have gone through a traumatic event and perceive it as life threatening while not presenting with acute post-traumatic stress symptoms. Bonanno (2004) also proposed a resilience group (Figure 6-1) which present mild symptoms for a short period of time before recovery, as one of the four prototypical response patterns following PTEs. But, does such a group exist?

Whereas ample studies have consistently reported positive correlations between peri-trauma panic/perceived threat and chronic PTSD (Memarzia, Walker, & Meiser-Stedman,

2021; Trickey et al., 2012), little evidence was found with regards to peri-trauma panic/perceived threat and *acute* stress. Nevertheless, in the trajectory study, peri-trauma panic was the strongest factor attributed to the high PTSS group compared to the group who demonstrated minimum symptoms across the three time points. A review of PTSD studies of children injured in traffic accidents reported that perceived threat was significantly associated with PTSS at 1-2 months in all the 12 studies it reviewed (Olofsson, Bunketorp & Andersson, 2009). So, it is apparent that perceived threat is associated with acute stress symptoms. This implies that people do not develop acute stress symptoms not because they are more resilient but rather, because the event is not perceived as frightening enough to them.

The other group among the four prototypical patterns that might not display apparent PTSS during the acute phase is the delayed group. Delayed PTSD was listed as a diagnostic subtype of PTSD in DSM-III (1980) but was not retained in DSM-IV or DSM-5. A review on this matter found that delayed-onset PTSD in the absence of any prior symptoms was rare (Andrews et al, Brewin, Philpott, & Stewart, 2007), while another systematic review showed that participants with initial subthreshold PTSD were at increased risk of developing delayed PTSD (Smid, Mooren, Van Der Mast, Gersons, & Kleber, 2009). In brief, delayed PTSD in fact occurs in cases where the subthreshold PTSS has deteriorated.

We can now address Q-1 ("why and how do individuals develop different responses to trauma exposure in the first place?") after eliminating the resilient group because, whether recovery, or chronic, or delayed, all groups presented with *some* acute stress symptoms, and the individual differences basically lie in the different routes taken from the early symptoms. It is then reasonable to expect the physiological, cognitive and behaivoural reactions at the acute stage to be at least partially responsible for the disparities in developmental courses following trauma exposure.

Apart from the cognitive processes investigated in the trajectory study and the NLP study, the ML study also recognized the arousal cluster as a strong influence on chronic PTSD. The hyperarousal cluster encompasses four symptoms: exaggerated startle response, sleep disturbance, irritability and hypervigilance. As mentioned in the introduction, the physiological aspects of PTSD are less well studied: whether they are the mere markers of disruption or they exacerbate other symptoms is unclear. Recent developments in neuroscience suggest that sleep disturbance holds promise for advancing our understanding in this area. For example, a study compared the brain activities in normal sleepers and participants with insomnia when reliving emotional experiences. They found that limbic areas were activated during novel shameful experiences in both groups, but after a week, the reliving of the same experiences did not elicit a limbic response in normal sleepers anymore, while the insomnia group still recruited limbic circuits. The differential activity patterns with new and old emotions in normal sleepers suggest that reactivation of the long-term memory trace does not recruit the limbic circuit, which explains how emotional "hot" memory attenuates and turns into "cold" neutral memory over time (Wassing et al., 2019). Studies like this suggest that sleep supports persistent changes in the neuronal representation of emotional experiences such that they are remembered better and are less distressful when recalled than when they were first experienced. It is conceivable that sleep fragmentation by arousal, a key characteristic of PTSD, could hamper the downregulation of distress and maintain PTSD.

This section has discussed a few important logic issues concerning acute trauma responses and PTSD. Conclusions are summarized below:

1) Any trauma-exposed individual will develop acute post-traumatic stress symptoms;
2) Any individual with PTSD will exhibit stress symptoms during the acute phase;
3) The individual difference question can be revised as: why and how can someone recover from the initial stress while others do not?

4) Post-trauma responses during the acute phase, including physiological, cognitive and behavioral reactions, are crucial to explaining recovery and failure to recover, i.e. the emergence of chronic PTSD.

6.5.2. **Pre-trauma factors and long-term impact**

Pre-trauma factors are included in many PTSD theories, particularly in cognitive theories. In DRT, pre-trauma factors appear as the antecedent knowledge of the world in the social-cognitive account of emotional processing. The conflict between previous experiences and the new information the trauma brings, is used to explain PTSD symptoms. The cognitive model sees prior experiences and beliefs to play important roles in influencing the cognitive processing and behavioral coping during and after trauma, whereas the mnemonic model frames the prior (together with other predispositions) as the factors that affect the way the memory of an event is encoded, maintained and retrieved.

The most tested pre-trauma variables are demographic factors such as age, gender, ethnicity, education level, social-economic status and personal history such as childhood adversity, previous trauma exposure, history of psychiatric disorder. In comparison to peri- and post- trauma factors, these prior variables are relatively weaker predictors of PTSD. In general, they have a very mild to medium magnitude in increasing the risk in all age groups (Brewin, Andrews, & Valentine, 2000; Ozer et al., 2003; Trickey et al., 2012). Correspondingly, two predisposition variables (age and ethnicity) in the ML study had low to medium predictive importance among the 13 features. On the other hand, the same meta-analysis studies showed that personal characteristics that are more salient to psychological processing and functioning, including childhood adversity, previous trauma, psychiatric history and family history, have a larger effect than the other pre-trauma variables.

This observation is consistent with cognitive theories and gives rise to the hypothesis that pre-trauma mental states will have a larger impact on the trauma responses. However, it is

much more difficult to measure fluid psychological constructions than fixed predispositions. The trajectory study looked at pre-trauma emotional wellbeing measured by level of anxiety, sadness, anger, relationship and perceived social support (CPAS). Interestingly, the result showed that CPAS did not correlate with an increased chance of having higher PTSS while it was the second strongest risk factor for depression in the 10 examined variables. A straightforward interpretation would be that poor psychological wellbeing effects depression more than it does PTSD. But this conclusion would be premature if we consider that the "pre-trauma" variable was actually measured retrospectively. In the depression literature, evidence has exhibited that more depressed people tend to recall negative affective experiences more negatively than non-depressed controls (Ben-Zeev, Young, & Madsen, 2009; Colombo et al., 2020). It is possible that the higher depression group reported worse pre-trauma wellbeing, hence the "pre-trauma" emotional wellbeing factor was actually the mirror of current mental conditions instead of a true precursor.

This example represents a stumbling block in PTSD research. That is, because data collection typically only starts after exposure, measures that concern pre- or peri-trauma factors depend on retrospective recalls that are prone to bias and distortion. However, this is not to deny the significance that pre-trauma factors have in PTSD, as mounting evidence suggests pre-trauma stress (e.g., childhood adversities, multiple trauma exposures) increases the risk of PTSD.

An alternative to understanding the impact of pre-trauma factors, in particular pre-trauma stress, is to study the long-term impact of trauma. Although it sounds contradictory, if the time axis in Figure 1-1 is stretched further, the first trauma exposure will become a prior factor when the person has another exposure; thus, through the long-term impact of stress we will be able to make sense of the role of pre-trauma stress in PTSD.

Among the four empirical studies included in this thesis, the MA study considered the impact of trauma on mental health in a different way and did not address PTSD. The study explored the long-term impact of childhood adversities on the risk of developing panic disorder. As PTSD at young age is a form of childhood adversities, and panic disorder is a common mental illness that shares presentations with PTSD, the study can be seen as attempt to investigate the general effect of early stress. An important observation made by the study is that regardless of the type of adversity experienced in childhood, the long-term impacts tended to be homogeneous. In the case of this meta-analysis, the risk of panic disorder in adulthood following childhood adversity was elevated, regardless of the type of adversity experienced. Similar results prevail in associations between ACEs with other psychiatric disorders. Smith and Pollak (2021) recommend that, in order to determine the difference in the neurobiological effects of ACEs, researchers should look at factors such as developmental period and intensity of exposure instead of the *type* of ACEs.

Support for the developmental period hypothesis in comparatively short-term impact can be found in our ML study. The IML analysis revealed that the risk of PTSD six months post trauma surged at age 16, a phenomenon that could be linked to developmental stage. In stress literature, Lupien, McEwen, Gunnar, and Heim (2009) conducted an extensive review on the effects of stress throughout the lifespan on the brain, behavior and cognition. They built a life cycle model of stress based on the activation of the hypothalamic-pituitary-adrenal (HPA) axis during stress exposures. The model attempts to explain why different disorders emerge in populations exposed to stress at different stages of their lives. PTSD research in youth has already paid attention to the influence of developmental aspects and have been seeking solutions to integrate these into PTSD theories (Meiser-Stedman, 2002; Salmon & Bryant, 2002), but understanding of differentials in long-term effects caused by trauma occurring at various developmental stages remains very limited. More research is needed in this area as this

will not only advance knowledge about stress but compensate for limitations in estimating the effect of pre-trauma factors.

In respect of the intensity of exposure, animal and human data show that increased intensity is linked with increased reactivity in brain areas including hippocampus, amygdala, and frontal cortical regions. It also increases responses in the sympathetic noradrenergic, adrenomedullary and HPA (Smith & Pollak, 2021). More importantly, these effects hold for the objective intensity of the stimulus as well as for subjectively perceived levels of stress (Jepma, Koban, van Doorn, Jones, & Wager, 2018), suggesting that these physiological responses could be used to measure intensity. In PTSD, exposure intensity is usually indexed by self-report peri-trauma panic. Peri-trauma panic is a reliable predictor of PTSD (Trickey et al., 2012) but whether the level of panic makes substantial differences in long-term pathology has yet to be ascertained. It also would be beneficial to compare peri-trauma panic cognitions and emotions to physiological measurements such as stress hormones to assess which aspect is a more reliable method to rate intensity.

6.5.3. **Evaluation of cognitive model of PTSD**

Based on the review of PTSD theories in chapter 1, it is conceivable that there are significant overlaps between EPT, DPT and the cognitive model, which all endorse a cognitive-behavioral framework. Given that the three major theories share similar features and the cognitive model provides the most detailed account of PTSD, we only review the cognitive model using the findings from the trajectory, NLP and ML studies.

Evidence for the cognitive model is clear. The three studies examined various aspects of the three main ingredients in the model: trauma memory, appraisals and cognitive/behavioral coping and the results all support the predictions made by the model. With regards to trauma memory, the model acknowledges disorganization as part of the nature of trauma memory while the NLP study confirmed the correlation between coherence level in trauma narrative

and severity of PTSD symptoms. The role of trauma-related appraisals was examined by the trajectory study and the NLP study, both of which showed that more negative appraisals predicted higher level of PTSS. Cognitive avoidance was studied via thought suppression in the trajectory study and was a predictive feature in the ML study. Thought suppression was found to significantly increase the risk of falling into the high PTSS trajectory group whereas cognitive avoidance symptoms during the acute phase was the second most influential factor in the model of 13 features that predict chronic PTSD. Importantly, methodologies used to measure PTSS level, appraisals and cognitive avoidance varied across studies. PTSS level was indexed by self-report questionnaire (UCLA PTSD Reaction Index) scores in the NLP study; in the trajectory study, it was described by the trajectories over nine months, and in the ML study, level of distress was marked according to whether the overall symptoms met the DSM-IV PTSD diagnostic criteria. The degree of negativity in trauma-related appraisals was measured by questionnaires in the trajectory study while the NLP study computed the same construct by NLP modeling. Lastly, cognitive avoidance was rated through a specific strategy though suppression, but in the ML study, it was taken as a gross PTSD symptom based on the harmonized questionnaire items. Applications of different measurements to the same construct are cross validations and they demonstrate the robustness of the findings, which in turn attest the robustness of the cognitive model of PTSD.

Based on our findings, there is no evidence against the cognitive model; nevertheless, the author sees two major defects in the model. Firstly, it neglects the part that the physiological aspect plays in PTSD. In DSM-5, two clusters describe physiological presentations: the intrusion cluster (cluster B) addresses the involuntary memories and the intense physical reactions accompanying the reliving of the memories whereas the cluster E narrates five hyperarousal symptoms (irritability, startle, hypervigilance, concentration problem and sleep disturbance) that are not directly linked with trauma memory. The cognitive model admittedly

acknowledges the bodily feelings but attributes them as part of the "nature of trauma memory". However, the stress literature has found that the brain produces various peptides, steroids and biogenic amines as adaptive responses to stress. These hormones (e.g., corticotrophin-releasing hormone, arginine vasopressin) are released into the brain and circulation during and after exposure. They not only operate as drivers of the stress hormone system but also act as neuromodulators in the brain, affecting higher mental functions including emotion, cognition, and behavior (Blair & Diamond, 2008; Holsboer & Ising, 2010). Following this theory, despite some of the physical feelings being triggered by trauma memory, a large part of physiological reactions is independent of trauma memory; the intrusive, incoherent characteristics of trauma memory are more likely to be the results of stress hormones rather than the cause of them. Interestingly, the cognitive model does not mention the physiological phenomena that can be detached from trauma memory and arousal is not listed as a key component that maintains chronic PTSD. In other words, it includes cluster B but not cluster E. Our model interpretation analysis in the ML study, however, revealed that cluster E (hyperarousal symptoms; cluster D in DSM-IV criterion) had much higher predictive power compared to cluster B (reexperiencing symptoms), and that this pattern holds at the individual symptom level. Whereas feature influence in a data mining model is not equivalent to causality, the pronounced contrast suggests that the physiological aspect is a promising area that deserves more research.

Second, the model relies on appraisals to explain other trauma-related cognitions and emotions. For instance, the model states: "…appraisals concerning one's responsibility for the traumatic event or its outcome lead to guilt, appraisals concerning one's violation of important internal standards lead to, and appraisals concerning perceived loss lead to sadness…" (Ehlers & Clark, 2000). Reasonable as it sounds, according to the data from the trajectory study, the effect of appraisals on other cognitive processes is overstated. More precisely, the trajectory study measured the levels of four post-traumatic cognitive processes: rumination, thought

suppression, adaptive processing and self-blaming. We list their crude linear coefficients with negative trauma-related appraisals (measured by CPTCI) and arousal (measure by score of CPSS arousal subset) respectively in table 6-1. It is evident that appraisals do correlate with most other trauma-related cognitions, but their magnitude is far weaker in relation to those with arousal. Of course, it can be argued that the CPTCI does not reflect the specific type of appraisal that gives rise to rumination or adaptive processing but except for the intuitive speculation proposed by the model, there is no study to suggest what appraisal leads to what cognition. On the other hand, more direct connections between the stress hormone and cognitions such as rumination and negative thoughts are supported by empirical studies (Zec, Antičević, Lušić Kalcina, Valić, & Božić, 2022; Zoccola & Dickerson, 2012).

Table 6-1: correlations between cognitive processes and appraisal vs correlations between cognitive processes and appraisal and arousal

	Appraisal (CPTCI)	**Arousal (CPSS Arousal)**
rumination	.129***	.415***
thought suppression	.191***	.658***
adaptive processing	.079***	.303***
self-blaming	.017	.013

*** p < .001

To give another example, when the cognitive mode explains "affect without recollection" (i.e. a person experiences emotional/physical distress without awareness of the reactivation of trauma memory), a phenomenon that can be easily accounted for by the physiological route, the model says: "…retrieval from associative memory is cue-driven and unintentional so that the individual may not always be aware of the triggers for reexperiencing …and may not be aware that his/her emotional reaction is due to activation of the trauma memory…". Such a statement cannot be falsified.

To summarize, the cognitive model of PTSD withstands scrutiny regarding the cognitive-behavioral aspects. That being said, as it predominantly omits physiological factors, it counts on cognitive appraisals functioning as the fundamental drive to explain the cognitive, emotional and behavioral presentations in PTSD. Although appraisal-based explanation is not necessarily wrong, as we have argued, it is less optimal in explanatory efficiency in comparison to the alternative inducing physiology-cognition/behavior route.

6.6. A Preliminary Computational Model of PTSD

Through the four studies - phenotyping post-traumatic responses, indexing trauma memory impairment, predicting chronic PTSD and searching long-term impact - we have so far demonstrated how computational methods are powerful tools to study PTSD in new ways. Computational approaches, however, are not just methodologically incisive; they offer a new theoretical perspective through which to look at mental dysfunction (computational modelling, section 1.5.2). We thereby introduce a provisional computational model of PTSD as our tentative attempt of moving towards a computational perspective. Based on the arguments made in the previous sections, the model makes two assumptions: 1) PTSD is caused and maintained by impaired memory related to the trauma event; 2) all trauma-exposed individuals develop acute stress; the main task of the model is to explain individual differences following the initial period of acute stress in the development of chronic traumatic stress symptoms.

First, we present a computational framework to look at interactions between the environment and a living organism. Figure 6-2 illustrates the exchange between environment and human brain, where the exchange is mediated by sensory and active states (e.g., behaviors). More precisely, external states are behind the mediating layer; internal states gain knowledge about the external states by inferring the hidden causes of sensory states and actively influence those causes (i.e., active inference) (Friston, 2013). Notably, the layer formed by sensory states and active states is called a Markov blanket or Markov boundary.

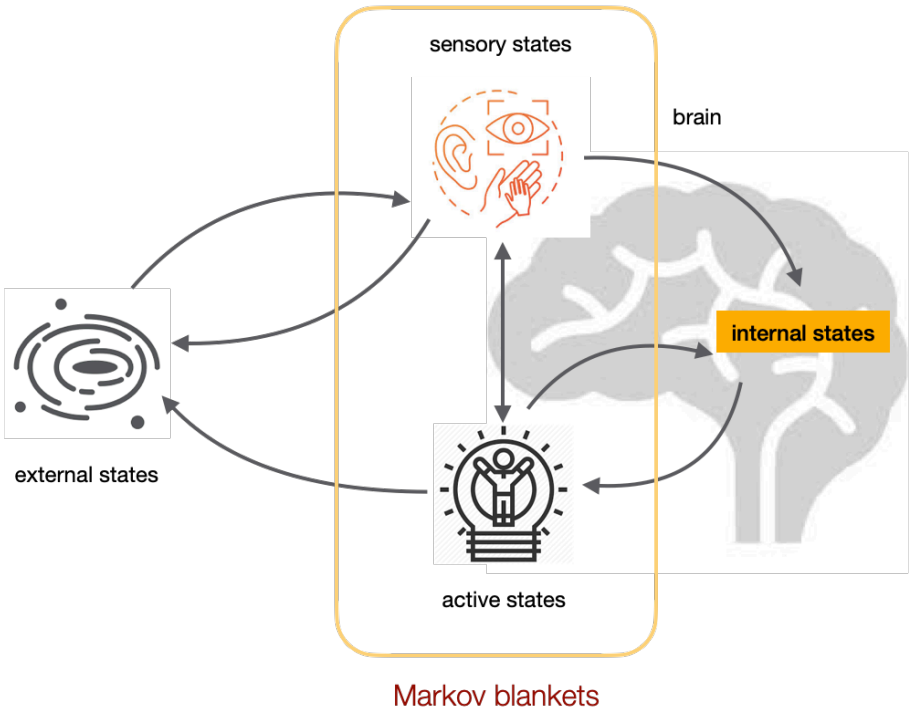


Figure 6-2: exchange between environment and human brain

Pearl (1988) first coined "Markov blanket" to describe the minimal set of variables required in order to infer the state of a variable in a Bayesian network. A Bayesian network is a probabilistic graphical model that represents a set of variables and their conditional dependencies via a directed acyclic graph (DAG) . In DAG, if a node (P) has a line pointing to another node (C), then P is C's parent and C is P's child. In figure 6-3, let variable A be the target variable, information from the subset of A's parent nodes, children and children's other parents is enough and other variables are irrelevant to extrapolate the state of A. Variables in the dashed circle constitute a Markov blanket of A. Applying the definition to figure 6-2, one can conclude that the sensory states and active states make up the Markov blanket of the internal states.

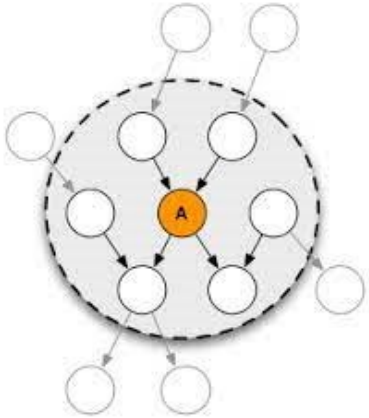


Figure 6-3:Markov blanket

As human mental states sit in a complex network of innumerable factors, having this boundary is immensely helpful when screening variables that are pertinent to the variable of research interest. More importantly, Friston (2010) synthesized brain theories in biological and physical sciences to put forward the free energy principle (FEP). Free energy denotes "the difference between the probability distribution of environmental quantities that act on the system and an arbitrary distribution encoded by its configuration" (p. 127). The FEP states that such systems always try to minimize free energy by changing its configuration to affect the way it samples the environment or changes the distribution it encodes. In the case of human beings, the FEP can be translated as: the environment is a set of factors that can affect an individual, and the individual develops their models of the external environment through sensory and active states. These models are part of the internal states and the difference between environment and internal modes is called "surprise". Abiding by the rule of FEP, we are compelled to reducing surprise to self-evidencing. That is, we are always actively seeking evidence to support our models of the world. Self-evidencing is achieved by active inference, the processes whereby the individual changes their perceptions of the environment or changes the environment, which in turn alters the sensory states or updates their models of the environment.

Although the theoretical framework is constructed in a computational architecture with technical terms, the interpretation of FEP at a high human behavioural level matches psychological theories closely. It is known that the brain is a result of environment, and evidence like neuroplasticity from neuroscience suggests the brain is able to change and adapt based on experience. According to the cognitive theories, individuals form schemas about themselves, other people and the world throughout life experiences. These schemas function as inner models that shape one's perceptions as well as steer their behaviors. Applying the FEP framework, a person in general tends to avoid changing schemas once they are established. The inner models are maintained by active engagement with various mental and behaivoural activities (e.g., selective attention). Clinically, individuals hold rigid models that do not reflect environment accurately are more prone to cognitive biases and mental illnesses. For example, attention to negative information is linked to depression.

Likewise, in Figure 6-4, we transformed the maintenance of current threat from the cognitive model into a similar network. The central component of the model is trauma memory, as the model takes the position that PTSD is a disorder of impaired memory. Physiological, cognitive and behavioral reactions are active states and physiological feelings are listed as part of the sensory states. Moreover, internal states include another key element: models of environment to represent the sum of current and prior experiences. The model proposes that trauma exposure or the external environment after the trauma event are excluded from the Markov blanket, indicating that they are immaterial to estimating the state of trauma memory or models of environment. Essentially, if active inferences such as cognitive/behavioral avoidance, negative appraisals, sleep disturbance and so on, manage to sustain the idiosyncratic models of environment that the world is too dangerous and too threatening for the person to deal with, then the emotional part of trauma memory cannot be attenuated and impaired memory will not restore; therefore, elevated stress symptoms are retained or deteriorate.

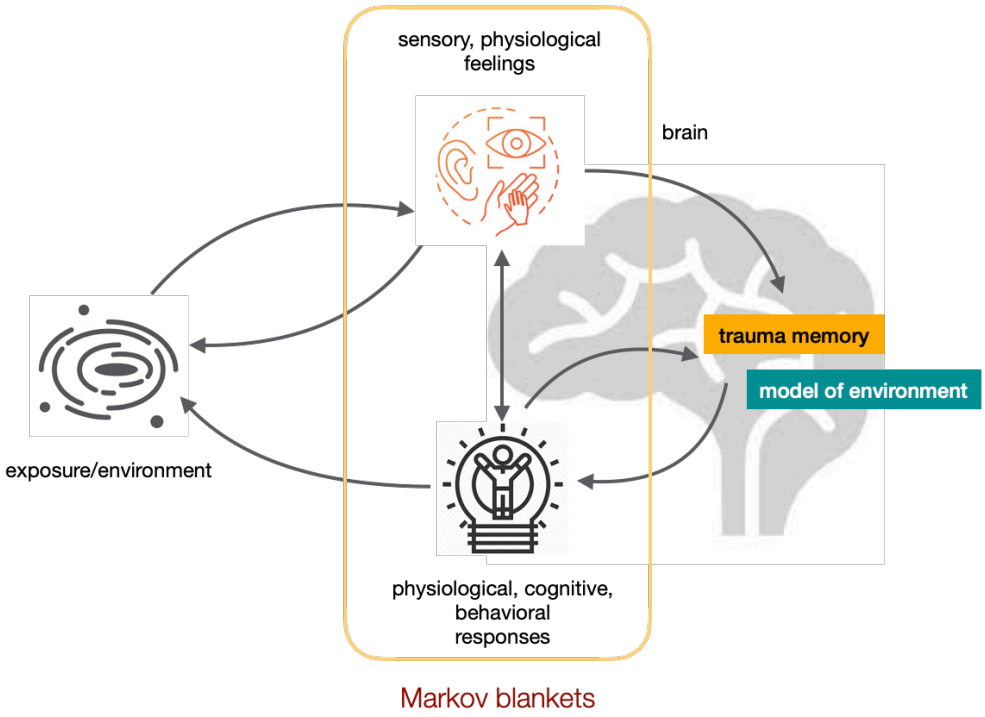


Figure 6-4: Maintenance of trauma memory

This model does not appear to differ much from the cognitive model of PTSD except for reframing the components and rearranging their positions. We expound its advantages as follows. Firstly, since the model is derived from the most successful model of PTSD, components in the model and their relations are tested and supported by empirical data. Secondly, employment of the Markov blanket diagram warrants a parsimonious account for the maintenance of PTSD. Thirdly, by incorporating models of environment, the model solves the retrospective sampling problem of prior trauma factors. It also embraces conscious as well as unconscious processes since models of the world can be at any level of the brain function hierarchy. Fourthly, as illustrated in figure 6-5, the FEP has suggested a set of unified formulae acting as constraints that can narrow down the search for explicit patterns in specific human behaviours. Lastly and most importantly, FEP theory assumes that active inferences are Bayesian inferences; as a result, mental functioning can be expressed by probabilistic models and operations of internal and blanket states. For example, model evidence can be simply computed by $\mathrm{p}(b|m)$, i.e., the probability of a particular blanket state if the model is true; value

in RL can be denoted as: - F (b, μ) = ln p($b|m$) while surprise is the negation of value, i.e., F (b, μ) = - ln p($b|m$).

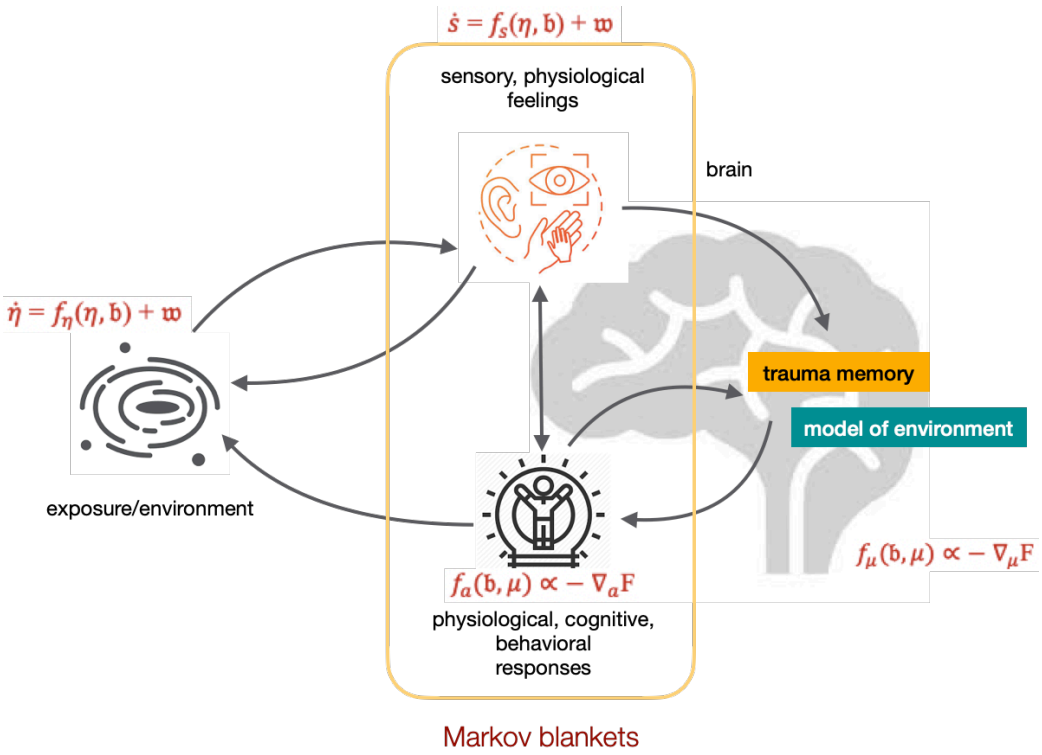


Figure 6-5: Computational model of PTSD. η: external states; μ: internal states; s: sensory states; a: active states; b: blanket states; m: Markov blanket

Fully unpacking the technique details of the FEP is beyond the scope of this thesis. Evidence supporting FEP mostly comes from studies in perception; whether FEP applies to high level mental functioning is yet to be tested. Even if FEP holds in human behaviours, there is a long way to go before researchers identify FEP functions that can be practically utilized in building the details of the model. Nevertheless, the message that we wish to convey is that following the steps of FEP, this computational model of PTSD, albeit preliminary, makes a leap from classic psychological models that are bounded to crude qualitative explanations and predictions, to models that are capable of giving complete, precise and quantitative accounts of a dynamic explanation of the etiology of PTSD.

7. Chapter 7: Limitations and Future Research

"The highest forms of understanding we can achieve are laughter and human compassion."

- *Richard Feynman*

The computational movement in mental health research is only just emerging; many methodological issues may overshadow its application. Some of these issues are due to the nature of the methods themselves while others can be classed as historic reasons. This thesis reflects these struggles and the limitations are reviewed in this chapter. In addition, two PTSD-specific limitations are discussed as they are above the individual study level and are linked with some of the points made in the discussion (chapter 6). Last, the chapter and the thesis conclude with an outlook for the prospect of the computational approach in PTSD and the short/long-term tasks the field needs to address.

7.1. Building a Cohesive Body of Knowledge

Data-driven research is the primary method in the computational approach. While it yields more robust patterns, the downside is also clear. Because the pattern that will emerge is unknown and the type of pattern feasible for inspection depends on the availability of data, it is difficult to design studies that are logically cohesive. For example, the ML study suggested that acute hyperarousal symptoms were important predictors, as might be expected. A study looking into biological measures such as heart rate, stress hormones should be followed, but physiological data are scarce in PTSD research, and it was not possible to design or conduct such a study to be included in this thesis. Whereas data-driven studies may appear to be disjointed in the short-term, in the long term, unified insights about a phenomenon will eventually be formed.

The four studies included in this thesis represent this loose connection when the number of planned studies is small. The trajectory study analyzed symptomatic courses and the cognitive factors associated with high symptom groups; the NLP study checked PTSS and memory coherence and appraisal extracted from trauma narratives; the ML study built a model to predict chronic PTSD, then broke down the relationship between variables in the model; the MA study synthesized the risk of childhood adversities to panic disorder. Among the studies, one is not successive to another regarding the research questions, and there are insufficient overlaps between the dependent/independent variables that allow the overall discussion to stay within a focused scope. Even within studies that share computational methodologies as a common feature, the specific methods are diverse. The thesis has to take a broad angle to include all computational components and all PTSD major theories to pull the studies together. Inevitably, evidence supporting/against certain speculations is reduced.

7.2. Using Cross-study Secondary Data

The trajectory study, NLP study used secondary data that have been collected for a particular project, then made available for this thesis; the ML study used a cross-study data depository and the MA study is also a secondary data study, as meta-analysis operates the results of existing studies. Whereas they are all secondary data studies, the ML study differs from the trajectory and NLP study in respect of data processing, and in a way shares some similarities with the MA study. The main reason behind the difference is that data in trajectory and NLP study came from one source while those of the other two studies came from multiple sources. In particular, the ML study went to great lengths to process the data during which a number of challenges arose that are common when using cross-study secondary data. These are summarized as follows.

7.2.1. **Quantity vs quality**

One of the reasons for utilizing pooled data is that larger data promote robustness of findings; therefore ,the principle of data inclusion is to have as many observations as possible, at the same time. However, involvement of more studies increases heterogeneity, a major setback to the quality of data. Given that sample size and heterogeneity are mutually exclusive, it takes fine judgment to balance the demands. ML comes with toolkits that can mitigate the damages caused by "messy" data and ML algorithms are in general more tolerant to less formalized data. Nevertheless, ML is not immune to the heterogeneity problem. Moreover, in meta-analysis, a type of study synthesizes cross-study data, assessing and reporting data heterogeneity is a routine procedure so that conclusions are interpreted within the appropriate context. However, no protocol is established in machine learning applications using cross-study data to address the concerns for data heterogeneity. There is also a lack of tools with which to evaluate the potential impacts to the downstream analysis between choices in order to inform decision-making; researchers hence have to rely on common sense, expertise or sometimes arbitrarity. For example, the ML study looked for data with PTSD diagnosis after 6-months post-trauma and there are studies conducting assessment at 6-9 months, 10-12 months and even longer. They are theoretically all eligible for inclusion, considering the major source of heterogeneity is PTSD measures rather than sampling times. In this study, the decision was taken to include records with diagnosis at as late as 15 months after exposure. However, without means of estimation, it is hard to judge whether the justification is reasonable, and with many ambiguous situations like this, errors can accumulate and amplify.

7.2.2. **Data harmonization**

Data harmonization is a procedure that cannot be avoided when using cross-study data. In the ML study, the primary task of data harmonization is to unify the measurement of PTSD symptoms. For various reasons, the child and adolescent PTSD literature uses a vast selection

of questionnaire-based measures, some of which are compatible with DSM-III, DSM-IV and DSM-5, and some of which do not follow any particular diagnostic criteria. Given that inconsistency at the measurement level is irreparable, the overall strategy was to break down the measures into items and map each of them onto the acute symptoms listed by the latest DSM-5 diagnostic criteria for PTSD. The implementation had to solve problems at the meaning (i.e., content), scale and missing data handling levels; these problems are outlined in greater detail below.

The meaning problem is about how to determine which item(s) measures which symptom. In usual cases, expertise is sufficient to develop the mapping, while it does not always guarantee consensus over some symptoms described in ambiguous terms, for instance: “an altered sense of the reality of one’s surroundings or oneself”. The ML study relied on a previous study that was coincidentally able to give a complete solution; but in many similar situations, researchers face novel challenges so that existing expertise will need a fallback system to catch the exceptions that cannot be solved solely by an individual researcher or a team.

The scale problem arises from the fact that measures have different scales. For example, a score of 2 on a scale of 1-2-3 is different from the same score on a scale of 0-1-2. To unify the scores of different scales, the original scores were transformed to a decimal between zero and one by dividing it by the maximum scale of the measure, i.e., score of 2 at a Likert scale of 0-1-2-3 will be .667. Although it seems straightforward, the conversion introduces a shift in the distributions of the unified score across studies. Precisely, if the multi-item symptoms which used the mean value are ignored, the possible converted values from a 3-level scale are (.33, .67, 1) and (.25, .5, .75, 1) from a 4-level scale. Even in a hypothetical scenario where the true distribution of the symptoms from the two studies are identical, because the levels in the measures are small (<= 4), the distributions cannot be smoothed out easily; as a result, more

errors will be introduced and the adjusted distributions will not be the same. Figure 7-1 shows that the distributions of two studies can be vastly different.

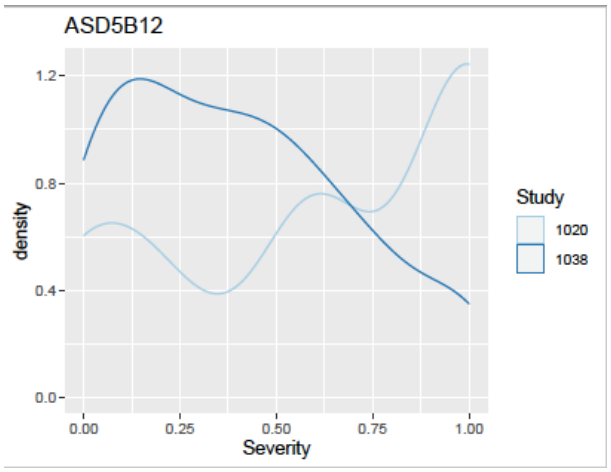


Figure 7-1: Distributions of hypervigilance scores from two studies after scale transformation

The third problem is missing data. Imputation is well developed and in general, is competent enough to make up the missing values. The basic idea of imputation techniques is to make reasonable guesses based on existing data and then applying sampling strategies to generate the missing data. But some early measures do not contain items for newly defined symptoms in DSM-5; therefore, for certain studies, all values of a symptom will be missing, meaning that imputation at the study level will not be possible as there is no data to inform the guess. As a solution, imputation was carried out at the pooled data level; in other words, all studies were assumed to follow the same distribution, which is obviously violated given the sample in Figure 7-1.

7.2.3. **Mitigating heterogeneity**

Data heterogeneity is inevitable, and the study tried to mitigate its impact. Besides the usual measures to control the nature of the studies, technical solutions were also sought. In clinical studies, differently calibrated measuring instruments and different demographic distributions are the usual factors to document/index? heterogeneity. In a recent study, Zhou et al. (2018) explored the method of shifting the distribution of one study to be in more accordance

with another. They correctly identified that age significantly contributed to the distributional difference of the two protein levels in Alzheimer data. They then successfully transformed the data from one study and rendered them more harmonious with one another (Figure 7-2).

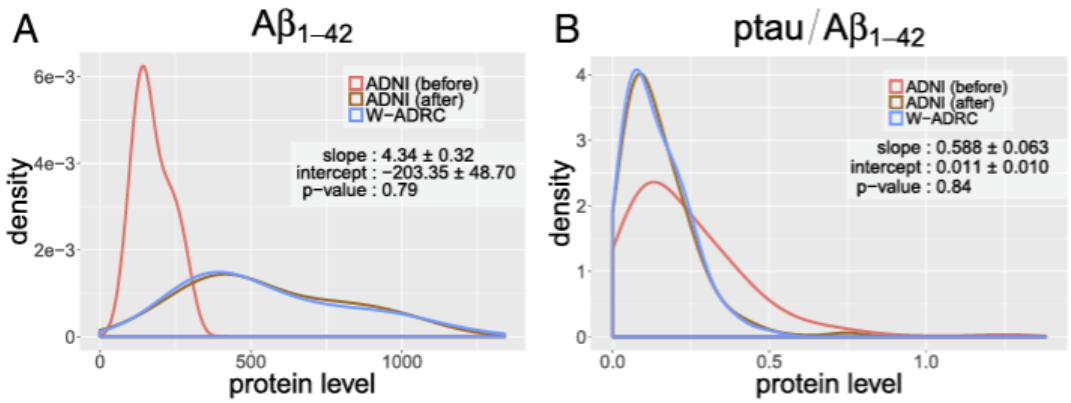


Figure 7-2: shift distributions of two protein levels from ADNI study towards the another (W-ADRC) study using identifiability conditions. The shifted distribution (brown) matched the target distribution (blue) nicely (Zhou et. al, 2018)

Zhou et al.'s study gave explicit identifiability conditions using a graphical causal model and executable algorithms to make the shift, a method followed closely in this study. Evidence in the literature suggests that age, trauma type and gender might explain the distributional differences between studies; a shifting algorithm was therefore applied using the identified three parameters. In the end however, the distributional differences could not be reduced by this method, possibly because in PTSD, age, trauma type and gender are not sufficient to account for the differences.

Overall, the ML study suffered a lot of issues using cross-study data. The difficulties are in part because of the novelty of the study; lack of systematic support in the data processing method also exacerbated the difficulties. Moreover, although peer-reviewed studies are a valuable source to learn from others' experiences, details of data processing are often compressed into very few lines of description, and organized communication on the topic is scarce in the field, making the building of a shared knowledge base regarding data harmonization practically stalled.

7.3. Trajectory Standardization

Computational phenotyping of PTSD phenomena is an important theme of the thesis and trajectory modelling has been shown to be a good option to phenotype post-traumatic responses. The advantage of computational phenotyping is that it provides a formative description of a phenomenon so as to facilitate data sharing and comparison. Although trajectory modelling has seen many successful applications in the PTSD literature, without standardizing the configurations, the purpose of big data sharing cannot be fulfilled. Specifically, the sampling times and the number of sampling times shape the structure of trajectories; trajectory modelling requires longitudinal data sampled at minimum three times, but there is no agreement on how many sampling times and what times a standardized trajectory should encompass to generate the most representatively structured trajectories. Furthermore, the absolute value on the y axis depends on the reading that measures the phenomenon, which again is not normalized. Consequently, the absent specification and normalization determine the description of a trajectory to be purely verbal (e.g., "recovery", "persistently low", "chronically high", etc) and quantitative comparison to be impossible. It is not surprising that the authors of a review of PTSD trajectory studies remarked that making sense of trajectories across studies is like "comparing apples and oranges" (Galatzer-Levy et al., 2018).

The technical part is fairly easy to solve. If a normalized trajectory is assumed to be defined on 4 sampling times of 1 day, 1week, 1 month and 6 months post-trauma with y axis values at range of [0, 1], any trajectory can be denoted as a vector $\vec{T} = (V_{t1}, V_{t2}, V_{t3}, V_{t4})$; the difference between the two trajectories can be operated by $\overrightarrow{T_2} - \overrightarrow{T_1}$. The difficult part, however, is how the PTSD field can work together to reach an agreement on the specifications or on the recommendations for the specifications of a standardized trajectory.

7.4. Data Attrition & Exclusion

PTSD studies usually collect longitudinal data and attrition is a common problem. The Cochrane handbook states that "Missing outcome data, due to attrition during the study or exclusions from the analysis, raise the possibility that the observed effect estimate is biased" (Cochrane, 2022). The delicate part in dealing with attrition is that drop out in clinical studies are often not random. The trajectory study reported that participants with higher symptoms, especially with higher depression symptoms, were estimated to have much higher dropout rate. It is likely that this pattern may persist in most PTSD data, whereas methods to evaluate and adjust the impact from nonrandom attribution are limited. The tool the trajectory study employed is the only one known to the author that offers estimation as well as adjustment, but it is restricted to group-based trajectory modeling and highly tied to the traj program (a STATA software, see details in 2.2.5). In the ML study, substantial data missingness was observed (Table 4-1); while current imputation techniques embrace flexible strategies, they all assume the attribution to be random. As such, the issue could not be properly addressed.

A more visible consequence of the inability of imputing non-random missing values is in the trajectory study. In the study, 10 participants were excluded from T3 as they were referred for treatment due to high symptoms. Although the modeling programme was able to estimate the missing patterns and to adjust the trajectory groups accordingly, the scenario is slightly different from nature attrition. An extensive discussion in chapter 2 was dedicated to the implications of exclusion, highlighting its potential link with the absence of chronic/increase group often presented in other similar studies. An ideal solution would be to build an alternative model upon data with imputed counterfactual values if those participants had not taken intervention, then inspect the original and alterative models for material distinctions. Such an exercise would provide a valuable reference for future studies on whether intentional data exclusion has a real impact on trajectory identification.

7.5. Addressing Unique Questions about Children and Adolescents

The title of the thesis indicates its dedication to PTSD in children and adolescents; in fact, except for the MA study, all studies referred to in this thesis used youth data. At the same time, none of the studies looked at research questions specific to this age group. Developmental factors, for instance, are unique to children and adolescents, while the only two occasions in the thesis that remotely touched on this area are: age being one of the predictors in the trajectory study (chapter 2); and the justification of controlling age in the NLP study (chapter 3). The reasons for this apparent limitation are as follows.

As has been discussed (section 7.1), in building a cohesive body of knowledge there is an inherited drawback of data-driven research, which is that it is bounded by the availability of the data. In order to answer developmental-related research questions, data should be made available to measures of developmental factors like cognitive abilities, linguistic levels or social development and so on. Unfortunately, whereas the idea of incorporating developmental elements into PTSD has been around for decades, apart from age, developmental information is not commonly collected, even in PTSD studies that focus on children; such data was not obtainable for our studies.

While little attention is given to developmental factors, the PTSD literature is nonetheless separated into adults and youth seems to be an unnecessary artefact. Till now, differentials between PTSD in adults and in children, mainly reside in peripheral areas such as children's assessment/treatment/research require consent by parents or guardians and the languages used in these activities need to be adapted. The fundamental theories in understanding trauma responses and the first line treatments of PTSD are exactly the same in the two age groups. With reference to the findings of the thesis, age was not a significant predictor to high PTSS or depression groups in the trajectory study, and no other evidence in

our findings suggest material difference in the cognitive-behaivoural understanding of PTSD in children compared to adults.

This is not to deny the importance of developmental factors in understanding the impact of trauma to young people. Consistent neuroscience evidence suggests trauma occurring at a critical stage has a significant effect on brain structure and functioning. However, translation of the neuroscience findings into mental health is lagging behind. The fact that the thesis has to neglect such a crucial element in youth research reflects the current status of the matter in early trauma literature. Recalling the MA study, even in childhood adversity research, developmental factors are absent from all the studies reviewed. There is an urgent need in phenotyping developmental factors so that links between developmental-specific phenomena and PTSD can be discovered.

7.6. Baseline Selection

The review of acute stress symptoms (section 6.5.1) concluded that the "resilient group" who do not develop stress symptoms after experiencing trauma is less germane to the research of clinical populations. The main reason is that it is unlikely that low symptoms can be attributed to true resilience: symptoms remain low because people in this group perceive relatively low threat during the exposure. In clinical populations where individuals had subjectively threatening experiences, a more cogent comparison is to the group where people are able to recover from the initial stress. This conclusion has an important implication for the baseline selection. In the trajectory study, a set of risk factors associated with the high symptoms groups were compared using the low symptom groups as references. This seemed to be an automatic choice when conducting the analysis since it is the default option for trajectory studies. If the observation had taken place earlier, we would have used the recovery group as the reference group, and the risk factors would have focused on the cognitive processes that differentiated natural recovery and no recovery. Clinically, this approach will be

more meaningful as it reveals factors more pertinent to the recovery process, which could be used in treatment to facilitate recovery.

7.7. Future Research Towards Computational Approach

The limitations of this thesis effectively summarize the problems computational approach in PTSD and mental health research have to address. Nevertheless, the prospect and opportunities opened up by computational research make these hurdles worth overcoming. Three short-term tasks have been identified: data processing protocols, phenotyping and phenotype normalization, and two long-term tasks: causal interpretation and computational modeling for the considerations of future research in PTSD.

Computational research relies on big data but big data without standardization are of no use. The three short-term tasks in brief are to formalize data and the making process of data so that shared data can be utilized effectively. Unlike conventional approaches where studies are relatively more independent, computational research is a collective effort. Phenotyping is to record phenomena in a digital form and phenotypes are the building blocks to studying the links among phenomena.

Besides data, the operations of data like data harmonization also need to be normalized. Computational research is like assembling a machine made of many parts. When the number of the parts is large, small errors will build up and completely overturn the machine. Having data processing protocols would help to reduce the errors introduced by operations on data, to ensure the robustness of integrated parts, i.e. the results.

Ultimately the long-term goals are to discover causality to inform intervention, and to build computational models that advance understanding and prediction. Both of these goals are desirable outcomes, but they will not be a matter of course until solid work focusing on short-terms tasks is accomplished. A thousand miles begins with a single step: it is hoped that this thesis is a single step in the right direction towards achieving this.

List of Tables

List of Figures

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