Computational Psychiatry in Post-Traumatic Stress Disorder (PTSD)

Zhi Qi Lee

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School of Informatics
University of Edinburgh

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Abstract

In this report, we aimed to achieve a greater understanding of the landscape of computational psychiatry in PTSD, because there are no existing papers summarising different models in this field to our knowledge. We first explored the concepts in computational psychiatry in a general sense and the dominant hypothesis of PTSD: (1) abnormal fear learning and (2) exaggerated threat detection. Recent computational studies have used reinforcement learning (RL) models to fit behavioural experiments with PTSD patients. We exhaustively described three model-free RL: (1) Rescorla-Wagner (RW) model, (2) Pearce-Hall (PH) model and (3) Gain-loss model and one model-based RL: latent-state (LS) model. Besides, we discussed the distinctions between these computational models of PTSD. By investigating the current papers on PTSD, which use the quantitative abductive approach of computational psychiatry, we also discussed the research findings obtained using these models. We then illustrate this approach by reimplementing the RW model, following the procedure recommended by Wilson et al. [87] and simulating the experiment of Homan et al. [35]. This approach has shown differences in how prediction errors are weighted in PTSD, in which PTSD assign more weight to prediction errors during learning than normal people. In addition, the PTSD symptom severity score positively correlates with the weightage of prediction error in learning. Those results indicate the component of learning, which is impaired in PTSD, and PTSD can be characterised by abnormal attention to surprising events. Other than that, these findings suggest the possibility of using weight to prediction error as the computational marker of PTSD, which in turn aids the PTSD diagnosis. Moreover, further PTSD studies using RL models with fMRI analysis might explain how the altered neural response to surprising events relates to PTSD patients and help pharmaceutical scientists discover the drug specifically for PTSD treatment.

Acknowledgements

I would like to express my special gratitude to my supervisor, Peggy Seriès, for providing guidance and feedback throughout this project. Thank you for having so much patience with me. You have truly inspired me to be a better person and student.

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Chapter 1

Introduction

1.1 Motivation

Unlike other somatic diseases that could be detected with a blood test or other lab test, mental illness like PTSD does not have a distinct biomarker. The diagnosis of PTSD is based primarily on self-assessment questionnaires and diagnostic manuals such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD). Therefore, the diagnosis might be inconsistent between doctors because doctors might use different decision-making rules. For example, showing a persistent inability to experience positive emotions for a period is a sub-criterion of diagnosing PTSD. Different doctors might interpret "a period" differently. Doctor A might think one week is long enough to tell, whereas Doctor B might think the period is one month. Besides, there is considerable overlap in criteria between mental illness. For example, diminished interest in activities, difficulty concentrating, and sleep disturbance are symptoms of PTSD and depression. Thus, people with the same symptoms might be categorized as having different mental illnesses. All these situations emerged since ICD and DSM are descriptive in terms of symptoms instead of the causes of symptoms. Hence ICD and DSM provide little information about the severity of diseases and treatment design.

However, the situation is improving through advancements in computational psychiatry. Computational psychiatrists construct mathematical modelling of mental illness. They aim to relate symptoms of mental disorders to dysfunction in brain neuro-circuitry and find a quantitative marker that can differentiate healthy people from mental illness patients. Researchers might even address the variability in clinical trajectory and treatment response across patients with the same mental illness with a quantitative marker.

Previous studies of depression in this field have been able to predict patients' clinical outcomes ([27][76]), while Brodersen et al. were able to detect subgroups of schizophrenia patients in their study ([8]). These studies imply that computational psychiatry studies in PTSD can also improve diagnosis and provide treatment guidance.

1.2 Research goals

The main objective of this work is to attain greater knowledge and understanding of computational psychiatry in Post-Traumatic Stress Disorder (PTSD). To realize this principal goal, the following research questions should be answered:

RQ 1: What are the dominant models of PTSD?

RQ 2: What are the current situation of computational psychiatry in PTSD?

RQ 3: What are the distinctions between the computational approaches in those papers?

RQ 4: What are the steps involved when using computational modelling techniques in PTSD research?

1.3 Contribution summary

We do an extensive background reading about the pathophysiology of PTSD and answered *RQ1* in chapter 3 of this dissertation.

To address *RQ2* and *RQ3*, we conducted a literature review on the bibliography of computational models in PTSD. A data search using the specific keywords ”computational” and ”ptsd” was performed on Google Scholar and we downloaded all the publications that appeared on the first five pages of the results. Besides, an additional search on the PubMed, a bibliographic database search engine, with the keywords ”computational model” and ”ptsd” appeared in title or abstract was also performed. We then removed conference abstracts and papers about animal models without computational modeling. Besides, we excluded computational models that were not constructed in accordance with the pathophysiology of PTSD (e.g., models that developed using data-driven approach) from this literature review. In chapter 4, we perform a critical assessment and comparison of the computational models in PTSD studies.

To answer *RQ4*, we set up an imaginary experiment as the setting in Homan et al.’s PTSD study [35] and implemented the Rescorla-Wagner model from scratch accordingly to the imaginary experiment by following Wilson et al.’s guideline [87] in chapter 5.

1.4 Dissertation structure

The remaining chapters is structured as follow:

Chapter 2: background knowledge of PTSD and Computational Psychiatry

Chapter 3: possible etiological model of PTSD

Chapter 4: algorithmic models of PTSD in theory-driven approach

Chapter 5: implementation of Rescorla-Wagner (RW) model

Chapter 6: conclusion

Chapter 2

Background

This chapter provides the background knowledge required to accomplish the work specified in the section 1.2, including clinical account of PTSD and concepts of Computational Psychiatry.

2.1 Post-Traumatic Stress Disorder (PTSD)

PTSD, sometimes known as post-traumatic stress disorder, is a trauma and stressor-related disease. It can develop due to exposure to a potentially traumatic incident beyond a typical stressor. The traumatic incident could be something that directly affects the person or indirectly happens to someone they care about. PTSD can develop even after witnessing a traumatic event. Violent personal assaults, natural or human-caused disasters, accidents, combat, and other types of violence are all examples of events that can trigger PTSD.

After a traumatic occurrence, it is typical to experience panic, fear, guilt, or anger. Some people may experience changes in their everyday routines, such as eating habits, sleeping habits, and personal hygiene habits. Some people may experience concentration issues as well as persistent flashbacks to the traumatic event. These are typical reactions to traumatic events and usually, fade over time. People with PTSD, on the other hand, may experience similar symptoms for more than a month, and the situation may worsen, leaving them unable to lead a normal life.

2.1.1 Diagnosis of PTSD

A psychiatric doctor will interview the person about their subjective experience of the symptoms. A PTSD diagnosis may necessitate long-term monitoring of the person's symptoms as well as various medical tests. Although PTSD does not have a distinct biomarker, these lab tests are done to rule out other somatic disorders and medication use. The diagnosis is based primarily on PTSD self-assessment questionnaires and the experience of the mental health professional. Depending on where he/she practises, the doctor will make an official diagnosis using a diagnostic manual such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification

of Diseases (ICD). However, one multinational study revealed the problem of low concordance across DSM-4, DSM-5, ICD-10 and proposed ICD-11 [80]. Only one-third of PTSD cases satisfied the criteria in all four systems, and another one-third only in one system. In order to capture all clinically meaningful instances of PTSD, the authors suggest that people who meet full criteria in at least one diagnostic criterion should be assessed as PTSD patients.

2.1.2 Main Symptoms of PTSD

The criteria for PTSD in DSM have changed over editions to correspond to the changing in clinical view and scientific understanding. Nevertheless, three main characteristics remain as the core criteria for being diagnosed with PTSD:

- Intrusive symptom:
  Patients replay the traumatic experience involuntarily and intensely through flashbacks, nightmares, or physical sensations such as nauseous and feelings of pain.
- Avoidance symptom:
  Patients avoid thoughts and feelings about the traumatic event and even cues that remind them of the traumatic experience.
- Hyperarousal symptom:
  Patients always feel themselves in a life-threatening situation and find it difficult to relax.

2.2 Computational Psychiatry

To overcome the deficiencies of the current symptom-based psychiatric classification systems, we desperately need a new diagnosis tool which is based on mechanisms and causes. Besides, the new diagnosis tool should be able to explain heterogeneity across patients and answer clinically relevant questions such as treatment response and disease trajectory. Considering all that has been mentioned so far, one may suppose that a new approach to understanding mental illness is urgently required. With recent developments in computational neuroscience, machine learning, and the accumulated scientific understanding of mental illnesses, a new field called Computational Psychiatry is gaining attention. In 2007, the phrase “computational psychiatry” was first used in a paper [78]. The first scientific journal dedicated only to Computational Psychiatry research was established in 2015 [1], and in 2020, Peggy Seriès edited the first introductory textbook in Computational Psychiatry.

Computational Psychiatry is an emerging research field that uses computational techniques to address topics in psychiatry, such as mechanism, diagnosis and treatment of the mental disorder. Generally, computational psychiatry consists of two different but complementary approaches: (a) data-driven and (b) theory-driven [4][38]. We will discuss these two cultures in the following sections and then briefly discuss how the hybrid model, which employs two approaches, could be developed. Besides, our main focus of this dissertation is the algorithmic models of PTSD in a theory-driven approach

which will be reviewed in Chapter 4. Hence we will include a brief introduction about the types of computational model in theory-driven approach at the end of this chapter.

2.2.1 Data-driven approaches in Computational Psychiatry

Data-driven approaches utilise methods from machine learning to answer clinically relevant problems such as diagnostic classification, treatment prediction, and selection [38]. Computational psychiatrists apply the methods to high-dimensional datasets, including medical, demographic, phenotypic, neuroimaging and other data types [54]. For example, under the category of diagnostic classification, computational psychiatrists may employ Support-Vector-Machine (SVM) to identify imaging biomarkers of psychiatric illness [65] and apply pattern recognition methods to neuroimaging data for psychiatric diagnostics [88]. For prediction of treatment outcome, they may use Gaussian process classifiers with neuroimaging data and clinical characteristics in the prediction of the naturalistic course of major depressive disorder [76], employ the mixture of factor analysis (MFA) method with electroencephalogram (EEG) data to predict selective serotonin reuptake inhibitor (SSRI) treatment response for major depressive disorder [41] and use gradient boosting machine with cross-validation and feature selection techniques to predict clinical remission of depression patients [14]. When comes to selection of treatment options, they may use fit generalized linear regression model (glmfit) to assist treatment selection [22] and employ referenced-EEG (rEEG) to aid medication selection for depression treatment [21].

Studies which employ data-driven approaches are promising in clinical application. However, they are like magic black boxes which lack descriptions of the mechanisms underlying clinical symptoms since the free parameters of the machine learning models are not presumed to correlate to any generative psychological process.

2.2.2 Theory-driven approaches in Computational Psychiatry

In contrast to the data-driven, theory-driven part of Computational Psychiatry seeks to simulate the computations performed by the brain with mathematical equations and redefine symptoms of mental illness (behaviours of a psychiatric patient) as cellular or molecular dysfunctions in specific brain circuits (aberrancy in neural activity) [51]. They extend models of normal function (see Figure 2.1) that capture main characteristics of behaviour , neural activity, or both through [52]:

- abductive approach: adjust the model of normal function according to the mental illness hypotheses and choose the most potential hypothesis by seeing which modified models give the best fit to patients' data (see Figure 2.2)
- quantitative abductive approach: find the computational marker of mental illness by fitting the algorithmic model to behavioural data(see Figure 2.3)
- deductive approach: use the most potential hypothesis of the mental illness to construct computational model of the mental illness (see Figure 2.4)

Since the data-generating process is the main interest of these explanatory models, the computational models in theory-driven field are also called generative models [4].

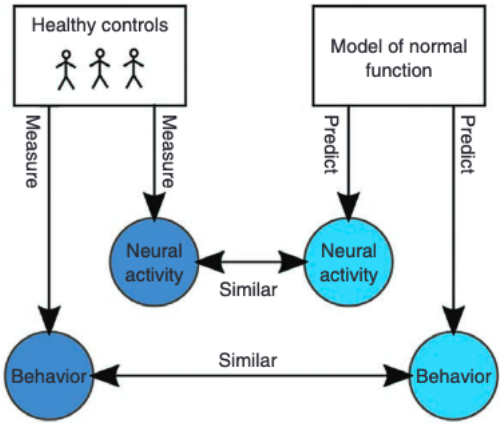


Figure 2.1: Model of normal function from [52]. Prediction of behavioural data from the model must be similar to the measurement of behaviour (for example, heart rate or skin conductance response) and/or the prediction of neural activity from the model must be identical to the measurement of neural activity, such as functional Magnetic Resonance Imaging (fMRI), magnetoencephalography (MEG) or electroencephalography (EEG). Only then can the model be considered a successful model of normal function that grasps the main trait of behaviour, neural activity or both.

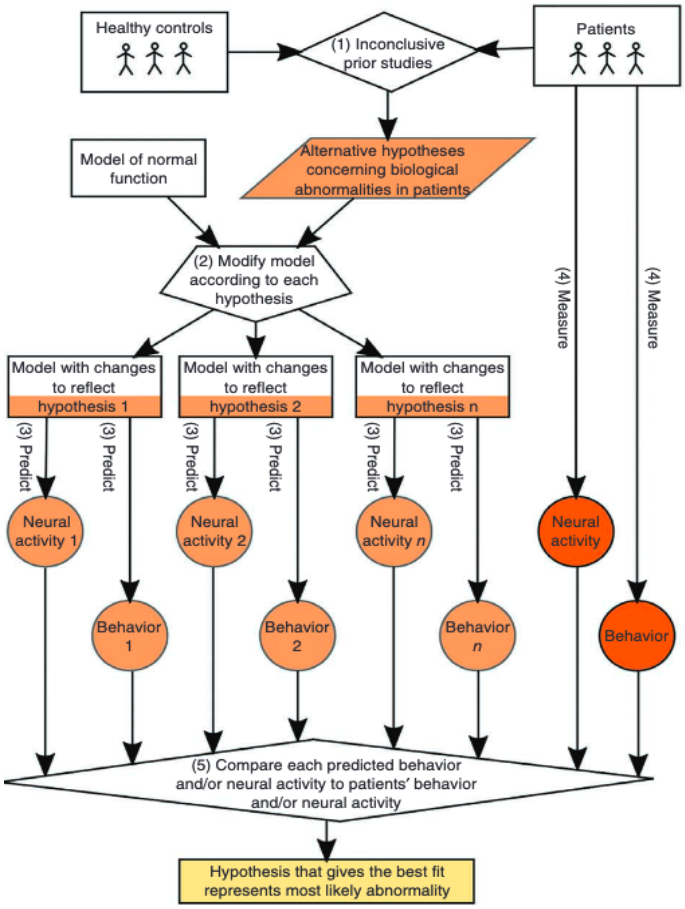


Figure 2.2: Abductive approach in theory-driven field of computational psychiatry from [52]. Given the consequences (the observed disturbances in behaviour or neural activity), abductive approach researchers infer their probable reasons (the latent biological abnormalities). They modify the model of normal function based on each possible hypothesis and fit these models to real patient data. They then use model selection techniques such as Bayesian Model Selection (BMS) to choose the hypothesis that accounts best for the patients' behaviour and/or neural activity. However, the chosen hypothesis is only probably true since the prior studies for generating the hypothesises might be incomplete, and further investigations are required for the hypothesis to become a fact.

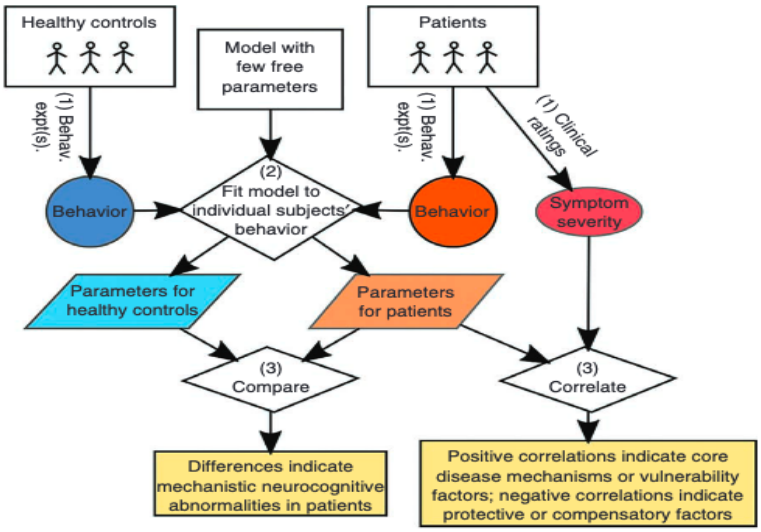


Figure 2.3: Quantitative abductive approach in theory-driven field of computational psychiatry from [52]. For this approach, researchers commonly use an algorithmic model as a model of normal function since this type of model contains fewer free parameters than the neural model. Researchers first collect behavioural data of participants (which consist of healthy controls and patients) from the experimental task(s) in psychology, such as the Think/No-Think (TNT) task or bandit task. After that, they fit the algorithmic model's free parameters to individual subjects' collected behavioural data. If there are differences in fitted parameters between the healthy control group and diseased subject group, the differences indicate plausible mechanistic neurocognitive abnormalities in patients. Besides, the correlation between patients' parameters and symptom severity from clinical ratings might imply factors about the psychiatric disorder.

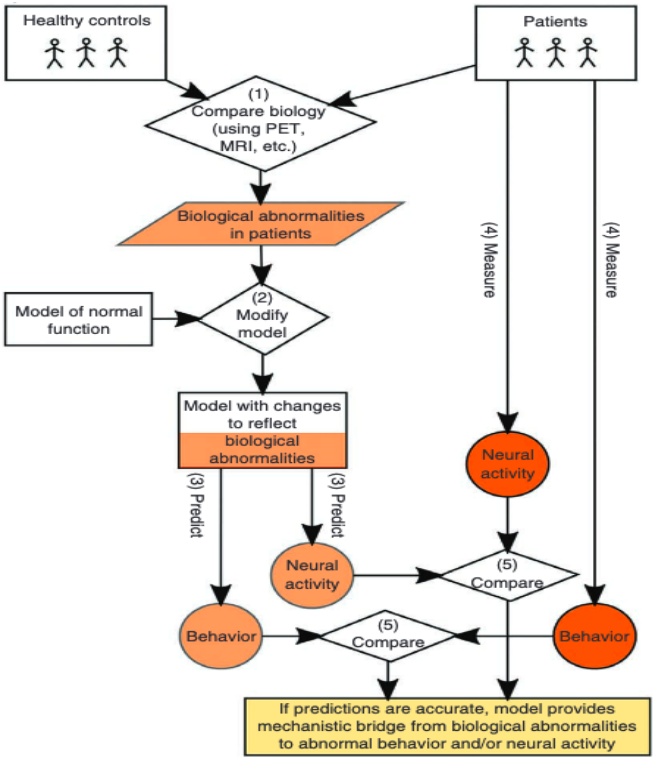


Figure 2.4: Deductive approach in theory-driven field of computational psychiatry from [52]. By comparing the biological data of healthy controls and patients, researchers may identify biological aberration in patients. Deductive approach researchers modify the neural model of normal function to reflect the observed biological anomaly. Suppose the outputs of the modified model match the measurements from patients. In that case, the altered model offers a feasible mechanistic account that links low-level biological features (e.g. low dopamine level) with high-level cognitive features (e.g. low motivation), thus bringing novel insights to aid the theory development of mental illness.

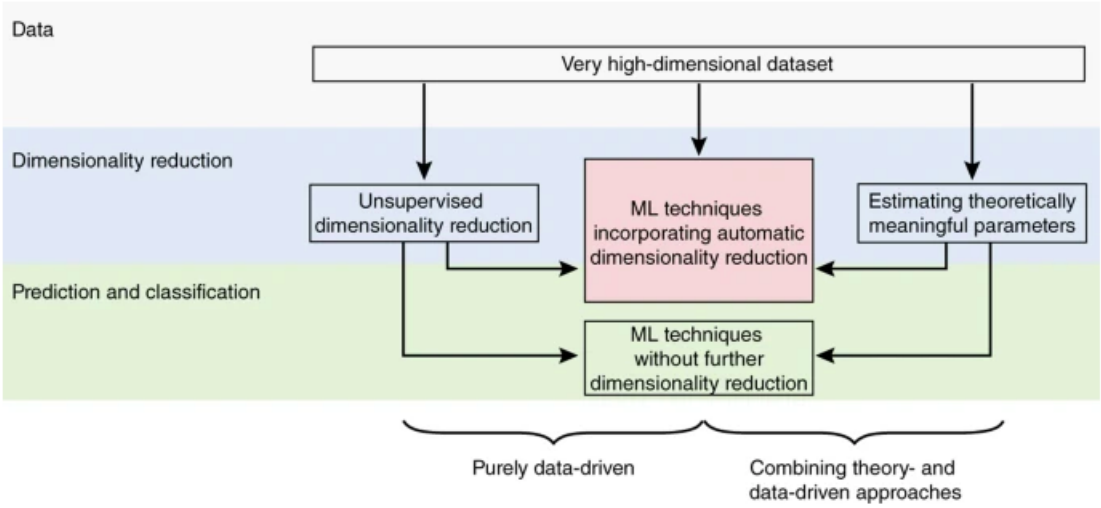


Figure 2.5: Pipeline of using high-dimensional psychiatric datasets in prediction and classification from [38]. Dimensionality reduction is a preprocessing step to avoid overfitting. In order to derive useful clinical applications, purely data-driven approaches (left and middle branches) and the generative embedding approaches (right branch) can be utilised in the data analysis of psychiatric datasets.

In theory-driven field, computational psychiatrists construct mathematical modelling of the neural or cognitive phenomena related to psychiatric dysfunction to generate an integrated mechanistic interpretation of psychiatric disorders. However, knowledge obtained from this approach is at the theoretical stage, and more work must be done before it can be applied in real-world clinical practice.

2.2.3 Combined use of data-driven and theory-driven

Due to the characteristics of machine learning algorithms and high-dimensional datasets, data-driven approaches often suffer overfitting problems, in which the statistical model will perform well on trained data but badly on new data. Hence extra techniques such as dimensionality reduction and regularisation are required to handle the overfitting problem.

Other than those data-driven approaches, the joint use of data-driven and theory-driven can also be utilised to avoid overfitting (see figure 2.5). Researchers employ theory-driven models to extract significant parameters relevant to mental illness. These informative parameters are the low-dimensional representations of the high-dimensional datasets and may reflect the underlying mechanism of the disorder. A machine learning algorithm for prediction or classification can then be applied to low-dimensional datasets.

If the theory-driven models precisely illustrate the pathophysiology of the psychiatric disease, the hybrid models of these two cultures may have better performance than data-driven models, which do not encompass the generative procedures[38][8][86].

2.2.4 Types of computational model in theory-driven approach

In 1982, Marr suggested that any complex information processing system such as the brain can be analysed at three independent but interrelated levels: computation, algorithm, and implementation. The computational level describes the calculation that the system is performing (e.g. "search an element in a tree data structure"). The algorithmic level describes the algorithm the system uses to perform the computation (e.g. "depth-first search", "breadth-first search"). The implementational level describes how the physical parts of the system implement the algorithm (e.g. specific programming language) [78]. Marr's three levels framework has become an organising principle in theory-driven approaches to Computational Psychiatry.

Diverse computational models are under the algorithmic level of Marr's three levels framework. The types of computational models in the theory-driven approach could be at various levels of abstraction, from algorithmic models close to the computational level of Marr's framework to biophysical models close to the physical level of Marr's framework. Here, we will introduce three types of computational models based on classification from [38]: (a) biophysical model, (b) algorithmic model and (c) optimal (bayesian) model.

In computational psychiatry, the biophysical model simulates biological interaction within the brain. Biological communication comprises multiple analysis levels ranging from molecular processes, single neurons, and groups of neurons to neuronal models of cognition such as the decision-making model. The mathematical equations used in the simulation are constrained by the physical properties of the complex system, for instance, the electrical properties of the cell membrane and neuronal dynamics [85]. Even under constraints, a biophysically realistic model tends to have numerous parameters due to the complexity of the biological system. Occasionally, a degree of extraction is necessary to decrease complexity and focus on the portion of the scientific topic we desire to answer [38]. Since the design of a biophysically model is based on the real biological system, a biophysically realistic model that successfully predicts the measurements collected from psychiatric patients could provide a mechanistic bridge between biological abnormalities of patients and symptoms of the disorder, e.g. from low concentration of GABA (an inhibitory neurotransmitter) to the feeling of nervousness [52]. Before conducting experimental studies, which are often limited by practical or economic considerations, researchers can perform many simulated experiments on the biophysical model to determine the most feasible research directions in pharmaceutics, therefore reducing the waste of research resources.

An algorithmic model is a quantitative computational model that illustrates the probable algorithms about how behaviour is generated. The probable algorithms work by taking a set of stimulus inputs and producing model outputs related to a group of behavioural responses (e.g. choices, reaction times or galvanic skin conductance response) [87]. Unlike the biophysical model that is verified through qualitative analysis of their predictions, the algorithmic model is generally validated through quantitative statistical methods such as model comparison and model selection techniques [38]. Thus, instead of establishing causal links, the algorithmic model can only provide insight into correlations between neural activity, and behaviour [63]. Besides, it is simpler and contains

a smaller number of model parameters compared to the biophysical model. Hence, researchers can create a concise abstract for the collected behavioural data using the model parameters best fitted for real behavioural data. Researchers can then compare the differences in model parameters across the healthy control group and diseased subject group [38]. They can answer questions about, for instance, how a patient's fear learning system, modelled computationally, differs from a typical person in terms of specific model parameters (aka computational marker). Furthermore, the correlation between a patient's computational marker and symptom severity from a clinical scale might aid mental illness diagnosis [52]. The psychiatrists can create a dimensional diagnosis as opposed to the current category diagnostic, thus addressing the variability in clinical trajectory. In chapter 5, we will use the quantitative abductive approach with the guideline from Wilson et al. [87] to implement the Rescorla-Wagner (RW) model (an algorithmic model of PTSD) from scratch.

The third model is called the optimal (bayesian) model. It originated from the concept of "unconscious inference" by Von Helmholtz. He suggests that the brains utilise prior knowledge to infer the causes of sensory inputs. Researchers adopt Helmholtz's theory and see the human perceptual system as a statistical inference engine [19] where the inference process can be formalised as Bayesian inference [81]. The "Bayesian brain" concept could be implemented in the brain through predictive coding schema [81]. Within the Bayesian predictive processing framework, the brain maintains a mental model of the surrounding world. The brain constantly uses the model to generate a prediction about sensory information. The prediction is then compared with the actual sensory information to form prediction error [34]. The goal of the brain is to minimise the prediction error; hence the mathematical model framed under this assumption is named the optimal model. To minimise the prediction error, the brain either updates the mental model to suit the input sensory information (perception inference) or acts on the surrounding world to gather more sensory information that validates the prediction about sensory information (active inference) [13]. The brain's internal model is the prior probability of the Bayes theorem, which can be combined with the sensory input (the likelihood probability) to form the prediction about sensory information (the posterior probability). Hence, the optimal model is also known as the Bayesian model. Predictive coding then uses the prediction to compute the prediction error; the brain will then update the prior probability based on the prediction error. However, the weighting of prediction error on belief update depends on the relative precision of sensory input and prediction [34]. Researchers suggest that many psychiatric symptoms are the result of improper weighting to either prior (prediction from the internal model) or likelihood (sensory evidence) [81]. For example, strong prior belief might be the cause of hallucinations [17] and significant weighting of sensory input might characterise autism [66].

Chapter 3

Pathophysiology of PTSD

Exposure to traumatic events is a necessary condition for the onset of PTSD. Surprisingly, it is not the sole determinant for the acquisition of PTSD. Several studies have revealed that only 5-30% of traumatic victims will develop PTSD [29] [58] [18]. Indeed, one of the most critical questions about PTSD is why some victims of traumatic events develop PTSD, while others seem to have certain resilience to trauma. According to a meta-analysis conducted by Brewin et al. (2000), pre-trauma factors such as reported childhood abuse, psychiatric history, and family psychiatric history have prognostic value for PTSD. In addition, factors during or after the trauma, such as trauma severity, lack of social support, and additional life stress, contribute more to the development of PTSD than the pre-trauma factor. [7]

The exact mechanism of PTSD has remained unknown. However, research in this field has identified two possible etiological models of PTSD that we will describe in the next section: (1) the fear learning model and (2) the threat detection model. The fear learning model originated from the behavioural psychology field. At the same time, the threat detection model is derived from the brain imaging field. These two models focus on a specific brain region and can explain certain symptoms of PTSD, but they are not mutually exclusive.

3.1 Fear learning model

Associative learning is a cognitive process that links two initially unrelated elements in the brain. Ivan Pavlov discovered the simplest form of associative learning, known as classical conditioning, during his famous experiment with dogs in 1927. Before conditioning, the dog will salivate (unconditioned response) when it sees the food (unconditioned stimulus) but shows no response to the sound of a bell (neutral stimulus). After a few trials of the ringing bell before sending food, the sound of the bell and the arrival of food will be paired. The dog will involuntarily turn the sound of the bell into a conditioned stimulus and show a conditioned response, which is salivating even though there is only the sound of the bell.

Fear conditioning is one form of classical conditioning which connects environmental

stimuli with unpleasant events. Under the pressure of natural selection, mammal animals learn the relationship between environmental stimuli such as the sound of their predator with the presence of a threat to promote the chances of survival. Fear conditioning in animal studies [20] shows four characteristics of fear learning:

- A single trial is typically enough to construct the pairing of CS and US.
- The association will normally last for the rest of the organism's life once the organism has learned
- Through extinction learning, conditioned responses to stimuli formerly paired with negative events may decrease. However, the strength of association might be restored either spontaneously or because of new stressful experiences months or years after the extinction learning.
- Fear motivates behaviour, including avoidance and approach.

These characteristics have high similarities with the features of PTSD, and the abnormalities in fear learning have been important in explaining the development of PTSD. Different aspects of fear learning, such as fear acquisition, fear extinction/ safety learning, and fear generalization, are the dominant hypothesis about the causes of PTSD. [49]

3.1.1 Fear acquisition

In the fear conditioning paradigm, repeated appearance of the conditioned stimulus (CS) and unconditioned stimulus (US) ultimately lead to fear acquisition. Generally, PTSD patients show successful fear acquisition, which shows conditioned response (CR) even without the presentation of US [32][64][69] [10]. However, they take longer to differentiate the US-predicting CS (CS+) and non-US-predicting CS (CS-) compared to the control group [32]. Instead of defecting to pay attention to the CSs or defecting to learn the CS-US contingency, Grillon et al. suggest that there may be a disconnection between cognitive awareness of the CS-US link and emotional responses in PTSD patients. In order to examine the participants' knowledge of the CS-US relationship, Grillon et al. request them to indicate whether the shocks were related with CS+ or the CS- or were appeared in a non-systematic way at the end of each conditioning session. Participants could also answer "they do not know" to this question. Except for one patient, all of the patients in their study accurately answered the correct association between the CS+ and the shock, suggesting the declarative knowledge learning mechanism of PTSD patients is normal. According to Orr et al., the emotional processing of threat cues in PTSD patients might differ from non-PTSD people. The PTSD group exhibits a gradual rise in fear response across CS+ acquisition trials, whereas anticipation of fearful stimuli produces decreasing emotional responses for the control group [64]. Besides, evidence for a heightened fear response during the fear conditioning is contradictory. Several studies have shown that the PTSD group presents an elevated fear response during conditioning [64] [69] [10]. On the other hand, some studies observed no significant group differences during acquisition or extinction learning [55][56].

3.1.2 Fear extinction/safety learning

Fear inhibition in humans has been studied through fear extinction in the fear conditioning paradigm. Fear extinction, sometimes known as safety learning, describes the phenomenon that after the repeated appearance of CS without the US in extinction learning, the human participants learn shortly that the CS loses predicting power for the arrival of US. Thus, the fear response to CS disappears, and CS is a safe cue now. Typically, the extinction is not permanent and might reappear under three situations: (1) exposure to the un-signalled US, (2) exposure to the signalled US in a context different from the context where extinction training occurred, and (3) after the flow of time following extinction training without any further training [61].

Various studies illustrate that the PTSD group shows a higher level of conditioned fear response during the late extinction training compared to the non-PTSD group [5][64] [69][62]. The reduced extinction of fear under a safe setting might indicate impairment in the fear inhibition of PTSD people. Guthrie et al. propose that reduced extinction of a conditioned emotional response is a risk factor for PTSD. In their study, 84 firefighters were evaluated during cadet training (before the trauma), and 70 were re-evaluated within 24 months after beginning active firefighting responsibilities (after trauma). Reduced extinction of fear-conditioned responses observed before trauma predicted 31% of the symptoms in later traumatised individuals [33].

By contrast, other studies observed no significant differences during extinction learning, but the PTSD group showed impaired extinction retention [55] [56]. Instead of the predisposing factor for PTSD development, Milad et al. propose that deficit in extinction retention results from combat trauma. During the extinction recall stage in their study, PTSD Vietnam veterans have a greater conditioned fear response than their non-combat exposure twins and those of non-PTSD combat veterans and their co-twins [55].

3.1.3 Fear generalisation

Fear generalisation indicates situations where the fear response is elicited toward cues other than US and CS. Normally, the cues share high similarity towards the CS or environmental context, which presents when the CS and the US are paired. The ability for generalisation helps us to immediately respond to new situations that are highly similar to the previous traumatic experience and thus minimise the risk from the horrible new situations. For example, a fire in the living room might elicit a fear response even if the person has only seen wildfire news. However, over-generalisation of conditioned fear might lead to a heightened startle response to safe stimuli. For example, the wildfire victim might feel startled even from seeing a red object.

In order to measure the fear generalisation rate, a continuous generalisation gradient can be formed by measuring the fear response toward a continuum of stimuli with increasing similarity to US-predicting CS (CS+) (see figure 3.1). Liessek et al. demonstrated that continuous generalisation gradient of conditioned fear is an applicable method for accessing the fear generalisation rate of humans in research. The flatter the generalisation gradient, the higher the fear generalisation rate [48].

PTSD patients tend to generalise their fear across stimuli compared to non-PTSD people

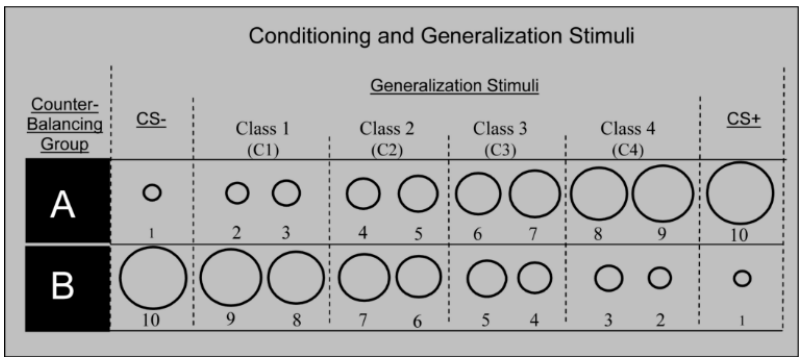


Figure 3.1: A continuum of stimuli used to measure fear generalisation in [48]. The numerals 1-10 at the bottom of the rings label the stimuli in descending order from smallest (1) to largest (10) but did not appear when the rings were shown to participants. Class 4 constituted the two rings closest in size to the CS+ in both counterbalancing groups A and B, whereas Classes 3-1 steadily reduced in similarity to the CS+.

[32] [69]. Several animal studies have reported that the intensity of fearful stimuli affects the breadth of the generalisation gradient. A powerful US widen the generalisation gradient [3][23][28]. Compared with animal studies, human studies about generalisation of fear are scant. In 2017, Dunsmoor et al.'s study observed that participants who experienced fear conditioning with high intensity of US presented broad generalisation of skin conductance responses as compared to participants who experienced a low-intensity US [24]. This result may explain the hyperarousal symptoms of traumatic victims as the strong intensity of traumatic events has led to high fear generalisation rate of victims. Thus, the victims treat all the safety cues in their daily life as threat predicting cues and show persistent "flight or fight" responses. Although no research proposed that the fear generation rate could be a good marker for differentiating PTSD people from healthy people, the connection between PTSD and over-generalisation could still be used to treat PTSD. For example, exposure therapy for PTSD patient can start from stimuli with less similarity to traumatic cues and then increase the similarity as the patient reduce avoidance behaviour [74].

3.1.4 Neuroanatomy of fear-related process

The key brain region responsible for fear-related processes is the amygdala. Many studies have shown hyperactivation of the amygdala during fear processing and fear learning [59][72][70][30]. Within the amygdala, there are various specialised groups of neurons named nuclei. The nuclei most relevant to fear conditioning are lateral (LA), basal (B), accessory basal (AB), and central (CE) nuclei. LA is the sensory gateway responsible for almost all the information input to the amygdala. CE is the exit door of the amygdala that is responsible for eliciting bodily responses related to fear, such as behavioural, autonomic nervous system (e.g., blood pressure and heart rate), and endocrine (pituitary-adrenal hormones) response through projections to brainstem areas [43][70].

When we are exposed to a conditioned fearful stimulus, the thalamus immediately sends sensory information about that stimulus to the LA in two routes (see Figure 3.3). Information received from LA is transferred to CE, the amygdala's output region, to

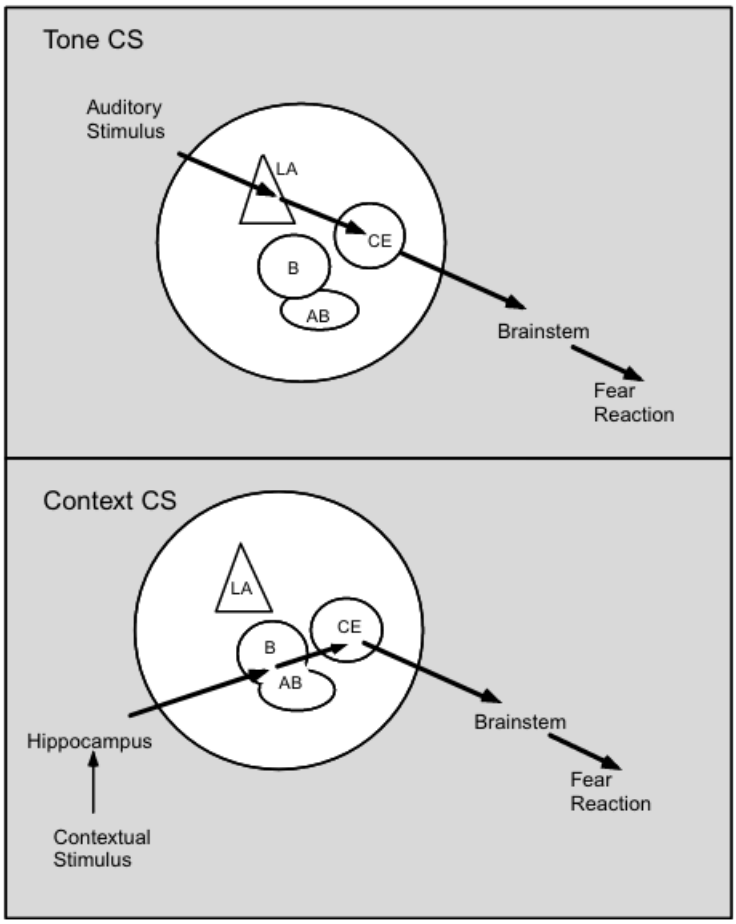


Figure 3.2: A comparison of the amygdala pathways involved in conditioning to a tone [conditioned stimulus (CS)] and to a context from [43]. The circle refers to amygdala. Conditioning to a tone CS involves projections from the auditory system to the LA (lateral nucleus) and from LA to the CE (central nucleus) in the amygdala. Conditioning to the environment and other contextual cues present when the CS and unconditioned stimulus (US) are paired, on the other hand, involves the context representation by the hippocampus and the communication between the hippocampus and the basal (B) and accessory basal (B) nuclei in the amygdala, which then project to CE.

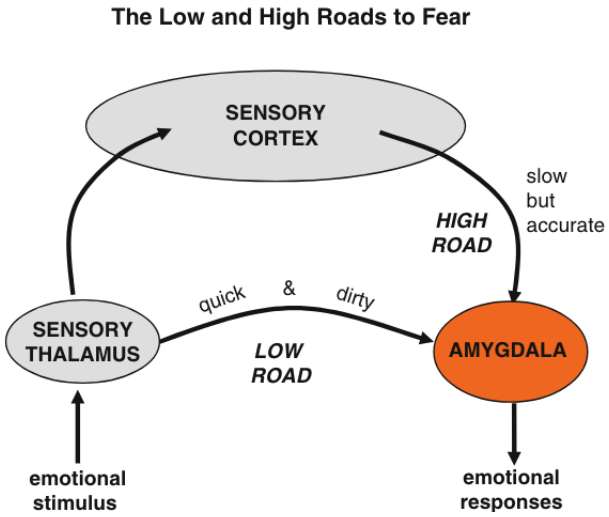


Figure 3.3: The two-road model of signal transmission from [20]. Emotional stimulus reaches the LA (lateral nucleus) in the amygdala via two independent sensory inputs: The “high road” or thalamic pathway sends a quick but imprecise signal. In contrast, the “low road” or thalamus-cortical pathway provides the amygdala with a more complex and detailed representation for conscious processing in humans.

elicit physiological and behavioural reactions. The low road is the pathway from the thalamus directly to LA in the amygdala. It is a quick and inaccurate route but allows immediate response to the fearful stimulus. In comparison, the high road is the pathway from the thalamus, sensory cortex to LA in the amygdala. It is slow but contains more accurate processed information about the fearful stimulus. For example, when we see a curled shape object in our garden, our low road will exhibit a jump-back reaction, and our high road will make a judgement about it: whether it is a real snake or just a garden hose. The cortex offers its interpretation of the stimulus based on previously learned knowledge. Therefore, the deficit in the amygdala and both pathways to the amygdala might be a risk factor for developing PTSD or/and contribute to the maintenance of PTSD symptomatology.

During fear acquisition, conditioning to the places and other information about the environmental context available when the CS and US are paired happens simultaneously. Both the amygdala and the hippocampus in the brain are involved in contextual conditioning. Contextual conditioning consists of the context representation by the hippocampus and the communication between the hippocampus and the basal (B) and accessory basal (AB) nuclei of the amygdala. The resulted communication is then projected to CE, which controls the expression of the responses (see Figure 3.2). The impairment of the amygdala and this pathway might produce the over-generalisation of fear in PTSD.

3.2 Threat detection model

Organisms are bombarded by a tremendous number of stimuli in their internal and external environments all the time. Therefore, preferential processing of threat-related stimuli is essential for the survival of organisms. Along with the advancement of functional neuroimaging studies, researchers have identified a core set of functionally connected brain regions named salience network (SN), responsible for bottom-up processing of salient stimuli, including threat stimuli [77]. The dysfunction of the salience network may alter the brain's threat detection functions and has been suggested to be involved in hypervigilance and hyperarousal symptoms of PTSD.

3.2.1 Salience Network (SN)

Out of enormous internal and external stimuli, the salience network (SN) picks out the stimulus that warrants our attention and requires immediate handling to maintain homeostasis. The salience network then assigns emotional weightage to the salient stimuli [77]. Commonly, a threat stimulus related to pain will always be imbued with more significant emotional weight than a non-threatening stimulus that does not associate with pain or discomfort [71]. The prominent nodes in the Salience network responsible for these functions are (1) anterior insula (AI) and (2) dorsal anterior cingulate cortex (dACC). AI is the input hub of SN. It monitors internal states and detects the interoceptive signal. Whereas dACC is the output hub of SN, which is responsible for producing appropriate visceral, autonomic, behavioural, and cognitive responses [77][83].

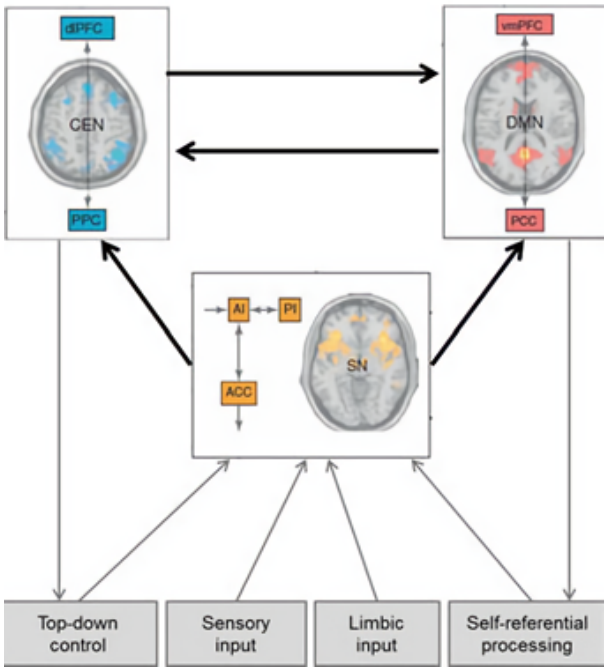


Figure 3.4: Interactions between Salience Network (SN), Central Executive Network (CEN) and Default Mode Network (DMN) from [44]. The SN receives and integrates sensory and limbic input from the anterior insula (AI). SN then switches between CEN and DMN, depending on homeostatic demands. CEN and DMN are inversely connected and communicate with the SN through top-down control and self-referential processing signals.

After emotional processing of the salient stimuli, SN facilitates access to the brain's attentional and working memory resources by causally influencing the switching between the default mode network (DMN) and the central executive network (CEN) (see figure 3.4). The default mode network is activated when an individual is not focusing on the outside world, such as daydreaming. In contrast, the central executive network is activated when individuals do tasks that require conscious control and rational thought, such as goal-oriented activity. These two networks are negatively correlated, which means only one of them is activated by SN at a time [77].

3.2.2 Exaggerated threat detection caused by abnormalities in SN

During task-free conditions, the SN is generally anti-correlated with DMN. However, in PTSD patients, the correlation is different. In a study investigating the relationship between DMN and SN in PTSD, Sripada et al. observed a higher level of connectivity between SN regions and DMN regions in PTSD veterans than in non-PTSD combat veterans and non-combat exposure controls during resting-state [79]. Other than that, higher coupling within SN is also related to PTSD. In Sripada et al.'s analysis, a greater coupling between SN seed regions (regions of interest during brain imaging) and peri-insula (a superset of anterior insula) was linked with a higher CAPS score (a measure of PTSD symptom severity). These findings have led to a plausible neural substrate for excessive attention to stimuli in a resting state, which could contribute to hyperarousal symptoms of PTSD.

The brain activity of SN is predictive of the PTSD treatment results. In a study of brain changes after trauma-focused cognitive–behavioural therapy, Cisler et al. found reduced functional connectivity between the amygdala (a subcortical node in SN) and anterior insula during cognitive reappraisal of negative images was connected to a higher level of post-treatment symptoms reduction in PTSD patients [15]. Moreover, compared to remitted PTSD patients and combat controls, persistent PTSD patients had a stronger dACC and AI response to negative images before and after therapy. Persistent PTSD patients also had heightened amygdala activity in response to negative images than remitted patients and combat controls before treatments. These results have suggested that the aberrancy in the salience network might lead to exaggerated threat detection in PTSD, and the brain activity pattern of nodes in SN could be a biomarker to indicate the effectiveness of PTSD treatment [84].

3.3 Concluding comments

As seen from the above sections, the fear learning and threat detection models are derived from different fields and focus on a specific brain structure which explains certain symptoms of PTSD.

The persistence of fear responses in PTSD patients, which were associated with intrusive symptom presentations, has been linked to impairments in fear extinction and safety learning. Research about the fear learning model has emphasised mechanistically a core brain region named the amygdala, which dominates these activities. Although there are other fear-related activities such as fear acquisition, fear generalisation, memory consolidation, and extinction recall which require brain regions like the thalamus, sensory cortex, hippocampus, and medial prefrontal cortex, they are often studied through their effects on the amygdala under the paradigm of fear learning. [47]

On the other hand, exaggerated threat detection has been a strong candidate for explaining the hyperarousal symptom of PTSD. The threat detection model has focused on a salience network that reacts to salient stimuli. Aberration in the salience network is characterised by hyperconnectivity of brain regions involving the anterior insula (AI) and dorsal anterior cingulate cortex (dACC). It might lead to abnormally alert to stimuli.

Apart from the two mentioned models, the emotional regulation/executive function (ER/EF) model is also an etiological model of PTSD. The ER/EF model hypothesises that insufficient regulatory power of executive function areas over limbic structures, which generates emotion, might contribute to the PTSD pathophysiology. The ER/EF model focuses on the central executive network (CEN), primarily comprised of the prefrontal cortex. The prefrontal cortex is linked with thinking and high-order awareness, responsible for decision-making and emitting fear inhibition signal. A deficit in the prefrontal cortex might lead to problems in fear extinction and extinction recall.

Since these models are not mutually exclusive and each focus on a specific brain region, it is highly possible that PTSD is a heterogeneous disorder resulting from different pathophysiological mechanisms. Exposure to a traumatic event can result in different levels of damage to these pathophysiological mechanisms, which might explain why there exist several PTSD sub-categories.

Chapter 4

Algorithmic Models of PTSD in theory-driven approach

Algorithmic models of PTSD are mainly instantiated by reinforcement learning (RL) models. In section 4.1, we will introduce the reinforcement learning framework and discuss the suitability of RL model in PTSD studies. Then, we will introduce three model-free RL: (1) Rescorla-Wagner model, (2) Pearce-Hall model and (3) Gain-loss model in sections 4.2 to 4.4 and one model-based RL: latent-state model in section 4.5.

4.1 Overview of Reinforcement learning (RL) model

Within the reinforcement learning framework, learners aim to create the association between the conditioned stimulus and the unconditioned response so that the association is as strong as the biological pre-established association between the unconditioned stimulus and the unconditioned response. The unconditioned stimulus, such as food and electric shock, are primary reinforcers that possess inherent biological properties and can affect the behaviour of organisms. For instance, Pavlov's dog, which is mentioned in section 3.1, learns to build the association between bell-ringing (conditioned stimulus) and salivation (unconditioned response) through food (reinforcer). During the learning process, prediction errors will be formed if the bell-ringing cannot sufficiently predict salivation. The prediction error is calculated by subtracting the expected associative strength (the degree to which a conditioned stimulus predicted a response) from the strength of the reinforcer. The prediction error will then be used to update the association strength in order to improve the next prediction.

Furthermore, neurophysiology studies have found the neuronal coding of prediction error, a major signal for guiding the reinforcement learning, in the brain [50] [52]. When an animal experiences an unexpected reward, dopaminergic neurons exhibit phasic firing. Nevertheless, dopaminergic neurons burst to the conditioned stimulus (CS) instead of the following reward if the animal learned the pairing of the CS and the reward. Besides, suppose the learned CS is delivered without the expected reward. In that case, the dopaminergic neuron fires below baseline nearly at the same moment that the reward should have been presented. The above results support the hypothesis that

the phasic activity of dopamine neurons encodes prediction errors: unexpected rewards generate positive prediction error; fully expected rewards do not generate any prediction error; the absence of expected rewards generates negative prediction error.

One form of pavlovian conditioning is fear conditioning. The reinforcement learning model can mathematically formalise the pavlovian conditioning; thus, it can also formalise fear conditioning. In addition, the prediction error, the key signal in reinforcement learning, is highly related to the phasic activation of dopamine neurons. Therefore, the reinforcement learning algorithm becomes a strong candidate for bridging the computational level of the fear learning system and the implementation level of the fear learning system.

On the computational level, abnormalities in fear learning have been crucial in explaining the development of PTSD (more details in section 3.1). On the implementation level, researchers have suggested disturbances of the dopaminergic system might play a role in forming the pathophysiological basis for psychiatric disorder [31]. Hence, the reinforcement learning algorithm is a powerful computational model to provide insights into the mechanism underlying PTSD, which aids the psychiatric research of PTSD. Over the years, many variations of RL models have been proposed in PTSD studies. In the following sections, we will discuss four RL models in more detail.

4.2 Rescorla-Wagner (RW) model

The Rescorla-Wagner (RW) model is a reinforcement-learning model proposed by Robert A. Rescorla and Allan R. Wagner in 1972 to describe Pavlovian conditioning formally [73]. The RW model was constructed around a central notion: (1) learning only occurs when the actual event differs from the expectation, (2) expectation could be built up by many stimuli and its component stimuli are modified when the subsequent events differ from the composite expectation.

4.2.1 The mathematical account of RW model

By making several modifications to the ”Bush & Mostellar” model [11], the authors introduce the model in terms of the associative strength between stimulus A and unconditioned stimulus (V_{A}) that indicates the degree to which a conditioned stimulus predicted an unconditioned response. The associative strength of the compound (V_{total}) is the summation of all the component stimuli present in the trial:

$$V_{\mathrm{total}} = V_{\mathrm{A}} + V_{\mathrm{B}} + ... + V_{\mathrm{Z}} \tag{4.1}$$

The changes in the strength to each of the component stimuli depend on the strength of the compound instead of the strength of the respective components. For instance, the changes in associative strength of stimulus A and unconditioned stimuli (ΔV_{A}) is represented as:

$$\Delta V_{\mathrm{A}} = \alpha_{\mathrm{A}} \cdot \beta_{\mathrm{us}} \cdot (\lambda_{\mathrm{us}} - V_{\mathrm{total}}) \tag{4.2}$$

where α_{A} is the salience of stimulus A, β_{us} is the learning rate associated with the unconditioned stimulus and λ_{us} is the asymptotic level of associative strength which

each unconditioned stimulus will support. Both α and β are limited inside a range $0 <= \alpha, \beta <= 1$. The stimulus salience (α) represents the authors' idea that different stimuli may obtain associative strength at different rate despite equal reinforcement. Whereas the learning rate associated with the unconditioned stimulus (β_{us}) reflects the authors' assumption that different learning rate may be employed during reinforcement or non-reinforcement. The learning rate is also indicating the importance of the prediction error (PE) in the learning process where the PE is defined by the discrepancy between the actual event and the expected value of the compound:

$$PE = \lambda_{us} - V_{total} \tag{4.3}$$

A higher learning rate or a higher stimulus salience will lead to a quick learning process but also dramatic fluctuation in expectations as greater amount of prediction error will be used for value updating. The highest value of the actual event (λ_{us}) is the maximum associative strength that the unconditioned stimuli will support. Unlike other model parameters, λ_{us} is not formally bounded. Since the range of λ will determine the interval on which V_{total} is falling on. For simplicity, researchers typically set λ_{us} to 1 if the unconditional stimulus is present at the trial (reinforcement) and 0 if the unconditioned stimulus is absent at the trial (non-reinforcement). On the other hand, V_A^0 usually is set as 0.5 to indicate that the learner's expected value of receiving an unconditioned stimulus or receiving a non-reinforcement trial is equally likely before the conditioning.

The new expectation toward stimulus A (V_A^{n+1}) is then updated through the addition of previously accumulated knowledge and the changes in associative strength of stimulus A and unconditioned stimuli:

$$V_A^{n+1} = V_A^n + \Delta V_A \tag{4.4}$$

Repeated co-occurrences of unconditioned stimuli and stimuli will lead to acquisition learning, whereas repeated occurrences of stimuli without unconditioned stimuli will lead to extinction learning.

To apply the RW model to experimental tasks, some researchers might need to provide some mapping of V values into the collected behavioural data. For example, several studies map linear regressions of expected value to the skin conductance response (SCR) data [2][35]. They assume the likelihood of each trial's SCR (S^n) to be distributed as a normal distribution with a mean determined by the scaled V value on that trial plus a constant term:

$$S^n \sim Normal(\theta_0 + \theta_1 V^n, \sigma) \tag{4.5}$$

4.2.2 The usage of RW model in PTSD studies

Exaggerated behavioural response of PTSD patients is one of the key symptoms of PTSD. A possible explanation for these responses may be the abnormalities in the Salience Network of PTSD patients (more details in section 3.2). Although brain imaging research about the Salience Network has identified the location of brain regions (e.g. insula, dACC and amygdala) involved in the modulation of attention, more research

is required to understand how the attention-related process is implemented in the human brain. The tendency to draw attention may be increase by surprising events, as several studies have shown [36] [39]. Therefore, the RW model, which involves surprise-driven learning, can be used to probe the neural computation underlying the salience-related brain regions and explain how the altered neural response to surprising events is related to PTSD patients.

Among a sample of combat veterans, Howlett et al. found that trial-by-trial prediction errors derived from the RW model were significantly associated with the neural activation of two salience-related regions of the brain (left precuneus/inferior parietal lobule and right inferior parietal lobule) [37]. In addition, the symptom severity score of veterans was positively correlated with the degree of neural activation to prediction errors in the left precuneus/inferior parietal lobule. These findings indicate that the PTSD symptom severity is particularly related to excessive neural response to unexpected events in salience-related brain regions.

The RW model has become one of the most influential models in the conditioning field as it successfully describes some sophisticated phenomena in conditioning, such as overshadowing and blocking [57]. Nevertheless, the RW model still has flaws when addressing some fundamental aspects of conditioning. For instance, latent inhibition, where pre-exposure of CS before the conditioning will reduce the efficiency of learning during the conditioning. The failure of RW model in describing the latent inhibition phenomenon arises from the model's assumption that the associability of a stimulus will not be changed by past experience, i.e. the α for a particular CS and β for a particular US are constants [57]. A reasonable approach to tackle this issue could be a model with dynamic associability (more details in section 4.3).

4.3 Pearce-Hall (PH) model

To accommodate circumstances in which the pairing of CS and US does not result in effective learning (e.g. Hall-Pearce negative transfer and latent inhibition), John M. Pearce and Geoffrey Hall proposed another conditioning model named Pearce-Hall (PH) model in 1980 [68]. The PH model was built on the ground that the effectiveness of a CS might change (as contrast to fixed stimulus salience in RW model). More specifically, the effectiveness of a CS, i.e.the associability of a stimulus, depends on how inaccurate it is in predicting its consequence (as contrast to its predecessor, the Mackintosh model, which suggests the associability of a stimulus is decided by how correctly it predicts its consequences).

In addition, Pearce et al. mentioned that the PH model can also be interpreted as a model of attention in learning: the degree of associative strength learnt at any given trial is determined by the amount of attention towards the stimuli [6]. Specifically, more attention will be paid to a stimuli (the stimulus salience increase) if the stimuli has higher prediction error thus higher amount of learning will occur.

4.3.1 The mathematical account of PH model

There are a number of similarities between PH model and RW model. The definitions of the associative strength of the compound (V_{total}) (see equation 4.1), the prediction error (PE) (see equation 4.3), the new expectation toward stimulus A ($V_{\text{A}}^{\text{n+1}}$) (see equation 4.4), the learning rate associated with the unconditioned stimulus (β_{us}) and the asymptotic level of associative strength which each unconditioned stimulus will support (λ_{us}) is the same as RW model.

Unlike the RW model which treat the salience of stimulus A as constant, the salience of stimulus A in PH model has trial-by-trial changes. Hence, in PH model, the changes in associative strength of stimulus A and unconditioned stimuli(ΔV_{A}) is defined as:

$$\Delta V_{\text{A}} = \alpha_{\text{A}}^{\text{n}} \cdot \beta_{\text{us}} \cdot (\lambda_{\text{us}} - V_{\text{total}}) \tag{4.6}$$

The value of the α_{A}^{0} depends on the setting of the experiment and normally obtained from the fitting process in PTSD-related studies. Furthermore, the associability of a stimulus is determined by its predictive accuracy. In the paper where Pearce et al. first introduce the PH model [68], the associability of the stimulus A on next trial ($\alpha_{\text{A}}^{\text{n+1}}$) is determined by the absolute value of PE on the current trial:

$$\alpha_{\text{A}}^{\text{n+1}} = |PE^{\text{n}}| \tag{4.7}$$

The higher the prediction error at current trial, the lower the predictive accuracy of the presented stimuli, thus the higher the associability of the stimulus A.

However, Kaye and Pearce suggests that the changes in α might be too intense since it is only determined by the immediately preceding trial without considering the cumulative effect of predictive accuracy from trial 0 [40]. To dampen the changes in α, Kaye and Pearce refine the relationship between the predictive accuracy of a stimulus and its associability by replacing the equation 4.7 with the following equation:

$$\alpha_{\text{A}}^{\text{n+1}} = \eta \cdot |PE^{\text{n}}| + (1-\eta) \cdot \alpha_{\text{A}}^{\text{n}} \tag{4.8}$$

From the equation 4.8, we can see associability weight (η) that control the extent to which α is affected by the immediately preceding trial. The η is confined to the unit interval, $0 <= \eta <= 1$. The equation 4.8 is the same as the equation 4.7 when $\eta = 1$. If $\eta \approx 1$, the α is greatly affected by the immediately preceding trial, with trials before the immediately preceding trial having little impact [42]. On the contrary, α is greatly affected by the earlier trials, with the immediately preceding trial having little impact, if $\eta \approx 0$. Thus, the higher the associability weight, more sensitive the learner to unexpected events.

As RW model, some researchers might need to provide some mapping of the trial-by-trial values of PH model into the collected behavioural data. Other than equation 4.5, researchers can have other kinds of mapping for PH model. For example, linear regression of associability or the combination of both expected values and associability can mapped to the skin conductance response (SCR) data [2][35]:

$$S^{\text{n}} \sim Normal(\theta_0 + \theta_1 \alpha^{\text{n}}, \sigma) \tag{4.9}$$

$$S^n \sim Normal(\theta_0 + \theta_1 V^n + \theta_2 \alpha^n, \sigma) \tag{4.10}$$

4.3.2 The usage of PH model in PTSD studies

Consistent with the theoretical discussion, several PTSD studies have shown that the PH model provides a better fit than the RW model for behavioural data [9][35][46]. Specifically, Homan et al. indicates that all three different versions of the mapping (equation 4.5, 4.9 and 4.10) of PH models outperformed the RW model. Overall, these cases support the view that attention-modulated learning plays a role in the associative learning of humans. Besides, the PH model may be a better choice of the computational model to probe the specific aspects of learning disrupted in PTSD patients compared to the RW model.

By applying the PH model to behavioural data, researchers have showed that an increased associability weight in the PTSD group compared to control group [9][35]. Besides, the higher associability weight was linked to higher PTSD symptom severity score in Homan et al.'s study [9]. Apart from these, the increased associability weight seems specific to PTSD patients in spite of the high comorbidity of PTSD and depression [9]. Brown et al. reveals that the PTSD patients had significantly higher associability weights compared to patients with only major depression disorder. These findings increase the possibilitiy of using the associability weight as a computational marker for the PTSD diagnosis.

On the neural level, PTSD has been found to have a significant relationship with the neural encoding of associability [9][35]. However, the localization of associability-related activation and the neural computation of associability varied across different studies. In Brown et al.'s study, both their whole-brain analysis and region of interest (ROI) analysis indicate higher tracking of associability in bilateral amygdala and insula (salience-related brain regions) have a significant relationship with PTSD [9]. Whereas, in Homan et al.'s study, lower tracking of associability in the striatum, hippocampus and dACC was linked to PTSD symptom severity [35]. Besides, Homan et al. observed that lower neural tracking of value in the striatum and amygdala, in addition to smaller amygdala volumes, were also related to higher PTSD symptom severity. Through a mediation analysis, they revealed the positive correlation between associability weight and PTSD symptom severity was complemented by decreased activity in the right striatum during associability computation. Apart from that, both the PTSD group and control group showed significant neural computation of prediction error (PE) in striatum [9]. These findings suggest that the processing of PE signals is unaffected by PTSD. Still, the aberrant gating of attention towards PE may cause an exaggerated reaction to unexpected stimuli in PTSD. People with PTSD may have increased attention to surprising events, which in turn facilitates learning.

As the participants of these studies were all veterans, future research should further develop and confirm these initial findings by conducting the same experiment setting with other cohorts of participants, such as victims of interpersonal violence. Besides, more investigations are required to explore the specificity of these differences in neural computation of associability.

4.4 Gain-loss model

Loss-aversion phenomenon observed by Amos Tversky and Daniel Kahneman suggests that humans tend to avoid loss rather than obtain equivalent gain during decision-making [82]. This phenomenon indicates humans have higher sensitivity toward punishment compared to reward. The central notion about the Gain-loss model: people may have different mechanisms for positive feedback (gain) learning and negative feedback (loss) learning [26].

4.4.1 The mathematical account of Gain-loss model

In the Gain-loss model, the initial expected value of stimulus A (Q_{A}^{0}) is determined by the experiment setting (see the different settings in [26][12][60]). The expected value of stimulus A at the subsequent trial ($Q_{\mathrm{A}}^{\mathrm{n}+1}$) is then updated by reinforcement feedback based on the sign of prediction error (PE):

$$Q_{\mathrm{A}}^{\mathrm{n}+1} = \begin{cases} Q_{\mathrm{A}}^{\mathrm{n}} + \alpha_G \cdot PE, & \text{if PE} > 0 \\ Q_{\mathrm{A}}^{\mathrm{n}} + \alpha_L \cdot PE, & \text{otherwise} \end{cases}$$

where α_G is the learning rate for gain learning and α_L is the learning rate for loss learning. Both α_G and α_L are limited inside a range $0 <= \alpha_G, \alpha_L <= 1$. A positive PE indicates the received feedback is better than expected and a negative PE indicates the received feedback is worse than the learner's expectation. Prediction error (PE) was calculated by:

$$PE = R - Q_{\mathrm{A}}^{\mathrm{n}}$$

where R is the feedback received by the learner at the trial. Typically, $R = 1$ for positive feedback and $R = 0$ for negative feedback. However, a different set of R is possible depends on the aim of the experiment. For example, Myers et al. measure how the participants treat the no-feedback outcome by setting R could be any one of the three values: +1 (reward), -1 (punishment) and R_0 (no-feedback). R_0 is a free parameter that could vary from 0 to +1 (the reinforcement value of reward), 0 to -1 (the reinforcement value of punishment); when $R_0 = 0$, the value of the no-feedback outcome is truly neutral [60].

4.4.2 The usage of Gain-loss model in PTSD studies

Some studies have suggested that humans may use distinct brain systems for reward and punishment learning [53][67]. The loss-aversion phenomenon indicates that humans have higher sensitivity toward punishment than reward. Thus, it is reasonable to ask whether this relationship changes in PTSD patients. The Gain-loss model in PTSD studies allows us to capture this dissociation and investigate it in more detail.

In a probabilistic classification task, veterans with severe PTSD symptoms (PTSS group) have better performance than veterans with few or no PTSD symptoms (control group) on the reward-based trial with no difference in punishment-based learning [9]. By fitting the behavioural data to the Gain-loss model, Myers et al. found that the

observed differences in performance are due to the differences in the interpretation of the ambiguous "no-feedback" outcome. According to the experiment setting, the ambiguous "no-feedback" outcome (R_0) can vary from 0 to +1 (successful in avoiding loss) and 0 to -1 (failure to obtain gain). Compared to the control group, the estimated values for the R_0 of the PTSS group were closer to 0, indicating that the PTSS group prefers to interpret ambiguous feedback as moderately neutral. Whereas the control group has a significantly greater weight of the R_0 than the PTSS group, the control group tends to treat the ambiguous feedback as successful avoidance of loss. During reward-based trials, this tendency will lead to a decreased amount of learning as the reinforcer is not strong enough. As the participants of this study are all veterans and some of them had been exposed to combat, the author suggested that the control group might have included individuals who have resistance to PTSD development and the resistance might be expressed as a tendency to interpret unclear feedback as reward.

PTSD research uses the Gain-loss model relatively less than the RW and PH models. There is much room for further progress in determining whether there are differences in gain or loss learning between PTSD people and healthy people. For instance, it might be possible to use the Gain-loss model with model-based fMRI analysis to examine the neural computation of reward and punishment in PTSD patients.

4.5 model-based RL

From sections 4.2 to 4.4, we have introduced three model-free reinforcement learning models. Although they have provided many insights into PTSD, these models, which only include simple trial-and-error learning, might not be enough to capture higher-order cognitive processes like inductive reasoning and the representation of conceptual knowledge [46][25]. For instance, model-free RL can explain how a person obtains the association between a tiger and a dangerous signal but not the conceptual knowledge that he is safe when he sees a tiger in the zoo and unsafe when he sees a tiger in the jungle. Besides, these models could not explain the learning phenomenon, such as the rapid recovery of conditioned response after extinction learning via reinstatement, context renewal, or spontaneous recovery [16]. Unlike model-free RL, learners who facilitate model-based RL develop an internal model of the environment. Thus, learners can develop distinct expectations for the various task conditions and weight their expectations depending on which situation they are in at the time [16][46]. For instance, a person, who utilises model-based RL, may assign different danger levels to the situations: (1) seeing a tiger in a zoo and (2) seeing a tiger in a jungle. He should feel very dangerous if he is in the "jungle situation" by weighing his warning expectations more than the "zoo situation". As there are many ways to construct model-based RL, we will only brief discuss the latent state (LS) model, a model-based RL which has been used in PTSD studies, in the next section.

4.5.1 The latent state (LS) model

The latent-state model defines the learning environment as a set of latent states [16][46][45]. Each latent state (l) is an association between stimulus and outcome under specific un-

observed hypotheses. Suppose the learner thinks only one latent state is in the learning environment. In that case, the LS model is like a typical model-free RL.

In the following description, we will build the latent-state model upon the RW model. Suppose the learner thinks there are two latent states in the task. In that case, the LS model contains two RW models where each is linked to a latent state and represents a mutually-exclusive association that the competing RW model did not capture.

The associative strength of stimulus a for latent state l at trial n (V_{al}^n) is then updated by the reinforcement feedback based on prediction error particular to each latent state (PE_l^n). The update of associative strength will be accelerated for latent states believed to be in active status. In contrast, associative strength for latent states believed to be in inactive status will be updated at a relatively slow rate. Besides, switching belief to a new latent state due to unexpected outcomes will also increase the update rate of associative strength.

The learner has to infer which latent state to use at each trial of the task by maintaining latent-state belief. Latent-state belief (p_l^n) is the degree of belief to which the learner think current observations reflect a given latent state l. p_l^n is a positive variable such that beliefs of all latent states sum to 1:

$$p_1^n + p_2^n + \ldots + p_L^n = 1 \tag{4.11}$$

For each trial, the learner uses an approximate Bayesian filtering equation to update the latent-state belief for the subsequent trial (please refer to [16] for a detailed mathematical account of the LS model). The changes in latent-state belief (*delta* beliefs, dB) represents the changes in the learner's internal representation of the learning environment. The associative strength of stimulus a at trial n is then calculated by using the weighted average of V_{al}^n with weights p_l^{n-1}:

$$V_a^n = \sum_{l=1}^{L} p_l^{n-1} \cdot V_{al}^n \tag{4.12}$$

4.5.2 The usage of model-based RL in PTSD studies

Previous studies have reported that a separate set of brain regions are involved in model-free RL and model-based RL [46]. Model-free RL is mainly implemented within areas of the ventral striatum, amygdala and salience network, which may correspond to the detection of salience stimuli and quick response to the stimuli (refer to "Salience Network" in section 3.2.1 and "low-road" in section 3.1.4). On the other hand, model-based RL is mainly implemented within areas of the prefrontal cortex and frontoparietal network (FPN), which may correspond to inferential and contextually derived learning (refer to "high-road" in section 3.1.4). These findings suggest that both model-free RL and model-based RL are not mutually exclusive and might both be involved in the learning process. As PTSD may be a heterogeneous disorder resulting from different pathophysiological mechanisms, the usage of model-based RL in PTSD research allows researchers to investigate the possible abnormalities in the "high-road" part of a PTSD patient.

To investigate whether the model-based RL process of women with interpersonal violence-related PTSD is impaired during fear conditioning, Letkiewicz et al. compared the LS model with two model-free RLs (RW model and PH model) [46]. The comparison is made by fitting these three models to the SCR data collected during the fear acquisition and extinction task. The LS model outperformed the RW and PH models in their study. This finding indicates that the LS model captures the learning dynamics, such as different learning for the acquisition and extinction context, that model-free RL does not capture.

Contrary to the author's prediction that frontoparietal network (FPN) encoding of delta beliefs would relate to PTSD symptom severity, fMRI analysis in Letkiewicz et al.'s study reports that decreased activity in visual processing brain regions (right calcarine gyrus/posterior cingulate cortex) during latent-state belief updates was associated with higher PTSD symptom severity [46]. Besides, they also reveal that higher tracking of value estimation in the left FPN during acquisition and lower tracking of value estimation within the dorsomedial prefrontal cortex (dmPFC/PCC) during extinction were related to higher PTSD symptom severity. Even though Letkiewicz et al.'s finding did not agree with their initial hypothesis, their study provides preliminary proof of model-based RL-related abnormalities, i.e. delta beliefs, in PTSD, which differ from model-free RL processes (e.g. value and associability).

In the future studies, more research is needed to apply and examine: (1) whether the hybrid RL model of model-free and model-based strategy provides a better fit for PTSD people's behaviours, (2) whether the PTSD group and healthy control group differ in the degree to which the use of a model-free vs model-based RL strategy and (3) whether the less or more use of model-based RL compared to model-less RL will lead to the PTSD development.

Chapter 5

Implementation of Rescorla-Wagner (RW) model

As mentioned in the last chapter, PTSD patients assign more weight to prediction errors than normal people. Thus, researchers can attempt to answer questions about PTSD by computational modelling the learning behaviour of PTSD people and mapping brain dysfunction to the importance of prediction error in PTSD people's learning.

Unlike running a typical program where its abnormal working could be detected by program error, incorrect computational modelling might not be easily noticed and might cause misleading findings. Hence, careful considerations are required during model-based analysis. Robert C Wilson and Anne GE Collins designed a guideline to help researchers avoid pitfalls in computational modelling [87]. In this chapter, we will implement a simple computational model of PTSD - RW model by following the recipe from Wilson et al. (see Figure 5.1). We will only perform section 1 to section 5 of the recipe as section 6 is about model comparison and the real behavioural data are required for steps after section 6. According to the paper, the same techniques are applicable to other more complex algorithmic models and can be used more generally for other observable behaviours.

5.1 Design experiment

As computational modelling tries to capture the computations underlying behaviour, it is fundamentally constrained by the behavioural data. Specifically, different implementations of the RW model may be required for different kinds of behavioural data (e.g. choice data, skin conductance response (SCR) data or pupil size response (PSR) data). The type of data to be used is then determined by the experiment protocol. Hence, designing a good experiment with computational modelling in mind became the first step in Wilson et al.'s recipe [87].

Since PTSD is characterised by inflexible modulation of behavioural and physiological responses to stimuli in changing environments, experiment tasks with only fear acquisition and fear extinction phrases might not be enough to understand the complete

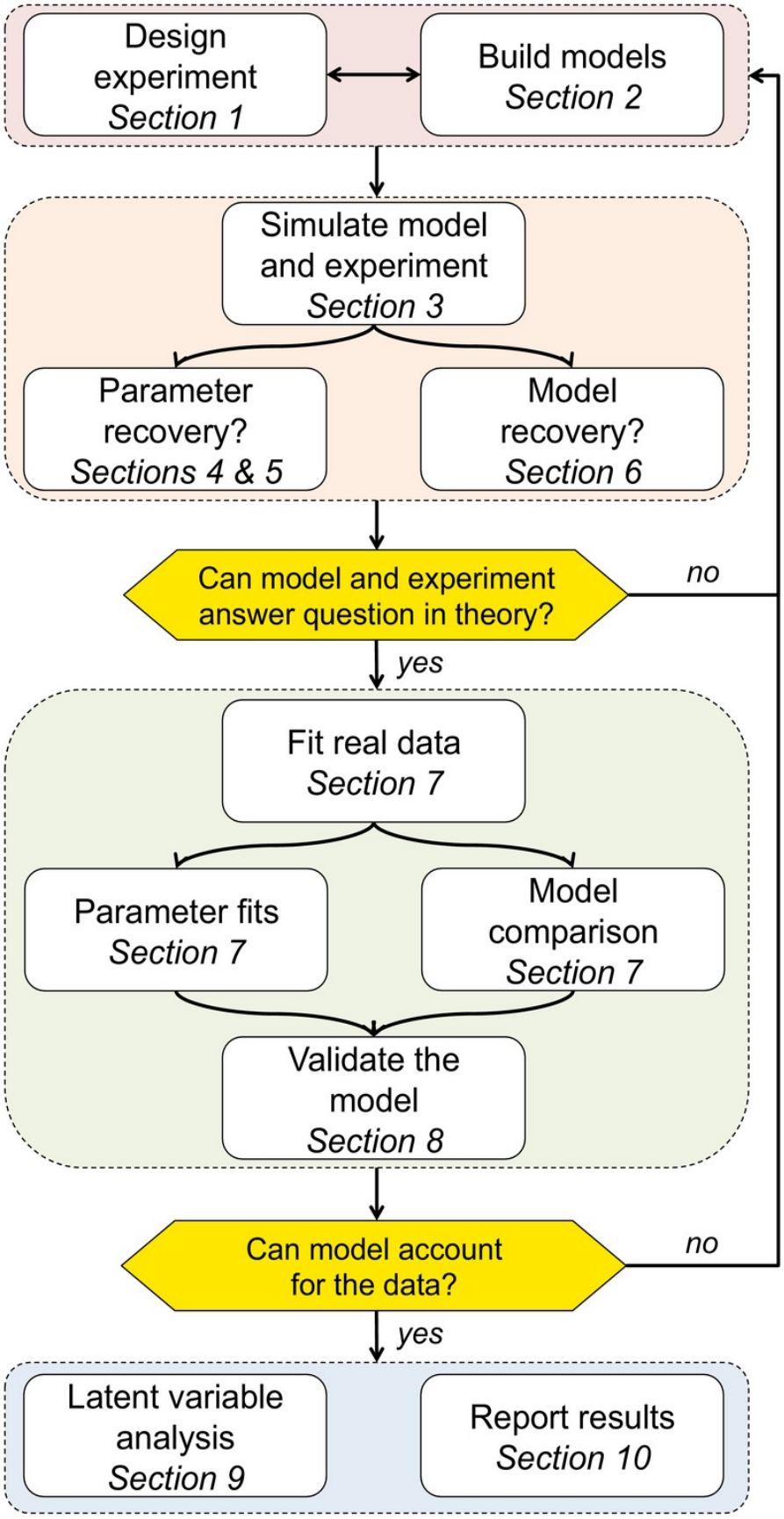


Figure 5.1: Schematic diagram of the 10 rules from [87]. Wilson et al. translate 10 rules for computational modelling of behavioural data into a process where each rule is mentioned in the corresponding section of their paper. In this report, We will only perform section 1 to section 6 of this procedure as the real behavioural data are required for steps start from section 7.

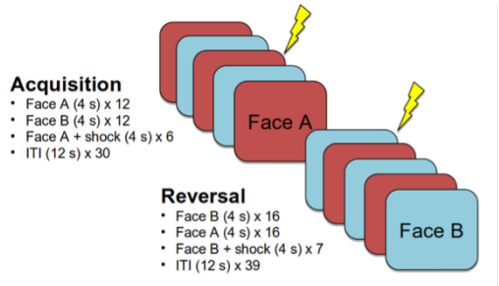


Figure 5.2: Experiment setup from [35]. A threat and safety reversal paradigm with partial reinforcement (reinforcement rate of 33%) was used. In acquisition stage, face A is a fear-inducing cue and associated with a electric shock on one-third of the trials. In reversal stage, face A becomes a safety-inducing cue and face B becomes the fear-inducing cue (ITI,inter-trial interval and s, seconds).

account of flexibility in fear modulation. In this report, we will use a threat and safety reversal learning task introduced by Schiller et al. [75] as our example experiment to investigate whether there is any difference in the gradual change of physiological response to cues that alternate in predicting danger in PTSD participants and healthy control participants.

Threat and safety reversal learning is an instance of associative learning that comprises two phases: acquisition and reversal. During the acquisition phase, the participant learned the association between the threat (e.g., electric shock) and the neutral cue (e.g., face). This association will be reversed during the reversal phase. The previous threat connection becomes safe, while another neutral cue becomes associative with the threat.

There are many possible ways to design a reversal-learning task, such as a different number of reversal phrases (once or twice) and how often the reversals occur [89]. We will set our experimental parameters as the setting in Homan et al.'s study [35]. There is one reversal phrase in our example experiment and 69 trials, each showing participants one of the two slightly angry faces for four seconds in a pseudo-randomised order (see Figure 5.2). We set the pseudo-randomised order that indicates which cue to present at given trial n as the order in Homan et al.'s study and attached it in appendix (see appendix A.1). During the acquisition, there were 18 trials of face A, and approximately one-third of face A were associated with electric shock, whereas 12 trials of face B were not. After 30 trials of face presentation, the transition from acquisition to reversal occurs, and the participants were not told of this transition. 16 face A trials became safe during the reversal phase, and 7 out of 23 face B trials were linked with an electric shock.

In this experiment, the skin conductance response (SCR) data of participants will be collected and reveal the participants' defensive responses, with a greater SCR indicating a higher stress level.

5.2 Build model

All of the reinforcement learning models in Chapter 4 can be used to model learning behaviour in reversal-learning task. Rescorla-Wagner (RW) model is one of such models. For demonstration, we will use RW model to model the behaviour of participants (see complete mathematical account of RW model in section 4.2.1).

Two associative strength, V_A and V_B, represented the expected value of the two cues, i.e. face A and face B, in the experiment respectively. Since only one cue will be present for each trial, the salience of the cue is set as 1 and the V^n_{total} is equal to the expected value of the cue which is present in the trial n, V^n_x where x can be A or B, given the learning rate (β):

$$\begin{aligned} V_{\mathrm{x}}^{\mathrm{n+1}} &= V_{\mathrm{x}}^{\mathrm{n}} + 1 \cdot \beta \cdot PE^{\mathrm{n}} \\ &= V_{\mathrm{x}}^{\mathrm{n}} + 1 \cdot \beta \cdot (\lambda^{\mathrm{n+1}} \text{ - } \mathrm{V}_{\mathrm{x}}^{\mathrm{n}}) \end{aligned} \tag{5.1}$$

The maximum associative strength that the electric shock will contribute at trial n (λ^n) is set as 1 if electric shock is delivered and 0 if electric shock is absent at trial n. To reflect the fact that both the cues are not predicting the electric shock before acquisition, both V^0_A and V^0_B are set to 0.5. Besides, only the expected value of the presented cue will be updated, whereas the expected value of the cue which absent in the trial remains unchanged for next trial. For example, cue A and electric shock are present together at first trial, then the updating will be performed in this way:

$$\begin{aligned} V_{\mathrm{A}}^{1} &= V_{\mathrm{A}}^{0} + 1 \cdot \beta \cdot (\lambda^{1} \text{ - } \mathrm{V}_{\mathrm{A}}^{0}) \\ &= 0.5 + \beta \cdot (1 - 0.5) \end{aligned}$$

$$\begin{aligned} V_{\mathrm{B}}^{1} &= V_{\mathrm{B}}^{0} \\ &= 0.5 \end{aligned}$$

For instance, cue B is present alone at second trial, then the updating will be performed in this way:

$$V_{\mathrm{A}}^{2} = V_{\mathrm{A}}^{1}$$

$$\begin{aligned} V_{\mathrm{B}}^{2} &= V_{\mathrm{B}}^{1} + 1 \cdot \beta \cdot (\lambda^{2} \text{ - } \mathrm{V}_{\mathrm{B}}^{1}) \\ &= 0.5 + \beta \cdot (1 - 0.5) \end{aligned}$$

During the value updating, two series of expected value, V_A (noted V^0_A,V^1_A,V^2_A ...) and V_B (noted V^0_B,V^1_B,V^2_B ...), will be maintained for cue A and cue B respectively. To map the expected values into the skin conductance response (SCR) data, the two series must be combined into a series of expected value. This is done by choosing one value from the two series, based on which cue appeared in that particular trial. For example, if in the trial, the sequence of cues appeared as ABBA, the final combined series of expected value will be $V^0_A V^1_B V^2_B V^3_A$.

By definition, V^n is between 0 to 1. However, the actual skin conductance response (SCR) data usually have a different range. Therefore, to map the expected values into

the SCR data, we assume the expected value V^n is in linear relationship with the actual SCR data S^n. Thus, we introduce three more free parameters: we note θ_0 as the intercept (the predicted value of S^n when the $V^n = 0$), θ_1 as the regression coefficient (how much we expect S^n to change as V^n increases) and ε as the error term (the variations of the participants' SCR from the baseline SCR). Then, we map linear regression of the expected values into the SCR data as below equation:

$$S^n = \theta_0 + \theta_1 V^n + \varepsilon \tag{5.2}$$

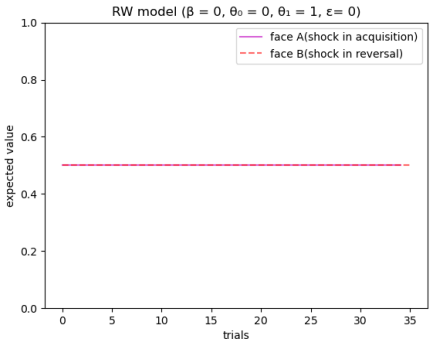
Combining the learning equation and mapping equation gives a simple model of learning in this experimental task with four free parameters: the learning rate (β), the intercept (θ_0), the regression coefficient (θ_1) and error term (ε). The implementation of RW model is in Python and attached in appendix (see Appendix A.2).

5.3 Simulate model

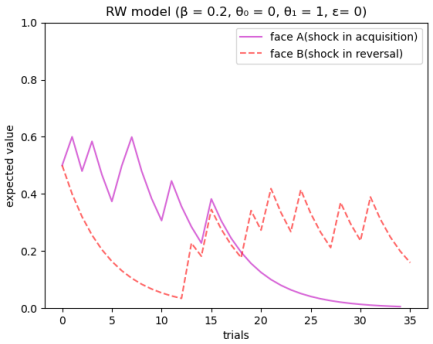
To ensure our RW model captures the behaviours that the experimental design is expected to generate, we use the RW model with different parameter setting to create artificial behavioural data.

As shown in equation 5.1, learning rate (β) is a weight parameter which quantify the amount of prediction error will be used in learning. To visualize the effect of β in learning without the influence of free parameters from mapping equation, we plot the learning behaviour of participants using different learning rate with only the expected values from the RW model. This can be done by setting the free parameter from mapping equation as $\theta_0 = 0$, $\theta_1 = 1$ and $\varepsilon = 0$. For data analysis purposes, we separate the expected value of Face A and Face B. The results obtained from the simulation are presented in Figure 5.3.

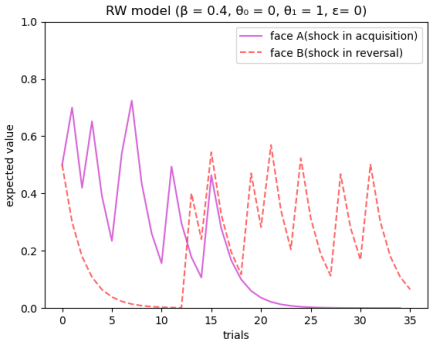
From Figure 5.3, we can see that the artificial participant shows successful reversal learning in the different settings of learning rate except when $\beta = 0$. Since zero amount of prediction error will be used in value updating so there is no learning can occur when the $\beta = 0$. When the learning rate is greater, the expected values of face B and face A converge to 0 more quickly during the acquisition stage and the reversal stage respectively. The reason for this phenomenon is high learning rate will cause a greater amount of prediction error to be used for value updating; thus, the expected value of both faces will converge to optimal learning, i.e. expected values of face A = 1 and face B = 0 during the acquisition stage and expected values of face A = 0 and face B = 1 during reversal stage, within fewer consecutive reinforcement or consecutive non-reinforcement trials compared to the RW model with a lower learning rate. However, this high learning rate also leads to participants' learning fluctuating more widely if there are interweave of reinforcement and non-reinforcement trials. For example, the expected values of face A during acquisition stage and face B during reversal stage fluctuate more widely when the learning rate is greater. In simple terms, a high learning rate accelerates a participant's learning but also causes the participant over sensitive to a surprising event. Whereas, a participant with a lower learning rate receives less effective learning during trials but is also less sensitive to a surprising event.



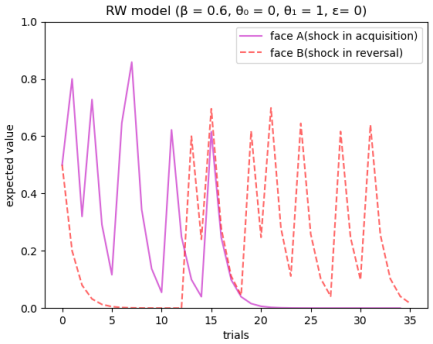
(a) learning rate = 0



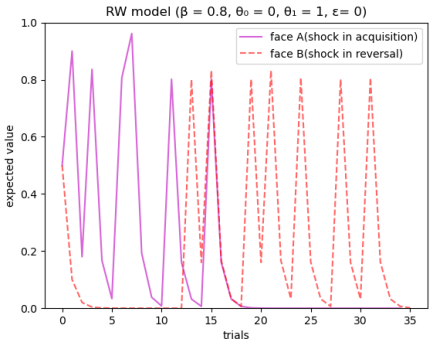
(b) learning rate = 0.2



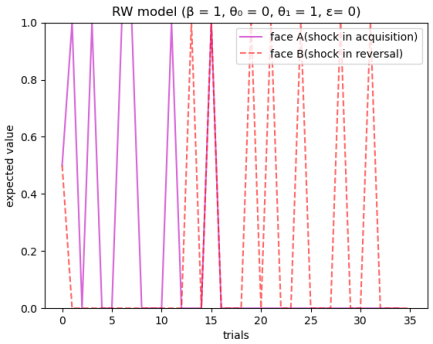
(c) learning rate = 0.4



(d) learning rate = 0.6



(e) learning rate = 0.8



(f) learning rate = 1

Figure 5.3: Simulation of RW model using different learning rate with the same setting for mapping equation ($\theta_0 = 0$, $\theta_1 = 1$ and $\varepsilon = 0$). The magenta line plot represents the expected value of face A in this experimental task, whereas the dotted red line plot represents the expected value of face B.

Compared to healthy control participants, we hypothesised that PTSD participants might assign more weight to the prediction error, facilitating their fear learning and leading to an over-sensitive and exaggerated behavioural response to novel stimuli represented by widely fluctuating SCR reading.

Apart from that, the rest three free parameters (from the mapping equation) are not as important as learning rate because they do not affect the learning pattern of RW model (see Figure B.1 and Figure B.2) thus do not disclose any details about learning of participants. The main functionality of the intercept (θ_0), the regression coefficient (θ_1) and the error term (ε) are used to model the relation between the estimation of threat and the actual physical stress response in the form of SCR.

5.4 Parameter recovery

Fitting a model to data is a process of finding the values of the model parameters that best describe the behavioural data. This process is a very important part in computational modelling as researchers can only explain the behavioural data in terms of model parameters (e.g. how a patient's fear learning system, modelled computationally, differs from a healthy person in terms of specific computational marker) if the fitting process gives meaningful parameter values. The fitting process can be evaluated on artificial data where the parameters generating the data are known to ensure the validity of the best-fitting parameter values. This evaluation method is called parameter recovery.

To running the parameter recovery process, we sample 60 β randomly from a continuous uniform distribution between 0 and 1 to represent the learning rate of 60 fake participants. As the humans' SCR should be relatively similar like the humans' heart rate, we assume that the participants will have similar mapping from the output of RW model to the SCR data. Hence, we generate a pair of θ_0 and θ_1 randomly from a normal distribution with mean = 0 and standard deviation = 1 respectively. The pair of generated θ_0 and θ_1 will be used in the mapping of all the participants. Besides, we also assume there are individual variations within the 60 participants and this will be capture by the ε of the mapping equation. We sample 60 ε randomly from a normal distribution with mean = 0 and standard deviation = 0.05 to account for the variations in each individual participant's SCR. We simulate artificial data with these known parameter values.

During the simulation of artificial data, the trials with electric shock are included in the computation of expected value. However, the trials with electric shock should be omitted during fitting to real data as the SCR are overwhelmed by the response to electric shock during reinforced trials and might affect the fitting process. Thus, we exclude all the trials with electric shock in our parameter recovery as well. Then, we fit the RW model to these fake data using hierarchical Bayesian model and Markov chain Monte Carlo (MCMC) sampling algorithm (see code of the hierarchical Bayesian model setting in Figure 5.4 and detailed code in A.3).

To compare the recovered parameters to their real values, we plot both the simulated and the recovered learning rates of 60 participants (each underwent 69 trials of value updating according to the experiment design) in a scatterplot (see Figure 5.5). As shown in Figure 5.5, there is a very good correlation between the simulated and the recovered parameters. Furthermore, the correlation coefficient between the simulated and the recovered parameters is 0.9114 (with p-value = 4.97e-24) also indicate a successful parameter recovery. Henceforward, we can fit the model to real behavioural data, including PTSD patients and healthy controls. Then, we can check if the best-fitting learning rates of PTSD participants are statistically higher than the healthy controls and if there is any correlation between the learning rate and the PTSD severity score of participants. However, a successful parameter recovery only increase our confidence that the estimated parameter can be used to explain the simulated dataset (the best-case scenario in model-based analysis) [87]. As the learning behaviour of human is much more complex than what the RW model can simulate, successful parameter recovery cannot be treated as the conclusive evidence that the fitted parameters completely describe the actual behaviours of human.

```
with pm.Model() as RW_model:
    ################################################
    # free paramters from mapping eqution
    beta0 = pm.Normal('beta0',0,20)
    beta1 = pm.Normal('beta1',0,20)
    ################################################
    # free parameter from learning equation

    # group-level mean and standard deviation of learning rate
    lr_hypermu = pm.Normal('lr_hypermu', 0,1)
    lr_hypersd = pm.HalfCauchy('lr_hypersd',beta=5)
    # individual learning rate is drawn from the group-level normal distribution
    lr_v = pm.Normal('lr_v',lr_hypermu,lr_hypersd,shape=no_subjects)
    # Convert unconstrained values into the interval [0,1]
    # as the learning rate is bounded between 0 and 1
    lr = pm.Deterministic('lr', pm.math.invlogit(lr_v))
    ################################################
    # step function
    vS = 0.5 * tt.ones((no_subjects,2), dtype='float64')
    combined_v = 0.5 * tt.ones((no_subjects,1), dtype='float64')

    outputs, updates = theano.scan(
        fn=update_RW,
        sequences=[stim_matrix, shock_matrix],
        outputs_info=[vS, combined_v],
        non_sequences=[lr, no_subjects])

    combined_v_ = outputs[1].reshape((no_trials,no_subjects))
    mapped_scr_model = beta1*combined_v_ + beta0

    #remove rows that represent shock to avoid contamination
    mapped_scr_model = mapped_scr_model[idx]
    ################################################

    # Model error
    eps = pm.HalfCauchy('eps', beta=5,testval=1.0)

    # Data likelihood
    scrs = pm.Normal('scrs',mapped_scr_model,eps,observed=mapped_scr_matrix)

    ################################################
    trace = pm.sample(1000,target_accept=0.9, chains=4,
                      cores=10, return_inferencedata=True)
```

Figure 5.4: Code of using hierarchical Bayesian model and Markov chain Monte Carlo (MCMC) sampling algorithm to fit the RW model

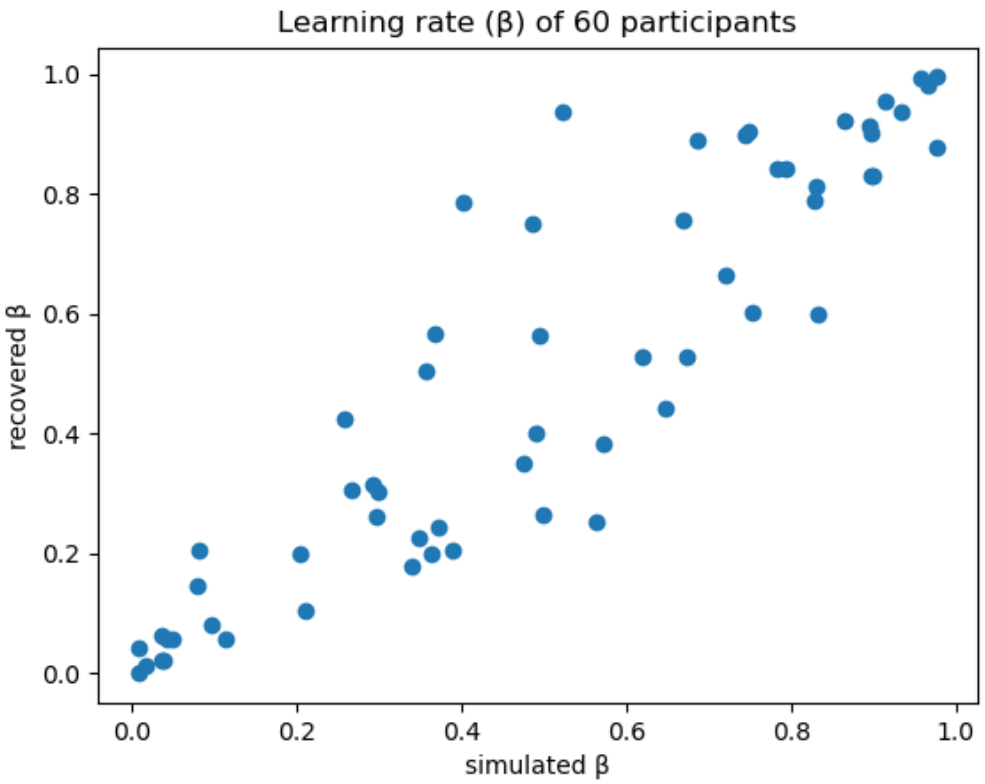

Learning rate (β) of 60 participants
recovered β
simulated β
0.0
0.2
0.4
0.6
0.8
1.0

Figure 5.5

Chapter 6

Conclusions

This report aimed to obtain greater understanding of Computational Psychiatry in Post-Traumatic Stress Disorder (PTSD). In chapter 2, we introduced the clinical account of PTSD and two different but complementary approaches of Computational Psychiatry: (a) data-driven and (b) theory-driven. We then mentioned how these two approaches can be combined to generate a hybrid model which has outperformed the data-driven model alone. We also briefly discussed three types of computational model in theory-driven approach based on the classification from Huys et al.'s paper [38]: (a) biophysical model, (b) algorithmic model and (c) optimal (bayesian) model.

After that, we discussed the two possible etiological models of PTSD : (1) the fear learning model from the behavioural psychology field and (2) the threat detection model from the brain imaging field in chapter 3. Fear-related activities are often investigated through their effects on the amygdala under the framework of fear learning model [47]. The persistence of fear responses in PTSD patients, which were associated with intrusive symptom presentations, has been linked to impairments in fear learning. Meanwhile, the threat detection model has focused on a salience network, including the anterior insula (AI) and the dorsal anterior cingulate cortex (dACC), that reacts to salient stimuli. Exaggerated threat detection has been a strong candidate for explaining the hyperarousal symptom of PTSD. Since these models are not mutually exclusive and each focus on a specific brain region which explains certain symptoms of PTSD, it is highly possible that PTSD is a heterogeneous disorder resulting from different pathophysiological mechanisms.

Apart from that, we talked about the algortihmic models of PTSD in theory-driven approach. Algorithmic models of PTSD are mainly instantiated by reinforcement learning (RL) models. We introduced the reinforcement learning framework and brief discussed the suitability of RL model in PTSD studies. We exhaustively described three model-free RL: (1) Rescorla-Wagner (RW) model, (2) Pearce-Hall (PH) model and (3) Gain-loss model and one model-based RL: latent-state (LS) model. Among them, RW model and PH model have been extensively used in the PTSD studies. Consistent with the theoretical discussion, several PTSD studies have shown that the PH model provides a better fit than the RW model for behavioural data [9][35][46]. In addition, the higher associability weight (parameter from PH model) was linked

to higher PTSD symptom severity score [9][35] which shows the potential of using associability weight as the computational marker in PTSD diagnosis. On the neural level, PTSD has been found to have a significant relationship with the neural encoding of associability [9][35]. However, the localization of associability-related activation and the neural computation of associability varied across different studies. Hence, future research should further develop and confirm these initial findings. In contrast to the RW model and PH model, there is not many papers about the Gain-loss model in PTSD research. However, the finding from Brown et al. indicate the veterans with severe PTSD symptoms have different interpretation of the ambiguous "no-feedback" outcome compared to the control group [9]. There is much room for further progress in determining whether there are differences in gain or loss learning between PTSD people and healthy people. Other than the three model-free RLs which only include simple trial-and-error learning, researchers applied model-based RL which develop an internal model of the environment in PTSD research. In Letkiewicz et al.'s study, the LS model outperformed the RW and PH models [46]. However, Letkiewicz et al.'s finding from fMRI analysis did not agree with their initial hypothesis. Thus, more research is needed to examine the usage of model-based RL in PTSD studies.

Researchers can answer questions about mental illness by mapping brain dysfunction to specific computational markers (e.g. associability weight and delta beliefs). However, careful considerations are needed during model-based analysis. In chapter 5, we used a threat and safety reversal learning task as our imaginary experiment where the experimental parameters are set up as the Homan et al.'s PTSD study [35]. To demonstrate a common practice of computational modelling in psychiatric research, we implemented the RW model in Python from scratch accordingly to the imaginary experiment by following Wilson et al.'s guideline[87]. We use the implemented RW model to generate artificial data. Through simulation, we ensure the RW model captures the learning behaviours that the experiment intends to generate and hypothesise that the PTSD participants might assign more weight to the prediction error. By running a successful parameter recovery on the artificial data, we increase the validity of the best-fitting parameter values in describing the real behavioural data. The RW model can then be fitted to behavioural data collected from the real experiment, and the best-fitting parameter values can potentially function as an indicator of PTSD. This is the approach used in Homan et al.'s study. From there, they fitted the RW model to real SCR data from trials of the healthy control group and PTSD patient group. They then analysed the model parameters to find out if there were any statistical differences between the two groups. Though several PTSD studies have shown that the PH model provides a better fit than the RW model for behavioural data [9][35][46], the RW model is sufficient for demonstrating the procedure and was chosen for simplicity.

Bibliography

[1] Computational Psychiatry (CPSY) http://computationalpsychiatry.org/home.html.

[2] Rany Abend, Diana Burk, Sonia G Ruiz, Andrea L Gold, Julia L Napoli, Jennifer C Britton, Kalina J Michalska, Tomer Shechner, Anderson M Winkler, Ellen Leibenluft, Daniel S Pine, and Bruno B Averbeck. Computational modeling of threat learning reveals links with anxiety and neuroanatomy in humans. *eLife*, 11:e66169, April 2022. Publisher: eLife Sciences Publications, Ltd.

[3] Elisabetta Baldi, Carlo Ambrogi Lorenzini, and Corrado Bucherelli. Footshock intensity and generalization in contextual and auditory-cued fear conditioning in the rat. *Neurobiology of Learning and Memory*, 81(3):162–166, May 2004.

[4] Daniel Bennett, Steven M. Silverstein, and Yael Niv. The Two Cultures of Computational Psychiatry. *JAMA psychiatry*, 76(6):563–564, June 2019.

[5] Jens Blechert, Tanja Michael, Noortje Vriends, Jürgen Margraf, and Frank H. Wilhelm. Fear conditioning in posttraumatic stress disorder: Evidence for delayed extinction of autonomic, experiential, and behavioural responses. *Behaviour Research and Therapy*, 45(9):2019–2033, September 2007.

[6] Mark E. Bouton. *Learning and Behavior: A Contemporary Synthesis*. Sinauer Associates, Sunderland, Mass, February 2007.

[7] C. R. Brewin, B. Andrews, and J. D. Valentine. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *Journal of Consulting and Clinical Psychology*, 68(5):748–766, October 2000.

[8] Kay H. Brodersen, Lorenz Deserno, Florian Schlagenhauf, Zhihao Lin, Will D. Penny, Joachim M. Buhmann, and Klaas E. Stephan. Dissecting psychiatric spectrum disorders by generative embedding. *NeuroImage: Clinical*, 4:98–111, January 2014.

[9] Vanessa M Brown, Lusha Zhu, John M Wang, B Christopher Frueh, Brooks King-Casas, and Pearl H Chiu. Associability-modulated loss learning is increased in posttraumatic stress disorder. *eLife*, 7:e30150, January 2018. Publisher: eLife Sciences Publications, Ltd.

[10] Louisa Burriss, Edwin Ayers, and D. A. Powell. Combat veterans show normal discrimination during differential trace eyeblink conditioning, but increased re-

sponsivity to the conditioned and unconditioned stimulus. *Journal of Psychiatric Research*, 41(9):785–794, 2007. Place: Netherlands Publisher: Elsevier Science.

[11] Robert R. Bush and Frederick Mosteller. *Stochastic models for learning*. Stochastic models for learning. John Wiley & Sons, Inc., Oxford, England, 1955. Pages: xvi, 365.

[12] Luke J. Chang, Bradley B. Doll, Mascha van 't Wout, Michael J. Frank, and Alan G. Sanfey. Seeing is believing: Trustworthiness as a dynamic belief. *Cognitive Psychology*, 61(2):87–105, September 2010.

[13] Charel van Hoof. Learn by example: Active Inference in the brain -1.

[14] Adam Mourad Chekroud, Ryan Joseph Zotti, Zarrar Shehzad, Ralitza Gueorguieva, Marcia K Johnson, Madhukar H Trivedi, Tyrone D Cannon, John Harrison Krystal, and Philip Robert Corlett. Cross-trial prediction of treatment outcome in depression: a machine learning approach. *The Lancet Psychiatry*, 3(3):243–250, March 2016.

[15] J. M. Cisler, B. A. Sigel, J. S. Steele, S. Smitherman, K. Vanderzee, J. Pemberton, T. L. Kramer, and C. D. Kilts. Changes in functional connectivity of the amygdala during cognitive reappraisal predict symptom reduction during trauma-focused cognitive–behavioral therapy among adolescent girls with post-traumatic stress disorder. *Psychological Medicine*, 46(14):3013–3023, October 2016. Publisher: Cambridge University Press.

[16] Amy L. Cochran and Josh M. Cisler. A flexible and generalizable model of online latent-state learning. *PLOS Computational Biology*, 15(9):e1007331, September 2019. Publisher: Public Library of Science.

[17] Philip R. Corlett, Guillermo Horga, Paul C. Fletcher, Ben Alderson-Day, Katharina Schmack, and Albert R. Powers. Hallucinations and Strong Priors. *Trends in Cognitive Sciences*, 23(2):114–127, February 2019. Publisher: Elsevier.

[18] Jonathan R. T. Davidson, Dan J. Stein, Arieh Y. Shalev, and Rachel Yehuda. Posttraumatic stress disorder: acquisition, recognition, course, and treatment. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 16(2):135–147, 2004.

[19] Peter Dayan, Geoffrey E. Hinton, Radford M. Neal, and Richard S. Zemel. The Helmholtz Machine. *Neural Computation*, 7(5):889–904, September 1995.

[20] Jacek Dbiec and Joseph LeDoux. The Amygdala and the Neural Pathways of Fear. In Joseph E. LeDoux, Terrence Keane, and Peter Shiromani, editors, *Post-Traumatic Stress Disorder: Basic Science and Clinical Practice*, pages 23–38. Humana Press, Totowa, NJ, 2009.

[21] Charles DeBattista, Gustavo Kinrys, Daniel Hoffman, Corey Goldstein, John Zajecka, James Kocsis, Martin Teicher, Steven Potkin, Adrian Preda, Gurmeet Multani, Len Brandt, Mark Schiller, Dan Iosifescu, and Maurizio Fava. The use of referenced-EEG (rEEG) in assisting medication selection for the treatment of depression. *Journal of Psychiatric Research*, 45(1):64–75, January 2011.

[22] Robert J. DeRubeis, Zachary D. Cohen, Nicholas R. Forand, Jay C. Fournier, Lois A. Gelfand, and Lorenzo Lorenzo-Luaces. The Personalized Advantage Index: translating research on prediction into individualized treatment recommendations. A demonstration. *PloS One*, 9(1):e83875, 2014.

[23] Otello Desiderato. Generalization of acquired fear as a function of CS intensity and number of acquisition trials. *Journal of Experimental Psychology*, 67(1):41–47, 1964. Place: US Publisher: American Psychological Association.

[24] Joseph E. Dunsmoor, Marijn C. W. Kroes, Stephen H. Braren, and Elizabeth A. Phelps. Threat intensity widens fear generalization gradients. *Behavioral Neuroscience*, 131(2):168–175, April 2017.

[25] Joseph E. Dunsmoor and Gregory L. Murphy. Categories, concepts, and conditioning: how humans generalize fear. *Trends in Cognitive Sciences*, 19(2):73–77, February 2015.

[26] Michael J. Frank, Ahmed A. Moustafa, Heather M. Haughey, Tim Curran, and Kent E. Hutchison. Genetic triple dissociation reveals multiple roles for dopamine in reinforcement learning. *Proceedings of the National Academy of Sciences*, 104(41):16311–16316, October 2007. Publisher: Proceedings of the National Academy of Sciences.

[27] Stefan Frässle, Andre F. Marquand, Lianne Schmaal, Richard Dinga, Dick J. Veltman, Nic J. A. van der Wee, Marie-José van Tol, Dario Schöbi, Brenda W. J. H. Penninx, and Klaas E. Stephan. Predicting individual clinical trajectories of depression with generative embedding. *NeuroImage: Clinical*, 26:102213, January 2020.

[28] Supriya Ghosh and Sumantra Chattarji. Neuronal encoding of the switch from specific to generalized fear. *Nature Neuroscience*, 18(1):112–120, January 2015. Number: 1 Publisher: Nature Publishing Group.

[29] Charles F. Gillespie, Bekh Bradley, Kristie Mercer, Alicia K. Smith, Karen Conneely, Mark Gapen, Tamara Weiss, Ann C. Schwartz, Joseph F. Cubells, and Kerry J. Ressler. Trauma exposure and stress-related disorders in inner city primary care patients. *General Hospital Psychiatry*, 31(6):505–514, November 2009.

[30] Liesbet Goossens, Stefan Sunaert, Ronald Peeters, Eric J. L. Griez, and Koen R. J. Schruers. Amygdala Hyperfunction in Phobic Fear Normalizes After Exposure. *Biological Psychiatry*, 62(10):1119–1125, November 2007.

[31] Anthony A. Grace, Stan B. Floresco, Yukiori Goto, and Daniel J. Lodge. Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. *Trends in Neurosciences*, 30(5):220–227, May 2007.

[32] C. Grillon and C. A. Morgan. Fear-potentiated startle conditioning to explicit and contextual cues in Gulf War veterans with posttraumatic stress disorder. *Journal of Abnormal Psychology*, 108(1):134–142, February 1999.

[33] Rachel M. Guthrie and Richard A. Bryant. Extinction learning before trauma and subsequent posttraumatic stress. *Psychosomatic Medicine*, 68(2):307–311, April 2006.

[34] Helene Haker, Maya Schneebeli, and Klaas Enno Stephan. Can Bayesian Theories of Autism Spectrum Disorder Help Improve Clinical Practice? *Frontiers in Psychiatry*, 7, 2016.

[35] Philipp Homan, Ifat Levy, Eric Feltham, Charles Gordon, Jingchu Hu, Jian Li, Robert H. Pietrzak, Steven Southwick, John H. Krystal, Ilan Harpaz-Rotem, and Daniela Schiller. Neural computations of threat in the aftermath of combat trauma. *Nature Neuroscience*, 22(3):470–476, March 2019. Number: 3 Publisher: Nature Publishing Group.

[36] Gernot Horstmann and Arvid Herwig. Surprise attracts the eyes and binds the gaze. *Psychonomic Bulletin & Review*, 22(3):743–749, June 2015.

[37] Jonathon R. Howlett, Jessica Bomyea, Katia M. Harlé, and Alan N. Simmons. Symptoms of Posttraumatic Stress Disorder are Associated with Exaggerated Neural Response to Surprising Errors. *Journal of Traumatic Stress*, 34(1):172–181, February 2021.

[38] Quentin J. M. Huys, Tiago V. Maia, and Michael J. Frank. Computational psychiatry as a bridge from neuroscience to clinical applications. *Nature Neuroscience*, 19(3):404–413, March 2016. Number: 3 Publisher: Nature Publishing Group.

[39] Laurent Itti and Pierre Baldi. Bayesian surprise attracts human attention. *Vision Research*, 49(10):1295–1306, June 2009.

[40] H. Kaye and J. M. Pearce. The strength of the orienting response during Pavlovian conditioning. *Journal of Experimental Psychology. Animal Behavior Processes*, 10(1):90–109, January 1984.

[41] Ahmad Khodayari-Rostamabad, James P. Reilly, Gary M. Hasey, Hubert de Bruin, and Duncan J. Maccrimmon. A machine learning approach using EEG data to predict response to SSRI treatment for major depressive disorder. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, 124(10):1975–1985, October 2013.

[42] M. E. Le Pelley. The role of associative history in models of associative learning: A selective review and a hybrid model. *The Quarterly Journal of Experimental Psychology Section B*, 57(3):193–243, July 2004. Publisher: Routledge _eprint: https://doi.org/10.1080/02724990344000141.

[43] Joseph E. LeDoux. Emotion Circuits in the Brain. *Annual Review of Neuroscience*, 23(1):155–184, 2000. _eprint: https://doi.org/10.1146/annurev.neuro.23.1.155.

[44] Elise Lesage and Elliot A. Stein. Networks Associated with Reward. In Donald W. Pfaff and Nora D. Volkow, editors, *Neuroscience in the 21st Century*, pages 1–27. Springer, New York, NY, 2016.

[45] Allison M. Letkiewicz, Amy L. Cochran, and Josh M. Cisler. Frontoparietal network activity during model-based reinforcement learning updates is reduced among adolescents with severe sexual abuse. *Journal of Psychiatric Research*, 145:256–262, January 2022.

[46] Allison M. Letkiewicz, Amy L. Cochran, Anthony A. Privratsky, G. Andrew James, and Josh M. Cisler. Value estimation and latent-state update-related neural activity during fear conditioning predict posttraumatic stress disorder symptom severity. *Cognitive, Affective, & Behavioral Neuroscience*, 22(1):199–213, February 2022.

[47] Israel Liberzon and James L. Abelson. Context Processing and the Neurobiology of Post-Traumatic Stress Disorder. *Neuron*, 92(1):14–30, October 2016. Publisher: Elsevier.

[48] Shmuel Lissek, Arter L. Biggs, Stephanie J. Rabin, Brian R. Cornwell, Ruben P. Alvarez, Daniel S. Pine, and Christian Grillon. Generalization of conditioned fear-potentiated startle in humans: Experimental validation and clinical relevance. *Behaviour Research and Therapy*, 46(5):678–687, May 2008.

[49] Shmuel Lissek and Brian van Meurs. Learning Models of PTSD: Theoretical Accounts and Psychobiological Evidence. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology*, 98(3 Pt 2):594–605, December 2015.

[50] Tiago V. Maia. Reinforcement learning, conditioning, and the brain: Successes and challenges. *Cognitive, Affective, & Behavioral Neuroscience*, 9(4):343–364, December 2009.

[51] Tiago V. Maia. Introduction to the Series on Computational Psychiatry. *Clinical Psychological Science*, 3(3):374–377, May 2015. Publisher: SAGE Publications Inc.

[52] Tiago V. Maia and Michael J. Frank. From reinforcement learning models to psychiatric and neurological disorders. *Nature Neuroscience*, 14(2):154–162, February 2011. Number: 2 Publisher: Nature Publishing Group.

[53] Aaron T. Mattfeld, Mark A. Gluck, and Craig E.L. Stark. Functional specialization within the striatum along both the dorsal/ventral and anterior/posterior axes during associative learning via reward and punishment. *Learning & Memory*, 18(11):703–711, November 2011.

[54] Maarten Mennes, Bharat B. Biswal, F. Xavier Castellanos, and Michael P. Milham. Making data sharing work: The FCP/INDI experience. *NeuroImage*, 82:683–691, November 2013.

[55] Mohammed R. Milad, Scott P. Orr, Natasha B. Lasko, Yuchiao Chang, Scott L. Rauch, and Roger K. Pitman. Presence and acquired origin of reduced recall for fear extinction in PTSD: Results of a twin study. *Journal of Psychiatric Research*, 42(7):515–520, June 2008.

[56] Mohammed R. Milad, Roger K. Pitman, Cameron B. Ellis, Andrea L. Gold, Lisa M. Shin, Natasha B. Lasko, Mohamed A. Zeidan, Kathryn Handwerger,

Scott P. Orr, and Scott L. Rauch. Neurobiological Basis of Failure to Recall Extinction Memory in Posttraumatic Stress Disorder. *Biological Psychiatry*, 66(12):1075–1082, December 2009.

[57] Ralph R. Miller, Robert C. Barnet, and Nicholas J. Grahame. Assessment of the Rescorla-Wagner model. *Psychological Bulletin*, 117:363–386, 1995. Place: US Publisher: American Psychological Association.

[58] Charles S. Milliken, Jennifer L. Auchterlonie, and Charles W. Hoge. Longitudinal assessment of mental health problems among active and reserve component soldiers returning from the Iraq war. *JAMA*, 298(18):2141–2148, November 2007.

[59] Rajendra A. Morey, Andrea L. Gold, Kevin S. LaBar, Shannon K. Beall, Vanessa M. Brown, Courtney C. Haswell, Jessica D. Nasser, H. Ryan Wagner, Gregory McCarthy, and Mid-Atlantic MIRECC Workgroup. Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. *Archives of General Psychiatry*, 69(11):1169–1178, November 2012.

[60] Catherine E. Myers, Ahmed A. Moustafa, Jony Sheynin, Kirsten M. VanMeenen, Mark W. Gilbertson, Scott P. Orr, Kevin D. Beck, Kevin C. H. Pang, and Richard J. Servatius. Learning to Obtain Reward, but Not Avoid Punishment, Is Affected by Presence of PTSD Symptoms in Male Veterans: Empirical Data and Computational Model. *PLOS ONE*, 8(8):e72508, August 2013. Publisher: Public Library of Science.

[61] K. M. Myers and M. Davis. Mechanisms of fear extinction. *Molecular Psychiatry*, 12(2):120–150, February 2007. Number: 2 Publisher: Nature Publishing Group.

[62] Seth D. Norrholm, Tanja Jovanovic, Ilana W. Olin, Lauren A. Sands, India Karapanou, Bekh Bradley, and Kerry J. Ressler. Fear extinction in traumatized civilians with posttraumatic stress disorder: relation to symptom severity. *Biological Psychiatry*, 69(6):556–563, March 2011.

[63] John P. O'doherty, Alan Hampton, and Hackjin Kim. Model-Based fMRI and Its Application to Reward Learning and Decision Making. *Annals of the New York Academy of Sciences*, 1104(1):35–53, 2007. _eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1196/annals.1390.022.

[64] Scott P. Orr, Linda J. Metzger, Natasha B. Lasko, Michael L. Macklin, Tuvia Peri, and Roger K. Pitman. De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. *Journal of Abnormal Psychology*, 109(2):290. Publisher: US: American Psychological Association.

[65] Graziella Orrù, William Pettersson-Yeo, Andre F. Marquand, Giuseppe Sartori, and Andrea Mechelli. Using Support Vector Machine to identify imaging biomarkers of neurological and psychiatric disease: A critical review. *Neuroscience & Biobehavioral Reviews*, 36(4):1140–1152, April 2012.

[66] Colin J. Palmer, Rebecca P. Lawson, and Jakob Hohwy. Bayesian approaches to autism: Towards volatility, action, and behavior. *Psychological Bulletin*, 143(5):521–542, May 2017.

[67] Stefano Palminteri, Damian Justo, Céline Jauffret, Beth Pavlicek, Aurélie Dauta, Christine Delmaire, Virginie Czernecki, Carine Karachi, Laurent Capelle, Alexandra Durr, and Mathias Pessiglione. Critical Roles for Anterior Insula and Dorsal Striatum in Punishment-Based Avoidance Learning. *Neuron*, 76(5):998–1009, December 2012.

[68] J. M. Pearce and G. Hall. A model for Pavlovian learning: variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psychological Review*, 87(6):532–552, November 1980.

[69] Tuvia Peri, Gershon Ben-Shakhar, Scott P Orr, and Arieh Y Shalev. Psychophysiologic assessment of aversive conditioning in posttraumatic stress disorder. *Biological Psychiatry*, 47(6):512–519, March 2000.

[70] Elizabeth A. Phelps and Joseph E. LeDoux. Contributions of the Amygdala to Emotion Processing: From Animal Models to Human Behavior. *Neuron*, 48(2):175–187, October 2005.

[71] Daniel Preciado, Jaap Munneke, and Jan Theeuwes. Was that a threat? Attentional biases by signals of threat. *Emotion (Washington, D.C.)*, 17(3):478–486, April 2017.

[72] Scott L Rauch, Paul J Whalen, Lisa M Shin, Sean C McInerney, Michael L Macklin, Natasha B Lasko, Scott P Orr, and Roger K Pitman. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biological Psychiatry*, 47(9):769–776, May 2000.

[73] R. Rescorla and Allan Wagner. A theory of Pavlovian conditioning: The effectiveness of reinforcement and non-reinforcement. *Classical Conditioning: Current Research and Theory*, January 1972.

[74] Barbara Olasov Rothbaum and Ann C. Schwartz. Exposure therapy for posttraumatic stress disorder. *American Journal of Psychotherapy*, 56(1):59–75, 2002.

[75] Daniela Schiller, Ifat Levy, Yael Niv, Joseph E. LeDoux, and Elizabeth A. Phelps. From Fear to Safety and Back: Reversal of Fear in the Human Brain. *Journal of Neuroscience*, 28(45):11517–11525, November 2008. Publisher: Society for Neuroscience Section: Articles.

[76] Lianne Schmaal, Andre F. Marquand, Didi Rhebergen, Marie-José van Tol, Henricus G. Ruhé, Nic J. A. van der Wee, Dick J. Veltman, and Brenda W. J. H. Penninx. Predicting the Naturalistic Course of Major Depressive Disorder Using Clinical and Multimodal Neuroimaging Information: A Multivariate Pattern Recognition Study. *Biological Psychiatry*, 78(4):278–286, August 2015.

[77] William W. Seeley. The Salience Network: A Neural System for Perceiving and Responding to Homeostatic Demands. *The Journal of Neuroscience*, 39(50):9878–9882, December 2019.

[78] Peggy Series. *Computational Psychiatry: A Primer*. MIT Press, November 2020. Google-Books-ID: U5QFEAAAQBAJ.

[79] Rebecca K. Sripada, Anthony P. King, Robert C. Welsh, Sarah N. Garfinkel, Xin Wang, Chandra S. Sripada, and Israel Liberzon. Neural Dysregulation in Posttraumatic Stress Disorder: Evidence for Disrupted Equilibrium between Salience and Default Mode Brain Networks. *Psychosomatic medicine*, 74(9):904–911, November 2012.

[80] Dan J. Stein, Katie A. McLaughlin, Karestan C. Koenen, Lukoye Atwoli, Matthew J. Friedman, Eric D. Hill, Andreas Maercker, Maria Petukhova, Victoria Shahly, Mark van Ommeren, Jordi Alonso, Guilherme Borges, Giovanni de Girolamo, Peter de Jonge, Koen Demyttenaere, Silvia Florescu, Elie G. Karam, Norito Kawakami, Herbert Matschinger, Michail Okoliyski, Jose Posada-Villa, Kate M. Scott, Maria Carmen Viana, and Ronald C. Kessler. DSM-5 and ICD-11 definitions of posttraumatic stress disorder: investigating "narrow" and "broad" approaches. *Depression and Anxiety*, 31(6):494–505, June 2014.

[81] Philipp Sterzer, Rick A. Adams, Paul Fletcher, Chris Frith, Stephen M. Lawrie, Lars Muckli, Predrag Petrovic, Peter Uhlhaas, Martin Voss, and Philip R. Corlett. The Predictive Coding Account of Psychosis. *Biological Psychiatry*, 84(9):634–643, November 2018.

[82] Amos Tversky and Daniel Kahneman. Loss Aversion in Riskless Choice: A Reference-Dependent Model*. *The Quarterly Journal of Economics*, 106(4):1039–1061, November 1991.

[83] L.Q. Uddin. *Salience Network of the Human Brain*. August 2016. Pages: 34.

[84] Sanne J H van Rooij, Mitzy Kennis, Matthijs Vink, and Elbert Geuze. Predicting Treatment Outcome in PTSD: A Longitudinal Functional MRI Study on Trauma-Unrelated Emotional Processing. *Neuropsychopharmacology*, 41(4):1156–1165, March 2016.

[85] Xiao-Jing Wang and John H. Krystal. Computational Psychiatry. *Neuron*, 84(3):638–654, November 2014.

[86] Thomas V. Wiecki, Jeffrey Poland, and Michael J. Frank. Model-Based Cognitive Neuroscience Approaches to Computational Psychiatry: Clustering and Classification. *Clinical Psychological Science*, 3(3):378–399, May 2015. Publisher: SAGE Publications Inc.

[87] Robert C Wilson and Anne GE Collins. Ten simple rules for the computational modeling of behavioral data. *eLife*, 8:e49547, November 2019. Publisher: eLife Sciences Publications, Ltd.

[88] Thomas Wolfers, Jan K. Buitelaar, Christian F. Beckmann, Barbara Franke, and Andre F. Marquand. From estimating activation locality to predicting disorder: A review of pattern recognition for neuroimaging-based psychiatric diagnostics. *Neuroscience & Biobehavioral Reviews*, 57:328–349, October 2015.

[89] Lei Zhang, Lukas Lengersdorff, Nace Mikus, Jan Gläscher, and Claus Lamm. Using reinforcement learning models in social neuroscience: frameworks, pitfalls

and suggestions of best practices. *Social Cognitive and Affective Neuroscience*, 15(6):695–707, July 2020.

Appendix A

A.1 order A from Homan et al.'s study [35]

Trial	Presented cue(s)
1	Face A + electric shock
2	Face B
3	Face A
4	Face A + electric shock
5	Face B
6	Face A
7	Face A
8	Face B
9	Face A + electric shock
10	Face B
11	Face A + electric shock
12	Face A
13	Face B
14	Face A
15	Face B
16	Face B
17	Face A
18	Face A + electric shock
19	Face B
20	Face A
21	Face A
22	Face B
23	Face A
24	Face A + electric shock
25	Face B
26	Face A
27	Face B
28	Face A
29	Face A
30	Face B
31	Face B + electric shock
32	Face A
33	Face B

Trial	Presented cue(s)
34	Face B + electric shock
35	Face A
36	Face B
37	Face A
38	Face B
39	Face B
40	Face A
41	Face B + electric shock
42	Face B
43	Face A
44	Face B + electric shock
45	Face B
46	Face A
47	Face A
48	Face B
49	Face A
50	Face B + electric shock
51	Face B
52	Face A
53	Face B
54	Face B
55	Face A
56	Face B + electric shock
57	Face A
58	Face B
59	Face A
60	Face B
61	Face B + electric shock
62	Face A
63	Face A
64	Face B
65	Face B
66	Face A
67	Face B
68	Face A
69	Face B

A.2 Package requirement for running the Python code in A.3

```
# save the lines as requirement.txt
# run below command in terminal
# pip install -r requirement.txt

numpy == 1.23.1
pandas == 1.4.4
matplotlib == 3.5.2
matplotlib-inline == 0.1.6
arviz == 0.12.1
pymc3 == 3.11.4
theano-pymc == 1.1.2
theano == 1.0.5
scipy  == 1.9.1
```

A.3 Python code in ipynb format

```
# %%
import matplotlib
import numpy as np
import pandas as pd
import matplotlib.pyplot as plt
import theano
import theano.tensor as tt
import pymc3 as pm
import scipy.stats
import arviz as az
%matplotlib inline


theano.config.compute_test_value = 'ignore'
np.random.seed(2022)

# %%
# ptsd_scr.csv is a csv file from Homan et al.'s work where
# filepath is ./preproc_NotInMakefile/scr/ptsd_scr.csv
# obtain stimuli order from Homan et al.'s work
df = pd.read_csv("ptsd_scr.csv")
orderA = list(df.loc[df["id"]=="RV001"]["stim"])

def order_to_stim_and_shock(order):
    '''
    convert stimuli order from Homan et al.'s work to format
```

```
    that can be used in RW model

    returns:
    stim(list of int with size (69)): pseudorandomized order that
    stimuli were presented (1 = faceA present at that trial,
    0 = faceB present at that trial)

    shock(list of int with size (69)): order that the shock were
    presented (0 = shock absent, 1 = shock present)
    '''
    stim = []
    shock = []
    for i in orderA:
        if i == "CSplusUS":
            # 1 = cs+ (aka face A)
            stim.append(1)
            # 1 for shock present
            shock.append(1)
        elif (i == "CSminusUS"):
            # 0 = cs- (aka face B)
            stim.append(0)
            # 1 for shock present
            shock.append(1)
        elif (i == "CSplus"):
            # 1 = cs+ (aka face A)
            stim.append(1)
            # 0 for shock absent
            shock.append(0)
        else:
            # 0 = cs- (aka face B)
            stim.append(0)
            # 0 for shock absent
            shock.append(0)
    stim = np.array(stim,dtype=np.int64)
    shock = np.array(shock,dtype=np.int64)

    return stim, shock

def separate_combined_v(combined_v,order):
    '''
    separate the series of expected values into two lists according
    the type of stimuli (only include trials without shock)

    returns:
    v_stim_A(list of float): expected values of trials where
    face A was presented (without shock trial)
```

```
    v_stim_B(list of float): expected values of trials where
    face B was presented (without shock trial)
    '''
    v_stim_A = []
    v_stim_B = []
    for i in np.arange(len(orderA)):
        if (orderA[i] == "CSplus"):
            v_stim_A.append(combined_v[i])
        elif (orderA[i] == "CSminus"):
            v_stim_B.append(combined_v[i])
        elif (orderA[i] == "CSplusUS"):
            v_stim_A.append(combined_v[i])
        elif (orderA[i] == "CSminusUS"):
            v_stim_B.append(combined_v[i])

    return v_stim_A, v_stim_B


# %%
def simulate_Rescorla_Wagner(theta0,theta1,epsilon,lr,stim,shock):
    """ Simulate the Rescorla-Wagner model
    params:
        theta0(float): constant term for SCR mapping
        theta1(float): scale value for SCR mapping
        epsilon(float): error term for SCR mapping
        lr(float): learning rate of RW model which is
        between 0 to 1

        stim(list of int with size (69)): pseudorandomized order
        that stimuli were presented (1 = faceA present at that
        trial, 0 = faceB present at that trial)

        shock(list of int with size (69)): order that the shock
        were presented (0 = shock absent, 1 = shock present)
    returns:
        V(2d-list of float with size (2,69)): list containing list
        of expected value for each face

        mapped_scr(list of float with size (69)): a list of SCR
        reading which mapped from list of expected value
        of presented face
    """

    # store expected value of cs- and cs+ in [cs-,cs+]
    # for each trials
```

```
    V_list = np.zeros((2, 69))
    # reflecting the assumption that getting a shock or not
    # was equally for the first trial
    V = [0.5, 0.5]

    combined_v = []
    for t in range(69):

        # store expected value of trial t
        V_list[:,t] = V
        # update expected values
        prediction_error = shock[t] - V[stim[t]]
        V[stim[t]] = V[stim[t]] + lr * prediction_error
        combined_v.append(V[stim[t]])

    mapped_scr = theta0 + (theta1*np.array(combined_v)) + epsilon
    return V_list,mapped_scr

def update_RW(stim_matrix,shock_matrix,vS,combined_v,
              lr,no_subjects):
    """
    update function of Rescorla-Wagner model, which will be used
    in pymc3 model fitting

    returns:
    vS: list of [[v_list for CS-, v_list for CS+],...] where
    shape = (no_subjects,2)

    combined_v: a series of expected value by combining expected
    value of face A and face B in the order of the
    appearance of cue
    """

    pe = shock_matrix - vS[tt.arange(no_subjects), stim_matrix]

    # vS is a list of [[v for CS-, v for CS+],...] where
    # shape = (no_subjects,2)
    vS = tt.set_subtensor(vS[tt.arange(no_subjects),stim_matrix],
         vS[tt.arange(no_subjects),stim_matrix] + lr * pe)

    #if stim = 1, append v for cs+, else append v for cs-
    combined_v =
    tt.set_subtensor(combined_v[tt.arange(no_subjects),0],
    (tt.switch(tt.eq(stim_matrix,1), vS[tt.arange(no_subjects),1],
    vS[tt.arange(no_subjects),0])))
```

```
    return vS, combined_v


# %%
#########################################################
# code for the fitting and parameter recovery part
#########################################################

### create fake data ###
stim, shock = order_to_stim_and_shock(orderA)
#no of trials is fixed at 69 to correspond the experiment design
no_trials = 69
no_subjects = 60
mapped_scr_matrix = np.zeros(shape=(no_trials,no_subjects))

lr_ = np.random.uniform(low=0.0, high=1.0, size=no_subjects)
theta0_ = np.random.normal(loc=0.0, scale=1.0)
theta1_ = np.random.normal(loc=0.0, scale=1.0)
for i in range(no_subjects):
    epsilon = np.random.normal(loc=0.0, scale=0.05)
    v_list,mapped_scr = simulate_Rescorla_Wagner(theta0_,theta1_,
    epsilon,lr_[i],stim,shock)
    mapped_scr_matrix[:,i] = mapped_scr

# remove trial with shock from scr data to avoid contamination
idx = [i for i in np.arange(len(shock)) if shock[i] == 1]
mapped_scr_matrix =  np.delete(mapped_scr_matrix, idx, axis=0)

# %%
### preparation for model fitting ###
# prepare stim matrix with shape = (no_trials,no_subjects)
# for feeding into the update_RW function
stim_ = stim.reshape(no_trials,1)
stim_matrix = np.repeat(stim_,no_subjects,axis=1)
stim_matrix = tt.as_tensor_variable(stim_matrix)

# prepare shock matrix with shape = (no_trials,no_subjects)
# for feeding into the update_RW function
shock_ = shock.reshape(no_trials,1)
shock_matrix = np.repeat(shock_,no_subjects,axis=1)
shock_matrix = tt.as_tensor_variable(shock_matrix)

# prepare index for row removal
idx = [i for i in np.arange(len(shock)) if shock[i] != 1]

# %%
```

```
### hierarchical Bayesian model fitting ###
with pm.Model() as RW_model:
    ################################################
    # free paramters from mapping eqution
    beta0 = pm.Normal('beta0',0,20)
    beta1 = pm.Normal('beta1',0,20)
    ################################################
    # free parameter from learning equation

    # group-level mean and standard deviation of learning rate
    lr_hypermu = pm.Normal('lr_hypermu', 0,1)
    lr_hypersd = pm.HalfCauchy('lr_hypersd',beta=5)
    # individual learning rate is drawn from the
    # group-level normal distribution
    lr_v = pm.Normal('lr_v',lr_hypermu,lr_hypersd,
           shape=no_subjects)
    # Convert unconstrained values into the interval [0,1]
    # as the learning rate is bounded between 0 and 1
    lr = pm.Deterministic('lr', pm.math.invlogit(lr_v))
    ################################################
    # step function
    vS = 0.5 * tt.ones((no_subjects,2), dtype='float64')
    combined_v = 0.5 * tt.ones((no_subjects,1), dtype='float64')

    outputs, updates = theano.scan(
        fn=update_RW,
        sequences=[stim_matrix, shock_matrix],
        outputs_info=[vS, combined_v],
        non_sequences=[lr, no_subjects])

    combined_v_ = outputs[1].reshape((no_trials,no_subjects))
    mapped_scr_model = beta1*combined_v_ + beta0

    #remove rows that represent shock to avoid contamination
    mapped_scr_model = mapped_scr_model[idx]
    ################################################

    # Model error
    eps = pm.HalfCauchy('eps', beta=5,testval=1.0)

    # Data likelihood
    scrs = pm.Normal('scrs',mapped_scr_model,eps,
           observed=mapped_scr_matrix)

    ################################################
    trace = pm.sample(1000,target_accept=0.9, chains=4,
```

```
                    cores=10, return_inferencedata=True)


# %%
pm.traceplot(trace)

# %%
a = az.summary(trace, var_names='lr')['mean']
print(a.values)

# %%
print(lr_)

# %%
# ################################################
# # code to produce correlation plot
# ################################################
plt.title("Learning rate (\u03B2) of 60 participants")
plt.ylabel("recovered \u03B2")
plt.xlabel("simulated \u03B2")
plt.scatter(lr_,a.values)
plt.show()
# std_error: 0.05 & no_subjects: 60 & std of lr_hypermu: 1
scipy.stats.pearsonr(lr_, a)


# %%
# ################################################
# # code to produce figures for simulation section
# ################################################

stim, shock = order_to_stim_and_shock(orderA)
for i in [0,0.2,0.4,0.6,0.8,1]:
    theta0 = 0 #[-1,0,1]
    theta1 = 1 #[-1,0,1]
    lr = i #[0,0.2,0.4,0.6,0.8,1]
    epsilon = 0
    v_list,combined_v = simulate_Rescorla_Wagner(theta0,theta1,
                        epsilon,lr,stim,shock)

    v_stim_A, v_stim_B = separate_combined_v(combined_v,orderA)
    plt.plot(range(len(v_stim_A)+1), [0.5]+v_stim_A, 'm-',
             alpha=.6, label='face A(shock in acquisition)')
    plt.plot(range(len(v_stim_B)+1), [0.5]+v_stim_B, 'r--',
             alpha=.6, label='face B(shock in reversal)')
```

```
    plt.xlabel('trials')
    plt.ylabel('expected value')
    plt.title('RW model ('+'\u03B2 = ' + str(lr) + ',
              \u03B8\u2080 = '+str(theta0)+ ',
              \u03B8\u2081 = '+str(theta1)+',
              \u03B5 = '+str(epsilon)+')')
    plt.legend()
    plt.ylim((0,1))
    # plt.savefig("RW_" + str(lr)+"_"+ str(theta0)+
                "_"+ str(theta1)+".png")
    plt.show()

# %%
```

Appendix B

Different settings of free parameters for the mapping equation

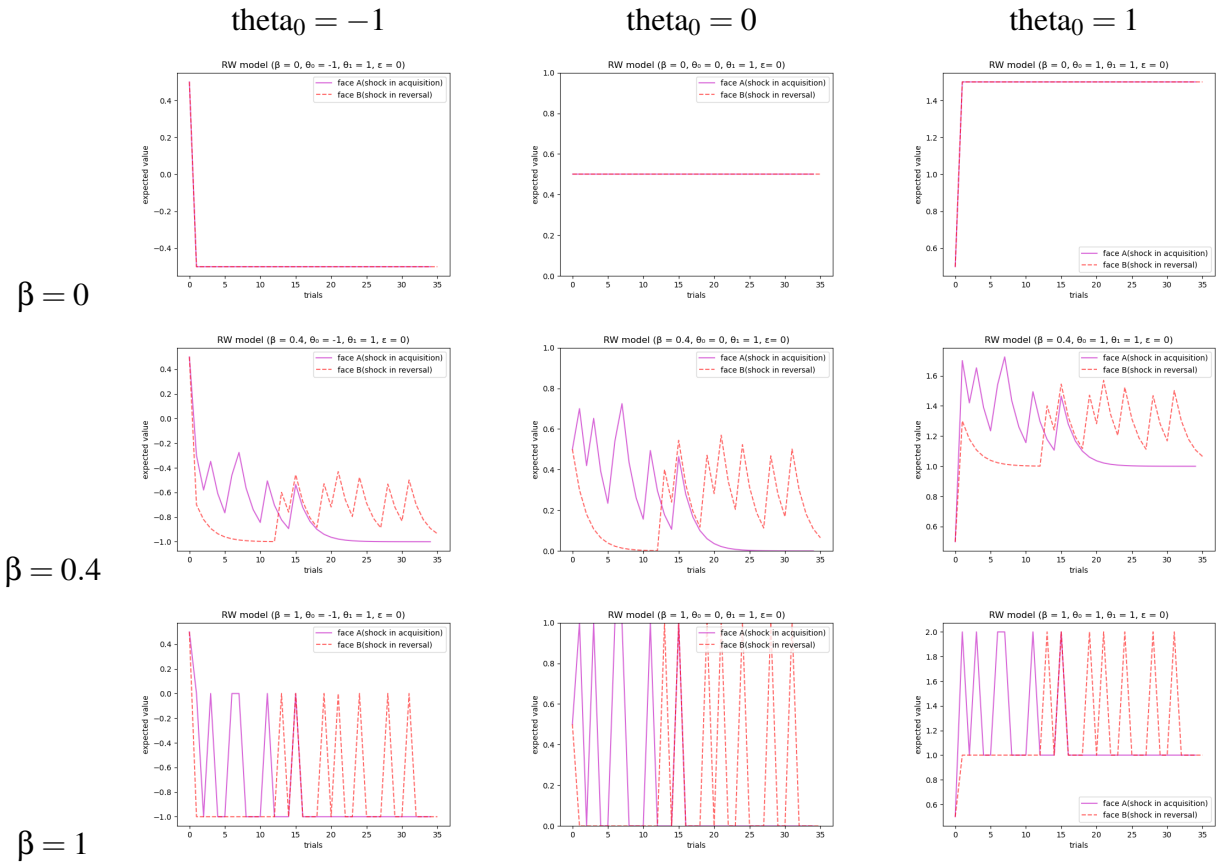


Figure B.1: Simulation of RW model where each row uses the same β and each column uses the same θ_0 with $\theta_1 = 1$ and $\varepsilon = 0$. The magenta line plot represents the expected value of face A in this experimental task, whereas the dotted red line plot represents the expected value of face B. We can see that the learning pattern varies along with the learning rate but not θ_0

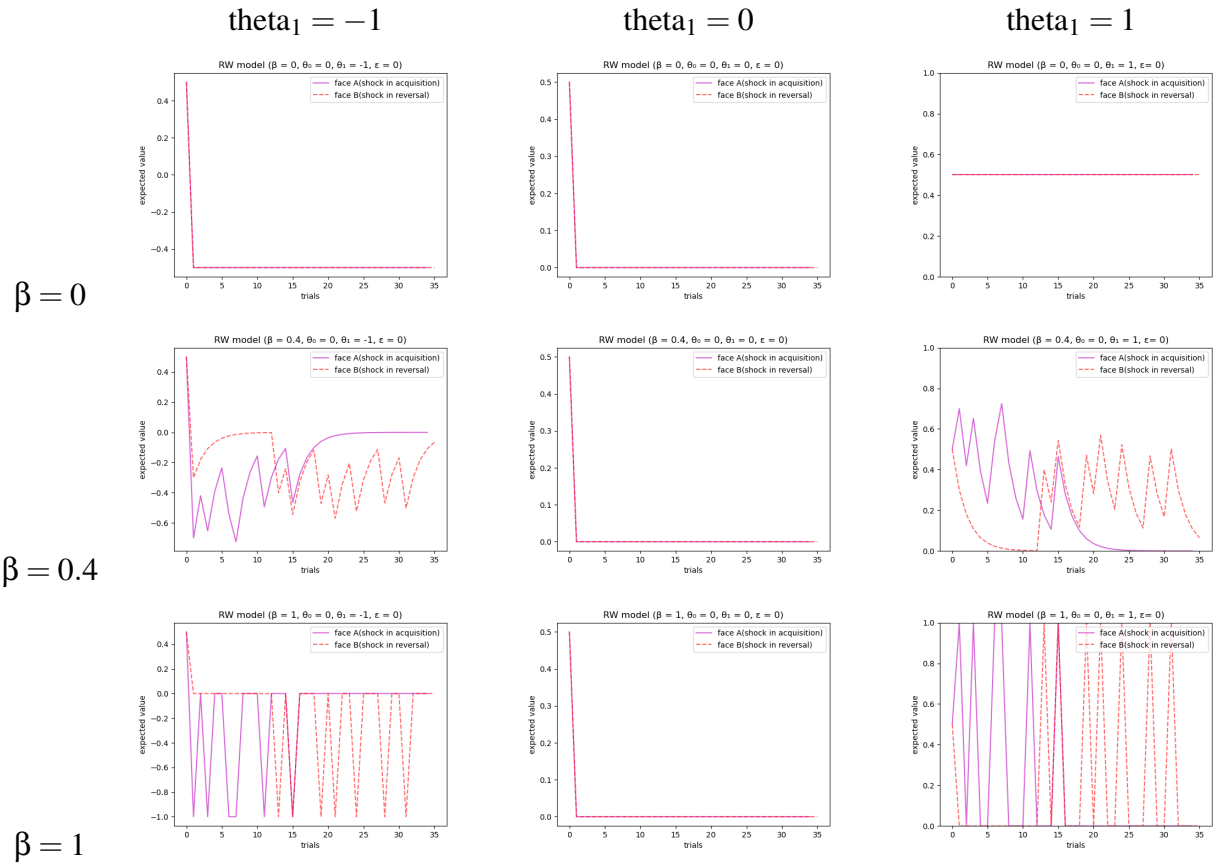


Figure B.2: Simulation of RW model where each row uses the same β and each column uses the same $theta_1$ with $\theta_0 = 0$ and $\varepsilon = 0$. The magenta line plot represents the expected value of face A in this experimental task, whereas the dotted red line plot represents the expected value of face B. We can see that the learning pattern varies along with the learning rate but not θ_1