CCN CW3

Reviewing *A Biologically Inspired Neural Network to Gain Insight Into the Mechanisms of Post-Traumatic Stress Disorder and Eye Movement Desensitisation Reprocessing Therapy*

April 2023

Word count: 3980

Contents

1 Introduction

Post-traumatic stress disorder (PTSD) is a psychiatric disorder characterised by recurrent intrusion symptoms and a persistent negative emotional state after directly experiencing or witnessing one or more connected traumatic events. These symptoms can be distressing memories or dreams, feeling detached from others or an inability to experience positive emotions. However, the arguably most characteristic symptom is the occurrence of flashbacks where triggered by a reminder (cue) of the event causing the individual to re-experiences the traumatic event as if it were happening again (American Psychiatric Association, 2013, pp. 271–280).

Two common short-term psychotherapy methods for PTSD are prolonged exposure therapy (PE) and eye movement desensitisation and reprocessing (EMDR). In exposure therapy, the patient is asked to gradually recall and process his experiences in a safe environment, typically over 8–12 weekly sessions. In EMDR sessions the patient is asked to imagine the traumatic experience while being stimulated bilaterally (Cusack et al., 2016). While it may seem somewhat natural that being able to process a traumatic event in a safe environment over an extended period is beneficial to reducing the stress associated with the event, the intuition behind EMDR's effectiveness is less obvious.

The publication by Mattera et al. (2022) that I am reviewing in this document, investigates the workings of EMDR therapy, in comparison to PE, by constructing a neural model of PTSD and subsequently simulating the two therapeutic methods. By fitting the model to experimental results from Nijdam et al. (2012), Mattera et al. attempt to gather evidence for a set of existing hypotheses that mean to explain the mechanics of EMDR.

In the following sections, I first introduce previous research on PTSD, PE and EMDR at the time of publication, and the background used by Mattera et al. to construct their model. I summarise the motivation behind their research and their hypotheses. Following, I provide a concise overview of their methods and results and finish the review by discussing the limitations and possible extensions.

2 Background

This section introduces prior research on the neurocircuitry of PTSD and the PE and EMDR therapy methods, which are relevant for understanding the model's construction, capabilities and limitations. It further provides a short background on prior models of PTSD as a comparison to the model proposed by Mattera et al. (2022).

Post-Traumatic Stress Disorder Across several neuroimaging studies, it has been found that PTSD patients tend to show a heightened activation of the amygdala (engaged in negative emotions; important for the consolidation of emotional memories) and insular cortex (responsible for self-awareness of emotion) in response to threatening stimuli or trauma cues. Activity in the hippocampus (engaged in contextual learning and memory) is also increased for stimuli associated with the trauma, which indicates that individuals have problems in identifying safe contexts (Fitzgerald et al., 2018; VanElzakker et al., 2018).

It is further found that the ventromedial, dorsomedial, ventrolateral, and dorsolateral prefrontal cortices (vmPFC, dmPFC, vlPFC, dlPFC) are under-engaged. These areas regulate the amygdala and their lower activation in PTSD patients can be a factor influencing the amygdala's stronger activity. The anterior cingulate cortex (ACC) is another brain region involved in modulating amygdala activation by judging the threat level, which has also been found to be under-engaged in PTSD patients (Fitzgerald et al., 2018; VanElzakker et al., 2018).

Prolonged Exposure Therapy From the neural description of the disorder, we can already presume that any therapy method will likely want to cause a lower activation of the amygdala for the negative stimuli, possibly by increasing regulation from the prefrontal cortex or the ACC. Indeed, prolonged exposure therapy has been shown to increase connectivity between the vmPFC, amygdala and hippocampus, thereby increasing inhibition of the amygdala by the vmPFC, causing it to be less active when exposed to trauma cues (Stojek et al., 2018).

Eye Movement Desensitisation and Reprocessing While 'the mechanisms of action of EMDR have been widely debated' (Mattera et al., 2022), research indicates that it may cause an increased blood flow and increased neural connectivity across the cortex in a state resembling Slow-Wave-Sleep (Miyamoto et al., 2017; Pagani & Cavallo, 2014). By activating this sleep-like state, EMDR supposedly leverages naturally occurring memory processing and consolidation.

Another observation is that AMPA receptors, which are partially responsible for synaptic transmission, on fear memory synapses in the amygdala are reduced. Harper et al. (2009) liken this to the removal of 'scarred tissue'.

Prior Models of PTSD While various computational models of PTSD have been proposed over the years, they tend to focus only on simulating a single symptom (Radell et al., 2017), such as Myers et al. (2013) for the avoidance of triggering situations or Smith et al. (2021) for hippocampal volume changes following the traumatic experience.

While Tryon (1998) theoretically proposed a mechanism to simulate flashbacks using a bidirectional associative network to allow for pattern completion, Mattera et al. (2022) appear to be the first to implement such a flashback mechanism for PTSD. To the best of my knowledge, they are also the first to simulate a therapy for the disorder.

3 Motivation and Hypotheses

As the mechanisms of action of PTSD, PE and in particular EMDR remain partially unknown, Mattera et al. (2022) attempt to gather evidence for existing hypotheses through computational means.

The hypotheses they aim to test regarding their regressive effect on PTSD are summarised from the previous sections as follows.

1. Prolonged exposure therapy increases the neural connectivity between the vmPFC and the amygdala, inhibiting the latter to better regulate the fear response (Stojek et al., 2018).
2. Eye movement desensitisation and reprocessing increases the blood flow and induces slow waves in the cortex, improving the connectivity across all cortical areas. This aids memory processing and consolidation, detaching the memory from the associated emotion (Harper et al., 2009; Miyamoto et al., 2017; Pagani et al., 2017).
3. Eye movement desensitisation and reprocessing increases the activation of the dlPFC, inhibiting the amygdala to better regulate the fear response (De Voogd et al., 2018).

As the above hypotheses on the mechanisms of PE and EMDR are phrased in physiological terms, Mattera et al. interpret said hypotheses as follows, to make them implementable in a simulation.

1. Increases in the neural connectivity between vmPFC and the amygdala, as a result of PE, can lead to faster learning. Thus, PE is expected to increase the learning rate between the vmPFC and amygdala.

2. An improved connectivity across the cortex, as a result of EMDR, can similarly be interpreted as an increase in the learning rate between all cortical areas.
3. A higher activation of the dlPFC, also caused by EMDR, increases the amygdala's inhibition and can thus be implemented as an increase in the connection strength (synaptic weights) between the dlPFC and its target, the amygdala.

By implementing a model that is capable of exhibiting the above mechanisms approximated by their interpretations and fitting it to real data, Mattera et al. (2022) aim to see whether the experimental data on the efficacy of each therapy, as gathered by Nijdam et al. (2012), can be reproduced. When relating the fitted learning rate parameters to the hypotheses, it is found that the hypotheses are indeed supported by the results. Additionally, the fitted parameters for each therapy are compared, and differences in their mechanisms are deduced.

Further experiments on the disposition of a simulated individual to develop PTSD were also run, although they were not the focus of this study.

4 Methods

This section details the methodology and specifically the models used by Mattera et al. (2022) to simulate post-traumatic stress disorder, prolonged exposure therapy and eye movement desensitisation and reprocessing.

As simulating the therapy methods requires having a simulated patient, I will first introduce how the PTSD model is constructed to then detail how it is treated using the two therapies. In the final subsection, I will specify the experiments that are used to test the model and therapies.

4.1 PTSD model

The neural model underpinning the simulations of PTSD, PE and EMDR, as shown in Fig. 1 entails four brain regions, which are based on the biological findings discussed in Section 2: (1) The sensory cortex is used to input patterns of auditory, visual and somatosensory perception that can trigger different behaviour. Each sense has two mutually inhibiting units (A1, A2 for the auditory cortex; V1, V2 for visual; S1, S2 for somatosensory) of which up to one can be activated at a time. (2) The hippocampus receives its input from all units of the sensory cortex and acts to process the sensory patterns. Its four units (H1, H2, H3, and H4) are pairwise inhibiting such that different input patterns activate distinct hippocampal units. It is connected to the sensory cortex in a bidirectional associative network to replicate flashbacks as theorised by Tryon (1998). (3) The amygdala, acting as a proxy for PTSD severity due to their strong correlation (Fitzgerald et al., 2018; VanElzakker et al., 2018), is activated in varying amounts by separate hippocampal units to differentiate between regular and traumatic patterns. The amygdala is regulated by (4) the vmPFC and dlPFC through an inhibitory connection. Their input comes from the sensory cortex, processed through a set of intermediate brain regions (which are left out and approximated by a direct excitatory plastic connection).

Each neural unit (eight in the sensory cortex, four in the hippocampus, one in the amygdala and one combining the vmPFC and dlPFC) is simulated using a leaky integrate-and-fire (LIF) neuron described in equation 1. It attempts to model the membrane potential V_i of a neuron i over time, given the firing rates F_{pre} of each pre-synaptic neuron and their connection strength $w_{pre,\,i}$. An additional input current I can be used to manually excite the neurons, as is done in Fig. 1 for "Sensory input", "Recalling", "Safety (PE) or Eye movement (EMDR)", and "Trauma".

$$\tau \frac{dV_i}{dt} = -V_i + I_i + \sum_{pre}(w_{pre,\,i} \cdot F_{pre}) \tag{1}$$

where pre-synaptic neuron's firing rate F_{pre} is calculated from its membrane potential using a tanh transfer function. Inhibiting connections have a negative weight.

The authors chose a LIF neuron for their implementation to strike a balance between biological plausibility and computability, as it is less computationally expensive than a Hodgkin-Huxley model (Hodgkin & Huxley, 1952) and more biologically accurate than a firing rate neuron.

To allow the network to learn, the excitatory connections between the sensory cortex and hippocampus, the sensory cortex and PFC, the hippocampus and amygdala as well as the inhibitory connection between the PFC and amygdala are made plastic (see Fig. 1, dashed lines), such that their weights can change. Specifically, the weight between a *pre*-synaptic and *post*-synaptic neuron updates according to the equation

$$w^{(t+1)} = w^{(t)} + \alpha \cdot (F_{post} - \rho) \cdot F_{pre} \tag{2}$$

where α is the learning rate and ρ is a threshold such that if the post-synaptic neuron's firing rate $F_{post} > \rho$, then the connection strengthens and undergoes long-term potentiation ($w^{(t+1)} > w^{(t)}$). It inversely undergoes long-term depression ($w^{(t+1)} < w^{(t)}$) if $F_{post} < \rho$.

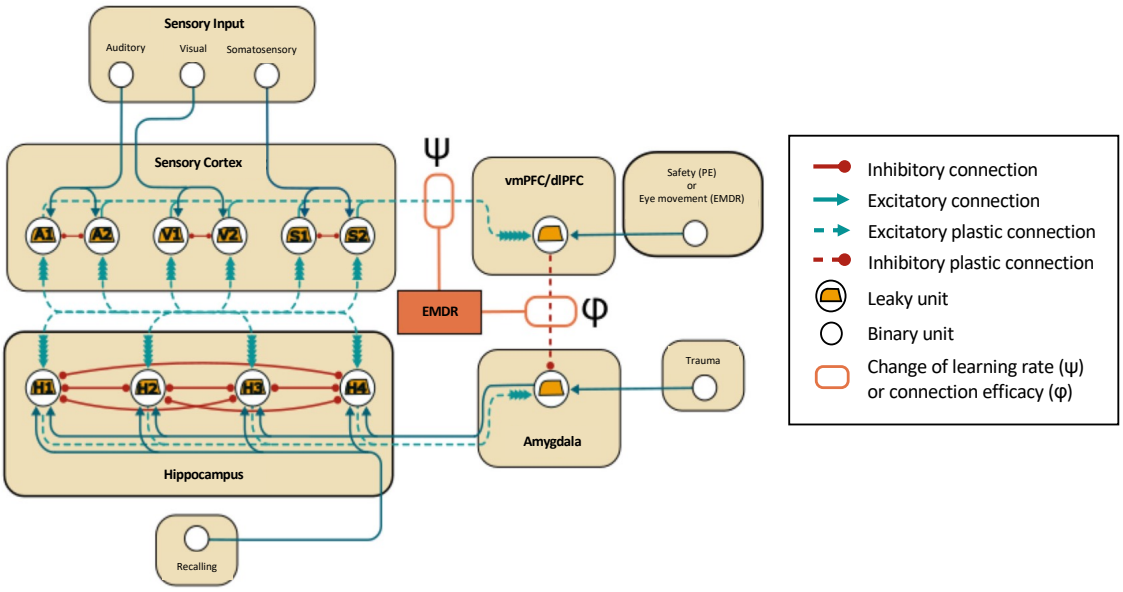


Figure 1: Diagram of the neural network proposed by Mattera et al. (2022) to model PTSD, as described in Section 4.1. Figure adapted from their publication.

4.2 Therapies

Each therapy is implemented by modifying part of the model, as follows.

Prolonged Exposure Therapy As PE therapy has been found to strengthen the connection between the vmPFC and amygdala (see 2 and 3), Mattera et al. (2022) model this mechanism by changing the weight of the inhibitory connection from the PFC unit to the amygdala. Specifically, it is initially set to $w_{\text{PFC,amygdala}} = \varphi = -1$ and then an optimal value is found by fitting the model to the experimental data (Nijdam et al., 2012). Recalling the traumatic event is simulated by manually setting the "Recalling" unit in Fig. 1 to 1, such that it sends an excitatory signal to all nodes in the hippocampus. However, as the nodes are laterally inhibiting, only the single node triggered by the sensory input gets amplified. The safe therapy environment is additionally simulated by activating the "Safety" binary unit, which excites the PFC neuron.

Eye Movement Desensitisation and Reprocessing Similarly, EMDR has been found to strengthen the connection between the dlPFC and the amygdala. As the vmPFC and dlPFC are combined into a single neural unit resembling the prefrontal cortex, the EMDR mechanism is also modelled by the same change of setting $w_{\text{PFC,amygdala}} = \varphi$ to the data. Additionally, EMDR seemingly also improves the connectivity across the entire cortex as induced by the slow waves (see Section 2), which is interpreted and implemented by the authors by modifying the learning rate. An additional tunable parameter ψ is added to equation 2 to give

$$w^{(t+1)} = w^{(t)} + \alpha \cdot \boldsymbol{\psi} \cdot (F_{post} - \rho) \cdot F_{pre} \tag{3}$$

The values of both parameters are determined by fitting the model to experimental data from Nijdam et al. (2012). Recalling is again simulated through the respective binary unit, as described above. Instead of a safe therapy environment, eye movement is simulated through the corresponding "Eye movement" binary unit, again exciting the PFC neuron.

4.3 Experiments

In order to validate the implementation of PTSD the two therapy methods, Mattera et al. (2022) run a set of experiments and inspect the learnt parameters.

Experiment schedule Each experiment consists of 35 trials, each lasting 104 time steps, and with 104 time steps between trials. The trial schedule is visualised in Fig. 2. To determine a baseline activity, the first trial is used to stimulate the visual cortex and measure the activation of each neural unit. In the second trial, the trauma is established. This is done by stimulating the full traumatic sensory pattern A1-V1-S1 and manually triggering the Amygdala by setting the "Trauma" unit's activation to 1. The model is allowed to rest for eight trials. Trials 11–30 are optionally used for treatment, after which the model rests for another 5 trials.

After each trial, the model's neuron activations are checked by stimulating the V1 or V2 unit (for testing the trauma or a neutral stimulus) without updating any weights.

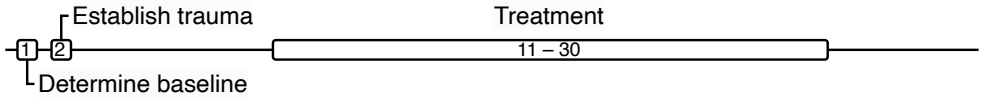


Figure 2: Visualisation of the experiment schedule. Trials are numbered from left to right.

Validating the PTSD model To check whether the intended symptoms are indeed expressed in the model, the authors simulated a single experiment without treatment. After the trauma is established in trial 2, they probe the hippocampus to confirm that different sensory patterns indeed activate distinct hippocampal units. To test for the presence of flashbacks, they also check whether stimulating a single sense (V1) will reactivate the full sensory pattern (A1-V1-S1). They further make sure that the trauma persists (amygdala activation does not decrease) throughout the 33 trials after establishment.

Disposition to develop PTSD Some studies comparing fear conditioning in PTSD and non-PTSD individuals have found a negative correlation between vmPFC activation and persistence of fear (Milad et al., 2009; Rougemont-Bücking et al., 2011). Thus, Mattera et al. (2022) devised a set of experiments in which the vmPFC's transfer function F_{PFC} is modified to express a higher firing rate at any membrane potential V_{PFC} than before. The authors interpret this decrease in vmPFC excitability as a reduction in emotional engagement.

Comparing therapies The final set of experiments targets the article's main objective, which is to gather simulational evidence for hypotheses on the mechanics of PE and importantly EMDR. To this end, Mattera et al. apply the treatments for 20 trials (11 to 30). PE is simulated by stimulating the V1 sensory unit as part of the traumatic pattern, while manually activating the "Recalling" unit to mimic imagining the trauma and activating the "Safety" unit to mimic the safe therapy environment (see Fig. 1). EMDR is simulated by again stimulating the V1 sensory unit and activating the "Recalling" unit. Instead of simulating safety, the authors activate the "Eye movement" binary unit (combined with the "Safety" unit in Fig. 1 as they have the same effect on the system) to excite the PFC.

To investigate the changes in the inhibitory connection strength between the PFC and amygdala (hypothesised to be higher in PE and EMDR), and investigate the changes in the cortical learning rate (hypothesised to be higher in EMDR), the model is fitted to the experimental data published by Nijdam et al. (2012). Specifically, the RMSE between their amygdala activation (from 0 to 1) and the normalised average (across all participants) reported PTSD score is minimised for each therapy method. The optimal values for the cortical learning rate ψ and regulatory connection strength φ are recorded.

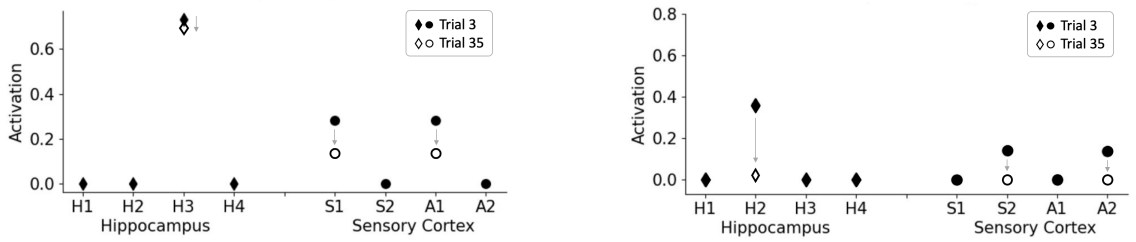
5 Results

This section presents the results obtained by Mattera et al. (2022) in the experiments presented in the previous section. The results will be briefly discussed and conclusions are drawn. A more detailed discussion is found in the next section.

Validating the PTSD model As shown in Fig. 3, different hippocampal units are activated when stimulating either the trauma-related V1 or the neutral V2 (acting as a control). It can also be seen that when stimulating V1, the other sensory units associated with the traumatic pattern are also activated. This flashback-like pattern completion persists. However, the pattern completion for the neutral unit is not only weaker but also fades.

To check that the PTSD persists as well as the flashbacks, the amygdala activation across trials is plotted in Fig. 4. It can be seen that when trauma is established but not treated, amygdala activation remains high and the trauma persists. This is in contrast to the neutral pattern A1-V1-S1 which is used as a control and does not activate the amygdala above the normal rate even after trauma is established for another pattern.

Thus, all aspects of PTSD that Mattera et al. (2022) claim to have attempted to replicate in their model appear to be validated. Other symptoms, such as feeling emotionally numb, or difficulty experiencing positive emotions (American Psychiatric Association, 2013) have not been replicated or tested for, as their implementation may require the addition of further brain regions.



(a) Traumatic pattern (A1-V1-S1)

(b) Neutral pattern (A2-V2-S2)

Figure 3: Activations of neural units in the hippocampus and sensory cortex after trials 3 and 35. No treatment is performed. The traumatic pattern is probed by stimulating the V1 unit in (a) while the neutral pattern is probed by stimulating V2 in (b). Figure adapted from (Mattera et al., 2022).

Disposition to develop PTSD The results produced by the authors' investigation into causality between the vmPFC's excitability and an individual's disposition to develop PTSD are presented in Fig. 4. The plot shows the amygdala activation across all 35 trials when stimulating the visual cortex for models where trauma is established and one where it is not. The trauma models have either the default vmPFC excitability, where the firing rate is computed by $F(V) = \max(\tanh(V - \theta_{PFC}), 0)$ and $\theta_{PFC} = 0.18$ or a more excitable vmPFC where $\theta_{PFC} = 0.09$. The latter parameter choice causes the PFC neuron to begin firing with a lower (halved) membrane potential than the first parameter choice, and fires at a higher rate, thus inhibiting the amygdala sooner and stronger. The figure shows that while a PTSD model with $\theta_{PFC} = 0.18$ retains its trauma across all epochs, the model with a more excitable vmPFC recovers from the trauma and does not develop persistent PTSD. Mattera et al. conclude that in their model, 'the PFC excitability determines the susceptibility to the trauma'.

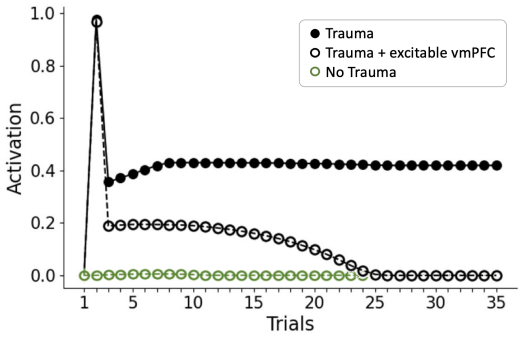


Figure 4: Amygdala activation for trauma, trauma + excitable vmPFC (lower emotional engagement), no trauma (control). The model was stimulated with V1 for the trauma measurements and with V2 for the control. The trauma was established in trial 2 and no therapy was applied. Adapted from (Mattera et al., 2022).

Comparing therapies By fitting the PE and EMDR therapy simulations to the experimental PTSD scores (see Section 4.3) the authors found that PE parameters ($\psi = 1.5$, $\varphi = 1$) and EMDR parameters ($\psi = 5$, $\varphi = 1.3$) best reproduce the experimental results. The normalised amygdala activation is plotted against the normalised experimental PTSD scores in Figure 5. The normalised amygdala activation forms an almost-linear trendline that resembles the true values well.

The extracted parameters indicate that, as hypothesised, the cortical learning rate is significantly increased by EMDR ($\psi = 5$) in contrast to PE ($\psi = 1.5$). Additionally, the amygdala appears to be inhibited more by the dlPFC which is activated by EMDR than by the vmPFC which is activated by PE.

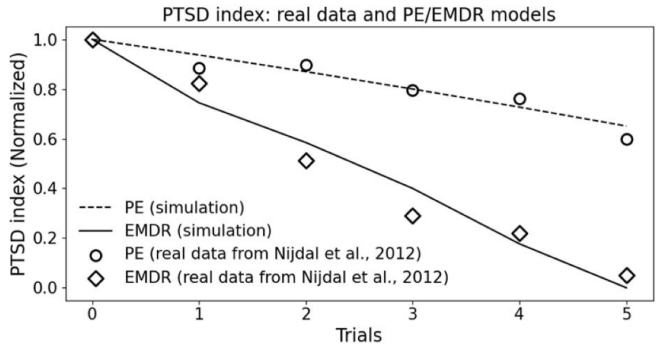


Figure 5: Comparison of simulated PTSD severity using the amygdala activation and the average PTSD scores from Nijdam et al. (2012) for PE and EMDR therapies for sessions 2-6. Ranges of the simulated and true results are normalised. Figure taken from Mattera et al. (2022).

6 Discussion

This section critically discusses the article, its methods, results, conclusions, limitations and extensions. I include arguments made by Mattera et al. (2022) and new ones. The section is split into three parts: First, the methods are reviewed in the context of the 'ten simple rules for the computational modelling of behavioural data' proposed by Wilson and Collins (2019), then other limitations are mentioned and finally extensions are suggested.

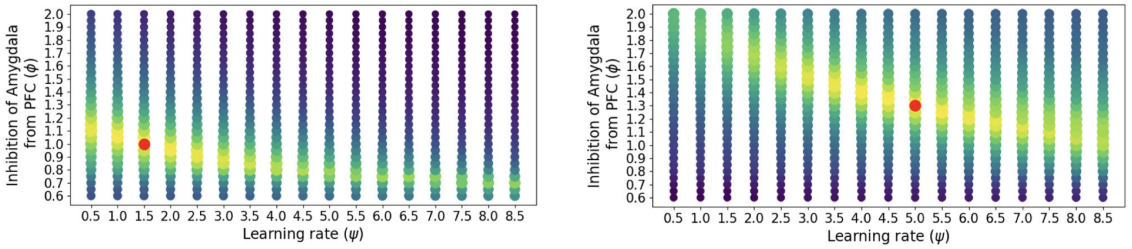
6.1 Rules for modelling

As Wilson and Collins's rules are meant to guide any investigation which uses 'computational models that instantiate different algorithmic hypotheses about how behaviour is generated', this encompasses the study being reviewed. More precisely, the study is one of parameter estimation, as it 'involves finding the set of parameter values that best account for real behavioural data for a given model.' (Wilson & Collins, 2019). For conciseness, I'll limit my discussion to only a few points ('rules') that are especially relevant to Mattera et al. (2022).

The first and second steps of the ruleset have been executed well. Though the authors could have stated the hypotheses more clearly, it is evident that they wish to (1) test whether a set of existing hypotheses on the mechanics of PTSD, PE and EMDR can effectively replicate the experimental results for these therapies, and (2) determine whether the vmPFC contributes to differences in susceptibility to PTSD. As the model is designed to capture the hypotheses by replicating only the brain regions that prior studies have found to be relevant, it is interpretable while maintaining simplicity. This interpretability extends to the model being designed to 'signatures' that are

typical of PTSD, such as flashbacks or the persistence of fear without therapy. The presence of these signatures has also been successfully tested by the authors.

Assuming the model was appropriately proposed and implemented, an important step in determining the reliability of the fitted parameters is to perform parameter recovery. In this phase, the model is first used to generate sample data from a set of randomly selected parameters within a reasonable range. The recovery method is then tested in this ideal scenario where the true parameters are known. A robust study should demonstrate a strong correlation between the true and recovered parameters. However, this has not been done in the current study. From the grid search results in Fig. 6, it is evident that there is a broad range of possible parameter values with similarly low RMSE, indicating that minor changes in other fixed parameters may significantly impact the fitted parameters. Thus, the determined parameters may not be as reliable as Mattera et al. suggest.



(a) Prolonged Exposure Therapy (PE)

(b) Eye Movement Desensitisation and Reprocessing (EMDR)

Figure 6: Grid search for the optimal PFC-amygdala connection strength φ (y-axis) and cortical learning rate ψ (x-axis). A brighter colour indicates a lower RMSE between the simulated and true results from Nijdam et al. (2012). The red dot indicates the local minimum. Figure taken from Mattera et al. (2022). No reference for the colour scale was available.

Despite not testing the robustness of parameter recovery, the authors effectively validate the model by visually comparing the simulated results with the experimental results in Fig. 5. This comparison offers an impression of how well the model fits the experimental results in absolute terms.

6.2 Further limitations

In addition to the limitations associated with the guidelines on modelling behaviour, Mattera et al. (2022) have mentioned further limitations, which I will briefly reiterate here and expand on with my observations.

The authors have identified that:

1. The model only includes few brain areas and in particular simplifies the connection between the sensory cortex and vmPFC/dlPFC. Their direct link between the two regions is not biological and forms a strong approximation. Instead, it has been suggested by prior research (also mentioned in Section 2) that the anterior cingulate cortex (ACC) may act as an intermediary between the specified regions (Alexandra Kredlow et al., 2022).
2. The model was fitted to the average PTSD score across all participants in Nijdam et al. (2012). While this may be reasonable for a pilot study, it would be significantly better to fit the model not only to individual participants' results but also to use actual measurements of the amygdala rather than a normalised self-reported severity score.

To these limitations, I add the following points.

3. To expand on the authors' argument of including the ACC, as stated in Section 2, the ACC and in particular the ventral and dorsal ACCs show increased activity in PTSD patients and during EMDR, the blood flow across the entire ACC increases. Thus, this region is likely relevant for a model of PTSD and EMDR.
4. The fixed model parameters appear to be very specific, though no justification for the chosen values is given. For instance, the maximum and minimum weights a synapse can take vary significantly depending on the regions it connects. Further, as mentioned in Section 6.1, having a wide range of parameter choices in Fig. 6 which are similarly good indicates that the fixed parameters can have a considerable impact on the fitted results. Thus, a justification for their choices or even a comparison of different fixed parameters would be favourable.
5. In addition to the previous criticism of the use of the dataset, I wish to comment on the compatibility of the data with the model. Although the use of sessions taken from brief eclectic psychotherapy (BET) instead of PE therapy may at first appear problematic, the therapies share many aspects and in particular the selection of sessions used by Mattera et al. (2022) are identical to those of PE. Importantly, however, the EMDR sessions executed by Nijdam et al. (2012) are slightly different from the ones implemented in the model, as they perform EDMR according to the Dutch Treatment Manual (de Jongh & ten Broeke, 2019): During each session, first focus on negative + stimulation 'until distress level is 0 or 1'. Then, 'a more positive cognition is introduced in relation to the target image' (Nijdam et al., 2012). The paper does not simulate the positive cognition part.
6. In humans AMPA receptors on fear memory synapses in the amygdala are removed or normalised by EMDR (Harper et al., 2009). This is not replicated in the simulation either.

6.3 Extensions

Based on these limitations, Mattera et al. (2022) propose the following extensions.

1. Fitting a model for each participant and investigating the trend.
2. Fitting to fMRI measurements of the amygdala instead of to PTSD scores.
3. Adding the ACC as a relay between the sensory cortex and the vmPFC.

These can be expanded as follows.

4. Evaluating the use of various fixed parameters
5. Recovering parameters from simulated experiments to validate the fitting accuracy.
6. Evaluating the model in contrast to one which includes positive emotions for better replication of the Dutch EMDR schedule.

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