New Interventions for the Treatment of PTSD

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Abstract. Post-traumatic stress disorder (PTSD) is a typical mental health problem, whose prevalence has increased rapidly following the global COVID-19 pandemic. Along with other mental health problems, it affects millions of people worldwide, and its effects can often be distressing and debilitating. However, research into more effective treatment is ongoing, including research into the use of medication such as the beta-blocker propranolol or the immunosuppressant rapamycin to treat PTSD by disrupting maladaptive memory reconsolidation, as well as a novel study using a cognitive task to prevent the formation of PTSD by interfering with memory consolidation. This paper adopts literature review as the research method, systematically evaluate the previous studies toward the treatments of PTSD. Finally, it concludes that, although further research must be carried out with larger sample sizes, there is a strong possibility that the use of new medications or innovative interventions could be more effective than traditional prolonged exposure therapy in many cases.

Keywords: PTSD; Maladaptive memory; Consolidation; Reconsolidation; Reactivation.

1. Introduction

PTSD is a debilitating mental health disorder characterized by symptoms such as extreme fear, anxiety, and flashbacks after exposure to traumatic events. These intrusive thoughts have a substantial negative impact on a person's quality of life and are frequently triggered by specific circumstances or environmental cues. A majority of theories suggest that the response to those trauma-related cues is due to the development of maladaptive fear memories after traumatic experiences that affect behavior and cognitive processes [1]. The traditional treatment of PTSD is prolonged exposure therapy - in order to attenuate the impact of maladaptive memory - which is based on the process of extinction [2]. This consists of clinicians creating a safe environment for the sufferers, allowing them to retrieve the traumatic memories, and then helping them to reduce their fear over time. Although this approach based on the traditional extinction strategies has been refined over the years, it has achieved only limited success, as some studies show that the maladaptive fear memories return in approximately half of the patients [3]. As such, further studies of new interventions are clearly needed.

However, research into more effective treatment is ongoing. One potential innovative treatment for PTSD is disrupting the initial traumatic memory itself. The approach may entail targeting the reconsolidation of memory. When previously consolidated memories are retrieved under certain circumstances, reconsolidation is the process that allows for the modification of those memories again [4]. Additionally, some investigators suggest that after a proper memory reactivation, even long-held memories can be susceptible to disruption [5]. However, it appears that reconsolidation only occurs in specific reactivated memories, which involve indirect re-exposure. Furthermore, other researchers have investigated the prevention of the formation of fear memory by directly targeting memory's initial consolidation within the 4-6-h consolidation 'window' after experiencing a traumatic event [6]. Both of these approaches were originally tested on animals, but small-scale experiments with human subjects have now been conducted, and initial results are available. As such, this paper will review the theory of memory, which is relevant to PTSD, before discussing and evaluating the research on existing treatment as well as these new interventions in order to determine what the better promising treatment might be.

2. The Theory of Memory

The process of memory is dynamic. Following an experience, memory is encoded over a period of time in a procedure known as consolidation, which primarily takes place in the hippocampus. During this time, the consolidation of memory is believed to depend on protein synthesis, which can be disrupted. For example, Daniel, Anthony & Randy (2000) found that the use of protein synthesis inhibitors prevented learning in participants [7]. However, research has also found that when memories are reactivated in the future, there is a period of time in which they are malleable and can potentially be updated, in a process known as reconsolidation - for example, Karim, Glenn & Joseph (2000) found that protein synthesis inhibition after the reactivation of memory could prevent it being expressed later [4]. This has implications for the treatment of PTSD because a maladaptive memory could be updated months or years after the event in order to reduce its negative effects on the patient.

2.1 Memory Consolidation

Consolidation of memory is the transformation of a temporary memory of a very recent event into more long-term memory. The theory was initially developed by Georg & Alfons (1900) to explain the malleability of memory for several hours after learning - within this window of opportunity. Short-term memories are more vulnerable to interference, such as suggestion or amnesia, than long-term ones [8]. While the hippocampus is essential for memory retrieval and storage during consolidation, more permanent memories also involve the neocortex. However, long-term memories may still be subject to errors or changes over time, meaning that false memories are possible [9]. Furthermore, the rate of consolidation may be dependent on various factors, including the extent of the subject's prior knowledge of the topic and whether the new information contradicts any previous information [10].

2.2 Memory Reconsolidation

Moreover, strong evidence has emerged that long-term memory can, at times, become labile again before returning to a fixed state - this process has been described as reconsolidation [11]. This may happen when memories are reactivated due to a cue. And indeed, research suggests that some aspects of memory, such as non-declarative conditioned reactions, can be altered during the process of reconsolidation. If this disruption occurs during reconsolidation, the memory may be permanently weakened, a situation which is referred to as "amnesic deconsolidation" [12]. Research on this topic appeared around 2000, with various researchers publishing papers which sparked a new interest, particularly because this research has significant therapeutic implications for the treatment of disorders like PTSD [13].

2.3 Declarative and Non-declarative Memory

Declarative memory and non-declarative memory are two commonly acknowledged primary memory systems in psychology. Declarative memory, also known as explicit memory, is a memory that can be reported, for example, episodic memory of an event or a memory of a fact. On the other hand, non-declarative memory, or implicit memory, is the memory that cannot be consciously reported, including procedural or emotional memory. Different brain areas are involved in different memory systems, with declarative memory primarily kept in the medial temporal lobe and non-declarative memory in the amygdala or striatum [14]. PTSD is a complex medical condition that typically involves both declarative memory, such as intrusive episodic memories of a traumatic event, and non-declarative memory, such as the conditioned emotional responses to a trauma cue [15]. As shown below, consolidation or reconsolidation of memory may allow for the targeted disruption of a particular aspect of memory. For example, researchers found that it was possible to disrupt non-declarative memories, such as fear without affecting declarative memories, such as the details of the traumatic events, or even to update one conditioned response without updating another [16].

3. Traditional Treatment for PTSD

The traditional treatment method for PTSD is the prolonged exposure (PE) method. It is believed that PE is effective as a treatment, because it works through the fear extinction mechanism, allowing the sufferers to break the link between the stimulus and the maladaptive fear response [17]. PE can be imaginal, meaning that a clinician will show a patient a visual image of a trauma cue in a safe environment in which the feared outcome does not occur in order to reduce the patient's conditioned response. PE is widely accepted as the standard treatment for PTSD and is recommended in PTSD treatment guidelines, such as those of the International Society for Traumatic Stress Studies [18].

There is evidence that PE is effective. Indeed, the Institute of Medicine reported in 2007 that PE was the only treatment for PTSD, which could be justified by existing research. PE and more generally cognitive behavioral therapy have been demonstrated to reduce symptoms of PTSD in a wide range of circumstances, with studies showing that it was effective with military veterans, victims of rape, domestic violence, etc [19].

However, although this approach has been refined over the years, its success is limited. In particular, one study found that maladaptive fear memories return in about half of patients [3]. Furthermore, many clinicians do not regularly use PE because they believe that the treatment will exacerbate comorbid diagnoses. For example, Carolyn et al. (2004) surveyed psychiatrists and found that 85% would not use PE for PTSD-sufferers with suicidality or psychotic disorders [20]. Note that PTSD may very often be linked to comorbidities. For example, one study found that there were comorbidities in 79-88% of PTSD cases [21]. As such, many clinicians would exclude the use of PE to treat the majority of PTSD patients.

4. Research on New Interventions

4.1 Research on New Interventions - Reconsolidation

In this section, the author will discuss several interventions using different drugs in order to inhibit the reconsolidation of maladaptive memories.

4.1.1 Reactivation + Rapamycin

Rapamycin, also known as Sirolimus, is a macrolide compound that is used clinically as an immunosuppressant. Reed et al. (2021) investigated whether rapamycin could disrupt the reconsolidation of traumatic memories in rats by indirectly reactivating those memories [22]. They divided rats into two groups and administered backward and forward conditioning to associate the fear memory with a cue. Then, they used that cue together with rapamycin to try to disrupt the reconsolidation of the traumatic memory. They found that the rats who had undergone forward conditioning retained their conditioned reaction even after treatment, whereas the rats who had undergone backward conditioning lost their conditioned reaction, and subsequent fear was reduced in these rats. The authors speculate that indirect reactivation of memories can also be used to trigger reconsolidation in humans. They suggest that the process of reconsolidation linked with backward conditioning may be linked to protein synthesis within the hippocampus, which can be prevented by rapamycin, whereas forward conditioning may be more associated with the amygdala.

The authors speculate that these results might be applicable to other mammals, including humans, and that indirect cues may therefore be used to reactivate memories as part of treatment. However, there are naturally many ways in which human and rodent psychology differ, so it must be careful not to draw unwarranted conclusions.

An earlier pilot study was carried out in 2013 using rapamycin on 54 war veterans who suffered from PTSD [23]. In this study, the experimental group received a dose of rapamycin combined with the reactivation of their traumatic memory, whereas a control group received only the reactivation and a placebo. The results of this study were mixed - combat veterans from the Vietnam war did not show any significant difference from the control group; however, veterans from more recent wars did

show an improvement. The authors speculate that rapamycin could be an effective treatment for a subpopulation of PTSD-suffers, depending on the length of time elapsed after the traumatic event. Naturally, the small sample size means that these results are only provisional, and the authors recommend further study with greater sample size.

4.1.2 Reactivation + Propranolol

Propranolol, also known as Inderal, is a beta blocker that is typically used to treat high blood pressure. There are several experiments using propranolol to disrupt fear memory reconsolidation. For example, Merel, Marieke, Bram (2009) used Pavlovian fear conditioning to create a conditioned response in human participants [24]. They tested whether propranolol could be used to disrupt the reconsolidation of this non-declarative memory by dividing the 60 participants into three groups. One group received propranolol before memory reactivation, another group received a placebo before memory reactivation, and the third group received propranolol without reactivation. The participants have exposed to the stimulus again, and only the propranolol + reactivation group did not display the conditioned response, whereas the other two groups retained it. On the other hand, all groups retained their non-declarative memory of the experiment. This implies that propranolol can disrupt non-declarative memory reconsolidation after memory reactivation, at least in the case of a conditioned fear response after a short period of time. Researchers from the same lab set up follow-up experiments to test the long-term effect, retesting memory one month after the intervention [25]. They found that the fear memory did not recover through the mere passage of time or in a different context. Moreover, participants did not re-formulate a differential fear-potentiated startle any more rapidly during reconditioning than they did during initial acquisition, implying that memories were not 'stored' in this case.

On the one hand, this approach shows advantages over traditional PTSD treatment, and in particular, exposure therapy. For example, a study by Emily et al. (2014) showed that the maladaptive fear memory returned in approximately half of the patients after exposure therapy [3]. However, the study by Merel, Marieke, Bram (2009) only used 60 participants, so its results may not be fully reliable [24]. Furthermore, while it found that there was a statistically significant difference between the reaction to the stimulus in the various groups, it did not provide the raw data of how many participants had the reaction. As such, it is difficult to know how effective this intervention is compared to traditional exposure therapy. In any case, further research with more participants would be helpful to confirm these results.

4.2 Research on New Interventions - Consolidation

Both the use of drugs and prolonged exposure therapy are designed to help sufferers of PTSD long after their original traumatic experience. However, there are experimental therapies that seek to prevent the consolidation of a traumatic memory only hours after patients experience trauma in order to prevent or weaken the permanent memory. Researchers carried out a preventive intervention on victims of car accidents while they were awaiting treatment in a hospital [6]. The experimental group was given a trauma reminder and was asked to play a demanding visuospatial game, namely Tetris, while the control group was asked to perform a placebo task. Participants were excluded if the accident had taken place more than 6 hours before. The authors found that the experimental group reported significantly fewer intrusive memories in the following week than the control group, with the experimental group suffering 62% fewer than the control group.

The authors theorize that using a visually stimulating game such as Tetris 'competes' with the consolidation of visual trauma memories by engaging this brain capacity. Their findings seem to support this theory, at least considering a test one week after the accident. They also noted that 48% of patients agreed to participate, compared to far lower numbers for psychotherapy or pharmacological trials. Their invention was completed in 97% of cases, and they reported the patients seemed to respond positively. Although it focuses only on visual memory, they hypothesize that this treatment can be viewed as a cognitive 'therapeutic vaccine' which is capable of preventing or

reducing the severity of PTSD in the timeframe of memory consolidation (i.e., under 6 hours). They particularly recommend it due to its ease of delivery, low cost, and the brevity of the treatment.

On the other hand, there are some limitations. Firstly, there was only one post-experiment test, which was carried out a week after the treatment. As such, the authors recommend further studies to determine long-term effectiveness, for example, by testing patients one month after a traumatic event. Furthermore, there are practical issues. Many subjects who undergo a traumatic experiment are likely unable to request cognitive therapy within the required timeframe of 6 hours. The case of victims of a car accident is thus quite unrepresentative of PTSD-suffers - soldiers, rape victims, domestic violence victims, childhood abuse victims, etc., are unlikely to be able to benefit from this therapy. Finally, the therapy focuses on visual memory. This is helpful, but PTSD may include other types of memory, which this approach would not address. Perhaps it could also be extended to other types of memory by trialing tasks that engage auditory processing.

5. Discussion

5.1 Traditional Treatments

The traditional prolonged exposure method has a proven track record, with studies showing an effect in various different environments [19]. Furthermore, it does not use medication and therefore reduces the risk of complications. However, it can be very unpleasant for patients to relive traumatic events. Furthermore, as discussed above, symptoms reoccur in a large number of cases and clinicians are often fearful of using PE when patients suffer from comorbidities [20，21]. Some research does suggest that PE can be carried out in many such cases and there are some grounds for encouraging clinicians to make wider use of PE than they currently do [17，18]. However, these problems have nonetheless shown the need for new treatments. While the limitations of PE do give impetus to new research, it remains a useful tool for clinicians in the present day.

5.2 New Interventions

Although some of the methods discussed remain experimental, there are good reasons to believe that the treatment of PTSD will evolve in the near future. Most research on new treatment has focused on disrupting the reconsolidation of traumatic memories, while some have also attempted to prevent fear memory consolidation immediately after the traumatic event.

To disrupt reconsolidation of traumatic memories, two main medications have become the focus of research - rapamycin and propranolol [22-24]. As discussed in 4.1.2, researchers were able to at least partially disrupt the conditioned response of participants in an experiment given propranolol (compared to a control group), whereas participants retained their declarative memory of the traumatic events [24]. This suggests that the use of propranolol can be targeted at non-declarative memory, conditioned responses or emotional memory. One possibility is that propranolol acts on the amygdala in order to affect emotional elements of memory, without affecting other areas, such as the medial temporal lobe circuits involved in the processing of declarative memory, consistent with the discussion in section 2 [14]. This could be beneficial from an ethical and legal point of view, as it would allow victims of crimes to give reliable eyewitness testimony even after treatment [16].

As discussed in 4.1.1, research on rapamycin also shows considerable potential for the disruption of reconsolidation when combined with a memory cue. Researchers found that it was effective at disrupting backward conditioning in rats, whereas it did little to disrupt forward conditioning. They speculated that this occurred because of its effect on protein synthesis in the hippocampus, and that it had less effect on the amygdala [22]. Given the role of the amygdala in processing non-delcarative memory, this suggests some limitations in how rapamycin may be used to treat maladaptive fear memories and PTSD. On the other hand, it may be that the disruption of declarative memory processed in the hippocampus reduces the fear reaction [15]. However, this was only a study on rats and may not be applicable to humans. Certainly, as discussed in 4.1.1, practical studies on PTSD-

sufferers found that rapamycin did have a positive effect on the severity of their symptoms, but the exact mechanism by which this occurs is not clear [23]. Furthermore, the reason why it was effective only on patients with more recent trauma is not clear - it may be that the conditioned response is so strong at that point that the effect of the intervention is negligible.

Some researchers have attempted to partially prevent the consolidation of traumatic memories, such as the study discussed in 4.2, which used Tetris to prevent the consolidation of the visual memory of victims of car accidents [6]. This relies on the theory of memory as discussed in section 2, namely that memories remain labile for a 4–6-hour window after an event before consolidation [8]. The researchers theorized that by occupying a part of the brain involved in visuospatial processing, they would interfere with the brain's ability to consolidate this aspect of the memory and therefore prevent the formation of PTSD [8]. They found that patients treated in this way had fewer intrusive visual memories of their accident than the control group [6]. However, given their focus on visual memories, it remains an open question what effect this intervention would have on the conditioned reaction of patients and whether PTSD itself would be reduced over the long term. While their study only had a follow-up test a week after, and therefore requires further research, it does show the potential for non-invasive treatment to prevent PTSD rather than to treat it. Its advantage over other types of treatment, such as PE and medication use, is that it is quite pleasant for patients and does not carry any risk of complication. However, there is a very narrow window of opportunity - perhaps only six hours - in which memory is consolidated, so this approach is unlikely to be effective in the majority of cases.

5.3 Limitations of the Research

As mentioned previously, most studies have a small sample size, which means the results are not fully reliable and further research should enlarge the sample size to make the conclusions more universal. Furthermore, some studies were carried out on rats, for whom memory may well be processed differently, and complex conditions such as PTSD are not easily comparable between species.

In the literature, there were two main approaches to experiment design, both with some advantages and disadvantages. The first approach was to take clinically normal human or animal subjects, provide them with some kind of negative stimulus, and then investigate the effects of the intervention [22]. This was an electric shock in the case of rats or exposure to unpleasant images in the case of humans. This allows experimenters to compare very similar experiences across many participants in order to reach more valid conclusions - for example, targeting visual memories. However, these negative stimuli were far more minor for ethical reasons than most traumatic experiences. As such, some conclusions from these studies may not be generalisable to the case of PTSD-sufferers, who experienced a more complex traumatic negative experience. The second type of study used existing PTSD-sufferers, and provided different interventions to an experimental group and a placebo group [23]. This has the benefit of investigating the real effect and utility of treatment on PTSD-sufferers. However, because PTSD is a complex condition including many kinds of memories, it also makes it more difficult to isolate the effect of the intervention on a particular type of memory and to determine the exact mechanism at work, even if the intervention is effective. It might well be expect many differences between PTSD-patients, and it may be that one intervention will not be effective for all.

5.4 Future Research

Many of the studies were trial studies, so more in-depth studies with a greater number of participants and a longer time frame are required to establish their results with greater certainty. In particular, research on the effects of these interventions on different groups is required - patients with comorbidities, PTSD-sufferers who were traumatised long ago, etc. And finally, more research into the exact effect on different memories is required - declarative, non-declarative, visual, auditory, emotional, etc. Where possible, the research could consider PTSD-sufferers who have a comparable history - for example, victims of domestic violence, former soldiers, etc. This would replicate the research already done on different groups for PE therapy.

6. Conclusion

Ultimately, the research on novel treatments for PTSD remains quite young. On the one hand, there is a large body of research demonstrating that PE can be used to reduce the severity of fear memories in many patients, even if it is not effective in many cases and clinicians often hesitate to make use of it in case of comorbidities. Research into new interventions which aim to disrupt the reconsolidation of fear memories remains relatively young. However, promising studies on animals and humans suggest this may be an effective treatment in some cases. Finally, some recent research into cognitive tasks suggests that they can be used to prevent the consolidation of some fear memories in a short window after a traumatic event, namely 4-6 hours. However, while these two new types of treatment are promising, further research is required to establish these results with larger sample sizes, to understand the exact mechanism at work, and to determine for which patients this may be an appropriate treatment.

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