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Bidirectional Synaptic Plasticity Mechanism Mediates the Abnormal Fear Memory Flashbacks in PTSD

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Abstract. Post-traumatic stress disorder (PTSD) is characterized by persistent traumatic memories and flashbacks, which may arise from dysregulated synaptic plasticity mediated by inflammatory and epigenetic mechanisms. Three intervention strategies are evaluated in this paper. They are exercise and exposure therapy, targeted drugs, and personalized repetitive transcranial magnetic stimulation (rTMS) respectively. Inflammatory and epigenetic pathways are integrated in this framework to provide a new perspective on PTSD synaptic pathology mechanism. Restoring the balance between long-term potentiation (LTP) and long-term depression (LTD) should be an important therapeutic target. Future studies should validate LTP and LTD changes in patients and develop personalized combination therapies based on plasticity subtypes. Studies have found that traumatic stress can promote excessive enhancement of the amygdala's LTP through abnormal activation of the hypothalamic–pituitary–adrenal (HPA) axis, leading to reinforced fear memories. Simultaneously, it can inhibit hippocampal LTD processes through Brain-derived neurotrophic factor (BDNF) DNA methylation and related signaling alterations, thus hindering the extinction of traumatic memories. The NF-κB inflammatory pathway and the BDNF methylation pathway may serve as key molecular nodes which regulate synaptic plasticity imbalance. Based on these mechanisms, this article further summarizes intervention strategies for restoring synaptic plasticity balance, including exercise combined with exposure therapy, targeted drug therapy, and personalized rTMS therapy.

Keywords: Post-traumatic stress disorder, Flashbacks, Synaptic plasticity, Hippocampus-amygdala circuit

1. Introduction

Post-traumatic stress disorder (PTSD) is a long-term, induced chronic mental and psychological disorder, caused by an event that endangers life or causes serious physical injuries experienced personally or experienced indirectly. It has several symptoms: intrusive symptoms (e.g., flashbacks), avoidance symptoms, negative alterations in cognitions and mood, and persistently heightened arousal. According to the DSM-5 standard, the flashback is a kind of typical intrusive symptom. It is manifested by the reappearance of traumatic frames and sensitive memories, and differentiated from subjectively recalled memories [1]. The global lifelong prevalence rate has reached 3.9%, causing a serious social issue [2]. This leads to the major research question: why can traumatic events form

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fear memories that have stability far exceeding ordinary memories and are difficult to fade naturally?

In research investigating how trauma modulates synaptic plasticity, there are two pathways that have garnered substantial attention: the Nuclear Factor-κB pathway in inflammation and the Brain-derived neurotrophic factor (BDNF) DNA methylation epigenetic pathway. Existing reviews have verified that trauma can interfere with the function of synapses in the hippocampus and amygdala by two pathways [2, 3]. Current research exhibits two core limitations: The one is the explanations of impaired synaptic plasticity are general, without differentiating excess potentiation of Long-term potentiation (LTP) and deteriorated long-term depression (LTD), and the other one is few of them link the imbalance of plasticity to intrusive flashback symptoms, which prevents the complete ecplanation of the implicit mechanism of persistent traumatic memories in cellular aspects [4].

LTP and LTD are two core ways of brain synaptic plasticity. Under normal physiological conditions, LTP consolidates memories by strengthening the synaptic connections, while LTD catalyses the process of natural fading of memories by weakening the synaptic connections. The dynamic balance between these two processes is the foundation of normal memory formation and attenuation in humans. This article is centered around bidirectional synaptic plasticity, integrating two upstream pathways including neuroinflammation and epigenetic modification, and constructs an analysis of the hippocampus-amygdala fear memory circuit [5].

The core purpose of this article is to explore the pathological mechanism of flashbacks in PTSD, based on the theory of bidirectional LTP and LTD synaptic plasticity. It systematically analyzes how traumatic stress disturbs the hippocampus-amygdala circuit that encodes fear memory and explains the cellular mechanism behind excessive LTP in the amygdala and impaired LTD in the hippocampus. At last, targeted intervention strategies based on restoration of the synaptic plasticity are summarized. This article aims to analyze existing research findings and provide a supplementary theoretical perspective to understand the pathogenesis of PTSD.

2. PTSD and abnormal fear encoding

2.1. Dysregulation of hypothalamic–pituitary–adrenal (HPA) axis cortisol after trauma

The HPA axis is the major neuroendocrine pathway that mediates the human body's responses to stress. It establishes communication between the central nervous system and the peripheral endocrine system. When the organism perceives any kind of stressors, such as fear, physical trauma, psychological shock, and so on, neural pathways are activated sequentially. The hypothalamus and the pituitary secrete corticotropin-releasing hormone(CRH) and adrenocorticotropic hormone (ACTH) respectively. The CRH acts on the pituitary gland. The ACTH travels through the bloodstream, reaches the adrenal glands, and stimulates the adrenal cortex to synthesize and release cortisol. The role of cortisol in the organism is the primary glucocorticoid hormone, helping humans respond to acute stress by facilitating the body's response. Healthy individuals possess intact negative feedback regulatory mechanisms. This means that once cortisol accumulates to a threshold concentration in the blood, it will exert an inhibitory effect on secretory activity within the hypothalamus and pituitary, preventing excessive hormone release and maintaining long-run endocrine homeostasis. However, extreme and enduring trauma stress breaks this regular cycle; some people may suffer from impaired long-lasting HPA axis function.

Severe trauma represents a high-intensity stressor that can keep the HPA axis activated persistently. Clinical and preclinical research identified that the most typical feature in patients with PTSD is impaired negative feedback pathways on the HPA axis. However, patients with PTSD do

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not necessarily represent sustained high levels of cortisol. The prevailing academic view shows that the core abnormality of this population is decreased flexibility of glucocorticoid regulation, which means the organism loses the ability to increase or decrease the level of cortisol to match the changes in the environment rapidly. As a result, the hormonal dynamic homeostasis is completely disrupted [6].

Although there is no universal cortisol concentration level in the peripheral circulation, the irregular and sharply fluctuating glucocorticoid signal would cause bidirectional damage in the hippocampus and amygdala, indicating the endocrine system loses its flexibility. There are a large number of glucocorticoid receptors (GRs) expressed on neurons in the hippocampus and amygdala. In addition, the GR has a low affinity for cortisol and is only activated at a high concentration level. The surging level of cortisol shortly after the trauma will strongly activate GR signals. When the GR is activated, a state called metaplasticity is induced, which means the ability of synapses to respond to different stimuli by changing the level of LTP and LTD will be changed. This state in PTSD manifests as abnormally strengthened LTP in the amygdala and damaged LTD in the hippocampus [5, 7]. This change in synaptic plasticity induced by the endocrine system provides an upstream basis for the bidirectional damage of LTP and LTD.

The hippocampus and the amygdala act as the core brain regions to regulate fear memories, having abundant GRs on the surfaces of their neurons, which means they are highly sensitive to changes in the concentration of cortisol. Sustained exposure of neurons in the two brain regions to long-lasting abnormal concentrations of cortisol alters neural resting excitability and disrupts normal signal transmissions. Such abnormal activity of brain regions induced by endocrine disorders acts as an upstream factor of subsequent bias on encoding the fear memory [6].

Persistent dysregulation of cortisol signalling disrupts normal information exchange and functional coordination between the hippocampus and amygdala, eventually triggering dysfunction of the fear memory regulatory circuit [6]. The circuit abnormality of these two brain regions will be analyzed in detail in the following section.

2.2. Functional disorder of hippocampus-amygdala circuit

Under normal physiological conditions, the hippocampus and the amygdala form a cooperative and balanced neural circuit. They jointly mediate the process of encoding, storing, and fading of fear memories. The amygdala is responsible for accepting the fear signals from the external environment and participates in the formation and primary consolidation of fear memories. It is the core brain region to response to fear. While the hippocampus undertakes the encoding of contextual information, integration of environmental memories, and memory discrimination, which can help the brain evaluate the safety of stimulus context [4].

Trauma-induced disruption of cortisol homeostasis severely disrupts the operation of the hippocampus-amygdala circuit, which leads to imbalanced differentiation of brain regions. Persistent abnormal levels of hormone stimulus overactivate the neurons in the amygdala, leading to high levels of excitation in the long term. As a result, the organism is hypersensitive to trauma-related signals, and the fear memory is easily consolidated. Meanwhile, chronically elevated levels of cortisol suppress the normal function of neurons in the hippocampus, leading to deceasing capacity for contextual recognition and memory regulation. The hippocampus fails to constrain amygdala excitation effectively [4].

The antagonistic functional imbalance between the two brain regions breaks the normal regulation mechanism of fear memories. The amygdala encodes the traumatic fear memory at an abnormally high level, and the hippocampus cannot distinguish safety contexts successfully. These

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lead to the organism failing to attenuate traumatic memory, which forms sustained pathological fear. The dysfunction of the circuit is the main reason that patients with PTSD retain the fear memory for a long time and are hypersensitive to trauma-related signals [4].

Overall, dysfunction of the hippocampus-amygdala circuit induced by trauma is ultimately indicated by changes in synaptic neuron function, providing a crucial foundation for the bidirectional imbalance of synaptic plasticity.

3. Bidirectional imbalance of LTP and LTD

3.1. Basic function of LTP and LTD under normal physiological conditions

As mentioned in the introduction, LTP and LTD represent the two core manifestations of synaptic plasticity in the brain, and constitute the cellular foundation of learning and memory activity in the neural system [5]. Under normal conditions, the

LTP and LTD mutually regulate the efficiency of synaptic transmission, ensuring the flexibility and accuracy of cerebral memory processing.

The LTP corresponds primarily to the long-term enhancement of synaptic transmission efficiency. When the brain accepts meaningful and salient external information, the activity of the related brain region rises markedly, and the signal transmission efficiency elevates consistently. Therefore, the encoding, consolidation, and storage process of memory is completed, forming long- lasting memories. LTD, by contrast, manifests as a persistent reduction in synaptic transmission efficiency. It is mainly responsible for eliminating redundant and irrelevant memory traces, weakening outdated neural connections, and mediating the processes of memory extinction and information filtering [5]. Current research shows that fear extinction is an active-learning process. The brain will code for a new inhibitory memory to suppress the fear memory competitively in a safe environment [4]. By weakening the efficiency of intrinsic fear synaptic transmission, providing more space and competitive merit for the consolidation of the new inhibitory memory [5]. However, for PTSD patients, this LTD-learning process is damaged dramatically.

The memory-consolidating function of LTP and the memory-attenuating function of LTD mutually constrain and balance one another. The LTP ensures that crucial information is saved efficiently, helping the organism accumulate survival experience, and the LTD prevents the brain from excessively saving useless memories, attenuating neural responses triggered by irrelevant stimuli, ensuring the brain can adapt to environmental shifts with flexibility. This dynamic balance of bidirectional plasticity constitutes the core cellular mechanism underlying the normal recognition, discrimination, and fading of fear memories [5].

3.2. Abnormal strengthening of LTP in the amygdala triggered by trauma

The amygdala is the core brain region encoding memories, so changes in synaptic plasticity in it directly determine the consolidation strength of traumatic memories. Under normal conditions, the amygdala only generates LTP enhancement in response to real danger, processing fear memory acquisition. This process can be reversible by the memory-fading mechanism. However, severe traumatic stimuli alter the regulation model of synaptic plasticity in the amygdala fundamentally, which induces persistent and pathological LTP enhancement [5].

High-intensity stress signals from trauma continuously activate synaptic pathways in the amygdala.This leads to long-lasting and marked elevation of synaptic transmission efficiency. The trauma-related LTP enhancement in the amygdala exhibits significant stability and resists reversal

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through conventional memory fading pathways. The abnormal synaptic enhancement consolidates trauma-related nervous connections consistently, which makes the trauma memory over-consolidated in the nervous system [5].

Sustained overexpression of pathological LTP directly renders patients highly sensitive to trauma-associated contexts like sounds and emotional cues. Ordinary, safe, and analogous scenarios are falsely interpreted by the brain as threatening stimuli. Therefore, it triggers intense fear, anxiety, and intrusive recollections, which are the flashback symptoms of PTSD. Accordingly, the trauma-induced abnormal potentiation of LTP in the amygdala is the key cellular mechanism forming the pathological consolidation of fear memories [5].

Aberrant enhancement triggered by LTP in the amygdala already disrupts normal memory equilibrium. The trauma concurrently impairs hippocampal LTD function, which further exacerbates the imbalance of bidirectional plasticity.

3.3. Abnormal weakening of LTD in the hippocampus triggered by trauma

Under a normal environment, the LTD in the hippocampus works to eliminate unrelated episodic memories, renew old memories, and distinguish safety and danger by attenuating synaptic connections, preventing inappropriate fear responses in a safe environment. As discussed in 3.1, the essence of fear memory extinction is actually a process of forming new inhibitory memory. The LTD of the hippocampus leaves synaptic space for the consolidation of the new memory by impairing the connections between synapses for the fear memory. But in PTSD, the traumatic stimuli markedly inhibit the inducing ability of the LTD in the hippocampus by dysregulation of the HPA axis. The dysregulation of the HPA axis leads to an unstable cortisol level. In addition, the hippocampus has a large number of GR, so these make the hippocampus become the target of the endocrine disorder [6, 7]. Animal studies have clearly shown that after traumatic exposure, the function of LTD in the hippocampus is clearly inhibited. The synapses in the hippocampus lose their inducibility, which means synapses cannot weaken their connections actively, leading to an inability to fear extinction [4, 5]. The molecular mechanism of this inhibition is that after the trauma, the GR is consistently activated by high levels of cortisol. The LTD is inhibited through changing the ability of synapses to respond by metaplasticity, so the synaptic connections tend to maintain the level they are connecting but not to weaken them [6, 7].

As a result of damaged hippocampus LTD, there are two aspects of the effects. First, the ability to cover or renew old memories is hindered. Due to the closure of the connection-weakening channel mediated by LTD, when exposed to a secure situation, new inhibitory memory cannot be effectively formed to suppress the fear, resulting in continuous dominance of the traumatic memory. Another one is that the ability of patients to distinguish safe environments and dangerous environments is lost. Patients cannot accurately distinguish the safe environment and the traumatic one, leading to erroneous judgment of stimuli.

The damage to LTD in the hippocampus and the strengthening of LTP in the amygdala form a malignant synergy. The amygdala over-strengthens the fear memory, and the hippocampus loses the ability of fear extinction. Both of them jointly lead to the abnormal persistence of the traumatic memory and the susceptibility to flashback symptoms.

The NF-κB inflammation and the BDNF DNA are both upstream molecules causing the bidirectional dysfunction of the hippocampus and the amygdala.

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3.4. Two upstream molecular pathways co-regulate plasticity imbalance

Current research has identified two pathways that are simultaneously activated under traumatic stress and jointly regulate the imbalance of bidirectional synaptic plasticity. The NF-κB mediated neuroinflammatory pathway and the BDNF DNA methylation-mediated epigenetic pathway [2, 3].

One pathway is NF-κB-mediated neuroinflammatory signals. Traumatic stress leads to the over-activation of microglia and astrocytes in the central nervous system, releasing a large number of proinflammatory cytokines like TNF-α, IL-1βand IL-6. These inflammatory mediators directly function in the synapses nearby by activating NF-κB to initiate the signal cascade. In the amygdala, the consistent activation of NF-κB lowers the threshold of the LTP inducibility, which means the synapses can be strengthened much more easily. This enables the fear signal to form a firm synaptic enhancement through slight stimuli, which corresponds to the pathological LTP in PTSD (discussed in 3.2). In the hippocampus, the NF-κB signal disrupts the synapse deactivation mechanism essential for LTD induction by interfering with the transmission of glutamic acid and inhibiting the function of inhibitory interneurons, thereby depriving synapses of the ability to actively weaken [3].

Another one is epigenetic modification, methylation of DNA in the BDNF gene pathway. The traumatic stimuli upregulate the activity and expression of the DNA methyltransferases(DNMTs) by activating the GR. This leads to the hypermethylation of the CpG island in the promoter region, thereby inhibiting the transcription and the translation of the BDNF gene [2].

BDNF is a crucial neuromolecule to maintain the bidirectional plasticity of the LTP and the LTD. In the amygdala, the reduction of BDNF causes a reduction in postsynaptic protein synthesis required for the maintenance of LTP. Simultaneously, the increasing NF-κB applies a stronger pro-inflammatory driving force, causing the enhancement direction of LTP in the amygdala to be over-amplified. In the hippocampus, the scarcity of BDNF directly damages the inducibility and the maintenance of LTD. LTD relies on the BDNF-induced AMPA receptor endocytosis and the rearrangement of synapses. The reduction of BDNF and the NF-κB inflammation form a superimposed effect, jointly leading to serious damage to LTD in the hippocampus [2].

Overall, the NF-κB pathway is a relatively fast pathway that directly changes the threshold of synaptic activation, and the BDNF methylation pathway is a relatively slow pathway that reshapes the ability of protein maintenance. They pull up LTP in the amygdala and push down LTD in the hippocampus together [2, 3]. The identification of NF-κB and BDNF methylation as the common upstream molecular regulators of the bidirectional plasticity imbalance provides a molecular basis for a double target strategy in clinical intervention.

4. Targeted clinical intervention of PTSD

4.1. Memory extinction training

Memory fading training (exposure therapy) is currently the first-line method in the psychological treatment of PTSD. Its core logic is to repeatedly expose patients to trauma-related cues in a safe therapeutic situation, thereby establishing a new association that cues are not equal to danger [4]. As discussed at the end of 3.1, the mechanism of fear extinction is to form a new competitive memory actively to inhibit the fear memory [4, 5]. From the synaptic plasticity aspect, the curative effect of exposure therapy relies on the successful inducibility of LTD in the hippocampus and the medial prefrontal cortex(mPFC). Only synapses can reduce the strength of the old fear memory connections, and the new memory has space to compete [5].

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However, the curative effect of typical exposure therapy is limited, and there are huge differences between individuals. Some patients still retain significant resistance to regression even after completing the treatment. Because of that, researchers have started to explore methods to enhance fading consolidation. Exercises have already proved to be an effective pathway for consolidation. The preliminary clinical trial by Powers et al. demonstrated that 30 minutes of moderate-intensity treadmill exercise before prolonged exposure therapy could improve the symptoms of PTSD by an effect size of d=2.65, and plasma BDNF levels increased (d=1.08), suggesting that exercise enhanced regression consolidation through BDNF-mediated synaptic plasticity [8].

This observation has similarities with the research concluded by Crombie et al. They observed among a group of female PTSD patients that after moderate-intensity aerobic exercise, the concentration of circular BDNF clearly mediates the reduction of the fear memory(BDNF 95% CI: The range of -0.941 to -0.005), further confirming that BDNF is a key molecular mediator of exercise enhancement and regression [9].

This research proves that through a behavioural pathway, increasing BDNF signals can indirectly promote the inducibility and maintenance of LTD in exposure therapy. However, there is a ceiling effect in behavioural intervention. Some patients cannot generate sufficient regression learning, or regression memory cannot generalize outside the treatment room. Therefore, drug interventions that directly target the molecular pathway of synaptic plasticity provide a more direct way for restoring LTP and LTD.

4.2. Targeted drug regulating bidirectional synaptic pathways

Two upstream regulatory pathways for the bidirectional synaptic plasticity imbalance are proven in Section 3.4, which provide targets for drug intervention. Furthermore, the GR, as the direct target of cortisol, the end product of the HPA axis, is also a key node for drug regulation of synaptic plasticity. The overactivation of GR is also a key reason for the damage of hippocampal LTD [6, 7]. Based on the above targets, the current drug strategies mainly follow three pathways: NMDA receptor regulation, GR antagonism, and anti-inflammatory regulation.

The first pathway is NMDA receptor regulation. The activation state of NMDA receptor decides that whether synaptic connections will be enhanced or regressed. D-cycloserine (DCS) is a partial agonist of NMDA receptors. It can induce bidirectional expression of synapses by lowering therapy(VRE) with 100mg DCS in a randomized controlled trial for patients with chronic PTSD. The results showed that the effect size of PTSD symptom improvements in the DCS-assisted group reached d=0.68 after treatment and increased to d=1.13 after 6-month therapy. The PTSD remission rate reached 69% at 6 months, while it was only 17% in the placebo group [10]. This indicates that DCS can enhance LTD learning by promoting NMDA-mediated synaptic plasticity, and the curative effect could last for 6 months [10].

The second pathway is targeting GR. As discussed above, abnormal cortisol changes metaplasticity by inducing GR, leading to damage to the hippocampus. As a result, GR antagonists may be expected to restore the induction ability of LTD in the hippocampus by blocking the GR signaling of cortisol. Currently, a Phase II randomized, double-blind, placebo-controlled trial is underway to evaluate the efficacy of the GR antagonist mifeprostone (1200 mg/ day for 7 days) in patients with refractory PTSD (N=60). The primary endpoint was the change in CAPS-5 scale score after 4 weeks of treatment [11].

However, drug-assisted regression is not always effective. There is a systematic review that included 13 RCTs, covering drugs such as D-cycloserine, propranolol, hydrocortisone, rapamycin, and mifepristone.The results showed that only 4 studies reported significant adjuvant efficacy, 7 had

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no significant effect, and even 2 indicated that the drugs actually weakened the efficacy [12]. This heterogeneity suggests that the drug-assisted effect would be affected by types of trauma, the gender of patients, comorbidity status, and administration time with a window, and also reflects that the precise understanding of "when, whom, and give what drug" to best restore the LTP and LTD balance needs to be explored more deeply.

In addition to pharmacological heterogeneity, drug intervention also faces bottlenecks such as blood-brain barrier permeability, side effects, and individual genetic differences. Currently, non-invasive neuromodulation techniques have reshaped synaptic plasticity by directly acting on specific brain region circuits, which provides an alternative path beyond drugs.

4.3. Non-invasive neuromodulation remodels overexcited synaptic connections

The mechanism of non-invasive neuromodulation is different from drugs. It directly applies physical stimuli like magnetic fields and electric currents to specific brain regions to alter the discharge patterns of neuron clusters, thereby inducing directional changes in synaptic plasticity of specific brain regions. The core dysfunction circuit for PTSD is that the over-activation in the amygdala and the regression in the hippocampus and mPFC. There are two pathways for neuron regulation. One is to inhibit the over-activation of the amygdala, and the other is to enhance the regulatory ability of the hippocampus and the mPFC [4].

Repetitive transcranial magnetic stimulation (rTMS) is currently the most studied neuroregulatory method. It usually enhances mPFC function through high-frequency stimulation or inhibits amygdala activity through low-frequency stimulation, thereby indirectly regulating the synaptic plasticity of the hippocampal-amygdala circuit. However, the highest-level evidence is not optimistic. There is a review that included 13 RCTS involving a total of 577 PTSD patients. Moderate-quality evidence showed that active rTMS had no significant difference in the immediate effect on the severity of PTSD compared to fake stimulation (SMD=-0.14, 95% CI: -0.54 to 0.27) [13]. The negative result suggests that the standardized rTMS treatment would not be so effective while facing huge individual differences in the mode of synaptic plasticity imbalance. Unlike standardized protocols, individualized rTMS (PrTMS) attempts to dynamically adjust the stimulation sites and frequencies based on the α oscillation characteristics of the patient's electroencephalogram (EEG) to achieve personalized stimulation treatment. In a current study including 185 veterans, 4 to 6 weeks of PrTMS combined with conventional PTSD treatment showed that over 50% of the patients achieved complete improvement of PTSD symptoms, accompanied by a significant increase in the synchrony of cortical α center frequency and α oscillations [14]. The writer believes that the curative effect of the PrTMS may originate from its precise regulation of the default mode network(DMN). The DMN experiences α -oscillation disorder after trauma. The PrTMS indirectly improves the information integration efficiency of the hippocampal-amygdala circuit by restoring the rhythmic activity of the DMN [14].

Combining 4.1 to 4.3, there are three intervention methods: exercises and exposure, molecular drugs, and physical stimuli. They all aim to restore the dynamic balance of LTP and LTD. The ideal treatment for PTSD should be based on different synaptic plasticity imbalance patterns for the patient, and combine multiple treatments for the best curative effect.

5. Conclusion

This article is based on bidirectional synaptic plasticity to analyze the mechanism of the PTSD flashback symptom. Traumatic stress drives the over-activation of LTP and the regression of LTD by

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the dysregulation of the HPA axis. This imbalance is controlled by the NF-κB inflammation pathway and the BDNF methylation pathway. Furthermore, this article also evaluates three kinds of clinical interventions for PTSD: the behavioural aspect, the molecular aspect, and the physical aspect, and suggests that personalized intervention is the core developing direction in the future. The overall structure indicates that the flashback symptoms of PTSD are not the abnormality of a single kind of molecule or a single region of the brain, and it is a systematic manifestation of bidirectional plasticity imbalance between LTP and LTD in the hippocampus-amygdala circuit. This article integrates two pathways of inflammatory signaling and epigenetics, which were previously studied separately, providing a more systematic view of the pathological mechanism of PTSD. For clinical interventions, effective therapy for PTSD should focus on the restoration of balance between LTP and LTD, which means that future research should draw attention to both the hippocampus and amygdala.

Further research in the future should aim to measure the plasticity of LTP and LTD directly for patients, using a transcranial magnetic stimulation-electroencephalogram (TMS-EEG pairing paradigm to ensure the bidirectional dysregulation is also the same in humans. In addition, precise intervention strategies based on individual plasticity imbalance subtypes are worthy of further exploration - this requires stratifying patients in combination with biomarkers and behavioral phenotypes, and designing targeted combination treatment plans.

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