Role of Neurotransmitters in Fear Memory Destabilization and Reconsolidation

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Abstract

Memory is stored in the strength changes of synaptic connections between neurons, and neurotransmitters play a critical role in regulating synaptic plasticity. Neurons that express specific types of neurotransmitters can form particular neurotransmitter systems, primarily including cholinergic, dopaminergic, noradrenergic, serotonergic, and glutamatergic systems, among others. Studies on the destabilization process of various types of memory have revealed that acetylcholine plays a crucial role in memory destabilization triggered by memory retrieval containing novel information; whereas the resistance of high-intensity fear memories to destabilization and reconsolidation is attributable to activation of the noradrenaline-locus coeruleus system during the encoding of such fear memories. Other important neurotransmitters, including dopamine, glutamate, GABA, and serotonin, also affect memory plasticity at different memory stages. Neurotransmitters play an important role in fear memory destabilization and reconsolidation, but these effects are typically not independent; rather, they involve interactive and mutually regulatory mechanisms, including dopaminergic-cholinergic and serotonergic-glutamatergic interactions, among others. Molecular-level research on neurotransmitters can provide valuable insights for studies on fear memory reconsolidation interventions. Future research should continue to explore key factors and methods for fear memory destabilization based on the molecular mechanisms of memory destabilization and neurotransmitter actions, in order to better improve clinical treatments for post-traumatic stress disorder based on memory reconsolidation interventions.

Full Text

The Role of Neurotransmitters in Fear Memory Destabilization and Reconsolidation

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Abstract

Memory is stored in the strength changes of synaptic connections between neurons, and neurotransmitters play a crucial role in regulating synaptic plasticity. Neurons expressing specific types of neurotransmitters can form distinct neurotransmitter systems, including cholinergic, dopaminergic, noradrenergic, serotonergic, and glutamatergic systems. Research on the destabilization processes of various memory types has revealed that acetylcholine plays an important role in memory destabilization triggered by retrieval of novel information. High-intensity fear memories resist destabilization and reconsolidation because of noradrenergic-locus coeruleus system activation during fear memory encoding. Other important neurotransmitters, including dopamine, glutamate, gamma-aminobutyric acid, and serotonin, also influence memory plasticity at different stages. Neurotransmitters play significant roles in fear memory destabilization and reconsolidation, but these effects are typically not independent; rather, they involve interactions and mutual regulation, such as dopamine-cholinergic interactions and serotonin-glutamate interactions. Molecular-level studies of neurotransmitters can provide valuable insights for research on fear memory reconsolidation interventions. Future research should continue to explore key factors and methods for fear memory destabilization based on molecular mechanisms and neurotransmitter functions, to improve clinical treatments for post-traumatic stress disorder through reconsolidation-based interventions.

Keywords: neurotransmitter; conditioned fear memory; destabilization; reconsolidation; synaptic plasticity

Introduction

Memory makes us who we are. However, as the saying goes, "it is better to forget and smile than to remember and be sad" —forgetting is also an important function for maintaining health. For clinical patients, the inability to forget negative memories or the overgeneralization of negative memories leads to persistent symptoms. Fear memory extinction is a major theme in basic research,

typically using classical conditioning to form conditioned fear memories through conditioned stimulus (CS)–unconditioned stimulus (US) associations, which are then eliminated through extinction training. Extinction training actually establishes an inhibitory CS–no US memory that competes with the original memory. Within a recent time window, the inhibitory memory dominates, manifesting as fear response extinction, typically measured through skin conductance response (SCR) and fear-potentiated startle (FPS). However, the new extinction memory does not completely destroy the original fear memory—the original memory association remains intact (Chen et al., 2021). Consequently, spontaneous recovery over time, reconstruction when facing the same negative stimulus again, or renewal when returning to the original fear memory context can all trigger relapse of the original fear. This is considered the main reason why exposure therapy has high relapse rates in treating anxiety disorders. How to utilize memory plasticity mechanisms to induce "forgetting" and explore the role of important factors in this process has become a key research focus.

The "retrieval-intervention" paradigm proposed around 2010 partially addressed these issues. Research demonstrates that after formation and stabilization, fear memories are not immutable. When properly retrieved and activated, they enter a transient unstable state, becoming sensitive to new information and requiring new protein synthesis to restabilize—a process called memory reconsolidation (Nader, Schafe, & Le Doux, 2000). Administering substances that directly or indirectly disrupt protein synthesis during this reconsolidation window interferes with the restabilization process, achieving destruction of the original fear memory. The retrieval-intervention paradigm, also called the reconsolidation interference paradigm, uses brief CS exposure to activate the original memory into a destabilized state, activating synaptic plasticity, followed by behavioral or pharmacological interventions to disrupt the original memory (M.-H. Monfils, Cowansage, Klann, & LeDoux, 2009; Schiller et al., 2010). Destroying the original fear memory connection is a method for completely eliminating fear and preventing relapse (Elsey & Kindt, 2017). Over the past two decades, based on this hypothesis, numerous studies have emerged using reconsolidation disruption to eliminate fear memories, combining with clinical practice for research and intervention on spider phobia, speech anxiety, post-traumatic stress disorder (PTSD), alcohol addiction, and drug dependence, demonstrating the vitality of this paradigm (Elsey et al., 2020; Kindt, 2018b; M. H. Monfils & Holmes, 2018; Paulus, Kamboj, Das, & Saladin, 2019).

Current views on memory reconsolidation stages fall into two categories: one considers reconsolidation an overall process that can be divided into memory destabilization and restabilization phases (J. L. C. Lee, 2008); the other treats reconsolidation as a separate process (restabilization), with memory updating including both destabilization and reconsolidation phases—the latter being the mainstream view in the field (Troyner & Bertoglio, 2020). This paper adopts the latter perspective, treating memory reconsolidation as a separate process and memory destabilization as the preceding phase that initiates reconsolidation, a parallel process with sequential relationship (Figure 1 [Figure 1: see original

paper]). The theoretical process of original memory from formation to updating is shown in Figure 1.

Figure 1. Utilizing memory destabilization and reconsolidation mechanisms to update original memory

Research shows that brief CS exposure does not necessarily retrieve memory into a destabilized state, but is subject to a series of boundary conditions (Zuccolo & Hunziker, 2019), which are considered one reason for many negative results in reconsolidation intervention research (Cahill & Milton, 2019). Currently recognized boundary conditions include: (1) memory-intrinsic conditions, such as fear memory intensity, age, and learning history (Li et al., 2023); (2) retrieval conditions: retrieval cue properties, presentation duration, presence of prediction error (PE) (Chen et al., 2020; Junjiao et al., 2019), and (3) pre-memory state conditions: exogenous stress before memory formation (Kindt, 2018b; Zuccolo & Hunziker, 2019). Therefore, how to induce destabilization of original memories has become an important prerequisite for using the reconsolidation intervention paradigm, and how to overcome boundary conditions caused by intensity in clinical disorders has become the primary problem for clinical application.

We hypothesize that neurotransmitters have advantages in solving this problem. As messengers of information transmission, neurotransmitters play crucial roles in regulating neuronal synaptic plasticity. Various neurotransmitters change human emotion, cognition, and behavior, having special effects on fear memory formation, maintenance, extinction, and updating. Therefore, studying neurotransmitter functions and mechanisms can help us understand the nature of learning and memory, and utilize these functional systems to better strengthen adaptive memories or extinguish non-adaptive memories, shaping human behavior and curing mental illnesses.

2.1 The Relationship Between Neurons, Synaptic Plasticity, and Memory

Donald Olding Hebb first described the basic principles of synaptic plasticity in his 1949 book *The Organization of Behavior*. Synaptic plasticity is defined as the long-term capacity for change in neuronal synaptic connections, and memory is stored in the strength changes of synaptic connections between nerve cells in the central nervous system. Synaptic plasticity has both structural and functional manifestations. Structural manifestations mainly involve dendritic spine generation and proliferation, while functional manifestations include long-term potentiation (LTP) and long-term depression (LTD). For learning and memory, mediating circuits directly produce behavior, while modulatory circuits fine-tune behavior through synapses between sensory and motor neurons during learning—these modulatory circuits constitute the basic neural components of memory.

Short-term and long-term memory formation involve different neural mecha-

nisms. Short-term memory involves changes in synaptic connection strength, including synaptic strengthening or weakening, but is limited to functional changes. Long-term memory formation involves anatomical structural changes: long-term sensitization causes neurons to grow new synapses, while long-term habituation eliminates certain old synapses. New learning can also activate inactive synapses or deactivate active ones.

Both short-term and long-term memory formation require neurotransmitter participation, but they have different neural bases. At the molecular level, when electrical signals are transmitted through axons to terminal nerve cells, neurons secrete neurotransmitters (such as serotonin) into the synaptic cleft, which then bind to receptors on the postsynaptic membrane, causing neurons to synthesize large amounts of cyclic AMP (cAMP). cAMP further activates protein kinase A (PKA), causing specific ion channels on the postsynaptic membrane to close, generating postsynaptic potentials that enhance corresponding reflexes —this forms the neural basis of short-term memory.

Long-term memory formation involves new synapse generation and has two independent processes: initiation of synaptic growth and maintenance of synaptic growth. After short-term memory formation, if learning and training are repeated, neurotransmitters cause PKA to translocate into the nucleus, where it activates cAMP response element binding protein (CREB), causing CREB phosphorylation that initiates special genes to establish new synaptic protein mRNA—this process is called synaptic growth initiation. After RNA transcription synthesizes proteins, CREB-regulated proteins activate synaptic protein synthesis. The combination of mRNA and CREB continuously synthesizes new proteins at synaptic terminals, leading to new synaptic growth—this process is called synaptic growth maintenance. These processes constitute the neural basis of long-term memory formation. Clearly, whether something can be remembered and enter long-term memory depends importantly on CREB. The cAMP-PKA-CREB signaling pathway is one of the most classic signaling pathways in memory molecular mechanisms, first discovered by Eric Kandel in sea slugs, but this learning mechanism also applies to other animals and humans.

2.2 Overview of Molecular Mechanisms of Fear Memory Destabilization

Memory destabilization is the gateway to memory reconsolidation, opening a temporary time window that provides the possibility for memory modification. How do consolidated long-term memories become unstable and changeable after retrieval? Molecular research indicates that the decisive factor for destabilization is protein degradation through the ubiquitin-proteasome system (UPS), which enhances memory destabilization by reducing synaptic connections of the original memory. Studies show that two glutamate receptors—α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) and N-methyl-D-aspartate receptors (NMDAR)—play important roles in memory destabilization.

Among AMPARs, calcium-permeable AMPARs (CP-AMPAR) are particularly important. In most cases, the presence of GluA2 subunits makes channels calcium-impermeable. If AMPARs lack GluA2 subunits, they become permeable to sodium, potassium, and calcium ions. When calcium-impermeable AMPARs (CI-AMPAR) are present, memories are relatively stable. When memories are activated by retrieval, the lack of GluA2 subunits causes receptors to become calcium-permeable CP-AMPARs, making synapses plastic and memories unstable. NMDARs and their subtypes also play important roles in memory destabilization and reconsolidation—for example, studies using the NMDAR antagonist ketamine to treat excessive drinking by disrupting memory reconsolidation (Das et al., 2019). Calcium/calmodulin-dependent kinase II (CaMKII) plays a central role in synaptic plasticity and may be important between CP-AMPAR/NMDAR activation and increased protein degradation required for memory destabilization.

Research on the molecular mechanisms of fear memory reconsolidation shows that mechanisms of fear memory consolidation and reconsolidation both overlap and differ (Orsi et al., 2019). In terms of overlap, both contextual fear memory consolidation and reconsolidation require CREB-mediated transcriptional activation and gene expression in the amygdala or amygdala/hippocampus. Recent studies also show that brain-derived neurotrophic factor (BDNF) is required for both memory consolidation and reconsolidation processes (Gonzalez, Radiske, & Cammarota, 2019), including fear memory and object recognition memory, correcting early research suggesting BDNF was not involved in reconsolidation (J. L. Lee, Everitt, & Thomas, 2004).

On the other hand, molecular mechanisms of fear memory consolidation and reconsolidation also differ. For example, transcription factor Zif268 is only required for memory reconsolidation, not consolidation, making it a molecular marker for activated memory reconsolidation. Research from Ma Lan' s group in China found that memory reconsolidation has unique molecular mechanisms, primarily involving β-arrestin-biased β-adrenergic receptor signaling pathway activation in memory reconsolidation (Liu et al., 2015).

3.1 Types and Functions of Neurotransmitters

Neurotransmitters are chemical substances that transmit information between neurons or between neurons and effector cells. Based on chemical composition, they are mainly divided into amino acids (including glutamate, aspartate, gamma-aminobutyric acid, glycine, and acetylcholine), monoamines (including norepinephrine, epinephrine, dopamine, and serotonin), neuropeptides, and other neurotransmitters. They are typically classified as excitatory or inhibitory based on whether they increase or decrease the probability of neuronal firing after acting on the cell membrane. Excitatory neurotransmitters include dopamine, norepinephrine, glutamate, and acetylcholine. Inhibitory neurotransmitters include serotonin, gamma-aminobutyric acid (GABA), endorphins, and oxytocin. However, this distinction is not absolute—a neurotransmitter may be

both excitatory and inhibitory depending on the target. For example, acetylcholine can be both.

A concept similar to neurotransmitters is hormones. The difference is that hormones are produced by specific glands, secreted into the bloodstream, and transported to specific locations to function, whereas neurotransmitters exist mainly in synapses, act directly on adjacent nerve cells, and are only found in the animal nervous system. Some substances serve as both neurotransmitters and hormones, such as norepinephrine.

Neurotransmitters are called "messengers" of information in the brain. The basic process involves chemicals stored in synaptic vesicles at nerve terminals. Upon receiving electrical signals conducted by axons, synaptic vesicles fuse with the presynaptic membrane, releasing transmitters into the synaptic cleft. After crossing the cleft, they bind to specific receptors on the postsynaptic membrane, causing ion channel opening and membrane potential changes, or indirectly affecting ion channels through second messenger systems, producing excitatory or inhibitory responses to complete information transmission. Remaining neurotransmitters in the synaptic cleft are either hydrolytically inactivated or undergo reuptake, being reabsorbed by the presynaptic membrane for reuse. Many psychiatric and neurological drugs work by inhibiting neurotransmitter reuptake, increasing neurotransmitter concentration in the synaptic cleft to alleviate disease symptoms, such as SSRIs for depression.

Neurons expressing specific neurotransmitters can form particular neurotransmitter systems, mainly including dopaminergic, noradrenergic, serotonergic, and glutamatergic systems, each with distinct pathways that regulate various cognitive processes and behaviors including arousal, circadian rhythms, motivation, emotion, cognitive control, learning and memory, feeding and energy balance, and reward.

3.2.1 The Role of Acetylcholine in Memory Destabilization

Acetylcholine (ACh) is generated from choline and acetyl-CoA under the action of choline acetyltransferase (ChAT). Due to its special role in memory, it is called the source of learning and memory. Its effects vary depending on the target, showing both excitatory and inhibitory actions. All ACh in the neocortex originates from the basal forebrain, located anterior and ventral to the striatum. Cholinergic neurons in the basal forebrain project widely, including to the hippocampus, olfactory bulb, and amygdala, regulating the "cortex-hippocampus-amygdala network" excitability. Studies show that basal forebrain cholinergic neurons are activated to release ACh when animals perform operant tasks, motor activities, face novel stimuli, and execute working memory and place preference memory (Pepeu & Giovannini, 2004).

Based on ACh' s important role in new memory formation, researchers have explored its potential role in destabilization processes of different memory types. Winters' team found that ACh plays an important role in remote object memory

and spatial memory destabilization, and this role appears or strengthens with salient novelty during memory retrieval. Stiver et al. studied the bidirectional regulation of cholinergic systems in object memory destabilization after retrieval, finding that injecting the muscarinic receptor antagonist scopolamine into rat perirhinal cortex (PRh) during memory retrieval could prevent novelty-induced long-term memory destabilization, while injecting muscarinic receptor agonists promoted object memory destabilization, demonstrating ACh' s important role in memory destabilization triggered by retrieval of novel information (Stiver et al., 2015).

Subsequent research further explored ACh' s role in hippocampus-dependent spatial memory. Weak spatial memory destabilization depends on activation of M1-muscarinic cholinergic receptors (mAChR) in the dorsal hippocampus (dHPC). Novelty-induced strong spatial memory destabilization requires activation of mAChR in dHPC, and inhibiting muscarinic receptors in dHPC prevents novelty-induced destabilization of high-intensity object location memory. If memory retrieval lacks novel information, pharmacologically induced activation of M1-mAChR in HPC can mimic the effect of novelty, destabilizing strong spatial memories (Huff, McGraw, & Winters, 2021).

Currently, research on ACh in conditioned fear memory is relatively scarce. The above team recently published research continuing to verify this mechanism in animal fear memory models, examining whether novel stimuli during memory retrieval in rats cause strong fear memory destabilization in a manner dependent on muscarinic cholinergic receptors (mAChR) (Abouelnaga, Huff, O' Neill, Messer, & Winters, 2023). This study distinguished two intensities of fear memory through different numbers of shocks, finding that for weaker fear memories, memory destabilization could be blocked by intraperitoneal injection of the mAChR antagonist scopolamine. For stronger fear memories, ordinary retrieval could not induce memory instability and required the presence of novel information during retrieval. Similar to previous object memory and location memory studies, intraperitoneal injection of M1-mAChR agonists could mimic or substitute for novelty information, eliminating intensity boundary conditions and triggering fear memory destabilization (Abouelnaga et al., 2023). These results support the consistency of ACh' s role in memory destabilization across memory types.

Regarding molecular mechanisms of ACh' s role in memory destabilization, research suggests this regulatory effect may be produced through activity at M1-muscarinic receptor subtypes rather than M2 subtypes, and may function through an intracellular pathway linking M1 receptors to ubiquitin-proteasome system (UPS) activation (Stiver et al., 2017). Protein degradation caused by UPS is considered the neurobiological basis of memory destabilization. Researchers verified the hypothesis that cholinergic receptor activation, especially M1-mAChR activation, stimulates UPS through inositol trisphosphate receptor (IP3R)-mediated intracellular calcium store release, thereby promoting object memory destabilization. Stiver et al. blocked UPS in PRh and found it pre-

vented object memory destabilization induced by novelty or pharmacological activation of M1 receptors, reporting a functional dissociation between M1 and M2 receptors: only selective M1 receptor antagonists could prevent novelty-induced remote object memory destabilization (Stiver et al., 2017).

All the above studies include novel information—unexpectedness or surprise during memory retrieval—called prediction error (PE) in fear memory reconsolidation research. Numerous studies show that prediction error is a necessary condition for fear memory destabilization and an important boundary condition for memory reconsolidation. PE primarily reflects a violation of expectation and the need to update original memory, considered a driving factor for memory modification or new learning. This mechanism has been demonstrated at the molecular level of neurotransmitters. The above studies found that salient novelty during memory retrieval promotes destabilization of strongly encoded spatial memories, and if unexpected information or PE signals are lacking, artificially activating M1-mAChR in dHPC can achieve the same effect, destabilizing strong spatial memories (Huff et al., 2021; Stiver et al., 2017). Therefore, we can speculate that one mechanism of PE' s action is through cholinergic signaling. Acetylcholine is a neurotransmitter that plays an important role in learning and memory, closely related to cognitive functions such as arousal and attention. Researchers hypothesize that PE signals or novelty information during retrieval enhance ACh levels, which then stimulate UPS for protein degradation, enabling memories that resist change due to intensity to successfully enter an unstable state (C. E. Wideman, Jardine, & Winters, 2018). However, this mechanism remains to be verified in conditioned fear memory.

3.2.2 The Role of Acetylcholine in Memory Reconsolidation

During memory reconsolidation, numerous studies show that blocking central cholinergic systems causes memory impairment, while enhancing cholinergic activity strengthens memory (Baratti, Boccia, & Blake, 2009; Blake, Boccia, Krawczyk, Delorenzi, & Baratti, 2012). Regarding the relationship with novel information, researchers used a mouse fear memory inhibitory avoidance task model, manipulating prediction error during memory retrieval (applying higher or lower US intensity or no US intensity than training), and observed behavioral changes in subsequent test phases. They found that cholinergic signaling only regulated memory reconsolidation when retrieval contained PE—administering mAChR agonist oxotremorine, mAChR antagonist scopolamine, or nAChR agonist nicotine after memory retrieval enhanced or impaired memory reconsolidation in a sex-specific manner (Krawczyk, Millan, Blake, & Boccia, 2021).

Wideman et al.' s recent research found that different ACh receptor subtypes—nicotinic acetylcholine receptors (nAChR) and muscarinic receptors (mAChRs)—show functional dissociation in mouse object memory reconsolidation. For object memory destabilization, mAChRs are required while nAChR is not necessary; conversely, for reconsolidation of already destabilized memories, nAChR is required while mAChRs are not. Therefore, researchers propose that nAChR

plays a selective role in the reconsolidation process of already destabilized memories (Cassidy E. Wideman et al., 2022).

3.3.1 The Role of Dopamine in Memory Destabilization

Dopamine is both a monoamine neurotransmitter and a hormone, also acting as a neurohormone released by the hypothalamus in the brain. Dopamine is secreted in the substantia nigra (SN), ventral tegmental area (VTA), periaqueductal gray (PAG), and hypothalamus. Dopamine has four main pathways in the brain (Figure 2 [Figure 2: see original paper]): (1) The nigrostriatal pathway projects dopaminergic neurons from the input region to the dorsal striatum (dStr), playing a major role in controlling motor function and learning motor skills. Damage to this pathway causes Parkinson' s disease. (2) The mesolimbic pathway from the midbrain limbic system to the nucleus accumbens regulates motivation, reward, biological instincts, and addictive behavior, representing an important neural pathway involved in drug abuse. (3) The mesocortical pathway projects extensively to the forebrain, with VTA projecting to the prefrontal cortex to maintain stability of higher brain functions including cognition, thinking, judgment, and analytical operations. (4) The tuberoinfundibular pathway involves hypothalamic dopaminergic neurons forming the tuberoinfundibular dopamine pathway, projecting from the arcuate nucleus to the median eminence and secreting DA as a prolactin inhibitor.

Figure 2. Dopamine projection pathways in the brain

Dopaminergic systems are closely related to memory destabilization. Dopamine receptors are a group of five G protein-coupled receptors (D1-D5) that function in many biological processes including learning and memory. To investigate dopaminergic roles in destabilization, researchers explored DA' s role in object recognition memory (ORM), finding that hippocampal D1/D5 receptors are not necessary for ORM trace formation, retrieval, or post-retrieval restabilization, but are essential for memory destabilization. Administering dopaminergic receptor antagonists to block D1/D5 before (but not after) memory updating prevents memory destabilization. DA functions during memory reactivation and when incorporating new information into original memory (Rossato et al., 2015). When D1/D5 in the dorsal hippocampal CA1 region are inhibited, it prevents novelty-induced object memory destabilization in rats. Researchers hypothesize that under these conditions, DA participates in initiating destabilization because presentation of novel objects may cause prediction error or violate previous expectations.

Since DA is massively released when prediction error occurs, researchers generally hypothesize that DA' s role in memory destabilization mainly accompanies the emergence of new information. Reichelt et al. demonstrated through animal experiments that VTA functional inactivation prevented reward memory destabilization in rats, and VTA is the main region secreting dopamine (Reichelt, Exton-McGuinness, & Lee, 2013). Merlo et al.' s research on reward

memory showed that administering dopamine receptor D1 and D2 antagonists in the amygdala before memory retrieval hindered memory loss caused by post-retrieval injection of protein synthesis inhibitor anisomycin, indicating it prevented memory from entering an unstable state. Results suggest that dopaminergic transmission in the basolateral amygdala (BLA) is a necessary condition during reward memory destabilization (Merlo et al., 2015).

Behavioral research has proven that prediction error is necessary but not sufficient for initiating memory reconsolidation—novel information alone during retrieval is insufficient for destabilization, with results also affected by other boundary conditions (Li, Chen, Shi, Dong, & Zheng, 2022). So as the biological indicator of PE, is DA' s role also necessary but not sufficient? In auditory cue fear memory, researchers examined dopamine receptor D1' s role in fear memory destabilization, finding that direct injection of D1 agonist before memory reactivation was insufficient to trigger auditory fear memory destabilization. However, Nefiracetam could induce memory destabilization, and this effect required DA signaling—when D1 was inhibited, Nefiracetam could no longer induce memory destabilization. These results suggest that DA is not directly and solely responsible for fear memory destabilization; DA alone is insufficient to trigger memory destabilization (Flavell & Lee, 2019). Thus, similar to behavioral-level prediction error, DA signaling also plays a necessary but non-sufficient role. Although DA is a necessary condition, memory destabilization also depends on many other signaling mechanisms, typically intracellular calcium signaling pathways leading to protein degradation (Milton, Das, & Merlo, 2023). Therefore, DA may regulate memory destabilization through interactions with other neurotransmitters including ACh, glutamate, and GABA (Flavell & Lee, 2019; Sippy & Tritsch, 2023).

3.3.2 The Role of Dopamine in Memory Reconsolidation

Dopamine also functions in memory consolidation and reconsolidation. During fear memory formation and consolidation, it is released in multiple brain regions including the hippocampus, prefrontal cortex, and amygdala, promoting memory consolidation and strengthening. In human fear memory formation, recent research using simultaneous PET and fMRI demonstrated dopamine release in the amygdala and striatum during fear learning, showing that dopamine release correlates with conditioned fear response intensity and linearly couples with learning-induced activity in the amygdala (Frick et al., 2021). Dopamine pathways also underlie human fear extinction learning, enhancing extinction by regulating nucleus accumbens prediction error coding during extinction learning (Esser, Korn, Ganzer, & Haaker, 2021).

Research has explored the role of reward-related DA elevation in interfering with fear memory reconsolidation. The principle involves administering the reward-associated drug methylphenidate (MPH) after memory retrieval to update or rewrite original fear memory. MPH can inhibit DA and NE reuptake and increase DA levels in the striatum and nucleus accumbens (NAc). Using

MPH after fear memory retrieval into the unstable state reduced conditioned fear responses, indicating fear memory was updated (Arellano Pérez, Popik, & de Oliveira Alvares, 2020).

3.4 The Role of Norepinephrine (NE) in Memory Destabilization and Reconsolidation

Norepinephrine (NE) is chemically similar to dopamine, formed by adding an oxygen atom to DA, making DA a precursor of NE. Epinephrine (EP) is synthesized in the body by adding a single methyl group to NE. NE, DA, and EP are all catecholamine neurotransmitters. While epinephrine acts on other body parts, norepinephrine concentrates in the brain. The locus coeruleus (LC) in the brain is the main region synthesizing NE, projecting widely to multiple brain regions in the central nervous system with excitatory effects. The LC-NE system is called the main regulator of arousal, alertness, and memory formation. Low NE causes attention deficits, but its most prominent role is regulating synaptic transmission and various forms of plasticity. In various sensory systems, both dopaminergic and noradrenergic systems can effectively reshape the modulatory properties of cortical neurons (Ranjbar-Slamloo & Fazlali, 2020). The extensive overlap of DA and NE in receptor expression and signaling pathways suggests they may mediate similar physiological functions, with behavioral specificity possibly depending on local concentration, timing of release and reuptake, and synaptic terminal activity.

Direct research verifying NE' s role in memory destabilization is limited, but recent studies found that high-intensity fear memories resist destabilization because of noradrenaline-locus coeruleus system (NOR-LC) activation during fear memory encoding. Preventing NOR-LC modulation of strong fear memory encoding allows the memory to undergo reconsolidation in the amygdala and become susceptible to interference (Haubrich, Bernabo, & Nader, 2020), suggesting NE' s potential role in memory destabilization. More research is needed to explore NE and its receptors' roles in memory destabilization and differences from DA.

In contrast, NE's role in memory reconsolidation is clearer. Adrenergic receptors are divided into α and β classes. The $ $1 receptor blocker propranolol is widely used to interfere with memory reconsolidation after memory activation, preventing new protein synthesis and thus preventing original memory restabilization to achieve memory disruption. Since propranolol is a commonly used drug for hypertension and arrhythmia that can be safely used in humans, it is widely used in human experiments and clinical treatments based on reconsolidation intervention. Note that this amnestic effect caused by propranolol is not due to the drug' s own pharmacological effects (i.e., propranolol does not treat anxiety disorders), but through its mechanism of affecting the β-AR/PKA/CREB signaling pathway and protein synthesis process, which should be clearly distinguished to prevent misuse (Kindt, 2018a).

3.5 Serotonin (5-HT) in Memory Destabilization and Reconsolidation

3.5.1 The Role of 5-HT in Memory Destabilization 5-hydroxytryptamine (5-HT) is an inhibitory neurotransmitter, also known as serotonin because it was first discovered in serum. 5-HT plays important roles in sleep-wake cycles, blood clotting, mood, bone health, sexual function, and memory formation and consolidation. In terms of emotion, normal 5-HT levels help individuals maintain good self-feeling, healthy mood, and well-being. Brain 5-HT deficiency is an important pathological feature of depression. An important type of antidepressant—selective serotonin reuptake inhibitors (SSRIs)—alleviates depression by reducing synaptic reuptake of 5-HT, increasing its concentration in the synaptic cleft. In the human body, 95% of serotonin comes from the small intestine. Recent research has confirmed the relationship between gut health and mental illness—the famous "gut-brain axis" system—with multiple neurotransmitters including 5-HT, DA, GABA, and NE found in the gut. Studies show that depressed patients have reduced probiotics in the gut, causing the 5-HT precursor tryptophan to be used for large-scale kynurenine production, reducing tryptophan conversion to 5-HT and making individuals more prone to depressive symptoms and impulsive, violent behavior (Agus, Planchais, & Sokol, 2018).

In cognition, 5-HT is considered an important neuromodulator for many cognitive processes including learning and memory (Ogren et al., 2008). Research found that mice with knocked-out genes related to 5-HT synthesis showed enhanced fear memory retention and increased intensity, while supplementing 5-HT in these knockout mice restored normal fear memory extinction, indicating that 5-HT deficiency leads to enhanced and difficult-to-extinguish fear memory (Dai et al., 2008). Chinese researchers using self-developed fluorescent probe technology for multiple neurotransmitters confirmed that 5-HT affects learning behavior by regulating synaptic plasticity during Pavlovian conditioning (Zeng et al., 2023).

Currently, few studies examine 5-HT' s specific role in memory destabilization, but researchers have begun noting 5-HT's role in memory retrieval and plasticity. Recent research using optogenetic manipulation of 5-HT nuclei found that optogenetic stimulation of 5-HT nuclei could restore lost memories in Alzheimer' s mice, achieved by closing inwardly rectifying potassium channel Kir2.1 on memory engram cells, thereby increasing engram cell excitability (Bostancıklıoğlu, 2019). Additionally, because 5-HT interacts with other neurotransmitters involved in memory destabilization such as DA, ACh, and Glu, it is thought to have potential involvement in memory destabilization. Based on serotonin' s important regulatory role in fear memory formation and extinction, it may become a promising target for intervening in memory stability, awaiting future research exploration.

3.5.2 The Role of 5-HT in Memory Reconsolidation In recent years, 5-HT' s role in memory reconsolidation has also received attention. Schmidt

et al. used selective inhibitors and agonists of 5-HT5A, 5-HT6, and 5-HT7 receptors, providing evidence that 5-HT in hippocampal CA1 may participate in contextual fear memory reconsolidation (Schmidt et al., 2017). Researchers injected 5-HT5A, 5-HT6, and 5-HT7 receptor inhibitors into rat dorsal hippocampal CA1 immediately after memory activation or with a three-hour delay, finding that only administration three hours after memory activation could prevent contextual fear memory reconsolidation, with reduced freezing behavior in tests the next day. Interestingly, injecting 5-HT7 receptor antagonists in CA1 seemed to promote reconsolidation, as rats showed more freezing behavior when returned to the context. These findings emphasize the importance and complexity of 5-HT receptor subtypes, especially 5-HT5A, 5-HT6, and 5-HT7, in memory reconsolidation, with different receptor subtypes potentially causing opposite results that require further study (Schmidt et al., 2017).

Other studies show that administering the 5-HT receptor antagonist methiothepin (MET) can disrupt aversive memory reconsolidation in snails (Nikitin, Solntseva, Kozyrev, Nikitin, & Shevelkin, 2018). Further research is still needed to clarify the complex potential roles of 5-HT in memory reconsolidation and whether these roles depend on different receptors.

3.6 Glutamate (Glu)

Glutamate is the most abundant neurotransmitter in the brain and central nervous system. Almost all excitatory neurons in the brain and spinal cord are glutamatergic, making it the most important neurotransmitter for maintaining healthy brain function. Particularly important is glutamate' s role in enhancing neural plasticity—the brain' s capacity to grow and adapt to constant change requires continuous learning, memory, and execution of various cognitive functions, all of which depend heavily on glutamate. In learning and memory, glutamate helps strengthen or weaken signals between neurons over time, thereby shaping memory. Too little glutamate causes learning difficulties, but excessive glutamate is excitotoxic, causing neuronal overactivation and death.

Glutamate functions in the central nervous system through two receptor types: (1) Ionotropic glutamate receptors, including NMDA receptors, AMPA receptors, and Kainate receptors, which contain an ion channel directly activated upon glutamate binding; (2) Metabotropic glutamate receptors (mGluR), which activate ion channels through G protein coupling. Each receptor has many subtypes. Glutamate and its receptors constitute the most important neurotransmitter system mediating synaptic plasticity. Glu functions in various neural plasticity mechanisms including long-term potentiation (LTP), long-term depression (LTD), and synaptic reorganization (Pal, 2021). In central nervous system structures, NMDA and AMPA receptor activation triggers LTP to strengthen synaptic connections necessary for memory formation (Lynch, 2004), while inhibiting NMDA receptor membrane trafficking significantly affects contextual fear memory consolidation, suggesting NMDA receptor membrane trafficking is required for memory consolidation (Yang et al., 2022).

3.6.1 The Role of Glutamate in Memory Destabilization Research examined Glu' s role in object recognition memory (ORM), finding that in adult male rats, memory retrieval conducted 24 hours after training—when ORM retrieval was activated in the presence of novel objects—administration of the non-subunit-selective NMDAR antagonist AP5 or the GluN2A subunit-containing NMDAR antagonist TCN201 in dHPC CA1 region 5 minutes after activation caused memory impairment in tests 24 hours later, indicating disrupted memory reconsolidation. In contrast, pre-retrieval administration of the GluN2B subunit-containing NMDAR antagonist RO25-6981 did not affect ORM in tests but prevented Zif268 inactivation and protein synthesis inhibitor-induced forgetting in CA1, indicating it blocked memory destabilization (Rossato et al., 2023). These results suggest that different NMDAR subunits have distinct roles in different stages of memory updating: the GluN2B subunit is required for memory destabilization, while GluN2A participates in memory reconsolidation. The GluN2A/GluN2B ratio determines whether memory can be successfully destabilized, verifying previous research conclusions (Milton et al., 2013).

Previous research found that whether retrieval induces memory destabilization is determined by the ratio of two NMDA receptor subunits (Vigil & Giese, 2018). The GluN2B subunit regulates memory destabilization, while GluN2A regulates memory restabilization, and their ratio determines the path after memory activation. When GluN2B receptors increase and the GluN2A/GluN2B ratio decreases, memory enters an unstable state. However, external factors such as memory encoding intensity and stress state during memory formation may reduce GluN2B receptors, making original memories less susceptible to destabilization activation (Solis et al., 2019).

Beyond NMDARs, glutamate' s other ionotropic receptor AMPAR also functions in memory destabilization. Hong et al.' s 2013 study found that memory retrieval activation causes calcium-impermeable AMPARs (CI-AMPAR) to exchange subunits for calcium-permeable AMPARs (CP-AMPAR). Since CI-AMPARs are more stable at synapses and CP-AMPARs are less stable, memory retrieval increases synaptic plasticity activity. They further found that during memory retrieval, blocking CI-AMPAR endocytosis or reducing NMDAR activity could prevent AMPAR subunit conversion to CP-AMPAR, making memory resistant to destabilization (Hong et al., 2013). Researchers examined whether autophagy (a major protein degradation pathway)-induced protein degradation could overcome intensity-related boundary conditions. Studies in mouse auditory fear memory models showed that autophagy induction facilitates fear memory destabilization dependent on AMPAR endocytosis. In contextual fear memory reconsolidation models, autophagy induced in the amygdala or hippocampus caused contextual memory destabilization, associated with AMPAR degradation in contextual memory cell spines (Shehata et al., 2018). These studies all indicate that glutamate and its receptors play crucial roles in memory destabilization.

3.6.2 The Role of Glutamate in Memory Reconsolidation Generally, glutamate is required for both memory consolidation and reconsolidation, but different glutamate receptor subtypes may act at different memory stages (Garcia-delaTorre, Pérez-Sánchez, Guzmán-Ramos, & Bermúdez-Rattoni, 2014; Gieros, Sobczuk, & Salinska, 2012). Research suggests amnesia results from impairing memory reconsolidation using NMDA glutamate receptor antagonists (Nikitin et al., 2018; Nikitin, Solntseva, Nikitin, & Kozyrev, 2015). In aversive memory, Glu receptor antagonists can prevent reconsolidation of taste aversion memory or long-term habituation memory (Garcia-delaTorre et al., 2014; Rose & Rankin, 2006). In addiction memory, glutamate signaling has also been shown to play an important role in drug addiction memory reconsolidation, becoming a target for eliminating addiction memory (Dennis & Perrotti, 2015).

In contextual fear memory, research shows that fear memory retrieval causes immediate but transient changes in synaptic plasticity mediated by altered expression of glutamate receptor subunits GluA1 and GluA2 in rodent hippocampus. Memory retrieval causes immediate LTP impairment, enhanced 6 hours after retrieval; memory retrieval also causes immediate LTD enhancement that decreases over time. Blocking GluA2 endocytosis during the initial reconsolidation period restores LTP and weakens LTD (Bhattacharya et al., 2017). Fear memory retrieval causes changes in GluA2 subunit-containing AMPARs, and preventing retrieval-induced GluA2 endocytosis can enhance subsequent fear expression and prevent long-term reconsolidation-based fear memory loss. Researchers propose that GluA2-containing AMPAR endocytosis is very important for maintaining memory plasticity, helping maintain memory adaptability through the reconsolidation process (Rao-Ruiz et al., 2011). Thus, glutamatergic synaptic plasticity, especially GluA2 endocytosis, is necessary for fear memory reconsolidation.

In summary, NMDAR subtypes GluN2A and GluN2B play dissociated roles in memory destabilization and reconsolidation, successively discovered across different memory types and brain regions including the amygdala in auditory fear memory, hippocampus in fear extinction memory, and perirhinal cortex in object memory, indicating this mechanism has cross-memory type universality (Rossato et al., 2023).

3.7 Gamma-Aminobutyric Acid (GABA)

Gamma-aminobutyric acid (GABA) is formed from glutamate through decarboxylation and is the main inhibitory neurotransmitter in the brain, responsible for synaptic inhibition throughout the nervous system, helping individuals experience relaxation and known as a natural "tranquilizer." The Glu-GABA balance in the brain is extremely important—these two neurotransmitters constrain each other to maintain normal brain function. GABA has three main receptors: GABA-A, GABA-B, and GABA-C. The A receptor is ionotropic, itself an ion channel; the B receptor is metabotropic, a G protein-coupled receptor; and the C receptor exists in visual neural pathways. GABA exerts corresponding physiological functions by binding to different receptors.

3.7.1 The Role of GABA in Memory Destabilization Research examining GABA in BLA on fear memory reconsolidation found that administering the GABA-A receptor agonist midazolam (MDZ) before memory encoding prevented stress-induced resistance to MDZ and propranolol's interference with fear memory reconsolidation (i.e., prevented stress-induced boundary conditions). Before memory encoding, injecting competitive GABA-A receptor antagonists in the amygdala induced resistance to memory interference caused by post-retrieval MDZ (i.e., created boundary conditions), producing effects similar to pre-encoding stress exposure. This indicates that GABAergic signaling in BLA during memory encoding is a decisive factor for inducing fear memory resistance to destabilization (Espejo, Ortiz, Martijena, & Molina, 2017). Enhancing GABA activity before memory encoding facilitates memory destabilization, while inhibiting GABA activity makes memory resistant to destabilization.

However, a recent study at another stage—before memory retrieval—examined the role of Glu receptors and GABA receptors in the nucleus reuniens (NR) of the thalamus in memory destabilization. In this contextual fear memory experiment, injecting GABA-A receptor agonist muscimol, protein degradation inhibitors, or NMDA-containing GluN2B receptor antagonists into NR before memory retrieval all prevented memory forgetting effects caused by post-retrieval anisomycin or clonidine administration, indicating these operations hindered fear memory destabilization (Troyner & Bertoglio, 2020). This suggests that enhancing GABA activity before memory retrieval actually inhibits memory destabilization. Therefore, GABA' s effects on memory plasticity may differ across memory stages.

3.7.2 The Role of GABA in Memory Reconsolidation As the main inhibitory neurotransmitter, GABA' s role in memory reconsolidation mainly involves regulating neuronal activity to affect memory formation and consolidation. Research found that reduced GABAergic neurotransmission is a shared mechanism in fear memory formation, retrieval, and extinction learning (Makkar, Zhang, & Cranney, 2010). Most evidence shows that using GABA agonists after CS re-exposure reduces fear responses, indicating GABA receptor activation interferes with fear memory reconsolidation.

GABA' s role in memory reconsolidation often manifests as synergistic effects with other neurotransmitters. Research injecting the cannabinoid receptor CB1 antagonist AM251 into the basolateral amygdala (BLA) combined with memory retrieval found that AM251 disrupted memory restabilization, an effect limited to post-retrieval conditions. The amnestic effect caused by AM251 could be compensated and restored by simultaneous use of GABA-A receptor antagonists during retrieval, indicating that AM251' s disruption of reconsolidation is mediated by altered GABAergic transmission in BLA. This result reveals that interaction between the endogenous cannabinoid system and GABAergic system in BLA is an important factor affecting fear memory reconsolidation (Ratano, Everitt, & Milton, 2014).

Recent research using optogenetics examined dorsal hippocampal neurotransmitters in an animal cocaine addiction memory model. Optogenetic inhibition of the dCA3 region immediately after memory retrieval for one hour reduced c-Fos expression (a neuronal activation index) in dCA3 stratum pyramidale (SP) glutamatergic and GABAergic neurons and stratum lucidum (SL) GABAergic neurons during memory reconsolidation compared to no-inhibition groups. Behaviorally, it selectively reduced drug-seeking behavior in the cocaine-paired environment in recall tests three days later, an effect also limited to conditions with memory retrieval, indicating that drug addiction memory was weakened by disrupting its reconsolidation process (Qi et al., 2022). Researchers infer that GABAergic transmission promotes addiction memory retrieval and maintenance of the unstable state by inhibiting irrelevant neuronal activity.

In summary, major neurotransmitters play important roles in fear memory destabilization, especially cholinergic, dopaminergic, glutamatergic, and GABAergic signaling. However, these neurotransmitter effects are typically not independent but involve interactions, mutual regulation, and joint production. For example, DA is a necessary but not sufficient condition for memory destabilization, consistent with behavioral-level PE; Glu and GABA also function synergistically. Among these, ACh' s role is relatively unique—ACh has been proven to be both necessary and sufficient for memory destabilization (Cassidy E. Wideman, 2023), seemingly able to independently trigger memory destabilization. But even so, its effects are still regulated by DA and other factors, influenced by prior modulatory actions, and not completed alone. Besides the neurotransmitters mentioned above, others including endocannabinoids and oxytocin also participate in neuroregulatory processes of memory destabilization and reconsolidation (J. Hu, Wang, Feng, Long, & Schiller, 2019). Thus, memory updating is a very complex multi-factor process. At the molecular level, changes in a single neurotransmitter alone cannot trigger synaptic destabilization. This also reflects that long-term memory has a delicate balance—mechanisms that protect its stability from external interference while retaining plasticity and elastic adaptation for memory modification potential. These processes are regulated by multiple factors at behavioral and molecular levels. Notably, both memory stability and plasticity are equally important. Research on clinical disorders such as Alzheimer' s disease, addiction memory, fear memory, and trauma memory extinction all seek drug targets based on long-term memory' s stable yet plastic characteristics and the influence of multiple neuromodulatory substances in this process. Memory stability and plasticity mechanisms and neurotransmitter involvement in memory destabilization are shown in Figure 3 [Figure 3: see original paper].

Figure 3. Memory stability and plasticity mechanisms (created with Figdraw)

4 Neurotransmitter Interactions in Memory Reconsolidation

The complexity of neurotransmitter action lies in that they do not work independently but interact and influence each other to exert combined effects on memory plasticity processes including formation, consolidation, destabilization, and reconsolidation. Additionally, as previously mentioned, different neurotransmitters can convert into each other when needed, adding difficulty to clarifying their roles. For example, 5-HT acts as a modulator of multiple neurotransmitters, co-localizing with other neurotransmitters in the same nerve terminals and interacting with them, activating GABA release and regulating glutamate levels (Ciranna, 2006). Therefore, examining neurotransmitter interactions is essential when investigating their effects on memory reconsolidation.

4.1 Dopamine-Cholinergic Interaction (DA-ACh)

Recent research further described the roles of dopaminergic and cholinergic neuromodulatory systems in memory modification based on reconsolidation. In an fMRI study of declarative memory, familiar video clips were replayed and suddenly stopped to induce PE during memory retrieval. When subjects were asked to recall details about the clips in subsequent test phases, PE during retrieval facilitated incorporation of misinformation into reactivated memory. During retrieval, PE seemed to guide hippocampal modification rather than just preserving explicit memory. This effect was supported by basal forebrain-HPC connections rather than HPC-VTA connections (Sinclair, Manalili, Brunec, Adcock, & Barense, 2021). The basal forebrain is the main source of ACh, and ACh release after PE can change HPC processing, enhancing memory updating. Previous research showed co-activation of HPC and VTA after unexpected events. The above study demonstrates synergistic roles of cholinergic and dopaminergic systems in hippocampus-based declarative memory updating, processing unexpected information and promoting original memory updating.

In fear memory research, the relationship between PE and cholinergic systems has also been found. Researchers using mouse inhibitory avoidance tasks found that PE-induced ACh release is a necessary condition for memory reconsolidation in this task, while ACh receptor antagonists disrupt memory reconsolidation (Krawczyk et al., 2021). Synergistic effects of dopaminergic and cholinergic systems in fear memory models await further research.

4.2 GABA-Cholinergic Interaction (GABA-ACh)

Many neurons that release acetylcholine also co-transmit the neurotransmitter gamma-aminobutyric acid (GABA) at synapses in the hippocampus, striatum, substantia nigra, and medial prefrontal cortex (mPFC). Recent research examined the role of ACh-GABA co-transmission in mouse cognitive function, comparing mice lacking ACh-GABA co-transmission with control mice across cognitive activities. Results showed that loss of GABA co-transmission from

ACh neurons did not disrupt social ability, motor skills, or sensation, but significantly changed social novelty preference, spatial and fear memory, and impaired cognitive flexibility in T-maze tasks. Fear memory research found that ACh-GABA co-transmission did not affect fear memory acquisition or extinction but enhanced context-dependent fear renewal (a type of fear relapse) (Goral et al., 2022).

4.3 Serotonin-Glutamate Interaction (5-HT-Glu)

Research found that although both Glu and 5-HT can hinder memory reconsolidation, their mechanisms may differ. For forgetting induced by NMDA receptor antagonists and 5-HT receptor antagonists after memory retrieval, reacquisition can be promoted in early forgetting stages (1, 3 days). In later forgetting stages (10, 30 days), NMDA-dependent forgetting is resistant to reacquisition, while 5-HT-dependent forgetting can still recover original memory from subsequent training (Nikitin et al., 2018). This suggests different roles and mechanisms of Glu and 5-HT in memory reconsolidation.

5-HT is both a neurotransmitter and neuromodulator, widely regulating excitation and inhibition of classic neurotransmitters including glutamate and GABA in the brain. 5-HT has extensive modulatory effects on glutamatergic systems in the hippocampus and prefrontal cortex, affecting cognitive ability and emotional processing such as memory and depression (Stan, 2014). In the lateral habenula (LHb), 5-HT also bidirectionally modulates and differentially regulates glutamatergic transmission. 5-HT increases glutamate release from nerve terminals of LHb neurons by activating its type 2 and 3 receptors. 5-HT may play important roles in processing information between LHb and its downstream target structures during decision-making (Xie, Zuo, Wu, Li, & Ye, 2016). The lateral habenula is the brain' s anti-reward center, associated with various mental illnesses especially major depression, and participates in functions including working memory and long-term spatial memory (H. Hu, Cui, & Yang, 2020). In traumatic memory research, 5-HT-glutamate receptor heterodimers, particularly 5-HT2A-mGlu2, play complex roles in hallucinogen memory modulation mechanisms. These dimers act through Gq and Gi proteins. 5-HT-Glu activation enhances CaMPKII through Gq protein while inhibiting cAMP-PKA through Gi protein. Both mechanisms contribute to activating scaffold protein degradation on proteasomes and inducing memory destabilization (Keri, 2022).

4.4 Dopamine-Norepinephrine Interaction (DA-NE)

The ventral tegmental area (VTA) and locus coeruleus (LC) are the main sources of DA and NE. Research shows that DA and NE neuromodulators have extensive overlap and many shared mechanisms across multiple domains, including shared biosynthetic pathways, co-release from LC terminals, convergent innervation, non-specificity of receptors and transporters, and shared intracellular signaling pathways. LC can propagate both DA and NE throughout the brain, leading researchers to propose that DA and NE may function in parallel to promote

learning and maintain states required for normal cognitive processes (Ranjbar-Slamloo & Fazlali, 2020).

A recent study found that in mouse conditioned reward learning models, NE promoted risk-taking behavior to obtain rewards under reward uncertainty. Simultaneously, NE was massively released when receiving unexpected feedback inconsistent with expectations. For example, when mice received unexpected rewards or unexpected reward omissions, LC released large amounts of NE, while the surge amplitude was small when receiving expected rewards. NE projects extensively in the brain, including the prefrontal cortex that performs higher cognitive functions. Meanwhile, mice continuously adjusted their lever-pushing behavior based on recent learning experiences, even after already learning the task (Breton-Provencher, Drummond, Feng, Li, & Sur, 2022). Previous views typically associated unexpected rewards or stimuli closely with DA release, but this study found LC also plays an important role in unexpected information encoding. Therefore, the researchers propose that NE may function synergistically with DA, and LC-NE activity may be subordinate to a larger network involving multiple neurotransmitters to promote learning (Breton-Provencher et al., 2022).

5 Summary and Outlook

5.1 Summary of Neurotransmitter Roles in Fear Memory Destabilization and Reconsolidation

Various neurotransmitters (including neuromodulators) play irreplaceable roles in activating long-term memory, promoting fear memory destabilization and memory reconsolidation, showing considerable complexity—like a symphony orchestra in the brain, regulating a series of cognitive and emotional functions including memory, and maintaining delicate balance. Once this balance is slightly broken, mental illness symptoms can manifest at the behavioral level. The main neurotransmitters and their roles in memory plasticity are summarized in the table below.

Table 1 Main neurotransmitters and their roles in memory destabilization and reconsolidation

Neurotransmitter	Main Source Region	Main Action Brain Region	Memory Destabilization	Memory Reconsolidation
Acetylcholine (ACh)	Basal forebrain	Hippocampus, Amygdala, Cortex	M1-mAChR activation	nAChR activation
Dopamine (DA)	VTA, Substantia nigra	Amygdala, Hippocampus, PFC	D1/D5 receptors	D1/D5 receptors

Neurotransmitter	Main Source Region	Main Action Brain Region	Memory Destabilization	Memory Reconsolidation
Norepinephrine (NE)	Locus coeruleus	Amygdala, Hippocampus	β-adrenergic receptors	β-adrenergic receptors
Serotonin (5-HT)	Raphe nuclei	Hippocampus, Amygdala	5-HT receptor modulation	5-HT5A, 5-HT6, 5-HT7 receptors
Glutamate (Glu)	Cortical neurons	Hippocampus, Amygdala	GluN2B subunit, CP-AMPAR	GluN2A subunit, AMPAR trafficking
GABA	Interneurons	Amygdala, Hippocampus	GABA-A receptor activity	GABA-A receptor activity

Note: VTA: ventral tegmental area; PFC: prefrontal cortex; CP-AMPAR: calcium-permeable AMPA receptor

5.2 Future Directions

5.2.1 Utilizing Neurotransmitter Research to Overcome Boundary Conditions Such as Intensity Neurotransmitters play extremely important roles in regulating neuronal synaptic plasticity and have special effects on fear memory formation, maintenance, extinction, and updating, providing beneficial insights for overcoming boundary conditions. Memory intensity and age factors produce protective mechanisms that prevent memory destabilization and destruction, creating boundary conditions for fear memory reconsolidation intervention—that is, difficulty activating memory into a plastic active unstable state through retrieval. However, memory' s inherent plasticity characteristics mean long-term fear memory still retains the possibility of overcoming boundary conditions to allow updating, which is also one of memory' s mechanisms. Therefore, for clinically relevant negative memories such as fear memory and addiction memory, research should focus on how to strengthen their plastic components, enhance their updatability, and thereby use the reconsolidation intervention paradigm to eliminate negative memories and reduce clinical mental illness symptoms. Under this guidance, molecular-level neurotransmitter research can provide good insights. For example, research involving ACh, DA, and NE shows that novel information must be present during retrieval for neurotransmitters to function and induce memory destabilization. Future research should continue exploring key factors and methods for negative memory destabilization based on molecular mechanisms and neurotransmitter functions.

5.2.2 Novelty or Prediction Error During Memory Retrieval Remains a Key Focus We believe that novelty during memory retrieval remains a key

focus. For strong and remote memories, we need to enhance novelty-induced memory updating. Sufficient research shows that new information must be present during retrieval for neurotransmitters to function and induce memory destabilization. Therefore, future research should continue focusing on PE or novelty effects. Specifically, we can strengthen behavioral-level design for memory retrieval, including: VTA DA release is closely related to error processing, so DA intervention can be reflected in specific PE settings; CS changes and other new information can trigger additional attention and activate the LC-NE system, so they can be combined with PE settings to enhance novelty intensity during retrieval; ACh has been shown to be instantly released through short-term stress, so applying stress before memory retrieval can increase ACh levels in brain intercellular spaces to some extent, promoting memory destabilization. Additionally, other theories and paradigms can be borrowed, such as novelty exposure paradigms and protein labeling theories, to explore multiple methods for enhancing novelty during retrieval.

5.2.3 Using Research from Different Memory Types to Inspire Fear Memory Elimination Different memory types share both commonalities and differences. Research results on memory reconsolidation and its boundary conditions show many commonalities and consistencies. This paper has referenced many research results from other memory types, including spatial memory, object memory, traumatic memory, and declarative memory. Research findings from different memory types provide rich and beneficial inspiration for fear memory elimination research, but whether results from other memory types can be directly transferred to fear memory remains unclear. Currently, research on fear memory destabilization is relatively lacking, and future studies should strengthen research on conditioned fear memory and avoidance memory in both animal models and human subjects.

5.2.4 New Technologies Provide New Insights into Understanding Memory Updating Essence Revealing the nature of memory requires ongoing interdisciplinary exploration. From behavior to brain imaging to molecular genetics, research at various levels is gradually unveiling the veil of memory, humanity' s most complex brain activity. The application of new technologies and methods always pushes this exploration forward. New technologies involved in this paper, such as optogenetics and calcium imaging, can directly and precisely activate or silence specific neurons, opening new perspectives for studying neurotransmitter mechanisms. With these technologies, we can more directly observe changes in neuronal synaptic plasticity and the roles of molecular-level factors in memory updating, providing more precise targets for drug treatment of mental illness and finding new therapeutic approaches. Meanwhile, multi-method and multi-modal research also provides more comprehensive perspectives for understanding memory updating essence.

5.3 Outlook

Reconsolidation intervention research toward clinical application typically targets negative and non-adaptive memories, such as fear memory, trauma memory, avoidance behavior, and addiction memory. Therefore, future research should strengthen studies on clinical and subclinical subjects and individual differences. Research shows significant differences in neurotransmitter release regulation between sexes in specific brain regions, so sex differences as an individual difference need attention (Zachry et al., 2021). Additionally, whether animal research can be fully transferred to humans should be considered carefully. Future research can strengthen comparative studies between animals and humans, as well as studies directly using human subjects, to increase generalizability of conclusions. In summary, the dynamic updating nature of memory and its utilization bring new hope for curing clinical mental illness. Through in-depth exploration of neurotransmitter roles in this process, we will comprehensively deepen our understanding of memory essence and enhance our ability to update memory in both laboratory research and clinical treatment, holding important significance and broad prospects.

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