The role of hippocampus in memory reactivation: an implication for a therapeutic target against opioid use disorder

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Abstract
Purpose of the review The abuse of opioids induces many terrible problems in human health and social stability. For opioid-dependent individuals, withdrawal memory can be reactivated by context, which is then associated with extremely unpleasant physical and emotional feelings during opioid withdrawal. The reactivation of withdrawal memory is considered one of the most important reasons for opioid relapse, and it also allows for memory modulation based on the reconsolidation phenomenon. However, studies exploring withdrawal memory modulation during the reconsolidation window are lacking. By summarizing the previous findings about the reactivation of negative emotional memories, we are going to suggest potential neural regions and systems for modulating opioid withdrawal memory.

Recent findings Here, we first present the role of memory reactivation in its modification, discuss how the hippocampus participates in memory reactivation, and discuss the importance of noradrenergic signaling in the hippocampus for memory reactivation. Then, we review the engagement of other limbic regions receiving noradrenergic signaling in memory reactivation. We suggest that noradrenergic signaling targeting hippocampus neurons might play a potential role in strengthening the disruptive effect of withdrawal memory extinction by facilitating the degree of memory reactivation.

Summary This review will contribute to a better understanding of the mechanisms underlying reactivation-dependent memory malleability and will provide new therapeutic avenues for treating opioid use disorders.

Keywords opioid withdrawal · memory reactivation · extinction · hippocampus · noradrenergic signaling

Introduction

Opioids comprise heroin, natural and semisynthetic opioids (such as morphine, codeine, hydrocodone, and oxycodone), and synthetic opioids other than methadone (such as fentanyl, fentanyl analogs, and tramadol) [1]. Chronic use of any of the above drugs could prompt opioid use disorder (OUD), which causes clinically serious suffering or impairment [2]. In the World Drug Report 2021 [3], an estimated 62 million people or 1.2% of the global population used opioids for non-medical purposes in 2019, which was nearly double over the past decades. Among that, almost 13 million people died, which accounted for 70% of the total deaths from drug use disorder. In particular, since the coronavirus disease (COVID-19) pandemic swept the world, opioid overdose deaths have increased observably. OUD is characterized by a high rate of relapse. In a large-scale survey, over 80% of those who completed opioid withdrawal relapsed within one year [4]. The transition from recreational to compulsive drug use has been proposed to entail a neuroadaptive process that shifts motivational processing from seeking positive reinforcement to avoiding the aversive effects of withdrawal [5]. Opioid users become physically dependent and are subject to aversive withdrawal symptoms (such as nausea, vomiting, and diarrhea) when drug levels fall too low or when the drugs are stopped abruptly [6]. Thus, withdrawing patients have intense opioid cravings associated with the feeling of
being unwell [7–9]. Although opioid withdrawal’s duration varies depending on the specific opioid being used, withdrawal response in most types of opioids only lasts several days. For example, symptoms of heroin withdrawal may last for 7–14 days [10]. However, conditioned withdrawal triggers opioid relapses that occur after the duration of withdrawal symptoms [11]. That is, one of the most important reasons for relapses is the retention of the opioid withdrawal memory induced by the conditioned context previously associated with withdrawal symptoms [12]. Therapeutic approaches to mediating withdrawal memory may be valuable in preventing opioid relapse.

Previous studies on drug abuse have considered approaches to weakening or removing maladaptive reward memories. Cue-exposure treatment in extinction was demonstrated as an important part of reward-related memory modulation [11, 13, 14]. Unfortunately, persistent maladaptive memories that maintain drug seeking and are resistant to extinction are a trademark of addiction. Additionally, extinction learning has several important limitations, the most important of which is the contextual specificity of extinction learning [15]. Despite the certain success of cue-exposure therapy, the long-term efficacy of this treatment remains extremely dubious because extinction learning might not thoroughly delete the previous memory traces but rather creates new learning that inhibits the original memory’s activation and thus is subject to relapse even after long periods of lessening [16–18]. Afterward, the reconsolidation phenomenon during the memory process was observed, and the disruption of memory reconsolidation after retrieval has received attention for its therapeutic potential [19]. Modification of memory after retrieval supports the hypothesis that reconsolidation is a true, specific process that maintains, strengthens, and possibly updates memory [20]. Many studies have shown that the memory reactivation–extinction pattern outperforms simple exposure to the context or cue in preventing addiction memory [13, 14, 21, 22]. Hence, whether memory has been activated or not and the degree of activation may be important factors in modulating the original memory. Nevertheless, studies regarding aversive withdrawal memory based on reconsolidation theory are lacking. Revealing the brain circuits handling the activation of opioid withdrawal memory may contribute to developing behavioral and neural regulation therapies for modifying pathological memory in OUD.

The hippocampus is one of the earliest attended brain regions in memory studies [23] and has demonstrated a crucial role in memory reactivation [24, 25]. Previous reports have shown that noradrenergic agents significantly affect memory modulation, which may be achieved by modulating the memory reactivation process [26–28]. Locus coeruleus (LC) is a major resource for noradrenergic neurotransmitters, projecting to the hippocampus [29, 30]. Meanwhile, LC is among the brain regions first studied for its response to opioid withdrawal [31, 32]. Here, we review hippocampus involvement in memory reactivation and suggest a potential role of noradrenergic signaling in the hippocampus and LC-hippocampus circuits for disrupting withdrawal memory based on the reactivation–extinction pattern. In particular, following this review’s aim, studies focusing on negative emotion-related memory are mainly discussed, and research on drug reward-associated memory is also mentioned.

**Memory is labile under active conditions**

Memory includes the acquisition, consolidation, and retrieval phases [33]. From an evolutionary perspective, it is highly functional to remember the most important events in life [34]. However, the putative indelibility of emotional memory can also be harmful and maladaptive, such as in drug abuse and post-stress traumatic disorder [35, 36]. In 2000, the reactivation–extinction pattern was proposed as a new approach targeting memory reconsolidation in a fear memory study [37]. This has been interpreted as proving that reactivated memories re-enter a state of lability and that the pulp will be re-stabilized through a protein-dependent process [37, 38]. Reconsolidation has a time window, and only if the memory is altered in this interval should the memory modification be successful. Much evidence has identified that the reconsolidation window is not fixed. For instance, some studies have shown that it was within six hours after memory reactivation [39, 40], while others have found that memory modification was not impaired beyond three hours after reactivation [41]. The difference may be related to the strength of the original memory [42], memory type [43], and the reactivation degree [44]. Anyhow, memories can be disrupted by amnesic treatments delivered shortly after their reactivation. The opportunity to eliminate pathological memories through pharmacological and behavioral treatment during the reconsolidation window has also been considered in the research field of drug abuse, especially focusing on drug-associated reward memory [21, 39, 41].

Previous research has revealed that a procedure that utilizes memory reactivation to make extinction more effective disrupts maladaptive memories, but the limitations of reactivation–extinction patterns have also recently been noticed for memory modulation. First, the preventing effect of the paradigm is selective to conditioned stimuli (CS) [39, 45]. Whether the memory could be efficaciously activated depends on the degree of similarity between the exposed environment during the memory retrieval phase and CS in the original memory acquisition. Second, the time elapsed since initial learning may be another important factor in context–exposure-induced memory reactivation. In some cases, the inhibition of response by the reactivation–extinction
manipulation only exhibits a short duration after the memory acquisition [46]. Some researchers have attempted to find other reliable ways to trigger memory activation to avoid these limitations. Unconditioned stimuli (UCSs) are another possibility to drive memory reactivation, such as a low dose of drugs for addiction-relative reward memory and a weak shock for fear memory [47]. Compared to CS, UCS seems more effective for reactivating memory. A study on drug reward memory showed that extinction after UCS exposure impaired the reinstatement of cocaine-seeking behavior and disrupted non-extinguished CS-induced cocaine-seeking behavior [47]. A similar result was found in the extinction of fear condition memory [48]. There is a possibility that UCS could induce more alterations in intracellular molecules, which implies that UCS could trigger a more unstable state of original memory than CS [48]. However, its neuronal mechanism remains unclear. Furthermore, this approach may paradoxically accelerate the reacquisition of the previously extinguished conditioned response or retard the memory’s extinction [21, 47]. Ethical issues still seem to face UCS usage in memory reactivation.

Collectively, although there are some uncertainties regarding CS in memory modulation, it has been generally accepted that memory is relatively labile when it is in an active state. Maximizing memory reactivation would contribute to the efficiency of the reactivation–extinction approach in modifying pathological memory. Since studies on the modulation of opioid withdrawal memory depending on reconsolidation theory are unexplored, understanding the neuronal mechanisms underlying negative emotion-associated memory reactivation is necessary.

The function of the hippocampus in memory reactivation

The hippocampus is often mentioned in studies for opioid withdrawal memory [49–51] and other types of aversive memory reactivation [52–56] (Table 1). Comprehensive presentation of the function of this brain region in memory reactivation comes from fear memory studies [24, 57]. The hippocampus cytoarchitectonically includes the dentate gyrus (DG) and the Cornu Ammonis subfields (CA1-3). Among them, DG, CA1, and CA3 have been demonstrated to be involved in the memory reactivation process [57–61]. In 1904, the term “memory engram” was first used to describe the memory representations by Richard Semon [62]. The hippocampus is mainly involved in studies of memory engrams [63, 64]. A landmark study identified a small subpopulation of granule cells in the DG but not in CA1 of the hippocampus as contextual memory-engram cells, and optogenetic stimulation of these cells is sufficient to activate behavioral retrieval of a context-dependent fear memory formed by foot shocks’ delivery [65]. In another recent study, a subset of memory retrieval-induced neurons in the DG became reactivated during extinction, and the degree of fear reduction was positively correlated with this reactivation after extinction training [57]. These findings further contribute to the understanding of the effect of reactivation–extinction patterns in memory modulation. Unlike DG, the hippocampal area CA3 is suggested to be of minimal importance for contextual memory reactivation [66]. Although it remains unknown whether the engram neurons in the hippocampal CA1 are also reactivated during extinction learning, the previous report that membrane excitability was increased in hippocampal CA1 neurons immediately after the retrieval of contextual fear memory may imply that CA1 is also involved in memory re-writing when the reactivation–extinction training is conducted [58]. It is possible that memory-associated information may flow through the DG-CA3-CA1 neural circuit during memory reactivation [67].

In particular, the induction of the immediate-early gene Arc in the DG was positively correlated with a higher aversion score in morphine-dependent animals [76], implying that the hippocampal DG participates in withdrawal memory reactivation. Recent studies have also revealed the role of hippocampal CA1 in withdrawal memory reactivation with some pharmacological and immunostaining methods [51]. However, how these hippocampal subregions engage in this process still requires further studies with advanced techniques in the neuroscience field.

The role of noradrenergic signaling in the hippocampus for memory reactivation

Several studies have demonstrated the critical and specific role of noradrenergic signaling in the hippocampus for reactivation in different types of memory (Table 2). By behavioral pharmacological manipulation, the causal relationship between noradrenergic signaling in the hippocampus and memory reactivation has been revealed. For example, the infusion of a β-adrenergic receptor antagonist into the hippocampal DG of rats shortly before testing impaired appetitive spatial reference memory expression [87]. Systemic administration or dorsal hippocampal infusion of a β-adrenergic receptor antagonist shortly before testing blocks the expression of cocaine place preference in rats [88]. Additionally, propranolol blocks membrane hyperexcitability in hippocampal CA1 neurons induced by fear memory retrieval [58], suggesting that aversive memory reactivation is also facilitated by β-receptor excitation in CA1. Furthermore, context exposure could evoke noradrenaline release in the hippocampus, stimulating β-adrenergic receptors and thereby causing an increase in intracellular cyclic

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adenosine monophosphate (cAMP), which then stimulates the activation of protein kinase A (PKA) [58]. PKA activation may increase neuronal excitability by phosphorylation ion channels and by increasing glutamatergic NMDAR-mediated calcium influx [58].

In the hippocampus, β-adrenergic receptors are mainly expressed by DG granular and CA1 pyramidal neurons [29, 30]. The LC is connected to the hippocampus via strong noradrenergic fiber projections [107]. Some studies have revealed that the LC plays a potential role in functional modulation of the hippocampus. Supporting evidence includes that the LC’s stimulation in the rats induced long-term potentiation in the hippocampus [108], that increased levels of hippocampal noradrenaline facilitated the synaptic

| Region or circle | Memory type | Treatment | Effect | Reference |
|-----------------|-------------|-----------|--------|-----------|
| CA1             | Fear conditioning | Electrophysiological recording | Membrane excitability increased | [58] |
| dCA1            | Fear conditioning | Phosphorylation of Erk1/2 | Enhancement | [68] |
| dCA1            | Fear conditioning | Scopolamine | Improvement | [69] |
| dCA1            | Fear conditioning | Optogenetics activation | Impairment | [24] |
| dCA1            | Fear conditioning | Optogenetics inhibition | Impairment | [70] |
| dCA1            | Fear conditioning | cFos IHC | Increased | [59] |
| dCA1            | Fear conditioning | excitotoxic lesions | Impairment | [71] |
| dCA1            | Inhibitory avoidance | Blockade of AMPAR endocytosis | Improvement | [52] |
| dCA1            | Inhibitory avoidance | mGlu1 agonist | Improvement | [53] |
|                 |              | mGlu2, mGlu3 agonist | Improvement | |
| dCA1            | Inhibitory avoidance | Arc WB | Improvement | [49] |
| dCA1            | passive avoidance | nicotine | Improvement | [60] |
| dDG             | Fear conditioning | Optogenetics inhibition | Impairment | [72] |
| dDG             | Fear conditioning | cFos IHC | Enhancement | [57] |
| dDG             | Fear conditioning | Electrophysiological recording | Membrane excitability increased | [73] |
| dDG             | Fear conditioning | Optogenetics activation | Improvement | [65, 74] |
| dDG             | Fear conditioning | Optogenetics activation | Impairment | [75] |
| dDG             | Morphine withdrawal | Arc WB | Enhancement | [49] |
| dDG             | Morphine withdrawal | CRF1R antagonist | Improvement | [50] |
| dDG             | Morphine withdrawal | adrenalectomy | Impairment | [76] |
| dHippo          | Fear conditioning | cFos IHC | Enhancement | [77, 78] |
| dHippo          | Fear conditioning | Zenk IHC | Enhancement | [79] |
| dHippo          | Fear conditioning | Zif268 WB | Enhancement | [80] |
| dHippo          | Fear conditioning | Calpain inhibitor | Impairment | [81] |
| dHippo          | Fear conditioning | GABAA receptor agonist | Impairment | [82] |
| dHippo          | Fear conditioning | AA-5-HT | Impairment | [83] |
| dHippo          | Inhibitory avoidance | MK-801 | Improvement | [55] |
| dHippo          | Inhibitory avoidance | CB1R antagonist | Improvement | [56] |
| vCA1            | Fear conditioning | Ca2+ imaging | Enhancement | [84] |
| vCA1            | Fear conditioning | Excitotoxic lesions | Impairment | [71] |
| vCA3            | Fear conditioning | Excitotoxic lesions | Impairment | [71] |
| vHippo–CeA      | Fear conditioning | Optogenetics inhibition | Impairment | [85] |
| Hippo           | Fear memory | Depth electrode recording | Oscillatory activity | [86] |
| Hippo           | Fear conditioning | Beta-AR antagonist | Impairment | [67] |
| dCA1–POR–BLA   | Morphine withdrawal | cFos IHC | Enhancement | [51] |

AA-5-HT N-arachidonoyl-serotonin, A (II) angiotensin II, AMPAR α-amino-3-hydroxy-5-methyl-4-isoxazole-propionamid receptor, BLA Basolateral amygdala, CB1R Cannabinoid receptor, CeA Central amygdala, CRF1R Corticotropin releasing factor (1) receptor, dCA1 dorsal CA1, dDG dorsal dentate gyrus, dHippo dorsal hippocampus, GABA γ-aminobutyric acid, IHC Immunohistochemistry, mGlu glutamate metabotropic, POR Postrhinal cortex, vCA1 ventral CA1; vCA3 ventral CA3, vHippo ventral hippocampus; WB Western blot.
delivery of glutamatergic AMPA receptors necessary for long-term potentiation [109], and that electrical activation of the LC induces noradrenaline release in the hippocampus, especially in the DG subregion [110]. Besides direct binding to β-adrenergic receptors on hippocampal neurons [111], astrocytes in the hippocampus may also participate in the process of memory retrieval modulated by noradrenergic signals. This is because β-adrenergic receptor distributions in hippocampal astrocytes provide the fundamentals for engaging astrocytes [112]. Previous evidence has shown the relationship between neurons and astrocytes in the hippocampus and that repeated stimulations to astrocytes cause CA1 pyramidal neurons to firing synchronously through the NR1/NR2B subunits of glutamatergic NMDA receptors [113]. Given that a crucial role of NR2B has been demonstrated in memory reactivation [114, 115], astrocytes in the hippocampus might be involved in the memory reactivation modulated by β-adrenergic signaling.

All noradrenergic neurons of the LC intensely expressed immediate-early gene c-fos mRNA during naloxone-precipitated morphine withdrawal [116]. Indeed, the LC and noradrenergic systems in this brain region have attracted much attention in opioid dependence studies since those early years. The withdrawal response has been attributed, at least in part, to elevated activity in the noradrenergic cells of LC [31, 32]. However, a total lesion of noradrenergic

### Table 2
Noradrenergic signal plays an important role in memory retrieval, and the LC is one of the major sources of noradrenaline transmitter in brain. The table lists the studies on the regulation of noradrenergic signal for memory retrieval in the hippocampus and other brain regions.

| Region       | Memory type              | Treatment                        | Effect            | Reference |
|--------------|--------------------------|----------------------------------|-------------------|-----------|
| dDG          | Spatial memory           | Beta-AR agonist                  | Improvement       | [87]      |
| dCA1         | Fear conditioning        | Beta-AR antagonist               | No effect         | [89]      |
| dCA1         | Fear conditioning        | Beta-AR antagonist               | Impairment        | [58]      |
| dCA3-dCA1    | Fear conditioning        | Beta1-AR agonist                 | Improvement       | [90]      |
| dHippo       | Cocaine CPP              | Beta-AR antagonist               | Impairment        | [88]      |
| dHippo       | Fear conditioning        | Beta1-AR agonist                 | Impairment        | [91]      |
| dHippo       | Fear conditioning        | Beta2-AR agonist                 | Impairment        | [92]      |
| dHippo       | Fear conditioning        | Beta-AR antagonist               | No effect         | [93]      |
| dHippo       | Ethanol–induced state–dependent memory | Beta1-AR agonist | Improvement | [94]      |
| dHippo       | Spatial memory           | Beta-AR antagonist               | No effect         | [95]      |
| Hippo        | Emotional memory         | Beta-AR antagonist               | Impairment        | [96]      |
| Hippo        | Fear conditioning        | Beta-AR antagonist               | Impairment        | [97]      |
| LC–BLA       | Taste associative memory | Chemogenetics activation         | Improvement       | [98]      |
| LC           | Emotional memory         | fMRI                             | Activation        | [99]      |
| LC–forebrain | Maze task for food reward| Alpha2-AR antagonist             | Improvement       | [100]     |
| LC–PFC       | Recognition memory       | LC lesion                        | Impairment        | [101]     |
| mPFC         | Taste aversion           | Beta-AR antagonist               | Impairment        | [102]     |
| IC           | Taste aversion           | Beta-AR antagonist               | Impairment        | [103]     |
| Ect, ACC, PPC| Inhibitory avoidance     | Beta1-AR agonist                 | Improvement       | [104]     |
| Amygdala     | Taste aversion           | Beta-AR antagonist               | Impairment        | [105]     |
| BLA          | Cocaine CPP              | Beta2-AR antagonist              | Impairment        | [106]     |
| CeA          | Fear conditioning        | Beta1-AR agonist                 | Improvement       | [107]     |

**ACC** Anterior cingulate cortex, **AR** Adrenergic receptor, **BLA** Basolateral amygdala, **CeA** Central amygdala, **CPP** Conditioned place preference, **dCA1** dorsal CA1, **dCA3** dorsal CA3, **dDG** dorsal dentate gyrus, **dHippo** dorsal hippocampus, **Ent** Entorhinal cortex, **fMRI** Functional magnetic resonance imaging, **IC** Insular cortex, **LC** Locus coeruleus, **mPFC** medial prefrontal cortex, **PFC** Prefrontal cortex, **PPC** Posterior parietal cortex.
neurons of the LC did not alter naloxone-precipitated morphine withdrawal [117], challenging the idea that this structure is vital in producing somatic signs [118, 119]. The LC may be involved in retrieving aversive learned associations, contrasting with the common idea of excluding the LC from the motivational component of withdrawal [116, 117].

**Other neurotransmitters and brain regions involved in LC-modulated memory reactivation**

The noradrenergic signal and the dopaminergic system are involved in LC-modulated memory reactivation [120]. The hippocampus may be the downstream area of this function of the LC [121]. Although the ventral tegmental area (VTA) is the main brain source for dopaminergic neurotransmitters but not the LC, the primary input from VTA is to the ventral subregion of the hippocampus with only minimal input to the dorsal hippocampus, and none is observed for the stratum radiatum of the dorsal hippocampus [122–124]. Given that activation of D1 dopaminergic receptors in proximity to CA3-CA1 synapses in the stratum radiatum of the dorsal hippocampus is required for hippocampal-dependent learning and memory [125, 126], noradrenergic fibers from the LC may be the primary source of dopamine release in the dorsal hippocampus [107, 127]. Therefore, combining the use of dopaminergic and noradrenergic receptor blockers or activation agents in a particular time window, behavioral treatment may develop a helpful approach against pathological memory.

In addition to the hippocampus, the amygdala is another important region in memory encoding and retrieval [97, 128–130]. Both the amygdala and the hippocampus are directly innervated by the LC [131, 132]. Noradrenergic modulation of memory likely occurs via projections of the LC to the hippocampus and the amygdala [133] (Table 2). The hippocampus and amygdala may control different aspects of memory. Case studies on lesions in humans suggest a double separation, with hippocampus lesions affecting declarative retrieval of fear conditioning and amygdala lesions affecting only arousal response [134]. Some studies have suggested that the connections between the LC and the amygdala are associated with arousal or aversive responses, while LC projections to the hippocampus are more relevant for the improved encoding of memories [135, 136]. This indication is supported by a previous study in which noradrenergic transmitter release increased in the amygdala during naloxone-precipitated withdrawal [137].

The cerebral cortex is another important brain region receiving the projection from LC [138]. There are few studies showing the involvement of the LC-prefrontal cortex circuit in the retrieval of reward memory or recognition [100, 102]. Direct evidence is lacking for the modulatory function of noradrenergic signaling in the prefrontal cortex in memory reactivation. However, some studies have shown that the prefrontal cortex plays a crucial role in fear memory retrieval [12, 139]. A new perspective suggests a pattern of hippocampal–neocortical interactions in memory retrieval [140]. In addition, the entorhinal cortex, which is closely located by the hippocampus, might be important in memory modulation by connecting a CA1 or a DG subregion of the hippocampus [141].

**Conclusions**

Although it is controversial whether the extinction learning process changes the original memory or establishes a new memory that links to the existing trace [22, 45, 142, 143], the above analysis and discussion suggest that noradrenergic signaling from LC (targeting the hippocampus and other limbic regions) may play a vital role in memory reactivation, providing a basis for the subsequent extinction in the reconsolidation window. Besides noradrenaline-related agents, selective neural stimulation is another choice for reducing pathological memory. Recently, non-invasive brain stimulations, such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS), have been applied to intervene in many types of neuropsychiatric disorders [144–147]. Although these techniques remain unsuitable for targeting deep brain regions, some applicable approaches, such as temporal interference (TI), have been developed recently [148, 149]. An animal study reveals that tDCS modulates excitability in a polarity-specific manner and selectively affects subregions of the hippocampus [150]. Additionally, indirect stimulation of LC seems to work by activating the vagus-nucleus tractus solitarii (NTS)-LC by TMS [151]. Moreover, LC can be activated by behavioral approaches, such as novelty exposure [152], which is based on LC’s physiological function of alertness and arousal [153, 154] (Fig. 1).

Theoretically, the idea of the reactivation–extinction paradigm has many advantages since the treatments may affect only the reactivated memory and not others, even closely related memories [155]. We raise the hypothesis that through pharmacological, behavioral, and even direct neural manipulations of the LC-hippocampal circuit, more engram cells are in an active state, and the original memory is more sensitive to modification in the extinction phase. However, noradrenaline from the LC is also involved in modulating the encoding and consolidation of hippocampus-based memory [138]. Thus, clarifying the mechanisms of the LC-hippocampal circuit underlying different memory phases may contribute to choosing the correct time window to conduct...
In this review, we only summarized the findings regarding the role of hippocampus in the retrieval of the memory, particularly in aversive memory and fear memory. This is a limitation that we did not cover other types or stages of memories, in which hippocampus has been demonstrated its involvements [156–158].

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![Reactivation-extinction pattern](image)

**Fig. 1** Potential frame work for withdrawal memory modulation. Withdrawal memory can be reactivated and become labile when the individual is exposed to the context which is associated with the withdrawal feelings. This labile state can last around 6 hours since the memory is reactivated, which is also called reconsolidation window. The reactivation–extinction pattern is proposed as an approach targeting memory reconsolidation. Maximizing memory reactivation will contribute to the efficiency of the reactivation–extinction approach in modifying pathological memory, such as withdrawal memory. We suggest that noradrenergic signaling from LC (specifically targeting the hippocampus) may play a vital role in facilitating memory reactivation, providing a basis for the subsequent extinction in the reconsolidation window. Optogenetics and chemogenetics are used to stimulate neural pathway directly in basic studies, while they are not suitable for the application in the human brain manipulation so far. The approaches of non-invasion brain stimulation, such as TMS, tDCS, tACS, and TI, have potential possibility for the indirect activation of LC and its projections. LC, locus coeruleus; Hippo, hippocampus; NTS, nucleus tractus solitarii; NA, noradrenaline; DA, dopamine; TMS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; tACS, transcranial alternating current stimulation; TI, temporal interference.

![Basic study](image)

![Potential clinical application](image)
to be paid attentions in our further investigation and idea organization. In addition, there may be distinct mechanisms between normal memory and pathological memories. Under normal conditions, the reconsolidation state after memory retrieval may act to update and maintain memories. In contrast, under altered conditions due to acute or chronic drug use, stress, or genetic predisposition, reconsolidation may enhance memories, contributing to persistent drug-related memories [159]. More studies are required to dissect how and why some memories become abnormally strong, and others do not, which may be important to avoid the wrong treatments used in memory modulation.

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Declarations

Competing of interest The authors declare no conflicts of interest.

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