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• REVIEW •
Special Focus on Brain Imaging and Addiction

Neuroimaging and intervening in memory reconsolidation of human drug addiction

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Abstract Reconsolidation refers to memory reprocessing when consolidated memory is being recalled and restored. Importantly, as memory is being recalled, it could further modify past memories. Memory reconsolidation has been identified as a critical role in various types of mental disorders, in particular drug addiction. In this review, we first review earlier studies related to reconsolidation. Secondly, we characterize memory reconsolidation processing in human brain via neuroimaging studies. Then we focus on the role of reconsolidation and reconsolidation-based interventions in drug addiction. Finally, we highlight the potentials of combining reconsolidation-based interventions and neuroimaging techniques as a therapeutic tool in drug addiction.

Keywords memory reconsolidation, human neuroimaging, drug addiction, retrieval-extinction

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1 Introduction

At synaptic level, memory is stored and referred as the long-term potentiation (LTP) and long-term depression (LTD) [1, 2]. When the synaptic consolidated memory is reactivated in the brain, memory can transiently switch to a labile state [3, 4]. During the time when the memory is about to re-stabilize (reconsolidate), the memory can be susceptible to interferences, such as weaken by memory suppressor, enhanced by memory enhancers or updated by new information incorporated [3–5]. The above-mentioned processes are defined as memory reconsolidation (see Figure 1). Memory reconsolidation processes are time-dependent (reconsolidation window), in rodents it would take less than 6 hours while in humans it is suggested less than 1 hour. When such processes have been accomplished, the memory trace becomes stable again and immune to interferences [3–5].

Memory reconsolidation plays a critical role in various mental disorders such as drug addiction [6]. The formation and persistence of drug-associated memory are crucial in addiction disorders and expose patients to relapse for years [6, 7]. Memory reconsolidation for drug addiction is one of the key process involving in drug memory maintenance [6, 7]. The curative effect of traditional therapy for drug addiction such as medication, cognitive behavioral therapy and extinction training is unsatisfactory [7]. Memory

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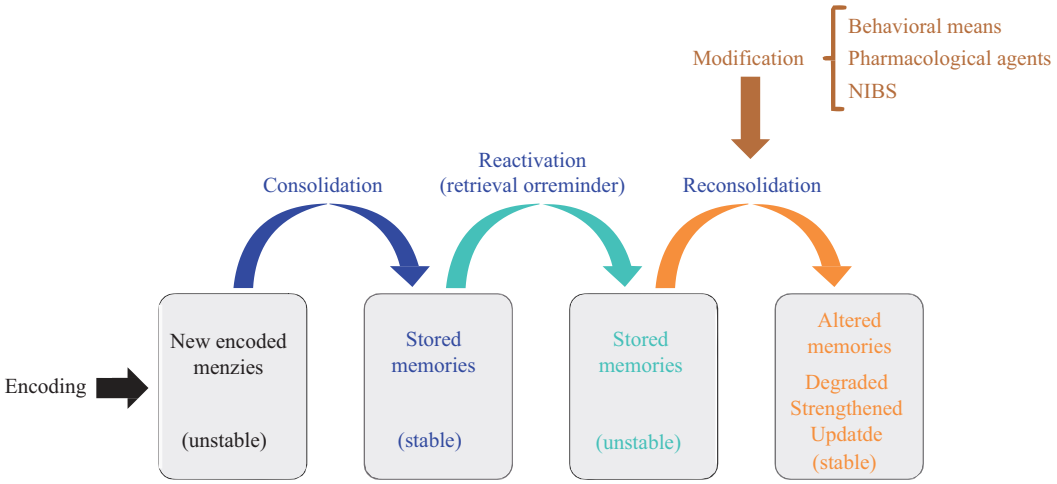

Figure 1 (Color online) Current theory of memory formation and reconsolidation-based intervention. After encoding, memories undergo an initial unstable phase for a limited time, before stabilized through the consolidation phase. Consolidated memories may return to a labile state when they are retrieved or reactivated by a reminder, thus requiring the so-called reconsolidation. During the time-limited reconsolidation window, memories can be degraded, strengthened or updated by the inclusion of new information. Memories can be modified through behavioral means (e.g, interference, extinction), pharmacological agents (e.g, propranolol), or noninvasive brain stimulation (NIBS) techniques. Modified from [5, 46].

reconsolidation has been considered as an updating to the original memory trace rather than generating new memory, therefore reconsolidation-based interventions could modify memory and have been considered as a promising treatment direction [8, 9]. Several human clinical studies also demonstrated long-time effect of reconsolidation-based intervention in addiction patients [10, 11].

There have been cumulating evidence for memory reconsolidation from systemic to cellular levels in animal models but the reconsolidation exploration in human studies mainly focused at behavioral level [1, 12]. Detecting the fundamental neural mechanisms of memory reconsolidation in human via neuroimaging techniques can provide insights in human memory reconsolidation processes. Comparing to traditional clinical interview or questionnaires, neuroimaging techniques can also provide objective data to assess the effect of reconsolidation-based intervention. In this study, we will first briefly introduce the history of memory reconsolidation. Next, we will introduce the human imaging studies focusing on memory reconsolidation. Finally, we will discuss the role of reconsolidation in drug-related memory, the interventions inspired from memory reconsolidation in addiction, and the future study directions on reconsolidation-based interventions combined with neuroimaging techniques.

2 Background of memory reconsolidation

Memory reconsolidation phenomena could date back to 1960s. It was found that rats showed selective memory loss when they received an electronic shock immediately after retrieval or reinstatement of a consolidated fear-condition memory [13, 14]. Similar findings were also reported in 1970s [15, 16]. The aforementioned studies were carried out by behavior analysis and seemed not convincing. The memory reconsolidation study began to show a remarkable progress in recent two decades. Nader and his colleagues infused the protein synthesis inhibitor-anisomycin into the lateral and basal nuclei of the amygdala (LBA) after reactivation of consolidated amygdala-dependent fear memory and produced fear memory amnesia, while the memory was intact with infusion anisomycin into LBA in the absence of memory reactivation [17]. Similar effect was observed with infusion of the protein synthesis blocker into hippocampus immediately following reactivation of consolidated hippocampus-dependent contextual fear memory [18]. Besides, reconsolidation inhibitor could reverse the glutamate receptor expression associated with learning which indicated the specific impairment induced by the reconsolidation inhibitor [19]. Those researches in animals showed memory reconsolidation existed directly at cellular/synaptic level.

The phenomena of memory reconsolidation were also discovered in humans, but most of human re-

searches indicating memory reconsolidation still stay at behavioral level. Schiller et al. [20] demonstrated that non-fearful information provided during the reconsolidation time window could result in old fear memory updating, and the effect could be observed even one year later. Similarly, providing a new motor sequence immediately after retrieval of a acquired sequence could make the original sequence memory fragile [21]. However, only behavioral observation is insufficient to unveil the characterization of the intriguing phenomenon, and more direct evidence supporting human memory reconsolidation is needed.

3 Human brain neuroimaging studies for memory reconsolidation

Reconsolidation has been widely confirmed in animal models with abundant direct evidence. However, invasive research approaches for human memory reconsolidation like animal models are forbidden in ethic. Neuroimaging data could provide direct human memory reconsolidation evidence.

3.1 Functional magnetic resonance imaging (fMRI) studies for human memory reconsolidation

The abundant molecular and cellular equipment available for the study of animal models are commonly invasive and, therefore, inapplicable to most research on people. fMRI is a very powerful tool for exploring the activity of identified brain structures and has revolutionized human brain function studies since it became available 20 years ago [22]. The blood-oxygenation level-dependent (BOLD) signals detected by fMRI are time-locked to performance in memory paradigm and could provide the instant activity data of relevant brain regions across the whole human brain [23]. More recently, fMRI methods, data analyses, and behavioral protocols have greatly improved and these improvements have led to higher resolution of the location of memory functions, and made it possible to better understand the functional interaction between brain regions.

Neuroimaging data could directly demonstrate human reconsolidation occurrence [24–26]. Fear memory is formed and reconsolidation in amygdala [27–30]. Agren et al. [24] designed a delicate reconsolidation-based retrieval-extinction experiment in human fear condition memory combining with fMRI. On day 1, fear conditioned memory was established. In the following day, participants received retrieval-extinction training (one group extinction training 10 min after retrieval, the other extinction training 6 h after retrieval). After the training, amygdala activities were major dependent variables and were acquired through fMRI scanning during renewal-induced fear test on day 3. On day 5, the skin conductance responses (SCRs) were used to assess fear response for fear reinstatement. They found extinction training during reconsolidation window (10 min after retrieval) prevented fear memory renaissance accompanied with decreased bilateral amygdala activity. In contrast, the group receiving extinction training involved outside reconsolidation window (6 h after retrieval) showed clear fear memory accompanied with bilateral amygdala activities and the magnitude of amygdala activities positively correlated with fear response [24]. This study demonstrated that neuroimaging techniques could be used to detect the appropriate memory reconsolidation-based behavior interfere paradigm [24]. Similar results has been documented in the research of Björkstrand's team [25]. Their research showed extinction training immediately following memory reminder (10 min) could greatly reduce fear memory response and this behavioral interfere effect even existed after 6 months. Consistently, attenuated activity in the amygdala was shown in following re-exposure and long-lasting attenuating amygdala activity was observed 6 months later. However, the group which took extinction training 6 h after memory reminder did not result in attenuated amygdala activity and the 6 h group induced less interfere effect than 10 min group [25]. Feng and his colleagues [26] used resting-state functional magnetic resonance imaging (rs-fMRI) to monitor the spontaneous brain activity following fear reminder of fear condition. Subjects were undertaken 10 min rest-state scanning immediately following fear reminder presentation. The reminder group showed increased amplitude of LFF (ALFF) in dorsal anterior cingulate (dACC) and ventromedial prefrontal cortex (vmPFC) contrasted with the no reminder group. The fear reminder group also demonstrated much stronger functional connectivity between the amygdala and vmPFC than the no reminder group [26]. These studies suggest fMRI

has broad application prospects to explore the underlying mechanisms of human memory reconsolidation.

In addition to using fMRI to measure the effect of the reconsolidation-based intervention, several researches used the neuroimaging technic to explore the notion of reconsolidation with pharmacological intervention [31, 32]. Schwabe et al. [31] employed fMRI to detect the neural signatures of reconsolidation impairment caused by reconsolidation-blocker in human brain. Emotional memory enhancement is related to arousal-induced noradrenergic activity in the amygdala, which then modulates memory in the hippocampus [33]. During reconsolidation, emotional memory become instable again and sensitive to amnesic agents such as β-adrenergic receptor blockade, propranolol. Thus, previous emotional memory can be attenuated [34, 35]. Schwabe and his co-workers found emotional memory reconsolidation impairment only following oral propranolol and the imaging data showed significantly increased activities both in amygdala and hippocampus in response to previous negative picture comparing to placebo group [31]. In reactivation stage, their results showed increased activations both in amygdala and hippocampus (comparing to no reactivation group) and there were no differences between the placebo reactivation and propranolol reactivation groups [31]. This indicates that propranolol did not change brain activation during memory reactivation [31]. Brunet's team adopted a pilot study using fMRI techniques to measure the effects after reconsolidation impairment with propranolol in post-traumatic stress disorder (PTSD) [32]. They recruited nine PTSD patients and undertook 6 weekly reconsolidation impairment treatment sessions. In each session, patients received brief exposure (5–10 min) to trauma reactivations under propranolol influence. Each patient received twice fMRI scanning separately before the whole treatment sessions and after completing treatment sessions. The fMRI data showed the right amygdala activation was higher in response to the fearful versus neutral faces before treatment and this difference declined after treatment [32]. Anterior cingulate cortex (ACC) activation diminished in PTSD patients which inversely associated with symptom severity [36]. Brunet et al's study [32] showed the right ACC activation in response to fearful versus happy faces increased after successful treatment in contrast with pre-treatment and the increase of ACC activation was correlated with PTSD symptom improvement. These researches indicate fMRI could be capable of measuring the reconsolidation-based interfere effects.

Neuroimaging data could also be applied to detect the neural mechanisms of reconsolidation-based behavior intervention [37, 38]. Retrieval-extinction paradigm has been widely applied in mental disorders such as anxiety, PTSD and addiction disorders [8]. Comparing to the standard extinction training, the retrieval-extinction training interferes the reconsolidation of original memory trace rather than generating a paralleled newly extinction learning memory [39, 40]. This indicates the retrieval-extinction can persistently prevent the original memory from renewal whereas the effects of the extinction training is hard to maintain and the original memory tends to reemerge months or years later [39, 40]. The failure in retrieval-extinction training mainly attributes to insufficient memory reactivation thus inducing the actual extinction training rather than retrieval-extinction manipulation [41]. With the help of neuroimaging techniques, it allows us to probe the distinction between retrieval-extinction paradigm and the standard extinction training [37, 38]. During standard extinction training in response to threat memory, the ventral medial PFC (vmPFC) was found to progressively activate and the activations will further suppress amygdala activations [42–44]. This relationship between vmPFC and amygdala has been associated with the generation of defense response [42–44]. However, during retrieval-extinction training, the researchers found the diminishment of PFC involvement [37, 38]. The vmPFC showed enhanced functional connectivity with the amygdala only during standard extinction learning, but not in the retrieval-extinction learning [37, 38]. The results also showed the reduced connecting strength between the PFC and amygdala after manipulating retrieval-extinction training while the connectivity between the PFC and amygdala increased after the standard extinction training [37, 38].

3.2 Non-invasive brain stimulation studies for human memory reconsolidation

Noninvasive brain stimulation techniques (NIBS) have been broadly applied for studying the physiological function of the central nervous system (CNS), exploring the functional role of specific brain regions, and, more recently, detecting large-scale network dynamics [45, 46]. NIBS stimulate the neurons at depth

through multiple electronic field and can selectively stimulate the target neurons without recruiting neurons of overlying brain area [47]. The two most widely used forms of noninvasive brain stimulation techniques are transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) [45, 46]. Both rTMS and tDCS are safe to human brain and have made remarkable contributions to neuroscience [45, 46]. They identify the causal links between the specific brain regions undertaking cognitive, affective, sensory and motor functions [45, 46]. They also provide insights into local and global brain network modality, dynamics and plasticity [45, 46]. Moreover, abundant evidence supports the use of rTMS and tDCS as tools for enhancing cognitive and motor function in healthy people and as therapeutic agents for patients suffering neurological and psychiatric disorders.

Noninvasive brain stimulation is a safe approach for studying brain mechanisms of memory reconsolidation [48, 49]. Sandrini et al. [48] used rTMS to stimulate the cortical regions associated with episodic memory during the retrieval interval. Their research [48] illustrated the causal role of the original memory trace in reconsolidation process. The right lateral prefrontal cortex (PFC) is a critical node in the neural network mediating the encoding and retrieval of episodic memories [50, 51]. Sandrini et al. [48] administrated 15 min-rTMS stimulating the right lateral PFC 10 min after the spatial-contextual reminder cue presentation and induced significant memory enhancement effects during memory recall test after 24 h. The rTMS enhancement effect was specific to memory retrieval and topographically specific owing to both participants with no-memory retrieval and participants with rTMS stimulating over the right lateral PFC showed no memory enhancement during memory recall test [48]. Moreover the memory enhancement was time-dependent because there was no memory enhancement effect if rTMS stimulation 1 h post-reactivation (outside of the reconsolidation window), which is in accordance with prediction from reconsolidation theory [48]. In another study, Censor et al. [52] utilized rTMS to interfere memory reactivation in the primary motor cortex (M1, a crucial region in acquisition of motor procedural memories) and produced existing procedural memory reconsolidation impairment in healthy participants [49]. In contrast, participants with intact memory modification showed no original procedural memory impairment [49]. Subjects with impaired memory modification had reduced activities in the supplementary motor area (SMA) and weaker functional connectives between M1, SMA, anterior cerebellum (consistently engaged in early learning), and sensorimotor striatum was active in late motor learning stage [49]. This suggests impaired original procedural motor memory trace with involvement of reconsolidation interfere [49]. The above researches indicate rTMS could be suited to explore the neural dynamics underlying memory reconsolidation and modulate the memory reconsolidation processes.

Similar effects in episodic memory reconsolidation interfere have been documented with tDCS applied to the PFC in young and older subjects [53,54]. The dorsolateral prefrontal cortex (DLPFC) plays a causal role in strengthening of verbal episodic memories through reconsolidation [55–57]. Javadi and Cheng [53] applied tDCS over the left DLPFC in 30 healthy university students. Subjects memorized words in the first session. Three hours later, in the second session, subjects in the reconsolidation group received tDCS while the existing memories were reactivated during retrieval. The final session for memory recognition task as a measure of memory performance was scheduled to occur 5 h after the stimulation session. Anodal tDCS strengthened episodic memory recognition compared to cathodal and sham stimulation. Contrary to the reconsolidation group, anodal stimulation did not enhance the memory performance for the control group (administration with anodal tDCS, no reactivation condition) [53]. This result suggests that anodal tDCS over the left DLPFC enhances the reconsolidation of long-term memory only when the existing memories have been reactivated during retrieval [53]. Sandrini et al. [54] applied anodal tDCS stimulating the DLPFC 10 min after receiving the episodic words memory reminder in elderly subjects. Memory recall were tested separately 24 h and 30 days after the DLPFC stimulating. Anodal tDCS over the left DLPFC enhanced existing verbal episodic memories and reduced forgetting compared to sham stimulation. In addition, subjects administrated with anodal tDCS after receiving reminder showed greater performance in memory recall test compared to those subjects without reminder [54]. Hence it seems that non-invasive stimulation techniques, such as rTMS or tDCS, could be applied to modulate the memory reconsolidation processes and to explore the neural mechanisms involving in memory reconsolidation.

4 The role of memory reconsolidation in drug addiction and reconsolidation-based intervention in addiction

At the drug memory acquisition stage, the rewarding properties of drug abuse can encourage individual to drug seeking and facilitate the transition from infrequent drug use into drug dependency [9, 58]. On the other hand, the negative consequences of drug withdrawal result in individual drug craving and relapse [59–61]. Repeated drug-taking behavior involves consolidation of memory for drugs and drug-related cues and contexts [62,63]. The memory of drug associated cues/contexts could induce drug craving and drug-seeking behavior rather than drug itself [62,63]. Neuroscientific study in rodents also found the synaptic LTP/LTD in amygdala, nucleus accumbens (Nac) and the prefrontal cortex which suggested the enhancement of connection between drug and drug associated cues/contexts [64, 65]. When drug-related memory is reactivated, it is suggested that these memories will be reconsolidated and further maintained for long-term even many years [66, 67].

Several animal studies demonstrated memory reconsolidation evidence in drug addiction. Post-reactivation administration of cocaine in rats significantly enhanced the rewarded-related memory performance [68]. Administrating protein synthesis inhibitors-anisomycin immediately after the reactivation of cocaine-conditioned place preference (CPP) memory significantly weaken the expression of reliable cocaine-CPP memory and this effect maintained for weeks [69]. Suppression of the immediate early gene expression, which is prominently increased following retrieval of drug-related memory [70], prevented the CPP reconsolidation and weakened the memory performance [71]. Therefore, the studies mentioned above provide the theoretical basis for the reconsolidation-based interventions in drug addiction.

Traditional extinguishing manipulation usually results in a newly formed separate inhibitory memory that might exist in parallel with the original memory trace [39,72]. Thus, it can make the original memory easy to reemerge spontaneously, reinstate and renew [39,72]. Reconsolidation-based interventions directly erased/updated the original memory trace [73,74]. As a result, it could persistently prevent drug craving and relapse in theory [73,74]. Xue et al. [10] applied the retrieval-extinction training to herion-addiction individuals and found that participants receiving retrieval-extinction training during the reconsolidation window (10 min after retrieval) showed significantly reduced drug seeking and craving. This effect even maintained 6 months later [10]. Similar results were found in Germeroth's research [11]. Germeroth et al. [11] adopted the retrieval-extinction training paradigms in nicotine-dependent subjects. Their participants with retrieval-extinction training significantly reduced nicotine-craving and substantially reduced the number of cigarettes intake per day [11]. This effect still maintained for 1 month [11].

5 Future study combined with neuroimaging techniques for the reconsolidation-based intervention in drug addiction

Despite memory reconsolidation-based interventions have received attention as a promising therapy for drug addiction in human, most studies still restricted on behavioral analysis and the effects were not consistent [8, 9]. One of the critical reason is a lack of robust neural data acquiring from neuroimaging tools [8, 9]. Here we summarize the fMRI and NIBS studies for memory reconsolidation (see Table 1) and are going to discuss future prospects using neuroimaging techniques for future reconsolidation-based intervention studies in human drug addiction.

First, when adopting the retrieval-extinction manipulation, actual memory reactivation should be observed in theory [8]. However, the effects based on such intervention are inconsistent. One of the critical reasons regarding the reconsolidation processes is that memory may not be activated during retrieval [3,8]. This could be attributed to the absence of effective cue reminders or the complexity of the memory [8]. Indeed, it is difficult to detect the memory retrieval processes at behavior level, therefore research adopting neuroimaging tools (e.g, EEG, fMRI) could provide useful temporal or spatial information. For example, event-related potentials (ERPs) with high time resolution (ms range) can provide noninvasive measures of neural instantaneous activity and are capable of examining the brain dynamics underlying human mem-

Table 1 Neuroimaging and intervening techniques in memory reconsolidation studies

	fMRI	NIBS
Advantages	High location resolution; Time-locked; Multiple analysis methods	Safe to human brain; Stimulate at depth precisely; Without affecting other regions
Current studies in exploring memory reconsolidation	Observe the memory reconsolidation processing; Evaluate the reconsolidation interfere effects; Explore the underlying mechanisms	Reveal the causal role of the target brain area; To modulate the memory reconsolidation process
Future direction in drug addiction	Explore the optimal retrieval-extinction paradigms; Explore the underlying mechanisms; Measure the interfere effect	Examine the causal links between brain regions; To modulate drug memory reconsolidation

ory [75]. Wirkner et al's study [76] had shown through behavior interference after reactivation of previous encoded emotional episodic pictures, and emotional memory impairment were observed accompanying with a reduced centro-parietal ERP old/new difference during retrieval of emotional pictures. Forcato et al. [77] used fMRI to assess the retrieval strength degree differences among various cue reminders. Their study demonstrated that different types of cue reminders could induce different levels of memory retrieval strength, which correlated with different left hippocampal activation during its presentation [77]. Hence, future clinical study could use neuroimaging tools to measure which drug-associated cue is best for addiction memory retrieval. Drug-related memory consists of several components including emotion related, context related memories, and drugs itself [7]. It is expected that when drug related memory becomes more complicated, it is more difficult to modify via reconsolidation-based intervention [78, 79]. It has been shown that complex memory could be better targeted by sequentially reactivating and extinguishing subcomponents of a whole [80]. Despite this intriguing behavior evidence, it is necessary to acquire more neural evidence to prove its value. Future studies could develop such manipulation in drug addiction to improve the effects of such intervention and with the neuroimaging technic neural mechanism could be explored at the same time.

Second, during reconsolidation interference stage, a suitable cue-presentation time and an appropriate interval between retrieval and interfere remain unclear [3, 8]. Hu et al's study [81] suggests that either too long or too short time for cue presentation could lead to a failure in reconsolidation, but these results still came from behavioral observation lacking in neuroimaging evidence. There are also several studies showing the proper interval between retrieval and interfere that is critical for successful intended manipulation [10, 17, 81]. Thomas' neuroimaging study mentioned above suggested that different intervals between retrieval and interfere could lead to different activities in reconsolidation-related brain regions [24]. Future studies could apply neuroimaging tools (e.g., fMRI) to explore proper time window for cue reminder presentation and the best interval between memory retrieval and the following modulation in drug addiction.

Moreover, future study should use neuroimaging techniques to explore brain regions and networks, which engage during the formation and persistence of drug-related memory reconsolidation. Most of studies for human memory reconsolidation in addiction were performed at behavioral level and required more direct corresponding biological evidence, such as neural data. According to the studies that we discussed above [48, 49], neuroimaging tools can be used to explore the neural mechanisms for the memory reconsolidation in drug addiction. Moreover, combining non-invasive brain stimulating techniques to target the memory related regions or networks could further improve reconsolidation-based intervention effects. A pilot study has showed that the combination of deep rTMS to the medial PFC with brief exposure to a traumatic event induced beneficial effects in patients with post-traumatic stress disorder [82]. There are also other types of non-invasive brain stimulation techniques with the capacity to modulate neural activity including transcranial alternating current stimulation (tACS), transcranial near-infrared

stimulation (tNIRS), functional electrical stimulation (FES), transcutaneous electrical nerve stimulation (TENS), pulsed radio-frequency, peripheral nerve stimulation and electro acupuncture. Although those newly mentioned non-invasive brain stimulation techniques here have not be applied in exploring the mechanisms and intervention of memory reconsolidation. Future studies should focus on whether combining non-invasive brain stimulation would improve intervention effects in drug addiction.

Finally, other neuroimaging techniques such as positron emission computed tomography (PET) and functional near-infrared spectroscopy (fNIRS) may also be capable of application to explore memory reconsolidation in drug memory and measure the interfere effect for drug addiction in future studies. PET has optimal sensitivity and specificity in identifying molecular metastases of neurons and early biochemical recurrence in neurons after therapy [83]. Combining with MRI, with high location resolution advantage, PET/MRI provides powerful application value for detecting underlying mechanisms of neuropsychological diseases and response to therapy [83]. Using PET/MRI in future studies may produce profound insight in memory reconsolidation. In recent years, fNIRS with characters of favorable spatiotemporal resolution, mobile portability, relative low cost and insensitivity to head motion has aroused wide attention in cognitive neuroscience [84]. With the help of fNIRS, future studies in drug memory reconsolidation may provide abundant information which would be much closer to the realistic mechanisms of drug addiction. Furthermore, other neuromodulation techniques such as tACS or tNIRS may also be considered as useful tools to provide information for drug memory reconsolidation and modulate drug addiction in future studies. The state of oscillations in the brain may involve in varies neural activity modulation including sensory, motor, cognitive and affective function, therefore tACS through applying weak oscillatory electrical currents over the scalp can modulate neural oscillations and result in the targeted brain region activity change [85]. Owing to the high dependence of neurons on oxygen metabolism, tNIRS mostly acts via photonics-bioenergetics mechanism and then induces metabolic and hemodynamic changes which facilitate targeted neurons functioning [86]. Although the above mentioned neuroimaging techniques or neuromodulation tools have not applied in memory reconsolidation, we believe these neuroimaging techniques and neuromodulation tools would likewise play an important role in future studies for exploring human drug memory reconsolidation.

Declaration and interests All authors report no biomedical financial interests or potential conflicts of interest.

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