MAJA PALOMA VÖLKER

Can Drug Addiction be Treated by Manipulating Memory?: A Literature Review of Memory-Based Treatments and a Qualitative Comparison with Conventional Treatments

Perspective

Drug addiction constitutes a major health problem in modern society. Most of the current treatments have demonstrated limited effectiveness in long-lasting treatment results because they focus on acute symptoms of the illness while neglecting important factors that maintain addiction. Memory manipulation therapies appear to be promising alternatives that act on mechanisms that maintain addiction. The aim of this review is to summarize the existing research about memory manipulation for drug addiction and to evaluate the potential as an

addition to currently used treatments. In this paper, memory-related processes that are associated with addiction etiology are explained. Additionally, several findings suggest the potential of memory manipulation to reduce the impact of drug-related memories and associated stimuli on behaviour. The reviewed studies provide support that targeting maladaptive drug memories might be a valuable therapeutic approach that seems to prevent relapse. Three types of memory manipulation treatment are reviewed; namely extinction training, reconsolidation therapy, and eye movement desensitization and reprocessing. Finally, the paper concludes with implications for treatment of addiction using the described approaches to adapt drug-related memories.

Keywords*:* memory, drug addiction, reconsolidation, retrieval, EMDR

INTRODUCTION

In recent years, several instances have contributed to the discussion about the use of recreational drugs. For example, the display of drug abuse has increased tremendously in mass media, with TV shows such as “Narcos” and “Breaking Bad” rising in popularity. Moreover, several countries have eased their regulations regarding the possession and consumption of cannabis to increase the control over drug-related problems. For example, in Canada, a law that legalizes recreational use of marihuana was passed in July 2018 with the purpose to improve control over consumption (Cox, 2018).

Another drug-related topic that is currently discussed is the problematic development with the opioid epidemic in the United States. Many doctors have become progressively liberal in prescribing opioids to chronic pain patients (Maxwell, 2011). Although these drugs are very effective in relieving pain, they also have a very high addictive potential (Ballantyne & Shin, 2008). The increase of opioid prescriptions in the US has been

associated with more cases of opioid addiction and death from overdose (Wilkerson, Kim, Windsor & Mareiniss, 2016).

The example of the opioid epidemic in the US illustrates that it is important to shed light on potential risks associated with excessive drug consumption. At first, the choice to consume drugs might have great appeal, as they promise pleasurable experiences and relieve negative affect. However, with repeated consumption the ability to control one's own behavior decreases (Volkow & Morales, 2015). Eventually, drugs may begin to interfere with daily life because activities other than drug consumption lose their pleasurable properties. The individual might neglect other activities for obtaining more drugs regardless of any sacrifice (National Institute on Drug Addiction, 2018).

Drug addiction is characterized by the uncontrollable craving for and intake of a substance despite the harmful effects. The drug interferes with the quality of life by impairing the drug user physically and mentally (American Psychiatric Association, 2013). Grant and colleagues (2016) report an estimated prevalence of 9.9% for a lifetime diagnosis of substance abuse

disorder (SUD) in the US, showing that it constitutes a common health issue. Extensive research on neural mechanisms has revealed that drug addiction can be partly explained by associative learning, including Pavlovian and Instrumental conditioning, meaning that situational or environmental cues present during the consumption of the substance will be stored and can elicit drug-seeking behaviors (Everitt, 2009). Pavlovian conditioning in addiction is a process that links drug effects to cues that are present in the environment. After repeated exposure within the context of drug use, these originally neutral cues become conditioned stimuli (CS) that are associated with the predicted drug effects. The CS will elicit anticipatory bodily responses that oppose these predicted effects (Siegel, 2005). Within this context, instrumental conditioning operates in conjunction with Pavlovian conditioning. By means of this process, an association between drug effects and drug-seeking behaviours is established. The pleasurable effects of the drug act as positive reinforcers, meaning that they increase the likelihood of drug-seeking behaviours (Everitt & Robbins, 2005). Given

sufficient repetition, the cue-induced drug seeking becomes habitual and behavioural control is lost (Milton & Everitt, 2012).

The treatment of drug addiction is a complicated and exhausting process for the drug addict due to the associated withdrawal effects, as the body must adapt to the absence of the drug. Additionally, current treatment forms for drug addiction leave the patient vulnerable to relapse as soon as being exposed to conditioned drug cues in an everyday context (Milton & Everitt, 2013). The National Institute on Drug Abuse (2018) reports relapse rates that range from 40-60% following treatment. These figures necessitate the development of treatment forms that prevent relapse in the long term.

Multiple research lines have identified a promising treatment approach to target the issue of relapse after the patient leaves medical care. Memory manipulation can be used to disrupt the ability of different environmental stimuli to elicit craving and drug-seeking behaviors. The intervention might result in effective long-term treatment for addiction by using the mechanisms of instrumental learning and classical Pavlovian conditioning. To counteract some of the underlying memory

mechanisms, potentially effective approaches that have been suggested include disruption of addiction memory reconsolidation, extinction treatments, and eye movement desensitization and reprocessing. This paper briefly describes established addiction treatments and their limitations before reviewing current findings to answer the question of whether memory manipulation is a suitable and perhaps better therapeutic approach to treat drug addiction.

Definition of Drug Addiction

The DSM-V (American Psychiatric Association, 2013) provides four main symptom categories to define addiction, clinically termed as substance use disorder (SUD). Firstly, there are several symptoms which can be classified as impairments in regulating drug consumption, for example taking increasingly larger amounts of the drug. Moreover, impaired functioning in social aspects, for example, the inability to cope with responsibilities, is given as diagnostic criterion. An additional

category covers the irresponsible usage of substances regarding situational factors, for example driving under the influence, and the harmful effects of the drug. Lastly, the DSM-V points out the pharmacological effects caused by the drug as an indicator for SUD, namely higher tolerance for the drug and withdrawal effects during abstinence. For a diagnosis of SUD, at least two criteria across a period of 12 months must be met.

Drug Addiction and Memory Mechanisms

Fundamental mechanisms of SUD can be explained in terms of an interplay between instrumental learning and classical conditioning. By means of instrumental learning, drugs are reinforcing the behaviours that are required to obtain them. This means that the individual learns what actions are required to receive the positive effects that the drug produces. By this process of instrumental learning, the drug behaviours that are required to experience the effects of the drug are reinforced (Everitt & Robbins, 2005). Over time, the ability to wilfully

modulate the behaviour in presence of stimuli decreases drastically (Everitt & Robbins, 2016). In the long run, drug-seeking behaviours may become habitual and compulsive. This means that the individual is unable to refrain from performing drug seeking behaviours despite the awareness that the consumption might entail negative consequences (Milton & Everitt, 2012).

The instrumental learning in drug addiction is mediated by classical conditioning. By means of classical conditioning, stimuli that are present in the environment during drug consumption gain incentive value and motivational salience (Everitt & Robbins, 2016). Initially, the drug effects constitute the unconditioned stimulus that triggers a biological response aimed at returning homeostasis. Cues that are repeatedly present during drug use become conditioned stimuli (CS) that are associated with the predicted drug effects (Siegel, 2005). The body will attempt to prepare for the drug effects by establishing opposite effects to the drug that are experienced as withdrawal symptoms and cravings (Milton, 2013). The CS imposes an uncontrollable motivational state upon the individual to engage

in reward-seeking behaviors that were reinforced by instrumental learning (Cartoni, Balleine & Baldassarre, 2016; Everitt & Milton, 2005; Milton & Everitt, 2012).

In a physiological context, one of the most important neural correlates of drug addiction is the limbic corticostriatal system. To delve deeper into the brain mechanisms, the basolateral and central parts of the amygdala are responsible for encoding the association between CS and the drug effects as an unconditioned stimulus (Everitt, 2009; Volkow & Morales, 2015). In addition, the repeated pairing of the stimulus with drugs leads to increased activation of the ventral striatum, most importantly the nucleus accumbens, by increasing the concentration of dopamine (DA) (Everitt & Robbins, 2005; Milton & Everitt, 2012). The concentration will also increase for subsequent encounters with CS and signal reward prediction (Volkow & Morales, 2015). This process is normally implicated in adaptive learning mediated by natural reinforcers such as food (Robbins, Ersche & Everitt, 2008; Milton & Everitt, 2012). The activation of the nucleus accumbens by the release of DA, therefore, increases behavioural motivation (Everitt, 2009). The

orbitofrontal cortex plays an important role in the acquisition of goal-directed behaviour as it links actions that are necessary to obtain a certain outcome with the representation of the predicted outcome value (Everitt & Robbins, 2005; Schoenbaum & Shaham, 2008). With sufficient repetition the drug seeking behaviour becomes habitual, which is represented by dorsal striatal activation. This mechanism accounts for the fact that the intake of drugs shifts from being a conscious decision to an automatic process in which the individual engages in drug seeking behaviour (Everitt & Robbins, 2016). Conjointly, the changes in activation patterns of these structures contribute strongly to addictive behaviour.

Current Treatments for Drug Addiction

Currently, various treatment approaches are used by therapists to treat SUD. In the following section, the most widely employed approaches, medication-based and behavioural therapies, will be

discussed to conclude how memory manipulation treatments might help to improve upon their effectiveness.

To begin with medication-based treatment, the clinician provides the patient with an alternative, relatively safe substance to replace the drug of abuse. By replacing the drug with a legal substitute, the withdrawal effects are reduced which usually interfere with the treatment and drug craving (Douaihy, Kelly & Sullivan, 2013). For an effective treatment, the alternative substance must be tailored to the mechanisms of the abused drug. For example, the therapist might prescribe buprenorphine or methadone to treat opioid addiction because they maintain the effects of illicit drugs. Both medications act as opioid agonists, meaning that they activate opioid receptors in the brain (Whelan & Remski, 2012). Compared to commonly misused drugs like heroin, these medications constitute a much safer alternative, mainly because of lower risk of overdosing (Soyka, 2017).

Nevertheless, the medications may have severe and sometimes even lethal side effects (Douaihy et al., 2013). Despite having a lower risk of overdose than their illicit counterparts, the

replacement medications can still cause respiratory depression if they are administered in wrong doses (Douaihy et al., 2013; Whelan & Remski, 2012). Additionally, buprenorphine may induce hepatitis while methadone may cause heart problems (Whelan & Remski, 2012). Moreover, there is no guarantee that patients comply with the medication schedule outside of treatment facilities.

Besides medication-based treatments, many psychosocial therapies have been used in a clinical context within the past few years. One form is contingency management (CM), during which the patient receives rewards for remaining abstinent. These rewards can take multiple forms depending on the individual patient (Jhanjee, 2014). For example, inpatients could be granted some time outside of the treatment facility in exchange for cooperative behaviour. To increase the effectiveness of CM, it might be useful to combine it with other therapeutic interventions. Recently, van den Brand and colleagues (2018) conducted a study to test whether financial incentives as an add-on to smoking cessation groups improve treatment outcomes. Both the control and the experimental

groups, consisting of smokers, received smoking cessation training in a group setting. The experimental group was additionally rewarded with vouchers during a period of 12 months following the training sessions if they remained abstinent. The results indicate that in the experimental group more participants remained abstinent with a proportion of 41% while in the control group only 26% of the participants remained abstinent.

On the one hand, CM has been found to improve compliance with treatment programs (Jhanjee, 2014). However, despite positive effects on abstinence outcomes during treatment (d=0.58, 95% CI=0.25 to 0.90), there is not much support for effectiveness on relapse prevention (Dutra et al., 2008; Blonigen, Finney, Wilbourne & Moos, 2015). Additionally, providing materialistic rewards for the patient is expensive. For that reason, CM is not employed often in the clinical context (Jhanjee, 2014).

As a final example of psychosocial treatments, the patient can engage in cognitive behavioural therapy (CBT) with a focus on identifying maladaptive beliefs and behaviours; and teaching

the patient appropriate coping strategies (Milton & Everitt, 2012). CBT seems to be effective for a broad range of drugs of abuse (Jhanjee, 2014). There are multiple interventions that have been put forward within the umbrella term CBT. Several studies have identified social skills training as the most effective intervention. The patient learns how to initiate social interaction and to cope with peer pressure regarding drug consumption (Blonigen et al., 2015). CBT was found to have a small, but significant effect for the treatment of SUD (g = 0.154, p < .005); with the largest effect for cannabis dependence (Hofmann, Asnaani, Vonk, Sawyer & Fang, 2012, Magill & Ray, 2009).

Even though CBT is a widely accepted therapeutic approach, it might not be suited for every patient. For successful treatment, cooperation by the patient is crucial as it requires recognition of and willingness to change dysfunctional beliefs. Therefore, it might not be effective for patients that have been obliged to complete treatment. Moreover, CBT requires sufficient cognitive capacities to identify maladaptive beliefs and behaviours and adapt them. Some patients might lack insight

into the underlying beliefs as contributing factors to their disorder.

In sum, it has to be noted that neither type of therapy described above sufficiently targets the conditioned responses that are a crucial component in maintaining addiction. Medication-based treatments are only suitable to temporarily replace drugs rather than treating causes and preserving aspects of SUD. CM provides an incentive to remain abstinent, but no attempt is made to identify the causes of SUD and triggers of relapse in form of CS. CBT approaches the causes and stimuli of abuse and relapse more, but it requires the patient to consciously adjust dysfunctional beliefs and behaviours. However, conditioning is a subconscious process. Even if the patient successfully identifies CS, this is not sufficient to prevent their impact on behaviour. A cognitive approach might not be suitable to reverse the influence of drug-associated stimuli on behaviour. Neglecting these maintaining factors leaves the individual more vulnerable to relapse in critical situations (Milton & Everitt, 2012). To treat SUD effectively in the long run, an alternative treatment approach that specifically targets

associations between CS and drug-seeking behaviours should be proposed. As the following part of the review argues, this might be accomplished with memory manipulation treatments. Rather than a single intervention, these treatments may be combined with the previously mentioned therapy forms to increase their effectiveness.

Memory Manipulation as Addiction Treatment

A memory manipulation treatment approach might be an effective way to reduce the risk of relapse after patients have left medical care (Milton & Everitt, 2012). It has been well-established that CS can elicit strong drug cravings and motivate drug-seeking behaviours, which in turn might result in relapse (Everitt & Robbins, 2005). The following approaches attempt to disrupt the impact of CS on behaviour.

Research in the field of neurobiology has identified two possible mechanisms of memory manipulation, extinction and reconsolidation (Torregrossa & Taylor, 2012). Firstly,

reconsolidation refers to the process by which reactivated memories are stabilized and updated before they are stored in long-term memory. One underlying molecular mechanism of reconsolidation has been identified as the synthesis of a neuronal protein which is regulated by the expression of the early immediate gene Zif268. The disruption of the synthesis of this protein may strongly interfere with reconsolidation (Milton, 2013). Addiction treatments can make use of this property by specifically manipulating maladaptive drug memories before they are updated and stored in long-term memory (Merlo, Milton & Everitt, 2015). As was discussed previously, some maladaptive memories can be identified as stored associations between a conditioned stimulus and drug seeking. Targeting those associations during retrieval by means of disrupting protein synthesis might decrease stimulus effects on behaviour. Reconsolidation can be disrupted by administering a pharmacological agent that interferes with protein synthesis just before drug-related CS exposure (Lee, Milton & Everitt, 2006). Ultimately, this might weaken the association between the

stimulus and the drug (Taylor, Olausson, Quinn & Torregrossa, 2009).

In a study by Lee and colleagues (2006), rats were conditioned to press a lever for a cocaine injection in response to a light cue. In subsequent sessions, at the basolateral amygdala (BLA) the rats were infused with Zif268 antisense oligodeoxynucleotides (Zif268 ASO), which suppress the expression of the early gene Zif286, just before exposing them to the CS again. The BLA has been found to be part of a mechanism by which CS exert control over drug seeking behaviour (Everitt, 2009). The suppression of Zif268 expression during memory retrieval effectively interfered with protein synthesis. Consequentially, the reconsolidation of memories that concerned the association between the conditioned light cue and cocaine administration was disrupted. As a result, the CS did not elicit the previously observed cocaine seeking behavior anymore ($p < .03$). Additionally, the rats did not show signs of relapse following reconsolidation training.

To disrupt reconsolidation in humans, propranolol has been put forward as a safe medication. The β-blocker disrupts

protein synthesis that is important for restabilising memory traces by binding to β-adrenoceptors in the brain. It is thought to be more effective in altering emotionally relevant memories because it reduces amygdala activity (Thomas, Saurnier, Pitman, Tremblay & Brunet, 2017). This property might be used to alter emotional drug memories of patients. So far, propranolol is the only medication to alter reconsolidation that has been approved to be used on humans (Lonergan et al., 2016).

In a pilot study, the effects of propranolol during retrieval periods were tested in patients with SUD (Lonergan et al., 2016). The subjects were randomly allocated to either a control (n=8) or experimental condition (n=9). In a total number of 6 sessions, the participants were given either propranolol or a placebo. An hour after ingestion, they were asked to read a text that described a personalized drug experience, meant to trigger drug cues and induce cravings. An analysis of the data showed that only the experimental group displayed a significant decrease in craving scores after completion of the last session (d= 1.40). These results suggest that propranolol can be used to reduce craving by preventing reconsolidation.

However, correct timing of propranolol administration has been found to be crucial to reproduce the desired effects. Thomas and colleagues (2017) found that only receiving the medication 60-75 min prior to retrieval effectively interfered with memory reconsolidation (*n*=50). Post-retrieval administration has failed to replicate the positive effects of reconsolidation interventions (*n*=36). A likely explanation for this phenomenon is that propranolol takes 1-2 hours to exert its full effects.

Treatment of SUD with propranolol has been found to have many advantages over conventional pharmacological manipulations. The intervention requires fewer treatment sessions and therefore significantly reduces treatment costs and effort. Additionally, patients do not have to take the medication daily. It is sufficient to administer propranolol prior to a therapy session. Moreover, the intervention could be translated into clinical settings easily and is accepted very well by patients (Lonergan et al., 2016). Additionally, propranolol has no addictive potential which is a big advantage for treating patients with SUD (Noyes, 1982).

Alternatively, extinction refers to the disruption of the association between the drug seeking and conditioned cues by preventing reinforcement (Torregrossa & Taylor, 2013). Consequentially, drug seeking behaviours should gradually decrease. The therapist exposes the patient to different stimuli that elicited drug-related behaviours in the patient's history of drug abuse. During the exposure periods, the patient is not allowed to consume any drugs. After multiple sessions, the procedure will eventually create a new association between the cues and the absence of reinforcement (Milton & Everitt, 2012).

Rather than eliminating the original association, maladaptive behaviours are inhibited by extinction (Taylor et al., 2009). Bouton (2004) proposes that the response to CS will depend on the context, which allows conditioned responses to be reinstated in critical environments. To improve treatment success, it might be useful to apply extinction procedures in real-life environments rather than treatment facilities (Taylor et al., 2009).

The extinction paradigm was tested in rats by Xue and colleagues (2012) using conditioned place preference (CPP),

meaning that a certain environment was used as the CS. The rats received injections of morphine in the same environment across multiple sessions. Due to the reinforcing effects of the drug, they developed a preference for that specific place compared to another environment where they merely received saline injections. In the following phase of the experiment, the rats were exposed to the conditioned place to retrieve the associated drug memories. Afterwards, they were withdrawn from the drug-associated environment and returned to it after varying delay periods. During this second exposure, the extinction training took place, meaning that there was no reinforcement by injecting morphine to the rats. If the delay between retrieval and extinction was of short duration, more precisely between 10 min to 1 hour, the association between the drug and the environment was weakened ($p < .05$, n= 9-11 per condition). These findings indicate that there is a limited time window in which extinction manipulation is effective.

The research group elaborated on this experiment by testing extinction procedures in abstinent heroin addicts. The subjects were tested for their reactivity towards neutral or

heroin cues following manipulation of memory retrieval and extinction training during which they were exposed to drug-related cues without drug reinforcement. The participants were assigned to one of three different conditions. A control group was exposed to a videotape that contained neutral cues whereas the two other groups saw clips that contained heroin cues. The manipulation with heroin cues was intended to elicit retrieval of drug-related associations. Afterwards, each group received extinction training during which they were exposed to different drug cues after varying delay periods. The subjects that were assigned to the neutral condition received the extinction 10 minutes after watching the video. The groups that were subjected to heroin cues experienced a delay period of either 10 minutes or 6 hours before the extinction training. Similar to the results from their previous experiment, the researchers found that only the group who had a short delay between memory retrieval and the training exhibited significantly lower levels of heroin craving and lower blood pressure following drug cue exposure compared to the control group ($p < .05$, n=16-18 per condition). Neither group showed reactivity in response to

neutral cues. These data add evidence to the notion that the delay between retrieving drug-related memories and extinction procedures should be short. More importantly, these results suggest that extinction could be a potential intervention for treating SUD.

Another alternative treatment approach that might be useful in SUD therapy is eye movement desensitization and reprocessing (EMDR). This approach makes use of the vulnerability of memories during reconsolidation. Originally, EMDR was developed to decrease the magnitude of traumatic memories (Qurishi, Markus, Habra, Bressers & Jong, 2017). More recently, attempts have been made to use EMDR for disrupting memories that are associated with drug consumption (Hase, Schallmayer & Sack, 2008). During therapy sessions, the patient is instructed to make horizontal eye movements (EM) during recall of drug memories to exhaust the capacity of working memory (WM). These drug memories can take multiple forms; patients may envision situations in which they felt an intensive craving, positive feelings that are associated with the drug or mental representations of CS (Wise & Marich, 2016). The limited

resources of the WM are allocated in favor of EM and do not suffice for maintaining a vivid representation of the drug memories (van den Hout & Engelhard, 2012). In this way, EMDR is supposed to desensitize the patient to these memories and reduce their impact on drug-related behaviour (Qurishi et al., 2017).

Hase and colleagues (2008) investigated the therapeutic effects of EMDR in 30 subjects with alcohol addiction. The experimental group received EMDR sessions in addition to treatment as usual (TAU). To retrieve drug-related memories, participants were asked to recall specific situations of craving or relapsing. Following the EMDR sessions, the patients reported more reductions in alcohol craving in comparison with a control group which only received TAU ($p < .001$). Moreover, it was found that EMDR might have the potential to prevent relapse in the long-term as the reduction in craving was maintained in most participants in assessments after 1 and 6 months. However, the success in relapse prevention has to be investigated further in real life situations in which patients encounter craving-

eliciting stimuli. Currently, this study constitutes the only randomized trial for EMDR therapy with addiction patients.

Some additional support for EDMR in addiction treatment is provided by a case study of a woman with treatment-resistant gamma-hydroxybutyric acid (GHB) addiction (Qurishi et al., 2017). EMDR sessions were added to her regular therapy. At the beginning of each session, patient and therapist identified a memory representation which triggered high levels of craving, mainly positive experiences with GHB consumption. The patient was instructed to maintain the identified representation actively while making horizontal EM. Following this intervention, the patient reported less craving when recalling the previously identified experiences. Additionally, she maintained abstinence during the treatment and 6 months later at the follow-up assessment.

In another study, the effects of EM on the vividness of substance-related memories and craving was tested in a sample of smokers (Littel, Hout, & Engelhard, 2016). Participants were instructed to recall a situation or emotional state in which they gave in to the craving to smoke a cigarette. During the main

task, the experimental group was asked to think of the previously identified memory while performing EM while the control group was asked to keep the eyes fixated. Results showed a significant increase in memory vividness (d = 0.71) and craving scores (d = 0.89) following recall of craving-related memory in the control, but not in the experimental group following recall combined with EM.

DISCUSSION

The use of memory manipulation appears to have potential for the treatment of drug addiction in the future, given that it has been supported by multiple research lines. The reviewed treatments target conditioned responses and stimulus associations that play an important role in the maintenance of SUD and relapse. Furthermore, memory manipulation stands out from most of the established treatments since it seems more effective in preventing relapse (Hase et al., 2008; Lee et al., 2006; Milton & Everitt, 2012; Xue et al., 2012) Nevertheless, one should

be cautious to translate those findings into a clinical context. Studies regarding the use of reconsolidation interference and EMDR to specifically treat SUD have been scarce. The experiments that have been mentioned need to be replicated to establish the robustness of results and to discern any potential side effects.

Especially regarding reconsolidation as a treatment tool, little is known about the impact on drug memories in human subjects. So far, successful treatment with pharmacological reconsolidation disruption in humans has been limited to propranolol (Lonergan et al., 2016). The manipulation of memories of an individual with pharmacological interventions is a rather intrusive approach. Further careful testing in humans should be conducted to investigate the impact of reconsolidation treatments and to rule out that non-related memories are affected. The effects of other pharmacological agents such as Zif268 ASO should be carefully examined for addiction treatments in humans before it can be fully utilized in a clinical context. As pharmacological agents may have various

side effects, extinction and EDMR therapies have an advantage over reconsolidation strategies.

One problem of extinction in comparison to reconsolidation is that drug seeking behavior might reappear after some time following the intervention, a phenomenon known as spontaneous recovery; after relapses from abstinence; or if a CS is encountered in a new context (Torregrossa & Taylor, 2013). An effort should be made to address this issue, as it is crucial for transferring extinction into treatment in real life. Improvement in outcomes of extinction might be accomplished by alternating the context of CS exposure in sessions. EMDR has to be studied more to draw conclusions whether it prevents the reinstatement of drug seeking behaviors.

Additionally, the studies by Xue and colleagues (2012) on extinction showed that there is a limited time window in which the intervention is effective. The associations between drug effects and CS in addicts have been established a long time before treatment in repeated fashion though. Future research may attempt to improve the outcomes of extinction for SUD,

possibly by combining it with other memory manipulation treatments or TAU.

In general, the long-term effects of memory manipulation should receive more attention in addiction research. In the study by Hase and colleagues (2008), the impact of EDMR was investigated across a span of 6 months, but it would be crucial to research whether the treatment success lasted for extended periods. It is of utmost importance to conduct careful testing trials across a few years to be able to make more general assumptions about treatment success and to dissect possible side effects with certainty.

Another limitation of memory manipulation treatments is that addiction is maintained by a complex pattern of associations between various cues and drug seeking behaviours. This imposes a major challenge for manipulation treatments, as it might not be feasible to target every single association. Taylor and colleagues propose that extinction training should be conducted in drug-related contexts, but they acknowledge that this might not be practical for clinicians. Regarding this, EMDR may have an advantage in comparison to the other treatments

since it covers complete memories of situations with multiple drug cues. However, the therapist must rely on the patient's ability to identify memories that are relevant to the maintenance of addiction. This might be difficult for some patients.

Future research should attempt to increase the number of subjects and investigate the effects of memory manipulation interventions across extended time periods. Moreover, it would be an interesting direction to explore how the described treatments can be combined with other therapy forms. There are multiple well-established therapies as for example CBT that have been found to be effective in the treatment of SUD. Memory manipulation treatments might be a valuable addition to TAU. Furthermore, additional studies should try to identify factors that constitute a suitable environment for memory manipulation therapies. If the manipulation-based treatments are found to have long-lasting positive treatment outcomes and to have few side effects, then it would be reasonable to include these interventions into regular SUD therapy.

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