TARGETING DRUG MEMORY RECONSOLIDATION: A NEURAL ANALYSIS

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HIGHLIGHTS

- Addiction is a disorder of maladaptive learning and memory.
- Different limbic corticostriatal regions support drug-associated memories.
- Disrupting drug-memory reconsolidation may provide a new addiction treatment.
- Regional manipulation makes specific aspects of drug memory tractable targets.

ABSTRACT

Addiction can be conceptualised as a disorder of maladaptive learning and memory. Therefore, maladaptive drug memories supporting drug-seeking and relapse behaviours may present novel treatment targets for therapeutic approaches based upon reconsolidation-blockade. It is known that different structures within the limbic corticostriatal system contribute differentially to different types of maladaptive drug memories, including pavlovian associations between environmental cues and contexts with the drug high, and instrumental memories underlying drug-seeking. Here, we review the mechanisms underlying drug memory reconsolidation in the amygdala, striatum, and hippocampus, noting similarities and differences, and opportunities for future research.

INTRODUCTION

Addiction, a complex disease [1], can be conceptualised as a disorder of maladaptive memory [2,3] for which preventing relapse is the greatest challenge. Drug-associated memories might therefore provide a novel anti-relapse treatment target [4-6]. Disrupting drug-associated memories was not considered feasible until memory reconsolidation was rediscovered [7]. The prospect of modifying well-established memories raised the possibility that disrupting the memories driving relapse could be a novel pro-abstinence therapy. This view was supported by early studies showing that pharmacological agents ranging from protein synthesis and protein kinase inhibitors [8,9] to β-adrenergic receptor antagonists [10,11] reduced subsequent drug-seeking in rodents, if administered

while the drug memory was 'reactivated' and unstable. This instability is usually achieved by briefly presenting discrete or contextual drug-associated conditioned stimuli (CSs) in the absence of drug or, less frequently, drug in the absence of associated CSs.

Any memory-modifying pharmacological treatment would need to be administered systemically in patients. However, understanding the neural mechanisms that support drug-associated memories remains important. We have previously reviewed how initially neutral environmental CSs (such as discrete cues, people, drug paraphernalia, contextual cues) become associated with drug highs in a pavlovian manner and subsequently increase drug-seeking [4]. Drug-seeking and drug-taking themselves are supported by instrumental memories that are initially goal-directed, associating the drug-seeking action with the drug-procurement outcome, but ultimately become habitual and driven by pavlovian CSs [12]. These memories are supported by different structures within the limbic-corticostriatal circuitry. Pavlovian CS-drug memories, particularly for discrete CSs, are represented within the amygdala, while the hippocampus is required for representing drug-associated contexts. Goal-directed and habitual memories are supported by different striatal regions, with a ventral-to-dorsal striatal shift as drug-seeking becomes habitual [12]. While all these regions contribute to drug-seeking behaviour and relapse, it cannot be assumed that the same plasticity mechanisms underlie memory persistence in all regions. We review the molecular and neurochemical mechanisms underlying drug memory reconsolidation in three key regions of the limbic corticostriatal circuitry: the amygdala, striatum, and hippocampus (Figure 1).

TARGETING THE RECONSOLIDATION OF PAVLOVIAN CUE-DRUG MEMORIES IN THE AMYGDALA

The amygdala is essential for associating environmental CSs with the affective value of the drug unconditioned stimulus (US). The basolateral (BLA) and central amygdala (CeA) differ in their representation of drug-associated CSs and may be differentially required for the reconsolidation of

memories induced by CS-based and US-based reactivation procedures [13]. As CS-drug memories are potent precipitators of relapse, both the BLA and CeA are logical targets for memory reconsolidation blockade [14].

The CeA appears engaged by US-based reactivation [15]. US-based alcohol memory reactivation leads to increased phosphorylation of S6 kinase (S6K), a critical component of the mammalian target of rapamycin (mTOR) pathway controlling mRNA translation (for review, see [16]) in the CeA, but not BLA [15]. Expression of excitatory transmission proteins, including Arc, PSD-95 and the GluA1 subunit of AMPA receptors is also increased. These increases appear necessary for reconsolidation in the CeA, as preventing S6K phosphorylation via upstream mTOR inhibition, concurrent with alcohol memory reactivation, prevented subsequent reinstatement of alcohol-seeking. Interestingly, this effect was specific to alcohol, not affecting sucrose memories. This suggests alcohol may recruit intracellular mechanisms, distinguishable from natural rewards, which may be specifically targeted.

More often reconsolidation-based interventions focus on the BLA, which represents the association between pavlovian CSs and specific outcomes [17]. As for US-based reactivation in the CeA, preventing mRNA translation in the BLA, concurrent with CS-based reactivation, disrupted drug memory reconsolidation [18]. Targeting intracellular pathways upstream of mRNA translation produces similar effects. The activation of protein kinases – or suppression of protein phosphatases – regulates mRNA translation, and several protein kinases in the BLA are necessary for CS-drug memory reconsolidation. Inhibiting protein kinase A (PKA) in the BLA during CS-based memory reactivation prevented both subsequent CS-induced and context-induced reinstatement [19-21], though not drug-primed reinstatement [19]. At reactivation, activating Exchange Protein Activated by cAMP (EPac) with 8-pCPT-cAMP disrupted subsequent CS-induced reinstatement of cocaine seeking [22]. Furthermore, while increasing PKA-mediated signalling via 6-Bnz-cAMP did not enhance CS-drug memory reconsolidation [22], co-administration of 6-Bnz-cAMP with 8-CPT at reactivation

rescued the deficit produced by activating EPac, suggesting antagonist feedback between the PKA and EPac pathways. Similarly, inhibiting another protein kinase, calcium-calmodulin-dependent kinase II (CaMKII), attenuated subsequent cue-induced reinstatement [23]. However, inhibiting CaMKII during CS-drug memory reactivation did not reduce subsequent context-induced cocaine seeking [20]. Overactivation of the calcium-triggered phosphatase calcineurin during reactivation inhibited both subsequent CS- and context-induced reinstatement of cocaine-seeking [24].

At the level of immediate early genes (IEGs), *zif268* has been repeatedly implicated in drug memory reconsolidation. Knockdown of *zif268* in the BLA before a CS-based reactivation decreased the acquisition of new, flexible cocaine-seeking [25] and cue-induced reinstatement of subsequent cocaine-seeking [26]. Upstream of Zif268 expression, antagonism of NMDARs in the BLA prior to memory reactivation not only prevented the acquisition of flexible cocaine-seeking, but also reduced the expression of Zif268 [27].

Taken together, the BLA and CeA seem differentially recruited by the use of context, discrete CSs and drug USs to reactivate the drug memory. Notably, the involvement of these regions in drug-induced habitual responding changes with extended drug exposure. The BLA projects densely to the nucleus accumbens core, which itself projects to more dorsal striatal regions. With limited drug self-administration, the pharmacological uncoupling of the BLA with the dorsolateral striatum reduced cocaine-seeking, whereas CeA manipulations had no effect until drug experience was extensive [28]. Therefore, we speculate that there may also be a BLA-to-CeA shift as drug experience becomes more extensive, and a consequent shift in the efficacy of CS-based and US-based reactivation procedures to destabilise the drug memory.

TARGETING THE RECONSOLIDATION OF PAVLOVIAN CUE-DRUG MEMORIES IN THE VENTRAL STRIATUM

The striatum consists of ventral (nucleus accumbens core, NAcbC, and shell, NAcbSh) and dorsal substructures. The BLA projects densely to the NAcbC, and both the BLA and NAcbC are required for pavlovian CSs to influence instrumental responding [29]. As for the BLA, expression of *zif268* increases in the NAcbC following cocaine CS exposure [30], and phosphorylation of specific proteins in the BLA and NAcbC is altered following CS-based drug memory reactivation [31].

However, the NAcbC supports different aspects of the CS-drug memory to the BLA. Unlike the BLA [25], the reconsolidation of CS-drug memories supporting flexible cocaine-seeking does not require Zif268 in the NAcbC [32], even though NAcbC-BLA interactions are necessary for drug-associated conditioned reinforcers to support flexible cocaine-seeking [33]. Similarly, inhibiting ERK in the BLA, but not NAcbC, at reactivation impairs subsequent context-induced reinstatement of cocaine-seeking [34], though manipulations targeting the NAcbC consistently disrupt the reconsolidation of drug-conditioned place preference (CPP) memories [8,9,32, 35-38] and memories for approach to drug assessed using the runway procedure [39]. The NAcbC may be an important target for disrupting reconsolidation of general motivational properties of pavlovian CSs, alongside disruption of their sensory-specific properties by targeting the BLA.

TARGETING THE RECONSOLIDATION OF CONTEXT-DRUG MEMORIES IN THE HIPPOCAMPUS

The dorsal hippocampus (DH) is necessary for the representation of contextual information, and inactivation of the DH acutely impairs the context-induced reinstatement of drug-seeking [40]. The hippocampus has a well-established role in context-drug memory reconsolidation as measured by CPP [41-43]. For instrumental drug-seeking behaviour, the requirement for the hippocampus

appears less straightforward. Inactivation of the DH with tetrodotoxin [44] or inhibition of GluN2A-containing NMDARs or Src family kinases [45] prevents context-induced reinstatement in a reactivation-dependent manner. However, inhibiting protein synthesis with anisomycin does not [44]. Instead, protein synthesis inhibition in the BLA, coupled with contralateral inhibition of the DH in a 'disconnection' procedure, persistently reduced context-induced reinstatement [21]. This likely indicates that although the DH is required to represent the contextual aspects of the context-drug memory, it is the BLA that stores the context-drug engram.

TARGETING THE RECONSOLIDATION OF INSTRUMENTAL MEMORIES UNDERLYING DRUG-SEEKING IN THE DORSAL STRIATUM

Drug-seeking and taking rely on instrumental memories. Instrumental learning recruits the dorsal striatum, with response-outcome (goal-directed) associations depending on the dorsomedial striatum (DMS), and stimulus-response (habitual) associations on the dorsolateral striatum (DLS) [46-49]. Originally, instrumental memories were thought not to reconsolidate [50]. However, this may have been due to unsuccessful memory destabilisation. Later studies disrupted instrumental memory reconsolidation by NMDAR antagonism with a change in reinforcement contingency at reactivation [51,52], preventing subsequent stress-induced, though not CS-induced, relapse to cocaine-seeking [53]. While the NMDAR antagonist was administered systematically, we speculate that it may have affected dorsal striatal regions. This remains to be tested with local injections, or by assessing the effects of NMDAR antagonism on local reconsolidation markers such as Zif268 expression. However, it notable that knocking down *zif268* in the posterior DLS during reactivation of a stimulus-response memory only transiently reduced habit-like behaviour on a T-maze task [54]. Whether this indicates that other IEGs are important for supporting the reconsolidation of instrumental memories, or other regions compensate for the loss of the memory in the posterior DLS, requires further investigation.

CONCLUSIONS

Addiction is a disorder of learning and memory that presents many different psychological targets for disruption, including pavlovian and instrumental memories, and their interactions. Different regions support distinct aspects of drug-related memories, from the BLA supporting sensory-specific memories of drug CSs, the CeA contributing to US-based reactivation, the DH supporting contextual information, and the striatum supporting instrumental memories (Figure 1). Though there are common principles regarding the molecular mechanisms underlying reconsolidation between these different regions – e.g. the recruitment of protein kinases and IEGs – it cannot be assumed that the mechanisms are identical between all structures. This may be particularly true for the relatively understudied (in the reconsolidation literature) GABAergic dorsal striatum. Further characterisation of reconsolidation mechanisms across brain structures would not only provide insight into the degree of conservation of plasticity mechanisms, but may also allow for systemic treatments to be used to target specific brain regions where a receptor or molecular pathway is uniquely associated with reconsolidation.

This review focused upon key structures within the limbic-corticostriatal circuitry, as they relate when drug-seeking is not yet compulsive. However, the progressively habitual and compulsive nature of drug-seeking in addiction leads to changes in the reliance on different structures within the limbic-corticostriatal circuitry [12]. While it is known that systems-level reconsolidation occurs between the hippocampus and the cortex [55,56], it remains unknown whether similar systems-level reconsolidation occurs, for example, between the BLA and CeA following extensive drug experience [28], or between different striatal regions as drug-seeking transitions from goal-directed to habitual. Coupled with potential differences in the molecular pathways supporting reconsolidation in different brain regions, changes in dependence on different parts of the limbic-corticostriatal circuitry could account for apparently dynamic boundary conditions. We suggest that in addition to characterising the molecular mechanisms of reconsolidation in different brain structures, research should focus on understanding how the memories that form the targets for reconsolidation-blockade move with time.

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AUTHOR CONTRIBUTIONS

Ursule Taujanskaite: Conceptualisation; Investigation; Writing – Original Draft; Writing – Review and Editing. **Emma N Cahill:** Conceptualisation; Investigation; Writing – Original Draft; Writing – Review and Editing; Supervision. **Amy L Milton:** Conceptualisation; Investigation; Writing – Original Draft; Writing – Review and Editing; Visualisation; Supervision.

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Developing their previous research examining the reconsolidation of instrumental memories, the authors showed that disrupting the reconsolidation of cocaine-seeking memories with the NMDAR antagonist MK-801 led to a reduction in cocaine-seeking at subsequent test, but only if cocaine-associated CSs were not presented. Furthermore, while disrupting the reconsolidation of the instrumental memory reduced subsequent stress-induced reinstatement of cocaine-seeking, it did not impair drug-induced reinstatement.

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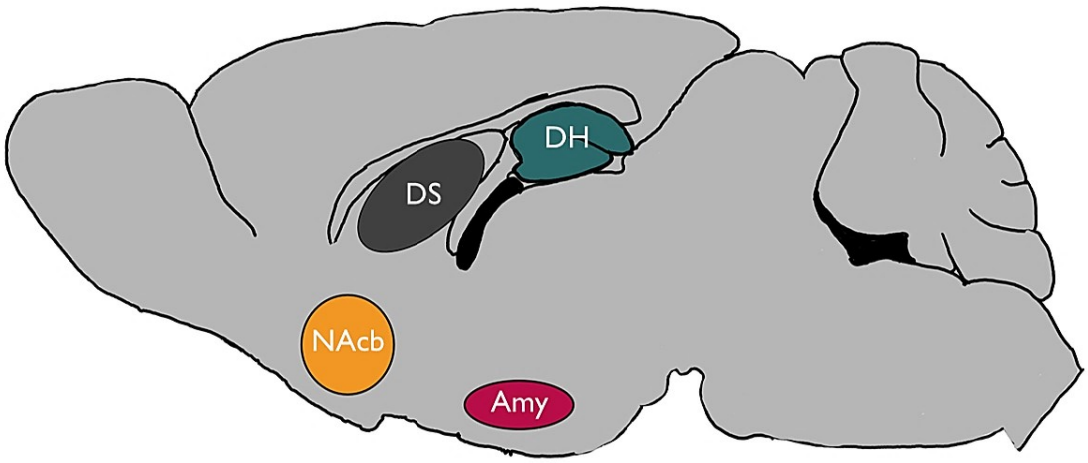
FIGURE LEGEND

Figure 1. (a) Sagittal section of the rat brain, with key locations implicated in drug memory reconsolidation highlighted. **(b)** Schematic of major connections between brain regions implicated in drug memory reconsolidation, indicating the aspect of the drug memory encoded by each region. The type of memory reactivation protocol that appears effective at recruiting each region is noted in brackets. Abbreviations: Amy, amygdala; DH, dorsal hippocampus; DS, dorsal striatum; NAcb, nucleus accumbens.

a


DH
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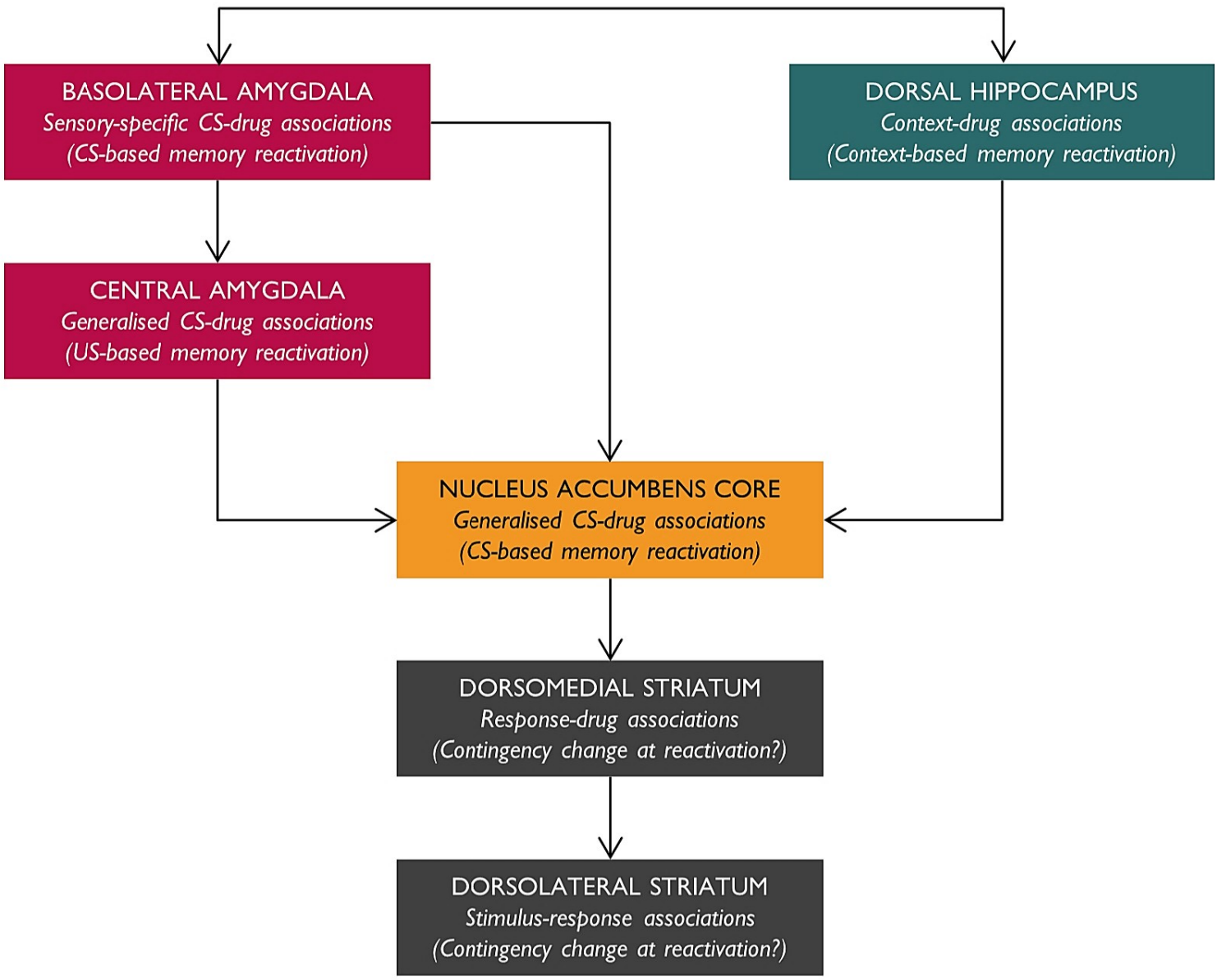
b


BASOLATERAL AMYGDALA
Sensory-specific CS-drug associations
(CS-based memory reactivation)
DORSAL HIPPOCAMPUS
Context-drug associations
(Context-based memory reactivation)
CENTRAL AMYGDALA
Generalised CS-drug associations
(US-based memory reactivation)
NUCLEUS ACCUMBENS CORE
Generalised CS-drug associations
(CS-based memory reactivation)
DORSOMEDIAL STRIATUM
Response-drug associations
(Contingency change at reactivation?)
DORSOLATERAL STRIATUM
Stimulus-response associations
(Contingency change at reactivation?)