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Integrating and fragmenting memories under stress and alcohol

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ABSTRACT

Stress can powerfully influence the way we form memories, particularly the extent to which they are integrated or situated within an underlying spatiotemporal and broader knowledge architecture. These different representations in turn have significant consequences for the way we use these memories to guide later behavior. Puzzlingly, although stress has historically been argued to promote fragmentation, leading to disjoint memory representations, more recent work suggests that stress can also facilitate memory binding and integration. Understanding the circumstances under which stress fosters integration will be key to resolving this discrepancy and unpacking the mechanisms by which stress can shape later behavior. Here, we examine memory integration at multiple levels: linking together the content of an individual experience, threading associations between related but distinct events, and binding an experience into a pre-existing schema or sense of causal structure. We discuss neural and cognitive mechanisms underlying each form of integration as well as findings regarding how stress, aversive learning, and negative affect can modulate each. In this analysis, we uncover that stress can indeed promote each level of integration. We also show how memory integration may apply to understanding effects of alcohol, highlighting extant clinical and preclinical findings and opportunities for further investigation. Finally, we consider the implications of integration and fragmentation for later memory-guided behavior, and the importance of understanding which type of memory representation is potentiated in order to design appropriate interventions.

1. Introduction

Our ability to recall past experiences represents a powerful and fundamental capacity of human cognition. The way in which we encode these experiences can have profound consequences for later adaptive and maladaptive actions. For example, how broadly will we generalize from a given experience? How readily can we update what we have learned? What cues do we need in order to evoke a feeling of fear or craving? Each of these processes requires applying acquired knowledge to new situations and is shaped by the extent to which our memories are integrated. In this review, we examine memory integration for distinct components of our experiences, or the extent to which they are bound together, at different levels of abstraction. We consider the neural and cognitive mechanisms supporting each level of integration. This framework, drawing from findings across fields and species, provides an opportunity to explain – and challenge – how stress impacts memory integration. It also builds a foundation for interpreting clinical and preclinical findings from the alcohol field, with the aim of fostering future experimental work targeting the effects of alcohol on this key mnemonic process.

We consider memory integration as a process that can occur at three levels (Fig. 1). First, for any given event, we can bind incoming sensory information to form a cohesive representation of our environment, leveraging spatial and temporal contextual information to place event features in an interpretable and meaningful space. We refer to the process of forming these distinct, discretized memories as *within-context binding* (Fig. 1B). For example, suppose a person drinking coffee and reading the morning paper on a bench witnesses an explosion. They can form links between features of that experience (coffee cup, newspaper, explosion), between those features and their environmental layout (where the bench is in the park), and their temporal characteristics (they sipped their coffee prior to opening the newspaper). Features, space, and

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time capture key dimensions along which to consider how information present during an event may be bound, offering an interpretable framework to evaluate how memories are encoded. At the next level, we can integrate across memory traces for related, but distinct events separated in time. We refer to this process as *between-context binding* (Fig. 1C). Continuing the example, this aversive event of witnessing the explosion may be linked to prior related events, like a prior time when the person purchased coffee. Finally, events can be integrated with information that is hidden, or not experienced directly. Such information includes pre-existing abstracted knowledge structures (schemas) or relevant comprehensions of how environmental variables behave in related situations (latent causes). We refer to this process as *extra-event binding* (Fig. 1D). Thus, the event of witnessing the explosion may be integrated into a broader set of associations with coffee.

This multi-level perspective provides insight into crucial embedding structures and neural mechanisms supporting the integration of information. It also helps broaden the ways in which integration or fragmentation may be influenced by stress and contribute to subsequent adaptive behavior. For example, although a long history of work indicates that stress leads to fragmented associations of features and context, or memory representations (Bedard-Gilligan and Zoellner, 2012; Brewin et al., 2010; Stout et al., 2018), emergent findings suggest that stress may enhance feature binding along with links to the underlying spatial geometry and temporal structure (Goldfarb et al., 2019; Meyer et al., 2013; Montijn et al., 2023). We discuss how stress can enhance the linking of these distinct events separated by time and promote integration with overarching abstracted knowledge or comprehension structures. These findings challenge our fundamental assumptions about the relationship between stress and memory integration, as well as the links between integration and later applications of these memories in novel situations (like generalization).

As is highlighted throughout this Issue, stress and alcohol intake are intricately and bidirectionally related. Here, we take a memory-guided approach to understanding this relationship and consider how findings regarding stress effects on memory integration may inform our understanding of distortions in alcohol-related memory. Stress and alcohol share physiological components (e.g., both elicit the release of the hormone cortisol) and can have overlapping effects on how events are remembered (for further discussion, see Goldfarb and Sinha, 2018). Such shifts in memory may profoundly impact subsequent drinking behavior. Memory has long been acknowledged to play an important role in alcohol use and relapse, with suggestions that different types of memory representations may each give rise to different addiction-relevant behaviors (Goldfarb and Sinha, 2018; Goodman and Packard, 2016; Hogarth et al., 2013; White, 1996). For example, strong memories for single alcohol-related cues can promote approach behavior or even act as reinforcers to potentiate learning new alcohol-seeking behavior, whereas strong memories for alcohol-related contexts may promote motivation and increased focus on alcohol when in those contexts (White, 1996). Although not part of the original formulation of these models, it is clear that these representations also vary in the extent to which they are distinct (e.g., remembering a single alcohol-related feature, like a wine bottle) or integrated (e.g., remembering having a drink within a specific spatiotemporal context). Thus, understanding whether acute or chronic alcohol intake facilitates certain levels of integration, perhaps informed by the stress literature, has important consequences for both fundamental mnemonic mechanisms driving maladaptive drinking and clarifying which

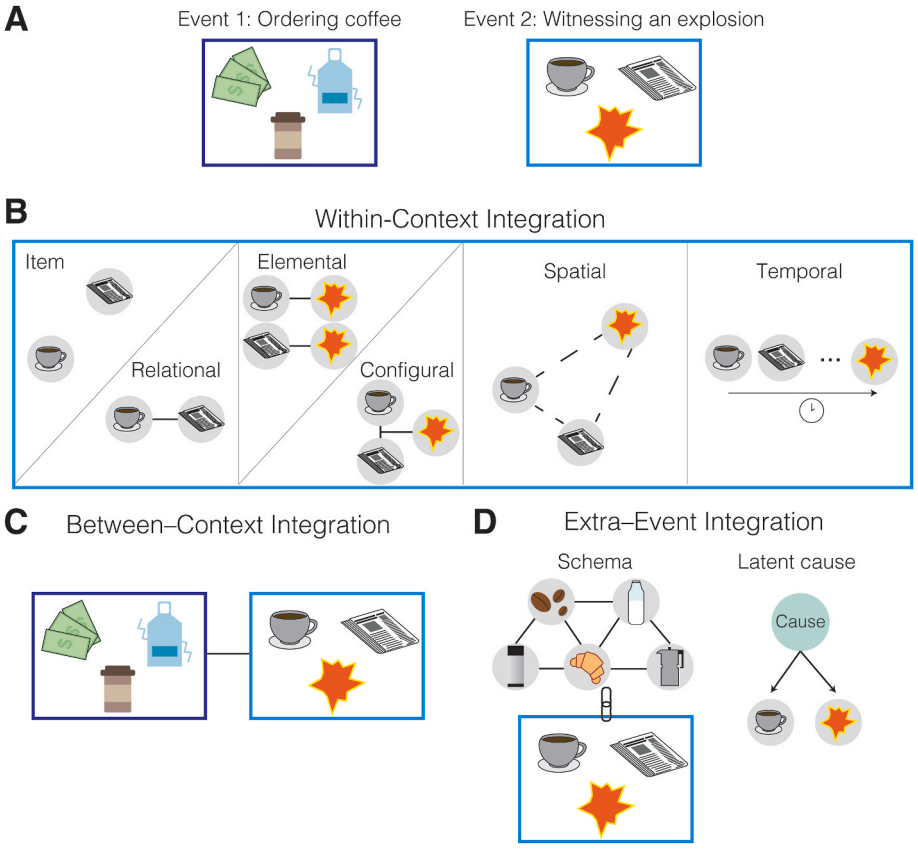

Fig. 1. Schematic of different levels of integration. **A,** Illustration of two events: one in which a person purchases coffee at a shop, and another in which the person witnesses an explosion while drinking a coffee and reading the morning paper. **B,** Examples of different ways that components of this experience can be integrated. These include more disjoint representations (item, elemental) as well as integration between features (relational, configural) and with the underlying spatiotemporal architecture (see Section 2). **C**, Linking of discrete events separated in time (Section 3). **D,** Integration of event with pre-existing knowledge or comprehension structure (Section 4).

representations should be targeted clinically.

In the following sections, we provide brief overviews of each level of integration, highlighting key experimental and computational examples, and neural mechanisms supporting these processes. We then discuss evidence for stress effects on each level of integration, focusing on the initial formation and consolidation of these representations. Based on the available literature, we chose to embrace a broad view of "stress" and incorporate findings from laboratory-based stress induction procedures, stress-related clinical populations (particularly post-traumatic stress disorder, PTSD), and experiences incorporating negative or highly aversive content. As there has been relatively little work exploring these questions in alcohol, we conclude each section with a consideration of implications for understanding alcohol, reviewing extant empirical findings from both acute and chronic alcohol exposure as well as clinical observations that may be benefited by this framework.

2. Within-context binding

Let us return to the situation illustrated in Fig. 1A, in which a person witnessed an explosion while drinking coffee and reading the newspaper. We consider each of these sensory inputs: the smell of the coffee, the newspaper, and the explosion itself as individual features of this event (Fig. 1B). At the simplest level, the person might remember features as individual *items*; for example, a sense of familiarity with the coffee cup. Beyond encoding individual items, the person can form more complex associations between multiple features (e.g., the coffee cup and the newspaper). The language describing such between-feature associations varies by field. In the associative learning literature, these fragmented *item* representations are contrasted with complex multi-feature *relational* associations (Davachi, 2006). In the threat learning literature, there is a focus on the links between sensory stimuli and salient outcomes or reinforcers (in our example, the explosion). Here, more fragmented representations are *elemental*, with singular feature-outcome associations (e.g., coffee-explosion and newspaper-explosion) that are separate and independent (Acheson et al., 2012; Rudy et al., 2004). More integrated representations are *configural*, with a coherent set of multiple features bound into a unified compound (Melchers et al., 2008), and it is this new compound that is bound with the reinforcer (e.g., coffee-newspaper is bound together and associated with the explosion (Honey et al., 2014; Rudy et al., 2004). We describe both sets of terms to frame relevant literature across fields (with threat learning dissociations particularly important with respect to PTSD; see Sections 2.1, 4.1) rather than to argue for the uniqueness of "reinforcers" compared to other sensory features. Framing memory representations in this way also serves to elucidate how neurocognitive mechanisms underlying learning may be differentially affected by stress in a fundamentally integrative or fragmentary manner. For example, forming *relational* rather than *item* memories corresponds to greater integration, just as *configural* representations are more integrated than simple *elemental* associations (Section 2.1, Table 1).

There is extensive empirical evidence to support differentiable neural systems underlying the encoding of individual features (items) versus associations between them (relational/configural binding). Encoding individual items appears to be most strongly represented in the perirhinal cortex, which may support both surface level features (e.g., blue) and higher level concepts (e.g., tasty; Davachi, 2006; Tompary et al., 2015). On the other hand, the hippocampus has been strongly implicated in relational binding. Convergent afferents from cortex and the intrinsic circuitry of CA3, involving high recurrency across excitatory cells, positions the hippocampus to rapidly encode associations between inputs in service of forming relations between features (Eichenbaum, 2004; Henke, 2010; Rolls, 2013). A parallel distinction may be made in the circuitry underlying threat learning. Here, the basolateral amygdala (BLA) has been strongly implicated in the formation of simple elemental associations between individual features and the reinforcer or outcome, whereas the hippocampus is theorized to form more relationally complex configurations of multiple features and the reinforcer (Fanselow and LeDoux, 1999; Rudy et al., 2004; Stout et al., 2018). These amygdala-driven elemental and hippocampal-driven configural representations may compete during encoding (Fanselow and LeDoux, 1999).

Table 1
Summary of stress effects for each level of integration.

Integration Level	Stress Effect on Integration	Primary Evidence		
		Stressor Type	Key Memory Finding	Citation
Within-Context	Enhance	CPT	Enhanced recognition of salient word/image pairs ↑ *relational*	Goldfarb et al. (2019)
		SECPT	Enhanced recognition of images encoded in room with stressor ↑ *spatial*	Sazma et al. (2019)
		SECPT	Enhanced recall and ordering of unique event images based on temporal sequence ↑ *temporal*	Montijn et al. (2023)
	Impair	Negative stimulus	Impaired recognition of negative item/neutral item pairs ↓ *relational*	Bisby and Burgess (2013)
		SECPT	Reduced skin conductance response to item-scene pairings that previously predicted shock ↓ *configural*	Drexler et al. (2018)
Between-Context	Enhance	Foot shock	Greater neural ensemble overlap and similar fear responses for high-shock and prior contexts ↑ *contextual*	Zaki et al. (2023)
Extra Event	Enhance	Modified TSST	Enhanced free recall for words from same schema as stressor ↑ *schema*	Smeets et al. (2007)
		PTSD	More likely to assign conditioning and extinction events to the same (singular) LC↑ *latent cause*	Norbury et al. (2021)

In addition to linking features to each other, features may also be integrated into their underlying *spatiotemporal context*. In the spatial domain, features can be situated within a coherent and stable spatial geometry, each bound to distinct locations. The spatial component of event memory is perhaps most apparent at retrieval; a mental reconstruction of a past event requires the appropriate placement of distinct objects in specific places in the environment (Bird and Burgess, 2008). A rich history of spatial memory in rodent models suggests hippocampal and entorhinal cortical involvement in encoding space (Hafting et al., 2005; O'Keefe and Dostrovsky, 1971), with parallel findings in humans (Ekstrom et al., 2003). The spatial quality of recalled information in human event memory may rely on reciprocal connections between hippocampal CA1 ("place cells") and neocortical ensembles (storing feature information) that together bind features to space (Bird and Burgess, 2008). The hippocampus may also serve a more domain-general binding mechanism, linking object identity (perirhinal cortex) with spatial context information (parahippocampal cortex; Davachi, 2006; Diana et al., 2007). By both accounts, hippocampal physiology provides a critical functionality in binding featural content to a spatial structure (Henke, 2010). We note that formulations of configural or relational encoding typically do not include the spatial environment, instead focusing on links between features (Acheson et al., 2012). Whether spatial coding is fundamentally different or an

instantiation of such relational binding processes is the subject of ongoing debate; nevertheless, considering this dimension of within-context binding provides further insight into whether stress promotes fragmentation or integration (see 2.1).

In the temporal domain, organizing information based on how it unfolds over time is a critical component of event encoding and recall (Eichenbaum, 2014; Tulving, 1972). The key role of temporal information are evident in effects like recency (enhanced memory for recent stimuli) and contiguity (facilitated recall for stimuli when cued with a temporally proximal stimulus; Howard and Kahana, 2002) as well as through sequential memory paradigms (DuBrow and Davachi, 2014). Recalling specific sequences of sensory information is highly conserved across species (Allen et al., 2014; Devito and Eichenbaum, 2011; Jenkins and Ranganath, 2010; Templer and Hampton, 2013). Thus, time may serve as a crucial embedding structure or architecture for binding features as they occur. As with featural and spatial binding, cortical and hippocampal contributions are theorized to play essential roles in temporal binding. For example, a slowly changing internal temporal context signal in prefrontal-cortical regions may be bound with featural information in the hippocampus to support memory (Polyn and Kahana, 2008). More recently, Buzsáki et al. (2022) posited that sequences of hippocampal assembly firing may provide a neural substrate for content-limited sequential ordering of place or events, acting as a pointer that concatenates fragmented representations of information stored throughout neocortex (Buzsáki et al., 2022).

2.1. Influence of stress

Extant research on stress and within-context binding appears to point in opposite directions (Table 1). Evidence from both the associative and threat learning literatures suggests that stress and negative emotionality lead to fragmentation, rupturing within-context binding. For example, when encoding a negative item and a neutral scene, there is robust evidence that people remember the (salient) negative item but forget the neutral scene (Bisby and Burgess, 2013, 2017), with the negative stimuli disrupting coherence dependency (Bisby et al., 2018). These discrepant effects of negative affect are posited to occur via uneven effects on hippocampus and amygdala (Bisby et al., 2016).

Theoretical models based on threat learning also propose that extremely stressful situations will prioritize fragmented memories, with a bias toward elemental rather than integrated configural representations. This is frequently considered in the context of PTSD, motivated in part by neurobiology: one known feature of PTSD is impaired hippocampal function as well as circuits involved in context processing more broadly (Liberzon and Abelson, 2016). Thus, impairment of this system may result in an overreliance on elemental rather than configural representations (Acheson et al., 2012; Rudy, 2009; Sutherland and Rudy, 1989). At the neural level, the hippocampus may serve a domain-general relational binding mechanism, with PTSD theorized to lead broad deficits in integration of "foreground cues" (features) to the "background" contextual features (Lambert and McLaughlin, 2019). One study found that direct infusion of glucocorticoids into rodent hippocampus led to elemental rather than configural threat memory (Kaouane et al., 2012). Trauma may also predispose the formation of item-level memories (Bisby et al., 2020) and lead to impoverished integration of the details of the event into the broader (or background) contextual features of its occurrence (Ehlers and Clark, 2000). Indeed, acute stress exposure in the laboratory was associated with the expression of elemental but not configural threat learning in experiments investigating fear conditioning and extinction (Drexler et al., 2018; Simon-Kutscher et al., 2019). Thus, stress may not affect elemental or configural encoding *per se,* but rather bias which of the two is more likely to be formed or recalled.

Such use of fragmented rather than integrated within-event representations may relate to gaps in memory for traumatic events (Brewin, 2011) and also help explain the tendency in PTSD to overgeneralize fear responses to similar, neutral stimuli in safe contexts (Acheson et al., 2012; Stout et al., 2018). That is, because the fear memory is fragmented, each elemental association may individually elicit fear, even in a safe context. For example, the smell of coffee alone may be sufficient to activate the explosion association and thus a fear response. In addition to laboratory models above, there is evidence of memory fragmentation from analysis of trauma narratives (see Foa et al., 1995 for an early example). For example, the degree to which trauma memories were coded as "disorganized" or "incoherent" (reflecting, in part, memory uncertainty, repetition, and lack of temporal integration) was higher in individuals with PTSD, with higher disorganization also predicting later development of PTSD (Brewin, 2016; Halligan et al., 2003; Jones et al., 2007). However, we note that evidence for fragmentation in trauma narratives is mixed (Bedard-Gilligan et al., 2017; O'Kearney and Perrott, 2006; Rubin, 2011; Rubin et al., 2008).

In contrast, recent laboratory findings suggest that stress and stress-related hormones may potentiate feature binding. For example, exposure to acute stress before learning strengthened memory for associations between features (i.e., relational binding), particularly for stimuli that participants found to be emotionally arousing (Goldfarb et al., 2019). Stronger memory for arousing feature associations also occurred with direct administration of hydrocortisone, and this benefit was associated with hydrocortisone-induced enhancement of intra-hippocampal connectivity (Sherman et al., 2023a). Similarly, memory contextualization was positively associated with acute stress-induced cortisol responses (van Ast et al., 2014). Examining neural representations using fMRI revealed that patterns of brain responses associated with different items become more similar, or "bound together", when the items were encountered under stress (Bierbrauer et al., 2021); see Section 3 for further discussion of pattern similarity). Indeed, even some models of PTSD propose that enhanced binding between stimulus features within a traumatic event may underly later involuntary re-experiencing (Ehlers and Clark, 2000).

There is also evidence that stress can enhance spatial context binding. For example, acute stress enhances memory for information encountered in the same spatial context, but not in a different context (Sazma et al., 2019; but see Riddell et al., 2023) for how this may differ depending on whether stress occurs before or after encoding). In addition, the ability to learn spatial contexts was enhanced with aversive images (Szekely et al., 2017; Zinchenko et al., 2020) and elevated stress-induced cortisol responses (Meyer et al., 2013; but see Meyer et al., 2020). Similarly, contextual threat conditioning was amplified by stress in rodents (Sandi and Pinelo-Nava, 2007; Shors, 2006). Stress-induced enhancements of spatial contextual binding are also supported by changes in neural function at the single-cell and population level. One study found that acute stress enhanced spatial encoding, expressed by computational models revealing increased spatial information contained in CA1 pyramidal place cell firing as well as sharper place cell tuning (reflected by lower sparsity; Markus et al., 1994; Tomar et al., 2021). Stress may also affect oscillatory activity in hippocampal ensembles; acute immobilization stress in rodents enhanced phase locking of single-cell firing, a critical component of the hippocampal temporal code that improves place encoding accuracy (O'Keefe and Recce, 1993; Tomar and McHugh, 2022; Tomar et al., 2021).

Finally, emergent evidence suggests that stress may enhance temporal context binding. For example, one consequence of learning a temporal sequence is that this can be generalized (e.g., your morning routine of making coffee, answering emails, and then driving to work has a similar temporal structure for each work day; Bellmund et al., 2022). Recent work indicates that acute stress can enhance generalization of such temporal structure between sequences in humans, while having no significant effect on the memory of the sequence itself (Montijn et al., 2023), suggesting that stress may facilitate integration of event features with their underlying temporal context. In another experiment, two groups of participants were exposed to acute stress or a control condition, were asked to memorize examples of short (300ms) and long (900ms) stimulus presentations, and then to classify whether

novel stimuli were more similar to this short or long interval (Cellini et al., 2023). Participants exposed to acute stress performed better on this task, suggesting better integration with these stored temporal representations. Thus, these results suggest that stress enhanced the integration of these distinct memory traces with each temporal gap. However, other reports indicate either no significant stress effects on spatiotemporal binding (Zerbes and Schwabe, 2019) or even the opposite pattern. A recent study showed that exposure to shock while viewing a sequence of scene images led to amplified memory for single scenes, but reduced priming effects between adjacent scenes, indicating less temporal binding (Grob et al., 2023a). This could be due to the fact that shocks were associated with individual scenes (indeed, participants were instructed that incorrect responses to a given scene would result in shock delivery), which may have led to the relevant "event" being a single item rather than a sequence.

In summary, although prevailing narratives posit that stress promotes memory fragmentation (especially in the PTSD literature), it is evident that there are situations in which stress enhances both featural and spatiotemporal within-context integration (Table 1). Specifically, stress can promote more complex feature binding rather than single item encoding, and can enhance integration of features into the spatiotemporal context in which they occurred. Although this discrepancy may in part be due to distinct methodological approaches, it also echoes earlier findings about seemingly contradictory effects of emotional arousal on memory integration. Thus, arguments applied to explain divergent effects of arousal on integration – namely, that binding will be enhanced for "whatever is considered to be an integral component of the emotionally arousing object" (Mather, 2007), or is more broadly considered task-relevant (Clewett and Murty, 2019) – may apply to considerations of stress effects as well. Further research is needed to understand the boundary conditions under which stress will promote within-context integration or fragmentation. The magnitude of stress, as well as whether the stress is intrinsic to or outside of the experience, may play important roles here (Goldfarb, 2019). Another avenue is to consider integration beyond what is immediately happening in the present moment. Specifically, integration between events separated in time (Section 3) and with generalized knowledge structures (Section 4) may provide insight into the conditions under which stress binds or ruptures mnemonic representations.

2.2. Implications for alcohol

To date, most studies of drinking-related memory biases have focused on the ability to remember individual features in the short-term. These studies have reported preferential encoding of alcohol-related items among individuals with alcohol use disorder (AUD; Franken et al., 2003; Fridrici et al., 2014; Klein et al., 2013). Although these findings appear consistent with a bias toward fragmented memory formation, these studies did not assess within-context binding.

By using a task that allowed us to measure long-term memory for both individual items and trial-unique associations between features, we could directly test whether individuals with AUD formed fragmented or integrated memories. Strikingly, despite having overall lower IQ and worse memory for individual items, we found that participants with AUD had significantly better memory for alcohol/scene associations than did social drinkers, consistent with enhanced within-context binding for these alcohol-related experiences (Goldfarb et al., 2020). This bias was particularly pronounced for alcohol/scene pairs that participants perceived as emotionally salient, similar to the effects of acute stress on feature binding reported above. The observed selectivity of enhanced within-context binding for (salient) alcohol-related events may explain why past investigations of associative binding for neutral stimuli did not find a benefit in individuals with AUD (De Rosa and Sullivan, 2003). Intriguingly, we were able to mimic the bias toward enhanced memory for salient alcohol/scene pairs in social drinkers by administering oral hydrocortisone prior to encoding (Harris et al., 2024). In both studies, within-context binding for alcohol-related events — but not memory for individual alcohol-related features alone — predicted subsequent drinking.

Other cross-species work indicates that alcohol history may potentiate within-context integration. For example, re-exposure to a context in which alcohol was available has been shown to reliably reinstate alcohol seeking in rodents, even if cue/alcohol associations had been extinguished (Crombag et al., 2008; Valyear et al., 2017). There is complementary evidence from humans for tight integration of contexts with drug use episodes, although this comes from the tobacco literature. In this study, both proximal (directly paired with actual smoking behavior, e.g. a lit cigarette) and distal (not directly paired, e.g. the environmental context) cues could elicit craving in smokers, suggesting that the context and features of smoking episodes were tightly integrated (Conklin et al., 2008). Highlighting the facilitatory effects of past alcohol use on context integration, chronic ethanol exposure potentiated contextual threat memory in rodents (Smiley et al., 2020).

Finally, acute alcohol administration may also modulate within-context binding, although these findings are more variable (Soderlund et al., 2007; Wetherill and Fromme, 2011). For example, low, but not high, doses of ethanol enhanced contextual threat memory in rodents (Gulick and Gould, 2007) and differentially impacted feature binding in humans (Bisby et al., 2010), with the timing relative to encoding also shaping feature binding (Doss et al., 2018; see Shields et al., 2017 for similar findings of acute stress effects over time). There is also preliminary evidence for alcohol-induced alterations in temporal binding in humans (Brown et al., 2010).

Together, by facilitating within-context binding, alcohol consumption may potentiate the integration of alcohol with its associated context, thus driving future intake in such contexts (Bornstein and Pickard, 2020; Kutlu and Gould, 2016; White, 1996). Although there is a need for further research in this area, the above studies provide suggestive evidence that both stress and alcohol use have the potential to enhance within-context binding, particularly for emotionally salient experiences, with important consequences for later behavior.

3. Between-context binding

In addition to linking information *within* an experience, we can also integrate *between* multiple events (Fig. 1C). These events can be temporally contiguous (e.g., sequential occurrences, like navigating from the train station to your new apartment) to more dispersed, occurring hours or more apart (e.g., attending lectures from your usual instructor and a substitute teacher in the same room; Clewett et al., 2019). Extracting distinct, but temporally contiguous, events from ongoing continuous experience may be achieved through a process of event segmentation where factors such as rapid context shifts induce mental boundaries (DuBrow and Davachi, 2013). The cognitive and neural mechanisms that link such events occurring sequentially as well as those remotely (in time) provide a useful perspective to understand how stress and alcohol promote integration or fragmentation (Sections 3.1-3.2).

One way that contiguous, but distinct, events may be integrated is through a common underlying goal or narrative structure. This theory posits that deliberative top-down processes may function to preserve temporal context integration between successive events (Clewett et al., 2019; DuBrow et al., 2017). For example, despite the rapid context changes you may encounter between the train station and your apartment, you may still integrate these distinct contexts into a singular coherent memory in the service of the goal of navigating home. In both rodents and humans, events that occur close together in time are more likely to be integrated than those that are farther apart (Cai et al., 2016; Rashid et al., 2016; Yetton et al., 2019), but memory integration also allows similar events separated by vast temporal distances to be bound together. This capacity represents a critical and adaptive form of between-context binding (Schlichting and Preston, 2015), and can be

measured using higher-order conditioning paradigms (Gostolupce et al., 2022). For example, seeing willow tree growing near a pond, then encountering a crocodile in a pond, may lead the fear of ponds to spread to willow trees (a process known as sensory preconditioning). The likelihood of integrating a previously formed memory with a novel situation is enhanced by a variety of factors including the memory representations being more distributed throughout the brain and conscious recollection of the previous memory (Kumaran and Ludwig, 2013; Schlichting and Preston, 2015). Thus, integration at this level is thought to support flexible knowledge updating and allow experiences to be applied to novel situations.

Powerful evidence for the idea that distinct memories can become integrated in the brain comes from nonhuman animal studies of sparsely distributed and interconnected cellular assemblies. These are thought to represent "engrams", event-specific neural signatures activated when an experience occurs and again when it is recalled (Josselyn and Tonegawa, 2020). For example, a landmark study by Liu et al. (2012) demonstrated that optogenetic activation of an ensemble of neurons that were active during threat conditioning was sufficient to induce freezing behavior, suggesting that the memory was stored in that ensemble (Liu et al., 2012). Thus, the integration of distinct events may result in overlapping cellular assemblies. This process of memory linking via overlapping ensembles can be promoted by locus coeruleus-CA1 projections (Chowdhury et al., 2022) and is associated with co-allocation of dendritic spines (Sehgal et al., 2021). These ensembles have been identified in distributed areas, including hippocampal subregions, amygdala, and prefrontal cortical regions (Abdou et al., 2018; Lavi et al., 2023; Roy et al., 2022). For example, hippocampal ensemble overlap in CA1 was associated with integration of memories for contexts separated by many hours (Cai et al., 2016), whereas ensemble overlap in BLA linked memories for distinct tone/shock pairings, allowing extinction to generalize from one tone to the other (Rashid et al., 2016).

Although human brain studies using fMRI do not enable the identification of cellular ensembles, unique memory traces can be identified via patterns of signal across voxels; for example, multi-voxel pattern classification algorithms have been leveraged to separately decode memory for newer (target) vs older (competing) stimuli in an associative learning task (Kuhl et al., 2012). There is evidence that training participants to recapitulate a pattern of activation associated with a threatening event promotes extinction, indicating that re-activating that brain pattern had a similar effect to retrieving the threat memory (Koizumi et al., 2016). Thus, similar to overlapping ensembles in rodents, more similar (that is, more highly correlated) neural activation patterns have been taken as evidence for integration in humans. Regions such as hippocampus and vmPFC have been shown to have more similar activation patterns for memories that share common associates (Schlichting et al., 2014, 2015; Schlichting and Preston, 2015) or overlapping features (particularly after a period of consolidation; Tompary and Davachi, 2017). Representational similarity of hippocampal activation across different contexts may serve as the neural substrate for temporal encoding spanning context changes. Further, the stability of hippocampal activity may also serve a critical function in maintaining order of information separated by event boundaries (Ezzyat and Davachi, 2014).

Highlighting the importance of communication between hippocampus and PFC for integration, functional coupling between vmPFC and hippocampus tracked formation of integrated memories (Zeithamova et al., 2012). Increased functional connectivity between these regions was also associated with serial learning of sequences of visual stimuli (DuBrow and Davachi, 2016), and damage to either hippocampus or PFC in mice resulted in loss of learned odor sequences in rodents (Devito and Eichenbaum, 2011). It is theorized that similar hippocampal/PFC binding mechanisms associated with linking temporally contiguous events are responsible for binding temporally disparate events as well (Clewett et al., 2019).

3.1. Influence of stress

As we have argued elsewhere, stress may be particularly well-suited to promote the gradual extraction of commonalities and integration across experiences (Sherman et al., 2023b). There is compelling evidence from nonhuman animal models that stress facilitates between-context binding (Table 1). In one such experiment, rodents were exposed to two contexts, two days apart. The first was affectively neutral (non-shock context) and the second included an electric shock (shock context). Critically, it was the animals who were exposed to a more stressful aversive event (high shock) in the shock context who went on to show greater freezing and greater ensemble integration with the non-shock context, thus demonstrating stress-induced facilitation of event binding across days (Zaki et al., 2023). In a similar design, Roozendaal and Mirone (2020) exposed rats to non-shock followed by shock contexts (here only 1–2 min apart), with the shock context exposure followed by injection of a stress-related agent (Roozendaal and Mirone, 2020). They found that post-encoding administration of corticosterone led to increased threat responses in both the shock and non-shock contexts. Although they did not assess whether this was driven by integration of the memories for these two contexts, they did demonstrate that threat responses were only elevated for those shock and non-shock contexts and did not arbitrarily generalize to a novel context (similar to the behavioral findings indicative of integration from Zaki and colleagues). Notably, Roozendaal and Mirone further demonstrated that administration of an adrenergic agent only increased threat responses in the shock context, and not the non-shock context (Roozendaal and Mirone, 2020). These findings suggest that distinct neuroendocrine components of the stress response may have divergent consequences for between-context binding.

Although there is less work on stress and between-context binding in humans, there are indications that threat learning leads to changes in memory for other related events. In one such study, participants viewed images of animals and tools. Then, shock electrodes were affixed and participants learned that images from one of these categories were associated with shock. After a delay, memory for images from the first (pre-conditioning) event were strengthened, but only if they were part of the category that was later paired with shock (Dunsmoor et al., 2015a; Hennings et al., 2021). This enhancement was associated with greater neural reinstatement of the first event during conditioning as measured by patterns of activation during the fMRI scan, potentially suggestive of greater integration between these events (Clewett et al., 2022). Finally, one recent study showed that stress promoted the formation of integrative links between experiences. After encoding a series of events A, B, and X, participants learned that events A and B were part of the same narrative. One week later, participants exposed to stress prior to learning were better able to remember that A and B belonged together (although they appeared to use different neural mechanisms to support this integrative knowledge compared to participants without stress; Grob et al., 2023b).

These facilitating impacts of stress and threat learning on binding to prior events have been framed in terms of the tag-and-capture model, which poses a neurobiological process through which experiences may be bound together in time. In this framework, a stressful occurrence may function as a "potentiating event" whereby neighboring events occurring either before or after, are bound together to form an integrated memory trace (Dunsmoor et al., 2022b). This is also consistent with conceptualizations of stress itself as a learning event, one which can potentiate synapses from related experiences, thus resulting in enhanced, linked memory (Cadle and Zoladz, 2015; Diamond et al., 2007). For example, in the context of PTSD, details of events leading up to the traumatic memory are often bound with the traumatic event itself (Dunsmoor et al., 2022a). Indeed, compared to individuals without PTSD, patients with PTSD were more likely to provide details from other episodes when recounting a stressful negative event (Memel et al., 2021).

In summary, both strong empirical work in animal models, as well as emergent findings in humans, point towards stress-induced enhancements in coupling distinct events. Work in rodent models suggest that distinct neuroendocrine components of the stress response may have differential effects on the extent to which events are bound, although further work is needed to clarify and test these findings in humans. In parallel, functional neuroimaging studies in humans indicate that threat learning promotes stronger memory and neural reinstatement of related events, strongly indicating an integration between multiple distinct contexts. The tag-and-capture model provides an attractive explanation for these effects and suggests that stress itself may serve as an intrinsically potentiating event. Together, these findings may explain how features in contexts temporally separated from a traumatic event may themselves elicit fear responses.

3.2. Implications for alcohol

Alcohol may also potentiate integration across contexts. From the clinical literature, there is evidence that situations which potentiate craving or relapse can be several steps removed from actual use-paired experiences. For example, in a recent thematic analysis of craving-inducing scenarios, a common environmental factor across substances including alcohol was money or payday. In an example from a patient with cocaine use disorder: "You have been working all week. You start thinking about how you to [sic] spend the money. Your heart beats faster. You know you want to get high." (Haeny et al., 2023). From an event memory perspective, payday is not a feature of the substance use experience (in contrast to, for example, a drinking companion or a wine glass). Instead, the capacity for this idea of income to induce craving requires binding between multiple events in addition to the substance use experience (e.g., being at work and receiving a check, bringing the check to an ATM to take out cash, taking money to a liquor store, purchasing liquor, consuming alcohol). Thus, the potential for even this many-context-removed cue of payday to elicit craving may reflect an increased tendency to integrate drug use events with other experiences. Similarly, common relapse-inducing situations can involve determinants that were not directly experienced as part of the substance use event (Marlatt, 1996).

Consistent with this clinical intuition, preliminary rodent evidence supports the idea of alcohol promoting integration of adjoining events. In one study, rodents performed a sequential learning task in which several events occurred prior to the presentation of alcohol. By integrating these distinct events, they developed a chain of behavioral responses promoting alcohol seeking (Cofresi et al., 2019). There is also preliminary evidence in juvenile rodents that moderate doses of ethanol facilitate sensory preconditioning, which requires linking across separate events that share a common associate (Chen et al., 1992). Together, these findings suggest that alcohol, like stress, may be associated with greater binding across contexts. Further work is needed to test this hypothesis directly.

4. Extra-event binding

In addition to linking information within an event and between distinct events, a key feature of using memory to guide adaptive behavior involves integrating events with information that is hidden, or not directly experienced. Two principal modes of extra-event information relevant to memory encoding are generalized, abstract knowledge structures, or *schemas*, and inferred rules that explain the environment, or *latent causes* (Fig. 1D). Here we consider how individual events are integrated with these previously learned schemas and inferred latent causes.

Schemas are knowledge structures that span multiple events, representing concepts, ideas, or commonalities extracted over potentially vast timescales (Gilboa and Marlatte, 2017; Richards et al., 2014). In psychology and neuroscience research, schemas are variously conceptualized as interconnected neocortical representations and mental templates that reflect concepts, categories, narratives, and statistical regularities (Gilboa and Marlatte, 2017; van Kesteren et al., 2012). A common underlying principle is that of an interconnected associative network that reflects information collated and abstracted from multiple individual events as well as outside knowledge. For example, a schema for "restaurant" could include the order in which events typically occur, experienced over many separate restaurant visits (enter, sit down, order food, food arrives; (Baldassano et al., 2018). Key features of these networks include retention of core (or repeated) content, but not incidental or idiosyncratic information.

Having an established schema can strongly influence encoding of new experiences (van Kesteren et al., 2012; Xue, 2018). Typical designs in humans probing this process leverage "congruency", or the extent to which novel information matches expectations arising from schemas. For example, novel associations that were schema-congruent (e.g., farm-tractor-farmer) were better recalled and recognized than associations which were schema-incongruent (e.g., farm-tractor-lawyer; (Frank et al., 2018). These benefits have been associated with greater ease of integration (Bein et al., 2015). Similarly, when learning associations between items and locations, locations were better remembered when they were consistent across items from the same category (Tompary and Thompson-Schill, 2021). These results suggest that schemas support flexible integration of new information with related nodes within the schema network. Schema congruence can also modulate the neural representations of new episodes, with congruent content associated with an earlier onset of memory-related neural activity (Packard et al., 2017) in mPFC days after encoding, suggesting enhanced memory-integrative neural processes (Audrain and McAndrews, 2022). Such designs differ from explicit instructions for participants to engage in "deep", elaborative, or semantic encoding (although it is notable that neural correlates of such processes may also be facilitated by stress; Kamp et al., 2019) in that they probe the extent to which participants incorporate their own pre-existing knowledge networks when encoding, consolidating, and retrieving novel information.

Although schemas are informed, and updated by, memories for individual experiences, there are substantial differences in their neural representation and characteristics. Reflecting their inherently broad informational content, schemas are thought to be distributed throughout, and rely heavily on interactions between PFC, OFC, angular gyrus and hippocampus (Gilboa and Marlatte, 2017). This is dissociable from memory for a single experience, which is thought to be supported by the hippocampus (see Section 2). Qualitatively, neocortical schemas are more "gist-like," lacking spatial and event-specific contextual information (Hardt and Nadel, 2018; Hardt et al., 2013; Rosenbaum et al., 2000). This may be driven in part by the hippocampus, which is thought to mediate the integration of neocortical contents via offline hippocampal reactivations, eventually rendering hippocampal storage of situation-specific information less essential in the network (Hardt et al., 2013; Richards and Frankland, 2017). In contrast, hippocampal-dependent episodic memories are more vivid and rich in detail (Bonnici et al., 2012; Sekeres et al., 2018). Supporting these distinction computations, viewing a movie in a scrambled order led to reduced schematic but unimpaired feature memory (van Kesteren et al., 2010). Showing that schema information is also represented, narratives with distinct features but a shared schema had consistent neural representations across participants (Baldassano et al., 2018). The neural mechanisms by which episodes transform into schemas, and the persistence (or lack thereof) of hippocampal representations along with distributed neocortical representations, is an active area of research (McClelland et al., 1995; Nadel and Moscovitch, 1997; Nadel et al., 2000; Squire et al., 2015). Despite the debates surrounding the precise roles of cortico-hippocampal interactions, general consensus emphasizes the importance of neocortical representations that collectively encode schemas and provide a functional template that facilitates the addition of schema-congruent novel information.

In addition to schemas, experiences can also be bound to an inferred hidden "state", or an internal representation of a situation which can be used to guide behavior (Langdon et al., 2019). Borrowing from the associative and reinforcement learning literature (Courville et al., 2005), such latent variables are not part of the immediate experience or event. Rather, in some cases they represent underlying rules or "causes" that one believes are responsible for generating the observed features in the environment (Gershman et al., 2015). In the simplest case of a rodent experiencing a tone followed by a shock, instead of binding the shock directly to the tone, the rodent infers that there is some underlying rule that governs why they may or may not be shocked on any given trial, an ability referred to as latent cause inference. The true latent cause in this case would be the stage set by the experimenter (Gershman and Niv, 2010). The appeal of this account is that it provides an explanation for phenomena like spontaneous recovery, or the return of threat responses after extinction, that are puzzling under other theoretical accounts of associative learning (Gershman et al., 2015). In a traditional framework, the process of extinction (for example, repeatedly experiencing a tone but no shock) should reduce the rodent's expectation of the shock when presented with the tone; thus, there should be no cause for the return of fear (i.e., spontaneous recovery). From a latent cause (LC) standpoint, the rodent may infer different LCs for contexts in which the tone leads to a shock and ones in which it does not. Thus, spontaneous recovery would arise when the rodent assigns the current context to the underlying LC that predicts shock. Based on this perspective, one way to improve extinction would be to make sure both threat learning and extinction were bound to the same LC (Dunsmoor et al., 2015b). Empirical work supports this idea, as introducing extinction more gradually (and thus allowing both threat learning and extinction to be integrated with the same LC) led to diminished spontaneous recovery in rodents (Gershman et al., 2013) and humans (Shiban et al., 2015). Recent computational work has aimed to elucidate how LC integration may be implemented (Cochran and Cisler, 2019; Song et al., 2022).

How the brain infers and uses LCs is an active topic of research, with features of striatal and dopaminergic signaling appearing to be consistent with state inference and integration (Langdon et al., 2019). Notably, orbitofrontal cortex (OFC) has been implicated both in state representations in reinforcement learning as well as schemas in episodic memory (Chan et al., 2016). Beyond this overlap, Chan et al. (2016) found that BOLD signal in OFC represented computations considered to be shared across inferring relevant schemas or latent causes, namely the inference of hidden unobservable factors that generate current observations. They demonstrated that OFC responses were best explained by the formation of a posterior distribution over latent causes compared to other related factors such as stimulus and uncertainty (Chan et al., 2016).

4.1. Influence of stress

Few studies to date have directly tested stress effects on memory integration at the level of schemas or latent states. In one such experiment, participants exposed to a stressor showed selectively amplified memory for content related to the stressor. That is, if participants were instructed to talk about their personality as part of the stress induction, they had significantly better memory for subsequently presented words that were relevant to personality (Smeets et al., 2007). This result suggests strengthened schema activation under stress that promoted enhanced encoding of schema-relevant features. Similarly, in a study in which participants judged relatedness of words to established schemas (e.g., whether "shower" was related to the schema "bathroom"), exposure to stress amplified responses to schema-related words throughout the brain, including in the hippocampus and in hippocampal/mPFC connectivity (Vogel et al., 2018). Conversely, a behavioral study found that exposure to stress or glucocorticoids interfered with schema integration, as these participants did not show the typical benefit for learning information related to a recently-learned schema (Kluen et al., 2017). One possibility is that stress and glucocorticoids impaired retrieval of the recently-learned schema information (which, in that study, was novel and learned the day prior; see (Gagnon and Wagner, 2016) for further discussion of stress effects on retrieval). Such effects may be distinct from retrieval of schemas gradually formed over many experiences, or even a lifetime, and stored for a longer period (Richards et al., 2014). Together, these studies provide some evidence that stress may enhance processing of long-established schemas.

Although not a direct test of stress effects, the phenomenon of "category conditioning" – in which individuals who receive an electric shock paired with category exemplars (e.g., an eagle, rabbit, and dog) then go on to show threat responses when presented with novel exemplars from the same category (e.g., a cat) – is predicated on the ability to extract a higher-order schematic representation of those individual learning events. That is, it requires the ability to learn that the *category* of animals is dangerous based on negative experiences with individual category exemplars. In this case, threat associations are spread through an extant schematic network, without requiring direct experience of these novel examplars paired with shock (Cooper et al., 2023). Category conditioning also follows classic logic from the category and schema literature; for example, people are more likely to abstract threat associations to the higher-order category when shock is paired with a prototypical, rather than atypical, category member (Dunsmoor and Murphy, 2014). This process of abstraction, or binding events to an existing schema of category-level knowledge, has been argued to play a critical role in threat generalization (Dunsmoor and Murphy, 2015). As with between-context integration, this process of spreading threat associations to schematically related content has been associated with neural pattern similarity (Cooper et al., 2023). Generalized fear responses in PTSD have been associated with this tendency to integrate traumatic events with prior schemas (Dunsmoor et al., 2022a), with clinical emphasis on addressing "fear structures" that include meaning and semantic associations (Foa and Kozak, 1986). Preliminary empirical evidence using category conditioning has also shown that patients with PTSD show stronger generalization of neural responses to the category paired with threat (Morey et al., 2020).

The relationship between stress and LCs, while also preliminary, is more complex and reflects a burgeoning area of scientific inquiry (Cisler et al., 2024). Both anatomical overlap of regions involved in inferring latent causes and those disrupted in PTSD (e.g., OFC and hippocampus), together with latent cause models providing strong fits to physiological markers of threat learning in PTSD, strongly implicate the importance of considering latent structure when examining memory biases in PTSD (Cisler et al., 2024; Letkiewicz et al., 2022). Some models of PTSD theorize that individuals with PTSD form more, and more event-specific, LCs (Rigoli, 2022). That is, having experienced more and variable negative experiences (a known risk factor for the development of PTSD), patients assign traumatic event(s) to a distinct LC (or set of LCs). Then, instances of trauma-related cues in safe contexts are assigned to yet more separate LCs. These new "interfering" LCs for safe environments then compete with trauma LCs in novel situations. Consistent with patients with PTSD tending to exhibit high fear sensitivity, this model posits that, when presented with a situation, patients will tend towards assuming the trauma LC rather than an interfering "safe" LC (Dretsch et al., 2013; Rigoli, 2022). Thus, a relative fragmentation of events into distinct LCs would explain overgeneralization of threat responses even in novel non-dangerous situations.

However, recent empirical work suggests the opposite pattern. In one study, behavior during acquisition and extinction of threat associations was fit to a LC model in order to determine whether data was best described as resulting from a single or many underlying LCs. Attribution to the same underlying LC for conditioning and extinction was associated with slower extinction learning, suggesting negative consequences of binding acquisition and extinction to the same LC. Critically, trauma-exposed participants who were best fit by a single LC also showed more severe PTSD-related symptoms (Norbury et al., 2021). By this account, stress may promote tighter integration between experiences and a single

underlying LC, in which case novel events could also be attributed to that same LC, thus allowing threat responses to predominate through generalization. This diverges from the model presented above: namely, that greater *fragmentation* of LCs would lead safety learning to be assigned to a distinct and less potent LC, thus allowing threat responses to predominate by threat LCs out-competing safety LCs. Nevertheless, further empirical evidence supports the idea of greater *integration*, rather than fragmentation, with a single LC. For example, recent evidence indicates that healthy participants misattributed cues presented during extinction as having been presented during conditioning (particularly for exemplars from the shock-paired category), perhaps reflecting broad integration with the same underlying LC (Hennings et al., 2021; Laing and Dunsmoor, 2023). A study of patients with PTSD also found that these individuals were impaired at differentiating their expectation of shock between contexts that were and were not paired with shock, and this impoverished differentiation was associated with more severe PTSD symptoms (Steiger et al., 2015). Here too, this effect may be due to patients attributing both contexts to an aversive LC. These studies provide suggestive evidence that, rather than creating fragmented associations with multiple LCs, integrating more events with the same LC may be deleterious. Nevertheless, further empirical studies directly testing the effects of stress and trauma on attribution of events to LCs are needed.

To summarize, preliminary evidence suggests that stress may promote the integration of incoming information into pre-existing knowledge structures and networks. Category conditioning provides one promising avenue to determine how distinct aversive events may become abstracted and integrated into existing category-level knowledge. Furthermore, computational work indicates that PTSD may bias integration of separate events (e.g., conditioning and extinction) to the same generative rule or latent cause. These examples also highlight that tighter integration is not necessarily beneficial. Indeed, spreading fear through a generalized network and attributing safe contexts to the same latent cause as dangerous ones are both deleterious. Understanding the mechanisms governing when and how stress enhances or impairs such extra-event binding may prove critical in designing more effective interventional strategies (see also Section 5).

4.2. Implications for alcohol

The relationship between alcohol and schemas or LCs remains an open question. In one study, participants who had acutely consumed alcohol showed greater benefit from a context-related word (e.g., "football") when encoding an opaque sentence ("the crowd cheered the block") compared to sober participants (Birnbaum et al., 1980). This finding may suggest alcohol-induced difficulty in generating schemas (thus leading to greater benefit when the schema is provided), or an alcohol-induced benefit in integrating new information with prior schemas; further studies are needed to clarify the underlying mechanism.

As in the case of between-context binding, there are also clues in the clinical literature to support the relevance of schemas and integration. One possibility is that a history of problematic alcohol use leads to a stronger and more inclusive alcohol schema. Consistent with this idea, heavier drinkers show a tendency toward associating a wider range of ambiguous cues with alcohol-related behaviors (Stacy, 1995, 1997; Woud et al., 2015). Furthermore, the accessibility of these schemas in memory moderated the association between positive expectations about alcohol and drinking (Palfai and Wood, 2001). Indeed, alcohol expectancies have been considered as having a schema-like memory network structure, with spreading activation between related nodes, and the organization of these networks may meaningfully differ with drinking history (Rather and Goldman, 1994).

Recent computational work also proposes a role for LCs in an addiction-relevant behavior: insensitivity to devaluation. This behavior is often explored in paradigms in which a rodent learns to press a lever to receive a drug reinforcer, after which the reinforcer is "devalued" (i.e., the drug is paired with a bitter tastant or shock). The key question is whether the rodent continues to lever press even when the drug reinforcer is no longer desirable. Persistent lever pressing, which is exacerbated by alcohol (Corbit et al., 2012; Dickinson et al., 2002; Mangieri et al., 2012), is typically interpreted as reflecting the formation of a habit (see Everitt and Robbins, 2016 for discussion). However, recent modeling work from Garrett et al. (2023) argues that this can also be explained using LCs. That is, the aversive experience of devaluation could simply be attributed to a different LC (i.e., LC_2) than the acquisition of the lever/reinforcer association (LC_1). Thus, if LC_1 is reactivated at test, the rodent would persist in lever pressing (Garrett et al., 2023). Although these model parameters have not yet been tested in the context of alcohol use, these findings suggest an intriguing possibility whereby positive alcohol use experiences are assigned to a distinct LC from either aversive alcohol experiences or alternative non-alcohol experiences, with the positive LC inferred at later drinking opportunities. A similar idea was recently proposed by (Bornstein and Pickard, 2020), in which relapse is precipitated by preferential retrieval of a drug "fantasy", a schema extrapolated from positive early drug use experiences, at the expense of alternative non-drug schemas. Finally, phenomenon like incubation of craving or cyclical dynamics of substance use were also recently explained via recurrence of latent causes (Pisupati et al., 2024).

Together, this work points to the potential significance of schemas and LCs in understanding alcohol use. It also suggests distinct hypotheses about these interactions. Does risky drinking lead to an easily accessible alcohol schema, creating a broader associative net that promotes alcohol seeking behavior in many situations? Or does drinking lead to a more exclusive alcohol schema, selective to positive (perhaps early) experiences, which is resistant to incorporating negative (perhaps later) episodes? These possibilities would point to different underlying mechanisms and targets for intervention, underscoring the need for more empirical work testing these integrative processes.

5. Conclusions

Memories for single features rarely exist in isolation. Adaptive behavior is facilitated by integrating new experiences with other relevant information present at the time, with related past events, and with existing knowledge structures. In this review, we discussed the computations and neural mechanisms involved in these different levels of integration, how they may be shaped by exposure to stress and alcohol, and the consequences of forming these different types of mnemonic representations.

From this discussion, it is clear that stress can enhance integration, including by linking events with other related experiences and existing schemas or latent causes (Table 1). This observation has important consequences for addressing the questions we raised at the start of this review, such as how broadly people will generalize from a given experience. Extant models of memory in PTSD, which focus on whether memory for the traumatic event itself is integrated (i.e., within-context integration), explain generalization as resulting from a *decrease* in binding. By forming fragmented representations, with weakly-bound features or elemental feature/outcome associations, threat responses to individual features can then become overgeneralized and expressed in inappropriate contexts (Acheson et al., 2012; Stout et al., 2018). However, from a between-context or extra-event binding perspective, it is an *increase* in binding that explains generalization. In this case, it is the process of forming strong links between events leading up to and following a traumatic event, as well as across the network of relevant schemas, that threat responses can become overgeneralized. In support of this idea, traumatic events in PTSD are theorized to be overly integrated with other autobiographical memories, leading them to act as a cognitive reference point in autobiographical knowledge; one consequence of this is inappropriate activation of the trauma event memory in future situations/events (Berntsen and Rubin, 2007; but see Lely et al.,

2019 for the efficacy of treatment interventions that aim to enhance integration of trauma memories with other autobiographical events). Yet these different perspectives – on the one hand, that trauma memories are fragmented, and on the other, that they are integrated – would yield distinct (even opposite) goals for clinical interventions. These observations underscore the importance of considering integration at multiple levels and highlight the need to consider consequences of stress-induced enhancements of integration as well as fragmentation.

Considering stress and alcohol effects on different levels of integration highlights striking parallels. As we have discussed previously, alcohol and stress share physiological correlates as well as mnemonic biases (Goldfarb and Sinha, 2018). We recently showed that heavier drinking is associated with greater generalization of alcohol-related responses to perceptually similar stimuli (Kang et al., 2023), consistent with a long line of evidence that both acute stress (Dunsmoor et al., 2017) and stress-related disorders (Cooper et al., 2022; Lissek et al., 2010) are also characterized by greater generalization of fear-related responses to perceptually similar stimuli. Similarly, alcohol intake has been associated with increased incidence of intrusive thoughts (dose--dependently; Bisby et al., 2009; Bisby et al., 2010) a central symptom of PTSD (DSM V). Does memory fragmentation (e.g., sensory representations separate from their context; Brewin et al., 2010) or integration (see Marks et al., 2018) promote these tendencies, and do the same mechanisms promote intrusive thoughts arising from stress and alcohol? Although we caution against considering memory integration arising from alcohol as a carbon copy of tendencies associated with stress and trauma, it is evident that there are fruitful opportunities for insights and hypothesis generation by applying findings from the stress field to elucidate the role of alcohol in memory integration.

In presenting this framework, we aim to both account for prior findings and present testable hypotheses for further research. Indeed, particularly for the alcohol field, there is an urgent need for further empirical work examining how both acute administration and prior history of alcohol exposure contribute to memory integration at multiple levels of abstraction. There are also important gaps in our understanding of how neural and computational mechanisms supporting these different forms of integration may be potentiated by stress and alcohol. For example, given robust evidence for impaired hippocampal function in chronic stress and PTSD (Kim and Diamond, 2002; Shin et al., 2004), and chronic alcohol exposure (Kutlu and Gould, 2016) how could memory integration – which, across levels of abstraction, appears to crucially involve the hippocampus – occur? One possibility is that distinct, perhaps extrahippocampal, mechanisms are employed under stress to facilitate integration (Grob et al., 2023b; Vogel et al., 2018). It is also possible that we need to reconsider the way that we quantify hippocampal involvement in encoding, particularly in human neuroimaging. For example, although we recently showed (consistent with past reports) that the stress-related hormone cortisol interfered with univariate BOLD signatures of within-context integration, it also amplified intrahippocampal connectivity, which in turn promoted within-context integration (Sherman et al., 2023a). This provides preliminary evidence in support of examining the relationship between stress, alcohol, and memory integration via hippocampal subfields and pathways, which are associated with different mnemonic computations (Schapiro et al., 2017) and have been shown to be differentially sensitive to these agents (see Avchalumov et al., 2021; Sawyer et al., 2020 for alcohol examples; stress effects discussed in Sherman et al., 2023b). In addition, a recent model suggests that states of "behavioral activation", associated with release of dopamine, can potentiate memory integration at multiple levels (Clewett and Murty, 2019). As dopamine is also a component of the body's response to stress (Joels and Baram, 2009) and alcohol (Nutt et al., 2015), this neurotransmitter may be a promising candidate for memory integration under both conditions. Furthermore, a recent quantitative model of emotional memory enhancement posits that emotional features are better remembered because they are more tightly integrated with an underlying emotional context. In this model, emotional features of stimuli continuously update the underlying emotional context in encoding such that later on, items sharing emotional context promote recall for each other. This shared context may further explain their competitiveness with non-emotional items at recall, a hallmark of emotion-enhanced memory (Talmi et al., 2019). Might stress or alcohol similarly serve as an underlying context for integration?

Further empirical work would also help expand the current framework. We based our discussion largely on data examining integration of external information. Given the importance of internal cues for memory retrieval in PTSD (Gross et al., 2023), further work is needed to assess how stress and alcohol influence the integration of internal states, like interoceptive and affective experiences, into memory representations (Maddox et al., 2019). In addition, we note that our framework could be augmented by considering memory integration at timepoints beyond the initial formation of the representation. In particular, contextual integration can also occur at the time of memory retrieval (Marks et al., 2018), and interpretation of context can govern which memories are retrieved through integrative processes like pattern completion (Liberzon and Abelson, 2016). Given the potential for stress to promote lapse and relapse, understanding what memories are preferentially retrieved under stress (and to what extent these memories are integrated) will be key to developing timely interventions to mitigate this risk (Bornstein and Pickard, 2020).

In conclusion, the current review discusses how our memories can be integrated: within an experience, between different events, and embedded within our sense of how the world works. We provide evidence that stress, and perhaps alcohol, can enhance each of these levels of memory integration. This framework aims to raise hypotheses for further empirical research and highlight novel mechanisms by which stress and alcohol shape our memories to guide subsequent adaptive and maladaptive behavior.

CRediT authorship contribution statement

Krystian B. Loetscher: Writing – original draft, Conceptualization. **Elizabeth V. Goldfarb:** Writing – review & editing, Conceptualization.

Declaration of competing interest

None

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