

## **Context in Spatial and Episodic Memory**

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## **Abstract**

In this chapter we discuss the role of context in shaping spatial and episodic memories. We first survey the psychological literature on the types of cues that define context and offer an inclusive definition that focuses on the adaptive role of contextual representations for guiding behavioral and mnemonic outputs. Using observations from both humans and non-human animals, we then review the neural basis of contextual memory focusing in particular on the hippocampus. We show that contextual representations in the hippocampus are organized by those same cues that define context cognitively. Finally, we characterize the inputs to the hippocampus mediating recognition of context-defining cues. Together, our review supports the hypothesis that a function of the hippocampus and its primary inputs is to form the holistic context representations that shape memory.

## **Introduction**

Theories of memory suggest that encoding and retrieval are facilitated or hindered by *context* (Davies & Thomson, 1988; Smith & Vela, 2001). For example, it is easier to recognize someone when that person is in the same setting as when you initially encountered her. Context plays a particularly important role in shaping spatial and episodic memories. Spatial memory reflects memory for spatial information defined relative to a particular contextual frame of reference (e.g., memory for the location of my seat in a movie theater). Episodic memories are detailed representations of the what, where, and when of past experiences (Tulving, 2002), and thus the ability to reinstate contextual information is one of the defining features of episodic memory (e.g., my memory of finding my seat in the movie theater). By contrast, other types of memory require no contextual information, such as knowledge of facts in the absence of memory for the context in which they were learned, or recognition of

stimuli based on a feeling of familiarity. A major scientific challenge has been to understand how the brain processes contextual information, and how this information shapes spatial and episodic memories. In this chapter, we review the cognitive role that context plays in memory and elucidate how contextual information is processed by the brain in service of such memories.

### **What cues define contexts?**

Despite the ubiquity of context in our lives, and its clear importance for shaping memory, “context” has proven to be a surprisingly difficult concept to define (Nadel & Willner, 1980). Confusion around the definition of context is not new; Smith and colleagues (1979) argued in the 1970s that context “is a kind of conceptual garbage... that denotes a great variety of intrinsic and extrinsic characteristics of the presentation or test...” of stimuli. Indeed, across studies purporting to interrogate contextual memory, ‘context’ has been operationalized in terms as nearly anything associated with items or locations in an event, ranging from something as simple as the color of text in a word list, to cues as complex as the physical environment. This ongoing lack of definitional clarity is due in part to the fact that general rules governing when cues do or do not define a context are unclear. Moreover, the type of context referred to in studies of memory is often underspecified, and it is not empirically clear that all types of cues used to operationalize context play identical mnemonic roles. To provide a handle for understanding the neural basis of context-dependent memory, it is thus critical to start by surveying the possible types of context-defining cues:

***Spatial cues.*** Everything we do occurs *somewhere*. The external sensory cues (visual, olfactory, auditory, and tactile) that denote this “somewhere” form the spatial context relative

to which memories are encoded and retrieved. Early research using “interference reduction” paradigms demonstrated that confusions between two lists of to-be-remembered items are reduced if the lists are learned in different spatial environments rather than the same environment (Canas & Nelson, 1986; Emmerson, 1986; Smith & Vela, 2001; Godden & Baddeley, 1975). In other words, people exhibit better memory when tested in the presence of the same external sensory cues as those experienced during learning compared to people tested in new spatial contexts. Studies with both rodents and non-human primates have likewise found that changes to spatial cues strongly influence memory (Bachevalier, Nemanic, & Alvarado, 2015; Bouton, 2002; Curzon, Rustay, & Browman, 2009; Dells, Fauchey, Le Moal, & Simon, 1997; Pascalis, Hunkin, Bachevalier, & Mayes, 2009). For example, although animals are able to recognize objects after moving from one experimental chamber to another, memory is stronger when the familiar environment is used during both learning and retrieval (Dix & Aggleton, 1999). Any external sensory cue could theoretically constitute a spatial contextual cue, though for reasons that will become clear in the next section, *landmarks*—stable and salient environmental features—are particularly critical.

***Situational cues.*** Everything we do occurs in *some way*, and this state of affairs or ‘situation’ surrounding an event is often an important contextual cue. For instance, a wedding and funeral are vastly different experiences even if they occur in the presence of the same spatial cues. Early reports noted that simple physical disruption between two lists of to-be-remembered items caused as much interference reduction as changes in spatial cues (Strand, 1970), and contextual interference is eliminated when participants tested in a new spatial context are instructed to recall the original learning environment just prior to recall (Smith, 1979). Such results show that situational cues, often operationalized in terms of task

or motivational demands, influence memory independent of spatial cues. Moreover, memories are best retrieved if the “brain state” at encoding and retrieval are similar. “Brain state” refers to the internal state of the individual, which we include as a kind of situational cues, such as mood (Bower, 1981; Eich, 1995), hormonal state (McGaugh, 1989), or feelings associated with administration of drugs (Overton, 1964). Whether external situational cues, such as the normative rules surrounding an event, and internal situational cues like brain state have qualitatively different influences on contextual representations remains an open question.

**Temporal cues.** Everything we do occurs at *some time*, and it is possible to remember that different events that occurred in the presence of similar spatial or situational cues occurred at different times. Two kinds of temporal cues influence memory. First, an internal representation of the time of day at which learning occurs, tightly linked an individual’s circadian rhythm, has an influence on retrieval (Mulder, Gerkema, & Van Der Zee, 2013). Time of day can serve as an important mnemonic cue in spatial memory tasks (Boulos & Logothetis, 1990). Time-of-day effects are also observed in contextual fear conditioning experiments that interrogate episodic memory, in which animals learn to fear a spatial context in which shock was previously experienced. Rodents display strongest context-dependent fear response during their “inactive phase” (the light period) (Chaudhury & Colwell, 2002). The second kind of temporal cue is the relative sequence in which learning takes place. Events experienced closer together in time are more similar than events experienced further apart. As a result, if a person experiences an event and her memory is later assessed, the ability to recall that event will decrease as the time between learning and retrieval increases (Rubin & Wenzel, 1996). Similarly, items encountered in close temporal proximity are more

likely to be recalled sequentially than items encountered further apart (Howard & Kahana, 2002).

This brief taxonomy of context-defining cues suggests that context is characterized by factors external to the agent, including the set of environmental cues that define a place or the situation that characterizes an event, and the internal factors (e.g., temporal, cognitive, hormonal, affective) against which mnemonic processes operate. The cinema provides an apt metaphor for summarizing these context-defining cues: a cinema contains multiple movie theaters (spatial cues) playing different movies (situational cues) at different times (temporal context) (Fig. 1A).

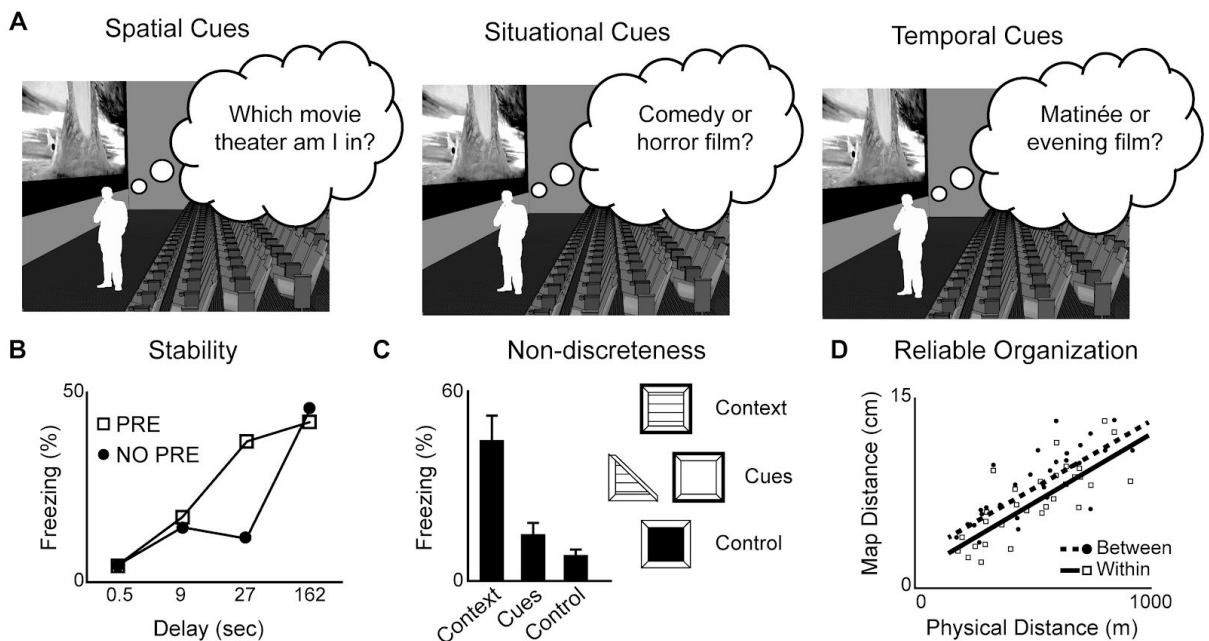


Figure 1.

### When do cues not define contexts?

For context to be a useful scientific construct there must be factors that differentiate contexts from other types of mnemonic cues. We suggest three important properties that limit the appropriate application of the term “context”:

First, for the brain to form contextual representations from statistical cue regularities, the cues that characterize context must be reliably present over time or *stable* (Biegler & Morris, 1993; Robin, 2018; Stark, Reagh, Yassa, & Stark, 2017). For instance, the location of seats that define a movie theater context must not change often for the seat locations to form an integral part of that context. In contextual fear conditioning experiments, if animals are briefly (e.g., less than 27 seconds) exposed to a context and shocked, they later show little fear of the context (Fanselow, 1990) (Fig. 1B). However, if they are first pre-exposed to the context, the shock elicits a fear response when the animal is subsequently returned to the conditioned context. Contextual conditioning thus only occurs if animals have an opportunity to learn the reliability of contextual cues through prolonged or repetitive exposure, indicating that experience of cue stability is critical for the formation of contextual representations that organize memory.

Second, just as eating popcorn does not define being in a cinema (one can also eat popcorn at home), contexts are *not defined by any single discrete cue* (Robin, 2018). In other words, contexts are not the same as cues that serve as discrete signals for other events. Unlike contexts, increased time spent with a discrete cue does not alter conditioning to that cue (Fanselow, 1990). As a corollary, contexts are tolerant to changes in any one discrete cue. The context of your local movie theater could be recalled as such independent of whether you have popcorn, or are seeing a horror or comedy film, or if you have consumed caffeine beforehand. This corollary suggests that context is not simply the set of cues associated with a particular event, but rather a holistic representation of those cues. Consistent with this idea, rodents do not exhibit a typical contextual fear conditioning response when exposed only to the cues individually that conjunctively form the conditioned context (Rudy & O'Reilly, 1999) (Fig. 1C). Therefore, context is a neural construct, rather than something that exists in



the world (Anderson, Hayman, Chakraborty, & Jeffery, 2003). As illustration of this point, suppose the locations of the seats in your local movie theater are moved in your absence.

When you later return to the theater, did you return to the same context or not? The answer to this question is not knowable *a priori*, but you could easily answer this question about your own memory.

Third, because contexts are not defined by any one discrete cue, different context-defining cues must have a *reliable organization* that allows them to be unified in a contextual representation. A common cue organization used by the brain to represent contexts is a hierarchy (Jeffery, Anderson, Hayman, & Chakraborty, 2004; Pearce & Bouton, 2001). There is an extensive literature demonstrating that the spatial environment is encoded as multiple hierarchically organized contexts, varying in spatial scale, instead of a single environmental context, and performance on memory tasks is influenced by this hierarchical structure (Han & Becker, 2014; Hirtle & Jonides, 1985; Holding, 1994; Marchette, Ryan, & Epstein, 2017; McNamara, 1986; McNamara, Hardy, & Hirtle, 1989; Montello & Pick Jr, 1993; Wiener & Mallot, 2003) (Fig. 1D). Situational and temporal contexts also have intuitive hierarchical structures. Purchasing movie tickets or purchasing movie snacks are both subordinate to the larger class of transactional situational contexts, and the relative sequence of events can be organized over minutes or days. Beyond hierarchical arrangements, the set of possible relational structures between cues necessary for such cues to be associated in a contextual representation is unknown.

### **What is context?**

Based on this survey of context defining cues and their boundary conditions, we offer the following inclusive definition of context:

*Context is a holistic representation of the internal and external (stable, non-discrete, and reliably organized) cues that predict particular behavioral or mnemonic outputs.*

This definition unifies the contextual cues by placing emphasis on the adaptive function of contextual representations, rather than on any one specific cue type (Mizumori, 2013; Stachenfeld, Botvinick, Gershman, 2017). Note that although this definition runs the risk of circularity, we have proposed three boundary conditions that limit the correct application of the ‘context’ construct—stability, non-discreteness, and reliable organization—that immunizes against circularity. Insofar as the role of context is concerned, this definition is consistent with theories of memory that do not place particular importance on any one contextual cue type, but rather focuses on the function of contextual representations (Eichenbaum, 1993, 1996; Howard & Kahana, 2002; Mensink & Raaijmakers, 1988; Schacter, 2012; Schacter, Addis, & Buckner, 2007; Ranganath, 2010).

By contrast, others argue that spatial cues play a particularly special role in memory by serving as an ineluctable component of all memories (Burgess, Becker, King, & O’Keefe, 2001; Hassabis & Maguire, 2007; Maguire & Mullally, 2013; Nadel & Moscovitch, 1997; Robin, Buchsbaum, & Moscovitch, 2018). There is empirical evidence in favor of this position. For instance, when recalling previously read scenarios, participants spontaneously generate spatial contexts for the scenarios, even when the scenarios did not include any spatial cues (Robin et al., 2018; see also Hebscher, Levine, & Gilboa, 2017). However, as eluded to above, situational and temporal context can also have strong influence over memory if they are behaviorally relevant. Our definition suggests that spatial cues may often be strong determinants of contextual representations because they are often experienced as most stable, thereby most predictive of context-appropriate behaviors, even if they do not necessarily have unique cognitive status. An important area for future research is the extent to

which different context-defining cues, matched in terms of their behavioral relevance—not just in an experimental situation, but also over the lifetime of an individual or evolution—are incorporated into contextual representations.

### **The hippocampal basis of contextual memory**

There is consensus that the hippocampus in the mammalian medial temporal lobe plays a crucial role in spatial and episodic memory, and neurobiological studies of contextual processing have focused on this brain area (for reviews see Maren, Phan, & Liberzon, 2013; Myers & Gluck, 1994; Ranganath, 2010; Rudy, 2009; Rugg & Vilberg, 2013; Smith & Mizumori, 2006; Winocur & Olds, 1978). In the 1970s, Hirsch (1974) first explicitly proposed that the hippocampus mediates retrieval of information in response to contextual cues that refer to the retrieved information. Since then, a wide variety of studies in both human and non-human animals have reinforced the importance of the hippocampus for context-dependent memory. Indeed, an automated meta-analysis ([www.neurosynth.org](http://www.neurosynth.org)) of functional magnetic resonance imaging (fMRI) studies of human context-dependent memory revealed common activation across these studies largely localized to the hippocampus (Fig. 2A).

Consistent with these neuroimaging findings, lesion studies have shown that the hippocampus is necessary for maintaining context-dependent memories (Anagnostaras, Gale, & Fanselow, 2001; Maren, 2001). When rodents are conditioned in one spatial context, for instance, they typically show a reduction of conditioned responses when tested in a new context, but animals with hippocampal damage continue to respond as if they did not notice the spatial context change (Bachevalier et al., 2015; Butterly, Petroccione, & Smith, 2012; Corcoran & Maren, 2001; Honey & Good, 1993; Penick & Solomom, 1991). Hippocampal

damage also impairs memory for situational contexts (Ainge, van der Meer, Langston, & Wood, 2007); for example, hippocampal lesions disrupt the ability of rats to approach different goal objects depending on the rats' internal motivational state (hunger or thirst), even though object and motivational state discrimination are preserved (Kennedy and Shapiro, 2004). Finally, hippocampal lesions impair the ability to recall the biological time of day at which an event occurred (Cole et al., 2016), and for remembering the temporal sequence of events (i.e., the relative temporal context) (Agster, Fortin, & Eichenbaum, 2002; Fortin, Agster, & Eichenbaum, 2002; Kesner, Gilbert, & Barua, 2002). Thus, the hippocampus is necessary for retrieval of memories associated with contexts characterized by the full range of context-defining cues.

At the cellular level, context is represented by the population activity of hippocampal neurons that fire whenever a navigator occupies particular environmental locations ("place fields") (O'Keefe & Dostrovsky, 1971). Within a context, different neurons have different place fields, and thus - as a population - are thought to reflect a cognitive map of locations within the local context (O'Keefe & Nadel, 1978). Neuroimaging studies in humans likewise support the idea that the hippocampus represents a map of local context (Epstein, Patai, Julian, & Spiers, 2017). Beyond distinguishing between locations within a context, however, the hippocampus also stores multiple maps that allows it to represent multiple contexts (Bostock, Muller, & Kubie, 1991; Muller & Kubie, 1987). The hippocampus' ability to distinguish between contexts is indexed by a process known as *remapping* (Fig. 2B). During remapping, when an animal changes contexts, all simultaneously recorded neurons shift their relative place fields to new locations or stop firing altogether, quickly forming a new map-like representation (Bostock et al., 1991; Save, Nerad, & Poucet, 2000).<sup>1</sup> Current

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<sup>1</sup> In contrast to remapping, in some cases the same neurons fire in the same locations across contexts, but with reliably different firing rates, a process termed "rate remapping" (Leutgeb et al., 2005). The conditions under

evidence suggests that a distinct ensemble of hippocampal neurons represents each different context (Alme et al., 2014; Anderson et al., 2003; Leutgeb et al., 2005; Leutgeb, Leutgeb, Treves, Moser, & Moser, 2004). If remapping mediates contextual memory, then remapping should occur between contexts defined by all contextual cue types and should be constrained by the same factors that limit when cues do not define contexts. As we will now review, this is indeed the case.

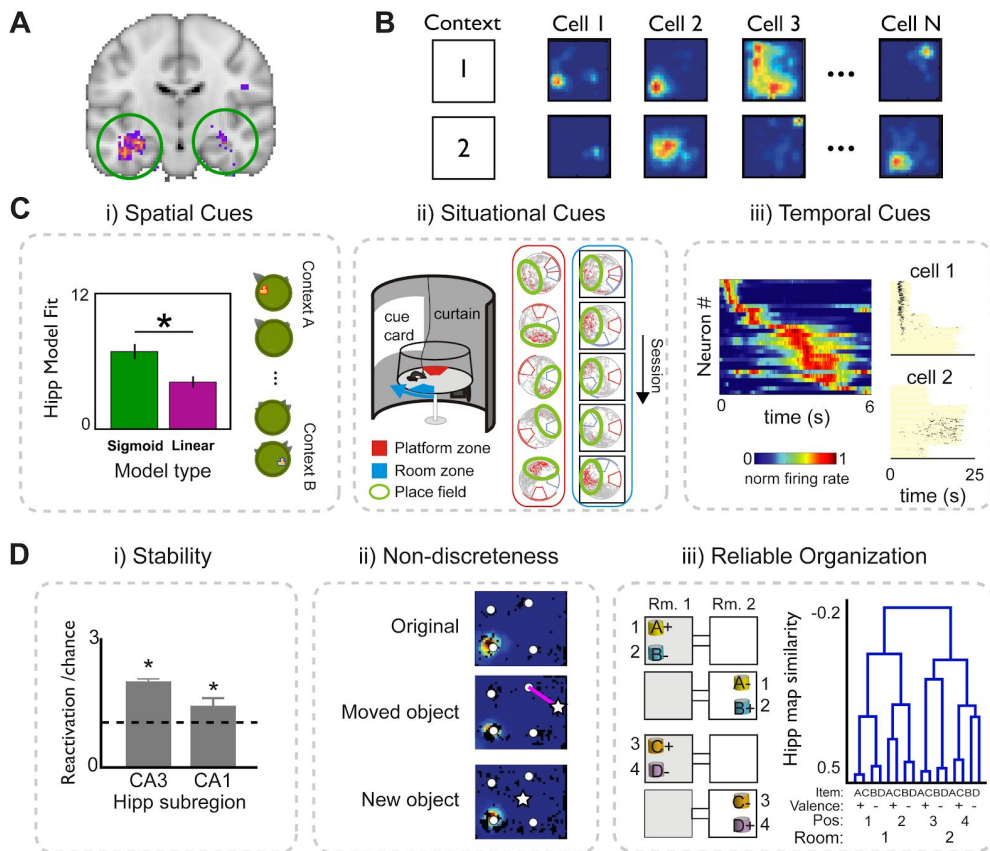


Figure 2

## What contextual cues induce hippocampal remapping?

**Spatial cues.** Remapping is induced by spatial cue changes such as when the walls of a familiar testing arena are replaced with walls of a different color (Bostock et al., 1991) or

which remapping (sometimes called “global” or “complex” remapping) versus rate remapping are observed are not currently well understood, but whereas global remapping may relate more to contextual changes, rate remapping may reflect non-contextual, non-spatial influences on hippocampal representations (Leutgeb et al., 2005).

when the shape of the environment is altered (Lever, Wills, Cacucci, Burgess, & O'Keefe, 2002). For example, Wills and colleagues (2005) observed that incremental changes in the squareness or circularity of the walls of an experimental chamber produced no change in hippocampal activity until the cumulative changes became sufficiently great, at which point all neurons suddenly remapped to the other pattern. Human fMRI studies provide convergent evidence for the idea that the hippocampus represents spatial context as well (Alvarez, Biggs, Chen, Pine, & Grillon, 2008; Chadwick, Hassabis, & Maguire, 2011; Copara et al., 2014; Kyle, Stokes, Lieberman, Hassan, & Ekstrom, 2015; Steemers et al., 2016; Stokes, Kyle, & Ekstrom, 2015) (Fig. 2C). Interestingly, rapid remapping following spatial cue changes is not always observed, but rather depends on several factors, including prior learning experience (Leutgeb et al., 2005; Bostock et al., 1991) and the extent of differences between cues. Moreover, if there are sudden shifts from one spatial context to another, the hippocampus spontaneously 'flickers' back to the original context representation (Jezek, Henriksen, Treves, Moser, & Moser, 2011). Remapping thus does not simply reflect changes to the perceived spatial cue constellation, but rather reflects contextual memory.

***Situational cues.*** Task and motivational demands strongly influence the firing of hippocampal neurons (Frank, Brown, & Wilson, 2000; Gothard, Skaggs, & McNaughton, 1996; Hampson, Simeral, & Deadwyler, 1999; Kobayashi, Nishijo, Fukuda, Bures, & Ono, 1997; Lee, LeDuke, Chua, McDonald, & Sutherland, 2018; Markus et al., 1995; Redish, Rosenzweig, Bohanick, McNaughton, & Barnes, 2000; Smith & Mizumori, 2006; Wible et al., 1986; Yeshenko, Guazzelli, & Mizumori, 2001). For instance, hippocampal neurons remap depending on the behavioral strategy used to solve a spatial memory task (Eschenko & Mizumori, 2007), or when navigators explore the same spatial context using different modes

of transport (Song, Kim, Kim, & Jung, 2005), or when an animal's future goal changes (Skaggs & McNaughton, 1998; Wood, Dudchenko, Robitsek, & Eichenbaum, 2000). In an even more striking demonstration of the impact of situational context cues, Kelemen and Fenton (2010) trained rats to avoid two shock zones on a rotating disk-shaped arena, one zone that was stationary relative to the larger room frame and the other rotated with the arena. Some neurons had place fields that were stationary relative to the broader room framework, while other fields rotated along with the local cues of the rotating arena (Fig. 2C). Thus, the hippocampus held distinct representations of two situational contexts in the same spatial context, one defined by the stable shock zone and the other defined by the rotating shock zone, and alternated between them when the situational contexts were placed in conflict. Human fMRI experiments provide convergent evidence for hippocampal coding of situational contexts (Milivojevic, Varadinov, Grabovetsky, Collin, & Doeller, 2016). Changes in affective brain state can induce remapping as well (Moita, Rosis, Zhou, LeDoux, & Blair, 2004; Wang, Yuan, Keinath, Álvarez, & Muzzio, 2015).

***Temporal cues.*** Circadian rhythms modulate the firing rates of hippocampal neurons (Munn & Bilkey, 2012), but whether changes in behaviorally-relevant biological times of day induces remapping is less well studied. Greater evidence supports the idea that that the hippocampus encodes the relative temporal context in which stimuli are learned and remaps between event sequences with different temporal structures. Temporal sequence information is represented by hippocampal cells that encode successive moments during a temporal gap between events (MacDonald, Lepage, Eden, & Eichenbaum, 2011; Sakon, Naya, Wirth, & Suzuki, 2014), even for sequences devoid of specific discrete cues (Farovik, Dupont, & Eichenbaum, 2010; Hales & Brewer, 2010; Meck, Church, & Olton, 1984; Moyer, Deyo, &

Disterhoft, 1990; Staresina & Davachi, 2009). Critically, many hippocampal neurons sensitive to temporal information remap (or “re-time”) when the main temporal parameter of a task is altered (Fig. 2C), suggesting that such neural populations encode temporal context. Human fMRI studies have likewise found that temporal sequence structure learning is associated with the hippocampus (Schapiro, Turk-Browne, Norman, & Botvinick, 2016; Lehn et al., 2009), and that the hippocampus generalizes across different sequences with similar temporal structures but not random sequences (Hsieh, Gruber, Jenkins, & Ranganath, 2014).

### **Effects of contextual boundary conditions on hippocampal codes**

***Hippocampal context representations are stable.*** Repeated visits to the same context reliably elicit activity in similar hippocampal populations. For example, Tayler and colleagues (2013) used genetically engineered mice that express a long-lasting marker of neural activity to compare the hippocampal population active at the time of initial exposure to a context with the population active in that same context two weeks later (Fig. 2D). Many neurons were active at both time points, but not re-activated in a different context, indicating that hippocampal context representations are stable over weeks. Inactivation of the hippocampus prior to context pre-exposure also eliminates the effect of pre-exposure in contextual fear conditioning paradigms (Matus-Amat, Higgins, Barrientos, & Rudy, 2004), suggesting that pre-exposure allows the hippocampus to form a contextual representation reflecting stable cues. Likewise, spatial cues that are previously experienced as unstable have little control over place fields (Knierim, Kudrimoti, & McNaughton, 1995).

Despite the stability of hippocampal context representations, hippocampal population activity changes over time in the presence of the same spatial and situational cues (Mankin et al., 2012). Ziv and colleagues (2013) used calcium imaging to monitor the activity of



hundreds of hippocampal neurons in mice over a 45-day period. Although many neurons had a place field on any given day, only 15-25% were present on any other given day. Indeed, the overlap between hippocampal populations activated by two distinct spatial contexts acquired within a day is higher than when separated by a week (Cai et al., 2016). Therefore, in addition to forming stable contextual representations, hippocampal neurons change firing patterns over time in a manner that may reflect gradually shifting temporal context information, an idea also supported by human fMRI and intracranial recording studies (Manning, Polyn, Baltuch, Litt, & Kahana, 2011; Copara et al., 2014; Deuker, Bellmund, Schröder, & Doeller, 2016; Nielson, Smith, Sreekumar, Dennis, & Sederberg, 2015).

***Hippocampal contextual representations do not reflect discrete cues.*** Hippocampal lesions selectively impair context-dependent learning in rodents, but not conditioned responses to discrete cues such as a tone, during both episodic (Kim & Fanselow, 1992; Phillips & LeDoux, 1992; Selden, Everitt, Jarrard, & Robbins, 1991) and spatial (Pearce, Roberts, & Good, 1998) memory tasks. Human patients with hippocampal damage likewise have greater deficits in memory for contextual associations compared to recall or recognition of discrete cues and events (Giovanello, Verfaellie, & Keane, 2003; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004). Human fMRI studies have also found that the hippocampus is more sensitive to contextual cues than information about the discrete cues learned within those contexts (Copara et al., 2014; Davachi, Mitchell, & Wagner, 2003; Hsieh et al., 2014; Ross & Slotnick, 2008). Importantly, consistent with these lesion and neuroimaging results, changes to discrete spatial cues does not always elicit remapping (Cressant, Muller, & Poucet, 1997; Deshmukh & Knierim, 2013) (Fig. 2D).

***Hippocampal representations reflect reliable organization of contextual cues.*** When spatial and episodic cues are hierarchically structured, hippocampal neurons differentiate between such cues using a hierarchical coding scheme (Takahashi, 2013). McKenzie and colleagues (2014) recorded hippocampal neurons while rats explored two rooms containing two objects (A and B) located in either of two positions (Fig. 2D). In one room, object A was rewarded, and in the other, object B was rewarded. The rats subsequently learned new room-object-reward contingencies using a second object set (C and D) within the same rooms. At the most general level, hippocampal activity encoded room identity. At the next level, the population responded similarly to objects at similar positions independent of the valence, and so forth. Thus, the hippocampus can represent cues using a hierarchical coding scheme in which each kind of response represents a subset of the responses at the next highest level of coding. Broadly, this suggests that the hippocampus represents contextual cues in a manner that reflects the reliable organization of those cues. Interestingly, rather than a distinct hippocampal ensemble representing each different context, this would imply that hippocampal neurons do not remap randomly across contexts; rather, the similarity between different hippocampal context representations may reflect the similarity in across-context relational cue structure, thus enabling across-context behavioral predictions. Consistent with this idea, when only a subset of cues change across contexts, partial remapping can occur in which place fields of only a proportion of neurons remap (Anderson & Jeffery, 2003).

### **Hippocampal context representations and behavior**

If the hippocampus mediates contextual memory, we would expect a link between hippocampal population activity and context-dependent behavior. Striking demonstrations of

this link come from studies using optogenetics to stimulate hippocampal populations (Liu et al., 2012; Tanaka et al., 2014). In one recent example, mice were exposed to a spatial context and the hippocampal neurons active in that context genetically labeled (Ramirez et al., 2013). The next day the mice were shocked in a different context while the labeled neurons from the original context were reactivated. When the mice were subsequently tested in the original context with no stimulation, they exhibited a fear response. Thus, the mice learned to fear an artificially reactivated representation of the original context, even though they had never been shocked there. Since hippocampal activity elicited by stimulation acted as a serviceable substitute for contextual cues—akin to how recalling the original learning context at retrieval eliminates contextual interference effects—hippocampal context representations mediate context-dependent behavior.

Despite this growing evidence that hippocampal activity is sufficient to induce context-dependent behavior, there is conflicting evidence regarding whether remapping is necessary for contextual memory under more naturalistic conditions. On the one hand, Kennedy and Shapiro (2009) observed remapping due to changes in motivational state (hunger vs. thirst) only when such situational cues were required to select among goal-directed actions, but not during random foraging when the situational cues were incidental to behavior. On the other hand, a consistent relationship between remapping and context-dependent behavior is not always found. Jeffery and colleagues (2003) trained rats to locate a reward in a chamber with black walls. When the wall color was changed to white, the rats still accurately chose the rewarded location despite the fact that the change in wall color induced remapping. This disconnect could have been due to the fact that behavior in this case was guided by discrete cues (i.e., behavior did not actually reflect contextual memory), even

though the hippocampus remapped. Understanding the link between remapping and contextual memory is a critical area for future research.

### **Context recognition inputs to the hippocampus**

For context to influence memory, an agent must first recognize the cues that denote their current context. This context recognition process is cognitively dissociable from other aspects of spatial memory (Julian, Keinath, Muzzio, & Epstein, 2015). Since the hippocampus mediates both contextual memory, as well as recall of locations, events, or items within a single context (Keinath, Julian, Epstein, & Muzzio, 2017; Redish & Touretzky, 1998; Ranganath, 2010; Eichenbaum, Yonelinas, Ranganath, 2007), this raises the possibility that context recognition is performed upstream of the hippocampus itself.

The primary inputs to the hippocampus originate in entorhinal cortex (EC; Witter & Amaral, 2004), which has medial (MEC) and lateral (LEC) subdivisions. There is mixed evidence for the idea that EC supports context recognition. On the one hand, lesions of the entire entorhinal region produce contextual memory deficits that mirror those caused by hippocampal damage (Ji & Maren, 2008; Majchrzak et al., 2006). Perturbation of hippocampal inputs from MEC also induces spontaneous hippocampal remapping (Miao et al., 2015) (Fig. 3A), suggesting that MEC in particular may be the source of hippocampal context representations. The MEC contains several types of place-modulated neurons (Hafting, Fyhn, Molden, Moser, & Moser, 2005; Sargolini et al., 2006), a subset of which are strongly contextually modulated (Kitamura et al., 2015). When contextually-modulated MEC neurons change firing patterns across different spatial contexts (Barry, Hayman, Burgess, & Jeffery, 2007; Fyhn, Hafting, Treves, Moser, & Moser, 2007; Marozzi, Ginzberg, Alenda, & Jeffery, 2015), coincident remapping is found in the hippocampus (Fyhn et al., 2007). MEC

sensitivity to behaviorally-relevant situational cues has not been extensively explored, but some MEC neurons are modulated by temporal sequence information (Kraus et al., 2015). On the other hand, lesions specifically targeting MEC or LEC do not cause selective contextual memory deficits (Hales et al., 2014; Wilson et al., 2013), and lesions localized to MEC do not eliminate hippocampal remapping (Schlesiger, Boubilil, Hales, Leutgeb, & Leutgeb, 2018). Thus, although EC is critical for transmitting contextual information to the hippocampus, it is unlikely to serve as a context recognition system itself.

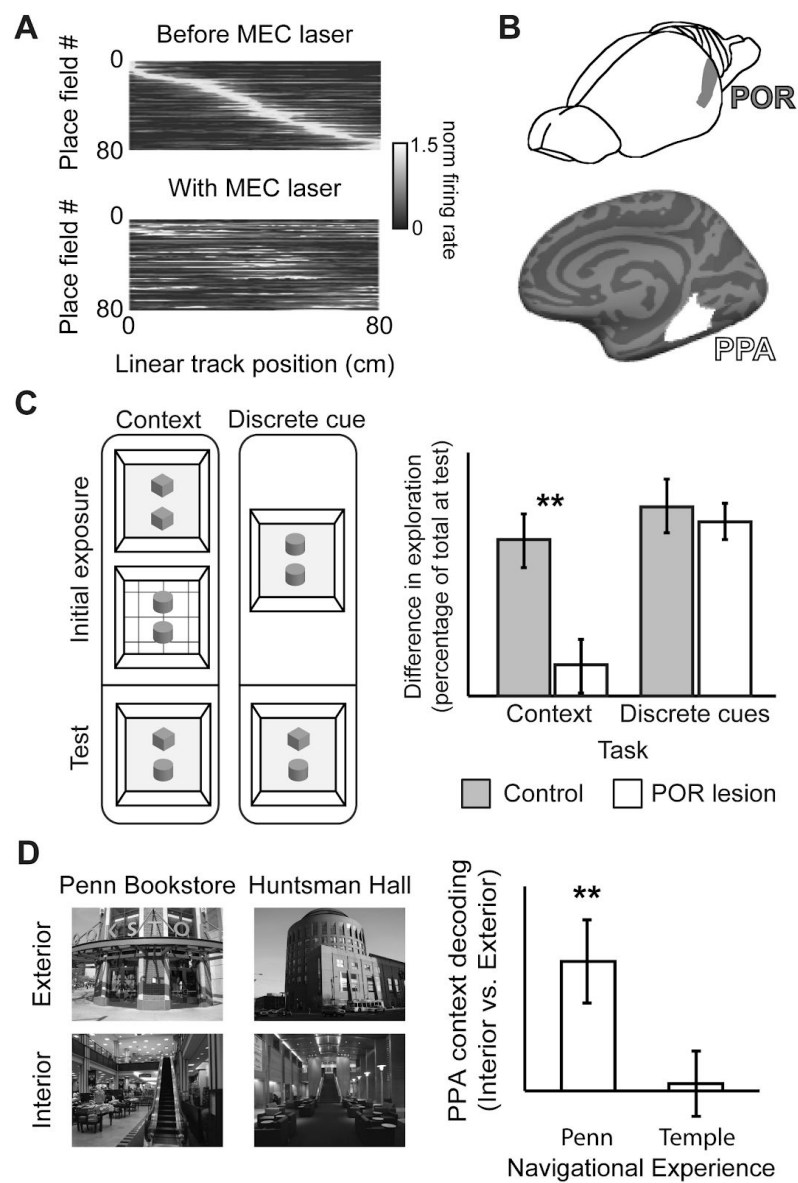


Figure 3

In rodents, one of the primary MEC inputs is postrhinal cortex (POR) (Ho & Burwell, 2014), which also projects directly to the hippocampus (Agster & Burwell, 2013). Cytoarchitectonic characteristics and anatomical connectivity suggest that POR is homologous to the primate posterior parahippocampal cortex (Burwell, 2001; Furtak, Wei, Agster, & Burwell, 2007), including a functionally-defined region known as the parahippocampal place area (PPA) in humans (Aguirre, Zarahn, & D'Esposito, 1998; Epstein & Kanwisher, 1998) (Fig. 3B). Growing evidence suggests that the POR / PPA plays an important role in context recognition (Julian, Keinath, Marchette, & Epstein, 2018). Damage to the human posterior parahippocampal cortex by stroke causes context recognition impairments (Aguirre & D'Esposito, 1999; Takahashi & Kawamura, 2002). Animal lesion studies have also confirmed the importance of the posterior parahippocampal / POR region for context-dependent memory (Okudzhava et al., 2009; Bucci, Phillips, & Burwell, 2000; Bucci, Sadoris, & Burwell, 2002; Burwell, Bucci, Sanborn, & Jutras, 2004; Norman & Eacott, 2005; Peck & Taube, 2017) (Fig. 3C). The magnitude of contextual memory deficits following POR lesions is not delay dependent, suggesting that the POR serves a context recognition function, rather than retrieval of contextual memories *per se* (Liu & Bilkey, 2002). POR lesions have little effect on the stability of hippocampal representations in a single context (Nerad, Liu, & Bilkey, 2009), but whether POR damage disrupts hippocampal remapping is unknown.

Recent human fMRI studies provide convergent evidence for the role of the PPA in processing contextual information. The PPA response pattern is similar for visual scenes depicting different views of the same spatial context, but only in participants that have learned that these views depict the same context (Marchette, Vass, Ryan, & Epstein, 2015) (Fig. 3C), and posterior parahippocampal cortex is activated when participants process cues

with strong contextual associations (Aminoff, Kveraga, & Bar, 2013; Bar & Aminoff, 2003; Bar, Aminoff, & Schacter, 2008; Davachi et al., 2003; Diana, 2017; Hayes, Nadel, & Ryan, 2007; Ross & Slotnick, 2008). The PPA is particularly sensitive to landmark cues that could serve as useful indicators of context (Troiani, Stigliani, Smith, & Epstein, 2012; Epstein, 2014), such as environmental boundaries (Epstein & Kanwisher, 1998; Kamps, Julian, Kubilius, Kanwisher, & Dilks, 2016; Kravitz, Peng, & Baker, 2011; Park, Brady, Greene, & Oliva, 2011) and large, stable objects (Julian, Ryan, & Epstein, 2016; Konkle & Oliva, 2012). The PPA is also modulated by the temporal sequence in which items are experienced (Turk-Browne, Simon, & Sederberg, 2012). However, one previous study found that the PPA is less strongly activated when participants identify scenes based on situational than spatial cues (Epstein & Higgins, 2006). Future studies are needed to resolve whether the POR / PPA is equally sensitive to all types of context-defining cues, and to determine whether contextual representations in this region are constrained by all contextual cue boundary conditions.

### **Concluding remarks**

Based on a survey of the cues critical for shaping contextual representations and their boundary conditions, we propose that context is a holistic representation of the spatial, situational, and temporal cues that reliably predict particular behavioral and mnemonic outputs. Extensive research supports the idea that context-dependent memory is mediated by the hippocampus. At a mechanistic level, context is represented by the hippocampus through remapping, driven by parahippocampal context recognition inputs. Together, our chapter shows that the brain learns in a dynamic world by forming holistic representations of the stable and reliably structured cue constellations (i.e., contexts) that in turn make it possible to generate precise predictions about the future.

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## Figure captions

**Figure 1. What is Context?** **A)** Contexts are defined by three cue types: Spatial, Situational, and Temporal. **B)** Cues must be experienced as stable to form an integral part of context. The longer rodents experienced a context prior to fear conditioning, the more likely they were to show contextual conditioning (% freezing). Context pre-exposure (PRE) also resulted in stronger conditioning than no pre-exposure (Fanselow, 1990). **C)** Contexts are not defined by single discrete cues. When rodents were pre-exposed to either a spatial context (Context), separately to each of the cues that conjointly define that context (Cues), or a completely different context (Control), they subsequently displayed fear response to the context only when initially exposed to the context itself (Rudy and O'Reilly, 1999). **D)** Contextual cues are represented as reliably organized. When participants recalled locations of landmarks in a city, their recall patterns showed evidence of hierarchical clustering into multiple smaller local contexts. Landmarks were drawn closer together on a map when recalled as being in similar local contexts (Within) than in different local contexts (Between) (Hirtle & Jonides, 1985).

**Figure 2. The hippocampal basis of contextual memory.** **A)** Reverse inference meta-analysis (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011) of 36 context-dependent memory human fMRI studies. Overlapping activation across studies was largely localized to the hippocampus (threshold  $p < 0.01$ , FDR-corrected). **B)** Contextual memory is indexed by hippocampal remapping, in which all simultaneously recorded neurons alter their firing patterns across contexts (Alme et al., 2015). **C)** Remapping is induced by contextual cue changes: i) Spatial Cues. As visual cues (mountains) were gradually morphed from Context A to B during a spatial memory task, a rapid remapping of fMRI response patterns (Sigmoidal) better characterized hippocampal activity than a gradual change (Linear) (Steemers et al., 2016). ii) Situational cues. Hippocampal neurons represented locations in two different situational contexts, one relative to a moving platform (left) and another relative to the stable room (right) (Keleman & Fenton, 2010). iii) Temporal cues. Left: hippocampal neurons modulated by time. Right: neurons changed firing patterns when the task's temporal parameters (yellow bars) were altered (MacDonald et al., 2011). **D)** Remapping reflects contextual boundary conditions: i) Stability. The same hippocampal neurons (in subfields CA3 and CA1) reactivated two weeks later after mice were placed in the same context as initial exposure (Tayler et al. 2013). ii) Non-discreteness. Example hippocampal neuron that did not remap when a discrete object (white circles) was moved (magenta line to star) or a novel object was added (star) (Deshmuck & Knierim, 2013). iii) Reliable organization. When rodents explored two chambers containing objects in different positions associated with different valences, hierarchical cue structure was reflected in hippocampal population activity patterns (McKenzie et al., 2014).

**Figure 3. Parahippocampal context recognition inputs to the hippocampus.** **A)** When rodents walked along a linear track, optogenetic (laser) inactivation of the MEC induced hippocampal remapping (Miao et al., 2015). **B)** A primary input to the rodent MEC is POR, which may be homologous to human PPA (shown on the inflated cortical surface; Julian, Fedorenko, Webster, & Kanwisher, 2012). **C)** POR lesions cause context recognition impairments. Control rats explore familiar discrete objects more when those objects appear in a different familiar context than they initially encountered them, but POR lesions eliminate this object-context novelty preference. POR lesions had no effect in a comparable discrete cue object recognition task (Norman & Eacott, 2005). **D)** PPA mediates context recognition

in humans. fMRI activity patterns in the PPA were similar for images of the interior and exterior of the same buildings, which share the same spatial context, but only students who have experience with those buildings (Penn), not in students who do not (Temple) (Marchette et al., 2015).

**Index keywords**

Hippocampus, hippocampal formation, medial temporal lobe, learning, memory, conditioning, remapping