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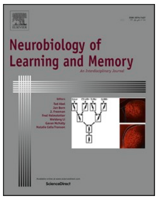

The limbic memory circuit and the neural basis of contextual memory

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ABSTRACT

The hippocampus, retrosplenial cortex and anterior thalamus are key components of a neural circuit known to be involved in a variety of memory functions, including spatial, contextual and episodic memory. In this review, we focus on the role of this circuit in contextual memory processes. The background environment, or context, is a powerful cue for memory retrieval, and neural representations of the context provide a mechanism for efficiently retrieving relevant memories while avoiding interference from memories that belong to other contexts. Data from experimental lesions and neural manipulation techniques indicate that each of these regions is critical for contextual memory. Neurophysiological evidence from the hippocampus and retrosplenial cortex suggest that contextual information is represented within this circuit by population-level neural firing patterns that reliably differentiate each context a subject encounters. These findings indicate that encoding contextual information to support context-dependent memory retrieval is a key function of this circuit.

1. Introduction

The hippocampus (HPC), retrosplenial cortex (RSC) and anterior thalamus (AT) are key components in a functional memory circuit. These three limbic structures are bidirectionally interconnected via an extensive array of direct and indirection connections. A simplified diagram is shown in Fig. 1 and more detailed illustrations of connectivity have been published elsewhere (for detailed reviews see Aggleton et al., 2010; Bucci and Robinson, 2014; Clark and Harvey, 2016; Sugar et al., 2011). The HPC sends extensive output to the RSC and AT, including direct projections from CA1 and the subiculum (Wright, Erichsen, Vann, O'Mara, & Aggleton, 2010; Wyass & Van Groen, 1992; Yamawaki et al, 2019). The RSC and AT project back to the HPC via the subiculum and entorhinal cortex (Van Groen & Wyss, 1995; Wyass & Van Groen, 1992). The AT nuclei are densely and reciprocally interconnected with the RSC, and include the anterior dorsal, anterior ventral and anterior medial nuclei (Van Groen, Vogt, & Wyss, 1993).

Given these anatomical relationships, it is not surprising that these three regions have strikingly similar functional characteristics. Lesions of any of these regions produce amnesia in human subjects (Mair, 1994; Scoville & Milner, 1957; Valenstein et al., 1987) and memory impairments in experimental animals (Nelson, 2021; Smith, 2008; Todd & Bucci, 2015). Lesion studies show that all three regions are also critical for spatial cognition (e.g., Byatt and Darymple-Alford, 1996; Eichenbaum et al., 1990; Keene and Bucci, 2009) and neurons within the circuit exhibit an array of spatial firing correlates, including spatially localized firing (O'Keefe & Dostrovsky, 1971), directional coding (Taube, 1995), boundary coding (Alexander et al., 2020), and encoding of goal locations (Miller, Mau, & Smith, 2019). Moreover, there is evidence for functional interactions between all components of this circuit (e.g., Alexander, Rangel, Tingley, & Nitz, 2018; Cooper & Mizumori, 2001; Jenkins, Vann, Amin, & Aggleton, 2004; Mao et al., 2018; Savage, Hall, & Vetreno, 2011; Smith, Wakeman, Patel, & Gabriel, 2004). However, we do not yet have a detailed picture of the functional contributions of each individual region or how specific interregional interactions produce particular memory functions (for discussion of this see Aggleton & Brown, 1999; Bucci & Robinson, 2014; Smith, Miller, & Vedder, 2018; Vann, Aggleton, & Maguire, 2009).

In this review, we focus on one particular function of this circuit, contextual memory. We will use the term 'context' to refer to the continuously present background cues within the environment, including the size and shape of the experimental apparatus, the color of the walls, the tactile features of the floor, and any ambient odors, sounds and illumination conditions. This is a commonly used operational definition and neural representations of the context are sensitive to these environmental variables. However, behavioral and neural data indicate that context representations also incorporate more abstract non-environmental features such as the behavioral strategies and task

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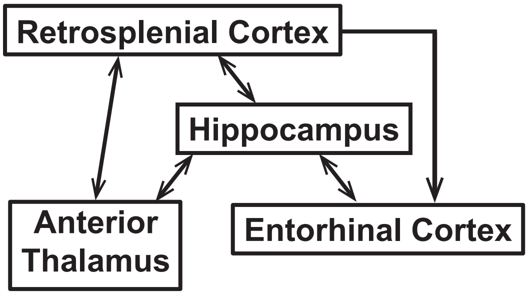

Fig. 1. Simplified illustration of the connections between the HPC, RSC and AT. See text for details.

demands of an experimental situation (for review see Smith & Bulkin, 2014).

The context plays an undeniably profound role in memory. Learned information is bound to the learning context, and the context is a remarkably potent retrieval cue. Empirical studies of contextual cueing of memory have a long history in psychology (Smith, 1988). Returning to a familiar context, such as one's childhood neighborhood, can evoke rich and detailed memories, even those thought to be long-forgotten. Items learned in one context are better recalled when testing takes place in the same context (Godden & Baddely, 1975). The context can also serve as a disambiguating cue that allows subjects to retrieve information associated with one context without interference from items learned in other contexts. For example, subjects who learn two lists of items in distinct contexts exhibit better recall than those who learn both lists in the same context (Smith, 1988). The association between context and memory is so strong that simply asking subjects to think about the learning environment is sufficient to improve recall (Smith, 1979). Well-known mnemonic techniques, such as the method of loci, memory palace and others are variations of this contextual cueing effect.

The context is important for the retrieval of many kinds of memory, including Pavlovian conditioned responses (Bouton, 1993), instrumental behaviors (Freeman, Cuppernell, Flannery, & Gabriel, 1996a; Smith et al., 2004; Thomas, McKelvie, & Mah, 1985), priming (Smith, Heath, & Vela, 1990), word list learning (Smith & Vela, 2001), object recognition (Tsivilis, Otten, & Rugg, 2001), motor skills (Ruitenberg, de Kleine, van der Lubbe, Verwey, & Abrahamse, 2012) and episodic memory (Yonelinas, Ranganath, Ekstrom, & Wiltgen, 2019). However, the notion of context is also closely related to spatial cognition. Although context representations frequently include non-spatial variables (e.g., Smith & Mizumori, 2006), the spatial geometry of the environment is typically a defining characteristic of the context and the brain regions known to be involved in context coding are also critical for spatial navigation. Moreover, navigational and contextual information both emerge from the same underlying neural computations, such as place fields and remapping, as we discuss below. Thus, the context occupies an intermediate position between spatial cognition and memory: It incorporates spatial information and is useful for spatial memory, planning, and decision making, but the contextual role in memory extends far beyond the spatial domain. Consistent with this idea, many of the aforementioned kinds of context-sensitive memory are not inherently spatial.

2. The hippocampal role in contextual memory

Most of the work on the neural encoding of context has been done in the HPC, where there is a large literature dating back to the 1970s (Hirsh, 1974). As mentioned above, early learning theorists noted the profound influence that contextual information has on learning processes. The subsequent discovery that this contextual influence is reliably disrupted by HPC lesions led to an extensive body of work on this topic (Kim & Fanselow, 1992; Penick & Solomon, 1991). A hallmark of the HPC role in contextual memory is that many kinds of HPC-independent learning become reliably dependent on the HPC when a contextual memory requirement is added. For example, HPC lesions selectively impair conditioned fear responses to the context but do not impair fear responses to phasic cues, such as a tone or light (Kim & Fanselow, 1992; Phillips & LeDoux, 1992). Similarly, standard Pavlovian delay eyeblink conditioning and instrumental discrimination learning do not require the HPC, but manipulation of the context reveals a HPC role. Intact subjects show decreased responding when the context is altered but subjects with HPC lesions do not (Burhans & Gabriel, 2007; Penick & Solomon, 1991). In these experiments, subjects with HPC lesions continue to perform as they did before the context change, suggesting that they failed to detect the change in context. A similar pattern of results has been reported in a wide variety of experimental tasks. For example, rats do not need the HPC to remember odor cues or their association with reward, but the HPC is needed when they have to remember which odors are rewarded within a particular context (Butterly, Petroccione, & Smith, 2012; Komorowski et al., 2013; Sill & Smith, 2012). This pattern of results suggests that the HPC selectively represents the context but not the individual items and associations of the basic (non-contextual) task.

The most extensively studied contextual memory task is contextual fear conditioning, in which rats learn to fear the context where foot shock occurs (for review see Maren & Holt, 2000; Maren, Phan, & Liberzon, 2013). Following the initial discovery that HPC lesions selectively impair conditioned fear responses to the context (Kim & Fanselow, 1992; Phillips & LeDoux, 1994), numerous follow up studies with various techniques and experimental procedures have confirmed that HPC disruption reliably impairs contextual fear memory (e.g., Akers et al., 2014; Cullen, Ferrara, Pullins, & Helmstetter, 2017; Hobin, Ji, & Maren, 2006). Perhaps the most striking evidence that the HPC represents the context comes from approaches using optogenetic and chemogenetic manipulation techniques (Liu, Ramirez, & Tonegawa, 2014; Ramirez et al., 2013; Ressler, Goode, Kim, Ramanathan, & Maren, 2021). This approach involves tagging the neurons that were active during a specific experience (e.g. contextual fear conditioning) and selectively expressing artificial ion channels in those neurons. The experimenter can then artificially reactivate the same population of neurons and observe the effects. In the case of contextual fear conditioning, artificial reactivation of these neural ensembles evokes a conditioned fear response, suggesting that the neural population encoded information about the context (Tonegawa, Liu, Ramirez, & Redondo, 2015). Initial studies found that artificial reactivation of the same neural populations that were active during contextual fear conditioning can evoke a fear response, even in a different context where the subject has never been shocked (Liu et al., 2014). This has been refined in several follow up studies that show that HPC neurons selectively represent the context and not the shock or other aspects of the learning situation (e.g., Ramirez et al., 2013). For example, one study tagged the HPC neurons that were active during exploration of context A (without shock) and subsequently paired the reactivation of those neurons with shock in a different context (context B), presumably forming an association between the HPC representation of context A and shock. During the test session, subjects were returned to context A where they spontaneously exhibited a fear response. Conversely, silencing the relevant HPC neural population blocks contextual memory (Tanaka et al., 2014).

Lesion and artificial reactivation studies provide strong support for the idea that HPC neural populations encode the context, but neurophysiological studies are needed to understand how contextual information is represented. HPC place cells typically fire in a circumscribed region of the environment (i.e. place fields, O'Keefe & Dostrovsky, 1971) and changing the environment causes changes in these firing patterns, commonly referred to as remapping (Fig. 2, Law, Bulkin, & Smith, 2016; Leutgeb et al., 2005). A given neuron may have place fields in both environments, with the locations being unrelated to each other

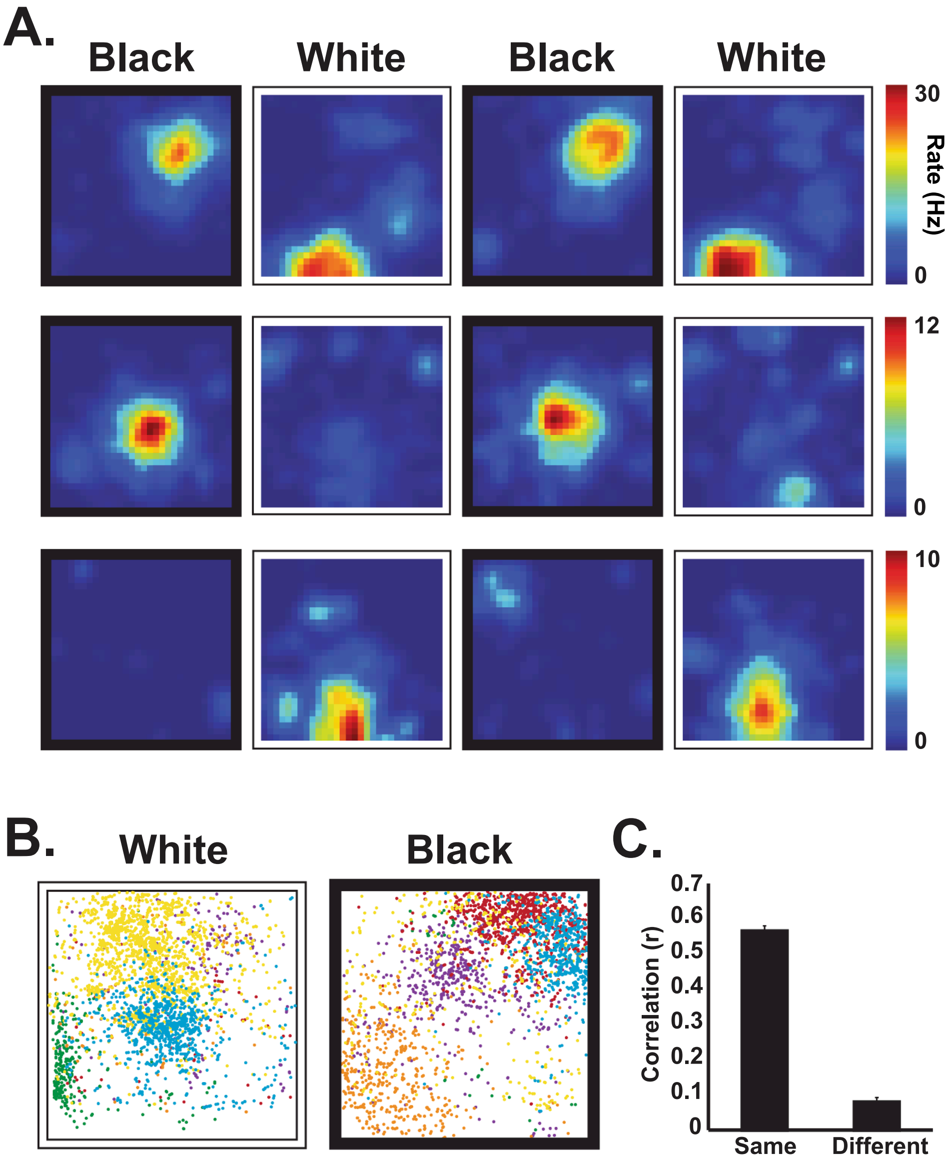

Fig. 2. Hippocampal neurons exhibit remapping in response to context change. A) Firing rate maps are shown for three CA1 neurons recorded while a rat foraged in two distinct environments, a black box and a white box. B) At the population level, this results in unique spatial firing patterns for each context a subject visits. Color coded spikes (dots) are shown for six neurons in the white and black box. C) The context-specific firing patterns are reliably reproduced when subjects return to a familiar context. Pixel by pixel spatial correlations are high for repeated visits to the same context, while low spatial correlations indicate that firing patterns are distinct for visits to different contexts (n = 296 CA1 neurons).

(e.g. top row Fig. 2A). However, the most common form of remapping in response to environmental change is for a given neuron to have a place field in one environment, but to be nearly silent in another (e.g. second and third rows Fig. 2A). As a result, a unique ensemble of neurons is active for each environmental context the subject visits and collectively, these ensembles emit a unique spatial firing pattern (Fig. 2B). There is no obvious limit to the capacity of this system to generate orthogonalized representations of the context (Alme et al., 2014) and whenever the subject returns to a familiar context, the appropriate firing pattern is re-expressed. HPC neurons also respond to a wide variety of non-spatial task stimuli and events, including auditory and olfactory cues (Freeman, Cuppernell, Flannery, & Gabriel, 1996b; Moita, Svetlana, Zhou, LeDoux, & Blair, 2003; Wood, Dudchenko, & Eichenbaum, 1999), rewards and aversive stimuli (Berger, Rinaldi, Weisz, & Thompson, 1983; Smith & Mizumori, 2006), objects (Manns & Eichenbaum, 2009), and events such as the start and end of training trials (Bulkin, Law, & Smith, 2016; Bulkin, Sinclair, Law, & Smith, 2020). These non-spatial responses also undergo 'remapping' in response to context change (Bulkin et al., 2016). The result is that each context a subject encounters has a unique HPC firing pattern associated with it, and any brain region that receives HPC output could readily use that information to identify the current context and thereby alter local processing in a context-dependent manner.

This mechanism for representing the context is apparent in tasks where the context must be used to guide memory and choice behavior. For example, McKenzie and colleagues (McKenzie et al., 2014; see also Komorowski et al., 2013; Komorowski, Manns, & Eichenbaum, 2009) recorded HPC neuronal activity while rats performed a context-dependent odor discrimination tasks with two discrimination problems (A vs B and C vs D). The rats were trained to dig for reward in cups containing odors A and C in one context, but B and D in the other context. Using representational similarity analysis, they found that although HPC neurons responded to spatial locations, the specific odors, and the valence of the odor cues, as well as combinations of these variables, the factor that was most clearly distinguished by population firing patterns was the context. In other words, ensemble firing patterns were organized hierarchically, with firing patterns being influenced most strongly by the context, followed by spatial location, then by cue valence and finally by specific odors. Although HPC neurons represented individual items of information, such as locations and odors, there was also an overarching representation of the context contained within these firing patterns (also see Bulkin et al., 2020).

In our laboratory, we explicitly examined the role of HPC context representations in memory retrieval (Bulkin et al., 2016; Butterly et al., 2012). Rats were trained on a proactive interference task, where they learned two sets of conflicting olfactory discrimination problems, one after the other. The second problem set contained half of the odors from the first problem set, with their valence reversed, along with several novel odors (see Fig. 3A). Therefore, memories acquired during learning of the first problem set were expected to interfere with learning the second problem set. However, this interference should be reduced if subjects learned the two problem sets in different contexts because the two problem sets can be segregated according to the context where they were learned. Any interference-reducing effect of the context should depend on the HPC. Accordingly, half of the rats were trained on the two problem sets in the same context, while the other half were trained in different contexts (black and white boxes). The rats were given muscimol or saline injections into the dorsal HPC during learning on the second problem set.

As expected, control rats that learned the two problem sets in different contexts were less susceptible to interference and consequently, they performed significantly better than controls that learned the two problem sets in the same context (Fig. 3B, solid bars). However, the contextual learning advantage seen in controls was completely absent in rats with HPC inactivation. Their performance was the same as controls that learned the two problem sets in the same context (Fig. 3B, open bars). Notably, muscimol rats did not perform worse than controls in the same context condition (Fig. 3B, red bars), suggesting that the rats could learn a complex set of conflicting discrimination problems without the HPC. It was only the ability to use contextual information to reduce interference which was impaired by HPC inactivation. This is another example of a HPC-independent task becoming HPC-dependent when a contextual component is added.

We next recorded HPC neuronal firing patterns in the same task in order to determine whether the characteristics of the HPC firing patterns are related to the ability to use contextual information to support

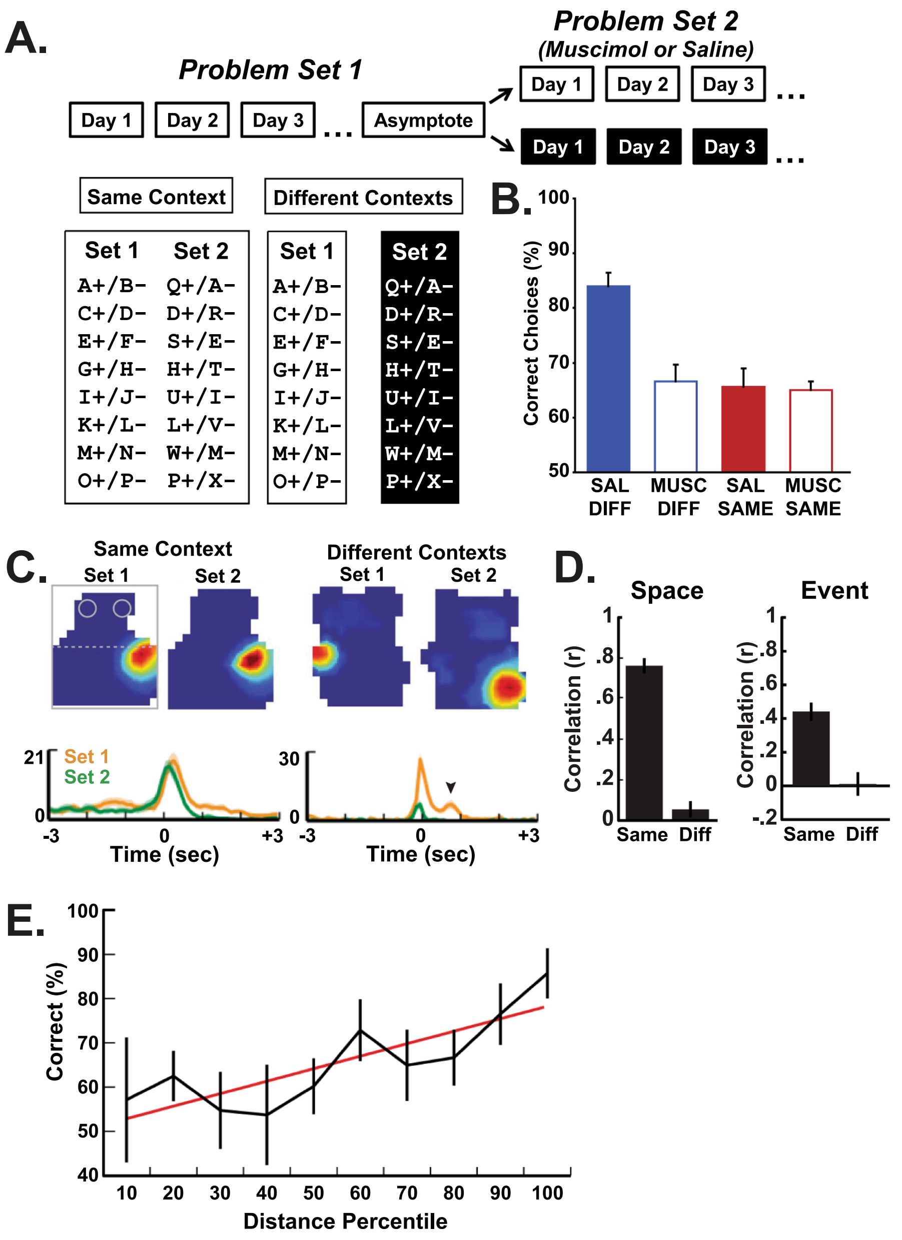

Fig. 3. Distinct hippocampal firing patterns are associated with good context-dependent memory performance. A) Schematic of the proactive interference task. Rats were trained on two sets of eight odor discrimination problems, with one odor in each problem reinforced (+) with a buried sugar pellet. Rats learned the first problem set in a white box until they reached asymptote (~98% correct), followed by three training sessions on the second problem set, either in the same white box or a different black box. Note that the two problem sets have conflicting items, designed to induce interference (e.g. odor A was rewarded in Set 1, but not rewarded when paired with a novel odor, Q, in Set 2). Muscimol or saline was infused into the dorsal HPC prior to each of the three training sessions of Set 2. B) Saline control rats that learned the second problem set in a new context (SAL-DIFF, solid blue bar) performed significantly better than control rats that learned the second problem set in the same context (SAL-SAME solid red bar). Rats that were given muscimol infusions did not exhibit any advantage from learning in different contexts (compare open bars). C) Spatial firing patterns were similar when the two problem sets were learned in the same context, but they remapped in different contexts. Firing rate maps are shown for two example neurons recorded during Set 1 and Set 2, one from the same context condition (left) and one from the different context condition (right). The outline of the box is shown in grey with the position of the digging cups (circles) and a removable divider (dotted line) which separated the trial area from the intertrial waiting area. Peri-event time histograms for two different example neurons (lower panels) show that event-related firing exhibited the same pattern, with similar responses in the same context (left) and distinct firing in different contexts (right, orange and green lines). Firing rates are shown for 3 s before and after the start of a trial (Time 0). Many neurons fired at the start of the trials. A second burst of firing at the time of arrival at the digging cup can be seen in the plot on the right (arrow). D) This pattern of results can also be seen in the full data set. Average spatial correlations (right) and correlations of event-related firing (right) is shown for all neurons (n = 99). E) The dissimilarity, or distinctiveness, of the firing patterns between Set 1 and Set 2 was measured using Mahalanobis distance. The distinctiveness (Distance Percentile) of the firing patterns was correlated with behavioral performance (% Correct), indicating that more distinct HPC firing patterns were associated with better memory performance (for details, see Bulkin et al., 2016; Butterly et al., 2012). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

olfactory memory. We reasoned that more distinct context representations would promote more selective cueing of the correct, context-specific odor memories and thereby reduce interference. Not surprisingly, we found that population level firing patterns were far more distinct when rats learned the two problem sets in different contexts, as compared to learning in the same context (Fig. 3D). This resulted from the remapping of spatial and non-spatial responses of individual HPC neurons (Fig. 3C). However, we also found that the firing patterns were clearly related to memory performance. The firing patterns during the second problem set showed some moment-to-moment variability. During some learning trials for problem set 2, the firing patterns were very distinct from those of problem set 1, but on other trials the patterns were less distinct. We compared the distinctiveness of the firing patterns to behavioral performance and found that the more distinct the firing patterns were for the two contexts, the better the rats performed (Fig. 3E). This suggests that the HPC capacity to generate highly distinct firing patterns is the mechanism that supports context-dependent memory retrieval.

Overall, these findings indicate that the HPC supports contextual memory processes. Moreover, there is a well-understood neurophysiological mechanism for representing contextual information: Spatial and non-spatial firing patterns of HPC neurons remap in a manner that results in unique population firing patterns for each context a subject visits. These context representations are adaptive because they provide a mechanism for automatically cuing memories that belong to the context and simultaneously reducing interference from memories that belong to other contexts.

3. The retrosplenial cortical role in contextual memory

Less is known about the RSC, compared to the HPC, but a growing literature indicates an RSC role in contextual memory. fMRI studies of human subjects have pointed to a likely role in contextual memory and the related function of scene perception for some time (for reviews see Chrastil, 2018; Epstein & Baker, 2019; Miller, Vedder, Law, & Smith, 2014). For example, Bar and Aminoff (2003) found that the RSC is preferentially activated by objects that have strong contextual associations, as compared to objects that are not closely linked to a particular context. The first experimental lesion studies to clearly identify an RSC role in contextual memory came from contextual fear conditioning studies in David Bucci's laboratory (Keene & Bucci, 2008a, 2008b). Since the initial reports, the RSC role in contextual fear memory has been confirmed in several studies using a variety of approaches. Temporary blockade of NMDA receptors in RSC blocked retrieval of contextual fear memory (Corcoran et al., 2011; Corcoran, Yamawaki, Leaderbrand, & Radulovic, 2018), inhibiting protein synthesis in the RSC blocked the acquisition of contextual fear memory (Kwapis, Jarome, Lee, & Helmstetter, 2015), and disruption of RSC outputs impaired contextual fear memory (Robinson, Poorman, Marder, & Bucci, 2012). As with the HPC, optogenetic reactivation of the RSC neurons that were active during contextual fear conditioning evokes a fear response (Cowansage et al., 2014). Interestingly, reactivation of the RSC neurons was sufficient to induce a fear response even when the HPC was temporarily inactivated, suggesting that the RSC contains an independent functional context representation that does not require HPC processing once it has been formed, although the formation of RSC representations may initially require the HPC (Mao et al., 2018).

Additional work on sensory preconditioning from the Bucci laboratory (Robinson et al., 2014) has identified a possible mechanism underlying the formation of RSC context representations. The context is made up of an array of stimuli of various modalities, which are thought to be bound together into a unitary representation of the context (e.g., Anagnostaras, Gale, & Fanselow, 2001; Holland & Bouton, 1999). Sensory preconditioning is a test of the capacity to spontaneously form associations between coincidentally occurring stimuli. Subjects are initially exposed to paired presentations of two neutral stimuli (e.g. a tone and a light) without any reinforcement. During the subsequent conditioning phase, one of the cues (e.g. the light) is paired with reinforcement, followed by testing with the second cue (the tone), which was never reinforced. Responding to the tone indicates that subjects must have formed an association between the light and tone during the initial preconditioning phase. Lesions or DREADD inactivation of the RSC impair sensory preconditioning (Robinson, Adelman, Mogul, Ihle, & Davino, 2018; Robinson et al., 2014). On the basis of these findings, Bucci and colleagues (Bucci & Robinson, 2014; Todd & Bucci, 2015) have proposed that the primary contribution of the RSC to contextual memory is to generate these stimulus–stimulus associations. Additional experimental work will be needed to determine whether this account fully captures the core function of the RSC, but it provides an important conceptual bridge between the contextual memory literature and the RSC role in various forms of stimulus encoding and non-contextual conditioning (for review see Smith, Miller, & Vedder, 2018).

The earliest neurophysiological evidence that the RSC might be involved in contextual memory processes came from studies of instrumental discriminative avoidance learning (for review see Gabriel, 1993). In this task, subjects learn to respond to a shock-predictive auditory tone and ignore a non-predictive tone. Neurons in the RSC and AT respond to the auditory tone cues and the pattern of activity across neural populations is specific to a particular environmental context. Training subjects in different contexts produced different firing patterns (Freeman et al., 1996a) and disconnection of the HPC from the AT and RSC disrupted these firing patterns and impaired the ability to match a learned discrimination to the appropriate context (Smith et al., 2004). Most of the modern neurophysiological studies have focused on spatial navigation and have revealed an array of spatial responses, including spatially localized firing patterns (Alexander & Nitz, 2015, 2017; Miller et al., 2019), directional coding (Jacob et al., 2017), boundary coding (Alexander et al., 2020), encoding of navigational landmarks (Vedder, Miller, Harrison, & Smith, 2017) and future goal locations (Miller et al., 2019). However, these studies did not include manipulation of the environmental context.

Recently, we explicitly examined RSC neural responses to context change by allowing rats to forage in two distinctive contexts defined by the background environmental cues (black and white boxes, Miller, Serrichio, & Smith, 2020), similar to previous studies of the HPC (Law et al., 2016; Leutgeb et al., 2005). Consistent with previous results (Alexander & Nitz, 2015; Miller et al., 2019), RSC neurons exhibited spatially localized firing patterns, although the neurons typically exhibited large areas of elevated firing rather than the compact, well-defined place fields typically seen in the HPC. Nevertheless, these spatial firing patterns exhibited clear and reliable remapping in response to the context change (Fig. 4A). At the population level, RSC firing patterns recorded in one visit to a given context could readily be used to decode the rat's position on a subsequent visit to the same context (Fig. 4C), indicating that the spatial firing patterns are reliably reproduced each time the subject returns to the environment. In contrast, decoding the rat's position was far less accurate when we used firing patterns from the other context, indicating that the firing patterns for the two contexts were different. These results suggest that, like the HPC, the RSC encodes contextual information through context-specific spatial firing patterns.

RSC neurons also exhibited a unique rate code for the context. Many RSC neurons showed little spatial specificity and fired throughout the environment, but fired at a consistently higher rate in one context as compared to the other (Fig. 4D). Responses ranged from a strong preference for the white box to a preference for the black box (Fig. 4E). These consistent rate differences produce a constant output that can readily be used to identify the current context. Using a decoding approach, we were able to correctly identify the context with ~90% accuracy from just a brief (250 msec) glimpse of the firing data from the RSC population (Fig. 4F). This rate code may represent a simple and effective mechanism for encoding contextual information.

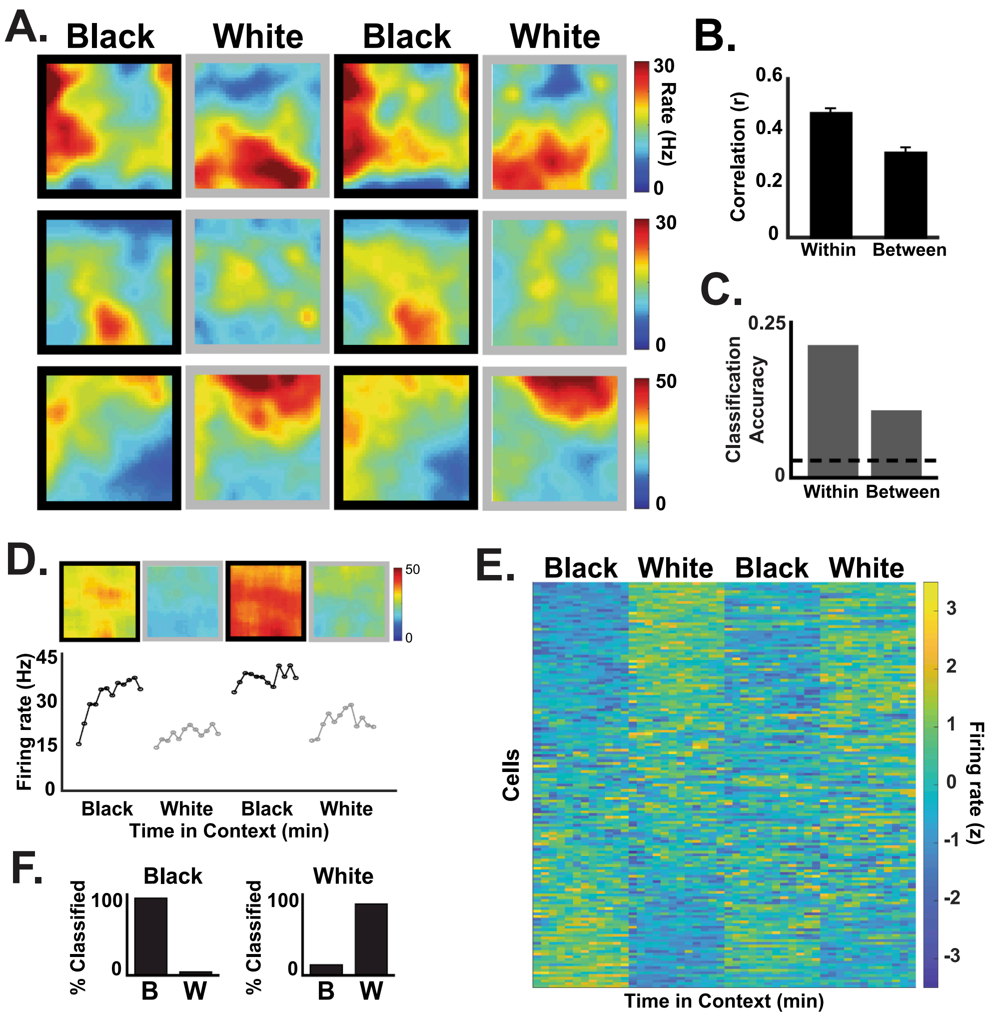

Fig. 4. Retrosplenial cortical neurons encode contextual information in two ways. A) RSC neurons exhibit spatially localized firing patterns that reliably differentiate the black and white boxes. Three illustrative examples are shown. B) Pixel by pixel spatial correlations are significantly higher for repeated visits to the same context than for visits to different contexts (n = 143 neurons). C) Although RSC spatial firing patterns are not as spatially specific as those in the HPC, population firing patterns can be used to decode the rat's current location significantly better than chance. Decoding accuracy is significantly better when training and test data come from the same context than when they come from different contexts, indicating that the spatial firing patterns are reliably different in the two contexts. D) RSC neurons also exhibit a rate code for the context. This example neuron fired at a reliably higher rate in the black box as compared to the white box. E) The firing rates 143 RSC neurons were binned in consecutive 1 min bins (rows) and sorted by firing rate in the black box. Many RSC neurons exhibited a clear preference for the white box (upper rows), while others preferred the black box (lower rows). F) Population firing rates could be used to decode the current context with high accuracy. Population firing rates sampled in the black box (left plot) were correctly classified as having come from the black box (B) more than 90% of the time and were rarely misclassified as coming from the white box (W). Similar accuracy was seen for the white box (right plot, for details see Miller et al., 2020).

The current literature indicates that the RSC, like the HPC, is involved in encoding contextual information. In addition to the HPC-like context representations produced by remapping of spatial firing patterns, the RSC also generates a striking rate code for the context. However, the study of RSC context coding has only begun. We do not yet know which environmental cues are the most important and how various cues influence RSC representations, unlike the HPC where manipulations such as cue rotations, deletions and cue scrambling have been studied extensively (e.g., Shapiro, Tanila, & Eichenbaum, 1997). We also do not know how RSC context representations emerge. RSC representations may depend on the HPC, at least during the initial stages of learning, although they appear to be independent of the HPC at later time points (Cowansage et al., 2014; Katche et al., 2013; Mao et al., 2018; Tayler, Tanaka, Reijmers, & Wiltgen, 2013). This suggests that RSC representations might be the product of systems consolidation of information from the HPC to the RSC (Alexander et al., 2018; De Sousa et al., 2019; Miller et al., 2019, also see Opalka and Wang, 2020).

4. The anterior thalamic role in contextual memory

The AT has a well-studied role in spatial cognition (for review see Clark & Harvey, 2016; Taube, 2007) and it is known to be involved in a variety of non-spatial memory tasks as well (for review see Nelson, 2021). However, the AT data on contextual memory is far more sparse than for the HPC or RSC. Nevertheless, a growing body of work suggests that the AT is also a key component of the contextual memory system. Studies of immediate early gene expression have shown that AT neurons are active when subjects are exposed to a novel environment and this AT activity may facilitate contextual memory processes in the HPC and RSC. For example, exposure to a novel context causes widespread c-fos activity in the HPC and RSC, but this is blocked by AT lesions (Jenkins, Dias, Amin, & Aggleton, 2002). Consistent with this idea, Savage and colleagues (Savage, Hall, & Resende, 2012; Savage et al., 2011) have found that AT damage is associated with widespread disruption of neurogenesis and acetylcholine activity in the HPC and RSC, along with behavioral deficits in HPC-dependent tasks. These observations suggest that the AT makes an important, if not completely understood, contribution to the broader contextual memory circuit.

The AT role in contextual memory has also been studied with fear conditioning. Anterior dorsal neurons showed increased c-fos activity when rats were re-exposed to a context where they had been shocked (Lopez, Gamache, Milo, & Nader, 2018; Yasoshima, Scott, & Yamamoto, 2007). Permanent lesions of the AT impaired acquisition of contextual, but not cued fear memory, and they impaired long-term retrieval of the contextual fear memory in rats (Marchand, Faugère, Coutureau, & Wolff, 2014), although another study found impairments in both cued and contextual fear conditioning in mice (Célérier, Ognard, Decorte, & Beracochea, 2000). Temporary inactivation of the AT impaired retrieval of a contextual fear memory one day after learning, but not thirty days after learning (Lopez et al., 2018), suggesting a time-limited role in contextual memory. Interestingly, anterior medial lesions impaired contextual fear memory induced by social defeat in rats (Rangel, Baldo, & Canteras, 2018). These results indicate an AT role in contextual fear conditioning, but details about the timing and other parameters that recruit AT involvement are not yet clear.

In our laboratory, we used the same context-based olfactory memory task described above (Fig. 3A) to examine the AT role in contextual memory (Law & Smith, 2012). We inactivated the AT with muscimol and found the same pattern of impairment we had seen with HPC inactivation (Fig. 5). Control rats that learned the two problem sets in different contexts performed better than controls that learned in the same context, but AT inactivation blocked that contextual learning advantage. Like the HPC, the AT is critical for the capacity to use contextual information to guide memory retrieval and suppress interference. AT lesions have also been found to impair object-location memory and object-in-place memory (Aggleton & Nelson, 2020). Although not a direct test of contextual memory, these tasks require subjects to associate objects with the background environment, which is a key component of contextual memory. However, the same laboratory found that AT lesions impaired conditional discrimination tasks when rats relied on distal spatial cues, but not when they relied on the kind of local environmental features commonly manipulated in contextual memory tasks (Dumont, Amin, & Aggleton, 2014). The reasons for this apparent discrepancy with findings of impaired contextual memory are not clear.

The neurophysiological evidence for an AT role in encoding contextual information is also sparse. As mentioned above, AT neurons exhibit context-dependent firing patterns during instrumental discrimination learning in coordination with their interconnected RSC layers (Freeman et al., 1996a) and these context-specific firing patterns are disrupted by disconnection from the HPC (Smith et al., 2004). Most of the neurophysiological studies of the AT have focused on the prominent head direction signal (for review see O'Mara & Aggleton, 2019; Peyrache, Duszkiewicz, Viejo, & Angeles-Duran, 2019; Taube, 2007; Tsanov & O'Mara, 2015), and these neurons do exhibit new directional preferences when the environment changes. However, the directional preferences of the whole population of neurons appear to shift as a coherent unit, suggesting that the directional system has realigned to a new set of environmental landmarks rather than producing an orthogonalized representation that is unique to the new context (Goodridge & Taube, 1995; Yoder & Taube, 2011; Yoganarasimha, Yu, & Knierim, 2006). Moreover, AT head direction cells continue to exhibit directional firing in the new context rather than acquiring entirely new correlates as HPC neurons have been shown to do (Bulkin et al., 2016; Smith & Mizumori, 2006; Wiener, Paul, & Eichenbaum, 1989). Thus, the directional signal does not appear to undergo the kind of remapping seen in the HPC and RSC. However, AT neurons have been shown to exhibit other kinds of spatial coding, such as place fields and border coding (Clark & Harvey, 2016; Jankowski et al., 2015), but these firing properties have not been extensively studied and we do not yet know whether they undergo HPC-like remapping in response to context change.

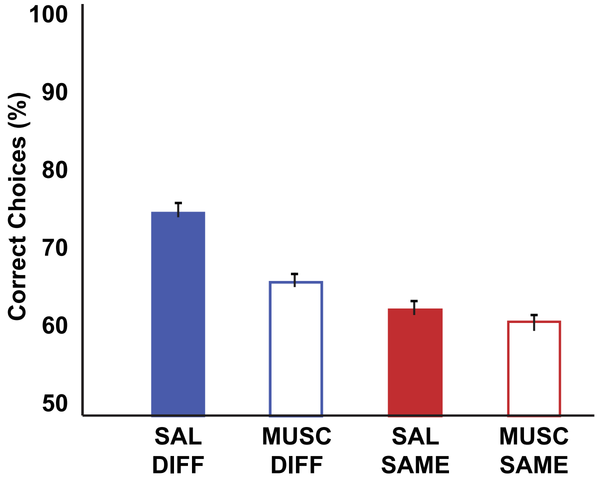

Fig. 5. Anterior thalamic inactivation blocks context dependent olfactory memory. The task and labels are the same as illustrated in Fig. 3A-B. Saline control rats that learned the second problem set in a new context (SAL-DIFF) performed significantly better than control rats that learned the second problem set in the same context (SAL-SAME). Muscimol infusions into the AT blocked the ability to use the context to guide olfactory memory (compare MUSC-DIFF to SAL-DIFF, see Law & Smith, 2012).

Overall, these results suggest that the AT plays a key role in contextual memory, but the precise nature of this contribution is not yet clear. Neurophysiological representations of the context in the form of complex population-level firing patterns have not yet been observed in the AT, although this has not been studied in detail. An important remaining question is whether AT neurons actually encode contextual information or instead act to facilitate context representations in the HPC and RSC. For example, AT neurons may respond selectively to contextual novelty, thereby providing a signal that triggers remapping in the RSC or HPC.

5. Conclusions

The data from the HPC, RSC and AT indicate a clear role in contextual memory processes. Neurons in many brain regions are sensitive to background variables (e.g., Olshausen & Field, 2005), suggesting that context sensitivity may be a common feature of neural systems, allowing for flexible information processing in varying conditions. However, neurons in the HPC, RSC and AT are not just sensitive to the context. Instead, they appear to construct and maintain coherent representations of the context which incorporate variables from a complex multi-modal array of features that define a learning situation. These neural representations of the context are critically important for memory. They provide a mechanism for promoting the retrieval of context-relevant memories while avoiding interference from irrelevant memories. More broadly, we suggest that the context representations generated by this circuit can be used by neural systems throughout the brain in order to promote context dependent processing in a wide range of sensory, emotional and cognitive functions.

We have accumulated substantial evidence for a contextual memory role of the HPC, RSC and AT individually, but contextual memory is complex and likely arises from the circuit-level interactions among these brain structures (e.g. Alexander et al, 2018; Corcoran et al, 2016, Opalka et al, 2020; Smith et al, 2004). We do not yet have a comprehensive model for how these interactions produce contextual memory. Nevertheless, the findings reviewed here provide a few key pieces to this puzzle, which are described below and summarized in Fig. 6. The local circuitry of the HPC is well suited for orthogonalizing inputs (Colgin, Moser, & Moser, 2008; Leutgeb et al., 2005), which results in an essentially limitless number of firing patterns that can be assigned to different contexts (Alme et al., 2014). This orthogonalization may act primarily on sensory inputs that arrive in the HPC via entorhinal cortical inputs, but the RSC and AT probably also provide important input to this process (Cooper & Mizumori, 1999; Smith et al., 2018). Output of these context-dependent HPC firing patterns likely modulates local processing widespread brain regions in order to promote flexible, context-specific cognitive, emotional and behavioral responses (Smith & Bulkin, 2014).

Accumulating evidence suggests that HPC-dependent memories are consolidated into the RSC (Alexander et al., 2018; Cowansage et al., 2014; Katche et al., 2013) and obtaining a clear understanding HPC-RSC consolidation processes will likely be critical for understanding contextual memory. However, at least one study suggests that the RSC may also play a time limited role in storing memories (Hart, Poremba, & Gabriel, 1997) and in any case, the RSC does not simply mirror HPC representations (Smith et al, 2012). RSC neurons encode navigational landmarks (Auger, Mullally, & Maguire, 2012; Vedder et al., 2017), which likely reflects extensive interactions with visual cortical regions (Powell et al, 2020), but also cues of other modalities (Smith et al, 2018). RSC encoding of environmental landmarks and other cues may be

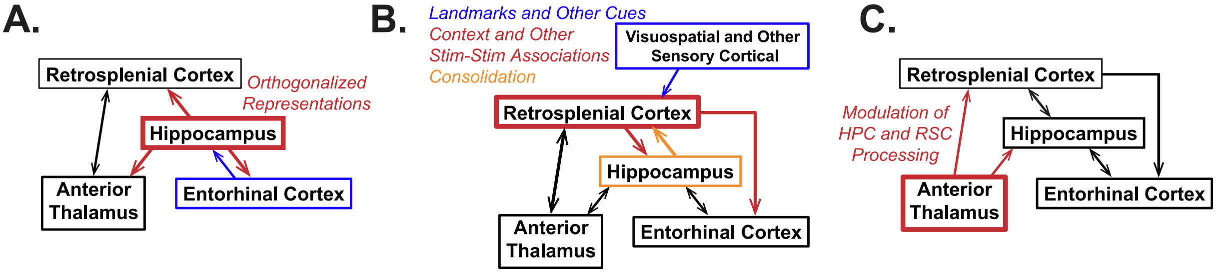

Fig. 6. Illustration of possible circuit interactions among the HPC, RSC and AT. A) The HPC orthogonalizes input from the entorhinal cortex (blue), resulting in unique firing patterns for each context a subject encounters. These HPC firing patterns support context-dependent processing in other brain regions via output to the entorhinal cortex, RSC/AT circuits, and other brain regions (not shown). B) HPC representations are consolidated into the RSC (orange), where additional processing incorporates information about landmarks and other multi-modal cues via inputs from the visual cortex and other sensory cortical regions (blue). C) AT input is critical for context processing in the HPC and RSC. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

important for linking HPC firing patterns to the cues that define each context. Additionally, the RSC is necessary for forming stimulus-stimulus associations as indicated by its role in sensory preconditioning (Robinson et al., 2014), but the HPC does not appear to be needed (Iordanova, Good, & Honey, 2011; Wimmer & Shohamy, 2012), suggesting that the RSC may play a special role in binding together diverse stimuli into a coherent context representation (Bucci & Robinson, 2014; Todd & Bucci, 2015). Whether the resulting RSC representations are a separate and independent source of contextual information (Cowansage et al., 2014), or instead feed back to influence HPC context representations is not presently known.

Interactions between the AT and the rest of this circuit are also critical for contextual memory. As described above, AT lesions impair contextual memory and disrupt processing in the HPC and RSC, suggesting that neural activity in the AT plays a key role in promoting context representations throughout this circuit. AT lesions severely impair processing in the RSC (Gabriel, 1993; Smith, Freeman, Nicholson, & Gabriel, 2002) and conversely, lesions of the RSC disrupt processing in the AT (Clark, Bassett, Wang, & Taube, 2010). The observation that fornix transection often produces memory deficits similar to those seen after HPC lesions (e.g., Dusek & Eichenbaum, 1998; Eichenbaum et al., 1990) suggests that HPC output to the AT is also critical for memory.

One possible model for the creation of context representations is illustrated in Fig. 6. The HPC generates the orthogonalized firing patterns that are the foundation of context representations. These representations become consolidated into the RSC where additional processing incorporates the landmarks and multi-modal stimulus associations that define that particular context. The AT input plays a critical, if not fully understood role in promoting coherent context representations. A comprehensive account of contextual memory, as well as episodic memory and spatial navigation, will depend on developing a more thorough model of the interactions among these components of the limbic memory circuit.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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