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Retrospective and Prospective Views on the Role of the Hippocampus in Interval Timing and Memory for Elapsed Time

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Abstract

The overlap of neural circuits involved in episodic memory, relational learning, trace conditioning, and interval timing suggests the importance of hippocampal-dependent processes. Identifying the functional and neural mechanisms whereby the hippocampus plays a role in timing and decision-making, however, has been elusive. In this article we describe recent neurobiological findings, including the discovery of hippocampal ‘time cells’, dependency of duration discriminations in the minutes range on hippocampal function, and the correlation of hippocampal theta rhythm with specific features of temporal processing. These results provide novel insights into the ways in which the hippocampus might interact with the striatum in order to support both retrospective and prospective timing. Suggestions are also provided for future research on the role of the hippocampus in memory for elapsed time.

Keywords

Medial temporal lobe, timing and time perception, decision-making, cortico-striatal circuits, time cells, neural oscillations

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1. Introduction

Previous research suggests that the hippocampus plays a secondary role in interval timing, with the effects of hippocampal or fimbria-fornix lesions being mainly observed in altered accuracy (e.g., proportional underrepresentation of target durations on the order of 20%), increased precision (e.g., sharper peak functions in the range of 10–40 s), and resetting of the timing process (e.g., internal clock) following the insertion of a gap or retention interval into the to-be-timed signal (Meck et al., 1984, 2013; Tam et al., 2013; Yin & Meck, 2013). A series of recent findings in rats, however, have dramatically expanded our understanding of the involvement of the hippocampus in duration discrimination, memory for elapsed time, and the representation of temporal sequences. In particular, the discovery of ‘time cells’ in the hippocampus that provide a framework for time stamping and binding sequential events in memory (MacDonald et al., 2011, 2013), as well as the observation that the hippocampus is crucial for resolving difficult duration discriminations in the multiple-minutes range (Jacobs et al., 2013), suggest that a reevaluation of the role of the hippocampus in temporal processing may now be appropriate. These issues are discussed in terms of the distinction between retrospective and prospective timing which leads to the proposal that the hippocampus may be involved in bridging the temporal gaps that inevitably occur in retrospective timing as well as in prospective timing on the order of minutes to hours. Finally, distinctive patterns of neural oscillations in the cortex, striatum, and hippocampus during temporal processing are described in order to argue for differential roles of cortico-striatal and hippocampal circuits in temporal integration (Gu & Meck, 2012; Hattori & Sakata, 2013). Individual-trials analysis of neural oscillations and spiking activity suggests that cortico-striatal circuits serve a timekeeping function while the hippocampus plays a complementary role by providing a temporal representation for the flow of events in memory (Allman et al., 2014; Lustig et al., 2005; MacDonald, *in press*; Meck, 2002a, b; Merchant et al., 2013a; Wimmer & Shohamy, 2011).

2. Hippocampal ‘Time Cells’ Bridge the Gap in Memory for Discontiguous Events

The hippocampus is essential to remembering the flow of events in distinct experiences and, in so doing, bridges the temporal gaps between discontiguous events. Recent electrophysiological recordings provide evidence of ‘time cells’ that appear to encode successive moments during an empty temporal gap between the key events composing a sequence in a behavioral task, while also encoding the subject’s location and ongoing behaviors (Eichenbaum, 2013; MacDonald et al., 2011, 2013). Furthermore, just as most hippocampal place cells ‘remap’ when a salient spatial cue is altered, most ‘time cells’ form qualitatively different representations and can be shown to ‘retime’ when the main temporal parameter is altered. Hippocampal

neurons also differentially encode the key events and disambiguate different event sequences to compose unique, temporally organized representations of specific experiences. These findings suggest that hippocampal neural ensembles segment and temporally organize memories in much the same way that they represent locations of important events in spatially defined environments.

Despite these observations, however, there have been serious challenges to identifying the role(s) that the hippocampus plays in timing and time perception given that hippocampal (or fimbria-fornix) lesions do not seem to produce dramatic impairments in duration discrimination using traditional psychophysical procedures in humans or lower animals such as rats and mice (e.g., Meck, 1988, 2006a; Meck et al., 1984, 2013; Melgire et al., 2005; Tam et al., 2013; Vidalaki et al., 1999; Yin & Meck, 2013). One possibility is that we have been looking at timing in the wrong way. Psychologists, for example, have distinguished between prospective and retrospective timing to highlight the difference between our sense of duration in an ongoing experience and our remembered duration of a past experience. Humans and other animals employ prospective timing in the seconds-to-minutes range in order to learn the durations of events and can organize their behavior based upon this knowledge when they know that duration information will be important ahead of time. In contrast, when temporal judgments are made after the fact, thus precluding the subject from consciously attending to the durations of events, duration information must be deduced or extracted from other memory representations. Interestingly, a recent meta-review of 117 timing studies by Block et al. (2010) shows an interaction between the way in which temporal judgments are made (i.e., prospectively or retrospectively) and cognitive load (e.g., attentional and memory demands) on participant's judgments of interval duration. For retrospective time judgments, estimates under a high cognitive load are *longer* than under a low cognitive load. For prospective judgments, the reverse pattern holds, with an increased cognitive load leading to *shorter* estimates. Whether or not different processes and/or neural circuits are involved in prospective and retrospective timing remains to be determined, but it is certainly intriguing to consider the possibility that the hippocampus is differentially involved in these timing processes as proposed by MacDonald (2013).

The neural circuits engaged by interval timing, as we currently understand them (Buhusi & Meck, 2005; Merchant et al., 2013a), overlap considerably with regions typically implicated in the learning and expression of procedural memories (Squire, 1992). In this way, interval timing is inextricably linked to the processes whereby we optimally organize specific behaviors and other cognitive resources in time (e.g., attending in temporal context — see Buhusi & Meck, 2009; Henry & Herrmann, 2014; Meck, 2005), and this process can operate independently of the hippocampus. Conversely, in retrospective timing paradigms, duration judgments involve remembering the temporal context of events that composed a past experience, and as such our attention is on the past. The hippocampus and sur-

rounding areas in the medial temporal lobe would be expected to be important for this latter process, but not necessarily the former. Consequently, the challenge is to understand how remembered duration is encoded in the hippocampus and medial temporal lobe, and how this representation differs from and contributes to prospective timing mediated by other neural circuits in service of cognition and emotion (Coull et al., 2013; Droit-Volet & Meck, 2007; Droit-Volet et al., 2013; Howard & Eichenbaum, 2013; Maguire & Mullally, 2013; Meck & Benson, 2002; Meck & MacDonald, 2007; Nadel & Peterson, 2013).

3. The Hippocampus and Memory for Elapsed Time

Episodic memory involves remembering specific events along with the spatial, temporal and/or situational context in which they occurred, a capacity that appears to have enjoyed a long and prosperous evolutionary history (Allen & Fortin, 2013). Most of our daily experiences have overlapping elements, including specific items and locations, but each experience occurs at a unique time. Thus, remembering *how long ago* specific events occurred, a form of temporal context memory, is important for distinguishing individual episodes. The discovery of timing signals in hippocampal neurons, including evidence of ‘time cells’ (Gill et al., 2011; Kraus et al., 2013; MacDonald et al., 2011, 2013; Pastalkova et al., 2008 — see also Naya & Suzuki, 2011) and of gradual changes in ensemble activity over the course of many minutes (Mankin et al., 2012; Manns et al., 2007), suggests that the hippocampus contributes to this capacity. Until recently, however, behavioral evidence supporting the role of the hippocampus in temporal context memory of this sort had been lacking. This is likely the result of previous studies using event durations typically in the range of 2–40 s when assessing hippocampal dependence (see Table 1 in Meck et al., 2013), a timescale known to require cortico-striatal circuits (e.g., Allman et al., in press; Jones & Jahanshahi, 2014; Lewis & Meck, 2012; Meck et al., 2008; Merchant et al., 2013a, b). A recent break-through occurred following the development of a non-spatial paradigm designed to test the hypothesis that the hippocampus is important for keeping track of elapsed time over several minutes (Jacobs et al., 2013).

Jacobs et al. (2013) trained rats on three conditions, each involving the presentation of three sample durations: (1) 1–3–12 min, (2) 1–8–12 min, or (3) 1–1.5–12 min. On each trial, rats were presented with a single row of three plastic cups, each filled with distinctly-scented sand (Odors A–C). In order to obtain a food reward, rats were required to determine how much time had elapsed since the previous trial, and to select the odor associated with that interval: Odor A (e.g., sage) signaled a 1-min interval, Odor B (e.g., cinnamon) signaled the intermediate interval (3, 8, or 1.5 min), Odor C (e.g., orange peel) signaled a 12-min interval. Following the animal’s choice, all experimental materials were removed from the test arena and the next to-be-timed interval began. To assess performance on each interval comparison separately, a plastic disk covered the sand in one of the two incorrect cups

(selected randomly); the covered odor could be smelled, but the rat could not dig in that cup on that trial. This resulted in three types of interval comparisons per condition (e.g., 1-min vs. 3-min, 1-min vs. 12-min, and 3-min vs. 12-min). This design allows a characterization of the rats' temporal resolution at these longer timescales, and the flexibility to control for potential confounding factors (e.g., frequency and location of stimuli, rewards, and interval comparisons).

Jacobs et al. (2013) found that rats have a robust ability to remember durations at this timescale and that the hippocampus was essential for discriminating smaller, but not larger, temporal differences (measured in log units), consistent with a role in temporal pattern separation. Importantly, this effect was observed at longer (e.g., 8–12 min) but not at shorter (e.g., 60–90 s) timescales, suggesting an interplay between temporal resolution and timescale in determining hippocampal dependence. These results offer compelling evidence that the hippocampus plays an important role in remembering how long ago events occurred. As a consequence, one of our goals should be the development of hybrid procedures that might prove useful in the study of a broader range of event durations than typically employed in laboratory studies with rodents (Buhusi et al., 2013; Cordes & Meck, 2013; Maggi et al., 2014).

The approach of Jacobs et al. (2013) may be used in future studies to test potential double dissociations between brain structures and time ranges (e.g., Fouquet et al., 2013; Jacobs et al., 2013, Fig. 4; MacDonald et al., 2012; Meck, 2006a, b; Yin & Meck, in press). For example, while maintaining the same ratio of durations (e.g., 1:1.5), but by changing their range (e.g., 1-min vs. 1.5-min, and 8-min vs. 12-min comparisons), a dissociation between the hippocampus and striatum might be observed such that inactivating the hippocampus would facilitate temporal discrimination at the shorter time range, but impair discrimination at the longer time range. In contrast, temporarily inactivating the striatum would impair temporal discrimination for the shorter time range, but facilitate discrimination at the longer range. At the moment, Jacobs et al. (2013) have presented compelling evidence for the role of the hippocampus in this exchange, and have set the stage for the investigation of the striatal component of this potential double dissociation.

4. Neural Oscillations in the Cortex, Striatum, and Hippocampus During Temporal Processing

Neural oscillations are an important feature of temporal processing and support communication among multiple brain areas. Increases in oscillatory activity and the specific phase relations of action potentials (neural spikes) to ongoing theta oscillations have been shown to sub-serve attention, working memory, and other cognitive processes (e.g., DeCoteau et al., 2007a, b; Fell & Axmacher, 2011; Gu et al., 2013; Tort et al., 2008). Cortico-striatal circuits in particular, are central to temporal processing and the coordination of timing and motor control (Meck et

al., 2008). The role of the hippocampus in temporal processing, however, is less clear and may depend upon task demands (Yin & Troger, 2011). In order to explore the relations among different patterns of neural oscillation in frontal-striatal-hippocampal circuits, local field potentials (LFPs) have been recorded simultaneously from the frontal cortex, dorsal striatum, and dorsal hippocampus (CA1 region) of rats performing temporal judgment and temporal reproduction tasks (e.g., Gu & Meck, 2012; Hattori & Sakata, 2013; Sakimoto et al., 2013). The oscillatory features recorded from these circuits allow for the determination of the underlying ‘temporal code’ as well as the relation among different brain areas during temporal processing (e.g., Sakata, 2006; Sakata & Onoda, 2003).

Gu and Meck (2012) reported increased power for low frequency (<15 Hz) oscillations in the cortex and striatum during the timing of signal durations in the range of 2 to 30 s. In contrast, the hippocampus showed increases in power at frequencies > 20 Hz, suggesting a broadening of the band size for low-frequency oscillations in this structure. An increase in gamma power (>100 Hz) was also observed with response preparation in the hippocampus and striatum. Spectrograms showed increased low-frequency oscillations in relation to temporal processing in both the frontal cortex and striatum. When trials were categorized into *early* vs. *late* responses, theta (4–8 Hz) frequency bands in the cortex and striatum showed leftward power shifts for *early* responses compared to those for *late* responses, suggesting the cortical-striatal circuits either produced or tracked the timekeeping process. Moreover, spiking activity in the striatum appeared to be entrained to striatal theta rhythm. This latter result is consistent with the findings of MacDonald et al. (2013) showing that ‘time cells’ are synchronized to ongoing hippocampal theta oscillations. These data suggest that hippocampal theta may be contributing to the organization of ‘time cell’ sequences, in part, by providing a timekeeping/clocking signal that is synchronized with the striatum (Gu et al., 2013). Evidence of cortical or striatal neuron spikes entrained to hippocampal theta oscillations and the coherence of theta oscillations among the cortex, hippocampus, and striatum implicates the importance of theta rhythms for communication across multiple brain areas (e.g., Berke et al., 2009; DeCoteau et al., 2007a, b; Dzirasa et al., 2010; Tort et al., 2008).

Hattori and Sakata (2013) recorded lever presses and LFPs of rats performing in a 30-s peak-interval (PI) procedure. The distribution of mean lever presses as a function of the signal duration since trial onset displayed a Gaussian-like function that peaked, as expected, at about 30 s (peak time). The LFP power spectra showed that striatal theta rhythm (4–8 Hz) was well correlated with timing performance during the trial and could be used to predict peak times on a trial-by-trial basis, suggesting that this frequency range is important for temporal processing (e.g., Onoda & Sakata, 2006; Sakimoto et al., 2013). Taken together with the findings of Gu and Meck (2012), the conclusion is that the power of low frequency (<15 Hz) neural oscillations is well correlated with temporal processing in the supra-seconds range.

Cortical, striatal, and hippocampal LFPs show differential patterns of neural oscillation, however. The fluctuation of theta power (4–8 Hz) in cortico-striatal circuits prior to the response used to classify signal durations showed leftward shifts in trials with *early* timing responses compared to trials with *late* responses, implicating its relation to the rate of temporal integration (i.e., clock speed). In contrast, neither hippocampal or cerebellar oscillations showed these correlations with trial-by-trial variation in performance (Onoda et al., 2003), although there were within-trial correlations suggesting a more general monitoring of the passage of time and/or the time of occurrence of specific events within a trial (e.g., signal onsets and offsets). These findings point to the importance of neural oscillations in temporal processing and cognition (Cheng et al., 2008; DeCoteau et al., 2007a, b; Gu et al., 2013) and lend support to the striatal-beat frequency model of interval timing (Allman & Meck, 2012; Coull et al., 2011; MacDonald & Meck, 2003, 2004; Matell & Meck, 2000, 2004).

5. Summary

The findings reviewed here indicate that the hippocampus, typically not considered to be involved in the measurement of event durations, makes use of ‘time cells’ to create timeframes for memory of elapsed time which may be applied to retrospective timing. Moreover, as durations enter the minutes-to-hours range there appears to be greater reliance on the hippocampus, especially when making difficult discriminations. These findings suggest a continuous interaction between the striatum and hippocampus, underlying the interplay between prospective and retrospective timing as well as time-based decision making, intertemporal choice, and episodic memory (Heilbronner & Meck, 2013; Jacobs et al., 2013; MacDonald, 2013; Meck et al., 2012; Raskin et al., 2011; Shi et al., 2013).

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