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Exploring the 4th dimension: hippocampus, time, and memory revisited

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Accurate and reliable timing is an essential component of nearly every purposeful behavior. Just as the brain contains mechanisms to track and orient the body in space, so too must it be able to orient itself in time. Coincidence detection – the integration of simultaneous activation of multiple inputs – is a proposed solution to the question of how the brain tracks the duration of events in the seconds-to-minutes range using millisecond-scale neural processes (Matell and Meck, 2000). The striatal beat-frequency (SBF) model is one of the most successful attempts at explaining the neural basis of interval timing in terms of coincidence detection of oscillatory processes (Matell and Meck, 2004; Lustig et al., 2005; Harrington et al., 2010; Oprisan and Buhusi, 2011, submitted). The SBF model involves a set of cortical timekeeper neurons that oscillate at regular, but distinct frequencies, allowing a unique pattern of activation to occur at each point in time. These activation patterns project onto striatal integrators that combine their information with feedback (e.g., reward input) and form the basis of interval timing.

Independent lines of research appear to converge on the conclusion that functional circuits composed of the prefrontal cortex, striatum, and thalamus are instrumental to both time perception and timed performance (Coull et al., 2004, 2011; Hinton and Meck, 2004; Buhusi and Meck, 2005; Meck, 2006a,b; Yin, 2009; Allman and Meck, 2011). This frontal–striatal system is hypothesized to correspond to the functional components of the SBF model (Meck, 1996, 2006a,b; Meck and Benson, 2002; Matell et al., 2003; Matell and Meck, 2004; Meck et al., 2008), wherein cortical oscillatory neurons, and reward input from the substantia nigra are integrated by striatal medium spiny neurons (MSNs). These neurons can hold temporal "memories" via dopamine-facilitated long-term potentiation and long-term depression that, possibly via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) trafficking (Centonze et al., 2001), modulate synaptic weights. Later, when the same signal duration is timed again, these neurons compare the current pattern of cortical activation with the stored "memories"; if coincidence is detected, then the spiny neurons fire to indicate the target duration has elapsed.

These neural structures contained within cortico-striatal circuits may not be the only ones involved in interval timing, however. The role of the hippocampus in timing and time perception for durations in the supra-seconds range was initially explored by Meck et al. (1984). Since then, numerous studies have demonstrated reliable changes in the accuracy and precision of interval timing following a variety of techniques impacting hippocampal function (e.g., transection of the fimbria fornix, lesions of the medial septal area, resection of the temporal lobe, selective lesions of the dorsal hippocampus, and destruction of the entire hippocampus – see Balci et al., 2009 for a review). Nevertheless, an explanation of the effects of hippocampal damage within the context of a theoretical model of interval timing has been elusive (Grossberg and Merrill, 1992, 1996; Lytton and Lipton, 1999; Onoda et al., 2003; Matell and Meck, 2004; Sakata, 2006; Lewis et al., 2011). As a consequence, the primary goal of this opinion article is to outline mechanisms by which the hippocampus could have specific effects on the modulation of the neural circuits specified by the SBF model of interval timing.

Rats and mice with lesions of the hippocampus and related areas demonstrate a proportional "leftward" shift in distributions of timing judgments for intervals in the range of 2–8 s for temporal bisection procedures and 10–40 s for peak-interval timing procedures – that is, when faced with tasks requiring them to estimate or reproduce a specific duration, they respond earlier on average than normal subjects indicating an over estimation/under production of duration proportional to the anchor durations or target duration(s) being timed (Meck et al., 1984, 1987; Olton et al., 1987, 1988; Buhusi et al., 2004; Balci et al., 2009). Similar effects on timing have also been observed in human participants with hippocampal damage following temporal lobe resection for anchor durations spanning the ranges of 50 vs. 200 ms, 1 vs. 2 s, and 2 vs. 8 s in temporal bisection procedures and 0.5–8 s for temporal reproduction procedures (Vidalaki et al., 1999; Melgire et al., 2005). Interestingly, in both rodents and humans, an increase in the precision of timing often accompanies the distortion in the accuracy of the temporal representations (Meck et al., 1984; Vidalaki et al., 1999; Meck, 2002, 2005; Melgire et al., 2005). These "classic" effects of hippocampal lesions on the performance of rats in the peak-interval procedure are illustrated in **Figure 1**.

Though there have been a number of studies that suggest a lack of any effect on peak-interval timing procedures in hippocampally lesioned animals (Dietrich et al., 1997; Dietrich and Allen, 1998), these experiments included extensive post-lesion training with explicit reinforcement contingencies for probe trials. Evidence suggests that, with extensive training, it is possible for timing behavior to become habitual and to enter a "locked" state where the "classic" horizontal shifts of response functions to pharmacological challenges are no longer apparent (Yin and Knowlton, 2006; Cheng et al., 2007a,b; Yin et al., 2009). It is also known that in cases of extensive training, hippocampal function can be transferred to other brain areas such as the cortex (Wiltgen and Silva, 2007; Wiltgen et al., 2010).

There are several important roles that the hippocampus could play in the SBF timing circuit. Firstly, it could function as a feedback control mediator (Meck, 1988), participating in the determination of temporal expectancy,

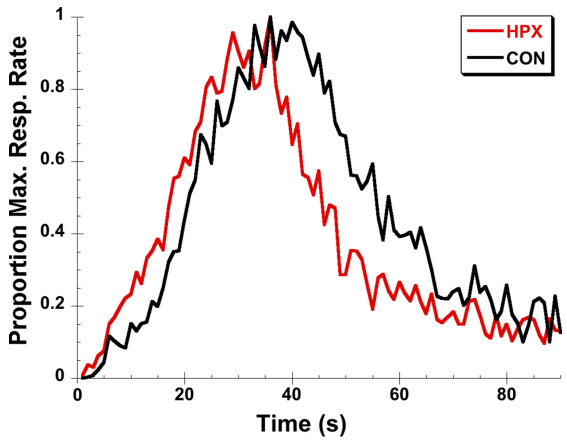

FIGURE 1 | An illustration of the "classic" effects of post-training hippocampal lesions for rats trained on a 40-s peak-interval procedure. The peak functions of rats with hippocampal lesions (HPX) rats are shifted leftward relative to control (CON) rats and are sharper with less spread around the observed peak time. Data are replotted from Buhusi et al. (2004).

which is a continuously updated function of memory, and clock-reading that supports the anticipation of outcomes tied to specific durations. Separate cortical areas exist that participate in the cortico-striatal and fronto-hippocampal circuits, respectively. The former is the basis of the "clock" stage while the latter may modulate the "memory" stage, updating temporal expectancy on a trial-by-trial basis. This memory-modulating cortical area also sends input to the striatal MSNs. Given that hippocampal lesions produce a progressive leftward shift (under production/over estimation) and frontal lesions produce a more or less symmetrical progressive rightward shift (over production/under estimation), it is possible that the hippocampus works in tandem with this frontal–temporal regulatory circuit to update temporal expectancy on a trial-by-trial basis (Meck et al., 1987; MacDonald and Meck, 2004; Lustig et al., 2005).

A second function that the hippocampus might serve in timing and time perception is as a regulator of the dynamic firing threshold of striatal MSNs (Matell and Meck, 2004). Hippocampal–striatal interactions have been previously documented (Devan and White, 1999; Poldrack and Packard, 2003; Lee et al., 2008; Graham et al., 2009). The MSN is essentially a two-state system with a "down-state" that does not allow neural firing and an "up-state" that facilitates firing. State transitions are driven by excitatory inputs. The interspike interval varies because the sub-threshold membrane potential fluctuates (Stern et al., 1997). Properties of sub-threshold signal integration in MSNs are determined by the distribution of synaptic inputs and differential activation of multiple postsynaptic conductances (Carter et al., 2007).

On this basis, we can suggest two possible ways that hippocampal input could directly contribute to modulating striatal neuron firing: phasic excitation and tonic inhibition. The hippocampus could desensitize membrane AMPARs on MSNs with its phasic excitatory output when it detects minor environmental changes, such as at the beginning of a new "to be timed" signal. This would render a varying set of MSNs unable to use "memories" of the previous signal duration. These MSNs must then update their "memories" on a trial-by-trial basis. This would produce more trial-by-trial variation, and would be expected to contribute to the Gaussian-like noise that generates scalar timing (see Matell and Meck, 2004; Oprisan and Buhusi, 2011, submitted).

The hippocampus could also tonically inhibit, and thus lower the sub-threshold membrane potential of striatal neurons such that firing is delayed by a small duration in some proportion of MSNs. Such an effect would be more pronounced in heavily weighted synapses of MSNs corresponding with the "representation" of the previous trial's temporal sequence of responding and reward outcome. In this case, striatal neurons could display "overexcitement" in the absence of hippocampal inhibition followed by habituation, resulting in a leftward shift of the timing function in early trials followed by a return to a more normal response distribution following repeated testing, again possibly explaining the lack of an observed shift in lesioned animals with extensive training.

A third possibility is that the hippocampus might function in a downstream decision-making process that controls motor output. It has been suggested that the decision-making processes downstream of the "clock stage" deserve further investigation (Harrington et al., 2004, 2011; Wearden, 2004; Meck, 2005). A subject's selection and execution of motor action based on the clock's output (which in the SBF model is determined by striatal firing rates) may depend on a "threshold gating" mechanism located in another brain region (Gibbon et al., 1997; Jin et al., 2009; Höhn, et al., 2011). This would predict variation in timing behavior between subjects that have identical perceptions of duration. For example, in a peak-interval procedure, an "impulsive" subject may press the lever well before its perception of the time in the current trial matches a sample taken from its memory distribution of times of reinforcement on previous trials. Conversely, a "less impulsive" subject demonstrating a higher degree of "self control" may be reluctant to press a lever until the time on the current time is much closer to the remembered target duration – or even past this duration (Church et al., 1994).

Regions that might be involved in this subsequent action–selection process are the ventral and dorsomedial striatum, orbitofrontal cortex, and possibly the hippocampus (Johnson et al., 2007; MacDonald et al., 2011). Indeed, it has been reported that the hippocampus may have a role in controlling impulsivity (Cheung and Cardinal, 2005; McHugh et. al., 2008; Sala et al., 2011). On the other hand, it has been shown that ventral/medial striatal neurons are entrained to the hippocampal theta rhythm (Berke et al., 2004). Therefore, it seems reasonable to speculate that the hippocampus might interfere with the downstream temporal control of action sequences (most likely via inhibitory control) in tandem with the ventral/medial striatal neurons. Lesions of the hippocampus may diminish this inhibitory control, thereby resulting in earlier start times, leading to leftward horizontal

shifts of the peak function in the peak-interval procedure (Meck et al., 1984, 1987; Balci et al., 2009; MacDonald et al., 2011). These three possibilities for the mapping of functional hippocampal connectivity within the SBF timing model are illustrated in **Figure 2**.

Further understanding of the hippocampus's role in interval timing could be achieved by examining the differences between pre- and post-hippocampal lesion training on a single-trial level (Church et al., 1994). This would allow us to narrow the range of possible roles the hippocampus might play in either attention, feedback, or memory consolidation mechanisms on a trial-by-trial basis (Meck, 1988; Buhusi and Meck, 2002; Buhusi et al., 2003, 2004). It could also provide us with clues as to whether or not the "clock stage" itself is affected, which would be reflected by a proportional horizontal shift of the response states (see Church et al., 1994; Matell et al., 2006, and MacDonald et al., 2011). Conversely, if the horizontal (e.g., leftward) shift in timing functions resulting from hippocampal damage is due to a change (e.g., decrease) in the latency to start timing rather than in the centering of the distribution of responses around the target duration, then it might suggest the third possibility discussed above. Furthermore, in order to examine the interaction between the hippocampus and either the cortex or the striatum, one could employ a cross-lesioning technique wherein one of each structure would be compromised contralaterally in addition to a transection of the corpus callosum (e.g., Christakou et al., 2001; Chudasama et al., 2003). Moreover, future studies would benefit from the use of optogenetic techniques (Yizhar et al., 2011) in terms of identifying the functional "connectome" among the hippocampus, striatum, and cortex (Chuhma et al., 2011). This would provide regions of interest for more traditional electrophysiological and pharmacological mapping studies of the role of the hippocampus and other brain structures in time – the fourth dimension of neural function (Coull et al., 2011).

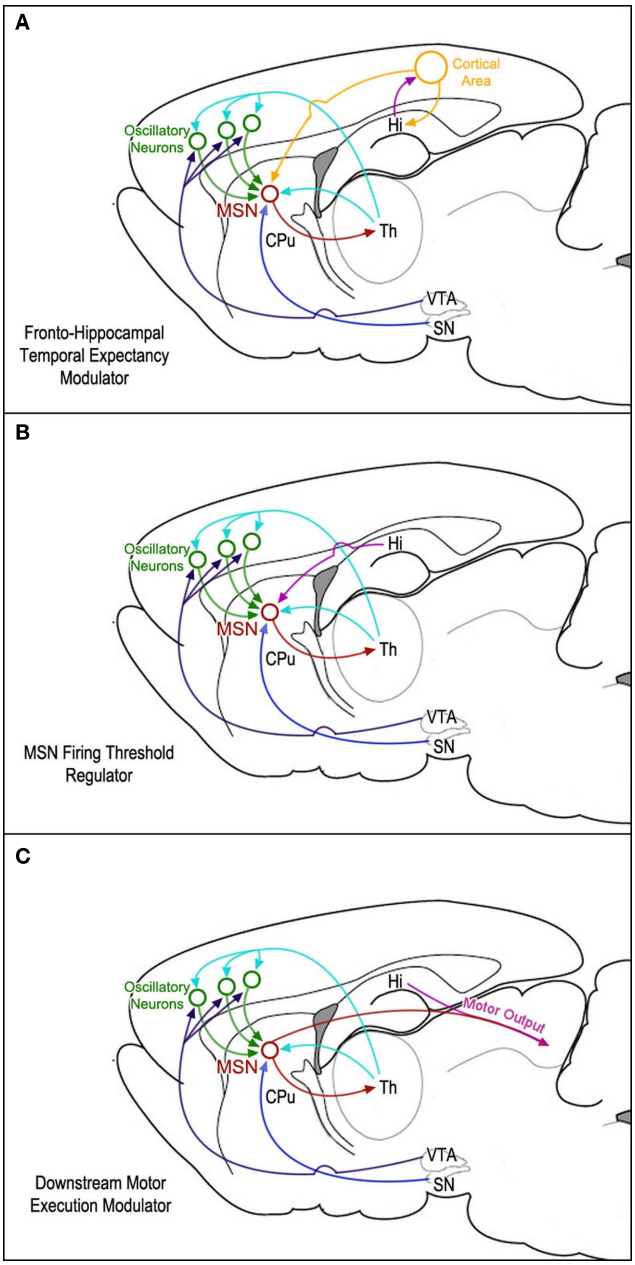

FIGURE 2 | Diagrams of three possible mappings of functional hippocampal connectivity within the neural circuits proposed by the striatal beat-frequency (SBF) model of interval timing: (A) the hippocampus is involved in a feedback mechanism designed to update temporal expectancy with a separate cortical area. This area's output is then integrated with clock and reward information by striatal medium spiny neurons (MSNs). **(B)** The hippocampus modulates MSN firing thresholds via either tonic inhibition or phasic excitation. **(C)** Hippocampal regulation downstream of the MSNs affects translation of temporal information into motor output.

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