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Hippocampus, Time, and Memory – A Retrospective Analysis

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Abstract

In 1984, there was considerable evidence that the hippocampus was important for spatial learning and some evidence that it was also involved in duration discrimination. The article *Hippocampus, Time, and Memory* (Meck, Church, and Olton, 1984), however, was the first to isolate the effects of hippocampal damage on specific stages of temporal processing. In this review, to celebrate the 30th anniversary of *Behavioral Neuroscience*, we look back on factors that contributed to the long-lasting influence of this article. The major results were that a fimbria-fornix lesion (a) interferes with the ability to retain information in temporal working memory and (b) distorts the content of temporal reference memory, but (c) it did not decrease sensitivity to signal duration. This was the first lesion experiment in which the results were interpreted by a well-developed theory of behavior (scalar timing theory). It has led to extensive research on the role of the hippocampus in temporal processing by many investigators. The most important ones are the development of computational models with plausible neural mechanisms (such as the Striatal Beat-Frequency model of interval timing), the use of multiple behavioral measures of timing, and empirical research on the neural mechanisms of timing and temporal memory using ensemble recording of neurons in prefrontal-striatal-hippocampal circuits.

There are several reasons that a scientific article might attain the status of ‘classic,’ innovation and significance chief among them. To the extent that the paper by Meck, Church, and Olton (1984) has attained that status, it’s worth noting that it had a very good title: “*Hippocampus, Time, and Memory*.” In 1984 each of these topics was “hot,” but the inclusion of all three in a single title was unusual, if not unprecedented. So the title helped. Our question now, however, is whether or not the article was innovative or significant. The article was focused on the behavioral effects of fimbria-fornix (FFx) lesions (which disconnect the hippocampus from subcortical innervation), and the cognitive interpretations of these results. The cognitive interpretations were based on scalar timing theory, which involved an information-processing (IP) model of interval timing that was developed in the early 1980’s by John Gibbon, Russell Church, Warren Meck, and others (Church, 1984, 2003; Gibbon, Church, & Meck, 1984; Meck, 2003). This IP model was expressed as a flow diagram with cognitive features of clock, memory, and decision stages, and as a

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computational model with closed-form equations as well as simulations. The model was consistent with the principles of scalar expectancy theory (Gibbon, 1977) and was being successfully fit to new experiments on timing and time perception (e.g., Church & Gibbon, 1982; Meck and Church, 1984). Meck, Church, and Olton (1984) explained the qualitative results with the IP model, but attempted to explain only a few of the quantitative results (e.g., Figure 8 on the effect of timing a stimulus with gaps, and Figure 10 on the probability that a choice was determined by previous choices).

The instructions to authors from *Behavioral Neuroscience* clearly required that "all manuscripts must include an abstract of 100–150 words." The 407-word abstract by Meck, Church, and Olton (1984) described the overall problem, the primary method and results of each of the five experiments, and the major conclusions. The abstract ended with three main conclusions about the effects of FFx lesions: (a) they interfere with temporal, as well as spatial, working memory, (b) they reduce the remembered time of reinforcement stored in reference memory, and (c) they have no effect on the rat's sensitivity to stimulus duration. Consequently, the extended abstract probably helped readers to appreciate interrelationships between hippocampus, time, and memory before reading the article.

Authors' background

In 1984, papers authored by single investigators or small groups of investigators with similar skills were typical in the field of behavioral neuroscience, but papers authored by teams of investigators with different skills were still relatively rare. The team that contributed to *Hippocampus, Time, and Memory* was ideal for this topic at that time. David Olton was a well-established physiological psychologist at The Johns Hopkins University, who now would be recognized as a behavioral neuroscientist. He was an expert in the function of the hippocampus, and in the use of the radial-arm maze. Most researchers then referred to it as the "Olton maze;" David Olton did not, but he occasionally referred to it as his "Tenure maze" and believed that investigators should be known for their discoveries and not the pieces of apparatus that they build. When he came to Brown University to do the brain surgeries, he was asked how many he had done previously, and he said "about 1000;" to the follow-up question about how many he had done recently, he said "two—I practiced before coming." Russell Church was an experimental psychologist at Brown University with considerable research experience on timing and animal learning. Warren Meck was a 1982 Ph.D. from Brown University who was focusing on the neural basis of interval timing. The Brown-Hopkins collaboration continued with four additional publications – Meck, Church, and Olton (1984), Meck, Church, and Wenk (1986), Olton, Meck, and Church (1987), and Olton, Wenk, Church, and Meck (1988).

Results and cognitive explanations

In 1984, knowledge of the role of the hippocampus in spatial learning was much more advanced than in temporal learning. The primary purpose of the radial-arm maze experiment (Experiment 5) was to determine that the FFx-lesions were sufficient to replicate the well-established findings that they impair spatial working memory (Olton, Becker, & Handelmann, 1979; Olton & Papas, 1979; Olton & Samuelson, 1976).

The article formulated some basic questions about the effects of a FFx lesion on temporal learning, and provided the basis for the three strong conclusions in the abstract. The conclusions were that a FFx lesion had strong effects of temporal memory (both on temporal working and reference memory), but it did not decrease the sensitivity to stimulus duration (and sometimes increased the subject's sensitivity to time). A basic finding was that a FFx lesion had no general impairment on a rat's ability to perceive time intervals. The sensitivity to stimulus duration or rate was unimpaired by this lesion in psychophysical choice procedures (Experiment 1), and the sensitivity to stimulus duration was unimpaired by this lesion in a standard peak-interval (PI) reproduction procedure (Experiment 4). Lesions that do not have general debilitating effects make it possible to identify specific effects.

FFx lesions also produced a sustained leftward shift in the psychometric functions for both duration and rate of a stimulus indicative of a systematic decrease in the clock readings stored in temporal memory. This timing distortion was interpreted in terms of a biased encoding/retrieval process whereby clock readings are transferred to and stored in reference memory (Experiment 1) and the same interpretation was made of the leftward shift in the PI procedure experiment (Experiment 4). However, the most dramatic effect of the FFx lesions is shown in Figure 1 (Figure 8 in the original article) in which rats in the control and lesion groups were trained in a 20-s PI procedure and tested with a 5-s gap in some of the probe-trial presentations. The peak times during unreinforced probe trials with and without gaps are shown for each rat in both the control and FFx-lesion groups. The amount of increase in peak time between the 'gap' and 'no gap' conditions indicated whether rats continued timing during the gap (run mode), paused their clocks during the gap (stop mode), or forgot the signal duration that occurred prior to the gap (reset mode) – see Allman, Pelphrey, and Meck, 2012; Buhusi and Meck, 2009b; Cheng, Williams, and Meck (2006), Matell and Meck (1999), Meck and Church (1983) and Roberts and Church (1978) for a description of how subjects can operate their internal clocks in these different modes. The major finding was that the control rats 'stopped' timing during the gap, but that rats with FFx lesions 'reset' their clocks sometime during the gap, i.e., the working memory of the control rats was normal, but the working memory of the FFx-lesioned rats was non-operational in this respect. In other words, normal rats estimate the total interval by adding together the time periods before and after the gap. In contrast, rats with hippocampal damage ignore the estimated time period before the gap and initiate timing anew after the interruption is removed as if the time before the gap never occurred (see Table 1 for the results of other PI-gap experiments as a function of the type of hippocampal lesion).

Combined with previous work reviewed by Church (1984), these findings demonstrated that subjects process temporal information as if they were using an internal stopwatch that can be run, stopped, and reset on command, and whose speed is adjustable (cf., Swearingen & Buhusi, 2010). Previous data suggest that dopaminergic drugs affect the speed of this internal clock (Maricq & Church, 1983; Maricq, Roberts, & Church, 1981; Meck, 1983, 1996 – see Coull, Cheng, & Meck, 2011 and Williamson, Cheng, Etchegaray, & Meck, 2008 for reviews). Using a paradigm in which rats have to filter out the gaps that (sometimes) interrupted timing, Buhusi and Meck (2002) found that methamphetamine (dopamine agonist) and haloperidol (dopamine antagonist) also affect the 'stop' and 'reset' mechanism of the internal clock, possibly by modulating attentional components that are dependent on

the content and salience of the timed events. This article was published in *Behavioral Neuroscience* and is the first report of both clock and attentional effects of dopaminergic drugs on interval timing in the same experimental setting. The behavioral methods relied on the use of the standard PI procedure with gaps as applied by Meck, Church, and Olton (1984) as well as the 'reversed gap' procedure as developed by Buhusi and Meck (2000) in order to isolate effects on attention, clock speed, and memory (e.g., Buhusi & Meck, 2006a, b, 2009b; Buhusi, Mocanu, & Meck, 2004; Buhusi, Perera, & Meck, 2005; Buhusi, Sasaki, & Meck, 2002; Buhusi, Scripa, Williams, & Buhusi, 2013). The basic discovery is that changes in attention can be observed in unreinforced peak trials with gaps where lesions and/or drugs have a more pronounced effect on the perceived salience of the gap relative to the 'to-be-timed' signal and the intertrial interval. In contrast, changes in clock speed are more easily detected in unreinforced peak trials without gaps using the same manipulations (drugs or lesions) presumably because the absence of a gap doesn't engage the same attentional processing (Buhusi & Meck, 2007, 2009a). Moreover, the proportional underestimation of time following neurotoxic lesions along the septotemporal extent of the hippocampus is reversed by the dopamine D2 receptor antagonist raclopride, suggesting a role for dopaminergic supersensitivity in the striatum following hippocampal damage (Buhusi & Meck, 2013; Yin & Meck, 2013).

From our current perspective, this work has been influential in multiple respects. First, the findings themselves have inspired numerous empirical reports investigating the role of the hippocampus in temporal processing (e.g., Abela & Chudasama, 2013; Abela, Dougherty, Fagen, Hill, & Chudasama, 2013; Brasted, Bussey, Murray, & Wise, 2003; MacDonald, Lepage, Eden, & Eichenbaum, 2011 – see Table 1 for a list of studies using prospective and retrospective timing procedures to investigate the effects of hippocampal lesions) and a variety of reviews (e.g., Allman, Teki, Griffiths, & Meck, in press; Balci, Meck, Moore, & Brunner, 2009; Kesner, 2002; Meck, 2002b, 2005; Squire, 1992; Wallenstein, Hasselmo, & Eichenbaum, 1998; Yin & Troger, 2011). Second, in addition to demonstrating that hippocampal damage contributes to distortions in long-term (reference) memory and impairments of short-term (working) memory as described above, it also revealed, by way of negation, that this type of short-term memory isn't necessary for the duration discrimination in basic timing tasks such as the standard PI and temporal bisection procedures in which the signal is present for the entire interval (see Church, 1984; Church & Deluty, 1977; Church, Miller, Meck, & Gibbon, 1991; Paule et al., 1999). This distinction is similar to the difference between trace and delay conditioning in terms of the temporal contiguity of the conditioned stimulus with the unconditioned stimulus (Bangasser, Waxler, Santollo, & Shors, 2006; Haritha, Wood, Ver Hoef, & Knight, 2013; Kehoe, Ludvig, and Sutton, 2009; Moyer, Deyo, & Disterhoft, 1990; Solomon, Vander Schaaf, Thompson, & Weisz, 1986).

The true importance of this work, however, extends beyond these specific findings, in that it began a theoretically driven systems neuroscience approach to the investigation of timing and time perception (MacDonald & Meck, 2004). While there were previous investigations of the impact of lesions on temporally controlled behavior using differential reinforcement of low rate and fixed-interval schedules (e.g., Ellen & Powell, 1963; Glickstein, Quigley, & Stebbins, 1964; Rawlins, Winocur, & Gray, 1983; Schmaltz & Isaacson, 1968; Spiegel,

Wycis, Orchinik, & Freed, 1955), this paper was the first lesion experiment in which the results were interpreted within a well-developed theory of behavior, i.e., scalar timing theory (Church, 2003; Church, Meck, & Gibbon, 1994; Gibbon, 1977; Gibbon & Church, 1984; Gibbon, Church, & Meck, 1984). Briefly, scalar timing theory proposes that time perception is achieved via a linear pacemaker-accumulator process (clock stage), a distributed reference memory store of previously reinforced clock times (memory stage), and a ratio-based comparison process (decision stage). Moreover, the standard deviation observed in timing behavior increases proportionally with the mean of the target duration – referred to as the 'scalar property' of interval timing – see Buhusi et al., 2009; Cheng & Meck, 2007; Gibbon, Church, & Meck, 1984. As the authors not only interpreted the data with respect to theory, but also designed this collection of experiments based on the information processing stages subsumed by the theory, this paper, as an anonymous reviewer stated, "still stands as an instructional example of how to mesh the psychological, biological and mathematical levels of explanation".

Search for neural mechanisms

As indicted above, the *Hippocampus, Time, and Memory* paper was quickly followed by a number of other neuroanatomical investigations of temporal processing by various members of the team (e.g., Meck, 1985, 1988, 2002a, b; Meck, Church, Wenk, & Olton, 1987; Olton, 1989; Olton, Meck, & Church, 1987; Olton, Wenk, Church, & Meck, 1988), leading to systematic growth in the field. Integrating the results from these and other studies investigating the roles of various temporal lobe structures (e.g., amygdala and hippocampus) in timing and temporal memory (Drane, Lee, Loring, & Meador, 1999; Droit-Volet & Meck, 2007; Lustig & Meck, 2009; Meck & MacDonald, 2007; Melgire et al., 2005; Olton, Meck, & Church, 1987; Vidalaki, Ho, Bradshaw, & Szabadi, 1999).

While these investigations have shown that the hippocampus organizes experiences in time and plays an important modulatory role in the translation (i.e., encoding/retrieval) of temporal sequences, this structure does not appear to be as critical for prospective timing and the detection of specific event durations as the striatum (Dalla Barba & La Corte, 2013; Eichenbaum, 2013; Meck, 2006b; Pastalkova, Itskov, Amarasingham, & Buzsáki, 2008; Shapiro, 2011; Shapiro & Ferbinteanu, 2006). Moreover, it has recently been proposed that the hippocampus may be preferentially involved in retrospective timing, which is more dependent on incidental memory for the number and temporal sequence of events than prospective timing (e.g., MacDonald, 2013; Ogden, Wearden, Gallagher, & Montgomery, 2011; Zakay & Block, 2004). As such, the remainder of this commemorative retrospective will highlight subsequent work by members of the original team and/or their colleagues that investigate the role of cortico-thalamic-basal ganglia circuits in time perception and timed performance (e.g., Allman & Meck, 2012; Coull, Cheng, & Meck, 2011; Gibbon, Malapani, Dale, & Gallistel, 1997; Gu, Laubach, & Meck, 2013; Matell & Meck, 2004; Matell, 2013; Meck, 1996; Merchant, Harrington, & Meck, 2013; Yin & Meck, 2013).

Following from other anatomical, pharmacological, and imaging work (e.g., Agostino et al., 2013; Allman & Meck, 2012; Buhusi & Meck, 2005; Cheng, Ali, & Meck, 2007; Cheng, Etchegaray, and Meck, 2007; Cheng, Hakak, and Meck, 2007; Cheng, MacDonald, & Meck,

2006; Gu, Cheng, Yin, & Meck, 2011; Hata, 2011; Jaldow, Oakley, & Davey, 1990; Jones & Jahanshahi, 2011; Lake & Meck, 2012; MacDonald, Cheng, & Meck, 2012; Matell, Bateson, Meck, 2006; Matell, King, & Meck, 2004; Meck, 2006a, b, c; Meck, Cheng, MacDonald, Gainetdinov, Caron, & Çevik, 2012; Meck, Penney, & Pouthas, 2009; Miller, McAuley, & Pang, 2006), combined with sophisticated behavioral and analytic techniques (Cheng & Westwood, 1993; Church, Meck, & Gibbon, 1994; Gibbon & Church, 1990; MacDonald, Cheng, Williams, & Meck, 2007; Meck, 2001; Penney, Gibbon, & Meck, 2008; Rakitin et al., 1998), a number of investigators have proposed that interval timing capacities rely on interactions between cortico-thalamic-basal ganglia and hippocampal circuits (e.g., Cheng, Jesuthasan, & Penney, 2011, 2013; Gu, Laubach, & Meck, 2013; Onoda & Sakata, 2006; Onoda, Takahashi, & Sakata, 2003; Sakata, 2006; Sakata & Onoda, 2003; Yin & Meck, 2013).

Neurophysiological realism

Unfortunately, these proposals lacked detail regarding the precise mechanisms that could be utilized to achieve control of timing in the seconds-to-minutes range at the same level as timing systems in the millisecond range (e.g., Buonomano & Mauk, 1994), and concerns regarding the physiological realizability of scalar timing theory were becoming apparent (Hinton & Meck, 1997a, b). Therefore, following the example of a theoretically driven research program set by this classic paper, Matell and Meck (2000, 2004) developed the Striatal Beat-Frequency (SBF) model of interval timing which provided a ‘neurophysiologically plausible’ mechanism for the temporal control of behavior (cf., Humphries, Stewart, & Gurney, 2006). Briefly, they proposed that striatal medium spiny neurons (MSNs) could learn, through synaptic strength changes, to recognize in a ‘perceptron-like’ manner, patterns or states of cortical activity, thereby providing a mechanism for the IP components of scalar timing theory. Specifically, the SBF model proposed that MSNs could be trained to represent target durations by detecting the coincident firing of an array of cortical neurons oscillating at different periodicities. See Gibbon (1991), Morell (1996), Bhattacharjee (2006), and Treisman (2013) for a historical perspective on the origins of pacemaker/accumulator conceptualizations of the ‘internal clock’ and the subsequent evolution of the SBF model of interval timing.

To assess the SBF model, Matell and Meck began recording from ensembles of dorsal striatal and anterior cingulate cortical neurons in rats trained on a two-duration (10 & 40 s) version of the PI procedure used by Meck, Church, & Olton, 1984. By using different reinforcement probabilities for the two durations, the rats lever pressed at approximately the same rate at each target duration. In this manner, neural activity associated with lever pressing at each duration could be meaningfully compared without the inherent confound of differences in motor output. They found that MSNs fired at different rates when the rat responded at the 10-s target duration than when it responded in an equivalent manner at the 40-s target duration, thereby suggesting that the striatum could represent different durations independently of the motor control exerted by the striatum and basal ganglia circuits. They also found that cortical neurons fired at differed rates when the rats responded at the two target durations, although the differences in firing rate were less robust than that seen in the striatum. Taken together, these data were broadly consistent with the SBF model in that the

striatum could represent specific target durations by integrating less-distinct cortical activity that co-varied with signal duration (Matell, Meck, & Nicolelis, 2003b.) While they found no evidence suggesting that neurons in the general area of the premotor and cingulate cortex fired in an oscillatory manner, the obvious possibility that other cortical areas provide this input has led to continued development of the SBF model (e.g., Buhusi & Oprisan, 2013; Oprisan & Buhusi, 2011, 2013; Lustig, Matell, & Meck, 2005; Meck & N'Diaye, 2005; Van Rijn, Gu, & Meck, 2013; Van Rijn, Kononowicz, Meck, Ng, and Penney, 2011). Of course, future theoretical work should examine the extent to which consistent, but non-oscillatory patterns of cortical activity could generate the same type of temporal control as specified by the SBF model (see Matell & Meck, 2004 for alternative descriptions of the time base for the coincidence-detection process specified by the SBF model).

Subsequent electrophysiological work by Matell and colleagues has followed up on these intriguing findings. In one study, they examined whether individual MSNs represented time in an 'abstract' manner, divorced from the motor behaviors necessary to obtain reinforcement (Meck & Church, 1982a, b; Portugal, Wilson, & Matell, 2011). Specifically, they trained rats that reinforcement could be earned for nose-pokes in one location at a specific time (i.e., 15 s), whereas nose-poking at a different location would be reinforced at random times. As a consequence, the rats responded at nearly constant levels during non-reinforced probe trials; they initially responded at a high rate on the random-interval nosepoke, abruptly switched to the fixed-interval nosepoke around 15s, and then abruptly switched back to the random-interval nosepoke. Critically, they found that the vast majority of MSNs had different firing rates for the same motor behavior as a function of the temporal phase in the task (e.g., initial responding on the random-interval nosepoke compared to responding on the fixed-interval nosepoke compared to terminal responding on the random-interval nosepoke), further supporting the notion that the striatum represents temporal information. On the other hand, this temporal modulation of firing rates was embedded within modulation related to the execution of overt motor behaviors (e.g., nose-poking, moving towards or away from the nose-poke location, etc.), thereby arguing against a purely 'abstract' representation of time – see Matell, Meck, & Nicolelis, 2003a. Again, these data were consistent with the coincidence-detection framework specified by the SBF model, which postulates that the temporally specific firing of MSNs serves as an instantiation of the 'decision stage' described by scalar timing theory (Gibbon et al., 1984).

Another follow-up study conducted by this research group (Matell, Shea-Brown, Gooch, Wilson, & Rinzel, 2011) examined neural activity in medial agranular cortex, a possible rodent homolog of primate pre-motor/supplementary-motor cortex (Reep & Corwin, 1999), which is one of the few cortical structures consistently activated in a variety of timing tasks (Wiener, Turkeltaub, & Coslett, 2010). As in the earlier study, they found that cortical neurons had firing rates that varied as a function of time, even though the rat's behavior during the analysis period was stationary. Using extracellular recordings, they found no evidence of oscillatory firing in this cortical area, further suggesting that the time base proposed by the SBF model may be less dependent upon oscillatory firing of cortical neurons than on other patterns of neural activity in the cortex or thalamus. However, they did find a wide variety of systematic firing patterns (i.e., positive and negative ramp patterns, as well as peak and dip patterns) that could be used by an 'ideal observer' to

distinguish the subject's 'location' in time. Subsequent computer simulations demonstrated that this variety of firing patterns provided an improved estimate of time (i.e., with less noise) than a single firing pattern. Notably, this article by Matell, Shea-Brown, Gooch, Wilson, and Rinzel (2011) received the D.G. Marquis award for the best paper in *Behavioral Neuroscience*, in 2011.

Given the massive anatomical convergence of cortical neurons to individual MSNs (i.e., 30,000 to 1), these findings suggest that investigation of the extent to which both oscillatory and non-oscillatory patterns of cortical activity can generate temporally structured behavior should prove fruitful for continued revision and/or expansion of the model (Allman & Meck, 2012; Coull, Cheng, & Meck, 2011; Gu, Laubach, & Meck, 2013; Gu & Meck, 2012; Lewis & Meck, 2012; Merchant, Harrington, & Meck, 2013). In this regard, current work is taking into account that the hippocampus normally provides tonic inhibition to the striatum, such that firing is delayed in some proportion of MSNs – perhaps those corresponding with the 'representation' of the previous trial's sequence of timed responding and reward outcome in order to provide feedback regulation of successive peak times (Lustig & Meck, 2005; Meck, 1988; Meck et al. 1987; Shi, Church, & Meck, 2013). Following hippocampal lesions, these MSNs may become sensitized or 'overexcited' in the absence of this tonic inhibition. It has been shown, for example, that hippocampal lesions can increase dopamine sensitivity in the striatum (Fidalgo, Conejo, González-Pardo, & Arias, 2012; Seeman et al., 2005) possibly altering the synaptic weights of the coincidence-detection processes predicted by the SBF model as illustrated in Figure 2 (Allman & Meck, 2012; Matell & Meck, 2004; Yin & Troger, 2011; Yin & Meck, 2012, 2013) and thereby providing an account of the memory-associated leftward shifts in PI functions first reported by Meck, Church, and Olton (1984). Such compensatory responses between the hippocampus and dorsal striatum, in terms of mutual inhibition and excitation, have become a focus of investigation for understanding complementary interactions among memory systems (e.g., Fouquet et al., 2013; Lee, Duman, & Pittenger, 2008; Packard & White, 1991; Poldrack & Packard, 2003).

Memory encoding and retrieval processes

While the horizontal leftward shifts observed by Meck, Church, and Olton (1984) were not evaluated for a gradual onset, subsequent work by this group confirmed that lesions of the FFx (Olton et al., 1987), as well as the medial septal area (Meck et al., 1987) produce sustained and gradual effects on temporal control. Such effects are identical in form to those seen following chronic modulation of the cholinergic system, and are consistent with a bias applied during memory encoding (Meck, 1983, 2002a, b; Meck & Church, 1987a, b). Remarkably, there have been no reports of pharmacological or anatomical manipulations that led to immediate and sustained changes in the content of temporal memory, which would be indicative of a bias in memory retrieval. Such a lack of effects is surprising, as it is difficult to imagine that the neural mechanisms underlying memory encoding would evolve in such a way that biases could be induced without a compensatory process to offset them. Indeed, Meck (1983, 1996, 2002a, b) proposed that the memory encoding bias might reflect a storage speed parameter (referred to as K* in scalar timing theory – see Church & Meck, 1988) whereby longer durations, i.e., larger accumulator values, took longer to store in memory due to the need to transfer the pulses in the accumulator into memory at a particular

baud rate. However, this notion implies that the stored memory is a proxy for the delay to reinforcement (i.e., the memory is of storage time rather than delay). Because the temporal control of behavior is viewed by scalar timing theory as reflecting a comparison between currently perceived time (i.e., current pulse accumulation) and a sample taken from reference memory (a distribution of previously reinforced times), it is logically necessary to have a process that performs the reverse transformation (from storage time to delay), so that the organism is comparing 'apples to apples'. However, the neural mechanisms by which such a retrieval process might be implemented largely remain to be determined.

As such, recent work by Matell and colleagues may provide an approach in which such retrieval processes can be specifically addressed. The timing task used by Matell et al. (2011) to examine medial agranular cortical activity produced some novel behavioral effects that suggested that rats engage in 'retrieval related' temporal computations. Specifically, they trained the rats that two different modal stimuli (i.e., tone and light) predicted two different times of reinforcement (i.e., 10 s and 20 s, respectively). Presentation of the compound stimulus (tone + light) in extinction led to maximal responding at an intermediate duration (i.e., 16 s). Importantly, this compound peak function was scalar, as was the distribution of responses on individual trials (see also Swanton, Gooch, & Matell, 2009). As such, the authors interpreted this effect as suggesting that the rats generated an average temporal expectation as a result of the simultaneous retrieval of discrepant memories, and then timed this estimate in an otherwise normal manner. Additional research suggested that the form and location of the compound peak function is influenced by the relative probability of reinforcement of the component cues (e.g., Kurti, Swanton, & Matell, 2013; Matell & Henning, 2013; Matell & Kurti, 2013; Swanton & Matell, 2011). Such averaging-like behavior is reminiscent of other effects seen when subjects are required to time multiple durations (e.g., Gu, Jurkowski, Lake, Malapani, & Meck, 2013; Lejeune & Wearden, 2009; Malapani et al., 1998; Meck, Komeily-Zadeh, & Church, 1984), suggesting that the interaction of multiple memories at encoding and retrieval is an important component of normal temporal processing. We anticipate that understanding the form and content of temporal memory and how these temporal memories interact will emerge as a fruitful line of investigation, particularly in the case of developmental changes in the hippocampus and the implantation of false memories (e.g., Buhusi, Lamoureux, & Meck, 2008; Cermak et al., 1999; Jones, Meck, Williams, Wilson, & Swartzwelder, 1999; Meck & Williams, 1997; Meck et al., 2007; Mellott et al., 2004; Ramirez et al., 2013). We hope that future work on these questions will meet the same success as the 'classic' team did in terms of generating an appreciation of the importance of 'internal clocks' for understanding interval timing and time-based decision making at both short-interval and circadian time scales (e.g., Agostino, Peryer, & Meck, 2008; Agostino, Golombek, & Meck, 2011; Caetano, Guilhardi, & Church, 2011; Cordes & Meck, 2013; Cordes, Williams, & Meck, 2007; Galtress & Kirkpatrick, 2010; Kurti & Matell, 2011; Doyère, & Gruart, 2012).

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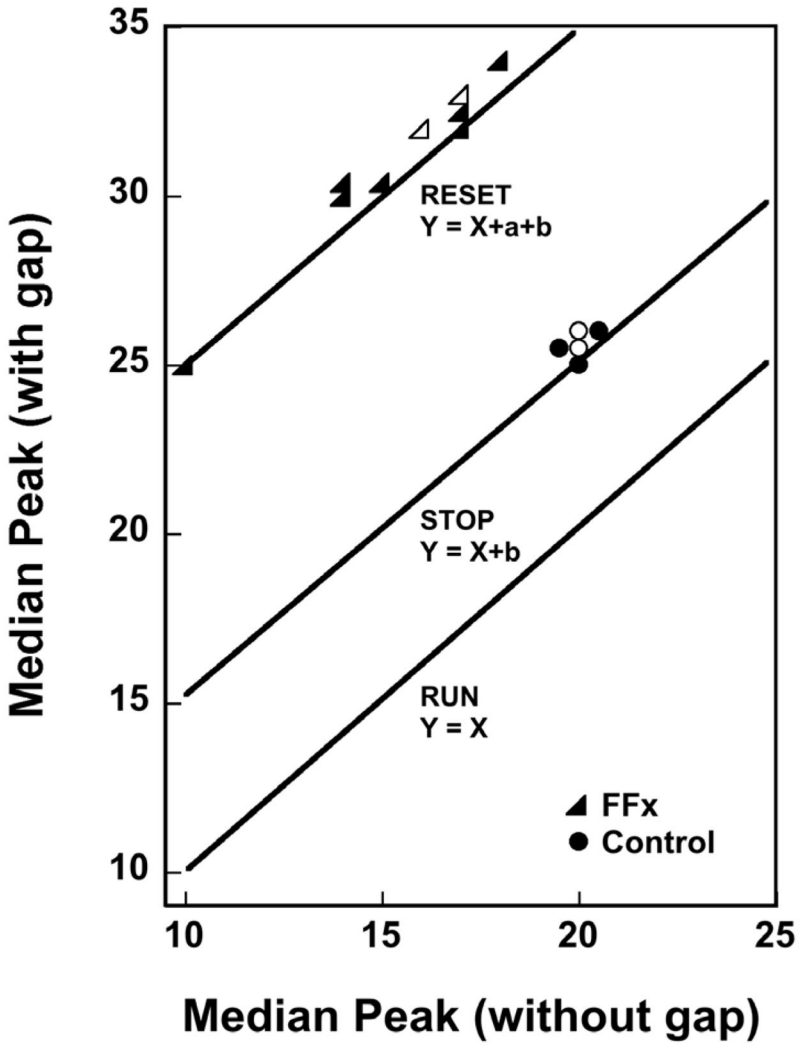

Figure 1.

The effect of a 5-s gap inserted during the white-noise signal for fimbria-fornix (FFx) lesioned and control rats performing in a 20-s PI procedure. The gap affected the control and FFx rats differently. The control rats typically responded about 5 s later on trials with a 5-s gap than without a gap (i.e., they stopped timing during the gap); the FFx rats responded about 15 s later on trials with a 5-s gap than without a gap (i.e., they reset timing during the gap). Open triangles represent multiple FFx rats (n=12) and open circles represent multiple control rats (n=8). The peak time on trials with gaps for rats with FFx lesions is approximated by a line $Y = X + a + b$, where X is the peak time without a gap, a is the duration of the signal before the gap, and b is the duration of the gap. In contrast, the peak time on trials with gaps for control rats is approximated by a line $Y = X + b$. The three diagonal lines show what would occur if subjects operated their clocks using the run, stop, or reset modes during the gap. Adapted from Meck, Church, and Olton (1984).

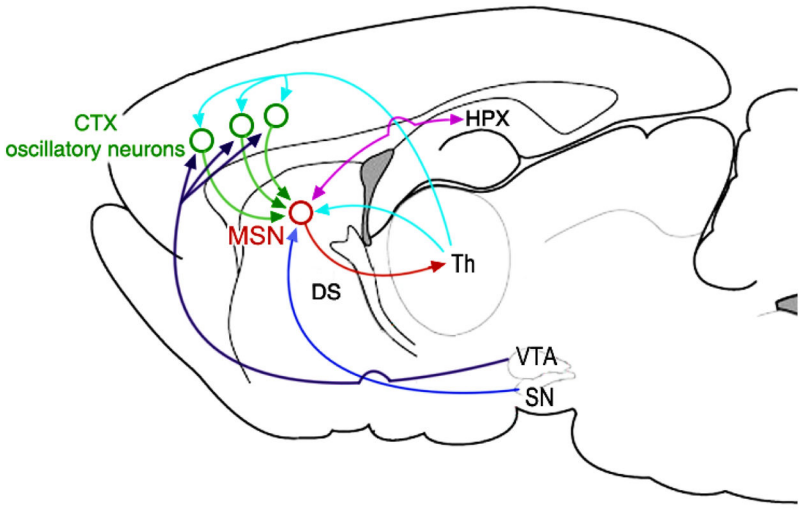

Figure 2.

Diagram of the possible mappings of functional hippocampal connectivity within the cortico-thalamic-basal ganglia circuit of the rat proposed by the striatal beat-frequency (SBF) model of interval timing (Matell & Meck, 2004). In this model, oscillatory neurons in the cortex (CTX) project to medium spiny neurons (MSNs) in the dorsal striatum (DS) which receives dopaminergic input from the substantia nigra pars compacta (SNc). Dopamine projections from the ventral tegmental area (VTA) to the CTX are able to modulate the frequency of CTX oscillations. Bi-directional projections from the hippocampus (HPX) to the DS modulate the firing thresholds of MSNs via either tonic inhibition or phasic excitation. Lesions of the hippocampus would be expected to release the DS from this inhibition, thereby reducing the firing thresholds for MSNs and producing proportional leftward shifts of timing functions (underestimation of duration). The timing circuit is completed by having the CPu project to the thalamus (Th) and back onto the CTX in order to provide feedback control of temporal processing (Lustig & Meck, 2005; Meck, 1988). Adapted from Yin and Troger (2011).

Table 1

Studies Investigating Hippocampal Involvement in Interval Timing.

Species	Manipulation	Procedure(s)	Major Findings	Reference
Rat	electrolytic lesions of ffx	2 vs. 8-s & 2 vs. 16-cps bisection; 20-s PI with gaps	leftward shifts of all functions (underestimation of target duration), sharpening of peak functions, reset following a 5-s gap	Meck et al. (1984)
Rat	ibotenic acid lesions of MSA	40-s PI with gaps	leftward shift (underestimation of target durations), reset following 5 & 10-s gaps initiated 10 or 20s into the signal	Meck et al. (1987)
Rat	electrolytic lesions of ffx	10-s & 20-s PI	proportional leftward shifts (underestimation of target durations); impaired regulation of peak time on sequential trials; normal transition from 20s to 10s	Meck (1988)
Rat	electrolytic lesions of ffx ibotenic acid lesions of MSA	10-s & 20-s PI	proportional leftward shifts (underestimation of target durations), reset following 10-s gap, normal STP	Olton et al. (1988)
Rat	aspiration lesion of hpx	12-s differential reinforcement of low-rate schedule	leftward shift of inter-response time distributions (underestimation of target durations)	Jaldow & Oakley (1990)
Rat	aspiration lesion of hpx	40-s PI with gaps	no effects - likely due to procedural limitations*	Dietrich & Allen (1998)
Rat	ibotenic acid lesions of dhpx	15-s and 30-s Pavlovian delay and trace conditioning with non-reinforced peak trials & gaps	proportional leftward shifts (underestimation of target durations) in both delay and trace conditioning; partial resetting in gap trials	Tam & Bonardi (2012a)
Rat	ibotenic acid lesions of dhpx	40-s Pavlovian delay conditioning with non-reinforced peak trials abd gaps	leftward shift (underestimation of target duration); resetting in gap trials, but no group differences	Tam & Bonardi (2012b)
Rat	ibotenic acid lesions of dhpx	15-s Pavlovian delay conditioning with non-reinforced peak trials and gaps	leftward shift (underestimation of target duration); partial resetting in gap trials	Tam et al. (2013)
Rat	ibotenic acid lesions along septotemporal extent of hpx	20-s & 40-s PI with gaps	proportional leftward shifts (underestimation of target durations) & sharpening of response functions, resetting with gaps	Buhusi & Meck (2013); Buhusi et al. (2004)
Mouse	ibotenic acid lesions of hpx	35-s PI	leftward shift of peak function (underestimation of target duration), including 'start' & 'stop' times	Balci et al. (2009)
Mouse	Close homolog to L1 ($CHL1^{-/-}$) gene deletion	20-s PI with 5 or 10-s gaps	leftward shift of peak function (underestimation of target duration), decreased effect of gaps	Buhusi et al. (2013)
Mouse	NMDA lesions of dhpx or vhpx δ opioid receptor ($Oprd1^{-/-}$) gene deletion	15-s & 45-s Bi-PI	leftward shift of peak functions (underestimation of target durations) for dorsal hpx lesions & $Oprd1^{-/-}$ mice; disruption of motivational effects for ventral hpx lesions	Yin & Meck (2012, 2013)
Rabbit	excitotoxic lesions of dhpx + vhpx	300-ms & 500-ms trace eye-blink conditioning	disruption of extinction for 300-ms & learning impairment for 500-ms condition	Moyer et al. (1990)
Rabbit	single-unit recording in CA1 area of hpx	10-s & 20-s trace eye-blink conditioning with non-reinforced peak trials	CA1 pyramidal neurons showed encoding of target duration on peak trials	McEchron et al. (2003)
Human	intracarotid AMO assessment following left or right temporal lobe resection in epilepsy patients	retrospective estimation of how much time had passed since AMO administration (multiple minutes)	underestimation of time for LTR & RTR, increased variability for RTR	Drane et al. (1999)

Species	Manipulation	Procedure(s)	Major Findings	Reference
Human	left or right medial-temporal lobe resection in epilepsy patients	1 vs. 2-s visual bisection	leftward shift (underestimation of anchor durations) for LTR; increased WF for RTR	Vidalaki et al. (1999)
Human	left or right medial-temporal lobe resection in epilepsy patients	5, 14, or 38 s reproduction and production tasks under conditions of silence, counting, or articulatory suppression	underestimation of duration in the production task for RTR	Perbal et al. (2001)
Human	left or right medial-temporal lobe resection in epilepsy patients	2 vs. 8-s auditory and visual bisection; 50 vs. 200-ms auditory bisection	decreased WF for LTR & increased WF for RTR in all conditions	Melgire et al. (2005)
Human	Left or right medial-temporal lobe resection in epilepsy patients	1 – 8 s verbal estimation and duration reproduction tasks	overestimation and underproduction for both LTR and RTR (effect larger for LTR)	Noulhiane et al. (2007)

AMO = amobarbital; ffx = fimbria-fornix; hpx = hippocampus; medial septal area = MSA; RTR = right temporal lobe resection; LTR = left temporal lobe resection; NMDA = N-Methyl-D-aspartic acid; PI = peak-interval procedure; Bi-PI = bi-peak-interval procedure in which both target durations are timed beginning at trial onset with no external cue provided to indicate which, if any, lever/target duration will be selected for reinforcement on any trial; STP = simultaneous temporal processing of an auditory and visual signal paired with different target durations presented in compound with asynchronous signal onsets; WF = Weber fraction used to measure sensitivity to signal duration, lower values indicate better sensitivity;

*study based differences in peak time on the number of sessions required to reach a criterion of 10% (± 4s) from the scheduled time of reinforcement (40 s), thus precluding observation of the nature of the deviations in peak time prior to this (typically more than 80 sessions). Moreover, 5-s gaps were contained in both fixed-interval and unreinforced probe trials used in the PI procedure, thus precluding their usefulness in evaluating working memory.

Note: Trace conditioning, a form of Pavlovian conditioning in which the presentation of the conditioned stimulus (CS) and the unconditioned stimulus (US) is separated in time by an interstimulus interval (ISI), requires an intact hippocampus (Moyer, Deyo, & Disterhoft, 1990). In contrast, Pavlovian conditioning procedures in which the CS and US are not separated by an ISI (i.e., delay conditioning procedures) typically do not (Solomon, Vander Schaaf, Thompson, & Weisz, 1986; Woodruff-Pak & Disterhoft, 2008). However, why trace conditioning is dependent on the hippocampus is unknown, but may be related to the absence of temporal contiguity (Bangasser, Waxler, Santollo, & Shors, 2006; Haritha, Wood, Ver Hoef, & Knight, 2013).