Contributions of Dorsal/Ventral Hippocampus and Dorsolateral/Dorsomedial Striatum to Interval Timing

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
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ABSTRACT

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Abstract

Humans and animals have remarkable capabilities in keeping time and using time as a guide to orient their learning and decision making. Psychophysical models of timing and time perception have been proposed for decades and have received behavioral, anatomical, pharmacological and physiological data support. However, despite numerous studies that aimed at delineating the neural underpinnings of interval timing, a complete picture of the neurobiological network of timing in the seconds-to-minutes range remains elusive. Based on classical interval timing protocols and proposing a Timing, Immersive Memory and Emotional Regulation (TIMER) test battery, the author investigates the contributions of the dorsal and ventral hippocampus as well as the dorsolateral and the dorsomedial striatum to interval timing by comparing timing performances in mice after they received cytotoxic lesions in the corresponding brain regions. On the other hand, a timing-based theoretical framework for the emergence of conscious experience that is closely related to the function of the claustrum and its interaction with the striatum is proposed so as to serve both biological guidance and the research and evolution of "strong" artificial intelligence. Finally, a "Double Summation Model of Interval Timing" that integrates the direct- and indirect- pathways of striatum is proposed to explain the set of empirical findings.

Dedication

To my extraordinary parents Shen Lin and Xinjian Yin for their endless support.

To all the insightful pioneers in the timing and time perception field for their efforts that have led us to believe in that “Timing is everything”.

To world peace and humanistic evolution of mankind.

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1. Introduction

Humans and other animals can be shown to process temporal information as if they use an internal stopwatch that can be “run”, “paused”, and “reset” on command and whose speed of “ticking” is adjustable. In addition, interval-timing behavior can be separated into “clock”, “memory”, and “decision” stages of information processing such that one stage can be modified without changing the others. 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 & 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 (Harrington, Zimbelman, Hinton, & Rao, 2010; Lustig et al., 2005; Matell & Meck, 2004a; Oprisan & Buhusi, 2011). 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.

1.1 Searching for functional neural circuits 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 (Allman & Meck, 2012; C. V. Buhusi & Meck, 2005b; Coull et al., 2011b; Coull, Vidal, Nazarian, & Macar, 2004; Hinton & Meck, 2004; Meck, 2006a, 2006c; Oprisan & Buhusi, 2011; H. H. Yin et al., 2009). This frontal-striatal system is hypothesized to correspond to the functional components of the SBF model (Matell & Meck, 2004a; Matell et al., 2003a; Meck, 1996, 2006a, 2006c; Meck & Benson, 2002c; Meck et al., 2008), wherein cortical oscillatory neurons and reward input from the substatia 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, Picconi, Gubellini, Bernardi, & Calabresi, 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, Church, 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, Meck, 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 & Merrill, 1992, 1996; Lewis, Couch, & Walker, 2011; Lytton & Lipton, 1999; Matell & Meck, 2004a; Onoda, Takahashi, & Sakata, 2003; Sakata, 2006). 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 2s to 8s for temporal bisection procedures and 10s to 40s 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 (Balci, Meck, et al., 2009; C. V. Buhusi, Mocanu, & Meck, 2004; Meck, Church, et al., 1984; Meck et al., 1987; Olton et al., 1987; Olton et al., 1988). 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. 2s, and 2 vs. 8s in temporal bisection procedures and 0.5s to 8s for temporal reproduction procedures (Melgire et al.,

2005; Vidalaki, Ho, Bradshaw, & Szabadi, 1999). 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, 2002b, 2005; Meck, Church, et al., 1984; Melgire et al., 2005; Vidalaki et al., 1999). These "classic" effects of hippocampal lesions on the performance of rats in the peak-interval procedure are illustrated in Figure 1.

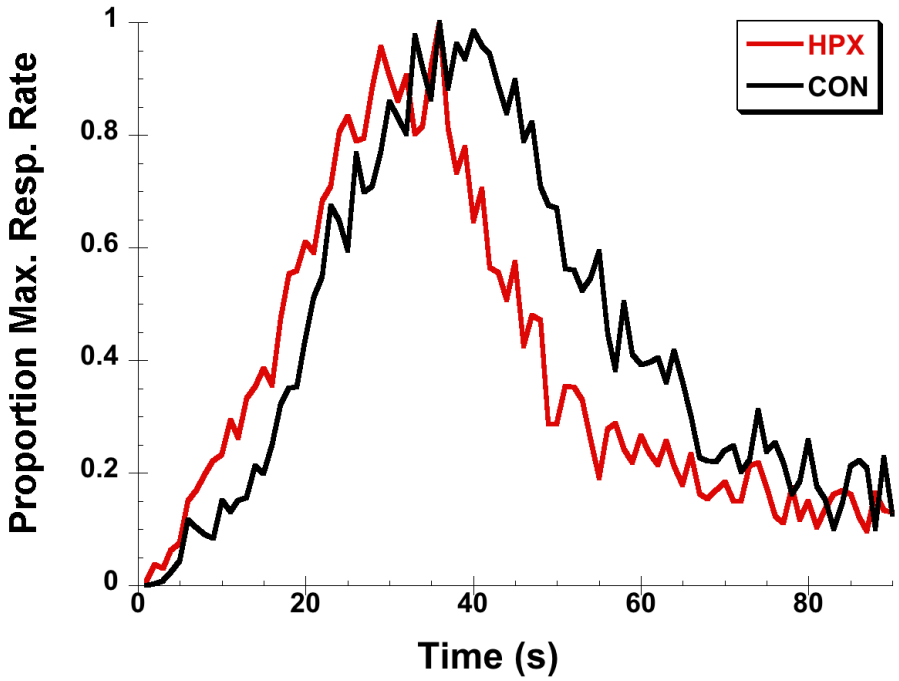

Figure 1: An illustration of the "classic" effects of post-training hippocampal lesions for rats trained on a 40-s peak-interval procedure. The peak functions of rats with hippocampal lesions (HPX) rats are shifted leftward relative to control (CON) rats and are sharper with less spread around the observed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

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 & Allen,

1998; Dietrich, Allen, & Bunnell, 1997), 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 (R. K. Cheng, Ali, et al., 2007; R. K. Cheng, Hakak, et al., 2007; H. H. Yin & Knowlton, 2006a; H. H. 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 & 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, 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 (Lustig et al., 2005; MacDonald & Meck, 2004; Meck et al., 1987).

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 & Meck, 2004a). Hippocampal-striatal interactions have been previously documented (Devan & White, 1999; Graham et al., 2009; Lee, Duman, & Pittenger, 2008; Poldrack & Packard, 2003). 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, Kincaid, & Wilson, 1997). Properties of sub-threshold signal integration in MSNs are determined by the distribution of synaptic inputs and differential activation of multiple postsynaptic conductance (Carter, Soler-Llavina, & Sabatini, 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 & Meck, 2004a; Oprisan & Buhusi, 2011).

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; Harrington, Castillo, Fong, & Reed, 2011; Meck, 2005; Wearden, 2004). 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; Hohn et al., 2011; Jin et al., 2009). 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., 2012). Indeed, it has been reported that the hippocampus may have a role in controlling impulsivity (Cheung & Cardinal, 2005; McHugh, Campbell, Taylor, Rawlins, & Bannerman, 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, Okatan, Skurski, & Eichenbaum, 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 (Balci, Meck, et al., 2009; Macdonald et al., 2012; Meck, Church, et al., 1984; Meck et al., 1987). These three possibilities for the mapping of functional hippocampal connectivity within the SBF timing model are illustrated in Figure 2.

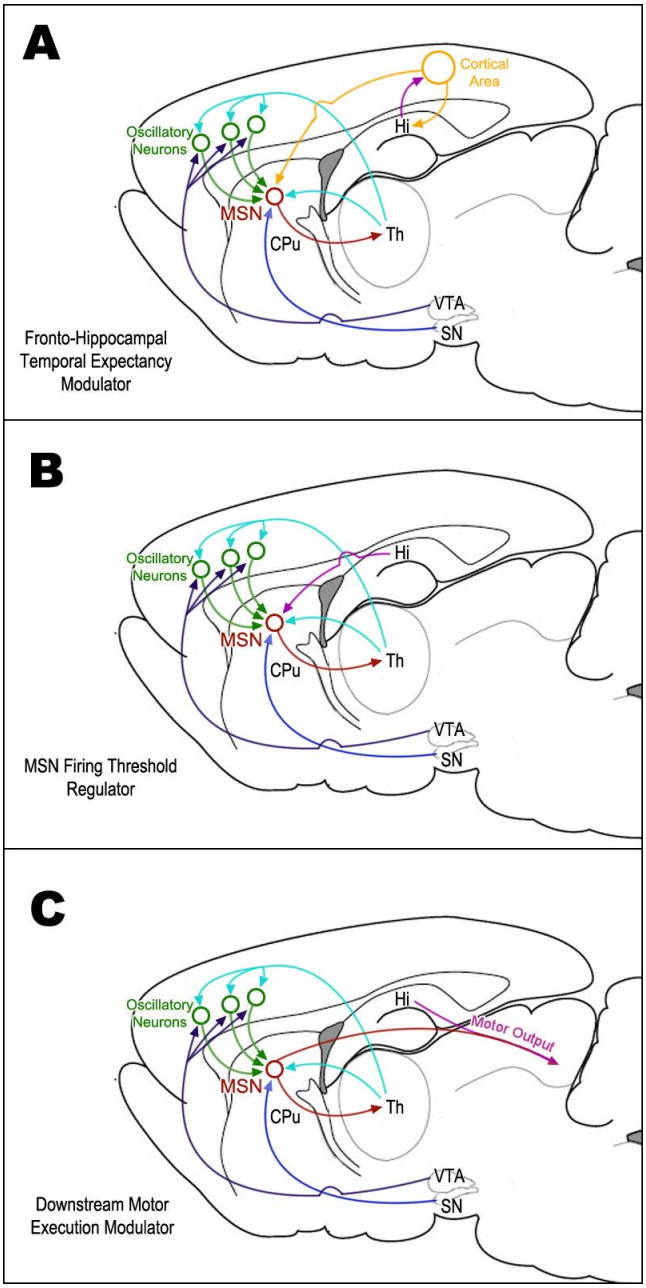

Figure 2: Diagrams of three possible mappings of functional hippocampal connectivity within the neural circuits proposed by the striatal beat frequency (SBF) model of interval timing: A) The hippocampus is involved in a feedback mechanism designed to update temporal expectancy with a separate cortical 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.

One important anatomical question is the whether the dorsal and ventral parts of the hippocampus play functionally distinct roles (Fanselow & Dong, 2010). It's known that the two parts projects differentially to other brain areas. Ventral hippocampus (VH) connects to the prefrontal cortex, the amygdala and ventral and rostral parts of the NAc shell associated with the regulation of locomotor activity, context-dependent learning and emotional behavior (Pennartz et al., 2011), whereas dorsal hippocampus (DH) connects to the rostral part of the ventral striatum including both core and part of shell, dorsal lateral septum, mammillary bodies, anterior thalamus, ventral medial hypothalamus and anterior cingulated cortex (Fanselow & Dong, 2010). Highly processed information from the sensory cortices entering the hippocampus mainly in its dorsal parts (Moser & Moser, 1995), and hence the DH is thought to be tightly related to memory and cognition (Fanselow & Dong, 2010). Therefore, teasing apart the potentially different roles of the dorsal and the ventral parts of the hippocampus in interval timing becomes an intriguing project, which is one of the main focuses in this manuscript.

On the other hand, the dorsal striatum itself is not a unitary entity either: at least the dorsolateral and dorsomedial striatum have been proposed to mediate functional distinctive roles, with the dorsolateral striatum participated in the more habitual, context-cue elicited control of behavior and the dorsomedial striatum participated in the more goal-directed, outcome-contingent control of behavior (Balleine, Delgado, & Hikosaka, 2007; Darvas & Palmiter, 2009; Gu, Cheng, Yin, & Meck, 2011; Hernandez, Sadeghian, & Kelley, 2002; Johnson, van der Meer, & Redish, 2007; Mitchell, Sexton, & Neumaier, 2007; P. Voorn, L. J. Vanderschuren, H. J. Groenewegen, T. W. Robbins, & C. M.

Pennartz, 2004a; H. H. Yin & Knowlton, 2006b). Previous timing studies have found that the temporal control of behavior is highly dependent on the extent of training (R. K. Cheng, Ali, & Meck, 2007; R. K. Cheng, Hakak, & Meck, 2007), contextual cues (Coull, Cheng, & Meck, 2011a; Jazayeri & Shadlen, 2010; Meck & Benson, 2002b; Shi, Church, & Meck, 2013) and is independent of its goals when trained (B. Yin & Meck, 2014b). These data raise questions of whether the two distinctive part of the dorsal striatum play different roles in the temporal control of behavior and how the two parts function together with other brain regions for spatiotemporal control of behavior. Therefore, while examining the roles of dorsal and ventral hippocampus, we also examined the roles of dorsolateral and dorsomedial striatum in interval timing using cytotoxic lesions similar to the ones used in the hippocampal experiments.

Once we solve the problem of hippocampal-striatal interaction in interval timing, one of the questions that would naturally come next is what would be the brain region that integrates these well-timed brain activities so as to make organisms “feel and think” like a cognitive machine. The claustrum has been proposed as a possible neural candidate for the coordination of conscious experience due to its extensive “connectome”. Herein we propose that the claustrum contributes to consciousness by supporting the temporal integration of cortical oscillations in response to multisensory input. A close link between conscious awareness and interval timing is suggested by models of consciousness and conjunctive changes in meta-awareness and timing in multiple contexts and conditions. Using the striatal beat-frequency model of interval timing as a framework, we propose that the claustrum integrates varying frequencies of neural oscillations in different

sensory cortices into a coherent pattern that binds different and overlapping temporal percepts into a unitary conscious representation. The proposed coordination of the striatum and claustrum allows for time-based dimensions of multisensory integration and decision-making to be incorporated into consciousness.

Finally, successful understanding of functional neural circuits underlying cognitive functions in animal models always rely on the successful application of suitable behavioral protocols. Therefore, it is important to examine available interval-timing protocols and envisage useful ones that could be widely applied to the study of temporal cognition and neurobehavioral genetics. Moreover, interval-timing procedures can be used to diagnose the behavioral abnormalities associated with transgenic, “knock-out”, and “knock-down” mouse models of human diseases. In conjunction with interval-timing tasks, evaluation of spatial memory and emotional regulation provides the necessary information for identifying the most-likely locus of behavioral deficits in genetically modified mice. Consequently, the Timing and Immersive Memory and Emotional Regulation (TIMER) test battery outlined here is recommended as a tool for behavioral phenotyping.

1.2 Interval-Timing Protocols and Their Relevancy to the Study of Temporal Cognition and Neurobehavioral Genetics

Birds, bees, fish, turtles, rodents, cats, primates, and quite possibly all living animals engage in a vast array of sensory-motor and social behaviors that evolve over milliseconds, seconds, minutes, hours, days, weeks, fortnights, months, seasons, years,

decades, and centuries (e.g., C. V. Buhusi & Meck, 2005b; Buonomano, 2007; Golombek, Bussi, & Agostino, 2014; Lejeune & Wearden, 2006; Mauk & Buonomano, 2004; Merchant, Harrington, & Meck, 2013; Richelle & Lejeune, 1980; Tucci, Buhusi, Gallistel, & Meck, 2014; Wittmann, 2013a). The timing of intervals on the scale of many hours to around a day is mediated primarily by circadian rhythms while in the range of milliseconds-to-minutes a different process, known as interval timing, is used that engages a 'stop-watch' like mechanism which is modulated by attention as well as the light/dark cycle (e.g., Agostino, do Nascimento, Bussi, Eguia, & Golombek, 2011; Agostino, Golombek, & Meck, 2011; C. V. Buhusi & Meck, 2009a; Bussi, Levin, Golombek, & Agostino, 2014; Church, 1984; Hinton & Meck, 1997b; Meck, 1991, 2003; Williamson, Cheng, Etchegaray, & Meck, 2008). Recent research has identified some of the behavioral and neural mechanisms supporting the interactions between these different timing systems and has focused attention on the neural circuits shared by interval timing and other cognitive processes such as working memory and decision-making (e.g., Allman, Teki, et al., 2014; Gu, van Rijn, & Meck, 2015; Hinton & Meck, 1997a; Lustig, Matell, & Meck, 2005; MacDonald & Meck, 2004; W. J. Matthews & Meck, 2014b; W. J. Matthews et al., 2014; Meck & Benson, 2002a; Meck, Church, & Matell, 2013; Merchant et al., 2013).

A classic example of interval timing comes from the fixed-interval (FI) procedure in which a subject's behavior is reinforced for the first response (e.g., lever press or nosepoke) made after a programmed interval has elapsed since the previous timemarker (e.g., signal onset or delivery of reinforcement – see (Freestone & Church, 2010;

Freestone, Maclnnis, & Church, 2013)). Subjects (e.g., primates, rodents, birds, and fish) trained on this procedure typically show what is known as the fixed-interval scallop. This pattern of behavior involves pausing after the delivery of reinforcement and beginning to respond after a fixed proportion of the interval has elapsed despite the absence of any external time cues. Interval timing of this type has been identified in the majority of animals in which it has been tested for (e.g., (Lejeune & Wearden, 1991; Paule et al., 1999; Richelle & Lehnen, 1980). The FI procedure gave rise to a discrete-trials variant known as the peak-interval (PI) procedure (Catania, 1970; S. Roberts, 1981) which is now widely used to study interval timing in a variety of animal species as cataloged in Table 1.

Table 1

Representative Publications Reporting on the Peak-Interval (PI) Timing Procedure

	Primary focus of Study				
Species	**Behavioral – Computational**	**Circadian**	**Anatomical – Biochemical – Electrophysiological**	**Pharmacological**	**Genetic**
Human (n=17)					
(Balci, Wiener, Cavdaroglu, & Branch Coslett, 2013)*	x				x
(Fortin et al., 2009)*	x				
(Hinton & Meck, 2004)			x		
(Hinton, Meck, & MacFall, 1996)			x		
(Kladopoulos, Brown, Hemmes, & de Vaca, 1998)*	x				
(Lake & Meck, 2013)				x	
(Levin et al., 1996)				x	
(Levin et al., 1998)				x	
(Lustig & Meck, 2005)*	x			x	
(Malapani, Rakitin, et al., 1998)	x		x	x	
(Malapani, Deweer, & Gibbon, 2002)	x		x	x	
(Malapani, Dubois, Rancurel, & Gibbon, 1998)			x		
(McAuley, Miller, Wang, & Pang, 2010)	x				
(Meck, Hinton, & Matell, 1998)			x		

(Rakitin et al., 1998)*	x				
(Rakitin, Scarmeas, Li, Malapani, & Stern, 2006)	x			x	
(Wearden & Mcshane, 1988)	x				
Rat (n=93)					
(Agostino, do Nascimento, et al., 2011)		x			
(Bayley, Bentley, & Dawson, 1998)				x	
(Brown, Richer, & Doyere, 2007)	x				
(C. V. Buhusi, Lamoureux, & Meck, 2008)				x	
(C. V. Buhusi & Matthews, 2014)	x				
(C. V. Buhusi & Meck, 2000, 2006a, 2006b, 2009a, 2009b)*	x				
(C. V. Buhusi & Meck, 2002a, 2007)				x	
(C. V. Buhusi, Perera, & Meck, 2005)	x				x
(C. V. Buhusi, Sasaki, & Meck, 2002)	x				
(Bussi et al., 2014)		x		x	
(Cevik, 2003a)				x	
(R. K. Cheng, Ali, et al., 2007)				x	
(R. K. Cheng, Hakak, et al., 2007)				x	
(R. K. Cheng & Meck, 2007)	x			x	
(R. K. Cheng, MacDonald, Gu, & Meck, 2014)			x		
(R. K. Cheng, Williams, & Meck, 2008)	x			x	
(Church, Meck, & Gibbon, 1994)*	x				
(Church et al., 2014)			x		
(Church, Miller, Meck, & Gibbon, 1991)	x				
(Drew, Fairhurst, Malapani, Horvitz, & Balsam, 2003)*				x	
(Eckerman, Segbefia, Manning, & Breese, 1987)				x	
(Elcoro, Thompson, Kelly, Pegan, & Aparicio, 2014)			x		
(Frederick & Allen, 1996)				x	
(Galtress, Garcia, & Kirkpatrick, 2012)*	x				
(Galtress & Kirkpatrick, 2009, 2010)*	x		x		
(Gharib, Derby, & Roberts, 2001)	x				
(Gooch, Wiener, Portugal, & Matell, 2007)	x			x	
(Gu et al., 2011)				x	
(Heilbronner & Meck, 2014)				x	
(Ho et al., 1996)				x	
(Holder & Roberts, 1985)	x				
(Holder & Roberts, 1985; Kaiser, 2008, 2009)	x				
(Kurti & Matell, 2011)*			x	x	

(Liu et al., 2002)				x	
(Macdonald, Cheng, & Meck, 2012)*			x	x	
(MacDonald, Cheng, Williams, & Meck, 2007)	x	x			
(MacDonald & Meck, 2005)				x	
(Malet-Karas, Noulhiane, & Doyere, 2014)	x				
(Maricq & Church, 1983)				x	
(Matell, Bateson, & Meck, 2006)*				x	
(Matell & Henning, 2013)					
(Matell, King, & Meck, 2004)					
(Matell & Kurti, 2014)*					
(Matell & Meck, 1999)					
(M. S. Matell, W. H. Meck, & M. A. Nicolelis, 2003a)			x		
(Matell & Portugal, 2007)*	x				
(Matell, Shea-Brown, Gooch, Wilson, & Rinzel, 2011)*			x		
(A. R. Matthews, He, Buhusi, & Buhusi, 2012)			x	x	
(McAuley, Miller, & Pang, 2006)	x			x	
(Meck, 1984)	x				
(Meck, 1987, 2006a, 2007)				x	
(Meck, 1988*; 2002a, 2006c, 2006e)			x	x	
(Meck & Angell, 1992)				x	
(Meck & Church, 1982, 1984)	x				
(Meck & Church, 1987a, 1987b)				x	
(Meck, Church, & Olton, 1984)*			x		
(Meck, Church, & Wenk, 1986)				x	
(Meck, Church, Wenk, & Olton, 1987)			x		
(Meck, Komeilyzadeh, & Church, 1984)*	x				
(Meck & Macdonald, 2007)			x		
(Meck & Williams, 1997a; 1997b*)				x	
(Miller, McAuley, & Pang, 2006)				x	
(Olton, Meck, & Church, 1987)			x		
(Olton, Wenk, Church, & Meck, 1988)			x		
(Pang, Yoder, & Olton, 2001)			x		
(Penney, Holder, & Meck, 1996)				x	
(Portugal, Wilson, & Matell, 2011)			x		
(S. Roberts, 1981, 1982)	x				
(S. Roberts & Holder, 1984)	x				
(Sanabria & Killeen, 2007)*	x				
(Swanton, Gooch, & Matell, 2009)*					
(Swanton & Matell, 2011)*	x				
(Swearingen & Buhusi, 2010)*	x				
(Taylor, Horvitz, & Balsam, 2007)*	x			x	
(Whitaker, Lowe, & Wearden, 2003)	x				
(Wiener, Magaro, & Matell, 2008)*			x		

(Yi, 2007)	x				
Mouse (n=21)					
(Abner, Edwards, Douglas, & Brunner, 2001)*				x	
(Agostino, Cheng, Williams, West, & Meck, 2013)			x	x	x
(Balci, Gallistel, et al., 2009)*	x				
(Balci et al., 2010)*					x
(Balci, Ludvig, et al., 2008)*				x	
(C. V. Buhusi et al., 2009)*	x				
(M. Buhusi, Scripa, Williams, & Buhusi, 2013)					x
(Cordes & Gallistel, 2008)*		x			x
(Cushing, 2009)					x
(Drew et al., 2007b)					x
(Carvalho, Silva, & Balleine, 2001)					x
(Gallistel, King, & McDonald, 2004)*	x				
(King, Gallistel, & McDonald, 2001)	x				x
(Lewis, Miall, Daan, & Kacelnik, 2003)		x	x		
(Meck, 2001)					x
(Meck et al., 2012)				x	x
(Meck & Yin, 2011)				x	x
(R. D. Ward et al., 2009b)					x
(B. Yin, Gainetdinov, Caron, & Meck, 2014)				x	x
(B. Yin & Meck, 2014a)					x
Chickadee (n=1)					
(Brodbeck, Hampton, & Cheng, 1998)*	x				
Pigeon (n=21)					
(S. Aum, Brown, & Hemmes, 2007; S. W. Aum, Brown, & Hemmes, 2004)	x				
(C. V. Buhusi, Paskalis, & Cerutti, 2006)	x				
(C. V. Buhusi et al., 2002)	x				
(Catania, 1970)	x				
(K. Cheng, 1992)	x				
(K. Cheng & Roberts, 1991)	x				
(K. Cheng & Westwood, 1993)*	x				
(K. Cheng, Westwood, & Crystal, 1993)*	x				
(Fetterman & Killeen, 1995)	x				
(KirkpatrickSteger, Miller, Betti, & Wasserman, 1996)	x				
(Knealing & Schaal, 2002)				x	
(Kraemer, Randall, Dose, & Brown, 1997)				x	
(Leak & Gibbon, 1995)	x				
(Odum, Lieving, & Schaal, 2002)				x	

(Rice, Grace, & Kyonka, 2014)	x				
(W. A. Roberts, Cheng, & Cohen, 1989)	x				
(W. A. Roberts & Boisvert, 1998)	x				
(Sanabria & Killeen, 2007)*	x				
(Sanabria, Thrailkill, & Killeen, 2009)*	x				
(Saulsgiver, McClure, & Wynne, 2006)				x	
Literature Reviews/Models (n=62)					
(Acerbi, Wolpert, & Vijayakumar, 2012)	x				
(Agostino, Golombek, et al., 2011)		x			x
(Allman & Meck, 2012)	x		x	x	x
(Allman, Teki, et al., 2014)	x		x	x	x
(Balci, 2014)*	x		x	x	x
(Balci, Meck, Moore, & Brunner, 2009)*	x		x	x	
(Balsam, Sanchez-Castillo, Taylor, Van Volkinburg, & Ward, 2009)	x	x			
(C. V. Buhusi, 2003; C. V. Buhusi & Meck, 2009a, 2010)	x		x	x	
(C. V. Buhusi & Meck, 2005b)	x	x	x	x	
(C. V. Buhusi & Oprisan, 2013)	x		x		
(Cevik, 2003b)				x	x
(K. Cheng & Miceli, 1996)*	x				
(Church, 1984)	x		x	x	
(Church & Broadbent, 1990)*	x				
(Church & Meck, 1988)	x		x	x	
(Church & Kirkpatrick, 2001)	x				
(Church & Meck, 1998)			x	x	
(Coull, Cheng, & Meck, 2011b)			x	x	
(Droit-Volet & Meck, 2007)	x		x	x	
(Gibbon & Church, 1984)	x				
(Gibbon & Church, 1990)*	x				
(Gibbon & Church, 1992)*	x				
(Gibbon, Church, & Meck, 1984b)	x				
(Gibbon, Malapani, Dale, & Gallistel, 1997)	x		x	x	
(Gu, Jurkowski, Lake, Malapani, & Meck, 2014)	x		x	x	
(Hasegawa & Sakata, 2015)	x				
(Hinton & Meck, 1997a, 1997b)	x	x	x	x	
(Lustig et al., 2005)	x		x	x	
(MacDonald & Meck, 2004)	x		x	x	
(Malapani & Rakitin, 2003)	x		x	x	
(Matell & Meck, 2000, 2004a)	x		x	x	
(M. S. Matell, W. H. Meck, & M. A. L. Nicolelis, 2003b)			x		
(Meck, 1996, 2002b, 2005)			x	x	
(Meck, 2001)*	x				x
(Meck & Benson, 2002c)	x		x	x	
(Meck et al., 2013)			x		
(Meck & Malapani, 2004)			x		

(Meck, Penney, & Pouthas, 2008)			x		
(Meck & Williams, 2003)	x			x	
(Merchant et al., 2013)			x		x
(Oprisan & Buhusi, 2011)	x		x	x	
(Oprisan & Buhusi, 2013, 2014b)	x		x		
(Paule et al., 1999)	x			x	
(S. Roberts, 1987, 1993, 2014)	x				
(Shapiro & Wearden, 2002)*	x				
(Shapiro, Wearden, & Barone, 2001)	x				
(Shea-Brown, Rinzel, Rakitin, & Malapani, 2006)	x		x	x	
(Shi et al., 2013)	x		x	x	
(Simen, Balci, deSouza, Cohen, & Holmes, 2011)*	x				
(van Rijn, Gu, & Meck, 2014b)	x				
(R. D. Ward, Kellendonk, Kandel, & Balsam, 2012)			x	x	x
(Wearden & Doherty, 1995)	x				
(Williamson et al., 2008)		x		x	
(Zentall, 2006)	x				

* = Individual-trials analysis applied and/or discussed.

In the version of the PI procedure typically used with rodents, a stimulus (e.g., light or tone) is tturned on to signal the beginning of the interval and in a proportion of trials (e.g., 50% FI – 50% probe trials) the subject's first response after the criterion time/target duration is reinforced (e.g., Church et al., 1994)). In the remainder of the trials, known as probe trials, no reinforcement is given and the stimulus remains on for two or three times the criterion time/target duration. When the mean response rate on probe trials is averaged over one or more sessions and plotted as a function of signal duration an approximately Gaussian distribution of responses is typically observed, centered around the criterion time/target duration (Church et al., 1991; Meck & Church, 1984; S. Roberts, 1981). The time at which this response rate function is at its maximum, also known as the peak time, gives an estimate of how accurately the subject is timing, precision is indicated by the spread of the timing function, motivation is measured by the

overall response rate as well as the response rate at the peak time, referred to as the peak rate (see Figure 3). These response measures have been shown to be independent in that one can be changed without changing the others. The use of these independent and correlated measures such as response duration and individual-trials analysis (described below) make the PI procedure an attractive tool for dividing duration discrimination into separate parts (e.g., R. K. Cheng & Meck, 2007; Gharib et al., 2001; Meck, 2001, 2006a, 2006c, 2006e; S. Roberts, 1981, 1993).

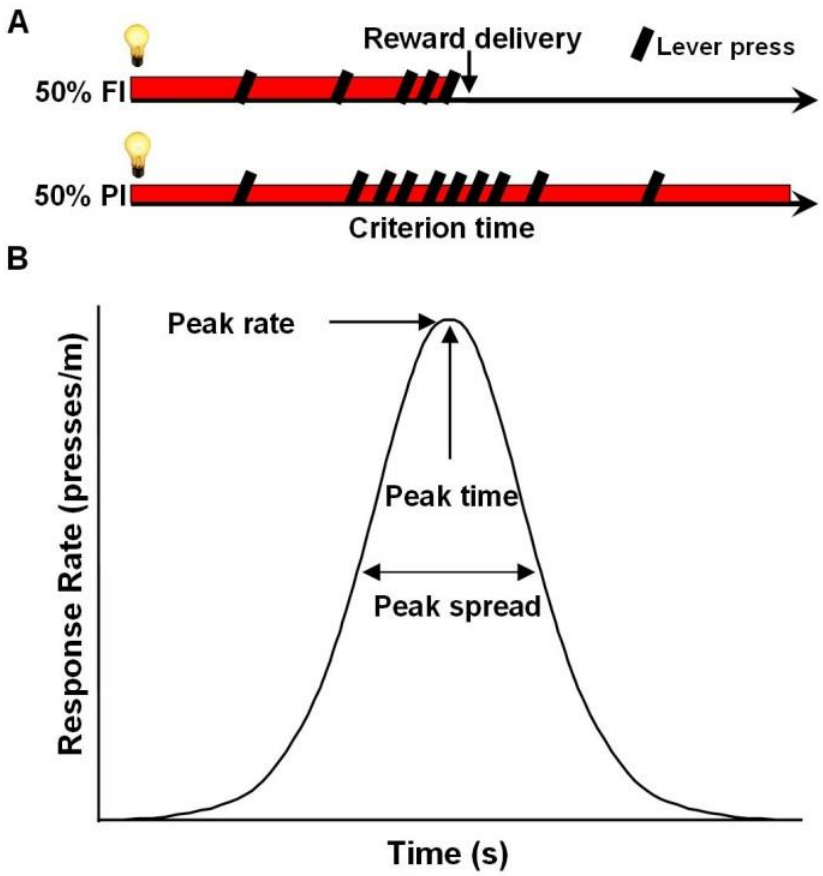

Figure 3: Schematic diagram of the peak-interval (PI) procedure. Panel A: Half of the trials are fixed-interval (FI) trials meaning that the first response after criterion time/target duration will be reinforced. The other half of the trials are unreinforced probe trials (PI) meaning that no reward is given and the signal remains on for up to 2 or 3 times of the criterion time/target duration. Panel B: Presents a Gaussian-shaped response function derived by averaging data across all probe trials. Peak rate is defined as the rate of responding around the expected time of reinforcement, which is defined by the mode of the distribution and referred to as peak time. Peak spread is a measure of the distance between the two points at which the responding curve ascends and descends through a threshold (e.g., 50%) of the peak rate for peak functions normalized by the peak rate (see (Allman & Meck, 2012; R. K. Cheng & Meck, 2007; S. Roberts, 1981).

Behavioral data derived from interval-timing tasks such as the PI procedure have contributed to the development of a number of different psychological theories of timing and time perception. Various behavioral, cognitive, computational, and neurobiological models of interval timing have been proposed (e.g., Buonomano, 2014; Church & Broadbent, 1990; Church & Kirkpatrick, 2001; Gibbon, 1977; Grossberg & Schmajuk, 1989; Hass & Herrmann, 2012; Ivry & Richardson, 2002; Killeen, 2002, 2014; Killeen & Fetterman, 1988; Lejeune, 1998; Machado, 1997; Matell & Meck, 2000, 2004a; Miall, 1989; Shapiro & Wearden, 2002; Shapiro et al., 2001; Shi et al., 2013; Simen et al., 2011; Simen, Rivest, Ludvig, Balci, & Killeen, 2013; van Rijn et al., 2014b; Wearden & Doherty, 1995). These models can be organized into different categories based upon the type of timing mechanism proposed and have been reviewed elsewhere (e.g., Church & Kirkpatrick, 2001; Matell & Meck, 2000). Of these theories, scalar timing theory stands out because not only does it explain much of the behavioral data including the key finding that variability in timing behavior increases proportionally with the duration of the interval being timed (scalar property), but it has also been useful in interpreting and guiding anatomical and pharmacological work in the attempt to identify the brain mechanisms responsible for these behaviors (e.g., Allan, 1998; Allman, Teki, et al., 2014; Church, 1984, 2003; Gibbon & Church, 1984; Gibbon et al., 1997; Lejeune & Wearden, 2006; Meck et al., 1987; Wearden, 1999; Wearden & Lejeune, 2008). Scalar timing theory can be expressed as a computational model of timing (e.g., Church, 2003; Gibbon, 1977; Gibbon, Fairhurst, Church, & Kacelnik, 1988) or as an information-processing model that postulates three distinct components: clock, memory and decision stages

(Allman, Teki, et al., 2014; Gibbon, Church, & Meck, 1984a; Shi et al., 2013). The clock stage is hypothesized to consist of a pacemaker that emits pulses that are transferred to an accumulator through a switch. When feedback (e.g., food reinforcement) occurs the current count in the accumulator is transferred to reference memory. As training with a particular target duration progresses, a distribution of the times of reinforcement is formed in reference memory ((Gibbon & Church, 1990, 1992; Meck, 1983). If the subject needs to compare the current clock reading with a time value sampled from reference memory this is done at the decision stage of the system by making a ratio comparison between the current accumulator value (i.e., clock reading) and a random sample from the appropriate target distribution drawn from reference memory. Scalar timing theory strongly favors a ratio-rule approach (i.e., relative error) for duration comparisons, largely because it is compatible with the scalar property introduced by the memory translation constant (e.g., Aghdaee, Battelli, & Assad, 2014; Meck, 1983; Shi et al., 2013). Working memory can be engaged if trial-specific information is required to complete the timing of the stimulus, e.g., if the stimulus is interrupted by a gap or retention interval (e.g., C. V. Buhusi & Meck, 2000, 2002a, 2006a, 2006b, 2007; C. V. Buhusi et al., 2006; C. V. Buhusi et al., 2002; Meck & Church, 1984; Meck et al., 2013; Swearingen & Buhusi, 2010). Finally, the scalar property of interval timing ensures ‘time-scale invariance’ such that the timing functions for different target durations in the PI procedure superimpose when plotted on a relative time scale – as illustrated in Figure 4 for C57BL/6 mice trained with 10, 20, and 40-s target durations (C. V. Buhusi et al., 2009).

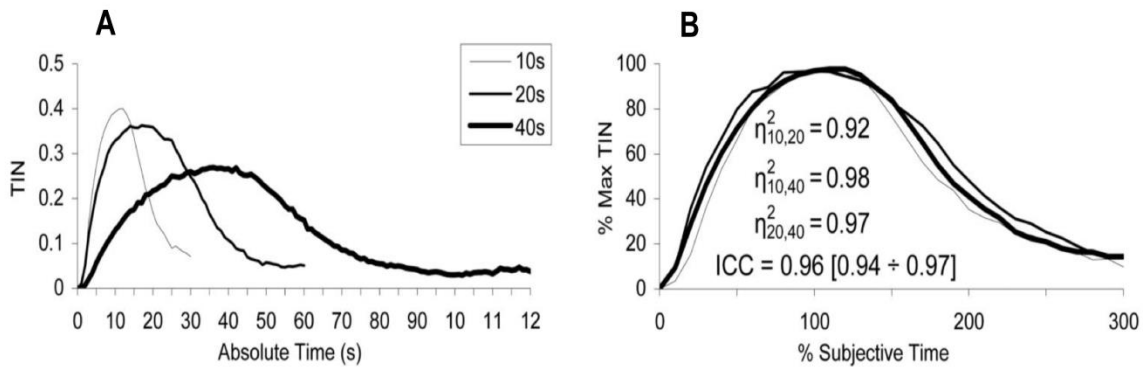

Figure 4: Nose poking in absolute and subjective time units in a peak-interval (PI) procedure with 10, 20, and 40-s target durations in C57BL/6 mice. Panel A: Average time in nose-poke (TIN) in absolute time units (s). Panel B: Average percentage TIN functions normalized in amplitude (peak TIN) and in time (percentage individual estimated peak time). The degree of overlap of functions is quantified by the superposition index (η2), with perfect superposition indicated by a value of 1.00, and by the intra-class correlation (ICC), with perfect superposition indicated by a value of 1.00, and its 95% confidence interval (S. Roberts & Church, 1978). Adapted from Buhusi et al. (2009).

1.3 Application of a Timing, Immersive Memory, & Emotional Regulation (TIMER) test battery

Recent progress in understanding brain and behavior has resulted from the crosstalk between the fields of genetics and neuroscience (e.g., Huang & Zeng, 2013; McCarroll & Hyman, 2013). Genetically modified mice, for example, have provided a means for examining structural and functional abnormalities as a consequence of the targeted genes. In mice, which offer an abundant source of genetic modifications that potentially mimic human diseases, behavioral test batteries (after evaluation of general health) typically include sensory and motor functions, neurological reflexes, learning and memory, feeding and drinking behaviors, social behaviors, reproductive behaviors, drug-seeking behaviors, and emotional behaviors (e.g., (Crawley, 2007). Confronted with such

a wide selection pool of available behavioral paradigms, which one(s) should neurogeneticists focus on? As a rule of thumb, the suspected core function of the modified genes is the primary guideline in determining which set of behavioral tests to be employed when evaluating the behavioral abnormality of the genetically modified animals. However, a particular behavioral paradigm may simultaneously depend on and thus evaluate multiple aspects of the behaviors mentioned above. For example, the Morris water maze is mainly used to evaluate spatial reference memory and spatial working memory (Vorhees & Williams, 2006). While the performance of the task may also depend on specific sensory and motor functions, as well as risk assessment and stress-related responses by the subject, which justifies additional behavioral tasks as a proper control. Moreover, one obvious caveat for some current tests for neurogenetic deficits in animals is that the major behavioral paradigms used are based on an individual-trial or a single-session outcome, thus could not eliminate the problem of state/context dependent behavioral fluctuations that could easily mask the differences between the wild-type group and the genetically modified group (yes, labor saving and craving for faster outcome usually comes with a price, which in the end slows down the speed of making important discoveries). Therefore, a carefully designed behavioral test battery for genetically-modified animals that centers on a multiple-session training design while also incorporating other core aspects of cognition is critical to the development of models for the functional genomics of neurogenetic disorders (e.g., R. K. Cheng, Jesuthasan, & Penney, 2014; R. K. Cheng, Jesuthasan, & Penney, 2011; Kabashi, Brustein, Champagne, & Drapeau, 2011). Interval timing fits nicely into this framework, not only because of the

multiple-session training methodology whose outcome is very stable across different laboratory environments (Maggi, Garbugino, et al., 2014)), but also because interval timing per se is at the core of cognitive and emotional processing (e.g., R. K. Cheng, MacDonald, Williams, & Meck, 2008; Droit-Volet & Meck, 2007; W. J. Matthews & Meck, 2014a, 2014b; Meck, 2001; Meck & Macdonald, 2007). The Battery for the Assessment of Auditory and Sensorimotor Timing Abilities (BAASTA) is one such tool that has been used successfully in humans; it includes duration discrimination, anisochrony detection, beat alignment, synchronization-continuation and tapping tasks, and has been used to compare musicians and non-musicians and to identify the specific timing impairments of patients with Parkinson's disease (Farrugia, Benoit, Harding, Kotz, & Dalla Bella, 2012) – see also Plotek et al., 2014.

1.4 Neural basis of interval timing

On the basis of the accumulation of evidence from drug and lesion studies investigators have suggested a potential mapping between the information-processing elements of scalar timing theory and structures in the brain. Specifically, the output from dopaminergic neurons in the substantia nigra pars compacta (SNC) has been suggested to serve as the "start gun" for interval timing with temporal integration occurring as a function of the coincidence detection of patterns of cortical oscillations by striatal medium spiny neurons (e.g., (Coull et al., 2011b; Matell & Meck, 2000, 2004a; Matell et al., 2003a; Meck et al., 2008)). Support for this hypothesis comes from the observation that indirect dopamine agonists, such as cocaine and methamphetamine, speed up the

clock whereas dopamine antagonists, such as haloperidol, slow down the clock (e.g., Cevik, 2003a; Heilbronner & Meck, 2014; Lake & Meck, 2013; Lustig & Meck, 2005; Maricq & Church, 1983; Maricq, Roberts, & Church, 1981; Matell et al., 2006; Matell et al., 2004; Meck, 1983, 1996). D2 dopamine receptors are specifically implicated in the function of the pacemaker by a study showing that the in vitro affinity of different neuroleptics for the D2 receptor predicts the magnitude of the rightward shift observed in timing functions (Drew et al., 2003; Meck, 1986). This hypothesis is further supported by the results of lesion studies which have shown that lesions of both the SNC and the dorsal striatum (DS) severely disrupt the temporal control of behavior, with the SNC deficits, but not the DS deficits, being partially restored by l-dopa treatment (Meck, 2006e). Moreover, lesions of the nucleus basalis magnocellularis or frontal cortex, but not the medial septal area or hippocampus, eliminate the clock speed effect of dopaminergic drugs (Meck, 2006c).

As one can readily see, the ability of the brain to process time in the seconds-to-minutes range is a challenging problem given that the basic electrophysiological properties of neurons operate on a milliseconds time scale. The striatal beat-frequency (SBF) model of interval timing integrates a multitude of cortical and thalamic oscillations with a “perceptron” processing system of the basal ganglia to arrive at the detection of times much larger than the oscillation periods (Matell & Meck, 2000, 2004a). This model is based on the observation that striatal spiny neurons receive input from 10,000-30,000 separate inputs from a wide variety of cortical and thalamic areas. These cortical and thalamic neurons oscillate with a mean periodicity of 10 Hz (Llinas, 1993, 1998). The

striatal medium spiny neurons have been hypothesized to be capable of detecting and responding to select patterns of cortical input. The particular pattern of excitatory input is selected by long-term potentiation and/or long-term depression which is believed to result from dopaminergic activity from the midbrain ventral tegmental area (VTA) and the SNC following the delivery of reinforcement. Additionally, these dopamine neurons have been shown to transfer their activation onset to the signals that predict subsequent reinforcement (e.g., Bermudez & Schultz, 2014; Schultz, Apicella, & Ljungberg, 1993; Schultz, Dayan, & Montague, 1997; Tomasi, Wang, Studentsova, & Volkow, 2015).

The above neurobiological properties of the cortico-striatal circuitry can be combined with a “beat frequency” model of timing (Miall, 1989) that suggests that after resetting a range of oscillatory inputs, a specific time can be encoded by selectively weighting which inputs are currently active at the criterion time. This model’s time coding is similar to the idea that one can code the number 15 by asking for the lowest common multiple of 3 and 5, thereby coding large numbers with much smaller numbers. Thus, the SBF model provides a manner to encode a long interval with very short neuronal mechanisms using the concept of coincidence detection which has been hypothesized as a major contributor to information processing in the basal ganglia (e.g., C. V. Buhusi & Oprisan, 2013; Gu et al., 2014; Houk, 1995; Matell & Meck, 2004a; Oprisan & Buhusi, 2011, 2013, 2014b).

Specifically, upon onset of a meaningful signal (e.g., a cue that predicts important outcomes), dopamine neurons fire in a burst pattern which transiently synchronizes the cortical and thalamic oscillations, as well as hyperpolarizes the striatal

membrane, thereby resetting the integrating mechanism. The level and reliability of this phasic dopamine response can vary as a function of age/disease state (e.g., Parkinson's disease – see Gu et al., 2014; C. R. G. Jones & Jahanshahi, 2014 or magnitude of reinforcement (e.g., Ludvig, Conover, & Shizgal, 2007), thereby producing a continuum of effects ranging from full reset/synchronization to partial reset/synchronization (Allman & Meck, 2012; R. K. Cheng, MacDonald, & Meck, 2006; T. Kononowicz & van Rijn, 2014). Following this dopamine burst, the cortical and thalamic neurons begin to oscillate at their inherent periods with associated variability, leading to a gradual reduction in synchronization and the emergence of the scalar property of interval timing while also allowing particular oscillatory patterns of neural activity to become meaningful. Upon detection of a previously reinforced pattern of oscillatory input, via the crossing of a coherent activity threshold, an ensemble of striatal spiny neurons fire thereby engendering a response that the encoded time has been reached. This striatal activity passes out of the basal ganglia to the thalamus and from there back to the cortex and striatum, thereby impinging on the current oscillatory inputs, allowing alterations of timing and time perception (Gu et al., 2015; Matell & Meck, 2000, 2004a; van Rijn et al., 2014b). Such information flow through cortico-striato-thalamo-cortical loops has been observed in functional magnetic resonance imaging data during psychophysical timing tasks with human participants and has been related to the timing dysfunctions observed in a variety of psychiatric and neurological disorders as well as related animal modals (e.g., Allman & Meck, 2012; Allman, Pelphrey, & Meck, 2011; Allman, Teki, et al., 2014; Allman, Yin, & Meck, 2014; Coull et al., 2011b; Harrington, Castillo, Greenberg, et al.,

2011; Harrington et al., 2014; Hinton et al., 1996; Hohn et al., 2011; C. R. G. Jones & Jahanshahi, 2014; Malapani, Dubois, et al., 1998; Meck, 2005; Meck et al., 1998; Meck & Malapani, 2004; Meck et al., 2008; Nichelli, 1993; Paulsen et al., 2008; Paulsen et al., 2004). A recent study by Valerie Doyere and colleagues is particularly relevant here because of its use of a transgenic rat model of Huntington's disease (HD) that recapitulates the late-onset HD phenotype (Hohn et al., 2011). In this study the authors assessed cortico-striatal function in this HD rat model using electrophysiological measures of input/output function and neural plasticity induced by theta-burst stimulation as well as the temporal bisection procedure (2 vs. 8-s anchor durations) to measure the accuracy and precision of interval timing. These findings suggest that timing in the supra-second range may represent one of the earliest forms of cognitive dysfunction in HD (Hohn et al., 2011; Rao, Marder, Uddin, & Rakitin, 2014).

1.5 What makes a mutant mouse "tick"?

The study of timing and time perception in wild-type and mutant mice has been successfully demonstrated and promises to become a fruitful area of inquiry for the study of the molecular basis of learning and memory (e.g., Brunner, Leahy, Edwards, & Abner, 2001; Carvalho et al., 2001; Cevik, 2003b; Huerta, Sun, Wilson, & Tonegawa, 2000; Sasaki, Wetsel, Rodriguiz, & Meck, 2001). For example, mice that display impairments in synaptic plasticity both at the presynaptic (synapsin I, synapsin II, synaptotagmin I, synaptogyrin and synaptophysin) and postsynaptic (alfaCaMKII Thr286Ala) level have been evaluated for their ability to form stable representations of event durations using the

peak-interval timing procedure (e.g., (Carvalho et al., 2001). These data suggest that impairments in the acquisition and retention of temporal memory are related to presynatic alterations in neural plasticity.

The major questions that many of these researchers seem to be asking about the internal clock used to make temporal discriminations in the seconds-to-minutes range are: What makes a mutant mouse "tick"? Or to put it another way, what brain mechanisms are involved in interval timing and what types of changes in interval timing are possible and/or interpretable using mutant mice? What follows is an outline of some of these possibilities that was initially proposed by Meck (2001) and updated to reflect the research findings and theoretical models developed since then.

i) The accuracy of a temporal discrimination can be affected by selective alterations in memory storage and retrieval processes. This type of change in interval timing has been described as a modification of the memory translation constant (K*) which is a multiplicative (i.e., scalar) constant (Gibbon et al., 1984a; Meck, 1983, 1996, 2002a, 2002b). Animals typically represent the psychological time of reinforcement veridically with the physical time of reinforcement, thus displaying a K* of 1.0. Systematic discrepancies in the psychological time of reinforcement can occur, however, with K* < 1.0 and K* > 1.0 leading to durations being remembered as being proportionally shorter or longer, respectively (Church & Meck, 1988; Meck, 1996, 2002a, 2002b; Meck & Church, 1987a; Oprisan & Buhusi, 2011; van Rijn et al., 2014b). Searching for a K* mutant is logically similar to the identification of hamsters, mice, and fruit flies bearing the circadian tau mutation (see Cordes & Gallistel, 2008; Hinton &

Meck, 1997a; King et al., 2001). One caveat to keep in mind, however, is that it seems unlikely to some researchers that this could be a single gene in the case of interval timing because of the reliance on the interactions of distributed brain areas, including frontal-striatal circuitry, rather than on rhythmic activity sustained by individual cells within the suprachiasmatic nucleus (see Allada, Emery, Takahashi, & Rosbash, 2001; Cordes & Gallistel, 2008; Golombek et al., 2014; Hinton & Meck, 1997a; Loudon et al., 2007; Lowrey et al., 2000; Maggi, Lassi, et al., 2014; Meng et al., 2008; Ralph & Menaker, 1988). Importantly, it has recently been observed that the circadian modulation of dopamine signaling in the basal ganglia affects the speed of the internal clock used to time intervals in the seconds-to-minutes range (Bussi et al., 2014) – see also Williamson et al., 2008).

ii) The precision of a temporal discrimination can be modified by selective alterations in the sources of variability associated with interval timing (e.g., R. K. Cheng & Meck, 2007; Church et al., 1994). Precision and/or sensitivity to time can be affected by the speed and variability of the "internal clock" as well as by variability in memory and the thresholds used to control responding. In practice, alterations in clock speed would be the primary factor of interest. Animals with higher clock speeds should (everything else being equal) exhibit greater sensitivity to duration and enhanced precision (e.g., Brunner et al., 2001). In contrast, animals with lower clock speeds should exhibit a lower sensitivity to signal durations and impaired precision in timing behavior. The identification of these source(s) of variability can be a pain-staking process, but it is feasible with current behavioral procedures and data analysis techniques (e.g., K. Cheng

et al., 1993; Church et al., 1994; Gibbon & Church, 1984; Rakitin et al., 1998). Indeed, recent work has successfully identified two genotypes that have highly specific and opposing effects on the precision with which mice represent interval duration (Gallistel et al., 2014), which has not been shown in many other measures of learning and memory.

Genes that modify clock speed should be identifiable with the combined use of pharmacological agents known to increase (e.g., methamphatamine) or decrease (e.g., haloperidol) clock speed in wild-type animals. Changes in clock speed lead to the observed "clock pattern" induced by dopaminergic manipulations (e.g., Coull et al., 2011b; Meck, 1983, 1996; Meck et al., 2012; Oprisan & Buhusi, 2011)). It would, of course, be possible to selectively "knock out" the clock – an extreme form of slowing it down. Presumably tyrosine hydroxylase knock-out (-/-) mice would have a completely dysfunctional "internal clock", but this is hardly a selective manipulation unless it is limited to the SNC or the VTA (e.g., Suri, Fung, Tischler, & Chikaraishi, 1993). Dopamine transporter (DAT) "knock-out" (KO) and "knock-down" (KD) mice as well as mice exhibiting striatal D2 receptor overexpression (Ward et al., 2009) are also of great interest in this regard. These mice have been shown to demonstrate paradoxical effects to dopaminergic drugs and have become an important model of attention-deficit hyperactivity disorder, obsessive-compulsive disorder, and schizophrenia (e.g., Cevik, 2003a, 2003b; Gainetdinov et al., 1999; Giros, Jaber, Jones, Wightman, & Caron, 1996; Gu et al., 2011; S. R. Jones et al., 1999; Meck et al., 2012; R. D. Ward et al., 2012) – see alsoBalci et al., 2013 for a discussion of the epistasis effects of dopamine genes on

interval timing and reward magnitude in humans evaluated using the PI timing procedure).

Other types of changes in the functioning of the “internal clock” are also possible. These might include:

iii) The rate of acquisition of a temporal discrimination, e.g., the setting of response thresholds (upper and lower thresholds in the peak-interval procedure) can be selectively modified (e.g., Church et al., 1994; Macdonald et al., 2012; Meck & Church, 1984). Differences in the thresholds to start and stop responding would be expected to affect the symmetry of the response distributions and the degree of independence in the setting of these proportional thresholds (e.g., Church et al., 1994; Church et al., 1991). Contrast, for example, the high degree of symmetry observed in the peak functions reported by Miller et al., 2006 – Fig. 1A, R. K. Cheng, Hakak, et al., 2007 – Fig. 1, left column), and Meck et al., 2012 – Fig. 5A & B, VEH functions with the large asymmetrical skew reported by Miller et al., 2006 – Fig. 1D), R. K. Cheng, Hakak, et al., 2007 – Fig. 1, right column), and Meck et al., 2012 – Fig. 5A & B, MAP functions. In the first two cases, the increased skew is due to drug administration (MK-801 or methamphetamine) and in the third case is due to the interaction between gene deletion (DAT +/+, +/-) and methamphetamine administration. Other data sets are also likely to exhibit these multiple response components which are typically modeled by a combination of a Gaussian distribution representing responses controlled by time (e.g., the target duration) plus a ramp function for responses controlled by other factors (e.g., general levels of arousal, impulsivity, and/or the anticipation of the end of the probe trial

and the beginning of the intertrial interval (Carvalho et al., 2001; Church et al., 1991; Drew et al., 2007b; B. Yin & Meck, 2014a). Unfortunately, an individual-trials analysis (described below) has difficulty in separating timing from non-timing components in this manner (Matell & Portugal, 2007).

iv) Changes in the probability of attention and/or attentional time-sharing (e.g., the latency to start and stop timing or the ability to divide attention among multiple events or signal durations as in simultaneous temporal processing – e.g., C. V. Buhusi & Meck, 2006a, 2006b, 2009a, 2009b; Fortin & Masse, 2000; Meck, 1984, 1987; Meck & Williams, 1997a; Olton et al., 1988; Pang et al., 2001; Penney, Gibbon, & Meck, 2008; Penney et al., 1996).

v) Changes in working memory or the ability to bridge a retention interval or break inserted into the ongoing timing signal (e.g., "PI-GAP" procedure) have demonstrated the involvement of the hippocampus in interval timing (e.g., C. V. Buhusi & Meck, 2000, 2006a, 2006b, 2007; C. V. Buhusi et al., 2006; C. V. Buhusi et al., 2002; Fortin et al., 2009; Fortin & Masse, 2000; Meck, 1988; Meck et al., 2013; Meck, Church, et al., 1984; Meck et al., 1987; Swearingen & Buhusi, 2010).

vi) Selective changes in the range of intervals that can be timed (e.g., the possibility of missing oscillators). Assuming that a continuum of oscillators are used to time a wide range of signal durations, it would be possible that a mutation could lead to the effective deletion of or more of these oscillators. Such a deletion could result in the inability to time specific durations; i.e., a loss in sensitivity to certain ranges of durations. This would tend to increase the discontinuities or "nonlinearities" that are sometimes

observed in interval-timing behavior (e.g., (Crystal, 1999, 2001; Crystal, Church, & Broadbent, 1997).

vii) Individual probe trials taken from PI timing sessions can be analyzed for sequential dependencies in the start, stop, middle, and spread of the response sequence generated on each trial as well as their covariance patterns (Church et al., 1994; Gibbon & Church, 1990, 1992; Matell et al., 2006) and transition states when switching from one target duration to another (e.g., (Macdonald et al., 2012; Meck & Church, 1984)). Unlike the mean response rate functions, individual peak trials are not typically characterized by a gradual increase and then a decrease in response rate centered around the time of reinforcement, but by a period of a relatively constant, high response rate, preceded and followed by a low response rate as illustrated in Figure 5. The covariance patterns among measures of the low–high–low (LHL) response pattern on individual trials (e.g., start, stop, middle, and spread) have been shown to support a parallel, scalar timing model in which subjects used a single sample from memory of the time of reinforcement and separate response thresholds on each trial to decide when to start and stop responding (Church, Gibbon, & Meck, 1986; Gibbon & Church, 1984, 1990, 1992; Gibbon, Meck, & Church, 1987). Application of the “break-run-break” pattern to individual trials can also assist in the identification of the sources of variance (e.g., clock, memory, and decision) and the nature of horizontal shifts in temporal discriminations (e.g., Balci, 2014; Balci et al., 2010; K. Cheng et al., 1993; Church et al., 1994; Galtress et al., 2012; Galtress & Kirkpatrick, 2009, 2010; Kurti & Matell, 2011; Macdonald et al., 2012; Matell et al., 2006). In addition to the traditional way of fitting a step function to individual trials in

order to determine start times (S1) and stop times (S2), one can also use S1 rate index and S2 rate index to represent the mean start response thresholds and stop response thresholds, respectively. The rate index can be calculated by taking the response rate in a specified interval (e.g., 20% of the target duration) just prior to or after the observed peak time as a ratio of overall response rate within the first (S1) or second (S2) half of the trial as defined by the target duration. Higher values of S1 and S2 rate index indicate sharper FI or PI timing functions and better duration discrimination (cf., Agostino, do Nascimento, et al., 2011; Agostino, Golombek, et al., 2011; R. K. Cheng & Meck, 2007). There are, however, some limitations and concerns associated with applying an individual-trials analysis to data obtained from the PI procedure as described in Appendix I.

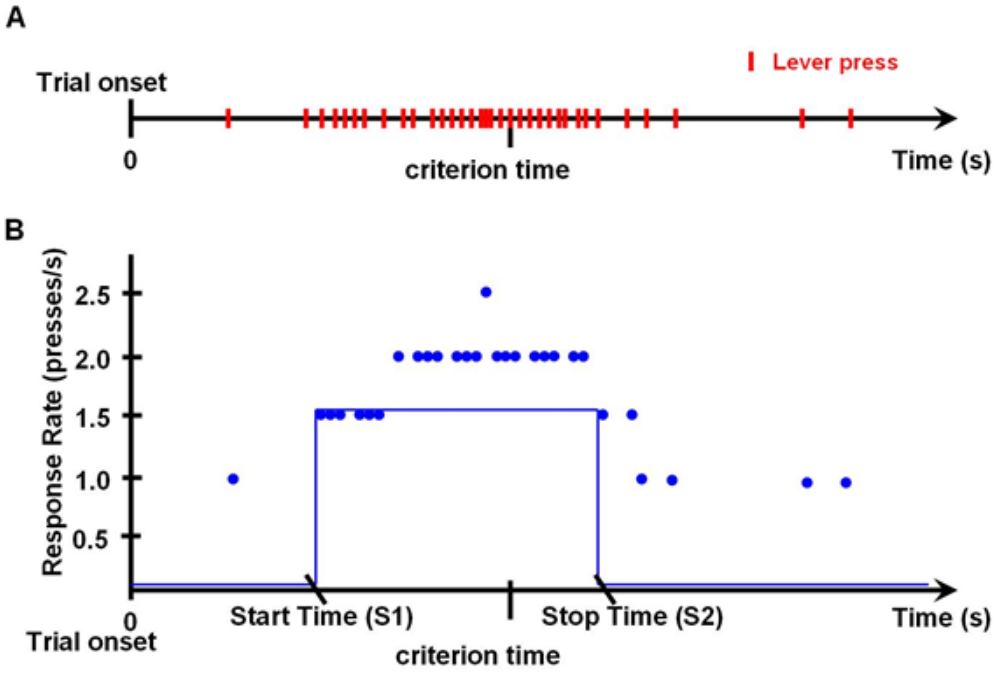

Figure 5: Schematic diagram of individual-trials analyses in the peak-interval (PI) procedure. Panel A: Represents lever-press data in an individual probe trial. On the X-axis, each red tick indicates one lever press. Panel B: Provides a conversion of the data displayed in panel A into response rate as a function of time. Each blue dot represents the response rate in a particular time bin. The blue lines represent the step functions that best fit the current response patterns in this trial. Start time (S1) and stop time (S2) are derived by the time points that the subject abruptly transitions from a low state of responding into a high state of responding before the criterion time/target duration and back into a low state of responding following the criterion time/target duration (e.g., (Church et al., 1994; Kurti & Matell, 2011; Macdonald et al., 2012; Matell et al., 2006; Matell & Portugal, 2007).

viii) The bi-peak and tri-peak procedures (e.g., Agostino et al., 2013; C. V. Buhusi & Meck, 2009b; Matell et al., 2004; Matell & Meck, 1999; Meck et al., 2012; B. Yin & Meck, 2014a) can also be used to examine the scalar variability of interval timing, and if there is any deviance in the multiple peak times obtained from the same trial. In this case, it would be possible to dissect whether the influences of an experimental manipulation affect clock speed or K* proportionally or not, and determine whether the affected peak functions still obey the scalar variability, i.e. whether the variances come from the clock, memory or decision thresholds (Meck, 1996; B. Yin & Meck, 2014a). Interestingly, a novel variant of the temporal bisection (e.g., R. K. Cheng, Etchegaray, & Meck, 2007; Church & Deluty, 1977; Meck, 1983; Penney et al., 2008) and bi-peak procedures (e.g., Meck et al., 2012; B. Yin & Meck, 2014a) in which subjects switch from the response associated with a 'short' duration to an alternative response associated with a 'long' duration has recently been developed (e.g., Balci, Freestone, & Gallistel, 2009; Balci, Papachristos, et al., 2008; Gallistel et al., 2014; Kheifets & Gallistel, 2012; Maggi, Garbugino, et al., 2014; Maggi, Lassi, et al., 2014; Meck et al., 2012; B. Yin & Meck, 2014a). In this 'timed-switching protocol', subjects (in this case mice) are provided with two flanking hoppers, one associated with a 'shorter' delay to reward availability and the other associated with a 'longer' delay after which a nosepoke will result in food reward as illustrated in Figure 4. The optimal behavior for the mouse is to begin poking its nose into the 'shorter' hopper and if there is no food delivery within a certain time period, switch to the 'longer' hopper. The distribution of switch latencies depends on both the 'shorter' and 'longer' durations, and therefore, the estimated mean of

the distribution of switch latencies measures the accuracy with which the subject can target the center of the 'temporal goalposts' so to speak (i.e., the point of subjective equality, PSE, between the two anchor durations), while the coefficient of variation (CV) measures the precision with which it does so. Changes in the 'switch point' can be analyzed by systematically varying the probability of reward at each hopper, thereby providing a highly efficient way of measuring temporal sensitivity and reward optimization in wild-type and mutant mice (e.g., Balci, Freestone, et al., 2009; Maggi, Lassi, et al., 2014).

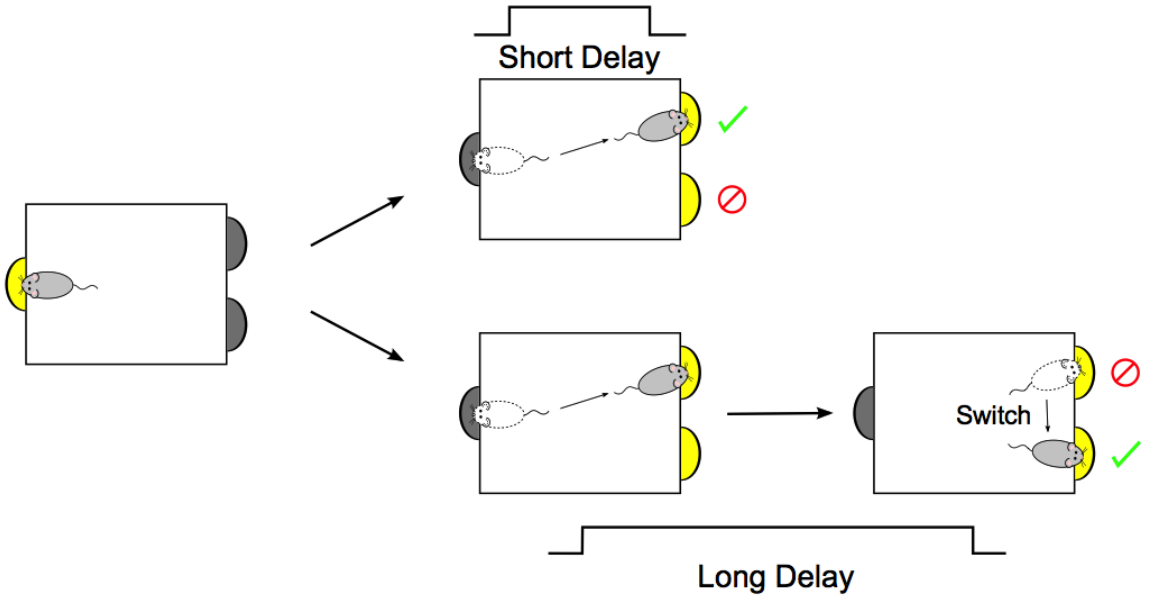

Figure 6: Schematic diagram of the 'timed-switching protocol'. Trials are self-initiated by a nose poke in the rear "hopper" which is registered by the breaking of an infrared beam. These trials are divided into short-delay (top) or long-delay (bottom) and mice are rewarded for correctly selecting the hopper associated with that delay duration. Adapted from (Balci, Freestone, et al., 2009; Balci, Papachristos, et al., 2008; Gallistel et al., 2014; Maggi, Garbugino, et al., 2014; Maggi, Lassi, et al., 2014).

ix) Modulation of peak times and peak rates under selective behavioral manipulations, such as reversal of temporal contingencies (e.g.,R. K. Cheng, Etchegaray, et al., 2007; B. Yin & Meck, 2014a) and pre-feeding (e.g., S. Roberts, 1981; B. Yin & Meck, 2014b). When using a bi-peak procedure, the contingency between specific inputs (e.g. the left or the right lever) and the corresponding to-be-timed durations can be reversed, and thus allowing the mice to switch their internal representations of the learned durations with specific motor programs, which are reflected by gradually changing peak times of the two to-be-timed durations. Again, the rate of reversal learning as reflected by the peak times changing can be modulated by interactions of different genes or different brain areas. On the other hand, mice that are prefed prior to testing in the PI timing procedure typically lack motivation to respond vigorously for food reward, which is reflected by reduced peak rates. However, even under these conditions, they are still able to time quite accurately and display the normal peak function (B. Yin & Meck, 2014b). Consequently, the sensitivity of peak rate reduction to pre-feeding can provide a useful measure of the functional interactions between different genes or different brain circuits.

x) The mere raw response rates, such as lever presses, nosepokes and/or foodcup entries, can be evaluated to measure the general motivational states of the mice performing the tasks irrespective of whether they can time or not. In addition, some secondary signs of timing, such as foodcup entries as a function of signal duration, can be evaluated as a potential parallel mechanism of timing, memory and emotional regulation (B. Yin & Meck, 2014b).

xi) Spatial-temporal integration can be studied by incorporating interval-timing components into a spatial mapping task, such as has been done in M. Buhusi et al. (2013). Animals can be confined in an area for a fixed duration before entering spatial exploration, during which animals spontaneously start timing immediately being placed in the confinement, or immediately upon entering the spatial maze, and the temporal cues are used to plan out the spatial action sequence based on past experiences (see van der Meer, Johnson, Schmitzer-Torbert, & Redish, 2010). In this way, if an animal actively integrates spatial-temporal information in planning action sequences, a change in the duration of confinement will have significant effects on the success rate of the spatial exploration task. A classic interval-timing task, such as the PI procedure introduced above, should be accompanied to determine whether the animal indeed has distortions in the interval timing abilities per se.

xii) Last but not least, contextual calibration using Bayesian optimization of interval timing has recently been proposed (e.g., Cicchini, Arrighi, Cecchetti, Giusti, & Burr, 2012; Jazayeri & Shadlen, 2010; Shi et al., 2013). In the Bayesian model, the likelihood function, prior distribution and loss function can be related to the three information-processing stages of the classic internal-clock model – clock, memory and decision-making stages. Evidence has shown that Bayesian inference provides strong predictions and a sound theoretical basis for contextual calibration in time perception. Therefore, the application of Bayesian inference to interval-timing paradigms should provide a deeper understanding of the perceptual and decision-making capabilities of genetically modified mice.

1.6 Proposal of a TIMER test battery and its application in reverse genetics

In this section, we describe the test battery for the Timing and Immersive Memory and Emotional Regulation (TIMER) and its ability to fulfill the need of most neurogenetic studies as outlined in Table 2. There are three main reasons why we think this test battery is a priority choice in evaluating cognition in genetically modified mice: 1) The test battery consists of both multiple-session training paradigms and single-session training paradigms, and includes almost all possible behavioral deficits that could be shown in relation to cognition. 2) Because the memory and emotional regulation components are also nested within the timing tasks, the cross-validation among the different components of the test battery can provide excellent structural validity. 3) The test battery consists of tasks that depend both on specific brain regions and on interactions among brain regions involved in interval timing, including the prefrontal cortex, striatum, hippocampus, amygdala and midbrain (Allman, Teki, et al., 2014; Coull et al., 2011b; Jin, Fujii, & Graybiel, 2009; Macdonald, Fortin, Sakata, & Meck, 2014; Meck et al., 2013; Meck et al., 2008; Xu, Zhang, Dan, & Poo, 2014; B. Yin & Meck, 2014a); therefore, the test battery is sensitive to both gene dose effects and brain-region specific effects as a result of genetic modifications; 4) Timing, memory, and emotional regulation are three fundamental aspects underlying consciousness (see Allman, Yin, et al., 2014; B. Yin, Terhune, Smythies, & Meck, 2016): as long as an organism is able to detect something novel that changes in time (as well as duration itself), and is able to record the changes in memory combined with emotional regulation that modulate its

strength, it has consciousness. Therefore, the TIMER test battery can potentially specify genes that directly link to one of the most mysterious aspect of cognition – consciousness.

Table 2

Test Battery for Timing, Immersive Memory, and Emotional Regulation (TIMER)

Timing Component	**Memory Component**	**Emotional Regulation Component**
Peak-Interval Procedure	PI-GAP Procedure	Fear Learning & Extinction
Bi-Peak Procedure	Morris Water Maze tests	Elevated Plus Maze Tests
Prefeeding procedure (modulates peak rates)	Barnes Maze Tests	Open Field Tests (novel environment)
Reversal of timing contingency (modulates peak times)	Novel Object Recognition Tests	Lever presses & Food-cup entries (familiar environment)

Note: Although this table separates paradigms into three categories, the memory and emotional regulation components are typically nested within the timing paradigms. The tasks listed in the memory and emotional regulation components provide selective comparisons to the deficits that may be observed in the timing paradigms per se.

PI-GAP = peak-interval timing procedure with a gap/break inserted in the signal.

An example of application of the TIMER test battery is in calcium-response factor gene-knockout mice. Calcium-response factor (CaRF) is an unique transcription factor that functions as a binding protein for a calcium-response element in the gene encoding brain-derived neurotrophic factor (Bdnf). CaRF knock-out (CaRF-KO) mice were generated to study its behavioral functions in vivo (e.g., Agostino et al., 2013; McDowell

et al., 2010). Several behavioral paradigms were adopted, including the 15-s & 45-s bi-peak procedures, the 30-s uni-peak procedure, the Morris water maze tests, the novel object recognition tests, and contextual fear conditioning and extinction. This array of behavioral tests can be seen as a variant of the TIMER test battery, as three key elements, i.e. timing, memory, and emotional regulation were all examined in these tests. Results demonstrated that the CaRF-KO mice were impaired in their ability to acquire timed 'start' and 'stop' response thresholds (Agostino et al., 2013). CaRF-KO mice did, however, show normal spatial learning and normal context-dependent fear conditioning. They also displayed enhanced reversal learning in the Morris water maze and extinguished fear-conditioned responses more slowly than their wild-type littermates. Finally, CaRF-KO mice showed normal short-term and long-term memory in a novel object recognition task, but exhibit impairments during the remote-memory phase of testing (McDowell et al., 2010). The fact that the tasks that the mice performed poorly on are considered to be striatal-dependent and the tasks that the mice performed well on are considered to be hippocampal-dependent (Macdonald et al., 2014; B. Yin & Meck, 2014a) suggests that the cognitive functions of cortical-striatal circuits were impaired while hippocampal functions remained largely spared. The timing component of the TIMER test battery strongly supports this view, because the PI procedures require multiple sessions of training and stable performance, which exclude the possibility of state/context dependent changes in behavior that may display floor/ceiling/carryover effects. Therefore, this battery of behavioral tests links a molecular-level analysis with a circuit-level analysis, and provides useful insights on how particular genomic information

is selectively expressed in different neural circuits under precise spatiotemporal regulation during development.

Another example of the application of the TIMER test battery is the dopamine transporter knock out (DAT-KO) or knock-down (DAT-KD) mouse. The plasma membrane dopamine transporter mediates uptake of DA into presynaptic neurons and thus a KO and KD of DAT normally creates chronic hyperdopaminergic states in the genetically modified mice with contributions from glutamatergic and serotoninergic systems as well (Gainetdinov, Mohn, Bohn, & Caron, 2001). In one study, DAT-KD mice exhibited earlier start times, but normal stop times in the standard PI procedure with 30-s and 45-s target durations (Balci et al., 2010). In a more recent report, DAT-KO -/- mice exhibited severe impairment in the temporal control of responding as illustrated in Figure 7. Moreover, DAT-modified mice displayed an increased sensitivity to the disruptive effects of a high-dose methamphetamine challenge in a gene-dose-dependent manner when performing in both the bi-peak procedure with 15-s and 45-s target durations and the standard PI procedure with a 20-s target duration (Meck et al., 2012). These studies nicely demonstrate the gene-dose effects that are not typically shown in single-session behavioral paradigms. In addition, the interaction between pharmacological challenges and genetic effects is best seen in timing procedures of this sort given the feasibility of within-subject control over multiple drug-no drug alternative sessions (note that timing performances are typically evaluated at the asymptotic-level of training and are not vulnerable to repeated exposure effects). Therefore, a TIMER test battery based on interval-timing tasks that incorporate other memory and emotional

regulation components can give the investigators an edge in deciphering most interesting aspects of animal cognition. Given the successful evaluation of DAT mice, one might also look into the timing performances of DARPP-32 mice (see (Gould & Manji, 2005) for an introduction to DARPP-32 mice), which in theory might perform in opposite ways from the DAT mice.

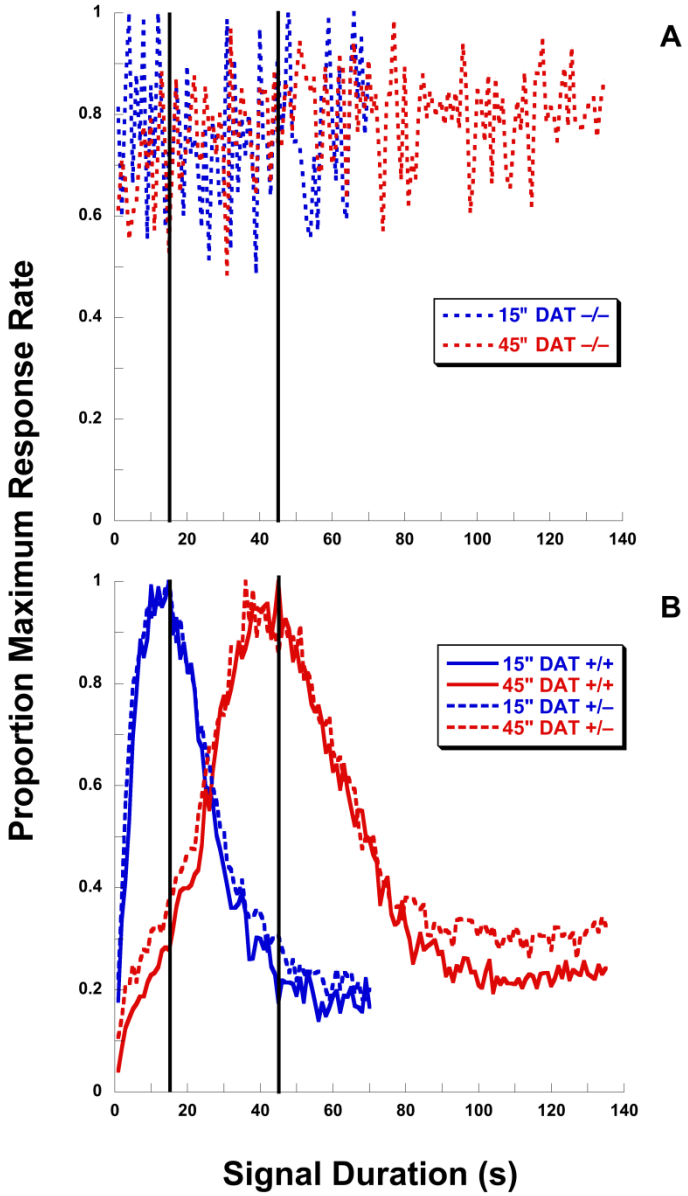

Figure 7: Mean proportion of maximum response rate (lever presses) plotted as a function of signal duration (s) during 15-s and 45-s peak-interval (PI) training. Panel A: Shows peak functions for DAT -/- mice. Panel B: Shows peak functions for DAT +/+ and +/- mice. Data are reported for the unreinforced probe trials from the last 7 sessions of baseline PI training. Adapted from Meck et al. (2012).

Furthermore, the serotonin transporter knockout (SERT-KO) mouse has also been extensively studied (e.g., (Gingrich & Hen, 2001; Gould & Manji, 2005), though no studies on timing performance have been reported to date. We have reasons to speculate that SERT-KO mice would also have interesting timing profile because: 1) Fluoxetine, a selective serotonin reuptake inhibitor, normalizes peak functions and restores superimposition in DAT mice (Meck & Yin, 2011); 2) DOI, a serotonin-2 receptor agonist, left-skewed the peak functions (unpublished data; also see (Body et al., 2003); 3) increased expression of serotonin-6 receptors in the rat dorsomedial striatum impairs instrumental learning with a timing component (Mitchell et al., 2007). Therefore, it would be beneficial to add the timing component to the behavioral profile of SERT-KO, which could give indications of the interactions of the serotonin, dopamine and glutamate systems (see Body et al., 2014; Body et al., 2013);

An interesting example is the close homolog to L1 (CHL1) knock-out mouse. The CHL1 gene has multiple functions in the formation of normal neuronal connections during development and in synaptic function and plasticity in the adult, processes which are thought to be disrupted in intellectual disabilities and schizophrenia. By using the PI procedure and a spatial-temporal procedure, (M. Buhusi et al., 2013) examined the timing abilities of CHL1 knock-out mice. It was discovered that while wild-type mice can use their temporal perceptual abilities to facilitate their spatial planning, the mutant mice failed to show this integration. This was also supported by their left-skewed peak functions and lack of modulation of their responses after gap retention intervals, which are direct measures of their timing abilities. It was also found that timing precision is

increased in the CHL1 heterozygote females compared with the wild type control (Gallistel et al., 2014), suggesting a gene-dose effect that was also evident in the DAT-KO mice.

The most complete case that utilizes the TIMER test battery is our recent evaluation of dorsal and ventral hippocampal lesioned mice – the results of which are partially summarized in Table 3, together with examples of other genetically modified mice (Meck et al., 2012; B. Yin et al., 2014). As can be seen, data from the test battery not only demonstrate a strong case for functional dissociations along the septotemporal axis of the hippocampus in terms of emotion/motivation, timed response thresholds, and encoding in spatial and temporal memories, but also provide important insights into how the hippocampal-striatal network potentially underlies and support various aspects of daily behavior in mice, including its "consciousness" (B. Yin & Meck, 2014b; B. Yin et al., 2016; B. Yin & Troger, 2011).

Table 3

Examples of the TIMER Test Battery Applied to Genetically Modified or Cytotoxic Lesioned Mice

Behavioral profiles	CaRF	DAT	SERT	CHL1	DH	VH
Peak Times	No change [1]	No temporal control* [3]	Not evaluated	Leftward shifts [14]	Leftward shifts [9]	Rightward shifts** [9]
Peak Rates	No change [1]	Increased? [3]	Not evaluated	Not evaluated	No change [9]	No major change*** [9]
Proportionality in Shifts of Peak Times	Not applicable	Not applicable	Not evaluated	Not evaluated	Yes [9]	No [9]
Superimposition (Scalar Property)	Preserved [1]	Severely disrupted [11]	Not evaluated	Not evaluated	Almost preserved [9]	Severely disrupted [9]
Start Times	Earlier [1]	Earlier [4]	Not evaluated	Not evaluated	Earlier [9]	No change [9]
Stop Times	Later [1]	No change [4]	Not evaluated	Not evaluated	Mildly earlier [9]	Later [9]
Peak Times in GAP Trials	Not evaluated	Not evaluated	Not evaluated	Hold on to pre-gap durations [13]	More prolonged [11]	More prolonged [11]
Prefeeding on Peak-Interval Procedure	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Reduced sensitivity [10]	No change in lever presses but enhanced sensitivity in foodcup entries [10]

Reversal of Target Duration Associations	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Facilitated peak time changes [9]	Peak rate changes [9]
Spatial Navigation	Normal spatial learning and reference memory but enhanced reversal [2]	Delayed spatial acquisition; normal spatial reference memory but impaired reversal [6]	Normal spatial learning; impaired spatial reference memory [7]	Normal spatial distinction [14]	Impaired spatial learning and reference memory [10]	Impaired spatial learning only [10]
Foodcup Entries	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Increased [10]	No change [10]
Locomotor Activity (Familiar Environment)	Not evaluated	Increased [3]	Not evaluated	No change [14]	No change [10]	No change [10]
Locomotor Activity (Novel Environment)	Normal [2]	Increased [5]	Decreased [7]	Decreased thigmotaxis [12]	Increased [10]	No change but increased thigmotaxis [10]
Fear Learning	Normal learning; but impaired retention of extinction [2]	Not evaluated	Normal learning; impaired retention of extinction [8]		Not evaluated	Impaired contextual learning; intact cue learning [10]

** DAT -/- showed no temporal control; whereas DAT +/- did not differ from controls unless challenged with methamphetamine.*
*** Rightward shifts were observed in earlier peak-interval training sessions, but not later sessions.*

*** *Although peak rates were not significantly different from controls, the ratio of peak rates for the shorter duration versus the longer duration were different from controls.*
[1] Carf-KO – (Agostino et al., 2013)
[2] Carf-KO – (McDowell et al., 2010)
[3] DAT-KO – (Meck et al., 2012)
[4] DAT-KD – (Balci et al., 2010)
[5] DAT-KO – (Gainetdinov et al., 2001)
[6] DAT-KO – (Morice et al., 2007)
[7] SERT-KO – (Kalueff, Jensen, & Murphy, 2007)
[8] SERT-KO – (Wellman et al., 2007)
[9] DH & VH –(B. Yin & Meck, 2014a)
[10] DH & VH – (B. Yin & Meck, 2014b)
[11] Unpublished data
[12] CHL1-KO – (Montag-Sallaz, Schachner, & Montag, 2002)
[13] CHL1-KO – (M. Buhusi et al., 2013)
[14] CHL1-KO – (Gallistel et al., 2014)

1.7 About this manuscript

In the remaining chapters, I will first describe the experiments on dorsal and ventral hippocampal lesions, then I will describe the experiments on dorsolateral and dorsomedial striatal lesions, and then I will propose a timing-based framework for the emergence of conscious experience, introducing the plausible role of the claustrum. Finally, I will propose a double saturation model of interval timing which leads to future directions.

2. Contributions of the Dorsal and Ventral Hippocampus to Interval Timing Behavior

2.1 Introduction

Timing and time perception are fundamental properties of cognition (Allman, Teki, et al., 2014; C. V. Buhusi & Meck, 2005b, 2009a; Meck, 2003) with numerous studies conducted to investigate its neural basis (Agostino et al., 2013; Coull et al., 2004; Hinton & Meck, 2004; Matell et al., 2003a; Meck, 2006a, 2006c, 2006e). In particular, considerable attention has been directed to cortical-striatal pathways that are essential in maintaining timing abilities in the range of hundreds of milliseconds to multi-seconds (Allman & Meck, 2012; Coull et al., 2011b; Matell & Meck, 2004a; Meck et al., 2008; Merchant et al., 2013). Interestingly, although neglected by many of the current models of interval timing (van Rijn et al., 2014b), the hippocampus has long been considered a site of spatial-temporal interaction, which provides a basis for generation, maintenance and retrieval of episodic memories (Dickerson & Eichenbaum, 2010; Macdonald et al., 2014). Since the initial evaluation of the effects of post-training fimbria-fornix lesions on timing and temporal memory (Meck, Church, et al., 1984), studies investigating the role of the hippocampus in the temporal control of behavior have generated consistent, though not always conclusive, results (Tam & Bonardi, 2012a, 2012b; Tam, Jennings, & Bonardi, 2013; Vidalaki et al., 1999). Specifically, both humans and rodents with a variety of different types of hippocampal lesions have been shown to underestimate target durations, and/or to exhibit increased sensitivity to signal duration (Gu et al., 2014; B. Yin & Troger, 2011). However, to date, no studies have examined the concurrent timing

of multiple target durations as a function of pre-training lesions to the dorsal (DH) or ventral (VH) hippocampus. As a consequence, adequate explanations for the source of the changes in timing behavior observed after selective hippocampal lesions are still lacking due to the inability to evaluate the scalar property of interval timing which posits that the sensitivity in temporal processing as measured by the standard deviation of timed performance increases in proportion to the target durations. Distortions in timing and time perception are often revealed by changes both in accuracy and precision, thus requiring that multiple durations be examined in order to determine the nature of the distortion (Gu et al., 2014; Meck, 2002a, 2002b).

The current study sought to evaluate the behavioral effects of cytotoxic lesions of either the DH or VH on interval timing in an effort to better characterize the nature of hippocampal-striatal interactions in timing and time perception in the multi-seconds range. A bi-peak procedure was used in order to evaluate changes in accuracy and precision as a function of multiple target durations (Agostino et al., 2013; R. K. Cheng & Meck, 2007; Meck et al., 2012). 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 (C. V. Buhusi & Meck, 2002b; C. V. Buhusi et al., 2004; M. Buhusi et al., 2013; Meck, 1988). 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; Macdonald et al., 2012; Matell et al., 2006). 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 (Figure 2).

2.2. Methods

2.2.1 Subjects

The subjects used in the experiments were male C57BL/6J mice (n= 66, Charles River Laboratories, Raleigh, NC) or male mice homozygous for the δ-opioid receptor (Oprd1-/-) backcrossed to C57BL/6J mice for at least 12 generations (n=10), plus wild-type littermates (n=10, Oprd1+/+ – Jackson Laboratory, Bar Harbor, ME). All mice were between 5-7 weeks of age when first delivered to our climate-controlled animal colony with a 12:12 light/dark cycle (lights on at 7.00 A. M., off at 7:00 P.M.). Mice were group housed (4-5 mice per cage). Standard rodent chow (5001 – Purina LabDiet®, Purina Mills Inc., St. Louis, MO) and water were available ad libitum in the home cages except during the food-restricted period of behavioral testing described below. Body weights were monitored on a daily basis throughout the course of the experiment.

Behavioural testing started at 8-9 weeks of age and occurred between 9:00 A. M. and 5: 00 P.M. The mice in each cohort were assigned to one of the 20 lever boxes with different lesion or genetic conditions randomly distributed – with mice trained in the same lever box at approximately the same time of day throughout the course of the

experiment. Sessions were conducted 7 days/week unless otherwise stated. During behavioural training, mice were maintained at 85-90% of their *ad lib* body weights by food restriction. All experiments were conducted under a protocol approved by the Duke University Institutional Animal Care and Use Committee in accordance with the National Institutes of Health guidelines for the care and use of animals.

2.2.2 Surgery

Mice were anesthetized with an intraperitoneal injection of ketamine/xylazine cocktail (100/10mg/kg). The mouse's head was shaved and mounted into a standard stereotaxic instrument (David Kopf, Tujunga, CA). A sterile lubricant (ointment) was generously applied to the eyes. The scalp was incised, and the skin was retracted. The head was leveled by equating bregma and lamda in the dorsoventral plane. Four (DH) or eight (VH) small holes were drilled into the skull according to the coordinates measured from bregma as shown in Table 4. A 1.0- µL Hamilton syringe (Model: 65458-01) was lowered into each of these holes, and N-Methyl-D-aspartic acid (NMDA; 20ug/ µL; Sigma, St. Louis, MO), dissolved in sterilized phosphate-buffered saline, was infused. An automatic syringe pump (Nanojet, Chemyx, Stafford, TX) attached to the Hamilton syringe mounted on the stereotaxic instrument was used to deliver 0.1 µL NMDA over 3 min. The syringe remained in place for an additional 2 min to allow for diffusion of the drug. In sham mice, the syringe was lowered to the same sites as lesioned mice but no injection was placed in order to minimize the physical damage to the target brain areas. After the final infusion, the incision was closed with stainless steel wound clips. Mice

were allowed to recover in a heating-pad-warmed cage with food and water easily accessible nearby. Upon awakening, DH mice (and their sham controls) were intraperitoneally injected with a single dose (~0.03mL) of diazepam (5mg/mL; Hospira, Lake Forest, IL) to help control potential seizures that would typically be observed after successful neurotoxic DH lesions (lab observation). No diazepam was needed for VH mice and their sham controls. After they regained full mobility and were actively running and consuming food and water for 12 hr, mice were returned to their home cages and allowed to recover for 10 days before post-lesion behavioral training began.

Table 4: Coordinates for Dorsal / Ventral Hippocampal Lesions
Reference: Bregma and skull surface

Location of Lesions	Anterior / Posterior (mm)	Medial / Lateral (mm)	Dorsal / Ventral (mm)
DH	-1.3	±1.0	-2.0
	-2.1	±1.5	-2.2
VH	-2.9	±3.0	-3.5
	-3.3	±3.6	-4.0
	-3.6	±2.85	-4.0
	-3.8	±2.75	-4.8

2.2.3 Behavioral Procedures

Apparatus

The experimental apparatus consisted of 10 matching lever boxes (Model ENV-307A, Med Associates, St. Albans, VT) housed in sound-attenuating chambers (Model ENV-021M; Med Associates). The dimensions of each lever box were 21.59 x 17.78 x 12.70 cm. The ceiling, side walls, and door of each box were made from clear Plexiglas.

The front and back walls were stainless-steel panels and the floor was made of parallel stainless-steel bars. The front wall of each box contained left and right retractable levers; a food cup was located between the levers; and a cue light was located directly above the food cup. A pellet dispenser delivered 20-mg grain-based food pellets (Research Diets, Inc., New Brunswick, NJ) into the food cup. The back wall of each box contained a house light (14-W, 100 mA) directed towards the ceiling. The operant chambers were controlled by the Med-PC IV software package. The fan was on throughout the session. An IBM-PC compatible computer attached to an electronic interface (MED Associates, Inc., Model DIG-700 and SG-215) was used to control the experimental equipment and record the data. The time of each lever press was recorded to an accuracy of 10 ms and placed into 1-s time bins.

Bi-Peak Timing Procedure

Lever-press training (Sessions 1-10).

All mice were given ten daily sessions of lever-press training. During the session, one of the two side levers was continuously retracted and inserted in a 1-s cycle every 120 s to attract attention from mice. The delivery of a food pellet in the foodcup was primed every 90s, which was signaled by the blinking of the cue light. In addition to the free food pellet delivered, a food pellet was delivered for every lever press (FR-1). Every 10 lever presses resulted in alternation of the two levers. Sessions ended after 3600 s and there was no limit for total pellets that could be earned within a single session (in reality, all mice earned between 40 to 150 pellets altogether per session). After 7 sessions, the

feed pellets were withdrawn in order to further encourage mice to earn food by pressing the lever. All mice that participated in the experiment learned to press the lever for food pellets after this stage.

15-s and 45-s fixed-interval training (Sessions 11-20).

During these sessions, the onset of the house light was used as a signal for the duration to be timed, i.e. fixed-interval (FI) trials were signaled by the onset of the house light and the appropriate lever(s) was primed for reinforcement at the associated target duration(s). The target duration used on each trial (15-s or 45-s) was randomly selected with equal probability and no external cue was given to indicate which lever/duration resulted in the delivery of a food pellet, signal termination, and the onset of a variable inter-trial interval (ITI), range 30-150s. The assignment of target durations to response levers was counter-balanced both within and across groups of mice. After 7 sessions of FI training, two levers were set to be simultaneously available (inserted) throughout the session, and mice were trained to press the lever associated with the 15-s duration first and then to switch to the other lever associated with the 45-s duration.

15-s and 45-s bi-peak training (Sessions 21-40).

Bi-peak training was used to assess the start and stop times with which mice timed the target duration(s). Sessions consisted of two trial types: FI trials (as described above) and unreinforced probe trials. The two levers were set to be simultaneously

available throughout the session. During probe trials the house light was turned on for a minimum of 3× the longer target duration (45-s) plus an additional random amount of time with a mean of 20s and a Gaussian distribution. No food was available for lever pressing on these unreinforced probe trials. FI and probe trials were ordered randomly with 50% probability each. Thus, one of the two target durations (15-s or 45-s) was presented in conjunction with non-reinforced probe trials in a random sequence. No external cue was provided to indicate which, if any, lever/target duration would be selected for reinforcement on any trial. Mice were free to respond on the lever(s) at any time during the session, though only responses made to the appropriate lever following the target duration during FI trials were reinforced.

Bi-peak reversal training (Sessions 41-75).

The reversal experiments used the same Bi-PI procedure as described above, with the exception that the association between the lever (Left or Right) and the target duration (15 s or 45 s) were switched for each individual mouse. For example, if a mouse was trained to associate the left lever with the 15-s target duration and to associate the right lever with the 45-s target duration, then during reversal learning, the left lever was switched to providing reinforcement for responding on a PI 45-s schedule of reinforcement and the right lever was switched to providing reinforcement for responding on a PI 15-s schedule of reinforcement. The adjustment in peak times of responding on the two levers was observed as a function of sessions. Previous studies have shown

reversal learning for duration discrimination procedures to be sensitive to cortico-striatal-hippocampal damage (R. K. Cheng, Etchegaray, et al., 2007).

DH Lesions – Post-Operative Bi-Peak Training

Pre-training DH lesions

In order to examine the effects of DH lesions on interval timing, a bi-peak procedure (see Methods) was employed. Fifteen mice were randomly assigned into the sham control group (Sham, n=6) and the DH lesion group (pre-DH, n=9). Surgeries were performed after mice were shaped to press the lever for food pellets in order to exclude any effect that DH lesions might have on instrumental learning per se (Cheung & Cardinal, 2005; Corbit & Balleine, 2000). After mice recovered from surgery, they were trained with the bi-peak procedure as described above.

VH Lesions – Post-Operative Bi-Peak Training

Pre-training VH lesions

Similarly, we examined the effects of VH lesions on interval timing using the same bi-peak procedure. Fifteen mice were randomly assigned to the sham control group (Sham, n=7) and the VH lesion group (pre-VH, n=8). Experiments were performed in an identical manner to the behavioural procedures used for the pre-DH condition described above.

DH Lesions – Pre-Operative Bi-Peak Training

Post-training DH lesions

Ten mice were randomly assigned to the sham control (Sham, n=5) and the DH lesion (post-DH, n=5) treatment groups. The experiment was performed in an identical manner to the previous two experiments, with the exception that surgeries were performed after the mice had already received FI training and 20 sessions of bi-peak training. Such post-training lesions are the most common procedure used to evaluate the effects of hippocampal damage on timing behavior [(Meck, 1988; Meck, Church, et al., 1984; Meck et al., 1987; Olton et al., 1987; Olton et al., 1988), but see (Tam & Bonardi, 2012a; Tam et al., 2013)]. Behavioural training was resumed after the mice recovered from the surgery and no reversal learning was conducted.

2.2.4 Histology

After behavioural testing was complete, all mice in the lesion groups were deeply anesthetized with ketamine and then intracardially perfused with saline and 4% paraformaldehyde. The brains were removed and stored in paraformaldehyde. Sections (100 µm) were cut coronally on a vibratome and stained with cresyl violet. Outlines of the relevant hippocampal tissue characteristics and lesions were examined under a Zeiss SteREO Lumar.V12 stereoscope and then traced onto line drawings of 16 coronal sections covering the entire hippocampus (Paxinos & Franklin, 2008). The outlines were then digitized to display the minimum and maximum lesions for each treatment group.

2.2.5 Data Analysis

Individual peak functions for each target duration (15 and 45 s) were fit using a Gaussian curve with the addition of a linear ramp function to account for right-tailed skew. These fits accounted for over 90% of the variance for all groups of mice and did not reliably differ as a function of treatment condition. The Gaussian fits were used to obtain peak time (a measure of accuracy), peak spread (a measure of precision), and peak rate (a measure of motivation) as previously described (R. K. Cheng & Meck, 2007; Church et al., 1994; Matell et al., 2006). Peak time divided by peak spread at the 50th percentile can be used as a measure of the relative standard deviation or sensitivity to time – also referred to as the Weber fraction (WF) or coefficient of variation (Church et al., 1994; Matell et al., 2006). The scalar property of interval timing predicts a constant WF across multiple target durations.

A rate index representative of the mean S1 response thresholds was also determined for FI response functions averaged over blocks of sessions. This rate index was calculated by taking the response rate in a specified interval (20% of the target duration) just prior to the observed peak time as a ratio of overall response rate within the first (S1) half of the trial as defined by the target duration. Higher S1 values indicate sharper FI timing functions and better duration discrimination (Agostino et al., 2013; R. K. Cheng & Meck, 2007).

2.2.6 Single-trials Analysis and Its Limitations

Response states defined by 'Start' (S1) and 'Stop' (S2) response thresholds were identified on individual trials that contained at least 5 lever presses as previously described (C. V. Buhusi & Meck, 2009b; Church et al., 1994; Macdonald et al., 2012; Matell et al., 2006). Briefly, in a single trial, the location of a 'high, relatively continuous' state of lever pressing during a trial is determined by fitting three contiguous, but non-overlapping horizontal lines to the response series over time during a single unreinforced probe trial. Therefore, the intercept of each line represents a response rate over an interval that is defined by the length of the line. The goal is to iteratively maximize the difference between the response rate defined by the middle horizontal line ('high' state) and the response rate defined during the flanking horizontal lines ('low' states). This calculation effectively fits a boxcar-like step function, referred to as a 'low-high-low' pattern of responding. The S1 and S2 times are defined as the time points in the fitted function at which the 'high' state begins and ends, respectively.

A single-trials analysis has certain limitations with this particular data set due to the mice being able to switch back and forth between levers in the Bi-Peak procedure. In particular, switching between the 15-s and 45-s levers interferes with the determination of the 'Stop' times for the 15-s target duration as well as the 'Start' and 'Stop' times for the 45-s target duration. As a consequence, the measures obtained from the single-trials analysis may not correspond with the measures obtained from the mean peak function as well as in other experiments using a single target duration (Church et al., 1994).

Nevertheless, the application of a single-trials analysis is robust enough to look for group differences as well as session effects.

i) No universally agreed upon method for identifying the start (S1) and stop (S2) response thresholds in the low–high–low (LHL) analysis or for defining for “good trials”, i.e., trials with a minimum number of responses and “reasonable” starts and stops, i.e., the start has to be before the target duration and the stop has to be after the target duration (see (K. Cheng & Westwood, 1993; Church et al., 1994; Galtress et al., 2012; Galtress & Kirkpatrick, 2009). This, of course, can lead to serious problems when using the peak-interval procedure in genomic and pharmacological studies (e.g., (Agostino et al., 2013; Matell et al., 2006).

ii) This leads to the concern that investigators may apply an individual-trials analysis to poor-quality timing data. In general, if the mean peak functions don't look good (i.e., centered around the target duration with a reasonable degree of symmetry and relatively small spread) then it doesn't make sense to apply such a sophisticated analysis.

iii) Asymmetrical response functions also present a problem for an individual-trials analysis (Church et al., 1991), particularly when the righthand tail (skew) of the response distribution is affected by the genetic manipulation and/or drug challenge in a manner different from the change in peak time (Carvalho et al., 2001; R. K. Cheng, Hakak, et al., 2007).

iv) The individual-trials analyses assumes a constant rate of responding during the “high state” which may be correct to a first approximation (Church et al., 1994), but

clearly isn't always the case (Church et al., 1994; Meck & Williams, 1997b) and may well differ as a function of genetic manipulations and/or drug challenges.

v) The individual-trials analyses gives all trials equal weight regardless of the quality of fit of the LHL analysis or the response rates on individual trials. This is a major difference from the way that individual trials contribute to the mean response rate function.

vi) Due to the manner in which the PI procedure is typically trained (e.g., substantial FI training prior to the insertion of unreinforced probe trials), subjects will have considerably more experience with setting a S1 (start) threshold in comparison with the S2 (stop) threshold. This would be expected to contribute higher levels of variance for the S2 measure, especially under conditions of genetic manipulations and/or pharmacological challenge where it may be more disrupted (R. K. Cheng, Hakak, et al., 2007; Drew et al., 2003). Furthermore, the S1 measure is always going to be lower than the S2 measure, making it more difficult to detect a change in the S1 threshold under experimental conditions than for the S2 threshold … especially if the effects are proportional to the durations. This makes the individual-trials analysis particularly susceptible to errors in the evaluation of genetic manipulations and/or drug effects and argues for the mean response rate function being a better measure of performance … although there may be significant value in utilizing both (cf., Balci, 2014; Balci, Day, Rooney, & Brunner, 2009; Balci, Gallistel, et al., 2009; Carvalho et al., 2001; Kurti & Matell, 2011; Macdonald et al., 2012; Matell et al., 2006; Matell & Portugal, 2007; Taylor et al., 2007).

vii) The PI procedure in general, isn't well-suited to studying short durations (e.g., durations less than 10-s) due to the "associative strength" of the signal causing the subjects to produce high-levels of responding at signal onset – referred to as loss of temporal control due to the subject's response output being "absorbed" by the associative value of the signal. This is particularly true of avian species, but can also be observed in rodents under pharmacological challenge. These factors undoubtedly play a role in the individual-trials analysis.

viii) An individual-trials analyses is limited to situations where a single target duration is used, i.e., it isn't readily applicable to the bi-peak or tri-peak procedures where subjects can switch back and forth between multiple levers (e.g., Matell et al., 2004; Matell & Meck, 1999; Meck et al., 2012; B. Yin & Meck, 2014a – but see Swearingen & Buhusi, 2010) for a novel application of the individual-trials analysis to the PI-GAP procedure.

2.2.7 Statistical Analysis

Statistical analysis was performed using GraphPad Prism 5 (GraphPad Software, Inc., La Jolla, CA). Single-factor and repeated measures analyses of variance (ANOVA) were used as appropriate. The alpha level was set at $p < 0.05$ for all statistical analysis.

2.3 Results

2.3.1 Effects of pre-training dorsal hippocampal lesions on the acquisition of temporal control in the bi-peak procedure

No significant differences in the S1 rate index were observed between the Sham and pre-DH lesion groups during the 10 sessions of FI training for either the 15-s, $F(1,13) = 0.51$, $p > 0.05$ or the 45-s target duration, $F(1,13) = 1.09$, $p > 0.05$.

The Gaussian+ramp functions fit to the mean response rate functions displayed in the upper portion of Figure 8 revealed no significant group differences in peak time early in training (Sessions 4-6 – Figure 8, panel a) for either the 15-s or the 45-s target durations, F's(1,13) < 1.0, p's > 0.05. In contrast, significantly lower peak times were observed for the pre-DH lesion group compared with the sham control group late in training (Sessions 16-18 – Figure 8, panel b) for both the 15-s and 45-s target durations, $F(1,13) = 4.68$, $p < 0.05$ and $F(1,13) = 5.46$, $p < 0.05$, respectively. Taken together, these data suggest that a leftward shift in peak times emerged over the course of post-operative Bi-PI training in pre-DH lesioned mice. Peak time and peak rate measures for these conditions are reported in Table 5.

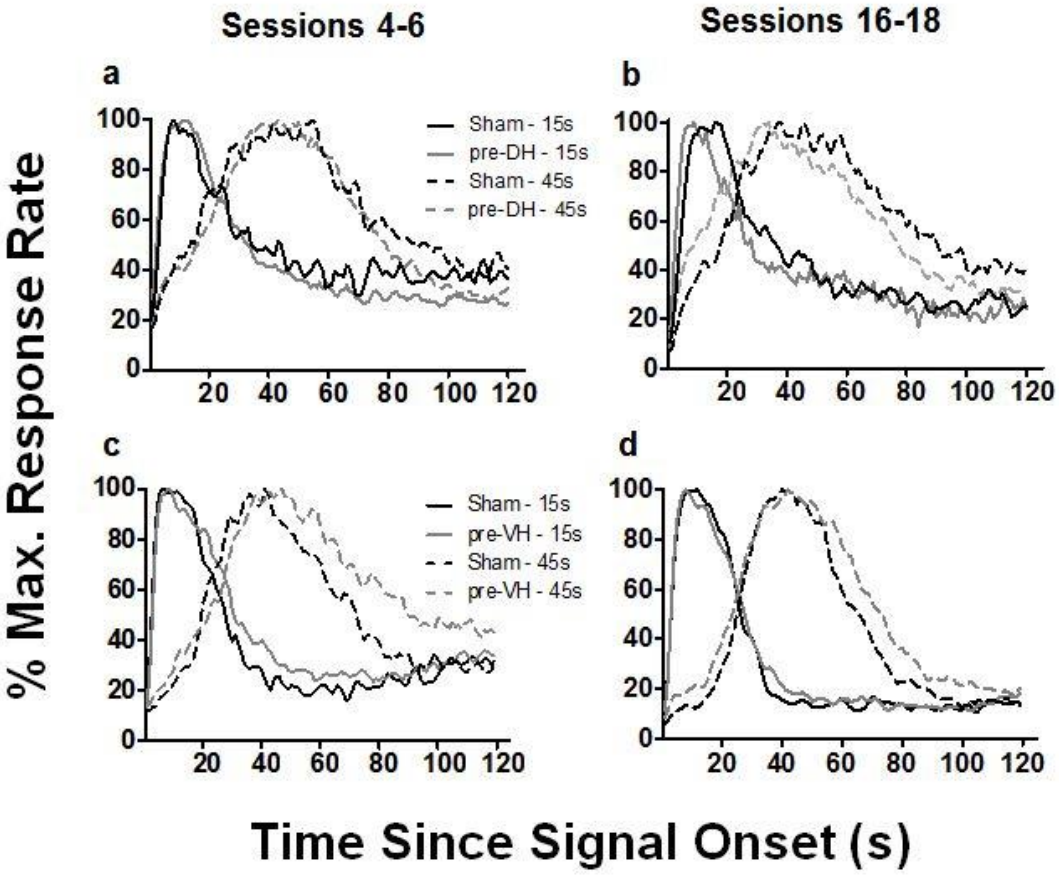

Figure 8: Bi-peak timing functions during post-operative sessions 4-6 and 16-18. The bi-peak functions for mice with pre-training cytotoxic lesions of the dorsal hippocampus (DH) are shown in panels a and b, and the functions of mice with pre-training lesions of the ventral hippocampus (VH) are shown in panels c and d. Black and grey lines represent the sham and the lesioned groups, respectively; whereas solid lines and dashed lines represent the 15-s and 45-s peak functions, respectively. Response rates as a function of time since signal onset were calculated from the pooled lever presses from all trials in a session and then normalized by the maximum response rate for each subject. Data were then averaged across three sessions for all the subjects in a group and then re-normalized to the maximum response rate.

Table 5: Peak Time (s) and Peak Rate (responses/minute) Measures

Groups/Sessions	Sessions 4-6		Sessions 16-18	
	15s	45s	15s	45s
Sham (pre-DH) n=6	13.62 s ± 1.11 71.26 r ± 14.30	45.43 s ± 2.79 72.70 r ± 15.39	16.06 s ± 1.12 84.59 r ± 15.85	46.78 s ± 2.22 63.64 r ± 13.44
pre-DH lesion n=9	13.30 s ± 0.98 73.04 r ± 12.83	44.52 s ± 1.28 77.34 r ± 7.01	11.89 s ± 0.90 53.63 r ± 8.87	36.00 s ± 2.84 72.02 r ± 10.62
Sham (pre-VH) n=7	12.71 s ± 0.70 126.05 r ± 27.77	42.74 s ± 3.01 80.15 r ± 21.43	15.00 s ± 2.01 138.14 r ± 29.83	44.10 s ± 1.15 112.69 r ± 21.68
pre-VH lesion n=8	13.90 s ± 0.56 126.97 r ± 29.97	51.67 s ± 2.03 90.49 r ± 13.03	13.46 s ± 0.68 122.81 r ± 18.30	46.46 s ± 1.13 139.11 r ± 17.59
Sham (post-DH) n=5	17.80 s ± 1.77 74.84 r ± 7.29	50.33 s ± 1.75 93.57 r ± 12.95	15.58 s ± 0.84 126.63 r ± 14.93	45.83 s ± 1.21 130.20 r ± 18.73
post-DH lesion n=5	14.40 s ± 1.81 116.27r ± 27.05	51.00 s ± 2.18 112.62 r ± 16.15	14.13 s ± 0.90 130.26r ± 42.33	41.13 s ± 1.83 147.18 r ± 27.78

Note. Numbers are means ± standard errors. s = seconds; r = response/minute

Single-trials analyses for the 15-s and 45-s target durations as a function of blocks of training sessions are illustrated in the upper portion of Figure 9. Significantly lower 'Start' times were observed for the mice in the pre-DH lesion group compared to the sham control group for both the15-s and 45-s target durations, $F(1,65) = 4.66$, $p < 0.05$ and $F(1,65) = 5.91$, $p < 0.05$, respectively. There was also a significant effect of session block, $Fs(5,65) \geq 4.53$, $p's < 0.05$, but no reliable group x session block interaction, $F's(5,65) < 1.0$. (Figure 9, panel a). In contrast, the apparent reductions in 'Stop' times observed for the mice in the pre-DH lesion group were unreliable when compared with the sham control group for both the 15-s and 45-s target durations, $F's(1,65) < 1.0$, $p's >$

0.05, with no reliable effects of session block or the group x session block interaction (Figure 9, panel b).

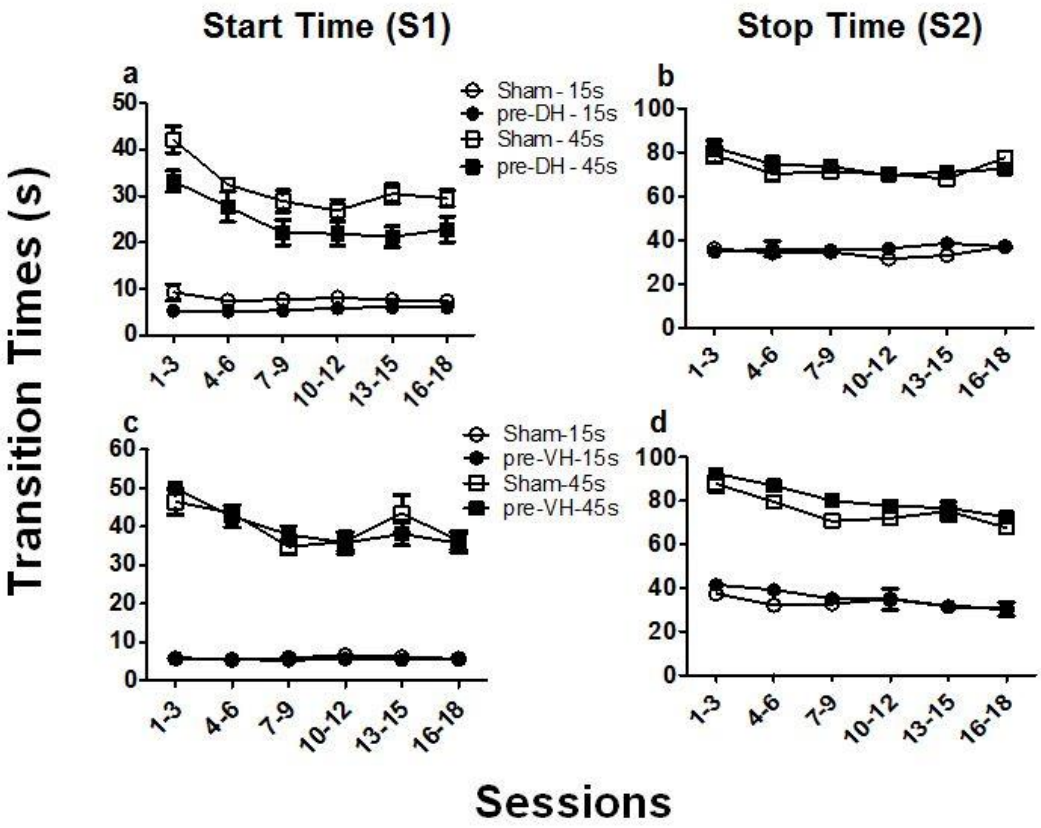

Figure 9: Start (S1) and Stop (S2) transition times obtained from the single-trials analysis plotted as a function of 15-s and 45-s peak-interval training sessions for mice with pre-training cytotoxic lesions of the dorsal (DH) or ventral (VH) hippocampus. The effects of pre-DH lesions are shown in panels a and b, and the effects of pre-VH lesions are shown in panels c and d. Empty circles and filled circles represent the sham and lesioned groups, respectively; whereas circles and squares represent the 'Start' and 'Stop' transition times for the 15-s and 45-s target duration, respectively. Data are means (± S.E.M) averaged over three sessions. Note that when the errors bars are contained within the symbols used to plot the means they are effectively invisible.

2.3.2 Effects of pre-training ventral hippocampal lesions on the acquisition of temporal control in the bi-peak procedure

No significant differences in the S1 rate index were observed between the Sham and pre-DH lesion groups during the 10 sessions of FI training for either the 15-s or the 45-s target duration, $F's(1,13) < 1.0$. $p's > 0.05$.

The Gaussian+ramp functions fit to the mean response rate functions displayed in the lower portion of Figure 8 revealed significant group differences in peak time between the pre-VH lesion and sham control groups during both early (Sessions 4-6 – Figure 8, panel c) and late (Sessions 16-18 – Figure 8, panel d) stages of training for the 45-s target duration, $F's(1,13) > 4.74$, $p < 0.05$, but not the 15-s target duration, $F's(1,13) < 1.0$, $p's > 0.05$ — although there was a trend of an effect for the 15-s target duration early in training, $p < 0.06$. Peak time and peak rate measures for these conditions are reported in Table 1.

Single-trials analyses for the 15-s and 45-s target durations as a function of blocks of training sessions are illustrated in the lower portion of Figure 9. No reliable differences in 'Start' times were observed for the mice in the pre-VH lesion group compared to the sham control group for either the15-s or the 45-s target durations, $F's(1,65) < 1.0$, $p's > 0.05$ (Figure 9, panel c). In contrast, significant differences in 'Stop' times were observed for the mice in the pre-VH lesion group when compared with the sham control group for both the 15-s and 45-s target durations, $F(1,65) = 4.63$, $p < 0.05$ and $F(1,65) = 12.17$, $p < 0.01$, respectively (Figure 9, panel d). The effect of session block was significant for both ‘Start’ and ‘Stop’ times for the 15-s and 45-s target durations, $F's(5,65) \geq 4.78$, $p's <$

0.05, whereas the group x session block interactions were unreliable, F’s(5,65) < 1.0. These data suggest that pre-VH lesions mainly affect 'Stop' times as evident by the “elevated tails” observed in the mean peak functions (Figure 8, panels c & d). The increase in 'Stop' times for mice in the pre-VH lesion group diminished with continued training as demonstrated in Figure 9, panel d.

2.3.3 Effects of pre-training dorsal/ventral hippocampal lesions on discrimination reversal learning

Discrimination reversal learning has been shown to be sensitive to impairments in timing associated with neurotoxic regimens of methamphetamine intoxication that contribute to neuronal death in the striatum and hippocampus (R. K. Cheng, Etchegaray, et al., 2007; Drew et al., 2007b). The current experiment was conducted in order to evaluate the performance of pre-DH and pre-VH lesioned mice as a function of blocks of 5 sessions following the switch in reinforcement contingencies, e.g., 15-s to 45-s target durations and 45-s to 15-s target durations for the left and right response levers, respectively. The pre-DH lesioned mice displayed faster reversal learning (as indexed by changes in peak time) than their sham controls in both the 15-s to 45-s condition, $F(1,78) = 15.11$, $p < 0.01$ and the 45-s to 15-s condition, $F(1,78) = 6.81$, $p < 0.05$, as shown by the transitions in peak time displayed in the upper panels of Figure 3. In contrast, the pre-VH lesioned mice were not significantly different in reversal learning compared with their shams controls in either the 15s to 45s condition, F’s(1,78) < 1.0, p’s > 0.05, as shown by the transitions in peak time displayed in the lower panels of Figure 10.

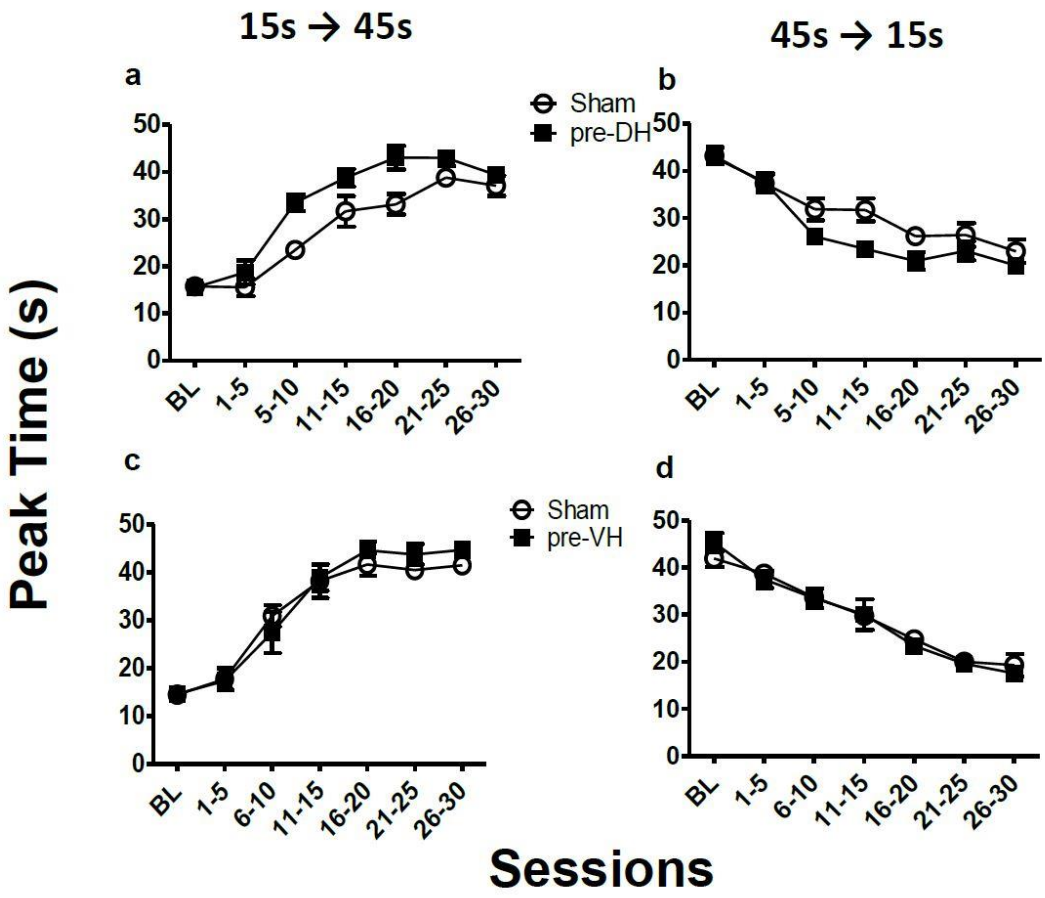

Figure 10: Fitted peak times plotted as a function of the 15-s to 45-s and 45-s to 15-s reversal sessions for mice with pre-training cytotoxic lesions of the dorsal (DH) or ventral (VH) hippocampus. The effects of pre-DH lesions are shown in panels a and b, and the effects of pre-VH lesions are shown in panels c and d. Empty circles and filled squares represent the sham and lesioned groups, respectively. Data are means (± S.E.M) averaged over five sessions. Before the reversal conditions, five sessions of bi-peak training with 15-s and 45-s target durations were used as a baseline (BL) for comparison.

A different pattern of results was observed between the pre-DH and pre-VH lesion groups, however, when response rates during reversal learning were compared. Peak rates calculated from the 'high' state of the single-trials analysis for pre-DH lesioned mice (101.3 ± 10.12) did not reliably differ from their shams controls (116.3 ± 22.63), F's(1,78) < 1.0, p's > 0.05. In contrast, the pre-VH lesioned mice displayed significantly enhanced peak rates (187.7 ± 24.04) during all phases of reversal learning compared with their shams control (111.8 ± 13.07), F's(1,78) ≥ 5.47, p's < 0.05.

Taken together, these data demonstrate that pre-DH, but not pre-VH lesions lead to an enhancement of reversal learning in timing tasks, which suggest that DH may be more relevant to core timing mechanisms than the VH. Nevertheless, VH lesions had reliable effects on peak rate when peak times were in transition, suggesting a possible interaction between the motivational and memory components of timing behavior (Drew et al., 2007b).

2.3.4 Superimposition of 15-s and 45-s bi-peak functions as a result of dorsal and ventral hippocampal lesions

Figure 11 displays mean bi-peak functions for the 15-s and 45-s target durations for each of the treatment groups (sham, DH, and VH) plotted on a time scale normalized by the observed peak times for each mouse prior to averaging. If the scalar property of interval timing holds, then these bi-peak functions should superimpose when plotted on a relative time scale (C. V. Buhusi et al., 2009; R. K. Cheng & Meck, 2007; Gibbon et al., 1984b). As one can see from visual inspection, the degree of superimposition is relatively

good for the sham and DH-lesion groups, but characteristically fails for the VH-lesion group with the 45-s peak function being consistently sharper (i.e., narrower) than the 15-s peak function. This type of failure of the scalar property has been observed in Parkinson's disease patients tested off of their dopaminergic medication (Gu et al., 2014; Malapani, Rakitin, et al., 1998) as well as in some types of timing procedures involving systematic error and impulsive responding in mice (Gallistel et al., 2004).

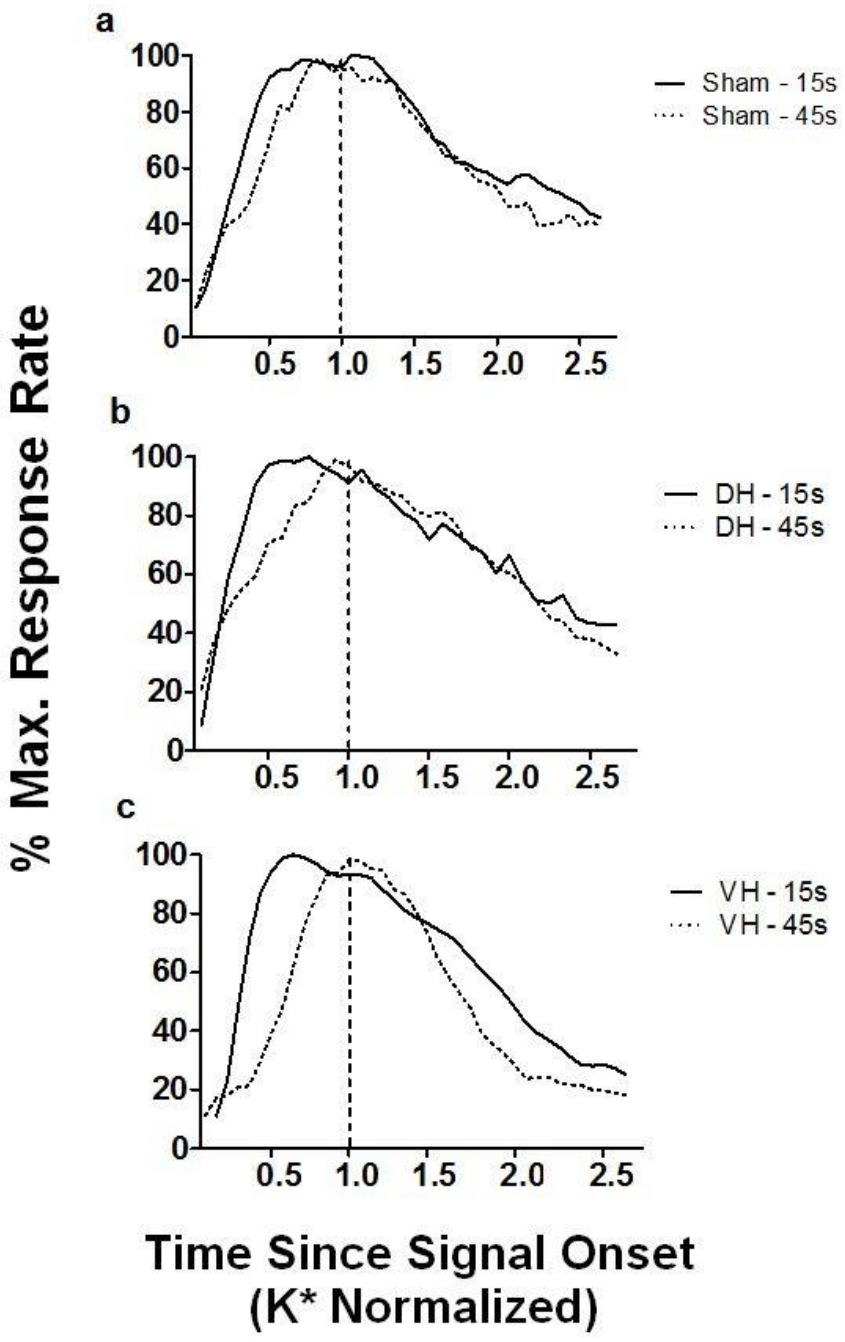

Figure 11: Superimposition plots of 15-s and 45-s bi-peak functions obtained from post-operative bi-peak sessions 16-18 for sham, dorsal (DH), and ventral (VH) hippocampal pre-training cytotoxic lesion groups. The 45-s peak functions were first normalized to the same relative percentage scale of the 15-s functions, and then re-normalized by their observed peak times.

2.3.5 Effects of post-training dorsal hippocampal lesions on the maintenance of temporal control in the bi-peak procedure

Because training itself may recruit certain brain areas that may not be required after learning, we also performed post-training DH lesions to examine whether this hippocampal region is still essential after mice had learned the timing tasks. The Gaussian+ramp functions fit to the mean response rate functions displayed in the upper portion of Figure S1 in the supplemental materials section exhibited non-significant group differences in peak time between the post-DH lesion and sham control groups during both early (Sessions 4-6 – Figure 12, panel a) for both the 15-s and 45-s target durations, $F's(1,8) < 1.0$, $p > 0.05$. In contrast, significant group differences were observed in peak time for the later stages of training (Sessions 16-18 – Figure 12, panel b) for both the 15-s and 45-s target durations, $F's(1,8) \geq 7.74$, $p < 0.05$. Peak time and peak rate measures for these conditions are reported in Table 5.

Single-trials analyses for the 15-s and 45-s target durations as a function of blocks of training sessions are illustrated in the lower portion of Figure 12 – panels c and d, for "Start' and 'Stop' times, respectively. Interestingly, similar to the pre-training DH lesion experiment, significant differences were found between the Sham and post-DH lesion groups for the 'Start' times for both the 15-s and 45-s target durations, $F's(1,8) \geq 8.27$, $p's = 0.05$, but no significant differences were found for the 'Stop' times, $F's(1,8) < 1.0$, $p's > 0.05$.

These data suggest that even after acquisition of the bi-peak procedure, post-DH lesions are still capable of producing gradual leftward shifts in the peak times of a magnitude similar to pre-DH lesions.

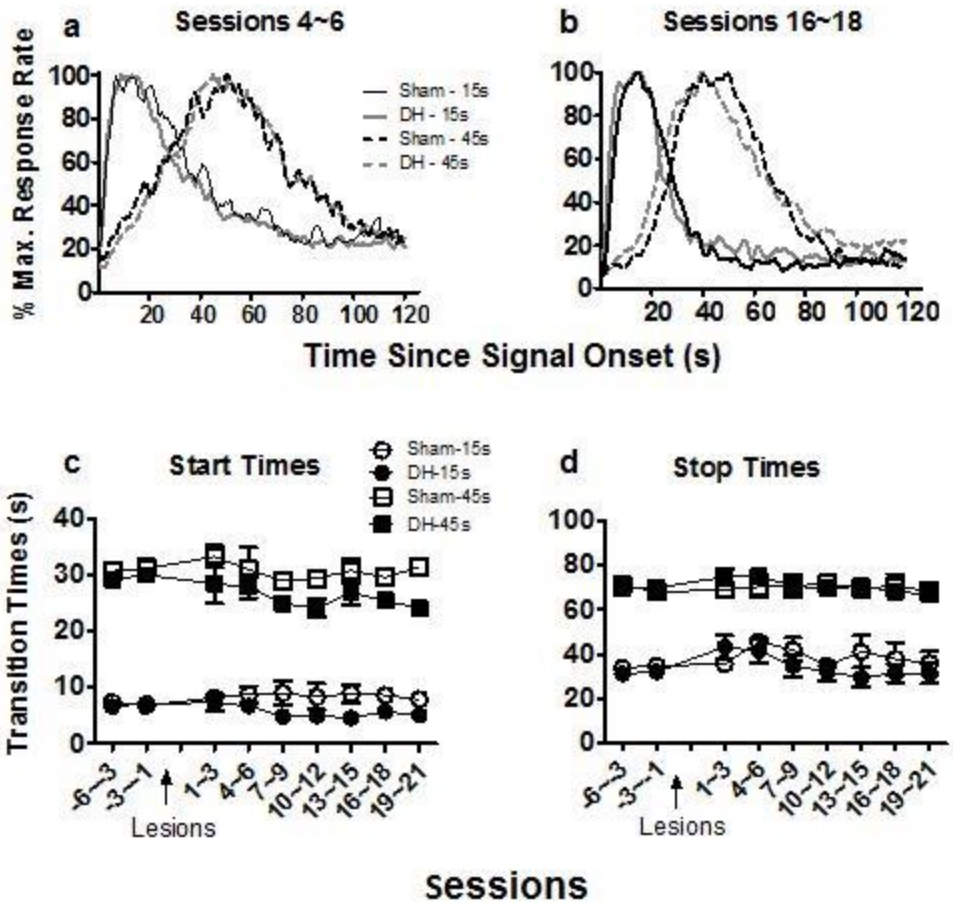

Figure 12: Effects of cytotoxic lesions of the dorsal hippocampus (DH) after having completed 20 sessions of bi-peak interval training. Bi-peak functions during post-operative sessions 4-6 and 16-18 are shown in panels a and b, whereas single-trial 'Start' and 'Stop' times as a function of post-operative training sessions are plotted in panels c and d. In panels a and b, black and grey lines represent the Sham and the DH-lesioned groups, respectively; whereas solid lines and dashed lines represent the 15-s and 45-s peak functions, respectively. Response rates as a function of time since signal onset were calculated from the pooled lever presses from all trials in a session and then normalized by the maximum response rate for each subject. Data were then averaged across three sessions for all the subjects in a group and then re-normalized to the maximum response rate. In panels c and d, empty symbols and filled symbols represent the Sham and DH-lesioned groups, respectively; whereas circles and squares represent the 'Start' and 'Stop' transition times for the 15-s and 45-s target duration, respectively. Data are means (± S.E.M) averaged over three sessions. Arrows on the time axis indicate where surgery occurred.

2.3.6 Histology

Histology confirmed that both DH and VH lesions were complete and successful as illustrated in Figure 13. This illustration displays the maximal extent of the lesions for each group. The lesions were consistent in their placement in either the DH or VH and variability in the extent of the lesions did not correlate in any obvious way with the observed behavioral measures.

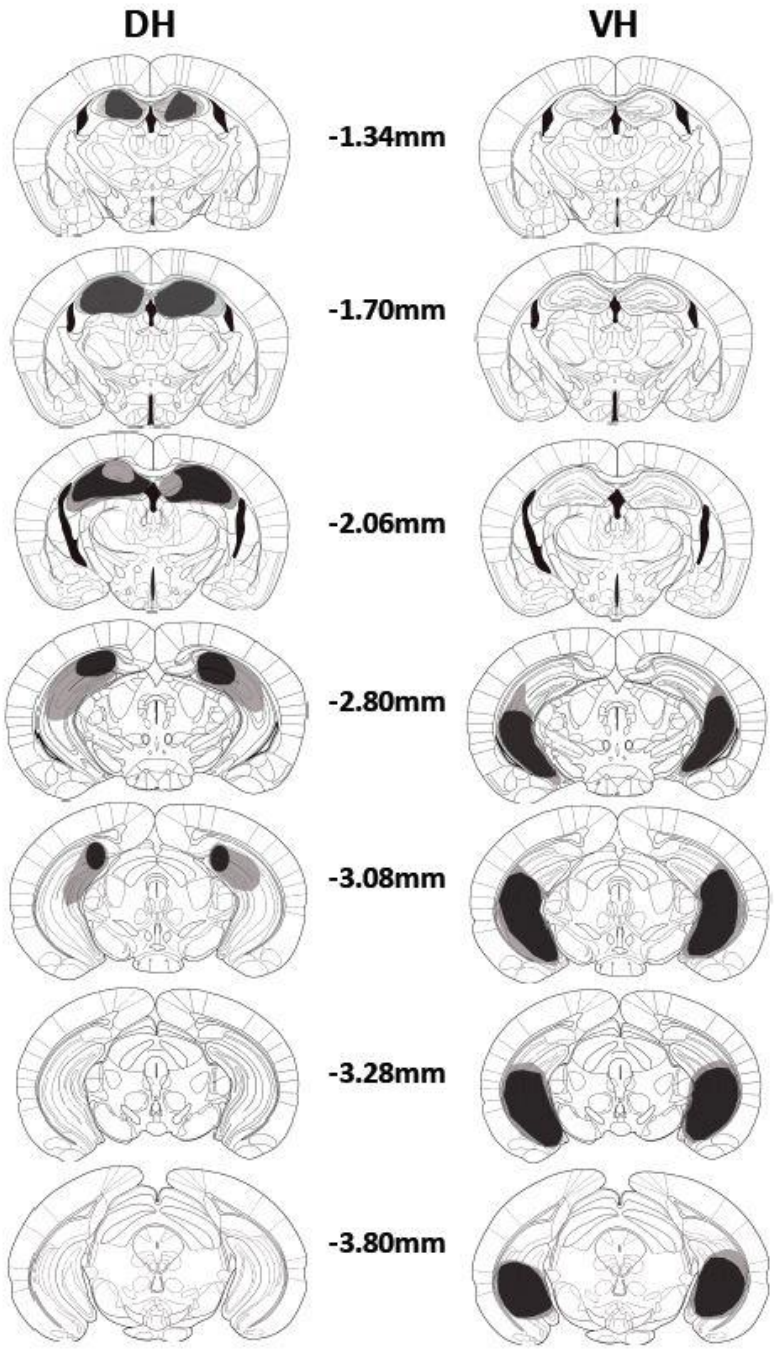

Figure 13: Schematic representations of the extent of (a) dorsal (DH) and (b) ventral (VH) hippocampal lesions on the coronal sections of the mouse brain [56]. The light grey areas represent the maximum scope of lesions within a lesion group and the dark grey areas represent the minimum scope of lesions within a lesion group.

2.4 Discussion

Dorsal and ventral hippocampal lesions differentially affect bi-peak performance

In previous work, rats with hippocampal damage (e.g., fimbria-fornix lesions or complete hippocampal cytotoxic lesions) responded earlier than the scheduled time of reinforcement in a variety of peak-interval procedures (C. V. Buhusi & Meck, 2013; Meck, Church, et al., 1984) suggesting that the hippocampus plays a role in temporal memory (Meck et al., 2013). Hippocampal lesions also disrupt responding in differential reinforcement of low rates (DRL) schedules. In DRL, rats are trained to withhold responding for food until after a set time has elapsed (e.g., >15 s). Rats with dorsal, ventral, or complete hippocampal lesions are highly inefficient in this task because they are less able to wait for the defined temporal interval to elapse (Bannerman et al., 1999). Consequently, the hippocampus has been proposed to play a role in temporal memory and/or inhibitory processes (B. Yin & Troger, 2011).

Hippocampal lesions have been suggested to affect peak times in the peak-interval procedure and the subjective equivalence points in the temporal bisection procedure (Balci, Meck, et al., 2009; Meck, Church, et al., 1984; Meck et al., 1987; Melgire et al., 2005). Therefore, our first priority was to determine whether DH and VH lesions affect the peak times in the bi-peak procedure, and whether the ‘Start’ and ‘Stop’ times during individual trials were equally affected by the lesions.

Importantly, both pre-training and post-training DH lesions produced leftward shifts in peak times confirming previous investigations and suggesting a possible role for the DH in the cortical-striatal based timing mechanisms (Balci, Meck, et al., 2009; Meck et al.,

2013; Meck, Church, et al., 1984; Merchant et al., 2013; Tam & Bonardi, 2012a; Tam et al., 2013). Importantly, examination of the individual-trial performance revealed that earlier ‘Start’ times rather than earlier ‘Stop’ times or a combination of both could well be the reason for the observed leftward shifts of peak times. In contrast, VH lesions produced a temporary rightward shift of peak times, which could be explained exclusively by later 'Stop' times. Moreover, when peak times and peak rates were modulated by reversal learning, pre-DH lesions appear to have dramatic effects on the adaptability of temporal associations, whereas VH lesions only have effects on response levels. These data suggest that the DH is more closely related to the core timing mechanisms involved in duration encoding (Matell & Meck, 2004a; Meck, 2002a, 2002b; Merchant et al., 2013) and the VH is more closely related to motivation and context-dependent modulation of timing performance (Drew et al., 2007b; Meck, 2006c).

Implications for hippocampal-striatal interactions

Do the effects observed here indicate a role for the hippocampus in timing per se or suggest an indirect effect by its modification of striatal function? The hippocampus is thought to be involved in navigation and memory in both spatial and temporal space (Eichenbaum, 2013a; Foerde, Race, Verfaellie, & Shohamy, 2013; Gorchetchnikov & Grossberg, 2007; Hirel et al., 2013; Teki et al., 2012). In addition, both hippocampal “time cells” that integrate episodic information across events (Macdonald et al., 2014; MacDonald, Lepage, Eden, & Eichenbaum, 2011) and a hippocampal neuronal coding mechanism that represents the recency of an experience over extended intervals (Mankin

et al., 2012) have been reported. These constructs demonstrate the importance of the hippocampus to interval timing per se; however, from an evolutionary standpoint, it would be hard to believe that each brain area works in isolation. Indeed, although knowledge about the action-outcome contingency can be regarded as a type of declarative memory, few reports have suggested a role for the hippocampus to be directly involved in striatal-mediated functions, such as goal-directed exploration and habit formation (H. H. Yin & Knowlton, 2006a). (Corbit & Balleine, 2000) showed that electrolytic lesions of the DH impairs contingency degradation, but not outcome devaluation – two forms of behavioural tests designed to evaluate the boundaries between goal-directed learning and habit formation. (Corbit, Ostlund, & Balleine, 2002), on the other hand, showed that damage to the entorhinal efferents, rather than the DH itself, accounts for the effect on delayed match-to-sample performance and goal-directed behavior. Interestingly, our work demonstrates that DH lesions enhance reversal learning in the bi-peak timing procedure, a form of contingency reversal. A similar case was recently demonstrated (Graybeal et al., 2011) in which lesions of ventromedial prefrontal cortex, known to inhibit dorsolateral striatum-mediated learning, enhance reversal learning. Therefore, these data suggest that DH lesions may cause substantial changes in the dorsal striatum, as dorsomedial striatum and dorsolateral striatum are believed to be the mediator for goal-directed learning and habit formation, respectively (B. Yin & Troger, 2011; H. H. Yin & Knowlton, 2006a). The route of influences could be through the prefrontal cortex (Degenetais, Thierry, Glowinski, & Gioanni, 2003) or by way of the nucleus accumbens and mid-brain dopamine systems (Grace, 2012; Gu et al., 2011; Luo, Tahsili-Fahadan,

Wise, Lupica, & Aston-Jones, 2011; P. Voorn, L. J. M. J. Vanderschuren, H. J. Groenewegen, T. W. Robbins, & C. M. A. Pennartz, 2004b) though the long-range GABAergic projections from the DH to the striatum have also been considered (Melzer et al., 2012). Interestingly, MacDonald et al. (Macdonald et al., 2012) have demonstrated that the acquisition of ‘Start’ and ‘Stop’ response thresholds in peak-interval timing procedures is differentially sensitive to protein synthesis inhibition in the dorsal and ventral striatum. Disruption of the dorsal striatum resulted in altered 'Start' times whereas disruption of the ventral striatum resulted in altered 'Stop' times. Combined with the results from the current study, we propose that the DH typically expresses an inhibitory influence on the dorsal striatum, whereas the VH has a excitatory influence on the ventral striatum.

(M. Buhusi et al., 2013) recently demonstrated that mice deficient in a close homolog to L1 (CHL1) cell adhesion molecules related to the immunoglobulin superfamily exhibit distortions in temporal memory such that they consistently under reproduce the target duration when trained on a PI timing procedure. These CHL1 deficient mice have morphological changes in hippocampal and thalamocortical pathways and display abnormalities in exploratory behavior (Montag-Sallaz, Baarke, & Montag, 2003) and sensorimotor gating (Morellini, Lepsveridze, Kahler, Dityatev, & Schachner, 2007). As a consequence, they have been used as a model of schizophrenia and other types of intellectual disabilities in humans. Because the behavioral phenotype of these CHL1 deficient mice displays some of the qualitative (e.g., under reproduction) changes observed in interval timing following DH lesions (M. Buhusi et al., 2013; Meck et al.,

2013), we considered it important to establish additional parallels between alterations in gene expression and selective changes in hippocampal/striatal interactions that might alter interval timing in the multi-seconds range.

Facilitated striatal activity resulting from the loss of hippocampal inhibition and/or internal changes in the balance between nigro- and pallidal-striatal pathways might contribute to an alteration in the memory translation constant (K*) and provide an explanation for maintained leftward or rightward shifts in timing functions. Previous work has shown that speeding up or facilitating memory storage results in a K* < 1.0 and slowing down or impairing memory storage results in a K* > 1.0. Changes in K* can either lead to under-reproductions (K* < 1.0) or over-reproductions (K* > 1.0). Moreover, changes in timing behavior that reflect the memory translation constant are uncorrected by feedback and are maintained throughout extended training (C. V. Buhusi & Oprisan, 2013; Meck, 1983, 1996, 2002a; Oprisan & Buhusi, 2011, 2013). Such changes in K* have been observed following fimbria-fornix (K* < 1.0) or frontal cortex (K* > 1.0) lesions or the administration of cholinergic agonists (K* < 1.0) or antagonists (K* > 1.0) (Coull et al., 2011b; Meck, 1983, 1996, 2006a, 2006c, 2006e; Meck & Church, 1987a). Here we report changes in K* (leftward shifts) following both pre- and post-DH lesions, but not VH lesions.

2.5 Summary

In summary, the data reported here establish that mice can be trained to perform in a bi-peak timing procedure with a degree of accuracy and precision similar to previous

studies (Agostino et al., 2013). Moreover, control mice exhibited the scalar property of interval timing as previously demonstrated (C. V. Buhusi et al., 2009) – a hallmark of short-interval timing shared by numerous species (Gibbon et al., 1997; Meck, 2003). The underestimation of target durations, i.e., leftward shifts in psychometric functions as a result of earlier 'Start' (and possibly 'Stop') times, produced by hippocampal lesions was demonstrated to be a result of DH damage, as opposed to VH damage – which leads to a broadening of the timing functions as a result of increases in the 'Stop' times and failure of the scalar property (Abela, Dougherty, Fagen, Hill, & Chudasama, 2013). In contrast, the changes in K* produced by the DH lesions was proportional to the target durations and scaled in a normal manner when the bi-peak functions were plotted on a relative time scale. These results strongly support a change in temporal memory resulting from hippocampal-striatal interactions such that the coincidence detection mechanism of the striatal beat-frequency model of interval timing (Agostino, Golombek, et al., 2011; Matell & Meck, 2004a) is biased towards shorter durations by the increased dorsal striatal activity resulting from the inhibition of DH function (Allman & Meck, 2012; Coull et al., 2011b; Dalla Barba & La Corte, 2013; Eichenbaum, 2013b; MacDonald & Meck, 2004; Matell & Meck, 2004a; Meck & Macdonald, 2007; Meck et al., 2008). Although speculative, this proposed mechanism receives support from the proportional leftward shifts (decreases in K*) observed in Oprd1-/- mice (data not shown) which have also been shown to exhibit impaired hippocampal-dependent and facilitated striatal-dependent learning in a manner similar to rodents with DH lesions (Eckart, Huelse-Matia, & Schwarting, 2012; Hinton & Meck, 1997a; Jacobs, Allen, Nguyen, & Fortin, 2013; Le

Merrer, Rezai, Scherrer, Becker, & Kieffer, 2013; MacDonald, Carrow, Place, & Eichenbaum, 2013).

3. Contributions of the Dorsolateral and Dorsomedial Striatum to Interval Timing Behavior

3.1 Introduction

The dorsolateral and dorsomedial striatum have been proposed to mediate functional distinctive roles, with the dorsolateral striatum participated in the more habitual, context-cue elicited control of behavior and the dorsomedial striatum participated in the more goal-directed, outcome-contingent control of behavior (Balleine et al., 2007; Darvas & Palmiter, 2009; Gu et al., 2011; Hernandez et al., 2002; Johnson et al., 2007; Mitchell et al., 2007; Voorn et al., 2004a; H. H. Yin & Knowlton, 2006b). Previous timing studies have found that the temporal control of behavior is highly dependent on the extent of training (R. K. Cheng, Ali, et al., 2007; R. K. Cheng, Hakak, et al., 2007), contextual cues (Coull et al., 2011a; Jazayeri & Shadlen, 2010; Meck & Benson, 2002b; Shi et al., 2013) and is independent of its goals when trained (B. Yin & Meck, 2014b). These data raise questions of whether the two distinctive part of the striatum play different roles in temporal control of behavior and how the two parts function together with other brain regions for spatiotemporal control of behavior. Therefore, we examined the roles of dorsolateral and dorsomedial striatum using cytotoxic lesions of either dorsolateral, dorsomedial or both in the same bi-peak procedure as in the hippocampal experiments.

3.2. Methods

3.2.1 Subjects

The subjects used in the experiments were male C57BL/6J mice (n= 41, Charles River Laboratories, Raleigh, NC). All mice were between 5-7 weeks of age when first delivered to our climate-controlled animal colony with a 12:12 light/dark cycle (lights on at 7.00 A. M., off at 7:00 P.M.). Mice were group housed (4-5 mice per cage). Standard rodent chow (5001 – Purina LabDiet®, Purina Mills Inc., St. Louis, MO) and water were available ad libitum in the home cages except during the food-restricted period of behavioral testing described below. Body weights were monitored on a daily basis throughout the course of the experiment.

Behavioral testing started at 8-9 weeks of age and occurred between 9:00 A. M. and 5: 00 P.M. The mice in each cohort were assigned to one of the 20 lever boxes with different lesion or genetic conditions randomly distributed – with mice trained in the same lever box at approximately the same time of day throughout the course of the experiment. Sessions were conducted 7 days/week unless otherwise stated. During behavioural training, mice were maintained at 85-90% of their *ad lib* body weights by food restriction. All experiments were conducted under a protocol approved by the Duke University Institutional Animal Care and Use Committee in accordance with the National Institutes of Health guidelines for the care and use of animals.

3.2.2 Surgery

Mice were anesthetized with an intraperitoneal injection of ketamine/xylazine cocktail (100/10mg/kg). The mouse's head was shaved and mounted into a standard stereotaxic instrument (David Kopf, Tujunga, CA). A sterile lubricant (ointment) was generously applied to the eyes. The scalp was incised, and the skin was retracted. The head was leveled by equating bregma and lamda in the dorsoventral plane. Four (DLS/DMS) or eight (Dual/Sham) small holes were drilled into the skull according to the coordinates measured from bregma as shown in Table 6. A 1.0- µL Hamilton syringe (Model: 65458-01) was lowered into each of these holes, and N-Methyl-D-aspartic acid (NMDA; 20ug/ µL; Sigma, St. Louis, MO), dissolved in sterilized phosphate-buffered saline, was infused. An automatic syringe pump (Nanojet, Chemyx, Stafford, TX) attached to the Hamilton syringe mounted on the stereotaxic instrument was used to deliver 0.1 µL NMDA over 3 min. The syringe remained in place for an additional 2 min to allow for diffusion of the drug. In sham mice, the syringe was lowered to the same sites as lesioned mice but no injection was placed in order to minimize the physical damage to the target brain areas. After the final infusion, the incision was closed with stainless steel wound clips. Mice were allowed to recover in a heating-pad-warmed cage with food and water mixed and easily accessible nearby. After they regained full mobility and were actively running and consuming food and water for 12 hr, mice were returned to their home cages and allowed to recover for 10 days before post-lesion behavioral training began. In the event that a mouse lost more than 15% of its pre-operative weight due to the inability to consume the food after striatal lesions, 10% dextrose (provided by

Duke Division of Laboratory Animal Research) was injected subcutaneously once a day until it regained its weight to normal.

Table 6: Coordinates for Dorsolateral / Dorsomedial Striatal Lesions
Reference: Bregma and skull surface

Location of Lesions	Anterior / Posterior (mm)	Medial / Lateral (mm)	Dorsal / Ventral (mm)
DLS	+0.5	±2.6	-2.5
	+1.0	±2.1	-2.5
DMS	+0.25	±1.5	-2.5
	+0.75	±1.2	-3.0

3.2.3 Behavioral Procedures

Apparatus

The experimental apparatus consisted of 10 matching lever boxes (Model ENV-307A, Med Associates, St. Albans, VT) housed in sound-attenuating chambers (Model ENV-021M; Med Associates). The dimensions of each lever box were 21.59 x 17.78 x 12.70 cm. The ceiling, side walls, and door of each box were made from clear Plexiglas. The front and back walls were stainless-steel panels and the floor was made of parallel stainless-steel bars. The front wall of each box contained left and right retractable levers; a food cup was located between the levers; and a cue light was located directly above the food cup. A pellet dispenser delivered 20-mg grain-based food pellets (Research Diets, Inc., New Brunswick, NJ) into the food cup. The back wall of each box contained a house light (14-W, 100 mA) directed towards the ceiling. The operant chambers were controlled by the Med-PC IV software package. The fan was on throughout the session. An IBM-PC

compatible computer attached to an electronic interface (MED Associates, Inc., Model DIG-700 and SG-215) was used to control the experimental equipment and record the data. The time of each lever press was recorded to an accuracy of 10 ms and placed into 1-s time bins.

Bi-Peak Timing Procedure

Lever-press training (Sessions 1-10).

All mice were give ten daily sessions of lever-press training. During the session, one of the two side levers was continuously retracted and inserted in a 1-s cycle every 120 s to attract attention from mice. The delivery of a food pellet in the foodcup was primed every 90s, which was signaled by the blinking of the cue light. In addition to the free food pellet delivered, a food pellet was delivered for every lever press (FR-1). Every 10 lever presses resulted in alternation of the two levers. Sessions ended after 3600 s and there was no limit for total pellets that could be earned within a single session (in reality, all mice earned between 40 to 150 pellets altogether per session). After 7 sessions, the feed pellets were withdrawn in order to further encourage mice to earn food by pressing the lever. All mice that participated in the experiment learned to press the lever for food pellets after this stage.

15-s and 45-s fixed-interval training (Sessions 11-20).

During these sessions, the onset of the house light was used as a signal for the duration to be timed, i.e. fixed-interval (FI) trials were signaled by the onset of the house

light and the appropriate lever(s) was primed for reinforcement at the associated target duration(s). The target duration used on each trial (15-s or 45-s) was randomly selected with equal probability and no external cue was given to indicate which lever/duration resulted in the delivery of a food pellet, signal termination, and the onset of a variable inter-trial interval (ITI), range 30-150s. The assignment of target durations to response levers was counter-balanced both within and across groups of mice. After 7 sessions of FI training, two levers were set to be simultaneously available (inserted) throughout the session, and mice were trained to press the lever associated with the 15-s duration first and then to switch to the other lever associated with the 45-s duration.

15-s and 45-s bi-peak training (Sessions 21-40).

Bi-peak training was used to assess the start and stop times with which mice timed the target duration(s). Sessions consisted of two trial types: FI trials (as described above) and unreinforced probe trials. The two levers were set to be simultaneously available throughout the session. During probe trials the house light was turned on for a minimum of 3× the longer target duration (45-s) plus an additional random amount of time with a mean of 20s and a Gaussian distribution. No food was available for lever pressing on these unreinforced probe trials. FI and probe trials were ordered randomly with 50% probability each. Thus, one of the two target durations (15-s or 45-s) was presented in conjunction with non-reinforced probe trials in a random sequence. No external cue was provided to indicate which, if any, lever/target duration would be selected for reinforcement on any trial. Mice were free to respond on the lever(s) at any

time during the session, though only responses made to the appropriate lever following the target duration during FI trials were reinforced.

Post-Operative Bi-Peak Training (Sessions 41-60)

Ten mice were randomly assigned to the sham control (Sham, n=11), the dorsolateral striatal lesion (DLS, n=11), the dorsomedial striatal lesion (DMS, n=10), and the dorsolateral / dorsomedial dual lesion (Dual, n=9) treatment groups. The experiment was performed in an identical manner to the previous post-training hippocampal lesions experiments, i.e. surgeries were performed after the mice had already received FI training and 20 sessions of bi-peak training. Behavioural training was resumed after the mice recovered from the surgery.

3.2.4 Video recording

Life videos were recorded throughout the whole session for selective post-operative sessions for all subjects. Cameras (1.0 Megapixel 720p USB Camera with Infrared Cut and Infrared LED for Day & night Smart Video Surveillance, ELP) purchased from Amazon.com were mounted at the ceiling of the sound-proof box and the angles were adjusted so as to have an all-around view of the lever box. The Infrared sensors were covered by black electric tapes so as to keep the cameras working in the night mode (black and white) in order to avoid significant disturbances when the cue light is turned on. The ELP-cctv video recording software downloaded from www.elpcctv.com was used to record the videos. Frame rates were set at 25 frames per second. In order to

make better contrasts between the mouse and the background, the ground and all four sides of the walls of the lever box were customized and wrapped by white coated paper covers made from 5" X 7" heavyweight blank white greeting cards purchased from Amazon.com, except for where the houselight, the cue light, the food cup and the two levers locate. Due to the large size of video files (~30 gigabytes per animal per 2.5h session), Seagate Expansion 5TB desktop external hard drives were purchased to transfer and store the video files.

3.2.5 Histology

After behavioural testing was complete, all mice in the lesion groups were deeply anesthetized with ketamine and then intracardially perfused with saline and 4% paraformaldehyde. The brains were removed and stored in paraformaldehyde. Sections (100 µm) were cut coronally on a vibratome and stained with cresyl violet. Outlines of the relevant hippocampal tissue characteristics and lesions were examined under a Zeiss SteREO Lumar.V12 stereoscope and then traced onto line drawings of 16 coronal sections covering the entire dorsal striatum (Paxinos & Franklin, 2008). The outlines were then digitized to display the minimum and maximum lesions for each treatment group.

3.2.6 Data Analysis

Using custom Matlab scripts the data was analyzed from text files generated by MedPC. The data was binned for all peak trials in a single session. The mean responses

were then taken across sessions for each animal. The peak rate was calculated separately for the 15 and 45sec duration and was considered to be the maximum of the average responses per bin. This data was then normalized by peak rate. Double gaussians were fit separately for each duration using Matlab's curve fitting toolbox. The peak time was calculated as the maximum of the gaussian function. Peak spread was calculated as the width of the peak at 50% of maximum responding.

3.2.7 Video Analysis

Video frames are cropped to include only regions available to the animal and converted to gray scale before applying an inverse binary threshold. The crop size and threshold parameters are specific to each video. Regions with pixel values of 0 post thresholding (i.e. white regions) are bound using contour tracing and regions are ordered by size. As frame manipulations are optimized to maximize the contrast between the animal and the surrounding environment, the largest region is always the animal. This region is then bound by a rectangle and the center of this bounded region is found. The center point is taken to be the center of mass for the animal in that frame and the corresponding pixel coordinate is recorded, as shown in Figure 14.

For "Time-Elapsed Heat Map" plotting, the location data obtained from the above process is first segregated by trial type. An array of zeros is created with the dimensions of the processed video frame. The animal's coordinates from each frame are expanded to a 23 by 23 pixel region and those coordinates are assigned a value of 1. Time points are then stacked with pixel values being additive over a specific trial type. An animated plot

is then created with the frame rate captured from the original video (30 fps in this case). An example of the plotted heat map is shown in Figure 19.

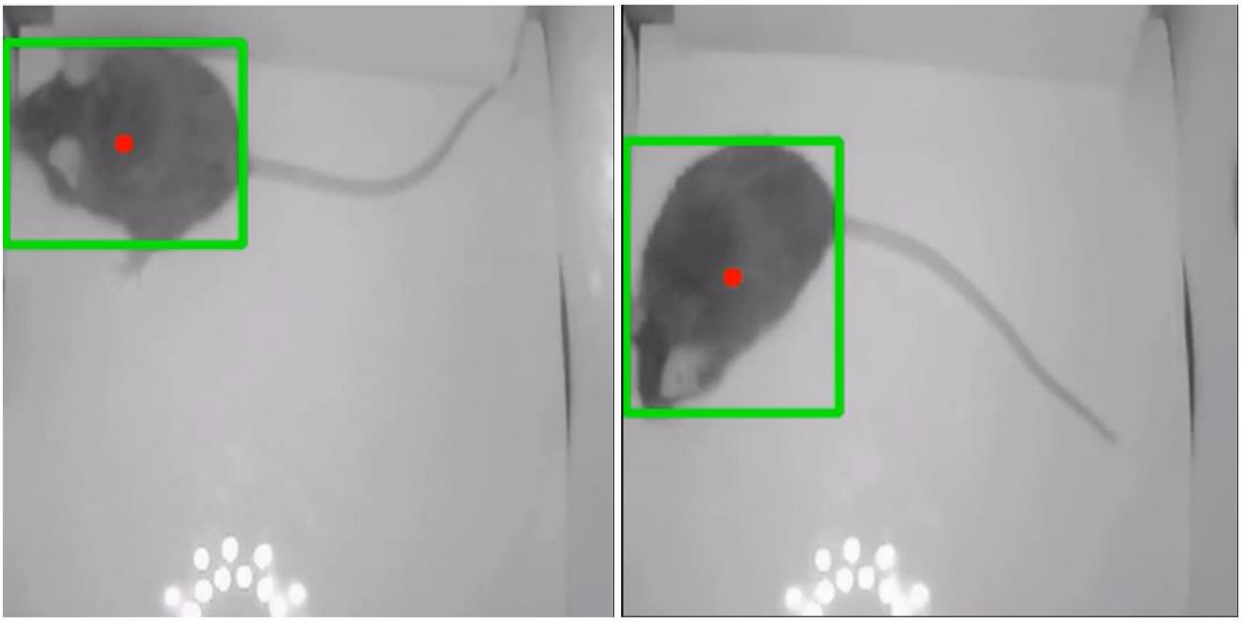

Figure 14: Video tracking of mice moving around in the lever box during a Bi-Peak procedure. The left and the right are two different postures of mice; therefore, the square that tracked the mouse dynamically changed its shape in order to keep the center red point constant at the body center of the mouse.

3.2.8 Statistical Analysis

Statistical analysis was performed using GraphPad Prism 5 (GraphPad Software, Inc., La Jolla, CA). Single-factor and repeated measures analyses of variance (ANOVA) were used as appropriate. The alpha level was set at $p < 0.05$ for all statistical analysis.

3.3 Results

3.3.1 Effects of post-training dorsolateral striatal (DLS) lesions or dorsomedial striatal (DMS) lesions on the maintenance of temporal control in the bi-peak procedure

The double Gaussian functions fit to the mean response rate functions before lesions did not show any significant differences among Sham, DLS and DMS groups (data not shown). The same analysis applied to the post-operative training functions displayed in the upper portion of Figure 15 revealed no significant group differences in peak times in both early and late training either (Sessions 4-6 – Figure 15, panel a; Sessions 16-18 – Figure 15, panel b) for either the 15-s or the 45-s target durations, F's(1, 29) < 1.0, p's > 0.05. However, there were significantly more animals in the DLS group whose peak times could not be identified and thus excluded from the ANOVA analysis (Sessions 4-6: 36% for the 15-s duration and 27.3% for the 45-s duration versus only 10% for the 15-s duration and none for the 45-s duration for the sham control group; Sessions 16-18: 36% for the 15-s duration and 27.3% for the 45-s duration versus none for either the 15-s or the 45-s durations for the sham control group). In contrast to the DLS group, there were no animals in the DMS group whose peak times could not be identified.

No significant group differences in peak rates in either early (Sessions 4-6) or late training (Sessions 16-18) for either the 15-s or the 45-s durations, F's(1, 29) < 1.0, p's > 0.05. However, there exists a trend for the DLS group to have much lower overall responding rates compared with the sham control group. There also exists a trend for the DLS group to have much wider peak spreads compared with the sham control group for

both the 15-s and the 45-s durations, though not approaching the significant level. Peak time, peak rate and peak spread measures for these conditions are reported in Table 7.

Taken together, these data suggest that an impairment in their maintenance of temporal control emerged immediately in post-operative Bi-PI training in DLS lesioned mice and 18 sessions of post-operative training were not sufficient to overcome the deficits. In comparison, no significant impairment in their maintenance of temporal control was found in post-operative Bi-PI training in DMS lesioned mice.

3.3.2 Effects of post-training dorsolateral striatal (DLS) or dorsomedial striatal (DMS) lesions on the “tail responses“ in the bi-peak procedure

{Drew, 2007 #526} found notable differences in the right-hand tails of peak functions of D2 receptor over expression group. Similar differences can be found through visual inspections of the peak functions among Sham, DLS and DMS groups for both the early (4-6) and late (16-18) sessions (Figure 15, a and b). In order to quantify the differences, the percentages of maximum responding rates corresponding to 160%~260% trained duration (i.e., 24s-39s for 15s trained duration, 72s-117s for 45s trained duration) were pooled from each individual's peak functions and the averages of them were compared among the three group. Repeated two-way ANOVAs using group (Sham, DLS and DMS) and trained duration (15s or 45s) as factors were used to examine the group differences. For the 4-6 post-operative sessions, strong effects were show in groups ($F=13.45$, $p<0.001$), trained duration ($F=160$, $p<0.001$) and interaction ($F=5.63$, $p<0.001$). For the 16-18 post-operative sessions, strong effects were show in groups

($F=4.75$, $p<0.05$), trained duration ($F=186.2$, $p<0.001$) and interaction ($F=3.98$, $p<0.01$). Results of Bonfferoni Post hoc tests in both comparisons were revealed in Figure 15, panels c and d.

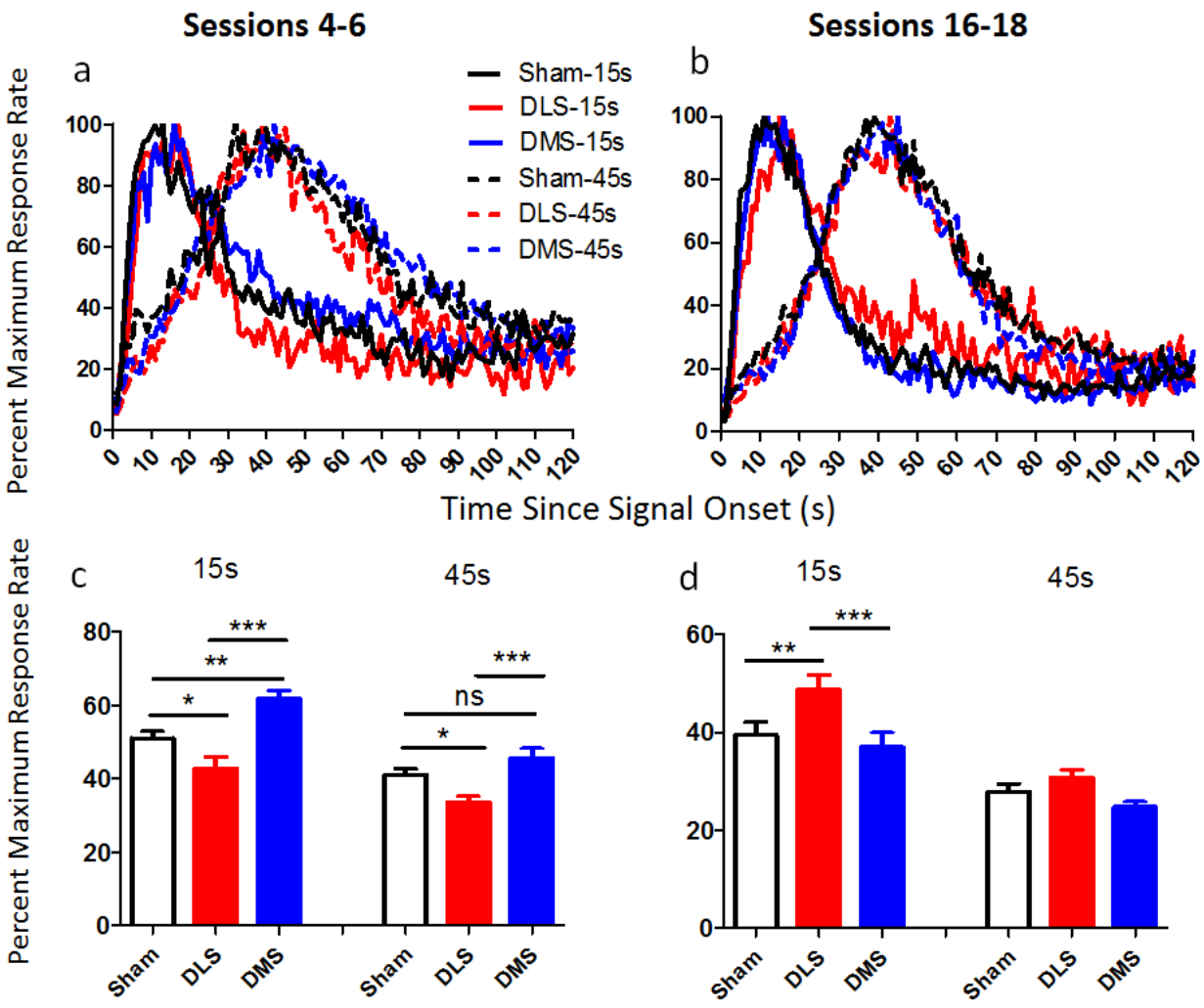

Figure 15: Bi-peak timing functions during post-operative sessions 4-6 and 16-18 are shown in panels a and b. The bi-peak functions for mice with post-training cytotoxic lesions of the dorsolateral striatum (DLS) and the dorsomedial striatum (DMS) are shown in red and blue, respectively, whereas black lines represent the sham control group. Solid lines and dashed lines represent the 15-s and 45-s peak functions, respectively. Response rates as a function of time since signal onset were calculated from the pooled lever presses from all trials in a session and then normalized by the maximum response rate for each subject. Data were then averaged across three sessions for all the subjects in a group and then re-normalized to the maximum response rate. Statistical analysis of the tail differences (defined as percentages of maximum response rates at the window of 160%-260% of trained duration are shown in panels c and d. Note: *p<0.05; **p<0.01; ***p<0.001.

Table 7: Peak Time (s), Peak Rate (resp/min) and Peak Spread (s) Measures

Groups/Sessions	Sessions 4-6		Sessions 16-18	
	15s	45s	15s	45s
Sham n=11	13.55 s ± 1.02[1] 25.33 r ± 4.47 22.00 s ± 3.85	41.28 s ± 1.57 26.67 r ± 3.95 45.37 s ± 3.26	14.03 s ± 0.75 29.69 r ± 4.44 20.60 s ± 1.37	42.10 s ± 1.13 31.28 r ± 4.97 37.91 s ± 4.24
DLS lesion n=11	14.09 s ± 0.70[4] 17.15 r ± 4.53 33.89 s ± 6.27	39.88 s ± 1.50[3] 16.69 r ± 4.39 65.51 s ± 11.94	16.84 s ± 0.57[4] 23.58 r ± 5.44 33.57 s ± 6.33	42.10 s ± 1.19[3] 20.55 r ± 5.11 57,94 s ± 12.32
DMS lesion n=10	18.81 s ± 2.29 17.90 r ± 1.61 28.46 s ± 4.21	44.67 s ± 1.62 25.73 r ± 5.64 56.75 s ± 4.04	13.94 s ± 0.79[1] 26.77 r ± 3.54 22.99 s ± 4.29	41.42 s ± 0.98[1] 28.20 r ± 6.60 44.88 s ± 8.46
Dual lesion n=9	14.03 s ± 1.97[5] 15.82 r ± 4.84 50.75 s ± 9.93	44.52 s ± 3.93[5] 19.48 r ± 5.76 83.67 s ± 12.37	14.03 s ± 1.10[3] 18.42 r ± 5.26 36.37 s ± 7.12	42.50s ± 1.76[3] 20.75 r ± 5.81 70.31 s ± 11.55

Note: Numbers = means ± standard errors; s = seconds; r = response rate (resp/min). Superscripts = number of mice for which peak times could not be determined. For peak spread calculations, 60s was assigned to the 15-s function that had indeterminate peak times, and 120s was assigned to the 45-s functions that had indeterminate peak times.

3.3.3 Effects of post-training dorsolateral and dorsomedial striatal dual (Dual) lesions on the maintenance of temporal control in the bi-peak procedure

As shown in Figure 16, panel a and Table 7, the double Gaussian functions fit to the mean response rate functions could not determine the peak times for the majority of mice in the Dual group in the early post-operative training sessions (Sessions 4-6: 55.6% for both the 15-s and the 45-s durations), although in the late post-operative training sessions some mice (20-30% of the entire group) in the Dual group had recovered some extent of their temporal control of responses and thus their peak times could be determined (Figure 16, panel b). No significant group differences in peak rates in both early (Sessions 4-6) and late training (Sessions 16-18) for either the 15-s or the 45-s durations, F's(1,17) =3.01, p's =0.10. However, there exists a trend for the Dual group to

have much lower overall responding rates compared with the sham control group (data not shown). Significant differences in peak spreads between the Dual group and the sham control group for both the 15-s and the 45-s durations, $F's(1,17) = 4.85$, $p<0.01$, with the Dual group to be much wider. Taken together, these data suggest that a very significant impairment in their maintenance of temporal control emerged immediately in post-operative Bi-PI training in the dorsolateral and dorsomedial striatal lesioned mice and 18 sessions of post-operative training were not sufficient to overcome the deficits, though some recovery were seen. Peak time, peak rate and peak spread measures for these conditions are reported in Table 7.

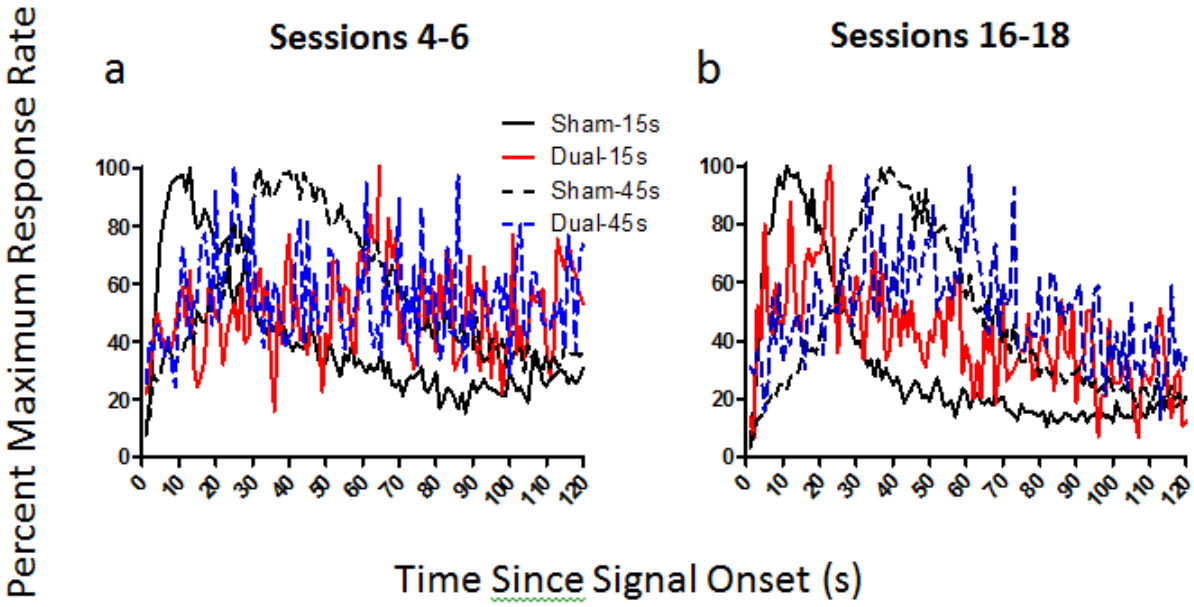

Figure 16: Bi-peak timing functions during post-operative sessions 4-6 and 16-18. The bi-peak functions for mice with post-training cytotoxic lesions of both of the dorsolateral and the dorsomedial striatum (Dual) are compared with those of sham controls. Black lines represent the sham group and the red and blue lines represent the lesioned group; whereas solid lines and dashed lines represent the 15-s and 45-s peak functions, respectively. Response rates as a function of time since signal onset were calculated from the pooled lever presses from all trials in a session and then normalized by the maximum response rate for each subject. Data were then averaged across three sessions for all the subjects in a group and then re-normalized to the maximum response rate.

Taken together, these data demonstrate that DLS and especially Dual, but not DMS lesions lead to an impairment of the maintenance of temporal control in timing tasks, which suggest that DLS may be more relevant to core timing mechanisms than DMS, while DMS could play a complementary role.

3.3.4 Superimposition of 15-s and 45-s bi-peak functions as a result of dorsolateral/dorsomedial striatal lesions

Figure 17 displays mean bi-peak functions for the 15-s and 45-s target durations for each of the treatment groups (sham, DLS, DMS and Dual) plotted on a time scale normalized by the observed peak times for each mouse prior to averaging. If the scalar property of interval timing holds, then these bi-peak functions should superimpose when plotted on a relative time scale (C. V. Buhusi et al., 2009; R. K. Cheng & Meck, 2007; Gibbon et al., 1984b). As one can see from visual inspection, the degree of superimposition is relatively comparable for the sham, DLS and DMS groups, with the Dual group being an outlier. This suggests that DLS and DMS are complementary to each other in maintaining the scalar property in the temporal control of behavior.

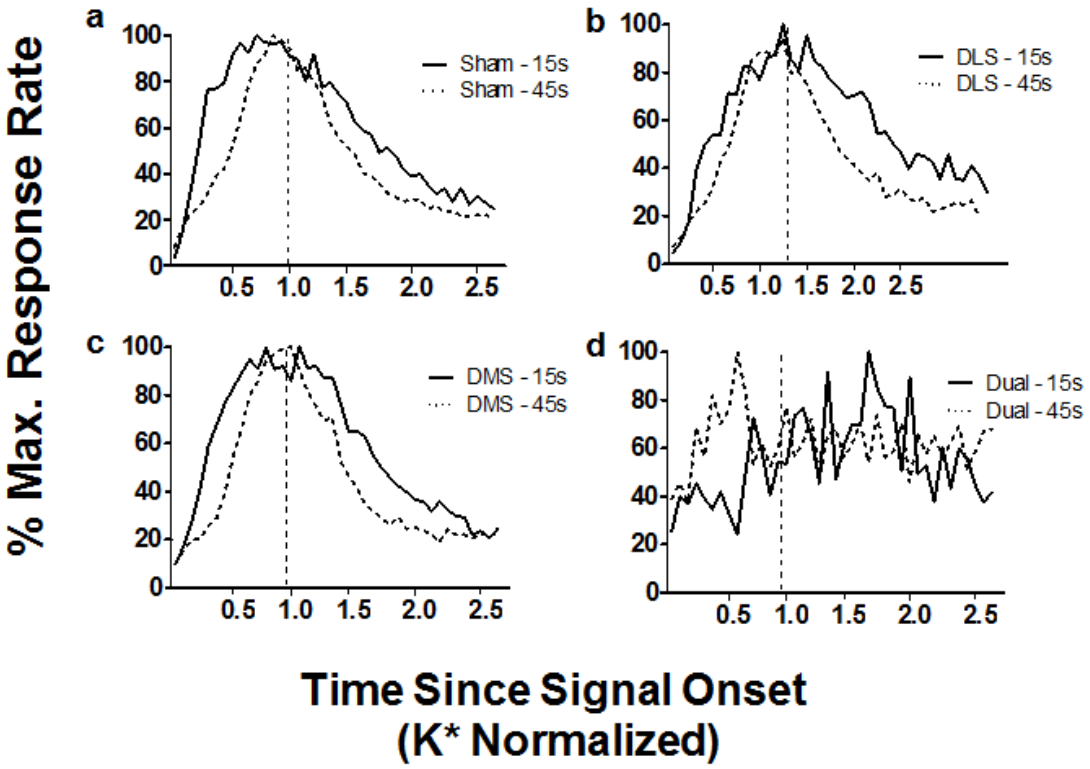

Figure 17: Superimposition plots of 15-s and 45-s bi-peak functions obtained from post-operative bi-peak sessions 16-18 for sham, dorsal (DH), and ventral (VH) hippocampal pre-training cytotoxic lesion groups. The 45-s peak functions were first normalized to the same relative percentage scale of the 15-s functions, and then re-normalized by their observed peak times.

3.3.5 Video analysis revealed differences between mice that had good or bad temporal control of their behavior in the bi-peak procedure

Video analysis demonstrates that the animals' body locations within a trial correlate nicely with their lever pressing rates as a function of time since signal onset within a trial (Figure 18). The Time-elapsed heat map revealed striking differences between a good timer (Figure 19, panel a) and a bad timer (Figure 19, panel b).

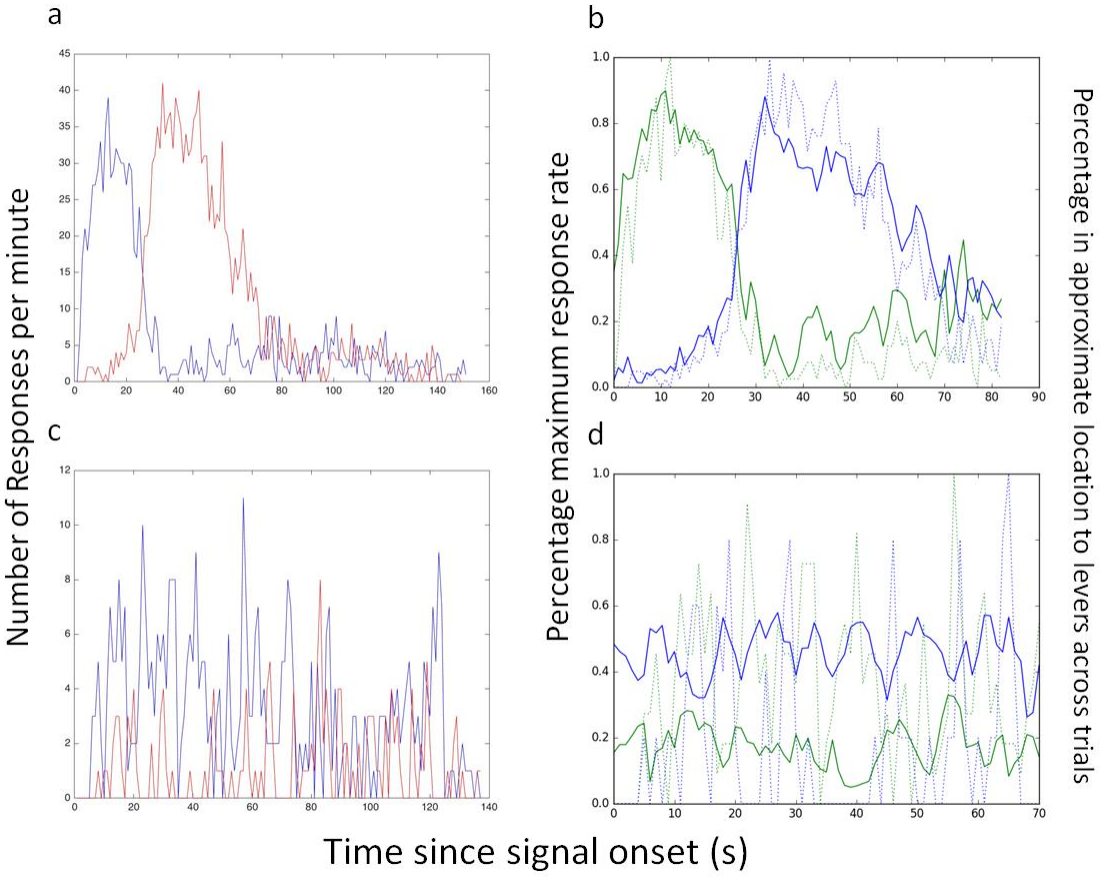

Figure 18: Demonstration for the lever press – body location correlation for a single mouse in a single session. The location bi-peak graph is calculated as the percent of video frames during a 1 sec bin that the animal spent in the region closest to a particular lever. Six regions were created by dividing the arena in half with one lever in each half. Then two perpendicular lines were drawn dividing each half into thirds (i.e. 6 equal regions). An animal was considered "near" the lever if its centroid location was inside the region corresponding to where the lever was located. Panels a-b and c-d demonstrates a good timer and a bad timer, respectively.

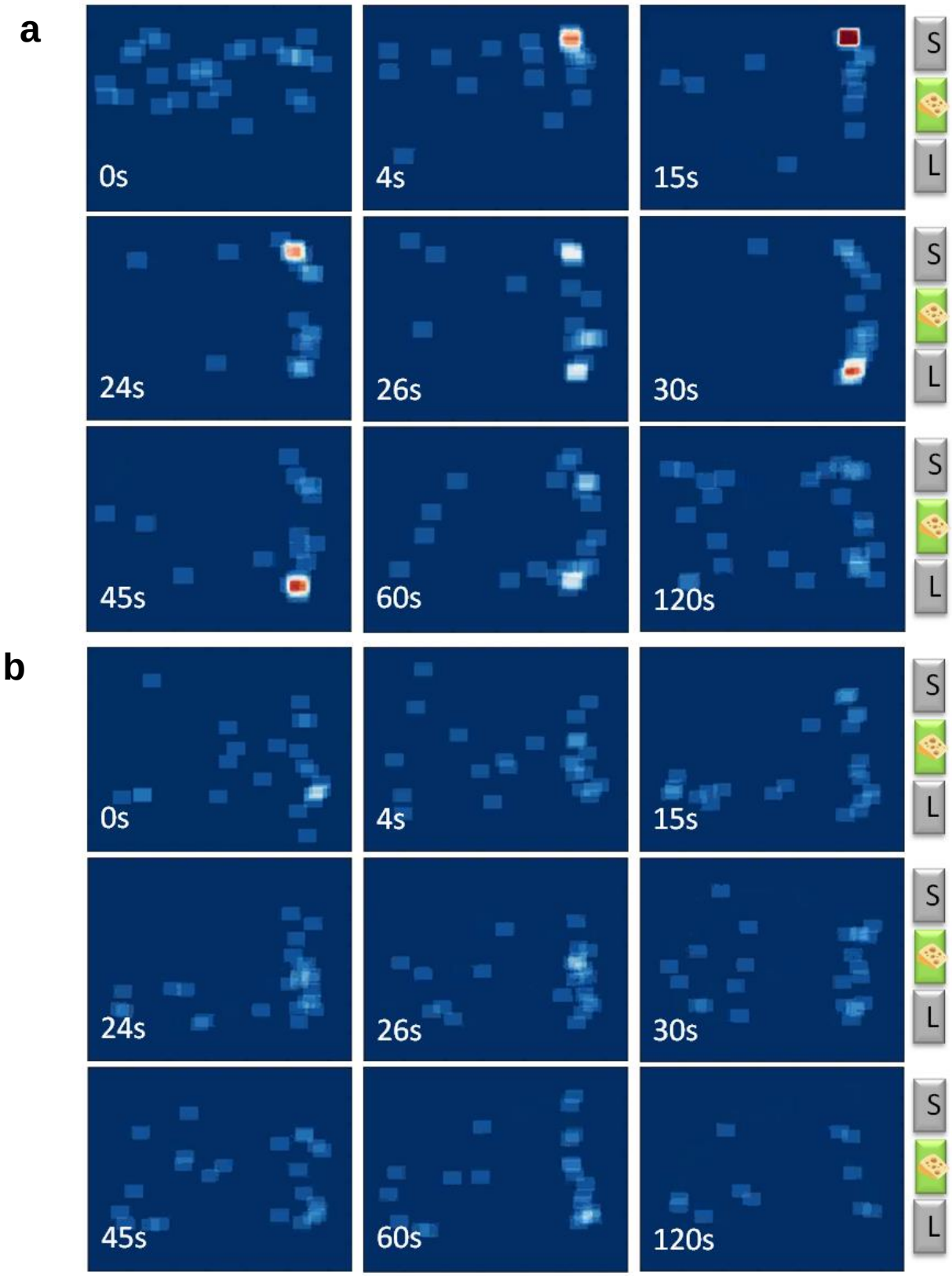
a
0s
4s
15s
24s
26s
30s
45s
60s
120s
S
L
b
0s
4s
15s
24s
26s
30s
45s
60s
120s
S
L

Figure 19: Demonstrations of "Time-Elapsed Heat Map". All levers and foodcups locate at the right side of each heat map, whereas "S" represents "the short lever" (associated with 15-s reward), "L" represents "the long lever" (associated with 45-s reward), the cheese logo represents the foodcup. Each light blue square represents the body location of the mouse at a given time point since signal onset in one trial. The color range is from 0 (blue) to 12 (red) with the value corresponding to the number of trials in which the animal occupied that space at each time point. The upper panel (a) demonstrates the heat map for a sham control mouse and the bottom panel (b) demonstrates the heat map for a dual lesioned mouse.

3.3.6 Effects of prefeeding/satiation on the maintenance of temporal control in the bi-peak procedure

In order to figure out whether the animals' body locations were authentic indicators of their spatiotemporal control of their behavior, all groups were prefed/satiated (Food *ad libitum*) before entering the bi-peak session. While prefeeding/satiation significantly reduces responding rates (Figure 20a), sham controls could still maintain nice temporal control of their body locations across all trials (Figure 20b).

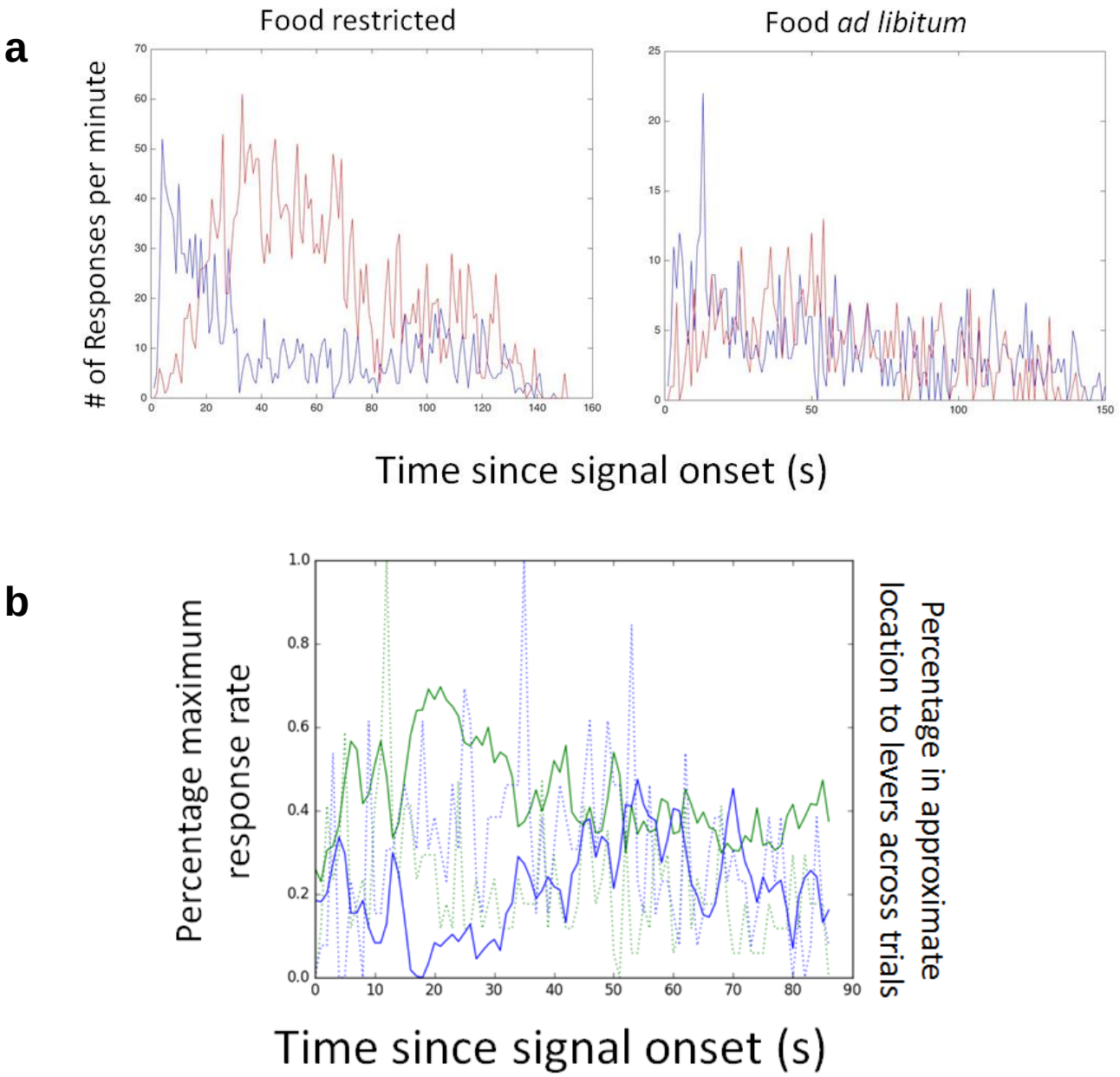

Figure 20: Satiation experiments. Satiation (Food *ad libitum*) dramatically reduces responding rates (panel a); however, sham controls could still deliver nice spatial-temporal control of their responses (panel b).

3.3.7 Histology

Histology confirmed that DLS, DMS and Dual lesions were complete and successful (data not shown). This illustration displays the maximal extent of the lesions for each group. The lesions were consistent in their placement in either the DLS or DMS and variability in the extent of the lesions did not correlate in any obvious way with the observed behavioral measures.

3.4 Discussion

Functional distinctions between DLS and DMS observed in timing behavior

There have been abundances of data showing that DLS lesions preserve outcome expectancy but disrupt habit formation in instrumental learning (H. H. Yin & Knowlton, 2006a; H. H. Yin, Knowlton, & Balleine, 2004), but few studies have clearly answered the question of whether timing is outcome oriented or habitual (or both). Recently, H. H. Yin (2010) demonstrated that DLS lesions produce severe deficits in the acquisition of serial order learning. Our data by and large support this study in the sense that 40% of the animals in the DLS group did not display temporal control of their behavior post lesions while all the animals in the DMS group displayed the same accuracy as sham controls. Given that all animals had been welled trained in the bi-peak procedure before lesions, we have reasons to believe that habit formation plays an important role in well-maintained temporal control of behavior, or timing itself is somewhat habitual. The almost complete “mess-up” of their temporal control of behavior in the DLS/DMS dual lesioned group provides further insights into possible complementary roles of both

outcome-oriented action learning and stimulus-triggered habit formation in the learning process of timing behavior. We previously showed that the effects of leftward shifts of peak times were independent of training (B. Yin & Meck, 2014a); therefore, it would be intriguing to learn about whether pre-training DLS and/or DMS lesions would produce similar effects to post-training lesions observed here.

On the other hand, we found that DMS lesions produced a significantly elevated "tail" of peak function at least in the early stage of post-operative sessions (Figure 15c) while DLS lesions produced a significantly suppressed "tail". These data are consistent with Castane et al. (2010)'s finding that DMS lesions produced a deficit in serial reversal learning of an instrumental spatial discrimination and produced more perseverative errors (also see Clarke et al., 2008), demonstrating a role of DMS in controlling obsessive/impulsive behavior when the targeted reward is no longer likely to be available; or possibly more specifically, the balance between the DLS and DMS in keeping excessive action that was previously rewarded in cognitive control (Johnson et al., 2007; Macdonald et al., 2012). It is also notable that DLS group demonstrated an opposite effect, i.e. an elevated "tail", in the late stage of post-operative training (Figure 15d), which is consistent with the idea that DLS is involved in late stages of skill learning (H. H. Yin et al., 2009), or re-learning in this case.

"Time-Elapsed Heat Map" is a useful tool to study spatiotemporal integration

Spatiotemporal integration in learning and memory as well as decision making has been an important though understudied topic given the complexity of devising a

behavioral task that integrates both temporal and spatial components while being able to tease them apart. By applying the timed-switching task, a variant of the bi-peak procedure used in our study, Tosun et al. (2016) showed that mice can abruptly adopt temporal decision strategies by directly integrating their previous knowledge of task parameters such as spatial location and reward probability into their timed behavior, supporting the model-based representational account of temporal risk assessment. On the other hand, Dallal et al. (2015) demonstrated that space and time are separable entities but can be integrated into a common metric using gravity and self-initiated movement as a reference. Here we develop a simple new technique named "Time-Elapsed Heat Map", which demonstrates that the timing behavior of the mice can be reflected by its spatial location, i.e. knowing where to go at the right time, thus the probability of being in the approximate location of its intended timing behavior (e.g. pressing the lever) could be an indicator of when the animal "starts timing" and "stops timing" in a given trial. A notable example is demonstrated in Figure 19a: the mouse "starts" timing the 15-s duration at 4s since signal onset, reflected by the first emergence of redness (i.e. trial overlapping) near the 15-s lever, "peaks" at 15s, and "stops" timing the 15-s duration at 24s, reflected by the last moment of redness near the 15-s lever; then it "switches" to the 45-s lever at 26s (the geometric mean of 15s and 45s), reflected by an equal distribution of its locations near the 15-s lever and the 45-s lever; then it "starts" timing the 45-s duration at 30s, reflected by the first emergence of redness near the 45-s lever, "peaks" at 45s, and finally "stops" timing the 45-s duration before 60s, reflected by the last moment of redness near the 45-s lever; its locations become random again during the remaining of the trial (an

example is seen at 120s). The percentage of its spatial location correlates well with its timing function (Figure 18a). In contrast, a mouse incapable of using temporal clues to guide its spatial orientation displays randomness in its spatial locations throughout the trial (e.g. Figure 19b), which correlates with its "messy" timing function (Figure 18b).

Prefeeding/satiation experiments revealed dissociation between habit-controlled, temporally-guided spatial location and goal-directed lever pressing

The intention-behavior discrepancies have widely been reported in humans (Ajzen, Brown, & Carvajal, 2004; Ajzen & Fishbein, 1974; Sheeran, 2002) but few are reported in animals possibly due to the difficulty of study animals' "intentions". Prefeeding or satiation is a form of outcome devaluation and shall impact goal-directed behavior but not habit formation (Balleine & Dickinson, 1998; Nelson & Killcross, 2006; H. H. Yin & Knowlton, 2006a; H. H. Yin et al., 2004). Here we used the "Time-Elapsed Heat Map" to demonstrate that while an animal's lever pressing response rate decreases dramatically as a result of prefeeding/satiation, as well as its temporal structure of response rate (Figure 20a, right), its temporal structure of its body location may still be relatively intact (Figure 20b), reflecting a possible dissociation between the habit-controlled, temporally-guided spatial orientation behavior and the goal-directed lever pressing more susceptible to outcome devaluation. It worth noted that the animal did not engage in some stereotypical "action chain" of behavior (Killeen & Fetterman, 1988) but instead displayed a variety of behavior including grooming, chewing the lever, climbing the wall, jumping from wall to wall, freezing in a corner, circling, etc. that did not

necessarily lead to getting its body near the reward-contingent lever (lab observation through the video) – this is also evident in the "Time-Elapsed Heat Map" that the body locations scattered randomly throughout the space across all trials, except for when aggregated near the reward-contingent lever under temporal control. Therefore, the key role of dorsal striatum in temporal control of behavior could be proved in the observation that sham controls were able to orient its body location under temporal control no matter what behavior it was actually engaging in while most dual-lesioned animals were not able to.

It is also known that the ventral striatum, a major part of which is the nucleus accumbens, controls the appetitive motivation (Cardinal, Parkinson, Hall, & Everitt, 2002; Kelley, 2004; Robbins & Everitt, 1996). It would therefore be interesting to inactivate the ventral striatum (Johnson et al., 2007; van der Meer et al., 2010; Voorn et al., 2004a) and see if the animal would still be oriented in the right approximate location as a function of time but do not "want" to press the lever.

The "tutoring" role of dorsal striatum on the cortex might explain the residual timing behavior in DLS/DMS dual-lesioned mice

In recent years growing evidence suggests that the connectivity and physiology of the basal ganglia is ideally suited for fast "directed" formation of reward-relevant associations, which over the course of practice train slower Hebbian learning in the downstream thalamocortical circuits (Ashby, Ennis, & Spiering, 2007; Houk et al., 2007). This means that basal ganglia is crucial in new skill learning but far less important in the

retention and recall of well learned skills (Barnes, Kubota, Hu, Jin, & Graybiel, 2005; Pasupathy & Miller, 2005; Tang et al., 2009; Z. Williams & Eskandar, 2005; Z. M. Williams & Eskandar, 2006), which may be the function of cortex (Calvo-Merino, Glaser, Grezes, Passingham, & Haggard, 2005; Kleim et al., 2004; Matsuzaka, Picard, & Strick, 2007). It is therefore reasonable to speculate that some dual-lesioned mice could still perform well in the bi-peak procedure under the guidance of the intact cortex, which has been "tutored" by the dorsal striatum during training prior to surgical lesions to the dorsal striatum was done. Indeed, there were signs that during the initial sessions after the context of the lever box where the animals were trained was modified (e.g. wrapping the ground and the wall with white cardboard in order to enhance the contrast for video analysis), the sham control mice displayed disoriented timing behavior while some dual lesioned mice actually performed better than in the original context (data not shown). This could be explained by that hippocampal-dependent fast learning system might be activated in the new context which might interfere with striatal-dependent behavioral expression, (Ghiglieri et al., 2011; Johnson et al., 2007; Lee et al., 2008; Packard & McGaugh, 1996; Wiltgen et al., 2010) but with striatal lesions the cortex might take the role of guiding behavior given that it has been "tutored" by the basal ganglia " (Botreau et al., 2004; Brooks, 1995; Turner & Desmurget, 2010; Wildgruber et al., 2001; Woolley & Kao, 2015). If this were true, then those dual-lesioned mice might not be able to learn new durations even though they were still able to perform suboptimal timing of well-learned durations.

3.5 Summary

In summary, these data have lent support to the idea that the dorsolateral and the dorsomedial striatum are complementary to each in timing-based decision-making, as illustrated in Figure 21.

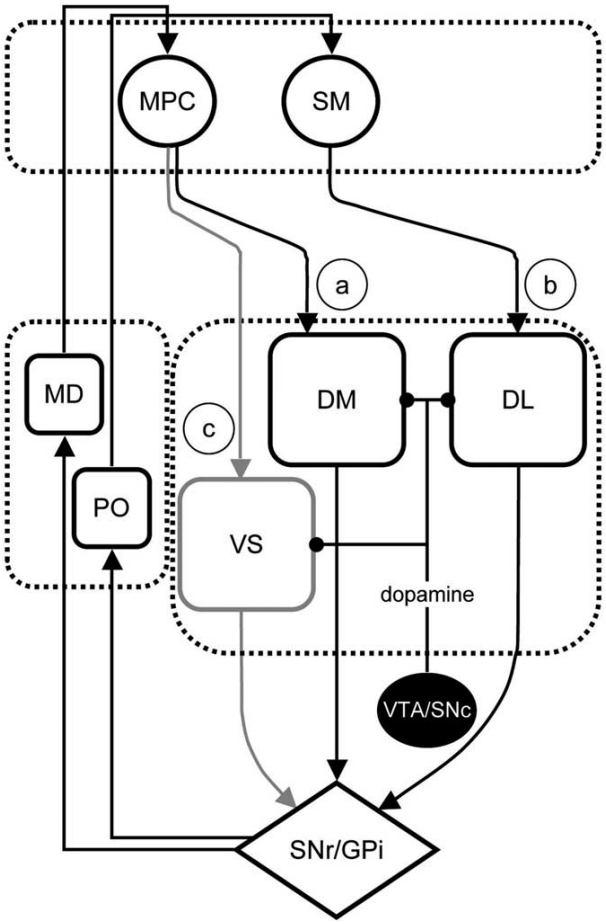

Figure 21: Corticostriatal circuits involved in decision-making. a, b, The learning processes controlling the acquisition of reward-related actions are mediated by converging projections from regions of anteromedial prefrontal cortex (MPC) to the rodent dorsomedial striatum or primate dorsomedial striatum (DM), whereas the processes mediating the acquisition of stimulus-bound actions, or habits, are thought to be mediated by projections from sensorimotor cortex (SM) to the rodent dorsolateral–primate dorsoposterior striatum (DL) (b). These corticostriatal connections are parts of distinct feedback loops that project back to their cortical origins via substantia nigra pars reticulata (SNr)/globus pallidus internal segment (GPi) and the mediodorsal (MD)/posterior (PO) nuclei of the thalamus. c, Reward and predictors of reward are the major motivational influences on the performance of goal-directed and habitual actions that are thought to be mediated by corticostriatal circuits involving, particularly, ventral striatum (VS) and regions of the amygdala. Dopamine is an important modulator of plasticity in the dorsal striatum, whereas its tonic release has long been associated with the motivational processes mediated by the ventral circuit. VTA, Ventral tegmental area; SNc, substantia nigra pars compacta. From Balleine et al., 2007a.

4. Claustrum, consciousness, and time perception

4.1 Introduction

Consciousness is not a unitary phenomenon, but a class of states that can be viewed as distributed along a continuum of arousal or awareness ranging from none to full awareness (Anzulewicz et al., 2015; Churchland, 1992; Mormann & Koch, 2007). Conscious awareness varies considerably within an individual across different contexts, such as non-conscious (or minimally-conscious) states as in non-REM sleep to fully conscious states as in normal wakefulness (Casali et al., 2013). The identification of the neural correlates of consciousness is both an enduring challenge in consciousness science and the focus of much research although our understanding of how the brain enables conscious states and how shifts in brain states contribute to fluctuations in consciousness remains in its infancy (Tsuchiya, Wilke, Frassle, & Lamme, 2015). Emerging evidence from studies of awareness across time, alterations in meta-awareness involving changes in neural synchronization, and clinical populations characterized by distortions in awareness, suggest a close intersection between conscious states and interval timing. Consequently, temporal integration mechanisms have been implicated in the neural substrates of consciousness (Meck, Vatakis, & van Rijn, 2014; Naish, 2014). Moreover, the primary neurophysiological correlates of consciousness in these studies has been neural synchronization as a function of alternation between phasic and sustained activity (Crone et al., 2015; Doesburg, Green, McDonald, & Ward, 2009; Terhune, Cardena, & Lindgren, 2011; Tononi & Koch, 2015; L. M. Ward, 2011).

In recent years, the claustrum was proposed as a possible neural candidate for the coordination of conscious awareness (Smythies, Edelstein, & Ramachandran, 2012; Smythies, Edelsten, & Ramachandran) and to play a key role in integrating diverse sources of neural information during the formation of unified conscious percepts (F. C. Crick & Koch, 2005; F. Crick & Koch, 2003). The interhemispheric connections of the claustrum enable the coordination of bilateral cortical functions by way of its ipsilateral and contralateral connections with prefrontal, premotor, and motor areas. Working from the starting point that subjective time constitutes the “infrastructure of consciousness” (Zahavi, 1999) we propose that the claustrum plays a crucial role in consciousness by supporting the temporal integration of cortical and thalamic oscillations involved in the multiplexing of sensory input used for interval timing and working memory (Gu et al., 2015).

The continuity of experience transduced by temporal integration is one of the defining features, if not the defining feature, of consciousness (Bodovitz, 2008). Accordingly, a first step in addressing the relevancy of time in consciousness requires a re-evaluation of what is *meant* by "conscious processing” and the control of an internal clock (Allman, Teki, et al., 2014; Velmans, 1991). On closer examination, a process might be said to be "conscious" in three distinct senses.

(a) one is aware *of* the process

(b) the operation of the process is *accompanied* by awareness (of its *results*) and

(c) awareness *enters into* or *causally influences* the process.

Crick and Koch provided an outlined for the scientific study of consciousness (F. Crick & Koch, 2003). In this framework, the authors proposed that an alternative to tackling the "hard problem" of qualia (Howell & Alter, 2009) would be to identify some neural correlate(s) of consciousness in causal terms, that is, "finding a minimal set of neuronal events that gives rise to a specific aspect of a conscious percept". As a consequence, they focused exclusively on neural activity related to a specific sensory modality, i.e. the visual system of primates, leaving unexplored other aspects of consciousness, such as emotion and self-awareness. Although we, in principle, agree with Crick and Koch's perspective, we maintain that consciousness science should investigate how inputs from different sensory channels can emerge as a complete picture of our ever-changing conscious experience. As a consequence, any specific sensory percept is construed as one input to this emergent principle of coalition. In other forums, this has traditionally been referred to as the 'neural binding' problem (Revonsuo, 1999).

It's easily overlooked that humans share with other animals a remarkable ability to estimate the durations of events and subjectively experience a sense of time passing (Lloyd & Arstila, 2014). It is also tempting to assume that the experience of conscious states, and in particular self-awareness, is dependent upon the ability to perceive duration and to understand the concepts of past, present, and future (Allman, Yin, et al., 2014), but see (Meyer, 2016) which leads researchers to face the dilemma of whether non-human animals have human-like conscious experience. Although performing a classic timing task such as the peak-interval procedure (Church et al., 1994; Rakitin et al., 1998) may not require the total awareness of time passing, more fundamentally our conscious

experience may actually be organized by an underlying timing mechanism. Indeed, distinct from physical entities that have multiple dimensions (at least three dimensions in space and one dimension in time in classical physics), time is arguably the only dimension for mental entities (e.g., thought, feeling, sensory perception, etc.), unless they have other dimensions that could only be measured in a phenomenal world (Smythies et al., 2012). Therefore, it is intriguing to question whether our subjective experiences coalesce mainly because we have a built-in temporal integration process that coordinates different channels of inputs into uniform subjective states. This is particularly important not only because of the "hard problem" of consciousness that has lingered for centuries, but also because timing is disrupted in various mental disorders (Allman & Meck, 2012) that can be regarded as "disorders of conscious experience" and thereby may prove valuable in elucidating basic mechanisms and developing treatments. One example is schizophrenia, because schizophrenic patients have a distorted sense of reality and temporal structure (Ciullo, Spalletta, Caltagirone, Jorge, & Piras, in press; Martin et al., 2014). Another example is pathological gambling, because pathological gambling can be directly associated with an altered state of consciousness, dysfunctional risk assessment, and a skewed perception of time and rate of return (Brevers et al., 2013). The observation that pathological gamblers exhibit reduced gamma synchronization in paralimbic cortical structures during rest as well as an impairment in task-related changes compared to controls has been associated with a loss of conscious coherence (Thomsen et al., 2013). Behavioral studies suggest that gamblers may be ultra-sensitive to time and experience a delusional high rate of return in various aspects of their lives (Wiehler, Bromberg, &

Peters, 2015). Consequently, disrupted optimization of timing abilities and impaired self-awareness may contribute to compulsive gambling behavior (Brevers et al., 2013; Wiehler et al., 2015; Wittmann, 2013b).

4.2 Consciousness, metacognition and interval timing

By definition, consciousness refers to awareness of one's unique thoughts, feelings and sensations of the environment. A key characteristic is that these experiences are constantly shifting. The ever-shifting stream of thoughts can change dramatically from one moment to the next, but one's experience of it seems smooth and effortless. How does the brain enable such continuity of experience and what are the essential mechanisms for the emergence of conscious experience? Three possible criteria can be derived from 'higher-order' theories of consciousness (Rosenthal & Werisberg, 2008) and 'integrated information theory' (Tononi, 2015):

1. The ability to select one state out of the indefinite possibilities (differentiated information) e.g., differences between a light sensor and a conscious agent.
2. The ability to have awareness of mental representations (metacognition; second-order representations).
3. The ability to tag personal meaning to the state.

It is important to note that there exist fundamental differences between sensitivity (non-conscious) and awareness (conscious): sensitivity relies on the first-order representation in the system, whereas awareness relies on the second-order representation in the system. That is, sensitivity entails the ability to respond in specific ways to certain states of

affairs, whereas awareness requires the agent to have the knowledge of the fact that she or he is sensitive to some state of affairs and also cares about a certain state of affairs. For example, a camera doesn't lack consciousness because it's only sensitive to light, but because it has no awareness of being sensitive to light. One could only make the camera conscious by enabling a second-order mechanism that could coordinate its moments of recording light with its memory of past recordings of light, as well as its own preference for that particular moment of light-sensing and memory traces – this mechanism could obviously be the time-keeping mechanism described above. For such a higher-order timing mechanism to work, each channel of inputs must have its own clock(s) so that these clock phases can be synchronized to form a representation of the present — "now". The proposal that we present in this review is that the claustrum is critical for the type of temporal integration required by consciousness.

A further link between metacognition and interval timing is suggested by psychological manipulations that alter conscious states and distort time perception as well as by disorders of consciousness. Two such psychological techniques include hypnosis, which involves the administration of a hypnotic induction, involving suggestions for reduced awareness and meta-awareness (Oakley & Halligan, 2013) and meditation, which involves a variety of practices with the intent to foment awareness of mental representations (Jo, Hinterberger, Wittmann, & Schmidt, 2015). A hypnotic induction reliably produces a tendency to underestimate time, particularly in highly suggestible individuals (Naish, 2014; Terhune et al., 2011), who comprise approximately 10-15% of the population (Oakley & Halligan, 2013). Alongside distortions in time perception,

highly suggestible individuals routinely experience states of depersonalization and derealization spontaneously following a hypnotic induction (Oakley & Halligan, 2013). Although they have not been systematically studied, depersonalization disorder patients are similarly known to experience pronounced disruptions in time perception (Spiegel et al., 2013) and drugs that elicit distortions in time perception also induce depersonalization (Wittmann et al., 2007). In contrast, preliminary evidence suggests that meditation training produces a tendency to overestimate intervals (Kramer, Weger, & Sharma, 2013).

The mechanisms underlying these distortions are not well understood but may lie in atypical metacognition in these populations. A common theme in models of hypnosis is that highly suggestible individuals are characterized by impaired executive monitoring and that the ability to respond to hypnotic suggestions is facilitated by reduced awareness of intentions underlying responses (Dienes & Perner, 2007; Oakley & Halligan, 2013). Following a hypnotic induction, highly suggestible individuals exhibit reduced medial prefrontal cortex activity (McGeown, Mazzoni, Venneri, & Kirsch, 2009) as well as reduced frontal-parietal alpha [8] and frontal-central-central beta synchrony (Jamieson & Burgess, 2014) relative to low suggestible individuals. These changes implicate default mode, executive attention, and motor networks involved in metacognition, cognitive control, and interval timing (Miele, Wager, Mitchell, & Metcalfe, 2011). In contrast, there is evidence suggesting that meditators have greater awareness of their intentions to act (Jo et al., 2015). Cumulatively, these results suggest that awareness of mental representations is closely intertwined with one’s perception of time.

4.3 Striatal Beat Frequency (SBF) model of interval timing

In the striatal beat frequency (SBF) model of interval timing (Allman & Meck, 2012; C. V. Buhusi & Meck, 2005b; Coull et al., 2011b; Matell & Meck, 2004a; van Rijn, Gu, & Meck, 2014a) duration estimation is based upon the coincidence detection of oscillatory processes in cortico-striatal circuits. The SBF model supposes that at the onset of a "to be timed" signal, populations of cortical (and thalamic) neurons phase reset (and synchronize) and begin oscillating at their endogenous periodicities. Dopamine release from the ventral tegmental area at the onset of the signal is believed to play a part in this resetting function for cortical neurons while also acting as a 'start gun', and dopamine release from the substantia nigra pars compacta at signal onset works in a similar fashion to reset the weights of the synaptic connections in the dorsal striatum (T. W. Kononowicz, 2015). The detection of coincident activation of specific cortical oscillatory patterns is the role of striatal medium spiny neurons (MSNs). The adjustment of cortico-striatal synaptic weights allows the MSNs to discriminate and become 'tuned' to specific patterns of coincident oscillatory activity, thus increasing their likelihood of firing upon similar patterns of cortical activation in the future. This property accounts for the close correspondence between interval timing and working memory performance, which are held to depend on the same neural representation of a specific stimulus (Gu et al., 2015).

Given that oscillatory activation repeats itself at regular intervals (its period) and changes in a systematic manner as a function of time (its phase), these cortical oscillatory patterns, when observed across neurons differing in their intrinsic periodicity, can represent time intervals in the seconds-to-minutes range although their neural firing

occurs in the milliseconds range. The MSNs are able to detect these patterns, which bear resemblance to musical chords, by acting as coincidence detectors or ‘perceptrons’ (C. V. Buhusi & Oprisan, 2013). Striatal output travels to the thalamus along two pathways: the direct (dopamine D_1 receptor-mediated) and indirect (dopamine D_2 receptor-mediated), then loops back to the cortex and striatum, influencing the rate of oscillatory activity and permitting alterations in clock speed by changing the input to MSNs (Oprisan & Buhusi, 2011). Differential activity in the direct and indirect pathways of the basal ganglia may serve to start, stop, or reset the timing process (Matell & Meck, 2004a). Consequently, the SBF model has the advantage of being consistent with the known psychophysics, neuropharmacology, and neuroanatomy of interval timing while at the same time making testable predictions regarding the functioning of its components (Allman, Teki, et al., 2014; Coull et al., 2011b; Hashimoto, 2015; T. W. Kononowicz, 2015; W. J. Matthews et al., 2014; Oprisan & Buhusi, 2014a). A unified timing model that incorporates the SBF model of beat-based timing using cortico-striatal circuits and duration-based models using olivocerebellar circuits is outlined in Figure 22. This model is based on coordinated activity in the core striatal and olivocerebellar networks that are interconnected with each other and the cerebral cortex through multiple synaptic pathways (Allman, Teki, et al., 2014; Teki et al., 2011a).

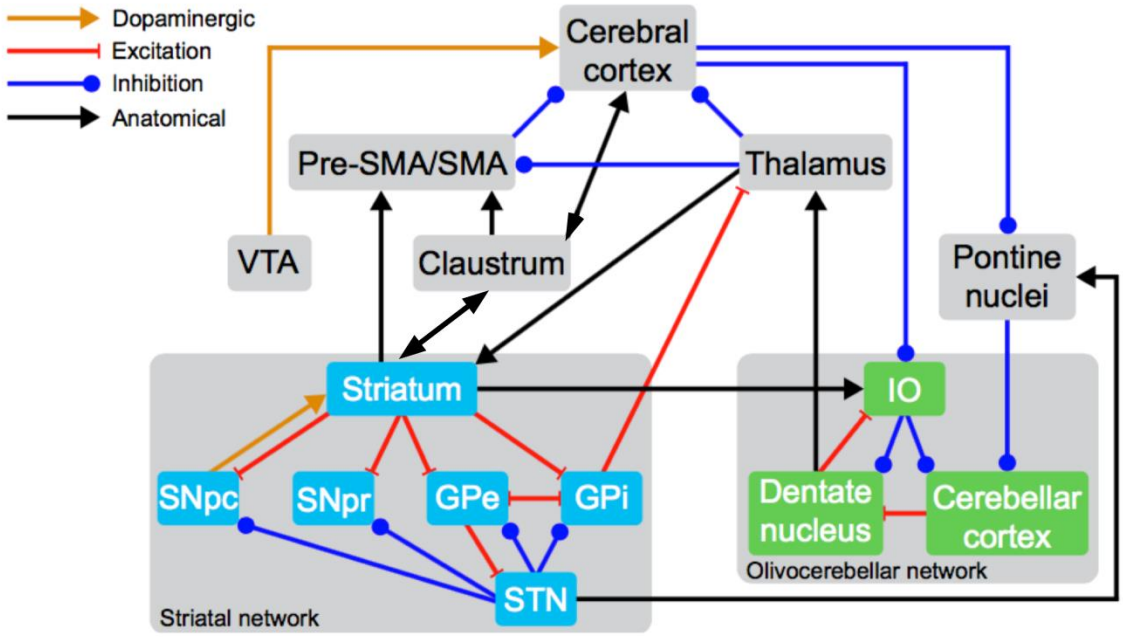

Figure 22: A unified model of interval timing. The striatal network (blue) and the olivocerebellar network (green) are connected to each other via multiple loops, and with the thalamus, pre-SMA/SMA, and the cerebral cortex. Separate bi-directional circuits connect the claustrum to the cortex and the striatum. Dopaminergic pathways are shown in orange, inhibitory projections in blue, excitatory projections in red, and known anatomical connections in solid lines, respectively. Abbreviations: GPe, globus pallidus external; GPi, globus pallidus internal; IO, inferior olive; SMA, supplementary motor area; SNpc, substantia nigra pars compacta; SNpr, substantia nigra pars reticulate; STN, subthalamic nucleus; VTA, ventral tegmental area. Adapted from (Allman, Teki, et al., 2014; Nyberg et al., 2010; Teki et al., 2011a).

Importantly, (Darvas & Palmiter, 2009) showed that restoring dopamine to the dorsolateral striatum using gene therapy in dopamine-deficient mice was sufficient to restore temporal processing and spatial memory. (Palmiter, 2011) subsequently argued that dopamine depletion to striatal median spiny neurons produced unconsciousness in mice and proposed dopamine signaling as a neural correlate of consciousness, thereby setting the stage for the consideration of interval timing as an integral component of consciousness.

4.4 Claustrum and consciousness

Crick and Koch described how the claustrum might play a role in integrating separate sensations into the unitary percepts that we experience as consciousness (F. C. Crick & Koch, 2005). Smythies and colleagues (Smythies, 2014; Smythies et al., 2012; J. Smythies, L. Edelstein, & V. Ramachandran, 2014a; Smythies et al.) subsequently presented a more detailed hypothesis about how such temporal integration might occur based on higher-order temporal synchronization and the neuroanatomy of the claustrum. The claustrum is broadly divided into 3 sub-regions, the anterior-dorsal region connected with somatosensory and motor cortices, a posterior dorsal region connected with the visual cortex, and a ventral area connected to the auditory cortex (Baizer, Sherwood, Noonan, & Hof, 2014; Mathur, 2014; Milardi et al., 2015a; Reser et al., 2014; Smith & Alloway, 2014; Torgerson, Irimia, Goh, & Van Horn, 2015; Torgerson & Van Horn, 2014). The claustrum has reciprocally distributed projections to virtually all regions of the cortex (e.g., frontal, premotor, ventral anterior cingulate, ventral temporal, visual,

motor, somatosensory, olfactory, and entorhinal cortex), as well as sub-cortical structures (e.g., caudate nucleus, putamen, globus pallidus, and lateral amygdala) that are illustrated in Figure 23. These extensive bilateral and interclaustral connections support the hypothesis that the claustrum serves as a ‘synchrony detector’, thereby coordinating information sharing and binding throughout the brain (F. C. Crick & Koch, 2005; Smythies et al., 2012).

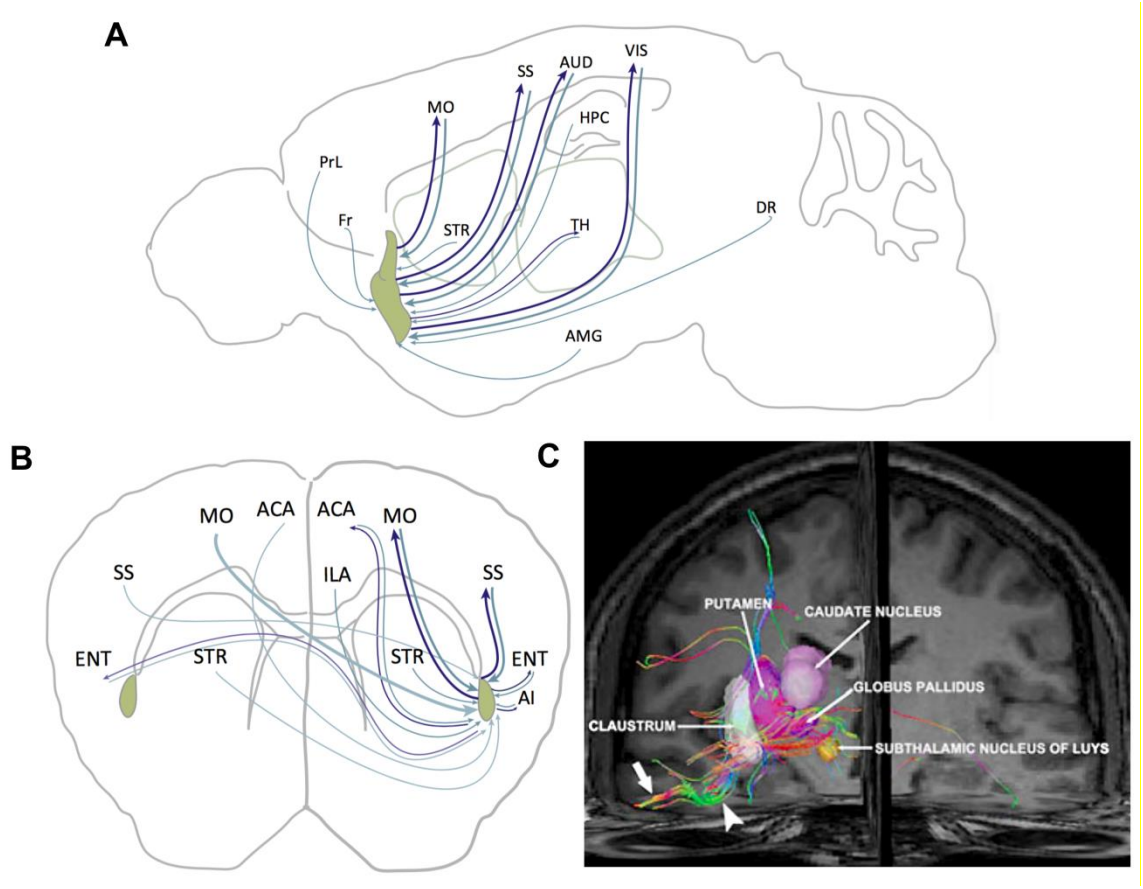

Figure 23: Input–output connectivity of the claustrum. The architecture of the input–output connectivity of the claustrum is charted in sagittal (A) and coronal (B) sections of the rodent brain. The primary inputs to the claustrum are from the cortical modalities, which display symmetrical reciprocal connections. Additional inputs come from the prefrontal cortex as well as subcortical inputs from the striatum, thalamus, amygdala, and dorsal raphe. Abbreviations: PrL, prelimbic cortex; ACA, anterior cingulate area; ILA, infralimbic area; MO, motor cortex; SS, somatosensory cortex; ENT, entorhinal area; AI, agranular insular area; PIR, piriform area; PrL, prelimbic area; Fr, frontal cortex; AUD, auditory cortex; VIS, visual cortex; STR, striatum; TH, thalamus; AMG, amygdala; HPC, hippocampus; DR, dorsal raphe. Coronal (C) section of the human brain showing the cortico-claustral medial pathway spreading between claustrum and basal ganglia using constrained spherical deconvolution tractography to map white matter fibers. Phylogenetic differences in the organization of the sensory systems of different species makes it difficult to identify homologous areas, consequently these illustrations should be taken as a general outline. Adapted from (Goll, Atlan, & Citri, 2015a; Milardi et al., 2015b).

White et al. (2016) have recently reported unanticipated findings relating to the anatomy of connections between the claustrum and the cortex. These include the observation that the projections from non-cingulate cortex to the claustrum are discrete, sparse and mainly directed to the contralateral claustrum while projections from the claustrum to the non-cingulate cortex are discrete, sparse and directed to the ipsolateral cortex. In contrast, the cingulate cortex projects mainly to the contralateral claustrum and the claustrum projects to the ipsolateral cortex as above. The connections between the claustrum and the cingulate, however, are both diffuse and massive with discrete regions in the cingulate cortex projecting to most of the claustrum and vice versa. These anatomical connections suggest that the main output of the claustrum to the motor-control system doesn't go via the sparse direct route, but via the dense route with a relay in the cingulate cortex. This allows the claustrum to play a modulatory role in all the many functions of the cingulate cortex besides controlling motor output and behavior via the premotor cortex. These findings also require an extension of the proposed functions of the claustrum as outlined by Smythies and colleagues (Smythies, 2016).

Although other brain areas have extensive interconnections (e.g., amydala, parietal cortex, thalamus), one way in which the claustrum is distinctive is in the proportion of claustral-cortical neurons that use synaptic zinc. Traditionally, Zn+ neurons have been associated with hippocampal mossy fibers and the generation of synchronized oscillations associated with activity-dependent neuroplasticity. The relatively dense zinc-positive (Zn+) terminations in the claustrum suggest the ability to coordinate multisensory processes more effectively given that synaptically released zinc is thought

to control a 'window' of postsynaptic excitability without altering firing rates (Pochwat, Nowak, & Szewczyk, 2015; Rockland, 2014).

Cortico-claustral-cortico circuits provide for strong feed forward inhibitory (FFI) processes. An FFI is composed of a group of pre-synaptic neurons that directly excite both glutamaterigic excitatory and GABAergic inhibitory interneurons and provide greater synaptic input to the latter (Pochwat et al., 2015). The post-synaptic neurons are interconnected and circuits that lack inhibition simply relay pre-synaptic activity to post-synaptic neurons. In contrast, post-synaptic neurons in an FFI are highly sensitive to the relative timing of action potentials, and this allows for the modulation of neural synchrony as transmitted by the pre-synaptic neurons (Smythies et al., 2014a). Neuromodulators and feedback connections may modulate the temporal sensitivity of such circuits and gate the propagation of synchrony into other layers as well as sub-cortical and cortical areas (Smythies, 2014). The prevalence of strong FFI circuits throughout the brain suggests that synchrony codes in conjunction with time-sensitive cortico-thalamic-basal ganglia (CTBG) circuits are the basis for the temporal integration required for consciousness. In this manner, the claustrum is able to support the full continuum of consciousness through the coordination of CTBG timing circuits in conjunction with cortical-striatal-hippocampal-insular networks, thereby creating a timing-based conscious experience (Merchant & Yarrow, 2016; B. Yin & Meck, 2014a).

This hypothesis also suggests that the claustrum plays an important executive function. Our proposal is that decision-making is mediated by select assemblies of neurons, with synchronized oscillations at different gamma frequencies, that carry

integrated sensory information modulated by saliency (reinforcing) mechanisms. These assemblies compete on a winner-take-all basis for access to the output from the claustrum to the prefrontal and premotor cortices. In this way the winner directs the voluntary decision-based behavior of the subject. Exact timing of these events plays a crucial role in the system.

Goll, Atlan, & Citri (2015b) have recently proposed a hypothesis that the claustrum is closely involved in selective attention. They hypothesize that a widespread top-down input from the prefrontal cortex to the claustrum competitively modulates the output from the claustrum to various cortical localities. This allows the claustrum initially to process many different sensory objects simultaneously, and then to allow just one of these at any moment to constitute the center of attention with the inhibition of its competitors. The claustrum is further subject to down-up modulation by unexpected stimuli from sensory cortices that can over-ride the selective attention strategy. The claustrum also has a projection to the motor cortex including the frontal eye fields that promote motor movements, such as eye and neck movements, which modulate the focus of attention and has been likened to a mechanism for moving the ‘spotlight’ of attention.

Some recent evidence has cast doubt on the role of the claustrum in consciousness (Chau et al., 2015). Combat veterans with penetrating traumatic brain injuries were studied in terms of the effects of claustrum lesions and loss of consciousness on long-term cognitive functions. The extent of claustrum damage was associated with the *duration*, but not the *frequency*, of loss of consciousness. This could be interpreted as indicating that the claustrum plays an important role in regaining consciousness, but not

in maintaining cognitive function. In contrast, other researchers have reported that selective bilateral lesions of the claustrum and external capsule resulting from herpes simplex encephalitis and Sugihiritake mushroom poisoning leads to severe encephalopathy with disruptions in consciousness, psychotic symptoms and seizures (Milardi et al., 2015a). A specific role for the claustrum in auditory scene analysis as reflected by sensitivity to sensory change has also been identified (Remedios et al., 2014). Cogent to the current hypothesis, Wittmann and colleagues (2004) assessed the effect of size and localization of brain lesions on the perception of the temporal order of two acoustic stimuli. Although a moderate association of lesion size and temporal-order threshold was observed among all brain-lesions patients, a clear temporal discrimination deficit was specifically observed in those patients with damage to the claustrum. Unfortunately, no assessment of consciousness was made in this study; hence correlations between temporal processing and consciousness couldn't be performed. Similar types of impairments in temporal order and spatial reversal learning have been observed in rats following lesions of the anterior claustrum (Grasby & Talk, 2013). Moreover, the impairments in duration discrimination produced by lesions of the dorsal striatum were magnified as a function of the extent of collateral damage to the claustrum (Meck, 2006c).

In support of the role of the claustrum in timing and time perception, a meta-analysis of fMRI studies (Wiener, Turkeltaub, & Coslett, 2010) showed activation of the claustrum during the timing of supra-second durations, particularly in reproduction tasks. Subsequent neuroimaging studies have shown activation of the insula/insular cortex (a

region closely related to the claustrum) in a variety of timing tasks (Pfeuty et al., 2015; van Wassenhove et al., 2011). Moreover, Koubeissi et al. (Koubeissi et al., 2014) recently reported a case study in which the researchers were apparently able to turn consciousness "on and off" by stimulating a small area of the claustrum/insular cortex.

4.5 Conclusions

We endorse the “attention hypothesis” for claustrum function (Goll et al., 2015b), which can readily be combined with the SBF model whereby the claustrum serves an executive function for the selection of the stimuli to be processed within the multiplexing system of interval timing and working memory (Gu et al., 2015). In this manner, the claustrum is able to modulate synchronized oscillations from widely distributed cortical regions in order to determine which patterns of spike coincidence-detection should be processed by cortico-striatal-thalamo-cortical timing circuits – either individually (selective attention) or in parallel (divided attention). The anatomical details and attentional functions of this type of time-sharing system have been previously described (Goll et al., 2015b), but the specific neurophysiological mechanisms remain to be delineated. The basis for this mechanism is suggested by recent evidence indicating the role of competitive synchronized gamma oscillations organized by the Pearson mechanism (Pearson et al., 1982; Smythies et al., 2014a). In addition, we propose that the motor output from the claustrum mediates the selection of all voluntary behaviors as well as the movements modulating the focus of attention (Smythies, 2016). Future experimental work addressing the relation between self and time (Wittmann, 2015)

should be designed to test these predictions regarding duration and temporal order discrimination as well as attentional time-sharing and simultaneous temporal processing (C. V. Buhusi & Meck, 2009a, 2009b; Meck & Macdonald, 2007) using optogenetic and designer receptor exclusively activated by designer drug (DREADD) techniques within the claustrum and CTBG (Farrell, 2011; Milardi et al., 2015a; Narayanan et al., 2012b; J. Smythies et al., 2014b). Such studies should allow for the dissection of beat-based versus interval-based timing (Teki et al., 2011a) within temporal windows defining past, present, and future states of awareness (Nyberg et al., 2010; Poppel, 2009; Sitt, King, Naccache, & Dehaene, 2013) while taking into account the flow of time from temporal sensation to time perception and production in the service of consciousness and the relation between time, self, and the specious present (Craig, 2009; Merchant et al., 2013; Montague, 1904; Stiefel et al., 2014; Wittmann, 2015; B. Yin & Troger, 2011).

5. General Discussion

Although a variety of models have been proposed to account for time perception and timed performance (e.g., Buonomano, 2014; Hass & Durstewitz, 2014; Matell & Meck, 2000; van Rijn et al., 2014b), relatively few of them are based on the known electrophysiological properties of neural networks (e.g., Hardy & Buonomano, 2016; Hass & Durstewitz, 2014). Likewise, there are various examples of neural ramping that are put forward as candidates for a putative timing mechanism (Narayanan, 2016) despite the fact that ramping functions are typically unable to account for the scalar property of interval timing or the continued ability to keep track of time once they've resolved (van Rijn et al., 2011).

On the other hand, various lines of research have claimed that independent brain areas are underlying timing and time perception (e.g., Leon & Shadlen, 2003 (C. V. Buhusi & Meck, 2005a; Leon & Shadlen, 2003; MacDonald et al., 2011; Matell & Meck, 2000, 2004b; Mita, Mushiake, Shima, Matsuzaka, & Tanji, 2009; Teki, Grube, & Griffiths, 2011b; Xu et al., 2014). Unfortunately, few of them have a solid psychophysical background, i.e., these studies typically can't differentiate the neural circuits that generate the "timing" signal versus areas that represent and/or monitor timing signals generated in other areas. Coincidence detection – the integration of simultaneous activation of multiple inputs – currently seems to be the solution for explaining how the brain detects the durations of events in the seconds-to-minutes range using millisecond-scale neural processes (Allman & Meck, 2012).

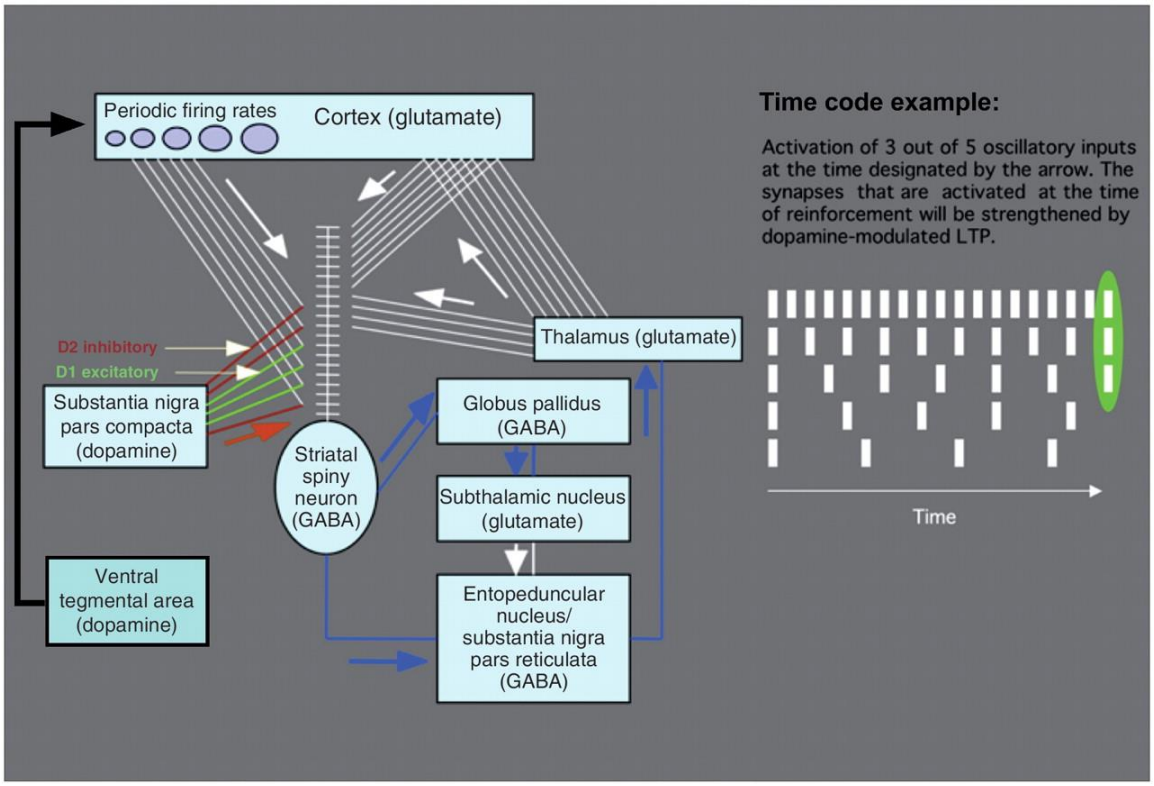

Figure 24. Striatal beat frequency model of interval timing. In this model, intervals are timed via striatal spiny neurons that monitor activation patterns of oscillatory neurons in the cortex. These cortical neurons have patterns of activity that fire with different frequencies and converge onto spiny neurons, as illustrated. At the beginning of an interval, these oscillating neurons are synchronized and the status level of the spiny neurons reset by phasic dopaminergic input from the ventral tegmental area and substantia nigra pars compacta, respectively. The delivery of reinforcement at the target duration produces a pulse of dopamine thereby strengthening the synapses in the striatum that are activated as a result of the beat frequency pattern of these cortical neurons at that specific point in time. In this manner, mechanisms of long-term potentiation (LTP) and long-term depression are used to strengthen and weaken synaptic weights in order to produce a record in memory of the target duration. Later, when the same signal duration is timed again, neostriatal GABAergic spiny neurons compare the current pattern of activation of these cortical neurons with the pattern stored in memory in order to determine when the target duration has been reached. When the clock and memory patterns match as determined by coincidence detection, the spiny neurons fire to indicate that the interval has elapsed. From Allman and Meck 2012).

Independent lines of evidence converge on the conclusion that functional circuits composed of the prefrontal cortex, striatum, and thalamus are instrumental to both time perception and timed performance (Allman & Meck, 2012; Coull et al., 2011a; Coull et al., 2004; Hinton & Meck, 2004; Jin et al., 2009; Meck, 2006b, 2006d; H. H. Yin et al., 2009). Other studies have focused on time-based decision making while recording from or manipulating cortico-striatal circuits (e.g., Eskenazi & Neumaier, 2011; Guitart-Masip et al., 2011; Tanaka et al., 2004). Therefore, this frontal–striatal system is hypothesized to correspond to the functional components of the SBF model (Meck, 1996, 2006a, b; Meck & Benson, 2002; Matell et al., 2003; Matell & 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 (LTP) and long-term depression (LTD) 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. This model succeeds at integrating the psychophysical model of interval timing and neurobiological findings, and is widely used to explain the distortions of time perception and timed performance in psychopathology (Allman & Meck, 2012).

Because of the important role the hippocampus plays in memory research, investigators initially proposed that the hippocampus might coordinate time. 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 and Meck et al. 2013 for reviews). Typically, 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 PI 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 (Balci et al., 2009; Buhusi et al., 2004; Meck et al., 1984, 1987; Olton et al., 1987, 1988). 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 (Melgire et al., 2005; Vidalaki et al., 1999). 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, 2002, 2005; Meck et al., 1984; Melgire et al., 2005; Vidalaki et al., 1999).

Nevertheless, an explanation of the effects of hippocampal damage within the context of a theoretical model of interval timing has been elusive (e.g., Grossberg & Merrill, 1992, 1996; Lewis et al., 2011; Lytton & Lipton, 1999; Matell & Meck, 2004; Onoda et al., 2003; Sakata, 2006). Yin and Troger (2011) proposed three possible roles that the hippocampus may have in the framework of the SBF model (Figure 2): 1) frontal-hippocampal temporal expectancy modulator, 2) striatal MSN firing threshold regulator, and 3) downstream motor execution modulator. These proposed mechanisms await further empirical support, whereas an important avenue should be added: the prefrontal-striatal-hippocampal interactions could be dynamic. The following sections first review the traditional views on the hippocampus and the striatum, and then explore the dynamic interactions among this network.

5.1 Traditional Views on the Hippocampus and the Striatum

5.1.1 Functional organization of the hippocampus

The hippocampal formation consists of the entorhinal cortex (EC), dentate gyrus (DG), cornu ammonis (CA)1–4 subfields, and the subicular complex (Swanson et al, 1978). Information from the organism's environment is received in the EC through extensive input from all cortical sensory association areas. This information then flows to the DG via the perforant path and subsequently to the CA3, the CA1, the subiculum, and then backs to the EC. The major output of the hippocampus is the fimbria-fornix that

connects bidirectionally to the subcortical regions including the lateral septum, nucleus accumbens (NAc), mammillary bodies, anterior thalamus and ventral medial hypothalamus. The other major hippocampal output is to the entorhinal cortex via subiculum and to the cingulate and prefrontal cortices (Swanson & Kohler, 1986).

Interest in studying the hippocampus emerged from the famous case of the patient H.M. (Scoville & Milner, 1957). Since then, it has widely been accepted that the hippocampus is involved in memory acquisition and short-term retrieval (Turner, 1969). Later the phenomena of LTP and LTD were first discovered in the dentate area of the hippocampus (Bliss & Gardner-Medwin, 1973; Bramham & Srebro, 1987), and has long been regarded as plausible cellular mechanisms for learning and memory (Morris, 2003). At the same time, hippocampal "place cells" were discovered (O'Keefe & Conway, 1978), and the hippocampus was been viewed as providing a "cognitive map" (O'Keefe & Nadel, 1979). Another point of view sees the hippocampus as a hesitation/inhibition device (Kimble, 1968) that coordinates "vicarious trial and error" (VTE), a conflict-like behavior in discrimination learning that enables the "micro-choice" among available options (Amsel, 1993; Hu & Amsel, 1995). Related to the role of inhibition, recent reports suggest that the ventral but not dorsal hippocampus play a role in context-specific inhibition (McDonald et al, 2006).

Recognition and episodic memories that have been attributed to the hippocampus clearly demands the ability for pattern separation and pattern completion, which has been intensively studied (e.g., Bakker et al, 2008; Leutgeb et al, 2007; McHugh et al, 2007; Yassa & Stark, 2011). It can be summarized as the follows: the hippocampal CA1 area

unified/linear coding of the general availability of the environment, whereas the CA3 area judges the threshold of pattern separation/completion, i.e. it judges how different the environment is in order to trigger pattern separation; the DG sparse coding, i.e. it has separate neuron populations firing to the details of the environment but every time it fires somewhat differently when entering a new or even old environment. Therefore, the information flow starts from the EC receiving inputs from sensory cortex and sends the information to the DG, and the DG calculates the information in guidance with the CA3 and feeds back to the EC for outputs and for system consolidation. Some other studies have also shown that EC sends inputs to the CA1 as well (Wohrl et al., 2007), and the CA1 also directly sends and receives inputs from other regions, making the circuit more complex – but it is possible that the role of EC-CA1 connection is for quick retrieval after system consolidation by neglecting the details of the environment.

Nevertheless, current debate in the literature regarding the role of the hippocampus in recognition memory involves recollection and familiarity. Recognition memory is said to be recollective if it includes contextual details. Sauvage et al. (2008) and Farovik et al. (2011) provided convergent evidences that recollection and familiarity dissociate by selectively damaging the hippocampus and the amygdala, respectively, whereas Smith et al. (2011) argued that when the strengths of recollection and familiarity are equated and strong in the task the hippocampus equally support the two functions. Memories once formed, regularly go into the cycle of reactivation and reconsolidation (Myers & Davis, 2002). Hippocampal replay of recent experiences occur during both during sleep (Ji & Wilson, 2007; Louie & Wilson, 2001; Skaggs & McNaughton, 1996)

and awake states (Carr et al., 2011; Davidson et al., 2009; Foster & Wilson, 2006), which not only contributes to consolidation and recall of recent experiences (Kali & Dayan, 2004) but also provides predictions for physically available trajectories in the environment (Gupta et al., 2010).

One important anatomical question is the whether the dorsal and ventral parts of the hippocampus play functionally distinct roles (Fanselow & Dong, 2010). It's known that the two parts projects differentially to other brain areas. Ventral hippocampus (VH) connects to the prefrontal cortex, the amygdala and ventral and rostral parts of the NAc shell associated with the regulation of locomotor activity, context-dependent learning and emotional behavior (Pennartz et al., 2011), whereas dorsal hippocampus (DH) connects to the rostral part of the ventral striatum including both core and part of shell, dorsal lateral septum, mammillary bodies, anterior thalamus, ventral medial hypothalamus and anterior cingulated cortex (Fanselow & Dong, 2010). Highly processed information from the sensory cortices entering the hippocampus mainly in its dorsal parts (Moser & Moser, 1995), and hence the DH is thought to be tightly related to memory and cognition (Fanselow & Dong, 2010).

5.1.2 Functional organization of the striatum

The striatum is the main component of the basal ganglia (BG) and comprises of the dorsal striatum and the ventral striatum. The dorsal striatum can be further divided into the dorsolateral striatum (DLS) and dorsalmedial striatum (DMS). The DLS is also called the sensorimotor striatum, as it primarily receives inputs from sensorimotor cortex

and is critically involved in stimulus-response (S-R) habit learning; the DMS is also called the associative striatum and is largely involved in action-outcome (A-O) learning, i.e. goal-directed behavior (Balleine et al., 2007; Yin & Knowlton, 2006). The main component in the ventral striatum is the nucleus accumbens and it can be furthered divided into the core area and the shell area, which mediate various forms of Pavlovian and instrumental learning and consolidation (Hernandez et al., 2002; Pennartz et al., 2011; Voorn et al., 2004). Lesions of the core impair control over the response to conditioned reinforcers, whereas enhancement of this control by psychostimulant drugs depends on the shell (Parkinson et al., 1999). Therefore, the role of the shell is to invigorate certain behavioral responses that are coordinated through the core.

Dopamine system is intimately associated with striatal activity not only because of the well-established importance of mesolimbic dopamine pathway and nigrastriatal dopamine pathway, but also due to the prominent role that dopamine plays in striatal-dependent behavioral signaling (Schultz, 2007), such as decision making, reward-dependent learning and action selection. During reinforcement learning, shifts in phasic dopamine signals from primary rewards to cues that predict the reward are thought to reflect the acquisition of the incentive salience for the conditioned stimuli.

One of the most influential models of how dopamine shapes striatal activity was advanced over 17 years ago by Albin et al. (1985) and is illustrated by Figure 25. The model posits the interaction of the direct pathway and indirect pathway in determining the output of the BG system. Briefly speaking, activation of the direct pathway MSNs lead to inhibition of the internal segment of globus pallidus (GPi) and substantia nigra

pars reticulate (SNpr), which disinhibits the downstream nuclei in the thalamus, superior colliculus, the pedunculopontine nucleus, etc and then feeds back to the cortex; whereas activation of indirect pathway MSNs leads to inhibition of the external segment of the globus pallidus (GPe), which disinhibits the subthalamic nucleus (STN) and the GPi, the STN excites the SNr and thus competes with the output from the direct pathway.

The primary neurons in the striatum are the gama-aminobutryic-acid (GABA) –ergic medial spiny neurons (MSNs). An interesting property regarding MSNs is that they have two distinct states: the inresponsive "down-state" and the responsive "up-state" (Wickens & Wilson, 1998). The "down-state" is maintained by inwardly rectifying potassium channels that hold the membrane potential near the potassium equilibrium potential, far from spike threshold; whereas the "up-state" is triggered by temporally and spatially convergent glutamatergic cortical inputs that overwhelm the potassium current and promotes the closure of potassium channel (Shen et al., 2007). It is during the hundreds of milliseconds lasting of the "high-state" that MSNs fire. On the other hand, if cortical-striatal synapses receive coincidental dopamine and glutamate inputs during conditional learning, long-term potentiation (LTP) will be formed which is thought to be underlying reinforcement memory, including temporal memory. Pharmacological or genetic deletions of dopamine D1 receptors (D1Rs) disrupt reinforcement learning in various behavioral paradigms, suggesting a critical role for D1R-mediated "dopamine stamping" of stimulus-response associations (Lisman & Grace, 2005). D2 receptors (D2Rs) are thought to modulate intrinsic excitability and glutamatergic signaling (Surmeier et al, 2007).

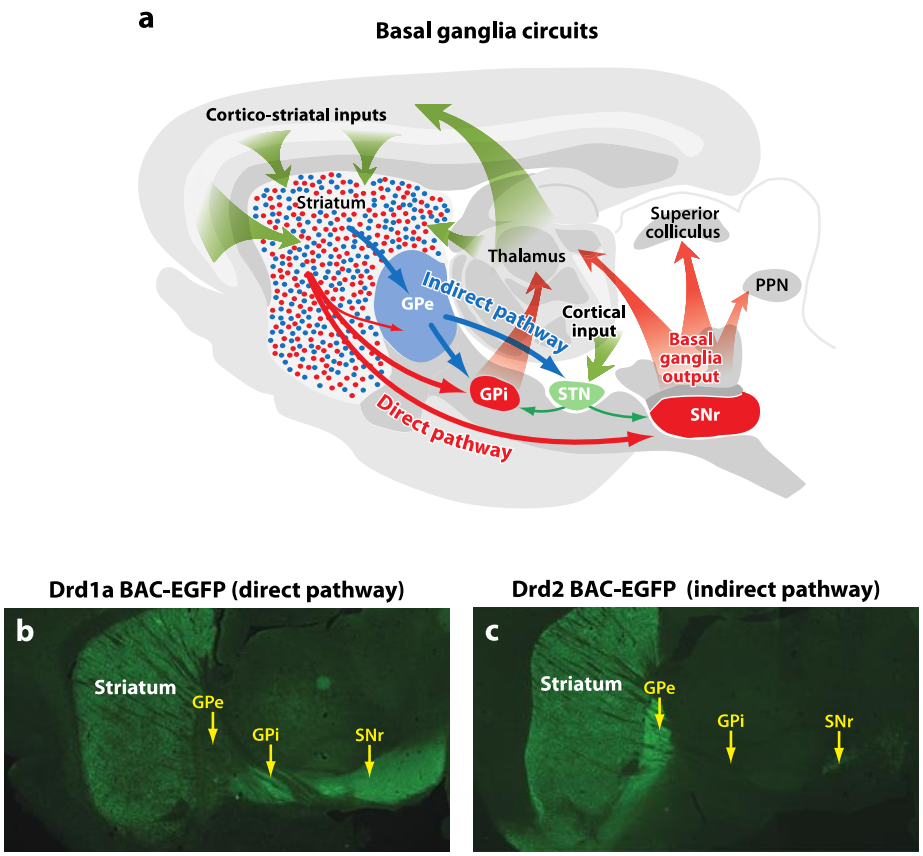

Figure 25. Diagram of select basal ganglia circuits. (a) The striatum receives excitatory corticostriatal and thalamic inputs. Outputs of the basal ganglia arise from the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr), which are directed to the thalamus, superior colliculus, and pendunculopontine nucleus (PPN). The direct pathway originates from Drd1a-expressing spiny projection neurons (SPNs) that project to the GPi and SNr output nuclei. The indirect pathway originates from Drd2-expressing SPNs that project only to the external segment of the globus pallidus (GPe), which together with the subthalamic nucleus (STN) contain transsynaptic circuits connecting to the basal output nuclei. The direct and indirect pathways provide opponent regulation of the basal ganglia output interface. (b) Fluorescent imaging of a brain section from a mouse expressing enhanced green fluorescent protein (eGFP) under regulation of the Drd1a promoter shows Drd1a-expressing SPNs in the striatum that project axons through the GPe, which terminate in the GPi and GPe. (c) Fluorescent imaging of a Drd2-eGFP mouse shows that labeled SPNs provide axonal projections that terminate in the GPe but do not extend to the GPi or SNr. From Gerfen and Surmeier (2011).

MSNs consists 95% of the striatal neurons and various types of interneurons consists the remaining 5% (Calabresi et al., 2007). Three primary interneurons include the cholinergic tonically active neurons (TANs), the also GABAergic fask-spiking interneurons (FSIs) and the low-threshold spike neurons (LTS). Indeed, these interneurons participate in the feedforward and feedback mechanisms of dopamine-dependent corticostriatal LTD. For example, dopamine influences the modulatory action exerted by cholinergic interneurons, nitrogen-oxide releasing, NOS-positive interneurons and the endogenous cannabinoids (ECBs) system.

5.1.3 Functional prefrontal-striatal-hippocampal circuits

The prefrontal cortex, the striatum and the hippocampus constitute the circuits that underlie most fundamental cognitive, motivational and sensorimotor functions in everyday life (Pennartz et al., 2009). Prefrontal efferent primarily connect to the dorsal medial striatum (Yin & Knolton, 2007) as well as the nucleus accumbens (Pennartz, 2007), regulating motivation-based reinforcement learning and goal-directed behavior. With prolonged experiences, paradigms shifts occur that drive the behavior from the DMS-based action-outcome form into the DLS-based stimulus-response form (Graybiel, 2008).

The prefrontal-hippocampal connections are mainly studied in terms of working memory function and systematic memory consolidation. The posterior DH-PFC pathway is essential for working memory on the order of seconds in rats (Izaki et al., 2008),

whereas VH projecting to both the mPFC and amygdala via the ventral subiculum and ventral CA1 (Jay & Witter 1991) may play a role in contextual modulation of emotional responses. Damage to the hippocampal formation results in a profound temporally graded retrograde amnesia, implying that it is necessary for memory acquisition but not its long-term storage (Stickgold, 2005). It is therefore thought that memories are transferred from the hippocampus to the cortex for long-term storage in a process called systems consolidation (Weible et al., 2012). In addition, divided Attention may be related to hippocampal activity, and the hippocampal-ACC connection may be important because ACC is activated during focused problem solving (Allman et al., 2001). Indeed, the homogenous counterpart of ACC in the primate, the orbitofrontal cortex (OFC), is important in the assignment-of-credit task as a recent study shows that lesions of OFC impairs contingency learning under more complex situations without impairing the simple association of a cue with a reward (Walton et al., 2010).

The interactions between the hippocampus and the striatum have been much focused on the competition and cooperation of two distinct memory systems (Ghiglieri et al., 2011; Poldrack & Packard, 2003). In particular, it was thought that the hippocampus cooperates with DMS in goal-directed spatial learning; while it competes with DLS in S-R learning (Yin & Knowlton, 2006). A classical example is the T-maze task in which animals were trained to turn to one of the two directions at intersection point in order to receive food reward (Packard, 1999). When the animals learned the task, the T-maze was transversed so that the place dependent direction is opposite to response dependent direction. It was found that hippocampal lesioned animal preferentially use the response

strategy whereas the DLS-lesioned animal preferentially use the place strategy; DMS-lesioned animal displayed reluctance to turn to one direction in order to accomplish the task and get the reward. Although knowledge about the action-outcome contingency can be regarded as sort of declarative, few evidences have suggested a role for the hippocampus to be directly involved in instrumental learning: Corbit and Balleine (2000) showed that electrolytic lesions of the dorsal hippocampus impairs contingency degradation but not outcome devaluation, two forms of tests to evaluate the boundaries between goal-directed learning and S-R habit formation; whereas Corbit et al. (2002) showed that damages to the entorhinal efferents rather than dorsal hippocampus itself account for the effect on DMS-based goal-directed behavior. Moustafa and Gluck (2012) suggest that the hippocampus is mainly involved in stimulus-stimulus representational learning, the dorsolateral striatum is for S-R learning and the prefrontal cortex is for stimulus selection during learning about multidimensional stimuli. Early learning may preferentially recruit one system (S-S or S-R), and with extended training the other system takes over control of the behaviors (Packard & McGaugh, 1996). In the situation that the organism is forced to make use of one system by excluding the other, a competition between the two systems emerge (Pennartz et al., 2011). In the situation that both cognitive/flexible and automatic/habit-like choices are available, a role of the amygdala seems to emerge, suggesting that the emotional state could influence the utilization of a particular memory system (Packard, 2009). Another “hotspot” that emerges these three brain regions is the nucleus accumbens. Indeed, The NAc is well known to act as a limbic–motor interface, where learned associations of motivational

significance are converted into goal-directed behavior (Mogenson et al., 1980). Grace et al. (2007) described a way that the PFC afferent and hippocampal afferent interact with each other with doparminergic modulation to shift the balance of the information flow in favor of either inputs.

5.2 Double Summation (Sensorimotor Integration) Model of Interval Timing

5.2.1 Challenges: dynamical roles of hippocampus in frontal-striatal based timing

Empirical data on effects of dorsal hippocampal lesions described above have posted significant challenges to the traditional view of frontal-striatal based timing. The effect of dorsal hippocampal lesions on interval timing in mice has been investigated using a variant of the peak-interval procedure, the bi-peak procedure (Yin & Meck, 2014). In this procedure, the mouse is trained to simultaneously time two durations (15s and 45s) for food rewards . Well-trained mice displayed two Gaussian-shape functions that peak at 15s and 45s, respectively. Interestingly, both pre-training and post-training lesions produces double leftward shifts in the peak times (Yin & Meck, 2014), confirming previous investigations (Balci et al., 2009) suggesting a possible for the dorsal hippocampus in the frontal-striatal-based interval timing mechanisms. Nevertheless, variability in individuals is also observed, and the leftward shift generally display a memory pattern but the leftward shifts gradually normalized with training and “aging” at different speeds (B. Yin & Meck, 2014b), with some mice this effect could last for a year.

This heterogeneity is not due to the differential recovery of the lesioned area, however, because prolonged training experience “locks” the effects of dorsal hippocampal lesions similar to the reduced clock speed effects of cocaine challenge (Cheng et al., 2007), but the “clock-resetting” effect known to be produced by hippocampal lesions (Meck et al., 1987) still persists. In addition, in the absence of such left-shift effect, dorsal hippocampal lesioned mice still displayed higher foodcup entries enhanced locomotor activity in a novel environment without increases in active lever pressing in the peak interval procedure. They also displayed reduced sensitivity to prefeeding and enhanced reversal learning in a variant of the peak interval procedure (B. Yin & Meck, 2014a, 2014b).

In addition, our studies also show that mice with cytotoxic lesions of the dorsal hippocampus underestimated 15-s and 45-s target durations in a bi-peak procedure as evidenced by proportional leftward shifts of the peak functions that emerged during training as a result of decreases in both ‘Start’ and ‘Stop’ times. In contrast, mice with lesions of the ventral hippocampus displayed rightward shifts that were immediately present and were largely limited to increases in the ‘Stop’ time for the 45-s target duration. Moreover, the effects of the dorsal hippocampal lesions were congruent with the scalar property of interval timing in that the 15-s and 45-s functions superimposed when plotted on a relative time scale, whereas the effects of the ventral hippocampal lesions violated the scalar property. Mice with dorsal hippocampal lesions also showed enhanced reversal learning in comparison to control and ventral hippocampal lesioned mice. Taken together, these results suggest a balance between hippocampal-striatal

interactions for interval timing and demonstrate possible functional dissociations along the septotemporal axis of the hippocampus in terms of motivation, timed response thresholds, and encoding in temporal memory.

5.2.2 Dopamine system regulation: Changes in striatal dopamine as potential mechanisms

What mechanism can explain these dynamics observed? Traditional views on the hippocampus, striatum and their interactions reviewed above can only provide controversial explanations to the data. However, based on the idea that it is ultimately the altered neurochemical interactions within neural circuits that underlie "abnormal" behavior, and the observation of the central role of dopamine system in regulating these behaviors including interval timing, one could reason that these results could be explained by dynamic changes in dopamine/glutamate system regulation.

Indeed, Grace (1991) proposed a dual mechanism for dopamine system regulation: transient or phasic dopamine caused by dopamine neuron firing and quickly cleared up by reuptake (Floresco et al., 2003; Ford et al., 2010), and sustained "background" tonic release of dopamine regulated by presynaptic prefrontal cortical afferents which is glutamate-receptor-dependent (Borland and Micahael, 2004; Cheramy et al., 1986; Desce et al., 1992; Krebs et al., 1991; Verma & Moghaddam, 1998; Wang, 1991) and less influenced by reuptake (Floresco et al., 2003). Phasic dopamine release signals behaviorally relevant stimulus, whereas tonic dopamine release regulates the density of phasic dopamine release through its regulation of extracellular dopamine levels. Importantly, tonic dopamine release sets the background of dopamine receptor

stimulation and (both autoreceptor and postsynaptic) regulates dopamine receptor sensitivity and thus the responsivity of dopamine system. Over time, dopamine receptor sensitivity would be either up-regulated or down-regulated through homeostatic mechanisms (Hymen, 2005) and thus regulate subsequent phasic dopamine responses – a similar scenario is observed in NMDAR-dependent glutamatergic transmission (Slutsky et al., 2010). On the other hand, in the central nervous system, baseline level dopamine D1 receptors (D1Rs) are predominantly in the low-affinity state while dopamine D2 receptors (D2Rs) are predominately in the high-affinity state (Richfield et al., 1989). As a consequence, phasic dopamine release predominantly increases D1Rs occupancy and tonic dopamine release predominantly increases D2Rs occupancy (Dreyer et al., 2010). Moreover, a much larger proportion of D1Rs would be expected to enter the high-affinity state than D2Rs as a consequence of chronic suppression of tonic dopamine release, thus increasing the phasic-to-tonic-evoked DA signal ratio, which may contribute to the "sharper" peak function observed, i.e., enhanced temporal sensitivity. Importantly, in recent years evidence has shown that the D1Rs are predominately located on striatonigral direct pathway neurons, whereas D2Rs are predominately located on striatopallidal indirect pathway neurons (see Figure 24; Ade et al., 2008; Bertran-Gonzalez et al., 2008; Cepeda et al., 2008; Day et al., 2006; Durieux et al., 2012; Gerfen et al., 2011; Gertler et al., 2008; Kravitz et al., 2010; Kreitzer & Malenka, 2007, 2008; Shen et al., 2008; cf. Hersch et al., 1995; Smith et al., 2004). In D1R MSNs, activation of D1Rs with NMDARs evokes LTP, whereas activation of mGluR5 receptors and CaV1.3 channels evokes LTD; in D2R MSNs, the competition between D2Rs and A2A adenosine

receptors (A2ARs) regulates calcium influx: activation of D2Rs inhibits NMDA-dependent calcium influx, whereas activation of A2ARs enhances this activity (e.g., Higley & Sabatini, 2010; Shen et al., 2008). Therefore, both types of MSNs can display bidirectional Hebbian spike-timing-dependent plasticity (Shen et al., 2008). Moreover, the D1R MSNs and D2R MSNs display different temporal kinetics, with D2R MSNs more excitable than D1R MSNs, whereas D1R MSNs exhibit more prolonged plateau potentials and spike trains (Flores-Barrera et al., 2011; Gertler et al., 2008); as a result, the relationship between spiking frequency and injected current was shifted leftward in D2 MSNs compared with D1 MSNs. This is mainly due to the morphological differences between the two types of MSNs (Gertler et al., 2008): D1R MSNs have two more primary dendrites than D2Rs and thus receive much more glutamatergic inputs, but also contain much more hyperpolarization-inducing potassium channels (Kir2). In addition, D1R exclusively express substance P, and dynorphin, whereas D2R MSNs exclusively express encephalin (Gerfen & Surmeier, 2011). MSNs also differ in their activity level during cortically driven up-states in anesthetized rodents (Wickens & Wilson, 1998).

5.2.3 Proposed modifications/refinements of the SBF model – the Double Summation component

Because of the morphological and electrophysiological dichotomy observed in striatal MSNs reviewed above, it is intriguing to propose a modified version of the SBF model that can adopt these phenomena. In this modified SBF model (Figure 26a), the to-be-timed duration is still encoded by D1R-mediated “dopamine-stamped” coincidental cortical inputs into dorsal striatal synapses, and decoded by matching pattern of cortical

inputs. The difference is that the expression of the timing signal, i.e., the decision threshold, is now determined by the summation of D1R-direct-pathway MSNs and D2R-indirect-pathway MSNs, rather than the summation of single MSN outputs. The summation of two independent pathways is likely achieved at the level of substantia nigra pars reticulata (SNpr), as this nuclei is the major "station" that two BG pathways converge, although the internal segment of the globus pallidus (GPi) can also be a potential "second-level integrator". Because the D2R MSNs are more excitable than D1R MSNs, they tend to fire earlier, but with smaller amplitudes in response to synchronized cortical inputs, potentiating the indirect pathway. As time progresses, the D1R MSNs are activated by a matching pattern of cortical inputs with large amplitudes, potentiating the direct pathway. The net effects of D1R MSNs and D2R MSNs at BG output is computed by either SNpr or GPi, and if the differences surpasses a threshold, the BG output is initiated, providing a "Go" signal that can be regarded as the "Start" time in timing tasks such as the peak-interval procedure (e.g., MacDonald et al., 2012). The determination of the "Stop" times is less clear in this model. However, one could speculate that thalamic gaiting of glutamatergic signaling may also play a role (e.g., Ding et al., 2010). Briefly speaking, thalamic bursts in response to salient stimulus (e.g., reward or reward omission) efficiently drive cholinergic interneurons and generate a burst-pause firing pattern, that transiently release acetylcholine that can suppress release probability at corticostriatal synapses formed on both D1R and D2R MSNs. In addition, activation of nAChRs on FSIs can also lead to a transient postsynaptic inhibition of both types of MSNs. A pause in the cholinergic activity generated by recurrent collateral or

neighboring interneuron activation of dopaminergic terminals provide a time window in which D2R MSNs are strongly biased toward a second repertoire of cortical activations, the result of which is to enhance the indirect pathway outputs in order to pass the threshold that determines the “Stop” time. Indeed, during steady-state performance, the striatal neurons are known to fire in a pattern that “chunks” action repertoires (e.g., Barnes et al., 2005; Graybiel, 1998). Because the regulation of “Stop” times in this way is determined by the responsivity of D2R as well as D1R MSNs to cortical inputs, manipulations on dopaminergic or cholinergic systems could, in theory, either modulate the “Stop” times in accordance with, or independent of the regulation of the “Start” times, depending on the nature of the manipulations on the temporal dynamics of dopaminergic and cholinergic systems. It should be noted that although acquisition of the “Stop” times seems to be dependent on the normal functioning of the VS (MacDonald et al., 2012), the steady-state performance of the “Stop” times seems to be independent of the VS (Meck, 2006). Variations of “Start” times and “Stop” times in the “double-summation” version of the SBF model come from three levels: the variations in coincidental cortical inputs, variations in the states of D2R MSNs regulated by extracellular dopamine fluctuationsand complex feedback and feedforward striatal microcircuits, and 3) the variations in the states of the “second-level integrator” regulated by modulations on the GABAergic efferent or the glutamatergic afferent (e.g., Betarbet & Greenamyre, 2004; Ibanez-Sandoval et al., 2006; Lee et al., 2011; Schmitt et al., 1999).

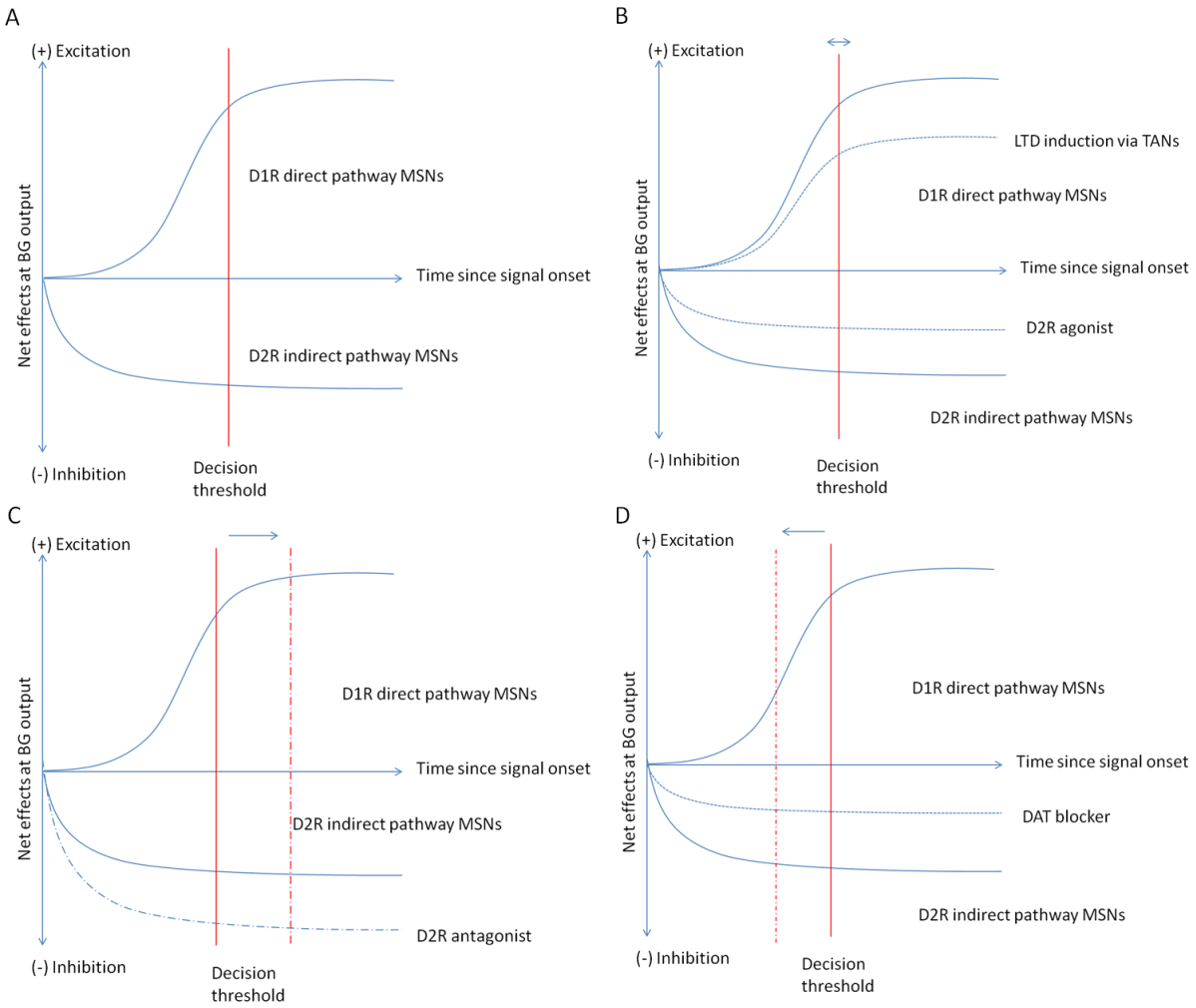

Figure 26. The Double Summation component of the SBF model. (A) the baseline situation. Coincidental cortical inputs activate both D1R direct pathway MSNs and D2R indirect pathway MSNs. Because the D2R MSNs are more excitable, they can be activated by less similar pattern of activation or simply by extracellular dopamine. D1R MSNs depend more on matching pattern of coincidental glutamatergic inputs. Therefore, D2R MSNs have smaller time constants than D1R MSNs. The net effects at basal ganglia outputs are summed for the direct pathway and the indirect way, and the decision threshold corresponds to the "Start" time. (B) D2R agonist suppresses D2R MSNs but also suppresses D1R MSNs via reduction of cholinergic tone, resulted in relatively unchanged "Start" time. (C) D2R antagonist disinhibit D2R MSNs, therefore produces a rightward shift of "Start" time. The extend of shift should be correlated to the D2R affinity of the drug used. Chronic blockade of D2Rs would lead to homeostatic upregulation of D2Rs, normalizing the effect. (D) DAT blocker (e.g. cocaine and methamphetamine) increases extracellular dopamine, and thus activates D2Rs that suppresses D2R MSNs without causing LTD at D1R MSNs, resulting in a leftward shift of "Start" time. Chronic elevation of extracellular dopamine leads to downregulation of D2Rs, normalizing the effect.

Now that a “double-summation” version of the SBF model has been outlined, it would be beneficial to test whether the SBF model in this form can account for previously observed effects of pharmacological modulations on interval timing (Meck, 1996). Remarkably, this “double-summation” model can clearly explain the effects of D2R agonists (e.g., quinpirole, see Gu et al., 2011), D2R antagonists (e.g., haloperidol – Meck, 1983), DAT blockers (e.g., cocaine – Matell et al., 2004) and DA release enhancers (e.g., methamphetamine - Meck et al., 2012) on interval timing without major difficulties (Fig. 15B-D). Interestingly, the atypical DA receptor blocker clozapine has been reported to have differential effects from haloperidol, i.e., it produces a leftward shift of peak time rather than a rightward shift (Buhusi & Meck, 2007; MacDonald & Meck, 2005). Clozapine decreases phasic DA release (White & Wang, 1983) while producing an increase in tonic extracellular DA levels (Burki et al., 1974; Meltzer, 1989), which according to the “double-summation” version of the SBF model would activate D2Rs which suppresses the D2R MSNs, leading to a leftward shift of peak time.

In addition to explaining the classic “clock pattern”, the classic “memory pattern” can also be accounted for with this modified model. It’s known that basal muscarinic tone suppresses the excitability of D2R MSNs (Shen et al., 2007), therefore, the pattern of cortical inputs is “stamped” earlier than it should be, resulting in a change in memory constant, $K^* < 1$ (Meck, 1983, 1996). This effect is relatively small and therefore gradually emerges as a function of multiple sessions, at which point it stabilizes and is maintained by continued drug administrations.

Balci et al. (2010) reported that in the DAT knockdown (KD) mice, the “Start” times were shifted earlier, but the “Stop” times were relatively unaffected, leading to a moderate increase in “Spread”, but relatively unchanged peak times despite a relatively large increase in peak rate. The DAT knockdown mice exhibit increased extracellular dopamine levels, therefore chronically activated D2R over D1R. This would be expected to lead to an earlier “Start” time according to the model, but does not change the “Stop” time possibly due to activation of D2Rs on cholinergic interneurons, and thus impeding the thalamic gating effects. In addition, higher tonic dopamine may also mediate enhanced motivation to work for food, resulting in increased peak rates. On the other hand, chronic increases of extracellular DA levels may lead to homeostatic down-regulation of D2R sensitivity, which may produce a reversing “memory effect” that balancing out the “clock effect” that higher [DA]o produces. This balance makes the peak time relatively unchanged in the DAT KD mice. Similarly, in DAT KO (-/-) mice, overwhelming of extracellular dopamine would not only shunt D2R MSNs, but also possibly reduces D2R sensitivity, which renders the mice unable to time (Meck et al., 2012). DAT KO (+/-) mice are able to time, but is disruptive under high-dose methamphetamine.

5.2.4 Explaining the dynamic effects of dorsal hippocampal lesions in interval timing

Based on the “double-summation” version of the SBF model, one could speculate that the dynamic effects of dorsal hippocampal lesions on interval timing and related behavioral paradigms (B. Yin & Meck, 2014b) are due to modulation of striatal tonic DA

release and/or D2R sensitivity. For example, the decreased tonic DA could activate the D2R MSNs via reduced activation of D2Rs, and thus potentiate the indirect pathway, leading to a leftward shift of “Start” time. Increased phasic-to-tonic-evoked DS signal could also account for the “sharper” timing functions typically observed. However, with training and “aging” going on, homeostatic enhancement of D2R sensitivity can produce a rightward “memory effect” that balance out the leftward “clock effect” produced by decreased tonic DA. Consequently, heterogeneity observed in the timing behavior of mice may be due to genetic variations of baseline D2R sensitivity and/or extracellular DA levels.

In addition, it is also reasonable to speculate that with extensive training, the glutamate-dopamine interactions “lock” the D2R MSN responsively to cortical inputs (e.g., Cheng et al., 2007), thus making the timing mechanism relatively insensitive to dorsal hippocampal lesions. However, effects originated from reduction of tonic DA release and enhancement of D2R sensitivity can still be observed. For example, the “clock-resetting” phenomenon can possibly be explained by a D2R-mediated “task switching” (Stelzel et al., 2010). It is also possible to speculate that active action for a defined goal (e.g. lever pressing for a food pellet) is mediated by tonic DA release, as selective knockout of NMDAR-dependent phasic DA release does not affect motivation to work for food after the acquisition is formed (Zweifer et al., 2009), whereas spontaneous exploration in the novel environment (e.g., locomotor activity in an open-field activity arena) is mediated by a high ratio of phasic-to-tonic DA release and/or enhanced D2R sensitivity, as selective ablation of D2R MSNs in the DMS dramatically

enhances such activity (Durieux et al., 2012). The data that dorsal hippocampal lesions increases locomotion in an activity box, but not baseline lever pressing inevitably suggest that DH lesions somehow lead to decreases of tonic DA levels, but not phasic DA levels, as well as enhancement of D2R sensitivity. Indeed, the D2R agonist quinpirole has been reported to increase rhythmic food-cup checking behavior (Gu et al., 2011); therefore, enhancement of D2R sensitivity could also explain the similar phenomenon in dorsal hippocampal lesioned mice. On the other hand, Zhang et al. (2009) found that the ratio of phasic-to-tonic-evoked DA was generally higher in the NAc compared with dorsolateral striatum (DLS). They also found that blockade of DAT and D2Rs enhanced the DA tone, whereas blockade of nicotinic acetylcholine receptors (nAChRs) containing the β2 subunit suppressed DA tone, the latter makes the DA dynamics more similar between the DLS and NAc, thus increasing the DLS gain over NAc. This may explain the insensitivity of DH mice to prefeeding, a form of habit-like response that is preferentially mediated by DLS. Finally, reversal learning has been suggested to be mediated by prefrontal-striatal interactions (Pasupathy & Miller, 2005) and striatal DA tone as well as D2R sensitivity also play a critical role (Cools et al., 2001, 2009), which could explain the enhancement of such behavior in DH-lesioned mice (B. Yin & Meck, 2014a).

How do dorsal hippocampal lesions lead to suppression of tonic DA release? One potential pathway is via modulation of midbrain DA neurons. Luo et al. (2011) discovered that dorsal CA3 predominately connects to the ventral tegmental area (VTA) via caudodosal lateral septum (cd-LS). A population of GABAergic neurons project to VTA GABA neurons and stimulation of dorsal hippocampal CA3 glutamatergic

pyramidal neurons excites these GABAergic cd-LS neurons, which inhibits the local GABAergic neurons within VTA, thus disinhibits the dopaminergic neurons. This study also found that neither ventral CA3 nor ventral subiculum (vSub) connect to VTA via cd-LS, and microjecting GABA into vSub does not block the effect of dorsal CA3 theta stimulation on excitation of VTA DA neurons and inhibition of VTA GABAergic neurons. Therefore, this pathway is independent of the hippocampal-VTA pathway via vSub (Lisman & Grace, 2005; Lodge & Grace, 2006; Grace, 2012). The vSub connects to VTA via nucleus accumbens (NAc) and ventral pallidum (VP) through similar mechanism of disinhibition. The subiculum activation is dependent on the context. When the vSub is activated in a novel context, it activates the NAc which inhibits VP GABAergic neurons. Release of tonic inhibition from VP leads to enhanced phasic firing of VTA DA neurons elicited by concurrent glutamertergic inputs from pedunculopontine tegmental nucleus (PPTg) associated with a salient stimulus in the context. Importantly, only those DA neurons fire spontaneously (i.e., released from VP tonic inhibition) can respond to the phasic input from PPTg with burst firing (Floresco et al., 2003). Therefore, the vSub controls phasic DA firing by controlling the number of DA neurons that can be phasically activated (Lodge & Grace, 2005). Based on these two independent pathways of DH/VH-VTA connections, two reasonable inferences can be drawn: 1) lesions in dorsal hippocampus, including the dorsal CA3 region, would likely lead to "perseverance" of local GABAergic inhibition of DA neurons within VTA, thus decreases tonic DA release in response to salient context; however, this local GABAergic inhibition would either not or only mildly block NMDAR-dependent phasic DA release

modulated by PPTg, due to normal functioning of the vSub-NAc-VP-VTA pathway; 2) lesions in ventral hippocampus, including the vSub, would likely lead to “perseverance” of the VP inhibition, thus massively reduce burst firing in VTA DA neurons in response to salient stimulus relayed by PPTg, in addition to possibly also reduced tonic DA release. This distinction is not only because the VTA receives much denser GABAergic projections from VP than from cd-LS (Kalivas et al., 1993), but also because the VP is a structure in which most neurons maintains high levels of spontaneous firing (Lavin & Grace, 1996).

On the other hand, Brene et al. (1994) found that kainic acid stimulation of the hippocampus increases D1R mRNA in the ipsilateral DMS and bilateral NAc whereas a 6-hydroxydopamine lesion alone increases D2R mRNA in the DLS and D1R mRNA in the NAc core ipsilaterally. Therefore, converging evidences suggest that hippocampal activations lead to up-regulation of the “Go” pathway in the associative/limbic regions in the striatum while hippocampal dopaminergic lesions lead to up-regulation of the “No-Go” pathway in the sensorimotor striatum as well as the “Go” pathway in amygdala-dependent appetitive cued learning (Ito & Hayen, 2011). Indeed, developmental or adult lesions of ventral hippocampus have been shown to alter function of the dopaminergic system in response to environmental and pharmacological challenge (Brake et al., 1999; Libska et al., 1994; Lillrank et al.,1999). On the other hand, Pezze et al. (2001) found that the compared with NAc shell, the extracellular dopamine level ([DA]o) in NAc core is significantly elevated during contextual fear retrieval but not during cued fear retrieval, whereas the opposite scenario was also true; while Manago et al. (2009) found that D1R

activation in NAc core and D2R activation in both NAc core and NAc shell are required for memory consolidation of inhibitory avoidance. Macedo et al. (2012) also showed that neonatal VH lesions lead to enhanced and non-extinguishing prefrontal DA release in response to food consumption.

An alternative route that dorsal hippocampal lesions could exert effects on decreasing tonic DA levels and hence enhances D2R sensitivity is via the interaction with the prefrontal cortex, as on one hand, the dorsal CA1 region directly interact with prefrontal neurons in terms of working memory regulation and system consolidation (Thierry et al., 2000); on the other hand, prefrontal efferent onto striatal DA terminals has been supposed to regulate tonic DA release (Borland & Micahael, 2004).

5.2.5 Sensorimotor integration as a core feature of the *Double Summation* model

Using a monosynaptic rabies virus system, (Wall, De La Parra, Callaway, & Kreitzer, 2013) has been able to demonstrate that direct-pathway neurons are preferentially innervated by sensory cortical and limbic structures whereas indirect-pathway neurons were preferentially innervated by motor cortex, while inputs from thalamus, substantia nigra, and specific cortical layers was similar between direct- and indirect- pathway (also see (Huerta-Ocampo, Mena-Segovia, & Bolam, 2014). Combined with the abundances of pharmacological manipulations in either D1 or D2 receptors as well as genetic enhancement or optogenetic inhibition of those dopaminergic receptors (Agostino & Cheng, 2016), one could safely assume that the D1R direct-pathway is more related to the perception of the valence or significance of the signal/cue of time whereas

the D2R indirect- pathway is more related to the action sequence of timing. Therefore, blocking the D1R signaling is equivalent to reducing the valence/significance of the signal/cue of timing, thus flattening the peak functions (Narayanan, Land, Solder, Deisseroth, & DiLeone, 2012a; Parker, Chen, Kingyon, Cavanagh, & Narayanan, 2014), or vice versa enhancing the attention to the previously rewarded timing cues (Hikida, Kimura, Wada, Funabiki, & Nakanishi, 2010; Kravitz, Tye, & Kreitzer, 2012); whreas blocking the D2R indirect-pathway is equivilant to blocking the timing action or letting other previously-unrewarded actions interfering with timing action (Hikida et al., 2010; Kravitz et al., 2012), thus resulting in rightward shifts of timing functions (C. V. Buhusi & Meck, 2002a; Drew et al., 2003; Lake & Meck, 2013), or vice versa sensitizing/obsessing the timing action (Drew et al., 2007a; Groman et al., 2014; Gu et al., 2011; R. D. Ward et al., 2009a). Indeed, (Wiener et al., 2008) has shown that lesions in the subthalamic nuclei, a critical part of the indirect pathway (Gerfen & Surmeier, 2011; Kreitzer & Malenka, 2008), did not affect the mainainence of temporal control in rats, but resulted in an impulsive/perseverative responding in the right tale of a peak trial when responding was unlikely to yield reinforcement. This result may be explaned by an increase in “spontaenous stereotypy” as a result of imbalances of the two pathways (McBride & Parker, 2015).

Furthermore, {Yin, 2009 #402} demonstrated that the potentiation of glutamatergic transmission observed in dorsolateral striatum after extensive training was preferentially expressed in striatopallidal neurons, rather than striatonigral neurons. This

is consistant with the idea that the DLS-D2R indirect-pathway might play a more important role in well-trained motor timing behavior.

5.3 Future Directions

The SBF model is currently the most successful model in explaining the neural correlates of interval timing. Ample evidences have suggested that this model has produced reliably predicted behavior (Buhusi, 2012; Coull et al., 2004; Jones & Jahanshahi, 2011; Matell et al., 2003, 2011; Meck et al., 2008; Oprisan & Buhusi, 2011; Teki et al, 2011b; van Rijn et al., 2011; Yin & Troger, 2011). It could also account for the pharmacological changes on the clock and memory components of interval timing that were independently manipulated (Meck, 1983). Indeed, the power of a model not only lies on its explanatory and predictive effects, but also lies on its flexibility to adapt itself into different situations without changing the main framework. In response to the evidences that suggest the existence of dichotomy in striatal MSNs, the author attempts to make a modification on the SBF model in order to continue exerting the power of this model on explaining time perception and timed performance. This does not suggest that the “double-summation” version is better or worse than the original SBF model, but provides a way in which different lines of research can be incorporated into the same framework. Indeed, the “double-summation” model is still under development and lacks several important features in order to fully account for timing behaviors, such as the generation of the scalar property, explaining clearly the dependence or independence of

“Stop” times on “Start” times, and being quantitative enough to allow mathematical simulations and make quantitative predictions for psychophysical studies.

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 contra-laterally in addition to a transection of the corpus callosum (e.g., Christakou, Robbins, & Everitt, 2001; Chudasama, Baunez, & Robbins, 2003). Moreover, future studies would benefit from the use of optogenetic techniques (Yizhar, Fenno, Davidson, Mogri, & Deisseroth, 2011) in terms of identifying the functional “connectome” among the hippocampus, striatum, and cortex (Chuhma, Tanaka, Hen, & Rayport, 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., 2011b).

Finally, as the Google Deepmind’s AlphaGo, an artificial intelligence software that uses human intuition-like algorithms to play the traditional Chinese chess *Go*, beat South Korean professional *Go* player and former World Champion Lee Sedol 4-1, I have been amazed by what level artificial intelligence could achieve in the near future and have changed my view: with the promise of “timing-based consciousness” research, the *strong* version of artificial intelligence will come sooner than later. We ought to think about what our roles are in that world.

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Biography

Bin Yin was born on January 3rd, 1986 in Fuzhou, Fujian, China and was raised there till entering college in Beijing. He majored in Biological Sciences and minored in Psychology at Peking University, graduating in 2008 with a Bachelor's in Science. He joined the Center for Learning and Memory at the School of Medicine at Tsinghua University since 2006 and worked as a research assistant there from 2008 to 2009. In the fall of 2009, he entered the Systems and Integrative NeuroSciences (SINS) Program in the Department of Psychology and Neuroscience at Duke University, working with Dr. Warren H. Meck. He received a Master's degree from Duke University in 2012. His work is published in such journals as *Journal of Neuroscience*, *Philosophical Transactions of the Royal Society – London B*, *Timing & Time Perception*, *Timing & Time Perception Reviews*, *Current Opinion in Behavioral Sciences*, and *Frontiers in Integrative Neuroscience*. He has been actively engaged in community services such as founding and managed an interdisciplinary knowledge-sharing platform among the graduate and professional students in the Triangle area named *Triangle SmartTalk*.