

Oscillatory Mechanisms Supporting Interval Timing in Cortical-Striatal Circuits

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Dissertation submitted in partial fulfillment of  
the requirements for the degree of Doctor of Philosophy  
in the Department of Psychology and Neuroscience  
in the Graduate School of Duke University

2014

ABSTRACT

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## **Abstract**

Numerous studies have explored brain activities in relation to timing behaviors from spike firing rates to human neuroimaging signals; however, not many studies have explored functional relations between neural oscillation and timing behavior. Neural oscillations are recently being considered as a fundamental aspect of brain function that modulate broad ranges of cognitive processes. Striatal-beat frequency model (SBF) also proposed that oscillatory properties of neurons are the critical feature that underlies timing behavior. In order to reveal the functional relations between neural oscillations and timing behavior, multiple timing paradigms have trained in groups of rats, and the neural oscillatory patterns during the timing tasks were recorded and analyzed. More specifically, oscillatory patterns that are involved in duration encoding and comparison have been identified using ordinal temporal comparison task. Then, the patterns of theta and delta rhythms have been explored in relation to duration judgment and production. Also, oscillatory patterns underlying interval timing have been compared to the patterns of working memory. The major target areas for those electrophysiological experiments were the cortical-striatal circuits which known for their critical role in timing behavior. Finally, excitatory and inhibitory oscillators (EIO) model has been proposed in order to address oscillatory features underlying interval timing and working memory.

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# 1. Introduction

The processing of temporal information is fundamental for many aspects of cognition and behavior; as for behavior to be adaptive, intact abilities of temporal processing is required from the millisecond range (e.g. for speech or motor movement) to the range of circadian rhythm (e.g. for foraging and sleep/wake cycle). Interval timing which ranges from second to minute is especially fundamental for cognition as this temporal range is critical for learning, decision making, working memory and attention. With the significance of temporal processing in various cognitive processes, the ability of animals to represent temporal information and the underlying neurological mechanisms have been the focus of much research (Buhusi and Meck, 2005; Merchant et al., 2013). For example, localization of relevant brain areas for timing and time perception are revealed by lesion or human imaging studies (Coull et al., 2004; Harrington et al., 2010; Hinton and Meck, 2004; Jones and Jahanshahi, 2011; Lewis and Miall, 2006; Meck, 2006a, b; Meck et al., 2008; Wiener et al., 2010). Also, neural responses such as spike firing patterns showed continuous changes of neural activity characterized by ramping up, decaying or peak-shaped firing rate with the development of time (Jin et al., 2009; Lebedev et al., 2008; Matell et al., 2003a; Matell et al., 2011; Mita et al., 2009; Narayanan and Laubach, 2009; Niki and Watanabe, 1979).

However, compared to the approaches of spatial localization in the brain or of firing rates of neural spikes, neural oscillatory properties have been less attended in the

research of timing behavior. Actually, neural oscillation is a fundamental property of brain function that modulates cognitive processes such as attention, memory, and decision-making (Buhusi and Meck, 2005; Cheng et al., 2008b; DeCoteau et al., 2007a; DeCoteau et al., 2007b; Matell and Meck, 2004; Varela et al., 2001; Wang, 2010). With recent increase of focus on the role of neural oscillations in cognition, numerous studies are exploring the functional significance of various frequency ranges of neural oscillations including gamma (30-70Hz), beta (13-30Hz), theta (4-8Hz), and delta (1-4Hz). For example, the role of gamma has been suggested in perceptual recognition or feature binding across various sensory modalities, and the role of theta has shown in relation to working memory and spatial navigation (Burgess and O'Keefe, 2011; DeCoteau et al., 2007a; DeCoteau et al., 2007b; Düzel et al., 2010; Fujisawa and Buzsaki, 2011; Huxter et al., 2003; Hyman et al., 2010; Jones and Wilson, 2005; Siapas et al., 2005; Tort et al., 2008). In addition, research into beta rhythm has proposed its role in motor planning or motor inhibition especially in basal ganglia and motor cortex (Brittain and Brown 2014; Jenkinson and Brown 2011). Also, the functional role of low frequency oscillations including delta (1-4 Hz) is suggested in attentional selection and anticipatory mechanisms in human and animal studies (Kim et al., 2007; Lakatos et al., 2008; Morgan et al., 1996; Schroeder and Lakatos, 2009; Stefanics et al., 2010).

Recent evidence suggested that neural oscillations especially in the range of theta and delta are involved in attention and stimulus timing in human and animal studies

(Cravo et al., 2011; Hsieh et al., 2011; Lakatos et al., 2008; Roberts et al., 2013; Stefanics et al., 2010). However, only a few studies have addressed the functional significance of neural oscillations in timing behavior; and to the best of our knowledge, no research has systematically explored the relation between neural oscillation and interval timing behavior. Therefore, in order to reveal the functional relations between neural oscillation and timing behavior, oscillatory mechanisms underlying interval timing will be explored by electrophysiological recordings during multiple interval timing paradigms. In addition, an excitatory and inhibitory oscillators (EIO) model will be proposed using computational modeling in order to address oscillatory features during interval timing as well as shared features between interval timing and working memory. EIO model is based on the SBF model but further developed to consider the population pattern of oscillatory individual neurons including both excitatory and inhibitory neurons.

### ***1.1 Interval Timing***

To begin with, temporal processing occurs across different time scales ranging from sub-second intervals to hours and days and has been categorized into millisecond, interval, and circadian timing (Buhusi and Meck, 2005; Buonomano, 2007; Lewis and Miall, 2009). Millisecond timing is frequently studied in reference to speech perception and motor control (Ivry et al., 2002; Kotz and Schwartz, 2010), whereas interval timing (ranging from milliseconds to minutes) is known to be important for computational learning and decision-making (Gallistel and Gibbon, 2001; Meck et al., 2012b). Multiple

lines of research suggest an important cut-off dividing sub-second and supra-second timing between 500 ms – 2 s, with evidence of different properties (e.g., scalar vs. non-variance, differential interaction/interference in dual-tasks, and the ability to make ordinal comparisons – see Buonomano et al., 2009; Cordes et al., 2007; Cordes and Meck, 2013; Fortin and Couture, 2002; Ivry and Spencer, 2004; Johnston et al., 2006; Michon 1985; Rammsayer and Ulrich, 2011; Rammsayer and Lima, 1991). In addition, Lewis and Miall (2003a, b, 2006) have considered other factors such as (1) whether the durations are in the sub-second or supra-second range; (2) whether they are continuous such as in a repeating cycle so that the specific temporal sequence could be predictable with relatively little (if any) attention; and (3) whether the durations are defined by movement. As a consequence, they proposed two different timing systems that engage different neuronal circuits – one that is automatic and another that is cognitively controlled (Lewis and Miall, 2003b).

In this manuscript, an emphasis will be placed on interval timing which can be also defined as cognitively-controlled temporal processing that involves supra-second intervals and not measured by specific movements or a continuous predictable pattern of stimulus presentation. Interval timing is not only fundamental to cognitive functions, but also it overlaps with the temporal ranges of working memory. Thus, the comparison of oscillatory features during interval timing and working memory will help us to better understand the neural features underlying interval timing.

## **1.2 Cortico-Striatal Circuits Involved in Interval Timing**

A variety of evidence from human neuroimaging (Harrington et al., 2010; Hinton and Meck, 2004; Lewis and Miall, 2006; Meck et al., 2008), clinical populations (Allman and Meck, 2012; Malapani et al., 1998), pharmacological (Buhusi and Meck, 2002; Cheng et al., 2006; Lake and Meck, 2013; Matell et al., 2004, 2006; Meck, 1983,1996; Meck et al., 2008), lesion or genetic mutation (Meck, 2006a, b, c; Narayanan et al., 2006; Meck et al., 2012a), and electrophysiological studies (Chiba et al., 2008; Macar and Vidal, 2002; Matell et al., 2003a, b; Merchant et al., 2013; Narayanan and Laubach, 2006, 2009) supports the critical role of cortico-thalamic-basal ganglia circuits in interval timing.

Lesions in the caudate/putamen (CPu) or loss of dopamine (DA) neurons in the substantia nigra (SN) generally produce a substantial loss of temporal control in humans and rodents (Jones and Jahanshahi, 2011; Meck, 2006b). Moreover, the disruption of interval timing ability by the loss of DA neurons in SN, but not the disruption by CPu lesions, can be restored by L-Dopa administration (Meck, 2006b), indicating the crucial role of CPu as well as the DA projection from the SN in timing behavior. In addition, clinical populations which have posited deficits in cortico-thalamic-basal ganglia circuits and DA regulation; such as attention-deficit hyperactivity disorder (ADHD), Huntington's disease, Parkinson's disease (PD), schizophrenia, autism and obsessive-compulsive disorder (OCD) also show evidence of abnormal timing ability (Beste et al.,

2007; Carroll et al., 2008; Gu et al., 2011; Jahanshahi et al., 2010 – for review see Allman and Meck, 2012; Meck, 2005; Meck and Benson, 2002).

Lesions of the frontal cortex (FC) also affect timing, for example, by reducing the effects of dopaminergic drugs on clock speed (Meck, 2006a – see also Smith et al., 2010), or by impairing simultaneous temporal processing and distorting temporal memory (Koch et al., 2002; Meck et al., 1987; Olton et al., 1988 – see Allman and Meck, 2012). The effects of dopaminergic drugs on clock speed refer to the phenomenon that DA agonists produce proportional leftward shifts and DA antagonists produce rightward shifts in the scaling of signal durations; reflecting increases and decreases in clock speed, respectively (Coull et al., 2011; Lake and Meck, 2013; MacDonald and Meck, 2004, 2005; Meck, 1983, 1996; Meck et al., 2012a; Narayanan et al., 2012). Repetitive stimulation of right dorsolateral prefrontal cortex (DLPFC) using transcranial magnetic stimulation (TMS) also produces timing impairments for durations in the multi-seconds range (Jones et al., 2004; Koch et al., 2003), further supporting the involvement of FC in supra-second timing.

Human neuroimaging studies have also localized functional brain areas involved in time perception and timed performance (Allman et al., 2014; Coull et al., 2011; Meck et al., 2008; Merchant et al., 2013). During duration discrimination or reproduction tasks, significant activation has been commonly reported in cortico-thalamic-basal ganglia circuits (including DLPFC, supplementary motor area (SMA), preSMA, striatum, and

thalamus), inferior parietal lobe, and cerebellum (Lewis and Miall, 2003b; Meck et al., 2008; Rubia and Smith, 2004 for review; Coull et al., 2004, 2008; Harrington et al., 2004; Meck and Malapani, 2004; Rao et al., 2001; Stevens et al., 2007). As an example, Coull et al. (2004) manipulated attentional allocation between time and color attributes of a stimulus with matched difficulty levels and minimal confounding in experimental procedures between the two tasks. They showed that a cortico-striatal network including the preSMA, putamen, and right frontal operculum was parametrically activated with attentional allocation to time (i.e., more attention to time produces more activation in the cortico-striatal network) while activation in the color-area V4 was parametrically related to the amount of attention allocated to color. Separate attempts to localize brain areas involved in interval timing have also revealed that the striatum and SMA are selectively activated during the encoding of durations compared to the encoding of other stimulus attributes (e.g., color or pitch – Coull et al., 2008; Harrington et al., 2004, 2010; Rao et al., 2001). Moreover, independent component analysis of fMRI data (Stevens et al., 2007) has identified cortico-thalamic-basal ganglia circuits as the primary common component across multiple timing tasks – see also Coull et al., (2011), Lewis and Meck (2012), and Merchant et al. (2013) for a fuller description of the properties of these “core” timing circuits.

In this regard, meta-analysis of the neuroimaging data from human timing studies reveals commonly activated brain areas for automatic (e.g., continuous, sub-

second, and involving movement) and more cognitively-controlled (e.g., discontinuous, supra-second, and not specifically defined by movement) forms of timing (Lewis and Miall, 2003b, 2006). Motor and pre-motor circuits such as the SMA, sensorimotor cortex, right cerebellum, lateral premotor area, and basal ganglia have been frequently activated by automatic timing; and in addition to these areas, cognitively-controlled timing additionally recruits the PFC and parietal cortices, with a bias to the right hemisphere (Lewis and Miall, 2003b; Meck, 2005). The additional involvement of PFC and parietal activations in cognitively-controlled timing has been hypothesized to represent encoding and attentional requirements during interval timing which could be shared with working memory processes (Buhusi and Meck, 2009a; Meck and Benson, 2002).

### ***1.3 Neuronal Features Involved in Interval Timing***

Electrophysiological findings from primates and rodents have provided rich neuronal evidence of interval timing via various firing patterns of neurons. Firing rates of spikes during timing often show linear ramping, descending, peak or dip patterns across time (Jin et al., 2009; Lebedev et al., 2008; Matell et al., 2003a, b, 2011; Narayanan and Laubach, 2006, 2009; Niki and Watanabe, 1979). These spike patterns have been shown in multiple brain areas, such as PFC, SMA, preSMA, motor cortex, parietal cortex, striatum, thalamus, and hippocampus (Jin et al., 2009; Komura et al., 2001; Leon and Shadlen, 2003; Matell et al., 2003a, b, 2011; Mita et al., 2009; Niki and Watanabe, 1979; Rainer et al., 1999; Young and McNaughton, 2000).

Ramping activity has received considerable attention due to its potential for encoding relevant temporal information (Wang, 2010). For example, if a response is required to be held for a specific target duration (e.g., 2 or 4 s), the slope of the 2-s ramping pattern of neuronal firing will be steeper than the slope of the 4-s ramping pattern such that both spike rates reach the same threshold when the response output is produced at the specific target duration (e.g., Lebedev et al., 2008). In some studies, the observed ramping patterns for neural firing are approximately linear – suggesting that firing rate may represent time veridically (e.g., Brody et al., 2003; Komura et al., 2001; Lebedev et al., 2008; Leon and Shadlen, 2003; Mita et al., 2009). Moreover, ramping functions that are too steep or too flat appear to produce direction-specific timing errors on those trials (Leon and Shadlen, 2003). The observed neural spike patterns are sometimes linear even during a single trial (Lebedev et al., 2008), which suggests that the ramping patterns shown for a population of neurons may not be a simple effect of averaging over multiple trials that have burst activities with different onsets.

However, the ramping slopes are also typically correlated with the expected reward value in many experiments. For example, a parametric modulation of slopes was shown for anticipated taste; such that an expectation for a sweet sucrose liquid produced a steeper ramping slope than expectation for water, and the slope for diluted sucrose liquid was in-between (Komura et al., 2001). In this respect, duration information encoded in the slope or degree of ramping activity is difficult to dissociate

from other representations such as reward value and/or response preparation. A separate mechanism of decoding each stimulus attribute (e.g., time or reward value) from the spike rates of each neuron or neural population might be a satisfactory explanation for the problem. At present, it remains uncertain whether any study reporting such ramping functions has isolated a pure timing signal given the failure to adequately control for these different factors (see Merchant et al., 2013; van Rijn et al., 2011).

In studies with human participants, electroencephalography (EEG) measures of brain activity have shown a slow negative waveform designated as the contingent negative variation (CNV – see Pouthas, 2003). This CNV occurs in relation to the participant's prospective timing of a signal and has been proposed as a possible neural representation of temporal accumulation in the brain (Macar and Vidal, 2003; Pouthas et al., 2000; Tarantino et al., 2010; Walter et al., 1964). CNV represents a slow brain potential wave of negative polarity mostly shown in fronto-central or parietal-central regions during interval timing, and the amplitudes of CNV peaks have previously been shown to be correlated with the reproduced durations (e.g., Macar et al., 1999).

However, there are controversies on the interpretation of the CNV; recently the major performance-dependent variations in the CNV have failed to replicate and habituation effects have instead been shown in the amplitude, both of which are inconsistent with the CNV serving as a direct reflection of stimulus duration (Kononowicz and van Rijn,

2011). Within this context, it has been suggested that the CNV may not be a direct reflection of temporal accumulation, but more likely represents response preparation or decision-making processes. Such processes monitor the accumulation of time, but they can be interrupted or terminated without a loss of temporal information (van Rijn et al., 2011).

### ***1.4 Oscillatory Features Involved in Interval Timing***

Neural oscillations are a fundamental property of brain function that modulate cognitive processes such as attention, memory, and decision-making, as well as duration and beat-based timing mechanisms involved in time perception and production (Allman et al., 2014; Buhusi and Meck, 2005; Cheng et al., 2008b, 2009; DeCoteau et al., 2007a, 2007b; Matell and Meck, 2004; Teki et al., 2011, 2012; Varela et al., 2001; Wang, 2001; Ward, 2003). Especially, low frequency oscillations (in the range of delta) have been implicated in attention and stimulus timing in human and animal studies (Lakatos et al., 2008; Stefanics et al., 2010).

In addition, stimuli with rhythmic or regular patterns have been proposed to entrain low-frequency oscillations, which then influence the neural activity of higher frequency bands such as beta and gamma activity (Lakatos et al., 2005, 2008). In this regard, a recent human EEG study has shown that the power of theta activity differs across conditions with different temporal expectations (Cravo et al., 2011). More specifically, in a Go/No-go task, when temporal expectations for the appearance of

targets were manipulated, increased theta activity was shown for conditions in which there was a high probability of a target appearing at a predictable time.

The oscillatory feature related to temporal-order information was identified in relation to the pattern in item or spatial information maintenance (Hsieh et al., 2011; Roberts et al., 2013). During maintenance of multiple items, specific feature or temporal-order information could be focused on separately for upcoming target selection. Accordingly, different oscillatory frequencies would be specifically involved in item or temporal-order maintenance. EEG measured in humans showed that frontal theta (5-7 Hz) oscillation power was increased during the temporal-order component compared to item maintenance, while parietal and lateral occipital alpha (9-12 Hz) oscillation power was increased during item compared to temporal-order maintenance (Hsieh et al., 2011). Similarly, oscillatory responses to spatial or temporal-order information for multiple items in working memory were compared to each other, and the results showed that left frontal theta (5-8 Hz) and posterior alpha/beta (9-12 Hz/14-28 Hz) oscillation power levels were increased with right frontal gamma (30-50 Hz) oscillation power decreased for the temporal-order component compared with the maintenance of spatial information in working memory (Roberts et al., 2013). Because the levels of task difficulty were matched between the temporal-order and item/spatial information, these findings suggest that the modulation of oscillatory power results from the extraction of different stimulus dimensions for the items maintained in working memory. These

studies also emphasize the importance of frontal theta power in the maintenance of temporal-order information.

Other oscillatory features related to the temporal components of working memory have been also identified using frequency entrainment in humans (Wimber et al., 2012). In this study, participants were presented with words to be remembered on either 6-Hz or 10-Hz flickering backgrounds. Interestingly, the recorded EEG signal showed a corresponding 6-Hz or 10-Hz power increase specifically for the words presented with those flickering background frequencies (e.g., 6-Hz frequency power of the EEG was increased during the encoding of words presented with 6-Hz flickering backgrounds compared to the words presented with the 10-Hz flickering background). More importantly, this EEG pattern presented during encoding has shown reactivated even in the recognition phase without the presence of a flickering background (see Sumbre et al., 2008 for a similar example of visual entrainment of neural ensembles involved in rhythmical timing). Furthermore, the degree of oscillatory brain reactivation at the corresponding background flickering frequencies was correlated with memory performance, suggesting that the memory encoding of an object is related to certain frequencies of the object that can be directly represented by neural oscillations (Lustig et al., 2005).

## ***1.5 Shared Features between Interval Timing and Working Memory***

Subjective time can be modulated by various factors; one of those being cognitive load which has been shown to affect timing and time perception in multiple (concurrent) task designs (Block et al., 2010; Block and Zakay, 1997; Brown, 1997). Findings show that subjective time tends to pass more quickly in difficult or attention-demanding situations such as those present in a high-load working memory task, while time is perceived to pass more slowly in less attentional-demanding situations (Block et al., 1980; Block and Zakay 2008; Brown 2008). However, these findings differ depending on whether participants are required to make a prospective duration judgment (participants are required to attend to stimulus duration prior to or immediately upon the onset of the to-be-timed signal) or a retrospective duration judgment (participants are not required to attend to the duration of a stimulus during the task, but instead are asked to provide a duration judgment following task completion). With increases in cognitive load, prospective duration judgments tend to decrease, while retrospective duration judgments tend to increase (e.g., Bisson et al., 2012; Tobin et al., 2010; Zakay and Block, 2004). Potential explanations for these distortions in time perception include the proposal that prospective timing has to share attentional resources and/or executive control processes with other non-temporal cognitive tasks (Buhusi and Meck, 2009a). In contrast, retrospective duration judgments rely more on memory components such as

the amount of contextual change or interval segmentation is correlated with estimated duration (Grondin, 2010).

In relation to the effect of cognitive load on interval timing, working memory is also affected by concurrent-timing procedures (e.g., Brown, 1997, 2006; Fortin and Breton, 1995; Fortin et al., 2007, 2009; Fortin and Couture, 2002; Fortin and Masse, 1999; Macar et al., 1994; Rammsayer and Ulrich, 2005), showing that these interactions are not uni-directional, but rather bi-directional. For example, in a concurrent temporal and non-temporal working-memory task, attending toward time has a detrimental effect on non-temporal task performance, and attending toward a non-temporal task has been shown to reduce the accuracy of time perception by shortening duration judgments (e.g., Brown, 1997; Macar et al., 1994). In addition, increasing the size of the search set in a working-memory task also reduces the accuracy of temporal reproduction (Fortin et al., 1993). Some studies have shown that the interfering effect between two simultaneous tasks is augmented when the working-memory component requires a high level of executive control or capacity such as in mental arithmetic (e.g., Brown, 1997; Rammsayer and Ulrich, 2005). Under the assumption that two different behavioral tasks sharing the same processing mechanisms will interfere with each other when they are performed simultaneously, this bi-directional interaction between interval timing and working memory further supports the notion that they share some common properties, such as attentional resources and/or executive control.

Additional evidence that interval timing and working memory are not independent of each other comes from studies examining individual differences in timing accuracy and working memory capacity. For example, correlations among the individual differences observed in the performance of interval timing and working memory tasks indicate that these processes are co-dependent (e.g., Broadway and Engle, 2011a, b; Woehrle and Magliano, 2012). Individuals with high-capacity working memory tend to show more accurate and unbiased temporal reproduction (Broadway and Engle, 2011b) and also more sensitive temporal discrimination (Broadway and Engle, 2011a). In addition, these differences in timing in relation to working memory capacity are evident even after general fluid intelligence is accounted for. A separate study explored the relation between interval timing and working memory using simultaneous duration judgment and non-temporal working memory components (Woehrle and Magliano, 2012). These researchers found that low-capacity individuals show less accurate performance on a non-temporal task, but more accurate duration judgments compared to individuals with high-capacity working memory. Although this finding seemingly contradicts the previous reports of Broadway and Engle (2011a, b), the important task distinction is whether the interval timing and working memory components are simultaneously engaged or activated separately. Moreover, these findings suggest that when simultaneous performance is required, high-capacity working memory participants attend more strongly toward the non-temporal dimension of the task at the

cost of monitoring the temporal dimension. In contrast, participants with low-capacity working memory couldn't help but allocate some attention to the secondary time-keeping task, thus making them more aware of the passage of time. As a consequence the low-capacity working memory participants' time perception was actually more accurate, while their performance on the non-temporal task component suffered (Woehrle and Magliano, 2012).

Limitations in working memory are frequently defined as reductions in the capacity of holding items in memory. The limitation of working memory capacity was traditionally hypothesized as seven plus or minus two (Miller, 1956); more recent studies, however, suggest four items without engaging the processes of rehearsal and/or chunking (e.g., Cowan, 2001; Dallal and Meck, 1990). In addition to the capacity limitation, temporal limitations of working memory have also been revealed by loss of information as a function of increases in the retention interval (e.g., Buhusi and Meck, 2000, 2006a, b; Fuster 1995; Pasternak and Greenlee, 2005). The limitations and failures of working memory are commonly attributed to the decay properties of maintained information as time passes, or proactive/ retroactive interference (Jonides et al., 2008). Time-based decay theory explains that the maintained information erodes as time passes so that it becomes less available for later retrieval. Decay properties in working memory were shown even when rehearsal and/or interference effects were carefully controlled which reduced the possibility of other factors occurring during the retention interval

(McElree, 2001; Roediger et al., 1977). Delayed-response tasks in primates and rodents (Fuster 1995; Pasternak and Greenlee, 2005) further support the decay proposal by showing steady declines in performance and neural activity over a prolonged retention interval (e.g. 10-s delay). In further support of this decay process, Barrouillet and colleagues proposed a time-based resource-sharing (TBRS) model that explains how forgetting is time related (Barrouillet et al., 2004) as well as the manner in which time plays a crucial role in working memory load (Barrouillet et al., 2007).

Similarity-based interference theory proposes that maintained representations compete with other representations held in working memory, which could be similar and/or stronger, and result in interference and forgetting (Nairne, 1990; Oberauer and Kliegl, 2006; Saito and Miyake, 2004). The observation of proactive and retroactive interference (e.g., interference from prior trials in the case of proactive interference or interference from later trials in the case of retroactive interference) on current trials and increased interference with higher similarity support this proposal. Oberauer and Kliegl (2001, 2006) have provided further support for the interference model by fitting the time-accuracy data from a working memory task with a nonlinear mixed effect (NLME) model. The basic idea underlying this study was that more similar conditions provoke more interference because interference arises from overlapping features of item representation, and the estimated interference from the NLME model could successfully account for the time-accuracy data in the working memory paradigm.

According to Oberauer and Kliegl (2006), no alternative model incorporating decay theory can account for the time-accuracy data as well as the NLME interference model. However, as a contradictory point to this argument, Portrat and colleagues (2008) showed that a time-related decay effect is present as a function of processing time and recall performance in a different working memory paradigm, consistent with the TBRS model proposed by Barrouillet et al. (2004). However, these decay and interference hypothesis, which provide seemingly contradictory accounts for the loss or inability to access stored information, may be supported by the same neuronal properties (Jonides et al., 2008). The possibility of such a common mechanism based upon attributes of neuronal oscillations will be explored in greater detail later in this manuscript.

## 2. Neural Oscillations in Duration Encoding and Comparison

Neural oscillations have been considered as essential to the various brain operations. Specific frequency ranges of oscillations have been suggested their role in specific cognitive functions. For example, theta rhythms are reported during working memory (Düzel et al. 2010; Fujisawa and Buzsaki 2011; Hyman et al. 2010; Jones and Wilson 2005; Siapas et al. 2005), spatial information processes (Burgess and O'Keefe 2011; Huxter et al. 2003), and also during learning and decision making processes (DeCoteau et al. 2007a; b; Tort et al. 2008). On the other hand, gamma rhythms are suggested to be involved perceptual recognition or feature binding across various sensory modalities. In addition, the role of delta rhythms has suggested in attentional selection and/or anticipatory mechanisms in human and animal studies (Kim et al. 2007; Lakatos et al. 2008; Morgan et al. 1996; Schroeder and Lakatos 2009; Stefanics et al. 2010).

While dense research has explored oscillatory properties of brain in relation to various cognitive functions, the relation between neural oscillations and timing behaviors has been less focused. In order to investigate this relation, we recorded local field potentials (LFPs) from multiple brain areas of rats during a timing task, specifically the ordinal/temporal comparison task. Ordinal/temporal task requires the rats to compare a pair of temporal durations and respond whether the second 'comparison' is longer or shorter than the first 'standard' duration by pressing left or right lever. The process of ordinal comparison includes timing and encoding of a standard duration, and

also the decision process of comparing the encoded duration to the secondly presented comparison duration. Oscillatory features during these cognitive phases will be explored separately, and common and distinct patterns will be examined across the cognitive stages.

## **2.1 Material and Methods**

### **2.1.1 Animals**

Fifteen adult male Sprague-Dawley (Charles River) rats were trained on the behavioral task. They were housed in a temperature-controlled room with 12h light /12 h dark cycles and were trained during the light phase. The rats were allowed continuous access to water in their home cages and their body weights were maintained at approximately 85% of their ad lib weights (300-400g) by restricting access to food. Of these, five (out of 15) rats with good behavioral performance contributed electrophysiology data. All studies were conducted in accordance with standard procedures approved by the Duke University Institutional Animal Care and Use Committee.

### **2.1.2 Apparatus**

Behavioral data were collected from eight identical lever boxes that were housed in sound- and light- attenuating chambers (all equipment from MED Associates). Each lever box had a transparent Perspex door, back panel and ceiling, with aluminum sidewalls, and a floor with 19 stainless steel bars. One of the aluminum walls had a

recessed food-cup positioned 1 cm from the floor (centered), into which food pellets could be delivered (45mg), and a photo-beam that detected food-cup entries. Above the food-cup were two retractable levers (to the left and right, respectively). Centered above the levers was a house-light (28-V, 80-ma, 2,500-lx) remained off for the majority of sessions, but whose illumination served as a warning cue in a subset of animals (see section 2.3.2). The stimulus to-be-timed was white noise presented through a speaker mounted on the opposite aluminum sidewall. All experimental events were controlled and recorded by an IBM-PC computer.

Lever boxes used during electrophysiological recording were the same as those used for behavioral training, with the following exceptions: The ceiling had a hole in the center (15 cm) for the headstage cable bundle, and the food cup was not recessed.

### **2.1.3 Behavioral procedures**

Rats received pre-training and training sessions prior to ordinal test sessions. Pre-training involved 5 sessions of combined magazine and lever training: During these sessions, only one of the levers was extended at a time (once 10 responses had been made on a lever, it was retracted and the other lever was extended) and each time it was pressed rats received a food pellet. In addition, a food pellet was delivered every 60-s with lever movement (insertion and retraction). Each session lasted until 60 food pellets had been delivered.

In the ordinal/temporal comparison task, the rats were presented with a pair of stimulus durations (white noise) separated by a brief inter-stimulus interval (ISI). The first duration in a pair is defined as the standard, and the second as the comparison duration. In an attempt to encourage rats to time both the standard and comparison durations (not just the comparison only), multiple standard durations are typically employed within a session. Immediately following the comparison stimulus, both response levers were extended into the chamber. Rats were required to determine whether the comparison duration was “shorter” or “longer” than the standard, on each trial, by pressing on the designated “shorter” or “longer” response lever. The left and right lever mappings for the “shorter” and “longer” durations were counterbalanced between the rats. For example, one group of rats (left-shorter) were trained to press the left lever if the comparison was shorter than the standard duration, and the right lever if it was longer; and another group of rats (left-longer) were trained to press the right lever if the comparison was shorter and the left lever if it was longer. If rats made a correct response, they received a food pellet, and if they made an incorrect response, or failed to respond within 8 seconds, they did not receive any food. At the end of a trial (once a response was made, or after 8-s) both levers were retracted, and there was a delay until the next trial (inter-trial interval; ITI).

Training stage: Training sessions were designed to allow rats to learn and generalize the required rule for the task. Training proceeded in four phases that got

progressively more difficult (discrimination difficulty indexed by ratio of standard: comparison; and number of standard vs. comparison arrangements). First, rats received 40 sessions of training, on some trials the standard duration was 0.5-s and the comparison was 2.5-s, and vice versa (i.e., 0.5 vs. 2.5-s; and 2.5-s vs. 0.5-s), and on other trials the standard was 2.5-s and the comparison was 12.5-s, and vice versa (i.e., 2.5-s vs. 12.5-s; and 12.5-s vs. 2.5-s). Second, rats received 5 sessions in which on some trials the standard and comparison durations were 1 and 5-s, and vice versa, and on other trials the standard and comparison durations were 5 and 25-s, and vice versa (i.e., 1 vs. 5-s; 5 vs. 1-s; 5 vs. 25-s; and 25 vs. 5-s). Third, pairs of stimulus durations were changed to 2 vs. 6-s (and vice versa) and 6 vs. 18-s (and vice versa) for 8 sessions. Fourth, rats received 10 sessions which employed standard and comparison durations of 0.3 vs. 0.9-s (and vice versa), 0.9 vs. 2.7-s (and vice versa), 2.7 vs. 8.1-s (and vice versa), 8.1 vs. 24.3-s (and vice versa).

Before surgery: All fifteen rats (un-cued paradigm) completed the test stage with a different pairs of durations (white noise) to those used during training. There were seven sessions, that each lasted 2 hours. There were three standard durations (0.5, 1, 3-s) and 12 comparison durations proportionally distributed around each standard (see Table 1). The identities of the standard and respective comparison durations were randomly selected on each trial, and there were approximately 120 trials per session. The ISI was 1.5-s and the ITI was between 25-80-s.

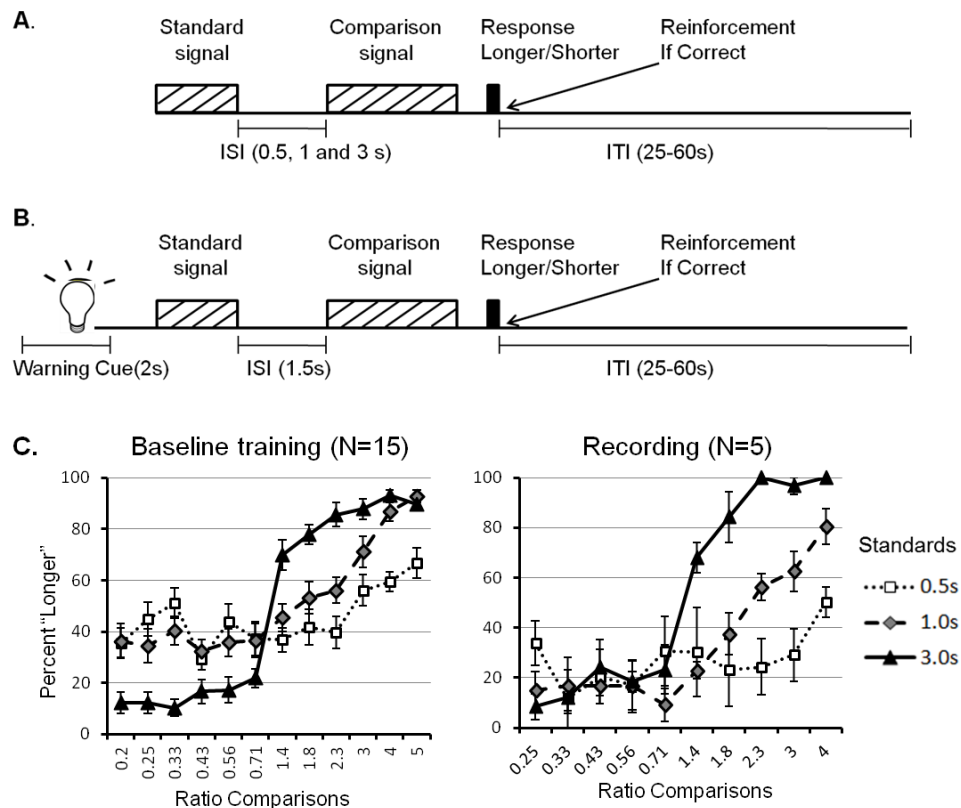
Following this training, seven rats (cued paradigm) received additional training with cued ordinal/temporal comparison task. Specifically, a “warning cue” (2-s illumination of the house-light) was presented 1-s before the onset of the standard duration. The “warning cue” served to alert the rats to upcoming standard duration stimulus. Ten ratios between the standard and the comparison were applied instead of 12 ratios (table 1).

**Table 1: Durations of Standard and Comparison White Noises**

Standard (s)	Comparison (s)											
0.5	0.10*	0.13	0.17	0.22	0.28	0.36	0.70	0.90	1.15	1.50	2.00	2.50*
1.0	0.20*	0.25	0.33	0.43	0.56	0.71	1.40	1.80	2.30	3.00	4.00	5.00*
3.0	0.60*	0.75	1.00	1.30	1.67	2.14	4.20	5.40	6.90	9.00	12.00	15.00*
Ratios to standard	0.20*	0.25	0.33	0.43	0.56	0.71	1.40	1.80	2.30	3.00	4.00	5.00*

After surgery: Three rats (2 left-longer, 1 left-shorter) received a micro wire array (MWA) implant and were tested again on the ordinal/temporal comparison task following recovery from surgery. Test sessions were identical to those previously described un-cued ordinal/temporal comparison task (before surgery) with the following exceptions, which were designed to optimize electrophysiological data acquisition (see Figure 1A). Sessions lasted 1.5 hrs.; the ISI was matched to the standard duration (e.g., if the standard was 1-s, the ISI was also 1-s); the ITI was between 25-60-s, and included ten (not twelve) ratios between the standard and the comparison (see Table 1 and Figure 1A).

Two additional rats (both left-shorter) also received a micro wire array implant, and were tested on the cued ordinal/temporal comparison task. ISI was 1.5-s irrespective of the Standard duration and sessions lasted 1.5hr with ten ratios between the standard and the comparison (Figure 1B).



**Figure 1: Task Design and Behavior Result.** (A). Un-cued ordinal/temporal comparison task. No warning cue was presented. (B) Cued ordinal/temporal comparison task. House light warning cues (2s) were presented 1s before the initiation of Standard duration. (C) Behavioral performances during the baseline training (un-cued comparison task) and during the LFPs recordings (3 rats with un-cued and 2 rats with cued comparison task). ISI=Inter-Stimulus Interval, ITI=Inter-Trial Interval.

### **2.1.4 Surgery and LFPs data acquisition**

The rats (3 rats with un-cued paradigm and 2 rats with cued paradigm) that performed well in the ordinal/temporal comparison task were selected and chronically implanted with a micro-wire array of 16 electrodes. Rats were anesthetized with ketamine (60mg/kg, i.p.) and xylazine (5 mg/kg, i.p.), and also injected with atrophine (0.02mg, i.p.) for airway secretion, and fixed in a stereotactic frame. Eight electrodes were targeted to the right striatum (AP between 0.90 and -1.2 mm; ML between 2 and 3.5mm; and between 3.5 and 4.5mm deep) and eight electrodes were targeted to the right sensorimotor cortex (AP between 0.90 and -1.2 mm; ML between 2 and 3.5mm; between 1.5 and 2.5mm deep). The ground screw was implanted in the skull right above the cerebellum and touching the brain. The local field potential (LFP) data were referenced against the reference electrode that was located in the cortex (AP between 0.9 and -1.2mm; ML between 3.5 and 4mm; between 2 and 2.5 mm deep) and had a 2mm exposed tip.

After 1-2 weeks of recovery, neural activity was recorded using the Multi-Neuron Acquisition Processor system (Plexon Inc, TX) while the rats performed an ordinal/temporal comparison task. LFPs were continuously sampled at 1kHz, preamplified with 10000 x, and bandpass filtered at 0.7-170Hz.

The LFPs were recorded during the cued or un-cued ordinal/temporal comparison task from multiple days and the data of two sessions, which displayed satisfactory performance, were selected for further analysis in each rat.

### **2.1.5 LFPs data analysis**

Before all analyses, the electrode data of each session were screened to determine if they show a significant 60 Hz noise. As a result, all 4 striatum LFPs data from one rat with cued paradigm, and 3 cortex and 1 striatum LFPs from 2 rats with un-cued paradigm were excluded from further analysis. Power spectral analyses were conducted using the MATLAB Chronux toolbox (<http://www.chronux.org/>; Mitra and Bokil 2008) and in-house matlab programs.

Power spectral analyses were done using “*mtspectrumc*” routine with multitaper methods (5, 9 tapers) on ITI and task trial segments. ITI segments were from 8s to 16s data point after the termination of each trial to exclude the period of chowing pellet. The task trial segments include from the initiation of Standard signal to the point of lever pressing.

Multi-taper spectrograms (3, 5 tapers) were calculated using a 0.5-s window sliding in 0.05-s increments using “*mtspecgramc*” routine. The spectrogram for each trial was constructed by averaging the data from multiple electrodes in the specified brain region. Then, the power of the spectrograms was normalized by dividing the power during the ITI (segment from -3s to -0.5s with respect to onset of the Standard signal or

the warning cue presentation) in each frequency so that the normalized value represent the relative increase of oscillation power compared to the baseline. All the following analysis was conducted using these normalized spectrograms. Trials containing outlier intensities (relative power of more than 20x) or those with no behavioral response were excluded from the analyses. Also, to average the spectrograms including Comparison signal which have various durations across trials (Figure 5 and 6), each time point was calculated by averaging over the trials that have a Comparison signal on and excluded the trials with Comparison signal terminated. This indicates that as the Comparison signal gets longer, the less number of trials was averaged for that time point.

Because the main changes in the oscillation power occurred in low frequency, changes in the low frequency (<10Hz) was especially focused in the following analysis. The power of the low frequency oscillation was calculated by averaging the normalized power below 10Hz in each trial. To display individual trial examples during the Standard duration, the low frequency power was shown in a relative power to the peak power in each trial so that the peak power can be more noticeable. For statistical analyses on the oscillation power of the comparison signal, the low frequency power of 0.5-s segment at the end of the comparison signal was averaged in each trials to see the relation between the response chosen and the oscillation power at the last point of the comparison signal.

## **2.2 Result**

### **2.2.1 Behavioral performance**

All rats successfully acquired the ordinal comparison rule in the first phase of training (first vs. last session, paired t-test,  $p < 0.001$ ), and generalized this rule to the subsequent three phases of training, performing significantly above chance during each phase (Phase2:  $M=85.9$ ,  $p < 0.001$ ; Phase3:  $M=83.7$ ,  $p < 0.001$ ; Phase4:  $M=72.4$ ,  $p < 0.001$ ).

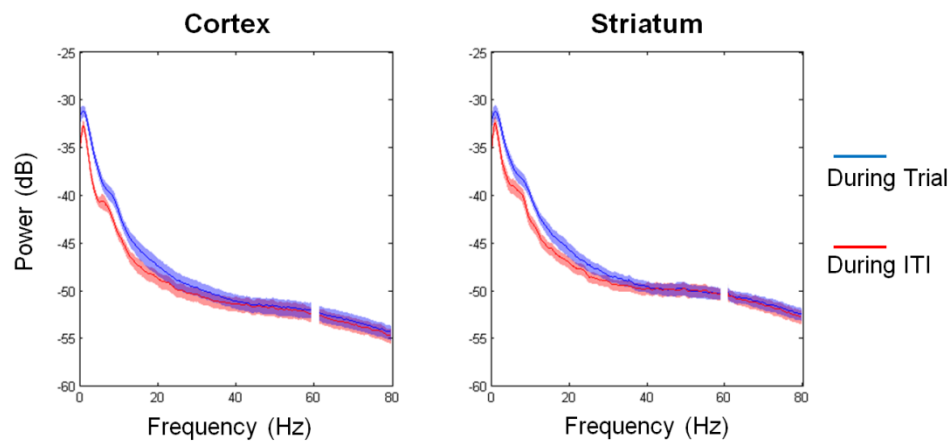
Before surgery: The percentage of “longer” responses was calculated for each ratio Comparison ( $\text{long}/\text{short} + \text{long} \times 100$ ) and plotted as a function of Standard duration (see Figure 1C left). In a group with un-cued paradigm, ANOVA on the %longer responses with two within-subject factors (Standard duration, ratio Comparison) revealed a significant main effect of Standard duration ( $F(2,504)=98.1$ ,  $p < 0.001$ ), a significant main effect of ratio Comparison ( $F(11,504)=8.9$ ,  $p < 0.001$ ), and a significant Standard  $\times$  Comparison interaction ( $F(22,504)=1.7$ ,  $p < 0.05$ ). This indicates the increase of %longer response with the increase of ratio Comparison; however, the rats showed good performance on supra-second timing and poor performance on sub-second timing as like shown in the previous study (Cordes and Meck 2013). The general performance between left-shorter and left-longer groups were similar and the performance of each condition were not significantly different between the two different lever-mapping groups.

Similarly to the findings of un-cued group, ANOVA on the performance with cued paradigm showed a significant main effect of standard ( $F(2,119)=69.8$ ,  $p<0.001$ ), a significant main effect of comparison ( $F(9,119)=32.3$ ,  $p<0.001$ ), and a significant standard x comparison interaction ( $F(18,119)=14.4$ ,  $p<0.001$ ).

After surgery: Figure 1C (right) reveals performance on the ordinal comparison task during LFPs recording. Inspection of this figure reveals performance across each of the three standard durations remained relatively stable after the surgery.

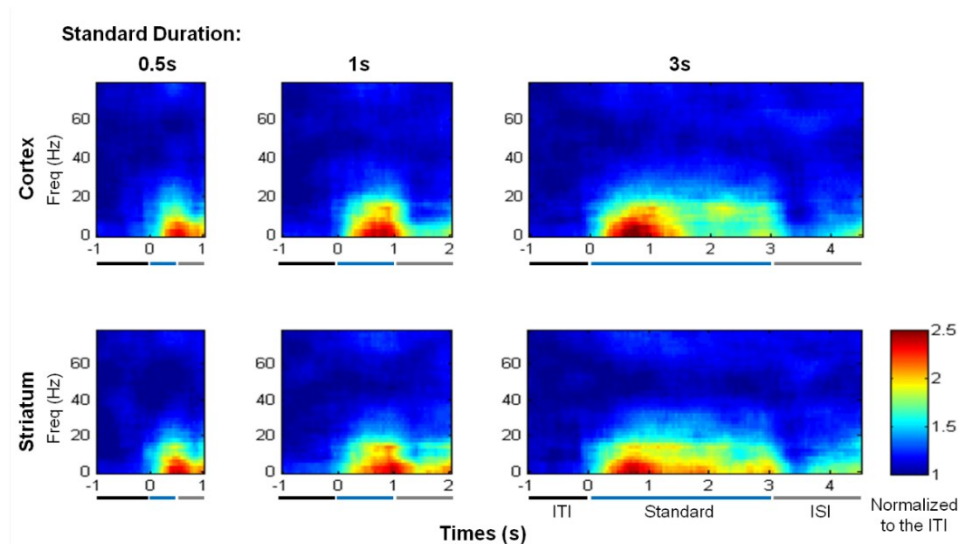
## 2.2.2 Timing of the Standard durations

Power spectral analyses shows that the power of low frequency including theta and delta bands are increased during the task trials compared to the 8s segments of ITIs in both of the Cortex and Striatum (Figure 2).



**Figure 2: Power Spectrum during Task Trials and Inter-Trial Intervals (ITIs).** Low frequency power during task trials increased compared to the power during ITIs. Shaded areas indicate 95% confidence interval of 10 sessions (5 rats x 2 sessions).

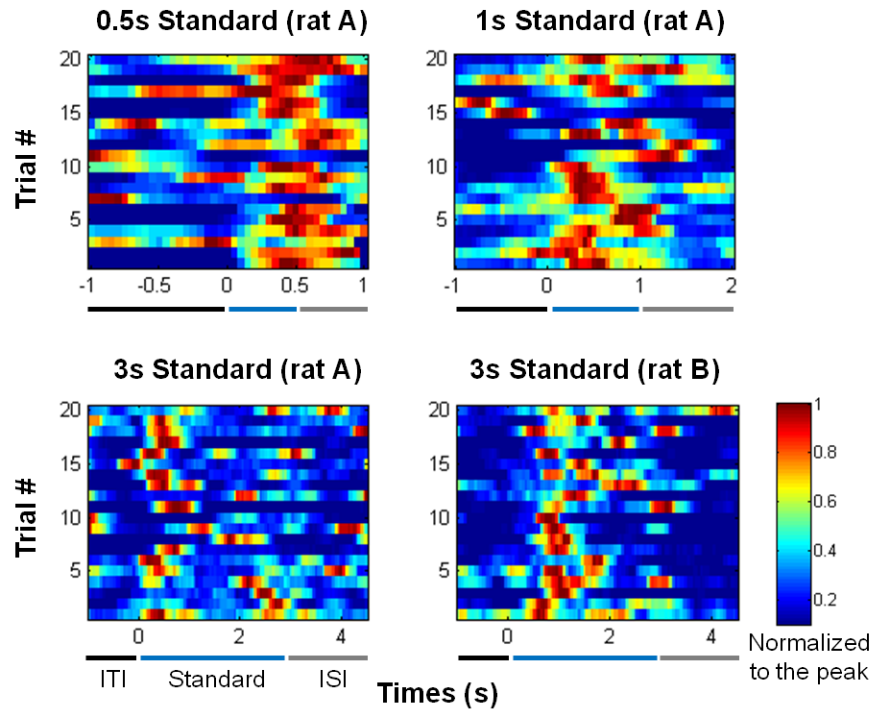
To further show the temporal changes of the oscillatory power, the spectrograms of each Standard duration were shown in figure 3. Low frequency power was robustly increased up to 2.5 times higher than the power during the ITI baseline (from -3s to -0.5s with respect to the onset of Standard or warning cue) in the LFPs from both the cortex and striatum (Figure 3). The increase of low frequency power was shown similar across the 3 different Standard durations and reached their maximum at around 0.5-1s after the onset of the Standard signal.



**Figure 3: LFPs Oscillations in Cortex and Striatum during the Encoding of the Standard.** The spectrograms were normalized to the power during the ITI (from -3 to -0.5s relative to the onset of Standard signal) separately in each frequency.

In addition, although the averaged spectrogram seems to show a sustained increase of low frequency power until the end of the Standard signal (especially in the 3s Standard duration), individual trial analysis shows that the increase is rather discontinuous in each trail, but it seems like averaging over multiple trials produce the

pattern that looks like continuous. In each trial, the increase of oscillation usually continued for about 0.5-1s and the increase often occurs multiple times in a trial with various temporal delays from the Standard onset (Figure 4).



**Figure 4: Low Frequency Oscillations (<10Hz) in Individual Trials during the Encoding of Standard Duration.** For a better visualization, the power of low frequency oscillation was normalized to the peak of the power in each trial.

The data of cued and un-cued tasks are shown averaged together because the behavioral performance did not differ from each other and also the inspection of spectrograms looks similar between the cued and un-cued tasks. To see if there is any difference in the low frequency oscillation according to the warning cue presentation, the power of low frequency oscillation of Standard was analyzed using ANOVA (cued

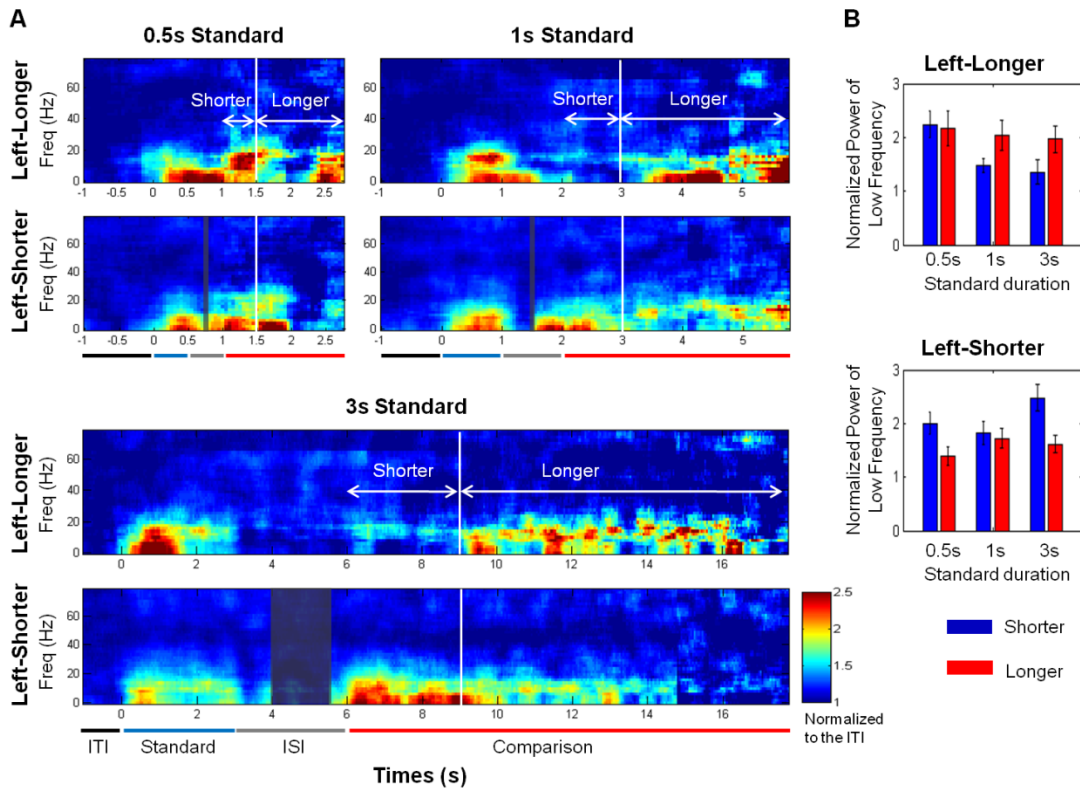
or un-cued group  $\times$  Standard duration) and there was no significant main effect nor an interaction between factors.

### **2.2.3 Timing of the Comparison durations**

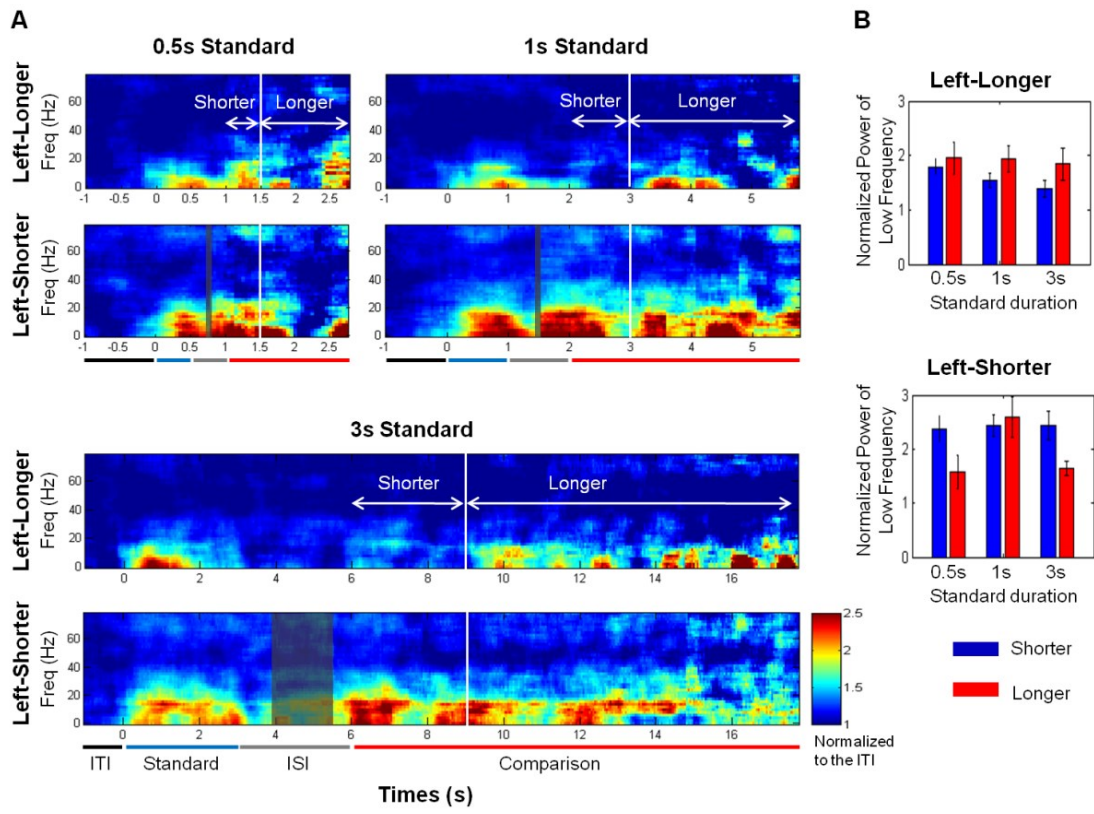
The low frequency oscillation power of the cortex and striatum during the Comparison duration was strongly modulated as a function of the lever-mapping. Left and right lever-mapping was counterbalanced between rats, so "left-longer" group (2 rats with un-cued paradigm) should press left lever for "longer" responses, and "left-shorter" group (1 rat with un-cued and 2 rats with cued paradigm) should press left lever for "shorter" responses.

The result showed that the low frequency oscillation power of "left-longer" group was reduced when the Comparison was "shorter" than the Standard, and increased when the Comparison continued to be "longer" than the Standard especially in trials with 1s and 3s Standard (Figure 5, 6). The "left-shorter" group showed the opposite pattern of increased low frequency power until Comparison signal reached to the duration of Standard and the power has reduced afterwards. The LFPs were recorded from the right cortex and striatum in both groups of rats, so this finding indicates that the increased low frequency oscillation in the right hemisphere would be related to the attention to the left lever or to the timing to press the left lever. This pattern corresponds to the rats' behavior that they initially wait near the "shorter" lever to be extended and then, switched to wait near the "longer" lever if Comparison

continues longer than the Standard (lever extended when the Comparison signal off). For example, the “left-shorter” rats waited to press left lever at the beginning and move to the right lever while the “left-longer” rats waited at right lever and later switch to the left lever.



**Figure 5: LFPs Oscillations in the Right Cortex.** (A). Spectrograms of correct trials were averaged. The left lever represented “longer” for 2 rats, and “shorter” for the other 3 rats. With respect to the point where the Comparison signal is same to the Standard (white line), “left-longer” group rats showed reduced low frequency oscillation power in “shorter” durations compared to the “longer” durations. “Left-shorter” group rats showed the opposite pattern. In order to average the cued and un-cued comparison tasks which have different durations of ISIs, certain time windows of ISI were cut out or extended accordingly, and the cut points are indicated by the gray shaded areas. (B). Normalized powers of low frequency oscillation (<10Hz) in the cortex during the last 0.5s with the Comparison signal are shown. A significant interaction between the left-shorter/left-longer group  $\times$  shorter/longer Comparison durations was shown ( $p < 0.05$ ).



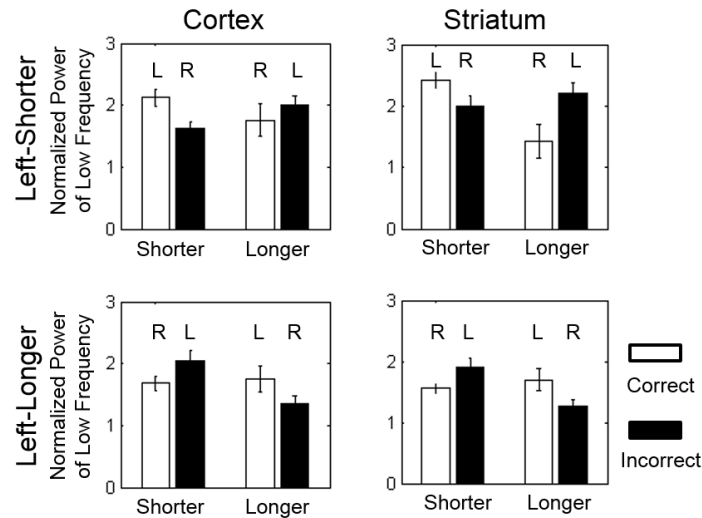
**Figure 6: LFPs Oscillations in the Right Striatum.** All the other parameters are same as in the Figure 5 except that the “left-shorter” group data are averaged over 2 rats.

To confirm this finding, the oscillation power of low frequency (<10Hz) for a 0.5s window right before a comparison signal off was averaged and compared using an ANOVA (Standard duration × left-shorter or left-longer group × shorter or longer Comparison). A significant interaction was shown in the left-shorter/left-longer group × shorter/longer comparison ( $F(1,600)=9.14$ ,  $p<0.01$  for Cortex;  $F(1,547)=7.71$ ,  $p<0.01$  for Striatum), confirming the increase of low frequency oscillation during a Comparison duration is related to a left-lever pressing.

## 2.2.4 Correct and incorrect trials

To compare the low frequency oscillation power between correct and incorrect trials, the power of Comparison signal (again, the 0.5s window before a comparison signal off) was analyzed using an ANOVA (correct or incorrect trials  $\times$  shorter or longer comparison) in each of the left-shorter and left-longer lever-mapping group. Findings showed significant interactions between the two factors which indicate that the increased oscillation power represents the left-lever choice rather than representing that the choice is correct or incorrect or the Comparison is shorter or longer than the Standard duration (Left-shorter group:  $F(1,492)=4.03$ ,  $p<0.05$  for Cortex;  $F(1,369)=5.90$ ,  $p<0.05$  for Striatum; Left-longer group:  $F(1,371)=4.98$ ,  $p<0.05$  for Cortex;  $F(1,405)=7.85$ ,  $p<0.01$  for Striatum) (Figure 7).

To see if there is any effect of encoding of Standard to the correct or incorrect responses, an ANOVA (left-shorter or left-longer group  $\times$  correct or incorrect trials  $\times$  shorter or longer comparison) was also conducted on the low frequency power of Standard duration; however, there was no significant main effect of factor nor an interaction between factors both in the cortex and the striatum.



**Figure 7: Power of Low Frequency Oscillation (<10Hz) during Comparison Signal in Correct and Incorrect Trials.** As all the LFPs were recorded from the right hemisphere, the findings indicate that the low frequency oscillation increases with the preparation or timing of a left lever pressing irrespective of the Comparison durations. Significant interactions ( $p < 0.05$ ) between shorter/longer Comparison durations  $\times$  correct/incorrect responses were shown in each lever-mapping groups in the cortex as well as in the striatum. L=left lever response; R=right lever response.

### 2.3 Discussion

Our simultaneous recordings from the cortex and striatum during ordinal/temporal comparisons show increased brain oscillation correlated to the task demands of timing/encoding and comparison processes. Low frequency oscillations including theta and delta bands increased both in the striatum and the cortex during the encoding of Standard durations in both of the cued or un-cued paradigms and also in both lever-mapping groups of left-shorter and left-longer. However, the low frequency oscillation during Comparison duration shows lever-mapping dependent pattern; low frequency power of the right cortex and striatum increases when rats are waiting to

press or attending to the left lever, regardless of whether the Comparison is longer or shorter than the Standard duration. Little research has explored LFPs oscillatory patterns in relation to timing and comparison processes; therefore, current findings of selective increases of low frequency oscillation in relation to the ordinal/temporal comparison processes is first to be shown, and it suggest that low frequency neural oscillation plays a crucial role in temporal processes.

Especially, it supports that both of the temporal and spatial aspect of neural functions are important in the processing of specific duration information. For example, while the duration information is attended and maintained by the oscillatory aspect of neural function (theta and delta-bands), the selected lever is represented by the spatial localization of the neural oscillation into a specific brain area (contralateral cortico-striatal areas to the lever choice).

A variety of evidence ranging from human neuroimaging, clinical populations, pharmacological and lesion studies supports the critical role of cortico-striatal circuit in timing and time perception (Allman and Meck 2012; Harrington et al. 2010; Hinton and Meck 2004; Jones and Jahanshahi 2011; Lewis and Miall 2006; Meck 2006a; b; Meck et al. 2008; Wiener et al. 2010). In addition, electrophysiological studies in rodents and primates have reported various firing patterns of neurons in cortico-striatal circuit in relation to timing, such as linear ramping, descending, peak or dip patterns across time

(Jin et al. 2009; Lebedev et al. 2008; Matell et al. 2003a; Matell et al. 2011; Mita et al. 2009; Narayanan and Laubach 2009; Niki and Watanabe 1979).

In relation to the functional role of the cortico-striatal circuit in timing, SBF model suggests that a coincident pattern of cortical neurons can be detected by striatum medium spiny neuron (MSN) at a specific time (Matell and Meck 2004). Oscillatory patterns of cortical neurons are emphasized in the SBF model as the core mechanisms of representing different durations. However, little study so far has examined oscillatory patterns in cortico-striatal circuit in relation to timing, therefore the current findings of low frequency oscillation in the cortex and striatum suggest the importance of neural oscillations in timing and support the SBF model.

However, the current findings need further considerations to be explained precisely within the neural prediction of SBF model. Because the current understanding to the origins of LFPs and neural oscillations are controversial (Baranauskas et al. 2012; Buzsáki et al. 2012), it is difficult to connect the oscillatory findings of LFPs to the SBF model prediction of individual neurons. However, recently proposed EIO (excitatory and inhibitory oscillators) model (in section 5), which is based on the SBF model but further developed to consider the population pattern of oscillatory individual neurons including both excitatory and inhibitory neurons, could suggest the underlying mechanisms of the neural oscillations and feasible predictions in relation to timing processes.

Only a few studies have reported theta or delta oscillation in the cortical-striatal circuit with relation to a specific cognitive function, and most of them were concentrating on tasks dealing with spatial information (Berke et al. 2004; DeCoteau et al. 2007a; b; Tort et al. 2008). In this regard, the current study is providing a new evidence of relation between the theta/ delta oscillations in the cortical-striatal circuit and temporal comparison processes. Especially, the increase of neural oscillation during a comparison phase was evident on the contralateral cortico-striatal circuit to the direction of the chosen lever, and this suggest that the cortico-striatal oscillation is related to an active maintenance of a direction to the selected lever. In accordance, intact cortico-striatal circuit has known to be important to the operant delayed alternation performance (Dunnett and White 2006; White and Dunnett 2006), which needs active maintenance of previously selected lever.

The findings show that low frequency oscillations including theta and delta are increased during the encoding and comparison phases in a lever-mapping dependent manner. Various interpretations can be considered with respect to which cognitive components in this timing and comparison task are relevant to the increased low frequency oscillation. First, the low frequency oscillation is not simply dependent to the stimulus presentation because the power has increased or decreased depending on the lever choice while there was a continuous presentation of comparison signal.

Moreover, the low frequency oscillation would not simply represent only a motor preparation because the power has also increased during the Standard duration which doesn't involve any specific motor preparation. Also, it is worth to note that rats usually use both paws to press a lever so the increased oscillation in the contralateral hemisphere is not representing left or right body movement. Previous studies on motor cortex have shown the event-related desynchronization (ERD) in the beta-band (15-30Hz) in relation to the motor preparation and its dynamic modulation (Pfurtscheller et al. 1996; Sanes and Donoghue 1993; Swann et al. 2009; Tzagarakis et al. 2010). However, the current finding does not present any noticeable changes of beta-band ERD.

The performance on sub-second timing was poor in the ordinal/temporal comparison task as shown in the previous study (Cordes and Meck 2013). It has been suggested that distinct neural structures are involved in sub- and supra-second timing (Breukelaar and Dalrymple-Alford 1998; Buhusi and Meck 2005; Koch et al. 2007; Lewis and Miall 2003a; Lewis and Miall 2003b; Wiener et al. 2010), and the dissociation of the mental time line between sub- and supra-second timing contributes to the poor performance exhibited in the sub-second timing (Cordes and Meck 2013). With the finding, it was proposed that rats were able to generalize an ordinal rule to durations in the suprasecond range but not for subsecond ranges.

The oscillatory pattern of sub and suprasecond timing looks similar during the encoding processes both in the cortex and the striatum. The low frequency oscillation

was increased during the Standard duration showing its peak at around 0.5-1s after the Standard onset. Examination of the individual trials revealed that the increase of low frequency oscillation continues for about 0.5-1s and then, the power has dropped close to the level of baseline. The peaks of oscillation power present with a various temporal delay after the onset of Standard and often show multiple peaks in a trial, which would have produced the pattern of sustained oscillation when averaged over multiple trials, especially as shown in the 3s Standard.

With the finding of 0.5-1s delay of the oscillation peak from the Standard onset, we speculated the possibility that the subsecond Standard duration is too short to attend properly considering the relatively long ITIs (25-60s). In order to test if the temporal cost of directing attention have produced the difficulties in subsecond ordinal comparison, we tested a group of rats with that cued design where the cue indicates the upcoming onset of Standard. However, the subsecond timing showed poor performance also in the cued task, and the low frequency oscillation pattern looks similar to the un-cued task. The finding reveals that the inefficiency of predicting the Standard onset is not related to the delay of oscillation peak nor to the difficulties in the subsecond comparisons.

### **3. Neural Oscillations in Duration Judgment and Production**

Acting at a proper time or expecting reward at a certain time is fundamental properties underlying learning and behavior. Interval timing is very closely related to motor preparation or reward expectation, thus, research on interval timing has mostly involved aspects of motor preparation, movement or reward. The motor components are often intermixed with the findings of interval timing so it is difficult to dissociate the neural features involved in interval timing from that of motor preparation or motor output. However, the components of motor preparation can be differently integrated with the interval timing components, for example, when one measures a stimulus duration for making a decision, specific motor preparation would be less involved compared to the case of timing a duration for an action.

Therefore, in order to find any neural differences between interval timing for an action and duration judgment for decision making, a duration judgment and production task has been designed and trained in a group of rats. The procedure has two phases in each trial which are 1) measuring a duration of the first signal and choose which lever to press depending on the duration (duration judgment for decision making), and then, 2) making a lever response at a target time with the second signal (interval timing for an action). The later part of this procedure, so called duration production phase is similar to

a differential reinforcement of low rates of responding schedule (DRL) (Cheng et al., 2008a; Cho and Jeantet, 2010; Young and McNaughton, 2000).

In a DRL procedure, an animal is required to withhold its responses until an imposed delay has passed because a premature responding will not be rewarded. However, the current design has couple of modifications from the typical DRL procedure in order to optimize the task paradigm for an electrophysiological recording. First, while a target duration starts from the previous responding in a typical DRL procedure, initiation of second white noise indicates the timing onset in this modified design. This is to extract the neural changes during interval timing in comparison to the neural patterns during trial by trial baseline (inter-trial-interval). Second, relatively shorter durations (2.1s) instead of the typically utilized durations in DRL procedure (e.g. 5, 10, 18 and 36 s) will be used in the modified paradigm. Typical DRL procedure requires the ability of behavioral inhibition in addition to the ability of time estimation to hold the response; therefore, by using shorter durations, the confounding from behavioral inhibition can be minimized in addition to the advantage that the task can be easy to learn.

The previous ordinal/temporal comparison task has mainly involved duration judgment and encoding of the first signal and we have shown the increase of low frequency oscillation during the procedure. In this paradigm, we expect to see similar findings of low frequency oscillation increase during the duration judgment phase, and

to be able to differentiate oscillatory patterns that are corresponding to motor preparation by a comparison between duration judgment and production phases.

In addition, the oscillatory frequency and power in relation to the temporal variations of responding will be examined by comparing early versus delayed responses. Temporal variations in behavior have been a focus of much research (Gibbon et al., 1984; Gu and Meck, 2011; van Rijn et al., 2013), and the variations in reaction times could be produced by multiple reasons like speed of clock (rate of pacemaker) or threshold for responding (decision making). Thus, exploring the oscillatory features involved in variations in response times would provide better understanding of the functional relations between neural oscillations and interval timing behaviors.

### ***3.1 Material and Methods***

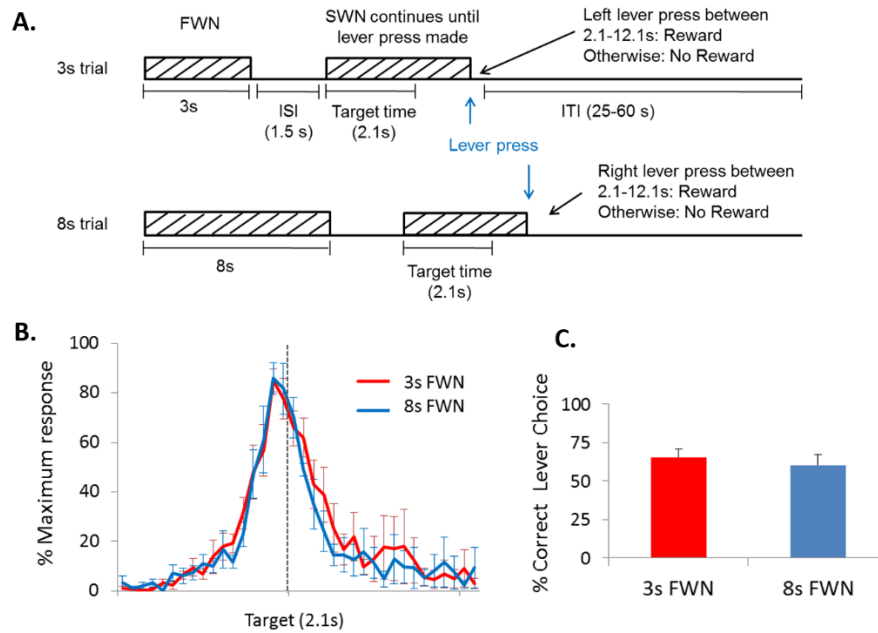
#### **3.1.1 Animals and apparatus**

Fourteen adult male Sprague-Dawley (Charles River) rats were trained on the behavioral task, and 6 rats showing good performances were selected for micro-wire array implanting surgery. Housing, food restriction procedures and training apparatus are identical to the previous experiment as described in the section 2.1.1 and 2.1.2. All studies were conducted in accordance with standard procedures approved by the Duke University Institutional Animal Care and Use Committee.

### 3.1.2 Behavioral procedures

Before training the duration judgment and production task, rats were pre-trained with 5 sessions of combined magazine and lever training as described in the previous section (2.1.3.1). After successful pre-training, rats were trained with the duration judgment and production task for more than 20 sessions.

In the duration judgment and production task (Figure 8), 3s or 8s of first white noise (FWN) was presented for duration judgment, and then, second white noise (SWN) was followed with both lever insertion for duration production. If the FWN was 3 s, a food pellet was dispensed only if a rat wait for 2.1 s after a SWN onset AND press left lever. Otherwise, for example, when a rat press left lever before 2.1s or press right lever after 2.1s, a food pellet was not provided. On the other hand, if the FWN was 8s, a rat should wait for 2.1s after a SWN onset AND press right lever in order to get the reward. Left or right lever mapping to 3s or 8s FWN was counterbalanced across rats, so 3s FWN indicated to pressing left lever in 2 rats and right lever in 4 rats to get a food pellet. When a response was made, the SWN was terminated and the both lever was retracted. Also, if a rat did not make any response, the lever was retracted and the trial was terminated without any reward. ISI was 1.5s and ITI was randomly chosen among 25-60s.



**Figure 8: Task Design and Behavioral Result.** (A) Rats were trained to time the first signal (FWN) to make a lever choice and wait for a target time with second signal (SWN) to press the chosen lever. (B) Response function shows its peak right before the target time. (C) Lever choices were over the chance level (50%).

### 3.1.3 Surgery and recording procedures

The general surgery and recording procedures are identical to the previous experiment except the target areas of electrodes and reference. The 6 rats that performed well in the duration judgment and production task were selected and chronically implanted with a micro-wire array of 16 electrodes. Eight electrodes were targeted to the right striatum (AP between 1 and -2 mm; ML between 2 and 3.5mm; and between 3.5 and 4.5mm deep) and 4 electrodes were targeted to the right sensorimotor cortex (AP between 1 and -2 mm; ML between 2 and 3.5mm; between 1.5 and 2.5mm deep) and the other 4 electrodes were targeted to the hippocampus. In order to the target the three

areas, the micro-wire arrays have a 30 degree angle between electrodes and a headstage. However, the recording data from hippocampus is not shown here due to uncertainty of recording sites.

One reference electrode was located in the cortex (AP between 0 and -2mm; ML; between 3 and 4mm; 2.5 mm deep) and the other reference electrodes was located in the striatum (AP between 0 and -2mm; ML between 3 and 4mm; 4.5 mm deep). Both reference electrodes had a 2mm exposed tip. The LFP signals from cortex and striatum was referenced to the cortex and striatum reference signals respectively.

The LFPs were recorded during the duration judgment and production task for multiple days and the recording data of three sessions, which displayed satisfactory performance, were selected for further analysis in each rat.

### **3.1.4 LFPs data analysis**

Before all analyses, the electrode data of each session were screened to determine if they show a significant noise. As a result, LFPs data from one cortex electrode from one rat was excluded from further analysis. The trials that shows obvious noise which probably have caused by scratching headstage also removed from further analysis. FieldTrip (<http://fieldtrip.fcdonders.nl/>) and in-house Matlab programs were used for the following analyses.

First, using “ft\_freqanalysis” routine of FieldTrip toolbox with hanning window and ‘mtmconvol’ method with specified length of time windows (5 cycles long, e.g. 0.5 s

window for 10 Hz) for each frequency, spectrograms of oscillatory power were calculated. Then, the power was normalized by the baseline power (with the time window of -9s to -0.5s from trial onset) in each frequency range in each trial. As mentioned in the previous analysis (section 2.1.4), the normalized power indicates the relative increase of oscillatory power from the baseline.

Trials of each session were categorized into early and delayed responses with respect to the target time. For a better comparison of theta power, 4 - 12 Hz band power was extracted from each trials and compared between the two response categories.

In order to see cross-frequency coupling, LFPs for ITIs and task trials were segmented into 8s for 3s FWN trials and into 13s for 8s FWN. Therefore, the each trial segment has included FWN, ISI and SWN until a lever press made. ITI segments included from 8s to 16s after a 3s FWN trial, and from 8s to 21s after a 8s FWN trial in order to match the length of segment to the task trial. First, using “ft\_freqanalysis” routine of FieldTrip toolbox with hanning window and ‘mtmconvol’ method, power spectrum of each time point was calculated in each frequency ranges. Then, “ft\_freqanalysis” routine was applied again with hanning window and ‘mtmfft’ method to the calculated time series of frequency power. Using this analysis, the envelope frequency bands (lower frequency) in which the power of each frequency band (higher frequency) entrained could be shown. Difference map between trial and ITI was shown by subtracting the powers of cross-frequency coupling from each other.

## **3.2 Result**

### **3.2.1 Behavioral performance**

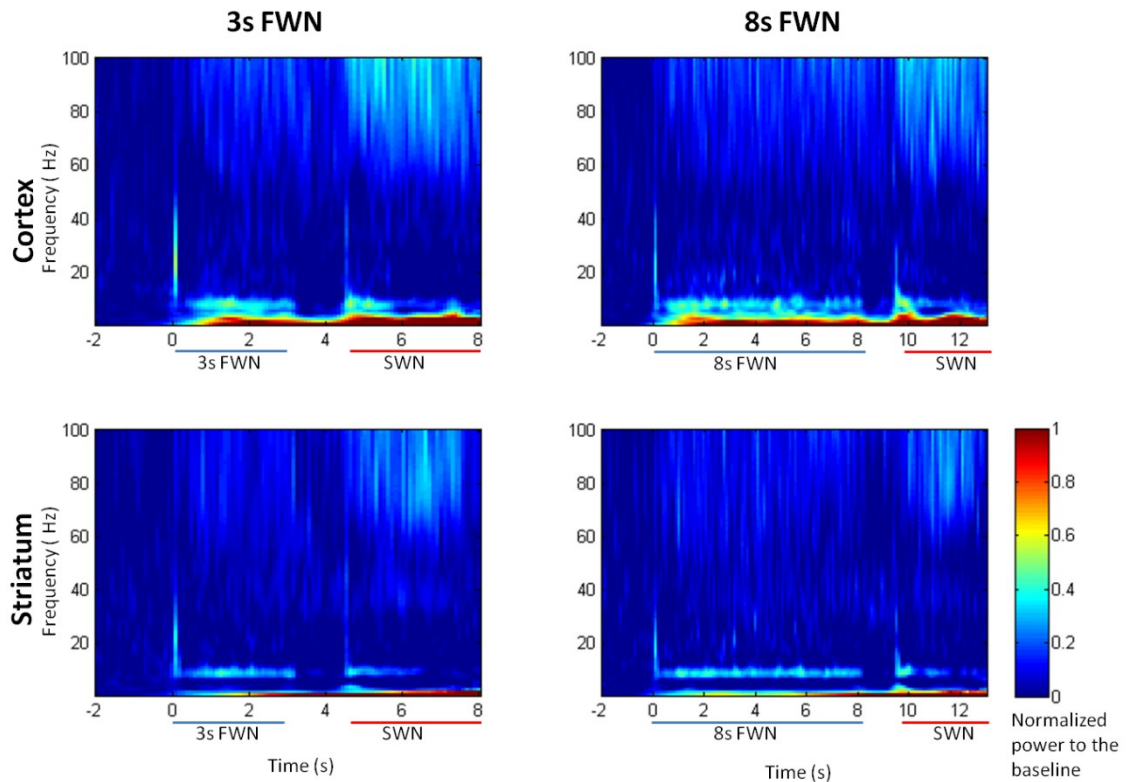
Behavioral performances during electrophysiological recording shows the peak of responses right before the target time (2.1s) and the shape response functions were not significantly different between the trials with 3 and 8s FWN (Figure 8 B). The correct lever choice was over the chance level for both 3s FWN (65.4%) and 8s FWN (60.4%) (Figure 8 C). Therefore, the result indicates that rats timed both the FWN and SWN during the recording sessions.

### **3.2.2 Oscillatory power during duration judgment and production**

Spectrograms show increased low frequency oscillations including theta and delta during the task in the cortex and the striatum (figure 9). Sustained theta (at around 8Hz) and delta power (1-3Hz) was shown during the duration judgment phase (FWN) as well as during production phase (SWN). Although cortex and striatum shows similar pattern in overall, the increased delta power was especially prominent in the cortex. In addition to the increase of theta and delta, high gamma power (60-100Hz) increase was also observed during the production phase (SWN).

The displayed values are normalized power to the baseline (ITI segment from -9s to -0.5s before the trial onset), therefore, it shows the relative increase of power in each frequency ranges. Spectrograms of absolute power also showed high power in the low

frequency ranges including theta and delta (data not shown).

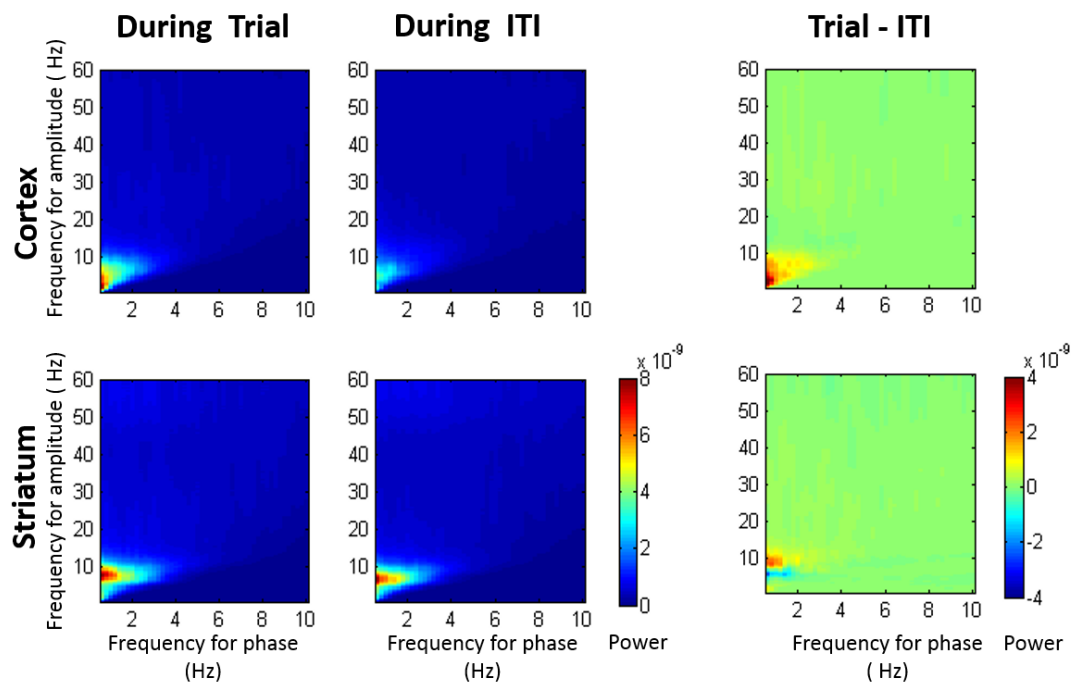


**Figure 9: LFPs Oscillations in Cortex and Striatum.** Both in the duration judgment and production phases, theta and delta powers were increased compared to the baseline.

### 3.2.3 Coupling of theta and delta rhythms

In order to see the relations between different frequencies, cross frequency coupling was examined. By showing the oscillatory patterns of the power of each frequency rhythm, it was shown that the power of theta rhythm oscillates in delta or lower frequencies (Figure 10). This finding of theta and delta coupling was shown both in the cortex and the striatum. Also, the finding was shown not only during the task trial (8s segments for the trials with 3s FWN and 13s segments for 8s FWN trials) but also

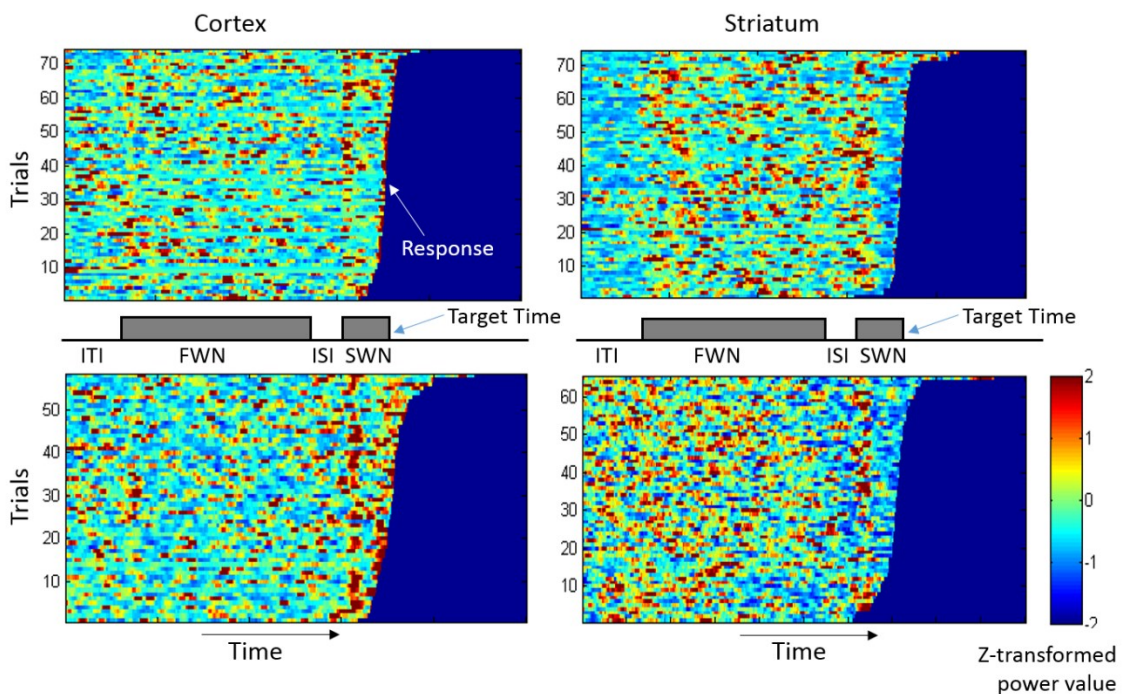
during the ITIs (same length segments corresponding to the trial segments). However, when the power was compared by subtracting the power mapping between the trial and ITI segments, the theta and delta coupling was shown stronger during the trials than during the ITI. Although the coupling was shown only between theta and delta (or lower frequencies), it should be noted that the relations of high frequency oscillations (e.g. high gamma and theta) could be ignored in this scale and visualization due to their smaller power compared to the low frequency power.



**Figure 10: Cross-Frequency Coupling between Theta and Delta Rhythms**

In order to see the patterns of theta and delta relations more closely in individual trials, power of theta rhythms were shown in individual trials. Four different electrodes were selected and the trials of each electrodes were aligned with the order of response

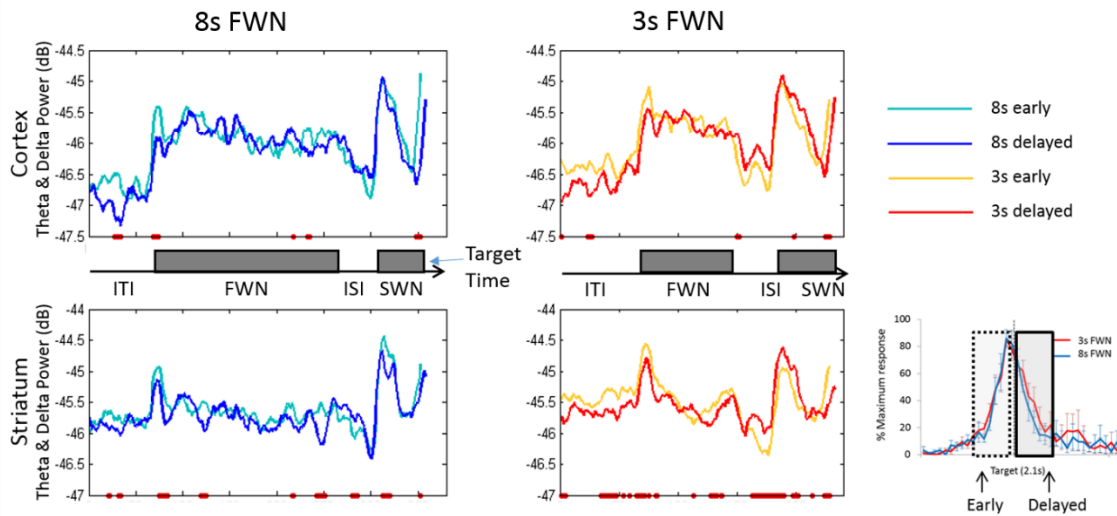
times from shorter to longer (Figure 11). Visualization of theta power in individual trials revealed various patterns such as that the power of theta shows its peak at the signal onset and/or right before the responses. Also, it should be noticed that the peaks of theta power are oscillates in time rather than showing sustained increase such as shown in the averaged data in the cortex during duration judgment phase (Figure 9). Due to the different peak times of oscillatory power over trials, the averaged power over multiple trials could have shown the sustained increase of power.



**Figure 11: Theta Power Changes in Individual Trials.** LFPs signal from 4 different electrodes from two rats were selected for example. Trials are aligned with the order of response times of lever pressing.

### 3.2.4 Oscillatory power during early versus delayed responses

In order to show the relations between response times and neural oscillations, the power of theta rhythm has been plotted separately for early and delayed responses (Figure 12). Comparison between the two response categories showed similar pattern of theta power in overall but differed at certain time points. Red dots indicates the time points where the powers were significantly different ( $P < 0.5$ , not corrected for multiple comparison) between the trials with early and delayed lever pressing. Especially theta power before the trial onset was increased in the trials with early responses compared to the trials with delayed responses indicating that the oscillatory status before the trial onset is related to the timing behavior.



**Figure 12: Theta Power Differences between Early and Delayed Responses.** Theta powers were plotted across trial time in each response condition. The right bottom panel shows how the early and delayed responses were categorized.

### **3.3 Discussion**

The findings of this experiment show that the power of theta and delta bands in the sensorymotor cortex and striatum fluctuates with temporal processes. During the duration judgment and production, low frequency power including theta and delta was increased. Although the averaged finding shows sustained increase of theta activity, the inspection of individual trials revealed that the theta power fluctuates across a task trial showing multiple peaks. Similarly to the inspection of theta fluctuation in each trial, the cross-frequency coupling finding showed that the power of theta was oscillating in delta rhythm, and this phenomenon was stronger during timing task trial phases compared to the inter-trial intervals. Therefore, the finding indicates that the strong interaction between theta and delta rhythm presents during temporal processes.

Lots of speculations on the functional role of neural oscillations have been suggested (e.g. efficient information selection), and the suggested functional roles differ depending on the frequency ranges of oscillation. The theta or delta ranges of oscillations are mostly shown in the tasks that involve working memory, spatial navigation, attention or decision making (DeCoteau et al. 2007a; b; Düzel et al. 2010; Huxter et al. 2003; Hyman et al. 2010; Jones and Wilson 2005; Lakatos et al. 2008; Siapas et al. 2005; Tort et al. 2008). Especially, the role of theta oscillation in working memory was supported with the evidences of hippocampal theta oscillation and the neural firings that are entrained to a specific phases of theta rhythm (Hyman et al. 2010; Jones

and Wilson 2005; Siapas et al. 2005). Primate (Pesaran et al. 2002; Siegel et al. 2009) and human studies (Fell et al. 2011; Rizzuto et al. 2003; Tesche and Karhu 2000) also support the idea that the increased theta oscillation or phase encoding to theta in the brain areas including frontal cortex, parietal cortex, and hippocampus are important in working memory. Regarding to the delta oscillations, it has long been considered as indexing a deep sleep state (Steriade 2006), but recent evidence support its functional role in cognitive processes such as in attentional selection (Kim et al. 2007; Lakatos et al. 2008; Morgan et al. 1996).

Considering the hypothesized role of theta and delta oscillations in working memory and attention, the functional role of low frequency oscillation during the duration judgment and production could be hypothesized to be involved in attention to the stimulus duration, maintenance of the duration information and/or timing to press a selected lever.

In addition to the theta and delta power increase, high gamma power was also increased during the duration production phase. The increase of high gamma was not evident in the previous study of ordinal/temporal comparison task, and stronger during the duration production phase than the duration judgment phase. The critical difference of duration production phase from the other timing phases (ordinal comparison or duration judgment) is that it involve inhibition of premature responses. During the ordinal/temporal comparison task and duration judgment phase, the lever is not

available, however, the lever is already inserted into the chamber during the production phase, but rats should wait the target time to press the lever in order to receive a food pellet. Further research should investigate what is the functional role of high gamma in timing tasks, and whether response inhibition is related to the increase of high gamma.

In addition, the oscillatory power at the pre-trial period was different between early and delayed responses. Increase pre-trial theta power was related to the early response. Evidence showing that the pre-trial oscillatory power is related to successful encoding of a stimulus or information processing speed was previously shown in human or primate EEG studies (Buschman et al., 2012; Guderian et al., 2009; Kleberg et al., 2014), however, to our best knowledge, the relation between pre-trial oscillatory power and interval timing was first to shown. This finding suggests that the preparatory state or the ongoing oscillatory states at the moment of duration onset is related to the timing of lever pressing. It cannot be explored whether the pre-trial oscillation power is related to the speed of time or the threshold for responding in this task design, so the relation should be further explored by different task design which can differentiate those two factors controlling response time (e.g. peak interval time paradigm).

## 4. Interval Timing and Working Memory

A stimulus has a multiple dimensions of information such as, identity, intensity and duration. Underlying neural circuits and neuronal modulation of the circuit will determine which feature will be extracted and attended from a stimulus. In this sense, interval timing and working memory are closely related and may largely be distinguished in terms of the type of information that is extracted and maintained from the underlying mechanisms, i.e., duration and temporal order information in the case of interval timing and specific auditory, visual, or semantic information in the case of working memory (see Baddeley, 2012; Lustig et al., 2005).

In the sense that both interval timing and working memory requires a continuation of certain neural representation across time in a brain, they are tightly related to each other. Or, interval timing reflects a specialized form of working memory in that an internal representation of time needs to be maintained in order to control temporal processing in the absence of an external stimulus (Hälbig et al., 2002; Meck and Benson, 2002; Wiener and Coslett, 2008). Both in interval timing and working memory, neural oscillation would be the crucial mechanism that enables the continuation of representation or information processing across time through recurrent characteristics of neural networks.

Interval timing and working memory shared lots of characteristics including behavioral features (section 1.5), brain areas involved, and neural features. It has been

suggested that interval timing and working memory rely not only on the same gross anatomical structures, but also on the same neural representations (Buhusi and Meck, 2009b; Lewis and Miall, 2006; Lustig et al., 2005; Lustig and Meck, 2005).

The literature supports the common involvement of the PFC, basal ganglia, and parietal lobe in addition to the specific sensory areas related to the stimuli to be remembered into working memory (e.g., D'Esposito, 2007; Postle, 2006; Wager and Smith, 2003). Especially, the cortical-striatal circuit has been suggested to play a crucial role in selecting and updating the relevant information into the working memory (e.g., Frank et al., 2001; Hazy et al., 2006, 2007; O'Reilly and Frank, 2006). Not only the cortical-striatal circuit is also known critical in interval timing as previously explained (section 1.2), the same types of dopaminergic drugs affect both supra-second timing and working memory. Neural features during working memory also show sustained neural activity or systematic ramping or decreasing activity during a delay period (e.g., Brody et al., 2003; Kojima and Goldman-Rakic, 1982; Niki and Watanabe, 1979; Quintana and Fuster, 1999), which are also similarly observed during interval timing procedures (section 1.3). Thus, taken together, this evidence supports the notion that same anatomical/neural properties are likely shared between the two processes (Buhusi and Meck, 2002, 2009a; Lewis and Miall, 2006; Lustig et al., 2005; Lustig and Meck, 2005).

However, previous human neuroimaging studies showed that different brain patterns, especially different oscillation frequencies are involved in item and temporal-

order maintenance of sequential objects (Hsieh et al., 2011). EEG measured in humans showed that frontal theta (5-7 Hz) oscillation power was increased during the temporal-order maintenance compared to item maintenance, while parietal and lateral occipital alpha (9-12 Hz) oscillation power was increased during item compared to temporal-order maintenance. Similarly, oscillatory responses to spatial or temporal-order information for multiple items in working memory were compared to each other, and the results showed that left frontal theta (5-8 Hz) and posterior alpha/beta (9-12 Hz/14-28 Hz) oscillation power levels were increased with right frontal gamma (30-50 Hz) oscillation power decreased for the temporal-order component compared with the maintenance of spatial information in working memory (Roberts et al., 2013).

With this evidence, neural oscillations in the frontal/motor and striatum are compared between interval timing and working memory procedures. Although the same anatomical/neural properties are shared between interval timing and working memory, specific differences will be observed between the two procedures depending which component (e.g. temporal or spatial) is attended and more engaged. In order to reduce subject variance as well as the recording site, rats were initially trained for a task that requires both interval timing and working memory. Afterwards, LFPs were recorded from the same rats while they do interval timing task as well as while they do working memory task, and the neural oscillation patterns during the two tasks were compared in each electrodes of the same rat.

## **4.1 Material and Methods**

### **4.1.1 Animals and apparatus**

Fourteen adult male Sprague-Dawley (Charles River) rats were trained on the behavioral task, and 3 rats showing good performances were selected for micro-wire array implanting surgery. Housing, food restriction procedures and training apparatus are identical to the previous experiment as described in the section 2.1.1 and 2.1.2. All studies were conducted in accordance with standard procedures approved by the Duke University Institutional Animal Care and Use Committee.

### **4.1.2 Behavioral procedures**

Before training the timing and working memory task, rats were pre-trained with 5 sessions of combined magazine and lever training as described in the previous section (2.1.3.1). After successful pre-training, rats were trained with the following timing and working memory combined task for 2 weeks.

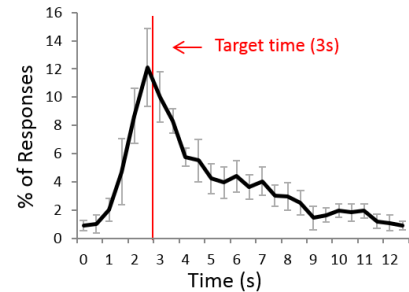
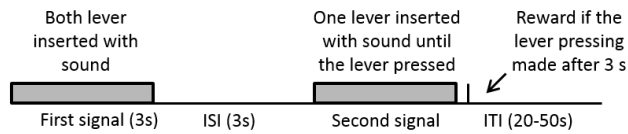
In the timing and working memory task, 3s white noise (first signal) was initiated with a left or right lever insertion into the chamber, and the lever was retracted when the signal turned off. After 1-3 s of ISI, the same white noise (second signal) was initiated again with the same lever insertion in the half trials of the sessions. On these trials, if a lever pressing made after 3s, a food pellet was dispensed into the food cup, otherwise, no pellet was provided and the trial was terminated. On the other half trials, both levers were inserted into the chamber with second signal, so choosing the same

lever that was inserted with the first signal was required in addition to the 3s timing like in the other half trials in order to get a food pellet. After a lever pressing with the second signal, the trial is terminated with the white noise off and the lever(s) retraction, and followed by 20-50s of ITI. Daily training session was continued for 2 hours and each session contained at around 160 trials.

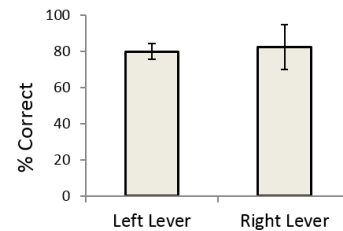
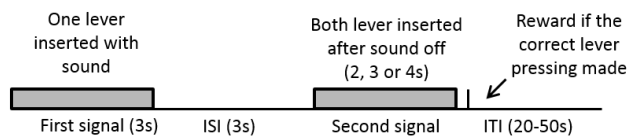
After a micro-wire array implanting surgery, the rats were retrained with the interval timing task (figure 13 A) for 3-5 sessions and followed by LFPs recording for 3 sessions of interval timing task. Then, the same rats were retrained with working memory task (figure 13 B) for 3-5 sessions as well, and LFPs were recorded during the working memory task for 2 sessions. Task designs of timing task and working memory are similar to each other in order to reduce other variables. In the timing task, both levers were inserted with first signal and one (correct) lever was inserted with the second signal and a reward was given with the timed (after 3s) lever pressing. In the working memory task, one lever was inserted with first signal and both levers were inserted right after the second sound end. The duration of second sound was randomly chosen among 2, 3 or 4s in order to give variations in response time. If the correct lever (the same lever to the first signal) was chosen, a reward was provided regardless of the response time. In both timing and working memory tasks for LFPs recording, ISI was maintained as 3s for the convenience of data analysis, and each session was continued for 1.5 hours as

including at around 120 trials.

### A. Timing task



### B. Working memory task



**Figure 13: Task Design and Behavioral Result**

## 4.1.3 Surgery and recording procedures

The general surgery and recording procedures are identical to the previous experiment except the target areas of electrodes and reference. The 3 rats that performed well during the training procedures were selected and chronically implanted with a micro-wire array of 16 electrodes. Eight electrodes were targeted to the right striatum (AP between 1 and 2 mm; ML between 1 and 3.5mm; and between 4 and 6mm deep) and 8 electrodes were targeted to the bilateral frontal cortex (AP between 1.5 and 2 mm; ML between -1 and 2mm; and 2.5 deep). Reference electrode was located in the striatum (AP between 1 and 2mm; ML; between 2 and 3mm; and between 4 and 6 mm deep) with a 2mm exposed tip.

The LFPs were recorded during the timing task (3 sessions) and working memory task (2 sessions) for each of 3 rats. However, due to 60Hz noise contamination, data from one rat was excluded from further data analysis.

#### **4.1.4 LFPs data analysis**

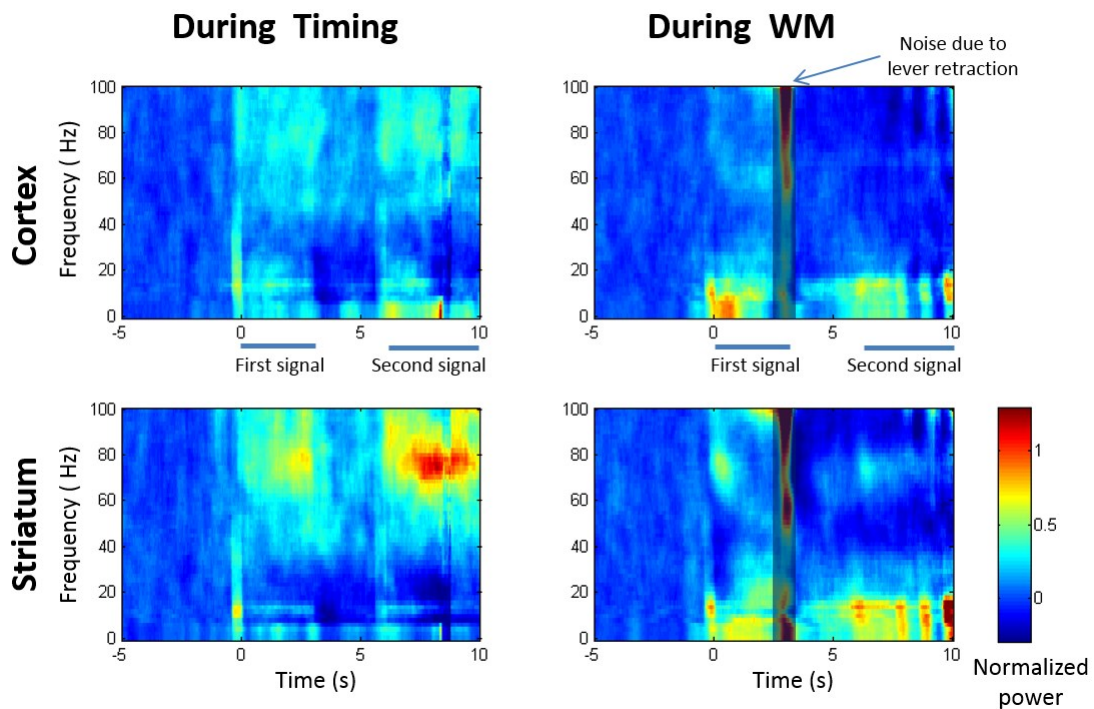
Before all analyses, trials from each electrode were screened to determine if they show a significant noise, and the trials that shows obvious noise were removed from further analysis. Chronux toolbox (<http://www.chronux.org/>; Mitra and Bokil 2008) and in-house Matlab programs were used for the following analyses.

Power spectral analyses were done using the similar methods described in the previous section (2.1.4). Power spectral analyses were done using “*mtspecgramc*” routine of Chronux toolbox with multitaper methods (3, 5 tapers) with 0.5-s window sliding in 0.5-s increments. LFPs data was segmented from -10 s of the trial onset to the lever pressing response. Then, the calculated spectrogram of each trial in each electrode was normalized by the frequency power during the previous ITI (segment from -10 to -1s before the first signal onset).

In order to see the differences of oscillation powers between timing and working memory, the normalized spectrograms were calculated separately for timing and working memory sessions, and subtracted from each other.

## 4.2 Result

The cortical and striatal LFPs from 2 rats were analyzed separately for timing (3 sessions for each rat) and working memory (2 sessions for each rat) paradigms. The spectrograms show similar patterns in overall as showing increase of delta, theta and gamma rhythms (Figure 14).

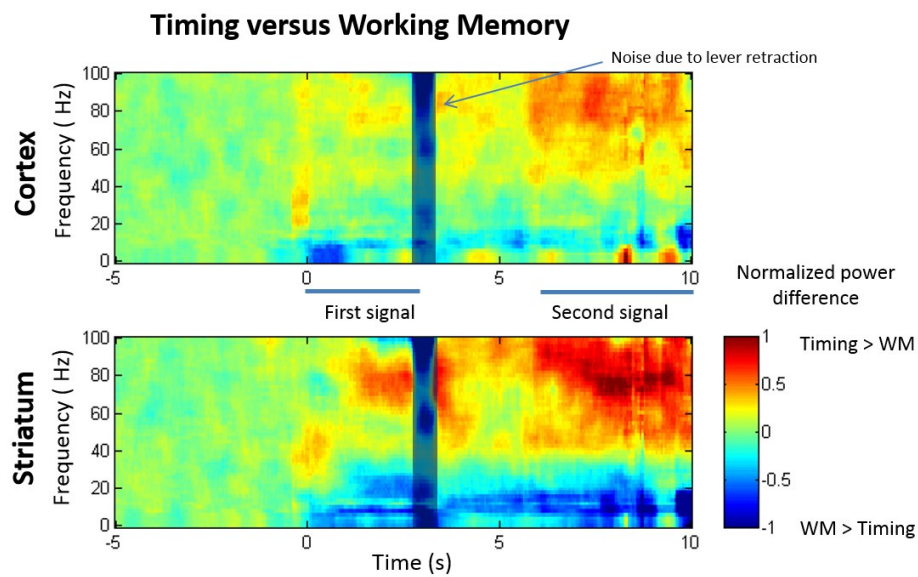


**Figure 14: Neural Oscillations during Interval Timing and Working Memory.**

However, the comparison between the two tasks revealed that interval timing involved bigger power in gamma (40-100Hz) in both cortex and striatum and in low frequency ranges (including delta and lower theta) in the cortex. On the other hand,

working memory involved bigger power in high theta and beta power (around 10-20Hz) compared to interval timing both in cortex and striatum (Figure 15).

During working memory, there was a noise when the first signal ends and lever retracted mainly because one rat often bite the lever when it is retracted. This period with noise was indicated with transparent shades in the figure 14 and 15.



**Figure 15: Oscillatory Power Differences between Interval Timing and Working Memory.**

### **4.3 Discussion**

The current experiment has compared oscillatory power during interval timing and working memory by applying two task paradigms to the same rats. The finding shows increase power in gamma, theta and delta ranges for both task paradigms, but the comparison revealed increased power in gamma and delta ranges during timing while the power in high theta and beta ranges were higher during working memory.

The clear increase of high gamma power in the striatum during timing was not expected considering the findings from the previous experiments (section 2 and 3), which showed mainly theta and delta rhythm increase although small increase in high gamma was observed during duration production. The differences in recording sites might have caused the different finding because the current recording sites were more medial and anterior than the previous experiments. Especially, high gamma (around 80Hz) was shown to be modulated in the ventral striatum by dopaminergic drug or reward sites and delivery (Berke, 2009; van der Meer and Redish, 2009; Kalenscher et al., 2010, for review, van der Meer et al., 2010).

The findings are in line with the human EEG findings of Hsieh et al., 2011 which showed that frontal theta (5-7 Hz) oscillation power was increased during the temporal-order compared to item maintenance, while parietal and lateral occipital alpha (9-12 Hz) oscillation power was increased during item compared to temporal-order maintenance. However, decrease in the right frontal gamma power (30-50Hz) during temporal-order compared to the spatial information maintenance was shown in the previous study (Roberts et al., 2013), as inconsistent with our findings of high gamma increase in interval timing compared to the working memory of left or right lever maintenance. However, the increase of frontal gamma was in low gamma ranges (30-50Hz), and the high and low gamma rhythms were known to be involved in different contexts and status (Berke, 2009; van der Meer et al., 2010).

Previous research has explored the relation of neural oscillations to working memory across humans, primates, and rodents (e.g., Howard et al., 2003; Lee et al., 2005; Pesaran et al., 2002; Raghavachari et al., 2001, 2006). Findings typically demonstrate an increase of gamma and theta activity as well as phase locking of gamma activity to the ongoing theta activity in working memory (Liebe et al., 2012; Lutzenberger et al., 2002; Pesaran et al., 2002; Raghavachari et al., 2001). However, the current finding does not show prominent gamma activity in relation to maintenance of working memory. With regard to the previous human intracranial EEG findings showing that gamma power is well correlated with working memory load (Axmacher et al., 2007, 2008; Howard et al., 2003; Meltzer et al., 2008), it can be also suggested that the less gamma power during working memory compared to interval timing task is related to the task difficulties (e.g. maintaining left or right lever information could be relatively easy).

The current finding was shown from only two rats, so it needs to be validated with additional subjects. Also, the interval timing task was trained and recorded a week before the working memory task, thus, the order of implanting task design should be counterbalanced in the future study.

## 5. Excitatory and Inhibitory Oscillators Model

Numerous models of interval timing and working memory have been proposed from varying perspectives (e.g., Buhusi and Meck, 2005; Miyake and Shah, 1999; van Rijn et al., 2013). Neural models of interval timing attribute the encoding and detection of time either to intrinsic neural networks, pacemaker/accumulator systems, or coincidence-detection of oscillatory patterns (e.g., Buonomano, 2000, 2007; Matell and Meck, 2000; Merchant et al., 2013; Oprisan and Buhusi, 2011). For example, the state-dependent network (SDN) model proposes that temporal information is locally encoded in an intrinsic spatio-temporal neural network along with representations of other stimulus attributes (e.g., Buonomano, 2000; Buonomano et al., 1995, 2009; Karmarkar and Buonomano, 2007); the stochastic ramp and trigger (SRT) model, which is an integration-based model, proposes that time is encoded as an average firing rate of neural populations and detected with a fixed threshold (Simen et al., 2011); the striatal-beat frequency (SBF) model of interval timing proposes that time is encoded by utilizing the oscillatory processes of cortical neurons and their coincident pattern can be detected by medium spiny neurons (MSNs) in the striatum (Coull et al., 2011; Matell and Meck, 2004; Oprisan and Buhusi, 2011).

In the working memory literature, various models also have been proposed in an effort to explain the underlying mechanisms of working memory, such as the TBRS model with emphasis on processing time in the determination of working memory load

(e.g., Barrouillet et al., 2004, 2007), the cognitive model of working memory with a central executive (e.g., Baddeley, 1986, 2000; Baddeley and Hitch 1974; Repovs and Baddeley, 2006), or the model defining working memory as an emergent property of activated neural systems (D'Esposito, 2007; Postle, 2006). However, given the complexity of working memory, the precise information-processing mechanisms and the underlying neuronal properties have yet to be fully revealed, and there are multiple working memory models currently being debated (Wiley and Jarosz, 2012).

As one of the models explaining neuroanatomical localization of working memory, the prefrontal cortex, basal ganglia working memory (PBWM) model (Frank et al., 2001; Hazy et al., 2006, 2007; O'Reilly and Frank, 2006) suggests a critical role for cortico-striatal circuits in selecting and maintaining relevant information in working memory. The PBWM model explains that PFC actively maintains task-relevant information that is dynamically gated/updated by the basal ganglia. In addition, the posterior cortex and hippocampus play a role in automatic sensory/motor processing and the rapid learning of arbitrary associations, respectively (e.g., Collins and Frank, 2012).

The proposed neural mechanisms of the PBWM model share some similarities with the SBF model of interval timing in numerous ways. For example, both rely on the posited involvement of the same brain areas—emphasizing a role for the striatum in detecting/gating cortical inputs. Specifically, the role of the striatum has been suggested

as detecting the coincident pattern of cortical inputs in the SBF model and as gating/updating information by integration of cortical input and DA signals in PBWM model. The selected (gated) signals are hypothesized to pass through the thalamus to the cortex in both models and to be modulated by DA (see Hazy et al., 2006, 2007; Matell and Meck, 2004). Also, both models accommodate a role for DA signaling in learning so that the synapses of MSNs in the striatum can be weighted appropriately. In the SBF model, feedback and/or the delivery of reward for responses occurring just after the target duration induces phasic DA input to the striatum which can strengthen the synapses of MSN receiving inputs from the relevant subset of cortical oscillating neurons in order for them to serve as “detectors” for specific target durations (van Rijn et al., 2013). Similarly, the PBWM model explains that phasic DA input modulates the MSN synapses so that the relevant cortical inputs can trigger the gating/updating of the relevant information. Given these similarities, it has been suggested that interval timing and working memory rely not only on the same gross anatomical structures, but also on the same neural representations (Buhusi and Meck, 2009b; Lewis and Miall, 2006; Lustig et al., 2005; Lustig and Meck, 2005).

In addition to the emphasis on the neuroanatomical localization of interval timing and working memory, the oscillatory components of the SBF model of interval timing (Coull et al., 2011; Matell and Meck, 2004) and certain working memory models (e.g., Burke et al., 2013; Jensen, 2006; Jensen and Lisman, 1998; Lisman, 2010; Lisman and

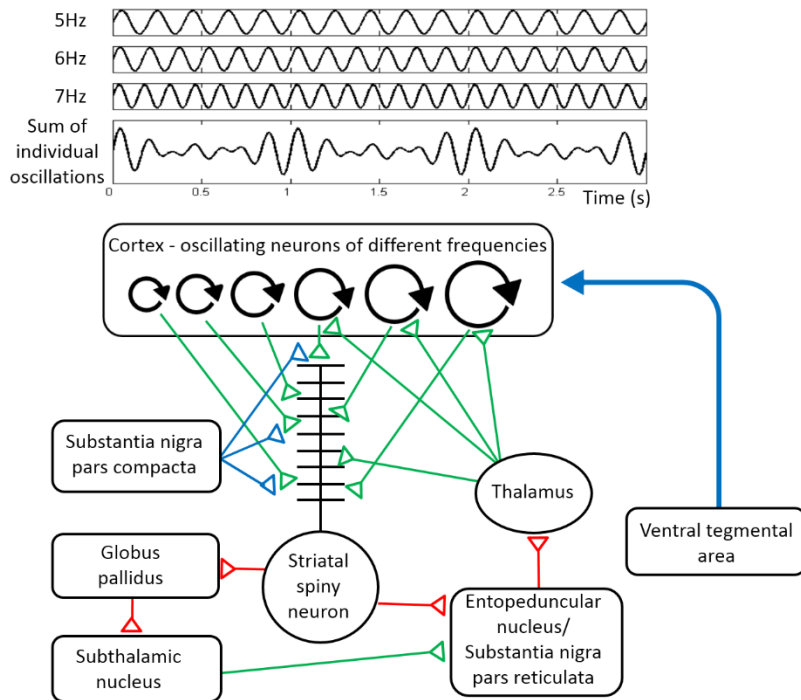
Idiart, 1995) have recently received considerable attention (Allman and Meck, 2012; Deiber et al., 2007; Jonides et al., 2008; Lustig et al., 2005). The oscillatory model of working memory proposes that maintenance of multiple items is organized by activity in the gamma and theta range of neural oscillations (Jensen, 2006; Jensen and Lisman, 1998; Lisman, 2010; Lisman and Idiart, 1995). In order to develop these ideas further, we review below the main oscillatory models of interval timing and working memory, and how these models can be integrated with a dual-oscillator model of hippocampal place-cell activity in conjunction with hippocampal models of interval timing (Burgess and O'Keefe, 2011; Meck, 2002; Meck et al., 1984; Yin and Troger, 2011).

## ***5.1 Complementary Models of Interval Timing and Working Memory***

### **5.1.1 Oscillatory models of interval timing: Coincidence detection**

The beat-frequency model of interval timing proposes that duration estimation arises from the coincidence detection of oscillatory processes (Miall, 1989, 1996), and in addition to this basic concept, the SBF model of interval timing (Buhusi and Meck, 2005; Matell and Meck, 2004; van Rijn et al., 2013) further details the possible neural mechanisms that correspond to each component in the model, such as neural oscillators and coincidence detectors and how these might be affected pharmacologically and/or by pathophysiological conditions (e.g., Allman and Meck, 2012; Coull et al., 2011; Oprisan and Buhusi, 2011).

Specifically, the SBF model suggests that each cortical neuron oscillates at a preferred oscillatory frequency covering the alpha and theta frequency bands (for example). With the onset of a stimulus to-be-timed, the phases of multiple oscillators are reset by a burst of dopaminergic input from the ventral tegmental area (VTA). Then, these cortical neurons continue to oscillate according to their endogenous oscillatory periods, and their coincident activation pattern can be detected by striatal MSNs during the course of the to-be-timed signal as illustrated in Figure 16. MSN's have the potential to serve as coincidence detectors because one MSN receives tens of thousands of inputs from divergent cortical and thalamic neurons and needs simultaneous input to be activated (Groves et al., 1995; Wilson 1995, 1998). Temporal information can be encoded in the pattern of synaptic weights between the MSN and oscillating cortical neurons whose synchronous firing will be detected by the relevant MSN. Even with drift in the oscillatory periods over time, the synchrony provided by the resetting at the start of a signal is sufficient to maintain the a constant coefficient of variation across signal durations in the seconds-to-minutes range and match the level of sensitivity to time observed in humans and other animals (Gibbon et al., 1984, 1997; Matell and Meck, 2004; Penney et al., 2008).



**Figure 16: Striatal-Beat Frequency Model.** At the beginning of an interval, dopaminergic input synchronize the oscillatory neurons in the cortex, and the cortical neurons begin oscillating at their endogenous frequencies. Upper panel shows the different frequencies of oscillation of individual cortical neurons and the sum of those oscillations. Through the connections between specific cortical neurons and a striatal medium spiny neuron, the coincident pattern of cortical neuron firing can be detected at the specific point of time, and those connections can be strengthened by the delivery of reinforcement at the target time (dopaminergic inputs). Glutamatergic (green), GABAergic (red) and dopaminergic (blue) connections are indicated separately. Adapted from Matell and Meck (2004).

According to this account, the learning of a new target duration can be explained within the same cortico-striatal circuit by modulating synaptic weights among MSNs and subsets of cortical neurons. For example, if the learning of a 6-s target duration has induced a MSN to be highly connected with a subset of cortical neurons whose firing rates are maximal 6 s after signal onset, the learning of a 10-s target duration will induce

a different set of synaptic weights as a result of stronger connections with a subset of cortical neurons that fire more frequently around 10 s. Phasic DA release into the striatum from the substantia nigra pars compacta (SNPC) is hypothesized to serve as the reinforcement signal for learning of new target durations, thus allowing modulation of the MSN synaptic weights and new learning (Agostino et al., 2011; MacDonald et al., 2012; Matell and Meck, 2004).

The strength of the SBF model lies in its biological specification which is based on known neural mechanisms, as well as its consistency with the available anatomical, behavioral, and pharmacological evidence (Allman and Meck, 2012; Coull et al., 2011; Merchant et al., 2013). MSNs in the striatum have the appropriate characteristics to serve as a large-scale coincidence detector system because they receive a large amount of convergent, multi-modal input from the cortex (Wilson 1995, 1998) and the coincident excitatory input from the cortex can drive the MSNs into the “Up state” (O'Donnell and Grace, 1995; Wilson, 1993). In addition, lesion studies of dorsal striatum (Meck, 2006b), as well as human brain imaging studies (Coull et al., 2004, 2008, 2011; Harrington et al., 2004, 2010; Hinton and Meck, 2004; Meck and Malapani, 2004; Rao et al., 2001; Stevens et al., 2007) contend that the striatum plays a central role in interval timing. Moreover, patients with apparent pathophysiology in DA systems in the cortico-striato-thalamic loop, such as Parkinson's disease, schizophrenia, autism, ADHD, and OCD show abnormal characteristics in interval timing (Allman and Meck, 2012; Beste et al., 2007;

Carroll et al., 2008; Gu et al., 2011; Jones and Jahanaahi, 2013; Meck, 2005). The purported role of oscillatory processes in interval timing can be readily addressed in SBF model, for example, variations in preferable frequencies of individual cortical neurons and increased theta oscillations during timing emphasizes the role of cortical oscillations as suggested by predictions of the SBF model (Matell and Meck, 2004; MacDonald and Meck, 2004).

In addition to the focus on coincidence detection of patterns of oscillatory activity over the course of temporal processing, the behavioral output of the subject can also be explained within the well-known mechanisms of cortico-striatal-thalamo circuits (Gu et al., 2011; Houk et al, 1995). When the detection of cortical patterns activates specific MSNs, it will in turn disinhibit the thalamus. Then, the activated thalamus in turn influences activation of the connected cortical neurons that can produce a particular response or representation. The systems downstream of MSNs (e.g., thalamus and output cortical neurons) can show increased firing patterns as the target duration approaches, and in relation, it has been shown in rats that striatal and cortical neurons have various firing patterns including peak-shaped activity that are similar to the observed behavioral output (Matell et al., 2003a, b, 2011).

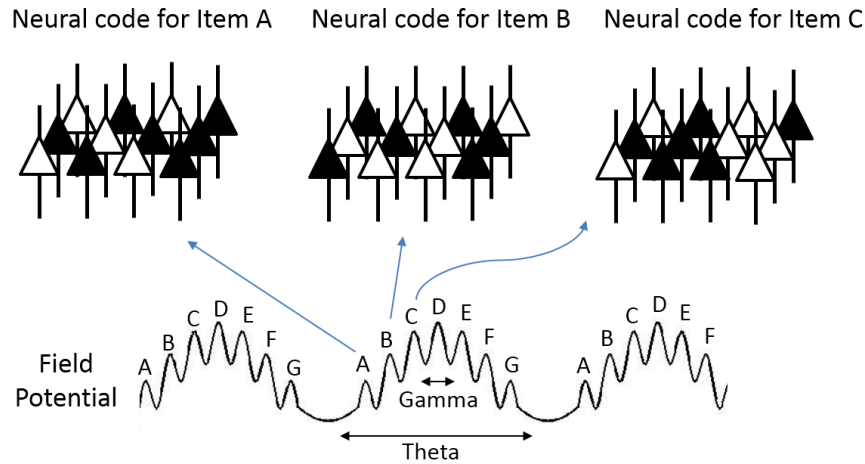
However, it has been suggested that this model can be susceptible to the variance of the oscillation periods. If the cortical oscillators are independent of each other so that they have different variations in their oscillation period, the ability of representing

detectable coincident patterns will be significantly impaired even with a small amount of variance if they aren't reset properly. The variance in oscillation period (i.e., variability in clock speed) that the model allows under this condition are quite small, i.e., less than 3% of the period, and considering that the variance can accumulate with time, the detection of longer durations in the minutes range could be much more debilitated. However, if the variance is introduced globally (e.g., all oscillation periods are increased by 4%), the models' detection ability is not affected, but only the clock speed will be changed (see Oprisan and Buhusi, 2011). Therefore, additional coupling mechanisms for cortical oscillators that can reduce the independence of oscillating neurons with different frequencies be investigated in order to incorporate a more biologically plausible level of variance into the system while still allowing for independence of multiple timing processes (Buhusi and Meck, 2009b).

### **5.1.2 Oscillatory models of working memory**

Oscillatory brain activity, especially in the theta and gamma bands, is modulated during working memory tasks and has been strongly implicated in memory performance. In addition to the oscillatory power modulations observed in the range of gamma and theta, PAC or “phase locking” of single neuron firing to theta oscillations is frequently observed during the maintenance of working memory (Maris et al., 2011; Schack et al., 2002), and has also been correlated with memory performance (Fuentemilla et al., 2010; Lee et al., 2005; Siegel et al., 2009).

In relation to the importance of theta and gamma oscillations for working memory, Lisman and colleagues (e.g., Lisman, 2010; Lisman and Idiart, 1995) proposed an oscillatory model of working memory. According to this model, gamma oscillations entrained within theta could represent maintained memory by repetitively activating relevant neuronal groups with temporal precision, and multiple items can be maintained in working memory by the multiple cycles of sequential gamma oscillations entrained within a theta oscillation (Jensen, 2006; Jensen and Lisman, 1998; Lisman, 2010; Lisman and Idiart, 1995 – Figure 17). For example, different items in memory are represented by different neuronal groups (e.g., spatial pattern of cells), and each neuronal group is activated during each gamma cycle. Because multiple gamma cycles of 30-80 Hz are present within each theta cycle of 4-10 Hz, multiple item information/memory represented by multiple gamma cycles is activated every theta cycle so that they can be maintained as separated from each other within a specific temporal sequence. The number of entrained gamma cycles in one theta cycle is approximately equivalent to the traditionally proposed memory capacity of seven digits, plus or minus two (Lisman and Idiart, 1995). This model addresses the importance of oscillatory properties shown by working memory, especially the PAC phenomenon between theta-gamma bands previously described (see Jackson et al., 2011; Maris et al., 2011).



**Figure 17: Oscillatory Working Memory Model.** Working memory of multiple items by temporal segmentation. Each item is represented by the synchronous firing pattern of selected neurons, and the different items are reactivated at different gamma cycles. In this way, the multiple item representations are sequentially reactivated in gamma (30-80Hz) cycles, and up to seven gamma cycles can be entrained in each theta cycle (4-10Hz). Adapted from Lisman & Idiart (1995) and Lisman (2010).

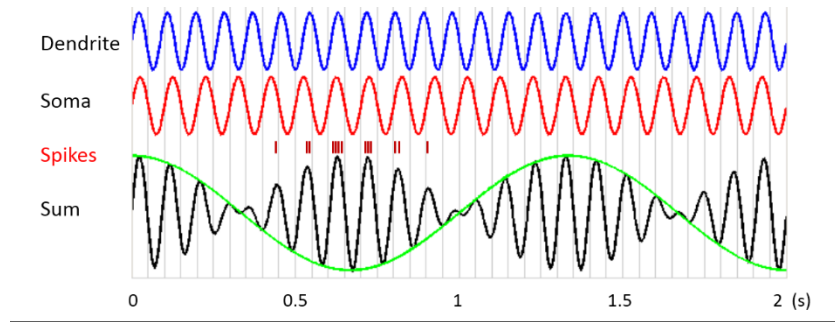
This oscillatory working memory model predicts that two separate items should be maintained within two different gamma cycles that are locked in different theta phases (e.g., the first and second gamma cycles of each theta cycle so that the first item in memory is activated earlier within the theta phase compared to the second item in memory). However, as of now no direct electrophysiological evidence supports this prediction. Moreover, two objects maintained in working memory are even more separable within gamma oscillation phases as opposed to theta phases based on electrophysiological recordings in monkeys (Siegel et al., 2009), which is inconsistent with this model. Possible modifications of the model could be extracted from the

relation between interval timing and working memory as well as from the dual-oscillator interference model of hippocampal function described below.

### **5.1.3 Dual-oscillator interference model of hippocampal function**

A dual-oscillator interference model has been proposed to explain the phase precession of place-cell firing to theta oscillations (Burgess et al., 2007; Burgess and O'Keefe 2011; O'Keefe and Burgess 2005; O'Keefe and Recce 1993). Features of place cells have been extensively studied especially in rodents, but also in humans (Huxter et al., 2003; Lever et al., 2002; O'Keefe and Recce 1993; Recce and O'Keefe, 1989; Skaggs et al., 1996). Place cells refer to the hippocampal neurons that fire when the subject enters a specific location in its environment. An interesting aspects of place cells is that they fire whenever the subject enters the place field of the cell irrespective of the subject's direction of movement (Muller et al., 1994), and the firing of place cells shows theta-phase precession during spatial navigation. For example, as a subject reaches its target area, the place-cell firing occurs at earlier phases of the theta oscillation of the LFP so that the firing phase of the cell reflects the relative distance that the subject has traveled through the cell's place field (e.g., firing at late phases of theta indicates that the subject has just entered the place field – Burgess et al., 1994; Skaggs et al., 1996). Moreover, this precession has been shown to be correlated with the subject's running speed, indicating that the phase of place cells represents the subject's traveled distance rather than the

time spent in the place field (e.g., Geisler et al., 2007; Lengyel et al., 2003; Maurer et al., 2005).



**Figure 18: Dual Oscillator Interference Model.** The sum of an oscillatory somatic (red) and dendritic (blue) inputs produce an interference pattern. The sum shows a high frequency ‘carrier’ oscillation (black) entrained in a low frequency ‘envelope’ oscillation (green). The spikes (red ticks) fire at the peak of the interference sum, and this produces the phase precession of spikes to the somatic input oscillations. Adapted from O’Keefe and Recce (1993) and Burgess et al. (2007).

In order to explain the features of place cells, the dual oscillator interference model hypothesized that the firing of place cells occurs at a slightly higher frequency than the LFP theta oscillation so that the firing precesses to the earlier phases of the LFP theta (Burgess et al., 2007; O’Keefe and Burgess, 2005). For example, if a neuron receives an oscillatory somatic input at 10 Hz – which is the LFP oscillation frequency – and an oscillatory dendritic input at 11.5 Hz, the sum of the two oscillators will show that a high-frequency oscillation (e.g., 10.75 Hz) is entrained within a low frequency oscillation (e.g., 0.75 Hz), which appears similar to the PAC phenomenon described above (Figure 18). At which point, the firing of the place cell occurs at the peak of the dual oscillator sum (oscillation of 10.75 Hz) so that the firing will show a phase precession compared to

the somatic oscillatory input (LFP oscillation of 10 Hz). In relation to this hypothesis, recent intra-cellular recordings from a virtual spatial navigation task with mice showed that the membrane potential oscillation (MPO), which may correspond to the dual oscillator sum, occurred at a higher theta frequency compared to the LFP theta oscillation, and the cell fired at the peaks of the MPO which resulted in the phase precession of spikes to the LFP theta oscillation (Harvey et al., 2009).

## ***5.2 Integrative Models of Interval Timing and Working Memory***

### **5.2.1 A model for the phase-amplitude coupling**

While the dual oscillator interference model (Burgess et al., 2007; O'Keefe and Burgess, 2005) defines an active dendritic oscillation (at a higher frequency than the LFP) and a baseline somatic oscillation (at the same frequency as the LFP) as the two oscillators interfering to each other, we propose excitatory and inhibitory oscillation (EIO) inputs to each neuron as the dual oscillator components for an integrative model of interval timing and working memory. Excitatory inputs are hypothesized to oscillate at a slightly higher frequency than that of the inhibitory inputs and the inhibitory inputs are assumed to oscillate at a similar frequency to the LFPs oscillation as a consequence of the information outlined below.

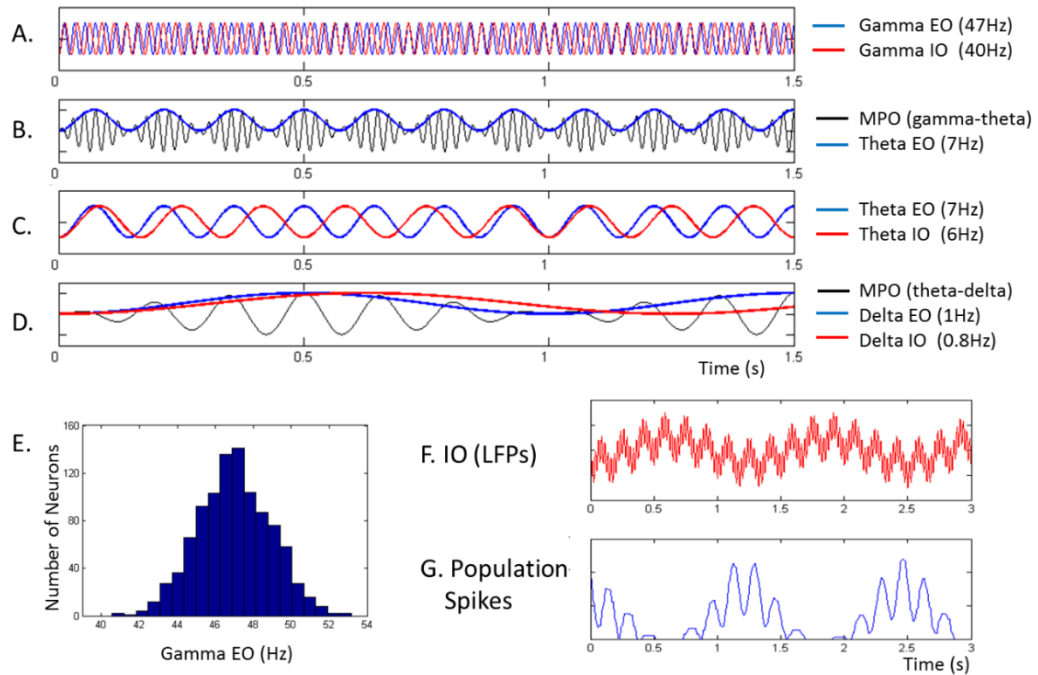
Previous findings have shown that typical neural firing oscillates faster than the theta frequency of the LFP (Burgess et al., 2007; Geisler et al., 2007; Harvey et al., 2009; O'Keefe and Recce, 1993). Geisler (2010) attempted to explain this discrepancy between

the mean oscillation frequency of individual neurons and the frequency of a neural population using a mathematical model. According to this model, the experimentally obtained parameters for the oscillation frequencies of individual neurons (mean frequency = 8.61 Hz) can produce the slower oscillatory frequency of the neural population output (7.97 Hz), which is similar to the experimentally measured LFP frequency (8.09 Hz) due to temporal shifts in cell assemblies. Then, via the recurrent connections between excitatory and inhibitory neurons and the extensive connections between inhibitory interneurons, the slower oscillation frequency of the population would drive the synchronized inhibitory oscillation at a frequency slower than the mean of the individual excitatory neurons. In other words, excitatory neurons would oscillate with difference frequencies from each other while inhibitory interneurons would show synchronized oscillation at the frequency of the population oscillation (similar to the LFP oscillation), which is slower than the mean of the excitatory oscillation frequencies.

Numerous controversies exist for the origins of LFP signals and the control of their oscillation frequencies; however, inhibitory interneurons are known to play a crucial role in the generation of LFP oscillations and also have a direct relation to the power of the LFP signal (Bartos et al., 2007; Buzsáki et al., 2012; Trevelyan, 2009). Moreover, a synchronized oscillation is a prominent feature of inhibitory interneurons; therefore, these features would support the assumption that the synchronized inhibitory

oscillation corresponds to the LFP oscillation as applied in the following integrative model.

The basic concept of our EIO model is similar to the original dual oscillator model (e.g., Burgess et al., 2007; O'Keefe and Burgess, 2005) although one of the dual oscillators, i.e., the baseline somatic oscillation at the frequency of LFP, is substituted with the inhibitory oscillation in the EIO model. The two models do not necessarily exclude each other, especially considering that inhibitory currents play a crucial role in LFP oscillation and also correlate with the power of the LFP signal (Bartos et al., 2007; Trevelyan, 2009). However, the EIO model can explain the PAC phenomenon at a neural population level and can provide a better foundation for oscillatory models of interval timing and working memory. Although PAC phenomena are currently receiving a great deal of attention in terms of its proposed role in cognitive processes, including working memory, not much has been revealed about the underlying neurobiological and computational mechanisms of PAC. Consequently, the proposal of a computational and neuronal network model involving PAC should help to explain the origins of PAC as well as its potential contributions to interval timing and working memory.



**Figure 19: EIO Model for Phase-Amplitude Coupling.** (A) Gamma range of excitatory oscillation (EO) and inhibitory oscillation (IO) inputs into a neuron. EO (47 Hz) in individual neuron is in higher frequency than the IO (40 Hz) which is synchronized over a small neuronal population. (B) Interaction of the EO and IO produces phase-amplitude coupling (PAC) between gamma and theta in the membrane potential oscillation (MPO). The gamma (carrier) amplitude is modulated by the 7-Hz theta (envelope) oscillation, whose frequency is determined by the frequency difference between the gamma EO (47 Hz) and IO (40 Hz). (C) The produced theta (7-Hz) oscillation interacts with theta IO (6-Hz). Theta IO is synchronized over a larger neuronal population than the gamma IO. The diagram shows EO and IO filtered in theta frequency bands for a simplification. (D) Interaction between theta EO (7 Hz) and IO (6 Hz), in turn, produces PAC between theta and delta. The delta envelope (delta EO) oscillates in 1 Hz and the delta IO is also modeled as in a lower frequency (0.8 Hz) than the EO. (E) Distribution of gamma EO frequencies of individual neurons ( $N = 1000$ ) is modeled as a mean of 47 Hz and SD of 2 Hz. (F) A simulation of total IO including gamma (40 Hz), theta (6 Hz) and delta (0.8 Hz) ranges of IOs. The simulated IO is hypothesized to assimilate LFPs. (G) Simulated firing rates of a neuronal population whose gamma EO frequencies are distributed as in panel E and receiving IO inputs as depicted in panel F. Population spikes plotted as a function of 100-ms time bins 10-ms sliding window show a pattern of theta oscillation entrained in delta.

The interaction between excitatory oscillation (EO) and inhibitory oscillation (IO) inputs can produce a membrane potential oscillation (MPO) for each individual neuron at a high-frequency oscillation (e.g., at the mean of the EO and IO) entrained at a low-frequency oscillation (e.g., at the differences between the EO and IO frequencies) as illustrated in Figure 19 A-D. Simulation of neuronal spike outputs from an excitatory neuronal population as well as the LFP resembles the PAC phenomenon of multiple frequency bands (e.g., theta entrained in delta) as illustrated in Figure 19 F and 19 G. This suggests that the differences among the frequencies of individual neural oscillations (corresponding to the EO) and the population oscillation (corresponding to the IO) will be the driving force for generating the PAC phenomenon. Consequently, the larger differences between the two oscillators will produce the higher frequency of envelope (low frequency).

Depending on the assumption of frequency bands for EO and IO, various ranges of PAC can be generated, and even the relation among frequency bands can be fractal. For example, given the assumption of a gamma range for EO and IO that will generate gamma entrained within the theta oscillation (as illustrated in Figure 19 A and 19 B), this generated theta oscillation will in turn produce theta entrained within the delta oscillation by way of interaction with the theta range of IO as illustrated in Figure 19 C and 19 D). The hierarchical organization of these frequency bands is one of the prominent features of our neural oscillation model and corresponds to the harmonics

observed in the SBF model of interval timing (Gu et al., 2011; Matell and Meck, 2004). Penttonen and Buzsáki (2003) showed the natural logarithmic relationship in the periods of delta, theta, gamma, and ultra-fast oscillations. Lakatos (2005) also showed hierarchical relations in gamma, theta, and delta activities. In this regard, the relations between these frequency categories are important for controlling neural activations, and the current simulations illustrated in Figure 19 A-D suggest that the logarithmic and hierarchical relationship can be produced by the interactions between the excitatory and inhibitory neural oscillations.

The role of inhibitory interneurons has been shown to be crucial in maintaining the PAC, such as the theta-gamma coupling (Wulff et al., 2009), and the different inhibitory neurons are thought to serve important roles in different frequency bands (Klausberger and Somogyi, 2008). In this regard, it's possible that the different types of inhibitory interneurons may work to filter the relevant frequency range of oscillations that are produced by the excitatory neuronal population. Precise functions of inhibitory interneurons in the oscillatory process should be studied further because the underlying mechanism will have important implications for interval timing, working memory, and other cognitive functions.

### **5.2.2 Integration of coincidence-detection and dual oscillator models**

Integrating the proposed EIO model into the SBF model of interval timing would provide better explanations for the behavioral and neural features of temporal

processing and working memory, as well as their interactions. The EIO model would add a realistic underlying oscillatory mechanism to the concept of oscillating cortical neurons with different frequencies as proposed by the SBF model. With emphasis on the neural oscillatory properties, the new integrative model will show that the temporal information present in the oscillatory interactions between excitatory and inhibitory neurons would be crucial for extracting information from the neural network during both of interval timing and working memory.

This new integrative model of interval timing predicts that a triggering event (e.g., DA input) will perturb the neural network such that this excitatory input causes the EO to achieve slightly higher frequencies than the IO, and the excitatory inputs to individual neurons oscillate at various frequencies while the inhibitory inputs show synchronized oscillation across neurons in a local neuronal network. For example, before any triggering event, both excitatory and inhibitory inputs oscillate (in balance) at a 6-Hz frequency so that they cancel each other out. The onset of a to-be-timed signal and the resulting DA input to the cortical neurons (see Allman and Meck, 2012; Matell and Meck, 2004) would trigger a sudden increase of EO frequencies in each neuron while leaving the IO synchronized at a slightly lower frequency than the EO. Depending on the density of synaptic connections or by any other reason of cellular diversity, the excitatory inputs to each individual neuron will oscillate at different frequencies, for

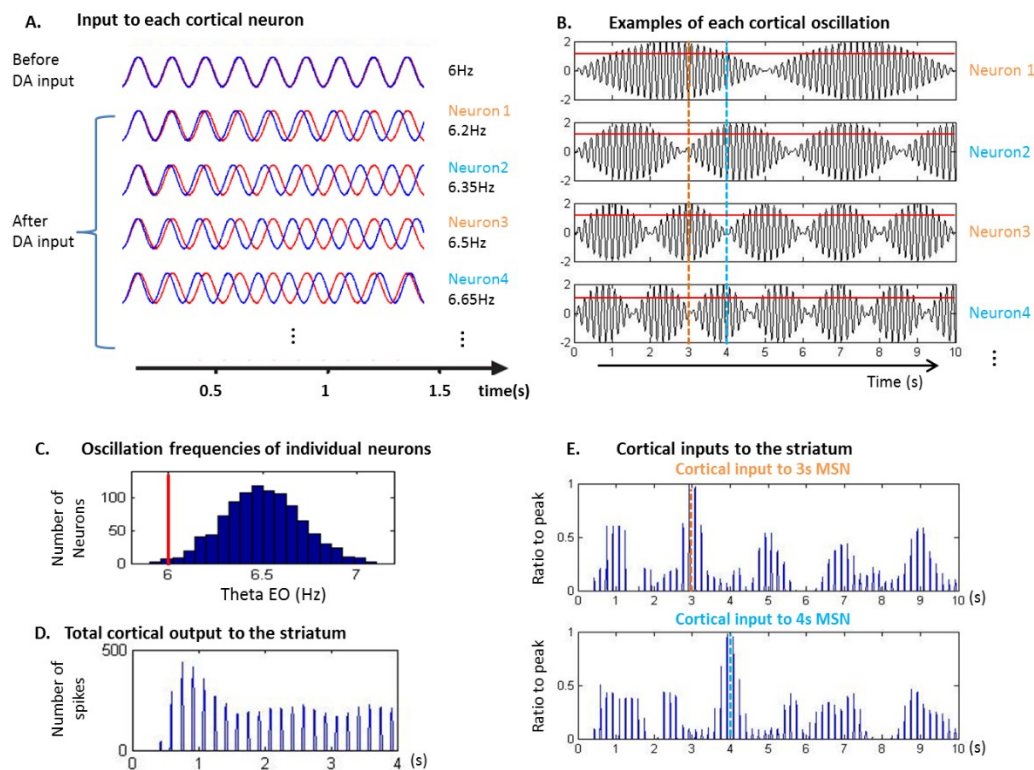
example, Neuron 1, 2, and 3 will receive 6.2 Hz, 6.35 Hz and 6.5 Hz of EO input, respectively as illustrated in Figure 20 A.

The summation of EO and IO inputs in each cortical neuron will produce a MPO of theta, enveloped in delta oscillations as previously described. The different frequencies of EO will produce different frequencies of theta MPO, entrained in different delta oscillations. For example, if IO inputs are synchronized at 6 Hz, the MPO of Neuron 1 will show a 6.1-Hz theta oscillation entrained within a 0.2-Hz delta oscillation, Neuron 2 will show a 6.175-Hz theta entrained within a 0.35-Hz delta oscillation, and Neuron 3 will show a 6.25-Hz theta entrained within a 0.5-Hz delta oscillation as illustrated in Figure 20 B. After applying a membrane potential threshold for generating spikes, each neuron will show a different pattern of firing rates across time. For example, Neuron 1, whose EO and IO summation produces a theta oscillation entrained within a 0.2-Hz delta oscillation, would show high firing rates of spikes with 0.2 Hz (every 5 s – so at 2.5 s, 7.5 s, 12.5 s, and so on). Similarly, Neuron 3 with a 0.5-Hz delta oscillation would show high firing rates of spikes with 0.5 Hz (every 2 s – so at 1 s, 3 s, 5 s, and so on).

Then, as the SBF model proposes, each MSN in the striatum could be trained to detect the coincident firing of a subset of cortical neurons to encode/detect a specific target duration, as well as strengthening the synaptic weights among the specific MSNs and cortical neurons. If both of the cortical neurons in our previous example (e.g.,

Neurons 1 and 3) are strongly connected to a certain group of MSNs, then those MSNs will receive a high firing rate of spikes at approximately 3 s as illustrated in Fig. 8E. On the other hand, if a different group of MSNs is strongly connected to other cortical neurons whose firing rates peak at 4 s (e.g., Neurons 2 and 4 as illustrated in Fig. 8B), then this group of MSNs will play the role of 4-s detector. In this way, each MSN (or group of MSNs) can detect the coincident firing of multiple cortical subunits, and different MSNs can encode different durations by being connected to a different subset of cortical neurons as illustrated in Figure 20 E.

This new oscillation model assumes that the frequency of EO varies across neurons and is predetermined in each cortical neuron. The underlying mechanisms of various EO frequencies (and the synchronized IO) should receive further consideration; however, different amounts of recurrent excitatory inputs to each cell or different effects of DA at each neuron could be major factors contributing to the variation in oscillation frequencies. In our simulated model as illustrated in Figure 20 C, the distribution of EO frequencies is defined as a normal distribution with a mean of 6.5 Hz and a standard deviation of 0.2 Hz. The IO frequency was fixed at 6 Hz for a particular neuronal population, based upon evidence from the previous reports (Geisler et al., 2010; Matell and Meck, 2004).



**Figure 20: EIO Model for Interval Timing.** (A) Theta range of EO (blue) and IO (red) inputs to each cortical neuron are balanced before dopamine (DA) input such as in 6 Hz theta oscillation. DA input at the timing onset drives the EO inputs to individual cortical neurons oscillate in the faster and various frequencies while IO inputs are synchronized in 6 Hz. (B) Summation of EO and IO inputs in each neuron generates MPO in theta entrained in delta oscillation. The envelope delta frequency differs by the theta frequency of each individual neuron. For example, larger theta frequency of Neuron 4 produces the faster delta frequencies. Neurons 1 and 3 (Orange) exhibit a peak around 3 s, but not at 4 s; Neurons 2 and 4 (Cyan) exhibit a peak at 4 s, but not at 3 s. Detection of coincident firing of the relevant neuronal groups such as Neurons 2 and 4 will produce the timing of the 4-s target duration. (C) Simulation of theta EO frequencies of 1000 cortical neurons is modeled with a mean of 6.5 Hz and SD of 0.2 Hz while IO frequency is fixed at 6 Hz. (D) Simulation of total spike inputs from the cortex to the striatum. It shows relatively little spiking between 0~ 0.5 s after the DA input and shows a peak at 0.5~1 s. (E) Spikes to each MSN neuron from the cortex show a peak at the target time of each MSN, but also exhibit fluctuating patterns across time. For example, 3 s MSN receives peak inputs at 3 s, however, the inputs fluctuate and oscillate in time.

Variation in the EO frequencies will play an important role in encoding various target durations and also a change in the frequency distribution can cause some important behavioral phenomenon. For example, if the EO frequencies are shifted rightwards (increased) without changes in IO, the same firing peak will be reached sooner than the physical time, so that the learned target duration will be reproduced shorter than it should be. As proposed in the SBF model, DA input to the cortex would be able to determine the clock speed by modulating the EO frequencies. However, compared to the SBF model where the whole network should speed up or slow down to same degree, this new model allows for more variation in the oscillation speed of each neuron. Each neuron can speed up by a slightly different amount independently (e.g., the EO frequency of Neuron 2 can change from 6.35 Hz to 6.36 Hz, while the EO frequency of Neuron 4 can remain constant at 6.65 Hz). This would result in an increase in the variability of the behavioral output without seriously disturbing the accuracy of the timing.

In addition, the degree of variation in EO frequencies could be related to periodic repetitive behaviors. Specifically, encoding a target duration within a narrow dispersion of theta EO frequencies would induce repetitive peaks at multiples of the target duration. For example, if most of the cortical neurons have a 6.5-Hz frequency, similar to Neuron 3 in Figure 20, it will produce strong 2-s periodic replay. This feature could be the underlying mechanism explaining the periodic repetitive behaviors shown in a rat

model of obsessive-compulsive disorder following quinpirole-induced sensitization (Gu et al., 2011 – see Meck, 1988).

It is also important to note that simulated spike outputs from the cortical neuron population shows firing within a theta frequency band with a peak around 0.5-1 s followed by a sustained theta oscillation as illustrated in Figure 20 D. This effect is consistent with the electrophysiological findings of a theta power increase during temporal processing as in the previous sections. Moreover, the simulation shows that the population spikes from these cortical neurons are sparse before 0.5 s due to the synchronized inhibitory inputs. This feature suggests a potential mechanism underlying the dissociation of sub- and supra-second timing (Cordes and Meck, 2013). While the supra-second timing can be encoded in the theta entrained within delta cortical oscillations and detected by MSNs in the striatum, sub-second (or below 500 ms) timing would be difficult for the MSNs to detect, thereby requiring other brain areas, such as the cortex or cerebellum, to be involved in the sub-second timing (Allman et al., 2014; Teki et al., 2011, 2012). Neuroimaging evidence supports the dissociation between sub- (<500 ms) and supra-second (> 500ms) timing with different brain involvement (Lewis and Miall 2003a, 2003b, 2006). Moreover, there are a variety of other neuronal models capable of explaining sub-second timing within cortical networks (e.g., Buonomano, 2000; Buonomano and Merzenich 1995; Buonomano et al., 2009; Karmarkar and Buonomano, 2007).

### **5.2.3 Integrative model for working memory with single or multiple items**

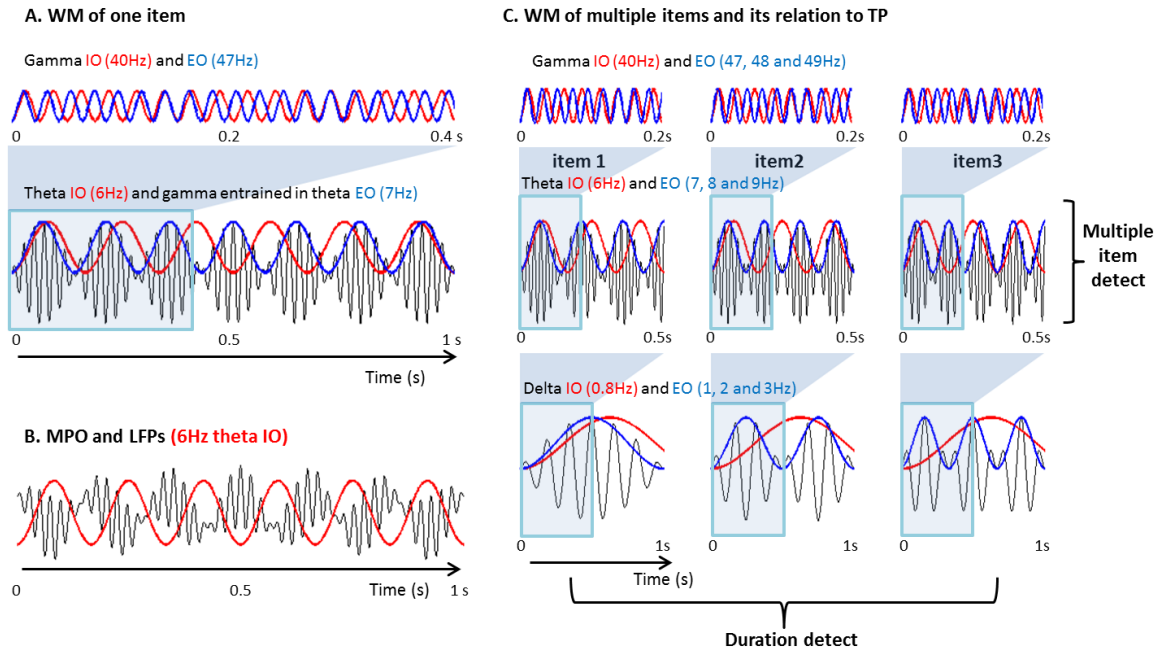
Neural oscillations are a crucial feature of both interval timing and working memory. The proposed EIO model can be further expanded into an oscillatory model of working memory, explaining the neural features of working memory as well as its temporal dynamics, especially in relation to interval timing. Due to the multiple layers of oscillatory properties of neuronal populations, the same oscillating neural firing is hypothesized to encode an item representation in working memory, as well as temporal order and duration information depending upon the range of oscillation frequencies focused on.

More specifically, MSNs in the striatum can detect cortical target representations from spatio-temporal patterns of gamma spikes entrained within theta (for stimulus attributes held in working memory) or from synchronous patterns of theta oscillations entrained within delta (for duration in interval timing). In this way, oscillatory patterns within a cortical network can represent both stimulus attributes and duration information simultaneously. However, a more optimal strategy for improved detection would utilize built-in differences between interval timing and working memory; a diverse range of theta frequencies is favorable for encoding a duration, whereas a synchronous theta oscillation is considerably better for retaining one item in working memory because it can increase the size of the neuronal network. Therefore, the behavioral interference observed between working memory and interval timing (e.g.,

Fortin et al., 1993) can be attributed to how the range of theta oscillation frequencies is set (e.g., multiple theta frequencies or one synchronized frequency of cortical oscillation).

Neuronal evidence indicates that working memory is maintained in the theta range of oscillatory reactivations. The proposed EIO model follows the concept that an item's representation is maintained by the gamma entrained theta replay as proposed in Lisman and Idiart's oscillatory working memory model (Lisman, 2010; Lisman and Idiart, 1995). However, integrating the EIO model with this concept should allow for more detailed predictions as well as an explanation of the underlying mechanisms. The observation that interactions between gamma ranges of EO and IO produces MPO with PAC between gamma and theta for individual neurons is shown in Figure 21 A. The produced MPO of individual neurons will also be interfered with by theta IO inputs, so the MPO will be modulated as shown in Figure 21 B. Spikes will be produced near the peak of MPO with certain thresholds, so the distribution of spikes will be "phase-locked" to the ongoing theta oscillation of the LFP as shown in Figure 21 B. In this way, a population of neurons will show a firing pattern of gamma entrained within theta, and also the spike firing will be "phase-locked" to the LFP theta oscillation. Although the EIO model predicts the phase precession of spikes to the LFP theta as a function of the retention interval, this effect has not been clearly reported in working memory literature – although it appears extensively in the spatial navigation literature (e.g., Buzsáki et al.,

2012). The involvement of other oscillatory components such as delta IO inputs or short retention intervals would make it more difficult to observe this type of phase precession.



**Figure 21: EIO Model for Working Memory.** (A) Working memory for a single item. Neurons encoding an item receive specific frequency of gamma EO (blue, 47 Hz) and IO (red, 40 Hz) inputs. The interaction of EO and IO produces a MPO (black) that is showing phase-amplitude coupling between gamma and theta oscillations. Thus, working memory of one item can be maintained in neuronal reactivations of a theta frequency. (B) Simulation of MPO (black) and LFPs (red). MPO was shown in relation to the theta IO which would correspond to filtered LFPs in a theta range. (C) Working memory of multiple items can be encoded in multiple theta oscillations while a target duration can be detected by multiple delta oscillations. Each item in working memory can be represented in each gamma oscillation entrained within each theta oscillation frequency. The capacity of maintaining multiple items in working memory would be related to how many theta oscillations of different frequencies can be maintained simultaneously. The multiple theta oscillations interacting with a theta IO would also produce multiple delta oscillations which has different temporal peaks of reactivation. Therefore, by depending on the related oscillation frequency, each item reactivation has their specific temporal characteristics.

If we extend the EIO model to working memory for multiple items, the maintenance of these items could be achieved through multiple replays at separate frequencies for gamma and theta oscillations as shown in Figure 21 C. For example, item 1, 2 and 3 are encoded in separate neuronal groups receiving 47, 48 and 49-Hz EO, respectively, and then, those neuronal groups interact with synchronized 40-Hz IO in order to produce 7, 8, and 9-Hz theta oscillations, respectively. Therefore, if separate but simultaneous multiple theta oscillations can be maintained at the same time (simultaneous temporal processing – see Buhusi and Meck, 2009b; Meck and Church, 1984) by different neuronal groups, simultaneous maintenance of multiple items would be also possible. However, the number of multiple theta oscillations that are possible will restrict the number of items in working memory. In this way, the model can account for both decay and interference features of forgetting. Simultaneous maintenance of different frequencies of theta oscillations (representing multiple items) would be easily disrupted by the interactions from other neuronal groups, especially when the two neuronal groups are tightly connected to each other – a result consistent with interference theory. Variations in the oscillations of multiple neurons will increase with time so that the temporal organization of spikes for different neuronal groups will be more disrupted at longer retention intervals, – a result consistent with decay theory.

Moreover, the TBRs model of working memory (Barrouillet, et al., 2004, 2007) suggests that forgetting is time related such that the proportion of time capturing

attention for each item is crucial to memory maintenance. This claim is consistent with the EIO model to the extent that it predicts the close relationship between interval timing and multiple-item working memory. As shown in the Figure 21 C, different theta oscillations representing different items will also produce different delta oscillations as a result of the interaction with synchronous theta IO. Therefore, the theta reactivations of item representations would also have delta oscillation components so that the different items-features would be reactivated at different times. For example, if the population neurons receive synchronized 6-Hz IO, the 7-Hz theta frequency encoding item 1 would be mainly reactivated at 1.5, 2.5, 3.5 s and so on (entrained within a 1-Hz delta oscillation) while the 8-Hz theta frequency encoding item 2 would be reactivated at 1.25, 1.75, 2.25 s and so on (entrained within a 2-Hz delta oscillation). In this sense, the time should be divided for the reactivations of each item to reduce the temporal overlap of reactivations between multiple items, so the restriction for the multiple-item maintenance originates from the temporal resource sharing (see Buhusi and Meck, 2009a) as proposed by the TBRS model.

The proposed temporal components of working memory explain the shared features between interval timing and working memory. According to the EIO model, temporal-order information for multiple items in working memory can be extracted by the reactivation order of theta entrained delta peaks while the item information can be extracted by the replays of relevant frequency of theta with gamma entrained.

Moreover, a specific target duration can be detected from a synchronous pattern of delta cortical oscillations that are generated by multiple theta oscillations, and the multiple theta oscillations are related to multiple item representations. In this way, interval timing and working memory are not independent processes, but rather inter-related processes that originate from the same neural representations.

Many aspects of the EIO model can be shared with the oscillatory working memory model proposed by Lisman and colleagues (Lisman, 2010; Lisman and Idiart, 1995); however, the neural prediction of multiple-item working memory differs in detail. The Lisman and Idiart model would predict that multiple items are maintained by the multiple cycles of sequential gamma entrained in a theta band so each item will fall into a specific phase of theta oscillation. In the new EIO model, the theta reactivations of multiple items will be produced in sequence that falls into each phase of theta IO (LFPs); however, the sequential reactivations will gradually precess in time so that the same item won't fall into the same phase of theta. Moreover, the sequential maintenance of multi-items will not only be present in the theta, but will also exist in the delta oscillations, so the maintained information can be extended or compressed in time depending on which oscillation ranges are captured.

This integrative model proposes the shared neural-oscillation properties underlying interval timing and working memory. Even in the absence of an ongoing stimulus, neural oscillations in the brain continue in time, and this property would

explain how we can perceive time and hold information in the brain. Certain frequency ranges of oscillation would include the specific dimension of information; such as theta activity entrained in delta for duration information and gamma activity entrained in theta for other stimulus attributes (e.g., pitch). In this way, interval timing and working memory would originate from the same cortical representations, but the specific connections between striatal and cortical neurons would be able to extract the different dimensions of that information.

### ***5.3 Implications and Future Directions***

With the exponential increase in neuroimaging studies focusing on the spatial localization of cognition, the field of cognitive neuroscience has accumulated a great deal of evidence concerning the functional role(s) of specific brain areas. In comparison, the temporal/oscillatory components of cognition have been largely ignored. Fortunately, recent focus on the temporal/oscillatory properties of brain and behavior has opened up another dimension for understanding the cognitive architecture of the brain. Interval timing and working memory in particular share the characteristic that some internal process must continue over the course of time regardless of the existence of an external stimulus. Moreover, spatio-temporal patterns of activation supporting these cognitive functions are sustained in neural networks over a time and these neural networks can be managed through the oscillatory fluctuations that reside in the recurrent networks. Because of the importance of these neural dynamics, the

temporal/oscillatory properties of the brain should be emphasized in future studies of interval timing and working memory.

As suggested in previous sections, information derived and maintained by interval timing and working memory can be conveyed through different ranges of oscillations involving theta entrained in delta and gamma entrained in theta, respectively. The functional role of neural oscillations wouldn't be restricted to interval timing and working memory, but also applied to most of other psychological functions via different frequency ranges of oscillations conveying different dimensional information (Düzel et al., 2010; Palva and Palva, 2011, 2012; Palva et al., 2005, 2010, 2011; Wang 2010). Gamma oscillation has been hypothesized as being responsible for the "binding" of features into a coherent cognitive unit (Engel et al., 2001; Gray et al., 1989), and the ultrafast oscillations, which are also known as ripples (150-250 Hz), shows replay of previously experienced firing patterns in a temporally compressed manner and has been shown to be vital for memory transfer and consolidation (e.g., Cheng et al., 2009; Girardeau et al., 2009; O'Neill et al., 2010). Moreover, increasing evidence supports the importance of infra-slow fluctuations ( $< 0.1$  Hz) in cognition as well as in brain signals (Palva and Palva, 2012). The variance in cognitive performance fluctuates over tens to hundreds of seconds and has largely been considered "noise"; however, the variance of cognition/behavior has shown to increase with time scales, showing  $1/f$ -type power distribution rather than just a random (white noise) distribution in the temporal

sequence of errors (Gilden et al., 1995; Gilden 2001). This suggests that the temporal variance of cognition originates from some systematic mechanism. In regard to this, the slow cognitive fluctuations measured by errors in a somatosensory detection task were shown to correlate with infra-slow EEG fluctuations, and in addition, the amplitudes of delta, theta and gamma oscillations were entrained in the phases of the infra-slow EEG (Monto et al., 2008).

Infra-slow fluctuations are not only evident in EEG brain signals, but also in the blood-oxygen-level-dependent (BOLD) signals of fMRI. Considerable attention has recently been focused on the infra-slow fluctuations of the BOLD signal that are temporally covariant over a large-scale brain network, and those networks are thought to represent an array of functional connectivity in the brain (Fox and Raichle, 2007). Various large-scale networks were extracted in relation to various cognitive functions such as attention, memory, and sensorimotor processes, as well as to the resting state “default network” (Fox et al., 2006; Fox and Raichle, 2007; Greicius et al., 2003). In particular, the default network has been shown to “anti-correlate” with cognitive effort, thus leading to speculation on its role and relation to infra-slow fluctuations. In concert with this, the measurement of infra-slow fluctuations in BOLD signals has been highly controversial and the underlying mechanism remains a mystery. Recent evidence, however, shows a relationship between electrophysiological signals and large-scale brain networks revealed by BOLD signals (He et al., 2008; Liu et al., 2010; Palva and

Palva 2012). Consequently, the EIO model of PAC proposed in this review could also be applied to these infra-slow fluctuations in large-scale brain networks – especially when the natural logarithmic relations among different frequency bands are considered (Penttonen and Buzsáki, 2003).

In the same manner that interaction between theta ranges of oscillation can produce a delta oscillation, the interaction between delta ranges of oscillations could produce the slow oscillations shown in the functional connectivity studies (see Buzsáki, 2006; Buzsáki et al., 2012; Palva and Palva, 2012). In this way, the different frequency ranges of oscillations are hierarchically interrelated to each other through the PAC – thus allowing slow and fast oscillations, as well as multiple ranges of oscillation to be present at the same time in the same brain regions (Buzsáki, 2006; Buzsáki and Draguhn, 2004; Lakatos et al., 2005). One thing to speculate about is the possibility that this hierarchical organization across oscillation frequencies would also include a hierarchical spatial organization, so that the slower-frequency oscillations are synchronized over the larger brain areas. In relation to this, it has been hypothesized that the slower-frequency oscillations are involved in long-range communication in the brain (e.g., Buzsáki, 2006; Buzsáki et al., 2012; Buzsáki and Draguhn, 2004).

In conclusion, there are various ways of manipulating neural oscillations such as “change-coupling” between multiple oscillations, synchronize/desynchronize switches in a local neuronal network, and increase/ decrease frequency modulations. These

dynamical modulations of neural oscillations represent crucial mechanisms for controlling brain function, and the temporal disorganization of these oscillations would likely contribute to many pathophysiological conditions such as autism, schizophrenia, OCD, or Parkinson's disease (Allman and Meck, 2012; Brazhnik et al., 2012; Gu et al., 2008, 2010, 2011; Lemaire et al., 2012). Problems with inhibitory GABA neurons and the abnormal organization of gamma frequency has long been implicated as one of the main problems in schizophrenia, which has also been shown to be related to deficits in interval timing and working memory deficits (Allman and Meck, 2012; Carroll et al., 2008; Lewis et al., 2005; Penney et al., 2005). Distortions in the oscillatory properties of neuronal networks would produce abnormal temporal relations among neural functions, thus contributing to a variety of disorganized thoughts and potentially hallucinations in the patients. In the case of OCD, the repetitive reactivations of certain thoughts (obsessions) is the core feature of OCD (Gu and Kukreja, 2011; Gu et al., 2008), therefore, understanding how oscillatory reactivations of certain neuronal groups continues in time might help to reveal the underlying neural mechanisms of obsession. This would also explain how the cognitive inflexibility shown in the patients with OCD (Gu et al., 2008, 2010) is related to the sustained neural oscillations that may capture them within a constrained oscillatory framework.

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## Biography

Bon-Mi Gu was born in Dangjin, South Korea on May 26, 1981. She received her Bachelor's degree in Biological Science and Master's degree in Neuroscience from Seoul National University, Seoul, South Korea in 2005 and 2007, respectively. She will receive her Doctor of Philosophy from Duke University, Durham, NC, USA in May 2014.

## Publications

### Journal Articles:

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