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Oscillatory multiplexing of neural population codes for interval timing and working memory

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Published in:
Neuroscience and Biobehavioral Reviews

DOI:
[10.1016/j.neubiorev.2014.10.008](https://doi.org/10.1016/j.neubiorev.2014.10.008)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Gu, B-M., van Rijn, H., & Meck, W. H. (2015). Oscillatory multiplexing of neural population codes for interval timing and working memory. *Neuroscience and Biobehavioral Reviews*, 48, 160-185.
<https://doi.org/10.1016/j.neubiorev.2014.10.008>

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Review

Oscillatory multiplexing of neural population codes for interval timing and working memory

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ARTICLE INFO

Article history:

Received 30 March 2014

Received in revised form 6 October 2014

Accepted 10 October 2014

Available online 18 October 2014

Keywords:

Episodic memory

Timing and time perception

Neural oscillations

Cortico-striatal circuits

ABSTRACT

Interval timing and working memory are critical components of cognition that are supported by neural oscillations in prefrontal–striatal–hippocampal circuits. In this review, the properties of interval timing and working memory are explored in terms of behavioral, anatomical, pharmacological, and neurophysiological findings. We then describe the various neurobiological theories that have been developed to explain these cognitive processes – largely independent of each other. Following this, a coupled excitatory – inhibitory oscillation (EIO) model of temporal processing is proposed to address the shared oscillatory properties of interval timing and working memory. Using this integrative approach, we describe a hybrid model explaining how interval timing and working memory can originate from the same oscillatory processes, but differ in terms of which dimension of the neural oscillation is utilized for the extraction of item, temporal order, and duration information. This extension of the striatal beat-frequency (SBF) model of interval timing (Matell and Meck, 2000, 2004) is based on prefrontal–striatal–hippocampal circuit dynamics and has direct relevance to the pathophysiological distortions observed in time perception and working memory in a variety of psychiatric and neurological conditions.

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Contents

1. Introduction	161
2. Interaction between cognitive processes supporting interval timing and working memory	162
3. Limitations in working memory and its temporal component	162
4. Selective neural patterns supporting interval timing and working memory	163
4.1. Lesion and inactivation studies	163
4.2. Neuroimaging studies	164
4.3. Electrophysiological studies	164
5. Oscillatory features of interval timing and working memory	166
6. Complementary models of interval timing and working memory	168
6.1. Basic features of timing and working memory models	168
6.2. Oscillatory models of interval timing: Coincidence detection	169
6.3. Oscillatory models of working memory	171
6.4. Dual-oscillator interference model of hippocampal function	171
7. Integrative models of interval timing and working memory	172
7.1. A model for phase-amplitude coupling	172
7.2. Integration of interval timing and dual oscillator models	173
7.3. Linking the EIO model to process models of interval timing	175
7.4. Integrative model for interval timing and working memory	176

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8. Implications	178
References	179

1. Introduction

Neural oscillations are a fundamental property of brain function that modulate cognitive processes such as attention, memory, and decision-making as well as the duration and beat-based timing mechanisms involved in timing and time perception (Allman et al., 2014; Benchenane et al., 2011; Buhusi and Meck, 2005; Cheng et al., 2008, 2009; DeCoteau et al., 2007; Matell and Meck, 2004; Teki et al., 2011, 2012; Varela et al., 2001; Wang, 2001; Ward, 2003). For example, in the context of working memory, oscillatory processes are thought to facilitate the encoding, maintenance, and synchronization of stimulus attributes presented in specific temporal sequences (Bonnefond and Jensen, 2012). This temporal structure provides us with the ability to compare the durations of relevant events (stimuli or responses), allowing us to perceive that ‘it’s time’ after a specific sequence of events has passed. In this sense, interval timing and working memory are intimately related and may largely be distinguished in terms of the type of information that is extracted 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). However, it’s important to note that 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 even in the absence of an external stimulus (Aagten-Murphy et al., 2014; Buhusi and Meck, 2000; Hålbjerg et al., 2002; Meck and Benson, 2002; Meck et al., 1984; Muller and Nobre, 2014; Wiener, 2014; Wiener and Coslett, 2008).

Various lines of research have examined the capacity and limitations of interval timing and working memory; however many issues remain unresolved and numerous controversies exist (Baddeley, 2003; Broadway and Engle, 2011a,b; Buhusi and Meck, 2009b; Fortin, 1999; Fortin et al., 2010; Taatgen and van Rijn, 2011; van Rijn et al., 2011). In order to get a clearer picture of the connections between interval timing and working memory, their shared features need to be viewed from multiple levels—including functional and neural mechanisms (Meck, 2003; Meck et al., 1984). Diverse evidence supporting co-variation between interval timing and working memory will be brought together so that the knowledge from each domain can inform and constrain the other. In an effort to achieve this goal, properties that are crucial to both interval timing and working memory will be selected and focused on such that the defining characteristics of each process are chosen and critically reviewed based on this overall goal.

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 (Kotz and Schwartz, 2010; Ivry et al., 2002; Schirmer, 2004), whereas interval timing (ranging from milliseconds to minutes) is known to be important for computational learning and decision-making (Gallistel and Gibbon, 2000, 2001; Gibbon, 1977; Meck et al., 2012b; Taatgen et al., 2007; van Rijn, 2014; van Rijn et al., 2014; Yin et al., in press). Multiple lines of research suggest an important cut-off dividing sub-second and supra-second timing between 500 ms and 2 s, with evidence of different properties (e.g., scalar vs. non-scalar variance, differential interaction/interference in dual-tasks, and the ability to make ordinal comparisons—see Buonomano et al., 2009; Cordes and Meck,

2014; Cordes et al., 2007; Fortin and Couture, 2002; Ivry and Spencer, 2004; Johnston et al., 2006; Michon, 1985; Rammsayer and Lima, 1991; Rammsayer and Ulrich, 2011). In addition to the sub- and supra-second distinction, Lewis and Miall (2003a,b, 2006) have considered other factors such as whether stimuli reoccur in a repeating cycle so that the temporal sequence can be predicted with relatively little (if any) attention; and whether the durations are defined by motor movement. As a consequence, they proposed two timing systems that engage different neuronal circuits—one that is automatic and another that is cognitively controlled (Lewis and Miall, 2003b). In this review, for better comparison with working memory, an emphasis will be placed on cognitively controlled temporal processing involving supra-second intervals not defined by specific movements or a continuous predictable pattern of stimulus presentation (see Matthews and Meck, 2014, in press; Matthews et al., 2014).

A “multi-component” model of working memory developed by Baddeley and colleagues (e.g., Baddeley, 1986, 2000; Baddeley and Hitch, 1974; Repovs and Baddeley, 2006) has been highly influential in the field. This model proposes that a central executive function provides attentional control over memory-storage systems that include a visuo-spatial sketch pad, phonological loop, and an episodic buffer for multimodal storage. This model, however, has been exclusively developed to account for data from human participants. Because this review includes both primate and rodent studies, a somewhat different working-memory model is preferred in order to support a more comparative perspective. Postle (2006), for example, has defined working memory as an emergent property of neural systems representing many different types of information. With evidence of diversity in the stimulus attributes maintained in working memory (e.g., egocentric and allocentric spatial information, olfactory and somatosensory cues, etc.), it seems reasonable to assume, as stated by Postle (2006, p. 29) “that if the brain can represent it, the brain can also demonstrate working memory for it”. In this regard, the definition of working memory in the current review represents an emergent property of neural systems, which in other words is “the temporary retention of information that was just experienced, but no longer exists in the external environment, or was just retrieved from long-term memory” (D’Esposito, 2007) and can be actively maintained, rehearsed, and also manipulated for its use in making predictions and guiding behavior (Borst et al., 2010).

From this perspective, shared features between interval timing and working memory will be identified and physiological accounts of these processes will be explored in an attempt to specify the common underlying mechanisms. The organization of this paper includes an overview of the behavioral, neuroanatomical, and neurophysiological features of interval timing and working memory, followed by a description of current theoretical models. Finally, a novel framework incorporating the shared features of interval timing and working memory will be proposed in order to better emphasize the common oscillatory mechanisms supporting these cognitive processes. This framework highlights the role of multiplexing, whereby multiple information streams share a common neural substrate. The basic idea is that such multiplexing, implemented as a function of the relative power in different frequency bands observed in local field potentials within and between different brain structures, enables the reconfiguration of effective connectivity and the types of information stored and/or extracted from the neural network (Akam and Kullmann, 2010, 2014).

2. Interaction between cognitive processes supporting 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 (e.g., Block and Zakay, 1997; Block et al., 2010; 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 and Zakay, 2008; Block et al., 1980; 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). Interestingly, if timing is a secondary aspect of an overall task, prospective duration judgments are not affected when cognitive load is manipulated while keeping the number of memory retrievals fixed (Taatgen et al., 2007). 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 distinctive memory components (e.g., amount of contextual change or interval segmentation) that are correlated with the estimated durations (Grondin, 2010; MacDonald et al., 2014).

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 and Couture, 2002; Fortin and Masse, 1999; Fortin et al., 2007, 2009; 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). This line of argument is supported by the finding that low working memory capacity participants show an increased neural response to irrelevant distractors in a Flankers task in comparison to high working memory capacity participants (Gulbinaite et al., 2014a). Interestingly, Harrington et al. (2004b) reported that poorer working memory correlated with increased variability in the 'clock' component of time reproduction, arguing for dissociation between temporal accuracy and precision with regard to working memory function.

3. Limitations in working memory and its temporal component

Limitations in working memory are frequently defined as reductions in the capacity for holding items in memory. Working memory capacity has traditionally been hypothesized to be seven plus or minus two items (Miller, 1956); more recent studies, however, suggest that it is only possible to hold four items in working memory when rehearsal and/or chunking and the use of other memory systems are prevented (e.g., Cowan, 2001; Dallah and Meck, 1990). In addition to this capacity limitation, temporal limitations of working memory have also been revealed by loss of information (either as decay or interference) as a function of increases in the retention interval (e.g., Buhusi and Meck, 2000, 2006a,b; Fuster, 1995; Pasternak and Greenlee, 2005). It is important to note that working memory capacity can vary as a function of the type of information stored (e.g., verbal vs. visuospatial) which in turn can affect temporal discrimination (e.g., Broadway and Engle, 2011a,b; Kane et al., 2004). Moreover, modality differences have been shown in working memory capacity, for example, lists presented in the auditory modality were maintained better than those presented visually (e.g., Drewnowski and Murdock, 1980; Penney, 1989). Interestingly, a similar modality effect has been also been demonstrated in time perception, such that auditory signals are perceived as being longer than visual signals (e.g., Cheng et al., 2011; Lustig and Meck, 2011; Penney and Turret, 2005; Penney et al., 2000).

The limitations and failures of working memory are commonly attributed to proactive/retroactive interference and/or the decay of information as time passes (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 have been shown even when rehearsal and/or interference effects are carefully controlled which reduces the possibility of other factors intervening during the retention interval (McElree, 2001; Roediger et al., 1977). Delayed-response tasks in rodents and primates (e.g., Fuster, 1995; Pasternak and Greenlee, 2005) further support the decay proposal by showing steady declines in behavioral 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-effects 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 successfully accounted for the time-accuracy data in the working memory paradigm, whereas decay theories could not account for the time-accuracy data. However, as a contradictory point to this argument, Portrat et al. (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 hypotheses, 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 review.

4. Selective neural patterns supporting interval timing and working memory

Timing in the milliseconds-to-minutes range is thought to be based on interactions between cortical areas, the basal ganglia, and the thalamus (Buhusi and Meck, 2005; Merchant et al., 2013a). The critical role of cortico-basal ganglia-thalamic circuits in interval timing is supported by a variety of evidence from human neuroimaging (e.g., Harrington et al., 2010; Hinton and Meck, 1997a,b; 2004; Lewis and Miall, 2006; Meck et al., 2008a), clinical populations (Allman and Meck, 2012; Harrington et al., 2011; Malapani et al., 1998), pharmacological (Buhusi and Meck, 2002; Cheng et al., 2006, 2007a,b; Heilbronner and Meck, 2014; Lake and Meck, 2013; Matell et al., 2004, 2006; Meck, 1983, 1986, 1996; Meck et al., 2008b), lesion or genetic mutation (Harrington et al., 1998; Meck, 2006a,b,c; Meck et al., 2012a; Narayanan et al., 2006), and electrophysiological studies (Chiba et al., 2008; Macar and Vidal, 2002; Matell et al., 2003a,b; Merchant et al., 2012, 2013a,b; Narayanan and Laubach, 2006, 2009).

4.1. Lesion and inactivation studies

Lesions in the caudate/putamen (CPu) or loss of dopamine (DA) neurons in the substantia nigra pars compacta (SNc) generally

produce a substantial loss of temporal control in humans and rodents (e.g., Cope et al., 2014; Jones and Jahanshahi, 2011; Meck, 2006b; Schwartz and Kotz, 2013; Schwartz et al., 2011). Moreover, the disruption of interval timing ability by the loss of DA neurons in the SNc, but not the temporal disruption produced by CPu lesions, can be restored by L-Dopa administration (Meck, 2006b), indicating the crucial role of the CPu as well as the DA projections from the SNc in timing behavior. In addition, clinical populations which have posited deficits in cortico-basal ganglia-thalamic circuits and DA regulation; such as attention-deficit hyperactivity disorder (ADHD), Huntington's disease (HD), Parkinson's disease (PD), schizophrenia, autism and obsessive-compulsive disorder (OCD) also show evidence of abnormal timing ability (e.g., Beste et al., 2007; Carroll et al., 2008; Cope et al., 2014; Gu et al., 2011; Jahanshahi et al., 2010—for reviews see Allman and Meck, 2012; Grahn et al., 2008; Jones and Jahanshahi, 2014; Meck, 2005; Meck and Benson, 2002; Moustafa and Gluck, 2011; Nombela et al., 2013; Parker et al., 2013). For example, patients with PD exhibit deficits in temporal processing (e.g., Allman and Meck, 2012; Gu et al., 2014; Malapani et al., 1998), and neuroimaging studies of PD patients support abnormal brain activation during timing tasks, especially in the cortico-striatal circuits (e.g., Harrington et al., 2011, 2014; Jones and Jahanshahi, 2014).

Lesions of the frontal cortex (FC) also affect interval 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 in a manner similar to age-related declines (e.g., Harrington et al., 1998; Koch et al., 2002; Lustig and Meck, 2001; Meck, 2002; Meck et al., 1986, 1987; Olton et al., 1988—see also Allman and Meck, 2012). The effects of dopaminergic drugs on clock speed refer to the phenomenon where 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 (e.g., Coull et al., 2011; Lake and Meck, 2013; MacDonald and Meck, 2004, 2005, 2006; Meck, 1983, 1986, 1996; Meck et al., 2012a; Narayanan et al., 2012). Especially, patients with lesions in right FC and inferior parietal cortex showed impaired temporal processing (Harrington et al., 1998), suggesting a critical role of the right hemisphere in timing. 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; Wiener, 2014), further supporting the involvement of right hemisphere in supra-second timing.

Many types PFC-dependent operant tasks have explicit temporal constraints that must be satisfied for the tasks to be performed correctly. For example, simple and choice reaction-time tasks require rats to sustain a response (lever press or nosepoke) over brief intervals (e.g., 0.5 to 2.0 s) and terminate the response when a stimulus is presented. Lesions or inactivations of medial PFC in these tasks typically results in rats making many “premature” responses, terminating the sustained response before the end of the delay period (e.g., Narayanan et al., 2006), an effect that does not occur with inactivation of adjacent medial motor areas of the frontal cortex (Smith et al., 2010). A common interpretation of these tasks is that the medial PFC exerts an inhibitory role in the control of behavior (e.g. Boulinguez et al., 2008; Hayton et al., 2010, 2011; Jaffard et al., 2008; Narayanan and Laubach, 2006, 2009; Narayanan et al., 2006; Risterucci et al., 2003; Totah et al., 2009). An alternative interpretation is that medial PFC encodes information about the passage of time and sends this information to the motor cortex, where inappropriate actions are inhibited (Merchant et al., 2013b; Narayanan and Laubach, 2006). Moreover, recent work showed that low-frequency oscillations within the medial frontal cortex are related to adaptive control over response time in a time-estimation

task. The finding was observed both in humans and rodents, suggesting a shared mechanism across mammalian species about how medial frontal networks guide behavior in accordance with behavioral goals (Narayanan et al., 2013).

4.2. Neuroimaging studies

Human neuroimaging studies have also localized functional brain areas involved in time perception and timed performance (Allman et al., 2014; Coull et al., 2011; Lewis and Miall, 2003c; Meck et al., 2008a; Merchant et al., 2013a; Penney and Vaitilingam, 2008). During duration discrimination or reproduction tasks, significant activation has been commonly reported in cortico-basal ganglia-thalamic circuits (including DLPFC, supplementary motor area (SMA), preSMA, striatum, and thalamus), inferior parietal lobe, and cerebellum (Lewis and Miall, 2003b,c; Meck et al., 2008a; Rubia and Smith, 2004; for review see Coull et al., 2004, 2008; Harrington et al., 2004a,b; 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 of 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., 2004a,b, 2010; Rao et al., 2001;). Moreover, independent component analysis of fMRI data (Stevens et al., 2007) has identified cortico-basal ganglia-thalamic circuits as the primary common component across multiple timing tasks—see also Allman et al. (2014), Coull et al. (2011, 2013), and Merchant et al. (2013a) for a more complete description of the properties of these “core” timing circuits and the importance of degeneracy in interval timing (Lewis and Meck, 2012).

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 motor 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 recruits the PFC and parietal cortices, with a bias to the right hemisphere (Lewis and Miall, 2003b; Meck, 2005; Meck and Malapani, 2004). The additional involvement of PFC and parietal activations in cognitively controlled timing has been hypothesized to represent encoding and attentional requirements which could be shared with working memory processes (Buhusi and Meck, 2009a; Meck and Benson, 2002; Borst et al., 2011).

Numerous attempts to localize working memory to specific brain areas have produced inconsistent findings and interpretations; however, at a general level, the literature supports the common involvement of the PFC, basal ganglia, and parietal lobe in addition to the sensory-specific areas related to the stimuli to be remembered (e.g., D'Esposito, 2007; Postle, 2006; Wager and Smith, 2003; Borst and Anderson, 2013). The roles of these areas in working memory are still controversial due to the complex nature of this process, such as the multiple components involved in working memory and the diversity in behavioral strategies and stimulus types used in different task designs. However, the role of the PFC has

been suggested as mediating interference, attentional monitoring, flexible control, transformations of mnemonic representations, and goal representations; while the parietal lobe has been implicated in engaging attentional control and working memory retrieval (e.g., Berryhill and Olson, 2008; Postle, 2006; Yantis et al., 2002). Moreover, the cortical-striatal circuit has been suggested to play a crucial role in selecting and updating the relevant information in working memory (e.g., Frank et al., 2001; Hazy et al., 2006, 2007; O'Reilly and Frank, 2006; Borst and Anderson, 2013).

There are some striking similarities in the shared neuroanatomical features between interval timing and working memory. For instance, the role of the PFC and basal ganglia network in controlling access to working memory via selective gating by DA modulation has many parallels with interval timing (e.g., Hazy et al., 2006; McNab and Klingberg, 2008; Meck, 1996). Not only do the same gross anatomical areas mediate cognitively controlled timing and working memory, but the suggested role/mechanisms of the PFC and basal ganglia are similar such as engaging attentional control and selective gating for relevant information (Stocco et al., 2010; Zakay, 2000; Zylberberg et al., 2010). Moreover, the same types of dopaminergic drugs affect both interval timing and working memory, thus, taken together, this evidence further supports the notion that the same anatomical/neuronal properties are likely shared between the two processes (Buhusi and Meck, 2002, 2009a; Gruber et al., 2006; Lewis and Miall, 2006; Lustig and Meck, 2005; Lustig et al., 2005).

4.3. Electrophysiological studies

Electrophysiological findings from rodents and primates have provided rich neuronal evidence of interval timing and working memory via various firing patterns of neurons. Firing rates of neural spikes during timing often show linear ramping, descending, peak or dip patterns across time (Fig. 1; Jin et al., 2009; Lebedev et al., 2008; Matell et al., 2003a,b, 2011; Merchant et al., 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). Moreover, a recent study reported longer duration temporal signals (on the order of many seconds) in the medial PFC during a delayed alternation task indicating the generality of linear ramping across a variety of different time scales (Horst and Laubach, 2012).

Ramping activity has received considerable attention due to its potential for encoding relevant temporal information (Durstewitz, 2003, 2004; 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 onset times.

However, the ramping slopes are also typically correlated with the expected reward value in many experiments. For example, a

Fig. 1. (A) Neural oscillations in the cortex during temporal ordinal comparison task in rats. Normalized power of low frequency oscillations (e.g. theta and delta rhythms) in the cortex increases during the encoding of standard duration of 0.5, 1 and 3 s. The peaks of oscillation power are shown at 0.5–1 s after signal onset consistently across different durations of standards. Adapted from Gu et al. (submitted) and Gu and Meck (2013). (B) Time-frequency spectrograms showed that the gamma LFP oscillations in parietal cortex of macaques increases during the maintenance period of the memory-saccade task. Increase of gamma is shown in the preferred direction, but not in the anti-preferred direction of the recording sites. Adapted from Pesaran et al. (2002). (C) Phase-amplitude coupling (PAC) shown in the intracranial EEG recordings in human hippocampus during a Sternberg working memory task. Filtered signal shows that the gamma activation modulated by theta phase (upper panel). The PAC pattern differed depending on the working memory load, so the frequency for phase (theta) was shifted toward lower frequencies with increasing memory load. Adapted from Axmacher et al. (2010). (D) Oscillatory power differences between order versus item maintenance in a working memory task recorded using EEG in humans. Finding shows that the frontal theta increases during order maintenance compared to item maintenance while posterior alpha is enhanced during item compared to order maintenance. Adapted from Hsieh et al. (2011).

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 (van Rijn et al., 2011; Boehm et al., 2014). 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., 2013a; van Rijn et al., 2011). Moreover, the observed ramping patterns can also be generated as a secondary effect of oscillatory processes that will be explained later as part of an integrative model of interval timing and working memory.

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). The CNV represents a slow brain potential wave of negative polarity mostly shown over 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 in 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; Ng et al., 2011). In addition, a comparison of the predictive value of the CNV amplitude and the predictive value of other EEG components has shown that the evoked response to the onset of a stimulus is a better predictor of subjective time than the CNV amplitude (Kononowicz and van Rijn, 2014), indicating that another source of temporal information must have been available for driving the evoked responses. 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 (Boehm et al., 2014) or decision-making processes. Such processes monitor the passing of time, but do not reflect accumulation per se (van Rijn et al., 2011).

One of the most prominent neural features associated with working memory is the sustained neural activity observed during a delay period (e.g., Funahashi et al., 1989; Fuster, 1973; Goldman-Rakic, 1995; Kubota and Niki, 1971; Miller et al., 1996). This sustained activity is commonly observed in the PFC and has been proposed to represent stimulus attributes. For example, in an oculomotor delayed-response (ODR) task where a monkey is required to maintain fixation throughout a cue and delay period before he makes a saccade to the direction where the cue is presented, it is the direction selective neurons in the dlPFC that exhibit sustained activity during the delay period even with continued fixation (Funahashi et al., 1989). It is worth noting that the duration of the delay periods used in these studies were fixed, and so it is just as likely that persistent activity in the dlPFC encodes the passage of time, and not the stimulus information per se. To date, no study has directly tested this issue using the ODR task. Other types of sensory information have been shown to be associated

with ramping and persistent discharge by dlPFC neurons. Sound frequency information (i.e., pitch) is parametrically maintained by the firing rates of primate PFC neurons during the delay period (e.g., high pitch stimuli produce high spike rates—e.g., Brody et al., 2003; Romo et al., 1999). Evoked or spontaneous disruptions of these sustained activities are correlated with the failure of maintenance (e.g., Fuster, 1973; Quintana et al., 1988; Sobotka et al., 2005; Wang et al., 2011), supporting the importance of sustained neural activity during the delay periods for the maintenance of information in working memory.

As described above for ramping firing patterns, some models have also been proposed to account for the sustained neural activity correlated with working memory as well as for other task-related variables (Durstewitz and Seamans, 2006; Durstewitz et al., 2000; Machens et al., 2005; Wang, 2001, 2008; Wei et al., 2012). A neural network consisting of two mutually-inhibiting neural nodes has been recently shown to support both the coding of an interval with ramping activity (Merchant et al., 2011) and its subsequent maintenance in working memory (Méndez et al., 2014). Moreover, this model also incorporates a decay of information as time passes, affecting performance in the manner described earlier. Taken together, this provides another piece of evidence in support of common mechanisms for interval timing and information storage.

The sustained neural activity usually isn't maintained at a constant firing rate, but more often exhibits various firing rates such as systematic ramping or decreasing patterns (e.g., Brody et al., 2003; Kojima and Goldman-Rakic, 1982; Niki and Watanabe, 1979; Quintana and Fuster, 1999). The diversity of firing patterns found in PFC regions during delayed response tasks is similar to the diversity exhibited by frontal cortical neurons during the performance of interval timing procedures (e.g., Brody et al., 2003; Kojima and Goldman-Rakic, 1982; Matell et al., 2003a,b, 2011; Niki and Watanabe, 1979; Quintana and Fuster, 1999). Future studies should attempt to relate neuronal correlates of timing delay periods and more extended intervals using novel task designs or by recording from the same neurons as animals perform these two types of tasks. Moreover, the retention interval is often difficult to separate from the timing component considering that the duration of the retention interval is often predictable (i.e., fixed in duration, or the probability onset follows a hazard function) and allows subjects to anticipate the presentation of the upcoming target. Consequently, the maintenance of specific stimulus attributes would typically occur simultaneously with timing, and the firing pattern of spikes could be related to both interval timing and working memory in a manner that would make them difficult to dissociate from each other.

5. Oscillatory features of interval timing and working memory

With the exponential increase of attention on the role of neural oscillations in cognition, numerous studies have explored the oscillatory mechanisms supporting working memory and interval timing. Compared to the extensive findings of gamma activity in working memory, low-frequency oscillations such as delta, theta, and beta activity have been proposed to convey temporal information. Low frequency oscillations (in the range of delta) have been implicated in attention and stimulus timing in human and animal studies (Kösem et al., 2014; 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). Phases of slow oscillations in auditory and visual cortical areas were systematically

shifted depending upon the perceptual simultaneity of auditory and visual stimuli (Kösem et al., 2014). Also, 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 (see also Cravo et al., 2013; Henry and Herrmann, 2014; Rohenkohl and Nobre, 2011; Rohenkohl et al., 2012).

In conjunction with these findings of oscillatory activity associated with interval timing, the encoding of specific signal durations has been shown to be related to slow frequency oscillations including the theta and delta ranges as illustrated in Fig. 1A (Gu et al., submitted; Gu and Meck, 2013). When rats are required to encode a standard signal duration in order to compare it with a subsequent comparison signal duration, theta/delta frequency oscillations increase with the onset of the standard duration and peak at approximately 0.5–1 s, followed by sustained theta/delta activity until the offset of the standard duration. The peak in theta/delta oscillations was similar across different standard durations (0.5–3 s) and was observed in both the cortex and striatum. These findings suggest that the fluctuation and maintenance of slow-frequency oscillations may partially underlie the mechanisms of duration encoding (Matell and Meck, 2004).

Beta and gamma rhythms have been observed to systematically fluctuate in relation to beat processing and/or rhythmical movement (e.g., Bartolo et al., 2014; Fujioka et al., 2009, 2012; Teki, 2014). Periodic beta desynchronization and rebound was shown during beat perception in the human auditory cortex and motor related areas even without movement, and the rate of beta power rebound represented the temporal information of the isochronous sounds (Fujioka et al., 2009, 2012). Moreover, information processing in the primate basal ganglia during sensory guided and internally driven rhythmic tapping suggests that gamma oscillations reflect local computations associated with stimulus processing, whereas beta activity involves the entrainment of large putaminal circuits in concert with other elements of a core timing system involving cortico-basal ganglia-thalamo-cortical networks (Bartolo et al., 2014; Merchant et al., 2013a). Interestingly, these effects generalize to the estimation of longer intervals (2.5 s) in a temporal reproduction paradigm. Reanalyzing data that questioned the link between the CNV and temporal accumulation, Kononowicz and van Rijn (submitted) demonstrated that beta power measured 500 ms after the onset of the reproduction predicted whether the current trial was going to be under- or overestimated.

An impressive series of studies have 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; Gulbinaite et al., 2014b). 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). For example, sustained gamma activity to the preferred stimulus has been shown in the lateral intraparietal lobe (LIP) of primates during the delay period of working memory, and oscillatory activity was often more predictable of the output behavior than the spike rates (Pesaran et al., 2002—see Fig. 1B). Also, a human intracranial EEG (iEEG) study has reported an increase of theta activity in multiple cortical areas during a Sternberg working memory task where visually presented multiple sequential letters were required to be maintained (Raghavachari et al., 2001)—again indicating the importance of oscillatory band frequency and power.

Other studies have shown that the peak frequency in the theta and alpha bands correlates with working memory capacity (Moran

et al., 2010; Myers et al., 2014a,b) and that gamma power is well correlated with working memory load (Axmacher et al., 2007, 2008). The number of items to be maintained in working memory was correlated with the power of gamma activity in frontal, parietal, hippocampal, and occipital areas measured by iEEG (Axmacher et al., 2007, 2008; Howard et al., 2003; Meltzer et al., 2008) or by magnetoencephalography (MEG—Roux et al., 2012). However, the relation of theta power to memory load has been shown to be inconsistent across measured brain areas and also dependent on task design, stimulus, or individual differences (e.g., Howard et al., 2003; Jensen and Tesche, 2002; Meltzer et al., 2008; Michels et al., 2008; Tesche and Karhu, 2000; van Vugt et al., 2010). For example, local-field potentials (LFPs) measured in the extrastriate visual cortex of primates showed increased theta power in relation to the increase of memory load in a delayed-matching-to-sample task (Lee et al., 2005). When the contrast of a sample image was lowered in order to make the task more difficult, the theta power (e.g., 4–8 Hz) recorded in the visual cortex increased during the maintenance as did the delta (e.g., 0–4 Hz) and gamma (e.g., 30–70 Hz) power. Another human iEEG study using a Sternberg working memory task, however, showed that the increased number of items to be maintained is negatively correlated with theta power in occipital and left frontal–parietal cortex while it is positively correlated with the theta power in the frontal cortex and posterior midline (Meltzer et al., 2008). Interestingly, the brain areas showing decreased theta power with memory load often showed a compensatory increase in gamma power. These inconsistent findings implicate the various functional roles of theta and gamma power across different brain areas, especially in relation to working memory load. Also, the findings of the relation between theta power and working memory load would have to be considered in light of the task characteristics, including the difficulty of the task. For example, whether the manipulation involves an increased number of items to be maintained in working memory or another type of increase in difficulty level for one-item maintenance (e.g., use of low-contrast images or an increase in the number of distracters).

There is also considerable evidence showing that beta rhythm increases during the delay period of working memory (e.g., Deiber et al., 2007; Siegel et al., 2009; Tallon-Baudry et al., 2001, 2004). These findings showed that beta rhythms increased during delayed matching to sample tasks in primates and humans, and the increased beta rhythms often coexisted with other frequency band rhythms such as delta, theta or gamma. Increase of beta rhythms have been mostly known to promote tonic motor contractions at the expense of voluntary movement (e.g., Brittain and Brown, 2014; Jenkinson and Brown, 2011), however, other functional relations of beta rhythms are also suggested such as in maintaining the current sensorimotor or cognitive state (Engel and Fries, 2010), endogenous top-down processing (Buschman and Miller, 2007, 2009), cue utilization (Leventhal et al., 2012) and short-term/working memory (Tallon-Baudry, 2003). The involvement of beta in working memory as well as in temporal behavior as previously described, in together with the evidence of other frequency bands of neural oscillations, suggests that oscillatory features could be shared between timing and working memory. In addition, beta rhythms are important in basal ganglia disorders and fluctuations in beta oscillations in the basal ganglia and sensorimotor cortex are frequently observed as a function of dopamine levels (Brittain and Brown 2014; Jenkinson and Brown, 2011; Gu et al., 2014), providing an anatomical link between beta rhythms and the cortico-striatal circuits involved in temporal processing and working memory.

In addition to the power of neural oscillations, the temporal relation of spike activity to the ongoing oscillations has received considerable attention in recent studies of working memory. Individual neurons that are related to the maintained representation often show “phase locking” of firing to the ongoing theta

oscillations (Lee et al., 2005; Rutishauser et al., 2010). This firing occurs at particular phases of the theta cycle, and the phase of theta has even been shown to reset by the arrival of the target stimulus (Tesche and Karhu, 2000). With this in mind, it has been proposed that “theta-coupled replay” is an important mechanism for maintaining information in working memory as a function of the periodic reactivation of the relevant information (Fuentemilla et al., 2010). Moreover, the “phase locking” of spikes during the maintenance phase is often exhibited without increases in firing rates (Lee et al., 2005), suggesting that the temporal coordination of spikes with ongoing neural oscillations may be even more important than the firing rates of spikes for the maintenance of information during a retention interval.

It's important to note that phase locking occurs in a stimulus-selective manner. For example, the phase-locked gamma synchronization is stronger in the contralateral position to the cued hemifield than in the ipsilateral hemifield and varies as a function of memory load, suggesting that phase locking occurs specifically to the relevant brain area (Sauseng et al., 2009). Also, the phase locking of a single neuron occurs selectively to the preferred target of the neuron (Lee et al., 2005). Moreover, multiple sequential items are associated with different phases of the LFP oscillation in the PFC of primates (Siegel et al., 2009). In this study, spikes and LFPs recorded from the PFC were measured during a working memory task where two sequential items (e.g., photos of apples and oranges) were required to be remembered in a specific temporal order. The findings showed that the oscillation powers at frequencies around 3 Hz and 32 Hz increased in relation to the task components and that the majority of spikes were phase-locked to the falling phase of the 32-Hz oscillation and to the trough phase of the 3-Hz oscillation. However, when the item's identity was considered, the first item was associated with earlier phases of the 32-Hz oscillation compared to the second item, with no differences in 3-Hz phases between the first and second items.

The degree of phase locking has also been shown to be predictive of working memory performance (e.g., Liebe et al., 2012) as well as for the successive encoding of information into long-term memory (Rutishauser et al., 2010; Tort et al., 2009). Specifically, Liebe et al. (2012) showed that the phase locking of spikes to the LFP theta oscillation increased during the maintenance of a visual stimulus in area V4 and the PFC of primates. Interestingly, these findings showed that the measured inter-area phase-locking value (e.g., phase locking of V4 spikes to the PFC theta oscillation and vice versa) was larger for correct trials compared to incorrect trials, supporting the idea that phase locking and theta oscillations are important for inter-area communication (see also, Fries, 2005) and maintenance of information in working memory (see also, Gulbinaite et al., 2014b).

In addition to the phase locking of spikes to theta oscillations, studies utilizing LFPs or EEG/MEG have reported that phase-amplitude coupling (PAC) between theta-gamma oscillations is involved in working memory (e.g., Axmacher et al., 2010; Jensen and Colgin, 2007; Lisman and Idiart, 1995; Maris et al., 2011; Mizuhara and Yamaguchi, 2011; Sauseng et al., 2009; Schack et al., 2002; van der Meij et al., 2012). PAC, also referred to as “nested oscillations”, refers to the phenomenon of coupling between the amplitude of a faster oscillation and the phase of a slower oscillation. Numerous studies have shown evidence of PAC in various species including humans, monkeys, and rats (e.g., Canolty et al., 2006; Chrobak and Buzsáki, 1998; Lakatos et al., 2005, 2008; Sirota et al., 2008; Tort et al., 2009; van der Meij et al., 2012). PAC has been most commonly observed between theta and gamma oscillations; however, recent evidence shows that PAC can occur at multiple frequencies with theta oscillations also being entrained to delta oscillations (e.g., He et al., 2010; Lakatos et al., 2005; Maris et al., 2011; Miller et al., 2010).

The functional role of PAC is thought to involve local neural computations and their communication across large-scale brain networks (Canolty and Knight, 2010). With the extensive evidence of PACs occurring over various frequencies and brain regions, PAC has been shown to be involved in multiple cognitive domains, important for working memory (e.g., Axmacher et al., 2010; Lisman and Idiart, 1995; Maris et al., 2011; Mizuhara and Yamaguchi, 2011; Schack et al., 2002; van der Meij et al., 2012), and also for decision-making, spatial navigation, learning, and perception (Kepecs et al., 2006; Lakatos et al., 2005). Canolty et al. (2006) examined the PAC patterns in different cognitive tasks by recording the electrocorticogram (ECoG) of epilepsy patients, showing that similar tasks evoked similar spatial patterns of theta and gamma PAC—suggesting that “cognitive architectures” can be described by these patterns of oscillatory activity.

In working memory tasks, the amplitude of gamma is modulated by theta phase in multiple brain areas, while PAC strength is modulated in a heterogeneous manner. Maris et al. (2011), for example, showed that working memory tasks are associated with increases in PAC strength in the parietal-temporal and right frontal areas, with an associated decrease in strength in right temporal lobe in humans. Moreover, when the amplitude- and phase-providing oscillations are spatially dissociated using decomposition techniques, the PAC was shown to be widely distributed across the brain, with the spatial extent of the phase-providing (slower) oscillations tending to be more widespread than the amplitude-providing (faster) oscillations (Maris et al., 2011; van der Meij et al., 2012). The widely distributed PAC networks demonstrated in these human studies, together with the evidence of cross-area couplings from rodents and primates (Liebe et al., 2012; Sirota et al., 2008; Tort et al., 2009), support the functional role of PAC in facilitating communication among brain areas by modulating the synchronous patterns of neural firing.

The PAC observed during working memory performance was also modulated by the degree of memory load (Axmacher et al., 2010—see Fig. 1C). The PAC between theta and gamma was increased during maintenance in working memory as measured by iEEG in human hippocampus, and with increases in memory load, the frequency for phase (slower frequency) was extended towards the lower frequency, while the frequency for amplitude (faster frequency) did not show any significant change. This systematic variation in PAC as a function of memory load indicates the critical role of theta and gamma PAC in working memory, and also highlights the underlying relations between PAC and multi-item working memory. The potential interaction of oscillatory features supporting working memory and interval timing has primarily been examined in terms of the temporal-order information associated with the items maintained in working memory (e.g., 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 as illustrated in Fig. 1D. As a specific example, 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 the maintenance of spatial information and temporal-order of multiple items 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 increased during temporal-order maintenance while the right frontal gamma (30–50 Hz) power increased 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 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. 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, the EEG pattern presented during encoding was reactivated in the recognition phase, even in the absence 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 characteristics of the object that can be directly represented by neural oscillations (Lustig et al., 2005).

6. Complementary models of interval timing and working memory

6.1. Basic features of timing and working memory models

Numerous models of interval timing and working memory have been proposed from varying perspectives (Buhusi and Meck, 2005; Méndez et al., 2014; Miyake and Shah, 1999; Shi et al., 2013; Taatgen and van Rijn, 2011; van Rijn et al., 2014; Wei et al., 2012). 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., 2013a; 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 and Laje, 2010; Buonomano and Maass, 2009; Buonomano and Merzenich, 1995; 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 (Allman and Meck, 2012; 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. 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 (Ullsperger et al., 2014; van Rijn et al., 2014). 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, 2009; Lewis and Miall, 2006; Lustig and Meck, 2005; Lustig et al., 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, 2005, 2010; Lisman and Idiart, 1995) have recently received considerable attention when trying to integrate these processes (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, 2005, 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 involvement in temporal processing (e.g., Burgess and O'Keefe, 2011; MacDonald et al., 2014; Meck, 2002; Meck et al., 1984, 2013; Yin and Meck, 2014; Yin and Troger, 2011).

6.2. 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., 2014) 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, for example, the alpha and theta frequency bands. 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 Fig. 2. 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). The synaptic weights between a MSN and cortical neurons with different endogenous oscillatory periods determine for which duration this MSN encodes. 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 a stable encoding of duration. The combination of drift on the one hand, and the reliance on slower oscillating cortical neurons for MSNs that encode for longer durations provide 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).

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 to a MSN 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 SNc 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 specification of 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., 2013a). MSNs in the striatum have the appropriate characteristics to serve as a large-scale coincidence-detector system because they receive a great deal of convergent, multi-modal input from the cortex (Wilson, 1995, 1998) and such coincident excitatory input from the cortex can drive the MSNs into the “Up state” (O'Donnell and Grace, 1995; Wilson, 1993). In particular, the importance of striatal function to interval timing and the acquisition of timed response thresholds has been demonstrated in studies using neurotoxin-induced lesions (Meck, 2006b), anisomycin-induced inhibition of protein synthesis (MacDonald et al., 2012), or calcium-responsive transcription factor-induced inhibition of brain-derived neurotrophic factor in cortico-striatal circuits (Agostino et al., 2013). Taken together, these studies reveal differential impairments in timing as a function of the striatal region (e.g., dorsal vs. ventral) and dopaminergic-glutamatergic interactions (e.g., Cheng et al., 2006, 2007a,b; Coull et al., 2011; Meck et al., 2012a).

Fig. 2. Striatal-beat frequency (SBF) 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 \(2004\)](#). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Human brain imaging studies have also shown that the striatum plays a central role in timing and time perception (e.g., [Coull et al., 2004, 2008, 2011](#); [Harrington et al., 2004a,b, 2010](#); [Hinton and Meck, 2004](#); [Meck and Malapani, 2004](#); [Rao et al., 2001](#); [Stevens et al., 2007](#)). Moreover, patients with apparent pathophysiology in DA systems in the cortico-striato-thalamic loop, such as HD, PD, schizophrenia, autism, ADHD, and OCD show abnormal characteristics in interval timing (e.g., [Allman and Meck, 2012](#); [Beste et al., 2007](#); [Carroll et al., 2008](#); [Cope et al., 2014](#); [Gu et al., 2011](#); [Harrington et al., 2011, 2014](#); [Jones and Jahanshahi, 2014](#); [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 predicted by the SBF model ([MacDonald and Meck, 2004](#); [Matell 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 be explained in terms of the well-known properties of cortico-striatal-thalamo circuits (e.g., [Alexander et al., 1986](#); [Gu et al., 2011](#); [Houk, 1995](#)). When the detection of cortical patterns activates specific MSNs, it will in turn

disinhibit the thalamus. Then, the activated thalamus in turn activates 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](#)).

It has been suggested, however, 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 overall clock speed will be changed (see [Oprisan and Buhusi, 2011, 2013, 2014](#)).

Fig. 3. 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 (30–80 Hz) cycles, and up to seven gamma cycles can be entrained in each theta cycle (4–10 Hz). The limited number of gamma cycles in each theta cycle corresponds to the limited number of different items that can be maintained. Adapted from Lisman and Idiart (1995) and Lisman (2010).

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).

6.3. 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, 2005, 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—Fig. 3). 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 seven (Lisman and Idiart, 1995). This model proposes that the main WM characteristics can be derived from oscillatory properties, especially the PAC phenomenon between theta–gamma bands previously described (see Dipoppa and Gutkin, 2013; Freunberger et al., 2011; Jackson et al., 2011; Maris et al., 2011).

This oscillatory working memory model predicts that two separate items should be maintained within two different gamma cycles (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

Fig. 4. (A) Place cell phase precession shown in the rodent hippocampus. Place cell fires in correlation to the specific position, and the spike firing occurs in higher frequency than the theta of local field potentials (LFPs). Therefore, the spike firings (red ticks) precess to the earlier phases of LFP theta (black). Adapted from Huxter et al. (2003). (B) Dual oscillator interference model of phase precession, showing 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). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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 beta oscillation phases as opposed to delta 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.

6.4. 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 and O'Keefe, 2011; Burgess et al., 2007; 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 aspect of place cells is that they fire whenever the subject's head 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 (Fig. 4A). 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).

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 (Fig. 4B). 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).

7. Integrative models of interval timing and working memory

7.1. A model for 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), we propose excitatory and inhibitory oscillation (EIO) inputs to each neuron as the dual oscillator components and expand this concept to a population of neurons for an integrative model of interval timing and working memory. A model of dendritic mechanisms explaining spike timing during theta rhythm (Gasparini and Magee, 2006; Magee, 2001) hypothesizes that proximal portions of pyramidal neurons (soma and proximal trunk) receive oscillating inhibitory inputs from the basket cell and axo-axonic cell network while distal dendrites receive inhibitory inputs that are in the opposite phase with the inputs to the proximal portions of pyramidal neurons. Increasing dendritic current injection caused a phase advancement of spikes to theta oscillation in this model (Magee, 2001). In the sense that the somatic inhibitory inputs guide the spike firing timing, this model shares some similarities with the EIO model.

In the EIO model, excitatory inputs to individual neurons are assumed to be various in oscillating frequencies (e.g. normal distribution, Fig. 5E) due to differences in the degree of dendritic inputs or conductance level of individual neurons. In addition, the population of these neurons is hypothesized to oscillate in a slightly slower frequency than the mean of oscillating individual neurons, and the inhibitory inputs are assumed to oscillate at a similar frequency to the oscillation of neural population 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 et al. (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. If we can bring this findings from hippocampus to the cortical network, 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 significant relation to the power of the LFP signal (e.g., Bartos et al., 2007; Buzsáki et al., 2012; Trevelyan, 2009). Therefore, these features would support the possibility that the synchronized inhibitory oscillation could be represented by the LFP oscillation.

The basic concept of our coupled 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 oscillators, the baseline somatic oscillation at the frequency of LFP, is substituted in the EIO model with the inhibitory oscillation which represents population feedback. The two models do not necessarily exclude each other, 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 their proposed role in cognitive processes, including working memory, not much has been revealed about the underlying neurobiological/computational mechanisms of PAC. Consequently, the proposal of a computational/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.

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 Fig. 5A–D. Simulation of neuronal spike outputs from an excitatory neuronal population as well as the inhibitory oscillation resembles the PAC phenomenon of multiple frequency bands (e.g., theta entrained in delta) as illustrated in Fig. 5F and 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 an increase in the 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 these 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 Fig. 5A and 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 Fig. 5C and 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 et al. (2005) also showed hierarchical relations in gamma, theta, and

Fig. 5. (A) Gamma range of excitatory oscillation (EO) and inhibitory oscillation (IO) inputs into a neuron. EO (47 Hz) in individual neuron is in larger 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.

delta activities. Moreover, the same neuronal firing sequences that are activated during previous theta states are shown to be replayed during ripple event in a compressed way (Lee and Wilson, 2002), and the fractal feature of EIO model can make it possible that the sequential neuronal firing during theta states are preserved during a ripple event.

In addition, depending upon the distribution of EO and IO frequencies, beta rhythms (instead of theta) can also be generated according to this model. For example, if the frequency difference between gamma IO and the mean of gamma EO is larger than in the case of theta rhythm generation, a higher frequency envelope oscillation, in the range of beta rhythms for example, can be produced. There is some evidence showing that the higher band gamma rhythms (~80 Hz) have different functional attributes in relation to dopamine than lower band gamma rhythms (~50 Hz), and the high or low gamma rhythms often coexist with theta or beta rhythms, respectively (e.g., Berke, 2009; Dejean et al., 2011). Thus, it is possible that specific inputs or depletion of dopamine can make changes in the distribution of gamma EO frequencies, which can result in the generation of beta rhythms instead of theta rhythms.

The relations between these frequency categories are important for controlling neural activations, and the current simulations illustrated in Fig. 5A–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 or amplify 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 (see Coull et al., 2011).

7.2. Integration of interval timing and dual oscillator models

Integrating the proposed EIO model with 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 coupled EIO model provides a realistic underlying oscillatory mechanism as proposed by the SBF model. With emphasis on the neural oscillatory properties, the new integrative model shows that the temporal information present in the oscillatory interactions between excitatory and inhibitory neurons is crucial for extracting information from the neural network during both interval timing and working memory (e.g., Buhusi et al.,

Fig. 6. (A) Theta range of EO (blue) and IO (red) inputs to each cortical neuron are balanced before a triggering event (e.g., dopamine input). The timing onset drives the EO inputs to individual cortical neurons oscillate in the faster and various frequencies while IO inputs are synchronized such as 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 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. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2013; Meck, 2001; Meck et al., 2008a). This new integrative model of interval timing predicts that a triggering event (resulting in a 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 at a 6-Hz frequency, cancelling 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) triggers 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, 3, and 4 will receive 6.2 Hz, 6.35 Hz, 6.5 Hz and 6.65 Hz of EO input, respectively as illustrated in Fig. 6A. The summation of EO and IO inputs in each cortical neuron will produce a membrane potential oscillation (MPO) of theta oscillations, 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, whereas Neuron

3 will show a 6.25-Hz theta entrained within a 0.5-Hz delta oscillation as illustrated in Fig. 6B. 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).

Under these conditions MSNs 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 (as originally proposed by the SBF model). 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. 6E. 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. 6B), 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 Fig. 6E.

This new EIO model assumes that the frequency of EO varies across neurons, but this varying frequency across neurons is relatively constant given a particular stimulus. 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 or different conductance ratios of neurons could be major factors contributing to the variation in oscillation frequencies (e.g., Gasparini and Magee, 2006; Magee, 2001). In our simulated model 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 as illustrated in Fig. 6C. 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).

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 phenomena. For example, if the distribution of EO frequencies is 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 target durations 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 Fig. 6, they will produce a 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 Fig. 6D. This effect is consistent with the electrophysiological findings of a theta power increase during temporal processing as illustrated in Fig. 1C. 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, 2014). 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 in this rhythm, thereby requiring other brain areas (e.g., cortex or cerebellum). It is important to note that although the model explains cognitively-controlled timing of supra-second duration ranges using theta and delta oscillations, it doesn't exclude the possibility of other frequency ranges such as beta or gamma oscillations being involved in timing. For example, there is evidence suggesting an important role for beta and gamma rhythms in temporal processing (e.g., Bartolo et al., 2014; Fujioka et al., 2009, 2012; Kononowicz and van Rijn, submitted), especially at the shorter end of the spectrum of durations (Allman et al., 2014; Teki et al., 2011, 2012). Neuroimaging evidence supports the

dissociation between sub- (<500 ms) and supra-second (>500 ms) timing with different brain involvement (Lewis and Miall, 2003a,b,c, 2006). Moreover, there are a variety of other neuronal models capable of explaining sub-second timing within cortical networks (e.g., Buonomano, 2000; Buonomano et al., 1995, 2009; Karmarkar and Buonomano, 2007). In sum, it is reasonable to assume that different duration ranges involve other frequency ranges of neural oscillations such as beta and gamma, and depending upon its specific characteristics different neural circuits might be involved in the estimation of these durations.

7.3. Linking the EIO model to process models of interval timing

At first, the oscillation-based model of interval timing described above might seem a large departure from the currently existing process models (e.g., Scalar Timing Theory, Gibbon et al., 1984; van Rijn et al., 2014) of interval timing that are used to explain broad spectra of behavioral effects. For example, the EIO account does not require a separate accumulator for temporal information, nor does it require a specialized pacemaker providing the temporal information, but it instead derives temporal information from the dynamics of other cognitive components such as the encoding and storage of new information in memory. Obviously, these changes raise the question whether the EIO model can still explain a similar spectrum of behavioral phenomena. To answer this question, it is useful to take the integrated timing model of Taatgen et al. (2007) in account. In this model, timing is not considered in isolation, but a temporal module inspired by Scalar Timing Theory is embedded within a cognitive architecture that provides further constraints on other cognitive faculties such as action-selection, memory retrieval, and interactions with the outside world. Using this integrated timing model, all aspects of a (behavioral) task can be modeled, from perception of a stimulus of which the display duration needs to be estimated, to the key presses required for the reproduction. In a series of papers, van Rijn and Taatgen (2008) have shown that this model is capable of explaining many different interval timing phenomena, from parallel estimation of multiple intervals to including context- or memory-mixing effects (Gu and Meck, 2011; Taatgen and van Rijn, 2011), but also that this integrated timing model can be used to explain the role of temporal information in higher level cognitive tasks such as driving a car or multitasking in a video game (e.g., Moon and Anderson, 2013; van Rijn, 2014).

The existing temporal system in the integrated timing model closely follows the outline of the Scalar Timing Theory, in that a separate start signal is needed to start the clock after which at any point the current state of the clock can be tested. Comparing the state of the clock with a previously experienced clock-state, and executing a key press as soon as these states are similar enough, straightforwardly implements a temporal reproduction task. This comparison process does not need to be an active process, as the striatal production rules (Stocco et al., 2010) in the decision making system are dormant until their conditions are matched, similar in functioning as the medium spiny neurons discussed earlier. This detection process is functionally identical to the firing of a MSN representing a particular duration, in both cases is the information that a specific interval is perceived made available to the other cognitive processes.

Interestingly, although not required by the original system, the onset of a temporal interval is in practically all models using the integrated timing theory accompanied by a change in the current memory state, either by updating the problem-specific memory representations or by changes in the declarative memory system. Although the neural substrate of the problem-specific memory representations is typically assumed to be located in the parietal cortex, recent work has shown links to the dlPFC (Borst and

Anderson, 2013) and all problem-specific memory representations are eventually stored in the declarative memory stores. Furthermore, although the declarative memory system is currently not implemented using oscillation-coding, earlier work has shown that the existing memory system can easily be extended to incorporate more detailed representational or retrieval mechanisms (van Maanen and van Rijn (2007); van Maanen et al., 2012). Assuming that these changes in memory representations result in the PAC discussed earlier, the encoding of the stimuli that trigger the onset of a relevant interval would automatically trigger phase-locking in the cortical neurons monitored by the MSNs. This combination of an extended Scalar Timing Theory model with a low-level model of neural oscillations thus allows for simpler models of timing tasks, as no explicit – and often considered ad-hoc – start signal needs to be implemented to start timing processes.

Fig. 7 shows the outline of an architecture that combines both the integrated timing theory and the EIO-based model of interval timing. As can be seen, interval timing and other cognitive processes are truly integrated, with the working memory system providing guidance to the oscillations on the basis of which interval timing decisions can be made.

7.4. Integrative model for interval timing and working memory

The proposed oscillation-based interval timing model can be expanded to include an oscillatory model of 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 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 hybrid EIO model follows the concept that an item's representation is maintained by the gamma entrained theta phase-amplitude coupling as proposed in Lisman and Idiart's oscillatory working memory model (Lisman, 2010; Lisman and Idiart, 1995). However, combining the EIO model with the additional PAC concept allows for more detailed predictions as well as an explanation of the underlying neural mechanisms. The observation that interactions between gamma ranges of EO and IO inputs produce a MPO with a PAC between gamma and theta is shown in Fig. 8A. The produced MPO of individual neurons will also be interfered with by theta IO inputs representing population feedback, so the MPO will be modulated as shown in Fig. 8B. Spikes will be produced near the peak of the MPO with certain thresholds, so the distribution of spikes will be “phase-locked” to the ongoing theta IO as shown in

Fig. 8B. 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 theta rhythm produced by inhibitory neural population. Although the coupled EIO model predicts the phase precession of spikes to theta rhythm 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.

If we extend the coupled 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 Fig. 8C. 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; van Rijn and Taatgen, 2008) 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 (see Jonides et al., 2008). Consistent with this view, explorations with a recurrent spiking network showed that some persistent activity of neural populations fades out or merges together as the working memory load increases, representing the decay and interference features of working memory (Wei et al., 2012).

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 hybrid EIO model to the extent that it predicts the close relationship between interval timing and multiple-item working memory. As shown in Fig. 8C, 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 hybrid EIO model, temporal-order

Fig. 7. The EIO-based interval timing model integrated in a process model of interval timing. The process model is based on the ACT-R cognitive architecture (see Taatgen et al., 2007). Labels in the upper left corner of some boxes refer to the default ACT-R name of this cognitive subsystem. Terms in the lower right corner reflect the neural structures assumed to implement the respective subsystems. See text for further explanation.

Fig. 8. (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. The relation of working memory to a theta corresponds to the relation of timing to a delta oscillation with theta entrainment; however, the optimal strategy for working memory involving one item would be entraining a large neuronal population into a single theta oscillation while timing requires multiple theta oscillations of various frequencies. (B) Simulation of MPO (black). MPO was recalculated with theta IO inputs (red, 6 Hz), and shown in relation to the theta IO which would correspond to population feedback 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. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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, specific target durations 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 coupled 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 a sequence that falls into each phase of theta IO; 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 multiple 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 hybrid 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 maintain 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.

8. Implications

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 (e.g., Cohen, 2011). 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, attention, and working memory (see, for example, Cohen, 2011; Henry and Herrmann, 2014; Lake et al., 2014; Rohenkohl and Nobre, 2011; Rohenkohl et al., 2012).

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 (Akam and Kullmann, 2010, 2014; 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., 2008, 2009; Girardeau et al., 2009; O'Neill et al., 2010; Rasch and Born, 2013). 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 2001; Gilden et al., 1995, see also Farrell et al., 2006). 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 coupled 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 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 a network of brain regions (Akam and Kullmann, 2010, 2014; 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 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 and Draguhn, 2004; Buzsáki et al., 2012; Murray et al., 2014).

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 may contribute to a number of pathophysiological conditions such as autism, schizophrenia, OCD, or PD (Allman and Meck, 2012; Brazhnik et al., 2012; Gu et al., 2008, 2010, 2011, 2014; 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 (e.g., 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 as described here for the hybrid EIO model of interval timing and working memory.

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