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Behavioural Processes

Phase resetting and its implications for interval timing with intruders ☆

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ABSTRACT

Time perception in the second-to-minutes range is crucial for fundamental cognitive processes like decision making, rate calculation, and planning. We used a striatal beat frequency (SBF) computational model to predict the response of an interval timing network to intruders, such as gaps in conditioning stimulus (CS), or distracters presented during the uninterrupted CS. We found that, depending on the strength of the input provided to neural oscillators by the intruder, the SBF model can either ignore or reset timing. The significant delays in timing produced by emotionally charged distracters were numerically simulated by a strong phase resetting of all neural oscillators involved in the SBF network for the entire duration of the evoked response. The combined effect of emotional distracter and pharmacological manipulations was modeled in our SBF model by modulating the firing frequencies of neural oscillators after they are released from inhibition due to emotional distracters.

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1. Introduction

Interval timing refers to the capability of perceiving and using the passage of time in the seconds-to-minutes range. Interval timing is essential for survival and adaptation, foraging (Moore et al., 1989), and decision making (Jozefowiez et al., 2005), speech recognition and music (Schirmer, 2004), and its impairment leads to cognitive and motor dysfunctions (Buhusi et al., 2005; Gallistel, 1990; Meck et al., 2008). Learning and memory abilities are altered in patients with depression, schizophrenia, and phobias (Davidson and Irwin, 1999; Rose and Ebmeier, 2006; Etkin and Wager, 2007; Gohier et al., 2009; Amir and Bomyea, 2011). A recent line of pharmacological treatment for these disorders involves norepinephrine (NE) and dopamine (DA) reuptake inhibitors, which indirectly increase neurotransmission in these pathways. In turn, both DA and NE modulate the internal clock (Buhusi and Meck, 2010). DA agonists speed-up, and DA antagonists slow-down timing (Buhusi et al., 2002; Buhusi and Meck, 2005; Matell et al., 2004, 2006; Taylor et al., 2007; Coull et al., 2011). Moreover, NE modulates interval timing in both human participants (Rammsayer, 1993;

Rammsayer et al., 2001) and rodents (Penney et al., 1996). Nevertheless, the specific roles of DA and NE in interval timing at various brain sites are less understood.

The peak interval (PI) procedure is commonly used for testing the capability of animals to perform interval timing. Temporal interval learning takes place during a fixed interval (FI) procedure (Fig. 1A1). At the beginning of a FI trial, a conditioning stimulus (CS), such as light or a tone, is turned on; the first response of the subject after a certain duration (called criterion time (T)) is reinforced and turns off the to-be-timed CS (Fig. 1A1). The ability to time intervals is tested in a PI procedure during which the CS is turned on for about three times longer than the learned criterion time without providing any reinforcement (Fig. 1A2). Typically, the average of responses over multiple PI trials produces a normalized response rate that follows a Gaussian-shaped curve centered on T (Fig. 1A3) (Church et al., 1994; Gibbon and Allan, 1984).

A common variation is the PI procedure with gap during which the CS is briefly interrupted (see Fig. 1B and C) and the position of the peak responses is measured. The results from PI procedures with CS gaps (Roberts, 1981) showed that in rats the peak response is delayed with the duration of the CS gap (Fig. 1B2). Such experiments support the hypothesis of a *stop/retain* mechanism that *retains* (maintains) the time of the stimulus before the gap and resumes timing when the stimulus is turned on again.

In contrast, experiments in pigeons (Roberts et al., 1989) indicated that the peak response was delayed with the sum of the pregap and gap durations (Fig. 1C3). Additionally, PI procedures
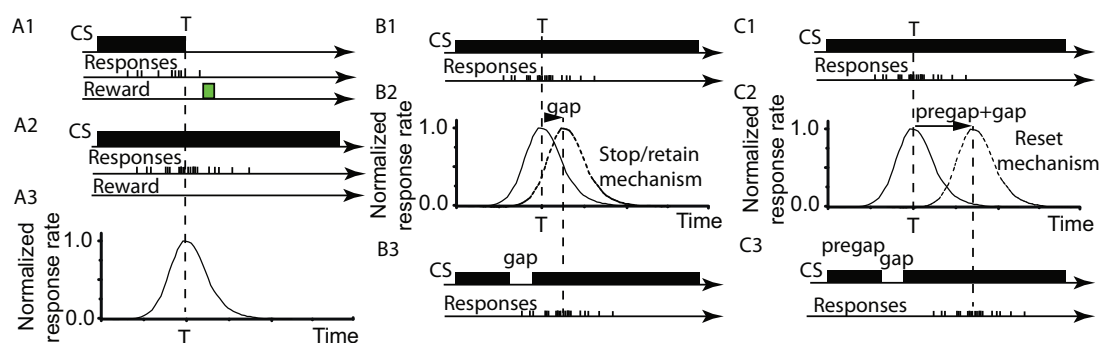
Fig. 1. Fixed interval (FI) and peak interval (PI) procedures with and without CS gaps. (A1) During FI trials, the first response after the criterion time, *T*, is reinforced and turns off the CS. (A2) In PI trials, the CS is on for about three times the duration of the criterion time without providing any reinforcement. (A3) The average of responses over many PI trials produces a normalized response rate curve that peaks around *T* and has a Gaussian-like shape. In PI trials with gap, the CS is briefly turned off (B3 and C3). In some experiments, the response rate curve is shifted with the duration of the gap (B2) supporting the hypothesis of a *stop/retain* of interval timing. In other experiments, the shift equals the sum of pregap and gap duration (BC2), supporting the hypothesis of a *reset*.

with gaps in starlings (Bateson, 1998), black-capped chickadees (Brodbeck et al., 1998), and pigeons (Cabeza de Vaca et al., 1994; Roberts et al., 1989) support the *reset* mechanism hypothesis.

Recent results indicate that rats *reset* their timing in PI trials upon presentation of reinforcement (Thorpe et al., 2002), that both rats and pigeons *stop* or *reset* depending on gap's content (Buhusi and Meck, 2000), gap discriminability (Buhusi et al., 2005), gap/signal contrast (Buhusi et al., 2002), and subjects' visual acuity. Recent studies showed that the outcome of PI procedure with CS gaps depends on many more factors than just the durations of gap and pregap. For example, non-temporal parameters of the to-be-timed event influence the response rule (*reset* or *run*) adopted by rats (Buhusi and Meck, 2000, 2005; Buhusi et al., 2002) and pigeons (Buhusi and Meck, 2002). When timing an illuminated stimulus, a (standard) dark gap prompts rats to stop timing, and when timing a dark stimulus, a (reversed) illuminated gap prompts rats to reset timing (Buhusi and Meck, 2000). Moreover, the response rule used by both rats and pigeons depends on the salience (discriminability) of the intruding event, affected by the contrast in intensity between the gap and the timed signal (Buhusi and Meck, 2002; Buhusi et al., 2005) and by the perceptual acuity of the subjects (Buhusi and Meck, 2005). Furthermore, in some PI procedures with gap no delay was found, i.e., the internal clock *run* through the gap and ignored it (see (Buhusi and Meck, 2005) for a review).

A more complex PI procedure could include another intruder, such as emotional distracters, e.g., electric shocks, paired with the uninterrupted to-be-timed CS. Delays of the peak response were obtained when the procedure includes intruders other than gaps (Buhusi and Meck, 2006; Buhusi et al., 2006; Kaiser et al., 2002). Presentation of emotionally charged distracters during the uninterrupted to-be-timed CS signal results in a considerable delay (*over-reset*) in PI procedure relative to neutral distracters (Aum et al., 2004, 2007; Brown et al., 2007). For example, anxiety-inducing task-irrelevant distracters severely alter timing. When asked to keep a face in working memory (primary task), the presentation of emotional faces (secondary task) impaired recognition memory (Dolcos and McCarthy, 2006). Context-dependent timing was also observed by manipulating the emotional content of stimuli (Evans, 2003; Flaherty, 1999; Lui et al., 2011; Matthews et al., 2012).

An abstract *internal clock* is the core of the influential scalar expectancy theory (SET) that offers a conceptual explanation of interval timing mechanism (Gibbon, 1977; Church, 1984) (see also earlier work by (Fraisse, 1957; Francois, 1927; Hoagland, 1933; Treisman, 1963; Woodrow, 1930)). The model consists of a clock, a memory and a decision stage. The clock consists of a pacemaker that emits pulses at regular intervals that are counted and temporarily stored in an accumulator (short-term memory).

At the reinforcement time, the content of the short-term memory is transferred to the long-term memory and serves as a subjective representation of *T*. At the decision stage, the current content of the accumulator (short-term memory) is compared against the long-term memory content and an appropriate response is produced (Church, 1984).

One of the first models that closely explored the relationship between the biological structure and its interval timing functionality was the connectionist model developed by (Church and Broadbent, 1990, 1991). The model assumed that a set of neural oscillators determines the peak time using multiple-period discrimination algorithms. The clock stage was represented by oscillators and the memory stage stored the oscillators' phases at reinforcement time. At the decision stage, the content of long-term memory was compared against the current phases of all oscillators and an appropriate decision was made. This connectionist model successfully duplicated the Gaussian-like shape of response rate and the scalar property (Church and Broadbent, 1991; Church et al., 1998). However, this connectionist model is limited to timing durations that do not exceed the longest period of the set of oscillators and requires a quite large coefficient of variation (Aschoff, 1989).

In this paper, we use a neurobiologically inspired striatal beat frequency (SBF) model (Matell et al., 2003; Matell and Meck, 2004; Miall, 1989; Oprisan and Buhusi, 2011, 2013) to explain recent experimental results obtained during PI procedures with intruders, both gaps and emotional distracters.

In this paper, we used a distributed neural network model that produces beats between multiple oscillators, presumably located in the prefrontal cortex, and is capable of timing intervals much longer than the durations of the intrinsic periods of individual oscillators (Miall, 1989; Matell et al., 2004; Matell and Meck, 2004). We implemented an SBF network with realistic, noisy Morris–Lecar (ML) model neurons (Morris and Lecar, 1981; Ermentrout, 1996) that mimic the activity of the frontal cortex neurons that are thought to provide the time base for the SBF (Coull et al., 2004; Olton et al., 1988). Elsewhere, we showed that the SBF-ML model produces both *precise* and *scalar* interval timing in the presence of variability of model's parameters such as the memorized criterion time and the firing frequencies of the oscillators (Oprisan and Buhusi, 2011, 2013; Buhusi and Oprisan, 2013).

Here, we showed numerically that our SBF-ML implementation is capable of producing both *reset*, i.e., delayed peak response equal to the sum of the pregap and gap durations, and *run* behavior, i.e., continue timing through the gap (ignore the gap). Crucial to the correct SBF modeling of gap effect is the ability to restart all oscillators in phase at the end of the CS gap. Such a strong phase reset could be due to postinhibitory rebound (Perkel and Mulloney, 1974;