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The clock that times us

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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):

Kononowicz, T. W. (2015). *The clock that times us: Electromagnetic signatures of time estimation.* [Groningen]: University of Groningen.

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Chapter 1

General Introduction

Humans, as well as other species, have the ability to perceive the passage of time (e.g., Buhusi & Meck, 2005; Ivry & Spemcer, 2004; Mauk & Buonomano, 2004; Merchant, Harrington, & Meck, 2013; Pöppel, 1997; Shi, Church, & Meck, 2013; Van Rijn, Gu, Meck, in press). The resulting sense of duration is essential for many everyday life activities such as speech, driving vehicles, or performing many types of physical activities. The first modern attempt to systematically study the ability to perceive and use temporal intervals is the work by Vierordt, published in his monograph *Der Zeitsinn: Nach Versuchen* (1868). Vierordt considered the ability to perceive time as one of the human senses, pointing out that the sense of time is sensitive to cognitive distortions. In the same era, Weber (1846) introduced his ideas about the just-noticeable-difference. The just-noticeable-difference is the smallest difference in a parameter defining a stimulus that can be reliably detected by comparing two stimuli that just differ on that parameter. Although he worked on more general psychophysiological phenomena, his just-noticeable-difference notion also held for discrimination of temporal durations. Where Vierordt and Weber studied time perception in isolation, in other research time played an important, although secondary role. For example, the canonical studies by Pavlov (1928) on animal conditioning have demonstrated that dogs can associate a conditioned stimulus - the sound of a bell - with an unconditioned stimulus - the delivery of food. Remarkably, the dogs do not salivate throughout the whole interval, but only at the end of the interval, with the latency of salivation increasing as a function of duration between conditioned and unconditioned stimulus. Moreover, if the duration between conditioned stimulus and unconditioned stimulus is too long, the animals will not learn the association. The important role of time in cognitive performance is also evident when taking into account that many studies focused on interval timing study the role of time in the context of other cognitive tasks or paradigms, such as temporal-orienting paradigms (e.g., Coull & Nobre, 1998), foreperiod paradigms (e.g., Niemi & Näätänen, 1980), or speech perception (Van Wassenhove, Grant, & Poeppel, 2005). In other words, in many phenomena, even those as robust as conditioning, interval timing is a crucial aspect of task performance (e.g., Gallistel & Gibbon, 2000, 2001; Kirkpatrick & Church, 1998, 2000, 2003).

Although the pioneering work of Vierordt, Weber, and Pavlov set a strong ground for more extensive studies on the sense of time, it took half a century (e.g., Creelman 1962, Treisman, 1963) before a general theory of interval timing was proposed that explains how interval timing in the range of seconds or minutes can be instantiated. Based on this work, more formal theories were proposed such as the Scalar Timing Theory (Gibbon & Church, 1984, Gibbon, Church, & Meck, 1984), often referred to as the Scalar Expectancy Theory (SET; e.g., Gibbon, 1977, 1991). This information processing model of interval timing still serves as the main theoretical basis for most current studies of interval timing.

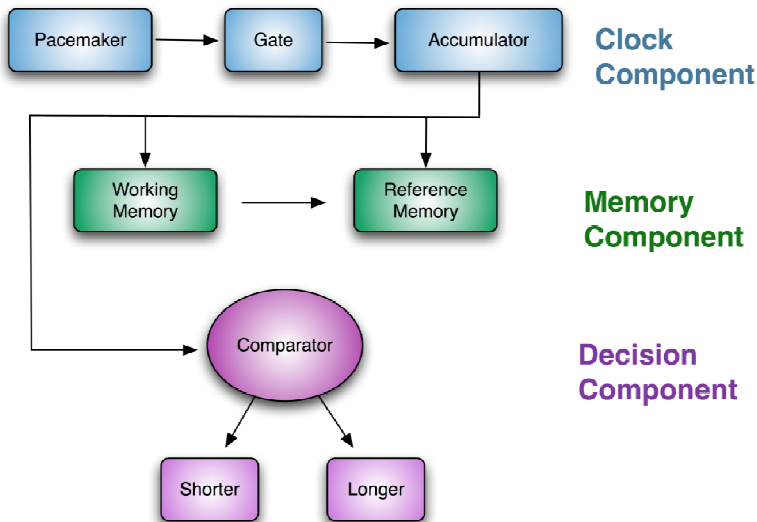


Figure 1. The information-processing model of interval timing as conceived by SET. Three colors depict the main components of that model: perception, memory, and decision.

Information Processing Theories of Interval Timing

The information-processing models are typically composed of three components (Figure 1). The central component of this model is an internal clock that contains a pacemaker that emits a stream of pulses (for a discussion on the effect of different pulse distributions see Komosinski, 2012; Komosinski & Kups, 2011) which are integrated by an accumulator. The current value of integrated pulses is stored in working memory and it can be compared with a previously stored value that is retrieved from reference memory. Based on the ratio of these two values, the model can decide whether the current duration is close enough to a memorized duration. Similar to a stopwatch, this time keeping mechanism can be started, paused, or reset to give an estimate of subjective time (Buhusi & Meck 2009, Meck & Church 1983).

The process of pulse integration is a crucial element of the clock component in SET, and modulations of this process have been proposed to explain a large number of phenomena related to biases in interval timing. For example, an "attentional gate" has been proposed which regulates the flow of pulses to the accumulator depending on the level of attention being paid to the timing task, explaining attentional effects (e.g., Hicks, Miller, & Kinsbourne, 1976; Lejeune, 1998; Meck, 1984; Thomas & Weaver, 1975; Zakay, 1992). Other psychological and physiological factors in interval timing such as arousal (e.g., Burle & Casini, 2001) or emotions (e.g., Droit-Volet & Meck, 2007) have been explained based on

modifications of other properties of the pacemaker accumulator model, such as the pacemaker rate. Summarizing, it seems that all identified factors modifying interval timing can be accounted for by altering the slope of the ramping function that describes the integration of temporal information. Interestingly, recent advancements in computational neuroscience has led to biologically plausible models of how such ramping process can be achieved (Durstewitz, 2003; Reutimann, Yakovlev, Fusi, & Senn, 2004; Simen, Balci, deSouza, Cohen, & Holmes, 2011).

Yet, another group of theories assumes that timing process are based on state modifications, such as a cascade of decaying memory traces instead of assuming ramping cumulative activity. For example, Staddon and Higa (1999; Staddon, 2005; also see Machado, 1997) proposed the multiple time scales model that relies on the assumption that subjective time estimates are obtained on the basis of decaying memory traces. The idea of neural state transitions over time has been also used in the Behavioral Timing Theory (Killen & Fetterman, 1988), which proposed a fixed sequence of neural states with a transition function following a Poisson pacemaker. Both theories mainly differ from the SET-type models by assuming a different clock component, but still (implicitly) assume a three-component system.

However, theories that posit that interval timing can occur in the absence of internal clock have also been proposed. Intrinsic theories of timing assume that timing is an ubiquitous property of neural networks (Buonomano & Laje, 2010; Karmarkar & Buonomano, 2007), and that a pacemaker or clock-system is not necessary at all. Along the same lines Miall (1989) and Church and Broadbent (1990) proposed a multiple oscillator model in which timing can be implemented by single neurons or neuronal ensembles oscillating at different frequencies. Over time, the phase of these basic units of the model would run out of phase as time progresses and thus different, unique and constantly changing coincidental patterns would emerge over time, providing an index to time (for a review, see Gu, Van Rijn, & Meck, 2014). This idea has been implemented in the striatal beat frequency (SBF, Buhusi & Meck, 2006; Mattel & Meck 2000, 2004) model that assumes that a striatal-cortical loop is the crucial timing network in the brain. The SBF model provides detailed descriptions of the neural mechanisms behind temporal processing, and can be integrated with aspects of information-processing models of interval timing (Van Rijn, Gu, & Meck, 2014). Nevertheless, SET is probably still considered to be the most successful theory, serving as a theoretical background for many contemporary neuroimaging studies investigating neural mechanisms of temporal processing in the human brain (e.g., Merchant, Harrington, & Meck, 2013). However, the specific neural mechanisms underlying the components of SET are not well understood.

Neuronal Underpinnings of Time Estimation

One of the main factors that makes the study of interval timing challenging is that unlike visual or auditory information that is coded in distinct sensory areas, time sense has no direct physical substrate. Unlike most other fields of cognitive

neuroscience in which there is at least agreement over where in the brain certain functions should reside, there still is a lack of agreement regarding the brain structures that play a crucial role in interval timing.

Nevertheless, several structures related to time processing have been identified. A recent meta analysis of fMRI studies showed that sub-second timing tasks activate the sub-cortical networks, such as the basal ganglia and cerebellum (Wiener et al., 2010), whereas supra-second timing tasks recruited the supplementary motor area (SMA) and prefrontal cortex. Interestingly, the SMA and the right frontal inferior gyrus were the only structures recruited across all types of timing tasks and all lengths of interval durations. These various brain structures are typically linked to certain modules of information processing theories of interval timing, such the clock component (Allman, Teki, Griffiths, & Meck, 2014; Buhusi & Meck, 2005; Merchant, Harrington, & Meck, 2013), the main function of which is pulse accumulation. Especially the SMA has been proposed to operate as an accumulator (Coull et al., 2004; Coull, Nazarian, & Vidal; Macar et al., 1999). However, although modern fMRI techniques provide images with highspatial resolution, the time course of activation of sub-second intervals is much more difficult to establish using fMRI.

Although most work exploring the role of the SMA has been done using fMRI technique, the other common technique allowing to track cognitive processes in fine temporal resolution, are the slow cortical potentials. Slow cortical negative shift are presumably caused by synchronous slow excitatory postsynaptic potentials in the apical dendrites in cortical layer I (Birbaumer et al., 1990; Birbaumer, 1999). These slow shifts have been associated with sensory, motor, attentional and even motivational states of the brain. Slow cortical potentials can be measured by electroencephalography (EEG) from the cortical sources oriented perpendicularly to the skull surface, and presumably using magnetoencephalography (MEG). However, in case of MEG, slow magnetic fields are measured from the cortical sources oriented tangentially to the skull.

Obviously, information regarding the time course of particular activation patterns during the perception or reproduction of temporal intervals is necessary to help establish the functional role of certain brain areas. Therefore, this thesis explores the neural mechanisms associated with the perception of time from the perspective of information processing theories of interval timing. In other words, this thesis addresses the question of how and where time is processed in the human brain.

Contingent Negative Variation and Time Estimation

The most extensively studied event related potential (ERP) component is a contingent negative variation (CNV). The CNV was introduced by Walter, Cooper, Aldridge, McCallum, and Winter (1964) who showed a slow shift of negative potential developing in a range of seconds between conditional and imperative stimuli. Already in the first decade after the first description of the CNV has it been

associated with several factors such as arousal, attention, and information processing (for a review, see Tecce, 1972).

The CNV has also been proposed as an index of interval timing, mainly based on a number of correlations between features of the CNV and behavioral performance in timing tasks (Macar & Vidal, 2004). According to this prominent view, the CNV could be driven by a climbing neural activity process often abbreviated to CNA (Durstewitz, 2003; Reutimann, et al., 2004, for reviews, Lewis and Miall, 2003, 2006; Wittmann, 2013) and directly reflects the temporal accumulation process as put forward by information processing theories of interval timing. This proposal assumes that the activity in the excitatory neurons builds up towards and peaks at the time of a behaviorally relevant event. The slope of neural activity could be, for example, adjusted by a firing rate adaptation in inhibitory neurons (Reutimann et al., 2004).

The most frequently used argument in favor of a direct link between pulse accumulation and the CNV recorded from the SMA was proposed by Macar, Vidal, and Casini (1999). Macar et al., (1999) reasoned that if trial-to-trial fluctuations in subjective timing are driven by differences in the current state of the accumulator, the observed fluctuations in behavioral responses should correlate with the CNV amplitude. This notion has been tested by asking participants to produce an earlier learned standard duration of 2.5 s by pressing a key twice. Trials were *post hoc* categorized into three groups: a group of “short” productions (2.2–2.4 s), of “correct” productions (2.4–2.6 s), and of “long” productions (2.6– 2.8 s). The CNV measured at the FCz electrode - which is typically assumed to measure activity in the SMA - was compared for the three conditions. Apparently in line with the notion that the CNA is reflected in the CNV (but see Chapter 3 of this thesis), Macar et al. (1999) found a higher CNV amplitude in the long condition, an intermediate CNV amplitude in the correct condition, and a lower CNV amplitude in the short condition. The positive correlation between produced duration and CNV amplitude has been taken as a strong argument suggesting that the unfolding of subjective time is directly linked with the amplitude of the CNV (but see Chapter 2 and 3).

Another important line of evidence in favor of the CNV as a component coding for subjective representations of time has been provided by temporal generalization tasks. In these tasks, participants are asked to compare an interval to a previously memorized standard. The CNV ramping pattern can be observed from the beginning of the interval until the offset of memorized standard interval, after which it deflects (Macar & Vidal, 2003; Pfeuty, Ragot, & Pouthas, 2003), even if the comparison interval still continues. This pattern has been proposed to reflect a timing process the accrual of subjective time, until the accrued value is similar to a neural representation of a memorized interval (Macar & Vidal, 2003). As the neural source of the CNV is typically determined to be in the SMA, evidence from EEG and fMRI converges with respect to the important role of the SMA in interval timing (Macar, Vidal, and Casini, 1999; Macar and Vidal, 2002; Pfeuty, Ragot, & Pouthas, 2003; Pouthas et al., 2000; Pouthas, Garnero, Ferrandez, and Renault, 2000). However, other studies have shown that other brain areas can also exhibit accumulation patterns during interval timing, for example fMRI studies in humans in which the anterior insula is observed to respond similar to a temporal accumulator (Wittmann et al., 2010). Also studies in animals have shown ramping

traces related to temporal behavior in various brain structures (e.g., Donchin, Otto, Gerbrandt, & Pribram, 1971; Janssen & Shadlen 2005; Kim, Ghim, Lee, & Jung, 2013; Lebedev et al., 2008; Merchant, Perez, Zarco, Gamez, 2013; Mita et al., 2009; Niki & Watanabe, 1976, 1979; Roux, Coulmance, & Riehle, 2003; Tanaka, 2007; for a review, see Wittmann, 2013).

Despite this large body of literature indicating that ramping activity in various parts of the brain can represent a one-to-one mapping between increasing activation of neuronal assemblies and subjective development of temporal interval, an often neglected fact is that a similar pattern of activation is often observed in other paradigms. For example, the slow waves can be observed in classical foreperiod studies (Leuthold, Sommer, & Ulrich, 2004; Niemi and Näätänen, 1981; Ulrich, Leuthold, & Sommer, 1998, Van der Lubbe, Los, Jaśkowski, Verleger, 2004) or temporal attentional orienting tasks (Miniussi, Wilding, Coull, and Nobre, 1999) in which temporal information is subserving the main task, but also in more perceptual tasks such as discrimination tasks (e.g., O'Connell et al., 2009; Rawle, Miall, & Praamstra, 2012), perceptual decision making (Boehm, Van Maanen, Fortsmann, & Van Rijn, 2014), and feedback evaluation processes (Brunia, 1988) in which timing is implicit at best. These results argue for a more general interpretation of the effects associated with ramping activation in the CNV: Although the evidence supporting the view that CNV is a neural signature directly reflecting time estimation might seem robust, it is implausible that such a prevailing property of neural dynamics could be exclusively linked with a one specific brain function such as accumulation of temporal pulses proposed by the pacemaker-accumulator model. In light of these considerations, the role of the CNA in the interval timing has to be scrutinized.

Overview

In Chapter 2 the hypothesis that the CNV amplitude can serve as a neural signature of subjective experience of time is assessed. Chapter 3 theoretically evaluates the findings of Chapter 2 and other experimental findings in the context of information processing theories of interval timing. Chapter 4 investigates whether the magnetic counterpart of the CNV can be used to track reproduction of supra-second temporal durations. It also attempts to determine which cortical sources are associated with reproduction of temporal intervals. Chapter 4 also demonstrates that the CNV is - to a large extent - driven by preparation. Unlike Chapters 2 to 4 that focus on event related potentials, Chapter 5 focuses on the role of oscillatory activity in the time production task. Contrary to previous studies that typically studied EEG markers at the end of the interval, Chapter 5 investigates interval timing processes at the interval onset and demonstrates that beta power oscillations at the onset of the interval are predictive of the subjective duration that will be produced. Chapter 6 evaluates one of the predictions of pacemaker-accumulator models and climbing neural activity, namely, that timing processes does not continue after the resolution of climbing neural activity as reflected in the CNV. In this chapter, the relationship

between CNV amplitude and subjective time estimations is further explored and compared with the ability of the offset components to discriminate between temporal intervals. Finally, Chapter 7 discusses the implications and future research directions on the basis of the empirical results presented in this thesis.

