Title: Timing and hippocampal theta in animals

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Synopsis

All animals have at least two different internal clocks, one governing cognition of time of day, and the other concerning awareness of seconds and minutes. In the latter case, organisms show scalar properties. The timing mechanisms in the brain may function similarly throughout the animal kingdom, but this is not yet clear. Previous studies have shown that the hippocampus is intricately involved with the process of interval timing. Data concerning electrophysiological field potentials in the hippocampus show obviously rhythmic activity, known as hippocampal theta activity. An information-processing model of interval timing postulates three distinct stages: a clock, a memory, and a decision stage /11/. The timing process includes memory processing, which means that the hippocampus works together with working memory to estimate current time passing.

Time is important for living animals, as all animal activity is related to timing. Timing activities can be divided into 1) the element of time of day and 2) interval timing /16/. Phenomena concerning time of day are directly related to circadian rhythm, which may be controlled by the phasic activity aspect of day. There is considerable evidence in mammals that the center of the nervous system of the circadian internal clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus /19,20,30,36/. Several genes regulate the controlled feedback loop that generates circadian rhythm at the intracellular level /18/. On the other hand, interval timing is like a stopwatch that has a starting switch and a stopping point /3/. This may be controlled by using of the counting activity aspect of events. Also, timing behavior may be affected by certain drugs /32/. However, the nature of the timing mechanisms remains a mystery, especially at the center of the nervous system. The aforementioned studies indicate that animals have at least two different internal clocks regarding timing.

It is generally accepted that timing mechanisms in the circadian range are different from those in the range of seconds and minutes. The internal clock of interval or hourglass timing in the seconds-to-hours range can be distinguished from that of oscillatory or circadian timing in at least three ways: counter-based versus phase-based, high flexibility versus low flexibility, and variability in scalar versus constant units /16/.

The behavioral property of timing is explained by its scalar property. That is, the standard deviation of timing functions grows in proportion to the mean of the interval being timed. The scalar property is demonstrated by some experimental results that are consistent with the distribution plotted on a relative time scale. Figure 1a shows original absolute response distributions and Figure 1b shows the relative distributions. In a landmark experiment, the peak-interval procedure was used to evaluate the timing of 8-, 12-, and 21-s intervals /33/. Response distributions appear normal as indicated by the good fit of the Gaussian curves to the data (Fig. 1a). Mean percentage of maximum response rate is plotted as a function of relative time at each target interval. These appear to fit well with each other (Fig. 1b). This reflects a Weber's Law-like property for the perception of time that is reflected in a wide variety of timing procedures.

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For what length of time does the scalar property retain its function? Crystal reported on the sensitivity to time for intervals in the circadian range /9/. In his

experiments, anticipation of restricted meals was examined for intermeal intervals near the circadian range (22, 22.5, 24, 25.5, and 26 h) and outside this range (3, 7, 14, and 34 h). The results showed that rats inspected the food trough before meals started. The data showed high precision in the circadian range and low precision in the other range /9/. The inspected timing was accurate in the circadian range. For example, in rodents circadian rhythmicity was shown to have a variablility as little as 1% of the 24-h cycle /1/. Intervals outside the circadian range showed a clear scalar property. Therefore, the scalar property continues to function from a range of seconds to several dozens of hours. There are only a few reports concerning the hours range. In this paper, the focus of the discussion will be on the interval timing behavior in the range of seconds to minutes.

Timing behavior in animals

Malapani and Fairhurst begin their paper as follows: “Evolution has selected for neurobehavioral mechanisms that anticipate events as well as react to them, making animals do the right thing at the right time. Whereas the ‘origin’ for time may be in the future (anticipatory timing), or may be set by a pattern of responses (coordinated timing), animals are often under the control of the time elapsed from some prior marker, called interval timing as opposed to periodic-oscillatory timing” /24/. Malapani and

Fairhurst reviewed animal and human data obtained with a variety of timing paradigms /24/. One of the fundamental properties of interval timing is the scalar property and it is well-retained behavioral property in all animals. They emphasized that Scalar Expectancy Theory (SET) /10/ remained the most prominent of the theoretical accounts of animal and human timing. All animals expect the events like foraging for foods that time scale depend on the scalar property. SET deals with the three principle psychophysical properties of timing data: flexible accuracy, multiplicative variance, and ratio comparisons.

Information-processing model with respect to timing

An information-processing model in the seconds and minutes range for interval timing was proposed by Gibbon, Church and Meck. This is the most effective model of interval timing /11/, and is based on SET /10/. In broad terms, the model is composed of clock, memory, and decision stages (Fig. 2). Almost all interval timing models can be conceived of in terms of these three stages /26/. The clock stage consists of a pacemaker that generates pulses which are gated by a switch controlled by attention processed into an accumulator. The pulse generator may be in the area of the striatum and cortex of the brain /27/. The value recorded in the accumulator may be temporarily stored into a

working memory buffer. If the signal is followed by a reinforcement event, the interval may be stored in reference memory. This is roughly equivalent to the memory stage which depends on the hippocampus and cortex /31/. In the decision stage, a comparison of the clock read for the current process with the working memory is found in the accumulator with a sample from the previously learned durations. A comparison between the current working memory and with stored reference memory allows the subject to determine when to respond. The brain regions where decision processes take place are not clear yet, but it can be hypothesized that the frontal cortex would be involved.

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Matell and Meck investigated various models and mechanisms concerning interval timing /26/. They listed the following models: Scalar Expectancy Theory, the Behavioral Theory of Timing, Multiple Time Scales, the Spectral Timing Model, the Multiple Oscillator Model, and the Beat Frequency Model. Numerous hypotheses based

on anatomical and electrophysiological evidence suggest that the functional role of the striatum is to act as a “coincidence detector” for cortical and thalamic input.

Hippocampal theta in animals

When an animal voluntarily moves and observes its environment, a hippocampal encephalography (EEG) shows very regular and high-amplitude synchronous waves. This wave pattern has long been called either “hippocampal theta activity” or “rhythmic slow activity” (RSA) on visual inspection. It is called hippocampal theta because it usually lies in the frequency spectrum of 4-7 Hz recorded from the hippocampal region, and it was first found in rabbits. Hippocampal theta rhythm is one of the most prominent EEG features of the mammalian hippocampus /37/. It is relatively easy to record in the rabbit and rat, more difficult in the cat and dog, and extremely difficult to observe in primates including humans /15/. One of the characteristics of theta rhythm is that the dominant frequency varies depending on species. The theta frequency bands in rats show a bandwidth from 6 to 12 Hz, and are of higher frequency than those in rabbits and cats. When a rat explores its surroundings, hippocampal theta can be detected predominantly in the dorsal area of the hippocampal CA1 as a local field potential /6/. During REM sleep, theta rhythm is observed in both the dorsal and

ventral hippocampus in the cat /22/. Only two studies have reported on hippocampal theta in humans. Kahana, Sekuler, Caplan, Kirschen, and Madsen recorded intracranial EEG in epilepsy patients, and described theta oscillations during computer maze tasks /23/. Not only in rodents, but also in humans, hippocampal theta waves have been recorded during rapid eye movement (REM) sleep /7/. The theta rhythm is evoked via pathways running from the septal area to the hippocampus, and these waves can be blocked by a section of the fornix or by septal lesions /14/.

There have been many theories concerning hippocampal functions, such as timing, cognitive learning, memory, spatial navigation, running, and sensory-motor integration /2, 4, 12, 13, 17, 21, 28, 35, 37/. In this paper, the main focus is on timing and hippocampal function. In timing behavior, the hippocampus may play a part in working memory as it relates to passing time. A previous study reported that the hippocampal damage interferes with temporal and spatial working memory /8, 29/. In that study, rats were trained to discriminate between 2-s and 8-s duration. After lesions of hippocampus, rats showed the point of subjective equality shifted to a shorter duration. As the information-processing model hypothesizes the memory stage, the main functional area must be the hippocampus. There is also evidence of hippocampal involvement with timing tasks. Sakata and Onoda found the hippocampus theta power at a frequency

range between 6 and 12 Hz to increase more during a temporal discrimination task than during another non-temporal simple reaction task in rats /34/.

Peak interval procedure and hippocampal theta

Peak interval (PI) procedure is the best method for studying seconds-to-minutes range interval timing behavior in animals. For example, rats have been trained for 30-s interval timing using a fixed interval (FI) reinforcement schedule in an operant chamber. In a typical discrete FI procedure, a stimulus (e.g. tone) is turned on to indicate the onset of the trial. Rats earn reinforcement (e.g. food pellets) at the first response after the criterion duration (e.g. 30-s), and the trial terminates. Early responses have no consequence, so after repeated FI training, the frequency of responses gradually increase towards the criterion time. This response pattern is called "a scallop pattern" as it resembles the shape of the shell. Many voluntary responses occur as the reflection of the temporal expectancy of the availability of reinforcement. In the PI procedure, half of the trials in one session are FI trials, and the other half are probe trials that have no reinforcement, with the length of a probe trial being three times that of the criterion duration. Responses in probe trials show typically Gaussian distribution at the peak of the criterion time. The PI procedure extend to two or three

kind of criterion durations. They called as bi-peak or tri-peak procedure. Matell and Meck reported on a tri-peak procedure that has three criterion durations /25/. They reported the well-conserved scalar property in three length of durations within subjects design in rats.

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How can we measure the passage of time in animals? To investigate the brain mechanisms, hippocampal theta rhythm may play an important role. Matell, Meck and Nicolelis reported that striatal and cortical neurons encode specific durations in their firing rate /27/. They showed a clear relation between neuron firing and behavioral pattern. Yet, they did not report about hippocampus activity. Their focus areas were the striatum, the substantia nigra pars compacta (SNPC), and the cortex. Recent electrophysiological studies have revealed that the precise timing of single neuron activity within neuronal networks might be able to represent information /4, 5/. An important function of the brain is the prediction of when future events will occur. The

subjective expectation for reward might reflect the firing circuit in the center of timing mechanism. The hippocampal theta activity may be able to explain this mechanism, including feedback and feed-forward networks.

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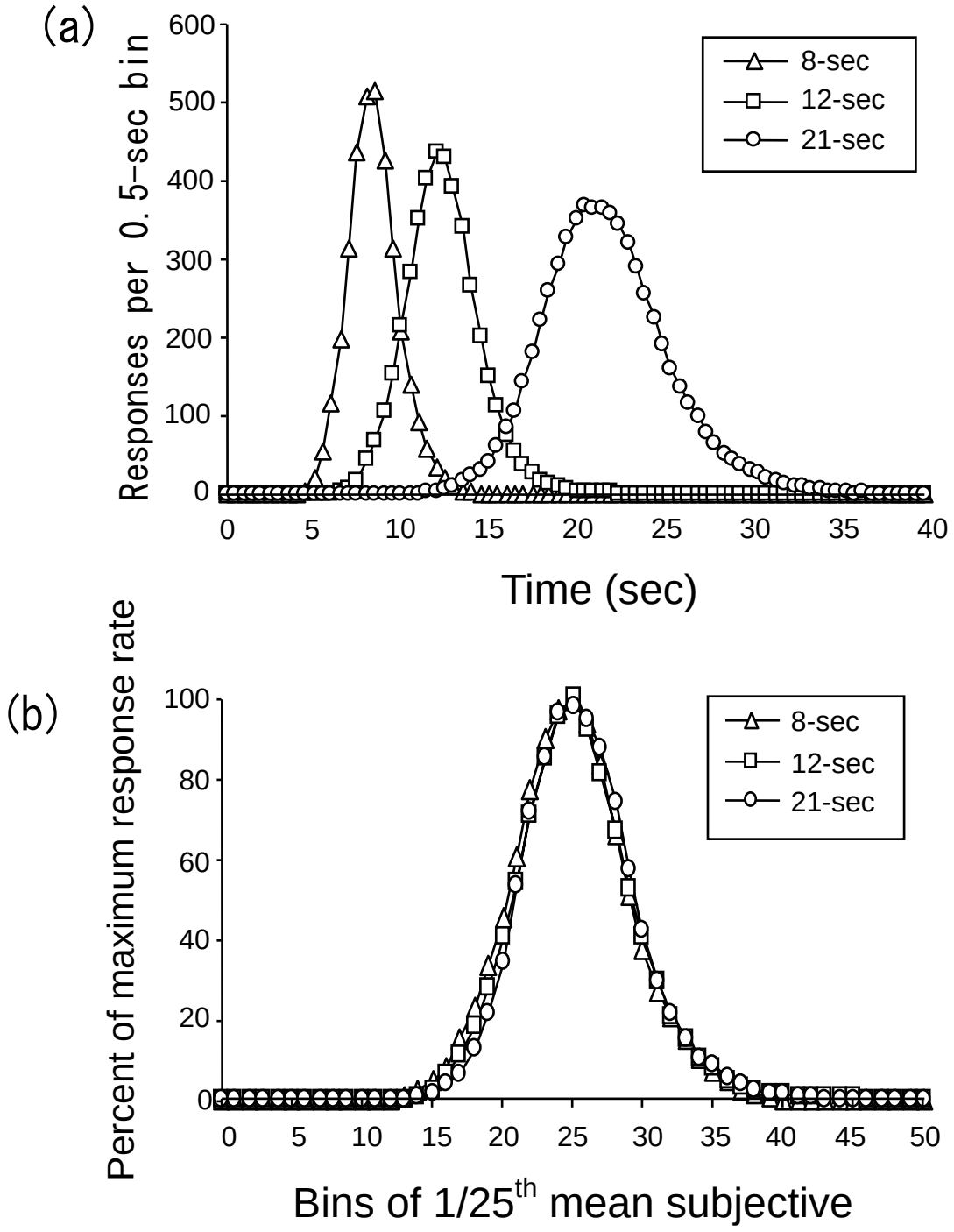
Legends

Fig. 1 Temporal estimation and scalar property in humans with a variety of interval timing using peak interval procedures. (a) The number of responses increases up to the setting time, and decreases in a symmetrical manner following setting time. (b) Relative response rate shows almost the same distributions that are normalized by each setting time and superimposed. X-axis transferred into relative time. Y-axis transferred into relative response rate, which means the maximum response rate is 100 percent. (Data were replotted from Rakitin et al., 1998. Permission from corresponding author, Meck.)

Fig. 2. A summary of the information-processing model of timing proposed by Gibbon, Church, & Meck (1984).

Fig. 3 Relative response distribution of interval timing using peak interval procedures in a rat. Response rate increases up to the criterion time (30-s) and decreases in a symmetrical manner following criterion time. The fitting curve

adapted to the data was calculated by 3-s bin. This is a typical distribution obtained in my laboratory.



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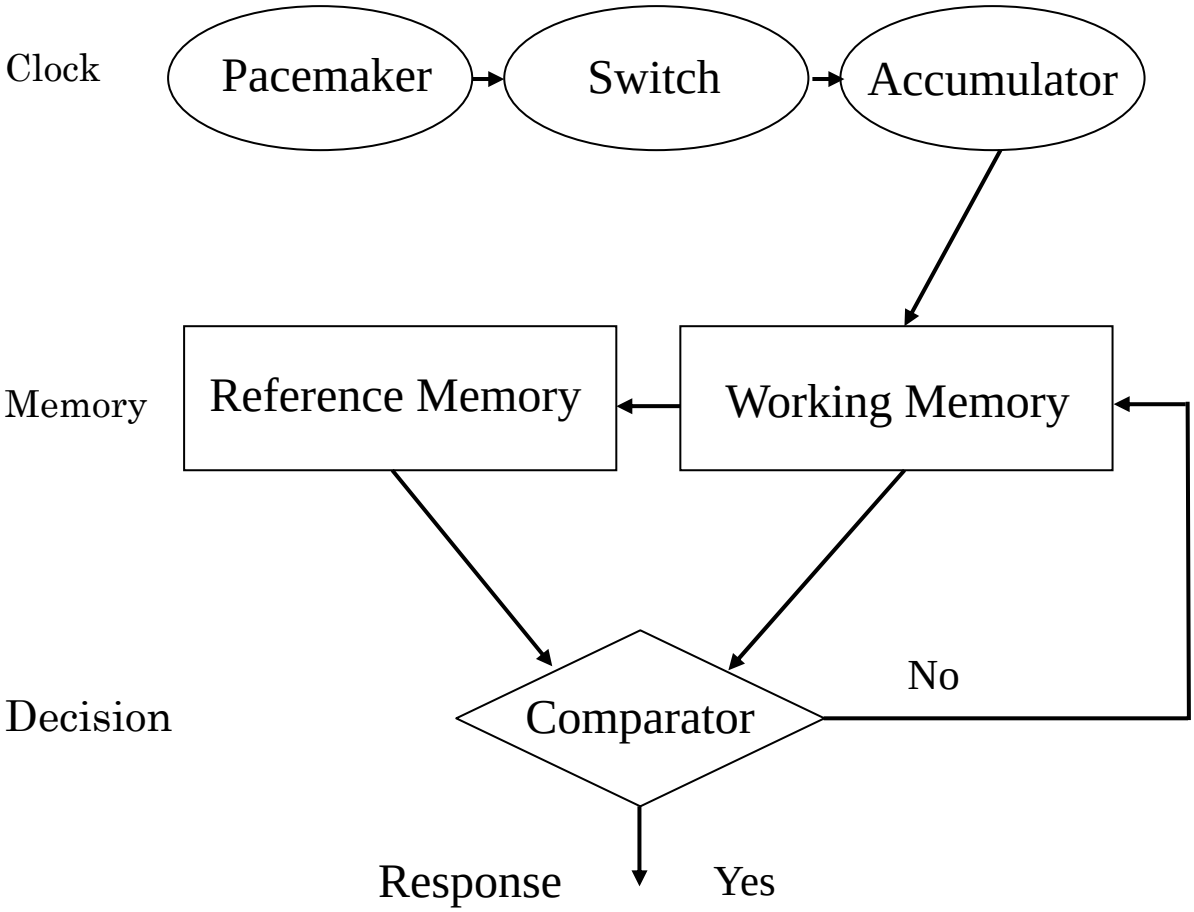

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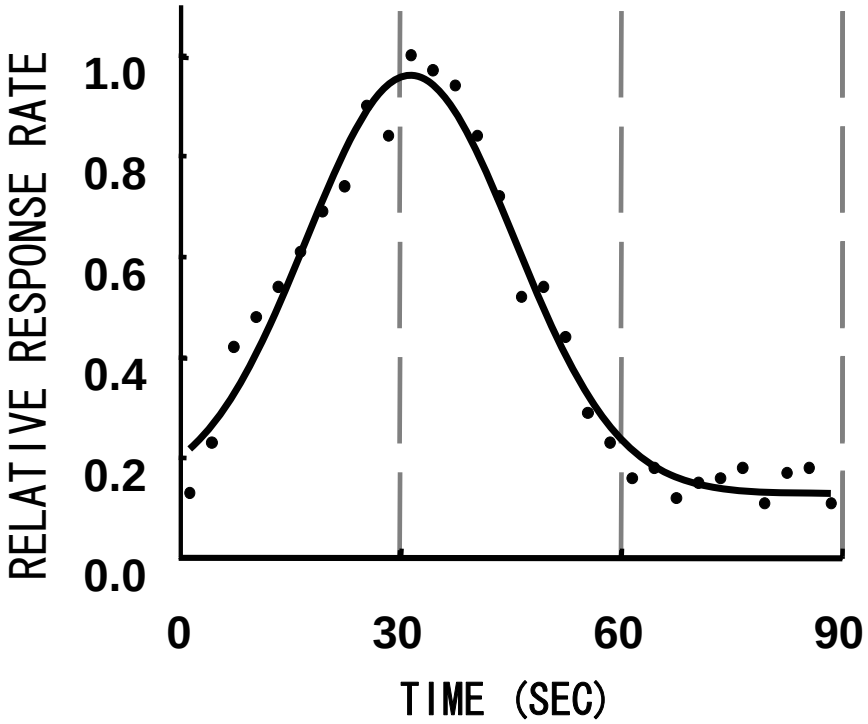

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