Interval timing: memory, not a clock

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Anticipation of periodic events signalled by a time marker, or interval timing, has been explained by a separate pacemaker-counter clock. However, recent research has added support to an older idea: that memory strength can act as a clock. The way that memory strength decreases with time can be inferred from the properties of habituation, and the underlying process also provides a unified explanation for proportional timing, the Weber-law property and several other properties of interval timing.

People and animals tell time in two main ways: circadian rhythms, the approximately 24-hour cycle that governs feeding, sleeping and other activities; and ‘interval timing’, the ability to anticipate delayed events signalled by a time marker, occurring at intervals on the order of seconds and minutes. Circadian timing depends on a clock located in the suprachiasmatic nucleus. A physiological clock has also been suggested as the basis for interval timing, but none has yet been identified and the two processes seem to be independent of one another: brain lesions that abolish circadian timing in mice leave interval timing unaffected, for example [1]. Recent theoretical and experimental work has instead added new evidence to support an older idea: that interval timing depends on temporal properties of memory [2,3].

An internal pacemaker clock?

Interval timing was first studied extensively by Skinner and his students as part of their explorations of schedules of reinforcement. This work led to two principles. In a well-trained organism, a dependent measure such as time to first response is roughly proportional to the to-be-timed interval (e.g. the time between food deliveries on a fixed-interval reinforcement schedule). This is termed ‘proportional timing’. The standard deviation of such a dependent measure is usually proportional to its mean, that is, a constant coefficient of variation (Weber-law property [4]). The latter property was termed ‘scalar timing’ by the late John Gibbon, who introduced the term in connection with a clock-type model for timing [5].

The clock model (scalar expectancy theory, or SET) has three main elements: a pacemaker that emits pulses at short, variable, intervals; an accumulator that counts pulses until a significant event such as food reinforcement; and a memory that stores pacemaker values. Responding is governed by comparison between the current value of the accumulator and a value sampled from stored values.

Some aspects of SET are shared by any conceivable model for interval timing. There must be some time-related variable that the organism can use to gauge time; and some way to compare its current value with a remembered value. But other aspects of SET are more contingent. Two decades of research has failed to reveal a neurophysiological pacemaker, for example. Moreover, by itself, a randomly varying pacemaker yields a coefficient of variation that is not constant but decreases as the mean increases. SET avoids this problem by postulating other sources of variability that overwhelm variation in the pacemaker. And finally, SET postulates a timing process *in addition* to other well-studied behavioral processes such as memory and behavioral competition. On these last two counts, SET fails the test of parsimony.

Memory, a parsimonious alternative

Thus, the search has been on for several years to find an alternative to SET. The account I will describe can be traced to an early observation [6] that not all events are equally effective as time markers. On a reinforcement schedule in which the time between food deliveries is constant (fixed-interval schedule), pigeons, rats and people will soon learn to wait before making the first response in each interval. This wait time is roughly proportional to the interval duration. If alternate reinforcers on a fixed-interval schedule are sometimes replaced by a neutral stimulus of equivalent duration (a ‘reinforcement omission’ procedure) then, despite the fact that the neutral stimulus signals the same fixed time to the next food as food itself, rats and pigeons fail to pause after it as they do after food. An obvious implication is that because food, or any other valued event, is better remembered than an arbitrary neutral stimulus, the failure to pause reflects a failure to remember, a phenomenon labeled ‘temporal overshadowing’. Perhaps interval timing uses memory strength as its clock? If so, the temporal properties of memory should correspond to known properties of interval timing.

Habituation: the clue to the memory trace

The way that memory strength weakens with time can be inferred from the simplest memory-related phenomenon, habituation: the progressively weaker reflex response to a repeated stimulus, such as a loud sound or novel event. Beginning with Sokolov [7], the dominant account of habituation explains it by a process that compares each stimulus presentation with an increasingly strong memory for the stimulus.

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Habituation has two basic temporal properties: (i) it is more rapid and complete if stimuli are close together than if they are widely spaced, but (ii) spontaneous recovery, after stimulation has ceased, is *slower* after more widely spaced stimuli ('rate sensitivity').

Figure 1a illustrates a simple comparator that can duplicate both these properties. A leaky integrator is 'charged up' (V increases) by each stimulus presentation (X). The above-zero difference between the stimulus input, X, and the 'memory,' V, determines response strength. As each stimulus is presented, V increases and then decays after the stimulus ceases. If the next stimulus presentation is soon enough, V continues to increase, the difference between X and V decreases, as does the response (the above-threshold difference) and the system habituates – property (i) above.

But this single-unit system does not show rate sensitivity, for which a cascade of at least two units, fast and slow, is necessary (Figure 1b) [8]. Closely spaced stimuli charge up mainly the first, fast, unit, thus blocking input to the second, slow, unit. The first unit also discharges quickly during spontaneous recovery. Conversely, in between widely spaced stimuli, the first, fast, unit discharges (i.e. recovers from habituation), allowing each stimulus to charge up the second, slow unit, which discharges slowly during spontaneous recovery. The two-unit system is the simplest comparator mechanism capable of rate sensitivity.

Exactly the same process, with a longer cascade of perhaps 10 or 12 slower and slower units, fits data on human long-term forgetting already known to correspond to a sum of declining exponentials [9]. This 'multiple-time-scale' (MTS) model also duplicates a range of phenomena related to Jost's memory law, that older memories decay more slowly than newer ones [10].

Most strikingly of all, perhaps, habituation experiments using magnetic source imaging (MSI) have provided direct evidence for a cascade of slower and slower exponential-decay processes in the human brain [2,11].

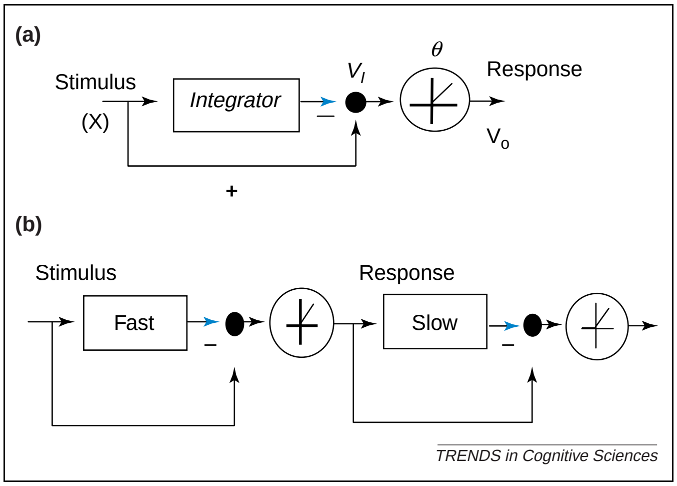

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Figure 1. (a) Single-integrator comparator habituation model. Response strength is equal to the above-threshold (usually set equal to 0) difference between the direct and remembered effects of the stimulus: θ(X–V). **(b)** Two-integrator system able to explain rate sensitivity. Closely spaced stimuli habituate the fast unit and block input to the slow unit; widely spaced stimuli the reverse. Response strength equals $\theta(X-V_1-V_2)$.

The MTS model is also consistent with a growing body of data showing that maintenance of neural activity seems to be essential for successful performance in short-term memory tasks [12].

Memory trace can also be a clock

Memory decay can be linked to interval timing in several ways. The simplest is just to assume that on fixed-interval schedules, wait time is linked to a threshold value: when the MTS memory trace decays below that value, responding begins. With this simple response rule, the activation trace generated by a cascade of integrator units of the type shown in Figure 1a (and definable with only two free parameters) can duplicate the two main properties of interval timing: proportional timing and conformity to Weber's law. The same model is also consistent with other data implying nonlinear time encoding, such as temporal bisection at the geometric, rather than arithmetic, mean [13].

Figure 2 shows how the MTS model, with a fixed response threshold, generates a trace compatible with proportional timing and Weber's law. The three steady-state traces shown in the figure are generated by periodic inputs over a range of 50–5000 time units and plotted as a proportion of the training inter-stimulus interval (ISI). The traces superimpose pretty closely. The center dashed line is the response threshold, with noise variation illustrated by the distribution on the y-axis. The peaked distribution on the x-axis shows how symmetrical threshold variation translates into slightly asymmetrical variation in wait times. Because all the curves superimpose for most of the proportional ISI, responding will show proportional timing and obey Weber's law (the scalar property). The MTS model has also been successfully applied to a range of temporal-tracking data and anomalous phenomena in temporal choice such as the choose-short and choose-long effects [13].

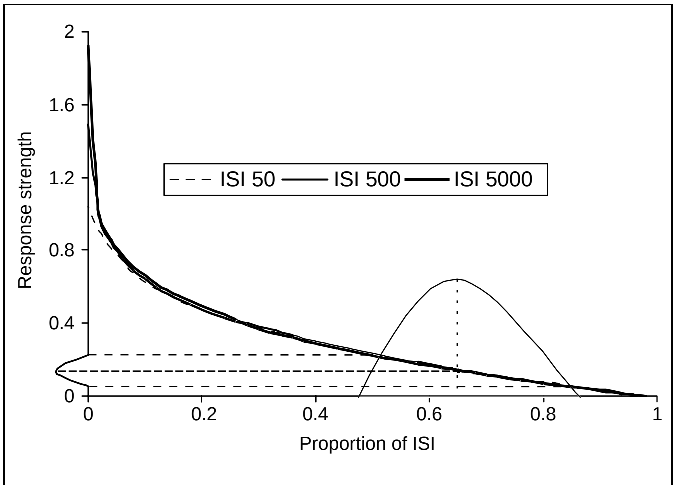

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Figure 2. Steady-state traces from a 10-unit magnetic source imaging (MTS) model plotted as a proportion of the training inter-stimulus interval (ISI) (x-axis) and translated along the y-axis so that the V-value (response strength) associated with reinforcement is zero for all traces (point 1,0). The center dashed line is the response threshold, with noise variation illustrated by the distribution on the y-axis. The larger distribution on the x-axis shows how symmetrical threshold variation translates into slightly asymmetrical (on a linear axis) variation in wait times.

Conclusion

The same dynamic process seems to underlie habituation, forgetting and interval timing, and it behaves like a cascade of thresholded integrators with progressively slower time constants. But many theoretical and experimental uncertainties remain. How exactly are the events that the organism uses as a time marker encoded? Tough questions have been raised about suggested applications of the MTS model to the choose-short effect, for example [14]. Exactly how best to generalize the memory-trace model to the learning of multiple time intervals has not been settled, nor are animals' limits in this regard well defined experimentally. Many other experimental questions remain. For an animal, as for a busy worker who might be late even if his watch is accurate, competing activities can affect timing: too much competition from other activities, and the target response might occur late; too little and it will be early [15]. Hence timing data can be affected by variables that act on activity levels rather than memory. And all the neurophysiological experiments necessary to cement the link between memory and timing have not yet been done. Do drugs or lesions that impair short-term memory (in delayed-match-to-sample tasks, for example) invariably impair timing of short intervals? Is the pattern of memory impairment matched by appropriate changes in temporal discrimination? Despite these uncertainties, the idea that the 'clock' that animals use in interval timing experiments is not a separate entity but a process based on memory strength looks like the best current view.

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The role of the inferior frontal junction area in cognitive control

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Cognitive control processes refer to our ability to coordinate thoughts and actions in accordance with internal goals. In the fronto-lateral cortex such processes have been primarily related to mid-dorsolateral prefrontal cortex (mid-DLPFC). However, recent brain-imaging and meta-analytic studies suggest that a region located more posterior in the fronto-lateral cortex plays a pivotal role in cognitive control as well. This region has been termed the inferior frontal junction area and can be functionally and structurally distinguished from mid-DLPFC.

In our daily life we continually alternate between different cognitive and motor operations with seemingly minimal effort. Cognitive psychology has assumed that this flexibility involves cognitive control processes [1]. Although several prefrontal and parietal areas have been discussed as being involved in cognitive control, the literature most consistently pointed to mid-DLPFC as the crucial fronto-lateral area in cognitive control [2]. However, a recent series of brain imaging studies and

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