■ REVIEW

How Do We Tell Time?

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Animals time events on scales that range more than 10 orders of magnitude—from microseconds to days. This review focuses on timing that occurs in the range of tens to hundreds of milliseconds. It is within this range that virtually all the temporal cues for speech discrimination, and haptic and visual processing, occur. Additionally, on the motor side, it is on this scale that timing of fine motor movements takes place. To date, psychophysical data indicate that for many tasks there is a centralized timing mechanism, but that there are separate networks for different intervals. These data are supported by experiments that show that training to discriminate between two intervals generalizes to different modalities, but not different intervals. The mechanistic underpinnings of timing are not known. However various models have been proposed, they can be divided into labeled-line models and population clocks. In labeled-line models, different intervals are coded by activity in independent and discrete populations of neurons. In population models, time is coded by the population activity of a large group of neurons, and timing requires dynamic interaction between neurons. Population models are generally better suited for parallel processing of interval, duration, order, and sequence cues and are thus more likely to underlie timing in the range of tens to hundreds of milliseconds.
NEUROSCIENTIST 8(1):42–51, 2002

KEY WORDS *Timing, Temporal processing, Models, Interval discrimination, Learning, Neural networks*

> Temporal integration is not found exclusively in language; the coordination of leg movements in insects, the song of birds, the control of trotting and pacing in a gaited horse, the rat running the maze, the architect designing a house, and the carpenter sawing a board, present a problem of sequences of action which cannot be explained in terms of succession of external stimuli.

This quote is from an article titled "The Problem of Serial Order in Behavior" by Karl Lashley (1951/1960). Lashley wrote the article because he felt that temporal processing was "the most important and also the most neglected problem of cerebral physiology." The article was written 2 years after Donald Hebb wrote the *Organization of Behavior*, the book in which Hebb presented his influential theory on the rules that govern synaptic plasticity. However, in contrast to the topic addressed by Hebb, the topic discussed by Lashley has not seen significant advances in the past half century.

A fundamental part of sensory processing is pattern recognition, that is, how central neurons develop selective responses to the spatial and temporal patterns of activity coming from primary sensory neurons. We can decompose sensory stimuli into spatial and temporal components. Spatial stimuli refer to those that can be discriminated based on a static "snapshot" of which neurons are active, that is, the spatial arrangement of active neurons. Discriminating the orientation of bars of light, or letters of the alphabet, falls into this category. In the past 50 years, much progress has been made on this front. Indeed, the fields of synaptic plasticity and self-organizing topographic maps explain how neurons can develop responses to simple spatial stimuli (for reviews, see Anderson and Rosenfeld 1988; Buonomano and Merzenich 1998). These advances, however, say very little about how neurons develop selective responses to temporal patterns. Temporal patterns refer to those in which the order, duration, or interval between the activation of sensory neurons is required for stimulus discrimination. The duration of flashed bars of light and the voice-onset time of phonemes are examples of temporal stimuli. Without an understanding of the neural mechanisms underlying temporal processing, it will not be possible to understand how the brain processes complex real-world stimuli, which are characterized by both their spatial and temporal features. For example, speech recognition, one of the most complex forms of pattern recognition, relies on both spatial and temporal processing (Tallal 1994). Indeed, one of the difficulties in understanding how the brain processes speech, and in the construction of artificial systems capable of speech recognition, stems from underestimating the importance of temporal information in speech (Shannon and others 1995). In addition to this and other forms of sensory processing, timing plays a fundamental role in motor coordination. Given

I thank Jason Goldsmith for comments on earlier versions of this manuscript. This research was supported by the Alfred P. Sloan and EJLB Foundations and by the NSF.

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ISSN 1073-8584

the inherent time-varying nature of our environment and our interaction with it, it is fundamental to understand the neural basis of how the brain processes time.

Temporal Processing: Time Scales

The terms *temporal processing*, *temporal integration*, and *timing* are used to describe a wide range of different phenomena, which often results in ambiguity in the literature. One source of ambiguity is the large scale over which animals process temporal information or generate timed behaviors. All together the brain processes temporal information over a range of at least 10 orders of magnitude from microseconds to daily circadian rhythms—and the above terms are used to refer to all of them. Based on the relevant time scales and the supposed underlying neural mechanisms, we can categorize timing into four different time scales: microseconds, milliseconds, seconds, and circadian rhythms (Fig. 1). These classes are not meant to represent discrete nonoverlapping types of processing. Instead, they represent a simplified division of the number of ranges of temporal processing that rely on different neural mechanisms.

Microseconds

Microsecond temporal processing is used primarily for the detection of interaural delays, the detection of electric fields in electric fish, and echo-location in bats (in which the relevant delays extend up to 10 msec). The best understood system is that used for sound localization. In humans it takes sound approximately 600 to 700 μs to travel the distance between the left and right ear. The auditory system uses these intervals to calculate the spatial location of the sound source. A relatively simple but extremely sensitive mechanism is used to determine the microsecond intervals for sound localization. A sound arriving in each ear will activate neurons in the cochlear nucleus. The axons from these neurons function as delay lines; that is, the distance a action potential has to travel is proportional to the time it takes. Neurons in the medial superior olive function as coincidence detectors and use the delays to respond selectively to different intervals. Together these neurons establish a topographic map of auditory space (Carr 1993).

Milliseconds

Millisecond processing will be defined as that above 10 msec and below 500 to 1000 msec. Sensory processing within this range is often referred to as perceptual timing: "below 0.5 sec information processing is of a highly perceptual nature, fast parallel and not accessible to cognitive control" (Michon 1985, p. 21). Millisecond processing is perhaps the most sophisticated and the least well understood. Virtually all the temporal cues for speech and vocalization discrimination, and many of the cues in music perception, fall within this range. Additionally, much of the motion processing in the visual and somatosensory system occurs on this scale. On the motor side, it is within the range of tens to hundreds of milliseconds that fine motor coordination operates in. Thus, the ability of athletes and musicians to perform extraordinary physical feats relies on sophisticated neural mechanisms capable of producing well-timed and orchestrated events in the millisecond range.

Seconds

Timing on scales longer than a second are often referred to as time estimation and thought to rely on conscious and cognitive control (Rammsayer and Lima 1991). Millisecond and second processing are thought to rely on different mechanisms based on psychophysical and pharmacological experiments. Rammsayer and Lima showed that interval discrimination of 50 msec intervals was unaffected by cognitive load, whereas intervals of 1 sec were. Additionally, pharmacological manipulations can differentially affect millisecond and second processing (see below). In addition to time estimation, there are various behaviors that rely on pattern generators operating in this time scale—such as breathing and locomotion. For reviews on timing in the range of seconds and minutes, see Gibbon and others (1997) and Matell and Meck (2000).

Circadian Rhythms

Animals also track time through daily circadian rhythms. In addition to the daily sleep-wake cycles, regulation of hormone levels, thermoregulation, and appetite cycles are occurring on the scale of hours and days. Sleep-wake cycles are a good example of a behavior controlled by an internal clock. Physiological measures in both plants and animals can be shown to exhibit an approximately 24-h rhythm, even in the absence of external stimuli. The clock controlling circadian rhythms is not immutable; its phase can be shifted and entrained by external cues. Studies in various organisms, including *Drosophila* and mice, have revealed that circadian clocks are composed of molecular/biochemical pathways regulating transcription and translation in autoregulatory feedback loops (for a review of the molecular mechanisms of circadian clocks, see King and Takahashi 2000).

In the current review, focus will be on time perception temporal processing occurring in the range of tens to hundreds of milliseconds. This time scale is fundamental to sensory processing in the auditory, visual, and somatosensory modalities. As mentioned above, motor coordination and speech perception exemplify how sophisticated temporal processing can be on the millisecond scale. During continuous speech, syllables are generated every 200 to 400 msec. The sequential arrangement of syllables is important in speech recognition (e.g., "la-dy" vs. "de-lay"). Similarly, the duration of each syllable is critical, as is the interval between syllables (e.g., by emphasizing the timing of Jimi Hendrix's famous mondegreen "kiss the sky," it is easier to distinguish it from "kiss this guy"). Additionally, the temporal structure within each syllable and phoneme also contributes to discrimination. For example, the voice-onset

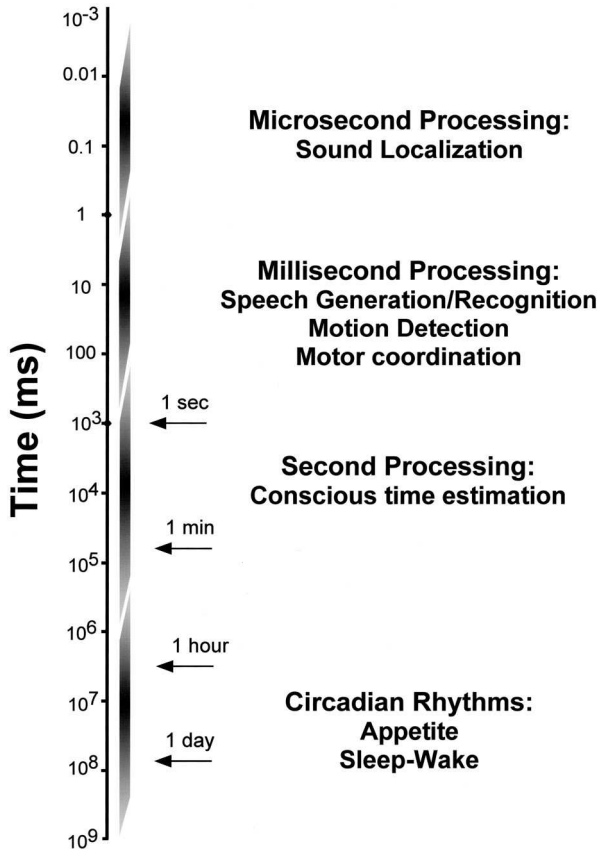


Fig. 1. Scales of temporal processing. Humans process temporal information over a scale of at least 10 orders of magnitude. On one extreme, we detect the delay required for sound to travel from one ear to the other. These delays are on the order of tens to hundreds of microseconds. On the other extreme, we exhibit daily physiological oscillations, such as our sleep-wake cycle. These circadian rhythms are controlled by molecular/biochemical oscillators. Temporal processing on the scale of tens and hundreds of milliseconds is probably the most sophisticated and complex and is fundamental for speech processing. Time estimation refers to processing in the range of seconds and minutes and is generally seen as the conscious perception of time.

time (the time between air release and vocal cord vibration) and transition duration of formants are used for the discrimination of individual consonant-vowel syllables (Tallal 1994). Prosodic cues such as pauses and duration of speech segments are used to determine semantic content (Lehiste and others 1976).

Temporal processing on the scale of microseconds, seconds, and days seems to be less complex than millisecond processing. For example, microsecond processing for interaural delay detection is not capable of duration or sequence discrimination. Timing in the range of seconds and minutes generally involves conscious estimation of intervals and is not used for sequence or parallel processing of multiple temporal cues or of periodic pattern generation. Circadian rhythms are likely to be controlled by biological clocks and exhibit less flexibility than temporal processing on the shorter time scales. For example, the internal clock controlling circadian rhythms cannot be instantly reset (thus jet lag). In contrast, time perception and time estimation can begin at the onset of any stimulus. Processing on the millisecond range seems to be the most complex. In speech we are processing the temporal structure of phonemes, the prosody of speech, and sequence of speech segments all in parallel. Additionally, temporal discrimination can exhibit a higher-order form of processing referred to as temporal invariance: we can identify the same speech segments or tone sequences at a range of speeds, as long as the ratios between different events are similar. Thus, the neural mechanisms underlying temporal processing in the millisecond range are likely to be complex and may or may not rely on independent mechanisms to solve specific components of temporal processing, such as order, duration, intervals, inter- and intramodality timing, and motor timing.

Central versus Distributed Mechanisms

A fundamental question regarding temporal processing is whether it relies on a single centralized mechanism or is distributed throughout different areas. If timing is centralized, then an interval discrimination task in the somatosensory, visual, or auditory modality would use the same group of neurons. Additionally, motor tasks requiring carefully timed responses would also rely on the same system. In this view, timing in the nervous system would be analogous to that in computers, in which a central clock sends out information to many other components of the computer. In contrast, in a distributed system various regions of the brain would process time, and the locations used would depend on the modality and task at hand. Thus, different parts of the brain would be involved in timing in somatosensory, auditory, visual, or motor tasks.

In the psychological literature on timing, by far the most influential model has been the internal clock model (Creelman 1962; Treisman 1963). Internal clocks are hypothetical mechanisms in which a neural pacemaker generates pulses; the number of pulses relating to a physical time interval is recorded by a counter. Internal clock models are generally centralized: one clock is used for all timing tasks.

Centralized and distributed mechanisms can be subdivided into models in which the same neurons are timing all intervals or models in which different neurons time different intervals. For example, we can use the same watch to time both 100 or a 500 msec intervals. However, one could imagine a system in which the initial event triggered an array of watches, each one devoted to a fixed interval: 100, 200, . . ., 500 msec. In this review, the former model will be referred to as a clock model and the latter as a labeled line or an interval-based model (Ivry 1996).

Correlations between Temporal Tasks

The majority of the timing studies in humans rely on interval discrimination tasks (Fig. 2*A*). In a typical task, two brief tones separated by a standard interval (e.g.,

100 msec) or a comparison interval (standard + ΔT) are presented to the subject. The order of the presentation of the standard and comparison intervals is randomized. The subject is required to make a judgment as to whether the longer interval was the first or second. Depending on the task design, the difference in milliseconds between the short and long interval (ΔT) is adaptively changed according to performance, which allows the calculation of an interval discrimination threshold (Wright and others 1997).

If timing relies on a centralized mechanism, a correlation between different timing tasks would be expected. That is, are individuals that are good at discriminating auditory intervals also good at discriminating somatosensory intervals? Two types of correlations can be analyzed, those between different modalities for the same interval and between different intervals in the same modality. High correlations in the former analysis would suggest a central timekeeping mechanism that is used in all modalities, but there could be independent timing mechanisms for each interval. In the latter, if a high correlation is observed between intervals, the analysis would support the notion that one central clock is being used for all intervals.

A study by Keele and others (1985) examined the correlations between a motor task and an auditory interval discrimination task. Moderate correlations (R^2 of approximately 0.5) between tapping and tone discrimination using target intervals of 400 msec were observed. A second study (Spencer and others 2000) also reports moderate correlations between both a 400 msec tapping and tone task ($R^2 = 0.39$) and an 800 msec target interval ($R^2 = 0.36$). This study also revealed a correlation between the 400 and 800 msec perception task ($R^2 = 0.54$). Figure 2*B* shows plots of the correlations between different conditions in an auditory discrimination task (Karmarkar and Buonomano, unpublished data). Four conditions were examined: 50 msec–1 kHz, 50 msec–4 kHz, 100 msec–1 kHz, and 200 msec–1 kHz. The results show significant correlations between 50 msec–1 kHz and 50 msec–4 kHz, as well as between 50 msec–1 kHz and 100 msec–1 kHz, but not between 50 msec–1 kHz and 200 msec–1 kHz. Together these results favor a centralized timing mechanism shared by sensory and motor systems for similar intervals. However, the lack of correlation between the 50 msec–1 kHz and 200 msec–1 kHz suggests that there may be distinct mechanisms for 50 msec and 200 msec timing. It should be stressed that the results from correlations studies are suggestive, in that they could also be attributed to experience-dependent generalization, rather than common underlying mechanisms.

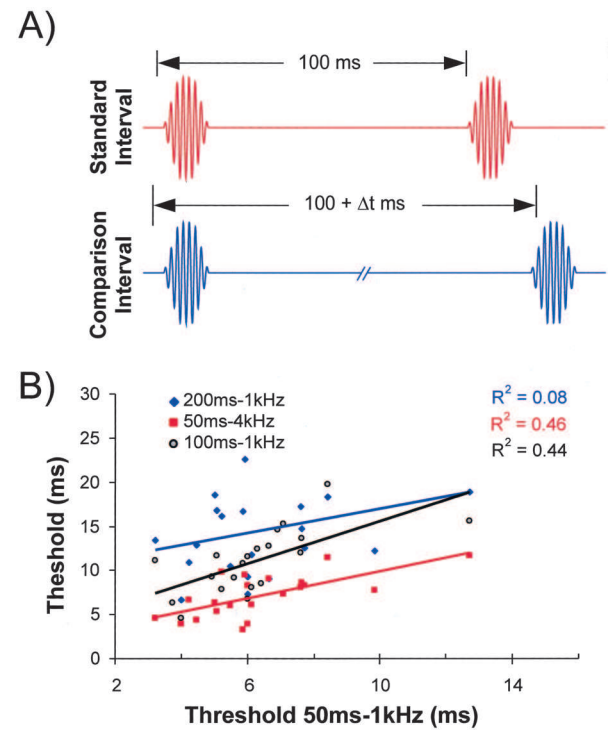


Fig. 2. Intrasubject correlations between interval discrimination tasks. *A*. Interval discrimination. Interval tasks can be designed in various ways. In one design, a standard and comparison interval are presented in random order, the subject has to decide whether the comparison interval (the longer one) came first or second. Both intervals are bounded by two brief tones of a fixed frequency. The standard interval is always the same length, whereas the comparison interval is equal to the standard + ΔT, where ΔT changes according to performance. Different task conditions are examined by varying the standard intervals and the frequency of the tones. *B*. Intrasubject correlations between different interval discrimination task conditions. Performance is well correlated for the same interval at different frequencies ($R^2 = 0.46$, $P < 0.005$). There is also a significant correlation between the 50 × 100 msec intervals ($R^2 = 0.44$, $P < 0.005$), but not between the 50 and 200 msec intervals ($R^2 = 0.08$, $P = 0.22$).

Intermodal Timing

Data from some interval discrimination tasks support the notion of distributed timing. Specifically, some studies have examined tasks in which intervals are bounded by intermodal stimuli. Interval discrimination of intervals bounded by a tone and a flash of light (or a flash and a tone) is significantly worse than intervals bounded by two tones or two flashes (Rosseau and others 1983; Grondin and Rousseau 1991). Interestingly, intermodality discrimination is impaired relative to intramodality timing for subsecond processing, but not for 1 sec intervals (Rosseau and others 1983). Not only is intermodality discrimination less accurate than intramodality discrimination, but even within a given modality, discrimination is impaired by using intervals bounded by different stimulus characteristics (Divenyi and Danner 1977; Grondin and Rousseau 1991). Thus, interval discrimination of a 250 msec interval marked by two 1 kHz tones is better than the same intervals marked by a 1 kHz tone and a noise burst (Grondin and Rousseau 1991).

These data can be used to argue for distributed timing because a centralized timer may be expected to time events arriving through different channels as well as events arriving through the same channel. However, an alternative explanation is that intermodal timing is sim-

ply a more difficult task because it requires a shift of attention from one modality to the other.

Anatomical Localization

If timing is centralized, it is important to ask: where is it located? Various structures have been implicated in timing. One such area is the right parietal cortex. A recent study showed that stroke patients with right hemisphere parietal lesions, but not left hemisphere lesions, exhibit a selective deficit for 300 and 600 msec interval discrimination (Harrington, Haaland, and Knight 1998). A second structure implicated in timing is the basal ganglia, although it is generally thought to contribute to timing on the scale of seconds. Two studies have shown that Parkinson patients exhibit deficits in temporal discrimination in the millisecond range, but not in frequency discrimination (Artieda and others 1992; Harrington and others 1998). These data are indirect because it is possible that Parkinson's effect on timing is due to secondary effects on structures other than the basal ganglia. In addition to the cortex and basal ganglia, the cerebellum has also been proposed to underlie timing. Because it is the structure that has been the best studied in relation to temporal processing, it will be discussed in detail below.

Cerebellum

Braitenberg (1967) suggested that one of the main functions of the cerebellum was timing. He made the specific proposal that the axons of the granule cells (parallel fibers) functioned as delay lines. This hypothesis is currently not accepted, primarily because given the conduction velocity of parallel fibers, it would require a 5-cm-long fiber to create a 100 msec delay. Furthermore, because granule cells are not excitatory, nor are there excitatory loops in the cerebellum, the cerebellar architecture does not support "excitatory chains" to implement longer delays.

Although the mechanisms are debated (see below), there is growing experimental support for a cerebellar role in timing (for a review, see Ivry 1996). This is particularly true for motor timing. One of the best studied systems regarding the timing of motor responses is eyeblink conditioning. In this form of conditioning, an animal receives paired presentation of a tone and a puff of air to the cornea. As a result of this training, animals learn to blink in response to the tone alone. Animals do not learn to blink arbitrarily on hearing the tone, but blink at a time equal to the interval between the tone and air puff presented during training. Lesions to the cerebellar cortex abolish the timing of the conditioned response, without eliminating it (Perrett and others 1993).

There is also support for a role of the cerebellum in forms of sensory timing, such as interval discrimination. Ivry and Keele (1989) showed that subjects with cerebellar lesions were less accurate in a 400 msec interval discrimination as compared with control subjects with cortical lesions. Other studies have shown deficits in the discrimination of phonemes differing in their temporal structure in subjects with bilateral cerebellar lesions (Ackermann and others 1997). Imaging studies have shown that the cerebellar vermis is activated during a 300 msec interval discrimination task (Jueptner and others 1995). However, in this study, the control task did not require decision making or stimulus comparisons, and other areas such as the right thalamus and basal ganglia were also active. Furthermore, it has been suggested that the observed increases in blood flow may reflect cerebellar involvement in complex stimulus analysis and not necessarily an explicit role in timing (Ackermann and others 1999).

Various lines of evidence suggest that one or more structures may play a predominant role in timing and function as a central time-keeping structure. However, to date no study has shown that a given lesion or disease eliminates temporal processing. This could be taken as indirect evidence for distributed timing mechanisms, in that none of the lesion studies produce a global multimodal sensory-motor breakdown in timing.

Interval Discrimination Learning

One question that has not been examined carefully until recently is whether interval discrimination undergoes perceptual learning. That is, does temporal resolution increase with practice. One of the first studies to examine this issue reported no perceptual learning (Rammsayer 1994). In this study, subjects were trained on 50 msec intervals for 10 min a day for 4 weeks. More recent studies have all reported improvement of interval discrimination with practice (Wright and others 1997; Nagarajan and others 1998; Westheimer 1999). In these studies, subjects were generally trained for an hour a day for 10 days.

Generalization of Interval Discrimination

In addition to showing that the neural mechanisms underlying timing can be fine tuned with experience, learning studies provide a means to examine the issue of central versus distributed timing. Specifically, we can ask if after training on a 100 msec interval bounded by 1 kHz tones the performance improves for different intervals and frequencies. If there is a single central timer that relies on a clock mechanism, generalization to both different intervals and different marker conditions should be observed.

The first study to address this issue revealed that after training on 100 msec intervals marked by 1 kHz tones, subjects showed complete generalization to the same interval marked by 4 kHz tones (Fig. 3) (Wright and others 1997). Subsequent work revealed that intermodal generalization was observed (Nagarajan and others 1998). Training on a somatosensory interval discrimination task resulted in improvement on an auditory task for the same intervals. Both studies revealed little or no generalization to novel intervals presented with the same markers as the trained condition. That is, despite improve-

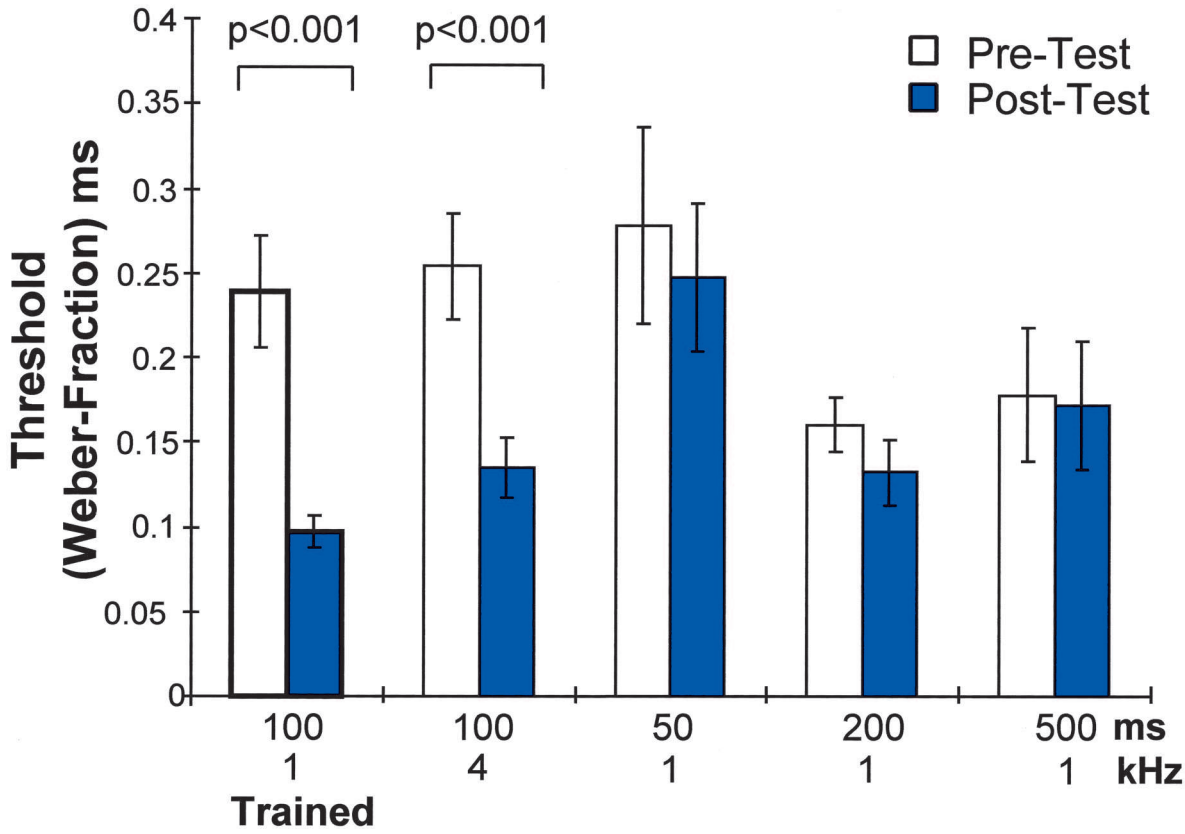


Fig. 3. Interval discrimination learning generalized across frequencies but not intervals. Subjects were trained on the 100 ms–1 kHz conditions for 10 days. The pre- and posttest thresholds revealed significant differences only for the trained condition, and the 100 ms–4 kHz condition. Modified from Wright and others (1997).

ment on the trained 100 msec interval, there was no improvement on 50 or 200 msec intervals. Together, these studies show that interval learning does not generalize in the temporal domain (different intervals) but does generalize in the spatial domain (different markers). This conclusion is also supported by results in the visual modality. Westheimer (1999) reported that training on a 500 msec duration visual stimulus presented to one visual hemifield generalized to the other hemifield. Even more surprising, training on an auditory task appears to result in an interval-specific improvement in a motor task requiring that the subjects tap their fingers to mark specific intervals (Meegan and others 2000).

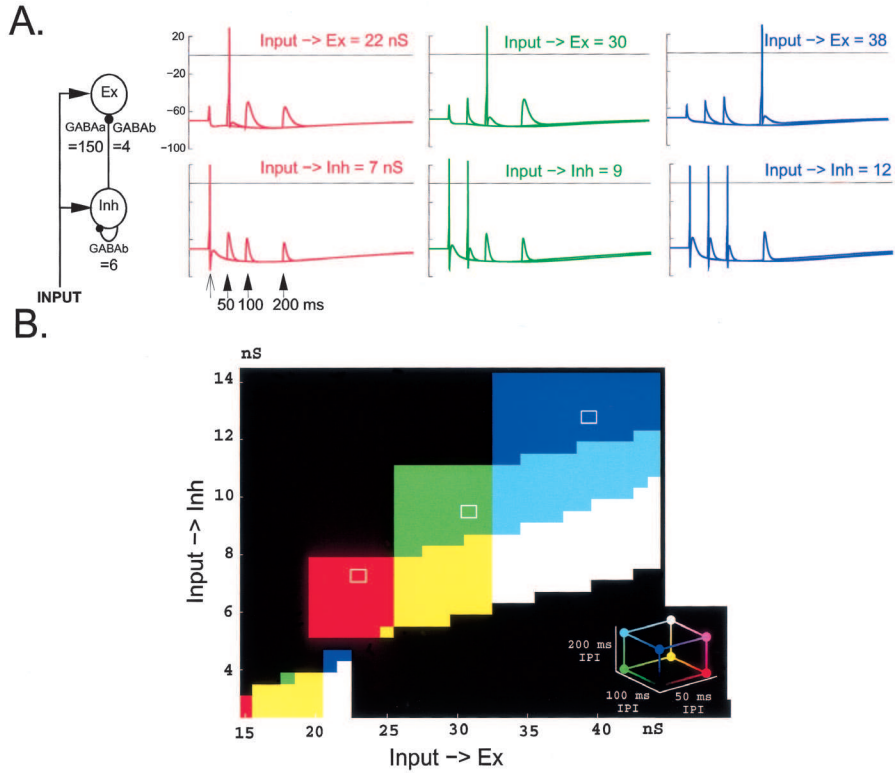
The simplest interpretation of these data is that there is a centralized clock for each interval, because the improvement is interval specific but generalized across modalities (somatosensory to auditory, and auditory to motor). The caveat in this interpretation is that it is possible that in these tasks learning occurs as a result of interval-specific cognitive processes other than temporal processing per se. For example, because interval discrimination requires comparing the test interval to a standard interval, improvement could rely on better representation or memory of the standard interval. Such an explanation would be consistent with the generalization across different stimulus markers and modalities, as well as the lack of generalization to novel intervals.

Psychopharmacology of Timing

Psychopharmacological experiments have also been used to probe the mechanisms underlying timing and to determine whether different time scales of processing rely on different neural systems. Numerous drugs have subjectively been reported to alter time estimation, that is, temporal processing in the seconds and minutes range, but few drug studies have carefully examined timing. One well-established finding is that dopamine antagonists produce temporal overshoot ("slowing of the clock"), and stimulants such as methamphetamine produce temporal undershoots ("speeding up the clock"; for a review, see Meck 1996). Few studies have examined pharmacological effects on temporal processing below a second. Rammsayer (1999) showed in human psychophysical experiments that the dopaminergic antagonist, haloperidol, significantly impaired discrimination thresholds for 100 msec and 1 sec intervals. Remoxipride, a dopamine antagonist that is more selective for D2 receptors, impaired processing on the scale of a second but not for 50 msec intervals (Rammsayer 1997). Experiments with benzodiazepines also support the dissociation between millisecond and second processing, by showing that performance in a 50 or 100 msec task is unaffected, whereas performance on a 1 sec task is made significantly worse (Rammsayer 1999, 1992). Together these results show that two distinct drug

Box 1: Interval Selectivity in Disynaptic Circuits

Computer simulations show how disynaptic circuits can exhibit interval selectivity. The circuit is composed of a single excitatory (Ex) and inhibitory (Inh) neuron, and there are five synapses: Input→Ex, Input→Inh, Inh_{fast}→Ex, Inh_{slow}→Ex, Inh_{slow}→Inh. The excitatory synapses exhibit paired-pulse facilitation (PPF), the inhibitory neuron produces both a fast ($GABA_A$) and a slow ($GABA_B$) inhibitory postsynaptic potential (IPSP) on the Ex neuron. Part *A* shows traces from the Ex and Inh cells for three different sets of synaptic strengths (red, green, and blue). Each graph shows the overlaid responses to three different intervals. By changing the strengths of the Input→Ex and Input→Inh connections in parallel, it is possible to tune the Ex unit to respond selectively to either 50, 100, or 200 msec intervals. With relatively weak inputs to both the Ex and Inh cell (red traces), the first pulse generates a supra- and subthreshold response in the Inh and Ex units, respectively. At 50 msec, the second pulse is suprathreshold in the Ex unit (even though it is riding a slow IPSP elicited by the first spike in the Inh unit), owing to PPF, which peaks at 50 msec. The second pulse, at any interval, does not generate a fast IPSP because the Inh unit did not fire owing to the $GABA_B$-mediated slow IPSP. If the strength of both inputs is increased (green traces), the Ex unit fires exclusively to the 100 msec pulse. It no longer fires to the 50 msec pulse because as a result of the increased input, the Inh unit fires in response to the second pulse at 50 msec producing a fast IPSP in the Ex unit, which prevents it from firing. If we continue to increase the strength of both inputs (blue traces), through a similar mechanism, the Ex unit fires exclusively to the 200 msec interpulse interval (IPI). Part *B* displays a parametric analysis of the interval selectivity described above in synapse space. The strength of the Input→Ex and Input→Inh was parametrically varied over a range of weights. The results are represented as a red-green-blue (RGB) plot, which permits visualization of the selectivity to the three intervals while varying two dimensions. As color coded in panel *A*, red represents regions of synapse space in which the Ex unit fires exclusively to the second pulse of a 50 msec IPI, but not to the 100 or 200 msec IPI; that is, a 50 msec interval detector. Similarly, green and dark blue areas represent regions of synapse space in which the Ex units respond only to the 100 or 200 ms interval, respectively. In the same manner that a computer screen makes yellow by mixing red and green, yellow in this RGB represents conditions in which the Ex unit responded to both 50 and 100 msec intervals, but not to the 200 msec interval. White areas represent regions that respond to all the intervals, but not to the first pulse. Black areas represent regions in which the cell was not interval selective: not firing at all or in response to the first pulse. The three unfilled white squares show the areas of synapse space of the traces in panel *A*. These simulations suggest that a computational function of short-term synaptic plasticity may be to allow neurons to exhibit interval selectivity and that circuits of neurons may be intrinsically capable of temporal processing. Modified from Buonomano (2000).



classes (dopaminergic antagonists and benzodiazepines) selectively interfere with second but not millisecond processing. To this author's knowledge, there have been no reports of drugs that interfere selectively with millisecond processing. Future experiments will be necessary to determine whether the above results are due to direct action on a timing mechanism or more nonspecific actions on arousal and/or cognition.

Neural Mechanisms Underlying Sensory Timing

The studies above addressed the psychophysical characteristics and localization of temporal processing, but not the actual underlying mechanisms. The term *mechanisms* refers to the neural properties that are actually sensitive to time, rather than involved in the readout. For example, looking at the readout of a watch does not necessarily provide us with any information about whether timing is occurring as a result of counting the revolution of mechanical gears or as a result of counting the oscillations of a quartz crystal. There have been a number of models of the possible neuronal mechanisms underlying timing. Rather than fully review these models, a summary of the general types of models will be provided. For simplicity, the models will be divided into two classes: labeled lines and population models. A third class is the clock model, of which internal clocks are the prototype. These models, which were described above, will not be discussed, because they are unlikely to be involved in millisecond timing, and few neurally realistic models have been put forth for them.

Labeled Lines

The majority of models that have addressed the neural mechanisms underlying timing have been influenced by the delay line model used for microsecond processing. In these models, there is an array of neurons, each of which responds selectively to a specific interval. This is considered a labeled line because there is a separate channel or neuron for each interval.

To implement labeled lines in the range of tens to hundreds of milliseconds, some temporal property must be present that allows neurons to respond selectively to a given interval. Because there must be a range of interval-selective units, whatever the time-dependent property is, there must be a spectrum of different time constants for different units. The time-dependent property can take various forms, including 1) oscillators (Fujita 1982; Miall 1989), 2) slow biochemical reactions such as the metabotropic glutamate receptor (Fiala and others 1996) or slow IPSPs combined with rebound excitation (Sullivan 1982; Margoliash 1983; Jaffe 1992), 3) intrinsic currents resulting in delayed spiking (Beggs and others 2000), and 4) cell thresholds combined with a constant rate of synaptic integration (Antón and others 1991).

What these models have in common is that in each case there are elements that are specialized for a given interval. Different elements are explicitly tuned to different intervals by adjusting the time constants, and different elements are set to different values. Because timing at different intervals is performed by independent groups of neurons, one prediction is that it is possible to abolish timing for a 250 msec interval, whereas 50 msec timing remains normal. Computationally, these models are very effective for simple tasks such as interval discrimination. However, in their simplest implementation, they are not well suited for complex forms of temporal processing such as sequences and speech.

Population Clocks

In population clocks (or population models), time is coded in the population activity of a network of neurons—any given neuron will contain little temporal information. An additional difference from labeled line models is that there is not an explicit range of time constants or time delays specifically set to capture specific intervals. Population models are a distributed type of timing; it should not be possible to create localized lesions that selectively impair one interval but not others. These models generally rely on local network dynamics and time-dependent changes in network state. The time-dependent changes in the state of the network can be the result of time-dependent properties such as short-term synaptic plasticity (Buonomano and Mauk 1994; Buonomano and Merzenich 1995), or they can be due to inhibitory feedback in local circuits (Buonomano and Mauk 1994; Mauk and Donegan 1997; Medina and others 2000).

One population model for sensory processing relies on the interaction between network dynamics and time-dependent synaptic properties (Buonomano and Merzenich 1995; Buonomano 2000)—short-term synaptic plasticity and slow synaptic events. Any initial event that arrives in a network of neurons can activate a population of neurons and will trigger a series of time-dependent properties. Thus, at the arrival of a second event 100 msec later, the same stimulus will arrive in a different network state. Due to synaptic facilitation/depression, the same synapses used 100 msec before are now stronger or weaker. Additionally, excitatory and inhibitory neurons may still be hyperpolarized by slow IPSPs. As a result, the same input can activate different populations of neurons dependent on the recent stimulus history of the network. In this type of model, a spectrum of different time constants is not present, but nevertheless neurons can respond selectively to a range of different intervals. Indeed, even in a simple network composed of two neurons it can be shown that neurons can be tuned to different intervals by changing synaptic strengths (see Box 1). Artificial network implementations of this model have been shown to be able to discriminate intervals and simple temporal sequences (Buonomano and Merzenich 1995; Buonomano 2000).

A different type of population model has been proposed to show how the cerebellar cortex may account for the timing of eye-blink conditioning (Buonomano and

Mauk 1994; Mauk and Donegan 1997; Medina and others 2000). Specifically, in the presence of a conditioned stimulus, the population activity of active granule cells changes dynamically owing to negative feedback through the granule→Golgi→granule loop. In this model, time is encoded in the population of active granule cells, and it can be read out by changing the weights of the granule-Purkinje synapses.

Conclusions

A half-century after Lashley wrote his article "The Problem of Serial Order in Behavior," the field of temporal processing is still in its infancy. However, the studies to date have allowed insights into the nature of timing. Multiple lines of evidence indicate that distinct neural mechanisms underlie millisecond and second timing. Both psychophysical and pharmacological data indicate that interval discrimination of 100 and 1000 msec tasks relies on different mechanisms, although it is not clear exactly where the boundary lies or how much overlap there is. Within the millisecond range, there is evidence that timing can undergo perceptual learning. Importantly, learning seems to generalize across modalities but not intervals. This suggests that there are central timing mechanisms in place (which does not exclude distributed timing) that are tuned to specific intervals. It is with regard to the neural mechanisms that underlie timing that relatively little progress has been made. How do neurons time external and internal events? It seems likely that the answer to this question will require an understanding of the temporal dynamics of networks of neurons. Progress is being made in recording from large numbers of neurons and analyzing the spatio-temporal patterns of activity within networks. Thus, as more neuroscientists start looking at responses to complex stimuli, and temporal discrimination tasks, we will be at last in position to make significant headway to the problem posed by Lashley 50 years ago.

References

Ackermann GS, Hertich I, Daum I. 1997. Categorical speech perception in cerebellar disorders. Brain Lang 60:323–31.

Ackermann GS, Hertich I, Daum I. 1999. Cerebellar contributions to the perception of temporal cues within the speech and nonspeech domain. Brain Lang 67:228–41.

Anderson JA, Rosenfeld E. 1988. Neurocomputing: foundations of research. Cambridge (MA): MIT Press.

Antón PS, Lynch G, Granger R. 1991. Computation of frequency-to-spatial transform by olfactory bulb glomeruli. Biol Cybern 65:407–14.

Artieda J, Pastor MA, Lacuz F, Obeso JA. 1992. Temporal discrimination is abnormal in Parkinson's disease. Brain 115:199–210.

Beggs JM, Moyer JR, McGann JP, Brown TH. 2000. Prolonged synaptic integration in perirhinal cortical neurons. J Neurophysiol 83:3294–8.

Braitenberg V. 1967. Is the cerebellar cortex a biological clock in the millisecond range? Prog Brain Res 25:334–6.

Buonomano DV. 2000. Decoding temporal information: a model based on short-term synaptic plasticity. J Neurosci 20:1129–41.

Buonomano DV, Mauk MD. 1994. Neural network model of the cerebellum: temporal discrimination and the timing of motor responses. Neural Comput 6:38–55.

Buonomano DV, Merzenich MM. 1995. Temporal information transformed into a spatial code by a neural network with realistic properties. Science 267:1028–30.

Buonomano DV, Merzenich MM. 1998. Cortical plasticity: from synapses to maps. Annu Rev Neurosci 21:149–86.

Carr CE. 1993. Processing of temporal information in the brain. Annu Rev Neurosci 16:223–43.

Creelman CD. 1962. Human discrimination of auditory duration. J Acoust Soc Am 34:582–93.

Divenyi P, Danner WF. 1977. Discrimination of time intervals marked by brief acoustic pulses of various intensities and spectra. Percept Psychophys 21:125–42.

Fiala JC, Grossberg S, Bullock D. 1996. Metabotropic glutamate receptor activation in cerebellar Purkinje cells as substrate for adaptive timing of the classically conditioned eye-blink response. J Neurosci 16:3760–34.

Fujita M. 1982. An adaptive filter model of the cerebellum. Biol Cybern 45:195–206.

Gibbon J, Malapani C, Dale CL, Gallistel CR. 1997. Toward a neurobiology of temporal cognition: advances and challenges. Curr Opin Neurobiol 7:170–84.

Grondin S, Rousseau R. 1991. Judging the duration of multimodal short empty time intervals. Percept Psychophys 49:245–56.

Harrington DL, Haaland KY, Hermanowicz N. 1998. Temporal processing in the basal ganglia. Neuropsychology 12:3–12.

Harrington DL, Haaland KY, Knight RT. 1998. Cortical networks underlying mechanisms of time perception. J Neurosci 18:1085–95.

Ivry R. 1996. The representation of temporal information in perception and motor control. Curr Opin Neurobiol 6:851–7.

Ivry RB, Keele SW. 1989. Timing functions of the cerebellum. J Cognit Neurosci 1:136–52.

Jaffe S. 1992. A neuronal model for variable response latency. In: Eeckman FH, editor. Analysis and modeling of neural systems. Boston: Kluwer. p 405–10.

Jueptner M, Rijntjes C, Weiller C, Faiss JH, Timmann D, Mueller SP, and others. 1995. Localization of a cerebellar timing process using PET. Neurology 45:1540–5.

Keele SW, Pokorny RA, Corcos DM, Ivry R. 1985. Do perception and motor production share common timing mechanisms: a correlational analysis. Acta Psychologica 60:173–91.

King DP, Takahashi JS. 2000. Molecular genetics of circadian rhythms in mammals. Annu Rev Neurosci 23:713–42.

Lashley K. 1951 [1960]. The problem of serial order in behavior. In: Beach FA, Hebb DO, Morgan CT, Nissen HW, editors. The neuropsychology of Lashley. New York: McGraw-Hill.

Lehiste I, Olive JP, Streeter LA. 1976. Role of duration in disambiguating syntactically ambiguous sentences. J Acoust Soc Am 60:1199–202.

Margoliash D. 1983. Acoustic parameters underlying the responses of song-specific neurons in the white-crowned sparrow. J Neurosci 3:133–43.

Matell MS, Meck WH. 2000. Neuropsychological mechanisms of interval timing behavior. Bioessays 22:94–103.

Mauk MD, Donegan NH. 1997. A model of Pavlovian eyelid conditioning based on the synaptic organization of the cerebellum. Learn Mem 3:130–58.

Meck WH. 1996 Neuropharmacology of timing and time perception. Cognit Brain Res 3:227–42.

Medina JF, Garcia KS, Nores WL, Taylor NM, Mauk MD. 2000. Timing mechanisms in the cerebellum: testing predictions of a large-scale computer simulation. J Neurosci 20:5516–25.

Meegan DV, Aslin RN, Jacobs RA. 2000. Motor timing learned without motor training. Nature Neurosci 3:860–2.

Miall C. 1989. The storage of time intervals using oscillating neurons. Neural Comput 1:359–71.

Michon JA. 1985. The complete time experiencer. In: Michon JA, Jackson JL, editors. Time, mind and behavior. Berlin: Springer-Verlag. p 21–52.

Nagarajan SS, Blake DT, Wright BA, Byl N, Merzenich MM. 1998. Practice-related improvements in somatosensory interval discrimination are temporally specific but generalize across skin location, hemisphere, and modality. J Neurosci 18:1559–70.

Perrett SP, Ruiz BP, Mauk MD. 1993. Cerebellar cortex lesions disrupt learning-dependent timing of conditioned eyelid responses. J Neurosci 13:1708–18.
Rammsayer T. 1992. Effects of benzodiazepine-induced sedation on temporal processing. Hum Psychopharmacol 7:311–18.
Rammsayer TH. 1994. Effects of practice and signal energy on duration discrimination of brief auditory intervals. Percept Psychophys 55:454–64.
Rammsayer TH. 1997. Are there dissociable roles of the mesostriatal and mesolimbocortical dopamine systems on temporal information processing in humans? Biol Psychol/Pharmacopsychol 35:36–46.
Rammsayer TH. 1999. Neuropharmacological evidence for different timing mechanisms in humans. Q J Exp Psychol 52B:273–86.
Rammsayer TH, Lima SD. 1991. Duration discrimination of filled and empty auditory intervals: cognitive and perceptual factors. Percept Psychophys 50:565–74.
Rosseau R, Poirier J, Lemyre L. 1983. Duration discrimination of empty time intervals marked by intermodal pulses. Percept Psychophys 34:541–8.
Shannon RV, Zeng FG, Kamath V, Wygonski J, Ekelid M. 1995. Speech recognition with primarily temporal cues. Science 270:303–4.
Spencer RM, Zelaznik HN, Ivry R. 2000. How do we time movements. Soc Neurosci Abstr 26:178.
Sullivan WE. 1982. Possible neural mechanisms of target distance coding in auditory system of the echolocating bat *Myotis lucifugis*. J Neurophysiol 48:1033–47.
Tallal P. 1994. In the perception of speech time is of the essence. In: Buzsaki G, Llinas R, Singer W, Berthoz A, Christen Y, editors. Temporal coding in the brain. Berlin: Springer-Verlag. p 291–9.
Treisman M. 1963. Temporal discrimination and the indifference interval: implications for a model of the 'internal clock'. Psychol Monogr 77:1–31.
Westheimer G. 1999. Discrimination of short time intervals by the human observer. Exp Brain Res 129:121–6.
Wright BA, Buonomano DV, Mahncke HW, Merzenich MM. 1997. Learning and generalization of auditory temporal-interval discrimination in humans. J Neurosci 17:3956–63.