Annu. Rev. Neurosci. 2004. 27:307–40
doi: 10.1146/annurev.neuro.27.070203.144247

First published online as a Review in Advance on February 26, 2004

# THE NEURAL BASIS OF TEMPORAL PROCESSING

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**Key Words** timing, cerebellum, cortex, dynamics, interval, conditioning

■ **Abstract** A complete understanding of sensory and motor processing requires characterization of how the nervous system processes time in the range of tens to hundreds of milliseconds (ms). Temporal processing on this scale is required for simple sensory problems, such as interval, duration, and motion discrimination, as well as complex forms of sensory processing, such as speech recognition. Timing is also required for a wide range of motor tasks from eyelid conditioning to playing the piano. Here we review the behavioral, electrophysiological, and theoretical literature on the neural basis of temporal processing. These data suggest that temporal processing is likely to be distributed among different structures, rather than relying on a centralized timing area, as has been suggested in internal clock models. We also discuss whether temporal processing relies on specialized neural mechanisms, which perform temporal computations independent of spatial ones. We suggest that, given the intricate link between temporal and spatial information in most sensory and motor tasks, timing and spatial processing are intrinsic properties of neural function, and specialized timing mechanisms such as delay lines, oscillators, or a spectrum of different time constants are not required. Rather temporal processing may rely on state-dependent changes in network dynamics.

## INTRODUCTION

In his chapter "The Problem of Serial Order in Behavior," Karl Lashley (1951) was among the first neurophysiologists to broach the issue of temporal processing.

> 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.

Lashley emphasized the inherently temporal nature of our environment. He explains that without an understanding of the neural mechanisms underlying our

ability to process the order, interval, and duration of sensory and motor events, it is not possible to gain insight into how the brain processes complex real-world stimuli.

All sensory and motor processing ultimately relies on spatial-temporal patterns of action potentials. For the purpose of this review it is useful to draw clear distinctions between spatial and temporal processing. We use the former term to refer to the processing of stimuli defined by which sensory neurons are activated. For example, in the visual domain the orientation of a bar of light can be determined based on a static snapshot of active retinal ganglion neurons. Similarly, the discrimination of the pitch of two high-frequency tones (that activate different populations of hair cells in the cochlea), or the color of a bar of light, or the position of a needle prick to the skin, can be discriminated solely upon the spatial patterns of activation, that is, by which afferent fibers are active. In contrast, other stimuli, such as the duration of a flashed bar of light or the interval between two tones, cannot be characterized by a snapshot of neural activity. These stimuli require the nervous system to process the temporal pattern of incoming action potentials. We refer to the analysis of these stimuli as temporal processing. In contrast to these simple examples, most sensory stimuli are not purely spatial or temporal but, like speech and motion processing, require analysis of the spatial-temporal patterns of activity produced at the sensory layers.

In the 50 years since Lashley's chapter, much progress has been made on understanding the neural basis of sensory and motor processing; however, much of this progress has been made regarding the spatial components of processing. Hebb's postulate, published two years before Lashley's chapter on temporal integration, plays a fundamental role in our understanding of spatial processing. Hebbian or associative synaptic plasticity presents a means by which neurons can develop selectivity to spatial input patterns, and it provides the underlying basis for the emergence of self-organizing maps (e.g., von der Malsburg 1973, Bienenstock et al. 1982, Miller et al. 1989, Buonomano & Merzenich 1998a). In contrast, associative plasticity alone cannot underlie the discrimination of a 100- or 125-ms presentation of a vertical bar or a 2-kHz tone.

Here we review the behavioral, electrophysiological, and theoretical data on temporal processing. We first define the different timescales over which the brain processes information and then focus on temporal processing in the range of a few milliseconds (ms) up to a second.

## SCALES AND TYPES OF TEMPORAL PROCESSING

The terms temporal processing, temporal integration, and timing are used to describe a number of different phenomena. One source of ambiguity is that these terms are used to refer to a wide range of timescales over which animals process time or generate timed responses. This range spans at least 12 orders of magnitude—from microseconds to circadian rhythms. Based on the relevant timescales and the presumed underlying neural mechanisms, we categorize

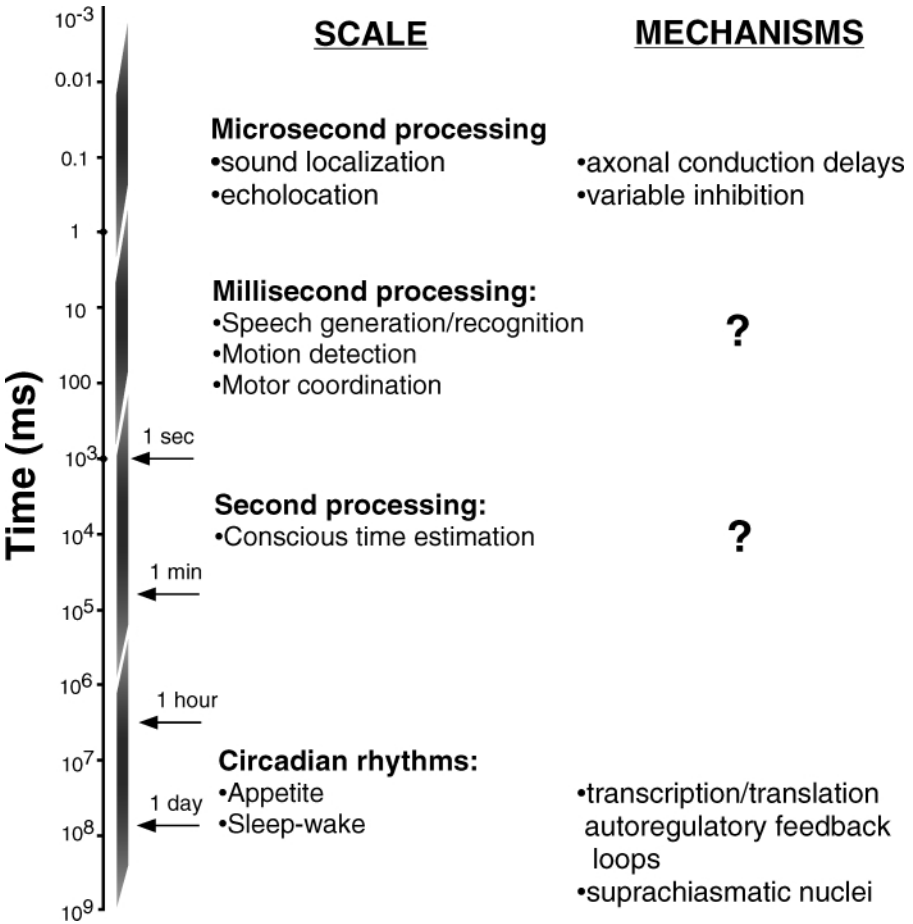


**Figure 1** Timescales of temporal processing. Humans process temporal information over a scale of at least 12 orders of magnitude. On one extreme we detect the delay required for sound to travel from one ear to the other. These delays are on the order of tens to hundreds of microseconds. On the other 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 ms is probably the most sophisticated and complex form of temporal processing and is fundamental for speech processing and fine motor coordination. Time estimation refers to processing in the range of seconds and minutes and is generally seen as the conscious perception of time.

temporal processing into four different time scales (Figure 1): microseconds (Carr 1993, Covey & Casseday 1999), milliseconds (Buonomano & Karmarkar 2002), seconds (Gibbon et al. 1997), and circadian rhythms (King & Takahashi 2000). These general classes are not meant to represent purely nonoverlapping types of processing or indivisible categories. Rather, they probably reflect the minimal set

of categories that serve different functions and rely on different mechanisms yet, nevertheless, exhibit significant overlap. Although there are numerous issues of interest at all these scales, here we focus on temporal processing on the scale of tens to hundreds of ms.

## Temporal Processing Versus Temporal Coding

Another important distinction and source of confusion is the difference between temporal coding and temporal processing (Figure 2). We refer to temporal processing as the decoding of temporal information or the generation of timed motor responses. In its simplest form, temporal processing may consist of neurons that respond selectively to the interval between two events. By definition, to process temporal information, one must start with spike patterns in which information is encoded in the temporal domain. In the sensory domain we focus on cases in which the temporally encoded information arises directly from external stimuli (e.g., duration discrimination, Morse code, rhythm perception, etc.). In addition to these external temporal codes, theoretical and experimental data suggest that temporal

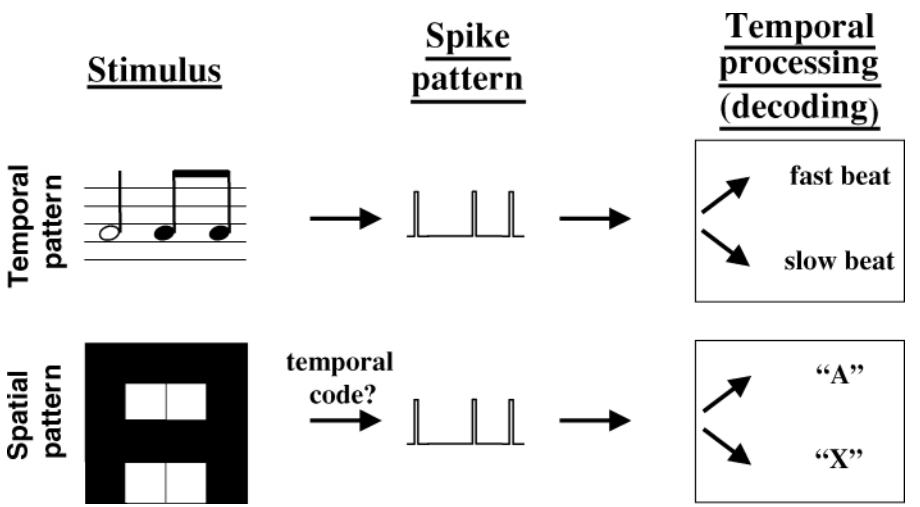


**Figure 2** Temporal processing and temporal coding. (*Upper panel*) Temporal processing refers to decoding of temporal information arriving from environmental stimuli such as music (*left*). A stimulus such as a piece of music will generate temporal patterns of action potentials that follow the beat of the music (*middle*). These action potential patterns must be decoded in order to decide whether the stimulus was played at a fast or slow tempo (*right*). (*Lower panel*) Spatial stimuli such as a statically flashed image of a letter (*left*) generate spatial patterns of action potentials. Even in response to a rapid spatial stimulus, all neurons will not fire in synchrony, and it is possible that temporal codes for spatial stimuli may be generated at early states of sensory processing (*middle*). In principle, this temporal encoding of spatial stimuli might be used by the brain for stimulus processing. However, the temporal code would also have to be decoded (*right*) as with stimuli that are inherently temporal in nature.

codes may also be internally generated. That is, static or steady-state stimuli may be partially encoded in the temporal patterns of spikes (e.g., Richmond et al. 1990, McClurkin et al. 1991, Middlebrooks et al. 1994, Laurent et al. 1996, Rieke et al. 1996, Mechler et al. 1998, Prut et al. 1998). For example, by taking into account the temporal structure of neuronal responses to static Walsh patterns there is more information about the stimuli than there is in the firing rate alone (McClurkin et al. 1991). Mechler et al. (1998) have shown that there is significant information about the contrast of transient stimuli in the temporal pattern of V1 neuron firing. Internally generated temporal codes may provide a means to increase the bandwidth (Rieke et al. 1996) or to perform computations such as invariant pattern recognition (Buonomano & Merzenich 1999, Wyss et al. 2003).

Although the studies above suggest that in some cases there is information in the temporal pattern of action potentials generated internally, there are few data showing that the brain uses this information (see, however, Stopfer et al. 1997). If internal temporal codes are generated by the brain, they must be decoded or processed, like the external temporal patterns discussed here.

## SENSORY TIMING

Temporal information in the range of tens to hundreds of ms is fundamental to many forms of sensory processing. Motion processing is a ubiquitous example in the auditory, somatosensory, and visual domains of a task that requires temporal information. However, it is arguably in the auditory domain that timing is most prominent, owing to its importance in vocalization and speech recognition.

A good example of the ability of the auditory system to process temporal signals is Morse code, in which language is reduced to temporal code. First, Morse code requires discriminating the duration of single tones (short versus long) and the interval between them (element, letter, and word pauses). Second, it requires perception of a sequence of tones, which represent auditory objects (letters and words). Third, the timing of the stimuli is not absolute but rather a function of the speed of transmission. At 15 words per minute (wpm), each dot and dash and interelement and intercharacter pause are 80, 240, 80, and 240 ms, respectively. Experts can understand Morse code at rates of 40–80 wpm; at 40 wpm the above elements' values are 30, 90, 30, and 90 ms, respectively. Thus, Morse code requires discrimination of continuous streams of sounds and discrimination of the duration, interval, number, and sequence of elements, as well as temporal invariance. The complexity of this analysis provides an example of the sophistication of temporal processing on the timescale of tens to hundreds of ms.

### Speech Recognition

To nonexperts, Morse code at high speed sounds much like noise, and considerable training is required to understand it. However, in many ways it is a simpler task than speech recognition, which shares much of the temporal richness of Morse code but exhibits additional features such as prosody, spectral information, and

speaker-specific recognition. During continuous speech, syllables are generated every 200–400 ms. The sequential arrangement of syllables is important in speech recognition (e.g., "la-dy" × "de-lay"). The pauses between syllables or words are also critical for parsing, as in "black bird" × "blackbird," or for example, the ambiguity in the mondegreen "kiss the sky" × "kiss this guy" can be decreased by longer interword intervals. The temporal structure within each syllable and phoneme also contributes to speech recognition. Specifically, temporal features are fundamental for phoneme discrimination. These features include voice-onset time (the time between air release and vocal cord vibration), which contributes to the "ba" × "pa" discrimination (Lisker & Abramson 1964), the duration of frequency transitions (e.g., "ba" × "wa"; Liberman et al. 1956), and the silent time between consonants and vowels (e.g., "sa" × "sta"; Dorman et al. 1979). Additionally, prosodic cues such as pauses and duration of speech segments are used to determine semantic content (Lehiste et al. 1976).

Owing to the multiple levels and scales of temporal information in addition to spatial information, speech is one of the most complex forms of pattern recognition and requires both spatial and temporal processing (Shannon et al. 1995, Tallal 1994, Doupe & Kuhl 1999). Various lines of evidence have revealed the degree to which speech recognition relies on temporal information. Indeed, in some cases it can rely primarily on the temporal structure. For example, experiments with cochlear implants show it is possible to achieve good levels of speech comprehension with 2–4 electrodes (Dorman et al. 1989, Dorman et al. 1997). Additionally, Shannon et al. (1995) showed that speech recognition could be achieved with relatively little spectral information. Near-perfect recognition of vowels, consonants, and sentences was observed with four broad spectral bands, and significant recognition of consonants and vowels was seen with a single band, in which only temporal and amplitude information was available.

Given the importance of temporal information in speech and language it would be expected that deficits in temporal processing would produce language deficits. Indeed, it has been suggested that certain forms of language-based learning disabilities may be caused by generalized sensory deficits in temporal processing (Livingstone et al. 1991, Eden et al. 1996, Tallal & Piercy 1973; for a review see Farmer & Klein 1995). However, even if some forms of language-based learning disabilities result from generalized sensory deficits, it is not yet clear whether those deficits are specific to timing or to more general features such as complex stimuli or rapidly changing stimuli.

## MOTOR TIMING

Because movements involve changes in muscle length over time, motor control and timing are inextricably related. Most movements involve the coordinated activation of agonist muscles to initiate motion and antagonist muscles as a brake. These activations require accurate timing on the order of tens of ms. Indeed, pathologies

that disrupt the timing between agonist and antagonist actions lead to dysmetric or inaccurate movements. Lesions of the cerebellum, for example, tend to delay the activation of antagonist muscles, which causes movements to be hypermetric or to overshoot (e.g., Hore et al. 1991). Cerebellar patients often display oscillating-like tremors during movements as they make a series of overshoots and corrections. A recent study shows that for saccade eye movements, which also involve agonist muscles to initiate and antagonist muscles to brake, the activity of populations of cerebellar Purkinje cells precisely encodes the onset and offset of a saccade (Thier et al. 2000). Motor control represents a clear example of an inherently timing-intensive computation in the range of tens to hundreds of ms.

Numerous studies focusing on timing have made use of repetitive movements as their readout. In particular, Keele, Ivry, and others have used such movements as rhythmic tapping of the finger to pursue the hypothesis that the cerebellum is a general-purpose timer in the tens-to-hundreds-of-ms range (e.g., Ivry & Keele 1989). In the prototypical experiment, subjects are first asked to tap their finger in time with a metronome (say at 400-ms intervals). After a brief training period, the subject continues tapping without the metronome. The main dependent measure is variability in the intertap intervals. This and similar paradigms have been used as screens to find brain regions for which damage disturbs the timing of the taps. These and related findings are discussed in more detail below in the section on the cerebellum.

## Timed Conditioned Responses

One of the more experimentally tractable forms of motor timing is seen in the precise learned timing of classically conditioned eyelid responses. In a typical eyelid-conditioning experiment, training consists of repeated presentation of a tone paired with a reinforcing stimulus such as an air puff directed at the eye. Over the course of 100–200 of such trials the animals acquire conditioned eyelid responses: The eyelids close in response to the tone (Figure 3*a*). The time interval between the onsets of the tone and the puff influences the nature of this learning (Figure 3*b*). Conditioned responses are acquired only when the tone onset precedes the puff by at least 100 ms and by less than ~3 s. Within this range, the timing of the conditioned responses is also affected by the tone-puff time interval. Short intervals promote the learning of responses with short latencies to onset and fast rise times. As the interval increases, the learned responses have longer latencies to onset and slower rise times. The result is that, in general, the responses peak near the time at which the puff is presented.

Several studies have demonstrated that these responses are a genuine example of timing and exclude the previously generally accepted alternative that response timing derives from response strength. For example, Millenson et al. (1977) and Mauk & Ruiz (1992) trained animals by presenting the puff on alternate trials at two different times during the tone. The responses the animals learn have two peaks, each corresponding to one of the times at which the puff was presented.

## PSYCHOPHYSICAL STUDIES

The predominate working hypothesis in the psychophysical literature has been a centralized internal clock model (Creelman 1962, Treisman 1963; for a review see Allan 1979), in which an oscillator beating at a fixed frequency generates tics that are detected by a counter. These models often assume that timing is centralized, that is, the brain uses the same circuitry to determine the duration of an auditory tone and for the duration of a visual flash. The alternate view is that timing is distributed, meaning that many brain areas are capable of temporal processing and that the area or areas involved depend on the task and modality being used. In addition to the question of centralized versus distributed mechanisms, there is the issue of timescale specificity. A universal clock (of which there could be a single instantiation or multiple instantiations) could be the sole timing mechanism for all intervals/durations, or there could be a set of dedicated circuits, each specific to given lengths of time (referred to as interval-based mechanisms; Ivry 1996).

### Interval and Duration Discrimination

The best-studied temporal tasks in humans are interval and duration discrimination (Divenyi & Danner 1977, Getty 1975, Wright et al. 1997). In a typical interval discrimination task two brief tones separated by a standard interval (T, e.g., 100 ms) or longer interval ($T + \Delta T$) are presented to the subject. The presentation order of the short and long intervals is randomized. The subject may be asked to make a judgment as to whether the longer interval was the first or second. $\Delta T$ can be varied adaptively to estimate the interval discrimination threshold. Duration discrimination tasks are similar, except each stimulus is a continuous tone (filled interval).

The relationship between the threshold and the standard interval constrains the underlying mechanisms. Figure 4 shows the relationship between threshold and the standard interval for a compilation of interval and duration discrimination studies in the range of tens of ms to one second. In untrained subjects the threshold for a 100-ms standard interval is $\sim$20 ms (Weber fraction of 20%). Note that although in absolute terms the threshold increases with increasing intervals, the Weber fraction (threshold/standard interval) decreases for short intervals (50 to 200 ms). For intervals from 200 to 1000 ms, the Weber fraction is fairly constant, perhaps suggesting that different neural mechanisms are responsible for interval discrimination at these intervals.

INTERMODAL TIMING Psychophysical studies have attempted to address the issue of centralized versus distributed timing by comparing performance on intra- versus intermodal tasks. In the intermodal tasks a standard interval may be demarcated by a tone at 0 ms and a flash of light at 100 ms. Performance on the intermodal condition is then compared to pure auditory and visual discrimination. The first observation that comes from these studies is that interval discrimination

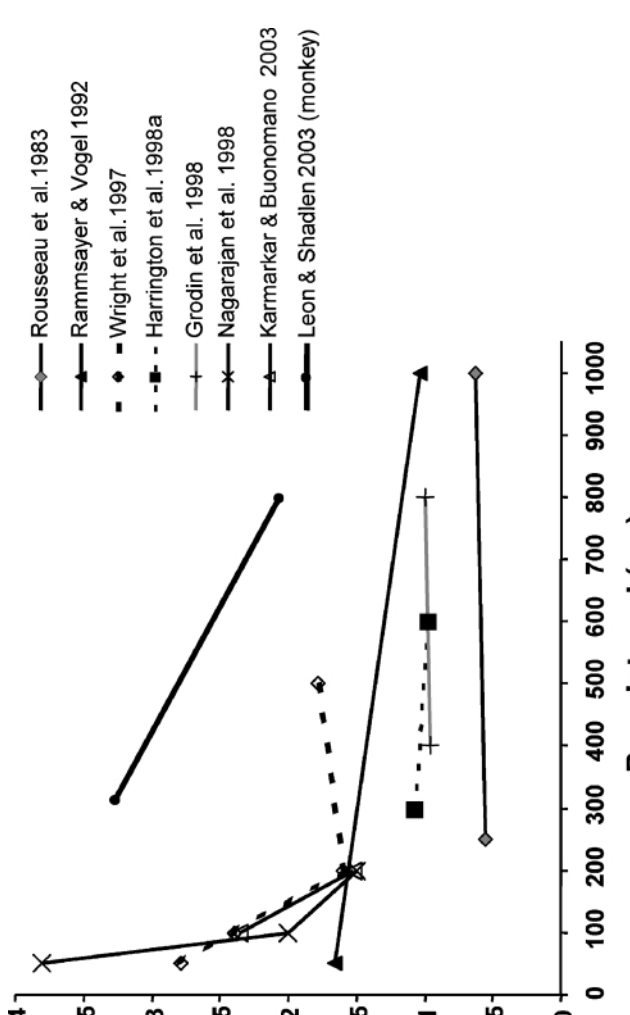


**Figure 4** Cross-study interval discrimination thresholds. The standard or base interval is represented on the X axis, and thresholds are plotted in the Y axis as Weber fractions (threshold/standard interval). Thresholds are calculated differently in different studies, thus comparing absolute thresholds across studies is not appropriate. Lines join the thresholds from different intervals within studies. These data indicate that, at short intervals, temporal discrimination thresholds do not follow a Weber fraction. However, at longer intervals, above 200 ms, thresholds are fairly constant in relation to the standard interval.

in the auditory modality is better then that in the visual modality (Rousseau et al. 1983, Grondin & Rosseau 1991). Additionally, these studies show that interval discrimination between modalities is significantly worse than that within modalities (Rousseau et al. 1983, Grondin & Rousseau 1991, Westheimer 1999). Specifically for standard intervals in the range of 100–250 ms, the threshold for tone-light discrimination can be 50%–300% worse than for light-light discriminations. Interestingly, Rousseau et al. (1983) showed that intermodal discrimination was significantly more effected for a 250-ms interval as compared to a 1-s interval. Within a modality, changing stimulus features also decreases performance. If the first tone is played at 1 kHz and the second tone is played at 4 kHz, interval discrimination is significantly worse than if both tones were played at the same pitch (Divenyi & Danner 1977).

These data are consistent with the notion of distributed timers. Specifically, because the stimulus features that delimit the interval in a cross-modality task are arriving at different timers, performance is decreased. However, an alternative explanation is that timing is still centralized, but intermodal timing is simply a more difficult task because it requires a shift of attention from one modality to the other.

## Psychopharmacology of Temporal Processing

On the timescale of seconds, dopamine antagonists produce temporal overshoot, and stimulants such as methamphetamine produce temporal undershoot (for a review see Meck 1996). On the timescale of a second and below, Rammsayer (1999) has shown in human psychophysical experiments that the dopaminergic antagonist, haloperidol, significantly impaired discrimination thresholds for 100-ms and 1-s intervals. Remoxipride, a dopamine antagonist more selective for D2 receptors, impaired processing on the scale of a second but not for a 50-ms interval (Rammsayer 1997). Experiments with benzodiazepines also support the dissociation between millisecond and second processing by showing that performance in a 50- or 100-ms task is unaffected, whereas performance in a 1-s task is significantly worse (Rammsayer 1992, 1999). Together these results show that two distinct drug classes (dopaminergic antagonists and benzodiazepines) can selectively interfere with second but not with millisecond processing. Future experiments will be necessary to determine whether the above results are due to direct action on a timing mechanism or to more nonspecific actions on arousal and/or cognition.

## Interval Discrimination Learning

Can temporal resolution improve with practice? One of the first studies on this issue reported no perceptual learning (Rammsayer 1994). In this study, subjects were trained on 50-ms intervals for 10 min a day for 4 weeks. Subsequent studies revealed robust learning with training (Wright et al. 1997, Nagarajan et al. 1998, Karmarkar & Buonomano 2003). In these studies subjects were generally trained for an hour a day (400–800 trials) for 10 days.

GENERALIZATION OF INTERVAL DISCRIMINATION The perceptual learning studies, in addition to suggesting that the neural mechanisms underlying timing can be fine-tuned with experience, provide a means to examine the issue of central versus distributed timing. We can ask, after training on 100-ms intervals using 1-kHz tones, if performance improves for different intervals and frequencies.

Generalization studies reveal that interval discrimination learning is specific to the temporal domain, and generalization occurs in the spatial domain (Wright et al. 1997, Nagarajan et al. 1998, Westheimer 1999, Karmarkar & Buonomano 2003). Figure 5 shows the results from a study in which subjects were trained on a 100-ms–1-kHz interval discrimination task. Subjects were pre- and posttested on conditions that varied across the temporal and spatial domain: 100-ms–4-kHz, 200-ms–1-kHz, and a 100-ms–1-kHz continuous tone condition. Generalization to the 100-ms–4-kHz tone was virtually complete, and there was no generalization to the 200-ms interval. This eliminates the possibility that learning was due to a nonspecific improvement such as task familiarization.

Interval learning has also been reported to generalize across modalities. Nagarajan et al. (1998) show that training on a somatosensory task can produce

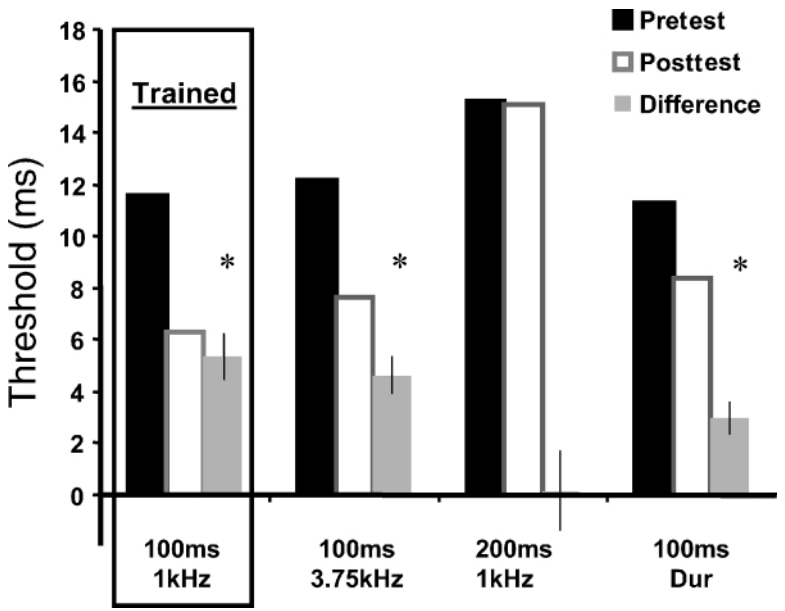


**Figure 5** Generalization of interval discrimination learning. A group of 10 subjects underwent training on a 100-ms–1-kHz interval discrimination task. After 10 days of training (an hour a day), they exhibited significant learning (*left bars*). Pre- and posttests on 3 different conditions revealed generalization to the same interval played at a different frequency, as well as to the duration discrimination task (continuous tone) at the same absolute time (100 ms). However, no generalization to novel intervals was observed. Modified from Karmarkar & Buonomano 2003.

improvement on an auditory interval discrimination task similar to the interval used for somatosensory training. 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 et al. 2000).

The simplest interpretation of these data is that centralized circuits exist for each interval, and with training, either the temporal accuracy or the downstream processing of these circuits undergoes plasticity. In this interpretation, timing is centralized but interval based. However, 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 tasks require comparing the test interval and a standard interval, improvement could rely on better representation of the standard interval or improved storage or retrieval from working or short-term memory. Such alternative explanations would be consistent with the generalization across different stimulus markers and modalities, as well as the lack of generalization to novel intervals. Alternatively, it could be argued that, although many circuits are capable of temporal processing, the relatively simple nature of these temporal tasks allows the brain to use multimodal pathways and a single timing circuit.

## TEMPORAL SELECTIVITY AND ANATOMICAL LOCALIZATION

A fundamental step in understanding the neural basis of temporal processing is finding neurons that are selective to the temporal features of sensory stimuli or responsible for the generation of timed motor responses. To date, interval, duration, or temporal-combination sensitive neurons have been described in a variety of different systems. These findings range from simple interval or duration-sensitive cells in bats and amphibians to more complex temporal-combination sensitive cells involved in song-selectivity in birds. Below we examine the electrophysiological and anatomical data that address the potential mechanisms and location of temporal processing. We believe that the range of tasks and behaviors that rely on temporal processing, and the number of areas putatively involved, suggest that temporal processing is distributed and a ubiquitous intrinsic property of neural circuits.

### Brainstem: Frogs and Bats

To communicate, some anuran amphibians (frogs and toads) use vocalizations rich in temporal information. The temporal structure of some frog calls is used to discriminate between vocalizations (Klump & Gerhardt 1987, Rose & Brenowitz 2002). Specifically, calls can be distinguished based on the number and frequency of pulses. Alder & Rose (1998, 2000) show that neurons in the auditory midbrain can be tuned to both the frequency and the number of auditory pulses. Selectivity was not sensitive to intensity. Neurons exhibited a preferred pulse frequency (e.g., 80 Hz) at which they would produce their maximal number of spikes. Lower or

higher frequencies elicited fewer or no spikes. These studies provide an elegant example of temporal tuning curves, a temporal analog to orientation tuning curves in V1 neurons. It is not yet known whether the temporal tuning arises primarily from synaptic/cellular or network properties.

Neurons in the bat auditory brainstem also respond selectively to specific temporal features such as the pulse-echo delay and sound duration (Covey & Cassidy 1999). Neurons in the inferior colliculus can be tuned to pulse-echo delays or to sounds of specific durations. Temporal tuning in these cells is known to rely on inhibition (Casseday et al. 1994, Saitoh & Suga 1995). One hypothesis is that stimulus onset produces inhibition, and the offset of inhibition causes rebound depolarization. If this rebound coincides with the second excitatory input (produced by sound offset), a duration-specific response can be generated. However, this mechanism may be a specialized brainstem process, and it is not clear if it will generalize to more complex patterns (see below).

## Temporal Selectivity in Songbirds

One of the best-studied systems regarding temporal processing is in songbirds. Similar to human language the songs of birds are rich in temporal structure and composed of complex sequences of individual syllables. Each individual syllable and the interval between syllables is on the order of tens of ms to 200 ms. The areas involved in the generation and learning of song have been identified (Bottjer & Arnold 1997, Doupe & Kuhl 1999). Song selectivity is often established by comparing the response to the normal song against the same song in reverse or reversing the syllable order. Recordings in the HVc (Margoliash 1983, Margoliash & Fortune 1992, Mooney 2000) and in the anterior forebrain nuclei (Doupe & Konishi 1991, Doupe 1997) reveal neurons that are selective to playback of the birds own song, specifically syllable sequences played in the correct order. Additionally, song selectivity of neurons in cmHV can be modified by a behavioral task requiring song discrimination (Gentner & Margoliash 2003). Thus, experience can lead to selectivity of complex temporal-spatial stimuli in adult birds.

Figure 6 shows an example of an order-sensitive cell in the HVc (Lewicki & Arthur 1996). Two syllables (A and B) are presented in all combinations with a fixed interval between them. The cell is selective to the AB sequence, and it does not respond well to either syllable individually or to BA. The order selectivity in neurons from HVc has been well established. Interval and duration selectivity have been less studied. Although, in some cases the neurons are also sensitive to the interval between sounds (Margoliash 1983, Margoliash & Fortune 1992). The mechanisms underlying this selectivity are not understood. Unlike simple detection of the interval between two tones, these cells are selective to both the spatial-temporal structure within each syllable, as well as to the sequence in which these elements are put together. This selectivity emerges in stages because neurons in earlier auditory areas of the songbird respond selectively to syllables but not to the sequence (Lewicki & Arthur 1996).

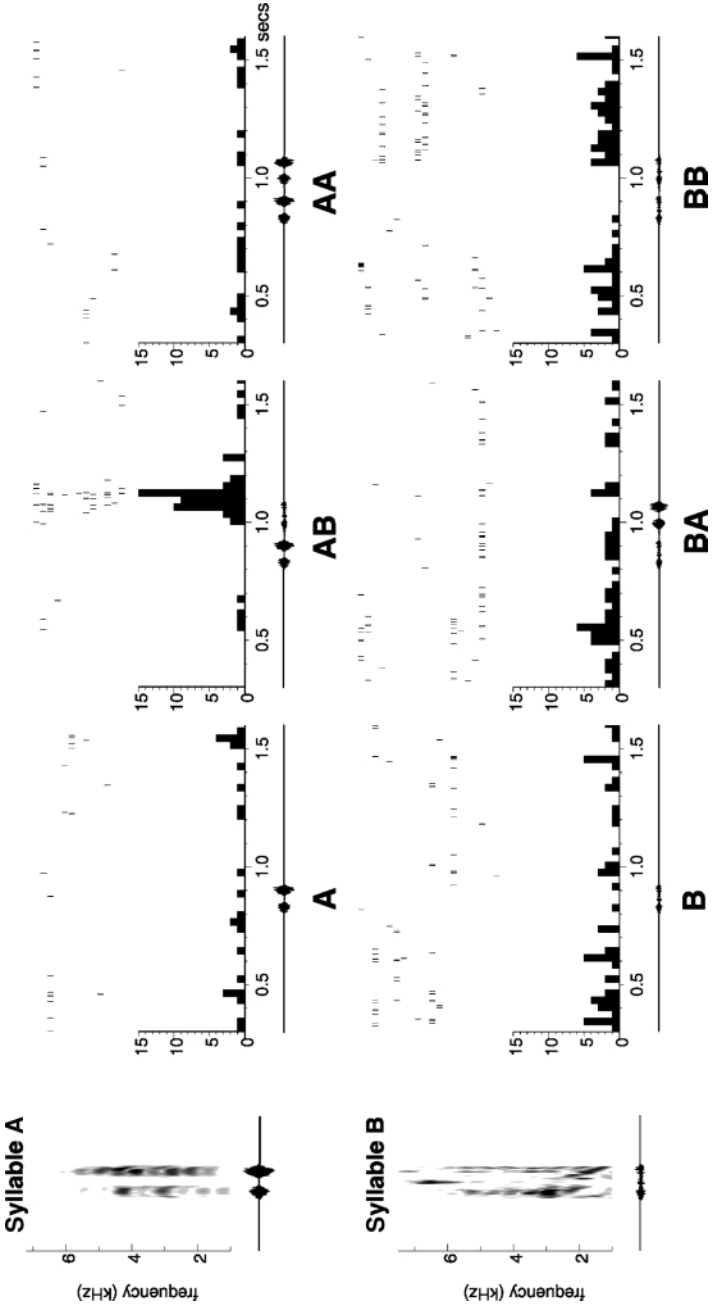


**Figure 6** Example of a temporally combination-sensitive neuron of a songbird. Recordings from a neuron in HVc in response to two syllables from the bird's own song. Spectrograms of each syllable are shown to the left. Above each histogram is the response of the neuron to each presentation of the stimuli. This cell is selective to syllable B only if preceded by syllable A. Modified from Lewicki & Arthur 1996.

Because HVc neurons can respond selectively to the auditory presentation of songs (these studies are generally done under anesthesia), these neurons are clearly sensitive to temporal information in the sensory domain. However, these same cells are also active during singing and can be activated at precise times during song production. A subset of HVc neurons may be responsible for generating the timed responses that drive the sequence of syllable production (Hahnloser et al. 2002). Whether or not this is true, it is clear that the song circuity is capable of temporal processing because cross correlations with peaks in the tens-to-hundreds-of-ms range have been reported (Hahnloser et al. 2002, Kimpo et al. 2003).

## Basal Ganglia

There are numerous studies suggesting the basal ganglia is involved in timing; however, most of the data focus on the timescale of seconds rather than in the range of tens to hundreds of ms. Much of these data relies on pharmacology studies. Specifically, drugs that act on the dopaminergic system interfere with timing. Because the basal ganglia is important in the dopaminergic system, the basal ganglia is likely involved in temporal processing (for a review, see Meck 1996). Studies of Parkinson patients, who in some cases have shown specific deficits in temporal tasks, support this claim (Artieda et al. 1992, Harrington et al. 1998a, Riesen & Schnider 2003).

Imaging studies have reported changes in BOLD signals in the basal ganglia. Rao et al. (2001) showed an increase in the BOLD signal in the basal ganglia during a duration discrimination task of 1.2 s. No significant basal ganglia activation was observed during a control frequency discrimination task using a similar stimulus protocol. Similarly, an fMRI study by Nenadic et al. (2003) revealed activation of the basal ganglia (putamen) during a 1-s duration discrimination task compared to a frequency discrimination task. This study also revealed activation of the ventrolateral prefrontal and insular cortex, but not the cerebellum, in the temporal condition.

Thus the basal ganglia likely plays a role in timing of sensory and motor events on the timescale of seconds. However, to date, there are few data that suggests involvement of the basal ganglia in temporal processing in the range of tens to hundreds of ms.

## Cerebellum

Although the cerebellum is generally viewed as primarily a motor structure, it has also been proposed to be a general-purpose interval timer in the range of tens to hundreds of ms. "General purpose" in this sense encompasses both sensory and motor timing. One advantage of such a theory is that the synaptic organization and physiology of the cerebellum are known. Much is known about the relationships between the cerebellum and forms of motor learning such as eyelid conditioning and adaptation of the vestibulo-ocular reflex (Raymond et al. 1996; Boyden et al. 2004, in this volume).

Support for the role of the cerebellum in timing is based on both motor and sensory timing experiments. Ivry and others presented a variety of evidence demonstrating cerebellar involvement in timing tasks. The fundamental observation was made in experiments in which the task required human subjects to make rhythmic taps with their finger. Analysis was based on a hypothetical construct that divides errors (tapping at the wrong time) into those attributable to motor execution versus those attributable to a timer (Wing & Kristofferson 1973). Ivry et al. (1988) showed that patients with lesions of the medial cerebellum have increased motor errors, whereas lesions that were more lateral increased timer errors. Cerebellar patients also display deficits in interval discrimination (Ivry & Keele 1989) and are impaired at judging the speed of moving visual targets (Ivry & Diener 1991, Nawrot & Rizzo 1995). Ackermann and colleagues (1997) observed that patients with lateral cerebellar lesions are impaired in their ability to discriminate phonemes that differ only in the timing of consonants. Imaging studies also suggest a potential connection between timing and the lateral neo-cerebellum in humans. PET imaging was used to detect activation in lateral portions of the cerebellum during an interval discrimination (Jueptner et al. 1995).

The timing hypotheses of cerebellar function attempt to explain the various tasks for which the cerebellum is engaged or is necessary in terms of the need to gauge the explicit timing between events in the hundreds-of-ms range. Despite the intent that these theories build on a computational base, supporting data remain mostly task-based. Most data involve demonstrations that the cerebellum is activated during, or is required for, tasks that we view as examples of timing.

CEREBELLUM IN TIMING OF CONDITIONED RESPONSES Lesions and reversible inactivation studies have shown that learned response timing of conditioned eyelid responses is mediated by the cerebellar cortex. Perrett et al. (1993) used a within-subject design to demonstrate the effect of cerebellar cortex lesions on eyelid response timing. Animals were trained to make a fast response to one tone and a slower response to a second tone. Using this two-interval procedure, it was demonstrated that lesions of the cerebellar cortex in already trained animals spare conditioned responses but abolish response timing (Figure 3*c*). The results demonstrated that the lesions do not produce a fixed shift in timing. Rather, the postlesion timing defaults to a short, fixed latency independent of the prelesion timing. Subsequent studies have replicated this effect on response timing using reversible inactivation techniques. Garcia & Mauk (1998) showed that disconnection of the cerebellar cortex with infusion of a GABA antagonist into the cerebellar interpositus nucleus (the downstream target of the relevant region of cerebellar cortex) also cause response timing to default to very short latency (Figure 3*d*). Recent studies have demonstrated similar results with infusions of lidocaine in the cerebellar cortex (W.L. Nores, T. Ohyama & M.D. Mauk, manuscript in preparation).

The implications of conditioned eyelid response timing involve much more than the finding that the cortex of the cerebellum is necessary. Eyelid conditioning is an especially useful tool for studying the input/output computations of the cerebellum,

owing to the relatively direct ways in which eyelid conditioning engages the cerebellum. Several decades of research, beginning with the studies of Thompson and his colleagues (e.g., Thompson 1986) have solidified three important findings in this regard (see Figure 7):

1. During eyelid conditioning the conditioned stimulus, often a tone, is conveyed to the cerebellum via activation of mossy fiber afferents from the pons.
2. Similarly, the reinforcing or unconditioned stimulus, usually a mild shock around the eye from a puff of air directed at the eye, is conveyed to the cerebellum via climbing fiber afferents from the inferior olive.
3. Output from the cerebellum, in the form of increased activity of particular neurons in the cerebellar interpositus nucleus, drives the efferent pathways responsible for the expression of the learned responses.

Because of these three findings, the extensively characterized behavioral properties of eyelid conditioning can be applied as a first approximation of what the cerebellum computes (Mauk & Donegan 1997, Medina et al. 2000, Medina & Mauk 2000, Ohyama et al. 2003).

The involvement of the cerebellum in both interval timing tasks and in the timing of learned responses raises the question: Is the computation performed by the cerebellum best understood as an interval timer or clock, or does cerebellar involvement in eyelid conditioning reveal a more learning-related computation? Based on recent evidence we support the latter. Specifically, cerebellar involvement in both tasks can be explained by the hypothesis that the computation performed by the cerebellum is a learned, feed-forward prediction. Additionally, the temporal portion of the computation would not rely on fixed timers or clocks but instead on network mechanisms that can perform both temporal and spatial computations. Several authors have argued that the cerebellum makes a feed-forward prediction, or generates forward models (e.g., Ito 1970, Kawato & Gomi 1992). Here we focus on the feed-forward computation itself and implications of its temporal specificity. Although it is easier to introduce the feed-forward prediction idea in the context of motor control, the computation is presumably applicable to nonmotor tasks influenced by the cerebellum as well (see Schmahmann 1997).

FEED-FORWARD PREDICTION AND THE CEREBELLUM To help make movements accurate, sensory input can be used in two general ways: feedback and feed-forward. Feedback is like a thermostat; outputs are produced by comparing sensory input with a target. When input from its thermometer indicates the room is too cold, a thermostat engages the heater. Although accuracy is easily achieved with feedback, it has the inherent disadvantage of being slow. Adjustments are only possible once errors have already occurred.

In contrast, feed-forward use of sensory input can operate quickly but at the cost of requiring experience through learning. To react to a command to change

room temperature quickly, a hypothetical feed-forward thermostat would predict the heater blast required from current sensory input. This prediction would draw upon previous experience and require associative learning in which error signals were used to adjust decision parameters for errant outputs. If our hypothetical feed-forward thermostat undershoots the target temperature, then learning from the error signal should adjust the connections of recently activated inputs so that in subsequent similar situations the heater is activated a little longer. Thus, through associative, error-driven learning it is possible to acquire the experience necessary to make accurate feed-forward predictions.

Eyelid conditioning reveals that cerebellar learning displays precisely these properties (see Mauk & Donegan 1997, Ohyama et al. 2003). Learning associated with feed-forward prediction should be associative, and there should be a precise timing to the association. An error signal indicates that the prediction just made was incorrect. For example, an error signal activated by stubbing one's toe when walking indicates that in similar circumstances the leg should be lifted higher. Thus, error signals should modify feed-forward predictions for the inputs that occurred approximately 100 ms prior (Figure 8*a*). This means the results of the learning will be timed to occur just prior to the time error signals arrive. Eyelid conditioning displays these properties. The conditioned responses are timed to occur just before the time at which the error signal (puff to the eye) normally occurs (Figure 8*b*).

The timing displayed by conditioned eyelid responses reveals both temporal specificity and flexibility to this associative learning, both in ways that are useful for feed-forward prediction. Timing specificity is revealed in the way conditioned eyelid responses are time locked to occur just before the arrival of the puff. This is consistent with what feed-forward associative learning must accomplish. When a climbing fiber error signal arrives, learning should selectively alter the cerebellar output that contributed to the faulty movement. Thus, learning should produce changes in output that are time locked to occur around 100 ms prior to the climbing fiber input, as is seen in the timing of eyelid responses. The flexibility of the timing is revealed by the way in which eyelid conditioning can occur with a range of time intervals between the onsets of the tone and puff. Even though learning can occur for mossy fiber inputs that begin 100 to ~2500 ms prior to the climbing fiber input, the changes in output remain time locked to occur just before the climbing fiber input (Figure 8*b*). To accomplish this, the learning must have the capacity to delay the responses with respect to the onset of the mossy fiber input—again, as eyelid conditioning reveals. These examples show the utility for feed-forward control of learning that is time locked to occur just before error signals (when the decisions actually have to be made) but that can vary with respect to the timing of predictive sensory signals (see Ohyama et al. 2003).

TEMPORALLY SPECIFIC FEED-FORWARD PREDICTION AND TIMING Considering cerebellar function in terms of its feed-forward computation provides an example of the cerebellum's role in timing. Feed-forward prediction helps determine the force required for agonist muscles and the force and timing of activating

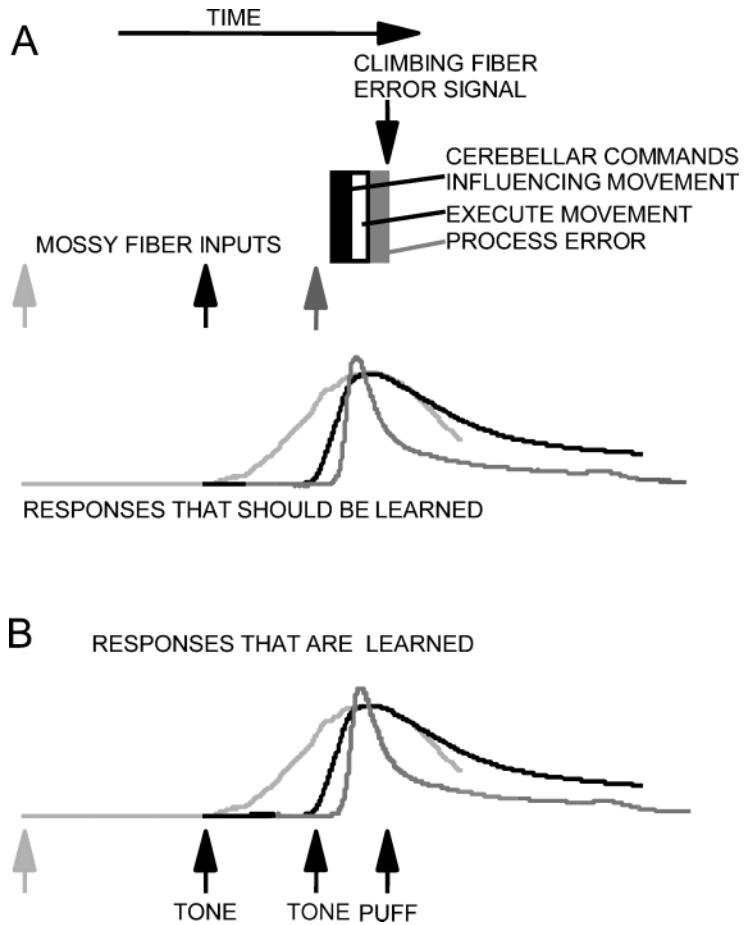


**Figure 8** Feed-forward learning is enhanced by temporal specificity. (*A*) A schematic representation of the timing required for error-driven associative learning supporting feed-forward predictions. A climbing fiber input to the cerebellum (*gray*) signals movement error as detected by an inappropriate consequence (e.g., stubbing the toe while walking). The cerebellar output that contributed to this errant movement (*black*) occurred approximately 100 ms prior, owing to the time required to execute the movement (*white*) and the time required to detect the error and convey the signal to the cerebellum. To improve subsequent performance, learning must alter cerebellar output for the time indicated by the black region. Because mossy fiber inputs that predict this error may occur at varying intervals prior to the output commands (*light gray, black, and dark gray*), the cerebellar learning mechanism must be able to delay learned responses elicited by the mossy fiber input so that they can be time locked to occur just before arrival of the error signal (*corresponding light gray, black, and dark gray traces*). (*B*) The learned timing of eyelid responses indicates that cerebellar learning displays temporal specificity in its learning. Response timing is delayed with respect to the tone (mossy fiber) onset so that it can be time locked to peak when the puff (climbing fiber) occurs.

antagonist muscles. Deficits from the absence of this contribution would be especially notable for movements that involve stopping and starting, as in the timing experiments that require finger tapping. This is consistent with the deficits seen from medial cerebellar damage (vermal and intermediate cerebellum), whose outputs contribute relatively directly to movement execution through descending pathways.

This view is also consistent with recent findings that apparent timing deficits are specific to discontinuous timing tasks relative to continuous ones. Spencer et al. (2003) tested cerebellar patients on two similar timing tasks. Two groups of subjects were required to draw circles at regular intervals. The "discontinuous" group was required to keep a beat by pausing at the top of each circle. The "continuous" group was instructed to keep a beat by drawing circles using a steady continuous motion. Cerebellar damage affected discontinuous drawing and not continuous. The authors interpret these findings as evidence that the cerebellum is required for tasks where timing is explicitly represented, as in the discontinuous task. In this view, the cerebellum is not required by the continuous task because timing can be implicit—that is, timing can be produced by maintaining a constant angular velocity. Alternatively, such findings can be seen as examples of the contributions of feed-forward prediction in the starting and stopping of movements. Holmes (1939) made a similar observation (see also Dow & Moruzzi 1958). He asked a patient to first draw squares with the hand affected by the cerebellar lesion and then by the unaffected hand. Holmes found that the motor deficit of the affected hand was most notable at the corners of the square, where stopping and starting movements are required.

Although more speculative, the feed-forward computation of the cerebellum may provide a way to understand the activation of the cerebellum in many timing tasks and explain the timing deficits observed with lateral cerebellar damage. Feed-forward prediction in lateral cerebellum may be a mechanism for predicting when the next tap should occur in a timing experiment. The cerebellum therefore underlies some forms of motor timing. This timing relies on distributed network mechanisms as opposed to a dedicated clock or timer (see below).

## CORTEX

The cortex has also been proposed to be the the primary site for temporal processing. If the cortex is involved in timing, whether virtually all cortical areas can processes time, or if specialized cortical areas devoted to temporal processing exist, is a fundamental issue.

### Anatomy

Based on data from stroke patients Harrington et al. (1998b) suggested the right parietal cortex may be involved in temporal processing. Specifically, right hemisphere, but not left hemisphere, lesions produced a deficit for 300- and 600-ms

interval discrimination. Imaging studies also reported changes in blood flow during temporal tasks in various cortical areas. In a PET study Belin et al. (2002) report activity in the right fronto-parietal network and prefrontal cortex during a 300-ms duration discrimination task. However, this study did not include a control task, and thus activation could be related to any form of processing. A second PET study in the visual modality reported activation in a number of cortical areas during a 700-ms duration discrimination task but no significant difference regarding an intensity discrimination task (Maquet et al. 1996). Onoe et al. (2001) showed activation of the dorsolateral prefrontal cortex in a monkey PET study. This study used a visual duration discrimination task in the range of 400 to 1500 ms. They report activation of the dorsolateral prefrontal cortex. Although there was no control task, they did report that bicuculline administration to the dorsolateral prefrontal cortex impaired duration discrimination more so than position discrimination.

Two fMRI studies revealed specific increases in BOLD signal, and both reported activation of the right parietal and dorsolateral prefrontal cortex (Rao et al. 2001, Nenadic et al. 2003). In both these studies the increases were in comparison to a pitch discrimination task using stimuli in the 1-s range. As mentioned above, both these studies also revealed increased signal attributed to temporal processing in the basal ganglia but not in the cerebellum.

## Electrophysiology

In addition to imaging data a few studies attempted to find, in the mammalian cortex, neurons that respond selectivity to temporal features. Vocalization-sensitive neurons were reported in primary auditory cortex of marmoset monkeys (Wang et al. 1995). Neurons responded more robustly to conspecific vocalizations compared to the same vocalization played in reverse. Additionally, vocalization-sensitive neurons were also reported in early auditory areas of Rhesus monkeys (Rauschecker et al. 1995). Creutzfeldt et al. (1989) described speech-specific neural responses in the human lateral temporal lobe. However, to date, no areas have been described in which the neurons exhibit the same degree of selectivity to vocalizations as that observed in songbirds. Other investigators have looked for combination or interval-sensitive neurons using tone pairs or sequences. Selectivity has been observed in primary auditory areas in cat (McKenna et al. 1989, Brosch & Schreiner 1997) and monkey (Riquimaroux 1994). Kilgard & Merzenich (1998, 2002) characterized the temporal selectivity of auditory cortical neurons to sequences of tones. In one study three element sequences such as high tone (H), low tone (L), noise burst (N) were paired with basal forebrain stimulation in awake rats (Kilgard & Merzenich 2002). A significant increase was reported in the number of sites that exhibited facilitated responses to the target sequence, indicating experience-dependent plasticity. For example, after training in H-L-N sequence, an enhanced response to N preceded by H–L was reported, as compared to N alone. The enhanced responses often generalized to degraded stimuli such as L-H-N. The temporal feature selectivity of cortical neurons undergoes experience-dependent plasticity. However, future research is necessary to determine the degree

of selectivity and whether these areas represent the primary locus for features such as interval, duration, and order.

To date, one study has looked for neurons that may code for time in awake-behaving monkeys. Leon & Shadlen (2003) recorded in the lateral intraparietal cortex in two monkeys trained on a duration discrimination task in the visual modality. Two standard durations were examined: 316 and 800 ms. The individual neurons contained information about time from stimulus onset. Time from stimulus onset was encoded in the instantaneous firing rate, which changed predictably with time. The encoding was very dynamic; specifically, the same neuron would show an upward or downward ramping of its firing rate depending on the location of the short or long target used for the response. Additionally the rate of change was slower for long durations than for short durations. Thus timing might be achieved by complex network mechanisms capable of dynamically changing firing rates in a context-specific manner. Whether the same neurons would contain temporal information if the task was auditory, or whether neurons in other areas contained the same information, has not been determined.

## In Vitro Studies

It has been proposed that cortical neural networks are intrinsically capable of processing temporal information (Buonomano & Merzenich 1995). If this is the case it may be possible to observe timed responses in vitro. In vitro studies cannot address whether the observed timing is behaviorally relevant. They can, however, establish whether neurons and neural circuits are capable of processing temporal information or whether specialized mechanisms are present. Long-latency timed action potentials in response to continuous synaptic stimulation (Beggs et al. 2000), or in response to single stimuli (Buonomano 2003), have been observed. In organotypic cortical slices, neurons can respond reliably at latencies of up to 300 ms after a single stimulus (Buonomano 2003). Thus cortical circuits are intrinsically capable of generating timed responses on timescales well above monosynaptic transmission delays. Mechanistically, timing relied on network dynamics, specifically, activity propagated throughout functionally defined polysynaptic pathways. The propagation path was a complex function of the functional connectivity within the network and was not simply a result of spatial wave-like propagation.

To date, relatively few studies have revealed cortical neurons strongly tuned to the interval or duration of tones or to complex sounds on the scale of hundreds of ms. These data contrast sharply with the tuning of cortical neurons to spatial stimuli such as orientation, ocular dominance, tonotopy, and somatotopy. It is more difficult to study temporal selectivity because temporally tuned neurons may not be topographically organized. In the visual cortex, if we record from a cell selective to vertical bars, the neighboring cells may also be tuned to vertical bars. Given the vast number of possible spatio-temporal stimuli, and the potential absence of chronotopy, it may prove difficult to localize temporal selective neurons with conventional extracellular techniques.

## NEURAL MECHANISMS AND MODELS OF TIMING

Analyses of the neural basis of timing have generally focused on three general computational strategies: mechanisms based on neural clocks, mechanisms based on arrays of elements that differ in terms of some temporal parameter, or mechanisms that emerge from the dynamics of neural networks. In general, these models must accomplish some variant of the same computational task. They must recode the temporal information present in an input into a spatial code. That is, in some way different cells must respond selectively to temporal features of the stimulus. For example, to discriminate differences in the duration of two stimuli, there must be differential neuronal responses to each duration.

### Clock Models

When considering the mechanisms of timing it is perhaps most intuitive to think in terms of clocks or interval timers. The basic computational unit of clock theories involves an oscillator and a counter (Creelman 1962, Treisman 1962). Conceptually, the oscillator beats at some constant frequency, and each beat would then be counted by some sort of neural integrator. These ideas have not yet been expressed concretely in terms of the synaptic organization of a specific brain region. Indeed, in its simplest form, if such a clock were used for the discrimination of 100-ms intervals (and allowed the discrimination of a 100- and 105-ms interval) the period of the oscillator would have to be at least 200 Hz. At the neurophysiological level, oscillating at this frequency, as well as accurately counting each beat, seems unlikely. However, as proposed by Meck and colleagues, clock-like mechanisms could be involved in timing on the scale of seconds and minutes (Meck 1996, Matell & Meck 2000).

OSCILLATOR-PHASE MODELS In addition to the oscillator/counter models mentioned above, more sophisticated models based on oscillators have been proposed (Ahissar et al. 1997, Ahissar 1998, Hooper 1998). These include the use of oscillators placed in phase-locked loop circuits. Specifically, Ahissar and colleagues have proposed (Ahissar et al. 1997, Ahissar 1998) that the thalamo → cortical → thalamo loop may use dynamic oscillators (oscillators that can change their period in an adaptive manner) to decode temporal information from the vibrissa during whisking in rodents.

### Spectral Models

Many of the proposed models share the characteristic of decoding time using arrays of neural elements that differ in terms of some temporal property. The most generic of these is the spectral timing model of Grossberg and colleagues (Grossberg & Schmajuk 1989), which has been expressed in varying forms. The original model assumed a population of cells that react to a stimulus with an array of differently timed responses. Two variants of this motif have also appeared. One is a variant of

clock models: Stimuli activate arrays of cells that oscillate at different frequencies and phases. By doing so, points in time following the onset of a stimulus can be encoded by activity in a subset of neurons that differs, at least somewhat, from the subsets of cells active at other times (Miall 1989, Gluck et al. 1990). In another model generally referred to as tapped delay lines, simple assumptions about connectivity lead to a sequential activation of different neurons at different times following a stimulus (Desmond & Moore 1988, Moore 1992, Moore & Choi 1997).

A number of studies propose biologically plausible implementations of spectral models. In these models all elements share a common implementation, but at least one of the variables is set to a different value, which allows each unit to respond selectively to different intervals. A wide range of biological variables have been proposed, including the kinetic constants of the metabotropic receptor pathway (Fiala et al. 1996), the time constant of slow membrane conductances (Hooper et al. 2002; see also Beggs et al. 2000), the decay time of inhibitory postsynaptic potentials (IPSPs) (Sullivan 1982, Saitoh & Suga 1995), short-term synaptic plasticity (Buonomano 2000, Fortune & Rose 2001), or even cell thresholds (Antón et al. 1991).

Spectral models have the advantage of encoding the time since the arrival of a stimulus by having different subsets of cells active at different times. Combined with simple learning rules where a teaching or error signal modifies connections for only active cells, spectral models can learn outputs that are properly timed and can even show the Weber effect of increased variance with increased delay. However, to date, neither arrays of elements with different time constants, arrays of elements that oscillate at different phases and frequencies, nor connectivity that supports tapped delay lines are supported by identified properties of neurons or networks. Additionally, these models focused on simple forms of temporal discrimination and may not generalize well to more complex forms of temporal processing without additional network layers (see below).

## Network or State-Dependent Models

The above models represent top-down approaches where timing is addressed by inferring a computation and then implementing the computation with neurons. An alternative bottom-up approach is to start with biologically realistic assumptions and then to ask the extent to which temporal processing can be found as an emergent property. These models have no built-in temporal processing or selectivity with ad hoc assumptions. That is, they do not rely on explicitly setting oscillators, synaptic or current-time constants, or some other variable that, in effect, functions as a delay line.

CORTICAL MODEL It has been proposed that cortical networks are inherently able to process temporal information because information about the recent input history is inherently captured by time-dependent changes in the state of the network (Buonomano & Merzenich 1995, Buonomano 2000, Maass et al. 2002). One set

of studies has examined how interval selectivity can be encoded in a population of cortical neurons (Buonomano & Merzenich 1995, Buonomano 2000). In an interval discrimination task, when the first of a pair of tones arrives in a cortical network, it will stimulate hundreds of excitatory and inhibitory neurons, a subset of which will fire. In addition to producing action potentials in some neurons, a series of time-dependent processes will also be engaged. In this model the time-dependent properties were short-term synaptic plasticity (Deisz & Prince 1989, Stratford et al. 1996, Reyes et al. 1998, Zucker 1989) and slow IPSPs (Newberry & Nicoll 1984, Buonomano & Merzenich 1998b), but it could include many other time-dependent properties. In this model all synapses exhibit the same short-term plasticity temporal profile, as opposed to spectral models. Because of these time-dependent properties, the network will be in different states at 50, 100, and 200 ms. Thus, at the arrival of a second event at 100 ms, the same stimulus that arrived at 0 ms will arrive in a different network state. That is, some synapses will be facilitated/depressed, and some neurons may be hyperpolarized by slow IPSPs. As a result, the same input can activate different subpopulations of neurons dependent on the recent stimulus history of the network. The differences in the population activity produced by the second and first pulse can be used to code for the 100-ms interval. Given the high dimensionality and abundance of time-dependent properties of cortical networks, this type of model could provide a realistic means to decode complex temporal and spatial-temporal patterns of sensory information (see below).

CEREBELLAR MODEL The evidence from the cerebellum illustrates how timing and performance on experimental tasks designed to study timing are mediated by computations that include temporal processing. For example, cerebellar-mediated, feed-forward prediction may be the computational basis for the temporal processing responsible for timing tasks in the millisecond range.

Buonomano & Mauk (1994) used the correspondence between eyelid conditioning and the cerebellum to test the timing capabilities of a network model of the cerebellar cortex. Although this model failed in many of its key properties, it showed how the connectivity of the cerebellar cortex could represent the time since the onset of a stimulus with subsets of different granule cells that become active at different times (Figure 9*A*). This time-varying stimulus representation was similar in many respects to the activity assumed in certain of the spectral timing models described above. The key mechanistic difference was that this activity was the natural consequence of the sparse, distributed, and recurrent connectivity of the cerebellar cortex.

By incorporating a more complete representation of the connectivity of the olivo-cerebellar circuitry, and by including recent findings regarding the specific synaptic conductances found in cerebellar neurons, a second-generation model now accounts for all key temporal properties of eyelid conditioning (Medina & Mauk 2000). As shown in Figure 9*B*, the timing of conditioned eyelid responses was partly derived from a competitive learning mechanism that increases the

temporal specificity of the cerebellar learning was one of the key findings from these simulations (Medina et al. 2000). The key process involves the bidirectional learning in the cerebellum that eyelid conditioning and other forms of learning reveal (Raymond et al. 1996).

Thus, computer simulations and related eyelid conditioning experiments suggest that timing mechanisms in the cerebellar cortex involve three interacting processes (Figure 9). First, sparse recurrent interactions between cerebellar Golgi and granule cells lead to the activation of different granule cells at different times during a stimulus. The activity in granule cells therefore not only codes stimuli, as suggested in seminal theories of cerebellum (Marr 1969), but also codes time elapsed during stimuli. With this temporal code it is then possible for a coincidence-based form of plasticity, such as cerebellar LTD (see Hansel et al. 2001), to mediate learned responses that can be specific for certain times during a stimulus. Finally, competition between excitatory and inhibitory learning sharpens the temporal resolution of the timed responses.

In these network or state-dependent models, timing does not arise from clocks or even from brain systems specifically dedicated to temporal processing. Rather, the evidence from the cerebellum, for example, illustrates how timing and performance on experimental tasks designed to study timing may be mediated by computations that include temporal processing but that are not accurately characterized as interval timers or clocks.

## FUTURE CHALLENGES: COMPLEX STIMULI

Most of the experimental and theoretical studies discussed above have focused on relatively simple stimuli. In particular, much of the work has been on the discrimination of the interval or duration of stimuli or on the generation of a single, timed motor response. The mechanisms underlying speech and music recognition, as well as the ability to process Morse code, require sophisticated mechanisms that can process multiple temporal cues in parallel and sequences composed of a continuous stream of elements with no a priori first and last element. Thus, a fundamental issue, particularly in relation to the computational models, is whether these models are sufficiently robust to account for more complex data. Indeed, if a model is limited to the discrimination of simple first-order stimuli (interval and duration), then this model is unlikely to represent the biological mechanisms underlying temporal processing in the range of tens to hundreds of ms.

### Higher-Order Stimuli

Consider the stimuli shown in Figure 10, in which a subject must discriminate between 2 sequences composed of 2 intervals (3 tones): 50–150 and 150–50. In reality, in this task one would include 50–50- and 150–150-ms stimulus

conditions to prevent the use of simple strategies. In clock or spectral models, neurons would have to respond selectively to the 50- and 150-ms intervals. Additionally, because both stimuli would activate the 50- and 150-ms interval detectors, another circuit would have to keep track of the order of activation, to discriminate between (50–150 and 150–50). Thus as sequences become more complicated, additional circuitry is generally required to keep track of the higher-order features.

## Reset Problem

The processing of sequences, as opposed to a single interval or duration, also imposes another constraint on the potential mechanisms underlying temporal processing. Let us consider how a spectral model will perform in response to the sequences shown in Figure 10. In a model based on a slow conductance such as an IPSP, the first tone will activate an IPSP of a different duration in each cell. If the second pulse arrives at 50 ms, the 50-ms detector will fire (owing to the interaction between IPSP offset and arrival of the second stimulus). However, the second pulse is also the first pulse of the second interval, and thus to detect the subsequent 150-ms interval, the second pulse would essentially have to reset the inhibitory conductance. We refer to this as the reset problem. When stimulus elements arrive on the same timescale as the intervals being processed, discrimination requires that the event that marks the end of one interval engage the initiation of the timing of the next interval. Resetting of synaptic conductances, in particular, is unlikely. In spectral models, a potential solution for this problem is to look at the above task as detecting two intervals 50–200 (50 + 150) versus 150–200 (150 + 50). In this manner the second pulse would not have to reset the timer because all timing would be relative to the first pulse. Nevertheless, the second pulse could not interfere with the ongoing computation of the 200-ms interval. This could perhaps be achieved by assuming that the first pulse saturated or depleted the mechanisms responsible for inhibition. However, we believe it is unlikely that spectral models are robust enough to generalize to complex temporal processing involved in speech and music recognition and complex motor patterns.

In contrast, models based on network dynamics may better generalize to the processing of more complex temporal patterns. In state-dependent network models (see above; Buonomano & Merzenich 1995, Buonomano 2000, Maass et al. 2002), the current state of the network is always dependent on the recent history of activity. Thus, in the above example, if the third input arrives at 200 ms, the network will be in a different state depending on whether the second pulse arrived at 50 or 150 ms. In these models, time-dependent properties, such as short-term synaptic plasticity, slow PSPs (e.g., $GABA_B$ or NMDA-dependent currents), or, potentially, slow conductance, function as state-dependent memory traces of the recent stimulus history. In contrast to single-cell models, these time-dependent properties are not tuned for any particular interval; rather these states are expressed as changes in the probability of different neurons becoming activated.

Figure 10 shows results from a state-dependent network model capable of discriminating intervals as well as simple sequences (Buonomano 2000). The network was composed of 400 excitatory and 100 inhibitory units; all synapses exhibited short-term synaptic plasticity, and a slow IPSP was also present. As a result of the time-dependent properties, the network is in a different state at 50 and 150 ms; thus different neurons will respond to the second pulse depending on its arrival time. Because different neurons responded to the second pulse, state-dependent change will be cumulative and alter the response to the third pulse in a different manner depending on the stimulus history. There are two potential shortcomings of state-dependent networks. First, the network must be in a specific regime that allows that expression of the state-dependent changes, which can be nontrivial because a balance between excitation and inhibition is required. Specifically, inhibition must enable excitatory neurons to fire while preventing run-away excitation. Second, because these networks encode time as relative to previous stimuli, they would be least effective at identifying specific intervals embedded in sequences, for example, comparing a 100-ms interval defined by two tones with a 100-ms stimulus embedded within a sequence of tones.

## CONCLUSIONS

The study of the neural basis of temporal processing is in its infancy. Few agree on whether temporal processing is centralized or distributed and which structures are involved. Indeed, if all neural circuits can intrinsically process temporal information, then virtually any circuit could be involved, and the location of temporal processing would depend on the nature and modality of the task at hand. Despite the fact that these important questions remain unanswered, the studies, to date, allow several insights into the nature of timing. First, although researchers do not agree on which areas are involved in sensory timing, it seems clear that the cerebellum is responsible for some forms of motor timing. Whether it is the sole source of motor timing and whether it is involved in sensory processing remain open to debate. Second, much evidence indicates that distinct neural mechanisms underlie millisecond and second timing.

Many models of timing have focused on specialized synaptic and cellular mechanisms aimed specifically at processing temporal information, and investigators assumed that spatial and temporal information are essentially processed separately. Given the inherent temporal nature of our sensory environment, and the continuous, real-time motor interaction with our environment, we favor the view that temporal and spatial information are generally processed together by the same circuits, and that there is no centralized clock for temporal processing on the scale of tens to hundreds of ms. Additionally, we propose that temporal processing does not rely on specialized mechanisms, such as oscillators or arrays of elements, as with a spectrum of different time constants. Rather, we believe that neural circuits are inherently capable of processing temporal information as a result of state-dependent changes in network dynamics.

ACKNOWLEGMENTS

We thank Uma Karmarkar and Tatsuya Ohyama for helpful comments on this manuscript, and Michael Lewicki for Figure 6. This work was supported by NIH grant MH60163 to D.V.B., and MH57051 and MH46904 to M.D.M.

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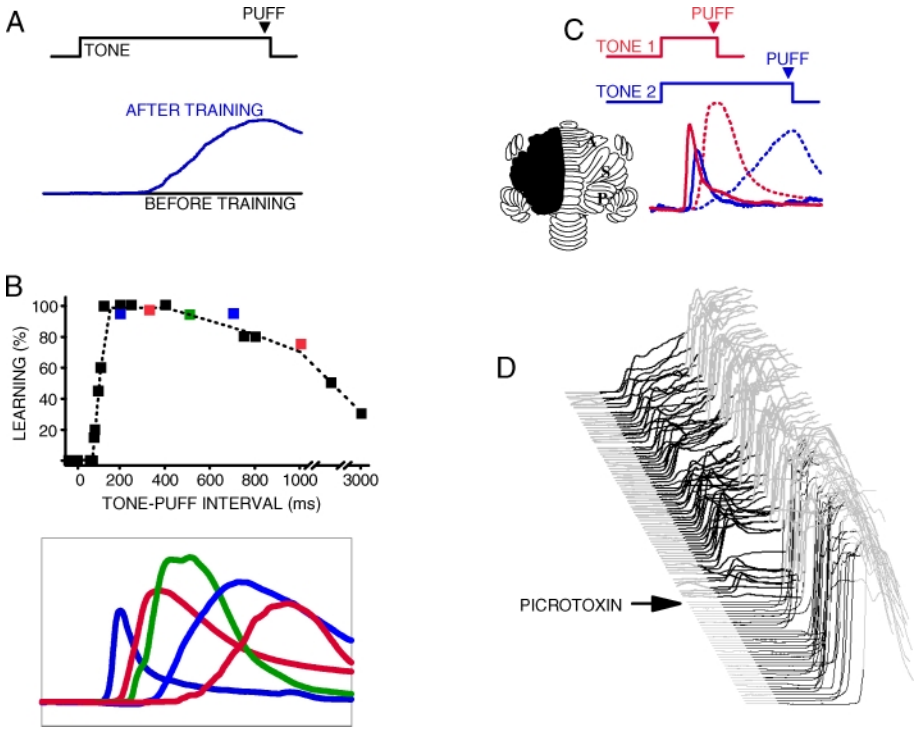


**Figure 3** Temporal properties of learned eyelid responses. Classical or Pavlovian eyelid conditioning displays learned timing. (*A*) In a typical experiment, training involves presentation of a neutral stimulus, such as a tone, paired with a reinforcing stimulus, such as a puff of air directed at the eye. (*Lower traces*) Repeated presentation of such trials leads to the acquisition of learned eyelid responses. Before training the tone does not elicit an eyelid response, whereas after training the upward deflection of the trace indicates that the tone elicits learned eyelid closure. In this case the tone-puff interval is 500 ms. (*B*) The time delay between the onsets of the tone and puff influences learning in two ways. First, learning only occurs for delays between approximately 100 and 3000 ms. Best learning is produced by delays ranging from 200 to 1000 ms. The tone-puff delay also determines the timing of the learned responses. These are sample learned responses for animals trained with the delays coded by the color of the points in the graph. (*C*) Lesions of the cerebellar cortex disrupt learned response timing. Animals trained using two tones and two tone-puff delays were then subjected to lesions of the cerebellar cortex (*example shown in inset*). The lesions produced a short and relatively fixed latency-to-onset interval independent of prelesion timing. Modified from Perret et al. 1993. (*D*) Reversible lesions or disconnection of the cerebellar cortex produce the same effect on timing. These are example responses from a training session in which the cerebellar cortex was functionally disconnected via infusion of the GABA antagonist picrotoxin into the cerebellar interpositus nucleus. The darker portion of each trace indicates the tone; responses are chronologically organized front to back. Modified from Medina et al. 2000.

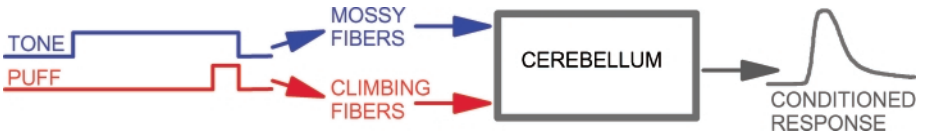


**Figure 7** Eyelid conditioning engages the cerebellum relatively directly. This is a schematic representation of the relationship between eyelid conditioning and the cerebellum. Output of the cerebellum via its anterior interpositus nucleus drives the expression of conditioned responses. Stimuli such as tones are conveyed to the cerebellum via activation of mossy fiber inputs. Reinforcing stimuli such as the puff of air directed at the eye are conveyed to the cerebellum via activation of climbing fibers.

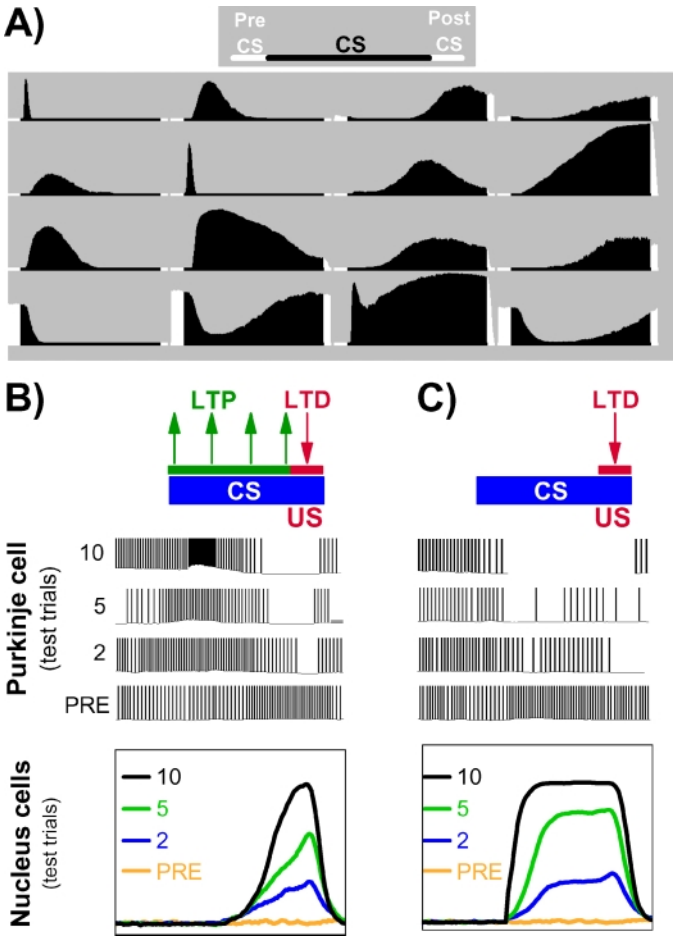


**Figure 9** Mechanisms of timing-specific learning in the cerebellum. Computer simulations of the cerebellum in the context of eyelid conditioning suggest mechanisms for learned response timing. (*A*) Peri-stimulus histograms of simulated granule cells for the presentation of a tone-like mossy fiber input to the cerebellum. This sample shows how different granule cells respond at different times during this stimulus. These simulated granule cells have identical temporal properties; these differently timed responses arise from network interactions with mossy fiber inputs and with cerebellar Golgi cells. (*B*, *C*) The simulations suggest that learned timing is enhanced by competitive learning within each trial. Proper timing requires mechanisms both for learning (LTD) responses, when a climbing fiber is present, and unlearning (LTP) responses, when it is absent. (*B*) Through these two mechanisms, the simulated cerebellar Purkinje cells can learn well-timed modulation of their activity during learning. (*C*) In simulations with unlearning disabled, timing of Purkinje cell response and of the learned responses of the simulation is impaired. Modified from Medina & Mauk 2001.

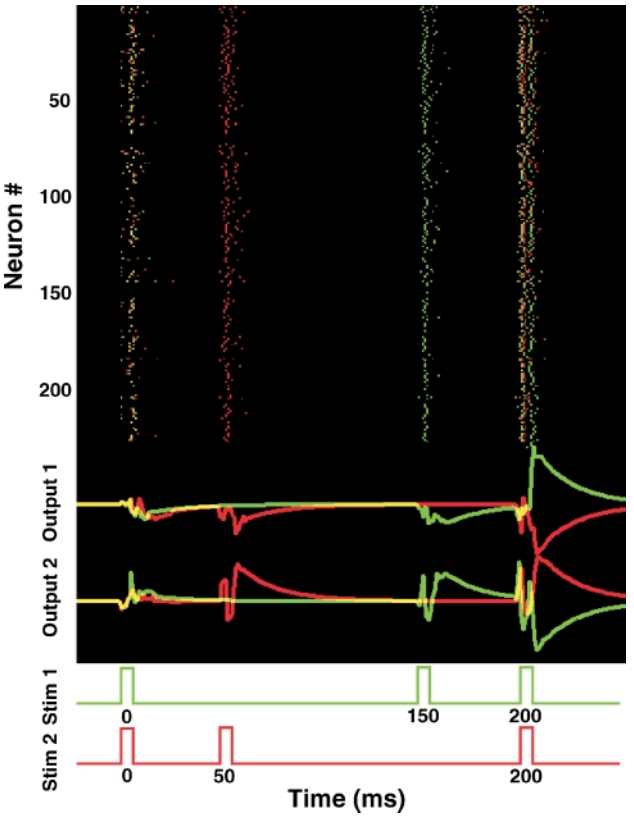


**Figure 10** State-dependent model of sequence recognition. The model is composed of excitatory and inhibitory neurons. The connectivity and synaptic weights are randomly assigned, the synapses exhibit short-term synaptic plasticity, and a slow-IPSP is present. The time constant of the short-term plasticity and slow IPSP is the same for all synapses in the network. The raster plot shows which excitatory neurons fired to the long-short stimulus (*green*) and to the short-long stimulus (*red*). If the neuron responded at the same time to both stimuli the spike is plotted in yellow. Note that there is more yellow in response to the first pulse than to the last (all points in response to the first pulse are not yellow because of intrinsic noise). Each pulse of a stimulus will activate a population of neurons and trigger short-term plasticity; thus at the arrival of the second pulse the network will be in a different state, depending on whether the second pulse arrived at 150 (*green*) or 50 ms (*red*). For both stimuli (long-short or short-long) the third pulse arrives at 200 ms; however, the network will be in a different state depending on the stimulus, allowing the network to respond differently to the same pulse. The two lower traces represent the voltage of two output neurons that receive input from all the excitatory neurons above. The weights on the output neurons were set by training (using a nontemporal learning rule) on different stimulus set presentations. Outputs 1 and 2 respond selectively to the long-short and short-long stimuli, respectively.