Appendix B: Copies of select “foundational” temporal processing (mental timing) articles

■ 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.
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> 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

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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

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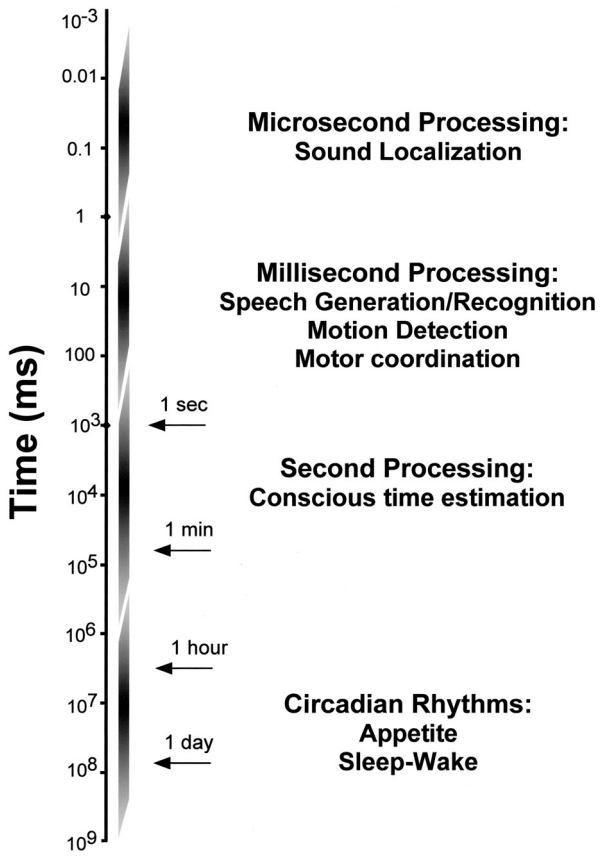

Fig. 1. Scales of temporal processing. Humans process temporal information over a scale of at least 10 orders of magnitude. On one extreme, we detect the delay required for sound to travel from one ear to the other. These delays are on the order of tens to hundreds of microseconds. On the other extreme, 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.,

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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.

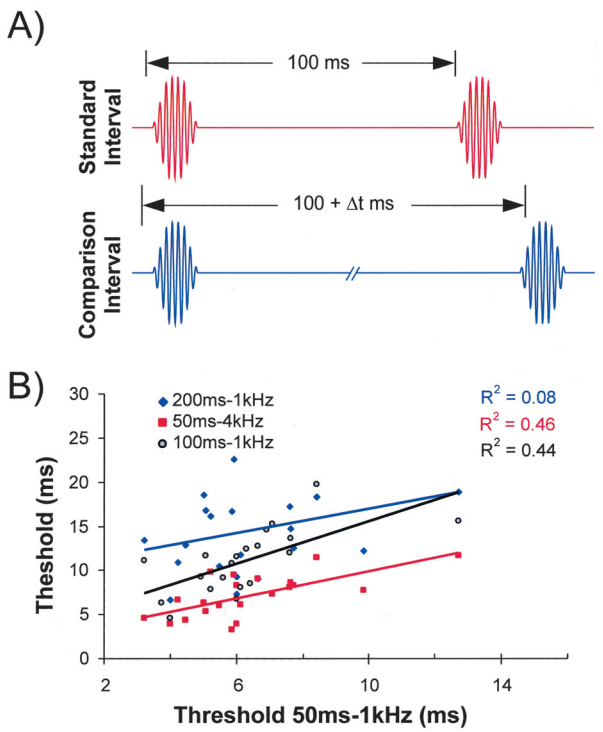

Fig. 2. Intrasubject correlations between interval discrimination tasks. *A*. Interval discrimination. Interval tasks can be designed in various ways. In one design, a standard and comparison interval are presented in random order, the subject has to decide whether the comparison interval (the longer 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-

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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-

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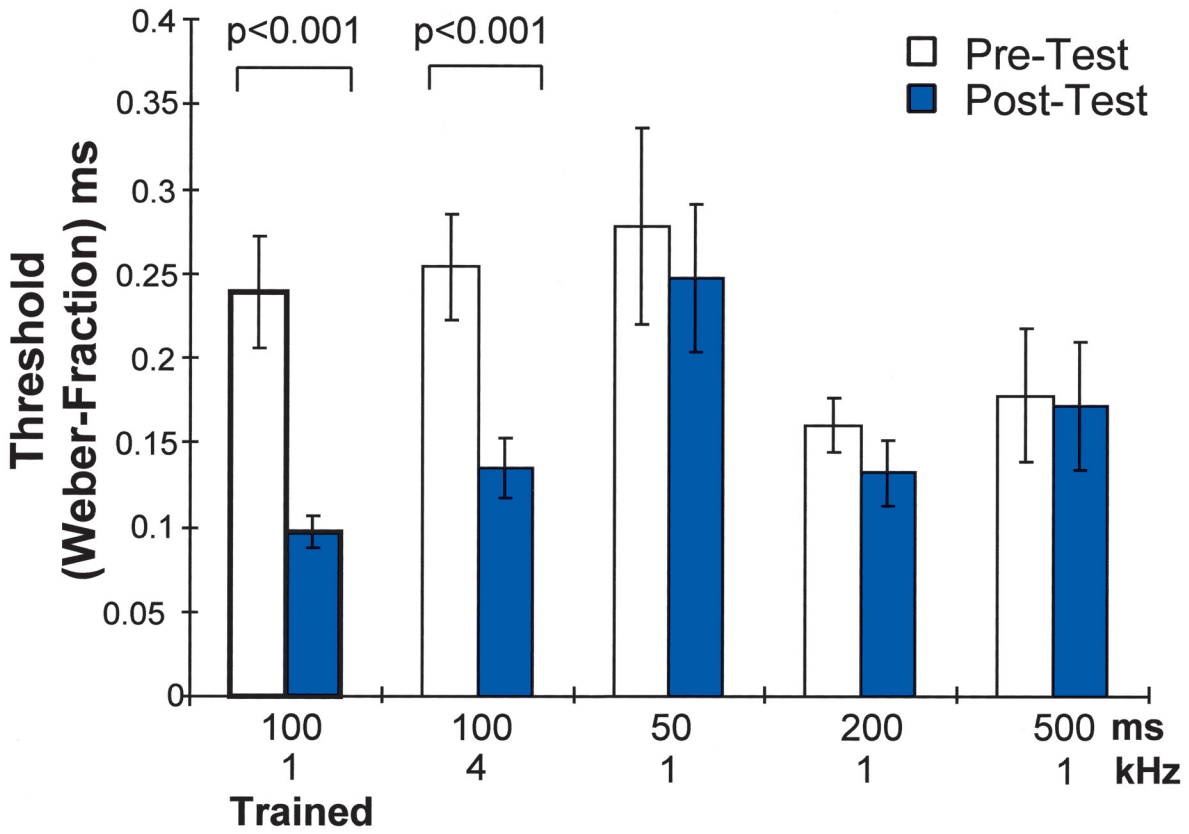

Fig. 3. Interval discrimination learning generalized across frequencies but not intervals. Subjects were trained on the 100 ms–1 kHz conditions for 10 days. The pre- and posttest thresholds revealed significant differences only for the trained condition, and the 100 ms–4 kHz condition. Modified from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

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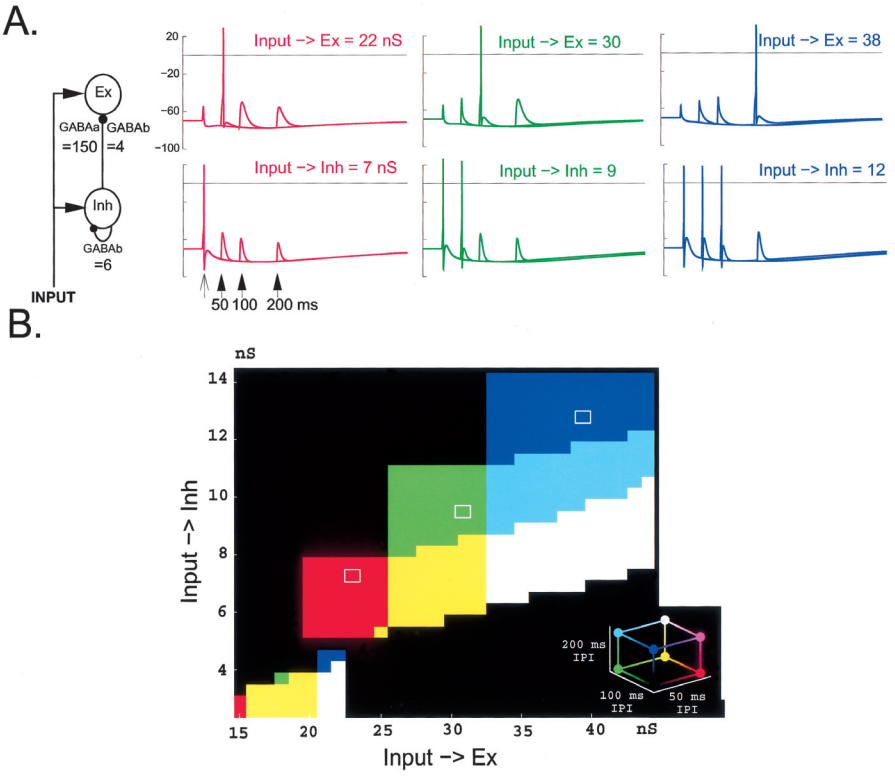
Box 1: Interval Selectivity in Disynaptic Circuits

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).



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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

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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.

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Review

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Dedicated and intrinsic models of time perception

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Two general frameworks have been articulated to describe how the passage of time is perceived. One emphasizes that the judgment of the duration of a stimulus depends on the operation of dedicated neural mechanisms specialized for representing the temporal relationships between events. Alternatively, the representation of duration could be ubiquitous, arising from the intrinsic dynamics of nondedicated neural mechanisms. In such models, duration might be encoded directly through the amount of activation of sensory processes or as spatial patterns of activity in a network of neurons. Although intrinsic models are neurally plausible, we highlight several issues that must be addressed before we dispense with models of duration perception that are based on dedicated processes.

Perceiving the passage of time

Cognition is dynamic, with our perceptions, actions and comprehension of the world unfolding over time. A generation ago, research on timing was limited, emphasizing the study of behaviors marked by temporal regularities [1]. More recently, a renaissance has taken hold in the study of time perception, with researchers addressing a broad range of temporal phenomena. Behavioral studies have revealed a host of puzzling effects in which our perception of time is far from veridical [2]. Neuroscientists have described how activity in single neurons varies with time and how this might relate to psychophysical judgments [3–5]. Theorists have asked how the dynamics of neural networks might encode temporal patterns in a reliable manner [6–11].

As has long been noted by philosophers and psychologists, we lack a sensory system devoted to the sense of time. Nonetheless, many percepts, and our actions in response to these percepts, are acutely dependent on the precise representation of time. Of course the terms 'time' and 'temporal processing' encompass a broad range of phenomena, including simultaneity, temporal order and the perception of duration. In this review we focus on the last of these, addressing how the nervous system encodes information concerning the duration of events in the range of hundreds of milliseconds, the units of time that are especially relevant for immediate perception and the actions we produce in relation to these events. In particular we focus on a fundamental question that has defined much of the recent discussion: is our perception of the passage of time the consequence of dedicated, clock-like neural mechanisms? Or is duration coded in an accessible manner as an intrinsic and ubiquitous property of neural activity?

Dedicated models of temporal processing

Dedicated models of time perception are, at their core, modular. As vision scientists speak of dedicated mechanisms for color or motion perception, modular models of time perception entail some sort of specialized mechanism that represents the temporal relationship between events. The pacemaker-counter model is one example of a modular system [12]. These two components define a clock with an interval specified by the accumulation of inputs from a pacemaker. Spectral models of timing constitute a second example of a modular process. The phasic interactions of a bank of oscillators [8,13] or the exploitation of differential activity patterns in a set of delay lines [14,15] can define different intervals. In dedicated models these representations are viewed as specializations, unique to particular neural structures, that provide a functional chronotopy that is recruited across diverse task domains.

One motivation for dedicated models comes from the observation that our sense of the passage of time appears to transcend the sensory modality of a stimulus. We can compare the duration of a tone to a light (although not as well as we assume [16–18]) or metrically reproduce the duration of a visual stimulus with a keypress. Such interactions are less apparent in other perceptual domains; for example, only rare individuals describe the color of a tone. The facile manner with which we compare time across different modalities suggests some sort of internal clock.

Behavioral data provide additional motivation. Individual differences in temporal acuity correlate between perception and action [19]. Measures of variability or dispersion are proportional to mean duration, and when the tasks are appropriately matched this ratio is similar for perception and action [20]. Based on the assumption that this property arises from signal-dependent noise in a common system, these results point towards a dedicated system for timing.

A neural instantiation of a dedicated model is the cerebellar timing hypothesis [21]. Patients with cerebellar pathology are impaired on a range of tasks that require precise timing, including perceptual tasks such as judging the duration of brief tones [22,23] or categorizing speech sounds that vary in the duration of a silent period [24]. The timing hypothesis also provides a principled basis for specifying the cerebellar contribution to sensorimotor learning: this structure would be essential when learning

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requires the representation of the temporal relationship between events, as in eyeblink conditioning. Consistent with a modular perspective, the cerebellar timing hypothesis is based on the assumption that the cerebellum has a unique representational capability and is accessed whenever a particular task requires precise timing.

Similar arguments have been developed for other neural regions that might serve as dedicated timing systems [25]. These include the basal ganglia [26,27], supplementary motor area [28,29] and prefrontal cortex, especially in the right hemisphere [30,31]. For the most part, converging evidence has been offered in support of all of these candidate regions. Patients with lesions encompassing a particular region might be impaired in judging the duration of an auditory stimulus yet show no problems in judging other acoustic features [30]. Correspondingly, an area might be activated in an imaging study when the task requires attending to the duration of the stimulus in comparison to a nontemporal attribute [28]. These dissociations, whether from lesions, pharmacological manipulations or neuroimaging, favor dedicated mechanisms for temporal processing (Figure 1a).

Although dissociations across task domains have been obtained readily, considerable debate continues on the question of whether temporal-processing deficits are uniquely associated with damage to a particular neural structure. For example, patients with cerebellar degeneration, Parkinson's disease or prefrontal lesions all show a similar perceptual dissociation between duration and pitch [32]. The neuroimaging literature presents a similarly murky picture [32]. Not only have highly divergent patterns of activation been observed across studies but also substantive task differences amplify the problem [32,33]. Given the required investment, replication studies are rare in the imaging literature.

Other dedicated models avoid localization issues by postulating that the representation of time results from activity across a network of regions [34,35] (Figure 1b). Within such models the operation of some areas could be specific to timing (e.g. pacemaker function), whereas other

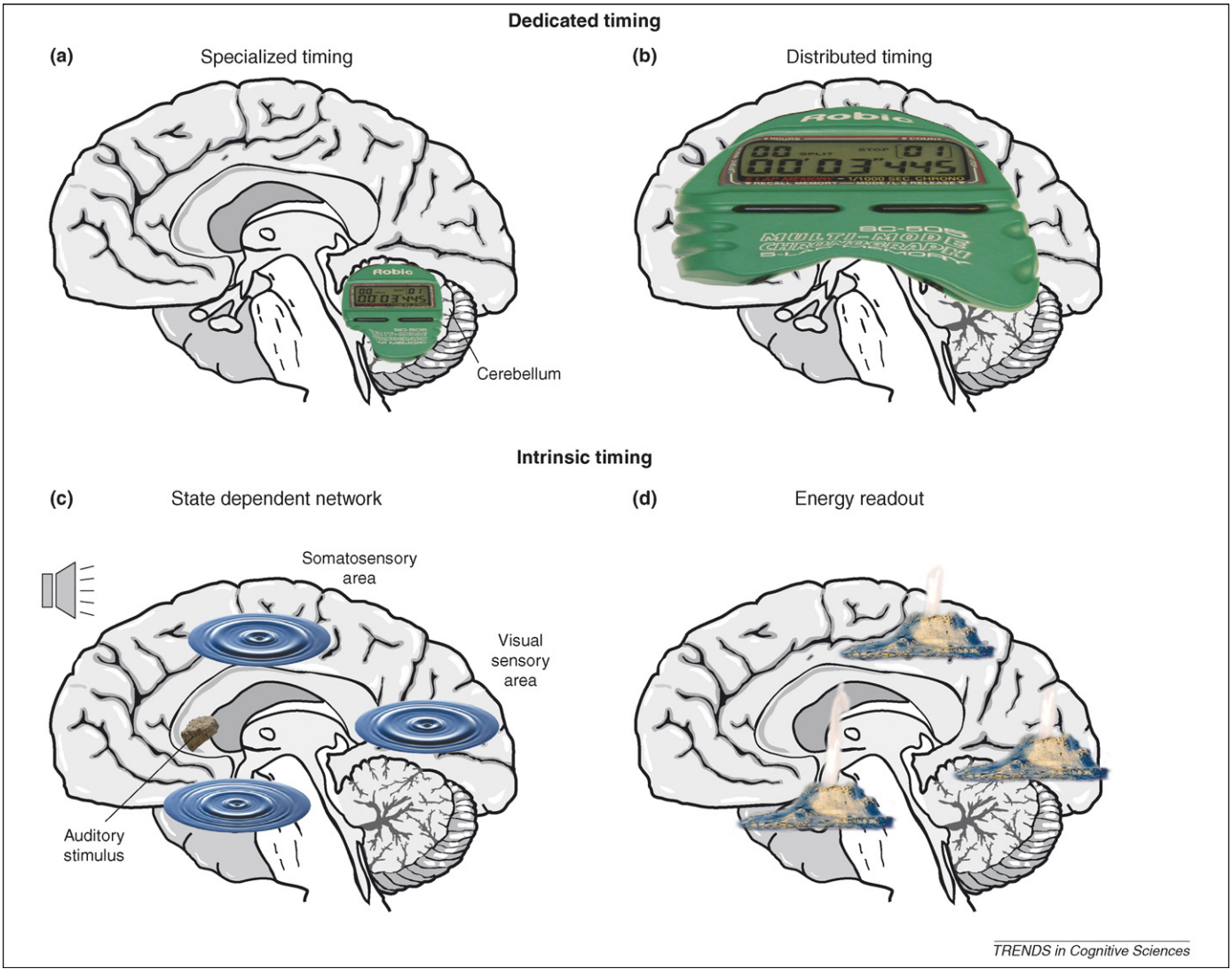

Figure 1. Neural models for temporal representation. The top two panels depict two dedicated models. **(a)** A neural structure might be specialized to represent temporal information. The example shows the cerebellum as a dedicated system, although some models postulate a specialized role for the basal ganglia, supplementary motor area or right prefrontal cortex. **(b)** A dedicated system could involve activity across a distributed network of neural regions. The bottom two panels depict two models for modality-specific intrinsic timing. **(c)** In a state-dependent network, temporal patterns are represented as spatial patterns of activity across a neural network. **(d)** In an energy readout model, elapsed time corresponds to the amount of neural activity.

areas might provide more general functions (e.g. working memory to store temporal information). Pathology in any node of this network would disrupt performance on timing tasks.

Intrinsic models of temporal processing

A spate of recent studies has promoted a more generic view of timing, which we will refer to as 'intrinsic models'. Intrinsic models offer a radically different perspective on the perception of time. These models assume that there is no specialized brain system for representing temporal information, asserting that time is inherent in neural dynamics (Figure 1c,d). In one class of models, this property might be limited to neural regions that are capable of sustaining their activity in the absence of sensory input [3,10]. For example, in delayed response tasks duration can be encoded in the ramped activity of neurons that provide a working memory representation of the stimulus or the time until the response [36].

Alternatively, timing might be ubiquitous and arise as part of modality-specific processing [37,38]. Thus, perceiving the duration of a visual event would depend on the dynamics of neurons in visual regions of the brain whereas the same duration of an auditory event would depend on similar operations in auditory regions. This idea contrasts with how modality-specific effects are conceptualized in dedicated models. For example, in our cerebellar model the duration of a tone is assumed to be represented in different cerebellar subregions than the representation of the duration of a light [15]. Nonetheless, both representations depend on a specialized cerebellar computation.

In a provocative paper titled 'Timing in the Absence of Clocks', Karmarkar and Buonomano [7] develop a neural network composed of excitatory and inhibitory neurons that exhibit a range of synaptic time constants and short-term plasticity mechanisms. This network is capable of representing different durations as unique spatial patterns of activity, even without any explicit mechanism that provides a linear metric of time. Judging the duration of a stimulus requires learning to recognize these spatial patterns.

An essential feature of this model is that temporal representation is context dependent. This property not only implies modality specificity but also that, even within a modality, the representation of a particular interval will be state dependent. Thus, the network's representation of the duration of a tone is related not only to activity occurring during the presentation of the tone but also to the state of the network at the onset of the tone. Consistent with this state dependency, perceptual acuity for duration is much poorer when the target interval is presented in a variable context compared to a fixed context [7]. Interestingly, this effect is limited to judgments involving relatively short intervals (e.g. 100 ms). Context manipulations had no effect on intervals of 1 s, consistent with the idea that the physiological processes underlying state-dependent networks are of limited temporal extent [39] (see Box 1).

A different mechanism for intrinsic timing is based on the idea that duration could be encoded in the magnitude of neural activity, in which the passage of time is gauged by some form of energy readout [40]. Consider a task in which participants view a stream of digits, each presented for a duration of around 500 ms [41]. If the same digit is presented repeatedly, the initial stimulus is perceived as longer in duration (or conversely, the perceived duration of subsequent stimuli is shortened). A similar effect is found when a set of digits are presented in their standard ordinal position (e.g. 1 2 3 4): the '1' is perceived as longer than the '2', '3' and '4'. However, if the order is scrambled (e.g. 1 4 3 2), there is no distortion of duration. Each digit cannot be anticipated and, thus, receives a similar degree of neural processing. Drawing on an intriguing parallel to the repetition suppression effect observed by functional magnetic resonance imaging (fMRI) [41], Pariyadath and Eagleman suggest that 'the conditions that lead to a suppressed neural response are the same as those that lead to a reduction in perceived duration' (p. 5). By extension,

Box 1. Different ranges, different mechanisms?

Time perception studies use intervals that extend from a 100 ms to tens of seconds or minutes. Does the requisite set of neural mechanisms change across this range? One important division is made between short intervals that range up to 1–2 s and longer intervals [35,66]. Within dedicated models of timing, the system can directly encode short intervals [15]. By contrast, longer intervals require the recruitment of attentional and working-memory processes. Repeated output of a timing mechanism might be used [23] or time perception could be indirect, the result of an inferential process [67].

Although evidence for such a division is compelling, the interpretation of time-perception studies frequently has favored a singular model across a large range of intervals. For example, clock-counter models have proved extremely useful in accounting for behavior. Nonetheless, it is unlikely that a single mechanism could operate at these different time scales. A pacemaker used to judge an interval of 40 s is unlikely to have the resolution to judge a 100 ms interval. The strength of these models is in their heuristic value: by specifying multiple components the model provides quantitative predictions to test how particular variables influence performance.

State-dependent networks suggest that an additional division is required. The physiological mechanisms that drive such networks are useful for differentiating patterns of a few hundred milliseconds. Beyond this range, time-dependent neural properties provide inadequate resolution [68,69]. By inference, intervals of a half-second or longer require additional processes. This division was anticipated at the end of the 19th century by Munsterberg, who suggested that short intervals might be directly perceived by sensory mechanisms [17].

To date only a few studies have examined whether distinct mechanisms underlie the perception of short intervals. Secondary tasks [17,70] or pharmacological manipulations [71] affect judgments of 1 s intervals while having little or no effect on intervals of around 100 ms. Secondary tasks that affect judgments of 1 s have little effect on intervals of 100 ms [17,70]. Temporal acuity normalized to mean duration is relatively constant for intervals between 200 ms to 2 s but becomes considerably poorer for intervals shorter than this range [7,72]. In preliminary work we (R.B. Ivry, *et al.*, unpublished) failed to find context effects in a replication of Karmarkar and Buonomano [7] when the base interval was increased to 300 ms.

It is possible that the distinction between intrinsic and dedicated mechanisms for duration perception will map onto temporal range, with the former applicable to relatively short intervals (e.g. a few hundred milliseconds) and the latter to longer intervals. Nonetheless, at present, variants of both classes of models have been applied to tasks spanning up to a few seconds. Thus, we focus in this review on outlining issues that allow for a comparison between these models when applied to a common set of phenomena.

events that capture attention produce an increase in neural activity [41,42] and, as would be predicted by an energy readout model, are perceived as longer in duration [43–45]. As with a state-dependent network [7] the perception of time is not attributed to mechanisms specialized for temporal processing but, rather, is based on generic and modality-specific features of neural activity.

Evaluating the evidence for modality specificity in intrinsic timing

Some of the most compelling evidence for intrinsic timing comes from physiological studies that emphasize local representations that are, at least implicitly, modality specific. In one study neurons in the lateral inferior parietal region LIP were recorded during a visual duration discrimination task [5]. Two lights, the first of a fixed duration (e.g. 316 ms) and the second a variable duration, were presented at fixation. The animal judged the relative duration of the second by making a saccade to one of two peripheral targets. Strikingly, perceptual judgments were well predicted by the activity of individual neurons. When the target for 'shorter' judgments fell within the neuron's response field, it would exhibit high firing rates at the onset of the second light. If the stimulus persisted, this response dropped off. When the target for 'longer' judgments fell within the response field of the neuron, the firing rate increased over time, eventually surpassing that of neurons with response fields tuned to the 'shorter' target.

This parallel between behavior and single-unit activity has been seen with other visual attributes. For example, psychophysical performance on motion perception tasks can be predicted from the activity of neurons in area MT (middle temporal, also known as area V5) [46,47]. By analogy, Shadlen and colleagues suggest that LIP neurons code the time of behaviorally relevant visual events. However, the authors acknowledge that activity in these eye-movement-related neurons might be driven by an upstream (dedicated) system for temporal processing [4].

A recent transcranial magnetic stimulation (TMS) study provides converging evidence in favor of modality-specific timing [48]. When judging the duration of a visual display, an increase in the difference threshold was observed on trials in which repetitive TMS was applied over V5/MT. Consistent with a modality-specific assumption, no change in performance was found when subjects judged the duration of a tone. Similarly, modality specificity was observed in an fMRI study when people were asked to tap a simple rhythm, initially specified by either a visual or auditory metronome [49]. In the visual condition only, activity remained high in area V5/MT after the metronome was terminated. One might suppose that, in terms of a state-dependent network, a persistent modality-specific pattern continues to provide a reference to time each response even in the absence of further sensory stimulation.

A further challenge to dedicated models comes from studies showing modality-specific distortions of perceived time. Morrone and colleagues reported a dramatic illusion in which time is compressed [50]. Just before the onset of a saccade to a peripheral target, a pair of bars was flashed with an onset asynchrony of 100 ms. Participants compared the duration of this interval to a variable one that was presented a few seconds later. Under these conditions, participants reported the stimuli to be of similar duration when the variable interval was around 50 ms long. This temporal compression was not seen if the initial interval was presented well before the saccade nor was it evident if auditory clicks were used to define the pre- and postsaccadic intervals. In subsequent work, similar compressive effects were spatially specific for intervals of a half-second [38].

Although evidence of modality and task specificity provides strong support for intrinsic timing, several crucial issues must be addressed as these models mature. For example, why would individual differences in producing consistent rhythms be selectively correlated with acuity in judging the duration (as opposed to the pitch) of a tone if these tasks engage distinct mechanisms? One might suppose that there are individual differences in noise properties associated with the time constants of neural activity. However, this would not account for the deficits observed after relatively focal brain lesions on a range of tasks that require precise timing [21]. Dedicated models offer a parsimonious way to computationally link disparate tasks.

Intrinsic models in their current form have difficulty accounting for crossmodal transfer. It is unclear how training on an auditory duration discrimination task would facilitate performance for judging the duration of a visual stimulus. Surprisingly, the empirical record on temporal transfer is rather thin. Humans [51] and rats [52] both show transfer between timing of visual and auditory signals. However, this work involves intervals of many seconds. Only a few studies have looked at transfer in the subsecond range, and these have not provided ideal tests for assessing intrinsic models. Meegan *et al.* [53] reported that, after extended training in judging the duration of a 300 ms tone, people were more consistent in producing a 300 ms interval compared with a 500 ms interval: an interval-specific transfer effect. Notably, participants were prevented from hearing sounds generated by their movements during production; thus, one cannot argue that they were reproducing sounds matched to their training. An intrinsic-based account of this form of transfer probably would require postulating that the movements were guided by an auditory temporal model. The auditory modality might have some special status compared to other senses with respect to the encoding of temporal information [54]; nonetheless, arguments of this sort are problematic for current versions of intrinsic models.

Moreover, intrinsic models that emphasize temporal encoding in early sensory areas could not fully account for transfer within a modality. Westheimer [18] gave participants extended training on a visual duration discrimination task, using a standard interval of 500 ms. During training the stimulus was always presented in the left visual field and acuity improved by ~60%. Perfect transfer was observed when the stimulus was presented in the right visual field. It is hard to reconcile this finding with the notion that activity in retinotopically organized areas provides the representation for temporal judgments.

The role of nontemporal factors on perceived duration

Performance on time-perception tasks entails several component processes, many of which are not specific to time. These include attention, working memory and long-term or reference memory [55]. To date few studies of intrinsic timing have asked which of these processes are affected by training. Perceptual studies of generalization have reported that benefits are interval specific [56,57], similar to the results observed by Meegen *et al.* [53]. Although this would rule out training effects related to processes of attention or working memory, it cannot be assumed that training has strengthened interval-specific timing elements or specific patterns in state-dependent networks. Consider a model in which there are patterns (or clock-like units) that correspond to 80 ms, 100 ms, 120 ms and so on. When given repeated training over this range, one might suppose that the strength of these patterns is enhanced. Alternatively, decision processes might become more reliant on neurons that recently provided relevant information, although the actual patterns remain unchanged. With either mechanism, improvement would be limited to the trained interval.

More generally, some of the behavioral effects attributed to intrinsic mechanisms probably are related to processes not directly involved in representing temporal information (see Box 2). As noted above, activity in LIP neurons that is predictive of psychophysical performance might reflect intrinsic dynamics that measure time or reflect fluctuations in decision and/or response preparation processes [4,58], with the perceptual analysis of duration occurring upstream. A transfer test would provide an important tool here. Suppose after extended training the monkey was presented with identical stimuli but now required to respond by using his fingers to press keys to indicate stimulus duration, rather than respond with an eye movement. If timing and the benefits of training were restricted to activity in LIP neurons, little transfer would be expected because LIP is involved mainly in preparing the saccades. Although not tested, this seems highly unlikely. We assume that humans would show immediate transfer.

Box 2. Outstanding questions

- Does training people on time-perception tasks in one modality transfer to other modalities? Are transfer benefits specific to judgments of time or do they reflect reductions in other sources of variability, such as those related to sensory detection or decision processes? Transfer designs also would be ideal for neurophysiological studies of time perception. For example, are the ramping functions evident in neural activity related to encoding the passage of time or preparation of specific responses? Could intermodal transfer be related to crossmodal projections between primary sensory areas [73], or would it depend on activity in association regions of cortex?
- In studies of patients with neurological disorders, deficits in temporal representation generally are manifest as increases in variability. By contrast, recent psychophysical studies have focused on manipulations that distort perceived duration, in other words, a change in the mean. How do changes in mean occur in intrinsic models of temporal processing, and what are the consequences of these changes on measures of variability? More generally, are temporal distortions the result of changes in the mechanisms used to represent temporal information, or do they reflect the influence of nontemporal processes on performance (see Figure 2)?
- What kinds of neural mechanisms can extend the temporal range for intrinsic models, or will these models be limited to the perception of very short intervals, similar to that proposed by Karmarkar and Buonomano [7]?

The nature of decision processes is also important for understanding how judgments of perceived duration might be influenced by task-irrelevant information. A 100 ms interval is more likely to be judged as 'long' when it is preceded by a long foreperiod compared to when it is preceded by a short foreperiod [59]. It is likely that the duration of the foreperiod is implicitly coded, providing a form of a congruency effect or introducing a response bias. Such biasing effects also can come from nontemporal information given congruencies that exist between axes of seemingly orthogonal dimensions (Figure 2a). Although 'small' and 'large' typically refer to space, these concepts map onto 'short' and 'long', respectively, in the temporal domain. This congruency can introduce biases that masquerade as distortions of time [60]. For example, when presented with a visual stimulus composed of an array of dots, people are more likely to report the duration as 'long' when the array contains more dots, larger dots or brighter dots. Even more abstract, for two stimuli of the same duration, the digit '7' is perceived as longer than the digit '1'.

At the earlier side of the processing stream, some temporal distortions are probable due to sensory or attentional effects in registering the onset or offset of a stimulus (Figure 2b). The observation that visual stimuli are perceived as shorter than auditory stimuli [61,62] might result from differences in the temporal resolution of the auditory and visual pathways. Similarly, attention and expectancies might influence the response to the onset and offset of a stimulus. Attended objects might reach a recognition threshold faster than unattended objects [44,63,64], which would result in an increase in perceived duration [44]. In contrast to the extended percept of attended objects, expected events might be perceived as shorter than unexpected objects because their hold on attention is reduced, leading to premature termination of stimulus processing.

A variant of these access effects also might account for the temporal compression illusion described above [50]. Compression occurs when a saccade target appears just before the first flash marking the start of the 100 ms interval. The abrupt onset of the saccade target might capture visual attention, delaying the recognition of the initial flash and, thus, result in a temporally shortened percept. Even when such masking-like effects are eliminated, compressive effects could be due, at least in part, to attentional effects. The spatial specificity observed in Burr *et al.* [38] occurs under conditions in which attention is biased away from the location of the standard stimulus (i.e. inhibition of return [65]). This would delay the recognition of this stimulus relative to other locations, resulting in an illusory compression of time.

Future directions

Following a modular paradigm, neuropsychological research generally has promoted models in which time is represented by dedicated neural systems. An appealing

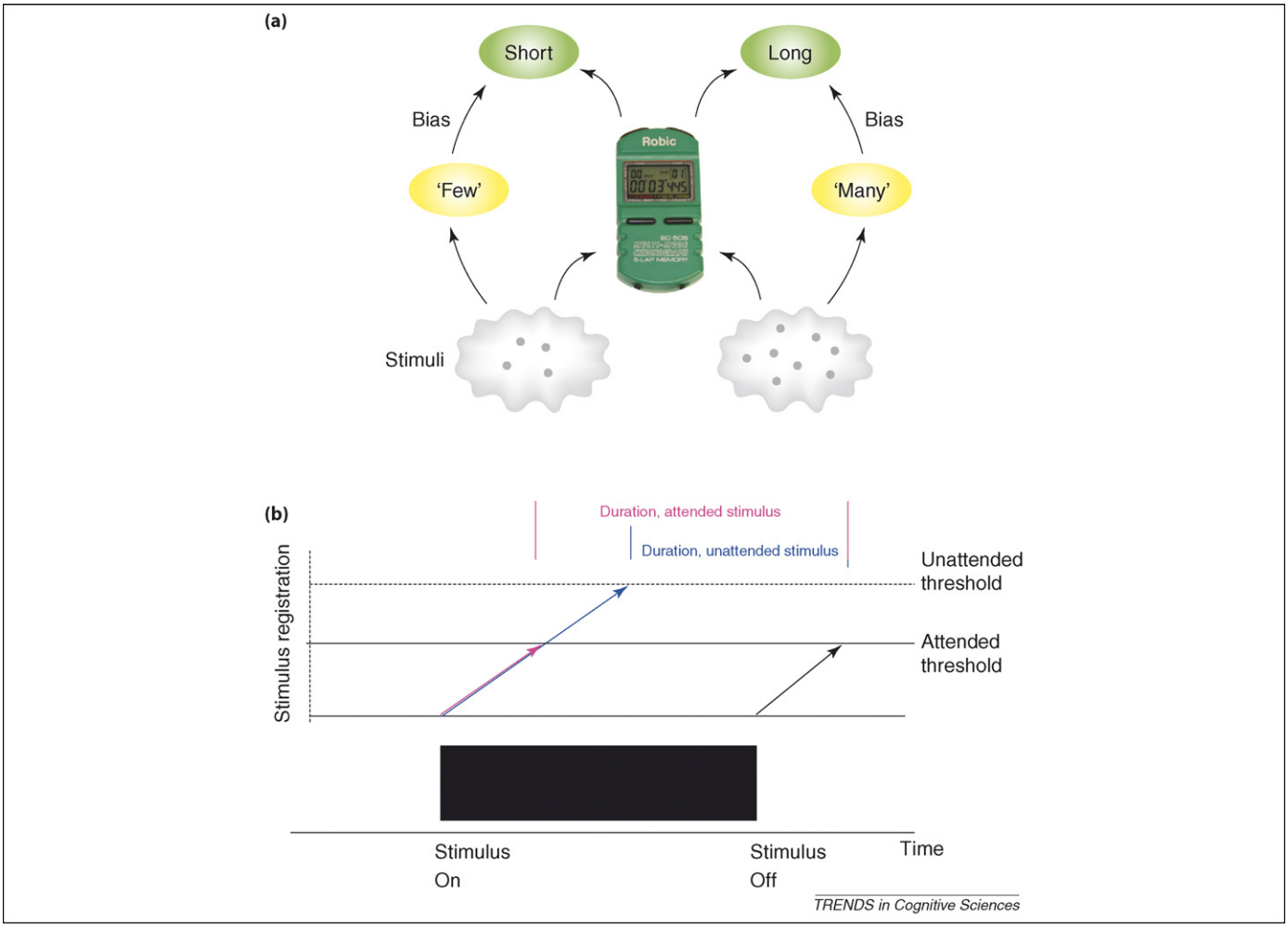

Figure 2. Nontemporal processes influence on the passage of time. **(a)** Decision processes in a time-perception task can be biased by nontemporal factors. For a stimulus presented for a fixed duration, a visual display composed of many dots is perceived as longer than a display composed of few dots. This illusion could result from the incidental activation of the overlap of spatial and temporal concepts. The spatial concepts 'few' and 'many' map onto 'short' and 'long', respectively. **(b)** Processes involved in detecting the onset and offset of a stimulus will influence perceived time. The registration threshold for an attended object is lower than for an unattended object. Assuming attention is then directed to the stimulus, the threshold for registering the offset will be the same for both stimuli, resulting in a longer perceived duration for the attended object. Similarly, faster detection times for the onset of an auditory stimulus might help explain why auditory stimuli are perceived as longer than visual stimuli. These nontemporal effects are relevant independent of whether temporal processing is dependent on dedicated or intrinsic mechanisms.

feature of these models is that they account for supramodal features of time perception and provide a principled basis for linking temporal processing in action, perception and cognition. By contrast, recent physiological and computational studies have highlighted how temporal information is reflected in the intrinsic dynamics of neural activity. This work complements behavioral studies showing distortions and disruptions of time perception that appear at odds with dedicated models.

Nonetheless, there remains much to be done in linking these behavioral and physiological signatures to a computational architecture of temporal representation. Intrinsic models need to account for some of the phenomena that provided the initial impetus for dedicated models; for example, these models need to account for commonalities, both in terms of behavior and neural systems, observed across disparate tasks requiring precise timing. Moreover, many of the effects now taken as evidence in favor of intrinsic mechanisms might, in actuality, be demonstrations of how nontemporal information can influence performance on temporal perception tasks. An important point to guide future research in this arena is that temporal and nontemporal mechanisms need not be married. Processes related to sensory registration, attention and decision making remain relevant, regardless of whether temporal representation is dependent on a dedicated process such as a pacemaker or tapped delay line or an intrinsic process such as the firing rate of sensory neurons or the spatial pattern across a state-dependent network.

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Timing in the Absence of Clocks: Encoding Time in Neural Network States

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SUMMARY

Decisions based on the timing of sensory events are fundamental to sensory processing. However, the mechanisms by which the brain measures time over ranges of milliseconds to seconds remain unclear. The dominant model of temporal processing proposes that an oscillator emits events that are integrated to provide a linear metric of time. We examine an alternate model in which cortical networks are inherently able to tell time as a result of time-dependent changes in network state. Using computer simulations we show that within this framework, there is no linear metric of time, and that a given interval is encoded in the context of preceding events. Human psychophysical studies were used to examine the predictions of the model. Our results provide theoretical and experimental evidence that, for short intervals, there is no linear metric of time, and that time may be encoded in the high-dimensional state of local neural networks.

INTRODUCTION

All forms of sensory processing are ultimately based on decoding the spatial and/or temporal structure of incoming patterns of action potentials. The elucidation of the neural mechanisms underlying the processing of spatial patterns has advanced considerably in the past 40 years. For example, the coding and representation of simple spatial patterns, such as the orientation of a bar of light, are well characterized in primary visual cortex (Hubel and Wiesel, 1962; Ferster and Miller, 2000). Indeed, much has been discovered about the mechanisms underlying the emergence of orientation-selective cells and their role in perception (e.g., Miller et al., 1989; Ferster and Miller, 2000; Gilbert et al., 2000; Schoups et al., 2001; Yang and Maunsell, 2004).

In comparison with spatial stimuli, there is a significant gap in our understanding of how the brain discriminates simple temporal stimuli, such as estimating the duration of time for which a light or tone is presented. Recent studies have begun to examine the neural (Kilgard and Merzenich, 2002; Hahnloser et al., 2002; Leon and Shadlen, 2003) and anatomical (Rao et al., 2001; Lewis and Miall, 2003; Coull et al., 2004) correlates of temporal processing. However, the neural mechanisms that allow neural circuits to tell time and encode temporal information are not clear. Indeed, it has not yet been determined if timing across different time scales and modalities relies on centralized or locally independent timing circuits and mechanisms (Ivry and Spencer, 2004).

Timing is critical in both the discrimination of sensory stimuli (Shannon et al., 1995; Buonomano and Karmarkar, 2002; Ivry and Spencer, 2004; Buhusi and Meck, 2005) and the generation of coordinated motor responses (Mauk and Ruiz, 1992; Ivry, 1996; Meegan et al., 2000; Medina et al., 2005). The nervous system processes temporal information over a wide range, from microseconds to circadian rhythms (Carr, 1993; Mauk and Buonomano, 2004; Buhusi and Meck, 2005). We will focus on the scale of milliseconds and seconds, in which the dominant model of temporal processing is the internal clock model. A prototypical clock model includes an oscillator (pacemaker) that emits pulses that are counted by an accumulator (Creelman, 1962; Treisman, 1963; Church, 1984; Gibbon et al., 1997). Within this framework, the pulse count provides a linear metric of time, and temporal judgments rely on comparing the current pulse count to that of a reference time. This model has proven effective in providing a framework for much of the psychophysical data relating to temporal processing (Church, 1984; Meck, 1996; Rammsayer and Ulrich, 2001). However, electrophysiological and anatomical support for the putative accumulator remains elusive, and mounting evidence indicates that clock models are not entirely consistent with the experimental data (for reviews see Mauk and Buonomano, 2004; Buhusi and Meck, 2005).

A number of alternate models of timing have been suggested (see Discussion; for reviews see Gibbon et al., 1997; Buonomano and Karmarkar, 2002; Buhusi and

Meck, 2005). One such class of models, state-dependent networks (SDNs), propose that neural circuits are inherently capable of temporal processing as a result of the natural complexity of cortical networks coupled with the presence of time-dependent neuronal properties (Buonomano and Merzenich, 1995; Buonomano, 2000; Maass et al., 2002). This framework, based on well-characterized cellular and network properties, has been shown to be able to discriminate simple temporal intervals on the millisecond scale, as well as complex spatial-temporal patterns (Buonomano and Merzenich, 1995; Buonomano, 2000; Maass et al., 2002). Here we examine the mechanisms and nature of the timing in this model and show that it encodes temporally patterned stimuli as single "temporal objects," as opposed to the sum of the individual component intervals. This generates the counterintuitive prediction that we do not have access to the objective (absolute) time of a given interval if it was immediately preceded by another event. This prediction is tested and confirmed using independent psychophysical tasks. Together, our results provide a mechanistic account of the distinction between millisecond and second timing and suggest that within the millisecond range, timing does not rely on clock-like mechanisms or a linear metric of time.

RESULTS

State-Dependent Networks

An SDN composed of 400 excitatory (Ex) and 100 inhibitory (Inh) recurrently connected integrate-and-fire units was simulated using NEURON. The synapses in the network exhibit short-term forms of synaptic plasticity and both fast and slow IPSPs (see Experimental Procedures). Short-term synaptic plasticity (Zucker, 1989) plays a critical role in SDNs by altering the state of the network in a time-dependent fashion after each input, which in turn produces time-dependent neuronal responses. In essence, in the same manner that long-term plasticity may provide a memory of a learning experience (Martin et al., 2000), SDNs use short-term synaptic plasticity to provide a memory trace of the recent stimulus history of a network (Buonomano, 2000).

The functional properties of an SDN can be understood if we consider the sequential presentation of two brief and identical events (e.g., two auditory tones) 100 ms apart (Figure 1A). When the first event arrives in the network, it will trigger a complex series of synaptic processes resulting in the activation of a subset of neurons. When the same event is repeated 100 ms later, the state of the network will have changed from S_0 to S_{100}. Due to the time-dependent changes in network state (imposed by short-term synaptic plasticity), the population response to the second stimulus inherently encodes the fact that an event occurred 100 ms before. In this fashion the network implements a temporal-to-spatial transformation—i.e., the presence, absence, or number of spikes from a given subset of neurons will depend on the temporal structure of the stimulus. The model is stochastic in the sense that determining which neurons will be interval sensitive is a complex function of the network's random connectivity, assigned synaptic strengths, and short-term plasticity (Buonomano, 2000). Once time is encoded in a spatial code, it can be read out by a set of output neurons (see below; Buonomano and Merzenich, 1995; Buonomano, 2000; Maass et al., 2002; Knüsel et al., 2004).

In this model, there is no explicit or linear measure of time like the tics of an oscillator or a continuously ramping firing rate (see Discussion; Durstewitz, 2003). Instead, time is implicitly encoded in the state of the network—defined not only by which neurons are spiking, but also by the properties that influence cell firing, such as the membrane potential of each neuron and synaptic strengths at each point in time. Thus, even in the absence of ongoing activity, the recent stimulus history remains encoded in the network. The simulation in Figure 1 consists of 500 neurons and a total of 12,200 synapses, allowing us to define the network's state in 12,700-dimensional space. Since the state of the network ultimately determines the response to the next input, we can think of its evolving trajectory through this space as encoding time. Principal component analysis was performed to provide a visual representation of this trajectory (see Experimental Procedures). In response to a single stimulus, the first three principal components establish a rapidly evolving neural trajectory through state-space, followed by a much slower path settling back toward the initial state (Figure 1B). When a second event is presented at t = 100 ms, it produces a perturbation in state-space different from the t = 0 event (Figure 1C). Similarly, additional presentations of the same stimulus at varying delays would continue to produce cumulative changes in network state.

The time it takes for the network to return to its initial state—its reset time—is a function of the longest time constants of the time-dependent properties. For short-term synaptic plasticity, this is on the order of a few hundred milliseconds (Zucker, 1989; Markram et al., 1998; Reyes and Sakmann, 1998). The dynamics of short-term plasticity must run its course; thus, the network cannot return to its initial state on command. As addressed below, this property has important implications for temporal processing.

Temporal Objects

An important feature of SDNs is that they naturally extend beyond simple interval discrimination to the processing of complex temporal sequences. This is due to the cumulative nature of changes in network state (Buonomano and Merzenich, 1995; Maass et al., 2002). However, potential weaknesses in SDNs arise because of both the absence of an explicit metric of time and their sensitivity to changes in initial state.

To examine these issues we investigated the ability of the network to discriminate between 100 and 200 ms intervals (we will use the notation [100] × [200] ms), as well as two simple patterns that contain these intervals, namely

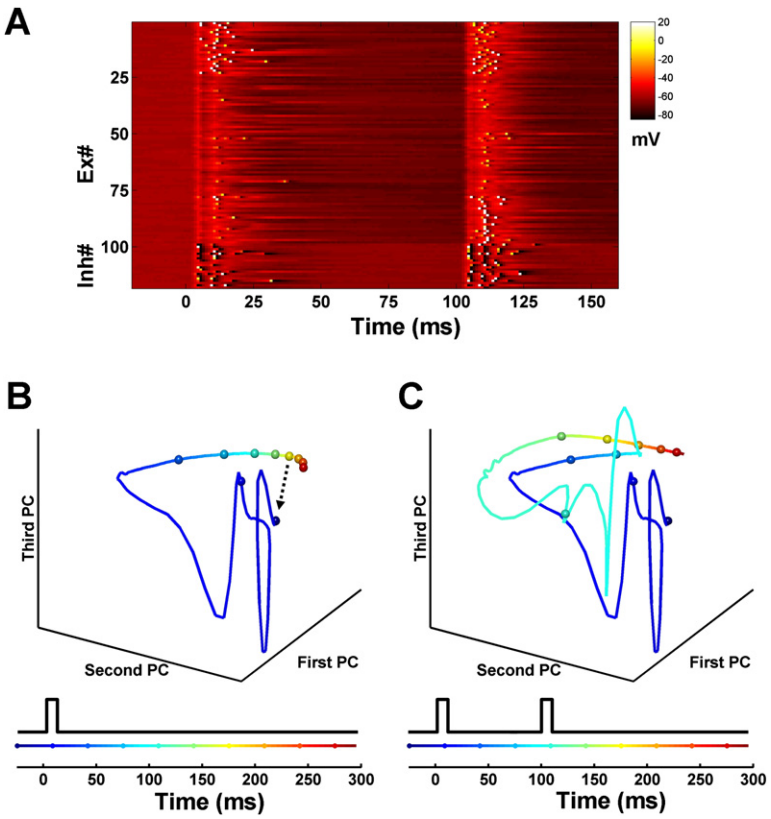

Figure 1. State-Dependent Network Simulation

(A) Voltage plot of a subset of neurons in the network. Each line represents the voltage of a single neuron in response to two identical events separated by 100 ms. The first 100 lines represent 100 Ex units (out of 400), and the remaining lines represent 25 Inh units (out of 100). Each input produces a depolarization across all neurons in the network, followed by inhibition. While most units exhibit subthreshold activity, some spike (white pixels) to both inputs, or exclusively to the first or second. The Ex units are sorted according to their probability of firing to the first (top) or second (bottom) pulse. This selectivity to the first or second event arises because of the difference in network state at t = 0 and t = 100 ms.

(B) Trajectory of the three principal components of the network in response to a single pulse. There is an abrupt and rapidly evolving response beginning at t = 0, followed by a slower trajectory. The fast response is due to the depolarization of a large number of units, while the slower change reflects the short-term synaptic dynamics and slow IPSPs. The speed of the trajectory in state-space can be visualized by the rate of change of the color code and by the distance between the 25 ms marker spheres. Because synaptic properties cannot be rapidly "reset," the network cannot return to its initial state (arrow) before the arrival of a second event.

(C) Trajectory in response to a 100 ms interval. Note that the same stimulus produces a different fast response to the second event. To allow a direct comparison, the principal components from (B) were used to transform the state data in (C).

a 100 or 200 ms interval preceded by a 150 ms interval ([150; 100] and [150; 200]). We calculated the information each neuron in the network contains for the discrimination of both sets of stimuli. Mutual information was determined based on the number of spikes in each neuron (see Experimental Procedures). The neurons containing information for the [100] × [200] and the [150; 100] × [150; 200] discriminations fall in largely nonoverlapping populations (Figure 2A). This occurs even though the discrimination could in principle be based on the same [100] × [200] interval. Since the individual intervals are encoded in the context of the whole stimulus, the network cannot recognize that the [100] and [150; 100] patterns share a common feature. Nevertheless, it can discriminate between all four stimuli (Figure 2B). Each stimulus is coded as a distinct temporal object regardless of its component features.

Reset Task

The prediction that emerges from the model is that if a distractor precedes a 100 ms target interval at random intervals, discrimination of the target should be impaired in comparison to a 100 ms interval with no distractor (or one preceded by a fixed distractor). This prediction was examined using psychophysical studies. We designed a task (Figure 3A) in which each trial consisted of a randomly interleaved presentation of a single two-tone (2T) or three-tone (3T) stimulus, and participants were asked to judge the interval between the last two tones. In the 3T case the first tone acts as a distractor. By independently and adaptively varying the intervals, discrimination thresholds were calculated for the 2T and 3T tracks (see Experimental Procedures). The randomly interleaved—and thus unpredictable—presentation of the 3T stimuli also ensured that the subjects did not adopt strategies to ignore the distractor. The standard interval (SI) was presented at the beginning of a trial and maintained implicitly as a result of feedback to each response (Grondin and Rammsayer, 2003; Karmarkar and Buonomano, 2003). Subjects were asked to judge whether the target interval was shorter or longer than the standard. Two classes of distractors, fixed (FIX) and variable (VAR), were examined. In the FIX condition, the distractor was always presented at a fixed interval before the target interval. In the VAR condition, the distractor was presented at a range of times (±50% of the standard).

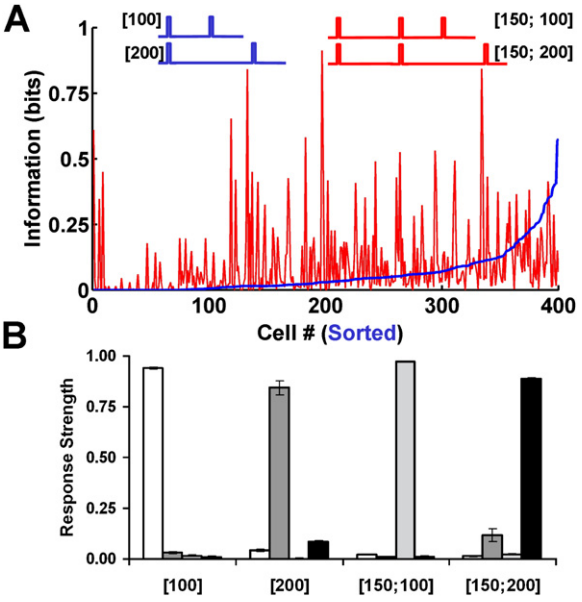

Figure 2. Encoding of Temporal Patterns

(A) Information per neuron. The blue trace displays the mutual information that each Ex unit provides for the discrimination of a 100 versus 200 ms interval (sorted). The red line shows the information for the same intervals preceded by a 150 ms interval; that is, discrimination of the pattern [150; 100] versus [150; 200]. While individual neurons contain significant information for both stimuli, a different population of neurons encodes each one.

(B) Discrimination of all four stimuli. All Ex units were connected to four output neurons trained to recognize the network activity produced by the last pulse of all four stimuli. Average responses were calculated from six independent (different random number generator seeds) simulations. Note that a mutual information measure based on total spike count to each stimulus, as in (A), would introduce a confound because the number of spikes is also a function of the number of events (see Experimental Procedures). Each group of four bars represents the responses of the four output neurons.

This task was termed the "Reset task" based on the unique constraints it places on the temporal encoding mechanisms. If a subject were using a simple stopwatch strategy, he or she would have to start the stopwatch at the first tone, even though it is irrelevant in the 3T trials. The true role of the second tone can only be determined retroactively by the presence or absence of a third tone. With a stopwatch, one approach could be to quickly record the time at t_2 and then reset the watch. Alternately, the time at t_2 and t_3 could be noted and then t_2 subtracted from t_3 to obtain the interval between the second and third tones. We will refer to the first strategy as a clock reset mechanism and the second as temporal arithmetic. Both can be implemented with internal clock models, either because the accumulator could be reset, or because the presence of a linear temporal metric would allow for temporal arithmetic. Both clock-based models predict that performance on the 2T and 3T tracks should be similar in both the FIX and VAR conditions because the predictability of the distractor should not affect the encoding of t_1-t_2 and t_2-t_3.

In contrast, in the SDN model, a reset strategy cannot be implemented because short-term plasticity cannot be reset on cue. Temporal arithmetic cannot be performed due to the absence of a linear metric of time. SDNs predict that performance on the FIX condition will be similar for the 2T and 3T stimuli because the feedback at the end of each trial can be used to establish consistent states on which to build internal temporal representations for both stimuli. However, they also predict an impaired performance in the 3T-VAR trials compared with the 2T or FIX conditions since the state of the network will not be reproducible across trials.

Subjects were first tested with a target interval of 100 ms (SHORT). Consistent with previous studies, thresholds for the 2T conditions were in the range of 20% of the target (Wright et al., 1997; Karmarkar and Buonomano, 2003). A two-way analysis of variance (ANOVA) revealed a significant interaction between conditions (FIX × VAR) and tone number (2T × 3T; $F = 57.75$; $n = 15$; $p < 0.0001$), demonstrating a dramatic impairment in the 3T-VAR condition only (Figure 3B). Indeed, the threshold in the 3T-VAR condition for a 100 ms interval was similar to that observed in independent (2T only) experiments on a 200 ms interval (46 ± 3.4 ms versus 45 ± 7 ms; data not shown). Thus, under the SHORT condition, the psychophysics supported the predictions of the SDN. In contrast, when the Reset task involved a target of 1000 ms (LONG), there was no effect of the variable distractor, as evident in the lack of interaction in the ANOVA (Figure 3C; $F = 0.087$; $n = 12$; $p > 0.5$). Importantly, the point of subjective equality (PSE) was approximately equal to the target intervals in both the SHORT and LONG experiments, independent of the presence or absence of the distractor in both the FIX and VAR conditions (Figures 3D and 3E). Therefore, a memory component of the task cannot account for the differences observed between the two target lengths.

The specific effect of the variable distractor on the SHORT group is consistent with the prediction of the SDN model. It is unlikely that this result is due to effects such as the increased uncertainty caused by the variable distractor, as the same degree of uncertainty was present in the LONG trials without an accompanying timing impairment. Additionally, the randomly interspersed presentation of the 2T and 3T stimuli ensures the same level of uncertainty for both stimuli (in both conditions), but the 2T-VAR performance was not affected. However, to further examine the general psychophysical effects of a variable distractor, we conducted two additional controls. The first was a task in which the distractor interval was 100 (FIX) or 50–150 ms (VAR) coupled with a 1000 ms target (Short-Long). In addition, subjects performed a frequency discrimination task in which the target frequency was preceded by a tone either at a fixed or variable interval (see Experimental Procedures). Neither the Short-Long [$F = 0.18$; $n = 10$; $p > 0.5$] or frequency [$F = 0.23$; $n = 14$; $p > 0.5$] experiments revealed a decrement in performance produced by the variability of the distractor (Figures 4A and 4B).

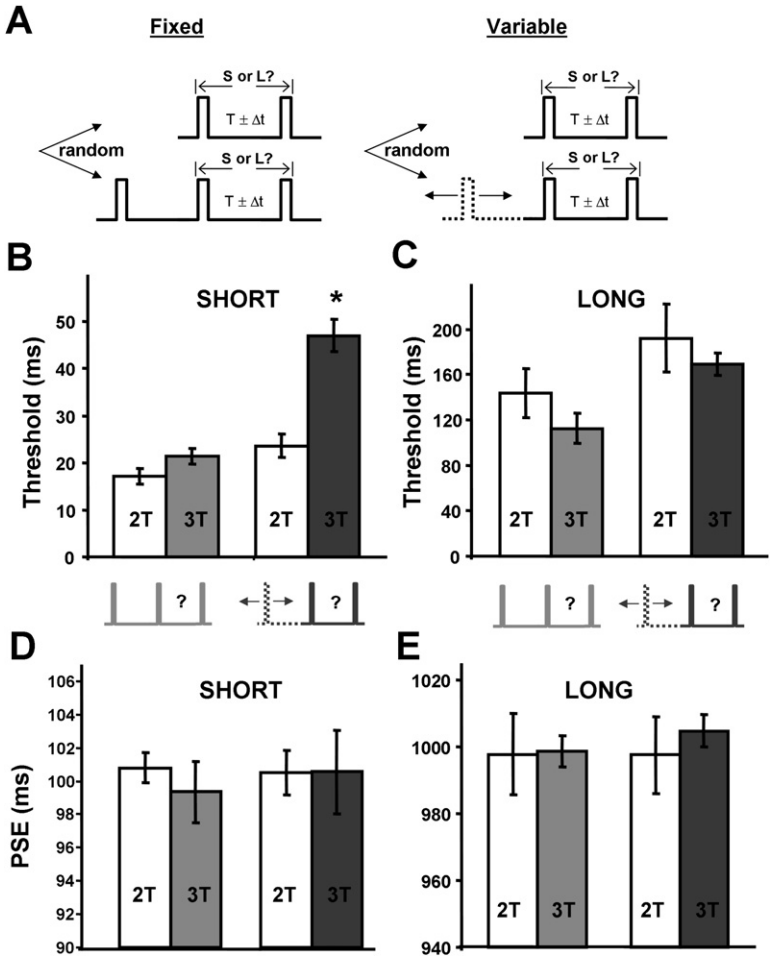

Figure 3. Reset Task: a Variable Distractor Impairs Discrimination of a Short, But Not a Long, Interval

(A) Reset task. Top rows represent the standard 2T interval discrimination task in a single stimulus protocol. Subjects are asked to press different mouse buttons if they judged the interval to be short (S) or long (L). The feedback across trials results in the creation of an internal representation of the target interval. Bottom rows represent the 3T task in which a distractor is presented at a fixed or variable (dashed) interval across trials.

(B) Thresholds for the 100 ms (SHORT) Reset task. (Left) Thresholds for the 100 ms 2T interval discrimination (open bars) and the 100 ms interval preceded by a distractor presented at the same interval across trials (3T-FIX, gray). (Right) Threshold for the standard 100 ms task (open) and 3T task in which the distractor was presented at variable intervals across trials (3T-VAR; gray). Error bars = SEM. The asterisk represents a significant difference from the other three groups.

(C) Reset task (represented as in A), using a 1000 ms (LONG) target interval. Neither of the main effects nor the interaction was significant.

(D and E) Point of subjective equality (PSE) values for the same experiments shown in (B) and (C), respectively. The PSE was not significantly different from the target intervals of 100 (D) and 1000 ms (E) in any condition.

Effect of the Interstimulus Interval on Performance

It is important to rule out the possibility that the impairments observed in the Reset task were not produced by some complex interaction between uncertainty and the intervals being judged, or that the distractor in the FIX condition was serving as a reference interval (see Discussion). Thus, we examined the prediction of the SDN model using a second independent psychophysical test. The SDN model predicts impaired performance under conditions when the network state at the time of the target stimulus varies across trials. This condition can also be produced by insufficient reset time before the next stimulus is presented. To test this directly, we examined performance on a traditional two-interval two-alternative forced-choice task (Wright et al., 1997) in which the interstimulus interval (ISI) was varied. In this paradigm, subjects heard both the 100 ms target and a longer comparison interval, then made a judgment as to whether the longer stimulus occurred first or second. We presented the two intervals with a mean ISI of either 250 or 750 ms. Since experimental data suggests that short-term plasticity operates on the time scale of a few hundred milliseconds (Markram et al., 1998; Reyes and Sakmann, 1998), the state-dependent model predicts that the network will not have completely returned to its initial state in the ISI_{250} condition, thus impairing temporal discrimination. Indeed, a comparison of the ISI_{250} to the ISI_{750} condition showed a significant decrease in performance for the shorter ISI [$t = 3.53$; $n = 10$; $p < 0.01$] (Figure 5A). Subjects also performed a frequency discrimination task under the short and long ISI conditions, for which they reported if the tone pitch was higher for the first or second stimulus. There was no difference between the two conditions [$t = 0.53$; $n = 10$; $p > 0.5$] (Figure 5A), indicating that the effect of the shorter ISI was specific to time discrimination.

The state-dependent framework predicts that the two intervals are more difficult to compare, resulting in higher temporal discrimination thresholds, because their state-space trajectories have different starting points which vary from trial to trial. The total length of time from the first tone of the first stimulus to the first tone of the second is determined by the exact duration of the ISI (250% ± ≤25%). As a result, the variability in the initial state for the second stimulus is caused by the first—the first interval interferes with the second. However, if the target and comparison stimuli were presented at the same ISI, but

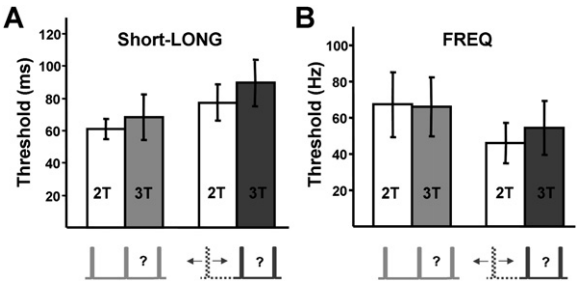

Figure 4. Control Interval and Frequency Discrimination Tasks

(A) Short-Long Reset task. The variable distractor in these trials was between 50–150 ms, and the target interval was 1 s. When a short unpredictable distractor preceded a long target interval, there was no effect of whether the distractor was fixed or variable.

(B) Frequency task. A tone was presented in the absence of a distractor (open bars) or in the presence of a distractor tone presented at a fixed (gray bar, left) or variable (gray bar, right) interval before the target tone. Conventions as in Figure 3.

to different local networks, the impairment produced by the short ISI should be decreased or absent. To examine this prediction, we took advantage of the known tonotopic organization of the auditory system. We performed interval discrimination tasks under two experimental conditions: (1) as above, a 100 ms standard and a comparison (100 + ΔT ms) played at 1 kHz at ISI_{250} and ISI_{750}; (2) a similar condition except that one of the stimulus intervals was played at 4 kHz and the other at 1 kHz. Replicating the

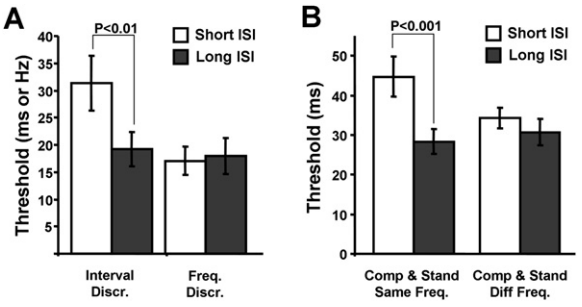

Figure 5. Short Interstimulus Intervals Impair Interval, but Not Frequency, Discrimination

(A) Bars on the left show the thresholds for a two-interval two-alternative forced-choice discrimination with a 100 ms target. When the interval between the stimuli was short (250 ms), performance was significantly worse compared with that in the long ISI condition (750 ms). In contrast, performance on a frequency discrimination task was unaltered by the ISI.

(B) Bars on the left illustrate the results for short (250 ms) and long (750 ms) ISI when both the standard and comparison intervals were presented at the same frequency. Bars on the right represent the interval discrimination thresholds when the standard and comparison stimuli were presented at different frequencies. We believe the difference in absolute interval discrimination between both studies (right bars in A and B) reflects interference between the different task and stimulus sets in both studies, as well as the inherent subject variability observed in timing tasks.

above results, Figure 5B shows that there was a significant increase in the threshold of the ISI_{250} compared with the ISI_{750} tasks [$t = 6.85$; $n = 9$; $p < 0.001$] in the same frequency condition. However, using different frequencies for the standard and comparison intervals eliminated any impairment in performance on the short ISI [$t = 0.85$; $n = 9$; $p > 0.3$].

Interval Discrimination despite Differences in Initial State

While the insufficient reset time in the above experiments (Figure 5A) impaired discrimination thresholds, it did not entirely prevent subjects from performing the task. We were thus interested in returning to the theoretical model to determine how performance varied as a function of ISI and whether some degree of timing was still possible with only a partial reset of the network. First, the trajectory of the network in state-space was calculated in response to two 100 ms intervals separated by a 250 or 750 ms ISI. As shown in (Figure 6A), a 750 ms ISI allows the network to return to a point very close to its "naive" initial state. As a result, the trajectory produced by the second stimulus closely traces that produced by the first one. In contrast, for the 250 ms ISI, the network does not return to the neighborhood of the initial state, and its trajectory for the second interval is significantly different. Measures of these distances are presented in Figure 6B.

To quantify the effect of initial state on interval discrimination, output units were trained to discriminate 100 ms from other intervals in the range of 50–150 ms. We then determined the ability of the model to perform this discrimination when the comparison intervals followed the 100 ms target by ISIs that varied from 250–750 ms. Performance worsened with decreasing ISIs (Figure 6C). Importantly, performance changed in a graded manner, indicating that the reset effect is not expected to be all or none. Thus, the behavior of the theoretical model is consistent with the results seen in the human psychophysical data.

DISCUSSION

The standard model of temporal processing postulates a single centralized internal clock, which relies on an oscillator and an accumulator (counter) (Creelman, 1962; Treisman, 1963; Church, 1984; Grondin, 2001). The clock concept is generally taken to imply that the passage of time is counted in units that can be combined or compared linearly. In contrast, SDN models propose that for spans on the scale of tens to hundreds of milliseconds, time may be represented as specific states of a neural network. Within this framework, a 50 ms interval followed by a 100 ms interval is not encoded as the combination of the two. Instead, the earlier stimulus interacts with the processing of the 100 ms interval, resulting in the encoding of a distinct temporal object. Thus, temporal information is encoded in the context of the entire pattern, not as conjunctions of the component intervals.

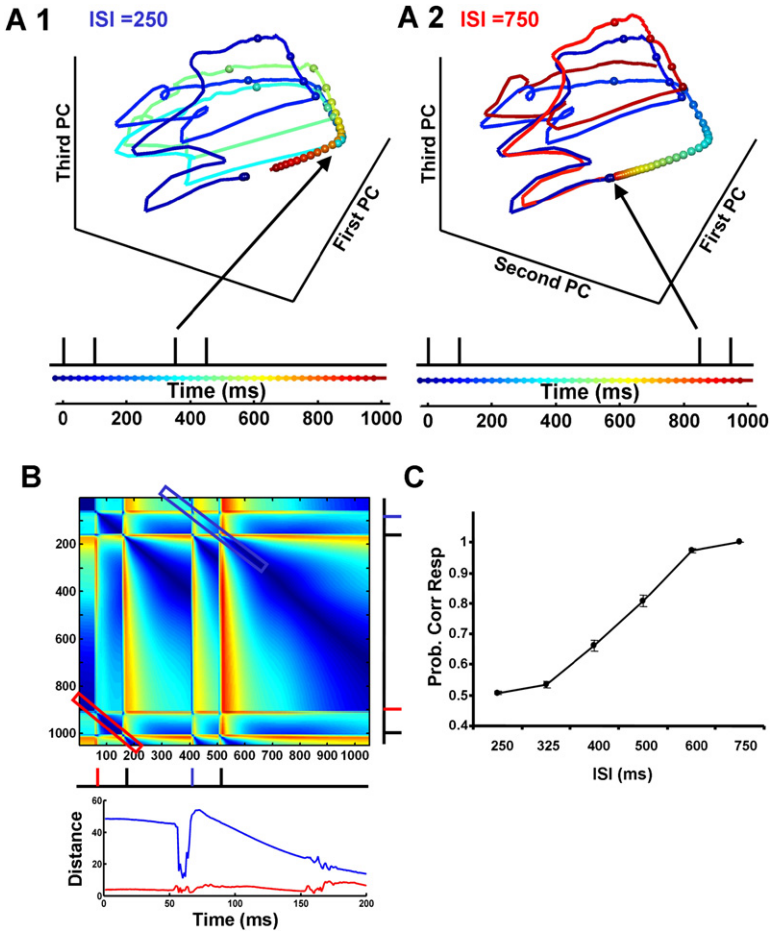

Figure 6. Dependence of the State-Dependent Network on Initial State

(A) Trajectory of the same network shown in Figure 1 and Figure 2, in response to two 100 ms intervals separated by a 250 (A1) or 750 (A2) ms ISI. Note that the trajectories under the 750 ms ISI are much closer to overlapping than they are in the 250 ms condition. Arrows indicate the times of the onset of the second interval.

(B) Distance matrix. The diagonal represents the distance in Euclidean space between the trajectories shown in (A1) and (A2) starting at 0. The distance is zero until the onset of the second tone (the noise "seed" was the same for both simulations). The secondary diagonals permit the visualization of the distances between two trajectories shifted in time. This allows the comparison of the trajectory starting at the onset of the second interval (for the 250 ms ISI) with that of the first interval (blue rectangle and blue line in lower panel), or the second interval of the 750 ms ISI with the first interval (red rectangle and red line in lower panel). These distances, shown in the lower panel, allow for quantification of the effect of the network not returning to its initial (resting) state before presenting the next stimulus. Note that while the initial distance is lower in the 750 ms ISI, it is not zero.

(C) Percent correct performance of networks trained to discriminate two intervals separated by varying ISIs. Average data from four stimulations. Output units were trained to discriminate intervals ranging from 50–150 ms. Performance was then tested by examining generalization to these same intervals when presented at varying ISIs after the presentation of a 100 ms interval. Results for the 100 × 150 ms discrimination are shown. Performance is highly dependent on the initial state of the network.

State-Dependent Networks and the Reset Task

SDN models propose that timing is a ubiquitous component of neural computations, and that local cortical circuits are inherently capable of processing both temporal and spatial information (Buonomano and Merzenich, 1995; Buonomano, 2000; Maass et al., 2002). In these models timing relies on mechanisms analogous to using the evolving state of a physical system—like the ripples on the surface of a lake—to tell time. However, as shown here (Figure 1 and Figure 2), reliance on the state of a complex system to tell time creates potentially serious limitations due to the resulting dependence on the initial state and the lack of a linear metric of time.

Interestingly, our psychophysical results reveal the same limitations—interval discrimination is impaired by the presence of a distractor that appears at unpredictable times. However, interval discrimination was not altered if the distractor occurred at a fixed time prior to the target. Thus, internal representations of the target interval can develop across trials for the 2T and 3T-FIX stimuli, but not for the target interval of the 3T-VAR stimuli. This is because the state of the system at the onset of the second tone is variable. The impairment in the 3T-VAR condition is not due to the unpredictability of the distractor's presence itself; since the 2T and 3T stimuli are randomly intermixed, the unpredictability is the same under all conditions. Rather, the impairment in the 3T-VAR condition is limited to the predictability (consistency) of the *interval* of the distractor.

An alternate interpretation of the 3T-VAR impairment is that in the 3T-FIX condition, the distractor interval served as a reference cue for the target interval. The two-interval discrimination task, in which both a standard and comparison interval are presented on each trial, was used to rule out this possibility (Grondin and Rousseau, 1991; Rammsayer, 1999; Wright et al., 1997). Performance was impaired if the time between the stimuli was 250 ms, but not 750 ms (Figure 5A). It could be argued that the impairment for short ISIs reflects a difficulty in segmenting or attending to rapidly presented stimuli. We find this

interpretation unlikely since performance on the short and long ISI conditions did not differ when the two intervals were presented at different frequencies.

The influence of preceding stimuli on temporal judgments is surprising because much of the timing performed by the nervous system on the scale of hundreds of milliseconds is based on a continuous barrage of incoming stimuli, such as speech or Morse code recognition. The subjects in the current study were naive; thus, a critical issue relates to the effect of learning. We speculate that training would allow subjects to improve their discrimination of intervals independent of temporal context. Indeed, SDN models do not predict that spatial-temporal patterns preceded by other events are impossible to process. Rather, they propose that there must be previous exposure to a large number of instances of the stimuli so that a correspondence between the target information in a number of different contexts can be learned.

Clock Models

The standard clock models predict a linear metric of time, which implies that the clock can time the sequential intervals independent of the presence of a variable distractor across trials. However, most of these models do not explicitly address the issue of the clock reset properties. Thus, it seems reasonable to consider whether a clock with some state-dependent properties could account for the impaired timing of short ISIs or intervals with a distractor. For example, one could assume that resetting or reading the time of the clock is state-dependent, and thus, the reset process could inject noise into the system or be delayed dependent on the initial state.

There are two aspects of our results which could argue against a state-dependent clock mechanism. First, though a state-dependent reset of a centralized clock could explain impaired timing in the short ISI condition (Figure 5A), it would not predict the lack of impairment in the short ISI condition with different frequencies (Figure 5B). The second issue concerns the specificity of the reset problem. In our Reset experiments (Figure 3), a clock would be started by the first tone and stopped and reset (restarted) by the second. The third tone would again stop the clock. As mentioned above, a state-dependent reset would take time or inject noise into the process, and impair the 3T-VAR sequence compared with the 2T one. However, such a clock would also be expected to impair timing of 3T stimuli in the FIX condition. In both cases, the second tone would stop and reset the clock, because there is a 50% chance that the second tone would be the end versus the beginning of the target interval. This prediction is counter to our psychophysical results. One might then propose the use of multiple clocks, in which the first tone activates a primary clock, the second tone activates a secondary clock (and stops the first), and the third tone stops the second clock. This explanation would correctly suggest that timing is not impaired in the FIX condition, but would also hold for the VAR, again violating the dissociation found in our data.

Nevertheless, we cannot eliminate the possibility that there exists a set of assumptions which can enable clock models to account for the observed millisecond timing results. However, we argue that the SDN model provides the most parsimonious explanation of the current psychophysical data on the processing of short intervals.

Other Models of Temporal Processing

A number of other mechanistic models have been put forth to account for measuring and encoding time. These include climbing firing rate models (Durstewitz, 2003; Reutimann et al., 2004), multiple oscillator models (Miall, 1989; Matell and Meck, 2004), and those based on ongoing network dynamics (Medina and Mauk, 2000; Buonomano, 2005). The latter focus primarily on generating appropriately timed motor responses and will not be discussed here.

The climbing or ramping firing rate models suggest that, like many other stimulus features, time is encoded in the firing rate of neurons. Experimentally it is established that some cortical neurons undergo a more or less linear ramping in their firing rate over time (Niki and Watanabe, 1979; Brody et al., 2003; Leon and Shadlen, 2003). In their simplest form climbing models propose that firing rate represents a linear metric of absolute time. However, recent data suggests that, at least in some cases, these neurons are coding expectation rather than absolute time (Janssen and Shadlen, 2005). Climbing rate models have been discussed primarily in relation to timing of intervals or durations; how they would account for timing of temporal patterns has not yet been addressed. Thus, their predictions for our tasks are not immediately clear. For the Reset task it could be argued that ramping would begin at the first stimulus. Time could be read out in the firing rate at the onset of the second and third tone, assuming activity is not reset by the second tone. However, climbing models would not predict the dramatic impairment observed in the 3T-VAR condition or the effect of short ISIs. We would speculate that ramping firing rates are likely to play an important role in the timing of expected motor responses, but less likely to be involved in the timing of rapid sensory stimuli, particularly for complex tasks such as speech or interpretation of Morse code.

The multiple oscillator model suggests that time is encoded in a population of oscillators with different base frequencies (Miall, 1989; Matell and Meck, 2004; Buhusi and Meck, 2005). Time can be read out by a set of coincidence detectors. This model has the advantages of not requiring an accumulator and being capable of timing multiple consecutive intervals once the oscillators have been triggered. However, how this model will behave in the tasks examined here is again dependent on its assumptions. If each event does not reset the oscillators, this model would be expected to produce a decrease in performance in the 3T-VAR condition, consistent with our results. However, it would not necessarily predict the decrease in performance observed with the short ISIs observed in Figure 5, since its reset mechanisms could be all or none. Furthermore, this model posits that timing is centralized. Thus,

it would not predict that any effect of a short ISI would be dependent on whether the frequencies of the comparison stimuli were the same. We would concur that a multiple oscillator model could contribute to timing in the range of seconds (Matell and Meck, 2004; Buhusi and Meck, 2005), but would argue that it is unlikely to account for the timing on the scale of a few hundred milliseconds.

Millisecond versus Second Timing

Timing in both the range of milliseconds and seconds has often been considered to rely on the same underlying mechanisms (Church, 1984; Macar et al., 2002). The results described here demonstrate qualitative differences in the processing of short and long intervals. Unlike the millisecond range, timing of intervals lasting one second or longer appears consistent with mechanisms that generate a linear metric of time. For a 1 s target subjects could accurately judge the first or second of two consecutive intervals in the Reset task, even though they did not know a priori which was the target. Performance was also independent of both fixed and variable distractors preceding the target interval. This implies that subjects could independently keep track of the objective time of two sequential second-long intervals and implies the presence of a linear metric of time. As described above, two simple strategies that a standard clock model could utilize to perform this task are resetting a clock at the second tone, or contributing values to the performance of temporal arithmetic. For the long intervals we did not observe any decrease in timing accuracy in the 3T versus 2T stimuli. We would suggest that this observation is more consistent with the temporal arithmetic scenario. Specifically, that timing on the order of seconds relies on a linear metric of time, and that the second of two consecutive intervals can be calculated by subtracting the first interval from the final count.

The theoretical framework and psychophysical results described here, together with previous psychophysical (Rammsayer and Lima, 1991), pharmacological (Rammsayer, 1999), and imaging studies (Lewis and Miall, 2003), support the existence of distinct loci for subsecond and second processing. The precise boundary between these forms of temporal processing cannot yet be established. However, it seems likely that they are highly overlapping, and that timing in intermediary ranges (e.g., 400–800 ms) may be accurately performed by both the mechanisms underlying time perception and time estimation. Based on the time constants of short-term synaptic plasticity and other time-dependent neural properties, we suggest that the SDN model is limited to intervals below 500 ms. Additionally, even within a specific time scale, there may be multiple mechanisms contributing to timing, and thus the above models are not mutually exclusive.

Relation to Previous Psychophysical Data

A comprehensive model of temporal processing should provide a detailed description of the neural mechanisms underlying timing, generate novel testable predictions, and account for existing experimental data. Two of the most robust features of temporal processing determined experimentally relate to the scalar property and the role of attention in subjective time estimation. The scalar property refers to the observation that the ratio of the absolute criterion interval and the standard deviation of temporal estimates tends to be constant for long intervals (Gibbon, 1977; Gibbon et al., 1997; Buhusi and Meck, 2005). However, this is not the case for interval discrimination in the range of a few hundred milliseconds (Wright et al., 1997; Mauk and Buonomano, 2004). Thus, we examined how performance scales with short intervals in the SDN model. Results showed that, consistent with the human psychophysical data, temporal resolution is proportionally worse for short intervals (see Figure S1 in the Supplemental Data).

Attention has been widely reported to alter estimates of time in the range of seconds (Hicks et al., 1976; Macar et al., 1994; Brown, 1997; Coull et al., 2004). Internal clock models can account for attention-dependent effects in the second range by assuming a gating mechanism that controls the number of events generated by the oscillator that are counted by the accumulator (Meck, 1984; Zakay and Tsal, 1989). In contrast, on the shorter time scale, divided attention or cognitive load does not appear to specifically alter temporal judgments (Rammsayer and Lima, 1991; Lewis and Miall, 2003). Therefore, the SDN model would be expected to be fairly insensitive to shifts in attention. However, recent studies have revealed that temporal distortions of short intervals can be produced by saccades or stimulus features (Morrone et al., 2005; Johnston et al., 2006). These studies suggest that on short scales, timing is local, and are generally consistent with the SDN model that predicts that temporal processing could occur in a number of different cortical areas on an as-needed basis.

Conclusion

We propose here that cortical networks can tell time as a result of time-dependent changes in synaptic and cellular properties, which influence the population response to sensory events in a history-dependent manner. This framework is applicable to the processing of simple intervals as well as more complex spatial-temporal patterns, and does not invoke any novel hypothetical mechanisms at the neural and synaptic level. Additionally, we propose that timing is not centralized, and can potentially occur locally at both early and late stages of cortical processing. The psychophysical experiments examined here emerged as a direct prediction of this model, and the results are supportive of this general framework. However, establishing the neural basis for timing will ultimately require the accumulation of converging evidence from a number of different fields; of particular relevance will be the use of more complex temporal stimuli in conjunction with in vivo electrophysiology to determine if the population response to ongoing sensory events also contains information about the preceding stimuli.

EXPERIMENTAL PROCEDURES

Neural Network Simulations

The simulated network was composed of 400 Ex and 100 Inh recurrently connected Hodgkin-Huxley units (Buonomano, 2000). Excitatory neurons were randomly interconnected with a probability of 0.2. The mean synaptic weights were adjusted so that neurons responded with zero to three spikes to a short stimulus, as is typical for primary sensory cortex in awake animals (Brody et al., 2002; Wang et al., 2005). Short-term dynamics of excitatory synapses were simulated according to Markram et al. (1998). Short-term synaptic plasticity of Ex→Ex synapses was facilitatory, based on experiments suggesting that paired-pulse facilitation is present in adult cortex (Reyes and Sakmann, 1998; Zhang, 2004). The mean U (utilization), τ_{rec} (recovery from depression), and τ_{fac} (facilitation) parameters were 0.25, 1 ms, and 100 ms, respectively. All three values were randomly assigned using a normal distribution with an SD of 20% of the mean. Short-term plasticity IPSPs in the form of paired-pulse depression was implemented as previously described (Buonomano, 2000).

Mutual Information and Network Readout

Mutual information was calculated using the total number of spikes in response to a stimulus, thus providing an assumption-independent estimate of the amount of information available (Buonomano, 2005). For the discrimination between stimuli with different numbers of pulses (Figure 2A), training of the output units was based on previously described supervised learning rules (Buonomano, 2000; Maass et al., 2002) using only the pattern produced by the last pulse. Training was performed on a set of 25 stimulus presentations and tested on 10 novel test presentations. In the stimulations shown in Figure 6, the outputs were trained to discriminate pairs of intervals (100 ms versus intervals ranging from 50–150 ms). In each case the shortest interval was defined as the short stimulus and the longest as the long stimulus.

Principal Component Analysis

The data set was comprised of the voltage of all Ex and Inh neurons, as well as the synaptic weights (which were time-varying) of excitatory and inhibitory synapses. To reduce the dimensionality of the data set, only 20% of all synaptic weights were used. The data were normalized and the principal components were calculated using the PRINCOMP function in Matlab. Although the dimensionality is very high, the dimensions are highly correlated during the silent period between events (if one cell is hyperpolarized, most cells are hyperpolarized). As a result, the first three principal components can account for a significant amount of the total variability (approximately 75% in Figure 1B). As expected, these components do not account well for the actual response to each event, which is dominated by highly nonlinear dynamics.

Psychophysics

Subjects consisted of graduate and undergraduate students between the ages of 18 and 30 from the UCLA community. All subjects had normal hearing.

Reset Task

These experiments were based on a single-stimulus two-alternative forced-choice protocol as described previously (Karmarkar and Buonomano, 2003). A within-subject design was used; thus, each subject performed the two distractor conditions (FIX and VAR) with each condition having two tracks (2T and 3T). Sessions of the FIX and VAR conditions were given on alternating days over a 1 day period (counterbalanced). Each block within a session consisted of 120 trials: 60 2T and 60 3T. Each tone (1 kHz) was 15 ms in duration and included a 5 ms linear ascending and descending ramp. In the FIX condition, a distractor tone was presented at a fixed interval equal to that of the SI prior to the target. In the VAR condition the distractor occurred before the target at an interval uniformly distributed between SI ± (0.5 × SI). Thresholds for the 2T and 3T tracks were obtained by presenting the target interval as SI ± ΔT, where ΔT varied adaptively according to a three-down one-up procedure (Levitt, 1971; Karmarkar and Buonomano, 2003). Threshold was defined as two times the mean of the reversal values, which corresponds to a 79% correct performance level.

In each trial subjects made a forced choice decision as to whether the stimulus seemed shorter or longer than the target interval by pressing one of two buttons on a computer mouse. They were provided with immediate visual feedback. All stimuli were generated in Matlab and presented through headphones.

The 2T and 3T stimuli were randomly interleaved to ensure that subjects did not develop a strategy that involved ignoring the distractor tone. Additionally, the simultaneous measure of performance on a conventional 2T task and a task with the presence of a distractor provided a control for nonspecific effects such as difficulty of the overall task, attention, and memory. Target intervals were either 100 or 1000 ms.

A similar protocol to the one used above was also used for the frequency discrimination task. Rather than adaptively varying the interval of the tones, their frequency was varied according to F ± ΔF (where F, the target frequency, was 1 kHz). Tone duration was 25 ms.

Two-Interval Forced Choice Procedure

In this task subjects were presented with two intervals on each trial: an SI and the comparison interval (standard + ΔT) (Allan, 1979; Karmarkar and Buonomano, 2003). Subjects were asked to press one of two buttons depending on whether they judged the first stimulus or the second interval to be longer. The SI was 100 ms, and the ISIs for the short and long ISI conditions were 250 and 750 ms, respectively.

The frequency task in the ISI experiments used the same type of stimuli, but shifted the frequency of both tones of the comparison stimulus. Note that in contrast to the single stimulus protocol, subjects could reference the target frequency on each trial as opposed to developing an internal representation of it across trials. We believe this difference, together with the absence of a distractor, is responsible for the improvement in the frequency thresholds as compared with the Reset task. All subjects performed all four tasks in a counterbalanced manner.

Statistics

In the Reset task, the key analysis was the performance on the 3T-VAR task in comparison with *both* the 2T-VAR and 3T-FIX tasks. A difference between only one of these comparisons would suggest a "cross-track" effect of the variable distractor independent of whether it was in the 2T or 3T condition, or impairment of 3T discriminations independent of whether the distractor was presented at a fixed or variable interval. Thus, we performed a two-way ANOVA to determine if there was an interaction between the 2T/3T and FIX/VAR factors.

Supplemental Data

The Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/53/3/427/DC1/.

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Finding the timer

Penelope A. Lewis

In a recent paper, Constantinidis *et al.* have shown that inhibitory relationships between pairs of dorsolateral prefrontal neurons can produce delays in cell activity of 200 to 1400 milliseconds. This is an important finding because it suggests that a simple form of timer might exist in the prefrontal cortex. This provides an alternative to the view that temporal processing occurs mainly in the basal ganglia.

Despite the experiences of the narrator in Proust's *À la Recherche du Temps Perdu* most of us will agree that once lost, time is something which can never be regained. It is thus essential that we keep careful track of our moments as they pass: evolution appears to have provided a system for doing just that. A network of cortical areas that includes the dorsolateral prefrontal cortex (dlPFC) and right hemispheric parietal cortex has been consistently associated with time measurement in neuroimaging and lesion studies (reviewed in [1,2]). Because the data showing involvement of these areas does not provide much information about the kind of activity occurring in them, their precise roles in time measurement, and how they work together to make up a putative 'clock' system, are not yet understood. Consequently we can only conjecture about the kind of neural activity and interaction involved and must therefore fall back upon models outlining possible scenarios.

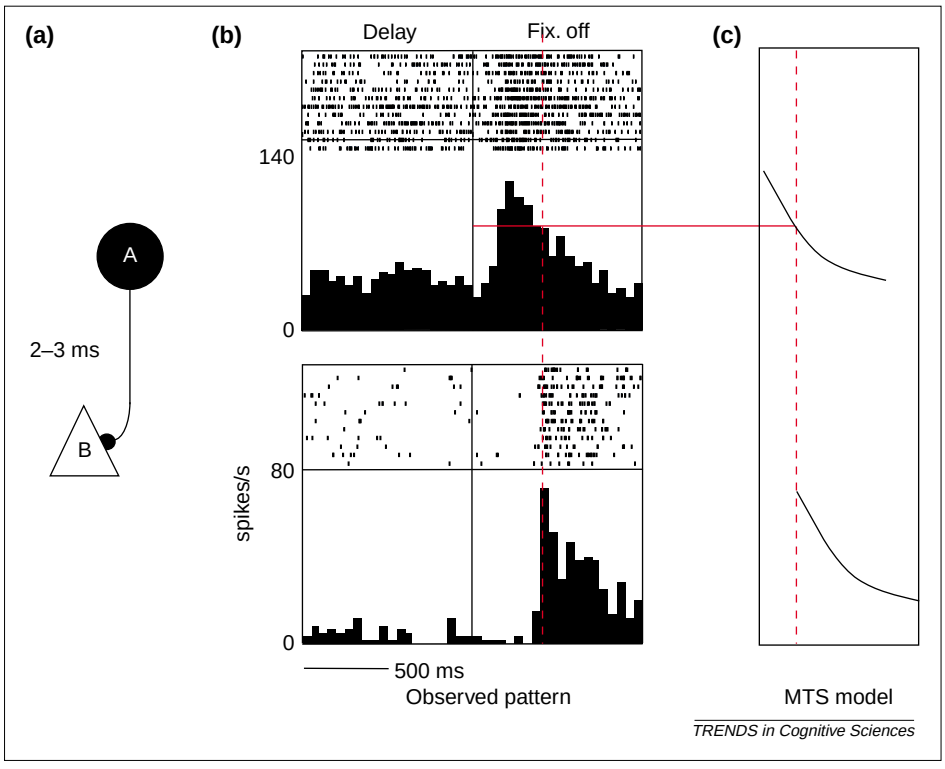

Fig. 1. (a) A feed-forward inhibitory relationship exists between cells A and B such that firing by A leads to a small decrease in activity of B after 2–3 ms. (b) The response function of cells in the dorsolateral prefrontal cortex. The cell at the top (equivalent to A) appears to inhibit the cell at the bottom (equivalent to B) when firing at above a critical frequency threshold of 80–90 spikes per second. Modified from Constantinidis *et al.* [3]. (c) Schematic, using the multiple time scales (MTS) model [5], illustrating how a decay process can be used to measure time if it consistently reaches a threshold height after the same delay.

Inhibitory relationships in the dlPFC

A recent paper by Constantinidis *et al.* has described a phenomenon that provides new avenues for these models [3]; it suggests a novel framework for how and where the measurement of time might occur. The authors recorded from pairs of neurons in the monkey dlPFC, and found an inhibitory relationship between cell pairs such that activity of one neuron was delayed by a time lag of 200 to 1400 milliseconds with respect to activity of the other. Their data suggest that this is likely to be an inhibitory effect because firing in the first neuron led to a brief decrease in activity of the second neuron after a lag of 2–3 milliseconds (Fig. 1a). The shape of the observed response functions (Fig. 1b) implies that activity in the inhibited cell only commenced when decaying activity in the inhibiting cell fell below a specific threshold level. This finding is important because it shows that inhibitory relationships between cells in the dlPFC can lead to sequencing of neural activities, which would provide a mechanism for temporal structure. It also shows that the delays induced by this type of inhibition can be as long as 1 s or more.

An earlier study showed that some cells in the dlPFC increase or decrease their firing rate along a temporally predictable curve during the delay period of a time-measurement task [4]. This curve bears more than a passing resemblance to the decay curves of the 'multiple time scales' (MTS) model of timing [5]. This model explains how time can be measured using increasing or decaying functions to mark off intervals if they consistently take a predictable amount of time to reach a specific threshold level of activity. It makes no attempt to suggest where in the brain such functions might be found. However, Constantinidis *et al.*'s finding that inhibitory interactions can delay the activity patterns of some cells for as long as 1 s, and that this inhibition appears to end when the firing frequency of the inhibiting cell has decayed beyond a certain threshold level, suggests that the predictable decay process observed in the dlPFC could be used, in combination with inhibition, to mark out a specific time interval. If linked into circuits, it would seem reasonable to suppose that temporally predictable inhibitory decay curves such as these might easily be used to measure intervals up to tens of seconds in duration.

Brain models of time measurement

To explain the full significance of this possibility for models of time measurement, it is necessary to outline existing frameworks. Some of the most dramatic data that has emerged in this context is that showing a link between dopamine levels and the rate of subjective time. In a classic paper, Warren Meck showed that rats pretrained to estimate a specific interval

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by pressing a button tended to produce a duration that was too long if their systemic dopamine levels were lowered, and too short if the levels were raised [6]. This effect has been replicated in a range of species. Meck explained the data neatly using a model in which time is tracked by a ticking internal clock, and changes in the speed of ticking relative to real time influence subjective estimates of the duration that has passed. Because this explanation specifies that the *rate* of ticking itself is altered, it is frequently interpreted as showing that the core process of the clock (equivalent to the swinging pendulum or piezo-electric crystal in a man-made mechanical clock) is controlled by dopamine levels. Approximately 80% of the dopaminergic receptors in the brain are localized to the striatum, and therefore this interpretation makes that structure a strong candidate for the locus of the 'central clock'.

This striatal hypothesis has been supported both by data from Parkinsonian patients, who have deterioration of the dopaminergic cells of the substantia nigra and show concomitant deficits in temporal processing tasks [7,8], and by neuroimaging studies that have documented activity in the striatum during time-measurement tasks (reviewed in [1,2]). Some proponents of this framework have suggested that the prefrontal cortex might be involved in memory and or attention functions, keeping track of the core clock process and helping to modulate it rather than being directly responsible for counting the passage of time [2,9].

An alternative framework, proposed in a well-argued article by Matell and Meck, shows how an array of cortical oscillators (periodic timers that repetitively measure the same duration) with different periods, could be used to feed into a striatal coincidence detector [10]. This coincidence detector could learn to use the coincidence of activity in an appropriate subset of oscillators to measure specified intervals. This framework has the advantage of providing an explanation at the cellular level, showing how the specific connectivity between cortex and spiny neurons of the striatum could be used to produce a timekeeper. Until now, however, it lacked a clear mechanism for the proposed cortical oscillators. The findings of Constantinidis *et al*. suggest a potential solution to this problem because the inhibition-induced delays they report could form the basis for an array of putative oscillators. One way in which this might work is by reciprocal inhibition between cell pairs in the dlPFC. Each cell could inhibit the other for a predictable duration, until its firing decreased enough for it to be inhibited in turn, thereby forming a classical oscillator system.

A third, more parsimonious, solution is the possibility that the central clock process occurs in the prefrontal cortex, relying on circuits using the types of delays described by Constantinidis *et al*., and the striatum is not involved at all. Although the striatum is heavily dopaminergic, it holds no monopoly on that transmitter, which is also found in many other regions of the brain including the dlPFC. It is entirely plausible that modulation of the dopaminergic dlPFC inputs might alter the observed delay relationships between cell pairs in a way that could lead to the classic dopaminergic effect seen by Meck and others. This third possibility is attractive for its simplicity, and is very much in line with current knowledge. Although striatal activity is seen during time-measurement tasks in some neuroimaging papers (for example [9,11,12]), it is absent from the results in at least as many others (for example [1,13–15]). Likewise, although patients with advanced Parkinson's disease and its associated deterioration of dopaminergic projections to the striatum show impaired temporal processing, these patients also have deterioration of the ventral tegmental area [7,8], a region that sends modulatory dopaminergic projections directly to the prefrontal cortex [16].

A framework for progress?

It will be difficult to determine which of these three frameworks is closer to the truth using lesioning and neuroimaging techniques, as these techniques cannot provide information about the behaviour of individual cells or local cellular circuits. Single-unit recording studies along the lines of Constantinidis *et al*.'s method might prove more useful, especially if combined with manipulation of dopamine, either systemically or in the dlPFC specifically. This kind of investigation could search for changes in the slope of increase (or decrease) in cell firing in the dlPFC, which might turn out to match the observed pattern of dopaminergic effect on time measurement.

Although developing models for how time measurement could be accomplished, and running experiments to test and differentiate between these models, is a fascinating pastime, it is important to keep the redundancy of biological systems in mind. Time measurement is such a basic function, which could be accomplished by any number of neural processes, and is so essential to many behaviours, that the existence of redundant mechanisms seems almost inevitable. Thus, work in this field may eventually show that evolution has done its best to help us 'regain' time by equipping us to measure it not just once, but many times using multiple clock mechanisms.

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Time Perception: Components of the Brain's Clock

We know the human brain contains some kind of clock, but determining its neural underpinnings and teasing apart its components have proven difficult. New work on the parietal cortex illustrates how single unit recording may be able to help.

Penelope A. Lewis[1] and Vincent Walsh[2]

Our brains measure time continuously. We are aware of how long we have been doing a particular thing, how long it has been since we last slept, and how long it will be until lunch or dinner. We are ready, at any moment, to make complex movements requiring muscle coordination with microsecond accuracy, or to decode temporally complex auditory signals in the form of speech or music. Our timing abilities are impressive, diverse and worthy of investigation. But they are not very well understood.

Many models of time perception have been put forward (for example, see [1–3]), collectively postulating a wide variety of different mechanisms. Regardless of their diversity, the models all agree that temporal information is processed in many ways: it is remembered, compared to other temporal information, combined with sensory information, and used in the production of motor outputs.

The holy grail of timing research is to understand the 'time-dependent process': a mechanism equivalent to a piezoelectric crystal in a man-made clock or the movement of a shadow on a sundial. This has proven an elusive goal, to the extent that ideas about how this mechanism might work remain near the level of conjecture. Researchers have had great difficulty in pinning timing-related activity in the brain to any specific type of function. This is largely because most time measurement tasks draw upon more than one process, making it difficult to tease the various components apart. In their recent study, Janssen and Shadlen [4] have shown how single unit recording can be used to partially bypass this issue.

Janssen and Shadlen [4] recorded time-sensitive responses in the lateral inferior parietal (LIP) cortex of the macaque. They trained two monkeys to perform a visual delay task: the monkeys first fixated a light, then, in response to a 'go' signal, moved their eyes to a peripheral visual target as quickly as possible (Figure 1). The delay between target onset and 'go' signal varied according to two schedules: a bimodal schedule in which the 'go' cue could come early or late, but not between 0.75 and 1.75 seconds, and a unimodal schedule in which it came between 0.5 and 2 seconds. The schedules were presented in alternating blocks. The observed neural spike frequency in LIP correlated with the expectancy — 'hazard function' — of the 'go' cue

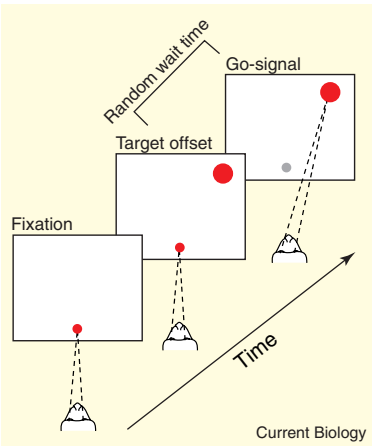

Figure 1. The task used by Janssen and Shadlen [4].

The monkey made eye movements to the red target as soon as the fixation point dimmed. Only trials in which the target appeared in the response field of the LIP neuron were reported. A bracket demarcates the random waiting time between target onset and 'go' signal. (Reproduced with permission [4].)

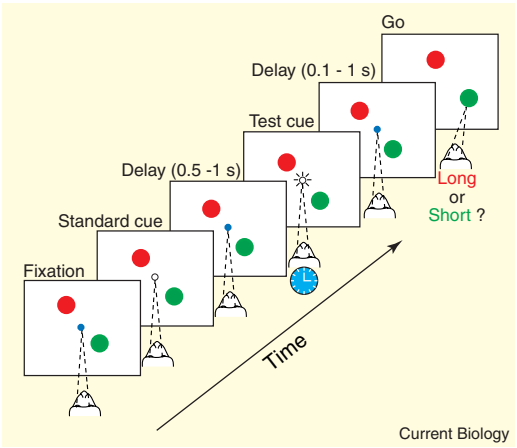

Figure 2. The time-discrimination task used by Leon and Shadlen [5].

A central, blue fixation point turned white for either 316 or 800 ms (the standard cue). After delay of between 500 and 1000 ms, the cue again turned white for a variable period (the test cue). Following a second variable delay between 100 and 1000 ms the blue fixation point disappeared and the monkey made a saccade to one of the two peripheral targets, indicating whether the monkey had judged the test cue to be longer (red) or shorter (green) than the standard cue.

for each of the two delay schedules.

These results build upon the findings of an earlier paper from the same group [5] in which LIP neurons were recorded during a temporal discrimination task. Monkeys fixated during presentation of a standard time interval, as defined by a light, followed by a variable probe interval defined in the same manner. They then indicated that the probe was *longer* than the standard by saccading to a peripheral green target, or *shorter* by saccading to a peripheral red target (Figure 2). Recordings from LIP neurons showed that those with the short (green) light in their receptive field responded at a high frequency until the duration of the standard had elapsed, at which time their response gradually decreased. Neurons with the long (red) light in their receptive field gradually increased responding, such that their response rates eventually 'crossed over' and exceeded those of the green light neurons.

Taken together, these datasets demonstrate that neurons in macaque LIP can respond to temporal information. The origin of that information and the purpose of such responses remain open for debate. If you are searching for the holy grail and you come across a shiny golden cup, it is natural to speculate that this is your object. Shadlen and colleagues have done so by suggesting that the neurons they observed measure time: ".. the monkey could base its judgement of time on the discharge of neurons with properties like the ones we observe" [5]. One of their arguments in favour of this interpretation is that the gradual change from high to low firing rates precludes input from an outside timer because the smooth shift in responding is inconsistent with information from a discreet decision. This pattern does not, however, exclude the involvement of input from a graded external timing signal [6].

In the more recent paper, Janssen and Shadlen [4] admit that they "cannot determine whether the timing-related anticipatory activity arises in area LIP or is simply passed to LIP from other structures that have been implicated in interval timing". Their results show that LIP responds along an expectation function or 'hazard rate' predicting the time of eye movements. It is unlikely that a central clock, providing time signals to a variety of brain regions for a variety of purposes, would compute such a function. These data therefore suggest either a localized parietal timer for eye movements or at least a localized calculation of the hazard rate based upon external timing signals. From the perspective of those not involved in finding the golden cup, the latter possibility appears just as likely as the former. It therefore seems imprudent to assume that these neurons actually measure time until more evidence is forthcoming. Furthermore, the pattern of response in these cells is not consistent with activity patterns predicted by network models of timing, for which one might expect either a periodic signal similar to the ticking of a clock [1,3] or a gradual and predictable ramping up or down of activity [2]. The authors have proposed no mechanism for such a function, and no mechanism is obvious from the literature at either the cellular or network level. Because LIP is widely connected, temporal information could easily be passed to it from other parts of the brain, a scenario which would be in better keeping with the large existing literature implicating structures such as cerebellum [7], basal ganglia [7,8], SMA [9] and dorsolateral prefrontal cortex [10,11] as the seat of time measurement. Thus, there is little evidence to suggest that this is the true grail, and quite a bit to suggest that it is not.

If LIP neurons do not measure time, what is the function of their temporally sensitive response? The most obvious possibility is a role in preparation for eye movements. This is certainly worth considering given that the neurons in question were selected because they responded during preparation for such movements. Leon and Shadlen [5] argue against this explanation, pointing out, amongst other things, that they did not find a correlation between the response functions of these neurons and eye movements. The subsequent demonstration by Janssen and Shadlen [4] of a correspondence between activity in these cells and the expectation that a movement will be cued undermines this argument, as does the observation that neural response frequency or 'expectation' is reflected in movement response times.

Taken together with the clear adaptive advantage conveyed by a tendency to prepare movement only when a cue to move is *expected,* these data provide

substantial support for the possibility that the LIP activity in question is associated with preparation for eye movement. The alternative interpretation offered by Janssen and Shadlen [4], "the intention-related signals seen in our experiments could underlie a shift in spatial attention that is not in competition with an eye movement plan" [4], is not obviously compelling. However, a related scenario in which these cells code for intentionality regarding a response, without being involved in a specific motor plan or tied to a specific motor affector, should also be considered.

The likelihood that LIP neurons do not actually measure time, and that their temporally sensitive responding codes instead for eye movement, do not render these findings uninteresting to the field of time measurement. The parietal cortex is frequently activated in neuroimaging studies of timing — for example, see [8,12], but see also review [11] — and damage to this region [13], as well as temporary disruption via transcranial magnetic stimulation, have both been shown to cause temporal deficits. A number of authors have speculated about the role of parietal cortex in temporal processing, with some papers [8,14] suggesting an attentional function, while another[15] suggests a system for calculating magnitude. Until now, little has been known about how these involvements could be manifest at the neural level.

The demonstration by Janssen and Shadlen [4] that individual LIP neurons can respond to visuo-temporal information confirms that temporal information is available to the parietal cortex. These findings also provide novel and welcome insight into what this area may be doing in time measurement tasks, suggesting that the role of parietal cortex in multisensory integration and the planning of action extends to the modality of time. Thus, by exploring temporal processing in the parietal cortex with single unit recording, Shadlen's group has taken a useful step towards describing the type of temporal processes performed in that region. Their work is also novel because it illustrates the potential of single unit recording as a tool for discrimination between the different forms of temporal processing: perception, memory, preparation for movement, and so on. Similar work in other structures associated with timing may lead to even greater insights. Thus, Shadlen and colleagues may not have found the holy grail of timing research, but they have certainly discovered a treasure trove of information which will undoubtedly lead to a better understanding of this system. And really, its about *time.*

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Axis Formation: Redundancy Rules

The role of BMP antagonists in the Spemann-Mangold organizer of vertebrate embryos is a controversial issue. A study using combined knock down of multiple antagonists finally reveals dramatic effects.

Christof Niehrs

The Spemann-Mangold organizer of vertebrate embryos plays a paramount role during embryogenesis by releasing a cocktail of molecules that induce the embryonic axes and various cell fates. Bone morphogenetic protein (BMP) antagonists are an important class of such inducers, as was discovered in *Xenopus*, where their over-expression has dramatic effects, such as inducing a secondary embryonic axis. By contrast, studies in higher vertebrates — such as chicken and mouse — have yielded less impressive results and have led to a controversy over how important BMP antagonists really are and what their precise role is. In a bold approach, Khoka *et al*. [1] have now knocked down in parallel three BMP antagonists in *Xenopus* embryos and observe dramatic effects on embryonic axis formation.

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Remembering the time: a continuous clock

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The neural mechanisms for time measurement are currently a subject of much debate. This article argues that our brains can measure time using the same dorsolateral prefrontal cells that are known to be involved in working memory. Evidence for this is: (1) the dorsolateral prefrontal cortex is integral to both cognitive timing and working memory; (2) both behavioural processes are modulated by dopamine and disrupted by manipulation of dopaminergic projections to the dorsolateral prefrontal cortex; (3) the neurons in question ramp their activity in a temporally predictable way during both types of processing; and (4) this ramping activity is modulated by dopamine. The dual involvement of these prefrontal neurons in working memory and cognitive timing supports a view of the prefrontal cortex as a multipurpose processor recruited by a wide variety of tasks.

Introduction

Awareness of the passage of time is inextricably intermingled with memory. This is not only true for the remembrance of things past. Sometimes we must remember the beginning of an event to judge its duration but often we must also remember the time as it passes, and if distracted we can 'lose track of time' and burn the muffins or miss the train. In this article, we propose that the same neurons which are used for working memory can also be used to index the passage of time.

Most models of how the brain measures time acknowledge the link between time and memory. In scalar expectancy theory [1], a framework which has dominated the field for almost 30 years, working memory takes the form of an accumulator process which collects quantized ticks from a hypothetical neural pacemaker. A more recent model [2], the multiple time scales (MTS) framework, dispenses with the pacemaker entirely and proposes that time can be measured using the decaying strength of memory traces. In this article, we expand upon this idea by suggesting that continuous, temporally predictable changes in firing rate could be used to measure time, and observe that some of the prefrontal 'delay' cells which are known for their role in working memory actually behave in this manner during timed intervals.

We propose that this temporally predictable ramping activity might serve as the timekeeping process during cognitively controlled time perception. Our hypothesis is supported by four crucial points. First, the dorsolateral prefrontal cortex, where these cells are located, is necessary for cognitively controlled time measurement tasks. Second, both working memory and cognitively controlled timing are modulated by dopamine and disrupted by manipulation of the mesolimbocortical dopamine pathway, which projects to the dorsolateral prefrontal cortex. Third, prefrontal neurons have been shown to ramp their activity in a temporally predictable way during timed intervals, and fourth, this ramping activity appears to be modulated by dopamine. We begin with an explicit definition of the form of time perception under discussion.

What is cognitively controlled timing?

Some timing processes help us to synchronize with our environment, including circadian and ultradian rhythms, for which the mechanisms are relatively well understood [3]. Other forms of time measurement, such as that needed for the coordination of complex movements, estimation of how long it takes to perform specific tasks, or prediction of when the train is about to depart, remain more mysterious. Because these tasks vary widely, it would be surprising if they all drew upon the same brain system.

Many researchers have suggested that distinct mechanisms exist for the measurement of different temporal durations [4–8], for motor versus nonmotor timing [9] and, more recently, for the timing of continuous cyclical versus discrete broken movements [8,10]. Several authors [8,11,12] have also suggested the existence of distinct mechanisms for automatic and cognitive forms of timing.

In a recent article [13], we built upon these findings by proposing that it is not any single characteristic, but rather a constellation of several characteristics which determines which timing system is recruited in any particular task. We tested this proposal using a meta-analysis of the neuroimaging literature on time measurement. Although other task characteristics might also be important, our analysis was constrained to consider just three: the duration measured, whether or not the timed intervals were defined by movement and, whether timing was continuous (e.g. an unbroken series of predictable intervals) or intermittent (e.g. broken into discrete measurements by the presence of unpredictable irregular intervals). Our findings indicated that tasks involving continuous measurement of a series of predictable subsecond intervals defined by movement (e.g. rapid paced finger tapping) tend to recruit primary

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sensorimotor and premotor areas, whereas tasks with the opposing characteristics tend to recruit right hemispheric prefrontal and parietal cortices (Figure 1). These results suggest that tasks recruiting only the sensorimotor system can be performed relatively automatically, whereas tasks which draw upon multipurpose prefrontal and parietal modules known for their involvement in working memory and attention might require more cognitive involvement.

Importantly, our analysis showed that having any two out of the three characteristics associated with a task type (cognitive or automatic) dramatically increased the probability that the areas associated with that timing system would be recruited. Accordingly, we can think of any task having two or more cognitive attributes (e.g. measuring more than a second, discontinuously, and without relying upon movement) as a 'cognitively controlled timing task', and any task with two or more of the opposing characteristics as an 'automatic timing task'. These definitions can be applied *post hoc* to any study of time measurement, a strategy which is useful in determining whether or not the existing literature supports the cognitive–automatic framework.

Cognitively controlled timing, right dorsolateral prefrontal cortex, and memory

Cognitively controlled timing activates the right hemispheric dorsolateral prefrontal cortex (DLPFC) more frequently than any other brain area [13]. The remainder of this article will focus specifically upon this region and its role in tracking the passage of time.

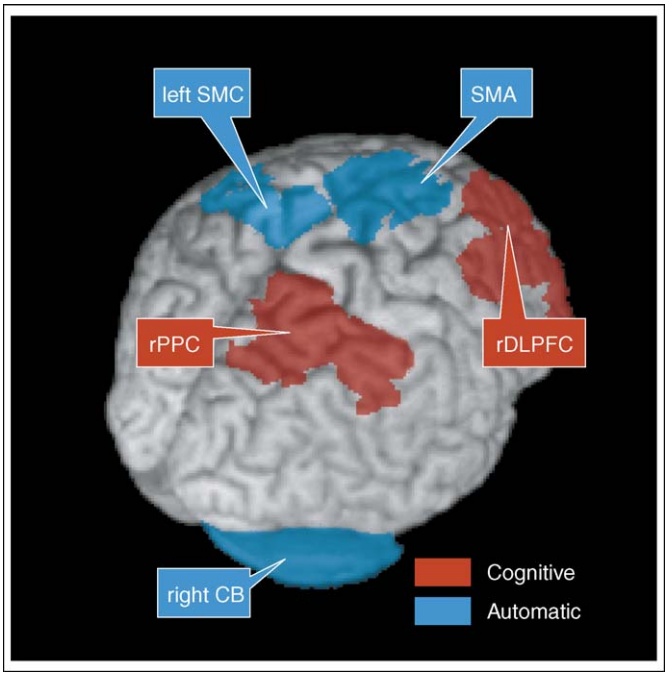

Figure 1. 3D depiction of the human brain regions associated with cognitively controlled (red) and automatic (blue) timing systems. These areas, identified in a meta-analysis of imaging studies [13], were defined for illustration using voxel-labelled templates in the automatic anatomical labelling atlas [50] and the mri3dX Brodmann atlas, rendered onto the SPM canonical brain (http://www.fil.ion.ucl.ac.uk/spm). Abbreviations: CB, cerebellum; SMA, supplementary motor area; SMC, sensorymotor cortex; rPPC, right posterior parietal cortex; rDLPFC, right dorsolateral prefrontal cortex.

The right DLPFC corresponds to the middle portion of middle and superior frontal gyri (e.g. Brodmann areas 9, 9/46 and 46) in humans, and to the region adjacent to the superior frontal sulcus in macaques [14]. That this part of the prefrontal cortex is strongly associated with working memory is evident from numerous studies using targeted lesions and single unit recording in monkeys, as well as from patient work and a vast collection of neuroimaging data [15]. Given the consensus that some form of working memory is important for timing, it is unsurprising that the DLPFC is essential to some timing tasks and that cells in this area exhibit a variety of time-sensitive behaviours [16]. Support for the right hemispheric lateralization of the involvement of this region in timing comes from neuropsychological work [17,18], examination of parkinsonian patients with unilateral deficits influencing the prefrontal cortex [19], and neuroimaging studies showing activity here during timing tasks (see Macar *et al*. [20] and Rubia and Smith [21] for reviews).

Importantly, right dorsolateral prefrontal activity is much more common in cognitively controlled timing tasks than in those classified as automatic [13]. Lesions to this area have been shown to disrupt cognitive timing [17], and the differential involvement of the right DLPFC in cognitive and automatic timing has been supported by a recent transcranial magnetic stimulation study showing impaired reproduction of suprasecond (more cognitive) but not subsecond (more automatic) intervals [22]. A parallel study showed that repetitive transcranial magnetic stimulation to the right but not left DLPFC disrupts the timing of suprasecond durations [23].

Overall, these data suggest that the region of the DLPFC that is known to be important for working memory is also essential for cognitively controlled time measurement but with an apparent bias to the right hemisphere. This area does not appear to be important for more automatic forms of timing.

Working memory and cognitive time measurement draw upon the same mental resources

Behavioural evidence that working memory and time measurement draw upon the same cognitive resources stems from dual-task studies showing interference between these two types of processing. Both visuospatial and phonological working memory tasks disrupt timing, and the extent of such disruption has been shown to correlate with the extent of working memory load (e.g. number of items to be remembered, number of syllables to be rehearsed or degrees of mental rotation) [24]. It is important to note that these experiments used timing tasks that would be classified as cognitively controlled.

Turning to pharmacology, manipulations targeting working memory can also disrupt cognitive timing. For example, benzodiazepines that influence working memory impair the processing of suprasecond intervals [6,8,11,25], whereas timing at the range of milliseconds appears to be unaffected by these drugs [26]. Similar dissociations have been shown for drugs thought to influence attentional processing such as the selective noradrenaline reuptake inhibitor reboxetene [25]. Rammsayer and co-workers [8,11,25] have interpreted this as evidence for two distinct

timing mechanisms: an automatic mechanism for the measurement of durations in the millisecond range and a cognitive mechanism, mediated by attention and drawing upon working memory, for the measurement of intervals in the range of seconds. This proposal differs from our cognitive–automatic framework [13] only in that these authors regard the timed duration as the prime discriminant between systems, whereas we propose that a combination of characteristics determines which system is recruited. Also, Rammsayer and co-workers investigated extremely brief intervals (~50 ms) and placed the cut-off between timing systems at around 500 ms, whereas we suggest that the critical value is closer to 1 s. Irrespective of these minor differences, both frameworks agree that separate systems exist for different types of time measurement and that at least one of these systems draws upon cognitive processors in the prefrontal cortex, with those regions known to be involved in working memory as prime candidates.

Dopamine, DLPFC, time, and memory

Additional evidence linking time perception to working memory stems from the observation that both are modulated by dopamine, a neurotransmitter which regulates activity throughout much of the brain, including the prefrontal cortex. The influence of prefrontal dopaminergic projections upon working memory is well documented [27]. Both increases in prefrontal dopamine and application of dopamine antagonists have been shown to disrupt this process [28], suggesting that deviation from an optimal level is detrimental to performance. Additionally, prefrontal dopamine levels increase during working memory tasks [29] and recording studies have demonstrated dopaminergic modulation of the layer III pyramidal cells associated with maintenance of information in working memory [30] (e.g. 'delay' neurons [28]). The importance of dopamine for temporal processing is also well established. A comprehensive review of work in nonhumans [31] argues that increasing levels of dopamine leads to a speeding up of subjective time. By contrast, decreasing dopamine leads to a slowing of subjective time [18]. In humans, both control subjects [8] and parkinsonian patients [4,19] have demonstrated a strong dopaminergic influence upon temporal processing, although it has been difficult to replicate the precise effects seen in the animal data [32].

Because the basal ganglia are heavily innervated by dopamine, and because their function is severely disrupted in Parkinson's disease, the influence of dopamine on subjective time measurement has typically been interpreted as support for the central role of these structures in timing. However, in addition to the mesostriatal dopaminergic pathway projecting from the substantia nigra to the striatum, the dopaminergic system includes a mesocortical pathway with projections from the ventral tegmental area to the prefrontal cortex. This provides a direct route by which dopaminergic inputs might act upon the prefrontal cortex to influence time perception [8,11,33,34]. The suggestion that mesocortical dopamine might influence cognitive time perception is informed not only by the anatomical overlap between the prefrontal regions innervated by this pathway and those known to be involved in time measurement, but also by the observation that parkinsonian patients experience more severe deficits in temporal processing in the late stages of the disease, when cells in the ventral tegmental area have been destroyed [35,36]. The recent demonstration of temporal deficits in several other dopaminergic disorders involving the prefrontal cortex, such as Huntington's disease [37], schizophrenia [38], and attention deficit hyperactivity disorder [39], are also in line with this view.

Pharmacological studies provide further evidence for the involvement of mesolimbic dopamine in cognitive timing. In a series of targeted investigations, Rammsayer and co-workers capitalized upon the differential influences of various dopamine antagonists upon mesostriatal and mesocortical pathways to determine the relative importance of each for different forms of time perception. They found that remoxipride, an atypical neuroleptic agent which blocks dopamine D2 receptors in the mesocortical system but not in the mesostriatal system, disrupts comparison of durations in the seconds range, without affecting comparisons of durations in the range of milliseconds, or movement timing [11]. The same study showed that haloperidol, which blocks D2 receptors in both systems, impairs the timing of both short and long duration processing and also interferes with movement timing. In conjunction with the results from studies with benzodiazepines and noradrenergic blockers discussed above [6,8,11,25], these data support the role of mesocortical dopamine in a cognitive timing system which draws upon working memory and attention, and of mesostriatal dopamine in both this cognitive system and a more automatic timing process [8,11,25]. Recent work with deep brain stimulation in the subthalamus has also supported a role for the mesostriatal dopaminergic system in cognitively controlled timing [40], with the suggestion that the observed effects might be mediated by striatocortical projections. This raises the possibility that the mesostriatal dopaminergic pathway influences cognitive timing via striatocortical projections, whereas mesostriatal influences on automatic timing are mediated in some other fashion – a proposal which could reconcile the broad literature on dopaminergic influences on timing with the evidence that prefrontal involvement is specific to cognitive timing. This possibility is also in good keeping with our suggestion that dopaminergic influences on cognitively controlled timing stem from the influence of this transmitter on pyramidal cells of the DLPFC because this region receives numerous striatocortical projections (Figure 2).

Overall, the data on dopamine suggest a selective influence of prefrontal dopamine on more cognitive timing tasks, thus implying that this form of timing might be mediated via the same dopamine-sensitive processors as working memory.

Time measurement and memory decay traces

The proposal of time measurement as a continuous process suggests that, rather than using a discrete ticking clock, we use something akin to a continuously fading memory trace of neuronal activity to track the passage of time. This idea was initially suggested at a theoretical level in the form of the MTS model [2]. This model proposes that forgetting

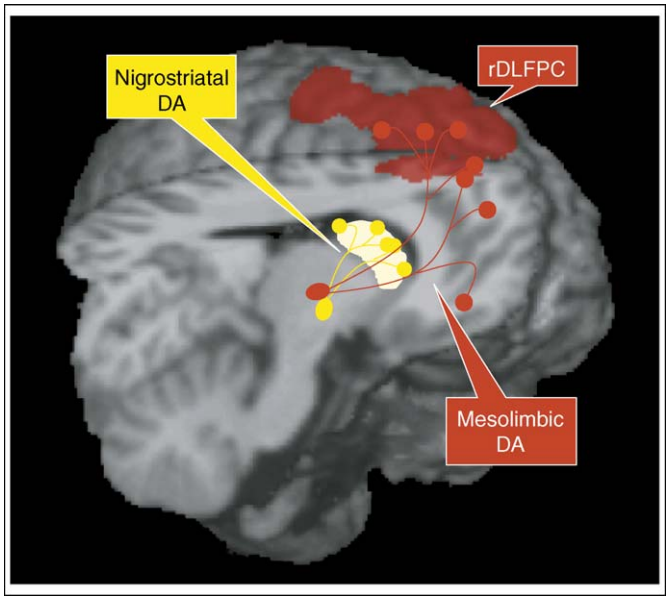

Figure 2. 3D depiction of a human brain which has been sliced to reveal the midbrain. The mesostriatal dopaminergic pathway, which projects from the substantia niagra pars compacta to the striatum, is depicted in bright yellow, with the caudate (one of the basal ganglia) shown in paler yellow. The mesocortical dopaminergic pathway, which projects from the ventral tegmental area to the cortex (particularly the frontal lobes), is represented in bright red, with the rDLPFC shown in darker red. These areas were defined using voxel-labelled templates derived from the mri3dX Brodmann atlas and rendered onto the SPM canonical brain. Abbreviations: DA, dopaminergic pathway; rDLPFC, right dorsolateral prefrontal cortex.

occurs along a predictable time course, which can be described as a sum of exponential curves [41] (Figure 3a), so the strength of a memory could be used to determine how much time has passed since it was formed. The MTS model involves several mathematical constraints that are not easily matched by individual prefrontal neurons, such as the requirement for logarithmic decay, and precise details of how the level of starting activity is stored and compared with the level of activity later in an interval. Nevertheless, a looser interpretation of the memory decay idea, in which the memory is held within a population of cells (Figure 3c), provides a compellingly parsimonious framework that can predict the fundamental psychophysical properties of interval timing (e.g. scalar timing and bisection at the geometric mean) [2,42].

The physiological feasibility of time measurement using a continuously decaying (or increasing) signal has become apparent as specific populations of cells behaving in this way during timing have been identified [34,43,44]. For instance, cells in the macaque prefrontal cortex have been shown to 'ramp' their activities in a predictable way during temporal comparison [45], and similar activities have been observed in rats during temporal production [43]. These firing patterns are highly reminiscent of the increases of firing rates ('delay activity') which occur when information is held online [46], and which are thought to serve as a basis for working memory (Figure 3b,c). Neuroimaging work in humans also supports this hypothesis; a recent study showed that functional magnetic resonance imaging signal in the DLPFC varies with the duration being measured [47]. Interestingly, some subregions of the DLPFC increased their average activity as the presented interval

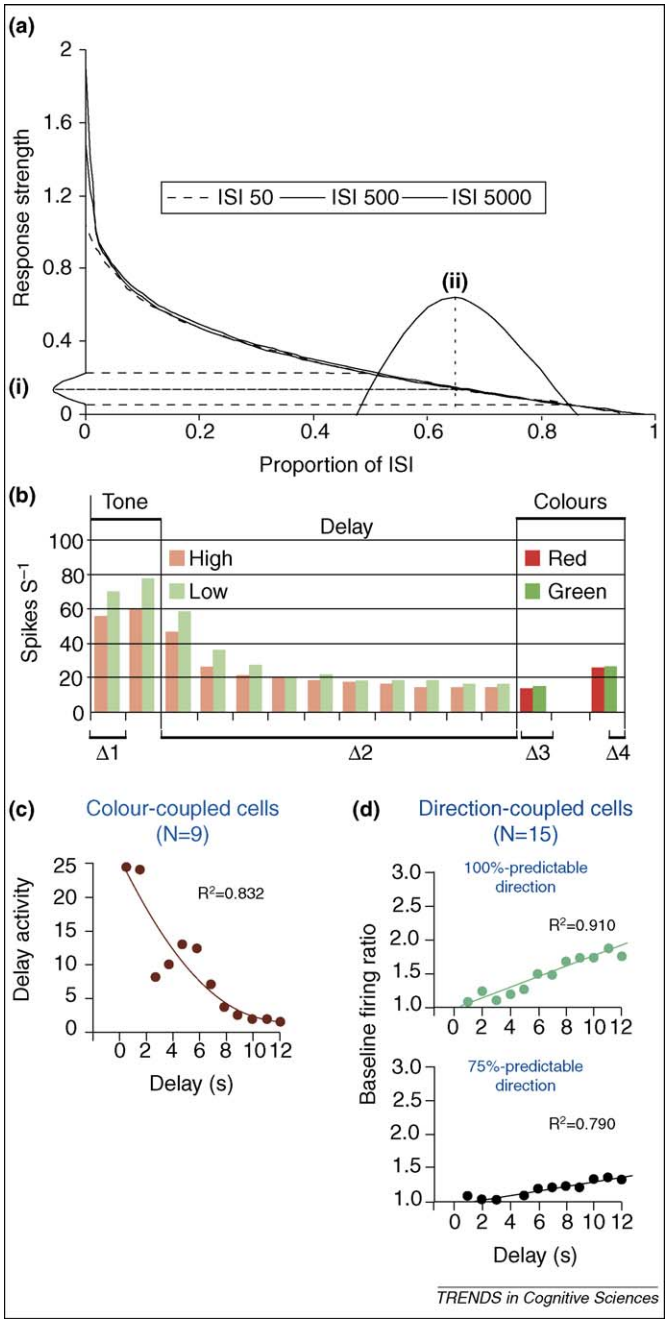

Figure 3. Memory for time. **(a)** Illustration of how 'forgetting curves' could be used to measure time under the MTS model. Three overlapping memory traces are shown for three intervals, all decaying along a predictable trajectory, such that measurements of strength at any given point can be used to determine how much time has passed. A threshold (horizontal line) with associated noise is assumed to trigger output from the system. The scalar property of timing arises naturally from this construct because a fixed uncertainty window in the memory strength (I) leads to variance in estimated duration (II), and the three curves have equal proportional variance. Modified, with permission, from Ref. [51]. **(b)** The activity of a monkey prefrontal neurone during the delay interval (Δ2) between presentation of tones and colours. The activity decays smoothly. Modified, with permission, from Ref. [46]. **(c,d)** Population data for similar prefrontal cells [46] showing decay (c) or ramping activity (d) across the 12-s delay interval.

increased, whereas other subregions decreased their activity, supporting the idea that both increasing and decaying activity could serve as a measure of time. Surprisingly, these correlations were observed in the left rather than the right hemisphere and were found in different locations during encoding and retrieval.

Concluding remarks: can time be measured using the same neural machinery as working memory?

We have outlined a substantial body of evidence suggesting that both cognitive time measurement and working memory rely upon the right hemispheric DLPFC. Dual-task interference suggests that both forms of computation place demands upon the same cognitive processing units. Both processes are influenced by dopamine, a neuromodulator known to effect function in this region, and we have argued that both types of processing might even draw upon the same cell population in this region – the dopamine-sensitive layer III pyramidal delay neurons.

The importance of memory for time perception is widely acknowledged. However, a traditional perspective has been to suppose that working memory is used in time perception – for instance, in the manner of an accumulator process keeping track of the ticks from a neural oscillator as proposed by the scalar expectancy theory model. In this article, we have drawn upon concepts from the newer MTS model to suggest that, instead of merely keeping track of the progress of a separate time keeper, these working memory processes might actually constitute the time-dependent process itself. This formulation can be taken one step further by proposing that the prefrontal time keeper function does not rely upon working memory *per se* but instead simply draws upon the same neural processors as working memory. Thus, the same regions – and potentially even the same cells – that are involved in working memory can be thought of as serving a distinct function when they are used for time measurement.

Our suggestion that the prefrontal processing units used in working memory can also be used to measure time is in keeping with the adaptive coding hypothesis [48], which proposes the prefrontal cortex as a multipurpose processor recruited for a wide variety of functions. This hypothesis explains why the same prefrontal regions are involved in so many cognitive tasks, including working memory, word generation, divided visual attention, problem solving, response suppression and cognitive time perception. A conceptually similar framework suggests that the parietal cortex might provide multipurpose calculations of magnitude [49], thus explaining its involvement in diverse tasks, including perception of size, number, and intensity, distance, as well as time. Taken together, the proposals of adaptive coding in the prefrontal cortex, and of generalized magnitude calculation in the parietal cortex, represent a move away from functional modularity and towards a more flexible and integrative view of the brain.

Although this article focuses on the right DLPFC, several other regions have consistently been shown to be important for cognitively controlled time measurement. Although the right DLPFC might serve as the time-dependent process within cognitively controlled timing tasks, this does not preclude the involvement of areas such as insula–operculum, basal ganglia, supplementary motor area and cerebellum in this and other forms of timing. These regions might work in conjunction with the right DLPFC or form alternate timing systems recruited in parallel with it. Because ramping neural activity is fairly common throughout the prefrontal cortex, it is also possible that timing activities in other parts of the prefrontal lobe might rely upon a similar mechanism. More research is needed both to test this proposed mechanism and to explore the roles of these other regions in timing (Box 1).

Box 1. Questions for further research

- Does concurrent performance of a working memory task disrupt automatic timing? How does this differ from the influence of identical tasks upon cognitively controlled timing?
- Do drugs like haloperidol and remoxipride (which antagonize the dopaminergic system), benzodiazepines (which influence working memory) and reboxetine (which influences attentional procession) show differential effects upon cognitive and automatic timing tasks?
- What is the relative importance of specific task characteristics (e.g. duration timed, continuousness of timing and involvement of movement in timing) for dissociation between cognitive and automatic timing via dual tasks and drugs (see above)?
- Are other task characteristics important for dissociating between cognitive and automatic timing?
- How does dopamine influence the pattern of ramping activity in dorsolateral layer III pyramidal cells during timing tasks? Is there a clear relationship between such influence and the observed behavioural effects?
- Can perturbation of the ramping activity in the right DLPFC (perhaps by microstimulation) influence the perceived duration of a stimulus?
- Might ramping activity in other areas [e.g. supplementary motor area (SMA) or pre-SMA and premotor cortex] underpin automatic timing?

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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.

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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

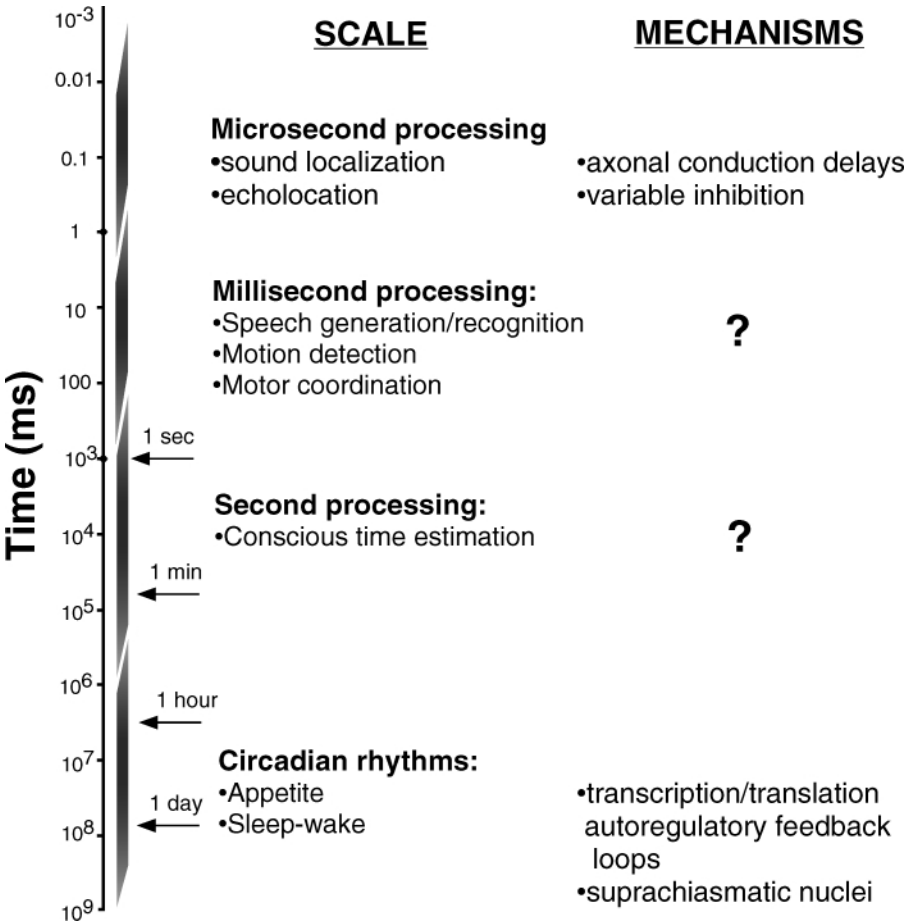

Figure 1 Timescales of temporal processing. Humans process temporal information over a scale of at least 12 orders of magnitude. On one extreme we detect the delay required for sound to travel from one ear to the other. These delays are on the order of tens to hundreds of microseconds. On the other extreme, 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

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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

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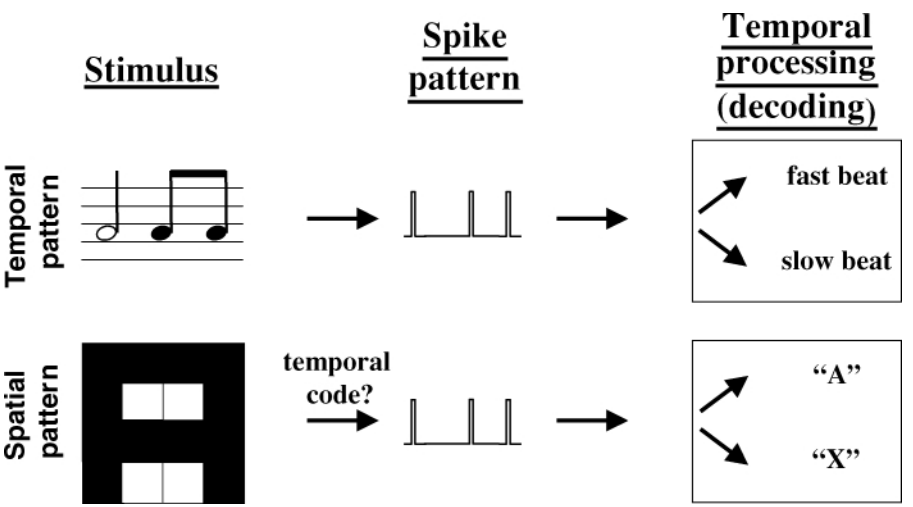

Figure 2 Temporal processing and temporal coding. (*Upper panel*) Temporal processing refers to decoding of temporal information arriving from environmental stimuli such as music (*left*). A stimulus such as a piece of music will generate temporal patterns of action potentials that follow the beat of 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.

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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

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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

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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.

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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. ΔT 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

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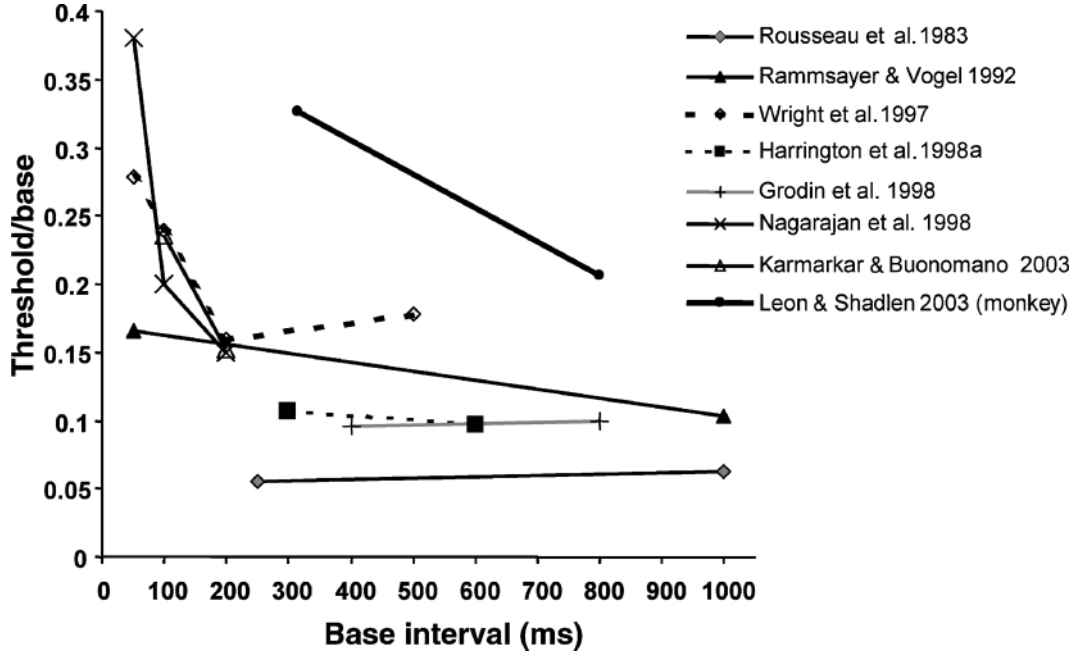

Figure 4 Cross-study interval discrimination thresholds. The standard or base interval is represented on the X axis, and thresholds are plotted in the Y axis as Weber fractions (threshold/standard interval). Thresholds are calculated differently in different studies, thus comparing absolute thresholds 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.

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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.

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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

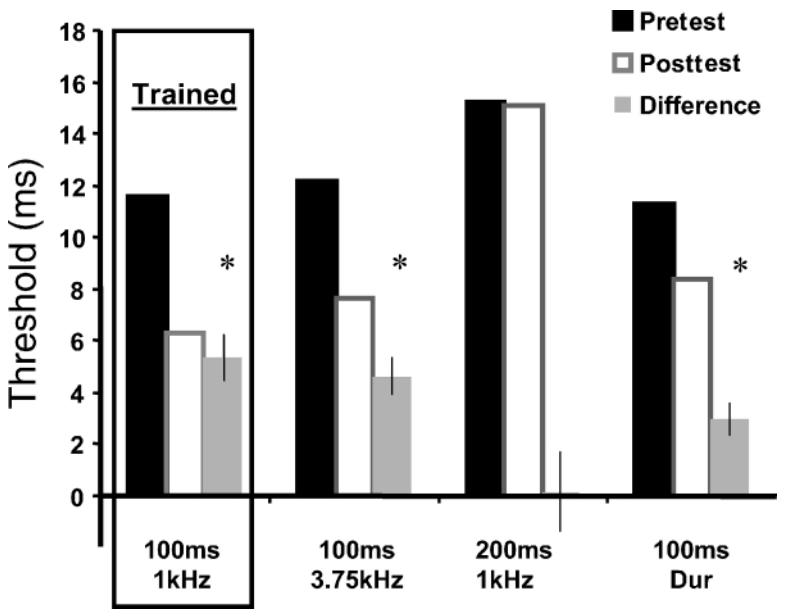

Figure 5 Generalization of interval discrimination learning. A group of 10 subjects underwent training on a 100-ms–1-kHz interval discrimination task. After 10 days of training (an hour a day), they exhibited significant learning (*left bars*). Pre- and posttests on 3 different conditions revealed generalization 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.

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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).

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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).

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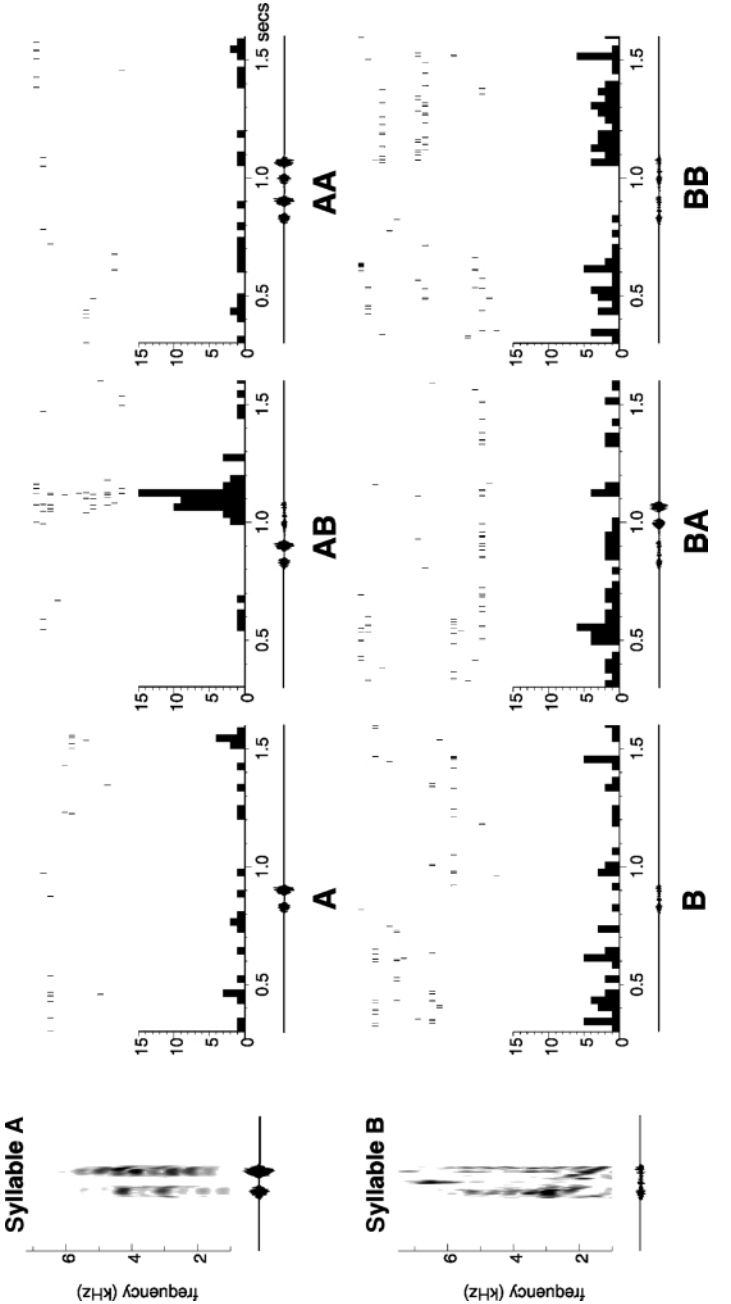

Figure 6 Example of a temporally combination-sensitive neuron of a songbird. Recordings from a neuron in HVc in response to two syllables from the bird's own song. Spectrograms of each syllable are shown to the left. Above each histogram is the response of the neuron to each presentation of the stimuli. 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).

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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).

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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).

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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

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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

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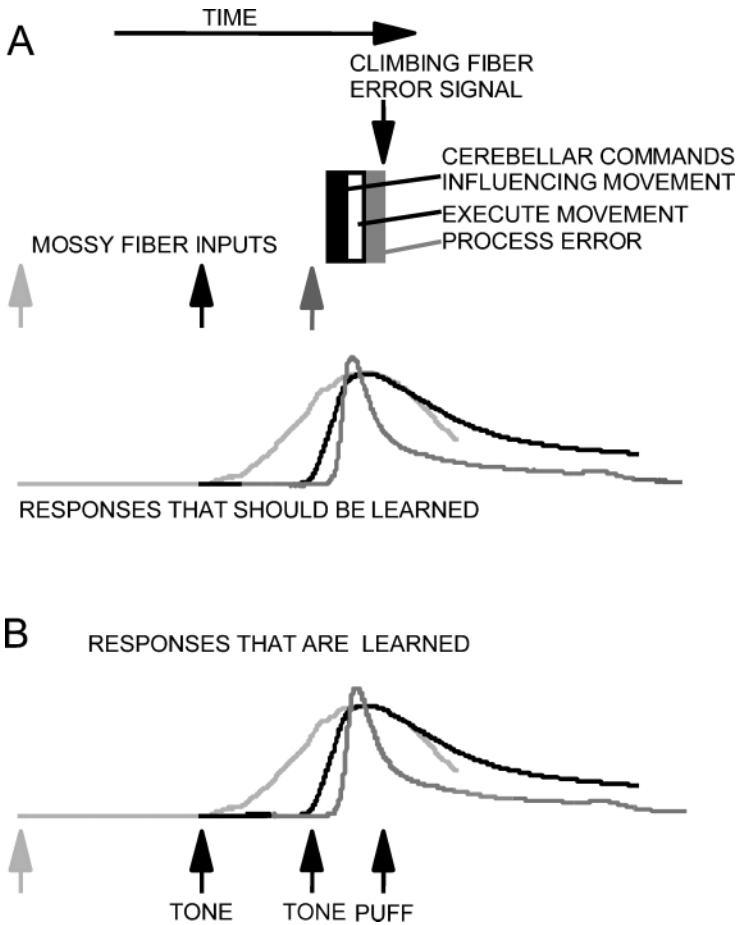

Figure 8 Feed-forward learning is enhanced by temporal specificity. (*A*) A schematic representation of the timing required for error-driven associative learning supporting feed-forward predictions. A climbing fiber input to the cerebellum (*gray*) signals movement error as detected by an inappropriate 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).

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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

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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.

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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.

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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

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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.

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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.

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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.

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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.

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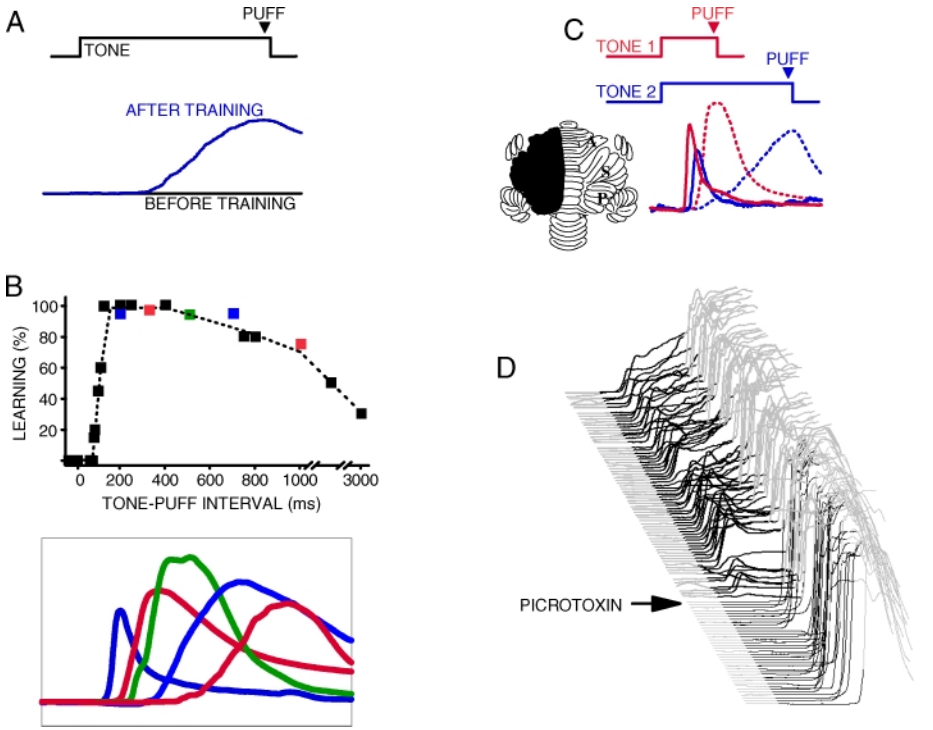

Figure 3 Temporal properties of learned eyelid responses. Classical or Pavlovian eyelid conditioning displays learned timing. (*A*) In a typical experiment, training involves presentation of a neutral stimulus, such as a tone, paired with a reinforcing stimulus, such as a puff of air directed at the 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.

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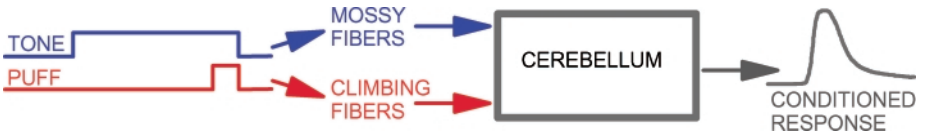

Figure 7 Eyelid conditioning engages the cerebellum relatively directly. This is a schematic representation of the relationship between eyelid conditioning and the cerebellum. Output of the cerebellum via its anterior interpositus nucleus drives the expression of conditioned responses. Stimuli such as 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.

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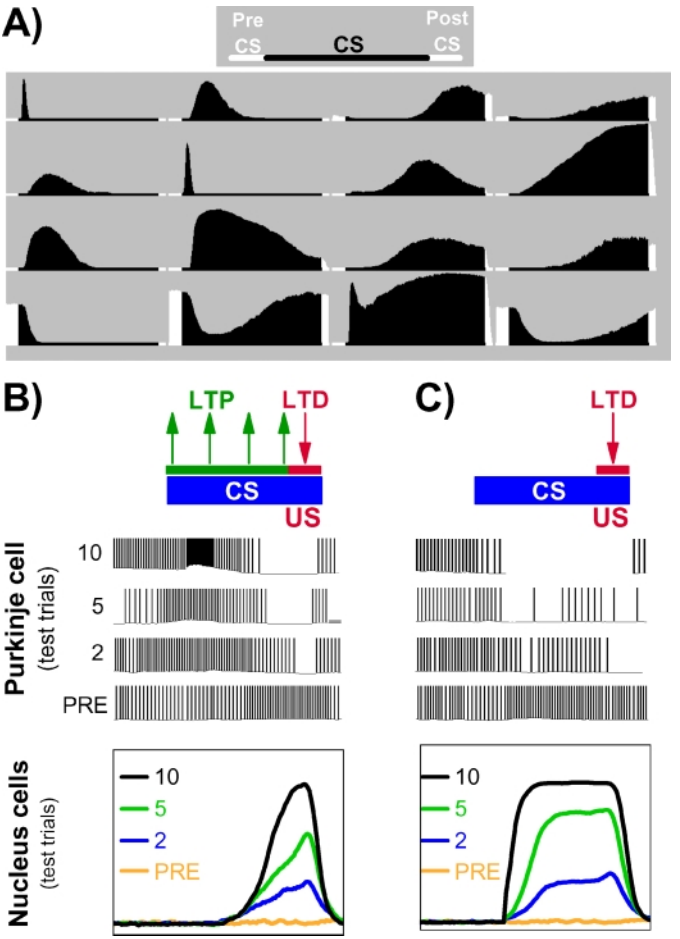

Figure 9 Mechanisms of timing-specific learning in the cerebellum. Computer simulations of the cerebellum in the context of eyelid conditioning suggest mechanisms for learned response timing. (*A*) Peri-stimulus histograms of simulated granule cells for the presentation of a tone-like mossy fiber input 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.

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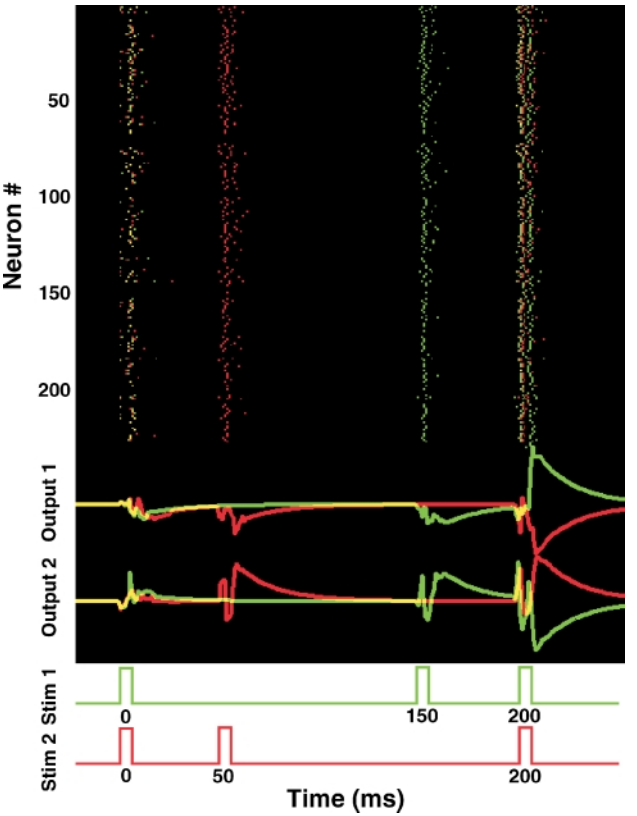

Figure 10 State-dependent model of sequence recognition. The model is composed of excitatory and inhibitory neurons. The connectivity and synaptic weights are randomly assigned, the synapses exhibit short-term synaptic plasticity, and a slow-IPSP is present. The time constant of the short-term plasticity 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.

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Research Focus

Time is of the essence

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Timing is essential to human behaviour, but the neural mechanisms underlying time perception are still unclear. New findings from a brain-imaging study by Coull *et al.* show that activity in a network of motor-related areas varies parametrically with attention to time. Given that a system in which timing is important (but not the primary function) is recruited when temporal judgements are required, we should perhaps reassess the notion of a dedicated timing system in the brain.

'Time is the primordial context' [1]. It frames most aspects of our behaviour, at scales ranging from the millisecond organization of motor actions to the annual cycle of celebrations, and beyond. It also has enormous impact on the flexible attentional modulation of perception and action. Limits on information processing exist in the temporal dimension, as demonstrated by phenomena such as the psychological refractory period [2], attentional blink [3], and inhibition of return [4]. Accurate expectations about the temporal 'position' of an event (temporal orienting) can optimize behaviour [5]. Finally, the passage of time itself can become the focus of attention (selective attention to time).

This last interaction between time and attention is the topic of a recent investigation by Coull and colleagues [6]. The authors use event-related fMRI to reveal brain areas involved in selective attention to time. There are several nice things about this paper. First, its prominent publication brings research on time to the forefront. Despite its central role in cognition, few imaging studies have ventured into the fourth dimension. Second, the authors addressed their experimental question in a simple and elegant way. They varied the degree of selective attention towards the temporal duration versus colour hue of stimulus pairs parametrically. In all trial types, a test and a comparison stimulus differed in both duration and colour. Participants were instructed at the start of each trial to attend to time only (T), time more than colour (Tc), both dimensions equally (tc), colour more than time (tC) or colour only (C). The cues indicated the probability that the participant would be asked to respond to each dimension, at the end of the trial. Task conditions were identical in visual stimulation and response requirements and the accuracy and speed of responses were well matched between conditions, minimizing the potential contribution of unrelated performance variables to the effects. To equate the time of engagement required for the discrimination across conditions, the colour task required integration of colour information throughout stimulus presentation (see also [7]).

The behavioural results demonstrated that people can explicitly decide the proportion of attention to devote to each task: Participants were increasingly more accurate and faster to make temporal (or colour) judgments, the higher the likelihood was of the time (or colour) task according to the cues. The cues therefore established effective task sets, and switching between these was behaviourally costly.

This parametric relationship between performance and strength of attention was reflected in the fMRI data: the strength of the BOLD signal from a network of areas increased parametrically, in line with performance, as subjects attended more strongly to the temporal aspects of the task. These areas were interpreted to constitute the neural system involved in selective attention to time; and included inferior parietal, superior temporal, prefrontal and premotor areas, specifically the inferior frontal cortex and the pre-supplementary motor area (preSMA). Their activation cannot be attributed only to task difficulty or response uncertainty, as these had a U-shaped relation to strength of attention to time (because of the competing colour task). Activity in V4 showed the same parametric variation with task set as the areas linked to temporal attention – except that activity there *decreased* as participants shifted their attention towards the temporal aspect of the stimuli (i.e. away from its colour). Activity in V4 is already known to be modulated by attention to colour [8], and the replication therefore serves as an internal control in the experiment. These findings are broadly compatible with those from previous experiments that have manipulated attention towards versus away from temporal aspects of stimuli to identify brain areas involved in time perception *per se* [7,9–11].

A motor network for time perception?

What light does this particular set of fMRI blobs shed on the understanding of attention to time or time perception? The authors suggest that a fronto-striatal loop is involved in timing-related functions. Involvement of the cerebellum in fast timing functions has also been suggested by some studies [7,12], but the structure was not imaged in the experiment by Coull and her colleagues. These areas are strongly implicated in motor control and motor attention. For example, the preSMA has been implicated in sequencing actions [13] and in switching intentional set [14]. This raises the possibility that a network with motor functions might also play a role in timing that is

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independent of motor actions. Interestingly, temporal orienting also engages structures involved in motor control [5,15] and modulates response-related aspects of stimulus processing [16,17]. A broader implication that could be drawn from the experiment is that systems in which timing is important (but not the primary function) are recruited when temporal judgements are required. Coull and colleagues have made the case for the motor system, but a similar case might have been made for the auditory system given that activations in auditory cortex were also observed (e.g. see [7]).

Converging evidence regarding timing at the systems level is relatively scarce, but does support a role for the basal ganglia, operating through fronto-striatal loops. As far as we know, there is no patient population whose primary deficit is centred on temporal aspects of cognition, in the way that spatial deficits are central to neglect for example. However, patients with Parkinson's disease, which is associated with degeneration of the nigro-striatal pathway, show deficits in both temporal production and temporal perception, which are exacerbated when they are off medication (e.g. [18], and see [1] for review). Deficits in temporal aspects of cognition have also been identified in patients with neglect and with frontal lesions [19,20].

Can brain imaging reveal the time-perception network(s)?

Coull and colleagues set out to investigate the perception of time itself, equating motor and perceptual demands in the task conditions they compared. If there is a core network that 'does' timing, their study should reveal it. The alternative is that temporal functions are embedded within different types of specialized circuits, although they may be more pronounced in some than others. To determine whether the motoric system revealed so far constitutes *the* centralized system for estimating and attending to temporal intervals, additional studies, including using convergent methodologies, will be essential.

To continue probing for centralized or distributed timekeeping circuits, imaging experiments should systematically manipulate the time scales, perceptual modalities and response-related variables (e.g. [7,21]). Although studies to date have not always emphasized speeded action, they have required decision making and motor responses, which engage motor-related circuitry similar to that reported. The neural network imaged so far could therefore result from a sampling bias to some extent.

However, imaging studies alone might not be able to resolve this interesting puzzle. Why? Because it is possible that some areas that are crucial to time functions cannot be modulated by directing attention towards or away from temporal functions. There may be areas that are crucial to timing whose activity is automatic and not under control by different task sets. Further, it is possible that activation of timekeeping mechanisms common to, say, motor and auditory systems [22] could cause epiphenomenal activation in one or both of those systems. Imaging is also likely to be limited in revealing activation in small subcortical regions that might be involved.

How do brain areas keep time?

Beyond identifying the brain areas that participate in perceiving and attending to time, lies the challenge of interpreting their functional role within time-keeping mechanisms. Theoretical models of time perception based on psychophysical data share core concepts but differ substantially in detail (for review see [23]). Core concepts include a repeatable mechanism that maps onto time (clock component), mnemonic mechanisms to store and retrieve relevant time values (memory component), and mechanisms to compare perceived and remembered temporal intervals (decision or comparator component). Interpretations of the functional contributions of brain areas lean heavily on specific models that authors embrace. For example, Coull and colleagues suggest that the preSMA 'is involved in invoking an imaginary ordinal scale or time line against which elements of a sequence, or "beats" in a duration can be aligned and quantified.' However, it is conceivable that the marking of temporal intervals could simply emerge without the need for explicit accumulators or comparators, for example through reinforcement of coincident firing in a specific subset of neurons with periodic firing properties [23,24]. Furthermore, it will be highly surprising if basic components of time perception models and their constituent parts, described at a theoretical and introspectively intuitive level of analysis, find direct instantiation in any one given brain area or circuit. More likely, models of time perception will have to be revised as the neural mechanisms are revealed, possibly towards less intuitively appealing explanations. Nevertheless, linking specific brain areas to testable timing functions is the first important step.

Where next?

What will be the next steps in understanding how time is represented in the brain? Many avenues are worth exploring. Electrophysiological studies might be particularly fruitful. Single-unit studies so far have shown that neurons in several brain areas are sensitive to temporal parameters of expected stimuli, including dopamine-containing neurons in the midbrain, striatum and orbitofrontal cortex [25], but also neurons in posterior parietal [26] and extrastriate visual cortex [27]. Studies measuring field potentials and oscillatory activity might be in a good position to detect markers of relevant time intervals, such as the synchronization of periodic activity in neuronal assemblies. Recordings of the magnetoencephalogram (MEG) might be able to reveal macroscopic markers of time keeping in the human brain with relatively good spatial resolution.

We may not quite have defined the core neuroanatomical substrates of timing behaviour, but at least we've got our hands wet. The temporal dimension is fundamental to many different functions, both perceptual and motor. Understanding how temporal judgements are made and implemented will be essential for understanding these processes, and investigation of the putative centralized and distributed mechanisms of temporal processing should lead to new revelations about the relations between brain systems.

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Asymmetries in face and brain related to emotion

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Research on the neural substrates of emotion has found evidence for cortical asymmetries for aspects of emotion. A recent article by Nicholls *et al.* has used a new imaging method to interrogate facial movement in 3D to assess possible asymmetrical action during expressions of happiness and sadness. Greater left-sided movement, particularly during expressions of sadness was observed. These findings have implications for understanding hemispheric differences in emotion and lend support to the notion that aspects of emotion processing might be differentially localized in the two hemispheres.

The study of facial expressions of emotion has a long and venerable history. Modern research on this topic was catalyzed by the publication of Darwin's *Expression of Emotion in Man and Animals* [1]. A celebration of 130 years of research on expression and emotion since Darwin was just recently published [2]. One of the abiding themes in research on facial expression since Darwin has been the observation of asymmetries in facial movement that accompany facial expression of emotion. Much attention over the past twenty years has been devoted to understanding the measurement, origins and significance of these asymmetries. The recent report by Nicholls and coworkers [3] is part of this ongoing effort and offers some promising methodological innovations. It also raises several important conceptual and methodological questions. In this brief commentary, we will first situate the Nicholls *et al.* report within the larger context of research on cerebral lateralization and emotion. We will then consider what Nicholls *et al.* did and what they found and will end with a brief discussion of why lateralization for affective processes might have evolved and what future research is suggested by these findings.

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Special issue: Editorial

The rhythmic brain

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Music is a universal but still poorly understood form of human communication in which abstract patterns of sound can cause people to cry, laugh, dance, reflect, bond and even mate. Rhythm is a basic organising principle of music, providing a strict temporal framework for an infinite variety of playful and expressive musical behaviours, from clapping and dancing in a group to a virtuosic violin solo. This temporal organisation exists on a number of hierarchical levels (the pulse, the bar, the phrase), allowing for the simplest forms of synchronisation and prediction as well as highly complex, large-scale musical structures.

Considering its primacy in musical behaviour, rhythm has not yet received the scientific attention it deserves. Perhaps due to the rich harmonic complexity of our Western tonal system, the focus of much music psychology and music neuroscience research has tended towards the hierarchical structures of pitch, melody, tonality and harmony. However, if we consider the diversity of musical languages across society, across cultures and across history, rhythm soon comes to the forefront as a ubiquitous component of human behaviour. Many cultures emphasize rhythm, with melody playing a less significant role. In addition, many music therapists and educators emphasize the role of rhythm in their work.

In June 2006, an interdisciplinary conference on the topic of Rhythm, Time and Temporal Organisation was held at the University of Edinburgh as the inaugural conference of the Institute for Music in Human and Social Development (IMHSD) (http://www.music.ed.ac.uk/Research/imhsd/Rhythm2006/programme.html). The conference brought together neuroscientists, therapists, philosophers, musicologists, musicians, psychologists, sociologists, educators and dancers to consider the nature of rhythm and timing from evolutionary, developmental, linguistic, motor and therapeutic perspectives. The event was both exciting and enlightening, leading to new collaborative ventures, and identifying clearly that musical rhythm is (a) intimately connected with movement (b) strongly related to temporal aspects of language and (c) potentially valuable in educational and therapeutic contexts.

This special issue includes contributions from several key speakers at the conference, in addition to contributions from other researchers currently exploring the neural basis of musical rhythm. The aim of the special issue is not only to bring together the latest research on this topic but also to juxtapose a diverse range of disciplinary perspectives and methodological approaches, from behavioural work, theoretical work and infant work, to evolutionary theory and genetics, to brain imaging using EEG, MEG, PET and fMRI. The editorial process was extremely interesting and even challenging, not least since the word *rhythm* can mean different things to different people, while terms such as *beat*, *metrical/non-metrical*, *simple/complex rhythm*, *conventional/unconventional rhythm* and so forth, can be the topic of heated debate. It is clear from such discussions that this area of research is still in its beginning stages, as the rhythmic brain begins to be charted and as researchers from different disciplines find agreement on terminology, conventions and assumptions. While it is evident that the classic behavioural work of a few individuals in particular has been extremely influential (e.g., Bruno Repp, Eric Clarke, Carolyn Drake and Mari Reiss Jones) there also remains much still to debate. We believe that this special issue represents the start of an explosion of interest in the rhythmic brain, and we hope it will be a source of interest and inspiration for future work in this area, including further debate on fundamental concepts and definitions.

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The volume begins with the topic of evolution and non-human rhythmic behaviour. In an extensive discussion of a wide range of animal and human research, Merker et al. (2009, this issue) consider the origins and motivation of the capacity to entrain to an isochronous stimulus. Amongst a variety of stimulating ideas, they suggest that this ability is not unique to the human species (occurring in certain insects, frogs and crabs), and propose that such synchronisation of animal calls results in signal amplification which allows groups of males to attract migrating females, giving them a reproductive advantage. In a very different and ground-breaking paper, Moran and Kyriacou (2009, this issue) discuss the rhythmic "love songs" of courting male fruit-flies and identify regions of the neural system that may mediate these song patterns, including regions involved in learning and memory. They also identify candidate genes for song behaviour, suggesting that a developmental defect at the earlier life history stage can generate later severe song defects as adults. Interestingly, both papers conclude from very different perspectives that a combination of numerous different neural systems must be involved in the rhythmic behaviour described.

We then move to humans and to a collection of papers examining the potential role of the motor system in rhythm perception, each focusing on a different brain region and using a different methodological technique. Trainor and colleagues (2009, this issue) use galvanically induced sensations of duple and triple metre to demonstrate that the vestibular system plays a primary role in metre perception, supporting their previous work in this area. Thaut and colleagues (2009, this issue) use tempo-tracking synchronisation tasks and PET to identify distinct cerebellar regions for separate rhythmic functions, putatively associated with motor control, changes in time magnitude during tempo modulations and conscious monitoring of synchronisation strategies. They suggest that the cerebellum has a critical role as a system for optimisation and coordination, and that its activation is associated with increases in complexity, novelty and learning rather than with pure timekeeping. Grahn and Brett (2009, this issue) compare the performance of Parkinson's disease patients with healthy control participants on rhythm discrimination tasks, confirming that the basal ganglia are involved in the detection (or possibly generation) of a steady beat, supporting her previous fMRI work in this area. Bengtsson and colleagues (2009, this issue) employ fMRI during passive listening to rhythms and identify a range of motor and pre-motor regions of interest, particularly during rhythm sequences that are more predictable/metrical. Interestingly, both Bengtsson and Thaut find relatively increased activation in the lateral cerebellum during their more complex rhythm discrimination tasks. But what is most clear from this collection of papers is that the neural bases of rhythm and movement are fundamentally connected, and distributed across a wide range of brain regions.

The next set of papers focuses more specifically on the role of hierarchical temporal organisation in rhythm processing. Grube and Griffiths (2009, this issue) present a carefully designed behavioural study which demonstrates convincingly that the precision of encoding for sequences increases with a stronger sense of metre and metrically plausible endings. They suggest that metre facilitates the storing of a rhythm as a coherent whole, rather than as a chain of durations. Vuust and colleagues (2009, this issue) present an interesting MEG study that examines responses to rhythmic incongruence in the context of strong metric anticipation. They show that, in keeping with predictive coding theory, event-related MEG components with the properties of an error term and a subsequent evaluation (mismatch negativity and a subsequent P3 component) are larger in musicians than non-musicians – that is, that the size of the error term is dependent on the quality of prediction. They interpret these data as support for predictive coding theory as an explanatory framework for the functional integration of musical processing, and also as evidence that the concept of metre is a cultural, mental construct. Geiser and colleagues (2009, this issue) also examine the effect of musical expertise on event-related potentials in a metrical context, using EEG. They show that in both musicians and non-musicians, rhythmic changes lead to an early negative deflection (N150) in both attended and unattended (pitch changes) conditions, while metrical changes show this negative deflection only in an attended condition. Since their behavioural data show that musicians and non-musicians respond very differently to metrical violations, they argue that this attention-related difference implies the existence of different neurophysiological processes underlying the auditory processing of metre and rhythm, where metre may rely on more Gestalt phenomena and hence takes longer to perceive. Potter and colleagues (2009, this issue) use EEG to examine the subconscious imposition of rhythm onto an isochronous stimulus by trained musicians. Confirming previous work, they find that the P300 evoked by deviant tones (intensity differences) is larger when it occurs in a putatively subjectively accented position in the tone sequence. In addition, they show that ERPs in the $<$100 msec range are observed in both standard and deviant tones from the onset of the stimulus, which they suggest supports both predictive coding models and attention synchronisation models of rhythm processing. The complementary data from these four different studies are complex and should be considered together, with detailed examination of the subtle differences in stimuli design, response analyses and interpretation.

Finally, we end the volume with two papers from the perspective of human development. Trehub and Hannon (2009, this issue) show that both 6-month-old infants and adults detect rhythmic changes more accurately in the context of a conventional rhythm (more metrical/less complex and previously identified as 'preferred' by adults), suggesting that temporal constraints on rhythm perception are present from a very early age. In addition, infants (but not adults) are shown to detect melodic changes more accurately in the context of a conventional rhythm, suggesting to the authors that infants may show more integrated perception of rhythmic and melodic aspects of a musical phrase than do adults. Corriveau and Goswami (2009, this issue) explore whether the rhythm perception deficits identified in children with speech and language impairment (SLI) extend to rhythmic motor entrainment. They show that children with SLI exhibit significant difficulties with synchronised rhythmic tapping and that task performance correlates with measures of language and literacy. They conclude that motor and language play focused on rhythm seems likely to be beneficial

for children in the development of speech and language skills, supporting previous work in this area.

The papers brought together in this special issue represent a wider range of research from across a number of different disciplines, providing a vivid 'snapshot' of current work in this area and exploring common themes such as sexual selection, neural complexity, motor behaviour, predictability and hierarchical rhythmic structures. We would like to thank the authors for their fascinating contributions and also for their discursive reviews. The similarities, differences, parallels, and occasional contradictions in findings and interpretations highlight the real complexities of research in this area, from stimuli design to subjects' individual experiences. We hope that this issue helps in the refinement of definitions and specific concepts and we look forward eagerly to future rhythm research, once the neural bases of the perception of pulse, beat and metre have been agreed, and we can begin to examine the neural basis of complex rhythmic behaviour such as polyrhythms, temporal flexibility, group performance, expert rhythmic learning and dancing….

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The evolution of brain activation during temporal processing

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Timing is crucial to many aspects of human performance. To better understand its neural underpinnings, we used event-related fMRI to examine the time course of activation associated with different components of a time perception task. We distinguished systems associated with encoding time intervals from those related to comparing intervals and implementing a response. Activation in the basal ganglia occurred early, and was uniquely associated with encoding time intervals, whereas cerebellar activation unfolded late, suggesting an involvement in processes other than explicit timing. Early cortical activation associated with encoding of time intervals was observed in the right inferior parietal cortex and bilateral premotor cortex, implicating these systems in attention and temporary maintenance of intervals. Late activation in the right dorsolateral prefrontal cortex emerged during comparison of time intervals. Our results illustrate a dynamic network of cortical-subcortical activation associated with different components of temporal information processing.

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Humans are remarkably proficient at perceiving the passage of time and producing precisely timed behaviors, many of which depend upon explicit prospective temporal judgments. For these events, multiple processes seem to determine our subjective perception of current time for intervals lasting several hundreds of milliseconds to several seconds. Most theories of prospective timing embody similar components[1], including an internal timekeeper, attention and memory[2,3]. A clock metaphor is used to describe the timekeeper mechanism, which represents subjective time through the accumulation or readout of pulses, possibly generated by oscillators. Our perception of time, however, is intimately related to the level of attention given to the passage of time. When attention is diverted, a systematic shortening of subjective duration occurs, implying that pulses from the timekeeper may be lost[4]. Attention may also mediate the flexible starting and stopping of pulses from the timekeeper, which enables anticipation of predictable events[5]. Hence, a representation of subjective time emerges from the interplay between timekeeping and attention mechanisms. This representation is then passed on to working memory, a short-term repository where interval representations are maintained and manipulated in accord with current goals (for example, comparing two intervals of time)[6]. Working memory functions can therefore alter stored representations of time as well. The combination of these different component processes gives rise to the subjective perception of time, although the relative contribution of each might differ depending on the interval duration or the cognitive demands of timing events[7].

The neural systems that support different component processes of time perception are a matter of debate. The basal ganglia and lateral cerebellum have been logical candidates for hypothetical timekeeping operations, as damage to these brain regions commonly disrupts behaviors that depend upon precise timing, such as rhythmic movements in Parkinson's disease[8] and regulation of agonist–antagonist muscle activity (for example, dysmetria) in cerebellar damage[9]. Although these movement abnormalities could be attributed to disruption of more generalized motor execution functions, the basal ganglia and cerebellum do seem to mediate time perception. Studies of Parkinson's disease patients[10,11] and pharmacological investigations in animals[12,13] have argued that timekeeping operations are regulated through dopamine neurotransmission in the striatum. Human lesion studies indicate that the lateral cerebellar hemisphere and its primary output, the dentate nucleus[14–18], are also involved in timekeeping mechanisms. Nonetheless, it has been difficult to isolate timekeeping and attention operations from working-memory and response implementation processes[1]. Timing deficits after basal ganglia or cerebellar damage could also be due to abnormalities in interconnecting cortical systems commonly associated with some or all of these processes[19,20]. Fewer studies have examined the involvement of the cerebral cortex in time perception. Focal lesion investigations in animals and humans have shown that the frontal and parietal lobes are also essential for accurate time perception, perhaps due to their purported attention and working memory functions[14,21,22]. Others have posited a role for the supplementary motor area[23], but this has been difficult to assess because focal lesions are uncommon in this region.

Functional imaging techniques can be used to dissect the contribution of each component of multiple neural systems, although studies of timing using these methods have produced conflicting or ambiguous results to date[7]. Most research[24–27] has focused on motor timing, making it difficult to separate activa-

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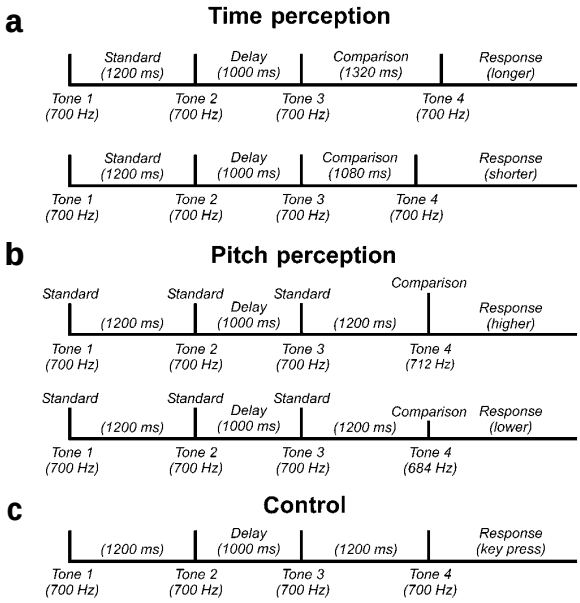

Fig. 1. Trial events in the time perception (**a**), pitch perception (**b**), and control (**c**) conditions. In the time perception condition, subjects indicated whether the comparison interval (defined by tones 3 and 4) was longer or shorter than the standard interval (defined by tones 1 and 2). In the pitch perception condition, subjects indicated whether the comparison tone (tone 4) was higher or lower in pitch than the standard tones (tones 1, 2 and 3). In the control condition, subjects pressed a key after the presentation of the four tones.

tion in systems traditionally associated with motor control, such as the basal ganglia and cerebellum, from those supporting timekeeping or other cognitive processes. Two PET studies[28,29] have specifically examined time perception. Unfortunately, the time scale of PET scanning is limited to blocked-trial designs that cannot disentangle processing associated with encoding an interval from processing associated with decision making and implementing a response. We reasoned that fundamental insights into this issue could be gained by studying the time course of brain activation patterns associated with different components of a time perception task. The present study exploited the finer temporal resolution of event-related functional magnetic resonance imaging (fMRI) to isolate patterns of brain activation that correlated with encoding time intervals from those associated with comparing two time intervals and implementing a response. Timing theory suggests that activation in systems integrally involved in encoding or formulating a representation of time (pacemaker and attention operations) should develop at the onset of a to-be-timed event[2,3], followed by activation in systems concerned with manipulating information in working memory (comparing intervals) and implementing a response.

We obtained fMRI scans of seventeen subjects as they performed three different tasks, the order of which was counterbalanced across subjects. In the time (T) discrimination condition, two tones (50 ms) separated by 1200 ms (standard tone-pair) were presented, followed by a 1-s delay and then a comparison tone-pair (Fig. 1a). Subjects indicated whether the comparison tone-pair was longer or shorter than the standard. To better separate neural systems specific to timing, subjects also performed a pitch (P) discrimination condition in which the auditory events were similar except that subjects indicated whether the fourth tone was higher or lower in pitch than the first three tones (Fig. 1b). Neural systems involved with processing time and pitch information were identified by contrasting imaging runs in each discrimination condition with a sensorimotor control (C) condition in which subjects responded after the presentation of two isochronous tone pairs of identical pitch (Fig. 1c). The T and P conditions were then contrasted to specify systems unique to time discriminations. These subtractions were conducted at each of four scanning intervals after trial onset (2.5, 5.0, 7.5 and 10.0 s). In all conditions, the typical motor response occurred approximately 4.5 s after trial onset (Fig. 2). Allowing 5 s for the hemodynamic response to peak, we proposed that the 2.5- and 5.0-s intervals after trial onset should reveal brain activation patterns specific to encoding time intervals. In contrast, the 10.0-s scanning interval should include activations associated with contrasting the standard and comparison intervals and implementing the response. Overlap between these processes should be particularly evident during the 7.5-s scan, due to encoding of the comparison interval. The results reported here show early sustained activation of the basal ganglia and right inferior parietal cortex, implicating these systems in formulating representations of time. Though activation in the cerebellum was more robust during time than pitch discriminations, activation was located in the vermis and unfolded late, suggesting a more general involvement in cognitive or sensorimotor functions. The evolution of activation in the bilateral premotor and right DLPF cortex differed from each other, consistent with previous work implicating these systems in different aspects of working memory.

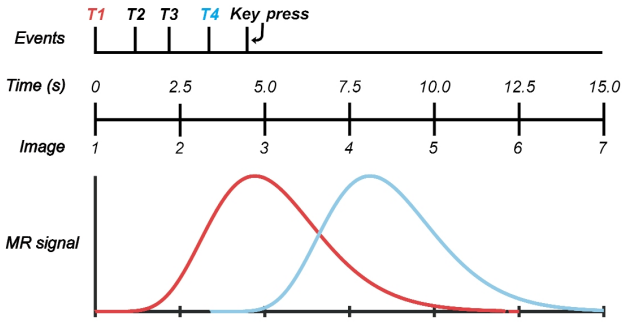

Fig. 2. Temporal relationship among the trial events, acquisition of images and hypothetical hemodynamic response functions to different task components. Seven scans were acquired during each 17.5-s trial (a 2.5-s interval between the seventh image and the first image of the next trial is not illustrated on the timeline). The first scan was acquired at the onset of the first tone (T1). The fourth tone (T4) was presented an average of 3.4 s after trial onset. The typical key press response occurred 4.5 s after trial onset. The two hypothetical time course functions illustrate early versus late MR signal responses to different trial events. An early response corresponding with the encoding of temporal information (red plot) would have a maximal signal change at 2.5 and 5.0 s after trial onset. In contrast, a late response due to decision making and response preparation processes (blue plot) would be observed primarily at 7.5 and 10.0 s after trial onset.

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RESULTS

Behavioral data collected during scanning showed that response times and accuracy correlated with the difficulty of time and pitch discriminations. Reaction time was typically longer (Fig. 3a, $F_{5,76} = 4.2$, $p < 0.01$; Fig. 3c, $F_{6,87} = 4.0$, $p < 0.01$) and accuracy poorer (Fig. 3b, $F_{4,57} = 8.1$, $p < 0.001$; Fig. 3d, $F_{7,112} = 2.7$, $p < 0.025$) when the comparison stimuli were closer in time or in pitch to the standard stimulus. There were no significant differences between the two discrimination conditions in overall accuracy (T, 83 ± 3%; P, 78 ± 3%) or reaction time (T, 1111 ± 76 ms; P, 1076 ± 54 ms). Reaction times for the C condition (707 ± 39 ms) were significantly faster ($F_{1,16} = 48.9$, $p < 0.0001$) than those for the time and pitch conditions.

During the early imaging epochs (2.5 and 5.0 s), which emphasize encoding of temporal information, subcortical activations specific to the T condition (Table 1) were observed within the right putamen, head of the caudate nucleus bilaterally, and right centromedian and ventroanterior thalamic nuclei (Fig. 4a). Early activation specific to the T condition was also observed in various cortical regions (Fig. 5): right intraparietal sulcus (BA 40), bilateral dorsal and left ventral premotor areas (BA 6), and bilateral lateral temporal cortex (BA 21/22). Activation specific to the T condition was sustained during the 7.5- and/or 10.0-s imaging epochs in most of these regions. In the P condition, areas of activation during the early imaging epochs overlapped with those in the T condition. In both the T and P conditions (Table 2), activity unfolded early within the medial wall (preSMA and SMA proper, BA 6, and anterior cingulate, BA 32; Fig. 4c) and the anterior insula/frontal operculum (Fig. 4a), but was sustained during later epochs as well.

During the later imaging epochs (7.5 and 10.0 s), which included decision and response selection components of the tasks, activation specific to the T condition (Table 1) was observed in the posterior vermis (tuber) of lobule VIIB of the cerebellum (Fig. 4b) and the right dorsolateral prefrontal (DLPF) cortex (BA 46/10/9; Fig. 5). All other activation foci were observed in the left hemisphere in both the

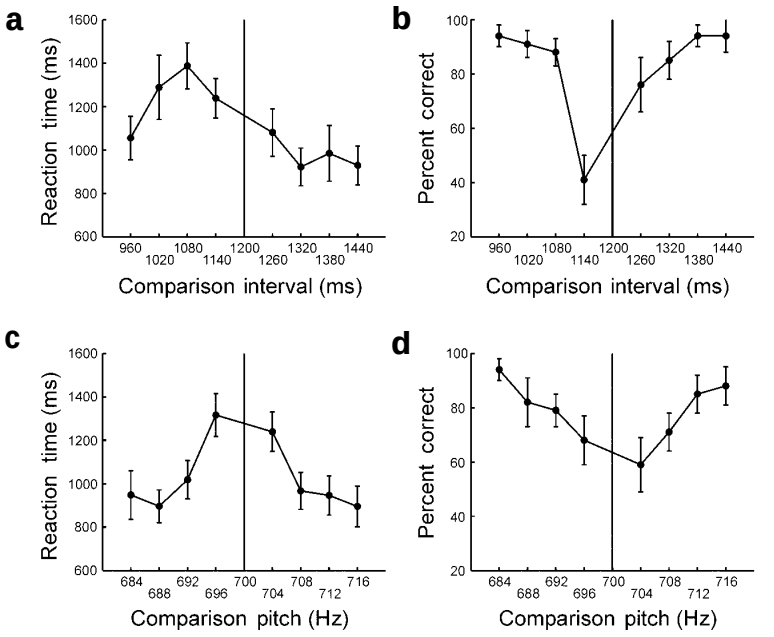

Fig. 3. Mean (± standard error of mean) reaction time and percent correct for the time perception (**a**, **b**) and the pitch perception (**c**, **d**) conditions. Data are depicted as a function of the comparison interval or comparison pitch.

Table 1. Stereotaxic brain atlas coordinates[49] for Time > Control subtraction.

Location (Brodmann Area)	Hemisphere	2.5	5.0	7.5	10.0
Basal Ganglia					
Medial caudate (head)	R		12, 7, 3	12, 6, 4	
	L		–12, 7, 5	–9, 7, 2	–8, 4, 8
Lateral caudate (body)	R				15, 6, 19
Putamen	R	22, 8, –1			23, 6, 8
					26, 6, –2
	L				–20, –1, 5
Cerebellum					
Vermis (tuber, lobule VIIB)	B			–3, –70, –30	2, –70, –29
Thalamus					
Centromedian nucleus	R		4, –21, 0	4, –21, 0	
Ventroanterior nucleus	R		4, –11, 0	5, –10, 0	
Frontal					
Dorsal premotor (6)	R		23, –7, 48	23, –3, 52	46, 1, 49
	L		–45, –7, 47		
Ventral premotor (6)	R		46, 8, 24		
	L	–54, –13, 26	–51, –15, 27		
Dorsolateral (46/10/9)	R			34, 23, 25	31, 46, 22
					41, 29, 22
Parietal					
Intraparietal sulcus, Angular gyrus (40)	R	38, –40, 41	36, –43, 40	37, –47, 38	30, –56, 35
Superior parietal lobule, Precuneus (7)	R				10, –68, 44
Temporal					
Superior temporal (22)	R		51, –39, 6		
Middle temporal (21)	L		–46, –56, 4		

R, right; L, left; B, bilateral. The activations reported in this table were not observed in the Pitch > Control subtraction.

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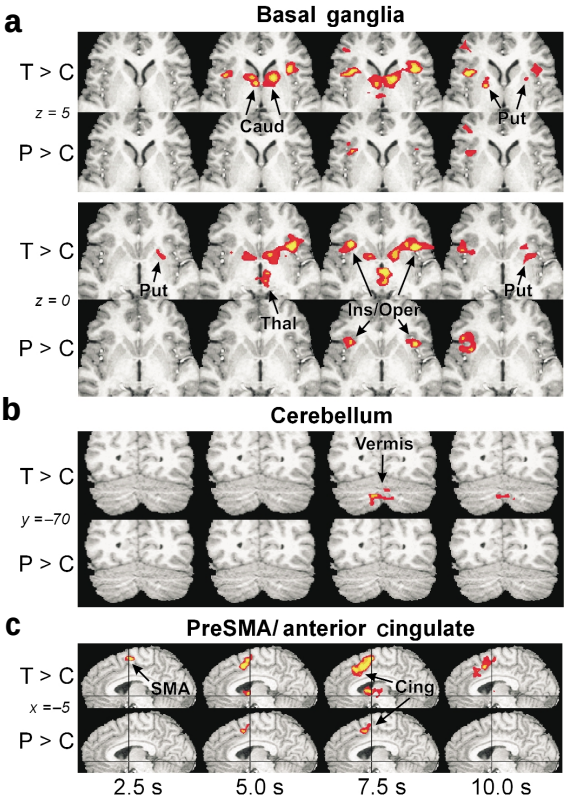

Fig. 4. Activation foci in the basal ganglia (**a**), cerebellum (**b**), and pre-supplementary motor area/anterior cingulate (**c**) resulting from subtraction of the control (C) condition from the time (T) and the pitch (P) perception conditions at 2.5, 5.0, 7.5 and 10.0 s after trial onset. Significant foci ($p < 0.001$) are displayed with a red-yellow intensity scale denoting greater activation for the T or P conditions. Slices are displayed in neurological view (left is on the viewer's left). Location of slices defined by the distance (mm) from anterior commissure: *x*, right (+)/left (–); *y*, anterior (+)/posterior (–); *z*, superior (+)/inferior (–). Caud, caudate nucleus; Cing, anterior cingulate area; Ins, insula; Oper, frontal operculum; Put, putamen; Thal, thalamus; SMA, supplementary motor area.

T and P conditions (Table 2), and included the inferior frontal gyrus (Broca's area, BA 44/45), intraparietal sulcus (BA 40), superior parietal lobule/precuneus (BA 7) and DLPF cortex.

The results from the T minus P subtraction were similar to the results for the T minus C subtraction (Fig. 6). During the earlier imaging epochs (2.5 and 5.0 s), subcortical activations unique to the T condition were in the right hemisphere and included the putamen (*x*, *y*, *z* = 24, 7, –2), caudate (15, 6, 13) and insula/frontal operculum (29, 16, 2). The later region, however, was also activated during the 7.5-s epoch in the pitch condition (Table 2, Fig. 4a). During the later imaging epochs (7.5 s), the right DLPF cortex (21, 21, 30) was also unique to the T condition (Fig. 6).

Discussion

The present findings provide compelling evidence for the involvement of the basal ganglia in formulating representations of time. Activation in the right putamen and caudate were uniquely associated with encoding time intervals. These results corroborate studies in Parkinson's disease showing that dopaminergic treatment improves motor timing[30,31] and time perception[32]. Pharmacological challenges in animals also suggest that dopaminergic antagonists and agonists respectively slow down and speed up timing operations[12,13]. Contrary to one proposal[33], these and other studies[10,11,27] show that the basal ganglia are involved in timing a wide range of intervals, from hundreds of milliseconds (300 ms) to tens of seconds (20 s). Collectively, these results implicate striatal dopaminergic neurotransmission in hypothetical internal timekeeping mechanisms.

Table 2. Stereotaxic brain atlas coordinates[49] for regions commonly activated in subtractions of Time and Pitch perception conditions relative to Control condition.

		Time > Control				Pitch > Control			
Location (Brodmann Area)	**Hemisphere**	**2.5**	**5.0**	**7.5**	**10.0**	**2.5**	**5.0**	**7.5**	**10.0**
Frontal									
Insula/operculum (47)	R		31, 17, 3	35, 16, 3	34, 17, 4			34, 17, 0	
	L		–35, 11, 5	–34, 15, 2	–36, 12, 4			–34, 18, 1	–36, 17, 0
PreSMA (6),									
Anterior cingulate (32)	L	–4, –1, 56	–4, 6, 49	–7, 10, 45	–5, 12, 43		–6, 7, 48	–4, 8, 49	
Inferior frontal gyrus (44/45)	R			37, 1, 32				37, 4, 28	
	L			–46, 4, 21	–47, 5, 18			–45, 4, 22	–44, 7, 26
Dorsolateral (46/10/9)	L			–39, 42, 12	–36, 46, 13				–36, 40, 8
				–42, 26, 28	–40, 14, 29				
Parietal									
Intraparietal sulcus,									
Angular gyrus (40)	L			–31, –49, 37	–29, –52, 33				
				–36, –53, 44			–32, –47, 38	–30, –55, 36	
Superior parietal lobule,									
Precuneus (7)	L			–21, –66, 49	–28, –49, 43			–13, –72, 50	–43, –57, 50
					–21, –63, 51				–25, –65, 50

R, right; L, left; B, bilateral

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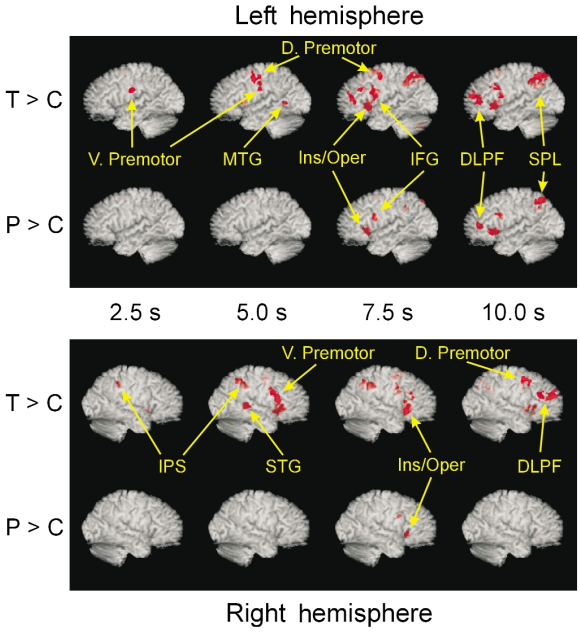

Fig. 5. Activation foci in the lateral surface of the left and right hemispheres denote greater activation for the time (T) and the pitch (P) perception conditions relative to the control (C) condition at 2.5, 5.0, 7.5 and 10.0 s after trial onset. Significant foci ($p < 0.001$) are displayed in red. DLPF, dorsal lateral prefrontal cortex; D. Premotor, dorsal premotor; IFG, inferior frontal gyrus; Ins, insula; IPS, inferior parietal sulcus; MTG, middle temporal gyrus; Oper, frontal operculum; STG, superior temporal gyrus; V. Premotor, ventral premotor.

Our findings did not support a unique role for the cerebellum in encoding time intervals. Nonetheless, cerebellar activation was observed during the time perception task (T minus C), consistent with several studies showing diminished time perception in patients with cerebellar damage[16,18,34]. However, in our study, activation was in the vermis rather than the lateral cerebellar hemispheres, contrary to reports that damage to the lateral cerebellum, but not the vermis, correlated with time perception deficits[15,18]. Cerebellar activation evolved later in the course of the trial, just before and during movement execution, suggesting an involvement in processes other than explicit timing. This is consistent with our previous fMRI study[27] showing that cerebellar activation was not specific to timing self-paced finger movements. Apart from its well-documented role in sensorimotor processing, neuroimaging research indicates that the cerebellum participates in many cognitive functions, including tactile perception[35] and working memory[36]. One lesion study has also shown that cerebellar damage produces pitch perception deficits[14]. Its broad role in sensorimotor and cognitive processing[37] has suggested that the cerebellum monitors and adjusts input from the cerebral cortex, but is not involved in computing a specific operation *per se*[38]. By this account, later activation in vermal lobule VIIB, which receives auditory and visual input[39], could be due to its involvement in optimizing sensory input from auditory systems, which facilitates the comparison of intervals in working memory. Although other explanations are possible, this account is appealing because it predicts that damage to the cerebellum will slow sensory acquisition, which should disrupt a broad range of behaviors, especially those involving timing. This view may explain why patients with cerebellar damage show deficits in timing[16,17], but not always in the perception of pitch or loudness[16,18].

Representations of time depend on the interplay of internal timekeepers with attention and working memory, functions more commonly identified with cortical systems. Neural systems associated with these functions should support a variety of computations, which may explain why they were not always unique to timing intervals (T minus P). However, in the comparisons involving the control condition (T minus C, P minus C), right hemisphere activations were observed during time but not pitch perception. These later results are consistent with findings from converging neuroscience approaches. Specifically, a neuroanatomical bridge for basal ganglia–cortical interactions is the thalamus[40], which was activated early during the encoding of intervals, along with two cortical regions, suggesting they work together in formulating representations of time. Coupled activation in the right inferior parietal cortex may suggest an interdependent role of this region in attention, which theoretically regulates the timekeeping mechanism. Neurological patients with right but not left inferior parietal damage show time, but not pitch, perception deficits that correlate with impairments in switching attention[21]. Electrophysiological recordings in humans have also shown a right hemisphere bias for temporal processing[41], especially in the parietal cortex[42]. The close relationship between timekeeping and attention is presumed by one influential theory[2], and has received empirical support in behavioral studies conducted on humans[4,5]. According to this view, representations of time are reflected in the pulse count accumulated over

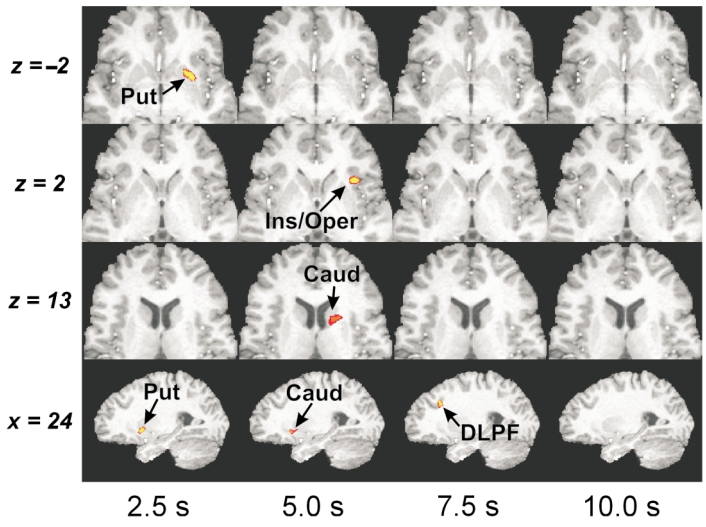

Fig. 6. Activation foci in the basal ganglia, insula/frontal operculum and dorsal lateral prefrontal cortex resulting from greater activation for the time (T) relative to the pitch (P) perception conditions at 2.5, 5.0, 7.5 and 10.0 s after trial onset. Significant foci ($p < 0.001$) are displayed with a red-yellow intensity scale. Slices are displayed in neurological view (left is on the viewer's left). Location of slices defined by the distance (mm) from anterior commissure. Caud, caudate nucleus; DLPF, dorsal lateral prefrontal cortex; Ins, insula; Oper, frontal operculum; Put, putamen.

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a particular physical time, which critically depends on the degree of attentional engagement. Our results point to the right inferior parietal cortex in regulating the accumulation of pulses, because of its well-documented involvement in attention[43]. Bilateral projections from the inferior parietal cortex to the putamen and caudate nucleus in monkeys[44] provide a neuroanatomic basis for the interaction of attention and timekeeping operations.

The perception of time also relies on stored representations of intervals in working memory[2]. During time perception, activation was observed in regions commonly associated with temporary storage functions, including the bilateral premotor (BA 6) and right DLPF cortex (BA 9, 10, 46)[19,20,45]. Right DLPF activation was also unique to performing time discriminations. This corroborates our previous finding that damage to these same regions in the right, but not left, hemisphere produces time perception deficits[21]. Controversy exists over whether these areas support different working memory functions[45–47]. However, a recent meta-analysis of neuroimaging studies[20] implicated the premotor cortex in a 'rehearsal circuit' in tasks involving mainly the temporary maintenance of information, such as item recognition. In contrast, the DLPF cortex was associated with an 'executive circuit' in tasks requiring manipulation of stored information, such as the two- and three-back working-memory tasks. Our findings are compatible with this process distinction, as premotor cortex activation began early, consistent with the need for maintaining the standard interval during the trial, whereas DLPF cortex activation unfolded later in association with comparing the two intervals and selecting a response. Independent evidence for the DLPF cortex in executive functions of working memory was observed in the pitch condition as well, in which activation unfolded later during the comparison phase, but was confined to the left hemisphere. Though premotor cortex was not activated in the pitch condition, repeated presentation of the standard pitch across the trial may have minimized the need for rehearsal.

In summary, the present results are compatible with prevailing cognitive theory, and provide new insights into the evolution of activation in cortical and subcortical systems that are specific to different cognitive components of a time perception task. The reciprocal interactions among these specialized systems give rise to our perception of current time. The results are in agreement with converging avenues of research implicating a perceptual system in which the basal ganglia act as a timekeeper that is tightly coupled with an attention system in the right inferior parietal cortex. This right hemisphere bias for the encoding of temporal information is in agreement with converging focal lesion and electrophysiological research in humans. The distinct evolution of activation in the bilateral premotor and right DLPF systems, together with previous neuroimaging studies, provides evidence for different working memory functions underlying time perception. Our results also showed that time and pitch discriminations are mediated by shared parietal and prefrontal systems mostly in the left hemisphere, which were activated during decision and response selection components of both tasks. Presently, we are investigating the dynamics of brain activation patterns during longer delay periods to more directly distinguish systems involved in encoding and short-term maintenance of time intervals.

METHODS

Subjects. Right-handed subjects (2 male/15 female; mean age, 23.9 years) gave written informed consent and were compensated for participation. The experimental protocol was approved by the institutional review board of the Medical College of Wisconsin.

Experimental design. Tone stimuli were presented binaurally using a computer playback system. Sounds were amplified near the scanner and delivered to the subject via air conduction through 180-cm paired plastic tubes, which were threaded through tightly occlusive ear inserts that attenuated background scanner noise to approximately 75 dB sound pressure level (SPL). Background scanner noise consisted of pulses occurring every 205 ms throughout the imaging run; the intensity of the tone stimuli averaged 100 dB SPL. For all three conditions, the standard tones were 700 Hz in pitch separated by a 1200 ms interval (Fig. 1). In the T condition, the eight comparison intervals were ±60-ms increments of the standard interval, and were presented twice in a randomized order (16 trials); pitch did not vary across the four tones. In the P condition, the eight comparison tone pitches were ±4 Hz increments of the standard 700 Hz tones and were presented twice in a randomized order (16 trials); duration did not vary during this condition. In the C task, 16 trials of identical standard tones were presented. The C task was a baseline condition used for removing the effects of low-level sensory and motor processing from the functional maps in the two discrimination conditions. Subjects pressed one of two keys with their right index or middle finger to indicate longer/higher or shorter/lower in the discrimination conditions; subjects pressed a key using their index in the control task. Accuracy and reaction time were measured with a nonferrous key-press pad. Subjects briefly practiced the three conditions before scanning.

Image acquisition. Event-related fMRI was done on a 1.5T GE Signa (Waukesha, Wisconsin) scanner equipped with a three-axis local gradient head coil and an elliptical endcapped quadrature radiofrequency coil. Foam padding limited head motion within the coil. Echo-planar images were collected using a single-shot, blipped gradient-echo echo-planar pulse sequence (TE, 40 ms; TR, 2.5 s; 90° flip angle; FOV, 240 mm; resolution, 64 × 64 matrix). Seventeen contiguous sagittal 7-mm-thick slices were acquired to provide coverage of the entire brain. Scanning was synchronized with the onset of the first tone so that 7 images were acquired during each 17.5-s trial (Fig. 2) with a total of 112 images per run (16 trials per run). An additional 4 images (10.0 s) were added to the beginning of the run to allow the MR signal to reach equilibrium, and were discarded from further analysis; 4 images were added to the end of the run to accommodate the delayed rise of the hemodynamic response. Before functional imaging, high-resolution three-dimensional spoiled gradient-recalled at steady-state anatomic images were collected (TE, 5 ms; TR, 24 ms; 40° flip angle; NEX, 1; slice thickness, 1.2 mm; FOV, 24 cm; resolution, 256 × 128) for anatomic localization and co-registration.

fMRI data analysis. Functional images were generated using Analysis of Functional NeuroImages[48] software. Time series images were spatially registered in three-dimensional space to minimize effects of head motion. A deconvolution analysis was used to generate impulse response functions (IRFs) of the fMRI signal on a voxel-wise basis. This analysis produced an estimate of the hemodynamic response for each condition (T, P and C) relative to a baseline state (rest) without making *a priori* assumptions regarding the shape, delay or magnitude of the IRF. Anatomical and functional images were then interpolated to volumes with 1 mm^3 voxels, co-registered, converted to Talairach stereotaxic coordinate space[49], and blurred using a 4 mm Gaussian full-width half-maximum filter. Voxel-wise analyses of variance (T versus C, P versus C, and T versus P conditions) were done separately for images obtained at 2.5, 5.0, 7.5 and 10.0 s after trial onset. Pooled-variance *t*-tests were applied on a voxel-wise basis to the IRF estimates for each epoch to identify regions showing greater activation in the T and P discrimination conditions relative to the C condition and greater activation in the T than the P condition. An activated region was defined by an individual voxel probability less than 0.001 ($t > 3.61$; df, 16), and a minimum cluster size threshold of 300 microliters[50]. These two thresholds were established based on 10,000 Monte Carlo simulations demonstrating that the chance probability of obtaining a significant activation cluster for an entire volume (type I error) was less than 10^{-6}.

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The evolution of brain activation during temporal processing

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Timing is crucial to many aspects of human performance. To better understand its neural underpinnings, we used event-related fMRI to examine the time course of activation associated with different components of a time perception task. We distinguished systems associated with encoding time intervals from those related to comparing intervals and implementing a response. Activation in the basal ganglia occurred early, and was uniquely associated with encoding time intervals, whereas cerebellar activation unfolded late, suggesting an involvement in processes other than explicit timing. Early cortical activation associated with encoding of time intervals was observed in the right inferior parietal cortex and bilateral premotor cortex, implicating these systems in attention and temporary maintenance of intervals. Late activation in the right dorsolateral prefrontal cortex emerged during comparison of time intervals. Our results illustrate a dynamic network of cortical-subcortical activation associated with different components of temporal information processing.

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Humans are remarkably proficient at perceiving the passage of time and producing precisely timed behaviors, many of which depend upon explicit prospective temporal judgments. For these events, multiple processes seem to determine our subjective perception of current time for intervals lasting several hundreds of milliseconds to several seconds. Most theories of prospective timing embody similar components[1], including an internal timekeeper, attention and memory[2,3]. A clock metaphor is used to describe the timekeeper mechanism, which represents subjective time through the accumulation or readout of pulses, possibly generated by oscillators. Our perception of time, however, is intimately related to the level of attention given to the passage of time. When attention is diverted, a systematic shortening of subjective duration occurs, implying that pulses from the timekeeper may be lost[4]. Attention may also mediate the flexible starting and stopping of pulses from the timekeeper, which enables anticipation of predictable events[5]. Hence, a representation of subjective time emerges from the interplay between timekeeping and attention mechanisms. This representation is then passed on to working memory, a short-term repository where interval representations are maintained and manipulated in accord with current goals (for example, comparing two intervals of time)[6]. Working memory functions can therefore alter stored representations of time as well. The combination of these different component processes gives rise to the subjective perception of time, although the relative contribution of each might differ depending on the interval duration or the cognitive demands of timing events[7].

The neural systems that support different component processes of time perception are a matter of debate. The basal ganglia and lateral cerebellum have been logical candidates for hypothetical timekeeping operations, as damage to these brain regions commonly disrupts behaviors that depend upon precise timing, such as rhythmic movements in Parkinson's disease[8] and regulation of agonist–antagonist muscle activity (for example, dysmetria) in cerebellar damage[9]. Although these movement abnormalities could be attributed to disruption of more generalized motor execution functions, the basal ganglia and cerebellum do seem to mediate time perception. Studies of Parkinson's disease patients[10,11] and pharmacological investigations in animals[12,13] have argued that timekeeping operations are regulated through dopamine neurotransmission in the striatum. Human lesion studies indicate that the lateral cerebellar hemisphere and its primary output, the dentate nucleus[14–18], are also involved in timekeeping mechanisms. Nonetheless, it has been difficult to isolate timekeeping and attention operations from working-memory and response implementation processes[1]. Timing deficits after basal ganglia or cerebellar damage could also be due to abnormalities in interconnecting cortical systems commonly associated with some or all of these processes[19,20]. Fewer studies have examined the involvement of the cerebral cortex in time perception. Focal lesion investigations in animals and humans have shown that the frontal and parietal lobes are also essential for accurate time perception, perhaps due to their purported attention and working memory functions[14,21,22]. Others have posited a role for the supplementary motor area[23], but this has been difficult to assess because focal lesions are uncommon in this region.

Functional imaging techniques can be used to dissect the contribution of each component of multiple neural systems, although studies of timing using these methods have produced conflicting or ambiguous results to date[7]. Most research[24–27] has focused on motor timing, making it difficult to separate activa-

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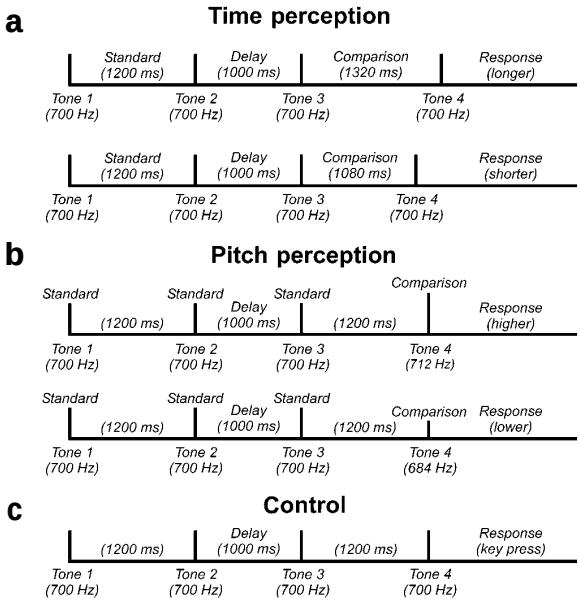

Fig. 1. Trial events in the time perception (**a**), pitch perception (**b**), and control (**c**) conditions. In the time perception condition, subjects indicated whether the comparison interval (defined by tones 3 and 4) was longer or shorter than the standard interval (defined by tones 1 and 2). In the pitch perception condition, subjects indicated whether the comparison tone (tone 4) was higher or lower in pitch than the standard tones (tones 1, 2 and 3). In the control condition, subjects pressed a key after the presentation of the four tones.

tion in systems traditionally associated with motor control, such as the basal ganglia and cerebellum, from those supporting timekeeping or other cognitive processes. Two PET studies[28,29] have specifically examined time perception. Unfortunately, the time scale of PET scanning is limited to blocked-trial designs that cannot disentangle processing associated with encoding an interval from processing associated with decision making and implementing a response. We reasoned that fundamental insights into this issue could be gained by studying the time course of brain activation patterns associated with different components of a time perception task. The present study exploited the finer temporal resolution of event-related functional magnetic resonance imaging (fMRI) to isolate patterns of brain activation that correlated with encoding time intervals from those associated with comparing two time intervals and implementing a response. Timing theory suggests that activation in systems integrally involved in encoding or formulating a representation of time (pacemaker and attention operations) should develop at the onset of a to-be-timed event[2,3], followed by activation in systems concerned with manipulating information in working memory (comparing intervals) and implementing a response.

We obtained fMRI scans of seventeen subjects as they performed three different tasks, the order of which was counterbalanced across subjects. In the time (T) discrimination condition, two tones (50 ms) separated by 1200 ms (standard tone-pair) were presented, followed by a 1-s delay and then a comparison tone-pair (Fig. 1a). Subjects indicated whether the comparison tone-pair was longer or shorter than the standard. To better separate neural systems specific to timing, subjects also performed a pitch (P) discrimination condition in which the auditory events were similar except that subjects indicated whether the fourth tone was higher or lower in pitch than the first three tones (Fig. 1b). Neural systems involved with processing time and pitch information were identified by contrasting imaging runs in each discrimination condition with a sensorimotor control (C) condition in which subjects responded after the presentation of two isochronous tone pairs of identical pitch (Fig. 1c). The T and P conditions were then contrasted to specify systems unique to time discriminations. These subtractions were conducted at each of four scanning intervals after trial onset (2.5, 5.0, 7.5 and 10.0 s). In all conditions, the typical motor response occurred approximately 4.5 s after trial onset (Fig. 2). Allowing 5 s for the hemodynamic response to peak, we proposed that the 2.5- and 5.0-s intervals after trial onset should reveal brain activation patterns specific to encoding time intervals. In contrast, the 10.0-s scanning interval should include activations associated with contrasting the standard and comparison intervals and implementing the response. Overlap between these processes should be particularly evident during the 7.5-s scan, due to encoding of the comparison interval. The results reported here show early sustained activation of the basal ganglia and right inferior parietal cortex, implicating these systems in formulating representations of time. Though activation in the cerebellum was more robust during time than pitch discriminations, activation was located in the vermis and unfolded late, suggesting a more general involvement in cognitive or sensorimotor functions. The evolution of activation in the bilateral premotor and right DLPF cortex differed from each other, consistent with previous work implicating these systems in different aspects of working memory.

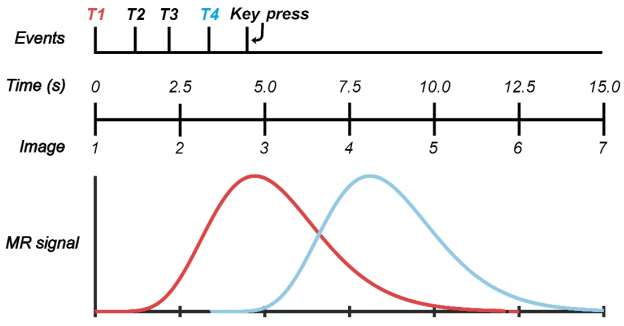

Fig. 2. Temporal relationship among the trial events, acquisition of images and hypothetical hemodynamic response functions to different task components. Seven scans were acquired during each 17.5-s trial (a 2.5-s interval between the seventh image and the first image of the next trial is not illustrated on the timeline). The first scan was acquired at the onset of the first tone (T1). The fourth tone (T4) was presented an average of 3.4 s after trial onset. The typical key press response occurred 4.5 s after trial onset. The two hypothetical time course functions illustrate early versus late MR signal responses to different trial events. An early response corresponding with the encoding of temporal information (red plot) would have a maximal signal change at 2.5 and 5.0 s after trial onset. In contrast, a late response due to decision making and response preparation processes (blue plot) would be observed primarily at 7.5 and 10.0 s after trial onset.

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RESULTS

Behavioral data collected during scanning showed that response times and accuracy correlated with the difficulty of time and pitch discriminations. Reaction time was typically longer (Fig. 3a, $F_{5,76} = 4.2$, $p < 0.01$; Fig. 3c, $F_{6,87} = 4.0$, $p < 0.01$) and accuracy poorer (Fig. 3b, $F_{4,57} = 8.1$, $p < 0.001$; Fig. 3d, $F_{7,112} = 2.7$, $p < 0.025$) when the comparison stimuli were closer in time or in pitch to the standard stimulus. There were no significant differences between the two discrimination conditions in overall accuracy (T, 83 ± 3%; P, 78 ± 3%) or reaction time (T, 1111 ± 76 ms; P, 1076 ± 54 ms). Reaction times for the C condition (707 ± 39 ms) were significantly faster ($F_{1,16} = 48.9$, $p < 0.0001$) than those for the time and pitch conditions.

During the early imaging epochs (2.5 and 5.0 s), which emphasize encoding of temporal information, subcortical activations specific to the T condition (Table 1) were observed within the right putamen, head of the caudate nucleus bilaterally, and right centromedian and ventroanterior thalamic nuclei (Fig. 4a). Early activation specific to the T condition was also observed in various cortical regions (Fig. 5): right intraparietal sulcus (BA 40), bilateral dorsal and left ventral premotor areas (BA 6), and bilateral lateral temporal cortex (BA 21/22). Activation specific to the T condition was sustained during the 7.5- and/or 10.0-s imaging epochs in most of these regions. In the P condition, areas of activation during the early imaging epochs overlapped with those in the T condition. In both the T and P conditions (Table 2), activity unfolded early within the medial wall (preSMA and SMA proper, BA 6, and anterior cingulate, BA 32; Fig. 4c) and the anterior insula/frontal operculum (Fig. 4a), but was sustained during later epochs as well.

During the later imaging epochs (7.5 and 10.0 s), which included decision and response selection components of the tasks, activation specific to the T condition (Table 1) was observed in the posterior vermis (tuber) of lobule VIIB of the cerebellum (Fig. 4b) and the right dorsolateral prefrontal (DLPF) cortex (BA 46/10/9; Fig. 5). All other activation foci were observed in the left hemisphere in both the

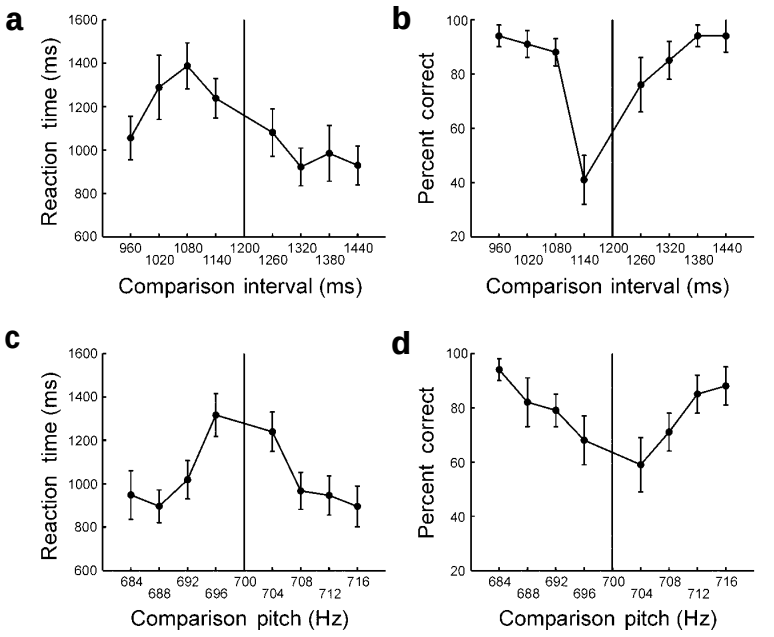

Fig. 3. Mean (± standard error of mean) reaction time and percent correct for the time perception (**a**, **b**) and the pitch perception (**c**, **d**) conditions. Data are depicted as a function of the comparison interval or comparison pitch.

Table 1. Stereotaxic brain atlas coordinates[49] for Time > Control subtraction.

Location (Brodmann Area)	Hemisphere	2.5	5.0	7.5	10.0
Basal Ganglia					
Medial caudate (head)	R		12, 7, 3	12, 6, 4	
	L		–12, 7, 5	–9, 7, 2	–8, 4, 8
Lateral caudate (body)	R				15, 6, 19
Putamen	R	22, 8, –1			23, 6, 8
					26, 6, –2
	L				–20, –1, 5
Cerebellum					
Vermis (tuber, lobule VIIB)	B			–3, –70, –30	2, –70, –29
Thalamus					
Centromedian nucleus	R		4, –21, 0	4, –21, 0	
Ventroanterior nucleus	R		4, –11, 0	5, –10, 0	
Frontal					
Dorsal premotor (6)	R		23, –7, 48	23, –3, 52	46, 1, 49
	L		–45, –7, 47		
Ventral premotor (6)	R		46, 8, 24		
	L	–54, –13, 26	–51, –15, 27		
Dorsolateral (46/10/9)	R			34, 23, 25	31, 46, 22
					41, 29, 22
Parietal					
Intraparietal sulcus, Angular gyrus (40)	R	38, –40, 41	36, –43, 40	37, –47, 38	30, –56, 35
Superior parietal lobule, Precuneus (7)	R				10, –68, 44
Temporal					
Superior temporal (22)	R		51, –39, 6		
Middle temporal (21)	L		–46, –56, 4		

R, right; L, left; B, bilateral. The activations reported in this table were not observed in the Pitch > Control subtraction.

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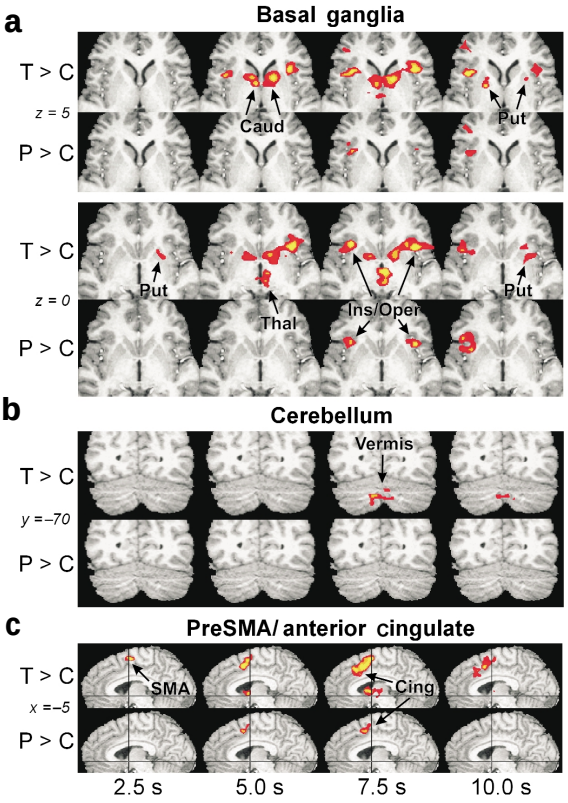

Fig. 4. Activation foci in the basal ganglia (**a**), cerebellum (**b**), and pre-supplementary motor area/anterior cingulate (**c**) resulting from subtraction of the control (C) condition from the time (T) and the pitch (P) perception conditions at 2.5, 5.0, 7.5 and 10.0 s after trial onset. Significant foci ($p < 0.001$) are displayed with a red-yellow intensity scale denoting greater activation for the T or P conditions. Slices are displayed in neurological view (left is on the viewer's left). Location of slices defined by the distance (mm) from anterior commissure: *x*, right (+)/left (–); *y*, anterior (+)/posterior (–); *z*, superior (+)/inferior (–). Caud, caudate nucleus; Cing, anterior cingulate area; Ins, insula; Oper, frontal operculum; Put, putamen; Thal, thalamus; SMA, supplementary motor area.

T and P conditions (Table 2), and included the inferior frontal gyrus (Broca's area, BA 44/45), intraparietal sulcus (BA 40), superior parietal lobule/precuneus (BA 7) and DLPF cortex.

The results from the T minus P subtraction were similar to the results for the T minus C subtraction (Fig. 6). During the earlier imaging epochs (2.5 and 5.0 s), subcortical activations unique to the T condition were in the right hemisphere and included the putamen (*x*, *y*, *z* = 24, 7, –2), caudate (15, 6, 13) and insula/frontal operculum (29, 16, 2). The later region, however, was also activated during the 7.5-s epoch in the pitch condition (Table 2, Fig. 4a). During the later imaging epochs (7.5 s), the right DLPF cortex (21, 21, 30) was also unique to the T condition (Fig. 6).

Discussion

The present findings provide compelling evidence for the involvement of the basal ganglia in formulating representations of time. Activation in the right putamen and caudate were uniquely associated with encoding time intervals. These results corroborate studies in Parkinson's disease showing that dopaminergic treatment improves motor timing[30,31] and time perception[32]. Pharmacological challenges in animals also suggest that dopaminergic antagonists and agonists respectively slow down and speed up timing operations[12,13]. Contrary to one proposal[33], these and other studies[10,11,27] show that the basal ganglia are involved in timing a wide range of intervals, from hundreds of milliseconds (300 ms) to tens of seconds (20 s). Collectively, these results implicate striatal dopaminergic neurotransmission in hypothetical internal timekeeping mechanisms.

Table 2. Stereotaxic brain atlas coordinates[49] for regions commonly activated in subtractions of Time and Pitch perception conditions relative to Control condition.

		Time > Control				Pitch > Control			
Location (Brodmann Area)	**Hemisphere**	**2.5**	**5.0**	**7.5**	**10.0**	**2.5**	**5.0**	**7.5**	**10.0**
Frontal									
Insula/operculum (47)	R		31, 17, 3	35, 16, 3	34, 17, 4			34, 17, 0	
	L		–35, 11, 5	–34, 15, 2	–36, 12, 4			–34, 18, 1	–36, 17, 0
PreSMA (6),									
Anterior cingulate (32)	L	–4, –1, 56	–4, 6, 49	–7, 10, 45	–5, 12, 43		–6, 7, 48	–4, 8, 49	
Inferior frontal gyrus (44/45)	R			37, 1, 32				37, 4, 28	
	L			–46, 4, 21	–47, 5, 18			–45, 4, 22	–44, 7, 26
Dorsolateral (46/10/9)	L			–39, 42, 12	–36, 46, 13				–36, 40, 8
				–42, 26, 28	–40, 14, 29				
Parietal									
Intraparietal sulcus,									
Angular gyrus (40)	L			–31, –49, 37	–29, –52, 33				
				–36, –53, 44			–32, –47, 38	–30, –55, 36	
Superior parietal lobule,									
Precuneus (7)	L			–21, –66, 49	–28, –49, 43			–13, –72, 50	–43, –57, 50
					–21, –63, 51				–25, –65, 50

R, right; L, left; B, bilateral

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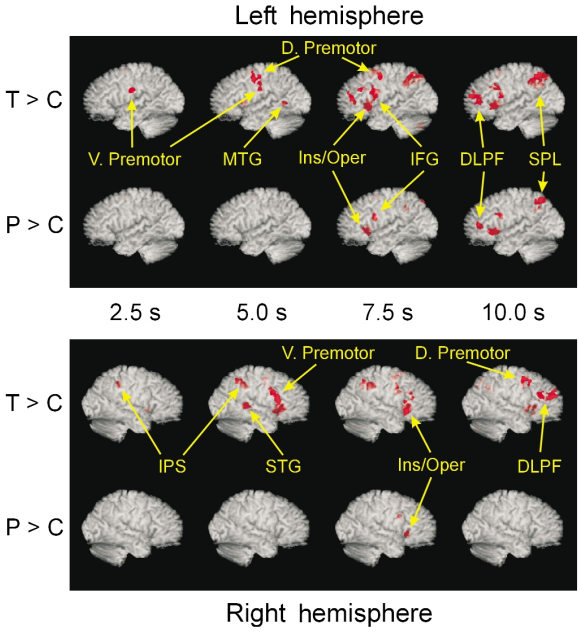

Fig. 5. Activation foci in the lateral surface of the left and right hemispheres denote greater activation for the time (T) and the pitch (P) perception conditions relative to the control (C) condition at 2.5, 5.0, 7.5 and 10.0 s after trial onset. Significant foci ($p < 0.001$) are displayed in red. DLPF, dorsal lateral prefrontal cortex; D. Premotor, dorsal premotor; IFG, inferior frontal gyrus; Ins, insula; IPS, inferior parietal sulcus; MTG, middle temporal gyrus; Oper, frontal operculum; STG, superior temporal gyrus; V. Premotor, ventral premotor.

Our findings did not support a unique role for the cerebellum in encoding time intervals. Nonetheless, cerebellar activation was observed during the time perception task (T minus C), consistent with several studies showing diminished time perception in patients with cerebellar damage[16,18,34]. However, in our study, activation was in the vermis rather than the lateral cerebellar hemispheres, contrary to reports that damage to the lateral cerebellum, but not the vermis, correlated with time perception deficits[15,18]. Cerebellar activation evolved later in the course of the trial, just before and during movement execution, suggesting an involvement in processes other than explicit timing. This is consistent with our previous fMRI study[27] showing that cerebellar activation was not specific to timing self-paced finger movements. Apart from its well-documented role in sensorimotor processing, neuroimaging research indicates that the cerebellum participates in many cognitive functions, including tactile perception[35] and working memory[36]. One lesion study has also shown that cerebellar damage produces pitch perception deficits[14]. Its broad role in sensorimotor and cognitive processing[37] has suggested that the cerebellum monitors and adjusts input from the cerebral cortex, but is not involved in computing a specific operation *per se*[38]. By this account, later activation in vermal lobule VIIB, which receives auditory and visual input[39], could be due to its involvement in optimizing sensory input from auditory systems, which facilitates the comparison of intervals in working memory. Although other explanations are possible, this account is appealing because it predicts that damage to the cerebellum will slow sensory acquisition, which should disrupt a broad range of behaviors, especially those involving timing. This view may explain why patients with cerebellar damage show deficits in timing[16,17], but not always in the perception of pitch or loudness[16,18].

Representations of time depend on the interplay of internal timekeepers with attention and working memory, functions more commonly identified with cortical systems. Neural systems associated with these functions should support a variety of computations, which may explain why they were not always unique to timing intervals (T minus P). However, in the comparisons involving the control condition (T minus C, P minus C), right hemisphere activations were observed during time but not pitch perception. These later results are consistent with findings from converging neuroscience approaches. Specifically, a neuroanatomical bridge for basal ganglia–cortical interactions is the thalamus[40], which was activated early during the encoding of intervals, along with two cortical regions, suggesting they work together in formulating representations of time. Coupled activation in the right inferior parietal cortex may suggest an interdependent role of this region in attention, which theoretically regulates the timekeeping mechanism. Neurological patients with right but not left inferior parietal damage show time, but not pitch, perception deficits that correlate with impairments in switching attention[21]. Electrophysiological recordings in humans have also shown a right hemisphere bias for temporal processing[41], especially in the parietal cortex[42]. The close relationship between timekeeping and attention is presumed by one influential theory[2], and has received empirical support in behavioral studies conducted on humans[4,5]. According to this view, representations of time are reflected in the pulse count accumulated over

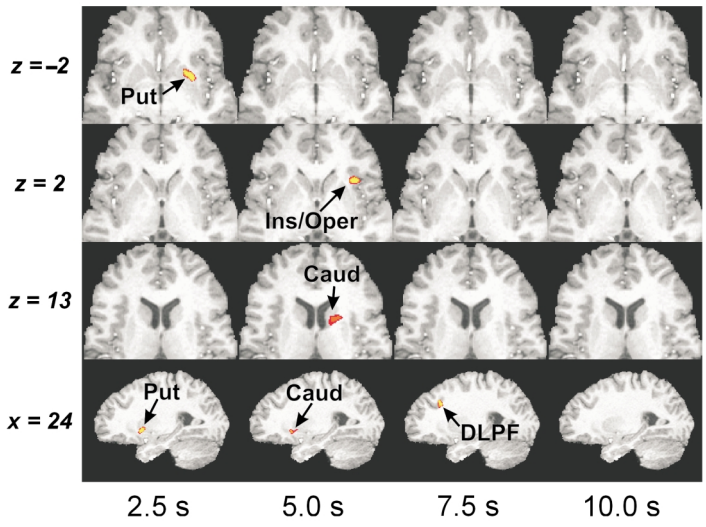

Fig. 6. Activation foci in the basal ganglia, insula/frontal operculum and dorsal lateral prefrontal cortex resulting from greater activation for the time (T) relative to the pitch (P) perception conditions at 2.5, 5.0, 7.5 and 10.0 s after trial onset. Significant foci ($p < 0.001$) are displayed with a red-yellow intensity scale. Slices are displayed in neurological view (left is on the viewer's left). Location of slices defined by the distance (mm) from anterior commissure. Caud, caudate nucleus; DLPF, dorsal lateral prefrontal cortex; Ins, insula; Oper, frontal operculum; Put, putamen.

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a particular physical time, which critically depends on the degree of attentional engagement. Our results point to the right inferior parietal cortex in regulating the accumulation of pulses, because of its well-documented involvement in attention[43]. Bilateral projections from the inferior parietal cortex to the putamen and caudate nucleus in monkeys[44] provide a neuroanatomic basis for the interaction of attention and timekeeping operations.

The perception of time also relies on stored representations of intervals in working memory[2]. During time perception, activation was observed in regions commonly associated with temporary storage functions, including the bilateral premotor (BA 6) and right DLPF cortex (BA 9, 10, 46)[19,20,45]. Right DLPF activation was also unique to performing time discriminations. This corroborates our previous finding that damage to these same regions in the right, but not left, hemisphere produces time perception deficits[21]. Controversy exists over whether these areas support different working memory functions[45–47]. However, a recent meta-analysis of neuroimaging studies[20] implicated the premotor cortex in a 'rehearsal circuit' in tasks involving mainly the temporary maintenance of information, such as item recognition. In contrast, the DLPF cortex was associated with an 'executive circuit' in tasks requiring manipulation of stored information, such as the two- and three-back working-memory tasks. Our findings are compatible with this process distinction, as premotor cortex activation began early, consistent with the need for maintaining the standard interval during the trial, whereas DLPF cortex activation unfolded later in association with comparing the two intervals and selecting a response. Independent evidence for the DLPF cortex in executive functions of working memory was observed in the pitch condition as well, in which activation unfolded later during the comparison phase, but was confined to the left hemisphere. Though premotor cortex was not activated in the pitch condition, repeated presentation of the standard pitch across the trial may have minimized the need for rehearsal.

In summary, the present results are compatible with prevailing cognitive theory, and provide new insights into the evolution of activation in cortical and subcortical systems that are specific to different cognitive components of a time perception task. The reciprocal interactions among these specialized systems give rise to our perception of current time. The results are in agreement with converging avenues of research implicating a perceptual system in which the basal ganglia act as a timekeeper that is tightly coupled with an attention system in the right inferior parietal cortex. This right hemisphere bias for the encoding of temporal information is in agreement with converging focal lesion and electrophysiological research in humans. The distinct evolution of activation in the bilateral premotor and right DLPF systems, together with previous neuroimaging studies, provides evidence for different working memory functions underlying time perception. Our results also showed that time and pitch discriminations are mediated by shared parietal and prefrontal systems mostly in the left hemisphere, which were activated during decision and response selection components of both tasks. Presently, we are investigating the dynamics of brain activation patterns during longer delay periods to more directly distinguish systems involved in encoding and short-term maintenance of time intervals.

METHODS

Subjects. Right-handed subjects (2 male/15 female; mean age, 23.9 years) gave written informed consent and were compensated for participation. The experimental protocol was approved by the institutional review board of the Medical College of Wisconsin.

Experimental design. Tone stimuli were presented binaurally using a computer playback system. Sounds were amplified near the scanner and delivered to the subject via air conduction through 180-cm paired plastic tubes, which were threaded through tightly occlusive ear inserts that attenuated background scanner noise to approximately 75 dB sound pressure level (SPL). Background scanner noise consisted of pulses occurring every 205 ms throughout the imaging run; the intensity of the tone stimuli averaged 100 dB SPL. For all three conditions, the standard tones were 700 Hz in pitch separated by a 1200 ms interval (Fig. 1). In the T condition, the eight comparison intervals were ±60-ms increments of the standard interval, and were presented twice in a randomized order (16 trials); pitch did not vary across the four tones. In the P condition, the eight comparison tone pitches were ±4 Hz increments of the standard 700 Hz tones and were presented twice in a randomized order (16 trials); duration did not vary during this condition. In the C task, 16 trials of identical standard tones were presented. The C task was a baseline condition used for removing the effects of low-level sensory and motor processing from the functional maps in the two discrimination conditions. Subjects pressed one of two keys with their right index or middle finger to indicate longer/higher or shorter/lower in the discrimination conditions; subjects pressed a key using their index in the control task. Accuracy and reaction time were measured with a nonferrous key-press pad. Subjects briefly practiced the three conditions before scanning.

Image acquisition. Event-related fMRI was done on a 1.5T GE Signa (Waukesha, Wisconsin) scanner equipped with a three-axis local gradient head coil and an elliptical endcapped quadrature radiofrequency coil. Foam padding limited head motion within the coil. Echo-planar images were collected using a single-shot, blipped gradient-echo echo-planar pulse sequence (TE, 40 ms; TR, 2.5 s; 90° flip angle; FOV, 240 mm; resolution, 64 × 64 matrix). Seventeen contiguous sagittal 7-mm-thick slices were acquired to provide coverage of the entire brain. Scanning was synchronized with the onset of the first tone so that 7 images were acquired during each 17.5-s trial (Fig. 2) with a total of 112 images per run (16 trials per run). An additional 4 images (10.0 s) were added to the beginning of the run to allow the MR signal to reach equilibrium, and were discarded from further analysis; 4 images were added to the end of the run to accommodate the delayed rise of the hemodynamic response. Before functional imaging, high-resolution three-dimensional spoiled gradient-recalled at steady-state anatomic images were collected (TE, 5 ms; TR, 24 ms; 40° flip angle; NEX, 1; slice thickness, 1.2 mm; FOV, 24 cm; resolution, 256 × 128) for anatomic localization and co-registration.

fMRI data analysis. Functional images were generated using Analysis of Functional NeuroImages[48] software. Time series images were spatially registered in three-dimensional space to minimize effects of head motion. A deconvolution analysis was used to generate impulse response functions (IRFs) of the fMRI signal on a voxel-wise basis. This analysis produced an estimate of the hemodynamic response for each condition (T, P and C) relative to a baseline state (rest) without making *a priori* assumptions regarding the shape, delay or magnitude of the IRF. Anatomical and functional images were then interpolated to volumes with 1 mm^3 voxels, co-registered, converted to Talairach stereotaxic coordinate space[49], and blurred using a 4 mm Gaussian full-width half-maximum filter. Voxel-wise analyses of variance (T versus C, P versus C, and T versus P conditions) were done separately for images obtained at 2.5, 5.0, 7.5 and 10.0 s after trial onset. Pooled-variance *t*-tests were applied on a voxel-wise basis to the IRF estimates for each epoch to identify regions showing greater activation in the T and P discrimination conditions relative to the C condition and greater activation in the T than the P condition. An activated region was defined by an individual voxel probability less than 0.001 ($t > 3.61$; df, 16), and a minimum cluster size threshold of 300 microliters[50]. These two thresholds were established based on 10,000 Monte Carlo simulations demonstrating that the chance probability of obtaining a significant activation cluster for an entire volume (type I error) was less than 10^{-6}.

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The neural correlates of cognitive time management: a review

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Review

Abstract. Cognitive time management is an important aspect of human behaviour and cognition that has so far been understudied. Functional imaging studies in recent years have tried to identify the neural correlates of several timing functions, ranging from simple motor tapping to higher cognitive time estimation functions. Several regions of the frontal lobes, in particular dorsolateral prefrontal cortex (DLPFC), inferior prefrontal cortex (IFC), anterior cingulate gyrus (ACG) and the supplementary motor area (SMA), alongside non-frontal brain regions such as the inferior parietal lobes, the cerebellum and the basal ganglia have been found to be involved in tasks of motor timing and time estimation. In this paper we review and discuss the involvement of these brain regions in different tasks of cognitive time management, illustrating it with own findings on motor timing and time perception tasks using functional magnetic resonance imaging (fMRI). The review shows that the same brain regions are involved in both motor timing and time estimation, suggesting that both functions are probably inseparable and mediated by common neural networks.

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Key words: time estimation, motor timing, timing, dorsolateral prefrontal cortex, DLPFC, inferior prefrontal cortex, supplementary motor area, SMA, anterior cingulate gyrus ACG, functional magnetic resonance imaging, fMRI

INTRODUCTION

Human behaviour is necessarily conducted in time and space, which makes cognitive time management an essential human function. Adequate timing of our behaviour and good time estimation skills are essential for normal social functioning and have an impact on a wide range of motor and cognitive functions such as movement, planning, speed of cognitive processing and speech.

In the timing literature, the distinction has been made between motor timing and time perception (Fuster 1990). In this article we use the term cognitive time management when we generalise across both forms of perceptive time estimation and motor timing. Motor timing refers to the timing aspects of the output of behaviour such as the temporal organisation of motor, speech or cognitive acts. Time perception refers to the more passive and perceptive aspects of cognitive time management such as perceiving temporal intervals and the ability to estimate temporal delays. In laboratory settings motor timing has so far been measured in tasks of finger tapping, rhythm production, rhythmic finger movements, sensorimotor synchronisation, and the temporal organisation of movements. The time range used with these methods range from the milliseconds' range to seconds and minutes. Time estimation has been measured in tasks of temporal estimation, where temporal intervals from milliseconds to minutes or even hours need to be estimated, in tasks of temporal production or reproduction, where subjects are told to (re)produce a time interval given to them in conventional time units, in time discrimination tasks, where two different temporal intervals need to be discriminated or in rhythm discrimination tasks.

Since cognitive time management is such an essential function of normal human behaviour, different behavioural pathologies have shown abnormalities in both motor timing and time estimation. Thus, abnormalities in time estimation have been observed in a wide range of pathologies including patients with brain lesions (Harrington et al. 1998, Rubia et al. 1997), attention deficit/hyperactivity disorder (Rubia et al. 1999a,b, 2001, 2003, Smith et al. 2002, Sonuga-Barke et al. 1998), antisocial personality disorder (Bauer 2001), dyslexia and dysphasia (May et al. 1988, Needham and Black 1970, Nicolson et al. 1995, Tallal et al. 1991), schizophrenia (Davalos et al. 2003, Rammsayer 1990, Ulferts et al. 1999, Volz et al. 2001), depression (Kuhs et al. 1991, Mundt et al. 1998, Rammsayer 1990), Parkinson's disease (Lange et al. 1995, Pastor et al. 1992, Riesen and Schnider 2001) and drug abuse (Mathew et al. 1998, Mintzer and Stitzer 2002, Solowij et al. 2002). Motor timing has been less extensively tested, but also been found to be abnormal in several psychopathologies such as attention deficit/hyperactivity disorder (Carte et al. 1996, Rubia et al. 1999a,b, 2001, 2003, Stevens et al. 1970), dyslexia (Denckla et al. 1985, Waber et al. 2000), Parkinson's disease (Elsinger et al. 2003, O'Boyle et al. 1996) and alcohol abuse (Parks et al. 2003).

It has been suggested that motor timing as an executive function would be mediated by prefrontal brain regions while time perception as a perceptive function would be aided by the activation of more posterior brain regions such as the parietal lobes (Fuster 1990). Over the last decades, brain lesion and imaging studies using a wide range of timing tasks, from simple motor tapping to higher complex time estimation tasks, have attempted to specify the neural correlates associated with the various functions of motor and cognitive time management. Several regions in the frontal lobes such as dorsolateral and inferior prefrontal cortices, supplementary motor area, and anterior cingulate, but also non-frontal cortical regions such as the parietal lobes and subcortical brain areas including the cerebellum and the basal ganglia have been found to be implicated in motor timing and time estimation. Interestingly, it appears that strikingly similar brain regions seem to subserve both motor timing and time perception. This may reflect the fact that cognitively, both functions can not be clearly separated. Time estimation tasks that involve a button press, for example, will be confounded by motor timing functions and most motor timing tasks involve an element of perceptive time estimation such as estimating a temporal delay in order to make a perfectly timed move. It is the aim of this article to review and discuss the brain regions that have been found to be involved in both functions of motor timing and time perception. Furthermore, we hope to show with this review that the two functions are mediated by similar brain regions suggesting that they cannot be as clearly separated as previously thought.

A further important distinction in the timing literature is to be made between different temporal domains in which both time estimation or motor timing are being measured (Szelag et al. 2004 – this issue). As different cognitive functions are being co-measured, for example, in time estimation or reproduction of several seconds or minutes, sustained attention to time and

working memory will be crucial basis functions to hold the time interval online. In reviewing the literature we will therefore clearly point out the time range that has been tested by the several studies.

DORSOLATERAL AND INFERIOR PREFRONTAL CORTICES

The prefrontal cortex was one of the first brain regions to be related to cognitive time management, based on animal and lesion studies of an involvement of the prefrontal cortex in planning and timing of behaviour and the perception of time (Fuster 1989). In recent decades, functional brain imaging studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) in combination with paradigms of motor timing and perceptive timing functions have confirmed the hypothesis of a predominant role of the prefrontal cortex in cognitive time management.

Lesion studies have shown that patients with lesions of right and left frontal brain regions appear to be impaired in their ability to estimate temporal durations of milliseconds, seconds and minutes (Casini and Ivry 1999, Harrington et al. 1998, Mangels et al. 1998, Nichelli et al. 1995, Rubia et al. 1997). In some of these studies, in particular the integrity of right DLPFC and right inferior parietal lobe has been shown to be critical for time discrimination and estimation deficits of several seconds (Harrington et al. 1998, Kagerer et al. 2002, Mangels et al. 1998, Rubia et al. 1997). Modern functional imaging studies using fMRI and PET have confirmed the role of DLPFC and IFC in mediating motor timing and time estimation. In most of these studies the prefrontal activation was in the right hemisphere. Thus, predominantly right hemispheric DLPFC, but also right IFC have shown to mediate time estimation of several seconds (Basso et al. 2003, Lewis and Miall 2002, Macar et al. 2002) and time discrimination of milliseconds (Maquet et al. 1996, Rao et al. 2001, Smith et al. 2003). DLPFC is also activated in motor timing tasks such as sensorimotor synchronisation of hundreds of milliseconds in finger tapping (Larsson et al. 1996) and of several seconds (Lejeune et al. 1997, Rubia et al. 1998, 2000). In our own studies of motor timing sensorimotor synchronisation was required for a stimulus that appeared every 5 s and contrasted to sensorimotor synchronisation of a 600 ms interval (Rubia et al. 1998, 2000). Sensorimotor synchronisation in the delay task of 5 s requires both adequate estimation of the

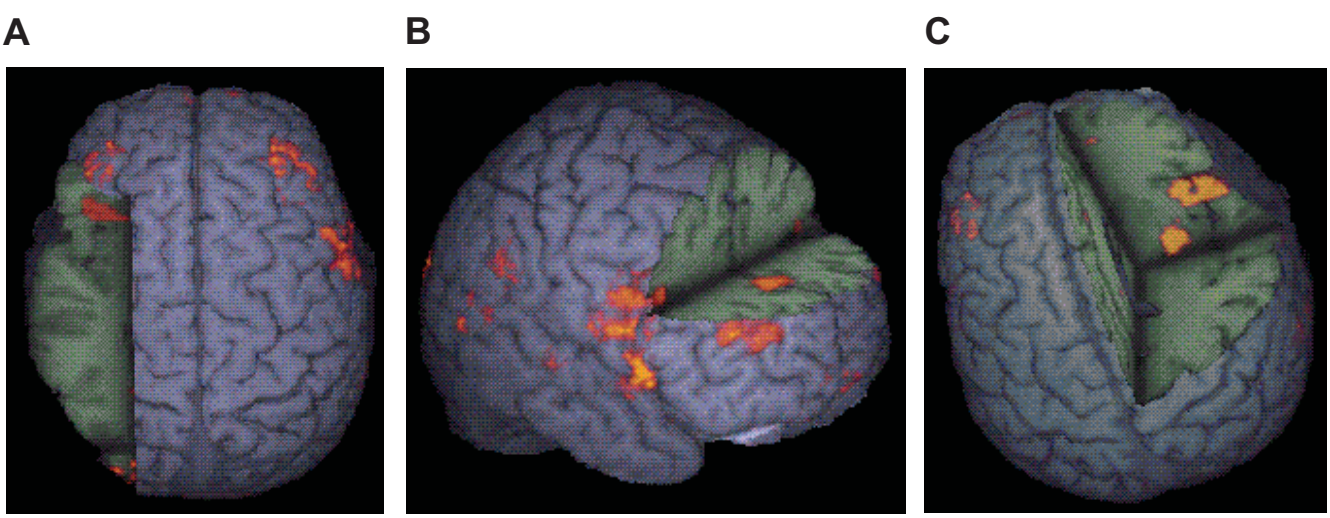

Fig. 1. Generic brain activation map of 8 right-handed male adults (aged 22 to 40 years; mean age 29 years) while performing a sensorimotor synchronisation task of 5 s, after contrasted with a sensorimotor synchronisation task (finger tapping) of 0.6 s in a block design fMRI study. Subjects were instructed to time their motor response to the regular appearance of the visual stimuli on the computer screen. For good sensorimotor timing subjects had to monitor the time interval elapsed since the presentation of the last visual stimulus. The long event rate condition imposes a higher load on time estimation and motor timing compared to the short event rate condition. Areas shown are brain regions that showed significant greater activation during the synchronisation task of 5 s in contrast to finger tapping, presumably reflecting both time estimation and motor timing (corrected $P<0.003$) (for further details see Rubia et al. 2000). (A) Activations in right and left dorsolateral (Brodmann area (BA) 46) and inferior prefrontal cortices (BA 45); (B) activation in anterior cingulate gyrus, right dorsolateral and inferior prefrontal cortices (BA 32) and right parietal lobe; (C) activation in right putamen and right inferior prefrontal lobe (BA 45).

5 s interval and accurate motor timing (see Fig. 1). In a posterior study we tested pure time estimation in a temporal discrimination task, where time intervals of about 1 seconds length differed by several hundreds of milliseconds; we observed a similar focus of right DLPFC and right IFC for pure time estimation (see Fig. 2).

A further distinction has been made between the neural correlates of long-term and short-term time estimations. Mangels et al. (1998) found that damage in lateral prefrontal cortex impaired the discrimination of long (4 s) but not short temporal durations (400 ms). This is in line with the studies of Rubia et al. (1998, 2000) where lateral prefrontal activation was only observed in the contrast of the longer synchronisation task with the tapping task, but not in the tapping task alone (see Fig. 1). These findings may suggest that regions of the prefrontal cortex have the function of a hypothetical accumulator within an internal clock model, which is required only with durations of more than several seconds. Indeed, prefrontal activation in timing tasks of durations of several seconds has often been related to other underlying functions besides pure timing processes, such as sustained attention to the time interval or working memory components (Macar et al. 2002, Maquet et al. 1996, Rao et al. 2001), based on the well-known role of DLPFC in working memory (Baker et al. 1996, Diwadkar et al. 2000, Manoach et al. 1997, Mull and Seyal 2001) and attention (Mazoyer et al. 2002, Posner and Peterson 1990, Sylvester et al. 2003). Thus, in some of the studies DLPFC activation was not only related to temporal discrimination but also to the attentional control conditions (Coull and Nobre 1998, Lejeune et al. 1997, Tracy et al. 2000). However, other studies have suggested that DLPFC may have a more primary role in time estimation processes (Constantinidis et al. 2002, Lewis 2002, Rubia et al. 1998, Zakay and Block 1996). Thus, studies using delay tasks with minimal working memory load have observed strong DLPFC and IFC activation (Rubia et al. 1998, 2000) (see Fig. 1). It has been argued that DLPFC activation often observed during working memory tasks such as the delayed response task (where a response is requested

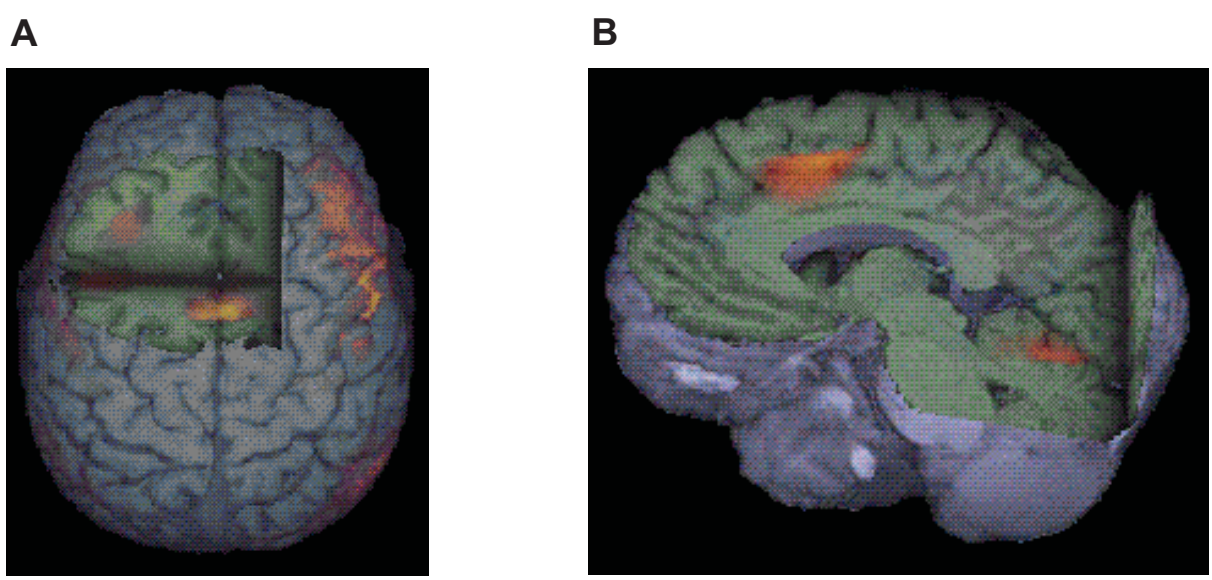

Fig. 2. Generic brain activation map of 20 healthy right-handed male adults (aged 22 to 42 years, mean age 29 years) while performing a time discrimination task after contrasted from an order discrimination task in block design fMRI. Subjects had to discriminate two time intervals. The standard interval lasted 1s, the comparison interval lasted either 1.3 s, 1.4 s, or 1.5 s. Both intervals were presented by a green or a red circle on a computer screen. Subjects had to decide which of the two circles that were presented consecutively on a computer screen lasted longer, the red of the green one (the standard and comparison intervals were counterbalanced in colour). The task was contrasted with an order discrimination task, where subjects had to indicate which of the two circles was presented first, the red or the green one (for details see Smith et al. 2003). Brain regions are shown of increased activation in relation to the temporal discrimination task when contrasted with the order judgement, thus representing areas responsible for pure perceptive temporal discrimination (corrected $P<0.05$) (A) Activation of right dorsolateral (BA 9/46) and inferior prefrontal (BA 45) cortices and the supplementary motor area (BA 6); (B) left hemispheric view: activation of left cerebellum and the supplementary motor area, that was activated bilaterally (see Fig. 2A).

after a certain temporal delay period), could in fact reflect underlying timing processes such as bridging the temporal gaps involved in these tasks or timing of the motor response (Rubia et al. 1998, 2000). Single cell recordings in prefrontal cortex in monkeys have been shown to be in line with this hypothesis. In an attempt to disentangle timing and working memory processes in delayed response tasks, Fuster (1973) found that different neurons in the DLPFC of monkeys were cue-coupled, presumably related to the mnemonic content, while others were showing sustained activity, presumably reflecting temporal processes. More recently, Constantinidis et al. (2002) studied cell pairs in DLPFC in primates and found that the firing of one of these paired neurons is then followed by inhibitory activity in the second cell of the pair. Temporally predictable decay curves in the first cell then determine the onset of activity of the second inhibited cell. These circuits could act as cortical oscillators and may even form the neural basis of a central clock mechanism (Lewis 2002). In support of this, an fMRI study found increasing activation in DLPFC with increasing delays in a working memory task, but not with increasing working memory load (Braver et al. 1997). Also, a study by Pochon et al. (2001) comparing a delayed matching task with a delayed response preparation task found that right-sided DLPFC activation was stronger for the response preparation than for the working memory task. Furthermore, there are also studies that have found DLPFC to be involved in shorter time estimation processes in the milliseconds' range, where sustained attention and working memory functions are less relevant (Larsson et al. 1996, Maquet et al. 1996, Ortuno et al. 2002, Rao et al. 2001 Smith et al. 2003). In our own study, the time intervals to be discriminated were about 1s long, but differed in hundreds of milliseconds (Smith et al. 2003). Thus, working memory or sustained attention demands were relatively small and well controlled by the control task and we still observed strong right-sided DLPFC and IFC activation (see Fig. 2).

It could also be argued, on the other hand, that working memory, i.e., holding the temporal interval online, is an important underlying cognitive component of time estimation processes which would also explain DLPFC activation during temporal tasks. DLPFC could then be thought to act as an "accumulator", storing information about a passing time interval and making it the working memory component of a hypothesised internal clock (Gruber et al. 2000, Mangels et al. 1998).

A third theory, probably the most likely, would assume that different regions within DLPFC subserve both timing and working memory functions (D'Esposito et al. 2000, Rubia et al. 1998, Zarahn et al. 2000).

Right IFC is another prefrontal region that has commonly been found to be activated during motor timing and time estimation processes. Thus, IFC has shown to be activated during motor timing tasks such as finger tapping (Rao et al. 1997), rhythmic finger movement (Kawashima et al. 1999), rhythm reproduction (Penhune et al. 1998), and sensorimotor synchronisation (Lejeune et al. 1997, Rubia et al. 2000) (see Fig. 1). It has, however, also found to be involved in perceptive timing paradigms such as temporal discrimination of hundreds of milliseconds (Maquet et al. 1996, Pedersen et al. 2000, Pouthas et al. 2000, Smith et al. 2003) (see Fig. 2), simple attention to synchrony/asynchrony (Gruber et al. 2000), rhythm perception (Schubotz et al. 2000), timed counting of hundreds of milliseconds (Ortuno et al. 2002) and temporal production of several seconds (Brunia et al. 2000). In a study that combined event related potentials (ERPs) with PET increased activation was observed in right IFC and ACG during time discrimination trials compared with intensity discrimination and the timing of the ERPs associated with right prefrontal regions were aligned with the durations themselves (Pouthas et al. 2000). As mentioned above, we observed right IFC and DLPFC activation in a motor delay task, where subjects had to adjust the motor response to a stimulus appearing every 5 seconds, which required both motor timing and time estimation (Rubia et al. 2000) (Fig. 1). IFC and DLPFC were, however, not activated during a motor tapping task of 600 ms, when contrasted with the synchronisation task of 5 s (Rubia et al. 2000). Very similar right IFC and DLPFC activation was observed during a temporal discrimination task of hundreds of milliseconds (Smith et al. 2003) (see Fig. 2). In an elegant attempt to disentangle the involvement of different prefrontal brain regions in timing aspects, Brunia et al. (2000) could attribute IFC activation to the execution of an anticipated timed movement (the production of a 3 s interval) based upon feedback on previous performance, while DLPFC appeared to use internal cues for temporal programming of the motor output. Furthermore, Gruber et al. (2000) and Schubotz et al. (2000) found activation in IFC where subjects were instructed simply to attend to rhythm and where no movement was required. It thus appears that IFC may be related more to perceptive time estimation processes rather than to motor timing aspects of behaviour.

SUPPLEMENTARY MOTOR AREA (SMA) AND THE ANTERIOR CINGULATE GYRUS (ACG)

The SMA forms part of fronto-striatal pathways. It has projections to and from the basal ganglia *via* the thalamus, and is also connected to frontal and parietal cortical attention areas (Schell and Strick 1984). Focal lesions in the SMA have shown to produce deficits in the timing of movements as tested in rhythm reproduction (Halsband et al. 1993). Activation of the SMA has consistently been found in motor timing tasks, including tasks of finger tapping and rhythm tapping of hundreds of milliseconds, and motor preparation, temporal production and temporal synchronisation of several seconds (Brunia et al. 2000, Lang et al. 1990, Penhune et al. 1998, Rao et al. 1997, Riecker et al. 2003, Rubia et al. 1998, 2000) (see Fig. 1). However, despite its postulated role in motor aspects of timing, the SMA has also been activated in tasks of pure perceptive time estimation. Thus, some studies have observed increased SMA activation during estimation of longer time intervals of seconds as opposed to milliseconds (Fernandez et al. 2003, Pouthas et al. 2001, Rubia et al. 1998, 2000) (see Fig. 1) and in time production of several seconds (Lewis and Miall 2002). However, SMA activation has also been found in studies of discrimination of short intervals in the milliseconds' range (Macar et al. 2002, Rao et al. 2001), of second intervals that differed by hundreds of milliseconds (Smith et al. 2003) (see Fig. 2), in rhythm discrimination involving milliseconds (Gruber et al. 2000, Schubotz et al. 2000), timed counting (Ortuno et al. 2002) and in temporal orienting to brief temporal intervals of hundreds of milliseconds (Coull and Nobre 1998). Indeed, Macar et al. (2002) found SMA activation in both short (milliseconds) and long time (seconds) interval discriminations. We observed a similar focus of the SMA in sensorimotor timing of 5 s (Rubia et al. 2000) (see Fig. 1) and in temporal discrimination of seconds intervals that differed by hundreds of milliseconds (Smith et al. 2003) (see Fig. 2). It thus appears that, while earlier studies have postulated a strong role of the SMA in motor timing processes, more recent studies have shown that the timing functions of the SMA also include purely perceptive timing.

The closely adjacent anterior cingulate gyrus (ACG) has also found to be activated in motor timing tasks such as sensorimotor synchronisation of seconds (Rubia et al. 1998, 2000) and sensorimotor synchronisation of hundreds of milliseconds (Lejeune et al. 1997, Rubia et al. 1998). It has, however, also been found to be activated in studies of time estimation such as time production and reproduction of seconds (Lewis and Miall 2002, Macar et al. 2002), temporal discrimination (Maquet et al. 1996) and timed counting (Ortuno et al. 2002) in the milliseconds range. Unlike the study of Maquet et al. (1996) we did not observe ACG activation when subjects had to discriminate time intervals that differed by hundreds of milliseconds (Smith et al. 2003) (see Fig. 2), but we observed ACG activation during sensorimotor synchronisation of hundreds of milliseconds and seconds (Rubia et al. 1998, 2000) (see Fig. 1). It has been suggested that ACG, rather than being specifically related to cognitive time management per se, might be related to motor attention functions. Thus, ACG has been found to show a biphasic activation in both a motor tapping task of 600 ms and a delay task of 5 s and has been suggested to play a role in switching and attention allocation (Rubia et al. 1998). The ACG forms part of the midline attention system and has therefore been attributed a role in attention to action as well as an evaluative comparator role assisting executive control (Carter et al. 1999, 2000, Gehring and Knight 2000, McDonald et al. 2000, van Veen et al. 2000), both important functions that are necessary for motor timing and distinguishing time intervals, respectively.

CEREBELLUM

Two important subcortical brain structures have been related to motor and cognitive time management, namely the cerebellum and the basal ganglia. The importance of the cerebellum in timing processes has been postulated long time ago (Braitenberg 1967) and is now fairly well established (Harrington and Haaland 1999). Lesion studies have shown that patients with cerebellar lesions display poor performance on both motor tapping and time estimation tasks such as velocity perception and temporal discrimination, both in the range of hundreds of milliseconds (Ivry and Diener 1991, Ivry and Keele 1989, Ivry et al. 1988). In one of the studies the poor performance of cerebellar patients on motor tapping and time discrimination contrasted with the performance of patients with cortical lesions, who showed deficits in a finger tapping but not a discrimination task, and patients with basal ganglia damage, whose performance did not differ from that of controls in either task (Ivry and Keele 1989, Ivry et al. 1988). Since temporal

discrimination is often thought to be the purest measure of time perception (Rubia et al. 1999a), this study was interpreted as evidence for a central role of the cerebellum in temporal perception. Other studies of cerebellar patients have shown them to be poor at time discrimination in both long (seconds) and short (hundreds of milliseconds) intervals (Casini and Ivry 1999, Mangels et al. 1998, Nichelli et al. 1996) and, in contrast with patients with prefrontal lesions, the temporal discrimination deficits of cerebellar patients were not alleviated by counting strategies and the use of short durations (Mangels et al. 1998). The above evidence, derived from focal lesion studies is supported by functional imaging studies where cerebellar activation has been found in temporal discrimination of short intervals of hundreds of milliseconds (Dupont et al. 1993, Jueptner et al. 1995, Maquet et al. 1996, Rao et al. 2001, Smith et al. 2003), temporal orienting of under a second intervals (Coull and Nobre 1998), rhythm discrimination (Schubotz et al. 2000), rhythm reproduction of hundreds of milliseconds (Penhune et al. 1998) and time production of several seconds (Lewis and Miall 2002, Tracy et al. 2000). Furthermore, apart from perceptive time estimation functions, the cerebellum has also been found to be activated in functional imaging studies on motor timing functions such as sensorimotor synchronisation of short intervals in the milliseconds' range (Inui and Hatta 2003, Larsson et al. 1996, Penhune et al. 1998, Rao et al. 1997) and longer time intervals of several seconds (Lejeune et al. 1997, Riecker et al. 2003). We observed activation in the left cerebellar hemisphere during a fine-temporal discrimination task of hundreds of milliseconds (Smith et al. 2003) (see Fig. 2a). Most imaging studies have found an involvement of the lateral portions of the cerebellar hemispheres in timing processes. It has therefore been suggested that motor execution may be subserved by medial regions of the cerebellum, while internal clock processes or temporal management may be subserved by lateral regions of cerebellum (Ivry et al. 1988). In line with this functional division is the difference in the connectivity of these two regions of cerebellum – the lateral cerebellum projects to premotor cortex and DLPFC, important for motor and perceptive timing, while medial cerebellum is connected with the spinal cord, affecting motor implementation (Middleton and Strick 1994, 2000). Two PET studies, however, found that besides the lateral portions of the cerebellar hemispheres also the vermis of the cerebellum was involved in temporal discrimination of hundreds of milliseconds (Jueptner et al. 1995, Maquet et al. 1996). In conclusion, based on the findings in the literature of an involvement of the cerebellum in motor timing and time perception tasks, it has been speculated that the cerebellum might be especially relevant to event timing (Ivry et al. 2002).

THE BASAL GANGLIA

Although basal ganglia lesion patients were not impaired in time discrimination in the study of Ivry and Keele (1989), the basal ganglia have been observed to be involved in time estimation and motor timing in several other studies. Thus, lesions in the right supralenticular white matter, presumably consisting of fronto-striatal pathways, have been found to be associated with impaired time estimation and production of several seconds in patients with brain lesions (Rubia et al. 1997). We observed right putamen activity in a sensorimotor task of 5 s in healthy adults using fMRI (Rubia et al. 2000) (see Fig. 1). Left and right putamen (Lejeune et al. 1997) and left putamen, globus pallidum and caudate nucleus (Riecker et al. 2003) have been found to be activated during other sensorimotor synchronisation tasks of several seconds and left putamen has been found to be activated during a finger tapping task of hundreds of milliseconds (Larsson et al. 1996, Rao et al. 1997) and left and right putamen during rhythm reproduction in the milliseconds range (Penhune et al. 1998). Furthermore, caudate and putamen have been also found to be activated in perceptive time estimation tasks. Thus, caudate and putamen have been found to be activated in time discrimination tasks in the milliseconds range (Dupont et al. 1993, Jueptner et al. 1995, Rao et al. 2001), in rhythm discrimination of hundreds of milliseconds (Schubotz et al. 2000), and in time production of several seconds (Lewis and Miall 2002). The role of the basal ganglia in time estimation and motor timing functions corroborates studies in patients with Parkinson's disease showing deficits in motor timing and time perception that can be ameliorated with dopaminergic treatments (Lange et al. 1995, O'Boyle et al. 1996, Pastor et al. 1992, Riesen and Schnider 2001). Furthermore, dopaminergic agents have also shown to have an effect on time estimation and motor timing functions in healthy subjects (Rammsayer 1993, 1997, Rammsayer and Vogel 1992). Animal studies show disruptions in response timing after focal lesions or drugs targeting the dopaminergic functions in the basal ganglia (for review see Meck 1996).

The role of the cerebellum and the basal ganglia in cognitive time management and timing of movements is not surprising giving the important role these two structures have in fine-modulation of the behavioural output and of movement in particular. Both the basal ganglia and the cerebellum have important reciprocal connections with the motor areas of the frontal lobes (Middleton and Strick 1994, 2000, Picard and Strick 1996), but also receive input from sensory brain regions such as the parietal lobes. Their role in fine-modulation of the motor and cognitive output makes them well suited to regulate the timing aspects of behaviour.

PARIETAL LOBES

Other cortical brain regions that have commonly been associated with time estimation, but less with motor timing, are the inferior parietal lobes. Focal lesion studies have found time estimation deficits of several seconds in patients with predominantly right parieto-occipital brain lesions (Harrington et al. 1998, Petrovici and Scheider 1994). Inferior parietal lobes have found to be activated during a sensorimotor synchronisation task of several seconds, which involved both time estimation and time estimation functions (Rubia et al. 2000) (see Fig. 1), during synchronisation of an interval of several seconds (Lejeune et al. 1997), during finger tapping (Larsson et al. 1996) and rhythm reproduction (Penhune et al. 1998) of hundreds of milliseconds, during time estimation tasks of several seconds (Basso et al. 2003, Lewis and Miall 2002, Macar et al. 2002), and in temporal discrimination (Dupont et al. 1993, Maquet et al. 1996, Pedersen et al. 2000, Rao et al. 2001), rhythm discrimination (Schubotz et al. 2000) and timed counting (Ortuno et al. 2002) of hundreds of milliseconds. It has been argued that the role of the parietal lobes in time estimation tasks could be related to aspects of sustained attention to time (Ortuno et al. 2002, Pardo et al. 1991). In our time discrimination task that was well controlled for sustained attention by a control task, we did not observe any parietal lobe activation (Smith et al. 2003) (see Fig. 2). Sustained attention to time intervals is certainly a necessary basis function for time estimation processes. Furthermore, the inferior parietal lobes are interconnected with the frontal lobes, the basal ganglia and the cerebellum (Cavada and Goldman-Rakic 1991, Schmahmann and Pandya 1990), all of which have shown to be important in time estimation. The parietal lobes with their connections to fronto-striatal and fronto-cerebellar circuits are thus strategically well placed to support cognitive time management processes by assisting them with sustained attention to time.

CONCLUSIONS

In conclusion, this review on the neural correlates of cognitive time management shows that predominantly right hemispheric dorsolateral and inferior prefrontal cortices, anterior cingulate, the SMA, the basal ganglia and the lateral cerebellar hemispheres appear to be involved in both functions of motor timing and time estimation.

Furthermore, the review shows that the dichotomy between motor and perceptive timing functions may be artificial. Both functions appear to be mediated by identical neural networks and may be inseparable.

There could be several reasons for the fact that motor timing and time perception are mediated by the same brain regions. The most likely reason is that the two timing functions are cognitively inseparable and therefore mediated by identical brain areas. This argument would suggest that timing a movement, for example, is not possible without good temporal perception functions, and, on the other hand, many time perception tasks involve elements of motor timing such as for example tasks of temporal and rhythm production and reproduction.

Another argument would be that third cognitive basic functions are underlying time estimation and motor timing such as sustained attention and working memory that would be responsible for the findings of common neural substrates. Several imaging studies, however, have controlled for sustained attention and working memory and it is therefore unlikely that the activation in timing tasks is due to timing-unspecific working memory or attention functions. It rather appears that each of these different brain regions has their specific role in contributing to cognitive time management.

Right dorsolateral and inferior prefrontal cortices – possibly in connection with their role in working memory – appear to play a special role in holding temporal intervals online which is essential for most time estimation and motor timing functions. The SMA, traditionally been related to motor timing, but, as the review shows, with recent involvement in purely perceptive temporal estimation, appears to be a crucial brain area to process temporal intervals in order to adjust movement in the temporal domain. The anterior cingulate has been suggested to have a more generic role in attentional

components necessary for both motor timing (attention to action) and time estimation (evaluative comparator). This area thus contributes to cognitive time management as comparator of temporal intervals in time estimation tasks or by assisting motor timing with allocation of motor attention. The cerebellum and the basal ganglia, known to be fine-modulators of emotional, cognitive and motor behaviour, appear to be crucial also for the fine-modulation of the temporal aspects of behaviours at both the motor and perceptive levels. Last, not least, the parietal lobes seem to contribute to time estimation and motor timing through allocation of sustained attention to time.

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