Toward a neurobiology of temporal cognition: advances and challenges
John Gibbon*†, Chara Malapani†‡, Corby L Dale† and CR Galliste§

A rich tradition of normative psychophysics has identified two ubiquitous properties of interval timing: the scalar property, a strong form of Weber’s law, and ratio comparison mechanisms. Finding the neural substrate of these properties is a major challenge for neurobiology. Recently, advances have been made in our understanding of the brain structures important for timing, especially the basal ganglia and the cerebellum. Surgical intervention or diseases of the cerebellum generally result in increased variability in temporal processing, whereas both clock and memory effects are seen for neurotransmitter interventions, lesions and diseases of the basal ganglia. We propose that cerebellar dysfunction may induce deregulation of tonic thalamic tuning, which disrupts gating of the mnemonic temporal information generated in the basal ganglia through striato-thalamo-cortical loops.

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Abbreviations
C
cycle duration
CR
conditioned response
CS
conditioned stimulus
T
trial duration
US
unconditioned stimulus
VLa
ventro-lateral anterior

Introduction
Time is the primordial context. For mobile organisms, evolution has selected for neurobehavioral mechanisms that anticipate predictable events rather than those that react to them after the fact. It has also selected mechanisms that assess resource quality based on the rate of return, that is, the inverse of the intervals between prey captures [1]. Many important events are not synchronized to a natural periodicity; hence, the interval timing mechanism must, like a stopwatch, be able to begin and end at arbitrary epochs. This feature is the hallmark of interval timing, as opposed to periodic, circadian timing (see e.g. Moore-Ede et al. [2]; for more on this distinction, see Church [3] and Gallistel [4]).

In this review, we first describe two essential properties of the normative psychophysics of temporal cognition and then outline the challenges these pose for neurobiology. Advances have been made, but much remains to be understood about the functional neuroanatomy of temporal information processing.

Psychophysics

Weber’s law: the scalar property
Interval timing systems are extremely flexible. They may start and stop at will and may cover a very broad range of times. This flexibility is bought at the cost of precision. In some species, circadian rhythmicity has a variability as low as 1% of the 24-hour cycle (see e.g. Aschoff [5]), whereas the precision of interval timing systems may vary from -5% to -60% of the interval being timed.

A hallmark of animal and human interval timing is the ubiquity of Weber’s law [6]. In the modern timing literature, Weber’s law has been taken to mean that variability of an underlying temporal distribution should show a constant coefficient of variation (σ/μ). We [7-10] have proposed that this reflects an underlying random variation in a multiplicative noise variable. Because uncertainty (noise) is proportional to the interval being estimated, entire time estimation distributions superpose in relative time, that is, when the time axis is normalized with respect to the mean of the distribution. This superposition reflects a rescaling in time, a scale-invariant error distribution for time estimation. It is as though the subjective time scale is a rubber ruler that may be stretched (multiplied) to accommodate any target time, but with a corresponding proportional error at any given proportion of that time.

The scalar property is a crucial feature of the information-processing, scalar timing model [3,7,11-14], developed from earlier seminal work by Treisman [15] (Figure 1a). An internal pacemaker/integrator monitors the passage of time (clock stage). Accumulated subjective time is occasionally a biologically important (reinforced) time, and these time records are transferred to working or reference memory (memory stage) for later comparison (decision stage) with the passage of current time. The decision stage compares current time with remembered time and identifies an appropriate response outcome. This general scheme has been used successfully to model a wide variety of temporally controlled behaviors (see e.g. [3,12,16,17]), in which the clock and memory stages are essentially the same, but differing comparison processes execute different computations for different tasks. Scalar variance may enter
in the clock or memory stage (Figure 1a), or through threshold variance in the decision stage.

**Time estimation**

An example of time estimation in Parkinson’s disease patients [18] is shown in Figure 1b. Patients were trained to reproduce 8s and 21s both ON (Figure 1b, top left) and OFF (Figure 1b, bottom left) levodopa and apomorphine medication. ON medication, time estimation is accurate and distributions superpose in time relative to the modal estimate (Figure 1b, top right). This is the general result with normal animal and human subjects [7,8,10,12,16,19]. OFF medication, accuracy is distorted (even though subjects received corrective feedback) and the scalar property is violated (Figure 1b, bottom right), implicating the basal ganglia in temporal processing. This finding typifies clinical investigations of basal ganglia disorders (as will be discussed below).

**Ubiquity of ratio comparisons**

Complementing the scalar variability of timing distributions is the ubiquitous use of ratios rather than differences in comparing remembered and currently elapsing temporal intervals. In virtually every kind of timing task, the decision to respond is based on the ratio of a currently evolving interval to a remembered standard [9,20]. Ratio comparison is a necessary complement to scalar variability of memory variables in the induction of scale invariance [11,21].

**Basic conditioning**

The learning of temporal intervals in conditioning protocols appears to be fundamental to classical or Pavlovian conditioning. Most simply, it has long been known that the peak of the conditioned response (CR) generally matches the reinforcement latency (i.e. the unconditioned stimulus [US] latency). But, just as important, an appreciation of basic timing principles is essential to understanding the effects of the two variables with the greatest impact on the rate of acquisition, the delay of reinforcement (i.e. the interval between a conditioned stimulus [CS] and an US) and the spacing of the trials. Since Pavlov’s earliest investigations [22], it has been known that delay of reinforcement retards acquisition, whereas trial spacing enhances it. More recently, it has been shown that these effects are intimately interlinked: neither matters by itself; when both are varied by the same factor (e.g. when the intervals in a protocol are scaled up or down), there is no effect on the rate of acquisition — another example of time-scale invariance. What determines the rate of...
acquisition is the cycle duration (C), which is the time between US presentations, divided by the trial duration (T), which is the interval between the CS and US. In other words, the C/T ratio—the interval of exposure to the conditioning environment, or background, per CS reinforcement relative to the interval of exposure to the CS—determines the rate of acquisition.

The most extensive data on the effects of delay of reinforcement, partial reinforcement, and trial spacing come from studies of pigeon autoshaping, which is the most widely used appetitive conditioning paradigm. It is identical to Pavlov's paradigm, except that the illumination of a round key replaces the ringing of a bell as the CS, the pigeon replaces the dog as the subject, and pecking the key replaces salivation as the CR. When a pigeon repeatedly sees the illumination of the key followed at some delay by the presentation of food, it eventually begins to peck the key, even though its pecking does not affect food delivery. This is called autoshaping because it permits the automated shaping of pigeon key pecking. The well controlled automated procedure has replaced the poorly controlled shaping of the CR by the experimenter, which was once thought to be essential.

In Figure 2, which is adapted from Gibbon and Balsam's [23] survey of the data on the rate of acquisition in autoshaping, the number of CS-US pairings (reinforced trials) required for acquisition is plotted as a function of the C/T ratio for a wide variety of studies and training regimes. This survey indicates that regardless of the reinforcement schedule, the delay of reinforcement, or the intertrial interval, reinforcements to acquisition is determined simply by the C/T ratio. Moreover, reinforcements to acquisition are inversely proportional to this ratio, because a straight line with a slope of -1 on the double log plot lies within the confidence limits for the best-fitting line through the data. The variability in trials to acquisition, which is indicated by the scatter of the data points around the regression line in Figure 2, is roughly constant on a log scale, which means that variability in reinforcements to acquisition increases in proportion to the mean number of required reinforcements—another example of time-scale invariance in error or noise.

In short, the acquisition process in Pavlovian conditioning exhibits the interval timing signature. First, the rate of acquisition and its variability are time-scale invariant. Second, acquisition appears to be determined by a ratio comparison between the rate of CS reinforcement, the estimate of which is proportional to T, and the rate of background reinforcement, the estimate of which after any given number of CS reinforcements is proportional to C, the amount of unreinforced background exposure per CS reinforcement.

Decisions mechanisms that take ratios as their inputs are a formidable constraint on timing models and on models of conditioning—one that is difficult to accommodate with any of the current neurobiological (network) process models. For example, the fact that the rate of acquisition in simple conditioning does not vary when the ratio of the CS-US interval to the cycle duration is held constant poses difficulties for models purporting to explain conditioning (e.g. Rescorla and Wagner [24], Grossberg and colleagues [25**,26], and Raymond et al. [27**]). At a minimum, it means that subjects assess the inter-reinforcement interval during the signal (CS) against the overall or background inter-reinforcement interval [23] and decide that the former is a significant improvement over the latter [28]. The ratio comparison of estimated reinforcement delays is the key to time-scale invariance, which, in turn, is a central feature of both CR timing and the acquisition of a CR.
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Figure 3

Coefficient of variation in timing tasks as a function of the magnitude of the interval being timed (both axes on log scales). In the ranges demarcated by vertical lines, coefficients of variation appear to initially decrease (less than 0.1 s to greater than 0.1 s), remain roughly constant for given tasks between 0.1 s and about 1.5 s, increase perhaps again between 1.5 s and 500 s, then increase again for times in the hours range at about 500 s. Large points denote studies spanning these ranges. Open points denote human studies, filled points animal studies.

The challenge for neurobiological models

A number of neural network models have been developed to explain timing in classical conditioning and operant learning. By extension, these models might apply to corrective feedback procedures in human timing (e.g. tapping or time estimation) as well. A general problem confronting most such models is the difficulty of suggesting plausible mechanisms for timing longer intervals, from half a minute to more than an hour.

Time ranges

Data on the variability of interval timing in animals and humans span at least six orders of magnitude in the intervals being timed. Ranges within this span may well involve fundamentally different temporal processing mechanisms at the neurobiological level. If so, one might be able to identify these different mechanisms and the ranges within which they operate by looking for changes in the coefficient of variation at different time ranges. Figure 3 presents coefficients of variation (Weber fractions) for humans and animals taken from a wide variety of studies and paradigms. This summary of the data is by no means exhaustive. We have imposed several restrictions. The species and paradigms included are common: temporal discrimination and bisection (excluding long/short time anchor ratios > 6), temporal production, and temporal generalization. A variety of less common procedures (aversive control [29,30], titration [31], and uncommonly studied species [32]) have been omitted. In general, coefficients variations from such studies tend to be high, suggesting other possible, non-temporal sources of variability. Potential ranges on this measure, which may be thought of as sensitivity to time, are indicated in Figure 3 by vertical lines.

These data do not give clear evidence for different coefficients of variation in different ranges, in part because different tasks tend to be used for different ranges, and there is clearly an effect of task on the coefficient of variation in the range below 1 s. The coefficient of variation is low (below 0.1) in rhythmic synchronization tasks (both the production and discrimination; see Ivry and Hazeltine [33**]). It is higher in studies of temporal generalization [34], temporal bisection [7] and temporal discrimination of crossmodal and intermodal intervals [35].

Within-task comparisons suggest that there may be an increase in the coefficient of variation between time
values below 1–2s and those above (large points in Figure 3); thus, three or four ranges, with possibly different neurobiological mechanisms, are suggested, but certainly not demonstrated. Work aimed at identifying neurobiological mechanisms of timing would benefit from coefficient of variation data from a single task spanning the whole range of intervals depicted in Figure 3.

**Recent neurobiological models**

Miall [36**] has suggested a mechanism similar to the generic pacemaker/integrator of scalar timing [11,12] in which a population of neural oscillators is integrated over time. His mechanism may be suited to the lower range of time estimation functions in animals—a relatively short number of seconds. Treisman et al. [37] have argued from a variety of results that a characteristic frequency for the pacemaker in the interval timing mechanism is around 50 Hz, a value commonly found in neural oscillations measured electrophysiologically [38,39]. In their model, Church and Broadbent [40] assumed that a set of synchronous oscillators at geometrically decreasing frequencies span the range of possible durations to be timed (about 30 suffice for periods up to the years range). However, oscillator models are not readily reconciled with Ivry and Hazeltine’s [33**] and Keele et al.’s [41] demonstration that in-phase and out-of-phase training and testing does not appear to change temporal sensitivity in the short range.

Miall [36**,42] has also described an alternative oscillator/clock system using a coincidence detector for simultaneous or close coincidence of outputs. Such a mechanism can work over longer time intervals, of the order of 20–30s, escaping some of the range limits inherent in other mechanisms. Still another temporal representation is a spatially distributed network for time in the cerebellum. These models have been developed by Mauk, Buonomano and their colleagues ([27**,43,44]; MD Mauk, NH Donegan, Soc Neurasci Abstr 1991, 17:869). Their clock mechanism requires unique Golgi/granule cell activity patterns that span the relevant range of latencies (200–400 ms). This mechanism also only appears plausible over very short time ranges; it is not clear that its range extends much beyond 2s, although eye-blink conditioning, for example, is readily obtained at CS-US intervals longer than that, provided that the intertrial interval and, hence, the C/T ratio, is sufficiently large [45].

Perhaps the most fully elaborated set of models for timing has been developed by Grossberg and colleagues (see [25**] for a summary). They propose one timing mechanism for the hippocampus and another for the cerebellum [46]. Both rely on a spectrum of activity in neural units with different time constants. This is plausible, however, only up to intervals on the order of 4s, which is the lower end of the range of mechanisms required to explain results from timing and conditioning experiments.

**Common features and problems**

**Memory**

In these models, a range of potential clock values undergoes selection by a teaching signal associated with reinforcement. This is a tuning property of self-organization. It selectively weights the spectrum of neural activity in the appropriate range, while uncorrelated ranges are damped out. The neuroanatomical locus of tuned activity is thus the locus of selectivity, that is, memory, although longer-term storage may occur elsewhere (e.g. in the deep cerebellar nuclei [27**]).

**Decision**

Decision processes are often the neglected stepchild in these models. When explicit, they are generally conceived as correlation gates. When the current input signal is sufficiently similar to the stored temporal memory, a response is permissively gated. This is explicit in the Church and Broadbent [40] multiple oscillator model, for example, as a cosine similarity computation exceeding a threshold (but see Wearden and Doherty [47] for the care with which one must choose such a threshold in order to avoid harmonics of the training time value). Decision mechanisms are not explicitly specified in the Miall models [36**,42] or in the cerebellar network models [27**,43,44]. In the adaptive resonance theory models (see [25**]), a threshold is applied to a similarity signal generated by a comparison of current input and remembered stored prototype patterns. When the input pattern is not matched to stored values, an orienting subsystem resets and continues to search for the appropriate prototype match. The orienting subsystem must be inhibited by an attentional subsystem that restricts search to the appropriate remembered times so that inappropriately timed orienting responses do not take subjects out of the timing task prematurely.

None of these decision mechanisms make ratio comparisons. Ratio decision rules that involve averages of local rates are most certainly not modeled by systems of this sort. Yet, they are a central feature of operant psychology (e.g. matching laws [48–52]) and of a burgeoning literature on local rate averaging for foraging choices in the behavioral ecology literature (see [1]). Information-processing models simply assume local rate averages as the statistics determining choice, as we have done [16,53], but a neurocomputational substrate for this kind of inversion and averaging is lacking at present.

The ratio invariance of the acquisition process in conditioning also poses a serious challenge for neurobiological models. An optimal interstimulus interval (ISI), which is a staple of models based on a concept of temporal pairing, does not exist in the autoshaping preparation, nor has it been demonstrated in others, including the eye-blink preparation [54–59]. Speed of acquisition is jointly determined by the CS-US interval and the intertrial interval in every preparation for which we have found relevant data. Models proposed for classical
conditioning in the cerebellum are impressively flexible in permitting blocking and overshadowing, as well as multiple timing, for multiple CS–US intervals. However, so far, they invariably fail to take into account the ratio comparison property of the decision mechanisms that operate in timing and conditioning tasks.

Scalar variability

In the Church and Broadbent model [40], the scalar variability property is built-in with the assumption that the noise in an oscillator is proportional to its period, but it is not clear whether, or how, this property arises in the other network models. The ubiquity of the Weber law-like processes in timing outlined above requires both scalar (multiplicative) variability in the underlying variables and ratio decision rules [11,20]. Neither is explicit in most of the network models. Neurobiologically oriented models need to specify explicitly the source of scalar variability if they are to come to grips with the psychophysical data.

Although scalar variability and ratio comparisons are central to scalar timing theory (see e.g. [3,12,16,17]) and are well understood at that level, tuning to appropriate time ranges is not. Realistic biological constraints on accumulation or integration mechanisms (cf. Miall [36*]) pose problems for use of the scalar timing system with a single integration mechanism because there is no known neural process capable of integrating over many minutes or even hours. A fruitful convergence of information-processing models and network models might center on this problem. For example, an array of accumulation mechanisms driven through a binary cascade from a pacemaker system might be an appropriate tuning mechanism. This would borrow differential time range selection from network theory. Conversely, the stochastic sampling mechanisms assumed in scalar timing theory might be incorporated usefully into network models to induce the scalar property. Such a mechanism might be a second (non-clock) source of scalar variability in a distributed network representation of the memory for duration.

Neuroanatomical locus of timing: experimental studies

The psychophysical models and analyses provide a conceptual framework and analytic tools to guide the search for the neurobiological mechanisms of the interval timing capacity. The first task, of course, is to localize these mechanisms. This task is hardly begun, although, so far, both the cerebellum and the basal ganglia appear to be important. Imaging studies, for example, have found activity during timing tasks in the cortex and basal ganglia [60] or in these areas and the cerebellum [61*]. Several of the advances in our understanding, especially of the cerebellar system, have been ably summarized in Ivry's [62**] recent review. We concentrate on the way in which these results interface with the other data. Table 1 summarizes a variety of drug and lesion studies.

Clock effects

The top section of Table 1 describes basal ganglia effects, seen in a number of studies using the peak and bisection procedures. The classic clock pattern is one indicating that the interval timing stage was affected. Meck and associates [63*,64*,65**] have shown that the nigrostriatal dopaminergic system is critical for interval timing because 6-hydroxydopamine lesions either in the substantia nigra pars compacta or in the caudate/putamen eliminate timing. However, dopamine supplementation produces recovery after substantia nigra pars compacta lesions, but not after caudate/putamen lesions.

Dopamine agonists and antagonists, like methamphetamine or haloperidol, produce a temporary distortion in accuracy when subjects are trained OFF the drug and tested ON, or vice-versa; however, this distortion disappears with continued training. When subjects are trained OFF dopamine agonists and tested ON, they show a temporary underestimation of the trained target time, as would be expected with a faster clock that reaches a stored criterion in memory early. Conversely, subjects trained ON dopamine agonists and tested OFF show a temporary overestimate of the target time, as would be expected with a slower clock that reaches a subjective criterion late. The reverse pattern is seen for dopamine antagonists. When the drug is removed, a rebound effect occurs in the opposite direction, followed by recovery as memory values again are overwritten under the normal clock speed. Importantly, these systematic over- and under-estimations are associated with scalar variability. For example, under dopamine agonists the clock reaches criterion early and variability is correspondingly decreased (the scalar property).

Several studies are consistent with dopamine regulation of clock speed (e.g. in pigeon [66] and in rat [67]), although often there is also increased variability under dopamine agonist treatment [67,68]. This increased variability was found in the Meck studies [63*,64*,65**] as well, but scalar variability for underestimation was found when analyzing only fast latency responses. Hence, dopamine appears to have at least two effects: one increasing overall variability, perhaps through variability at the decision stage, and the other increasing clock speed, which tends to lower variability.

Memory effects

The next series of studies in Table 1 show the effects of frontal and limbic system interventions on the memory stage. Cholinergic agonists cause the duration being stored (or being retrieved from) memory to be somewhat greater than the duration indicated by the clock at the conclusion of the interval, whereas antagonists cause the opposite distortion [65**]. The size of the distortion in memory is proportional to the target time, and, in both cases, variability shows a corresponding increase or decrease (the effects are scalar). The effect is gradually
Table 1

The effects of lesions and/or synaptic transmission manipulations on timing tasks.

<table>
<thead>
<tr>
<th>Timing experiment</th>
<th>Manipulation</th>
<th>Ranges</th>
<th>Accuracy (over/under estimation)</th>
<th>Variance</th>
<th>Functional system</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt, Bis; rat [63][111-115]</td>
<td>Basal ganglia</td>
<td>DA(a) 20-50 s</td>
<td>Under-recovery</td>
<td>Over-recovery</td>
<td>Decreased/Scalar</td>
<td>CLOCK PATTERN</td>
</tr>
<tr>
<td></td>
<td>DA(a)</td>
<td></td>
<td></td>
<td></td>
<td>Pacemaker/Integrator</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SNC</td>
<td>DA(a) 30-60-120 s</td>
<td>Timing abolished</td>
<td>Some recovery</td>
<td>Increased/Scalar</td>
<td>Pacemaker/Integrator</td>
</tr>
<tr>
<td></td>
<td>CP</td>
<td>DA(a) 1-5 s</td>
<td>Under</td>
<td></td>
<td>Pacemaker/Integrator</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DA(a) 1-60 s</td>
<td>No change</td>
<td></td>
<td>Memory or decision?</td>
<td></td>
</tr>
<tr>
<td>Pt; rat [116]</td>
<td>DMTS: pigeon [66]</td>
<td>DA(a) 50 ms</td>
<td>Not shown</td>
<td></td>
<td>Non-specific arousal</td>
<td></td>
</tr>
<tr>
<td>Fm; rat; DMTS; rat; pigeon [68,117-119]</td>
<td>Discrimination: humans [120]</td>
<td>DA(a) 10 s</td>
<td>No learning</td>
<td>Normal learning</td>
<td>Learning maintained</td>
<td>Clock/memoty needed for timed avoidance</td>
</tr>
</tbody>
</table>

Frontal and limbic system

| Pt; Bis; rat [64][116] | ACh(a) 10-50 s | No change-under | Under-recovery | Scalar | Reference memory | MEMORY PATTERN |
| | DA(a) | | | | Reference memory with no recovery, |
| FC | | Over | Over | Basal | Reference memory followed by gradual |
| NBH | | Over-recovery | | Not shown | Reference memory recovery when drug is |
| FF | | Under | | Not shown | Reference memory |
| MSA | | Under-recovery | | Not shown | Reference memory |
| Pt with gap; rat [125,126,128-130] | ACh(a) | 4-20 s | No reset | No reset-recovery | Not shown | WORKING |
| | | | | | No reset: accumulated time retained |
| | | | | | Reset: failure to |
| Amygdala | | 10-50 s | Normal | | Working memory |
| FF | | Reset | | | Working memory |
| MSA | | Reset-recovery | | | Working memory |
| Discrimination with | ACh(a) | 3-12 s | Over | | Attention-mediated |
| delay; rat [132] | | | | | Attention mediated |
| | | | | | Fast (Aud) and slow |
| | | | | | (Vis) memories mixed |
| Bis; humans [133] | | 3-12 s | Under | | Attention mediated |
| | | | | | gate closure |
| Aud within V/A | | | | | Retarded gate closure |
| | | | | | by constant amount |
| Pt; PE (PERI); rat [114,123] | He(a) | | Over | | NON-SPECIFIC |
| | | | | | PATTERN |

Cerebellum

| Bis; rat [103] | Cer | 300-800 s | Normal | Normal | Increased/Scalar | Deregulation of clock |
| | | 360-1200 ms | Under | | Memory or decision |
| Conditioning; rabbit | Cer | 400 ms | Impaired | | Impaired timing, some |
| | | | | | conditioning remains |

(A), agonist; (aa), antagonist; ACh, acetylcholine; Aud, auditory; Bis, bisection; Cer, cerebellum; CP, caudate/putamen; DA, dopamine; DMTS, delayed matching to sample; FC, frontal cortex; FF, fimbria/ fornix; Ft, fixed interval; MSA, medial septal area; NBM, nucleus basalis magnocellularis; NE, noradrenalin; PE, prior entry; PER, prior entry reversal; Pt, peak interval; SNA, substantia nigra, pars compacta; V/A, visual and auditory signals interpolated; Vis, visual.

achieved and permanent as long as the subjects are under the drug, which is the opposite of the pattern seen when a treatment affects the clock rather than memory. This pattern is characteristic of a memory effect, because distorted memory values gradually replace pre-drug values, and these distorted values continue to be written to memory until the drug is discontinued.

The next part of the frontal and limbic section of Table 1 describes short-term memory manipulations in which either a gap in the signal to be timed is inserted on a small proportion of the trials or a retention interval is inserted prior to a choice discrimination response. These procedures require a temporary, working memory to store the current accumulation of subjective time through the temporal gap or the retention interval. Frontal cortex, nucleus basalis magnocellularis and amygdala lesions do not affect the normal carryover of the value across the gap. This is what control rats in gap procedures do and is also found with partial reinforcement in the pigeon [69]. When a trial goes unreinforced during conditioning, it is as though there is simply a gap between it and its next occurrence. Subjects hold the accumulated time in short-term memory and continue timing when the signal reappears. In contrast, fimbria/fornix or medial septal area lesions produce a near complete reset of accumulated time. Subjects cannot accumulate intervals across gaps. They treat the reappearance of the signal after the gap as a new trial.

A few studies of cerebellar dysfunction on timing are described in the bottom part of Table 1. Increased variance is seen, but it is difficult to specify the affected temporal-processing components.
### Table 2

<table>
<thead>
<tr>
<th>Timing experiment</th>
<th>Manipulation</th>
<th>Ranges</th>
<th>Accuracy</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paradigm</td>
<td>Lesion/Disease</td>
<td>ON drug</td>
<td>OFF drug</td>
<td>Lesion</td>
</tr>
<tr>
<td>Tapping [134]</td>
<td>Deg/PD</td>
<td>DA1</td>
<td>450 ms</td>
<td>Under</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>550 ms</td>
<td>Under</td>
</tr>
<tr>
<td>Tapping [73]</td>
<td>Deg/PD</td>
<td>DA1</td>
<td>550 ms</td>
<td>Under</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>500 ms</td>
<td>Under</td>
</tr>
<tr>
<td>Tapping [71**]</td>
<td>Deg/PD</td>
<td>DA1</td>
<td>550 ms</td>
<td>Under</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>500–2000 ms</td>
<td>Normal</td>
</tr>
<tr>
<td>Tapping [72*] exp 1</td>
<td>Deg/PD</td>
<td>DA1</td>
<td>300–1000 ms</td>
<td>Under</td>
</tr>
<tr>
<td>Tapping [72*] exp 2</td>
<td>Deg/PD</td>
<td>DA1</td>
<td>550 ms</td>
<td>Under</td>
</tr>
<tr>
<td>PEST procedure [74]</td>
<td>Deg/PD</td>
<td>DA1</td>
<td>400 ms</td>
<td>Normal</td>
</tr>
<tr>
<td>Verbal estimation [75]</td>
<td>Deg/PD</td>
<td>DA1</td>
<td>3–9 s</td>
<td>Under</td>
</tr>
<tr>
<td>Reproduction [75]</td>
<td>Deg/PD</td>
<td>DA1</td>
<td>150 ms</td>
<td>Under</td>
</tr>
<tr>
<td>PI [18,83]</td>
<td>Deg/PD</td>
<td>DA1</td>
<td>8 s</td>
<td>Under</td>
</tr>
<tr>
<td>Discrimination threshold [81]</td>
<td>Deg/PD</td>
<td>DA1</td>
<td>150 ms</td>
<td>Under</td>
</tr>
<tr>
<td></td>
<td>Focal (thalamus)</td>
<td>DA1</td>
<td>95–21 s</td>
<td>Over</td>
</tr>
<tr>
<td>FrONTAL and limbic areas</td>
<td>Deg/PD</td>
<td>DA1</td>
<td>150 ms</td>
<td>Under</td>
</tr>
<tr>
<td></td>
<td>Focal (frontal)</td>
<td></td>
<td>550 ms</td>
<td>Under</td>
</tr>
<tr>
<td></td>
<td>Focal (frontal)</td>
<td></td>
<td>100–900 ms</td>
<td>Under</td>
</tr>
<tr>
<td>PEST procedure [74]</td>
<td>Deg/PD</td>
<td>DA1</td>
<td>400 ms</td>
<td>Normal</td>
</tr>
<tr>
<td>Verbal estimation [135]</td>
<td>Deg/AD</td>
<td>DA1</td>
<td>5–40 s</td>
<td>Normal</td>
</tr>
<tr>
<td>Reproduction [135]</td>
<td>Deg/AD</td>
<td>DA1</td>
<td>1 s</td>
<td>Under</td>
</tr>
<tr>
<td>PI [78]</td>
<td>Deg/Korsakoff</td>
<td>DA1</td>
<td>15 s and 30 s</td>
<td>Under</td>
</tr>
<tr>
<td></td>
<td>Deg/Post encephalitis</td>
<td>DA1</td>
<td>15 s</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Deg/A</td>
<td>DA1</td>
<td>30 s</td>
<td>Under</td>
</tr>
<tr>
<td>CEREBELLUM</td>
<td>Deg/PD</td>
<td>DA1</td>
<td>550 ms</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Focal</td>
<td>DA1</td>
<td>550 ms</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Deg/OPCA</td>
<td>DA1</td>
<td>100–305 ms</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Deg/OPC</td>
<td>DA1</td>
<td>100–900 ms</td>
<td>Under</td>
</tr>
<tr>
<td>PEST procedure [74]</td>
<td>Deg/OPC</td>
<td>DA1</td>
<td>400 ms</td>
<td>Under</td>
</tr>
<tr>
<td></td>
<td>Focal (mesial)</td>
<td></td>
<td>8–21 s</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Focal (lateral)</td>
<td></td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; DA1, dopamine supplementation treatment (levodopa, carbidopa, apomorphine); Deg, degenerative; HD, Huntington’s disease; OPCA, olive-ponto-cerebellar atrophy; PD, Parkinson’s disease; PEST, parameter estimation by sequential testing; PI, peak interval.

### Neuroanatomical locus of timing: clinical studies

Clinical studies of human patient populations are summarized in Table 2. Accuracy and variability measures are all relative to control populations studied using the same paradigm. The top section of Table 2 deals with basal ganglia disorders; the second section reports results from patients with focal and global lesions of the frontal cortex, premotor cortex, basal forebrain and limbic areas; and the last section describes work with cerebellar patients.

#### Accuracy

With one exception [70], focal lesions in, and degenerative diseases of, the basal ganglia cause subjects to underestimate time in the short range [71**,72*,73,74] while causing them to overestimate time in longer time ranges, from seconds to minutes. This latter effect is seen in both temporal estimation [75] and temporal reproduction [18,76] tasks.

Focal lesions of the frontal cortex produce underestimation in both short [74,77] and long [77,78] time ranges, when tested with tapping, bisection or peak interval procedures. In contrast, cerebellar lesions do not effect accuracy in either short [79] or long [80*] time ranges.

#### Variability

Not surprisingly, lesions in, and degenerative diseases of, a variety of structures tend to increase variability in timing tasks. This has been a common finding in studies of patients with degenerative basal ganglia disease, Huntington’s disease [72*] or Parkinson’s disease, where the increase is greater when they are OFF rather than ON medication [18,70,75,81]. It has also been found in
patients with focal lesions in the basal ganglia [76], the thalamus, and the premotor frontal cortex [82]. Similar increases are seen in patients with frontal lobe lesions [77] and frontal lobe dysfunction produced indirectly by lesions in the basal forebrain and limbic areas [78]. Cerebellar lesions also increase variability [74,80*].

Data from these studies are summarized in Figure 4, which shows coefficients of variation for patients in ratio to normal controls at the time ranges studied. Three points are evident. First, large differences between patients and normal controls are found at both short and long time ranges. In the few studies that span both ranges, these increases are not larger in the long time range than those seen in normative data (compare with Figure 3). Thus, a range effect is not seen in the studies that have comparable data in both ranges. This is an important point, because the difference in ranges between most of the work on cerebellar dysfunction (millisecond range) and that on basal ganglia dysfunction (seconds range) has been proposed as a possible dichotomy between cerebellar and basal ganglia function in timing (see e.g. Ivry [62**]).

Second, the size of the differences between patient groups and normals does not correlate well with the site of the lesion. Neither paradigm, nor site of lesion, nor time ranges appear to overcome sampling variability in these populations.

Third, in the few studies with more than one time range, the increased variability following cerebellar lesions is scalar [80*,83], whereas violations of the scalar property occur frequently in basal ganglia lesions [18,70,72*,76] and in frontal cortex lesions [77,78].

It is unfortunate that more than one time value was not examined in several of the studies reviewed here (see e.g. [71**,79]), because the scalar property and the Wing-Kristofferson [84,85] partition of variability into scalar (timing-related) and non-scalar (non-timing-related) variance components cannot be validated except indirectly with a single time value. Ivry and Hazeltine [33**] have demonstrated the importance of partitioning variability into time-dependent and time-independent components using a range of target intervals.
In summary, basal ganglia and frontal cortex but not cerebellar lesions impair accuracy in timing and time perception. Cerebellar, basal ganglia and frontal cortex dysfunctions usually increase variability in timing and time perception. The increased variability remains scalar in the case of the cerebellum and often violates the scalar property in basal ganglia diseases.

It is noteworthy that we were unable to include an interpretation column in Table 2. While increased variability is the norm, it is entirely possible that this increase could occur in clock, memory, or decision mechanisms. Often, it is not clear whether the increases would, within the same patient population, conform to the scalar property. If they did, and there is a suggestion in a few studies [80*,83] that this is the case, then an important advance would have been made. We would then be able to determine whether dysfunctions were isolated to a particular time value or range, which might implicate differing clock systems. From the present data alone, however, variability might be increased in memory or decision mechanisms and not involve the underlying clock at all. The analytic tools for dissecting these effects have not yet been applied in clinical studies.

Summary
This review has outlined a number of advances and challenges to our understanding of the neurobiology of temporal cognition. One class of challenges arises from what is currently known about the psychophysics of timing and time perception. Our current understanding of the psychophysics of temporal processing far exceeds our current understanding of their neural substrate. Two major psychophysical properties that are currently not well understood, even in speculative models of these systems, are the sources of scalar variability and the mechanism for ratio comparison. This is particularly important in the learning domain because ratio comparisons appear to underlie classical conditioning over a very broad range of massed and spaced training regimes.

Some advances have been made in specifying brain regions involved in temporal processing, especially the basal ganglia and the cerebellum. Controversy remains on how these two structures, independently or in conjunction, influence timing capacities. The detailed work on clock versus memory functions subserved by dopaminergic and cholinergic systems in the basal ganglia and striato-frontal loops is not presently matched by a similar level of detail in systems affected by cerebellar timing.

One question is whether there are multiple timing systems subserving different functions or a coordinated timing system involving the cerebellum for some tasks and the basal ganglia for others, with a convergence of central, perhaps cortical, control of both systems. In the schema depicted in Figure 5, striato-frontal loops through the thalamus, and the cerebellar-cortical connections and cortico-olivary/cortico-pontine projections to the output side of the cerebellar system are outlined. A first point of convergence for both systems is the thalamus, particularly the ventro-lateral (VL) structure. Both striato-cortical loops and cerebellar-cortical connections pass through the thalamus in close proximity at the ventro-lateral anterior (VLa) nuclei. Cerebellar connections are largely restricted to the VLa and ventro-lateral anterior pars caudalis (VLac) nuclei in humans—equivalent to ventro-lateral pars oralis (VLo) and ventro-lateral caudalis (VLa) and area X of Olszewski [86] in non-human primates. Putamen input from the basal ganglia to the thalamus largely projects to the ventro-lateral mesial (VLM) nuclei but also to VLa targets. A second point of convergence is the ventral anterior (VA) thalamic nuclei in which input from the cerebellum at the ventral anterior pars parvocellularis (VApC) is in close proximity to input from the caudate. Both points of convergence have common targets in frontal cortical and limbic areas (light/dark regions in Figure 5). The data suggest that cerebellar lesions generally produce an increase in variability, whereas a variety of variability and accuracy effects result for basal ganglia deregulation. Hence, it is unlikely, on these grounds alone, that the two systems are entirely independent. Both produce increased variability in common tasks.

One hypothesis espoused by Ivry and colleagues (see [62**]) has been that disparate time ranges are subserved by different timing systems, one in the cerebellum (milliseconds) and one in the basal ganglia (seconds to minutes). The evidence we have summarized argues against that possibility. Dysfunctions in the long as well as the short time ranges appear from lesions in both sites (Figure 4). Thus, time ranges are not the deciding factor in discriminating temporal-processing deficits.

A new hypothesis
We propose an alternative hypothesis. Cerebellar lesions may produce deregulation of tonic functioning in the thalamus. If the striato-thalamo-cortical loops are critical for mnemonic encoding of the comparison interval in timing tasks, then the additional noise observed after cerebellar lesions may be a result of deregulation of thalamic control. Hence, the likely culprit is not clock function, but mnemonic storage or retrieval, mediated perhaps by striato-thalamo-cortical loops. Simultaneous but reversible lesions in the cerebellum and substantia nigra, pars compacta in animals might illuminate this question. If lesions are present in both structures and thalamic deregulation impairs memory storage only, then, when clock function is restored by supplemental dopamine, noise in mnemonic processing would remain, due to cerebellar deregulation of thalamic tuning. Cerebellar lesion animal studies of explicit timing tasks are rare (Table 1). They show increases in variability but no loss of accuracy. Studies with both timing and conditioning tasks would confirm (or not) the specificity of putative timing loss in conditioning [87].
This proposal is highly speculative and goes against work implicating the cerebellum as a memory storage site for well-timed movements (for a review, see Thach [88]). However, Llinas and Welsh [89], as well as Hallet [90], have argued that the site of memory storage is unlikely to be in the cerebellum itself. Rather, they suggest that the inferior olive, through its influence on the cerebellar output, is responsible for motor coordination, but not for motor learning through information storage [89].

On these grounds, an alternative explanation for the increased variability that remains scalar in the case of cerebellar lesions might be a dysfunctional decision process that releases the timed motor response. Depending on the nature of the timing task, comparisons utilizing either the cortico-olivo-cerebellar output or, alternatively, the output from the prefrontal and limbic areas to the cerebellum through the pontine nuclei (Figure 5) may become more variable, yet remain scalar. Even though control tasks using other sensory dimensions seem to argue that decision processes are unimpaired after cerebellar lesions [74,80*], ceiling effects in the case of discrimination must be well controlled before this conclusion can be firm.

Conclusions
In summary, most of the data are consonant with an increase in variability with cerebellar dysfunction and with clock and memory effects from different kinds of basal ganglia intervention. The two converge on thalamo-cortical projections in close proximity, which suggests a mnemonic function for transmission of appropriate representations of comparison times through the thalamus, which may be disrupted in its tuning precision or gating efficacy under cerebellar dysfunction.

In any event, the psychophysical study of timing has created a solid behavioral foundation for the investigation of the neurobiological mechanisms that mediate this fundamental aspect of brain function. Essential features of temporal information processing are scalar variability and ratio comparisons. The search for the mechanisms subserving these two aspects of temporal cognition is an important challenge for neurobiology.

Acknowledgements
We are grateful to Stephen Fairhurst and Trevor B Penney for help on parts of this manuscript, and to Warren H Meck for comments on an early
References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


A well written and comprehensive summary of the adaptive resonance theory (ART), which has been developed over the past several years by Grossberg and colleagues. This architecture includes several subsystems: an attentional subsystem, an orienting subsystem, and a comparison subsystem (a vigilance parameter indexes the degree to which stimulus inputs match remembered prototypes). The theory includes a spectral timing component posted in the CA3 region of the hippocampus, as well as spectrally timed response outputs in the cerebellum. Timing, in both cases, is based on a population of neural units that react at different rates (spectrum) spanning the relevant temporal range. Concomitant habituation processes damp out irrelevant temporal ranges. Arousal from US sources can adaptively select co-active units, which when aggregated, focus attention during a CS that initiates orienting responses that would otherwise occur during a delay interval and, in the cerebellar timing network, releases appropriately timed behavior at about the CS–US interspike interval (ISI). Combining hippocampal and cerebellar timing permits an account of second-order serial learning. Spectral timing in these networks show something approximating Weber’s law. The distribution of appropriately tuned receptors is broader at longer ISIs than at shorter ones. However, it is not yet clear that the rate of increase is sufficient to handle the scalar property in detail.


27. Raymond JL, Lieberger SG, Mauk MD: The cerebellum: a neuronal learning machine? Science 1996, 272:1126-1131. A review of cerebellar architecture and circuitry relevant to two conditioned behaviors: the conditioned eye-blink response and the VOR (vestibulo-ocular response). The authors argue that similarities in synaptic plasticity of Purkinje cells induced by climbing fiber activation in these two, very different response systems provide a framework for adaptive timing in the cerebellum. They propose that temporally adaptive learning occurs in the cerebellar cortex, with memory storage in the deep cerebellar nuclei. Appropriately timed CR is modelled as a spatially distributed network representation of the delay between CS (parallel fiber activation) and US (climbing fiber activation) in the cerebellum.


Three experiments compare the underlying mechanisms of temporal perception and production in the short time interval (325-550 ms) range. The authors found that, when tasks were equated, perception and reproduction of these durations resulted in similar Weber fractions. One experiment also found similar Weber fractions comparing in-phase with out-of-phase test durations, arguing against the maintained oscillator model of clock of function. The perception and reproduction access similar interval representations of time, implicating a common interval timing mechanism used to measure and discriminate target intervals in both types of tasks.


A provocative review and exposition of neural network models for time. Miall analyzes problems and advantages of a variety of encoding mechanisms, with special emphasis on difficulties of most of these with intervals in the many seconds range. He describes two models that can handle longer times. One is his ‘beat frequency’ or coincidence detector mechanism that encodes synchronous beats from a population of oscillator neurons with significantly varying periods. This mechanism can robustly encode intervals up to about a half minute. A second mechanism described is an integrator of oscillatory pacemaker neurons that also has a broader range. Both mechanisms require a (possibly unrealistic) perfect reset common to many network models, so that several trials for learning a duration can encode the same values. The chapter is unusual in its thoughtful, frank evaluation of the strengths and weaknesses of these and other network models.


Comparisons of brain activation in a time estimation task relative to a compound motor task was assessed using positron emission tomography (PET) on six normal healthy subjects. Subjects discriminated between a 200 ms (raise right index finger) or 400 ms (raise right middle finger) interval. The authors found significant increases in the activity of superior portions of the cerebellar cortex and vermis and the time estimation as compared to the control task, concluding that these cerebellar areas are involved in timing in humans. Interestingly, they showed that thalamic activation, particularly in the right thalamus, increased 10.27% for 200 ms, the largest of any region in the control condition. The role of basal ganglia structures relative to that of the cerebellum is still unclear from these results, but all areas are probably involved in timing.


An articulate summary of recent contributions that support the roles of the cerebellum and basal ganglia in temporal processing. The data reviewed suggest that durations less than 1 s are under cerebellar control, whereas longer durations are modulated by structures within the basal ganglia and striato-cortical loops. Oscillator and distributed network models of the internal clock are described, with particular emphasis on the flexibility of distributed networks that appear best able to mimic data on cerebellar control of temporal processing in classical conditioning.


A two-part experiment examines the behavioral effects of caudate/putamen (CPu), substantia nigra (SN), and nucleus accumbens (NAS) lesions in rats on temporal discrimination in peak interval procedures. In experiment 1A, a single target interval (30 s) was trained preoperatively. Postoperatively, responding was flat (no improvement for the lesioned group) or increased for control (nonlesioned rats). The CPu lesions showed recovery of temporal discrimination. In experiment 1B, two target values were trained (10 s and 60 s) preoperatively with rats that subsequently received neurochemical lesions of the CPu or NAS. Results showed a double dissociation. Rats with CPu lesions retained differential responding to the two reward rates, but with a loss of temporal discrimination. NAS-lesioned rats showed no appreciation of the two reward rates, but maintained discriminability of the target times (peak responding remained the same). These findings suggest that the mesolimbic and nigrostriatal dopaminergic systems play different roles in temporal processing. The CPu and SN, through connections from A9, A10 and ventral tegmental area, may act as the clock system for temporal duration, while the NAS is not critical to duration discrimination but is important for hedonic appreciation of relative reward rate.

64. Meck WH: Frontal cortex or nucleus basalis magnocellularis lesions, but not hippocampal or medial septal area lesions, occasion the loss of control of the speed of an internal clock. Behav Brain Res 1997, 77:447–455.

A study of the role of cholinergic and dopaminergic lesions in the basal forebrain and frontal cortical loops on deficits in the clock and memory functions of temporal processing. Lesions in this system (i.e. nucleus basalis magnocellularis [NBM] and frontal cortex [FC]) are compared with those in the hippocampal cholinergic system known to affect temporal memory (i.e. medial septal area [MSA] and fimbria fornix [FF]). Rats were preoperatively trained on the peak interval (PI) procedure at a 40 s target interval. Postoperatively, rats with MSA and FF lesions underestimated the target interval, whereas NBM- and FC-lesioned rats overestimated the interval. After post-operative retraining, subjects received dopaminergic antagonists (haloperidol) and...
cholecystokinin) and agonists (methamphetamine and a 'surprise' session, representing an arousal condition) in balanced sessions. A double dissociation was found. Drug and arousal manipulations had no effect on MTA- and FFx-lesioned subjects who exhibited the normal horizontal displacement of the choice, as did control groups. This displacement was not seen in NBM- and FG-lesioned rats. The author concludes that the basal forebrain dopaminergic system increases or decreases clock speed based on training contexts, whereas hippocampal systems modulate temporal memory.


Two experiments examine accuracy and variability of Huntington's disease (HD) patients in auditory synchronization and continuation tapping tasks. Experiment 1 contrasted mean rates between both cued and uncued tapping for five intervals (frequencies from 1-5 Hz) and the variability (SD) around mean tapped intervals. The authors also employed the Wing and Kristofferson [85] model of variance partitioning of 'motor' and 'clock' variance, contrasting ON and OFF states of PD patients, as well as impaired and unimpaired offrotor in asymmetrical PD, to normal controls. PD patients generally displayed shorter IRIs than controls while response variance was greater in the ON, OFF and impaired effector conditions. A within-patient comparison of impaired versus unimpaired effector, and OFF versus ON states, also resulted in greater clock and motor variance for impaired and OFF, respectively. These results support dopaminergic/basal-ganglia involvement in the production of short time intervals, conflicting with an earlier report from Ivy and Keele [74] (but see Keele and Ivy [136]).


An extensive study of the temporal properties of food anticipation in pigeons in the hours range, manipulating three putative timing systems: a zeitgeber-driven circadian clock, a dawn-initiated interval clock, and a cued interval clock. Variance in responding during the cue was approximately scalar in the hours range, manipulating three putative timing systems: a zeitgeber-driven circadian clock, a dawn-initiated interval clock, and a cued interval clock. Variance in responding during the cue was approximately scalar in the hours range, manipulating three putative timing systems: a zeitgeber-driven circadian clock, a dawn-initiated interval clock, and a cued interval clock.


