Toward a neurobiology of temporal cognition: advances and challenges

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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

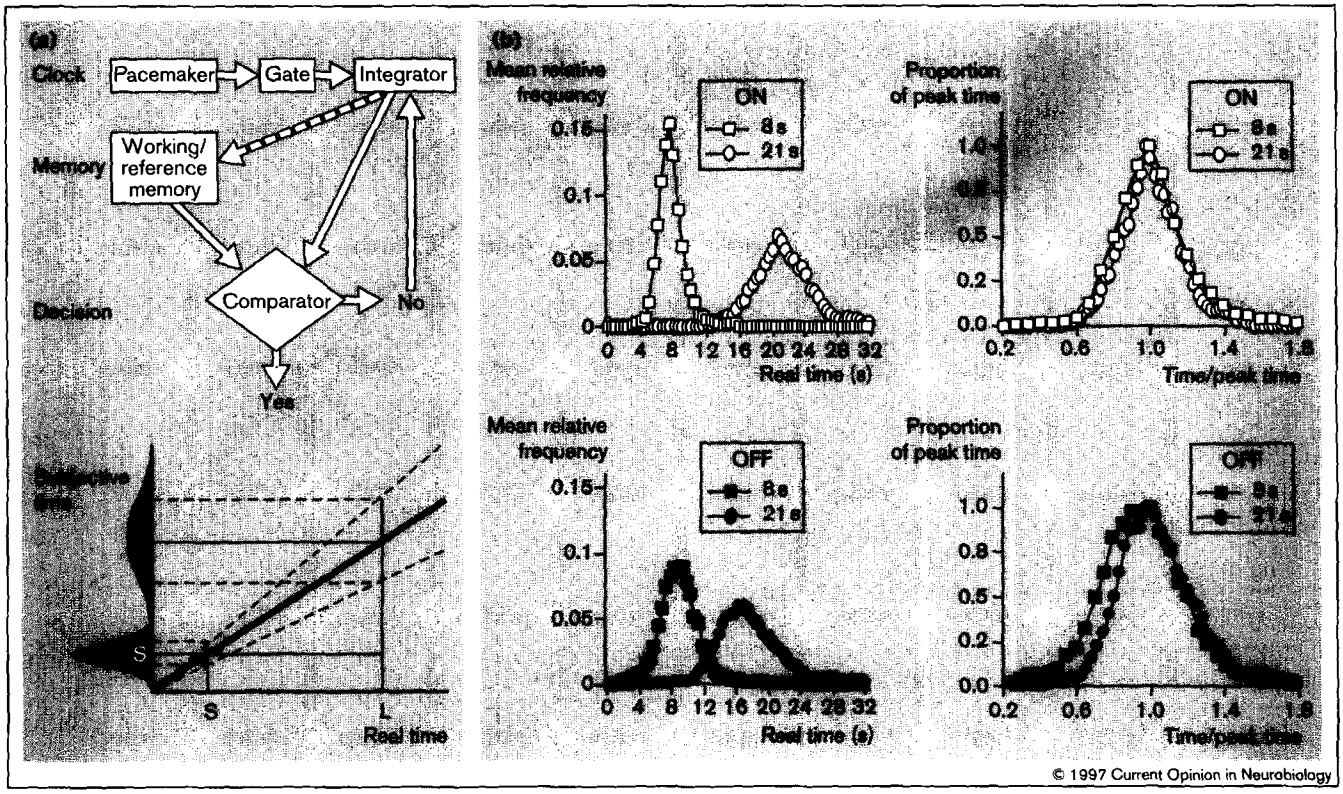
Weber's law: the scalar property

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

Figure 1



Scalar interval timing. **(a)** Information-processing components of the scalar timing model (top) generate subjective time distributions (bottom), which are scale transforms of each other. S, short (real) time; L, long (real) time. **(b)** Time estimation performance of Parkinson's disease patients (left column) exhibits scalar variability when they are ON medication (note that the normalized distributions in the upper right-hand panel superimpose), but not when OFF their medication (the normalized distributions in the lower right-hand panel do not superimpose).

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 8 s and 21 s 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.

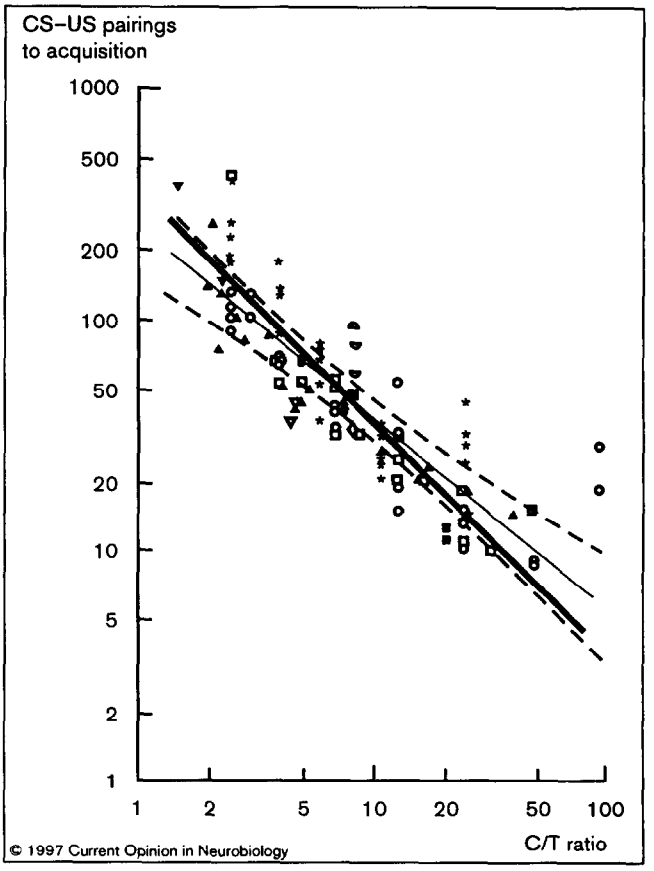
The most extensive data on the effects of delay of reinforcement, partial reinforcement, and trial spacing come from studies of pigeon autoshaping, which is the most widely used appetitive conditioning paradigm. It is identical to Pavlov's paradigm, except that the illumination of a round key replaces 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.

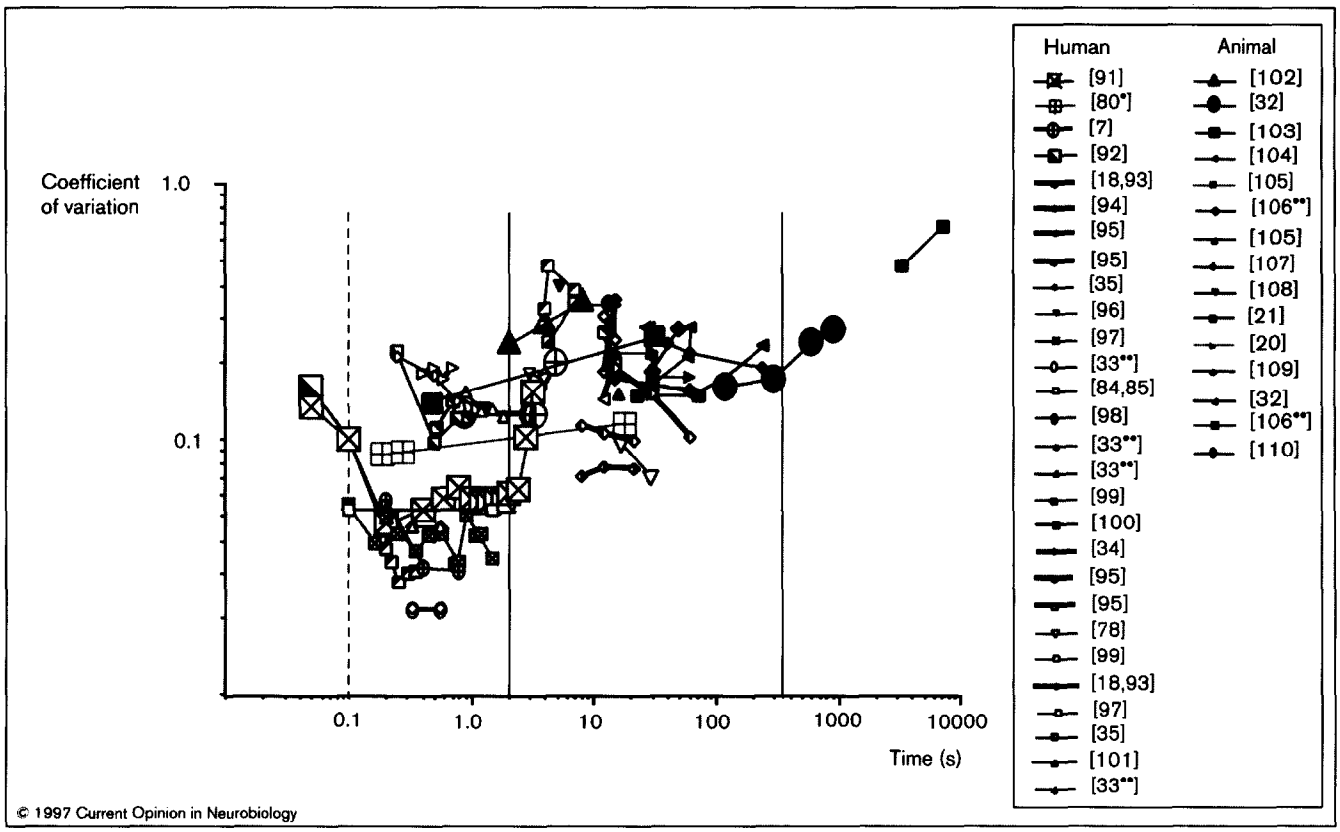
Decisions mechanisms that take ratios as their inputs are a formidable constraint on timing models and on models of conditioning—one that is difficult to accommodate with any of the current neurobiological (network) process models. For example, the fact that the rate of acquisition in simple conditioning 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.

Figure 2



The number of CS–US pairings (reinforced trials) to the acquisition of a CR (key pecking) as a function of the C/T ratio (both axes on log scales). The thin, solid straight line through the data is the best fitting line. The dashed lines are the confidence region. The thick, solid straight line has a slope of −1, indicating that, within the limits of uncertainty, the number of CS–US pairings required for acquisition and its variability, are inversely proportional to the C/T ratio. Equivalently, the rate of acquisition is proportional to the C/T ratio. These data refer to several studies (indicated by different symbols), details of which are included in [23].

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 1–2 s 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 20–30 s, 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 Neurosci 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 2 s, 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 4 s, 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 in (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.

Timing experiment	Manipulation		Ranges	Accuracy (over/under estimation)			Variance	Functional system	Interpretation
Paradigm: species	Lesion	Drug		Lesion	ON drug	OFF drug			
	Basal ganglia								CLOCK PATTERN
PI, Bis: rat [63*,111–115]		DA(a)	20–50 s		Under→recovery	Over→recovery	Decreased/Scalar	Pacemaker/Integrator	Abrupt estimation shift, followed by recovery
		DA(aa)			Over→recovery	Under→recovery	Increased/Scalar	Pacemaker/Integrator	Abrupt rebound when drug is removed
	SNc	DA(a)		Timing abolished	Some recovery			Pacemaker/Integrator	
	CP	DA(a)		Timing abolished	No timing			Gate/Integrator	Gate/Integrator in CP
FI: rat [116]		DA(a)	30–60–120 s		Under		Not shown	Pacemaker/Integrator	Clock effect
DMTS: pigeon [66]		DA(a)	1–5 s		Under		Increased	Pacemaker/Integrator	
FI, Bis, DMTS: rat, pigeon [68,117–119]		DA(a)	1–60 s		No change		Increased	Memory or decision?	Non-specific arousal
Discrimination: humans [120]		DA(aa)	50 ms		Not shown		No change		
			15 s		Not shown		Increased		Non-specific arousal
Avoidance: rat [121]	SNc	DA(a)	10 s	No learning	Normal learning	Learning maintained	Not shown		Clock/memory needed for timed avoidance Timing after DA(a) not shown
	Frontal and limbic systems								REFERENCE MEMORY PATTERN
PI, Bis: rat [64*,113 115,122,124–127]		ACh(a)	10–50 s		No change→under	Under→recovery	Scalar	Reference memory	Gradual estimation shift with no recovery, followed by gradual recovery when drug is removed
		ACh(aa)			No change→over	Over→recovery	Scalar	Reference memory	
	FC	DA(a)		Over	Over		Scalar	Reference memory	
	NBM			Over→recovery			Not shown	Reference memory	
	FF			Under			Scalar	Reference memory	
	MSA			Under→recovery			Not shown	Reference memory	
									WORKING MEMORY PATTERN
PI with gap: rat [125,126,128–130]	FC		4–20 s	No reset			Not shown		No reset: accumulated time retained
	NBM			No reset→recovery			Not shown		
	Amygdala		10–50 s	Normal			Not shown		Reset: failure to retain accumulated time during gap in signal
	FF			Reset			Not shown	Working memory	
	MSA			Reset→recovery			Not shown	Working memory	
Discrimination with delay: rat [132]		ACh(a)					Increased	Working memory	
		ACh(aa)					Increased		
Modality effects									ATTENTION PATTERN
Bis: humans [133]	Vis within V/A		3–12 s		Over		Decreased/Scalar	Leaky gate (slow clock)	Attention-mediated clock speed
	Aud within V/A				Under		Increased/Scalar		Fast (Aud) and slow (Vis) memories mixed
PI–PE, (PER): rat [114,123]		NE(aa)			Over		Increased/Scalar	Slow gate (long latency)	Attention-mediated gate closure Retarded gate closure by constant amount
	Cerebellum								NON-SPECIFIC PATTERN
Bis: rat [103]	Cer		300–800 s	Normal			Increased/Scalar	Deregulation of clock	
			300–1200 ms	Over			Increased/Scalar	Memory or decision	
			20–40 s	Normal			Normal		
Conditioning: rabbit [87]	Cer		400 ms	Impaired			Increased	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; FI, fixed interval; MSA, medial septal area; NBM, nucleus basalis magnecellularis; NE, norepinephrine; PE, prior entry; PER, prior entry reversal; PI, peak interval; SNc, 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 carrying 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

Effects of degenerative diseases and/or focal lesions on timing tasks in humans.

Timing experiment	Manipulation			Ranges	Accuracy			Variance		
Paradigm	Lesion/Disease (affected structure)	ON drug	OFF drug		Lesion	ON drug	OFF drug	Lesion	ON drug	OFF drug
Basal ganglia										
Tapping [134]	Deg/PD		DAt	450 ms and 550 ms	Not shown		Not shown	Increased/ Non scalar		Increased/ Non scalar
Tapping [74]	Deg/PD	DAt	DAt	550 ms	Under	Under	Under	Increased/Not shown	Normal	Normal
Tapping [70]	Deg/PD	DAt	DAt	400 ms and 500 ms	Over	Over	Over++	Increased/ Not clear	Increased/ Not clear	Not shown
				600–2000 ms	Normal	Normal	Over	Increased/ Not clear	Increased/ Not clear	Not shown
Tapping [71••]	Deg/PD	DAt	DAt	550 ms	Under	Normal	Under++	Increased/ Not shown	Normal	Increased/ Not shown
Tapping [72•] exp 1	Deg/HD	DAt	DAt	350–1000 ms	Under			Increased/Non scalar		
Tapping [72•] exp 2	Deg/HD			550 ms	Under			Increased/Not shown		
PEST procedure [74]	Deg/PD		DAt	400 ms	Normal	Not shown	Not shown	Normal	Normal	Normal
Verbal estimation [75]	Deg/PD	DAt	DAt	3–29 s		Under	Under++		Increased/ Scalar	Increased/ Non scalar
Reproduction [75]	Deg/PD	DAt	DAt	3–9 s		Over	Over++		Increased/ Scalar	Increased/ non scalar
PI [18,93]	Deg/PD	DAt	DAt	8 s		Normal	Over		Normal	Increased/ Non scalar
				21 s		Normal	Under		Normal	Increased/ Non scalar
Discrimination threshold [81]	Deg/PD	DAt	DAt	150 ms					Normal	Increased
Discrimination threshold [82]	Focal (thalamus)			150 ms				Increased		
PI [76]	Focal (putamen)			8–21 s	Over			Increased/Non scalar		
Frontal and limbic areas										
Tapping [74]	Focal (frontal)			550 ms	Under			Normal		
Bisection [77]	Focal (frontal)			100–900 ms	Under			Increased/Non scalar		
				8–32 s	Under			Increased/Non scalar		
Pest procedure [74]	Focal (frontal)			400 ms	Not shown			Normal		
Discrimination threshold [82]	Focal (frontal)			150 ms				Increased		
Verbal estimation [135]	Deg/AD			5–40 s	Normal			Increased/Not clear		
	Focal (forebrain)				Under			Increased/Non scalar		
Reproduction [135]	Deg/AD			1 s	Over			Increased/Not clear		
	Focal (forebrain)				Normal			Increased/Non scalar		
PI [78]	Deg/Korsakoff			15 s and 30 s	Under			Increased/Non scalar		
	Deg/Post encephalitis			15 s	Normal			Normal		
				30 s	Under			Increased/Non scalar		
Cerebellum										
Tapping [74]	Focal			550 ms	Normal			Increased		
Tapping [79]	Focal (mesial)			550 ms	Normal			Normal		
	Focal (lateral)				Normal			Increased/Not shown		
Bisection [80•]	Deg/OPCA			100–325 ms	Normal			Normal		
				100–600 ms	Normal			Increased/Scalar		
Tapping [79]	Deg/OPCA			100–900 ms	Under			Normal		
				8–32 s	Normal			Increased/Scalar		
PEST procedure [74]	Focal			400 ms	Not shown			Increased/Not shown		
PI [83]	Focal (mesial)			8–21 s	Normal			Normal		
	Focal (lateral)				Normal			Increased/Scalar		

AD, Alzheimer's disease; DAt, dopamine supplementation treatment (levodopa, carbidopa, apomorphine); Deg, degenerative; HD, Huntington's disease; OPCA, olivo-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

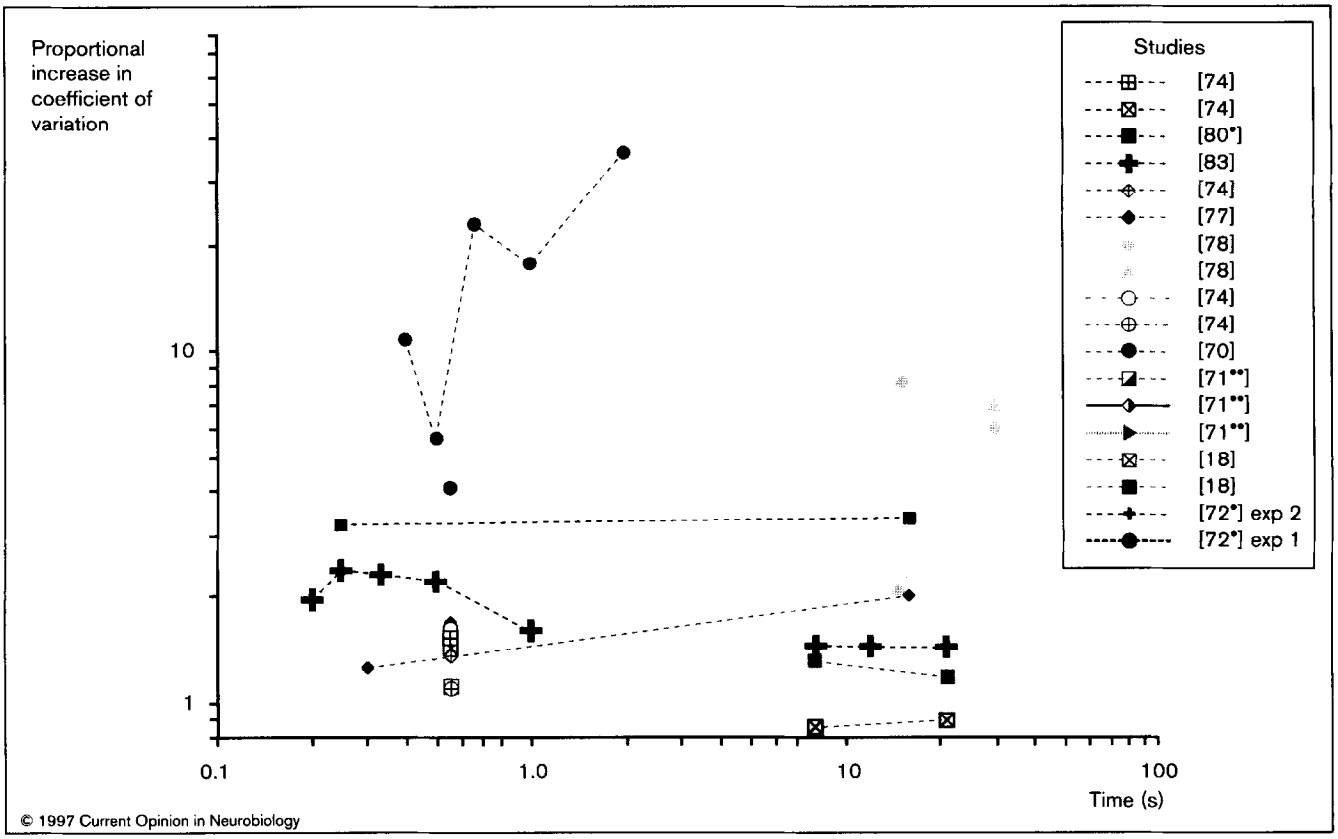
With one exception [70], focal lesions in, and degenerative diseases of, the basal ganglia cause subjects to underestimate time in the short range [71••,72•,73,74] while causing them to overestimate time in longer time ranges, from seconds to minutes. This latter effect is seen in both temporal estimation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

Figure 4



The effect of lesions in different brain structures on various timing tasks in humans. Proportional increase over normal controls of the coefficient of variation is displayed as a function of the time range (ordinate and abscissa on log scales). Comparable increases are found at both millisecond and seconds ranges.

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.

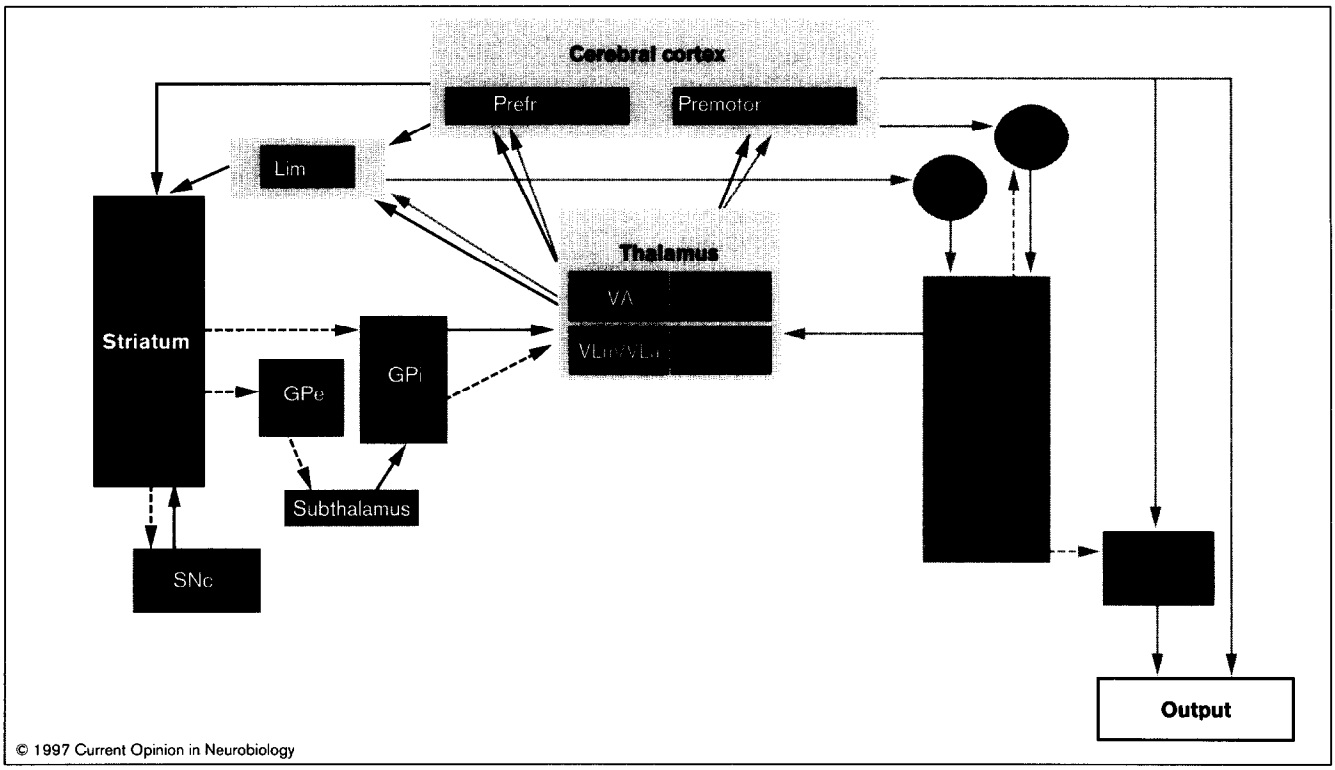
One question is whether there are multiple timing systems subserving different functions or a coordinated timing system involving the cerebellum for some tasks and the basal ganglia for others, with a convergence of central, perhaps cortical, control of both systems. In the schema depicted in Figure 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 (VLc) 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].

Figure 5



Schema of the connections between the structures commonly implicated in timing. Striato-thalamo-cortical connections (dark gray) and connections between the cerebellum and the cerebral cortex through the thalamus (light gray) are depicted. Excitatory (solid arrows) or inhibitory (dashed arrows) pathways are indicated. GPe, globus pallidus, external; GPi, globus pallidus, internal; IO, inferior olive; PN, pontine nuclei; RedN, red nucleus; RetN, reticular formation nuclei; SNc, substantia nigra pars compacta; VA, ventral anterior nuclei; VApc, ventral anterior pars parvocellularis nucleus; VLa, ventro-lateral anterior nuclei; VLac, ventro-lateral anterior pars caudalis nucleus; VLm, ventro-lateral mesial nuclei; VN, vestibular nucleus.

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 ease 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.

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- •• of outstanding interest

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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 posited 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 inhibits 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 ISI's than at shorter ones. However, it is not yet clear that the rate of increase is sufficient to handle the scalar property in detail.

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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 MSA- and FFx-lesioned subjects who exhibited the normal horizontal displacement of the timing function, as did control groups. This displacement was not seen in NBM- and FC-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.

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A definitive review of neuropharmacological data on properties of interval timing, particularly those manipulations dissociating attention, scalar variance, and clock and memory components of information processing. The author argues that dopaminergic manipulations affect clock function, whereas acetylcholine modulates memory for duration. Lesion studies compliment neuropharmacological investigations implicating structures of the basal ganglia in clock function and higher cortical areas in temporal memory and attention.

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A careful study of patients with Parkinson's disease (PD) and age-matched controls, investigating mean interresponse intervals (IRIs) and their variance associated with continuation tapping. A short time interval (550 ms) was tested in both groups. 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 effector in asymmetrical PD, to normal controls. PD patients generally displayed shorter IRI values than controls while response variance was greater in the ON, OFF and impaired effector conditions. A within-patient comparison of impaired versus unimpaired effectors, 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 Ivry and Keele [74] (but see Keele and Ivry [136]).

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