Title

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Journal

Reviews in the Neurosciences, 10(2)

ISSN

0334-1763

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Publication Date

1999

DOI

10.1515/revneuro.1999.10.2.91

Peer reviewed

Reviews in the Neurosciences, 10, 91-116 (1999)

Neural Underpinnings of Temporal Processing: A Review of Focal Lesion, Pharmacological, and Functional Imaging Research

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SYNOPSIS

The mechanisms by which the brain times events and stores them in memory for later use is increasingly of interest to neuroscientists. There are a variety of neurological disorders in which skilled behaviors are not coordinated and appear less than fluent, which may suggest a disorder in temporal processing. In this review, two influential models are described which suggest timing deficits may be due to impairments in a timekeeping mechanism or various nontemporal processes such as motor implementation, memory, and attention. We then review focal lesion, pharmacological, and functional imaging approaches to understanding the neural underpinnings of temporal processing. Converging findings from these approaches provide support for the role of the basal ganglia in timekeeping operations. Likewise, focal lesion and some functional imaging studies are compatible with a timekeeping role of the cerebellum, though specific regions within the cerebellum that control timing operations have not been identified. In contrast, the results from recent focal lesion research suggests the right middle-frontal and inferior-parietal cortices comprise a pathway that supports attention and working memory operations, which are crucial for timing. Functional imaging data provide some converging evidence for this proposal. Functional imaging work also indicates that a right superior-temporal inferior-frontal pathway sometimes aids timing through subvocal nonlinguistic rehearsal processes. These distributed pathways maintain timekeeping operations in working memory and store representations of temporal events, which is crucial for skilled performance.

KEY WORDS

timing, working memory, attention, basal ganglia, cerebellum, prefrontal cortex, parietal cortex, functional imaging

INTRODUCTION

Goal-directed behaviors are comprised of diverse cognitive processes including the timing of behavioral events. Timing impinges on many aspects of behavior including perception, memory, and movement. Yet most highly skilled activities are carried out automatically, without awareness of temporal processing. A skillful tennis player, for example, readily perceives the location, spin, and speed of an oncoming ball, while simultaneously planning the optimal body and arm position, and velocity and angle to hit the ball. The perception of the ball's motion must be precisely timed with the implementation of the motor patterns necessary to swing the arm to return the ball. Likewise, specific temporal patterns of muscle activity across the arm, trunk, and legs are essential. The fluency and automaticity of a highly skilled behavior such as this masks the complexity of the processes involved in timing. In the novice player, sequences of behaviors are carried out more deliberately, step-by-step, and the timing of perceptual and motor events is inaccurate and highly variable. It is only after practice that components of skills become coordinated, partially due to the reliance upon past experiences or memories of how these events should be precisely timed.

Accurate timing of these and other kinds of behaviors appears to depend on interval timing mechanisms, which are capable of anticipating predictable events and of flexibly starting and stopping timing. The cost of this flexibility, however, is less accurate and more variable timing than is found with oscillatory or circadian timing mechanisms (for a complete discussion see /32/). It also appears that

interval timing is greatly influenced by other processes, including attention and memory, which regulate or interact with the operation of hypothetical internal timekeepers or clocks. This review focuses on behavioral, neuroanatomical and pharmacological studies of the neural underpinnings of timing and closely associated processing mechanisms. We will first, however, describe two influential models of timing that have driven investigations into the neural substrates of temporal processing.

MODELS OF TIMING

Many models have been put forth to explain the regularity and coordination of complex skills, including those that do not require an explicit timing mechanism /41/. The two models that are the focus of this review were developed to predict elementary forms of timing, but there is evidence that both can be generalized to explain more complex timing behaviors /59,89/. Each model has been closely tied to a particular approach(s), so it is important to first take a brief look at the main paradigms used to investigate timing.

Interval scaling or discrimination methods are commonly employed /3/. Examples of interval scaling methods include (1) *paced-tapping procedures* in which subjects first produce repetitive movements in pace with a metronome at a constant rate (i.e., synchronization phase) and then without a metronome (i.e., continuation phase) and (2) *peak-interval procedures* in which subjects produce movements to designate the end of a previously learned target interval. Widely used interval discrimination methods include (1) *comparison procedures* in which a standard interval is presented followed by a comparison interval, which the subject then judges as longer or shorter than the standard and (2) *time-bisection procedures* in which subjects judge whether a comparison interval is more similar to previously learned short and long standard intervals.

Each of these methods reveal fundamental properties of timed behaviors, despite some differences in their measures of accuracy and variability. One property of timed behaviors is that trial-by-trial variability increases linearly with the duration of the interval being timed, such that the standard deviation (SD) of a distribution of intervals typically is proportional to the square of the mean interval being timed. This aspect of timing is referred to as the scalar property, a form of Weber's law, and implies the precision of temporal processing remains constant across a wide range of intervals. This property is consistent with a pacemaker that discharges pulses with a Poisson distributed interpulse interval. The accuracy of temporal processing (mean of the produced or perceived interval) is also related to the interval being timed, such that subjects tend to overestimate shorter intervals and underestimate longer intervals. These properties characterize time perception and production across different modalities (e.g., auditory, visual), leading most models to assume that a common timekeeping mechanism underlies perception and production (for a review see /3/). Although a detailed description of each model is beyond the scope of this review, our goal is to describe their hallmarks to set the stage for critically examining investigations into the neural underpinnings of temporal processing.

Two-Process Timing Model

Some models of timing attribute all of the variation in produced intervals to a central timekeeping mechanism or internal clock. This supposition was questioned by the observation of a negative correlation between adjacent responses when producing successive intervals of a fixed duration, as in the paced-tapping procedure. Although this finding might reflect a feedback mechanism that compensates for the production of intervals that are too long or too short, this explanation was rejected by Wing and Kristofferson /98/, who maintained it was

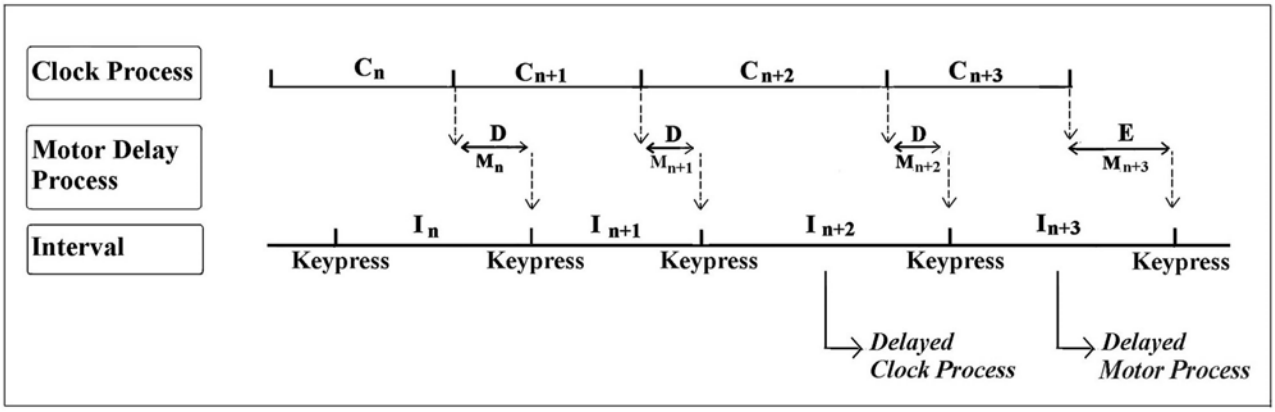

Figure 1. Diagram of the two-process model /98/. The model is based on the paced- tapping procedure, in which performance variability is ascribed to a clock and a motor delay process. Once the clock is entrained to the periodicity of the pacing cues (synchronization phase), the clock ticks at rate C. Every tick activates a motor delay process, which needs M msec to initiate the implementation of a response ($_n$). There is random variation in the duration of both processes, but each proceeds independently such that timing is under open-loop control. Consequently, delays (or hastening) in the clock process (e.g., C_{n+2}) has no effect on the duration of M, but will increase (or decrease) the duration of the interval (e.g., I_{n+2}). Similarly, delays in the motor delay process (e.g., M_{n+3}) has no effect on the duration of C, but increase the duration of the interval (e.g., I_{n+3}). The model contends that the duration of adjacent response intervals covaries negatively, due to random variation, so that if M_n is long then M_{n+1} will tend to be shorter. By comparison, the duration of the clock process is confined to a single interval.

due to random variation in a motor implementation process. Their two-process timing model consisted of a timekeeper or clock process and a motor delay or implementation process /98/. According to this model, the clock produces a pulse when the target interval passes and this activates the motor delay mechanism, which controls peripheral motor implementation processes. Figure 1 illustrates the model and shows that the total variability of the interresponse intervals (I) is equal to the additive variability of the clock (C) and the motor delay (MD) components. This is expressed as var(I) = var(C) + 2var(MD). The motor delay component is doubled because each interval is bound by two adjacent responses, hence, two motor implementation processes. The clock and motor delay processes are assumed to be independent in this formulation, even though the actual computation of clock variability depends on the computation of motor delay variability (i.e., first compute the I and MD variance terms and then make the appropriate algebraic manipulation). It is also notable that temporal processing is conceived of as open-loop, proceeding without the utilization of feedback mechanisms. This latter assumption, however, may not be valid for timing more complex behaviors /89/ or saccadic eye movements /12/, and is frequently violated in studies of patients with neurological disorders /29,35,67,70/.

A critical prediction of the two-process model is that clock variability will increase with the interval duration, but motor delay variability will not because the same peripheral implementation processes are required regardless of the interval duration. Empirical tests have confirmed this assumption /34,96/, but many exceptions have been noted /12,96,98/. However, only clock variance increases during a concurrent task /87/, consistent with a central or cognitive mechanism, and only motor delay variance was elevated in two patients with sensory loss below the elbow /35/. These studies support the functional specificity of the two-process model.

The two-process model implies that perception tasks should provide a relatively pure reflection of timekeeper processes since there is no motor requirement. This inference, however, is problematic because timing critically depends on other nontemporal processes, such as attention and memory. For instance, clock but not motor delay variability is elevated during the performance of a concurrent anagram-solving task /87/, which presumably utilizes nontemporal cognitive resources common to both tasks. Likewise, when attention to timing is diverted, intervals tend to be underestimated /9/, presumably because fewer pulses from the clock are counted during the remembered interval. Attentional factors may also explain why adults tend to overestimate short intervals and underestimate longer ones. Presumably more attention is paid to shorter intervals so that more pulses are registered during a remembered interval whereas attention wanes across longer intervals so that fewer pulses are counted. The above findings raise the possibility that clock variability also includes variance due to other processes, and further suggest that timing accuracy may provide additional insight into temporal processing mechanisms. We now turn to another model that addresses these issues.

Scalar Timing Theory

An information-processing approach to interval timing, scalar timing theory (SET) /24/, was derived from an impressive animal literature and has been applied in human studies of timing /49,80,91,92,93/ using peak-interval (PI) or time-bisection procedures. Similar to the two-process model, SET predicts that specific patterns of accuracy and variability represent different processes. Hence, a more detailed description of the procedures is necessary because they are directly tied to the assumptions underlying the model. In the *PI procedure*, subjects first receive a series of fixed interval (FI) trials in which they are rewarded (animal studies) or receive feedback (human studies) for making responses (e.g., lever presses) after a criterion period following a stimulus (e.g., light). During experimental trials, FI trials are randomly presented along with PI trials, wherein reward is withheld. On PI trials, a symmetric response distribution is obtained over a session such that the peak response rate is near the criterion time and variability around this time is proportional to the peak time (i.e., scalar property) /23/. In the *time-bisection procedure*, subjects are first trained to discriminate two standard stimulus intervals (e.g., 2 and 4 sec) and on experimental trials stimuli of intermediate durations are randomly presented without reinforcement or feedback /53,55/. Subjects must judge whether an interval is more similar to the short or long standard interval. The bisection point (i.e., point of subjective equality; PSE) measures accuracy of remembered intervals and is the interval in which there is an equal probability of subjects responding long or short (usually the geometric mean). The difference limen (DL) is the time half way between the intervals classified "long" on 25% and 75% of the trials, has a scalar property if it is constant in proportion to the bisection point, and measures temporal precision.

Figure 2 illustrates the three stages or components of SET, which contribute independent sources of variability. The clock component consists of a pacemaker that is Poisson in character and discharges pulses used for measuring time. The switch controls when pulses are started and stopped. The accumulator stores the total number of pulses, which represents the amount of time passed. Attention can affect both the switch and accumulator by altering the onset of the switch or the number of pulses entered into the accumulator. Accumulated pulses are encoded into a temporary working memory store, which represents the current time, and over trials, into a long-term reference memory store. A critical assumption is that the representation of time in memory depends on the pulse count in the accumulator and the amount of time or *rate* at which the accumulator count is transferred or encoded into memory.

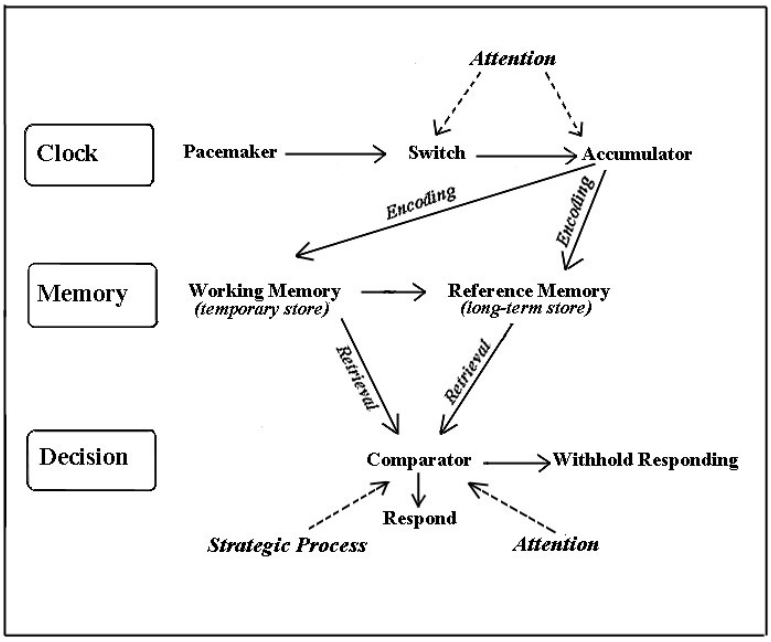

Figure 2. Diagram of the information-processing model of interval timing derived from scalar timing theory /24/. The clock stage component consists of a pacemaker that discharges pulses which are gated by a switch and then passed into an accumulator to be counted. Accumulated pulses are encoded into working memory on each trial and stored in reference memory over trials. The decision process compares pulse counts from the accumulator with those in memory to determine how or when to respond. Attention can influence the clock process, by delaying (or hastening) the onset of the switch or changing the pulse count in the accumulator. Attention and strategic processes influence the decision stage by biasing response thresholds.

The decision process involves comparing pulse counts from the accumulator relative to the ones in working or reference memory to determine when or how to respond. Here, strategic or attentional factors can operate by biasing response thresholds that determine when the current time is sufficiently close to the remembered time. This review will focus on the clock and the memory stages, because the neural underpinnings of decision processes have not been studied.

SET assumes that the scalar property of timing is due to multiplicative variance mechanisms that can be influenced by the clock, memory, and decision processes. However, isolating these processes can be complicated. SET predicts that each component will be represented by specific *patterns* of accuracy and variability (for a detailed discussion see /23,32,55/), which have been derived largely from pharmacological manipulations of processes. The logic of the patterns critically depends on the PI and bisection procedures, in which subjects are pretrained on an interval and then a pharmacological challenge is administered to evaluate the effects on timing relative to pretraining. Table 1 summarizes these patterns. The *clock pattern* is associated with proportional changes in *accuracy* (i.e., under-

Table 1. Scalar Expectancy Theory: Clock and Memory Patterns[1]

	Accuracy	Variability	Temporal Onset[2]	Duration[3]
Clock Pattern				
Increased Clock Rate	Underestimation	No Change	Immediate	Temporary
Decreased Clock Rate	Overestimation	No Change	Immediate	Temporary
Memory Pattern				
Increased Encoding Rate	Overestimation	Increased	Gradual	Long Lasting
Decreased Encoding Rate	Underestimation	Decreased	Gradual	Long Lasting

[1] The clock and memory patterns were derived from studies using the PI and time-bisection procedures where subjects are pre-trained and tested on an interval(s), after which a challenge (i.e., pharmacological, lesion) is administered and subjects are tested again. Therefore, the patterns represent performance after the challenge in comparison to pre-training.
[2] Temporal onset represents the latency at which a change in clock or memory encoding speed is found.
[3] Duration represents the time course of the clock or memory effect over multiple trials and testing sessions.

estimation or overestimation) that happen *immediately*, after the introduction of a variable that alters clock speed, but accuracy then returns to the criterion time because the clock can be *recalibrated* on reinforced or feedback trials /52,53,55,57,58/. It is assumed that clock variability is relatively small relative to memory or decision variability, so that changes in clock speed mostly affect accuracy. Time is *overestimated* when the clock slows down, presumably because the pulse count accumulates later in physical time than during pre-training of an interval (i.e., PI and bisection procedures). Time is *underestimated* when the clock speeds up, because the pulse count accumulates earlier in physical time relative to pre-training. This contrasts with the *memory pattern* which is represented by *gradual* changes in *accuracy* and *variability* that are *long lasting*, because memory-storage speed cannot be recalibrated quickly /55,60/. Memory deficits presumably slow down or prevent the encoding of the pulse count from the accumulator into memory (Figure 2), so that the pulse count is increased, which increases variability and produces an *overestimation* of time.

SET is conceptually appealing, but in practice it is difficult to separate clock and memory variance, because both can have similar trial-by-trial patterns /23/. Although manipulations of attention and working memory help sort out variance components /56,60/, this has been accomplished only in trial-by-trial analyses of responses using the PI procedure. A different approach to testing SET may be a component analysis method, wherein attention, memory, and strategic processing are assessed using other tasks and then correlated with timing measures /29,39,40/.

NEURAL UNDERPINNINGS OF TIMING

The remaining review analyzes the contributions of lesion, pharmacological, and functional imaging approaches to isolating neural systems involved in timekeeping from those that give rise to nontemporal processes, which support timing. The necessity of considering evidence from converging approaches should become apparent, because each clearly has advantages and drawbacks, which compliment one another.

Lesion and Pharmacological Studies of Timing

The lesion method is a bottom-up approach in which the role of a neural site in a behavior is investigated by directly manipulating the brain (e.g., focal lesions, neurodegenerative

disorders). This approach can validate areas essential for particular behaviors and can elucidate the neuroanatomical systems that support specific hypothetical processes by showing, for example, that damage to a particular site disrupts clock, but not motor delay variability. On the other hand, focal lesion studies are problematic because brain damage often affects multiple sites and recovery of function may confound inferences about brain-behavior relationships. The pharmacological method is another bottom-up approach that investigates the role of specific neurotransmitters in a behavior. While the underlying neural systems are implied by the prevalence of a neurotransmitter(s) in particular areas of the brain, pharmacological manipulations have indirect effects on other neurotransmitters, which may obscure interpretations of neural activity. Both approaches tend to focus upon one or two neural sites or neurotransmitters. In the case of temporal processing, the *basal ganglia* and the *cerebellum* have been the focus and the main source of controversy, with some studies supporting the role of the basal ganglia in explicit timing and others embracing the cerebellum. Interest has also been taken in the role of interconnected *cortical* sites, which most investigators identify with nontemporal processing, such as working memory or attention.

The Role of the Basal Ganglia in Timing

It has been hypothesized that the basal ganglia play a key role in controlling an internal timekeeping or clock process. There are several lines of evidence in support of this proposal, the first of which was derived from studies of a degenerative disorder of the basal ganglia, Parkinson's disease (PD), which produces disturbances in rhythmic movement /21,64/. One compelling finding is that the administration of dopamine (DA) agonists (e.g., methamphetamine) speed up the clock, while antagonists (haloperidol) slow down the clock. When subjects are first trained to discriminate a criterion interval(s) (i.e., pre-training) and then administered a DA agonist or antagonist, there is an abrupt change in timing accuracy (peak time, bisection point), but variability remains scalar /52,53,55,57,58,81/ (Table 1). This is ostensibly because when the clock slows down, the pulse count accumulates later in physical time than during pre-training, producing an overestimation of time. When the clock speeds up, the pulse count accumulates earlier in physical time, producing an underestimation of time. However, these distortions gradually disappear over trials as feedback is provided, presumably because the subject learns to adjust the faster or slower pulse count to the values stored in memory. Importantly, the physiological effect of neuroleptic drugs on timekeeping is due to its binding affinity for dopamine D2 receptors, rather than D1 or other receptors sites that are affected by these drugs (i.e., noradrenergic and serotoninergic receptors). Specifically, the affinity of 5 neuroleptics for D2, but not other receptors, correlated with shifts in timing accuracy /57/. These studies strongly implicate the basal ganglia in timekeeping operations because DA receptors are abundant in the caudate and putamen (CPu), the nucleus accumbens (NAS), and the substantia nigra (SN) /58/.

As an aside, manipulations of cholinergic activity, which is thought to affect the speed of encoding the pulse count into memory (Figure 2), have different effects than dopamine. Cholinergic challenges alter accuracy as well as variability of timing, and the effects are also gradual, because it takes time to establish new pulse counts in memory (Table 1). Increasing cholinergic activity (e.g., physostigmine) speeds up the rate at which the pulse count is transferred from the accumulator to memory (Figure 2). This decreases the pulse count in memory, which gradually produces an underestimation of intervals and reduced variability /60/. Likewise, decreasing cholinergic activity (e.g., atropine) slows down the encoding rate such that the pulse count in memory is gradually increased, thereby increasing variability and producing an overestimation of intervals. These effects are

long lasting because the memory process cannot be recalibrated quickly or at all, under some circumstances (e.g., hippocampal damage).

In human lesion studies, PD has served as the predominant model of dopaminergic dysfunction. However, the findings do not represent a typical clock pattern (Table 1), in part because clock patterns may be different when subjects are trained and tested in the same neurological state. This issue is relevant to a recent study using the PI procedure, in which separate groups of PD patients were tested either on or off medication (i.e., same neurological state) /49/. The results were equivocal in unmedicated PD patients, as they did not represent a typical clock or memory pattern as defined by SET (i.e., Experiment 1: elevated nonscalar-variability and over-and underestimation of 8 and 21 sec intervals, respectively; Experiment 2: normal variability and overestimation of a 21 sec interval). Additionally, timing was normal in medicated PD patients, despite the fact that medication does not fully restore normal dopaminergic functioning /37/. This latter finding raises the possibility that distortions in a timekeeping process might also be overshadowed by the significant memory demands of the PI procedure.

Other studies in PD patients have been more influenced by the two-process model. The associated experimental paradigms also minimize memory demands and therefore, might be a purer reflection of timekeeping processes. The first case study of timing in PD /97/ reported that the elevated variability in the produced intervals (i.e., paced-tapping procedure) of one patient was due to increased clock but not motor delay variability. Since then, group studies have shown that clock and motor delay variability are elevated in PD patients withdrawn from dopaminergic replacement therapy, but both improve substantially when medication is reinstated (/67,70/; for conflicting results see /35/). Although the study of unmedicated patients offers a more sensitive appraisal of basal ganglia dysfunction, increases in both sources of variance could confound the interpretation of clock variability, because it is directly derived from motor delay variability. For this reason, studying medicated PD patients has advantages because motor delay variability is normal /29,35,67/. Although earlier group studies of medicated PD patients reported normal motor-timing variability /17,35/, recent investigations have found elevated clock, but not motor delay variability /29,67/. Figure 3a and 3b show that elevated clock but not motor delay variability has been found for 300 and 600 ms intervals and is scalar /29/. Moreover, medicated PD patients tend to *underestimate* standard intervals shorter than 1 second (/29,35,67/; for conflicting results see /70/). While this pattern of findings is not consistent with the typical clock or memory patterns derived from pharmacological studies (Table 1), important differences in the experimental methods may explain the discrepancy.

A qualitatively similar pattern of accuracy and variability in produced intervals has been found in early-stage Huntington's disease (HD) patients /20/, which is a mystery given the different physiological mechanisms of HD and PD /16/. However, it is possible that the two-process model does not dissociate some neurological disorders from others because it does not differentiate timekeeper variability from variance due to attention or memory processes. Furthermore, the model's assumption of open-loop processing is also frequently violated in neurological patients, suggesting the assumption of independence between the clock and the motor delay variability may not be correct.

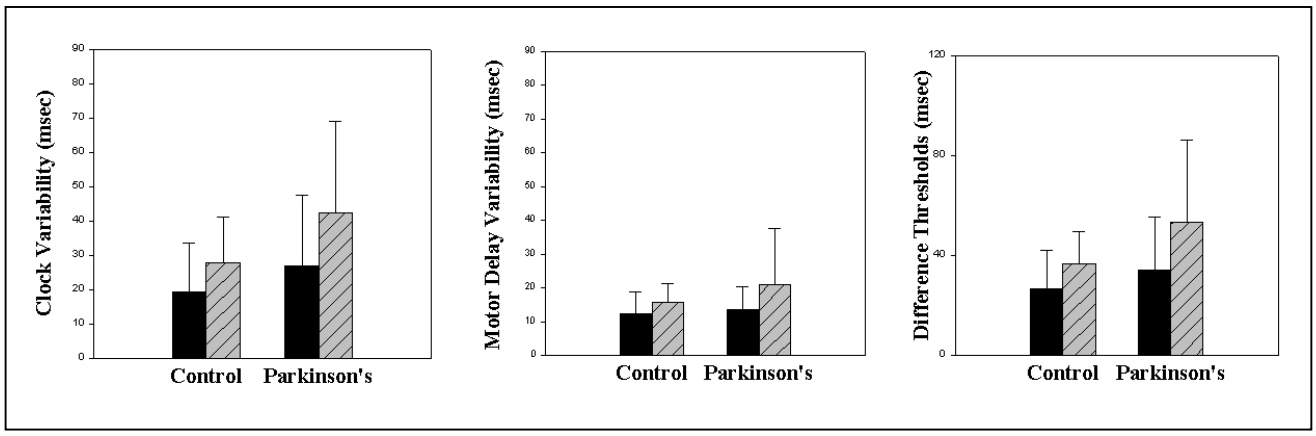

Figure 3. Means and standard deviations for control subjects and Parkinson's patients in the pace-tapping and time-perception tasks. Performance is graphed for the 300-ms (solid bars) and 600-ms (slashed bars) target intervals /29/. a and b. Clock and motor delay variability, respectively, from the paced-tapping task. These sources of variability was decomposed from the total interresponse intervals variability using the procedures of Wing and Kristofferson /98/. Variability is expressed as a standard deviation. c. Difference thresholds from the time-perception task. The difference threshold is a measure of perceptual acuity and was computed by subtracting the difference between the upper (longer) and lower (shorter) threshold and dividing that quantity by 2. The threshold was set to equal 1 SD from the point of subjective equality (PSE). A larger threshold indicates that a larger difference was required between the standard and comparison intervals to correctly discriminate the intervals.

Duration discrimination procedures seemingly offer a solution to the latter problem because there are no motor requirements. Although few studies have used these procedures in PD patients, most have found diminished time perception in medicated /29/ and unmedicated patients (/4,71/; for an exception see /35/). Nevertheless, duration discrimination may involve nontemporal processes too. For example, we used a *comparison procedure*, in which a standard tone pair separated by a fixed interval (e.g., 300 or 600 ms) was presented and then followed 1 sec later by a comparison interval, which the subject immediately evaluated (i.e., longer or shorter) relative to the standard interval /29/. Although this task appears to minimize memory demands because the standard interval is presented on each trial, performance could be affected by the ability to attend to and process sequential auditory stimuli. To control for this possibility, we included a frequency perception task in which the trial events were similar to the duration discrimination task, except that subjects judged the frequency of the comparison tone pair relative to the standard tone pair. We found that medicated PD patients were impaired on the time (Figure 3c) but not the frequency perception task. This suggests that timekeeping mechanisms are dysfunctional in PD patients, rather than other cognitive processes required for the performance of both tasks. Still, verification of this conclusion using other control conditions is needed to investigate other potential nontemporal processes that may be diminished in PD and contribute to impaired time perception.

In summary, the above studies generally provide convincing evidence for the role of the basal ganglia in timing intervals in the milliseconds to seconds range. Support for this proposal has been marshaled in both animal and human studies using lesion and pharmacological manipulations. Nevertheless, the experimental paradigms in studies of PD have not been well researched in terms of the different pattern of results that would be expected for clock versus memory effects. PD produces an increase in clock variability in pace-tapping, which suggests that clock distortions may indeed increase variability,

contrary to SET (Table 1), but in agreement with the two-process model. Increased variability might arise from damaging the clock (i.e., neuronal loss), which produces greater noise in the system, as opposed to simply altering its speed through pharmacological challenges in healthy subjects. This supposition is consistent with the greater variability in PI performance after levodopa (metabolic precursor of dopamine) injections in rats with SN lesions than presurgically /32/. Likewise, why do PD patients tend to *underestimate* intervals /29,67/ if their clock is slowed down? One possibility is that the direction of the accuracy bias predicted by SET depends critically on the procedures used to establish clock patterns. In pharmacological studies, an accuracy bias due to changing the clock speed is determined by comparing accuracy during a subject's normal state with accuracy during a dopamine challenge. In contrast, studies of PD patients assess timing only in an abnormal state, because dopamine levels are not normal even in medicated patients /37/. Therefore, the direction of the bias may be different from the pattern predicted by SET, because it is not possible to test patients in a normal state. In addition, in many of the procedures used to study neurological disorders (e.g., paced-tapping, time comparison) the standard interval is provided on every trial, so that the effects of clock versus memory factors may be difficult to disentangle.

It is also important to note that surprisingly few studies have directly examined whether basal ganglia damage or alterations in dopaminergic functioning compromise nontemporal processes that support timing, despite the attention and/or working memory deficits in PD patients /8,13,99/. Timing accuracy and variability could be due to distortions in multiple processes, because in PD there is neuronal loss in the SN (timekeeper) and atrophy of the CPu, which project via independent thalamocortical pathways to frontal areas /2/ implicated in working memory and attention. These avenues of research are essential for more critical tests of the basal ganglia hypothesis.

The Role of the Cerebellum in Timing

The cerebellum has also been implicated in motor and perceptual timing, but early findings were limited by the use of patients with cerebellar atrophy /19,35,65,95/, which is rarely focal and typically involves the cerebral cortex. Clinicians often assume that cognitive deficits in these patients are more reflective of the integrity of the cerebral cortex, which is consistent with the reduction in cerebral blood flow (rCBF) in cortical areas of the brain in patients with cerebellar degeneration /94/. For this reason, studying subjects with focal cerebellar lesions provides more direct information about the function(s) of the cerebellum.

Ivry and colleagues /36/ studied motor timing (paced-tapping procedure) in a case study of patients with focal lesions of the cerebellum. They reported that lateral cerebellar lesions (4 patients) were associated with elevated clock, but not motor delay variability, whereas medial cerebellar lesions (3 patients) produced the opposite pattern of results. The double dissociation between the two sources of variability for lateral and medial lesions provided a particularly compelling case for different temporal operations in the cerebellum, especially as these regions differ in terms of their connectivity with the cerebral hemispheres and the spinal cord. The lateral cerebellum contains the dentate nuclei. The dorsal and ventral dentate project to the premotor cortex and the dorsolateral prefrontal (DLPF) cortex, respectively /62,88/, such that timekeeping operations could directly influence neural systems involved in sensorimotor processing and working memory. In contrast, the medial cerebellum projects to the spinal cord, directly impacting muscle activity and therefore affecting motor implementation.

The findings from this study were intriguing, but did not address whether the results would extend to performance on time-perception tasks, which has been viewed as a

stronger test of timekeeping operations /35/. This was investigated in a study of 9 focal lesion cerebellar patients /50/, who showed impaired time-perception acuity (comparison procedure) at a 400 ms and a 4 sec standard interval. Although the group X interval interaction was not reported, perceptual acuity appeared more disrupted at the longer interval, which might imply that the deficits were partially due to working memory or attention problems. Strategic processing deficits might be an important factor if subjects normally employ strategies to sustain information in working memory, especially over longer intervals. The role of counting strategies in time perception was therefore examined, because counting helps to divide longer intervals into a series of shorter ones, which improves timing accuracy /42/. Subjects performed a time-perception task with and without strategic support (i.e., the 4 sec interval was divided into 10 subintervals), and with and without instructions to use the subintervals as a basis for computing time. Time-perception acuity was impaired in the cerebellar patients in all conditions, but could not be attributed to counting deficits. Specifically, neither the cerebellar or the control subjects used counting without stimulus support or instructions, but when both were given, the cerebellar patients used explicit counting strategies as efficiently as the control subjects to improve their performance (i.e., nonsignificant group X condition interaction). Although the authors concluded that the cerebellum subserves a timekeeping mechanism, this is arguable because counting involves timing /90/. If cerebellar patients had a deficient timekeeper, they should not have been able to use this strategy as well as the control subjects, which was not found. The study also did not rule out the possibility that timing deficits could be due to abnormalities in other processes, as cerebellar patients showed significant deficits in frequency perception.

A recent study suggests that working memory deficits may not explain the timing impairments after damage to the cerebellum /10/. In this study, patients with cerebellar damage (7 focal lesion, 1 cerebellar atrophy) performed a time (400 ms) and frequency perception task (i.e., comparison procedure) under single and dual task conditions. In the time-perception task, dual-task performance deteriorated to the same extent in the control and cerebellar groups, and frequency perception did not decline under dual-task conditions in either group. Still, cerebellar patients were impaired in both conditions of the time and frequency perception tasks, suggesting that other deficits might explain time-perception performance.

The above studies demonstrate that cerebellar damage consistently disrupts timing. However, it will be necessary to more carefully isolate variance due to temporal and nontemporal process, because cerebellar damage is not specific to time perception, but instead, more generally impairs nontemporal discrimination performance and also disrupts attention /1/. Importantly, recent investigations have not found a relationship between time-perception acuity and cerebellar lesion location /10,50/. This weakens the case for a timekeeping mechanism in the cerebellum and indicates that previous dissociations between the lateral and the medial cerebellum in clock and motor delay components of paced tapping /36/ also need re-examination.

The Role of the Cerebral Cortex

Most studies have focused on the role of the basal ganglia and cerebellum in temporal processing with limited attention directed to the cerebral hemispheres, despite the multiple cortical connections of both structures. Reciprocal thalamocortical pathways to the basal ganglia include the supplementary motor area (SMA), frontal eye fields (FEF), DLPF cortex, lateral orbitofrontal cortex (LOC), and anterior cingulate (AC) area /2,63/. Similarly, the dentate nuclei project to the DLPF and premotor cortex /62,88/. The frontal cortex could, therefore, play a role in time-dependent operations or an indirect role in nontemporal processes that support timing. In fact, damage

to the frontal cortex disrupts certain aspects of temporal processing.

One proposal is that the frontal cortex supports the encoding of temporal information into memory (see Figure 2) and another emphasizes its role in attention. Support for the memory hypothesis was provided by a study /61/ in which rats were trained to discriminate a 40 sec interval (i.e., PI procedure), after which they received control operations or lesions in the medial septal area (MSA; projects to the hippocampus), nucleus basalis magnocellularis (NBM; projects to frontal cortex), or frontal cortex (FC), all of which reduced ACH activity in the lesioned area only. Postoperatively, FC and NBM lesions produced a *gradual overestimation* of peak time, similar to the effects of cholinergic antagonists, and this was attributed to a slowing in the encoding of temporal information into memory. In contrast, MSA lesions produced a *gradual underestimation* of time, although the mechanism for this effect was not clear. These findings, which have been replicated /68,69/, represent a memory pattern because the effects developed gradually and persisted over sessions, in contrast to a clock pattern (Table 1).

The frontal cortex also appears to control attention during temporal processing. In a variation on the PI procedure, rats were trained to associate a 10 or 20 sec interval with a light or white noise /69/. After receiving NBM, FC, MSA, or fimbra fornix (FF; portion of hippocampal system) lesions or control operations, they then performed a simultaneous temporal processing (STP) procedure wherein the 20 sec stimulus was first presented and followed after a random delay by the 10 sec stimulus. The control, MSA, and FF rats timed the two stimuli in STP trials the same as for trials with a single stimulus. In contrast, the NBM and FC rats were not able to time the 20 sec stimulus while the 10 sec one was present. Rather, when the two stimuli were on simultaneously they stopped timing the 20 sec one, remembered its value, satisfactorily timed the 10 sec one, and then finished timing the 20 sec stimulus. Consequently, their peak times for the 20 sec stimulus were increased by approximately 10 sec. These results indicated that the frontal cortex is involved in divided attention during temporal information.

Studies in humans also support a role for the frontal cortex in temporal processing, although there are some conflicting findings. Ivry and Keele /35/ investigated time perception (comparison procedure; 400 ms standard interval) and motor timing (550 ms paced-tapping procedure) in 7 patients with lesions that extended into the posterior portions of the frontal lobe. Clock and motor delay variability were elevated, but these results were not interpreted as reflecting a dysfunctional timekeeper, because time perception was normal in these patients, contrary to the above animal studies. However, animal studies have used much longer intervals (seconds), which are more influenced by attention, working memory, and strategic processing than intervals in the hundredths of milliseconds.

Nichelli and colleagues /66/ investigated the role of memory in a study of 11 patients with frontal lesions (2 left, 6 right, and 3 bilateral hemispheric) on a short (100 to 900 ms) and a long (8 to 32 s) interval time-bisection task. Frontal lobe patients underestimated both intervals (bisection point) and their discrimination precision was impaired (nonscalar Weber ratio) relative to the control group. The results were consistent with a clock or a memory pattern (Table 1), but because the patients also showed impaired accuracy on a control spatial-bisection task, this suggests the time-perception deficits might be more reflective of impairments in nontemporal processes.

Similar issues were examined in a study of patients with lesions in the frontal cortex (5 left and 2 right hemisphere) /50/. The frontal patients showed impaired time-perception acuity (i.e., comparison procedure) when the standard interval was 4 sec but not 400 ms. Similarly, the frontal patients showed greater frequency perception deficits when the standard and comparison pitches were separated by 4 sec than by 400 ms. These findings demonstrated that frontal lobe damage produced

discrimination deficits that were not specific to timing and possibly related to maintaining information in working memory. However, it did not appear that impaired strategic processing could explain the working memory problems, because when subjects were instructed to count, performance in the frontal group improved to the same extent as in the control and cerebellar groups.

A recent study provides more direct evidence for an attention or working memory role of the frontal cortex in both temporal and nontemporal discriminations /10/. Patients with frontal lesions (4 left and 1 right hemisphere) were impaired in single and dual task conditions of a time (400 ms standard; comparison procedure) and a frequency perception task. Although time-perception performance deteriorated during the dual-task to a similar extent in the frontal, control, and cerebellar lesion groups, frequency-perception performance declined during the dual task only in the frontal group. These findings suggest that frequency perception depends on fewer resources than duration perception, because the dual task did not interfere with performance in the controls and cerebellar patients. However, when the ability to divide attention is disrupted by frontal lobe damage, deficits emerge even in frequency perception.

The above investigations implicate the frontal lobe in nontemporal aspects of timing, but the specific processes have not been well defined and the associated frontal sites have not been delineated. The role of other cortical areas has not been studied. The parietal cortex might be expected to be involved in timing because of its interconnectivity with the basal ganglia and cerebellum, which are both implicated in timing. The inferior parietal cortex has strong, bilateral projections to the putamen and caudate nucleus in monkeys /11/. There are also cerebellar-thalamic projections to the inferior and the superior parietal cortex /85/. Clinical observations suggest the left parietal cortex might play a direct role in timing because it is typically damaged in patients with limb apraxia /27/ who show disruptions in timing gestures /76/. On the other hand, damage to the right parietal cortex often produces neglect /77/, suggesting that underlying attentional operations could support timing.

We recently investigated the role of the cerebral hemispheres in time perception by studying individuals with focal left (9 anterior and 10 posterior lesion patients) or right (6 anterior and 12 posterior lesion patients) hemisphere cortical lesions /30/. The performance of patients and control subjects was studied in frequency and time-perception tasks (comparison procedure), in which the interval separating the standard tone pairs was 300 or 600 ms. We also investigated whether time perception was correlated with an independent measure of switching attention, to determine if timing deficits in patients with focal lesions could be attributed to impairments in attention.

The main findings showed that frequency perception and attention were impaired after left (LHD) or right (RHD) hemisphere damage. However, the incidence of frequency perception deficits was considerably higher in patients with left frontal lesions (67%) than in the other patient groups (20% or less). In contrast, the magnitude of deficits in switching attention did not differ among the patient groups. Figure 4 shows that when deficits in nontemporal discrimination processes were controlled by analyzing subjects with normal frequency perception, only the RHD group showed time-perception deficits (nonscalar), especially at longer intervals. Poorer time-perception acuity correlated with greater problems in switching attention in the RHD but not the LHD patients, despite attention deficits in both groups. In contrast, switching attention was not correlated with frequency perception (in any patient group), which suggests the attention deficits were more specific to timing events. These results are not necessarily discrepant with those of Casini and colleagues /10/, as our task assessed switching attention, rather than processes involved in dividing attention.

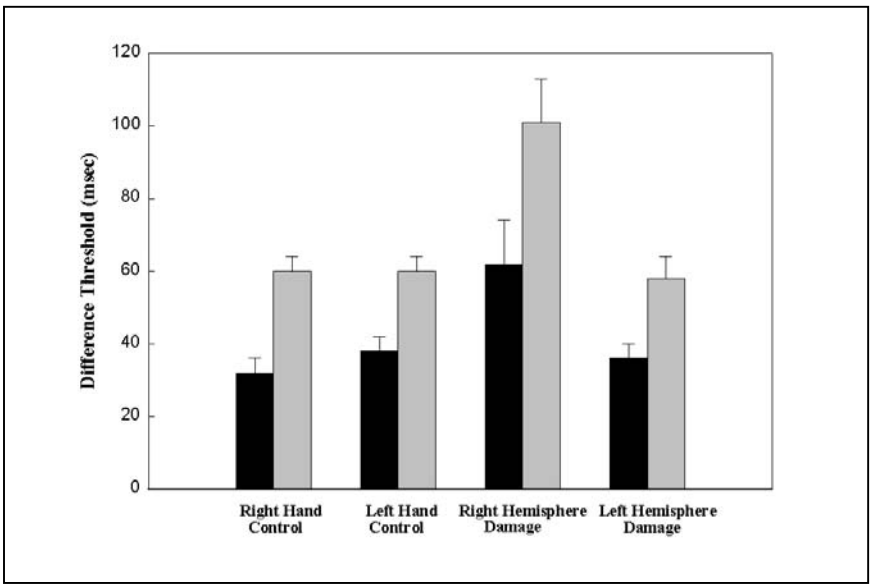

Figure 4. Difference thresholds (means and standard errors) for the time-perception task in control subjects and patients with unilateral left or right- hemisphere damage. Two groups of control subjects were studied, one who performed the task using their right hand and the other who used their left hand. Performance is graphed for the 300-ms (solid bars) and 600-ms (slashed bars) target intervals. Data are displayed for subjects with normal frequency perception /30/.

Figure 5 displays the lesion overlap in patients with damage primarily anterior (top row) or posterior (bottom row) to the central sulcus, who showed impaired (left column) or normal (right column) time perception. The lateral view shows the location of the greatest lesion overlap in patients with impaired time perception. There were no LHD patients with anterior lesions (Figure 5a) who showed time-perception deficits whereas all RHD patients with anterior lesions (Figure 5a; yellow) had lesions in the middle and superior frontal gyri (areas 46, 8). Damage to this same region in patients with LHD (Figure 5b; yellow) did not produce time-perception deficits. Figure 5c shows that the area of 100% lesion overlap (yellow) in RHD patients with posterior lesions involved the supramarginal (SMG; area 40) and angular gyrus (area 39). Damage to this same area in the left hemisphere did not produce time-perception deficits (Figure 5d; yellow). Only 3 patients with posterior RHD showed normal time perception. One of these patients had occipital damage (not shown in Figure 5) and two had lesions involving area 40, but time perception was borderline normal in one of these patients.

Overall, these results implicate a right prefrontal-inferior parietal network in temporal processing, associated with the right hemisphere's role in switching attention. Although the right inferior parietal cortex has been associated with spatial attention /77/, our results suggest a broader role in attention to time. Attention is also intricately linked to working memory. The middle and superior frontal gyri (designated areas 9 and 46 by some investigators /79/), have been implicated in various aspects of working memory /25/, which presumably is required to compare two intervals. On the other hand, the comparison procedure used in our study would

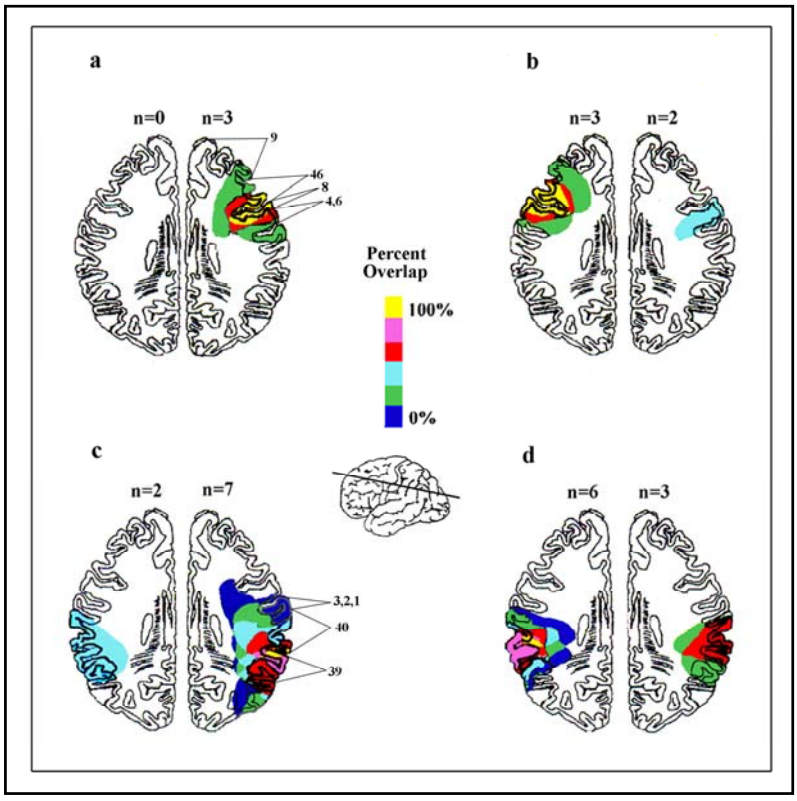

Figure 5. Lesion overlap in stroke patients with damage primarily anterior or posterior to the central sulcus. The axial sections show overlap for left hemisphere (on the *left* of each section) and right hemisphere (on the *right* of each section) lesions in patients with normal frequency perception /30/. The line on the lateral view shows the location of the axial sections. The color scale indicates the percentage of patients within a particular group with damage in an area, with yellow designating the common areas of infarction in 100% of the patients. The number of patients in each group is specified above each axial section. Brodmann areas are specified to the right of the sections in the left column (a and c). a. Overlapping lesions in patients with anterior lesions and *impaired performance* on the time-perception task. b. Overlapping lesions in patients with anterior lesions and *normal performance* on the time-perception task. c. Overlapping lesions in patients with posterior lesions and *impaired performance* on the time-perception task. d. Overlapping lesions in patients with posterior lesions and *normal performance* on the duration perception task.

procedure used in our study would seem to minimize the necessity for rehearsal or memory retrieval processes because the standard interval was presented on each trial and there was only a brief delay (1 sec) separating the standard and comparison intervals. This supposition is consistent with the absence of a relationship between time-perception deficits and damage to inferior frontal-superior temporal pathways, which support retrieval and rehearsal processes /72,100/. Our results indicated that the left hemisphere does not appear to play a role in these operations, at least in the analysis of nonlinguistic acoustic stimuli. A careful inspection of the lesion sites in LHD patients with impaired frequency *and*

duration perception also failed to uncover evidence of a common left-hemisphere network for time perception, consistent with studies of patients with frontal lobe lesions /10,50/. Nevertheless, it is possible that the left hemisphere supports other nontemporal mechanisms underlying timing that were not identified by our study.

The above studies are consistent with clinical neuropsychological perspectives on the functioning of the frontal and the parietal lobes /48/. It also appears that there may be a right-hemispheric bias for attending to temporal information, at least in the range of hundredths of milliseconds or longer. Although support for this idea has been found in only one lesion study /30/, the next section will show that functional imaging findings are compatible with this proposal. These lines of research, however, will be further strengthened by more research that directly evaluates the role of the cerebral cortex in nontemporal processes during timing. Here, it will be important to directly contrast the effects of cortical damage with basal ganglia and cerebellar damage on nontemporal and timekeeping processes. This is a crucial step towards advancing timing models by providing more precise empirical evidence for clock, memory, decision, and attention patterns, hopefully across a variety of timing procedures.

Functional Imaging Studies

More recently, the capacity to precisely time events has been investigated using functional imaging methods in healthy individuals. Functional imaging is a top-down approach that provides information about whether activation of a neuroanatomical site occurs in association with a behavior. An advantage of this method is that the importance of a neural site relative to others can be examined more readily than in lesion or pharmacological studies. Activation of a particular system can also provide insight into the cognitive processes underlying a behavior, when there is general agreement about that system's function. On the other hand, experimental manipulations of a cognitive function may alter brain activity in many sites and unlike lesion and pharmacological methods, it is difficult to directly associate brain activity in a specific area with one but not another behavioral measure (e.g., accuracy, variability), each of which represents distinct hypothetical mental operations. Additionally, functional imaging currently relies heavily on the subtractive logic, wherein the subtraction of two tasks is assumed to reflect functional activity associated with a mental operation in one but not the other task. Unfortunately, this assumption is often not tenable or difficult to test. These limitations can seriously obscure interpretations of causal linkages between brain structure and function, and need to be weighed when interpreting the neural mechanisms underlying a specific cognitive process.

Relatively little timing research has been conducted using functional imaging techniques. Table 2 summarizes studies representative of neuroimaging investigations into motor and perceptual timing. The table describes each study's main experimental conditions and lists the areas associated with an increase in activation after subtracting functional activity in one condition from another.

Table 2 shows that the results from studies of motor timing are discrepant, particularly with regard to the role of the basal ganglia and cerebellum. This may be due in part to the different 'control' or comparison conditions used across studies. One study using positron emission tomography (PET) concluded that the timing of visual information depends on the extrastriate cortex (area 19) because this area showed greater activation in comparison to other conditions, which presumably had similar visual processing requirements /18/. However, the main temporal task (TSD) required a visual discrimination (i.e., same or different visual grating), which might overshadow any demands on timing operations, and the timing component involved initiation of the discrimination response at a specific time, though no behavioral verification was provided. While intuitively the TSD condition seems to require timing, the temporal

Table 2. Summary of Functional Imaging Studies of Temporal Processing

Citation [Method]	Task	Subtraction	Areas of Increased Activation				
			Frontal	Parietal	Basal Ganglia	Cerebellum	Other
Motor Timing							
Dupont et al. (1993) [PET] [1]	*Conditions* • Temporal Same-Different (TSD); 600 ms response initiation; both hands • Detection (D); 400 ms response initiation; right hand • Identification (I); both hands • Passive Viewing (P) *Stimuli/Response* • Visual gratings/same-different (TSD) or vertical-horizontal (I)	• D – P* • TSD – I* • TSD – D*	• l. M1, PM • r. M1, PM	• r. 40	• r. put.	•r. cer. • l. cer.	• r. VC,AC • r. VC • r. VC
Larsson et al. (1996) [PET] [1]	*Conditions* • Self-Paced Rhythmic Movement (SPM) • Visually Triggered Movement (VTM); 250 and 2000 ms random intervals • Passive Viewing (P) *Stimuli/Response* • Visual (VTM, PF)/Tap right finger in synchrony (VTM)	• SPM – P* • VTM – P	• SMA, l. M1 l. mid. 6,9,10 • r. 44, 46	• l. S1 r. SMG • b. 40	• l. put.	• r. cer.	• l. VC • l. thal., b. VC r. TC
Lejeune et al. (1997) [PET]	*Conditions* • Synchronized Tapping (S); 2.7 sec fixed Intervals • Random Synchronization (R); 2 – 3.4 sec random intervals • Time-Bisection Procedure (T; Maquet et al. 1996); 700 ms standard *Stimuli/Response* • Visual/Right finger press in synchrony with light	• S – R* • S and T* Common Areas	• r. 47 • r. 46, 47	• r. 40 • r. 40	• l. put.	• r. vermis • l. cer.	

Table 2. (Continued)

Citation [Method]	Task	Subtraction	Areas of Increased Activation				
			Frontal	Parietal	Basal Ganglia	Cerebellum	Other
Motor Timing							
Rao et al. (1997) [FMRI]	*Conditions* • Synchronized Tapping (S) • Continuation Tapping (C) • Passive Listening (L) • Pitch Discrimination (D) • Baseline Resting (R) *Stimuli/Response* • Auditory 300 or 600 ms interval/Right finger press	• S – R • C – R* • L - R • D – R	• l. M1 • l. M1, r. 44 caud. SMA • rost. SMA		• l. put.	• r. cer. • r. cer.	• r. TC • l. thal. r. TC • b. TC • b. TC
Penhune et al. (1998) [PET]	*Conditions* • Perception Fixed-Interval Sequences (BASE) • Synchronized Tapping: Fixed-Interval Sequences (FIX) • Synchronized Tapping: One Repeated Sequence (REP); mixed intervals • Synchronized Tapping: Novel Sequences (NOV); mixed intervals *Stimuli/Response* • Auditory or visual 6-element sequences; 250 and/or 750 ms intervals/Right finger press	• FIX – BASE* • Auditory • Visual • REP – FIX* • Auditory • Visual • NOV – REP* • Auditory • Visual	• l. M1/S1 SMA, l. 10 • l. M1/S1 r. 44,45,47,11 • l. M1/S1 • SMA • r. 47,11	• r. 40	• l. GP • l. GP • b. put.	• r. paravrm. • r. paravrm. l. cer. • l. paravrm. • vermis b. cer. • vermis b. cer.	• r. TC • r. TC • l. VC • r. VC • l. thal.

Table 2. (Continued)

Citation [Method]	Task	Subtraction	Areas of Increased Activation				
			Frontal	Parietal	Basal Ganglia	Cerebellum	Other
Time Perception							
Jueptner et al. (1995) [PET][1]	*Conditions* • Comparison Timing Procedure (T); 300 ms standard; 200 and 400 ms comparisons • Movement Control Task (M) • Rest Condition (C) *Stimuli/Discrimination* • Auditory tone-pairs/Longer or shorter, right hand response	• M – C • T – M*	• b. 46,10		• r. caud. • r. caud. b. put.	• vermis b. cer. • vermis b. cer.	• b. TC • b. thal.
Maquet et al. (1996) [PET]	*Conditions* • Time-Bisection Procedure (T); 700 ms standard; 490 – 910 ms comparisons • Intensity Bisection Procedure (I) • Movement Control Task (C) *Stimuli/Discrimination* • Visual (light)/same-different, right-left hand response	• T – C* • I – C • T – I^2*	• r. 44,45,47 • r. 45	• r. 40 • b. 40		• vermis l. cer. • vermis l. cer.	• l. VC • b. VC
Roland et al. (1981) [PET] [1,3]	*Conditions* • Rhythm Discrimination Task (T) • Rest (C) *Stimuli/Discrimination* • Auditory 6-element rhythm pairs, each 1650msec/Same-different covert decision	• T – C* • Right – Left Hemisphere	• b. s. PF, i. PF b. FEF • r. i. PF	• r. IP r. IPS			• b. AC r. i. TC

Note: The table lists representative studies of temporal processing in which there was an explicit timing component in one or more tasks. Only directly relevant portions of the tasks and results are described. l. = left hand, r. = right hand, s. = superior, i. = inferior, M1 = primary motor cortex, S1 = sensory cortex, PM = premotor cortex, PF = prefrontal cortex, FEF = frontal eye fields, IP = inferior parietal, IPS = intraparietal sulcus, TC = temporal cortex, put. = putamen, s. nigra = substantia nigra, GP = globus pallidus, cer. = cerebellar hemisphere, paravrm. = paravermis, thal. = thalamus, VC = striate and/or extrastriate cortices, AC = auditory cortex, SMA = supplementary motor area, caud. SMA = caudal supplementary motor area, rost. SMA = rostral supplementary motor area, mid. = middle.

* The authors designated these subtractions as the ones reflective of timing operations.

[1] No behavioral data were reported in these studies to verify that performance was reflective of processes assumed to underlie the task..

[2] These subtractions did not show any significant areas of activation.

[3] This study did not have anatomical localization of activated regions.

requirements might be more related to processes involved in response preparation or selection. These issues aside, it is noteworthy that in the D – P subtraction, which perhaps was the purest test of temporal processing because the D condition only involved detection, increased activation was found in the putamen and the cerebellar hemisphere. In contrast, activation was not found in these areas in the TSD – D subtraction, perhaps due to the subtraction of a temporal component common to both tasks.

PET studies using synchronized tapping or self-paced rhythmic movements have also shown that timing correlates with activation of the cerebellum and/or the basal ganglia (Table 2). Nevertheless, the explanations of the findings differed, with some attributing a central timekeeping role to the cerebellum /73/, the basal ganglia and cerebellum /47/, or the SMA /45/. This illustrates the inherent subjectivity of subtractive procedures, especially in terms of the mental operations presumed to underlie tasks. For instance, an implicit assumption in one study /73/ was that the timing requirements increased across tasks with the fixed-interval sequences (FIX) being the easiest and the novel sequences with mixed intervals (NOV) being the most difficult to time. This assumption was not verified by the behavioral data. Moreover, neural activity in systems underlying timekeeping may not perfectly correlate with experimenter-defined complexity, so that subtracting two timing conditions (i.e., REP – FIX, NOV – REP) sometimes masks activations specific to temporal processing.

Only a few time-perception studies have been conducted, but the main findings are also controversial (Table 2). An early PET study /84/ reported activation of an inferior-frontal temporal-parietal network that was biased for right-hemispheric discriminations of auditory rhythmic sequences. However, rhythm discriminations did not activate the basal ganglia or the cerebellum. More recently, Jueptner and colleagues /38/ scanned individuals while they performed a comparison time-perception task (T) and a motor-control task (C), in which they alternately lifted the left and right fingers after the same sequence of stimulus events. They concluded that the vermis and cerebellar hemispheres controlled timing, but Table 2 shows that the basal ganglia were also activated in the same subtractive analysis (T - M). Maquet and colleagues /51/ performed a similar study using time-bisection and illumination-intensity procedures, to determine if the patterns of activation were specific to timing or more general to discriminating stimulus events. Table 2 shows that the vermis, cerebellar hemisphere, and a frontal-inferior parietal network, biased for right hemispheric processing, were activated by both discrimination tasks. These findings implicated both systems in nontemporal aspects of time and illumination discriminations, but suggested the basal ganglia were not involved in time perception.

The above studies illustrate the discrepant findings and the difficulties of interpreting activation patterns, when they cannot be directly associated with a specific temporal or nontemporal process. Nonetheless, they raise some interesting questions about the potential involvement of neural systems in nontemporal aspects of timing. Several studies reported activation in the prefrontal and inferior parietal cortex, consistent with focal-lesion studies /10,30,50/. This is particularly striking when subjects reproduce longer intervals (1 sec or more) /45,47/ or maintain information in working memory for at least several seconds before making temporal judgments /51,84/. Similar networks were also activated in nontemporal control tasks /18,45,51/.

To examine this issue more carefully, we conducted a whole-brain functional magnetic resonance imaging (fMRI) study of motor timing in healthy individuals /83/, which was similar to previous studies in patient populations. Using the pace-tapping procedure, subjects first tapped their index finger in synchrony with a series of tones separated by a constant 300 or 600 ms (synchronization phase; S). The tones were then discontinued and subjects continued to tap at the same pace (continuation phase; C). Timing competency

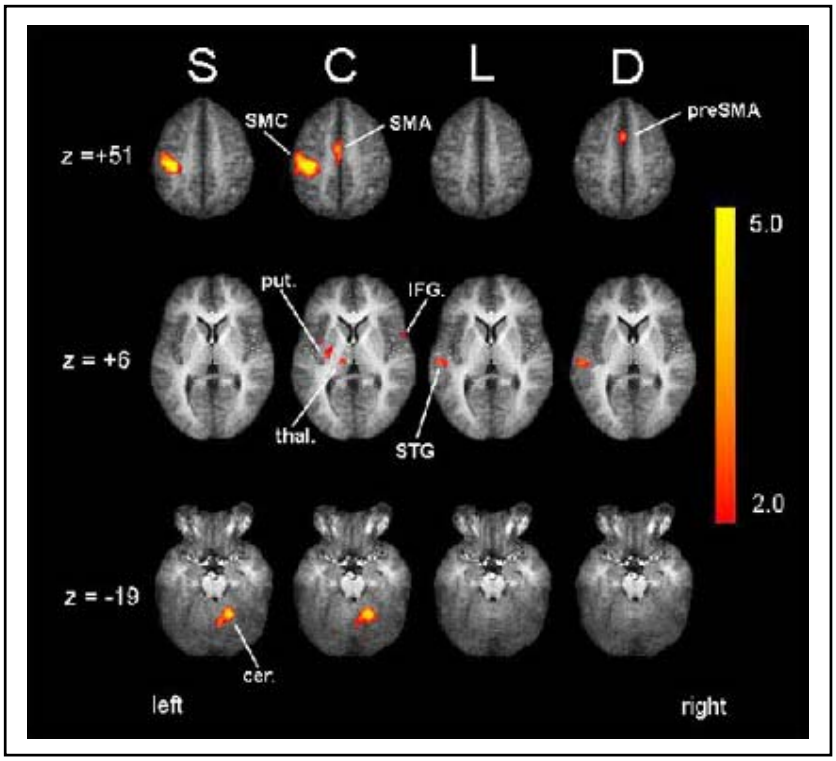

Figure 6. Areas demonstrating significantly increased MR signal intensity from t-tests comparing each of the four experimental conditions (S, synchronization; C, continuation; L, listening; D, discrimination) with rest. Data are from the 300 msec interval condition /83/. Functional activity (shown in color) is overlaid into averaged axial anatomic scans (right side of brain is on reader's *right*). *SMC*, Sensorimotor cortex; *STG*, superior temporal gyrus; *SMA*, supplementary motor area; *IFG*, inferior frontal gyrus; *put.*, Putamen; *thal.*, thalamus; *cer.*, cerebellum, *z* designates the number of millimeters above (+) or below (-) the anterior-posterior commissure line.

was assessed when the tones were discontinued (C) because performance depends entirely on an internal representation of the interval. Although the S condition also involves timing, performance depends largely on the perception of the synchronization error and afferent delays from stimulus events /43,54/. We predicted that the neural systems specific to timing should show greater activation in the C than in the S condition. Passive listening (L) and pitch discrimination (D) conditions were included to control for the auditory sensory processing in the S condition. Tones in the L and D conditions were presented at the same intervals as in the S condition. The analyses of the functional imaging data subtracted each of the conditions from a rest (R) condition, to minimize the more serious problems of the subtractive logic.

The behavioral findings showed that tapping accuracy was close to the criterion intervals and intertap variability increased with the interval being timed, demonstrating a pattern of performance characteristic of timekeeping processes. The variability in produced intervals was also greater when subjects had to time events without the benefit of a pacing signal (C). Table 2 summarizes the functional imaging results and Figure 6 displays the activation sites for the 300 ms condition, which showed the same activation pattern as the 600 ms condition. Only the C condition activated the caudal SMA, the left caudal putamen, and the left ventrolateral thalamus. This implicated a basal-ganglia medial-premotor pathway /2/ in

explicit timing, consistent with the motor-timing deficits in patients with PD and SMA lesions /28,29,67,70/, and recordings of cortical DC potentials in healthy individuals linking the SMA to precise timing /44/. Table 2 shows that comparable results have also been found during synchronized tapping with an auditory stimulus (FIX – BASE; NOV –REP), although only basal-ganglia, but not SMA activation was found during synchronized tapping with a visual cue /73/. Synchronized tapping clearly involves a timing component, but other processes like the perception of feedback and error correction processes might predominate /54/ and sometimes overshadow the timekeeping component, such that robust activation of the medial premotor pathway is not always found.

In our study, judgments of pitch (D) correlated with activation in the rostral portion of the SMA, consistent with our assumption that a nontemporal discrimination would activate different systems. There is speculation that different behavioral processes correlate with rostral and caudal SMA activation. While intracortical stimulation of caudal SMA elicits specific movements, stimulation of rostral SMA does not and is thought to be involved in more complex tasks (e.g., go-no paradigms) requiring response discriminations rather than simple movements /75/.

The C condition also uniquely activated the right inferior-frontal (Broca's area) (not shown in Figure 6) superior-temporal pathway. We hypothesized that this system might be involved in an internal nonlinguistic rehearsal of intervals. Specifically, subjects may use nonlinguistic strategies to sustain a representation of the criterion interval, which aids in pacing off time in the absence of external stimulation /100/. This speculation is in agreement with the proposal that the inferior-frontal superior-temporal pathway supports an articulatory loop of working memory, which includes a subvocal rehearsal system /72/. Most PET studies, with the exception of one /73/, have not shown activation of this system, which suggests that the alleged subvocal rehearsal processing is not essential for timing, but rather serves a strategic function, perhaps by highlighting attention to the pacing interval, which suppresses interference from the periodic background noise of the MRI scanner.

Activation of the left motor cortex and the right cerebellum was found in both the S and C conditions, in the vicinity of the dorsal dentate nucleus, which projects to motor cortex /62,88/. This pathway appears to support the sensorimotor processing requirements of the task /46/, which were similar for both the S and C condition. This explanation agrees with the absence of cerebellar activation in the D condition, wherein a low response rate (below 1 Hz) typically produces MR signal intensity changes that are similar to background noise levels /82/. Importantly, neither the S or C conditions showed activation in the ventral portion of the dentate nuclei or in the DLPF cortex, the ventral dentate's main output pathway /62/, ostensibly related to working memory /25/. In fact, the ventral dentate nuclei have not been a foci of activation in several previous studies (Table 2) /38,47,51,73/. However, similar to our findings, activation of the ipsilateral dorsal dentate and left sensorimotor cortex was found during paced tapping (right hand) with an auditory stimulus (FIX-BASE) /73/. These findings suggest that motor-timing impairments in patients with cerebellar damage /35,36/ may be secondary to deficits in sensorimotor processing /6/.

It was notable that we did not find activation of a frontal-parietal network in any of our experimental conditions, which contrasts with some functional imaging studies of motor and perceptual timing (Table 2) /45,47,51,84/ and the time-perception deficits in patients with focal right-hemisphere lesions /30/. We speculate that other functional imaging studies may have placed greater demands on attention and working memory than in our study. Specifically, both processes may contribute more to performance when produced intervals are long /47/, standard intervals are sustained over trials for several seconds or more /51/, time discriminations are more difficult /30,51/, or timing involves rhythms /84/.

The above studies show that multiple neural systems support temporal processing, consistent with SET. However, isolating systems associated with explicit timing from those involved in nontemporal processes is often circuitous in functional imaging studies, complicated by the limiting factors described earlier. It is largely through converging data from focal lesion and pharmacological studies of timing, neuropsychological and neuroimaging studies of nontemporal processes, and anatomical descriptions of neural pathways in the monkey that a reasonably coherent interpretation of the neuroimaging findings begins to emerge. Still, many of the explanations remain speculative and require further investigation.

CONCLUSIONS

In summary, several different avenues of research are beginning to converge and elucidate the neural underpinnings of temporal processing. There is mounting evidence for the proposal that timekeeping operations are supported by the basal ganglia, from converging findings in lesion /4,29,32,49,58,67,70,71/, pharmacological /52,53,55,57,81/, and functional imaging studies /38,45,47,73,83/. It also appears that the basal ganglia control timing for a wide range of short (milliseconds) and long (seconds) intervals, contrary to some proposals /33/. While there is some support for a role of the cerebellum in timing /10,36,50/, the findings have been weakened by the finding of deficits in nontemporal discrimination processes in patients with focal cerebellar lesions, and the failure to associate timekeeping processes to regions with major output pathways to the cerebral cortex (i.e., ventral dentate nuclei) instead of the spinal cord (i.e., vermis) /10,50/. Likewise, neuroimaging studies have not convincingly dissociated activation of the cerebellar hemispheres and vermis from temporal and nontemporal processing /38,47,51,73/, and activation of the ventral dentate nucleus has not been reported in any timing conditions. We speculated that the cerebellum plays a role in sensorimotor aspects of timing /83/, but clearly it is involved in non-motoric functions as well /7,22/. A current challenge is to figure out why cerebellar activation in healthy individuals or timing deficits after cerebellar damage are associated with many different regions of the cerebellum, depending on the study.

There appears to be consensus from lesion and pharmacological studies that the frontal cortex is important for temporal processing /10,30,50,56,60,66,68,69/, perhaps because of its purported role in attention and working memory. The specific role it plays needs clarification, as different regions likely sustain different processes. Insight into this problem might be advanced by considering the reciprocal pathways between the frontal cortex and the parietal and temporal cortices /74,86/, which are also implicated in temporal processing. Damage to the right middle-frontal or inferior parietal cortex produces time-perception deficits, which correlate with the severity of attention deficits /30/. This pattern of findings is consistent with the working memory function of the middle-frontal gyrus /25/ and the attention functions of the inferior-parietal lobe /31,78/. On the other hand, the right inferior-frontal superior-temporal pathway /83/ may assist in the retrieval and the nonlinguistic rehearsal of auditory information when reproducing a temporal pattern without the aid of external stimulus support. This is compatible with activation of this system during silent rehearsal of letter strings /72/ and the role of auditory cortex in auditory imagery /100/ Although these speculations require further investigation, it appears that distinct frontal-parietal and frontal-temporal pathways mediate nontemporal operations involved in timing in different ways, depending on the temporal processing demands of an event.

It is also notable that when frontal-parietal or frontal-temporal networks support timing, there is a right-hemispheric bias in both lesion /30/ and in functional imaging studies /47,51,83,84/. This is consistent with the right-hemispheric bias for sensory processing of nonlinguistic consonant-vowel-consonant

syllables when formant transitions were in the hundredths of milliseconds (i.e., 200 ms), but a left-hemisphere bias when transitions were in the tenths of milliseconds (i.e., 40 ms) /5/. The more rapid formant transitions are commonly found in language, which may partially explain the left-hemisphere bias for language processes. Here, it is worth mentioning that a recent functional imaging study reported a left-parietal hemispheric bias for attention to time /15/, which contrasts with most of the functional imaging studies of timing (Table 2). In this study, a visual stimulus cued the location (left/right) or time (300 or 1500 ms) after which a target would appear and a right finger response was made when the target was detected. It is unclear whether explicit timing was required in this task. Rather, the results could be more reflective of a left-hemispheric bias for response anticipation and selection /26/, which is consistent with the bias for contralateral (left) parietal activation in this study and the left inferior-parietal bias for attending to time-related information such as speed /14/.

The above studies illustrate the complexity of temporal processing and the many different ways in which neural systems might come to mediate different aspects of timing. Differentiating the reasons for impaired timing in focal-lesion patients will no doubt require the development of more sophisticated studies that isolate the clock from other nontemporal processes. This line of research should lead to a better understanding of the processes reflected by different patterns of accuracy and variability, hopefully across a range of experimental paradigms. Functional imaging research will facilitate this endeavor given its potential power in unmasking the contributions of different neural systems underlying a behavior.

ACKNOWLEDGEMENTS

Special thanks to Gabrielle Mallory for her technical support in all aspects of the research and Stephen Rao for his thoughtful comments. This work was supported by a grant from the Medical Merit Review, Department of Veterans Affairs and a NIMH Program Project Grant (2 P01 MH51358). Reprint address: Deborah L. Harrington, Ph.D., Psychology Service 116B, Veterans Affairs Medical Center, 1501 San Pedro SE, Albuquerque, NM 87108, USA; Tel: 505-265-1711, ext. 2389; Fax: 505-256-2877; E-mail: dharring@unm.edu

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