

# Neuropharmacology of timing and time perception

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## Abstract

Time is a guiding force in the behavior of all organisms. For both a rat in an experimental setting (e.g. Skinner box) trying to predict when reinforcement will be delivered and a human in a restaurant waiting for his dinner to be served an accurate perception of time is an important determinant of behavior. Recent research has used a combination of pharmacological and behavioral manipulations to gain a fuller understanding of how temporal information is processed. A psychological model of duration discrimination that differentiates the speed of an internal clock used for the registration of current sensory input from the speed of the memory-storage process used for the representation of the durations of prior stimulus events has proven useful in integrating these findings. Current pharmacological research suggests that different stages of temporal processing may involve separate brain regions and be modified by different neurotransmitter systems. For example, the internal clock used to time durations in the seconds-to-minutes range appears linked to dopamine (DA) function in the basal ganglia, while temporal memory and attentional mechanisms appear linked to acetylcholine (ACh) function in the frontal cortex. These two systems are connected by frontal-striatal loops, thus allowing for the completion of the timing sequences involved in duration discrimination.

*Keywords:* Internal clock; Attention; Temporal memory; Acetylcholine; Dopamine; Glutamate; Basal ganglia; Frontal-striatal loop

## 1. Introduction

Despite the fact that we are usually not aware of it, our perception of time is a guiding force in our behavior. Imagine you are driving your car and come to a red light. You seem to be waiting a long time for the light to change to green. How do you know when you can assume that the light is broken and you should drive through it? Two things are necessary for you to make this decision. (1) You need to have some timing mechanism like an internal clock to register the signal duration that has passed. (2) You need some criteria in memory against which this sensory input can be compared. You can only know that you have been waiting too long at the red light if you have previous experiences of red light durations stored in your memory. A student driver may not be able to tell when too much time has passed because s/he has not built up a temporal criterion for red light duration in her/his memory. This example illustrates how both the perception of the current signal duration and the memory of past durations are both essential for duration discrimination. How these different cognitive mechanisms can be studied from

the perspective of neuropsychopharmacology is the focus of this review.

As an initial attempt to understand the operating characteristics of the behavioral and neural mechanisms involved in timing and time perception, previous investigations have studied the effects of systemically administered drugs on the temporal control of behaviors for which the mechanisms of action could not be easily identified. Consequently, these studies were limited in terms of both the pharmacological and the psychological selectivity of the assays employed. The development of sophisticated behavioral paradigms, data analysis techniques, and accompanying theoretical models which provide independent measures for the various aspects of behavioral change that can be produced by drugs have greatly aided our interpretive abilities [15,65,71,76]. Likewise, improvements in the selectivity of the pharmacological tools that we employ, as well as the drug delivery techniques and advances in our understanding of the underlying neuroanatomy have contributed to the identification of brain-behavior relations that have previously been used mainly as heuristics to explain orderly and systematic changes in behavior. One of these heuristics that is rapidly becoming a physiological reality, due in part to neuropharmacological studies described below, is the internal clock used to measure the

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durations, rates of occurrence, and temporal order of events in the seconds-to-minutes range.

**2. Interval timing**

Interval or hour-glass timing in the seconds-to-minutes range can be distinguished from oscillatory or circadian timing in at least three ways. (1) Interval timing displays a greater degree of flexibility in terms of its range and operating characteristics compared to oscillatory timing. For example, an interval timer can be reset immediately upon command and does not display the harmonic properties typical of an oscillatory mechanism. (2) Flexibility in the initiation of the interval-timing process is bought at the cost of precision, i.e., interval-timing mechanisms are extremely flexible but relatively inaccurate compared to oscillatory-timing mechanisms. (3) Interval timing displays the scalar property, i.e., the standard deviation (S.D.) grows in a manner proportional to the mean of the interval being timed. Circadian timing does not display this scalar property; it is far more accurate and variance increases very little with the mean of the interval [14,28,107,112]. Many researchers study interval-timing behavior within the contexts of cognition, chronobiology, optimal foraging, psychophysics, and traditional learning theory [95]. Currently, there are a growing number of laboratories engaged in the analysis of the neuropsychological basis of interval timing and temporal memory. Studies of this type are crucial for determining the foundations upon which the

behaviors in question rest, especially given the observation that distortions in the perception of time accompany a number of different neurological disorders and pharmacological manipulations in animals and humans[16,23,34,60, 61,65,90,101,120,128].

*2.1. Scalar timing theory*

Scalar timing theory is a mathematical model that describes the formal properties of the cognitive processes that operate when an individual solves a variety of duration discriminations [28-30]. It has provided us with both the conceptual framework and the experimental procedures to develop quantitative models of duration discriminations, which are necessary to investigate the neural and pharmacological mechanisms involved in temporal processing. In an information-processing version of this model, a *pacemaker or oscillatory process* emits pulses that are gaited by a switch into an *accumulator* that integrates pulses in a linear fashion over time. The value in the accumulator is compared to a sample of the expected time of some relevant event which is taken from a distributed reference memory system. If these values are close enough according to a specific decision rule applied by a *comparator*, a response is made. If the response is correct, the value in the accumulator is transferred to memory. In this model, *reference memory* is used to store information about the expected time of an event, gained from experience with many trials. Sometimes a trial in progress will be temporarily interrupted and a retention interval imposed

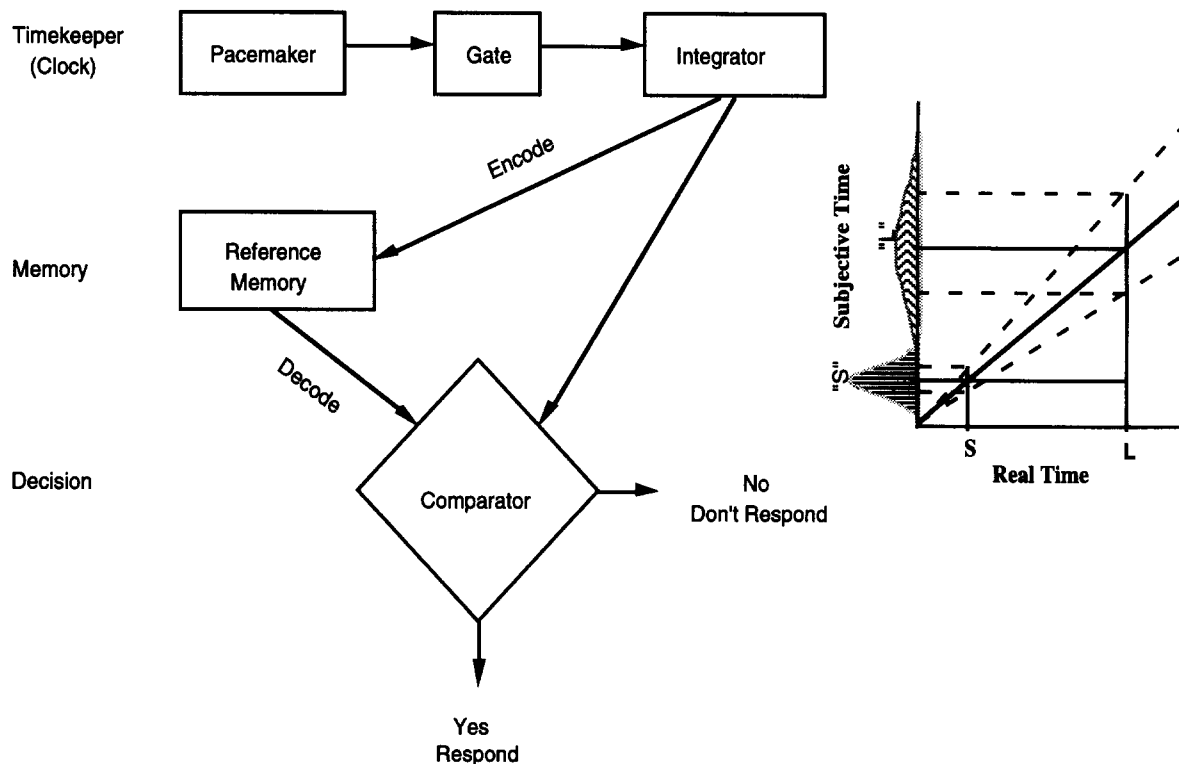


Fig. 1. An information-processing model of temporal processing representative of scalar timing theory.

such that the subject is required to combine the duration of the signal prior to the gap in the signal with the duration of the signal following the gap in order to determine the appropriate response. Under these conditions, the initial time value can not be maintained in the accumulator and these partial accumulations must be stored in a trial-specific or *working memory* buffer. *Divided attention* is required when two or more events require simultaneous temporal processing and can be distinguished from the working memory processes described above [60,68,78].

The central features of an information-processing model of the interval-timing process are shown in Fig. 1. As indicated above, a pacemaker or internal oscillator provides a stream of pulses (Poisson-generated) which, when a timing signal begins, are gated to an integrator appropriate to that signal (left panel). When the target duration is cued, the value in the integrator is transferred via an encoding system to reference memory for later retrieval and use in comparing remembered and current times. On subsequent probe trials the current integrator value is compared during its processing with a value retrieved from memory for the target. Responding occurs when the two are 'close enough' according to a decision rule appropriate to the task. In the peak-interval (PI) timing procedures described below the decision rule uses a threshold on a relative discrepancy. The criterion compares the percentage difference between the remembered time and the current time. In probe trials the signal stays on considerably longer than the target time, and responding begins when the percentage discrepancy drops below a threshold, and continues until the percentage discrepancy exceeds a threshold on the far side of the target. The storage and retrieval processes have been described in detail elsewhere [31,32], but for now we may conceive of them as roughly linear in the integrator value associated with the target time. An immediate result of this kind of processing is that variation in the rate of the pacemaker, or in the memory-storage/retrieval rate, produces a particular kind of variability in the output. This is shown schematically in the right panel of Fig. 1 with subjective time on the ordinate and real time on the abscissa. The heavy line diagonal represents the mean integration speed and the light lines represent  $\pm 1$  S.D. around this value. It is clear from the figure that subjective time variance increases rapidly, in fact proportionate to the square of the mean value being timed. This is called the 'scalar property' a strong form of Weber's Law, and is a hallmark of normative temporal processing [28,29]. It is this property that induces superposition of PI timing functions scaled in relative time.

According to scalar timing theory, variations in performance are caused by variations in clock, memory, threshold, and comparison processes. Attempts have been made to distinguish among these sources of variance by examination of the form of the mean response functions following various pharmacological manipulations. By making specific assumptions about distribution forms and sources

of variability scalar timing theory has been able to account for an extremely high percentage of the variability in performance of duration discriminations [33]. The model has also been extended to account for the behavioral patterns that are produced by changes in the speed of the internal clock used to measure event durations and changes in the speed of the memory processes used to encode these measured durations [65]. There have also been applications to situations where attentional bias toward different stimulus modalities occurs and the modulation of these attentional effects by pharmacological interventions [66,71,97].

### 3. Pharmacological isolation of an internal clock

One of the major findings concerning time perception in the seconds-to-minutes range is the ability to decrease clock-speed with neuroleptic drugs such as haloperidol and to increase clock-speed with stimulant drugs such as methamphetamine [63]. Systematic changes in the subjective experience of event duration following the administration of these drugs has been considered evidence that dopamine-releasing neurons are involved in temporal integration for time estimation. However, the conclusions that could be drawn from this evidence were limited by the identification of at least three distinct dopamine receptor subtypes; D1 (adenylate cyclase-linked), D2 (non-adenylate cyclase-linked), and D3 (presynaptic). In addition, neuroleptics and amphetamines interact with other neural receptor sites such as alpha noradrenergic (NE- $\alpha$ ) and serotonergic sites (S1 and S2). Consequently, it has been important to show that the dose of a neuroleptic drug required to produce a temporary rightward horizontal shift of 15–20% in psychophysical functions that relate responding to signal duration is correlated with its binding affinity to a particular dopamine receptor subtype. When such a comparison was made for five neuroleptics (chlorpromazine, haloperidol, pimozide, promazine, and spiperidol) it was discovered that affinity for the dopamine D2 receptor predicted neuroleptic potency in producing the criterion shifts of the timing functions that are associated with a decrease in clock-speed, whereas affinity for other aminergic receptors (D1, D3, the  $\alpha$ -noradrenergic receptor, S1, and S2) did not [67]. The conclusion is that dopamine D2 receptors play a major role in determining the rate of temporal integration for time perception.

Historically, the synapses essential for the behavioral effects mediated by the neurotransmitter dopamine (DA) have been thought to be located exclusively in telencephalic structures, primarily the caudate-putamen (CPu) and the nucleus accumbens (NAS). These regions receive dense dopaminergic innervation from mesencephalic A9 and A10 neurons [115], and pharmacologically distinct DA receptor subtypes, termed D1 and D2, are found there in abundance [18,45]. In rats, discrete stimulation or blockade of telencephalic DA receptors by intracerebral administra-

tion of DA agonists or antagonists mimics the effects of these agents when given peripherally. For example, apomorphine induces stereotyped motor behavior whether it is injected systemically or placed directly into the CPu [116] and rats will self-administer amphetamine either systemically or directly into the NAS [41].

Recent evidence suggests that mesencephalic DA receptors may also play an important behavioral role. The substantia nigra pars reticulata (SNr) is now known to be richly endowed with DA receptors, predominantly of the D1 type [18]. Moreover, the dopaminergic neurons of the substantia nigra pars compacta (SNc) innervate the SNr via their ventrally extending dendrites which are capable of releasing DA into this structure [12]. Because the SNr is a major output nucleus of the basal ganglia, dendritically released DA may interact with D1 receptors there to exert an important influence on striatal outflow. It has recently been demonstrated that D1 and D2 receptors play different but interactive roles in normal dopaminergic transmission. D1 receptor stimulation is required for the expression of D2 receptor mediated phenomena [118,123]. Thus, nigral D1 receptors may play an important role in all DA-mediated behavior in neurologically intact animals [54,98,99].

The large-scale inactivation of central nervous system DA function with DA-receptor antagonists and midbrain neurotoxin lesions results in a behavioral syndrome not unlike severe Parkinson's disease in man. Rats show akinesia, catalepsy, and are impaired in performance for a variety of behavioral situations that may involve the timing of stimulus events [43,53]. More specific impairments of DA systems induced by microinjection of DA-receptor antagonists or by neurotoxin terminal lesions has shown differential effects on behavior depending on the locus of the DA system and the type of behavior studied. For example: depletion of DA in the CPu, but not in the NAS, impairs reaction-time performance in a simple reaction-time task [1], impairs a conditional discrimination of temporal frequency [100], and impairs simple stimulus–response (S–R) associations in a variety of tasks, including the conditioned emotional response paradigm [124,126]. In contrast, neurotoxin-induced lesions of DA neurons in the NAS, but not the CPu, attenuate amphetamine self-administration and the enhanced responding to reward-related stimuli produced by intra-accumbens amphetamine injections [59,111] as well as the motor stimulation induced by this drug [46,48]. Furthermore, the differential behavioral effects of amphetamine microinjections into striatal subregions have been extensively mapped, suggesting that the NAS, but not the CPu, is the primary site underlying the registration of reward [46].

One hypothesis to explain this overall pattern of results is that the ventral striatum (subsuming the NAS) is implicated in the processes of incentive motivation and the determination of the rewarding (approach-eliciting) properties of a stimulus; both contribute to associative measures of response strength [100,125]. In contrast, the dorsal

striatum (subsuming the CPu) is implicated in processes of sensorimotor integration, as exemplified by simple S–R associations that are necessary for planning, initiating, and coordinating a conditioned movement (real or imaginary) to a sensory cue [1,35,100,124].

### *3.1. Dopaminergic–glutamatergic interactions in determining clock-speed*

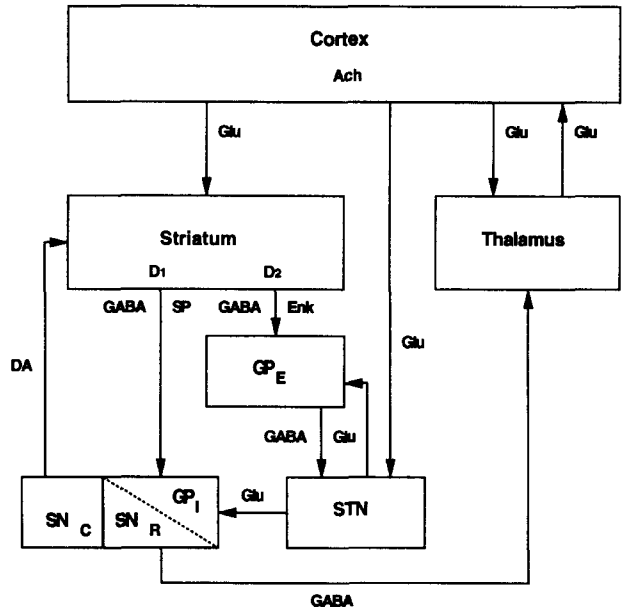
In the past few years there has been a growing interest in the interactions between DA and glutamate in the striatum [51,56,57,96]. It has been hypothesized that dopaminergic nigrostriatal fibers mediate a presynaptic inhibitory influence on striatal glutamate release via D2 receptors located on the terminals of corticostriatal neurons. This is one of the reasons why interval-timing data showing that lesions of the frontal cortex or its inputs from the nucleus basalis completely block the changes in the rate of temporal integration that are typically obtained with dopaminergic drugs are crucial to determining the extent of dopaminergic–glutamatergic interactions [74]. These data are suggestive of a deafferentiation of corticostriatal neurons containing D2 receptors following ibotenic acid lesions of the NBM or aspiration lesions of the FC that leads to a deregulation of clock-speed. It has also been suggested that the therapeutic effect of traditional neuroleptics might be brought about by strengthening glutamatergic transmission within the striatum. However, dopaminergic nigrostriatal neurons do not seem to inhibit striatal glutamatergic transmission tonically under normal conditions. It follows then that if the therapeutic effect of neuroleptics in schizophrenia, which also presents timing dysfunctions [67], is achieved by increasing glutamatergic transmission, then a hyperactive DA system, leading to a secondary deficiency in glutamatergic transmission must be postulated [10,11,13,44,117].

Another way of looking at the DA–glutamate interaction within the striatum involves the notion of a corticostriato-thalamocortical negative feedback loop, serving to protect the cortex from the overload of information and hyperarousal: excitatory (glutamatergic) neurons projecting from the cortex to the striatum, inhibitory (GABAergic) neurons projecting from the striatal complex (possibly via subthalamic nucleus) to the thalamus, and excitatory (glutamatergic/aspartergic) neurons projecting from the thalamus to the cortex provide the anatomical substratum for a negative feedback loop. The thalamus might be looked upon as a filter for sensory inputs, and activation of the corticostriato-thalamic loop would serve to close this filter. Conversely, activation of another neuronal system, namely the mesostriatal dopaminergic pathway, would yield opposite effects, i.e., a widening of the filter, and hence increase the flow of information to the cortex. Via collaterals from striathalamic GABAergic neurons, these two neuronal systems may, in an analogous manner, control the impulse flow from the mesencephalic reticular

formation to the cortex and hence control the degree of behavioral arousal and rate of temporal integration [113,114]. An advantage to this hypothesis from a morphological point of view is that it does not require the assumption that dopaminergic and glutamatergic terminals make direct synaptic contact in the striatum. It is, therefore, in line with morphological data indicating: (1) that axo-axonic synapses are rare or non-existent in the striatum [38], and (2) that corticostriatal/thalamostriatal glutamatergic and nigrostriatal dopaminergic neurons make synaptic contact with a common third neuron, i.e., with the dendritic spines pertaining to a GABAergic projection neuron [26]. Thus, the corticostriatal glutamatergic and nigrostriatal dopaminergic systems may operate independently of one another on the local level, sharing a common target neuron or final endpoint, influencing the state of the thalamic 'filter' in opposite directions. The observation that systemically administered dexamphetamine causes excitation of a population of striatal neurons in intact (awake, freely moving) rats [119], but inhibition in animals subjected to cortical ablation, also fits with the notion of a corticostriato-thalamocortical negative feedback loop. The recent findings that D2 receptors in the striatum play a major role in determining the rate of temporal integration for time estimation [67] and that the selective non-competitive NMDA receptor antagonist MK 801 increases response rate and shifts psychophysical timing functions leftward in a manner indicative of increased clock-speed [122] suggests a possible role for dopamine-glutamate interactions in the control of temporal integration in the basal ganglia.

**4. Interval-timing functions of the basal ganglia**

An overview of the neuropharmacological connections of the basal ganglia is provided in Fig. 2 and a mapping of the timekeeping, gating, and integrating functions of an information-processing model for interval timing onto this neuroanatomy in provided in Fig. 3. The predominant input to the basal ganglia is the excitatory input from the cerebral cortex (and from the thalamus) to the striatum. Striatal neurons are generally quiescent and activity is generated by this excitatory input [50]. These neurons, which utilize GABA as a transmitter give rise to two major output pathways. One pathway, the so-called direct striatonigral output pathway, provides inputs to the entopeduncular nucleus (internal segment of the globus pallidus in primates) and the substantia nigra. These two nuclei are considered part of one extended nucleus and the term striatonigral refers to the pathway providing inputs to both nuclei. The second striatal output pathway provides an indirect pathway between the striatum and the substantia nigra. Striatal neurons contributing to this pathway provide inputs to the globus pallidus. Neurons in the globus pallidus, which are primarily GABAergic, provide inhibitory inputs to the SN and to the STN. The STN provides



Schematic diagram of neuronal connections among the cortex, basal ganglia, and thalamus. Acetylcholine (Ach); dopamine (DA); D1 dopamine receptor (D1); D2 dopamine receptor (D2); enkephalin (Enk);  $\gamma$ -aminobutyrate (GABA); L-glutamate (Glu); substance P (SP); subthalamic nucleus (STN); external pallidum segment - globus pallidus (GPE); internal pallidum segment - entopeduncular nucleus (GPI); substantia nigra pars compacta (SNc); substantia nigra pars reticulata (SNr).

Fig. 2. Schematic diagram of neuronal connections among the cortex, basal ganglia and thalamus. Acetylcholine (Ach); dopamine (DA); D1 dopamine receptor (D1); D2 dopamine receptor (D2); enkephalin (Enk);  $\gamma$ -aminobutyrate (GABA); L-glutamate (Glu); substance P (SP); subthalamic nucleus (STN); external pallidum segment, globus pallidus (GPE); internal pallidum segment, entopeduncular nucleus (GPI); substantia nigra pars compacta (SNc); and substantia nigra pars reticulata (SNr).

excitatory input to the SN. Thus, these two striatal output pathways work antagonistically to modulate neurons in the SN. The indirect pathway, through connections with the globus pallidus and STN, moderates the excitatory inputs to the SN. Inhibitory inputs to the SN are regulated by the striatonigral pathway [21,49].

While striatopallidal and striatonigral neurons share some common morphologic and neurochemical character-

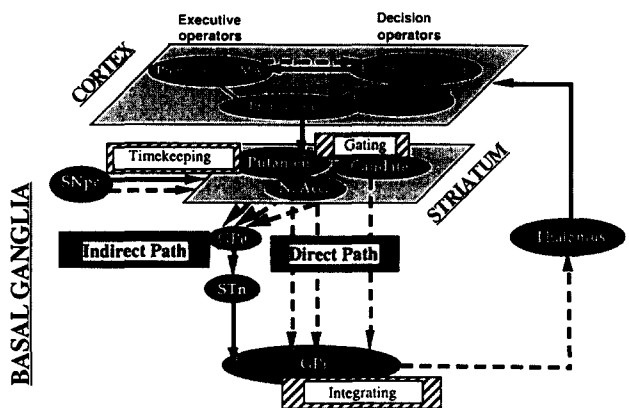


Fig. 3. A proposal for mapping an information-processing model of interval timing onto associated frontal-striatal pathways.

istics, they can be distinguished not only on the basis of their projections but also by their expression of different neuropeptides and dopamine receptor subtypes. As determined with *in situ* hybridization histochemistry, the majority of striatopallidal neurons express the peptide enkephalin and the D2 dopamine receptor [27], whereas the majority of striatonigral neurons express both substance P and dynorphin and the D1 dopamine receptor [27]. Dopamine-depleting lesions and pharmacologic treatments produce specific changes in the levels of peptide mRNAs expressed by striatal output neurons, which provide one assay of the dopaminergic regulation of these neurons. The consequences of dopamine's actions through D1 and D2 dopamine receptors on the circuitry of the basal ganglia, determined by data on gene regulation [27], together with studies of 2-deoxyglucose utilization [22], suggest that dopamine differentially affects striatonigral and striatopallidal output pathways in opposite ways. Following dopamine depletion in the striatum, increased activity of the striatopallidal system results in an increase in the tonic firing of nigral GABA neurons and other types of compensatory responses that may have an important impact on timing behavior [129]. In the dopamine-depleted striatum, D1 selective agonists specifically elevate the activity of striatonigral neurons, whereas D2 selective agonists reverse the lesion-induced increase in striatopallidal neurons. Thus, it appears that the direct action of dopamine through D1 and D2 receptors is to modulate striatonigral and striatopallidal neurons in opposite ways [49,98].

In a recent series of experiments we investigated the effects of lesions to the SN or the CPu (dorsal striatum) or NAS (ventral striatum) upon performance of a PI timing task [75]. Rats that sustained electrolytic lesions of SN or CPu could not express an interval discrimination. Treatment with L-DOPA restored the function in SN lesioned, but not CPu-lesioned rats in a manner similar to previous reports of reversal by L-DOPA of impaired learning due to destruction of the dopaminergic nigrostriatal projections [130]. In the second experiment, neurotoxic depletions of DA were made within the ventral or dorsal striatum and the ability of the rats to discriminate between a shorter (20-s) or longer (60-s) interval was tested. The latter lesion prevented the expression of a peak discrimination, but rats did show higher rates of responding to the stimulus paired with a 20-s interval rather than a 60-s interval. Ventral striatum lesions did not prevent the relatively higher maximal response rate to the stimulus signaling the shorter interval. These data indicate that the mesolimbic-mesocortical and nigrostriatal dopaminergic systems are both involved in duration discrimination and timing, but in complementary ways. Rats with SN lesions possess severe impairments in their ability to generate the pulses (timekeeping) required to quantify the temporal dimension of stimulus events and rats with CPu lesions possess severe impairments in their ability to accumulate (gating) those pulses. Furthermore, the inability to modify

duration discrimination in rats with NAS lesions, suggests that although this region may be involved in discriminating the relative reward value of a signal, it is not critical for basic aspects of temporal integration in duration discrimination.

## 5. Interval-timing functions of frontal and temporal systems

Previous work has shown that both the frontal and temporal systems in the brain are involved in the reference memory of the duration of an event, but in complementary ways. A double dissociation resulted from lesions of the FC and the nucleus basalis magnocellularis (NBM), on the one hand, and the HIP, fimbria-fornix (FFx), and the medial septal area (MSA), on the other. Lesions in the frontal system (NBM, FC) produced a rightward shift (overestimation) of the expected time of reinforcement, while lesions in the hippocampal system (MSA, FFx) produced a leftward shift (underestimation). Another dissociation was found in the effects of these lesions on working memory for the duration of a stimulus prior to a gap or retention interval interpolated during that stimulus. Here, lesions of the hippocampal system produced a complete amnesia for the memory of the duration of the event prior to the gap, while lesions in the frontal system had no effect [81,84,93]. Lesions of the hippocampal system also produced a total inability of animals to regulate the temporal criterion used on a trial-by-trial basis, whereas, lesions in the frontal system did not disrupt temporal regulation which requires an intact working memory [70,84].

### 5.1. Choline acetyltransferase (ChAT) inhibition and temporal memory

Recently, we have investigated the effects of a potent inhibitor of choline acetyltransferase (ChAT), BW813U, on timing behavior in mature (10 months) and aged (30 months) rats [83]. Rats were trained on a discrete trial 20-s peak-interval (PI) procedure. During baseline (non-drug) training the time of the maximum response rate (peak time) for mature rats was approximately at the time of scheduled reinforcement (20 s), but peak time for aged rats was reliably later than the time of scheduled reinforcement (25 s). A single administration of BW813U (50 mg/kg, *i.p.*) produced a rapid, long-lasting reduction in ChAT activity of about 70% in both the HIP and the FC. In addition, BW813U administration resulted in an approximately 20% increase in the remembered times of reinforcement as indexed by peak times for both mature and aged rats. This change in temporal memory occurred gradually and was long-lasting. These horizontal shifts in peak time indicate a change in the content of reference memory for the remembered time of reinforcement that is similar for aging processes and BW813U administration. When a 5-s

gap was interpolated in the signal, control rats of both ages summed the signal durations before and after the gap, whereas rats given BW813U showed no retention of the signal duration prior to the gap. This loss of trial-specific temporal information indicates a drug induced working memory dysfunction. Taken together, these results demonstrate that both working and reference memory for temporal information is sensitive to ChAT inhibition. These results suggest that BW813U may be a valuable tool for the study of the relationship between ChAT levels and memory processes because it can be microinjected into specific brain regions in order to produce 'reversible' lesions. A similar pattern in peak time has recently been reported following the repeated administration of pyrithiamine, a major antimetabolite of thiamine that can lead to a relatively specific inhibition of acetylcholine synthesis by limiting pyruvate dehydrogenase activity [36,76].

### 5.2. Aging, choline uptake, and temporal memory

The integrity of the choline (Ch) nervous system decreases with age [3,6]. On the basis of the lesion and drug data that has been reported in which the remembered time of reinforcement was inversely related to Ch activity, one would expect the remembered time of reinforcement to increase with age. In a study in which rats were trained on a temporal discrimination task from 10 months to 30 months of age, an age-related increase in the remembered time of reinforcement was demonstrated [82]. In addition to the control rats in this aging study, there was a group of rats that received injections of arginine vasopressin (AVP; 0.08 PU/kg, i.p.) 20 min before 30 training sessions when they were 10–13 months old. AVP administration prevented the age-related increase in the remembered time of reinforcement observed in the control group that had received saline injections. Biochemical analysis revealed that in the FC and HIP, there was an age-related decrease in muscarinic receptor density as measured by [<sup>3</sup>H]quinuclidinyl benzilate (QNB) binding, an increase in sodium-dependent high affinity choline uptake (SDHACU), and a modest, but reliable increase in ChAT. AVP administration reduced the age-related increase in SDHACU, but it did not affect the age-related decrease in QNB. SDHACU in the FC was significantly correlated with the subjective discrepancy in the remembered time of reinforcement as indicated by the peak time measures. These results suggest that certain endogenous peptides exert long-term effects on brain structure and function that are related to temporal memory processes. These effects may be related to the finding that long-term treatment of rats with a neural stimulant, pentylentetrazole, or with a potent and active analog of the ACTH [4–9] molecule (ORG 2766), can retard the development of both some neuromorphologic and some behavioral correlates of brain aging in rats [55]. Of particular importance to the work described here is the observation of a reliable relation between aging processes,

SDHACU, and the content of temporal memory such that SDHACU in the FC, but not in the HIP, is correlated with the *magnitude* but not the *direction* of the discrepancy in the content of temporal memory [73].

### 5.3. Simultaneous temporal processing

Simultaneous temporal processing (STP), a variation of the timing procedures described above, has some trials that require divided attention to two or more simultaneous events [68,78,94]. The FC has been strongly implicated in temporal processing, attention, and planning [24,52,58,87,89,92,127]. Consequently, we expected another, complementary dissociation so that lesions in the frontal, but not the hippocampal, system would impair attention to multiple temporal inputs. This result would confirm the importance of the frontal system in temporal discrimination, provide another important dissociation between the functional roles of the frontal and hippocampal systems, and introduce a useful procedure for the analysis of the neural mechanisms involved in attention in animals.

Our results indicated that lesions of the FC or the NBM produced a severe impairment in the ability to time two stimuli simultaneously. When the second stimulus was presented while the first was still in progress, control rats successfully timed the second stimulus and continued to time the initially presented stimulus as well. These rats gave two peak times, one at the expected time of reinforcement associated with each stimulus. In contrast, rats with lesions in the frontal system were unable to time both stimuli simultaneously. When the second stimulus was presented while the first one was in progress, these rats successfully timed only the second one. They stopped timing the first stimulus, remembered its value, and started timing the second stimulus. When they finished timing the second stimulus, they recalled the value of the first stimulus and continued to time it. For the first stimulus, however, they had a rightward shift of the peak time by an amount equal to the duration of the second, short stimulus (e.g., 10 s). These results support the hypothesis that the FC is important for tasks that require planning and temporal organization of behavior, and attention to different cognitive demands [88,108,128].

Dissociations between the effects of lesions of the frontal system and those of the hippocampal system are unusual in rats. In most cases, lesions of the MSA, FF, and HIP, or the NBM and FC, produce equivalent behavioral changes. Tasks finding no dissociations include: active avoidance, passive avoidance, spatial delayed discriminations, and swim maze [52,91]. The fact that the experimental procedures used in these timing tasks generated three striking dissociations of frontal and hippocampal function indicate that this particular testing procedure should be extremely useful in examining the functional organization of these two areas. First, in the peak trials in the PI procedure, frontal lesions produced an overestimation in

the remembered times of reinforcement (rightward shift) while hippocampal lesions produced an underestimation in the remembered times of reinforcement (leftward shift). This dissociation indicates complementary control of the values that are entered in reference memory. Second, in the gap trials in the peak interval with a gap (PI-GAP) procedure, hippocampal lesions produced an amnesia for the duration of the stimulus prior to the gap, while frontal lesions did not. This dissociation demonstrates that the hippocampal system, but not the frontal system, is involved in working memory. Third, in the simultaneous temporal processing (STP) procedure, frontal lesions produced an impairment in the ability to continue timing an ongoing stimulus when a second one was presented, while hippocampal lesions did not. This dissociation demonstrates that the frontal system, but not the hippocampal system is involved in attentional mechanisms. To our knowledge, no other conceptual approach or set of experimental procedures with rodents has been this successful in demonstrating functional dissociations between these two neural systems.

#### 5.4. Cortical modulation of the speed of an internal clock

In a second series of experiments we examined the effects of lesions to the FC, NBM, FFX or MSA upon temporal control of behavior in rats trained on a PI timing procedure [74]. The lesions caused anticipated changes in the ability of the rats to estimate the interval used in the training sessions. The novel result compared with our earlier work was the effects of lesions upon the ability of dopaminergic or related manipulations (e.g. systemic methamphetamine or haloperidol injections) to alter the estimation of the interval in a normal manner. The results clearly demonstrated that whereas lesions to the MSA and FFX do not affect the response to pharmacological challenge, rats that have sustained lesions of the FC or the NBM do not respond to such treatments. The emphasis here is less on the cholinergic systems that were directly lesioned (as has been the focus of our earlier work), but rather on the indirect effect of the lesions insofar as they lead to deafferentation of the striatum and therefore the dopaminergic drug treatments become ineffective. Studies of this type are crucial for demonstrating the interplay among the various neurotransmitter systems involved in duration discrimination.

An increasing amount of evidence indicates that the Ch modulation of neural networks in frontal and temporal systems is important for both working and reference memory in a variety of species [4,37]. We have previously reported that temporal memory processes involved in time discrimination are selectively sensitive to the destruction of Ch rich areas of the brain such as the MSA, HIP, NBM and FC. Additional evidence has indicated that the pharmacological modification of the Ch nervous system by the administration of Ch receptor blockers (e.g. atropine and

scopolamine), anticholinesterases (e.g. physostigmine), and Ch agonists (e.g. oxotremorine) leads to selective changes in the content of temporal memory [65,72,79]. In general, a decrease in Ch function produced by the repeated administration of atropine or related compounds leads to a proportional increase in the remembered times of reinforcement (rightward shift) that are stored in reference memory as well as a total inability to retain trial-specific temporal information stored in working memory. In contrast, the effects of an increase in Ch function produced by the repeated administration of physostigmine or related compounds leads to a proportional decrease in the remembered times of reinforcement (leftward shift) that are stored in reference memory with a facilitation of working memory.

## 6. Combining psychopharmacology with the psychophysical scaling of stimulus duration

It has long been known that physiological changes can alter the perception of time. An increase in body temperature seems to speed up the internal clock as indicated by faster production of time intervals [2,40,121]. Fraisse [23] reviewed the effects of several drugs on temporal production and concluded that drugs which accelerate vital bodily functions (like amphetamine and caffeine) also lead to an acceleration of temporal production, similarly drugs which slow down bodily functions (like pentobarbital and alcohol) lead to a slowing down of temporal production. Simply knowing whether a drug leads to the perception of time as being faster or slower however, does not inform us as to the psychological processes that underlie timing and time perception. To fully understand these processes and their biological basis it is crucial to differentiate whether these 'misperceptions' of time are due to changes in a clock process, a memory process, or a response latency process unrelated to the perception of time. An information-processing model of timing and time perception designed to differentiate among clock, memory, and decision stages has recently been developed by Gibbon, Church and Meck [33] (see Fig. 1). Recent pharmacological evidence has supported the view that these stages can be separated.

### 6.1. Curve-shift paradigms

Some recent studies investigating pharmacological effects on temporally regulated behavior have examined the role of peripheral mechanisms in controlling these behaviors and/or short-term memory for temporal stimuli [5,7,8,103,109]. These types of studies are often difficult to interpret in terms of a psychological model of timing per se because the effects observed may be due to a specific effect on timing or to other non-specific factors such as motivation or general malaise. Caution must be taken when interpreting pharmacological studies because of the far reaching effects systemically administered drugs can



have on an organism. Specific effects in the system of interest must be distinguishable from non-specific performance effects caused by the drug [62,65,79]. Studies which examine simple measures like response rate can be open to several different interpretations and may not be informative about the system of interest. One paradigm which allows specific vs. non-specific drug effects to be differentiated is the ‘curve-shift’ paradigm developed by Gallistel and his associates [19,20,25] for studying the neural substrates of brain stimulation reward. Meck and his colleagues [65,69] have used the curve-shift paradigm to study the pharmacological bases of interval timing and have also shown how different patterns of results within this paradigm can differentiate clock-speed vs. memory-storage speed effects.

In the study of timing and time perception the curve being ‘shifted’ is a psychophysical function relating the duration of a stimulus to the probability of a certain response. Factors that influence temporal processing will shift the curve horizontally rather than vertically. The two main types of behavioral procedures that have been used in these studies are the peak-interval and the temporal bisection procedures [14]. In the PI procedure animals (typically pigeons or rats) are trained on a fixed interval (FI) schedule to respond (peck or bar press) for food after a specified interval (50 s in this example) as signaled by a stimulus like a light or a tone has elapsed. Responses at other times are not reinforced. On some trials (‘peak trials’) the duration of the signal is extended and no reinforcement is given. On the average of these trials the animals show a gradual rise in response rate with a maximum rate at the expected time of reinforcement, responding then drops off in a fairly symmetrical fashion after this time has passed. This procedure generates two key independent pieces of data, the peak time, which is the time at which maximum responding occurred, and the peak rate, which is the highest response rate achieved. Only the peak time, which characterizes the horizontal placement of the curve, is effected by manipulations that influence temporal processing.

In the temporal bisection procedure subjects are trained to give one response (press the left lever) after a ‘short’ duration stimulus (e.g. 2 s of white noise) has been presented and to make another response (press the right lever) after a ‘long’ duration stimulus (e.g. 8 s) has been presented. The subjects are then presented with stimuli of varying durations. The curve plots the probability of making a ‘long’ response as a function of stimulus duration. If a pharmacological manipulation speeds up the temporal processing system, the curve will shift horizontally to the left as the subject will classify shorter stimuli as being proportionally ‘longer’ than normal. Factors which simply influence motivation will shift the curve vertically, lowering or raising the asymptotic response levels, but will not shift the curve horizontally because the horizontal placement of the curve is dependent on temporal processing. In

the bisection procedure the point analogous to the peak time, which characterizes the horizontal placement of the curve, is the indifference point, the signal duration that is equally likely to be characterized as short or long.

The difficulties in interpreting data from pharmacological studies that do not employ these types of curve-shift paradigms illustrate their advantages. In one study the effect of the dopamine antagonist haloperidol on temporally regulated behavior in dogs was examined using a differential reinforcement of response duration (DRRD) paradigm [9]. In this procedure dogs had to wait on a platform for a specified duration after which a tone signal was presented. After the tone was presented the dog could leave the platform and obtain reinforcement. In the test phase tones were sometimes presented before the specified duration had passed. Dogs receiving haloperidol injections were more likely to leave the platform after one of the early signals than dogs receiving saline injections. The authors interpret their results as showing that the haloperidol disrupted temporal regulation, making it harder for the drugged animals to discriminate the appropriate duration. This led the dogs to respond after the first reinforcement signal, regardless of its temporal placement. The authors acknowledge that their results could be due to non-specific performance effects of the drug like a lessening of the frustrative effects of errors or a lessening of the ability to wait for an expected reward. They further acknowledge that without some type of psychophysical function showing changes in performance to both early and late signals and without variation in the criterial response duration a temporal regulation hypothesis of their data cannot be confirmed or discounted. A primary advantage of curve-shift paradigms is that they provide these types of psychophysical functions.

## 6.2. ‘Clock patterns’ in the pharmacological distortion of time

On the basis of pharmacological data obtained using the curve-shift paradigm two main classes of distortion in temporal discriminations have been identified: the clock pattern, linked to dopamine (DA) function in the nigrostriatal system [65,67,75], and the memory pattern, linked to acetylcholine (ACh) function in the frontal cortex [65,79,84]. The manner in which peak times obtained from rats pretrained during baseline sessions on either a 20-s or a 40-s PI procedure were affected by pharmacological manipulations (e.g., systemic injections of 1.5 mg/kg methamphetamine or 0.12 mg/kg haloperidol) that influence clock-speed is shown in Fig. 4. When a drug affects clock-speed there is an immediate horizontal displacement in the peak time of responding. The values stored in reference memory and used by the comparison/decision process were initially laid down using the clock-speed of baseline training. Under the influence of the drug during the first phase of testing the clock is now running at a

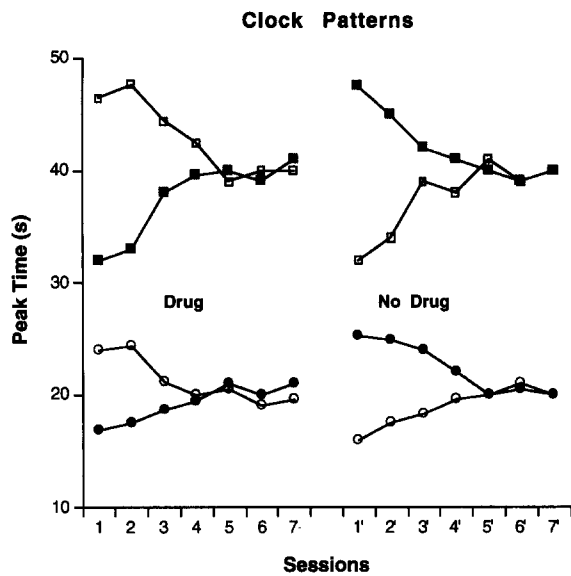


Fig. 4. Clock pattern: mean peak times from four different groups of rats ( $n = 10$ /group) initially trained on either a 40-s (squares) or 20-s (circles) PI-timing procedure and tested under the influence of dopaminergic drugs that affect clock speed (left panel) or after the removal of the drugs (right panel). The closed symbols represent rats treated with methamphetamine (1.5 mg/kg i.p.) and the open symbols represent rats treated with haloperidol (0.12 mg/kg i.p.).

different speed (faster for methamphetamine and slower for haloperidol). Therefore the criterial match of the current elapsing interval duration to the duration sampled from reference memory will occur at a different point in physical time than it had previously. If the clock stage is viewed as made up of a pacemaker system that generates pulses that are integrated over time by an accumulator than one can describe the quantification of stimulus duration in terms of the number of pulses contained in the accumulator at any particular point in time. For purposes of illustration please consider the following example, under the baseline clock-speed '100' pulses from the putative pacemaker may have equaled 20 s, this means that the comparator will set a criterion of '100' pulses for the time of maximal responding. If the clock is running faster due to the influence of a drug the '100' pulses will accumulate earlier in physical time than during baseline training and the peak response rate will occur at a time  $< 20$  s. Similarly, if the clock is now running slower the '100' pulses will accumulate later in physical time than during baseline training and the peak time will occur later than 20 s. Consequently, if a test is given under the influence of a drug that affects clock-speed an abrupt shift in the peak times that is proportional to the duration being timed is observed during the initial test sessions until the subjects learn to rescale signal duration.

Several studies have shown these types of abrupt shifts in the horizontal placement of psychophysical functions for signal duration when drugs that affect dopaminergic systems are systemically injected. Drugs that increase the

effective level of DA increase clock-speed as indicated by leftward shifts in the timing functions that are proportional to the intervals being timed. In rats, methamphetamine (1.0–1.5 mg/kg) has been shown to decrease peak times [62] and the indifference points of bisection functions [62,63,65,67]. In studies using simple FI procedures administration of *d*-amphetamine has been shown to decrease post-reinforcement pauses in both pigeons [8,109,110] and rats [64], a result predicted by an increase in clock-speed. Drugs that decrease dopaminergic activity decrease clock-speed. Haloperidol (0.1–0.3 mg/kg) has been shown to increase the indifference points of rats' bisection functions [63,67]. Humans show impaired duration discriminations after haloperidol injections consistent with a decrease in clock-speed [102]. In contrast, the DRRD study in dogs cited above appears to show, by one interpretation, haloperidol increasing clock-speed [9]. In that case, dogs left the waiting platform to obtain reinforcement too early after haloperidol injections. It is important to note, however, that temporal control of responding was competing with the Pavlovian control exerted by the auditory signal paired with reinforcement. The haloperidol may have slowed the speed of the internal clock down to such a degree that the temporal stimuli became irrelevant, allowing the Pavlovian cues to dominate.

The neurotransmitter activity crucial in both temporal production and estimation procedures appears to involve the dopamine D2 receptors. In a study with five neuroleptics (chlorpromazine, haloperidol, pimozide, promazine and spiperidol) affinity for the dopamine D2, but not D1 or D3, receptors predicted the amount of neuroleptic required to achieve a criterial shift in the horizontal placement of temporal bisection functions. Binding affinity for other receptor subtypes (e.g., norepinephrine NE- $\alpha$  and serotonin S1 and S2) were also uncorrelated with the observed changes in timing behavior [67].

Opioid effects on timing behavior have also been investigated in the rat using the PI timing procedure. Morphine (0–3 mg/kg) administered prior to an experimental session decreased the probability of attention to stimulus duration while at the same time it increased the sensitivity of the duration discrimination on those trials that rats attended to time. These effects occurred in a dose-dependent manner. No change in peak time was observed when morphine was administered alone, but morphine administration enhanced the temporary leftward shift in peak time produced by methamphetamine (1.5 mg/kg) which has been interpreted as an increase in the speed of the internal clock due to an increase in the effective level of DA. The effects of morphine and morphine + methamphetamine were antagonized by the opiate receptor blocker naloxone. Morphine was without effect on the rightward shift in peak time produced by haloperidol (0.12 mg/kg) induced blockade of DA receptors. Taken together, these data indicate a complex interaction between opiates, DA, and

temporal processing. It has been suggested that the effects of morphine on the speed of an internal clock are best explained by assuming that opiate administration inhibits GABAergic neurotransmission, thereby disinhibiting dopaminergic activity in the nigro-striatal system [77].

All of these studies looked for abrupt short-term changes in the horizontal placement of psychophysical functions when a drug was administered after baseline training without drug treatment. Returning to Fig. 4 we see what happens when continued training is given on these tasks under the influence of a drug that affects clock-speed. Peak times return to the appropriate interval of 20 s with continued training under the drugs that affect clock-speed. This occurs because the intervals preceding reinforcement, while under the influence of the drug at the new clock-speed, are being transferred to reference memory and rescaling of time in memory is allowed to occur. For example, for the rats treated with methamphetamine, it may now be that reinforcement occurs after '150' pulses have accumulated rather than after '100' pulses. As training proceeds more sample intervals at this new value are added to reference memory, eventually replacing the old, '100 pulse', samples and thus effectively producing a rescaling of time using the new clock-speed.

When drug administration and behavioral training are discontinued during a week-long 'wash-out' period the psychophysical data obtained immediately following this period strongly suggest that clock-speed abruptly returns to the normal baseline level thereby producing a mismatch of the accumulator reading at the time of reinforcement with criteria sampled from reference memory. Behavioral change results from this set of conditions and peak times 'rebound' in the direction opposite to the original drug-induced shift, as is shown in the right panel of Fig. 4. The methamphetamine treated rat now has a reference memory that indicates that reinforcement should come after '150' pulses have accumulated. After the removal of the methamphetamine the clock-speed slows down to its original rate, therefore only '100' pulses will accumulate in 20 s. The criterion for maximal responding will be reached later in physical time. Once again with continued training the peak times will readjust to the appropriate point in physical time as reference memory is rescaled according to the now 'normal' clock-speed.

### 6.3. 'Memory patterns' in the pharmacological distortion of time

While abrupt changes in peak time that readjust with continued training are the hallmarks of the clock-speed pattern, manipulations that affect memory-storage speed lead to a pattern of gradual but long lasting changes in the peak times, as shown in Fig. 5. When the drugs are first administered no change in the peak time is observed. This is because the vast majority of time values stored in reference memory were accumulated during baseline train-

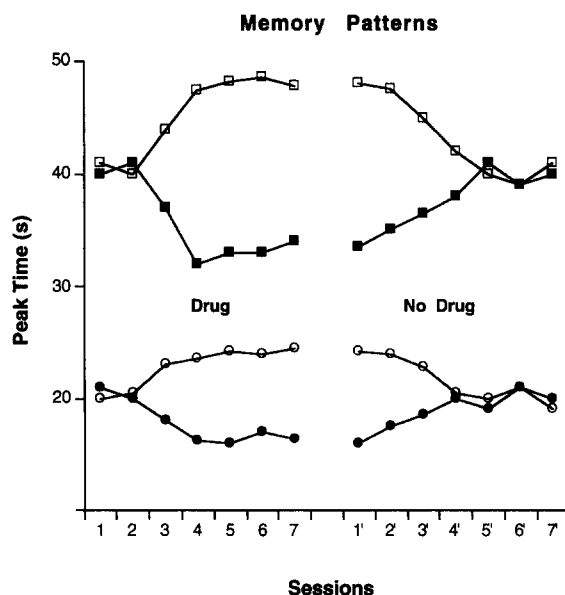


Fig. 5. Memory pattern: mean peak times from four different groups of rats ( $n = 10/\text{group}$ ) initially trained on either a 40-s (squares) or 20-s (circles) PI-timing procedure and tested under the influence of cholinergic drugs that affect memory-storage speed (left panel) or after the removal of the drugs (right panel). The closed symbols represent rats treated with physostigmine (0.01 mg/kg i.p.) and the open symbols represent rats treated with atropine (0.05 mg/kg i.p.).

ing under conditions of normal memory-storage speed, not one distorted by drug administration. Thus, if test sessions were given with a drug that affects memory-storage speed no effects on peak time would initially be noticeable until the original distribution of values stored in memory could be modified by the new experience.

With continued training under the influence of the drug the peak times show a gradual shift away from the appropriate physical time. Intervals are distorted as they are transferred to reference memory and with continued training these distorted intervals make up the majority of the memory samples. These distorted samples are then compared to current times in the accumulator that are the result of a normal clock-speed. For rats treated with physostigmine (0.01–0.09 mg/kg), which produces a carbamylated acetylcholinesterase enzyme that prevents the normal hydrolysis of ACh thereby increasing cholinergic activity, the speed at which information is transferred from the accumulator into reference memory is increased in a dose-dependent manner. Our model assumes that the content of temporal memory is dependent both upon the number of pulses initially accumulated by the clock stage and the amount of time required to transfer those pulses into memory. Thus, baud rate (otherwise referred to here as memory-storage speed) is a critical determinant of the content of temporal memory. Such a memory mechanism is able to represent stimulus duration as the period of time that is required to transfer a given quantity of pulses. For present purposes, we can assume that '100' pulses in the accumulator equal 20 s in physical time. If memory-stor-

age speed is increased it is as if those '100' pulses become '75' pulses in reference memory. The 'read out' from the accumulator to reference memory has been sped up so that reference memory now encodes '100' pulses as a shorter duration. The comparator therefore gets samples from reference memory that lead to a maximum response rate at '75' pulses and the peak will be too early in real time. Because the distortion is in the reference memory, as opposed to the clock, there can be no re-adjustment that will lead to a return to an appropriate peak in real time. When the clock-speed is affected memory adjusts to the new clock because the new accumulator readings are transferred to reference memory but the clock cannot compensate for a memory distortion because the clock-speed is independent of memory-storage speed.

If drug treatments affecting memory-storage speed are discontinued there is no immediate effect on peak times. The distorted times still make up a majority of the samples stored in memory. As new samples are added to memory and stored at a normal speed the peak times gradually shift back to normal as the clock and memory values are once again matched. The '100' pulses in the accumulator once again stay '100' pulses in reference memory and peaks occur at the appropriate point in physical time.

Administration of drugs or nutrients (e.g. choline) that affect cholinergic function has led to results that fit the memory-storage speed distortion pattern [72,79,80,85]. Systemic administration of physostigmine, which increases the effective levels of ACh, has been shown to lead to gradual, not abrupt, leftward horizontal shifts in psychophysical functions for time that are maintained by continued training on either bisection [65] or PI timing procedures [72,79,80]. Administration of ACh receptor blockers (e.g. atropine, 0.05–0.45 mg/kg), inhibitors of choline acetyltransferase (e.g. BW813U, 50 mg/kg) or antimetabolites of thiamine that inhibit ACh synthesis by limiting pyruvate dehydrogenase activity (e.g. pyrithiamine, 4 mg/kg), all decrease the effective level of ACh at the synapse and lead to gradual, not abrupt, rightward horizontal shifts in psychophysical functions for time that are maintained by repeated drug administration and continued training on either bisection [65] or PI timing procedures [36,76,79,83]. The magnitudes of the horizontal shifts observed are dose-dependent and proportional to the intervals being timed, indicating a change in the rate of temporal processing and not a change in the latency to initiate the timing or memory-storage process. In addition, these behavioral effects are not dependent on the peripheral actions of the cholinergic drugs as indicated by the lack of effect of neostigmine (0.03 mg/kg) or methylatropine (0.15 mg/kg) [79].

At present, it is uncertain whether the M1 or the M2 muscarinic receptor subtype mediates the behavioral effects on duration discrimination produced by cholinergic drugs. Recent data from bisection studies using relatively high doses of physostigmine (0.056–0.56 mg/kg), scopolamine

(0.075–0.237 mg/kg), or pirenzepine (1.0–10 mg/kg) suggest that changes in temporal processing produced by muscarinic agents do not involve the M1 receptor subtype due to the lack of any reliable effect of pirenzepine on timing behavior [106]. Because the ACh receptor blocker pirenzepine, in contrast to atropine and scopolamine, has a high affinity for the M1 muscarinic receptor subtype and a low affinity for the M2 receptor subtype these results suggest that the changes in the perception of stimulus duration by cholinergic drugs do not involve the M1 receptor subtype. Although intriguing, these results are limited in their ability to distinguish between clock and memory effects because of the relatively high doses used and the relatively brief exposure afforded the subjects to each of the doses.

#### 6.4. Hybrid drugs with both 'clock-speed' and 'memory-storage speed' effects

Tetrahydrocannabinol (THC), an active ingredient in marijuana, that can display atropine-like effects, has been shown to lead to rightward shifts in pigeon's bisection functions when administered repeatedly [17]. The commonly reported effect of marijuana distorting temporal experience may therefore be explained as a modification of memory-storage speed. However, a study that compared the effects of marijuana smoking and atropine injections on human duration production [39] brings this explanation into question. In this experiment subjects were asked to depress a foot pedal for an arbitrary number of seconds under no-counting instructions. Specific durations were produced after placebo injections, atropine injections, and smoking marijuana with different concentrations of THC. THC affected temporal production in a dose dependent fashion. Shorter durations were produced for any given objective time. The atropine injections had no effect on temporal production. This was despite the fact that the atropine dose used produces equivalent cardiac acceleration to the high THC dose. These data suggest that the initial effects of cannabinoids on temporal experience may stem from an effect other than their role as cholinergic antagonists. The behavioral reports resemble a clock-speed effect similar to that produced by stimulants such as methamphetamine. Thus, THC may possess both clock-speed and memory-storage speed effects that are in opposite directions (e.g. increased clock-speed with decreased memory-storage speed) and are revealed at different stages of training and/or testing. THC is clearly an interesting drug with respect to timing and time perception because of the recent identification of cannabinoid receptors in the basal ganglia and their interaction with dopamine systems. Its synergism with some of the sedative actions of sedative/hypnotic drugs as well as its synergism with some of the energizing effects of stimulant drugs suggests that it may act differentially on dopaminergic and cholinergic systems and that these interactions can be revealed by

observing the full time course of its actions on duration discrimination across repeated sessions of administration.

## 7. Conclusions

As a result of the curve-shift paradigm's separation of general performance effects from psychological process effects, and the dissociability of clock and memory patterns, it has been demonstrated that the clock system is to a large extent dopaminergically based while the memory system is to a large extent cholinergically based. This work represents a beginning from which a more specific understanding of the neural substrates of timing and temporal memory processes may be gained. Past research has used systemically administered drugs and the curve-shift paradigm has proven useful in differentiating global drug effects from specific effects of interest. We are now in a position to undertake a more detailed analysis utilizing microinjection techniques. These techniques have recently been used to identify which striatal subregions are crucial in controlling responding for conditioned reinforcement [46,47]. Specifically, injections of amphetamine into the nucleus accumbens, but not into posterior regions of the striatum, led to enhanced responding for conditioned reinforcement in rats. Given the physiological similarities that have been demonstrated between the mechanisms involved in the quantification of reward and temporal integration [69] this work provides a starting point for more detailed pharmacological specification of the neurobiological bases of the internal clock.

Recent experimental studies of patients with Parkinson's disease (PD) have suggested that the development of parkinsonian symptoms includes deficits in interval timing and temporal memory that may be associated with an abnormally high level of neuronal activity within the basal ganglia [61,75,105]. This excitation of the basal ganglia may be due to alterations in the action of the excitatory neurotransmitter glutamate. Antagonists of glutamate may have, not only antiparkinsonian actions, but may also be involved in the normal control of interval timing. The precise mechanisms by which activation of glutamate receptors produces changes in timing and motor control remain elusive. Studies performed in monkeys rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) show that striatal dopamine loss disinhibits the excitatory glutamatergic projection from the subthalamic nucleus (STN) to the internal pallidal segment (GPI) and substantia nigra pars reticulata (SNR), which act in concert at the basal ganglia output nuclei [86]. Glutamatergic transmission may also be enhanced in the neostriatum (STR) due to loss of inhibitory dopaminergic input from corticostriatal nerve endings [105]. Another unresolved issue is the role of the different glutamate receptor subtypes in the control of interval timing as well as the evolution of parkinsonism. Glutamate acts on at least three

pharmacologically distinct receptor types, two of which contain cationic channels and have been pharmacologically characterized as *N*-methyl-D-aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)/kainate (KA) receptors according to their preferred agonists. The third receptor type, named metabotropic receptor, is coupled with the intracellular phosphoinositide cycle and is activated by *trans*-( $\pm$ )-1-amino-1,3-cyclopentanedicarboxylate (*trans*-ACPD). The original pharmacological classification of glutamate receptors has been confirmed by the cloning, sequencing, and functional expression of gene products that conform to the properties of these receptors [42,104]. Although the glutamate receptor subtypes are differentially distributed within the basal ganglia and subserve different physiological and perhaps psychological functions, previous pharmacological studies employing different glutamate antagonists have not provided a consistent understanding of the specific role of glutamate receptor subtypes in either normal cognitive function or parkinsonism. To elucidate the role of glutamate receptors in interval timing future research will need to examine whether NMDA, AMPA, KA, and *trans*-ACPD mediate changes in temporal integration following microinjection into different parts of the basal ganglia.

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