Brain and Cognition **48,** 195–211 (2002)
doi:10.1006/brcg.2001.1313, available online at http://www.idealibrary.com on IDEAL®

Dissecting the Brain's Internal Clock: How Frontal–Striatal Circuitry Keeps Time and Shifts Attention

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Published online November 15, 2001

The ability of organisms to time and coordinate temporal sequences of events and to select particular aspects of their internal and external environments to which they will attend is vital to the organism's ability to adapt to the world around them. Numerous psychological theories have been proposed that describe how organisms might accomplish such stimulus selection and represent discrete temporal events as well as rhythm production. In addition, a large number of studies have demonstrated that damage to the frontostriatal circuitry appears to compromise the ability of organisms to successfully shift attention and behavior to adapt to changing temporal contexts. This suggests that frontostriatal circuitry is involved in the ability to make such shifts and to process temporal intervals. A selective review is accomplished in this article which focuses upon the specific neural mechanisms that may be involved in interval timing and set shifting. It is concluded that prefrontal cortex, substantia nigra pars compacta, pedunculopontine nucleus, and the direct and indirect pathways from the caudate to the thalamus may provide the neuroanatomical and neurophysiological substrates that underlie the organism's ability to shift its attention from one temporal context to another.

INTRODUCTION

Interval timing has been characterized as an organism's sensitivity to the passage of time in the seconds to minutes range. While some have argued that timing for durations in the millisecond range is subserved by a different system (for a discussion, see Ivry, 1993, 1996), this distinction is beyond the scope of this article. Instead, focus will remain upon an organism's ability to perceive and produce durations that fall within the range of seconds to minutes. This behavior has been demonstrated by a variety of different psychophysical tasks (for a review see Paule et al., 1999). What follows is an introduction to some of the theorizing that has guided research in determining the neuropsychological bases of interval timing and related processes.

The traditional heuristic used to describe interval timing is an information-processing (IP) model first proposed by Treisman (1963). This model has been developed to describe the workings of an ''internal clock'' that is presumed to mediate interval timing ability in humans and lower animals (e.g., Gibbon & Church, 1984; Gibbon, Church, & Meck, 1984). The model entails three distinct stages in which temporal information about an event is abstracted, encoded, and acted upon. For a diagram

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0278-2626/01 $35.00

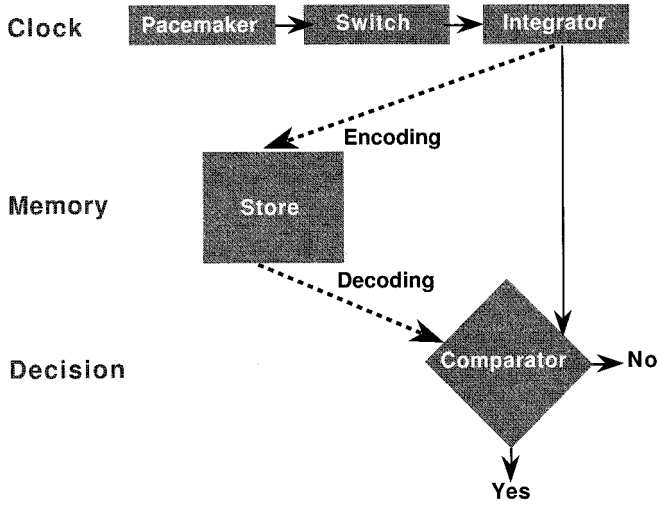

FIG. 1. A summary of the information-processing model of timing proposed by Gibbon, Church, & Meck (1984).

that illustrates these various stages, please refer to Fig. 1. The first stage of this model involves the transformation of physical time into psychological time (clock stage). In the IP model, the pacemaker emits pulses gated via attentional processes (Meck, 1984, 1996) into an accumulator, located in the striatum. These attentional processes are thought to take the form of a switch that can be closed (to allow the flow of pulses to pass) or opened (to stop the flow of pulses). The switch is closed whenever temporally significant information is detected (Meck & Church, 1983). Once the temporally significant information has ended, the switch then opens to stop the flow of pulses. The accumulator typically integrates these pulses in a linear fashion for the duration of an event. The value obtained in the accumulator (which under some conditions can be stored in working memory) is then compared with a sample value of the expected time of the event, which is stored in reference memory (memory stage). If the values are close enough according to a decision rule applied by a comparator, a response is made (decision stage). The value in the accumulator is then added to the distribution of samples stored in reference memory. In so doing, the new value stored in reference memory can come to affect subsequent behavior. Pharmacological manipulations and lesion studies in humans and lower animals have provided evidence of how these psychological processes might be linked to neural structures (e.g., Harrington & Haaland, 1999; Ivry & Richardson, 2001; Malapani et al., 1998; Meck, 1996; Meck & Church, 1987; Meck, Church, & Olton, 1984; Meck, Church, Wenk, & Olton, 1987; Nichelli, Venneri, Molinari, Tavani, & Grafman, 1993). These findings will be elaborated upon below.

Recently, a real-time neuropsychological model of interval timing behavior was proposed by Matell and Meck (2000, 2001). This Striatal Beat-Frequency (SBF) model was inspired by the theoretical work of Miall on the storage of time intervals using oscillating neurons (e.g., Miall, 1989, 1996). The SBF model is based upon a more physiologically realistic consideration of the functioning of frontal–striatal circuits than can be provided by traditional IP models. According to this neuropsychological model, the representation of time is due to the striatum's ability to detect coincident patterns of cortical oscillations. The detection of particular patterns of oscillations that could be related to specific signal durations of interest occurs via a

selective weighting of the cortical inputs into the striatum that are concurrently active when the specific duration is present. This change in the weighting of inputs is thought to occur via interactions in the striatum between dopamine (DA) inputs from the substantia nigra pars compacta (SNc) and glutamatergic inputs from the cortex. Although the SBF model is tied much closer to the physiological properties of the anatomical structures involved in interval timing, it shares all of the psychological properties of the earlier IP models of interval timing. Consequently, for the purposes of this article, reliance will be placed upon the traditional IP model that was proposed by Gibbon et al. (1984).

One of the ways that attention can function in the IP model is as a gate or switch for the pulses that pass from the pacemaker to the accumulator. Actually, whether attention at this location is thought to be a gate and/or a switch affects what sorts of predictions a model can account for (for a discussion, see Lejeune, 1998). Lejeune defined a gating function of attention as ''attentional allocation to time'' and a switching function as ''temporal meaning of stimuli'' (p. 136). As cited in their critical review, Block and Zakay (1996) have argued that timing behavior involves both an attentional gate and a switch at the clock stage. These researchers are uncertain which one should come first. However, interestingly, they attribute activity of the switch as being due to the organism's processing of external stimuli, whereas they attribute activity of the gate as being due to the organism's internal allocation of attentional resources. The views of these researchers stand in contrast to those of Gibbon et al. (1984), in which only an attentional switch is called for at the clock stage. Based upon her extensive review, Lejeune concluded that it is more parsimonious to suggest that attention acts as a switch at this clock stage, rather than proposing that attention acts as both a gate and a switch, but see Zakay (1999) for a rebuttal.

Macar, Grodin, and Casini (1994) and Thomas and Weaver (1975) proposed a model that allows for an interplay between temporal and nontemporal information processing. Even though this model was originally designed to handle durations shorter than 100 ms, the ideas that they elaborate are of relevance to longer durations. These researchers suggested that attentional resources were shared between a specific timing component and a more general stimulus processing component. These two components were thought to operate in parallel to one another. They proposed that the perception of a duration would be a weighted average of the information encoded by the temporal and nontemporal information processors. When attention is allocated to the timer, pulses would accumulate as a function of time and the subjective experience of duration would be directly proportional to the final number of pulses that had been accumulated. It was assumed that if attention were diverted away from this timer, then a certain number of pulses would be lost, and the subjective experience of time would be shorter than it should be.

The idea that pulses can be lost is also retained within the IP model of timing. In this situation, a ''flickering'' mode switch would be in operation. If an organism has some sort of deficit in attention (e.g., as in the case of attention deficit hyperactivity disorder—ADHD), then the possibility exists that the gating of pulses from the pacemaker to the accumulator could be impaired. In this case, the closing of the switch that allows pulses to flow could be irregular. There may an increased latency to close the switch at the beginning of a duration, the switch may close and open at random times during the interval, or there may be an increased latency to open the switch at the end of the duration. All of these situations would serve to increase the amount of time required to satisfy the duration requirement, because more pulses would need to be accumulated in order for the subjective experience of the duration to meet the objective duration.

NEUROPHARMACOLOGICAL AND NEUROIMAGING STUDIES OF INTERVAL TIMING

Dopamine and Nigrostriatal Pathways

Administration of dopaminergic agonists and antagonists has been found to cause horizontal shifts in the placement of interval timing functions (Meck, 1983, 1996). These horizontal shifts have been interpreted as indicative of effects upon clock speed. When dopaminergic agonists such as methamphetamine are initially administered, an immediate horizontal shift in the peak time or point of subjective equality (PSE) is found to correspond to an earlier time than when feedback was delivered (a leftward shift). Likewise, when dopaminergic antagonists such as haloperidol are administered, a horizontal shift in peak time or PSE is found to correspond to a time later than when feedback was delivered (a rightward shift). In particular, the affinity that the dopaminergic antagonist has for the D_2 receptor subclass seems to best predict how effective it will be in causing a decrease in the speed of the internal clock (e.g., Meck, 1986; Rammsayer, 1997).

It should be noted, however, that as testing continues, these under- and overestimations of stimulus duration begin to readjust. By the end of testing on these drugs, psychophysical functions have gradually shifted back to normal. However, if the drug is removed and testing continues, what one sees is an immediate rebound effect. That is to say, that subjects that had been tested with the dopaminergic agonists show a subsequent shift rightward upon removal of the drug, while those tested with dopaminergic antagonists show a leftward shift. This phenomenon has been interpreted as being due to the subjects relearning the criterion durations while under the influence of the drug (Meck, 1983, 1996). Those that were trained under the influence of dopaminergic agonists learned that fewer pulses needed to be accumulated in order for a response to be made, while those on the dopaminergic antagonists learned that they needed to accumulate more pulses. When the drug is removed and dopaminergic tone shifts back to normal, the subjects are still abiding by these updated ''response rules.'' Thus, when subjects tested with the agonist perform in this drug-withdrawl condition, they require more pulses to accumulate to equal what they had experienced on the drug, hence, a horizontal rightward shift. A similar (but opposite) situation occurs for those tested on the antagonist.

This effect of dopaminergic drugs has been interpreted as an effect on clock speed because the effects are proportional to the intervals being timed; i.e., the transformation is multiplicative rather than additive. This effect is believed to be mediated, in part, by changes in the effective level of striatal DA. The SNc is believed to be one source of this DA because lesions of the SNc have been shown to severely impair interval timing behavior (Meck, 1996).

Neuroimaging Evidence for Frontostriatal Circuitry Involvement in Interval Timing

Utilizing functional magnetic resonance imaging (fMRI), Hinton, Meck, and MacFall (1996) documented the first reported evidence for the involvement of the basal ganglia and frontal–striatal circuits in human interval timing. Participants performed in a peak-interval timing procedure (Rakitin et al., 1998) while brain scans were obtained. After controlling for both sensory-specific and motor effects, interval timing-related activation was demonstrated in the striatum, thalamus, and frontal cortex. Replicating this study, Meck, Hinton, and Matell (1998) showed similar activation in frontal–striatal circuits for both auditory and visual stimuli. They also demon-

strated inhibition of the hemodynamic response within cerebellar areas concurrent with task-dependent activation in the caudate/putamen.

In a related study, Rao et al. (1997) used fMRI to image subjects while they performed a finger-tapping task while listening to an auditory cue and in the absence of this cue. In comparing the activation patterns that resulted from these two conditions, they found that the striatum, thalamus, and cortex were activated only when the timing of the taps depended upon an internal representation of time; no such activation was evidenced when the participants were required to tap in time to the auditory cue. This suggests that these activated structures are critical to the ability to time. One caveat should be noted, however. Because a subtraction technique was utilized to discover the differences between these two conditions, the possibility remains that the striatum, thalamus, and cortex are also activated when the participants are coordinating their tapping to the tones. Perhaps the activation of these structures is less when an external cue is provided and this accounts for the difference. Regardless, this study and a more recent one by Rao, Mayer, and Harrington (2001) provide strong evidence for the role of frontostriatal circuits in the production of event durations and temporal sequences. Similar effects have been observed using positron emission tomography (PET) to map the basic patterns of activation in motor and sensory temporal tasks (e.g., Lejeune et al., 1997).

NEUROPSYCHOLOGICAL EVIDENCE FOR FRONTOSTRIATAL INVOLVEMENT IN INTERVAL TIMING

Parkinson's Disease (PD) Patients—Neurodegeneration of Dopaminergic Cell Bodies in the SNc

Marsden (1984) proposed that the basal ganglia serve both motor and cognitive functions, stating ''The sequencing of motor action and the sequencing of thought could be a uniform function carried out by the basal ganglia.'' In a similar vein, hypotheses of interval timing and coordination also construe both cognitive and motor functions to the involvement of the basal ganglia in coding time. Patients with basal ganglia pathologies (e.g., PD patients) are capable of performing motor tasks that require control of kinematic and dynamic features, such as force and direction, suggesting that their deficits are not simply due to elemental motor dysfunction. Rather, it appears as though their deficits may, in part, be due to difficulties with higher order functions (e.g., Dubois, Boller, Pillon, & Agid, 1991; Dubois & Pillon, 1997; Graybiel, 1997; Lawrence, Sahakian, & Robbins, 1998; Middleton & Strick, 1994).

A variety of researchers have noted a deficit in the ability of PD patients to correctly time behavior. For instance, Benecke, Rothwell, Dick, Day, & Marsden, (1987) noted that PD patients displayed a longer interval (or pause) between sequential self-paced movements than did controls. Likewise, Harrington, Haaland, and Hermanowicz (1998) tested medicated PD patients on their ability to synchronize finger taps to tones that were separated by either 300 or 600 ms. Participants then had to continue this tapping in the absence of these external cues. They found that PD patients were impaired when they had to reproduce the interresponse interval between the tones without the benefit of the external cue. This was true for both interresponse intervals tested. They also tested these patients on their ability to judge the relative duration of tones that were separated by either 300 or 600 ms. Again, they found that patients were impaired in their ability to time; PD patients performed significantly worse than controls on both of these duration perception tasks.

PD patients have also been found to have increased temporal discrimination thresholds (Artieda, Pastor, Lacruz, & Obeso, 1992). Temporal discrimination was defined

by these authors to be a measure of the minimum time interval that needed to come between two successive stimuli in order for these stimuli to be perceived as separate. These stimuli could be auditory, visual, or tactile. In this study, they tested one group of PD patients while they were off their medication and another group of PD patients while they were on their medication. They tested these patients on the three stimulus modalities mentioned above. Stimuli were separated by different durations in the millisecond range. The results of the study indicated an impairment of temporal discrimination for all three modalities in PD patients. Further, this deficit was partially ameliorated by treatment with L-dopa.

Another study by this group demonstrated that PD patients were impaired in their ability to estimate and to reproduce time intervals in the range of seconds (Pastor, Artieda, Jahanshahi, & Obeso, 1992). One group of PD patients was tested while off their medication, while another group was tested while on it. Patients were trained to verbally estimate the duration of 1 s by counting aloud at a rate of one digit per second, while looking at a stopwatch. They were then tested on their ability to perform a time estimation task in which a rectangle appeared on a screen for varying amounts of time (e.g., 3 s, 9 s). Participants were instructed to use the verbal counting method to try to estimate how many seconds the rectangle appeared for. They then made a verbal report of the total of this count. PD patients were found to estimate 1 s as being longer than it is in reality. Thus, they were found to be impaired on this time estimation task relative to controls.

For the reproduction portion of this task, participants were required to observe a screen upon which stimuli where presented for a certain period of time. These stimuli could be either numerical time markers for the interval presented at various frequencies (the ''filled'' time intervals) or a square remaining on the screen for a fixed amount of time (the ''unfilled'' intervals). For the filled interval conditions, the participants were asked to reproduce the interval by internally counting the time markers at the same speed with which they were presented. When the participant was finished counting, they were required to press a key. For the unfilled conditions, the participants were asked to reproduce the interval that the square had been present by any strategy they chose. Once they had completed reproducing the interval, they were again asked to press a key. As with the time estimation task, PD patients were found to respond at a time later than did controls. This suggests that the internal clock of these patients was running slower. When patients were tested on their L-dopa medication, a significant improvement in timing was observed. This again suggests that the level of DA is critical to how the internal clock functions.

One final study of interest is that of Malapani et al. (1998). This study used the peak-interval procedure to investigate the ability of PD patients on and off their medication to reproduce time intervals. In their first experiment, participants were trained to reproduce two target times (8 and 21 s). When PD patients were tested on their medication, their performance was similar to that of young and age-matched controls. However, when PD patients were tested off their medication, both the accuracy and the precision measures of their peak functions indicated an impairment. The impairment in the measure of precision was determined to be due to a nonscalar source of variability. This may be indicative of an impairment in attention or set shifting (e.g., Joosten, Coenders, & Eling, 1995). In addition, these patients demonstrated what Malapani et al. referred to as the migration effect. This means that the timing function for the 8-s signal was shifted toward the right (i.e., this interval was produced as longer), while the 21-s signal was shifted toward the left (i.e., this interval was produced as shorter). This migration effect was due to being trained on two intervals at the same time, because when PD patients off their medication were trained to only reproduce the 21-s interval, this function was shifted toward the right (i.e., indicative

of producing the interval as longer). In this second experiment, the variability evidenced in their timing function was determined to be due to scalar variability in agreement with a slower clock speed.

Malapani et al. (1998) attempted to explain this migration effect as being due to a memory dysfunction. They argued that the relatively permanent over- and underestimation of the intervals (8 and 12 s, respectively) despite intermittent corrective feedback is similar to the memory effects seen to occur with the administration of cholinergic antagonists and lesions of the frontal cortex (e.g., Lange et al., 1992; Meck, 1996). In such situations, participants are proposed to be unable to recalibrate their timing because of problems that occur when the memories are established or retrieved. These researchers further argue that when the memories for these durations are encoded or retrieved, they are somehow coupled together, such that they are now attracted to one another. In other words, the memory for the duration currently being timed is affected by the memory for the other duration.

However, given that nonscalar variability was present when PD patients off their medication were required to time two durations, while scalar variability was evident when they were required to time only one duration, another explanation for this migration effect could be proffered. The migration of the two durations toward one another could be due to a deficit in attentional set shifting in these patients. Many researchers have demonstrated that PD patients have a problem when they are required to switch their attention between two sets of responding (Flowers & Robertson, 1985; Robertson & Flowers, 1990). One could view the timing of an interval as yet another example of set; when the stimulus for timing occurs (in this case, a rectangle on a computer screen), the participant has learned to pay attention to its duration and to respond when s/he thinks that the duration is almost up. Because the same stimulus was used in this experiment for both durations, the PD patients would have to rely upon their internal representation for both durations (i.e., there would be no external cue that would signal which duration they should be timing). This situation has been shown to be difficult for PD patients in other situations that call for a reliance upon internally generated information (e.g., Brown & Marsden, 1988, 1991). Thus, when PD patients begin to time the duration of the stimulus, they may become confused about which duration they should be paying attention to or when they should switch their attention toward the other duration. Evidence for this proposition could be taken from the finding that for the shorter duration, the PD patients off their medication tend to start responding at about the same time that they do while on the medication. However, the function that is produced has a wider spread and is shifted toward the right. This suggests that these patients have some idea of when the short duration occurs, but that they shift, inappropriately, to the longer duration as the interval elapses. In contrast, the data from the longer duration suggest that PD patients off their medication begin responding much earlier than normal, well before the response threshold for the longer criterion duration has been reached. In this situation, perhaps they are confused about which duration they should attend to. They may start out timing the longer temporal criterion, but as time elapses and the threshold for the shorter temporal criterion approaches, thoughts of the shorter duration may intrude, causing confusion. The patient would then start to respond earlier than s/he should to try to make up for the elapsed short duration, while still entertaining the idea that they should be timing the longer one. This would result in the function being shifted toward the left and a wider (nonscalar) spread, which is what is observed in these patients. Unfortunately, this is a post hoc analysis and would need to be tested further to elucidate whether this sort of ‘‘interference effect’’ of temporal sequencing is indeed occurring.

As alluded to above, cognitive impairment and dementia are common even in the

early to middle stages of PD. Patients have characteristic cognitive deficits and they show impairment especially in neuropsychological tests thought to be sensitive for frontal lobe function. Therefore, some investigators have emphasized the ''frontal'' or ''frontostriatal'' nature of the cognitive deficits seen in PD, whereas other have suggested a more generalized profile of cognitive impairment or have used a wider concept of ''subcortical'' dementia (see Rubin, 1999). Recent brain imaging studies using PET have demonstrated reduced [^{18}F]fluorodopa uptake in PD in the caudate nucleus and frontal cortex that is related to impairment in neuropsychological tests measuring verbal fluency, working memory, and attentional functioning (e.g., Rinne et al., 2000). These results indicate that dysfunction of the DA system has an impact on the type of cognitive impairments observed in patients with PD. Although these findings clearly point to frontal lobe dysfunction, they do not exclude the possibility of more generalized cognitive impairment in PD that involves temporal integration and/or coincidence detection processes more specific to regions in the basal ganglia.

Schizophrenia (SZ) Patients—Hyperactivity/Dopaminergic Dysfunction of Frontal–Striatal Circuits

Pathophysiological models of SZ have implicated disturbances in specific brain structures including the frontal and prefrontal cortex, limbic system, and corpus striatum (Carlsson & Carlsson, 1990; Carpenter, Buchanan, Kirkpatrick, & Tamminga, 1993; Grace, 1993; Lieberman, Sheitman, & Kinon, 1997). Basal ganglia structures have been reported to be especially abnormal in SZ. A structural MRI study of schizophrenics showed enlarged brain volumes of specific DA-rich brain areas compared to controls: 14.2% for total basal ganglia, 27.4% for globus pallidus, 15.9% for putamen, and 9.5% for caudate (Hokama et al., 1995). In this study, increased volumes, especially in the caudate, were associated with poorer neuropsychological test performance on finger tapping and Hebb's Recurring Digits. The strongest correlations were found between basal ganglia volume and relatively pure tests of motor speed, timing, and dexterity. There was also evidence suggesting that basal ganglia pathology influenced attentional processes. By contrast, performance on tests of memory, abstraction, and categorization that strongly correlate with temporal lobe volumes did not correlate with basal ganglia volumes.

Antipsychotic drugs used to treat SZ exert their therapeutic effects by altering the chemical activity of neurons (particularly of DA among other neurotransmitter systems) in the cortex and striatum (Lieberman, 1993). It is important to note that one of the major findings concerning time perception in the seconds to minutes range is the ability to decrease clock speed with antipsychotic drugs such as haloperidol and to increase clock speed with stimulant drugs such as methamphetamine (e.g., Meck, 1983, 1996). In particular, animal studies have shown that when a comparison is made of DA receptor antagonists (e.g., chlorpromazine, haloperidol, pimozide, promazine, and spiroperidol) the binding affinity for the dopamine D_2 receptor predicts the pharmacological potency in producing the criterion shifts of psychophysical timing functions that are associated with a decrease in clock speed, whereas affinity for other neuroreceptors (D_1, D_3, the alpha adrenergic receptor, S1, and S2) does not (Meck, 1986). The conclusion drawn from this work is that D_2 receptors play a major role in determining the rate of temporal integration for time perception in the seconds to minutes range. Interestingly, a similar correlation holds for predicting an antipsychotic drug's potency for clinical treatment of schizophrenic symptoms (e.g., Creese, Burt, & Snyder, 1976) as well as its efficacy in blocking the reinforcing effect of electrical stimulation of the medial forebrain bundle (e.g., Gallistel & Davis, 1983).

Taken together, these results suggest that the physiological mechanisms involved in the quantification of reward magnitude and stimulus duration are quite similar (Meck, 1988) and that the symptoms of SZ should include the misperception both of hedonics and time.

Tysk (1983) studied the ability of various types of medicated SZ patients to estimate time in three separate tasks. One task involved the adjustment of a metronome to estimate one beat per second. The second involved a verbal estimation of various durations while listening to the ticking of a stopwatch. The final task was to produce various durations with a stopwatch. In all three cases, patients were instructed to count the seconds. The results of all three studies indicated that SZ patients of all types responded too early and displayed increased variability in their responding. This was true for patients who displayed active disease symptoms and for those who were classified as being in remission. The one exception to these findings was the results for patients with schizotypal personality disorders. These patients either were similar to controls or displayed a tendency to respond too late. These results suggest that the internal clock of SZ patients may run faster than that of controls.

A recent study investigated the ability of participants at high risk for the development of SZ, at high risk for affective disorder, and normal controls to perform on both an auditory and a visual duration bisection procedure (Penney, Meck, Roberts, Gibbon, & Erlenmeyer-Kimling, 2001). Participants were trained to classify auditory and/or visual signals as either ''short'' or ''long'' in duration. They were instructed not to count or subdivide the durations in any way. After the signal presentation ended, two choice boxes appeared on a computer screen. Participants indicated their decision about the length of the signal duration by selecting the appropriate box. Feedback was provided in the initial training phase regarding whether they were correct in their choice. During the testing phase, intermediate durations between the two anchor point training durations were also presented. On any given trial, the modality of the signal for discrimination of duration could be visual, auditory, or both. Feedback was provided only on those trials for the anchor points.

One of the striking findings of this study was that the duration of visual stimuli was classified as being shorter than the corresponding durations of auditory stimuli. This was true for all groups (high-risk SZ, high-risk affective disorder, and controls) tested. These results replicate those of a specific investigation of the effects of auditory and visual stimuli upon clock speed (Penney, Gibbon, & Meck, 2000b). Based upon both of these studies, these researchers put forth the argument that auditory stimuli cause the internal clock to run faster than do visual stimuli. This difference is proposed to be due to a difference in the ways that these two types of stimuli affect the attentional switch. They make the suggestion that less attention may be allocated to the switch in the case of visual stimuli, which would cause the switch to flicker between the closed and the open state. As discussed earlier, this state would result in some pulses being lost. With some of these pulses being lost, accumulation of pulses within the accumulator would be less. This could lead to the subjective experience of a shorter duration.

Another finding of the study by Penney et al. (2001) was that there was a greater difference in the separation between auditory and visual psychophysical functions for the participants at risk for SZ than for the normal controls or the participants at risk for affective disorder. This suggests that there was an enhanced effect of these two signal modalities on clock speed in these participants at risk for SZ. This again was thought to be due to effects of attention on the switch and the involvement of dopaminergic activity in frontal–striatal circuits (e.g., Cohen & Servan-Schreiber, 1992; Elliott, McKenna, Robbins, & Sahakian, 1995; Elliott & Sahakian, 1995; Eslinger & Grattan, 1993).

Attentional-Deficit Hyperactivity Disorder Patients—Hypoactivity/Dopaminergic Dysfunction of Frontal–Striatal Circuits

Adult participants with ADHD were evaluated not only on their timing ability, but also for the effect that nicotine might have on this behavior (Levin et al., 1996). Nicotine is known to act on nicotinic receptors in the ventral tegmental area and to stimulate DA release which may help alleviate some of the attentional problems suffered by adults with ADHD (cf., Hinton & Meck, 1996). Participants were trained on a 7- and 17-s peak-interval procedure, both while receiving a nicotine skin patch and while receiving a placebo skin patch. Feedback on both the precision and the accuracy of performance was given either after every trial or after a quarter of the trials. The effect of nicotine was the clearest for the longer duration with the least amount of feedback. Nicotine increased both the accuracy (i.e., peak time) and the precision (i.e., the spread) of the timing functions in this condition. Thus, when not on nicotine, ADHD patients demonstrated a deficit in their ability to produce temporal intervals under limited feedback conditions. The results of the administration of nicotine also suggest that the deficit for ADHD patients may be due to problems with attention (e.g., flickering mode switch). This is supported by the finding that the timing functions when given placebo were much broader and rightward shifted, indicating a possible deficit in attention.

Prefrontal Lesion Patients

Harrington, Haaland, and Knight (1988) investigated the ability of patients with focal lesions of the left prefrontal cortex, patients with focal lesions of the right prefrontal cortex, and controls on their ability to perform a duration perception task. In this task, participants were presented with a standard tone pair that was followed 1 s later by a comparison tone pair. Their task was to determine if the time between the comparison tone pair was longer or shorter than the duration between the standard tone pairs. They found that only patients with lesions of the right prefrontal cortex exhibited deficits in time perception.

Interestingly, the competency with which these right prefontal patients were able to time was correlated with an independent test of their ability to switch nonspatial attention. Nonspatial attention was assessed by requiring participants to make a response to a target stimulus (a circle or triangle). This stimulus was preceded by a neutral cue (a cross), a valid cue (circle or triangle), or an invalid cue. Reaction time to the target stimulus which appeared after a variable delay was measured. Both patient groups showed deficits on this task, compared with controls. However, only the data from the right prefrontal patient group correlated with timing performance. These results suggest that the right prefrontal cortex is intimately involved in the timing process. In addition, these results suggest that attentional switching and interval timing ability are independent, but related to one another.

FUNCTIONAL INTERPRETATIONS OF FRONTOSTRIATAL–THALAMOCORTICAL ACTIVITY

Interval Timing Behavior

One of the interpretations of the activity of frontostriatal circuitry as described by Alexander and Crutcher (1990) has been that it mediates interval timing behavior (Meck, 1996). Persuasive evidence has been presented to show that such circuitry does indeed subserve the sensitivity of behavior to time (e.g., Gibbon, Malapani,

Dale, & Gallistel, 1997; Meck, 1996, Matell & Meck, 2000, 2001). However, this does not preclude the involvement of these areas in other psychological functions, such as attentional and behavioral set switching. Indeed, it will be recalled that in the study conducted by Harrington et al. (1988), interval timing behavior and attentional switching were suggested to be independent, but correlated with one another.

Jueptner, Frith, Brooks, Frackowiak, & Passingham (1997) provided further evidence that the prefrontal cortex and basal ganglia nuclei are involved in attention and learning. They tested human participants on three separate tasks while they also performed PET scans of the activational patterns of areas during these different tasks. One task required participants to make random sequences of button presses. In this task, attentional mechanisms were required to make decisions and to keep track of previous responses, but no learning was involved. Another task required participants to use trial and error strategies to learn new sequences of button presses. The control task required participants to make a repetitive motion on all trials. In comparing the activational patterns generated during the random sequence with that generated during the learning task, they found significant activation of the prefrontal, medial prefrontal, and parietal cortices and of the caudate and ventroanterior and dorsomedial thalamic nuclei during the learning task. In comparing the patterns for the random sequence task and the repetitive task, they found significant activation in the prefrontal cortex and the cingulate gyrus. In comparing the activity for the learning task and the repetitive task, they found that the dorsal prefrontal cortex, cingulate gyrus, caudate, putamen, globus pallidus, and thalamus were all significantly activated during the learning task. Thus, this suggests that the prefrontal cortex and the caudate are important in situations where attentional demands are made. In addition, this lends further support for the involvement of frontostriatal–thalamocortical circuitry in the formation of new learning.

Another report by this group (Jueptner et al., 1997) investigated the role of the prefrontal cortex when particular attention to action was required. In this study, they performed PET scans upon participants while they were engaged in the learning of a new sequence of button presses, while they were required to pay attention to an already learned sequence that was considered to be automatic, and while they performed the already learned sequence without paying attention to it. As in the previous study reviewed above, these authors noted increased activity in prefrontal areas, medial frontal areas, the cingulate gyrus, caudate, globus pallidus, and the dorsomedial and ventroanterior thalamic nuclei while the participants were engaged in new learning compared to when they were required to perform the prelearned sequence. In addition, the prefrontal areas, anterior cingulate, and caudate nucleus were all found to be activated when attention was required. Thus, again, the prefrontal cortex was found to be more active in new learning, and not to be significantly involved in the production of automatic responses. In addition, both the caudate and the globus pallidus were found to be activated more during the new learning condition. Also, both the prefrontal areas and the caudate appear to be important in mediating attentional responses.

Attentional Set Shifting and Interval Timing

Perhaps one of the earliest conceptions of how the basal ganglia could regulate behavioral and cognitive sets was put forth by Buchwald, Hull, Levine, and Villablance (1975). To these researchers, ‘‘set’’ was thought to be represented in neural activity by the alteration of the probability that incoming information to a neuron would be transmitted further by that neuron. These researchers made a distinction between the terms ‘‘response set’’ and ‘‘cognitive set.’’ Response set was thought

to be due to a relatively short-term biasing effect that would enable the initiation and execution of movements. Cognitive set, on the other hand, was to be due to a relatively long-term biasing effect in these neurons that would serve to transfer neural information for a variable length of time before a response is initiated. Normal functioning of response sets was thought to entail the ability to initiate and execute a series of movements that constitute a response in a smooth and efficient manner. Normal cognitive set was defined by these authors as the ability to discriminate between situational contexts and to make an appropriate response to a given context. In addition, this sort of set was thought to be adaptable to changes that would occur in behavioral contexts.

A more recent view of attentional set switching was proposed by Brown and Marsden (1990). This view was intended to account for the cognitive deficits observed in PD patients, but it also has implications for set switching and interval timing. These authors suggest that dysfunctions within the corticostriatal circuitry may be responsible for the cognitive deficits observed in PD patients. As has been reviewed in this article, two of the most prominent deficits recorded in these patients, and in other patients that exhibit dysfunctions within the frontal cortex–basal ganglia system, are problems in switching from one attentional, cognitive, or response set to another and dysfunctions of interval timing. This would suggest that these areas are involved in the generation of these behaviors.

One final view that could be construed as suggesting a role for frontostriatal systems in both set shifting and interval timing is that put forth by Wise, Murray, and Gerfen (1996). In their review of the frontal cortex–basal ganglia system, they suggest that behavior is guided by rules or ''syntax'' that serve to determine which of several possible outputs to a given input will be selected when more than one response is possible. This idea is very similar to the early definition given for set. They go on to suggest that the frontal cortex is specialized to participate in the learning of new behaviors, in selecting rules to guide behavior, and in rejecting, or switching from, rules that no longer appear to work in a particular context. The basal ganglia, on the other hand, were proposed by these authors to be responsible for the potentiation of already acquired rules in the appropriate behavioral context and reward history. With repeated success in adopting a particular rule for a behavioral context, the basal ganglia is thought to ''train'' the cortex to respond efficiently and according to that particular rule via activation of appropriate thalamocortical loops.

SUMMARY

The results described earlier from Harrington et al. (1998) suggest that interval timing and attention are two separate, but complimentary, processes. Thus, interval timing behavior might be mediated by attentional processes, but these processes do not constitute interval timing itself. One may see deficits in attention, but no deficit in interval timing (as in the case for left prefrontal lobe patients). In addition, one may observe that interval timing behavior is disrupted when an attentional deficit is elucidated, but that the basic parameters that demonstrate timing ability are still present (e.g., temporally controlled peak functions). Scalar timing theory has attempted to promote a separate role for attention in timing (e.g., Hinton & Meck, 1997; Penney, Gibbon, & Meck, 2000a). However, somewhat surprisingly, it has not made independent tests that try to correlate timing and attention. Such information would be useful in determining the extent to which interval timing and attention are related to one another.

The review of the literature presented here suggests that the frontal cortex and

related basal ganglionic areas are involved both in the generation of attentional set shifting and in interval timing behavior. Furthermore, the temporal integration properties of interval timing may serve as the basis for attentional set shifting and sequence coordination. It is apparent that this is an idea whose time has come given the converging evidence for the types of behavioral dysfunction associated with frontal–striatal damage (e.g., Owen et al., 1993; Pantelis et al., 1997; Partiot et al., 1996). How these different types of psychological processes might be integrated into an unified theory is currently uncertain. What is clear is that a temporal basis (e.g, oscillatory or pacemaker process) for behavioral coordination and integration must exist in order to provide structure and coherence to response sequences.

Our curent view is that temporal information relevant to the context in which the organism finds itself is relayed from the thalamic–cortical connections to the striatum. If this incoming cortical information is coincident with an outcome that would have some motivational meaning to the subject, then another cascade of effects would occur (e.g., long-term potentiation). This would depend upon dopaminergic input to the striatum from the SNc. The interaction between DA and glutamate would affect the output effected by these striatal neurons. If both DA and extensive glutamatergic input occurred at dendritic spines in the striatum, then thalamic disinhibition would result via the direct striatal pathway. This would serve to potentiate contexts (including temporal sequences and the event durations they are composed of) and behavioral responses that would be appropriate to this state. This dopaminergic and glutamatergic input would also activate neurons in the indirect striatal pathway. The action of the indirect pathway would be to cause inhibition of unwanted behavioral responses and irrelevant aspects of the environment via inhibition of these areas of the thalamus. In addition, if glutamatergic input were to cause excitation within the striatal neuron without the concomitant input from dopaminergic fibers, then this would result in depression of activity in this neuron, which could ultimately result in long-term depression (Graybiel, 1998; Houk & Wise, 1995; Matell & Meck, 2000).

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