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Cortico-striatal representation of time in animals and humans

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Interval timing in the seconds-to-minutes range is crucial to learning, memory, and decision-making. Recent findings argue for the involvement of cortico-striatal circuits that are optimized by the dopaminergic modulation of oscillatory activity and lateral connectivity at the level of cortico-striatal inputs. Striatal medium spiny neurons are proposed to detect the coincident activity of specific beat patterns of cortical oscillations, thereby permitting the discrimination of supra-second durations based upon the reoccurring patterns of subsecond neural firing. This proposal for the cortico-striatal representation of time is consistent with the observed psychophysical properties of interval timing (e.g. linear time scale and scalar variance) as well as much of the available pharmacological, lesion, patient, electrophysiological, and neuroimaging data from animals and humans (e.g. dopamine-related timing deficits in Huntington's and Parkinson's disease as well as related animal models). The conclusion is that although the striatum serves as a 'core timer', it is part of a distributed timing system involving the coordination of large-scale oscillatory networks.

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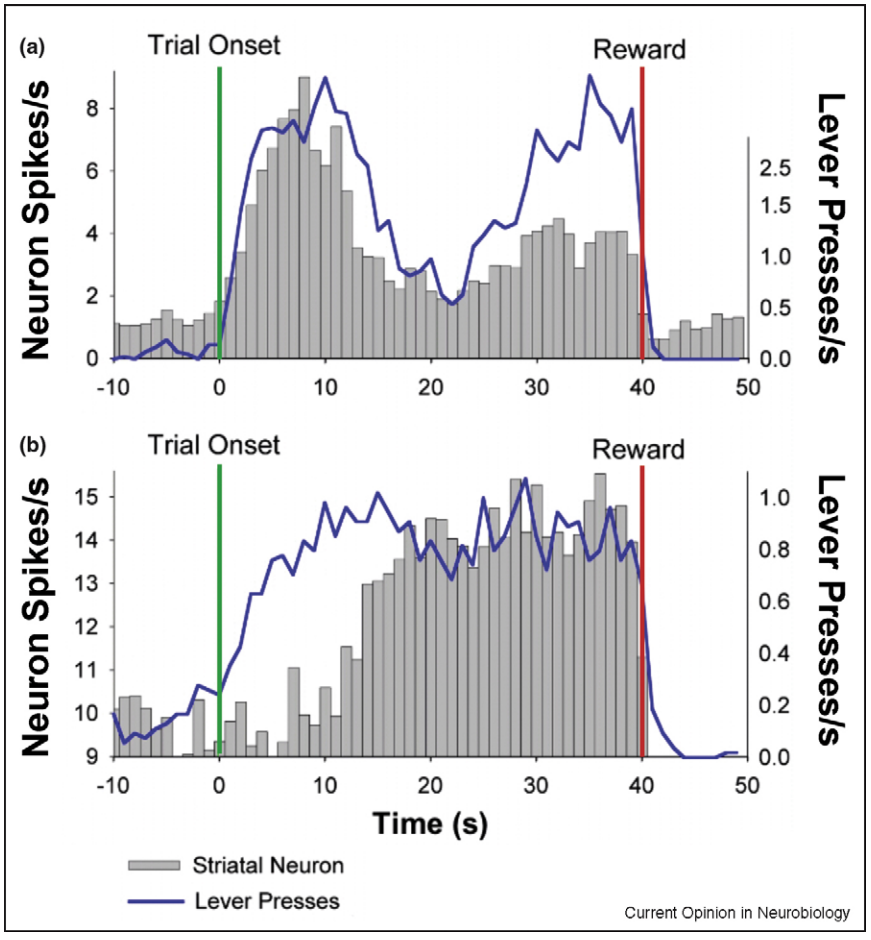
Diverse lines of evidence suggest that striatal neurons are crucial to duration discrimination in the seconds-to-minutes range through their participation in large-scale oscillatory networks involving functional links among mesolimbic, nigrostriatal, and mesocortical dopaminergic systems [1•,2••,3]. Pharmacological studies indicate that the administration of indirect dopamine (DA) agonists such as cocaine and methamphetamine produce proportional leftward shifts of timing functions, while DA receptor blockers such as haloperidol and raclopride produce the opposite effect [4••]. The D_2 receptor is crucial to the mediation of these pharmacological effects [5] and transient overexpression of striatal D_2 receptors impairs the acquisition of temporal control [6••]. In addition, deletion of the DA transporter (DAT) gene, but not the norepinephrine transporter gene, abolishes the ability to discriminate supra-second durations in homozygous mice and leads to a decreased sensitivity to the clock-speed enhancing effects of methamphetamine in heterozygous mice, indicating that excess levels of DA impair temporal integration [7]. Likewise, lesions of DA/DAT-rich areas such as the substantia nigra pars compacta (SNC) and dorsal striatum lead to decreased levels of DA and impairments in supra-second timing, while lesions of the ventral striatum eliminate the behavioral contrast observed between different delays to reward and lesions of the frontal cortex lead to the loss of pharmacological control over clock speed [8••,9]. Moreover, electrophysiological recordings from striatal spiny neurons that receive both dopaminergic and glutaminergic inputs show them to be directly involved in the coding of durations in the seconds-to-minutes range, as demonstrated in Figure 1 [10,11••], whereas compartmentalization of the human striatum, similar to that in other animals, has revealed correlations between D_2-receptor binding and cognitive performance related to temporal processing [12].

Recent neurophysiological modeling of interval-timing proposes that the neural inputs that constitute the time code arise from the activity of large areas of the cortex [2••,11••,13•]. The frontal cortex in particular contains neurons that oscillate at different rates (5–15 Hz) and striatal spiny neurons that receive their synaptic input from the cortex can monitor the oscillatory patterns of this cortical activity. According to the Striatal Beat Frequency (SBF) model [14••], coincidence detection in the striatum results in the identification of a pattern of oscillatory firings or beats (i.e. similar to a musical chord) among other beats that represent noise. The probability that a particular 'chord' will be identified as a signal increases as the number of detectors that simultaneously respond to such beats increases. In the SBF model, signal durations are translated into a particular cortical pattern formed by the firing of multiple neurons that have different oscillation rates. This coding scheme ensures that a large number of specific supra-second intervals can be produced by the integration of a limited number of primitives represented by different subsecond oscillation frequencies in the cortex. The relevant components of the SBF model of interval timing are illustrated in Figure 2. In comparison with traditional pacemaker/accumulator models of interval timing where DA is assumed to be the neurobiological substrate of the pacemaker pulses, in the SBF model the role of phasic DA

Figure 1



Representative patterns of striatal neuron activity with maximal firing at either 10-s or 40-s target durations plotted in conjunction with lever presses for a rat trained in a bi-peak procedure. (**a**) Striatal medium spiny neuron showing a strong increase in firing rate at the first target duration of 10 s, but failing to exhibit a robust increase in firing at 40 s despite an increase in lever pressing. (**b**) A different striatal neuron showing a large increase in firing rate at 40 s, with relatively little change around 10 s despite an increase in lever pressing. In both cases, the distributions of neural activity contrast with the lever-press distributions, which show equivalent peaks at both 10 s and 40 s. Other analyses indicate that the neurons are keeping track of signal duration and are not related to the frequency, topography, or duration of lever presses. Adapted with permission from [11••].

release is to serve as a 'start gun' by indicating the onset of a relevant signal — leading to the synchronization of cortical oscillations and the resetting of the membrane properties of the striatal spiny neurons [2••]. Consequently, this initial DA pulse coincides with the 'closing of the switch' to begin timing and later, at the end of the interval, a second DA pulse co-occurring with the delivery of reward serves to strengthen synaptic connections that are active within the striatum at the time of feedback — thereby building a 'coincidence detector' for a specific set of signal durations. In contrast, tonic DA release is considered to modulate the speed of the internal clock by altering the frequencies of cortical oscillations [14••]. Consequently, this cortico-striatal timing mechanism allows for the anticipation of future events [15–17,18•] and probably contributes to the DA-related timing deficits observed in individuals with attention-deficit disorders, Huntington's disease (HD), Parkinson's disease (PD), and schizophrenia (SZ) [19–21].

Evidence from patient populations and electrical potentials

Timing deficits in patients with impairment in cortico-striatal function are typically associated with reduced amplitude of slow brain potentials, particularly that of the contingent negative variation (CNV). This slow, negative potential shift develops over frontal and fronto-central areas in situations where a warning stimulus (S1) is followed by a predictable interval before a second (imperative) stimulus (S2) that cues a reaction time response. It was originally interpreted as a reflection of stimulus anticipation and preparation of the motor response [22]. Since then, relationships between processes involved in interval-timing and CNV features have

Figure 2

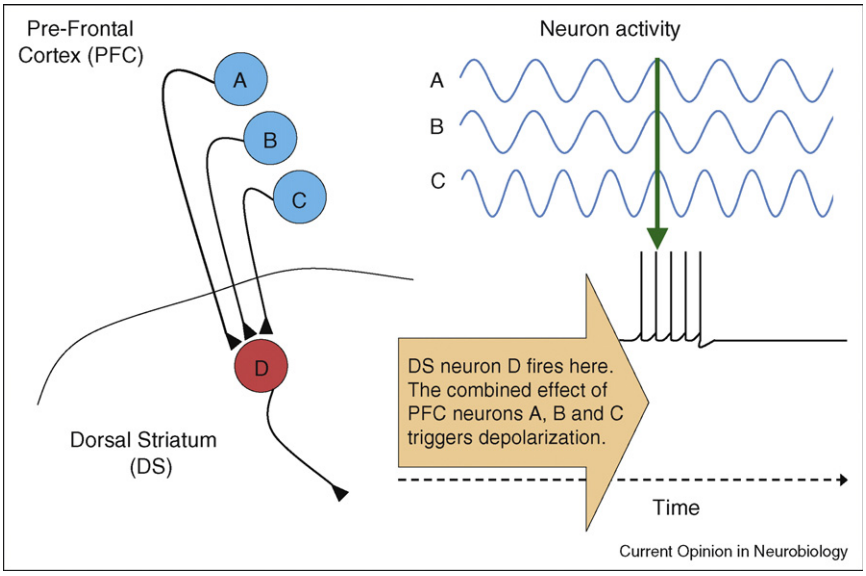
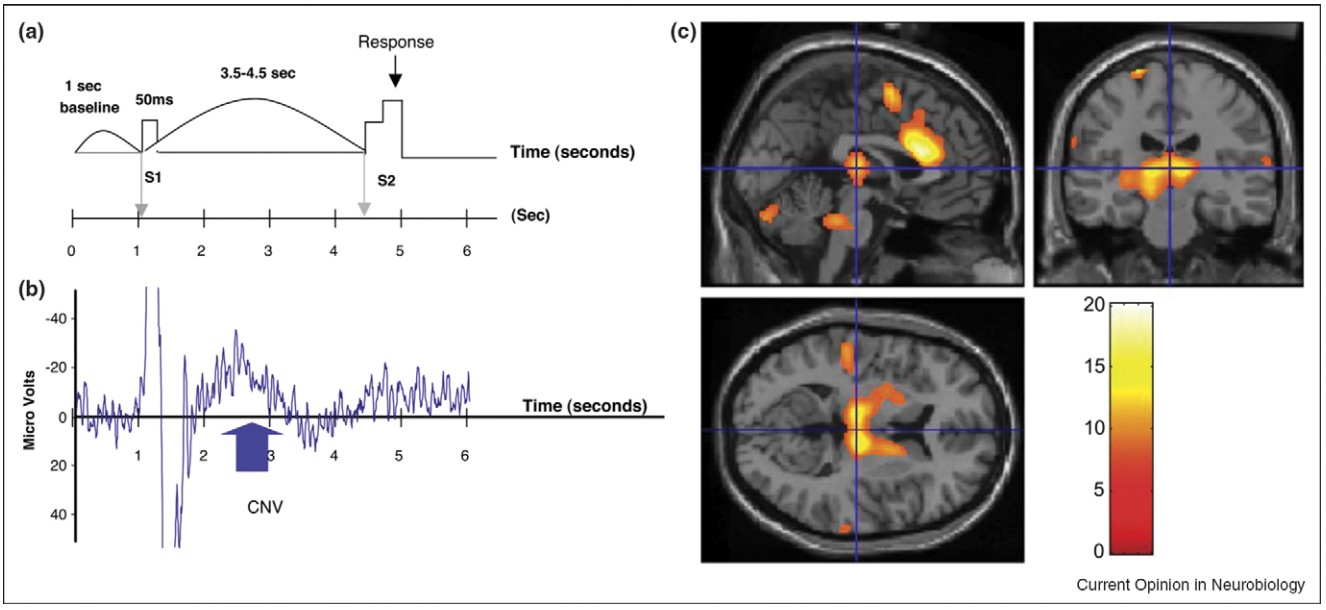


Illustration of the Striatal Beat Frequency (SBF) model of interval timing. In this model, the activation patterns of oscillatory neurons in the cortex (e.g. neurons A, B, and C) are monitored by striatal medium spiny neurons (e.g. neuron D). These cortical neurons have patterns of activity that fire with different frequencies and converge onto spiny neurons. At the beginning of an interval, these oscillating neurons are synchronized and the status level of the spiny neurons reset by dopaminergic input from the ventral tegmental area and substantia nigra, respectively. The delivery of feedback at the target duration produces a pulse of dopamine thereby strengthening the synapses in the dorsal striatum that are activated as a result of the beat-frequency pattern of these cortical neurons at that specific point in time as indicated by the green arrow. In this manner, mechanisms of long-term potentiation and long-term depression are used to strengthen and weaken synaptic weights in order to produce a record in memory of the target duration. Later, when the same signal duration is timed again, spiny neurons compare the current pattern of activation of these cortical neurons with the pattern stored in memory in order to determine when the target duration has been reached. When the clock and memory patterns match, as determined by coincidence detection, the spiny neurons fire to indicate that the interval has elapsed as illustrated for the 10-s and 40-s target durations presented in Figure 1. Adapted with permission from [14••].

been well documented [23,24]. Studies using various types of timing tasks showed the attenuation or even the absence of the anticipatory negative wave in PD patients [25]. Low CNV amplitudes before antisaccades are observed in SZ and are related to poor task preparation [26]. Bradykinesia scores in HD are significantly correlated with an early CNV amplitude reduction compared to controls [27]. In patients, decreased activation of frontal cortical areas, including the supplementary motor area (SMA) and prefrontal cortex, probably results from impaired thalamocortical output of the basal ganglia. Besides, L-DOPA treatment or subthalamic nucleus stimulation, shown to be effective in improving the clinical symptoms of PD, also improved cortical functioning as suggested by significantly increased CNV amplitudes over frontal and frontocentral regions [28,29]. These findings corroborate functional magnetic resonance imaging (fMRI) studies showing that brain activation patterns in PD patients are partially 'normalized' with DA supplementation [30]. Moreover, shifts in cortical activity from medial to lateral areas in PD or abnormal activation of the posterior part of anterior cingulate cortex in HD patients compared to controls appears to reflect a compensatory mechanism for the altered basal ganglia function [25,27–31].

CNV data have been obtained through scalp and cortical recordings. Therefore, studies using simultaneous recording of CNV and fMRI data acquisition [32] or using intracerebral recordings [33] in a CNV paradigm are of particular interest as illustrated in Figure 3. On the one hand, BOLD activity during the period of CNV generation was enhanced in SMA and adjacent cingulate cortex, thalamus, and bilateral insula. Interestingly, covariation of regional brain activity with CNV amplitude was found in the thalamus together with cingulate and SMA, confirming involvement of these structures in CNV generation. On the other hand, intracerebral recordings in epileptic patients showed that there were CNV generators in the basal ganglia, putamen, caudate, and pallidum, supporting the role of subcortical structures and the cortico-striatal-thalamo-cortical circuit in the generation of scalp-recorded CNV. These data are consistent with the amplitude decrease of the CNV found in PD patients and with the CNV restoration following L-DOPA treatment. Data from patients combined with neuroimaging studies show that normal CNV and accurate interval-timing mechanisms are dependent on intact basal ganglia function, which is consistent with the timing circuit proposed by the SBF model.

Figure 3



Relationship between regional brain activity and the Contingent Negative Variation (CNV). (**a**) Diagram illustrating the CNV paradigm: participants were presented with repeated trials of two tones, a warning stimulus (S1) and an imperative stimulus (S2) to which they were required to make a reaction time response. (**b**) Averaged EEG data of one subject, obtained during simultaneous fMRI data acquisition. (**c**) Brain regions modulated by CNV amplitude: bilateral thalamus, anterior cingulate, SMA, and cerebellum. Adapted with permission from [31].

It should be noted, however, that relationships between modulation of CNV features (amplitude and resolution time) and timing performance have typically been interpreted within a pacemaker/accumulator framework [34–36]. It has been proposed that CNV amplitude reflects the number of pulses accumulated during an interval with higher CNV amplitudes observed during intervals perceived as longer than the target duration as compared to intervals perceived as shorter than the target. Certain features of CNV activity have also been shown to be similar to those of climbing neuronal activity observed through intracerebral recordings in animals: CNV activity peaked at the end of the memorized duration, and its slope varied inversely with the length of this duration suggesting that both activities reflect the anticipation of the entrained interval termination [36]. Recent reaction time studies have renewed and generalized the idea of integration over time, and examined how the brain might accumulate evidence for a decision, whether perceptual, mnemonic, or otherwise. These results suggest that decision-making can be explained by a form of 'near perfect' temporal integration that stops when a criterion amount of evidence has been accumulated [37•,38•,39•]. In this manner, temporal integration within specific time ranges (e.g. <1–2 s) may be a fundamental computation underlying higher cognitive functions that are dissociated from immediate sensory inputs or motor outputs. Consequently, further studies must translate these issues involving different time ranges and frequency bands with respect to the SBF model and other forms of temporal integration [40••,41••].

Neuroimaging evidence using fMRI and PET

Assuming that the SBF model applies to interval timing in humans as well as it does in other animals, then two features of the model should be consistent with the extant neuroimaging literature. First, timing should elicit activation in a functional circuit that comprises the thalamus, the striatum, the substantia nigra, and distributed areas of cortex, with the precise cortical region/s perhaps depending on stimulus modality [42]. Although establishing a basic anatomical correspondence between the SBF model and the neuroimaging data supports the model, it is not, in itself, sufficient proof. This is because brain structures that are active during timing tasks may be involved in general attention, memory, and decision processes, whereas the SBF model allocates timing specific functions to particular brain structures. Consequently, the second crucial component is that modulation of brain activity during timing should be consistent with those hypothesized timekeeping roles. For example, showing that quantitative changes in brain activity parallel quantitative changes in behavior, that is the scalar property, is strong evidence that a given brain structure specifically underlies interval timing rather than merely reflects general memory and decision processes [43].

During the past decade, numerous human fMRI studies using timing tasks that are conceptually equivalent to the tasks used in animals, such as duration discrimination and reproduction, have revealed the involvement of many

Table 1

Summary of recent fMRI and PET studies of subsecond and supra-second timing revealing activation in cortical (blue) and subcortical (red) structures specified in the Striatal Beat Frequency (SBF) model of interval timing

	Task	Task Comp.	Study	Sig. Mod.	Timing Cond.	CORTEX				BASAL GANGLIA				TH
						FC	PC	OC	TC	P	C	G	S	
Sub-Second	DD	T > C	62	V	S & L	$_{pSMA}$ R_{DLPFC} B_{VLPFC} B_{LPMC}	R_{IPS}				R			
			63	A	D	$_{SMA}$ B $_{DLPFC}$ B_{FO} B_{dPMC} B_{vPMC}		L	B_{STG}	B	R			B
	DR	T > C	45	A	S & L	L_{LPMC}							L	
					S > L	L_{MFG} R_{SMFG} B_{SFG}			L_{STG} L_{MTG}		L			
			50	V		L_{IFG} B_{MFG} B_{SMA}	R_{SMG}			B		R		
	DE	T > C	50	V		L_{IFG}				L	R	R		
	RC	T > R	58	A		R_{IFG} B_{pSMA} B_{SMA} B_{PMC}			L_{STP} B_{STG}	B				
	TP	ICA	44	A		R_{SFG} R_{MFG} B_{SMA}	R_{SMG}		R_{MTG}	B	B	B		
Supra-Second	DD	T > R	59	A	Enc	R_{MFC} R_{IFC}	B_{Inf} L_{Sup} L_{AG} R_{prec}	R_{lg}	B_{Sup}	L	B_{bd} L_{tl}			
		T > C	62	V	S & L	$_{pSMA}$ R_{DLPFC} B_{VLPFC} B_{LPMC}	R_{IPS}				R			
					L > S	$_{pSMA}$ R_{IFG} B_{LPMC}					R			
		T > O	46	V		$_{pSMA}$ L_{VLPFC} R_{DLPFC} R_{FO} R_{dPMC}	B_{Inf}		R_{Sup} R_{Mid} R_{Inf}	L_{Ant}				
			61	V	C easy	B_{PFC} B_{IFG} B_{PMC}	R_{Inf}			B				
					C diff	B_{IFG}	L_{SMG}			L				
	DR	T > C	47	A & V		B_{DLPFC} B_{PFC}			$_{STG}$	B	L			R
			45	A	S & L	L_{LPMC}							L	
					S > L	R_{DLPFC} R_{SMA} B_{LPMC} R_{PMC}	$R_{IPS/AG}$ R_{Sup}			R				
			60	V		R_{IFG} L_{SFG} L_{SMA} L_{dPMC}	L_{SM1} L_{prec}	L_{lg}				R		

Task: DD = duration discrimination, DE = duration estimation, DR = duration reproduction, RC = rhythm comparison, TP = tapping. *Task comparison* (*Task comp.*): T = timing, O = other task (color discrimination [46••,61••]), C = nontiming control task (press response button after stimulus [45••,61••]; passively view stimulus [47••,60]), ICA = independent components analysis. *Signal modality* (*Sig. mod.*): A = auditory, V = visual. *Timing condition*: D = difficult, S & L = short and long duration versus control comparison, S > L = short versus long comparison, C easy = color discrimination task easier than timing task, C diff = color discrimination task more difficult than timing task, Enc = encoding condition, L > S = long versus short comparison. *Anatomical directions*: B = bilateral activation, L = left hemisphere activation, R = right hemisphere activation, Ant = anterior, Inf = inferior, Mid = middle, Pos = posterior, Sup = superior. *Brain structures*: AG = angular gyrus, bd = body, C = caudate, DLPFC = dorsolateral prefrontal cortex, dPMC = dorsal premotor cortex, FC = frontal cortex, FO = frontal operculum, G = globus pallidus, IFC = inferior frontal cortex, IFG = inferior frontal gyrus, IPS = intraparietal sulcus, lg = lingual gyrus, LPMC = lateral premotor cortex, MFC = medial frontal cortex, MFG = middle frontal gyrus, MTG = middle temporal gyrus, OC = occipital cortex, PC = parietal cortex, PFC = prefrontal cortex, prec = precuneus, pSMA = pre-supplementary motor area, P = putamen, SFG = superior frontal gyrus, SM1 = primary sensorimotor cortex, SMA = supplementary motor area, SMFG = superior mesial frontal gyrus, SMG = supramarginal gyrus, S = substantia nigra, STG = superior temporal gyrus, tl = tail, TC = temporal cortex, TH = thalamus, VLPFC = ventrolateral prefrontal cortex, vPMC = ventral premotor cortex. (See Refs. [58•,59•,62••,63]).

cortical areas, including the DLPFC, SMA, preSMA, STG, and inferior parietal lobule. Equally important for the SBF model is the evidence of activity in the striatum (both caudate and putamen), thalamus, and substantia nigra. A summary of recent fMRI studies showing timing-related activation in these areas is presented in Table 1.

Is there evidence that these regions comprise a functional network? If spatially distinct brain activations share similar hemodynamic changes over time, then this suggests that those areas form a functional circuit. Stevens *et al.* [44••] used spatial ICA to isolate a circuit comprising the right middle frontal gyrus, left cingulate, SMA (superior frontal gyrus), right MTG, right SMG, bilateral insula, bilateral caudate, bilateral putamen, bilateral globus pallidus, and bilateral thalamus. Their data analysis revealed activation of this network independent of whether or not the timing task had an explicit motor component. These results map exceedingly well onto the functional neuroanatomy of the SBF model described above.

Can the components of the functional circuit in turn be mapped onto specific timing roles? Using positron emission tomography (PET), Jahanshahi *et al.* [45••] obtained substantia nigra activation and interpreted it as reflecting a reinforcement signal and reset mechanism consistent with the SBF model. Moreover, Coull *et al.* [46••] reported that frontal cortical regions invoke a 'time scale or time line' and that the putamen then 'detects the target duration within the invoked time scale' which are precisely the functions prescribed for these brain areas by the SBF model [14••]. Although valuable, these demonstrations of a correspondence between brain area and

function are less compelling than evidence that changes in brain activity track behavior, such as demonstrating that variation in brain activity, measured as percent hemodynamic signal change, scales with the target duration being timed in a similar manner to the scalar property or Weber's law, that is, the variability in timing behavior grows in proportion to the mean of the interval being timed [2••]. Meck and Malapani [43] reanalyzed fMRI data from Hinton and Meck [47••] and showed scalar timing variance in brain activation only in the putamen, that is, normalized hemodynamic response functions showed superimposition in relative time, in an interval-timing condition, but not in a motor-timing condition. Similar findings have also been observed using ERP techniques in human infants and adults [48]. These findings are particularly important because isolation of psychological processes to subcomponents of a timekeeping network will require demonstration that brain activation patterns correspond to the psychophysical characteristics of interval timing.

Conclusion

The evidence presented here strongly suggests that the cortical and basal ganglia structures implicated in the SBF model are used by a wide variety of species [49] in tasks that present auditory and visual stimuli, durations ranging from hundreds of milliseconds to several seconds, and require duration discrimination, production, and reproduction decisions (see Figures 1 and 3, Table 1). As a consequence, a number of investigators have suggested that the dorsal striatum may serve as a 'core timer' because it is centrally active in both duration reproduction and duration perception tasks in both the subsecond and supra-second ranges [10,11••,14••,45••,47••,50•,51,–53], with the involvement of specific cortical areas being influenced by task factors such as signal modality, decision processes, and response requirements. In addition to providing an oscillatory 'time code' to the striatum, the cortex may also support 'satellite' temporal integration mechanisms that are able to function with some degree of independence from the 'core timer', which is ultimately required for the synchronization of these distributed timing mechanisms and shifts in dopaminergic sensitivity as a function of the level of training, emotional state, and circadian cycles [2••,7,21,40••,54–57].

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