The Interactions of Temporal and Sensory Representations in the Basal Ganglia

Pavel E. Rueda-Orozco, Ana E. Hidalgo-Balbuena,
Perla González-Pereyra, Mario G. Martinez-Montalvo,
and Ana S. Báez-Cordero

Abstract

In rodents and primates, interval estimation has been associated with a complex network of cortical and subcortical structures where the dorsal striatum plays a paramount role. Diverse evidence ranging from individual neurons to population activity has demonstrated that this area hosts temporal-related neural representations that may be instrumental for the perception and production of time intervals. However, little is known about how temporal representations interact with other well-known striatal representations, such as kinematic parameters of movements or somatosensory representations. An attractive hypothesis suggests that somatosensory representations may serve as the scaffold for complex representations such as elapsed time. Alternatively, these representations may coexist as independent streams of information that could be integrated into downstream nuclei, such as the substantia nigra or the globus pallidus. In this review, we will revise the available information suggesting an instrumental role of sensory representations in the construction of temporal representations at population and single-neuron levels throughout the basal ganglia.

Keywords

Basal ganglia · Timing · Action · Sensory processing

Introduction

The basal ganglia (BG) are a group of subcortical nuclei implicated in motor function. While their specific function is still debated, multiple streams of evidence in human and nonhuman primates, felines, and rodents indicate their involvement in action selection, postural control, and modulation of movement parameters, such as vigor, timing, and kinematics (Graybiel, 2008; Redgrave et al., 2010; Turner & Desmurget, 2010; Dudman & Krakauer, 2016; Yin, 2017; Robbe, 2018). In rodents, the main nucleus of the BG is the striatum, which in turn can be subdivided into three functional regions: the ventral striatum, receiving information mainly from limbic regions including the medial and orbital prefrontal cortex; the dorsomedial striatum, receiving information mainly from dorsolateral prefrontal and premotor cortices; and the dorsolateral striatum (DLS), receiving information mainly from sensorimotor

---

P. E. Rueda-Orozco (✉) · A. E. Hidalgo-Balbuena
P. González-Pereyra · M. G. Martinez-Montalvo
A. S. Báez-Cordero
Institute of Neurobiology, National Autonomous University of México, Querétaro, Mexico
e-mail: ruedap@unam.mx

H. Merchant, V. de Lafuente (eds.), *Neurobiology of Interval Timing*, Advances in Experimental Medicine and Biology 1455, https://doi.org/10.1007/978-3-031-60183-5_8

regions of the cortex and thalamus (Redgrave et al., 2010). The DLS, also known as sensorimotor striatum, has been more commonly implicated in motor control and time-related processes (Buhusi & Meck, 2005; Redgrave et al., 2010; Merchant et al., 2013). In humans, BG lesions produce chronometric dysfunctions; for example, patients with bilateral striatal lesions present problems with interval production and, to a lesser extent, with interval perception (Coslett et al., 2010; Schwartze et al., 2015; Nozaradan et al., 2017). Similar results have been found in patients with Parkinson's disease and Huntington's disease who were tested in different interval timing protocols. Both types of patients tended to present strong impairments not only in interval perception but also in interval production (Rowe et al., 2010; Beudel et al., 2013; Honma et al., 2016, 2018). In rodents, bilateral striatal lesions completely abolished timing behavior in a peak-interval timing procedure (Meck, 2006). In a protocol where rats were trained to execute a timed sequence of movements while running on a motorized treadmill, bilateral striatal lesions affected speed control and behavioral timing (Jurado-Parras et al., 2020). While the BG have been associated with various behaviors, little is known about the potential interactions between the well-characterized sensorimotor functions and other relevant functions, such as the perception or production of time intervals. With the objective of creating a conceptual bridge between these apparently different functions, in the following sections, we will analyze the available literature where, in our opinion, timing and sensorimotor functions intersect and arise from the neural dynamics of the same neural populations.

The Dorsolateral Striatum: A Sensorimotor Hub Implicated in Interval Perception and Production

Cortical activity has been typically associated with temporal processing from ramping spiking patterns at the single-cell level in the medial premotor cortex (MPC) (Merchant et al., 2011) to whole cortical regions containing temporal information embedded in the population activity, commonly known as "population clocks" (Buonomano & Laje, 2010). In these population dynamics, temporal information can be extracted from the sequential activation of neurons within the population (Zhou et al., 2020), that is, from the "temporal position" of each cell within an activation sequence triggered by a particular stimulus or behavioral transition (Jin et al., 2009). Furthermore, temporal information can also be extracted from the geometrical characteristics of the cortical population's neural trajectories (Gámez et al., 2019). Altogether, various lines of evidence in primate literature suggest that the MPC carries time-related information at the single-cell and population level. The evidence also supports the notion that in primates, this region is implicated in the perception and production of time intervals. However, sensorimotor cortices massively innervate the striatum, where single-neuron and population temporal-related dynamics have also been reported, making it difficult to understand if the temporal representations in the striatum are partially or completely inherited from cortical regions, or whether partially or completely produced locally (Wang et al., 2018). For example, in primates, striatal spiking activity has been associated with timing perception. In an interval discrimination procedure, the striatal bursting activity of individual neurons was associated with the presentation of different stimulus durations, delay periods, and final choices, suggesting a potential involvement in interval categorization (Chiba et al., 2015). Conversely, when animals were required to produce a particular time interval, individual striatal neurons tracked the passage of time in an adjustable ramping fashion during three different instructed intervals (Kunimatsu et al., 2018). Moreover, important examples of the role of the corticostriatal networks at the single-cell and population levels have recently emerged from the rodent literature. At the single-cell level, rodent cortical dynamics have been shown to present both ramping activity and sequential activation in relation to specific time intervals (Kim et al., 2013; Xu et al., 2014; Henke et al., 2021).

Likewise, subpopulations of DLS neurons have been described to discharge at specific time intervals associated with rewards, suggesting that this brain region could represent behaviorally relevant intervals (Matell et al., 2003). Similar to what has been found in primates, Gouvêau et al. (2015) demonstrated that in rats trained to discriminate between long- and short-time intervals on the scale of a few hundreds of milliseconds, striatal neural population dynamics are organized in sequences of activation, and population trajectories drawn from dimensionally reduced dynamics from the same activity adjust their speed depending on the duration of the interval (Gouvêa et al., 2015). Along the same line, in rats trained to lever press at different fixed-interval ratios ranging from 12 to 60 s, striatal population dynamics covered the interval to be estimated and the sequential activation order of the cells scaled with the target interval (Mello et al., 2015). In another example, Bakhurin and colleagues (Bakhurin et al., 2017) trained mice to lick from a water spout starting 2.5 s after the presentation of a particular odorant. In this work, striatal and cortical population dynamics were analyzed and compared, demonstrating that striatal activity was significantly more useful to decode the passage of time in the 2.5-s interval between the odor presentation and motor response.

The previous examples illustrate the striatal involvement in the perception of time intervals in rodents, but a few other examples have also addressed its participation in time interval production. Rueda-Orozco and Robbe trained rats to execute a timed sequence of accelerations and deaccelerations while running on a motorized treadmill at a fixed speed (Rueda-Orozco & Robbe, 2015). The authors found robust DLS speed and spatial representations of the sequence of movements, but interestingly and in contrast with the previous examples, they only found a few individual cells that presented correlations with elapsed time, suggesting that this variable may be better represented in the ensemble activity. In the same work, the authors were able to compare the sequential activation of neurons associated with execution sequences of movements in expert and naïve animals. While the kinematic representations were specific to the expert rats, the sequential activation elicited by movement execution was present in both groups. This observation suggested a strong learning-independent sequential organization evolving in time and triggered by relevant behavioral events, as a potential temporal structure to contextualize motor commands (Paton & Lau, 2015; Rueda-Orozco & Robbe, 2015). Recently, a similar idea was proposed and tested by Toso et al. (2021). In this work, rats were trained to estimate the duration of patterns of somatosensory stimulation applied to the animal's whiskers. These patterns changed in duration, frequency, and amplitude. As in all the previous examples, the authors found clear DLS sequential activations that spanned for the duration of trials, but inherently, these were decoupled from the animals' judgments of duration. The authors concluded that trial-related temporal representations in the form of sequential activation are inherent to the DLS but have no impact on the judgment of specific intervals presented during the same trial (Toso et al., 2021).

The previous examples support the notion that striatal sequential activations are a robust phenomenon that can be triggered by specific behavioral circumstances, such as odors or cutaneous stimulations, or the beginning of trained (or untrained) movement sequences. In fact, in a recent article, it has been demonstrated that these DLS sequences can also be evoked in anesthetized conditions by applying specific patterns of somatosensory stimulation (Hidalgo-Balbuena et al., 2019). While it is difficult to question the presence of this organized neural unfolding, its specific contribution to timed behavior, if any, is still yet to be fully determined. In this context, two future lines of research may help to clarify this point: first, determining the exact source of these sequential activations and whether they are linked to sensory feedback or can be self-sustained after being triggered by sensory or motor commands from cortical or thalamic inputs to the striatum, and second, manipulating these sequences during different behavioral contexts, for example, during behavioral protocols specifically designed to produce or sense time intervals.

In the following sections, we will address the latest evidence in both directions.

Sensory Processing in the DLS: Beyond Sensory Feedback for Sensorimotor Transformations

The somatotopic sensory representation in the striatum has been described for decades in primates and rodents (West et al., 1990; Carelli & West, 1991; West, 1998; Reiner et al., 2003; Coffey et al., 2016; Hintiryan et al., 2016). These representations have been accepted as the intrinsic anatomical organization of corticostriatal communication, and recently, it has been demonstrated that cortical activity permeates the striatum in a topographically organized fashion (Peters et al., 2021). However, the exact role of these representations is not entirely clear. In the context of motor control, a straightforward possibility is that these representations may be necessary to contextualize action maps and provide sensory feedback for movement control. In humans, somatosensory functions, such as somatosensory discrimination or tactile object shape recognition, have been reported to be impaired in Parkinsonian patients (Weder et al., 1999, 2000), and basic sensory processing and integration appear to be disrupted in rodent models of Parkinson's disease (Ketzef et al., 2017; Peña-Rangel et al., 2021).

How sensory information is processed in the striatum? In this section, we will focus on somatosensory processing, mostly from the whisker and forelimb systems. First, in the rodent, different streams of sensory information reach the DLS from the primary somatosensory cortex (Hoover et al., 2003) and sensory regions of the thalamus (Erro et al., 2001, 2002; Díaz-Hernández et al., 2018; Hidalgo-Balbuena et al., 2019). Second, it has been demonstrated that striatal medium spiny neurons (MSNs) from both direct (dMSNs) and indirect (iMSNs) pathways are able to integrate information from different sensory modalities, such as somatosensory and visual modalities (Reig & Silberberg, 2014; Coffey et al., 2017), and from ipsilateral and contralateral sensorimotor cortices (Reig & Silberberg, 2016). Third, it has been suggested that information is greatly "filtered" in its transition from the cortex to the striatum. In a rodent study, cortical layer 5 neurons from the barrel field projecting to the DLS were antidromically identified by stimulating the DLS. While most of the cortical neurons were responsive to whisker stimulation, only about a third of the neurons recorded in the DLS responded to the same stimulation (Pidoux et al., 2011). Fourth, striatal sensory representations are used to guide learning and reward associations. In an elegant work on the barrel system of mice, whisker stimulation was associated with water rewards, and conditioned responses were defined as "licks" to a waterspout. Whisker-related depolarizations associated with rewards (but not when animals made mistakes) were detected in the membrane potential of MSNs from the DLS (Sippy et al., 2015). In the same work, it was demonstrated that both dMSNs and iMSNs exhibited significant membrane potential depolarizations, but dMSNs presented the shortest response latencies and associated action potentials, while the iMSNs' depolarizations were not sufficient to trigger action potentials. The authors also reported that substituting whisker stimulation (in catch trials) with optogenetic activation of dMSNs, but not iMSNs, efficiently evoked the conditioned response (Sippy et al., 2015). These results are consistent with the role of the BG in sensorimotor transformation, which can either bias the behavior toward a reward or simply initiate a sensory-guided action, in this case "licking." Additional work has shown that the primary motor (M1) and sensory (S1) cortex provide differential inputs to the subpopulations of neurons in the DLS. Lee et al. have proposed that S1 (but not M1) provides stronger inputs to parvalbumin interneurons, typically known as fast-spiking interneurons, than to MSNs (Lee et al., 2019; Johansson & Silberberg, 2020). Interestingly, optogenetic S1-DLS terminal activation during a sensory discrimination protocol induced a response inhibition, while M1-DLS terminal activation induced a facilitated behavioral outcome.

Until recently, striatal sensory information has been studied in the context of stimulus-reward associations, providing a potential basis for movement timing; that is, the moment when movements may be initiated or repressed. However, movement initiation constitutes only a piece of the puzzle. Sensory information throughout the cortico-BG-thalamic circuits is a constant flow that accompanies motor execution, for example, when rodents freely explore the world with whiskers and forelimbs, usually in a rhythmic fashion (West et al., 1990; Shi et al., 2005; Rueda-Orozco & Robbe, 2015; Hidalgo-Balbuena et al., 2019). Hence, the study of sensorimotor processing in the BG has recently benefitted from sensory information analyses in the context of continuous motor execution or stimulation patterns that mimic motor execution. In this context, repetitive sensory stimulation of the whiskers or forelimbs induces different patterns of response adaptation in cortical and DLS neurons (Smith et al., 2012; Peña-Rangel et al., 2021). It has been proposed that different patterns of adaptation (short-term facilitation or inhibition) are related to the propensity of recurrent networks, such as the cortex or striatum, to generate sequential patterns of activation (Carrillo-Reid et al., 2015b; Goel & Buonomano, 2016). These striatal sequential patterns that can be observed in isolated brain slices (Carrillo-Reid et al., 2008) or in rodent behavior (Barbera et al., 2016) may be a mechanism through which a constant sensory flow to the BG helps to sense or to produce time intervals.

Sensory Information in the DLS: A Dynamic Pacemaker to Contextualize Motor Timing

One intrinsic characteristic of sensory systems is that, under particular circumstances, they are entrained to behavioral dynamics. For example, in the case of the olfactory system, the sensation is rhythmically organized and tightly linked to the respiratory rhythm (Cury & Uchida, 2010; Junek et al., 2010). The encoding consequences of this imposed rhythm are still under debate, but one possibility is that breathing may act as an oscillatory pacemaker creating windows for the integration of information at brain-wide scales that may be important for cognitive functions, such as memory consolidation (Karalis & Sirota, 2022). Similarly, rhythmic auditory and visual information have been probed to serve as external pacemakers that entrain cortical and subcortical activity into circular population dynamics to encode beats or complex rhythms which may ultimately guide rhythmic behavior (Cadena-Valencia et al., 2018; Gámez et al., 2019). Another important characteristic is that sensory-evoked responses at the single-cell and population levels appear to share temporal dynamics independently of the sensory modality, suggesting a common scaffold for information processing that can be used for cognitive and motor functions (Luczak et al., 2015). In the somatosensory system, at the single-cell level, these responses can be observed as complex patterns consisting of short-latency activations frequently followed by a transient inactivation and a rebound (Fig. 1a) (Chapin et al., 1981; Hidalgo-Balbuena et al., 2019; Peña-Rangel et al., 2021). These patterns present a variety of response latencies across the population, giving the impression of sequential activation covering hundreds of milliseconds following the stimulation onset (Fig. 1b, c). Furthermore, the temporal architecture of these population dynamics (Fig. 1c) appears to be spontaneous and recruited by the corresponding sensory stream (Luczak et al., 2007, 2009; Carrillo-Reid et al., 2015a). In this context, DLS activity is strongly permeated by topographically organized somatosensory representations (West et al., 1990; West, 1998; Reiner et al., 2003; Hintiryan et al., 2016). From these, forelimb, hindlimb, mouth, and whisker representations would be naturally prone to be rhythmically entrained during locomotion, mastication, or exploration. The whisking cycle, for example, oscillates at around 10 Hz (Deschênes et al., 2016; Sreenivasan & Petersen, 2016). These signals can be recorded in the DLS of unrestrained or anesthetized rodents (Alloway et al., 2009; Smith et al., 2012, 2014). The relevance of these rhythmic signals in the striatum has not been

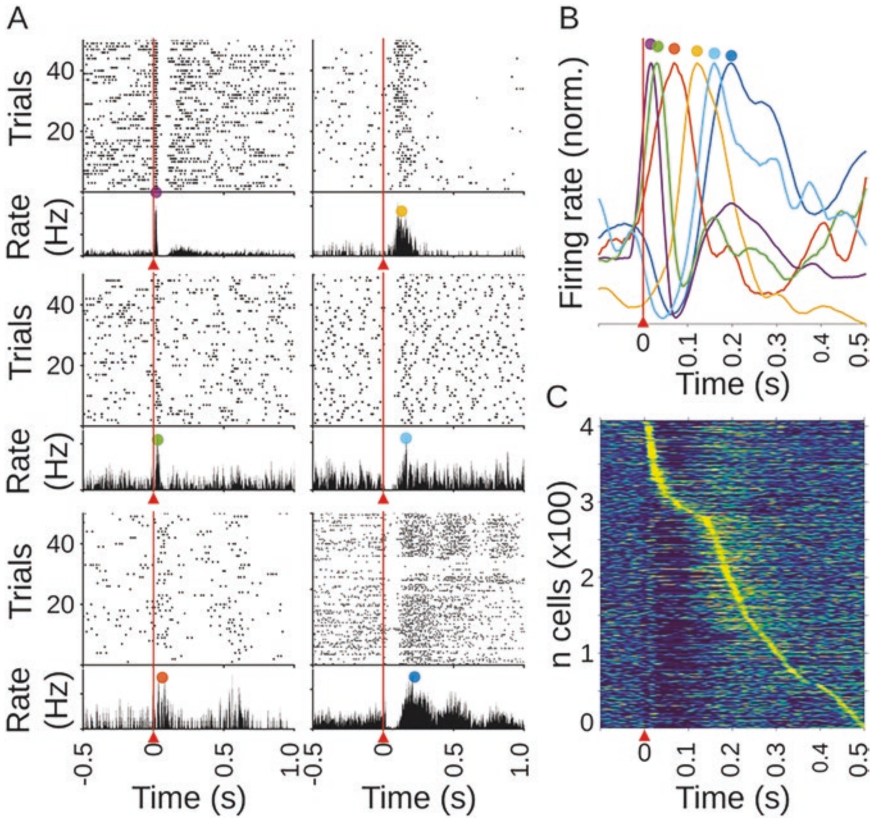

Fig. 1 Sensory-evoked responses organized in sequences covering hundreds of milliseconds. (**a**) Somatosensory-evoked activity in six representative neurons recorded in the dorsolateral striatum (color-coded). Spike rasters and peri-histograms are aligned to the onset of somatosensory stimulation (red lines and arrowheads) of the contralateral forepaw palm to the recording site. For each neuron, the moment of the highest firing rate after stimulus onset is indicated by a colored dot. (**b**) The average activity of neurons displayed in A was normalized to the highest peak, revealing a variety of latencies spanning hundreds of milliseconds. (**c**) Average firing rate (z-scored) for more than 400 neurons recorded in the striatum, sorted by the time of the highest activity after stimulus onset (red arrowhead). Cells displayed in this figure were collected in experiments reported in (Hidalgo-Balbuena et al., 2019; Peña-Rangel et al., 2021)

determined, but one possibility is that it may serve as a pacemaker to facilitate inter-region or interstructure communication. Along the same line of thinking, in rats, the forelimb cycle during locomotion typically oscillates between 2 and 3 Hz depending on movement speed (West et al., 1990; Carelli & West, 1991; Shi et al., 2004). In this case, in previous work from our group, we explored the relevance of these striatal rhythmic signals (Hidalgo-Balbuena et al., 2019). First, by using an anesthetized model where sensory signals can be reliably recorded in sensory regions of cortical, striatal, and nigral regions (Mochol et al., 2015; Peña-Rangel et al., 2021), we induced striatal population sensory responses evoked by 3.3 Hz trains of cutaneous stimuli mimicking the forelimb cycle when animals are running at speeds of ~30 cm/s. This stimulation protocol evoked cortical and striatal population dynamics organized in neural sequences that covered the 300-ms interval between stimuli (Hidalgo-Balbuena et al., 2019; Peña-Rangel et al., 2021). Interestingly, when activity was analyzed throughout the train of 5 stimuli, sensory-evoked striatal population dynamics were more useful to decode elapsed time as compared to the decoding from cortical activity (Hidalgo-Balbuena et al., 2019). These observations suggest a prewired striatal network configuration that can be recalled by sensory stimulation even in artificial experimental conditions and that is independent of motor commands. Such network dynamics have been observed in in vitro conditions in cortical culture cells (Goel & Buonomano, 2016) and similar dynamics have been reported in striatal slices (Carrillo-Reid et al., 2008), supporting the idea that an intrinsic functional property of neural networks is the organization in sequential dynamics from which time can be decoded (Goel & Buonomano, 2014). While this is an attractive alternative, there are still some important questions to answer. For example, what type of timing would these dynamics represent? Would these signals be useful to exclusively perceive time, or would they also be useful to guide timed actions? To address these possibilities, in a previous report, we optogenetically activated/inactivated sensory pathways to the DLS in rats performing a stereotyped sequence of movements in a temporal interval of 7 s. Inhibiting and exciting sensory pathways to the DLS induced the execution of shorter and longer sequences of movements, respectively. Further behavioral analysis revealed that changes in sequence duration were independent of movement speed or motor confounds, confirming that these changes were related to under and overestimation of the temporal interval, respectively (Hidalgo-Balbuena et al., 2019). These data indicate that rhythmic sensory inputs to the DLS may constitute a temporal reference for movement production. In this study, striatal neural dynamics were not assessed during movement execution; hence, it was not possible to determine if the sensory manipulations that induced behavioral changes also impacted DLS population dynamics. In this sense, a more recent work suggests that striatal neural sequences can guide temporal judgments (Monteiro et al., 2023). By manipulating striatal temperature in rodents, authors were able to speed up or slow down both striatal sequential dynamics and temporal judgments, strongly suggesting that scaling striatal temporal population dynamics is the mechanism used to estimate elapsed time (Monteiro et al., 2021). Further experiments would be necessary to elucidate the exact neural mechanism underlying the production of temporal intervals, but in our opinion, the previous evidence strongly suggests that rhythmic entrainment induced by different sensory streams to the BG may play a central role in this function.

Sensory- and Time-Related Signals Throughout Cortico-Basal Ganglia-Thalamic Circuits

The striatum belongs to a macrocircuit that includes BG and extra-BG structures; hence, an important question arises about the diversity of the temporal representations that reach the circuits of the BG. Are striatal sensory and sequential representations distributed homogeneously throughout the different subpopulations of striatal neurons and downstream BG nuclei? MSNs, the main striatal population, are further divided into two subpopulations expressing distinct subclasses: dopaminergic metabotropic receptors D1 and D2 (Albin et al., 1989; Gerfen et al., 1990). MSNs expressing the D1 receptor are the origin of the direct pathway (dMSNs), projecting directly to the output nuclei of the BG, the globus pallidus internal segment (GPi) and the substantia nigra pars reticulata (SNr). MSNs expressing the D2 receptor are the origin of the indirect pathway (iMSNs), projecting to the external segment of the globus pallidus (GPe). Both pathways exert opposing effects over movement control, with dMSNs and iMSNs facilitating and inhibiting movement, respectively (Albin et al., 1989; Gerfen et al., 1990; Kravitz et al., 2010; Cruz et al., 2022). The main source of dopamine to all BG nuclei is the substantia nigra pars compacta (SNc), and it has been reported that SNc neurons encode interval duration and that its activation or inactivation is sufficient to slow down or speed up time interval perception, respectively (Soares et al., 2016). These data suggest that both pathways are permeated by time-related signals, but whether each pathway would represent time or not is still unknown. In this context, a recent work in mice demonstrated that both subpopulations of neurons develop strong and reliable sequential activations associated with forelimb movements (Sheng et al., 2019). Importantly, the experimental design included fixed intertrial intervals, and it was during this period when more iMSNs were implicated in sequential organization. These data suggest that interval representation may not be homogeneously represented in the striatum. Whether these iMSN/dMSN sequential activations are exclusively training-dependent or also spontaneous or triggered by sensory streams is yet to be defined. However, the latter possibility would not be surprising since; for example, it has been shown that whole-body somatosensory representations (Coffey et al., 2017) and rhythmic signals related to licking (Chen et al., 2021) are present in both pathways, and both subpopulations display different patterns of recurrent connectivity with other elements of the striatal microcircuit, such as neurons of the opposite pathway or interneurons (Taverna et al., 2008; Chuhma et al., 2011). In this context, systemic, and intrastriatal administration of D2 but not D1 antagonist produced an overestimation of time intervals in a "peak-interval" procedure (Drew et al., 2003; De Corte et al., 2019; Kamada & Hata, 2021). However, earlier studies suggest that both D1 and D2 receptor agonists and antagonists may produce similar time overestimations and underestimations, respectively (Frederick, 1996). However, Cheung et al. found that systemic administration of quinpirole, a D2 receptor agonist, caused an overestimation of time, while the administration of a D2 antagonist produced no impact on timing (Cheung et al., 2007). More recently, it has been reported that the striatal optogenetic manipulation of the BG's direct pathway produced a temporal representation reset of a fixed interval (Bakhurin et al., 2020). Indirect pathway activation induced a pause on the interval that proportionally recovered as optogenetic stimulation ceased (Bakhurin et al., 2020). There are still many questions on whether the activity of a single pathway would be better to encode elapsed time; however, the available evidence arising from pharmacological and optogenetic research and experiments suggests that this may be the case.

The External Segment of the Globus Pallidus While there is a consensus on the participation of the dopaminergic system in temporal processing, the specific anatomical and functional mechanisms are far from being fully understood. An alternative possibility to explore the role of the different pathways in temporal processing would be to focus on different elements of the BG beyond the striatum. Additionally, time representation may be considered an emergent property of neural networks (striatal or extra-striatal), where the temporal dynamics could be mediated by their connectivity and the intrinsic properties of their elements (Goel & Buonomano, 2014). In this context, the GPe and the subthalamic nucleus (SthN) are anatomically independent entities typically associated with the indirect pathway. The GPe is a GABAergic nucleus considered the first relay of the indirect pathway. It targets the output nuclei of the BG (the internal segment of the GP and the SNr) with reciprocal connections with the striatum and SthN (Kita & Jaeger, 2016). Given that the GPe is centrally located within the BG, studying this area may be an interesting approach to explore the indirect pathway's contribution to movement control and other components of behavior, including timing. In primates and rodents, GPe neurons display firing rates between 30 and 80 Hz and adjust their activity patterns to passive and active movements of the arm and orofacial regions (DeLong, 1971; Alexander & DeLong, 1985). In addition, these neurons can also couple their spiking activity to different temporal phases of movement or movement sequences, firing before, during, or at the end of the sequence (Hegeman et al., 2016). Previous reports on non-human primates also demonstrate somatotopic representations of the different parts of the contralateral hemibody, inheriting the topographical organization from the sensorimotor cortices and the DLS (Bevan, 2002; Jaeger & Kita, 2011; Nambu, 2011; Iwamuro et al., 2017). In terms of intrinsic properties, GPe shares important features with time-related structures, such as the cortex of the striatum. For example, cortical sensory/motor stimulations or even task-relevant events produce complex response patterns in the firing rate of individual GPe neurons, characterized by an initial high-frequency discharge followed by a transient inhibition and a final burst rebound (Alexander et al., 1985; Bevan, 2002; Jaeger & Kita, 2011; Kita & Jaeger, 2016; Iwamuro et al., 2017). These complex response patterns have been described in cortical and striatal regions (Chapin et al., 1981; Hidalgo-Balbuena et al., 2019; Peña-Rangel et al., 2021) and have been proposed as "building blocks" of population spontaneous or evoked packets of information from which temporal representations can be extracted (Goel & Buonomano, 2014; Luczak et al., 2015; Hidalgo-Balbuena et al., 2019) (Fig. 1). In summary, while there are no network analysis studies directly exploring the contribution of the GPe to time interval estimation, the basic network elements observed in other brain regions would make this indirect pathway structure a suitable candidate to explore this possibility.

The Substantia Nigra Pars Reticulata The SNr is one of the two major output nuclei of the BG, receiving mostly inhibitory afferents from the striatum (direct pathway) and excitatory afferents from the SthN (indirect pathway) (Yoshida & Precht, 1971; Dray et al., 1976; Parent et al., 1984). SNr neurons synthesize and release GABA tonically to its main targets, the motor thalamus (ventral medial/lateral; VM/VL) and the dorsal midbrain (Carpenter et al., 1976; Parent et al., 1983; Hikosaka, 2007). In addition, SNr neurons display multiple collateral contacts with other SNr neurons, providing intrinsic feedback to regulate the output of the BG (Brown et al., 2014). SNr neurons show complex associations with sensory events (Nagy et al., 2005; Brown et al., 2014; Báez-Cordero et al., 2020) and different phases of movement, such as preparation and execution (Hikosaka & Wurtz, 1983; Turner & Desmurget, 2010; Schmidt et al., 2013). An interesting feature of SNr neurons is that changes in their firing rate are rarely related to a single event. For example, the same cell might have multisensory responses (Nagy et al., 2005) and be modulated by saccades triggered by visual stimulation. Regarding the potential contribution to temporal processing, Shultz (1986) studied the electrophysiological properties of SNr neurons with extracellular recordings from single neurons in monkeys performing a behavioral GO/NO-GO paradigm, employing an initial preparatory tone, visual stimuli, and forelimb reaching movements. SNr neurons showed consistent changes in activity during performance, and these changes were not simply related to sensory stimuli or forelimb movements. Some neurons increase or decrease their activity during the period between an initial sensory stimulus and the availability to move for reward. Similar complex responses have been seen in SNr neurons in relation to oculomotor mechanisms (Wurtz & Hikosaka, 1986). These complex responses have been typically described as neural mechanisms related to motor planning or movement onset; however, some of their temporal dynamics may also be related to temporal processing. For example, in mice trained to lick a waterspout for reward in a fixed-interval schedule, stimulation of the SNr to the superior colliculus pathway not only canceled licking (motor effect) but also delayed the initiation of anticipatory licking for the next interval, suggesting that SNr may play a role in initiating actions and in adjusting central timing mechanisms (Toda et al., 2017). However, in a cue-guided decision-making licking task in mice (Catanese & Jaeger, 2021), the authors recorded single-unit activity in the VM/VL thalamus; these neurons showed a prominent ramping of activity during a delay epoch in anticipation of a Go cue signaling the onset of movement, suggesting that ramping activity was related to the timing of action initiation. Next, the authors explored whether inhibition from the SNr during the delay epoch could affect behavioral outcomes through an alteration of ramping activity in VM/VL. To test this possibility, they optogenetically stimulated the SNr GABAergic terminals in the VM/VL thalamus during the delay epoch and found a decrease in impulsive licks and an increase in movement omissions. These behavioral changes were accompanied by a decrease in the ramping activity of multiple VM/VL neurons, further supporting the notion that SNr contributes to the appropriate timing of action initiation.

The Motor Thalamus So far, we have revised BG neural dynamics that can be linked to temporal processing. However, the concerted activity of these motor nuclei would be meaningless without a reader. The main target of the output of the BG is the motor thalamus (MTh), a group of nuclei linking subcortical and cortical areas. The MTh can be divided into three regions: ventral anterior (VA), VL, and VM. This complex receives the main projections from the cerebral cortex, the cerebellum, and the BG (Pare et al., 1987; Sommer, 2003). Even when its participation in behavioral outcomes is not completely understood, the evidence suggests that this complex is involved in motor functions such as timing, preparation, initiation, and vigor of movements (Guo et al., 2017; Gaidica et al., 2018; Catanese & Jaeger, 2021; Inagaki et al., 2022). In this context, imaging studies in humans suggest the MTh is part of a network that activates during perceptual timing tasks (Rao et al., 1997; Stevens et al., 2007; Teki et al., 2011). For example, in a synchronization-continuation tapping task for humans, functional magnetic resonance imaging revealed that both conditions produced equivalent activation on the sensorimotor cortex, cerebellum (dentate nucleus), and the right superior temporal gyrus, but only the "continuation" condition produced an activation of the premotor medial system: supplementary motor area, putamen, and thalamus (VL nuclei), suggesting that the internal generation of the motor interval also implicates MTh (Rao et al., 1997). This has been further confirmed in stroke patients whose MTh is affected, producing more variable motor intervals than healthy subjects or brain-injured controls (stroke in another brain region) (Mole et al., 2018). More specific studies from the group of Masaki Tanaka indicate that the MTh may be implicated in motor timing. For example, pharmacological inactivation of the VL thalamus delayed saccades in primates (Tanaka, 2006), and many of the thalamic neurons displayed ramping activity in anticipation of external stimuli that trigger the saccade or self-timed saccades, suggesting that MTh neurons carry preparatory signals that keep track of elapsed time until movement onset (Tanaka, 2007). More recently, the same group demonstrated that subpopulations of MTh neurons can extract temporal predictions from periodic sensory events (Matsuyama & Tanaka, 2021). The mechanisms behind these temporal computations are yet to be determined, but the previous evidence suggests that, as in the BG, time may be embedded as an emergent property of thalamic network dynamics.

Conclusions

In this work, we summarized relevant observations linking sensory processing with timed behavior throughout cortical, BG, and thalamic circuits. The first important observation is that sensory inputs to the sensorimotor striatum produce various robust complex patterns of activation at the single-cell level. These patterns are characterized by brief periods of bursting activity intermingled with silences with variable latencies after stimulation onset. These sensory-evoked responses can be observed under anesthetized conditions, suggesting a prewired configuration, and are not exclusive to the sensorimotor region of the striatum but can also be observed throughout the different relays of the BG, such as the GPe or the SNr, and extra-BG regions such as the MTh and the primary somatosensory and motor cortices (Fig. 2). When these type of responses are plotted together and sorted according to the moment of highest activity, ensemble activity appears to organize as neural sequences covering hundreds of milliseconds after the presentation of a triggering stimulus (even in anesthetized conditions) or a relevant behavioral event (Luczak et al., 2015; Rueda-Orozco & Robbe, 2015; Hidalgo-Balbuena et al., 2019; Monteiro et al., 2021; Peña-Rangel et al., 2021). This sequential dynamic appears to be a robust organization from which time can be decoded, but whose definitive function is still debated. A possible explanation is that these sequences can be a parallel and independent organization to the typical sensorimotor organization that includes visual, auditory, and somatosensory representations, or the representation of task-relevant events or motor-related parameters, such as rewards or kinematic

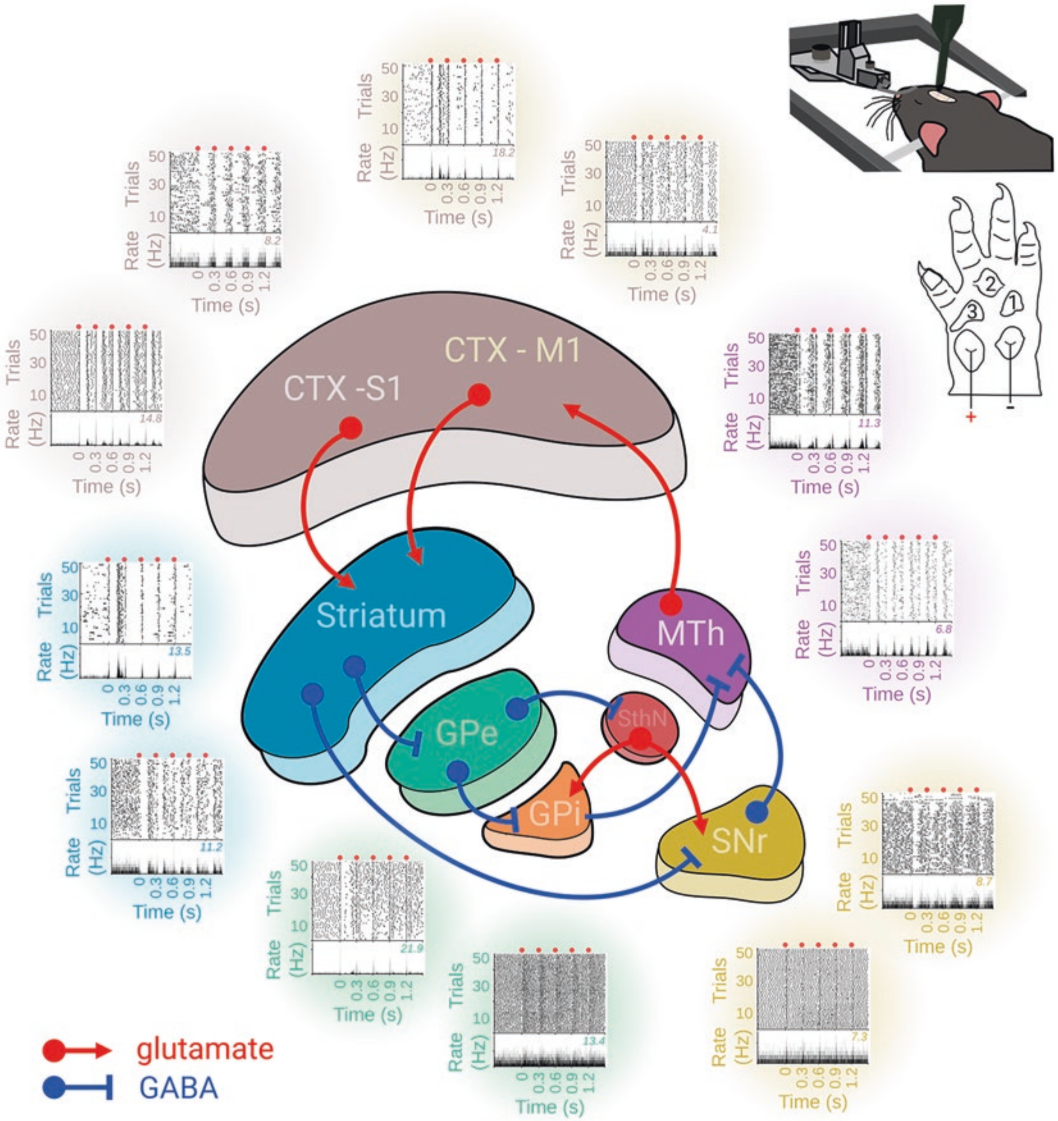

Fig. 2 Sensory representations throughout cortico-basal ganglia-thalamic circuits. Somatosensory-evoked activity of example neurons recorded at different relays within the cortico-BG-thalamic circuit (color-coded). Activity in spike rasters and peri-stimulus histograms is aligned to the first five consecutive stimuli delivered at 3.3 Hz to the forepaw contralateral to the recording sites (upper right corner). All recordings were performed in urethane-anesthetized animals. Representative neurons from primary motor (M1) and sensory (S1) cortices (brown), dorsolateral striatum (blue), and substantia nigra pars reticulata (SNr; golden) were extracted from experiments performed in the following publications (Hidalgo-Balbuena et al., 2019; Báez-Cordero et al., 2020; Peña-Rangel et al., 2021; Pimentel-Farfan et al., 2022). Representative neurons for the external segment of the globus pallidus (green) and the motor thalamus (MTh; purple) were collected in unpublished experiments from our group under identical conditions. No available data for the internal segment of the globus pallidus (GPi; orange) or the subthalamic nucleus (SthN, red). Maximum firing rates are indicated for each neuron on top of the histogram

representations, respectively. In support of this notion, researchers have recorded striatal sequential activation in behaving rats performing sequences of movements (Rueda-Orozco & Robbe, 2015) or sensory discriminations (Toso et al., 2021) and have shown that this activation is independent of the learning stage, kinematic encoding, or sensory discriminative properties of the striatal network. These sequences may provide a general sense of the passage of time, which might be useful to interval perception or to the temporal constraint of motor commands during interval production. These sequences may be started or entrained by sensory events, such as the rhythmic representation of the forelimb during locomotion (Hidalgo-Balbuena et al., 2019) or the clicking sound during lever pressing tasks (Cook et al., 2022).

The fact that the ensemble dynamics recruited by sensory inputs throughout the different relays of the cortico-BG-thalamic circuits share important features (e.g., sequential activation) suggests that to fully understand the role of sensory-evoked activity in perception and movement timing, it is necessary to determine the relationship between the sequential activation observed in different structures, for example, in the striatum and its anatomical targets—the GPe, GPi, and SNr. To this aim, a key challenge is developing experimental approaches to manipulate sequential activation at different stages of these circuits and then evaluating the impact of these manipulations on time perception and time production. This has been partially achieved by specifically manipulating somatosensory pathways to the DLS in animals performing behavioral protocols designed to produce time intervals (Hidalgo-Balbuena et al., 2019). However, it is still necessary to combine this manipulative approach with simultaneous high-density neural recording methods and more complete behavioral protocols where production and perception of time intervals can be compared.

References

Albin, R. L., Young, A. B., & Penney, J. B. (1989). The functional anatomy of basal ganglia disorders. *Trends in Neurosciences, 12*, 366–375. Available at: https://linkinghub.elsevier.com/retrieve/pii/016622368990074X

Alexander, G. E., & DeLong, M. R. (1985). Microstimulation of the primate neostriatum. II. Somatotopic organization of striatal microexcitable zones and their relation to neuronal response properties. *Journal of Neurophysiology, 53*, 1417–1430. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=4009227

Alexander, G. E., DeLong, M. R., & Delong, R. (1985). Microstimulation of the primate neostriatum. I. Physiological properties of striatal microexcitable zones. *Journal of Neurophysiology, 53*, 1401–1416. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=4009226

Alloway, K. D., Smith, J. B., Beauchemin, K. J., & Olson, M. L. (2009). Bilateral projections from rat MI whisker cortex to the neostriatum, thalamus, and claustrum: Forebrain circuits for modulating whisking behavior. *The Journal of Comparative Neurology, 515*, 548–564. Available at: https://onlinelibrary.wiley.com/doi/10.1002/cne.22073

Báez-Cordero, A. S., Pimentel-Farfan, A. K., Peña-Rangel, T., & Rueda-Orozco, P. E. (2020). Unbalanced inhibitory/excitatory responses in the substantia Nigra Pars Reticulata underlie cannabinoid-related slowness of movements. *The Journal of Neuroscience, 40*, 5769–5784. Available at: http://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.0045-20.2020

Bakhurin, K. I., Goudar, V., Shobe, J. L., Claar, L. D., Buonomano, D. V., & Masmanidis, S. C. (2017). Differential encoding of time by prefrontal and striatal network dynamics. *The Journal of Neuroscience, 37*, 854–870. Available at: http://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.1789-16.2017

Bakhurin, K. I., Li, X., Friedman, A. D., Lusk, N. A., Watson, G. D. R., Kim, N., & Yin, H. H. (2020). Opponent regulation of action performance and timing by striatonigral and striatopallidal pathways. *eLife, 9*, 1–25. Available at: https://elifesciences.org/articles/54831

Barbera, G., Liang, B., Zhang, L., Gerfen, C. R., Culurciello, E., Chen, R., Li, Y., & Lin, D. T. (2016). Spatially compact neural clusters in the dorsal striatum encode locomotion relevant information. *Neuron, 92*, 202–213. Available at: https://doi.org/10.1016/j.neuron.2016.08.037

Beudel, M., de Geus, C. M., Leenders, K. L., & de Jong, B. M. (2013). Acceleration bias in visually perceived velocity change and effects of Parkinson's bradykinesia. *Neuroreport, 24*, 773–778. Available at: https://journals.lww.com/00001756-201310020-00003

Bevan, M. (2002). Move to the rhythm: Oscillations in the subthalamic nucleus–external globus pallidus network. *Trends in Neurosciences, 25*, 525–531. Available at: https://linkinghub.elsevier.com/retrieve/pii/S016622360202235X

Brown, J., Pan, W.-X., & Dudman, J. T. (2014). The inhibitory microcircuit of the substantia nigra provides feedback gain control of the basal ganglia output. *eLife, 3*, 1–25.

Buhusi, C. V., & Meck, W. H. (2005). What makes us tick? Functional and neural mechanisms of interval timing. *Nature Reviews. Neuroscience, 6*, 755–765. Available at: http://www.nature.com/articles/nrn1764

Buonomano, D. V., & Laje, R. (2010). Population clocks: Motor timing with neural dynamics. *Trends in Cognitive Sciences, 14*, 520–527. Available at: https://doi.org/10.1016/j.tics.2010.09.002

Cadena-Valencia, J., García-Garibay, O., Merchant, H., Jazayeri, M., & de Lafuente, V. (2018). Entrainment and maintenance of an internal metronome in supplementary motor area. *eLife, 7*, 1–23. Available at: https://elifesciences.org/articles/38983

Carelli, R. M., & West, M. O. (1991). Representation of the body by single neurons in the dorsolateral striatum of the awake, unrestrained rat. *The Journal of Comparative Neurology, 309*, 231–249.

Carpenter, M. B., Nakano, K., & Kim, R. (1976). Nigrothalamic projections in the monkey demonstrated by autoradiographic technics. *The Journal of Comparative Neurology, 165*, 401–415. Available at: https://onlinelibrary.wiley.com/doi/10.1002/cne.901650402

Carrillo-Reid, L., Tecuapetla, F., Tapia, D., Hernandez-Cruz, A., Galarraga, E., Drucker-Colin, R., & Bargas, J. (2008). Encoding network states by striatal cell assemblies. *Journal of Neurophysiology, 99*, 1435–1450. Available at: http://jn.physiology.org/cgi/doi/10.1152/jn.01131.2007

Carrillo-Reid, L., Kang Miller, J., Hamm, J. P., Jackson, J., & Yuste, R. (2015a). Endogenous sequential cortical activity evoked by visual stimuli. *The Journal of Neuroscience, 35*, 8813–8828. Available at: http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.5214-14.2015

Carrillo-Reid, L., Lopez-Huerta, V. G., Garcia-Munoz, M., Theiss, S., & Arbuthnott, G. W. (2015b). Cell assembly signatures defined by short-term synaptic plasticity in cortical networks. *International Journal of Neural Systems, 25*, 1550026. Available at: https://www.worldscientific.com/doi/abs/10.1142/S0129065715500264

Catanese, J., & Jaeger, D. (2021). Premotor ramping of thalamic neuronal activity is modulated by nigral inputs and contributes to control the timing of action release. *The Journal of Neuroscience, 41*, 1878–1891. Available at: https://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.1204-20.2020

Chapin, J. K., Waterhouse, B. D., & Woodward, D. J. (1981). Differences in cutaneous sensory response properties of single somatosensory cortical neurons in awake and halothane anesthetized rats. *Brain Research Bulletin, 6*, 63–70. Available at: https://linkinghub.elsevier.com/retrieve/pii/S036192308180069X

Chen, Z., Zhang, Z.-Y., Zhang, W., Xie, T., Li, Y., Xu, X.-H., & Yao, H. (2021). Direct and indirect pathway neurons in ventrolateral striatum differentially regulate licking movement and nigral responses. *Cell Reports, 37*, 109847. Available at: https://doi.org/10.1016/j.celrep.2021.109847

Cheung, T. H. C., Bezzina, G., Hampson, C. L., Body, S., Fone, K. C. F., Bradshaw, C. M., & Szabadi, E. (2007). Effect of quinpirole on timing behaviour in the free-operant psychophysical procedure: Evidence for the involvement of D2 dopamine receptors. *Psychopharmacology, 193*, 423–436. Available at: https://link.springer.com/10.1007/s00213-007-0798-8

Chiba, A., Oshio, K., & Inase, M. (2015). Neuronal representation of duration discrimination in the monkey striatum. *Physiological Reports, 3*, e12283. Available at: https://doi.wiley.com/10.14814/phy2.12283

Chuhma, N., Tanaka, K. F., Hen, R., & Rayport, S. (2011). Functional connectome of the striatal medium spiny neuron. *The Journal of Neuroscience, 31*, 1183–1192. Available at: https://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.3833-10.2011

Coffey, K. R., Nader, M., & West, M. O. (2016). Single body parts are processed by individual neurons in the mouse dorsolateral striatum. *Brain Research, 1636*, 200–207. Available at: https://doi.org/10.1016/j.brainres.2016.01.031

Coffey, K. R., Nader, M., Bawa, J., & West, M. O. (2017). Homogeneous processing in the striatal direct and indirect pathways: Single body part sensitive type IIb neurons may express either dopamine receptor D1 or D2. *The European Journal of Neuroscience, 46*, 2380–2391.

Cook, J. R., Li, H., Nguyen, B., Huang, H., Mahdavian, P., Kirchgessner, M. A., Strassmann, P., Engelhardt, M., Callaway, E. M., & Jin, X. (2022). Secondary auditory cortex mediates a sensorimotor mechanism for action timing. *Nature Neuroscience, 25*, 330–344. Available at: https://www.nature.com/articles/s41593-022-01025-5

Coslett, H. B., Wiener, M., & Chatterjee, A. (2010). Dissociable neural systems for timing: Evidence from subjects with basal ganglia lesions Tell F, ed. *PLoS One, 5*, e10324. Available at: https://dx.plos.org/10.1371/journal.pone.0010324

Cruz, B. F., Guiomar, G., Soares, S., Motiwala, A., Machens, C. K., & Paton, J. J. (2022). Action suppression reveals opponent parallel control via striatal circuits. *Nature, 607*, 521–526. Available at: https://www.nature.com/articles/s41586-022-04894-9

Cury, K. M., & Uchida, N. (2010). Robust odor coding via inhalation-coupled transient activity in the mammalian olfactory bulb. *Neuron, 68*, 570–585. Available at: https://doi.org/10.1016/j.neuron.2010.09.040

De Corte, B. J., Wagner, L. M., Matell, M. S., & Narayanan, N. S. (2019). Striatal dopamine and the temporal control of behavior. *Behavioural Brain Research, 356*, 375–379. Available at: https://doi.org/10.1016/j.bbr.2018.08.030

DeLong, M. R. (1971). Of pallidal during movement. *The Journal of Physiology, 34*, 414–427.

Deschênes, M., Takatoh, J., Kurnikova, A., Moore, J. D., Demers, M., Elbaz, M., Furuta, T., Wang, F., & Kleinfeld, D. (2016). Inhibition, not excitation, drives rhythmic whisking. *Neuron, 90*, 374–387. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0896627316001860

Díaz-Hernández, E., Contreras-López, R., Sánchez-Fuentes, A., Rodríguez-Sibrían, L., Ramírez-Jarquín, J. O., & Tecuapetla, F. (2018). The thalamostriatal projections contribute to the initiation and execution of a sequence of movements. *Neuron, 100*, 739–752.e5. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0896627318308547

Dray, A., Gonye, T. J., & Oakley, N. R. (1976). Caudate stimulation and substantia nigra activity in the rat. *The Journal of Physiology, 259*, 825–849. Available at: http://doi.wiley.com/10.1113/jphysiol.1976.sp011497

Drew, M. R., Fairhurst, S., Malapani, C., Horvitz, J. C., & Balsam, P. D. (2003). Effects of dopamine antagonists on the timing of two intervals. *Pharmacology, Biochemistry, and Behavior, 75*, 9–15. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0091305703000364

Dudman, J. T., & Krakauer, J. W. (2016). The basal ganglia: From motor commands to the control of vigor. *Current Opinion in Neurobiology, 37*, 158–166. Available at: https://doi.org/10.1016/j.conb.2016.02.005

Erro, M. E., Lanciego, J. L., Arribas, J., & Gimenez-Amaya, J. M. (2001). Striatal input from the ventrobasal complex of the rat thalamus. *Histochemistry and Cell Biology, 115*, 447–454.

Erro, M. E., Lanciego, J. L., & Giménez-Amaya, J. M. (2002). Re-examination of the thalamostriatal projections in the rat with retrograde tracers. *Neuroscience Research, 42*, 45–55. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0168010201003029

Frederick, D. (1996). Effects of selective dopamine D1- and D2-agonists and antagonists on timing performance in rats. *Pharmacology, Biochemistry, and Behavior, 53*, 759–764. Available at: https://linkinghub.elsevier.com/retrieve/pii/0091305795021035

Gaidica, M., Hurst, A., Cyr, C., & Leventhal, D. K. (2018). Distinct populations of motor thalamic neurons encode action initiation, action selection, and movement vigor. *The Journal of Neuroscience, 38*, 6563–6573. Available at: https://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.0463-18.2018

Gámez, J., Mendoza, G., Prado, L., Betancourt, A., & Merchant, H. (2019). The amplitude in periodic neural state trajectories underlies the tempo of rhythmic tapping Zatorre R, ed. *PLoS Biology, 17*, e3000054. Available at: https://dx.plos.org/10.1371/journal.pbio.3000054

Gerfen, C. R., Engber, T. M., Mahan, L. C., Susel, Z., Chase, T. N., Monsma, F. J., & Sibley, D. R. (1990). D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science (80-), 250*, 1429–1432. Available at: https://www.science.org/doi/10.1126/science.2147780

Goel, A., & Buonomano, D. V. (2014). Timing as an intrinsic property of neural networks: Evidence from in vivo and in vitro experiments. *Philosophical Transactions of the Royal Society, B: Biological Sciences, 369*, 20120460. Available at: https://royalsocietypublishing.org/doi/10.1098/rstb.2012.0460

Goel, A., & Buonomano, D. V. (2016). Temporal interval learning in cortical cultures is encoded in intrinsic network dynamics. *Neuron, 91*, 320–327. Available at: https://doi.org/10.1016/j.neuron.2016.05.042

Gouvêa, T. S., Monteiro, T., Motiwala, A., Soares, S., Machens, C., & Paton, J. J. (2015). Striatal dynamics explain duration judgments. *eLife, 4*, 1–14. Available at: https://elifesciences.org/articles/11386

Graybiel, A. M. (2008). Habits, rituals, and the evaluative brain. *Annual Review of Neuroscience, 31*, 359–387. Available at: http://www.annualreviews.org/doi/10.1146/annurev.neuro.29.051605.112851

Guo, Z. V., Inagaki, H. K., Daie, K., Druckmann, S., Gerfen, C. R., & Svoboda, K. (2017). Maintenance of persistent activity in a frontal thalamocortical loop. *Nature, 545*, 181–186. Available at: http://www.nature.com/articles/nature22324

Hegeman, D. J., Hong, E. S., Hernández, V. M., & Chan, C. S. (2016). The external globus pallidus: Progress and perspectives Bolam P, ed. *The European Journal of Neuroscience, 43*, 1239–1265. Available at: https://onlinelibrary.wiley.com/doi/10.1111/ejn.13196

Henke, J., Bunk, D., von Werder, D., Häusler, S., Flanagin, V. L., & Thurley, K. (2021). Distributed coding of duration in rodent prefrontal cortex during time reproduction. *eLife, 10*, 1–24. Available at: https://elifesciences.org/articles/71612

Hidalgo-Balbuena, A. E., Luma, A. Y., Pimentel-Farfan, A. K., Peña-Rangel, T., & Rueda-Orozco, P. E. (2019). Sensory representations in the striatum provide a temporal reference for learning and executing motor habits. *Nature Communications, 10*, 4074. Available at: https://doi.org/10.1038/s41467-019-12075-y

Hikosaka, O. (2007). GABAergic output of the basal ganglia. *Progress in Brain Research*, 209–226. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0079612306600125

Hikosaka, O., & Wurtz, R. H. (1983). Visual and oculomotor functions of monkey substantia nigra pars reticulata. III. Memory-contingent visual and saccade responses. *Journal of Neurophysiology, 49*, 1268–1284. Available at: http://www.physiology.org/doi/10.1152/jn.1983.49.5.1268

Hintiryan, H., Foster, N. N., Bowman, I., Bay, M., Song, M. Y., Gou, L., Yamashita, S., Bienkowski, M. S., Zingg, B., Zhu, M., Yang, X. W., Shih, J. C., Toga, A. W., & Dong, H. W. (2016). The mouse cortico-striatal projectome. *Nature Neuroscience, 19*, 1100–1114.

Honma, M., Kuroda, T., Futamura, A., Shiromaru, A., & Kawamura, M. (2016). Dysfunctional counting of mental time in Parkinson's disease. *Scientific Reports, 6*, 25421. Available at: http://www.nature.com/articles/srep25421

Honma, M., Masaoka, Y., Koyama, S., Kuroda, T., Futamura, A., Shiromaru, A., Terao, Y., Ono, K., & Kawamura, M. (2018). Impaired cognitive modification for estimating time duration in Parkinson's disease Ginsberg SD, ed. *PLoS One, 13*, e0208956. Available at: https://dx.plos.org/10.1371/journal.pone.0208956

Hoover, J. E., Hoffer, Z. S., & Alloway, K. D. (2003). Projections from primary somatosensory cortex to the neostriatum: The role of somatotopic continuity in corticostriatal convergence. *Journal of Neurophysiology, 89*, 1576–1587. Available at: http://jn.physiology.org/cgi/doi/10.1152/jn.01009.2002

Inagaki, H. K., Chen, S., Ridder, M. C., Sah, P., Li, N., Yang, Z., Hasanbegovic, H., Gao, Z., Gerfen, C. R., & Svoboda, K. (2022). A midbrain-thalamus-cortex circuit reorganizes cortical dynamics to initiate movement. *Cell, 185*, 1065–1081.e23. Available at: https://doi.org/10.1016/j.cell.2022.02.006

Iwamuro, H., Tachibana, Y., Ugawa, Y., Saito, N., & Nambu, A. (2017). Information processing from the motor cortices to the subthalamic nucleus and globus pallidus and their somatotopic organizations revealed electrophysiologically in monkeys. *The European Journal of Neuroscience, 46*, 2684–2701. Available at: https://onlinelibrary.wiley.com/doi/10.1111/ejn.13738

Jaeger, D., & Kita, H. (2011). Functional connectivity and integrative properties of globus pallidus neurons. *Neuroscience, 198*, 44–53. Available at: https://doi.org/10.1016/j.neuroscience.2011.07.050

Jin, D. Z., Fujii, N., & Graybiel, A. M. (2009). Neural representation of time in cortico-basal ganglia circuits. *Proceedings of the National Academy of Sciences, 106*, 19156–19161. Available at: https://pnas.org/doi/full/10.1073/pnas.0909881106

Johansson, Y., & Silberberg, G. (2020). The functional organization of cortical and thalamic inputs onto five types of striatal neurons is determined by source and target cell identities. *Cell Reports, 30*, 1178–1194.e3. Available at: https://doi.org/10.1016/j.celrep.2019.12.095

Junek, S., Kludt, E., Wolf, F., & Schild, D. (2010). Olfactory coding with patterns of response latencies. *Neuron, 67*, 872–884. Available at: https://doi.org/10.1016/j.neuron.2010.08.005

Jurado-Parras, M.-T., Safaie, M., Sarno, S., Louis, J., Karoutchi, C., Berret, B., & Robbe, D. (2020). The dorsal striatum energizes motor routines. *Current Biology, 30*, 4362–4372.e6. Available at: https://doi.org/10.1016/j.cub.2020.08.049

Kamada, T., & Hata, T. (2021). Striatal dopamine D1 receptors control motivation to respond, but not interval timing, during the timing task. *Learning & Memory, 28*, 24–29. Available at: http://learnmem.cshlp.org/lookup/doi/10.1101/lm.052266.120

Karalis, N., & Sirota, A. (2022). Breathing coordinates cortico-hippocampal dynamics in mice during offline states. *Nature Communications, 13*, 467. Available at: https://www.nature.com/articles/s41467-022-28090-5

Ketzef, M., Spigolon, G., Johansson, Y., Bonito-Oliva, A., Fisone, G., & Silberberg, G. (2017). Dopamine depletion impairs bilateral sensory processing in the striatum in a pathway-dependent manner. *Neuron, 94*, 855–865.e5. Available at: https://doi.org/10.1016/j.neuron.2017.05.004

Kim, J., Ghim, J.-W., Lee, J. H., & Jung, M. W. (2013). Neural correlates of interval timing in rodent prefrontal cortex. *The Journal of Neuroscience, 33*, 13834–13847. Available at: https://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.1443-13.2013

Kita, H., & Jaeger, D. (2016). Organization of the globus pallidus. In *Handbook of behavioral neuroscience* (pp. 259–276). Available at: https://linkinghub.elsevier.com/retrieve/pii/B9780128022061000131

Kravitz, A. V., Freeze, B. S., Parker, P. R. L., Kay, K., Thwin, M. T., Deisseroth, K., & Kreitzer, A. C. (2010). Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. *Nature, 466*, 622–626. Available at: http://www.nature.com/articles/nature09159

Kunimatsu, J., Suzuki, T. W., Ohmae, S., & Tanaka, M. (2018). Different contributions of preparatory activity in the basal ganglia and cerebellum for self-timing. *eLife, 7*, 1–19. Available at: https://elifesciences.org/articles/35676

Lee, C. R., Yonk, A. J., Wiskerke, J., Paradiso, K. G., Tepper, J. M., & Margolis, D. J. (2019). Opposing influence of sensory and motor cortical input on striatal circuitry and choice behavior. *Current Biology, 29*, 1313–1323.e5. Available at: https://doi.org/10.1016/j.cub.2019.03.028

Luczak, A., Barthó, P., Marguet, S. L., Buzsáki, G., & Harris, K. D. (2007). Sequential structure of neocortical spontaneous activity in vivo. *Proceedings of the National Academy of Sciences, 104*, 347–352. Available at: https://pnas.org/doi/full/10.1073/pnas.0605643104

Luczak, A., Barthó, P., & Harris, K. D. (2009). Spontaneous events outline the realm of possible sensory responses in neocortical populations. *Neuron, 62*, 413–425. Available at: https://doi.org/10.1016/j.neuron.2009.03.014

Luczak, A., McNaughton, B. L., & Harris, K. D. (2015). Packet-based communication in the cortex. *Nature Reviews. Neuroscience, 16*, 745–755. Available at: https://doi.org/10.1038/nrn4026

Matell, M. S., Meck, W. H., & Nicolelis, M. A. L. (2003). Interval timing and the encoding of signal duration by ensembles of cortical and striatal neurons. *Behavioral Neuroscience, 117*, 760–773. Available at: http://doi.apa.org/getdoi.cfm?doi=10.1037/0735-7044.117.4.760

Matsuyama, K., & Tanaka, M. (2021). Temporal prediction signals for periodic sensory events in the primate central thalamus. *The Journal of Neuroscience, 41*, 1917–1927. Available at: https://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.2151-20.2021

Meck, W. H. (2006). Neuroanatomical localization of an internal clock: A functional link between mesolimbic, nigrostriatal, and mesocortical dopaminergic systems. *Brain Research, 1109*, 93–107. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0006899306017203

Mello, G. B. M., Soares, S., & Paton, J. J. (2015). A scalable population code for time in the striatum. *Current Biology, 25*, 1113–1122. Available at: https://doi.org/10.1016/j.cub.2015.02.036

Merchant, H., Zarco, W., Bartolo, R., Perez, O., & Prado, L. (2011). Measuring time with different neural chronometers during a synchronization-continuation task. *Proceedings of the National Academy of Sciences, 108*, 19784–19789.

Merchant, H., Harrington, D. L., & Meck, W. H. (2013). Neural basis of the perception and estimation of time. *Annual Review of Neuroscience, 36*, 313–336. Available at: https://www.annualreviews.org/doi/10.1146/annurev-neuro-062012-170349

Mochol, G., Hermoso-Mendizabal, A., Sakata, S., Harris, K. D., & de la Rocha, J. (2015). Stochastic transitions into silence cause noise correlations in cortical circuits. *Proceedings of the National Academy of Sciences, 112*, 3529–3534. Available at: http://www.pnas.org/lookup/doi/10.1073/pnas.1410509112

Mole, J., Winegardner, J., Malley, D., & Fish, J. (2018). Time perception impairment following thalamic stroke: A case study. *Neuropsychological Rehabilitation, 28*, 208–222. Available at: https://doi.org/10.1080/09602011.2017.1383273

Monteiro, T., Rodrigues, F. S., Pexirra, M., Cruz, B. F., Rueda-Orozco, P. E., & Paton, J. J. (2021). Using temperature to analyse the neural basis of a latent temporal decision. *bioRxiv*. Available at: https://doi.org/10.1101/2020.08.24.251827

Monteiro, T., Rodrigues, F. S., Pexirra, M., Cruz, B. F., Gonçalves, A. I., Rueda-Orozco, P. E., & Paton, J. J. (2023). Using temperature to analyze the neural basis of a time-based decision. *Nature Neuroscience*. Available at: https://doi.org/10.1038/s41593-023-01378-5

Nagy, A., Paróczy, Z., Norita, M., & Benedek, G. (2005). Multisensory responses and receptive field properties of neurons in the substantia nigra and in the caudate nucleus. *The European Journal of Neuroscience, 22*, 419–424. Available at: http://doi.wiley.com/10.1111/j.1460-9568.2005.04211.x

Nambu, A. (2011). Somatotopic organization of the primate basal ganglia. *Frontiers in Neuroanatomy, 5*, 1–9. Available at: http://journal.frontiersin.org/article/10.3389/fnana.2011.00026/abstract

Nozaradan, S., Schwartze, M., Obermeier, C., & Kotz, S. A. (2017). Specific contributions of basal ganglia and cerebellum to the neural tracking of rhythm. *Cortex, 95*, 156–168. Available at: https://doi.org/10.1016/j.cortex.2017.08.015

Pare, D., Steriade, M., Deschenes, M., & Oakson, G. (1987). Physiological characteristics of anterior thalamic nuclei, a group devoid of inputs from reticular thalamic nucleus. *Journal of Neurophysiology, 57*, 1669–1685. Available at: https://www.physiology.org/doi/10.1152/jn.1987.57.6.1669

Parent, A., Mackey, A., Smith, Y., & Boucher, R. (1983). The output organization of the substantia nigra in primate as revealed by a retrograde double labeling method. *Brain Research Bulletin, 10*, 529–537. Available at: https://linkinghub.elsevier.com/retrieve/pii/036192308390151X

Parent, A., Bouchard, C., & Smith, Y. (1984). The striatopallidal and striatonigral projections: Two distinct fiber systems in primate. *Brain Research, 303*, 385–390. Available at: https://linkinghub.elsevier.com/retrieve/pii/0006899384912241

Paton, J. J., & Lau, B. (2015). Tread softly and carry a clock's tick. *Nature Neuroscience, 18*, 329–330. Available at: https://doi.org/10.1038/nn.3959

Peña-Rangel, T. M., Lugo-Picos, P. I., Báez-Cordero, A. S., Hidalgo-Balbuena, A. E., Luma, A. Y., Pimentel-Farfan, A. K., & Rueda-Orozco, P. E. (2021). Altered sensory representations in parkinsonian cortical and basal ganglia networks. *Neuroscience, 466*, 10–25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/33965505

Peters, A. J., Fabre, J. M. J., Steinmetz, N. A., Harris, K. D., & Carandini, M. (2021). Striatal activity topographically reflects cortical activity. *Nature, 591*, 420–425. Available at: https://doi.org/10.1038/s41586-020-03166-8

Pidoux, M., Mahon, S., Deniau, J. M., & Charpier, S. (2011). Integration and propagation of somatosensory responses in the corticostriatal pathway: An intracellular study in vivo. *The Journal of Physiology, 589*, 263–281.

Pimentel-Farfan, A. K., Báez-Cordero, A. S., Peña-Rangel, T. M., & Rueda-Orozco, P. E. (2022). Cortico-striatal circuits for bilaterally coordinated movements. *Science Advances, 8*, 1–19. Available at: https://www.science.org/doi/10.1126/sciadv.abk2241

Rao, S. M., Harrington, D. L., Haaland, K. Y., Bobholz, J. A., Cox, R. W., & Binder, J. R. (1997). Distributed neural systems underlying the timing of movements. *The Journal of Neuroscience, 17*, 5528–5535. Available at: https://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.17-14-05528.1997

Redgrave, P., Rodriguez, M., Smith, Y., Rodriguez-Oroz, M. C., Lehericy, S., Bergman, H., Agid, Y., Delong, M. R., & Obeso, J. A. (2010). Goal-directed and habitual control in the basal ganglia: Implications for Parkinson's disease. *Nature Reviews. Neuroscience, 11*, 760–772. Available at: https://doi.org/10.1038/nrn2915

Reig, R., & Silberberg, G. (2014). Multisensory integration in the mouse striatum. *Neuron, 83*, 1200–1212. Available at: https://doi.org/10.1016/j.neuron.2014.07.033

Reig, R., & Silberberg, G. (2016). Distinct corticostriatal and intracortical pathways mediate bilateral sensory responses in the striatum. *Cerebral Cortex, 26*, 4405–4415. Available at: https://academic.oup.com/cercor/article-lookup/doi/10.1093/cercor/bhw268

Reiner, A., Jiao, Y., Del Mar, N., Laverghetta, A. V., & Lei, W. L. (2003). Differential morphology of pyramidal tract-type and intratelencephalically projecting-type corticostriatal neurons and their intrastriatal terminals in rats. *The Journal of Comparative Neurology, 457*, 420–440.

Robbe, D. (2018). To move or to sense? Incorporating somatosensory representation into striatal functions. *Current Opinion in Neurobiology, 52*, 123–130. Available at: https://doi.org/10.1016/j.conb.2018.04.009

Rowe, K. C., Paulsen, J. S., Langbehn, D. R., Duff, K., Beglinger, L. J., Wang, C., O'Rourke, J. J. F., Stout, J. C., & Moser, D. J. (2010). Self-paced timing detects and tracks change in prodromal Huntington disease. *Neuropsychology, 24*, 435–442. Available at: http://doi.apa.org/getdoi.cfm?doi=10.1037/a0018905

Rueda-Orozco, P. E., & Robbe, D. (2015). The striatum multiplexes contextual and kinematic information to constrain motor habits execution. *Nature Neuroscience, 18*, 435–460.

Schmidt, R., Leventhal, D. K., Mallet, N., Chen, F., & Berke, J. D. (2013). Canceling actions involves a race between basal ganglia pathways. *Nature Neuroscience, 16*, 1118–1124. Available at: http://www.nature.com/articles/nn.3456

Schultz, W. (1986). Activity of pars reticulata neurons of monkey substantia nigra in relation to motor, sensory, and complex events. *Journal of Neurophysiology, 55*, 660–677. Available at: https://www.physiology.org/doi/10.1152/jn.1986.55.4.660

Schwartze, M., Stockert, A., & Kotz, S. A. (2015). Striatal contributions to sensory timing: Voxel-based lesion mapping of electrophysiological markers. *Cortex, 71*, 332–340. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0010945215002610

Sheng, M., Lu, D., Shen, Z., & Poo, M. (2019). Emergence of stable striatal D1R and D2R neuronal ensembles with distinct firing sequence during motor learning. *Proceedings of the National Academy of Sciences, 116*, 11038–11047. Available at: https://pnas.org/doi/full/10.1073/pnas.1901712116

Shi, L. H., Luo, F., Woodward, D. J., & Chang, J. Y. (2004). Neural responses in multiple basal ganglia regions during spontaneous and treadmill locomotion tasks in rats. *Experimental Brain Research, 157*, 303–314. Available at: http://link.springer.com/10.1007/s00221-004-1844-y

Shi, L. H., Luo, F., Woodward, D. J., & Chang, J. Y. (2005). Dose and behavioral context dependent inhibition of movement and basal ganglia neural activity by delta-9-tetrahydrocannabinol during spontaneous and treadmill locomotion tasks in rats. *Synapse, 55*, 1–16. Available at: http://doi.wiley.com/10.1002/syn.20088

Sippy, T., Lapray, D., Crochet, S., & Petersen, C. C. H. (2015). Cell-type-specific sensorimotor processing in striatal projection neurons during goal-directed behavior. *Neuron, 88*, 298–305. Available at: https://doi.org/10.1016/j.neuron.2015.08.039

Smith, J. B., Mowery, T. M., & Alloway, K. D. (2012). Thalamic POm projections to the dorsolateral striatum of rats: Potential pathway for mediating stimulus-response associations for sensorimotor habits. *Journal of Neurophysiology, 108*, 160–174. Available at: http://jn.physiology.org/cgi/doi/10.1152/jn.00142.2012

Smith, Y., Galvan, A., Ellender, T. J., Doig, N., Villalba, R. M., Huerta-Ocampo, I., Wichmann, T., & Bolam, J. P. (2014). The thalamostriatal system in normal and diseased states. *Frontiers in Systems Neuroscience, 8*, 1–18. Available at: http://journal.frontiersin.org/article/10.3389/fnsys.2014.00005/abstract

Soares, S., Atallah, B. V., & Paton, J. J. (2016). Midbrain dopamine neurons control judgment of time. *Science (80-), 354*, 1273–1277. Available at: https://www.science.org/doi/10.1126/science.aah5234

Sommer, M. A. (2003). The role of the thalamus in motor control. *Current Opinion in Neurobiology, 13*, 663–670. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0959438803001697

Sreenivasan, V., & Petersen, C. C. H. (2016). Inhibition patterns the whisking rhythm. *Neuron, 90*, 211–213. Available at: https://doi.org/10.1016/j.neuron.2016.04.012

Stevens, M. C., Kiehl, K. A., Pearlson, G., & Calhoun, V. D. (2007). Functional neural circuits for mental timekeeping. *Human Brain Mapping, 28*, 394–408. Available at: https://onlinelibrary.wiley.com/doi/10.1002/hbm.20285

Tanaka, M. (2006). Inactivation of the central thalamus delays self-timed saccades. *Nature Neuroscience, 9*, 20–22. Available at: http://www.nature.com/articles/nn1617

Tanaka, M. (2007). Cognitive signals in the primate motor thalamus predict saccade timing. *The Journal of Neuroscience, 27*, 12109–12118. Available at: https://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.1873-07.2007

Taverna, S., Ilijic, E., & Surmeier, D. J. (2008). Recurrent collateral connections of striatal medium spiny neurons are disrupted in models of Parkinson's disease. *The Journal of Neuroscience, 28*, 5504–5512. Available at: https://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.5493-07.2008

Teki, S., Grube, M., Kumar, S., & Griffiths, T. D. (2011). Distinct neural substrates of duration-based and beat-based auditory timing. *The Journal of Neuroscience, 31*, 3805–3812. Available at: https://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.5561-10.2011

Toda, K., Lusk, N. A., Watson, G. D. R., Kim, N., Lu, D., Li, H. E., Meck, W. H., & Yin, H. H. (2017). Nigrotectal stimulation stops interval timing in mice. *Current Biology, 27*, 3763–3770.e3. Available at: https://doi.org/10.1016/j.cub.2017.11.003

Toso, A., Reinartz, S., Pulecchi, F., & Diamond, M. E. (2021). Time coding in rat dorsolateral striatum. *Neuron, 109*, 3663–3673.e6. Available at: https://doi.org/10.1016/j.neuron.2021.08.020

Turner, R. S., & Desmurget, M. (2010). Basal ganglia contributions to motor control: A vigorous tutor. *Current Opinion in Neurobiology, 20*, 704–716. Available at: https://doi.org/10.1016/j.conb.2010.08.022

Wang, J., Narain, D., Hosseini, E. A., & Jazayeri, M. (2018). Flexible timing by temporal scaling of cortical responses. *Nature Neuroscience, 21*, 102–110. Available at: https://doi.org/10.1038/s41593-017-0028-6

Weder, B. J., Leenders, K. L., Vontobel, P., Nienhusmeier, M., Keel, A., Zaunbauer, W., Vonesch, T., & Ludin, H.-P. (1999). Impaired somatosensory discrimination of shape in Parkinson's disease: Association with caudate nucleus dopaminergic function. *Human*

Brain Mapping, 8, 1–12. Available at: https://onlinelibrary.wiley.com/doi/10.1002/(SICI)1097-0193(1999)8:1%3C1::AID-HBM1%3E3.0.CO;2-E

Weder, B., Azari, N. P., Knorr, U., Seitz, R. J., Keel, A., Nienhusmeier, M., Maguire, R. P., Leenders, K. L., & Ludin, H.-P. (2000). Disturbed functional brain interactions underlying deficient tactile object discrimination in Parkinson's disease. *Human Brain Mapping, 11*, 131–145. Available at: https://onlinelibrary.wiley.com/doi/10.1002/1097-0193(200011)11:3%3C131::AID-HBM10%3E3.0.CO;2-M

West, M. O. (1998). Anesthetics eliminate somatosensory-evoked discharges of neurons in the somatotopically organized sensorimotor striatum of the rat. *The Journal of Neuroscience, 18*, 9055–9068.

West, M. O., Carelli, R. M., Pomerantz, M., Cohen, S. M., Gardner, J. P., Chapin, J. K., & Woodward, D. J. (1990). A region in the dorsolateral striatum of the rat exhibiting single-unit correlations with specific locomotor limb movements. *Journal of Neurophysiology, 64*, 1233–1246. Available at: http://www.physiology.org/doi/10.1152/jn.1990.64.4.1233

Wurtz, R. H., & Hikosaka, O. (1986). Role of the basal ganglia in the initiation of saccadic eye movements. *Progress in Brain Research, 64*, 175–190. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0079612308634123

Xu, M., Zhang, S., Dan, Y., & Poo, M. (2014). Representation of interval timing by temporally scalable firing patterns in rat prefrontal cortex. *Proceedings of the National Academy of Sciences, 111*, 480–485. Available at: https://pnas.org/doi/full/10.1073/pnas.1321314111

Yin, H. H. (2017). The basal ganglia in action. *Neuroscience, 23*, 299–313. Available at: http://journals.sagepub.com/doi/10.1177/1073858416654115

Yoshida, M., & Precht, W. (1971). Monosynaptic inhibition of neurons of the substantia nigra by caudatonigral fibers. *Brain Research, 32*, 225–228. Available at: https://linkinghub.elsevier.com/retrieve/pii/0006899371901703

Zhou, S., Masmanidis, S. C., & Buonomano, D. V. (2020). Neural sequences as an optimal dynamical regime for the readout of time. *Neuron, 108*, 651–658.e5. Available at: https://doi.org/10.1016/j.neuron.2020.08.020