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Review

The Neural Basis of Timing: Distributed Mechanisms for Diverse Functions

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Timing is critical to most forms of learning, behavior, and sensory-motor processing. Converging evidence supports the notion that, precisely because of its importance across a wide range of brain functions, timing relies on intrinsic and general properties of neurons and neural circuits; that is, the brain uses its natural cellular and network dynamics to solve a diversity of temporal computations. Many circuits have been shown to encode elapsed time in dynamically changing patterns of neural activity—so-called population clocks. But temporal processing encompasses a wide range of different computations, and just as there are different circuits and mechanisms underlying computations about space, there are a multitude of circuits and mechanisms underlying the ability to tell time and generate temporal patterns.

> The office of this faculty is to mark the passage of time, duration, succession of events, etc. It also remembers dates, keeps correct time in music and dancing, and induces to punctuality in the fulfillment of engagements.—Charles H. Olin (*Phrenology: How to Tell Your Own and Your Friend's Character from the Shape of the Head*)

Introduction

The above quote from a phrenology text from the 19th century describes the functions of the ''time organ'' within the brain (Olin, 1910). This phrenological view, in which a highly specialized area is responsible for timing in all its shapes and forms, captures an extreme version of the notion of a master clock. A less extreme form of the master clock theory influenced research on timing late into 20th century. For example, Aschoff (1985) asked whether the prolonged isolation from external cues that alters the period of the circadian clock also affected the ability of humans to time intervals on the order of seconds. His results did not reveal any relationship between timing on the scale of seconds and days. Other experiments, however, suggested such a link; for example, it was reported that the circadian clock gene *period* alters the timing of the courtship songs in fruit flies (Kyriacou and Hall, 1980, 1986). These experiments have not been replicated (Stern, 2014), and studies in rodents have confirmed the lack of any direct relationship between circadian timing and interval timing on the scale of seconds (Lewis et al., 2003; Cordes and Gallistel, 2008; Papachristos et al., 2011)—of course, because the circadian rhythms modulate a wide variety of cognitive and physiological functions, it can affect performance on a wide range of tasks, including timing tasks (Golombek et al., 2014).

We now understand that the brain has fundamentally different mechanisms in place to tell time across different scales. For example, the transcription-translation autoregulatory feedback loops that implement the circadian clock are entirely independent of the timing mechanisms responsible for the detection of interaural delays on the scale of microseconds. These mechanisms, which operate on the extreme ranges of biological timing, are relatively well understood. In contrast, the mechanisms underlying timing on the intermediate scale of tens of milliseconds to tens of seconds remains a mystery. It is this temporal scale that is the focus of the current review.

Tens of Milliseconds to Tens of Seconds

The ability to tell time, discriminate temporal patterns, and produce appropriately timed motor responses on the scale of milliseconds to seconds is critical to many, if not most, forms of learning and behavior. For example, on the sensory side many animals use interval, duration, and the overall temporal structure of vocalization elements to communicate. On the motor side, the brain must generate highly complex and well-timed motor patterns in order to capture prey or play a musical instrument. Furthermore, animals are able to anticipate when events will occur and adjust their behavior appropriately: rodents will anticipate a reward onset by licking, and humans anticipate when a traffic light will change to green by shifting their focus to the light.

Timing on the scale of tens of milliseconds to a few seconds, in particular, is unique in that it extends far beyond the need to time simple isolated intervals or durations. It allows for the recognition and generation of complex temporal patterns that cannot be characterized by the duration of any one element. For example, Morse code reduces communication to a purely temporal code, in which information is based on not only identification of the duration of individual elements (''dots'' versus ''dashes''), but the overall global temporal structure of sequences of tones and pauses. Similarly, speech and music rely on the on the ability to recognize the higher-order temporal structure of sequences of notes on the scale of tens of milliseconds to a few seconds, and outside this range the ability to detect prosody or rhythm is lost—if a musical piece is slowed or sped up too much, it ceases to be music.

Time and Space

Many theories and models have been proposed to account for timing (see Ivry and Spencer, 2004; Mauk and Buonomano,

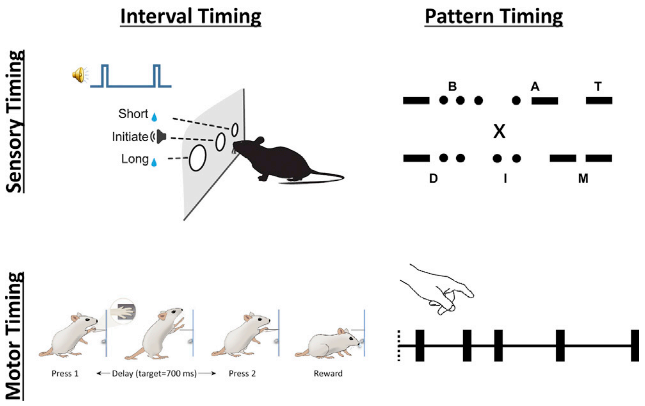

Figure 1. Taxonomy of Timing Tasks

The continuum along at least two task dimensions are likely to be important for understanding the neural basis of timing: sensory versus motor and interval versus pattern timing. Some tasks (Interval Timing) require the discrimination (Sensory Timing) or production (Motor Timing) of simple durations or intervals (or anticipation of an external event). Other tasks (Pattern Timing) require the discrimination or production of complex temporal or spatiotemporal patterns—such as deciphering Morse code signals (Sensory timing) or tapping a complex temporal pattern (Motor Timing). Upper left: adapted from Gouvêa et al. (2015). Lower left: adapted from Kawai et al. (2015).

2004; Buhusi and Meck, 2006; Coull et al., 2011; Merchant et al., 2013). Overall, these models loosely fit into two broad classes: *dedicated* and *intrinsic* models (Ivry and Schlerf, 2008). Dedicated models propose that the brain has a more or less centralized set of circuits for timing that account for timing across modalities, tasks, and scales within the range of hundreds of milliseconds to many seconds. In these models, timing relies on dedicated or specialized neural mechanisms. Intrinsic models propose that timing is an intrinsic computation of most neural circuits, and timing per se emerges from general properties of neurons and the inherent dynamics of neural circuits.

Here, we argue that converging data strongly support intrinsic models. Indeed, we suggest that given the importance and universality of temporal computations, dedicated models would not make computational sense. This does not imply that there are not some brain areas involved in a range of temporal tasks that share similar temporal processing requirements, but rather that distinct temporal computations, such as processing a Morse code message and anticipating when a traffic light will change, rely on distinct circuits and mechanisms. Under this view, areas that are consistently implicated in timing tasks should not be thought of as a central clock, but as areas that are involved in tasks that are inherently temporal in nature—e.g., since preparing and producing motor responses are inherently temporal in nature, motor areas should be consistently implicated in timing.

How the brain processes information about space provides a useful analogy for the intrinsic timing perspective. Like the temporal dimension, the spatial dimension permeates much of what the brain must accomplish, from localizing the position of objects in space, to guiding movements to grasp objects, and creating large-scale maps for spatial navigation. Mammals have many different maps of external space, including those in the colliculi, auditory cortex, visual cortex, hippocampus, and parietal cortex (Knudsen et al., 1987; Kandel et al., 2013). The multitude of spatial representations within the brain can map onto each other and form more general polymodal maps in the parietal cortex. Furthermore, consistent with the intrinsic perspective of timing, different maps of external space are computed in different ways and make distinct contributions to sensori-motor processing and cognition.

The Taxonomy of Time

Scientific advances sometimes rely not on a specific discovery or technical innovation, but on the clarity provided by the appropriate classification of the phenomenon being studied. For example, a critical breakthrough in the learning and memory field was the distinction between implicit and explicit memory, and the understanding that memory is not a unitary process—i.e., different forms of memory rely on different circuits and mechanisms (Squire, 1986). It is increasingly recognized that a major challenge in the timing field is to establish the correct taxonomy of time (Meck and Ivry, 2016). That is, to determine which of the many different forms of timing rely on the same circuits and mechanisms.

As a first step toward a taxonomy of time, it is critical to distinguish between true timing tasks and time-dependent tasks. Timing tasks refer to those that are directly based on interval or duration and that require some sort of timing device to solve. In contrast, some tasks are defined by their temporal properties but are not considered timing tasks, such as judging whether two sensory events occur simultaneously or not (asynchrony tasks) or which of two events came first (temporal-order tasks). These tasks do not require a clock or timing device to solve. Standard examples of timing tasks include (Grondin, 2010):

Interval/duration discrimination. discriminating which of two presented durations (or intervals) is the longest, or making a judgment as to whether an event is short or long relative to a standard (e.g., bisection task).

Reproduction. reproducing the duration or temporal structure of a presented sensory stimulus—e.g., tapping an interval demarcated by two tones or reproducing the complex temporal structure of a presented Morse code pattern.

Production. production of a simple or complex temporal pattern in the absence of any recent sensory presentation of the relevant interval or pattern—e.g., human subjects asked to press a key for "1 second," or a rodent that produces a timed anticipatory motor response (e.g., an eyeblink that precedes the US, or licking in anticipation of a predicted reward).

Each of the above categories encompasses a large number of different tasks that vary across sensory modality, temporal scale, and the temporal characteristics of the sensory or motor pattern. And they do not necessarily comprise a taxonomy of time because they provide few insights into which rely on similar underlying neural mechanisms and circuits. While the establishment of a taxonomy of time remains a major objective of the timing field, there is some consensus as to key dimensions that are likely to be critical to the formation of a taxonomy of time. Here, we highlight three dimensions: (1) subsecond versus suprasecond timing; (2) interval versus pattern timing; (3) sensory versus motor timing (Figure 1).

Subsecond versus Suprasecond Timing. There is ample evidence that timing of very short and very long intervals relies on different mechanisms and areas; however, there is no clear boundary between what constitutes a short or long interval. Nevertheless, a loose distinction between sub- and supra-second timing is often made. Pharmacological (Rammsayer and Vogel, 1992; Rammsayer, 1999), psychophysical (Karmarkar and Buonomano, 2007; Spencer et al., 2009; Rammsayer et al., 2015), and imaging (Lewis and Miall, 2003) studies suggest that discriminating a short interval (e.g., 50–100 ms) recruits different circuits than the discrimination of longer (>1 s) intervals.

Interval versus Pattern Timing. Imaging studies suggest that tasks that require the production of simple intervals or specific patterns recruit different neural circuits (Grube et al., 2010; Teki et al., 2011). Indeed, the distinction between simple and complex timing seems critical because these timing tasks can have fundamentally different computational requirements (Hardy and Buonomano, 2016). Discriminating the duration of a single musical note or anticipating the arrival of a reward relies on the timing of isolated durations or intervals and can easily be solved with timing mechanisms analogous to a stopwatch. In contrast, recognizing the tempo of a song, the prosody of speech, or producing Morse code are tasks that are defined by the duration and interval of components, as well as by the overall global temporal structure of a sequence of these components. Critically, when such patterns are scaled in time, they can be identified as the same pattern (a song played at different tempos is still the same song).

Sensory and Motor Timing. Time is not a sensory modality like vision or audition; rather, like space, time is a fundamental dimension of sensory data. Thus, it is important to consider the degree to which a task involves analyzing temporal relationships present in the external world versus imposing temporal structure onto the external world through action. To attempt to capture this difference, we distinguish between sensory and motor timing tasks—but emphasize that some tasks have both sensory and motor components. Duration and interval discrimination comprise prototypical sensory timing tasks: subjects report whether an external stimulus was ''short'' or ''long'' by performing a motor action such as pressing one of two keys, or nose-poking to the left or right. While these tasks require a motor response, the decision is based on the temporal properties of a sensory event, and the timing of the motor response is irrelevant. Sensory timing also includes many other distinct computations: from deciphering the temporal structure of speech and other forms of communication to learning about the statistical regularities between events in the environment that underlie associative learning and prediction. Motor timing tasks, such as motor production, require the brain to actively generate an internally timed response or prediction—such as licking, blinking, or shifting attention, at a given interval after a start cue.

The sensory versus motor dimension is, of course, a continuum: while some tasks can be considered to be exclusively sensory or motor in terms of the task constraints, many, perhaps most, require timing of both sensory inputs and motor outputs (e.g., reproduction tasks). While the distinction between sensory and motor timing is based primarily on the characteristics of the task, there is evidence for the involvement of distinct areas and mechanisms in some forms of sensory and motor timing. For example, interval- and duration-selective neurons that have been identified in the brainstem and sensory cortices (see below) bear the hallmarks of extraction of temporal information as opposed to the generation of timed patterns. Below we will use the sensory versus motor distinction to review the areas that have been implicated in timing, yet we stress that depending on the task and timescale in question many areas, such as the basal ganglia, have been implicated in both sensory and motor timing.

Models of Timing

An important step toward elucidating the neural mechanisms of timing is the development of theories and models of how the brain tells time and process temporal information. Models, however, differ significantly in the level of analyses they address, and in their ability to generate experimental predictions. David Marr distinguished between three levels of analyses: (1) a *computational* level that essentially defined the problem being addressed from a computational or information processing perspective; (2) an *algorithmic* level that sought to solve a problem algorithmically—that is, without regard to how the brain may actually implement such an algorithm; and (3) an *implementational* level, which, in the case of neuroscience, seeks to develop models implemented at the level of synapses, neurons, and neural circuits.

The first models of timing on the scale of hundreds of milliseconds and seconds were pacemaker-accumulator models (Creelman, 1962; Treisman, 1963)—and, by far, the most influential of these is referred to as scalar-expectancy theory (Gibbon, 1977). Like man-made clocks, pacemaker-accumulator models postulated a time-base or oscillator, and an accumulator or integrator that essentially provides a linear readout of elapsed time. Most pacemaker-accumulator models, however, concerned themselves with accounting for the behavioral data, such was whether Weber's law was satisfied, and not with a biological implementation. Weber's law (or the scalar property) is a general feature of timing and represents an important benchmark for models of timing (Gibbon, 1977). It refers to the observation that, for example, in motor timing tasks the SD of the response time across trials increases linearly with the mean time of the responses. While Weber's law is robust, it is not universal, and it generally applies to restricted temporal ranges, e.g., the Weber fraction (σ/t) can differ significantly for intervals of a few hundred milliseconds, seconds, and tens of seconds (Lewis and Miall, 2009; Grondin, 2014).

We will focus primarily on models implemented with attention to biological realism and supported by electrophysiological data. In the context of sensory timing, this includes a wide range of models that exploit the time-varying neuronal and synaptic properties to create temporal filters. In the context of motor timing, we focus primarily on ramping models and population clocks. Ramping models (e.g., Durstewitz, 2003; Simen et al., 2011; Balci and Simen, 2016) propose that time is encoded in monotonic changes in firing rate and that actions are produced when the firing rates reaches a threshold value. Such ramping neurons have been observed in a wide range of brain areas during timing tasks. An alternative to encoding time in the monotonic changes in firing rate is that the nervous system encodes time in the dynamically changing population of neurons (population clocks)—ranging from sequential chains of activity (Abeles, 1982) to complex patterns. This hypothesis, referred to as population clock, was first proposed in the context of the cerebellum (Buonomano and Mauk, 1994; Mauk and Donegan, 1997), and there is now a large amount of cumulative data supporting this hypothesis.

Sensory Timing

As defined above, sensory timing refers to tasks in which decisions are based on the temporal structure of stimuli. In humans, a prototypical sensory timing task is interval (or duration) discrimination, whereas in animal studies the bisection task is often used. In a bisection task, subjects are trained to make one choice when presented with a stimulus of a long duration, and another choice when presented with a stimulus of a short duration. After training, subjects undergo a procedure wherein the majority of trials are equivalent to the training phase, but on probe trials they are presented with stimuli of intermediate duration between the long- and short-duration standards. By fitting psychometric curves to the probability of choice data across the presented stimuli, it is possible to estimate the point of indifference, i.e., the interval that subjects are equally likely to judge as long and short. On probe trials, subjects are not rewarded; thus, their categorical choices have historically been thought to reflect the subjective similarity to the intervals that were reinforced during training. However, recent work suggests that, instead of reflecting perceptual similarity between short and long standards, the point of indifference may reflect the point where short and long choices are of equal value to the animal and is thus subject to factors such as the degree to which the value of future rewards are discounted relative to immediate ones (Kopec and Brody, 2018).

Sensory timing tasks represent the temporal equivalent of standard “spatial” sensory-discrimination tasks, such as orientation and pitch discrimination in the visual and auditory sensory modalities, respectively. Our understanding of the neural mechanisms underlying spatial processing and pattern recognition have benefited immensely from (1) studies of perceptual learning that significantly constrain the location and mechanisms of spatial pattern discrimination; and (2) identification of neurons that respond selectivity to specific spatial patterns, and how neural tuning changes with learning (Buonomano and Merzenich, 1998; Karmarkar and Dan, 2006; Gilbert et al., 2009). Thus, in this section we first address (1) whether sensory timing undergoes perceptual learning; (2) evidence that neurons in some early brain areas are tuned to the interval and duration of sensory stimuli; and (3) the areas of the brain that have been implicated in sensory timing. Last, we review models of sensory timing.

Temporal Perceptual Learning

While interval discrimination studies have been performed in humans for over 100 years (Mehner, 1885), it was not until the 90s that the question of whether interval discrimination thresholds improve with practice was systematically addressed. Although some studies demonstrated that musicians are superior at interval discrimination (Keele et al., 1985), other studies suggested interval timing does not improve with practice (Rammsayer, 1994). Subsequent studies, however, revealed that interval learning undergoes robust learning—however, unlike some forms of perceptual learning, temporal perceptual learning is relatively slow and requires training across days (for a review, see Bueti and Buonomano, 2014). One of the first studies to demonstrate temporal perceptual learning revealed that, after training subjects for 1 hr a day for 10 days, interval discrimination thresholds for a 100-ms interval improved from 24% to 12% (Wright et al., 1997). Importantly, despite the significant learning on the trained 100-ms interval, there was no detectable improvement on untrained 50-, 200-, and 500-ms intervals. This temporal specificity of temporal perceptual learning has been replicated in many studies and is now seen as a general characteristic of temporal perceptual learning (Nagarajan et al., 1998; Karmarkar and Buonomano, 2003; Buonomano et al., 2009; Wright et al., 2010; Bueti et al., 2012). Temporal specificity during interval-discrimination tasks constrain the neural mechanisms and models underlying sensory timing and argue against the notion of a single master clock. Specifically, if the overall precision of a clock improved with practice, it would be expected to enhance performance across a range of intervals, not just the trained interval. Another critical question relates to “spatial” generalization of temporal learning—e.g., after training on a 100-ms interval demarcated by brief 1-kHz tones, do humans improve on their ability to discriminate that same interval now bounded by 4-kHz tone? Interestingly, most studies have reported robust spatial generalization, but the interpretation of this finding is complicated by the fact that spatial generalization lags temporal perceptual learning—suggesting that generalization to different tones may result from top-down mechanisms independent of the timing mechanisms per se (Wright et al., 2010).

Interval- and Duration-Selective Neurons

It is well established that discrimination and learning of spatial patterns relies in part on the selectivity of neurons to the spatial structure of sensory inputs (Karmarkar and Dan, 2006; Gilbert et al., 2009; Froemke et al., 2013)—such as orientation or frequency-tuned neurons in V1 and A1, respectively. Although less common, neurons that respond selectively to interval or duration on the order of tens-to-hundreds of milliseconds have been identified in numerous brain areas.

Many forms of animal communication rely on temporal pattern recognition on the scale of tens to hundreds of milliseconds. Insects, frogs, fish, birds, and mammals have the ability to detect specific temporal patterns in sensory input as a means of intraspecies communication. And this ability relies in part on neurons that are tuned to the relevant temporal features of the vocalizations. Neurons in the *torus semicircularis* (TS) of frogs, for example, display variable tuning for ethologically relevant temporal features of either experimentally generated or natural calls (Elliott et al., 2011; Rose, 2014). Interval- and rate-tuned neurons have also been identified in the brainstem of weakly electric fish that use the temporal features of discharge from their electric organs to communicate (Figure 2A) (Carlson, 2009). The mechanism underlying temporal tuning in these cases is not fully understood, but it has been established that selectivity relies in part on dynamic changes in the balance of excitation and inhibition imposed by temporal summation and short-term synaptic plasticity (see below).

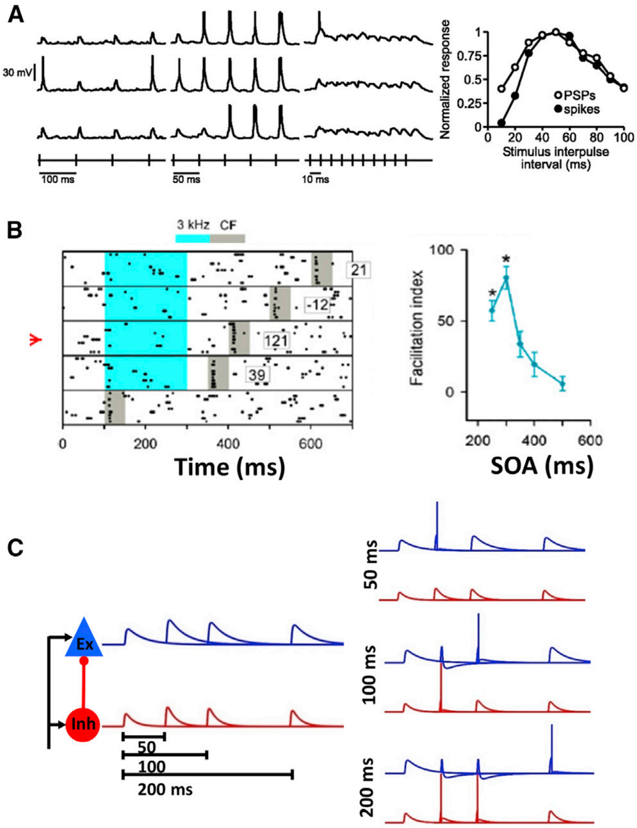

Figure 2. Example of Interval-Tuned Neurons

(A) Voltage traces from a neuron in the midbrain of an electric fish to trains of electrical pulses presented at intervals of 100 (left), 50 (center), and 10 ms (right). The rows represent three separate repetitions of each train. This neuron was tuned to pulses delivered at intervals of 50 ms (right). Adapted from Carlson (2009).

(B) Rastergram of a neuron from rat auditory cortex in response to five different stimuli, each composed of a 200-ms 3-kHz tone followed by a 50-ms 7-kHz (characteristic frequency [CF]) tone with different stimulus-onset asynchronies. Numbers represent the facilitation index. Rats were trained to detect an interval of 100 ms between both tones (red arrow), and this was the spatiotemporal pattern that elicited the maximal response across the population (right). Error bars represent SEMs. Adapted from Zhou et al. (2010).

(C) Model of how STP can generate an interval selective neuron in a disynaptic circuit composed of an excitatory (blue) and inhibitory (red) neuron (traces from three intervals are overlaid). Left, the input to both neurons exhibits paired-pulse facilitation. Right, by adjusting the weights onto both the Ex and Inh neurons, it is possible to create an Ex neuron that functions as a 50-, 100-, or 200-ms detector. Adapted from Buonomano (2000).

Temporally selective neurons have also been identified in the cortical circuits of birds and mammals. Indeed, some of the first examples of temporally selective neurons were described in the sensori-motor area HVC of zebra finches. Some HVC neurons are tuned to the interval between two tones, responding optimally to specific intertone intervals in the range of tens to hundreds of milliseconds (Margoliash, 1983). Other studies in song birds have confirmed the presence of neurons that are sensitive to a diverse array of temporal and spatiotemporal sensory features (Margoliash and Fortune, 1992; Lewicki and Konishi, 1995; Doupe, 1997).

In the mammalian cortex, studies have identified auditory neurons that are sensitive to the interval and duration of tones, as well as the overall spatiotemporal structure of auditory stimuli (He et al., 1997; Brosch and Schreiner, 2000; Sadagopan and Wang, 2009; Zhou et al., 2010). And duration-sensitive neurons have also been identified in V1 (Duysens et al., 1996). Importantly, as is the case with spatial perceptual learning, there is some evidence that the presence of temporally selective neurons is modulated by experience. In one study (Zhou et al., 2010), rats were trained to nose-poke in response to a 3-kHz tone followed by a 7-kHz tone with a 300-ms stimulus-onset asynchrony. After weeks of training, recordings in A1 revealed a bias toward the spectral and temporal features of the target stimulus. For example, Figure 2B shows a neuron that responded moderately to a brief 7-kHz tone; however, the response to the 7-kHz tone was facilitated by over 100% when it followed the 3-kHz tone by 300 ms, importantly in this neuron (and across the population) this facilitation was temporally tuned.

In contrast to the ordered topographic maps underlying spatial tuning, there have been few reports of chronotopic maps in sensory cortices. Nevertheless, there seems to be a sparse representation of temporal features in sensory cortices, as revealed by the presence of temporally selective neurons. It is reasonable to hypothesize that these neurons contribute to sensory timing in the tens-to-hundreds of milliseconds range (but see Pai et al., 2011). Furthermore, similarly to spatial perceptual tasks, there is significant evidence from animal (Kilgard and Merzenich, 2002; Yin et al., 2008; Zhou et al., 2010) and human (van Wassenhove and Nagarajan, 2007; Bueti et al., 2012) studies that perceptual learning of temporal stimuli in the tens-to-hundreds of milliseconds range rely on cortical plasticity.

Basal Ganglia

The basal ganglia (BG), a collection of subcortical nuclei that receive input from almost the entire cortical mantle as well as multiple thalamic areas, are often implicated in sensory and motor timing on the scale of hundreds of milliseconds to seconds. This is perhaps not surprising given that the BG contribute to reinforcement learning—forming predictions about future reward and selecting actions that lead to rewarding outcomes. A fundamental aspect of learning to predict something is the ability to detect temporal contingencies (Balsam and Gallistel, 2009), the degree to which some event or action reduces uncertainty about another, and there is behavioral evidence that animals represent the temporal statistics of events required for performing probabilistic inference thought to underlie this manner of associative learning (Kheifets and Gallistel, 2012; Li and Dudman, 2013). In addition, execution of behavior often involves proper timing and sequencing of action. Thus, the BG should at the very least have access to representations of timing information for both learning predictions and producing proper behavior. Evidence for BG involvement in timing comes from a variety of sources, including disease states, lesions, and pharmacological or genetic manipulations that affect BG functioning as well as functional neuroimaging and neurophysiology. Here, we will briefly discuss the evidence that the BG contribute to sensory timing and provide a more detailed discussion of the role of the BG in timing in the Motor Timing section.

While the BG have predominantly been studied in the context of what would fall under motor timing tasks, there is significant evidence that BG are involved in sensory timing. For example,

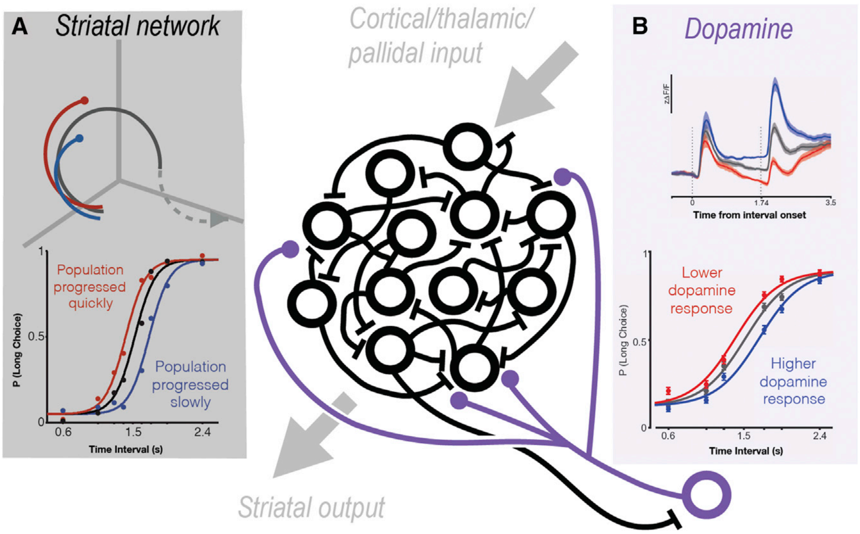

Figure 3. Midbrain Dopamine Neurons and Striatal Dynamics May Interact to Regulate Timing

(A) The speed with which striatal ensembles traverse neural space (top panel) predicts duration judgments (lower panel) in an interval-discrimination task. Colored schematic trajectories in top panel depict a quickly (red) or slowly (blue) evolving ensemble activity pattern during interval presentation in a space defined by the firing of simultaneously recorded striatal neurons. Psychometric curves for trials segregated on the basis of whether activity proceeded quickly or slowly during interval presentation. Adapted from Gouvêa et al. (2015).

(B) Calcium signals collected from dopamine neurons in the SNc exhibited trial-to-trial variability during interval presentations (top panel) that predicted the timing judgments of mice during the same interval-discrimination task used during the data collected in (A) (adapted from Soares et al., 2016). Given the dense innervation of striatal networks (in black, center) by nigro-striatal dopamine neurons (in purple, center) and the fact that SNc dopamine neurons receive significant input from striatum, these data support a hypothesis where the two brain areas reciprocally influence each other's timing functions.

multiple fMRI studies have described significant activation of the human striatum during an interval categorization task where subjects were trained to categorize intervals as longer or shorter than a cued decision boundary as compared to a control task (Rao et al., 2001; Pouthas et al., 2005). In addition, in monkeys trained to perform a duration comparison between two sequentially presented intervals, information related to both the categorical decision—was the current interval longer or shorter than the previously presented interval—and the elapsed time within an interval was encoded in the firing of neurons in the striatum (Chiba et al., 2015).

One piece of evidence that the BG play a causal role in sensory timing is data showing that inactivation via infusion of muscimol into the rat dorsal striatum impairs performance of a interval categorization task (Gouvêa et al., 2015). Recordings from single units around the site of muscimol infusions revealed rich and variable dynamics that, when viewed at the population level, encoded information about elapsed time during interval presentation. Furthermore, the timing information derived from simultaneously recorded ensembles of striatal neurons predicted the trial-to-trial variation in duration judgments produced by the animals (Figure 3). When population dynamics proceeded more quickly, rats were more likely to judge a given interval as being in the "long" category, and vice versa when population dynamics proceeded more slowly, indicating that striatal dynamics reflected the timing information that rats were using to guide their judgments (Gouvêa et al., 2015). These data demonstrate that the striatum was required, and striatal populations encoded information, for guiding what we would define as a sensory timing task. That said, it is possible that animals develop a motor strategy for solving this type of task. For example, animals might learn that reward is available to the left up to some state as a motor pattern is produced. Indeed, pigeons, mice, and rats have all been observed to initially move toward the location where a short categorical choice is reported and then move toward the location where a long categorical choice is reported as time elapses past the decision boundary in temporal discrimination paradigms (Machado and Keen, 2003; Gouvêa et al., 2014). Such observations have been interpreted as evidence that animals use embodied solutions to solve sensory timing tasks (Killeen and Fetterman, 1988; Machado et al., 2009). However, comparing simultaneously recorded high-speed video and neural population activity revealed a clear asymmetry between when timing information appeared in neural activity and behavior, with neural activity leading behavior by ~300 ms (Gouvêa et al., 2015). Thus, while time encoding by striatal neurons likely carries information about a plan for future action, it is unlikely to represent motor commands on their way out of the CNS, nor could it solely reflect the sensory consequences of action.

Mechanisms and Models of Sensory Timing

Computational models of timing have not generally explicitly distinguished between sensory and motor timing. We argue that such a distinction is important, because the temporally selective neurons in the brainstem and sensory cortex seem to behave as temporal filters as opposed to timers, and are unlikely to be directly responsible for the production of timed motor patterns. Mechanistically, we can think of the sensory and motor timing distinction as relying on *passive* versus *active* neural mechanisms, respectively. Passive neural mechanisms refer to those that react to the temporal structure of stimuli, but that are incapable of actively generating a timed response. A prototypical example of a passive mechanism is a band-pass temporal filter, which gates the information arriving at certain frequencies, but cannot actively produce a timed response. In contrast, motor and implicit timing require a circuit to actively generate a timed signal. We stress, however, that, while the distinction between sensory and motor timing is important, they can be overlapping, and indeed many models of motor timing can account for simple sensory timing (such as interval and duration discrimination).

Models of sensory timing have typically relied on the temporal characteristic of neurons and synapses to implement time delays or temporal filters. Axonal time delays that contribute to the detection of interaural time delays in the range of tens of microseconds were among the first example of models of sensory timing (Jeffress, 1948). Later models attempted to extend these axonal delay line models to the range of tens to hundreds of milliseconds by proposing that the parallel fibers of cerebellar granule cells may function as delay lines on the order of tens-to-hundreds of milliseconds (Braitenberg, 1967). Today there is little experimental support for the notion that axonal (or dendritic) delay lines contribute to timing at intervals above tens of milliseconds. But as we will see next, it is clear that the brain uses many other well-described neural and synaptic properties to implement temporal filters and solve some sensory timing problems.

Temporal Selectivity Based on Changes in the Excitatory-Inhibitory Balance. Much of the sensory timing required for animal communication—ranging from the interval and rate codes of insects and frogs to the complex vocalizations of birds and humans—takes place on the timescale of tens-to-hundreds of milliseconds. It is probably not coincidental that this is the range of the time constants of the vast majority of neuronal and synaptic properties, including the kinetics of K^+ and Ca^{2+} channels fast (tens of milliseconds) ionotropic and slower (hundreds of milliseconds) metabotropic receptors (e.g., $GABA_B$ and NMDA receptors), and short-term synaptic plasticity. Together these neuronal and synaptic properties provide a rich palette to generate neurons that are selective to the interval, duration, or temporal structure of sensory stimuli. Indeed, there is converging evidence across numerous systems that the temporally selective neurons reported in crickets, frogs, electric fish, bats, and rodents rely on dynamic shifts in the balance of excitation and inhibition produced by time-varying cellular and synaptic properties such as inhibition, rebound excitation, and short-term synaptic plasticity (Edwards et al., 2007; Aubie et al., 2009; Elliott et al., 2011; Kostarakos and Hedwig, 2012; Baker and Carlson, 2014; Rose, 2014; Goel and Buonomano, 2016).

Early models of duration selectivity in frogs and bats relied on coincidence arrival of a delayed excitatory input with the input generated by stimulus offset (Narins and Capranica, 1980; Sullivan, 1982; Saitoh and Suga, 1995; Aubie et al., 2009). Some of these early models relied on rebound excitation produced by the offset of inhibition. For example, interval selectivity to a 50-ms tone could result from stimulus onset triggering inhibition that produced rebound excitation at 50 ms, and when this rebound coincided with a subthreshold input produced by tone offset a spike would be generated. There is evidence that the temporally tuned neurons of the cricket rely on the convergence of delayed events imposed by rebound excitation and non-delayed inputs arising from a second sensory event (Kostarakos and Hedwig, 2012). And there is significant experimental evidence that duration-selective neurons in the inferior colliculus rely on a combination of mechanisms relating to the duration of inhibitory postsynaptic potentials (IPSPs) and rebound excitation (Covey and Casseday, 1999; Pérez-González et al., 2006; Aubie et al., 2009, 2012). More speculative models of interval and duration selectivity have focused on the filtering properties based on the time constants of K^+ channels (Hooper et al., 2002) or metabotropic glutamate receptors (Fiala et al., 1996).

Other models have proposed that short-term synaptic plasticity contributes to the formation of temporally selective neurons (Buonomano and Merzenich, 1995; Buonomano, 2000; Fortune and Rose, 2001). Short-term synaptic plasticity refers to a form of use-dependent synaptic plasticity in which the strength of an excitatory postsynaptic potential (EPSP) (or IPSP) can decrease (short-term depression) or facilitate (short-term facilitation) in response to a sequence of consecutive presynaptic spikes (Zucker and Regehr, 2002). For example, at cortical synapses that exhibit short-term facilitation (most exhibit depression), the second of a pair of EPSPs separated by 100 ms might be 25% larger than the first (Reyes and Sakmann, 1999)—this facilitation typically decays with time constant on the order of a few hundred milliseconds.

Figure 2C demonstrates how a simple disynaptic circuit composed of synapses that exhibit short-term facilitation can account for interval selectivity over a range of tens-to-hundreds of milliseconds. The circuit is composed of a single input, and an excitatory and inhibitory neuron—this disynaptic circuit comprises a virtually universal microcircuit architecture throughout the mammalian nervous system. We can see that if both the excitatory and inhibitory neurons receive input from synapses with short-term facilitation, one can create an interval selective neuron by adjusting the input weights. For example, let's assume the strength of the input synapse to the excitatory neuron is suprathreshold for the 50- and 100-ms interval and suprathreshold for the inhibitory neuron only at 50 ms, then the excitatory neuron can function as a 100-ms detector because the second potentially suprathreshold EPSP of the 50-ms interval can be vetoed by activity in the inhibitory neuron. By parametrically varying the weights of both synapses it is possible to create a neuron that response selectively to the 50-, 100-, or 200-ms intervals, or combinations of these intervals (Buonomano, 2000).

The interplay between short-term plasticity at excitatory and inhibitory synapses creates a flexible set of mechanisms to govern the temporal selectivity of neurons. Indeed, there is significant experimental support for the notion that the time-dependent shifts in the balance of excitation and inhibition produced by short-term plasticity (STP) contribute to temporal selectivity in electric fish and frogs (Carlson, 2009; Elliott et al., 2011; Rose, 2014).

State-Dependent Networks. The above examples demonstrate how time-varying neural and synaptic properties, such as rebound excitation and STP, can underlie interval and duration selectivity in simple circuits. Much more general and powerful computational models have been put forth to account for how cortical circuits might respond selectively to the spatiotemporal structure of complex stimuli such as spoken words, as well as intervals and durations. These interrelated models go by various names including, state-dependent networks (SDNs) and liquid-state machines (Buonomano and Merzenich, 1995; Maass et al., 2002; Buonomano and Maass, 2009). Conceptually, the SDN model proposes that the response of a population of neurons at any moment in time is intrinsically dependent on the interaction between the current input and the current state of the network (i.e., the context imposed by the previous sensory events). The internal state in turn is defined not only by which neurons are currently firing (the active state), but by the suite of time-dependent neural properties discussed above (referred to as the hidden state)—such as which synapses are currently facilitated or depressed state. If we imagine an interval defined by two tones separated by 100 ms, the first and second tone may activate the same population of input fibers, but the population of neurons activated by the first and second tone should be different because the second tone will arrive when the network is in a different state: e.g., the strength of some excitatory and inhibitory synapses (the hidden state) during the first and second tone should be different; thus, some neurons should respond differentially (Buonomano and Merzenich, 1995; Buonomano, 2000; Pérez and Merchant, 2018). As originally proposed, in SDN models the network is inactive in the absence of any stimulus—i.e., the recurrent weights are not strong enough to support self-perpetuating activity—thus, the model cannot account for anticipatory or motor timing.

SDNs are prototypical intrinsic models of timing in that they propose that temporal selectivity arises as an inevitable consequence of the rich collection of neural and synaptic properties with time constants on the order of tens-to-hundreds of milliseconds. Because each sensory event is naturally encoded in the context of the previous events, SDN models naturally account for the discrimination of complex temporal and spatiotemporal patterns, such as Morse code patterns or spoken words (Buonomano, 2000; Maass et al., 2004; Lee and Buonomano, 2012). The state dependency of SDN models generate the prediction that the detection of a specific interval should be impaired if it is preceded by a distractor tone presented at unpredictable time points (e.g., it is difficult to compare a pure 100-ms interval to a 100-ms interval that is embedded within a more complex sequence). This prediction and related predictions have been validated by psychophysical (Burr et al., 2007; Karmarkar and Buonomano, 2007; Spencer et al., 2009) and electrophysiological studies (Nikolić et al., 2009).

Motor Timing

As defined above, we use the term motor timing to refer to tasks that require an animal to actively produce a temporal pattern or anticipate an external event. Prototypical motor tasks include those in which animals or humans have to produce a simple interval or complex motor pattern (Figure 1), as well as those in which animals prepare or produce an anticipatory response to an expected stimulus. Importantly, prediction and anticipation do not only take the form of direct motor behaviors, such as anticipatory licking or blinking, but can also take the form of temporal attention. That is, much as we can focus our attention to specific points in space during a visual detection task, we can focus our attention in time during tasks in which a stimulus is expected to occur after a given interval. An example of a temporal attention task (and the related phenomenon of implicit timing) is the foreperiod task, in which a stimulus is presented at a fixed interval after a warning signal. Temporal attention decreases reaction time and increases performance—e.g., discrimination is better in trials in which the stimulus occurs at the expected time (Nobre et al., 2007; Jaramillo and Zador, 2011; Cravo et al., 2013; Nobre and van Ede, 2018).

Because of the universal importance of the generation of complex spatiotemporal motor patterns and of the ability to predict and prepare for external events, motor timing is critical to many forms of learning, behavior, and cognition. Thus, it would be surprising if all these abilities relied on a single neural circuit or mechanism. Indeed, electrophysiological and imaging studies have implicated a large number of brain areas in motor timing. We first review the brain areas that have most consistently been implicated in motor timing and then examine the neurocomputational models of motor timing.

Basal Ganglia

The neurologist Oliver Sacks described a group of patients that fell ill from an epidemic of encephalitis lethargica that swept the world between 1918 and 1923 (Sacks, 1991). These patients expressed a variety of symptoms with respect to the timing of their movements, some moving abnormally quickly, and others abnormally slowly. More modern examinations of cases of encephalitis lethargica have revealed apparent damage to BG structures such as the striatum and midbrain dopamine neurons that may be caused by an autoimmune response that preferentially affects the BG (Dale et al., 2004). Consistent with these observations, aberrant time estimation has also been described in those affected by Parkinson's disease (Pastor et al., 1992; Malapani et al., 1998), which is characterized by a loss of dopamine neurons in the substantia nigra pars compacta. In fact, a range of disorders affecting the BG including Parkinson's disease, Huntington's disease (Freeman et al., 1996), Tourette's (Vicario et al., 2010), substance abuse (Wittmann et al., 2007), and attention deficit disorder (Noreika et al., 2013) have been associated with altered sensation of time or temporally patterned behavior. Last, lesions as well as pharmacological and genetic interventions that affect striatal function in rodents have been shown to cause disturbances in timing behavior (Meck, 2006; Drew et al., 2007; Gouvêa et al., 2015; Mello et al., 2015). However, BG activation has not always been observed during temporal processing, and significant damage to the BG does not always produce clear timing deficits (Coslett et al., 2010), which may indicate either the degree of redundancy present among brain mechanisms for timing or a special dependence on the BG for timing processes with a motor component (Yin and Meck, 2014).

These observations broadly agree with data collected from healthy human subjects using functional magnetic resonance imaging (Schubotz et al., 2000; Nenadic et al., 2003), electroencephalography (Pfeuty et al., 2003), and positron emission tomography (Jahanshahi et al., 2006), all of which have frequently localized sensory and motor timing to circuits within or anatomically connected to the BG. For example, during an interval categorization task where subjects were trained to categorize intervals as longer or shorter than a cued decision boundary of either 450 or 1,300 ms, the right caudate was significantly activated as compared to a control task (Pouthas et al., 2005), irrespective of the cued condition, as assessed using fMRI. As in other studies (Rao et al., 2001; Ferrandez et al., 2003), this activation was accompanied by activation in premotor cortex. While these techniques combined with incisive behavioral task design can allow for the localization of interval timing to different regions of the brain, their spatial and/or temporal resolution is often too coarse to reveal the nature of time encoding in these areas. Electrophysiological studies in animal model organisms have provided important clues as to how timing information is encoded by BG circuits. For example, in monkeys performing a sequential saccade task, the varied response profile of striatal neurons could be used to encode time between individual task events (Jin et al., 2009). However, no explicit requirement to estimate time or to report a temporal judgment was present in this task, leaving open the question of whether time information encoded by neurons would correlate with time judgments produced by the animal.

By systematically varying the temporal predictability of cues eliciting movement, Sardo et. al (2000) were able to measure differences in reaction time that reflected monkeys temporal expectations of a stimulus. When tonically active neurons, presumed cholinergic interneurons, were recorded during this behavior, a large fraction of cells modulated their cue response depending on temporal predictability of the cue, demonstrating that tonically active striatal neurons have access to a timing signal (Sardo et al., 2000). Other studies have shown that information about elapsed time is continuously available to BG circuits. GABAergic neurons in the substantia nigra of mice trained to depress a lever for a minimum amount of time (Fan et al., 2012) and striatal neurons recorded in rats trained to press a lever for a reward delivered on a fixed interval reinforcement schedule (Matell et al., 2003; Mello et al., 2015), or mice trained to lick for reward delivered after a fixed delay (Bakhurin et al., 2017), also exhibited diverse temporal profiles that as a population encoded information about elapsed time—that is the network implemented a population clock. Interestingly, the response profiles of many striatal neurons temporally rescaled in association with changes in the interval between reward availability or timing behavior (Mello et al., 2015). This suggests that the striatum may encode information about relative as opposed to absolute time, adapting to the relevant timescale in the current environment. Time representations that temporally rescale may have important implications for the learning processes that BG circuits are thought to implement, as the temporal credit assignment required for associative learning is thought to rely on the statistics of relative, rather than absolute, timing of events in the environment. Importantly, across multiple behavioral paradigms, reversible inactivation of the striatum transiently reduced the sensitivity of animal's behavior to elapsed time (Meck, 2006; Gouvêa et al., 2015; Mello et al., 2015; Wang et al., 2018). Thus, it appears that the normal functioning of striatal populations is required and encodes information for guiding time-dependent behaviors.

It is important to point out that, in many behavioral tasks, behavior is continuously changing and non-repeating, and thus neural responses that simply reflect ongoing behavior might be misinterpreted as representing elapsed time. Indeed, many striatal neurons respond around behavioral events. However, these responses cannot be easily explained as simply motor in nature; rather it is often the case that information about time and action in multiplexed (Matell et al., 2003; Mello et al., 2015). In addition, removing cells with responses locked to observed behaviors does not remove all time information from striatal populations (Bakhurin et al., 2017).

The above studies suggest a mode of time encoding by the striatum wherein the speed with which populations of active neurons progress through a spatiotemporal pattern of activity reflects the speed of an internal clock that animals use to guide time-dependent behavior. What mechanisms might be responsible for this variability in the speed of this population clock? A recent neural network model demonstrated that sequential neural activity can be generated using a striatum-like inhibitory network, and that these sequences of activity across neurons can be stretched or contracted by simply varying the magnitude of a tonic excitatory input to the network or by varying the time-constant of short-term synaptic depression of the synapses between striatal neurons (Murray and Escola, 2017). In the model, tonic input is thought to originate in the thalamic or cortical inputs to the striatum and serves to "select" which sequence of firing to produce, whereas the cortical inputs act as a kind of tutor during learning, training the striatal network to produce a particular sequence via an anti-hebbian plasticity rule that is expressed at recurrent synapses. This work highlights a few mechanisms by which a kind of population clock may be instantiated and modified by experience within BG circuitry; however, at its core it is agnostic as to what upstream neurobiological factors may cause changes in the parameters of short-term synaptic plasticity or overall excitatory drive onto the network.

Midbrain dopamine neurons, in addition to encoding a reward prediction error (Schultz et al., 1997), have been implicated in timing (Malapani et al., 1998). These neurons project densely to the striatum (Gerfen and Bolam, 2010) and can modify circuit dynamics (Costa et al., 2006). For example, excitotoxic lesions of dopaminergic input to the striatum using 6-hydroxydopamine can render previously learned behavior insensitive to duration (Meck, 2006), and overexpression of D2 type dopamine receptors in the striatum can cause disruptions in timing behavior (Drew et al., 2007). Interestingly, there is evidence that dopaminergic projections to more ventral striatum may not play a large role in timing processes, as lesions of dopaminergic input to nucleus accumbens or local infusions of drugs affecting dopamine availability or receptor activation produce changes in the vigor of behavior, but not its timing (Meck, 2006). However, a recent study demonstrated that lesioning the ventral striatum in rats could abolish signatures of a time-dependent component of reward prediction error coding by dopamine neurons in the ventral tegmental area, indicating that some time-dependent computations might rely on more ventral regions in the striatum (Takahashi et al., 2016).

The most direct assessment of the role of dopamine neurons in time estimation comes from studies that measure and manipulate dopamine neuron activity on a fast timescale during timing behavior. During an interval categorization task, fiber photometric recordings of dopamine neuron activity in the substantia nigra pars compacta of mice revealed signals that reflected variation in internal time estimates (Soares et al., 2016). These data were consistent with voltammetric recordings of dopamine release in the striatum during a temporal bisection task (Howard et al., 2017). By encoding reward prediction error, dopamine neurons encode the degree to which an organism is surprised by a reward, including when that surprise originates from uncertainty about when a stimulus will occur (Pasquereau and Turner, 2015). However, optogenetic activation of substantia nigra pars compacta (SNc) dopamine neurons caused underestimation, and optogenetic inhibition of SNc dopamine neurons caused overestimation of interval duration, indicating that dopamine neurons not only reflect information about estimates of elapsed time but are capable of exerting control over those estimates (Soares et al., 2016). Putting together the above observations, an intriguing hypothesis emerges that dopaminergic projections from the SNc to the striatum modify striatal population dynamics in a manner that is linked with prediction error. When the world is better than expected, phasic increases in dopamine neuron activity may act to slow striatal population dynamics, either by causing a net decrease in the excitatory drive to the striatal network or by altering the dynamics of synaptic plasticity. Such an effect may underlie common observations that fearful or pleasurable experiences can have opposites effects on perceived duration (Falk and Bindra, 1954; Gable and Poole, 2012; Fung et al., 2017). Future work involving the simultaneous observation or manipulation of dopamine neurons while recording from striatal populations during timing behavior will be required to explore such hypotheses, and more generally to understand the relationship between dopaminergic neuromodulation and neural dynamics in recipient brain areas such as the striatum.

Cerebellum

The cerebellum is one of the first structures to be implicated in timing and hypothesized to serve as a critical structure for many forms of timing in the subsecond range (Braitenberg, 1967; Ivry and Keele, 1989). Lesion and imaging studies suggest the cerebellum is involved in sensory and motor timing tasks in the subsecond range (Ivry and Keele, 1989; Spencer et al., 2003; Grube et al., 2010; Teki et al., 2011). The most compelling evidence for a role of the cerebellum is probably in the context of motor timing of eyeblink conditioning. In this associative learning paradigm, an initially neutral conditioned stimulus (CS) is repeatedly paired with a delayed (e.g., 50–500 ms) unconditioned stimulus (US) composed of a shock or airpuff delivered to the eye of rodents or rabbits. Subjects learn to blink in anticipation of the US delivery as learning progresses. Lesions of the cerebellar cortex lead to the loss of proper timing of eye closure yet do not prevent the CS from eliciting a blink response (Perrett et al., 1993; Kalmbach et al., 2010). Mauk and colleagues first suggested that the diverse temporal profiles of granule cell firing triggered by CS input can act as temporal basis for learning proper conditioned response timing (Mauk and Donegan, 1997; Medina et al., 2000). In this model, the temporal structure of the granule cell activity forms a population clock that emerges from a negative feedback loop between granule and Golgi neurons. Coincident input from climbing fibers originating in the inferior olive that signal US delivery and input from granule cells active at the time of US delivery onto Purkinje cells are thought to drive long-term depression of granule cell to Purkinje cell synapses. Through learning, this would lead to a decrease in granule cell excitatory drive onto Purkinje cells (which are inhibitory) around the time of US delivery, leading to a decrease in Purkinje activity and downstream disinhibition the cerebellar nucleus generating a properly timed blink. While the mechanisms underlying timing in the cerebellum continue to be debated, it is well established that the cerebellum plays a role in some forms of motor timing (Kalmbach et al., 2010; Johansson et al., 2014; Kennedy et al., 2014).

Related cerebellar models account for how well timed predictions are formed by neural circuits. Most notably in how timed "negative images" of the sensory consequences of electric organ discharge (EOD) in mormyid fish is learned and generated (Kennedy et al., 2014). Again, the diverse profile of activity of granule cells acts as a temporal basis set, the weighted combination of which can approximate the sensory consequences of EOD alone. Interestingly, the kind of temporal basis functions that has been ascribed to granule cell activity in the cerebellum parallels a classical method for representing time within computational models of reinforcement learning (RL). RL models learn predictions about future reward. Whereas the cerebellum has been postulated to learn forward models that shape behavior through a supervised learning process, the objectives of which are to predict the sensory consequences of action, the BG are thought to help learn to select actions that maximize future reward.

Bird Song System

Studies in song birds have provided some of the clearest evidence that population clocks in the form of sequential activation of neurons underlie some forms of motor timing. The songs of zebra finches are characterized by the temporal structure of both individual syllables as well as of the entire sequence (Doupe and Kuhl, 1999). And there is evidence that this temporal structure is governed by a population of neurons in area HVC; specifically, the population of excitatory neurons that project to the motor area RA have been shown to be activated in a chain-like sequence (Figure 4D) (Hahnloser et al., 2002; Long et al., 2010; Lynch et al., 2016). Such sequential activation could be implemented by a simple feedforward connectivity; however, whole-cell recordings reveal that these neurons also receive well-timed subthreshold inputs at different times during the song (Long et al., 2010), suggesting that the underlying dynamics might be produced by a more complex recurrent architecture that results in functionally feedforward activity.

As in other areas of the brain in which population clocks have been observed, it is of course possible the sequential activation of neurons in HVC does not constitute the timer per se but rather reflects readout of a timer in upstream areas. However, the birdsong system has allowed for experiments aimed at establishing a causal relation between sequential neural activity and motor timing. Specifically, it has been shown that cooling HVC uniformly slows song speed, whereas cooling the motor nucleus RA does not dramatically alter song timing (Long and Fee, 2008). These experiments comprise some of the best evidence to date of a causal link between the dynamics generated within a local circuit and the timing of a motor behavior.

Cortical Circuits

Cortical circuits involved in the temporal control of behavior likely span the entire spectrum from sensory cortex, to higher-order associative areas, to motor cortex. For example, information about the expected time of sensory events such as visual cues has been observed in primary visual cortex of monkeys and rats (Shuler and Bear, 2006; Sirotin and Das, 2009; Chubykin et al., 2013; Gavornik and Bear, 2014), as has information about the timing of impending actions (Namboodiri et al., 2015). Furthermore, local optogenetic activation of rat visual cortex can produce shifts toward earlier action timing (Namboodiri

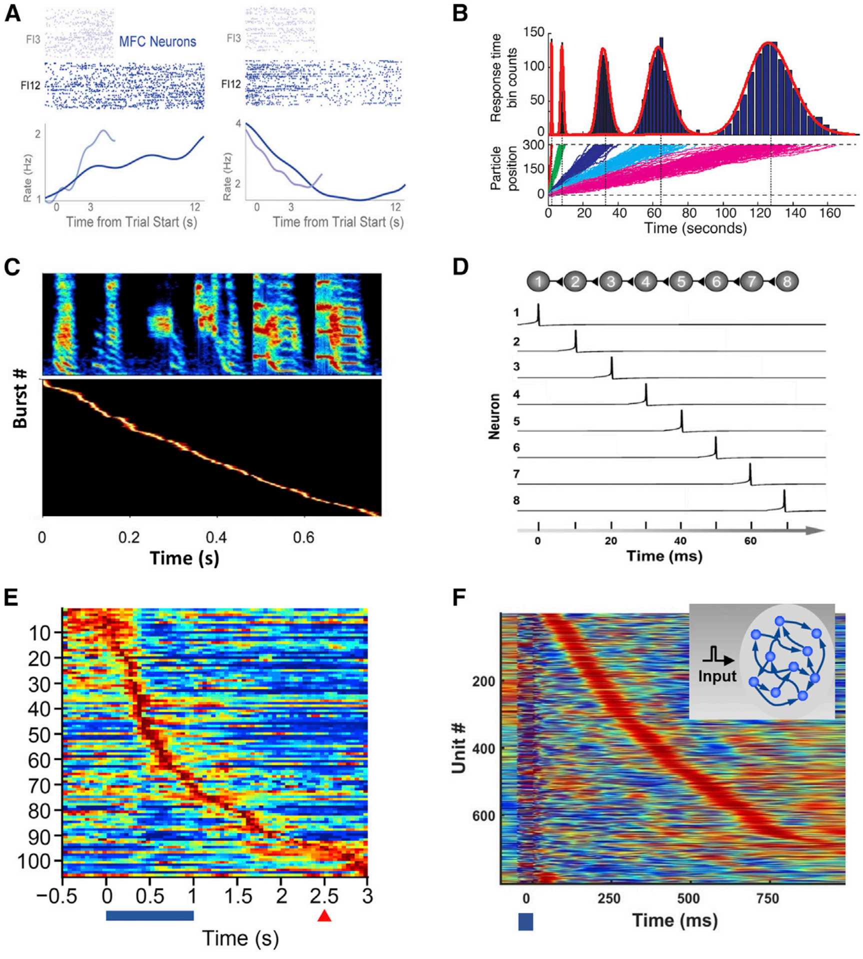

Figure 4. Examples of Experimentally Observed Neural Responses and Simulated Models of Timing

(A) Two ramping medial frontal cortex (MFC) neurons recorded during trials in which the animal anticipated reward availability at 3 or 12 s. Adapted from Emmons et. al. (2017).

(B) Model of an integrator that generates ramping and that can be rescaled to time different durations by changing the magnitude of the input. Adapted from Balci and Simen (2016).

(C) Example of the sequential activation of neurons in area HVC. Each line represents a burst in a neuron (neurons that bursted more than once are represented in different lines). The pattern drives the timing of the zebra finch song. Adapted from Lynch et al. (2016).

(D) Schematic of a simple feedforward network (a synfire chain) that can implement a sparse population clock.

(E) Example of the trial-averaged activity in simultaneously recorded orbito frontal cortex (OFC) neurons in response to an olfactory cue (blue bar) that predicts a delayed reward (red arrowhead). Cells are sorted according to the time of the peak firing rate. Adapted from Bakhurin et al. (2017).

(F) Simulation of a firing-rate based RNN that generates a complex population clock. Units are sorted according to the time of peak activity after the end of the input (blue bar). Adapted from Laje and Buonomano (2013).

et al., 2015), suggesting that primary visual cortex may have a causal role in the production of visually cued timed actions. Relatedly, single neuron and multiunit responses recorded in primary auditory cortex have been shown to encode information about the timing of motor responses during auditory but not visually cued behavior (Brosch et al., 2005). Thus, primary sensory cortex may play an important role in guiding motor timing by linking modality specific sensory signals with properly timed behavior.

At the opposite end of the sensory-motor continuum, and perhaps less surprisingly, primary and higher motor cortical areas have been repeatedly implicated in timed behavior. However, the specific contributions of different motor cortical regions to timed action is not entirely clear. In one recent study, lesions of primary motor cortex in rats trained to produce a 700-ms interval resulted in minimal changes in motor timing when lesions were performed in well-trained animals (Kawai et al., 2015). However, similar lesions performed before training blocked learning of appropriately timed behavior, suggesting that motor cortex may be specifically involved in tutoring subcortical motor structures during learning but no longer drives execution of timed actions after learning. Results of lesioning motor cortex in animals trained to perform a simple peak-interval timing procedure, which involves motor timing over the longer scale of tens of seconds, similarly do not seem to affect action timing. However, those same lesions do disrupt timing behavior during a modified peak interval procedure wherein two stimuli must be timed concurrently, suggesting that primary motor cortex may play an important role in splitting timing resources between multiple tasks (Olton et al., 1988), even after extensive training. Interestingly, many more neurons in primary motor cortex responded to concurrently presented timing cues but not to single timing cues than responded to any of the timing cues when they were presented in the simple, single-interval timing condition (Pang et al., 2001).

Electrophysiological studies performed in awake-behaving animals performing timing tasks have revealed that neural activity in a wide range of cortical areas encode time—i.e., it is possible to estimate elapsed time from the patterns of neural activity. Furthermore, the temporal variability of the neural code for time correlates with the timing of the motor responses—i.e., when the “neural code” runs faster than average the motor responses are produced earlier than average. In addition to the sensory areas described above, encoding of elapsed time has been reported in parietal (Maimon and Assad, 2006; Jazayeri and Shadlen, 2015), prefrontal (Xu et al., 2014; Emmons et al., 2017; Wang et al., 2018), premotor (Crowe et al., 2014; Murakami et al., 2014; Merchant and Averbeck, 2017), and motor cortices (Renoult et al., 2006), and, recently, responses reflecting the decision boundary in an interval-discrimination task were reported in pre-supplementary motor cortex (Mendoza et al., 2018). As described below, these neural codes for time take various forms—from monotonic ramping of single neurons, to sequential activation of neurons, to complex spatiotemporal patterns of activity (Figure 4). One recurring feature in some of these studies is the presence of response dynamics that temporally rescale with action timing. Such patterns of activity represent a widespread and powerful mechanism for motor timing. This is because if action initiation is triggered by entry into a particular network state, timed actions or decisions could be produced by simply modulating the speed with which neural populations progress from some initial condition to an action or decision initiation state (see below).

The above results suggest that cortical circuits are involved in a broad range of timing functions and that timing is a general computation of cortical circuits. Further support for this view is provided by studies showing that *in vitro* cortical circuits can adapt to, and in a sense anticipate, the timing of temporal patterns administered *in vitro* (Johnson et al., 2010; Chubykin et al., 2013; Goel and Buonomano, 2016). Overall, there is converging *in vivo*, *in vitro*, imaging, and lesioning data that suggest that cortical circuits are intrinsically able to process temporal information and do so on an "as-needed basis."

Models of Motor Timing

Traditionally, most models of timing have focused on motor timing—i.e., timers or clocks that can actively report elapsed time. As emphasized earlier, these models can certainly be used for sensory timing tasks—but sensory timing models are not well suited for motor tasks. Here, we review three broad classes of models of motor timing. Our classification is based on the fundamental basis of timing per se as opposed to the readout mechanism: (1) oscillator-based models; (2) ramping models; and (3) population clocks. We focus primarily on models that are implemented with attention to neurobiological plausibility.

Oscillator-Based Models. The first models of timing on the scale of milliseconds to seconds are referred to as internal clock or pacemaker-accumulator models (Creelman, 1962; Treisman, 1963). In their simplest form internal clock models mirror the principles of man-made clocks: an oscillator generates periodic events that are integrated or counted by an accumulator. While more sophisticated versions of the internal clock model—most notably scalar expectancy theory (Gibbon, 1977) have proved to be very valuable in guiding behavioral and psychophysical experiments, there is very little biological support for the standard pacemaker-accumulator models. It is important to note that many of these pacemaker-accumulator models can also be implemented as "accumulator" models in which the pacemaker is replaced with a tonic input that generally takes the form of a fixed firing rate with a Poisson distribution. Such models are essentially equivalent to the ramping models discussed below (Luzardo et al., 2017).

Other examples of oscillator-based models rely on the notion that time is encoded in a population of oscillators with different periods (Miall, 1989; Matell and Meck, 2000, 2004). For example, a 1-s interval might be encoded by the coincident activity of a 10-, 4-, and 3.33-Hz oscillator. The most detailed version of this multiple oscillator model is referred to as the striatal beat frequency model, which suggests that distributed cortical circuits contain a population of neurons oscillating at a range of different frequencies, and that the medium spiny neurons of the striatum function as coincidence detectors (Matell and Meck, 2004; Buhusi and Meck, 2005)—capturing the beats of the cortical oscillators. As discussed above, there is abundant evidence that the BG contribute to many timing tasks, but there is little evidence that detecting the beats of cortical oscillators represents the underlying mechanism. Indeed, it seems unlikely that the sequential activation of MSN neurons observed during timing tasks (Gouvêa et al., 2015; Mello et al., 2015) is consistent with the striatal beat frequency (SBF) model.

While there is little experimental support for oscillator-based mechanisms for timing, it is important to emphasize that it is well established that oscillators do contribute to timing of rhythmic motor behaviors. The distinction lies in the difference between supra- and sub-period timing. As proposed in the internal clock model the time intervals being measured are above the period of the time base (supra-period timing). Sub-period timing refers to cases in which the temporal structure being produced lies below the period of the oscillator—i.e., time is coded in the phase of the oscillator. The circadian clock provides a clear example of the subperiod and supraperiod distinction: the circadian clock accurately times intervals below its period, but the neurons in the suprachiasmatic nucleus do not keep track of supraperiod intervals (the number of oscillations they have undergone). Many rhythmic motor behaviors that require tightly timed sequential responses—such as walking, breathing, and swimming—are governed by the phase of neural oscillators (Marder and Calabrese, 1996; Grillner, 2003; Feldman and Del Negro, 2006).

Ramping-Based Models. Ramping models of timing refer to those in which a neuron or population of neurons undergo an approximately linear increase (or decrease) in firing rate over time—thus producing a metric of elapsed time encoded in neural firing rate (Figure 4A). There are abundant data showing that, during interval motor timing tasks, neurons in the parietal cortex (Leon and Shadlen, 2003; Janssen and Shadlen, 2005; Jazayeri and Shadlen, 2015), prefrontal cortex (Niki and Watanabe, 1979; Kim et al., 2013; Emmons et al., 2017; Kim et al., 2017), and premotor and motor cortex (Mita et al., 2009; Murakami et al., 2014) all exhibit approximately linear ramping of firing rates during motor timing tasks. It is generally the case that a timed motor response is generated when a population of ramping neurons reaches a given firing rate threshold. Importantly, the slope of the ramp generally decreases as the interval being timed increases, while the peak firing rate remains approximately the same. (Leon and Shadlen, 2003; Murakami et al., 2014; Jazayeri and Shadlen, 2015; Merchant and Averbeck, 2017).

Since neurons have time constants on the order of tens of milliseconds, and ramping has been observed over scales of seconds, ramping models generally require some sort of positive feedback mechanism to integrate information and counterbalance membrane "leak." Cellular- and network-based mechanisms have been proposed to underlie ramping. Cellular-based mechanisms refer to those in which a single neuron can integrate input and produce a ramp in firing rate. One such model proposes that tonic synaptic input opens voltage-gated Ca^{2+} channels, which in turn activate depolarizing currents resulting in positive feedback and a linear increase in firing rate (Durstewitz, 2003; Hass and Durstewitz, 2014). Most ramping models, however, rely on network mechanisms in which positive feedback is implemented via recurrent excitatory connections (Reutimann et al., 2004; Gavornik et al., 2009; Simen et al., 2011; Lim and Goldman, 2013). In their simplest form, such ramping or drift-diffusion models do not generally account for Weber's law. However, a model that has been implemented at the neural level, and referred to as a time adaptive opponent Poisson drift-diffusion model, captures Weber's laws by incorporating both excitatory and inhibitory feedback (Simen et al., 2011; Balci and Simen, 2016; Merchant and Averbeck, 2017).

While many neurons exhibit ramping during tasks in which animals produce a timed motor response or anticipate a reward, it is not clear whether ramping neurons are the actual timer or rather reflect the preparation of a motor response—and are thus better thought of as the readout of upstream timing circuits. During most tasks, timing and motor response preparations are confounded, but it is possible to dissociate them if the timing of an expected stimulus is bimodally distributed. For example, if a stimulus is expected at either 0.5 or 2 s, animals can learn the hazard rate (reaction times will be minimal around 0.5 and 2 s). If ramping neurons encode absolute time, they would be expected to exhibit an increase in firing throughout the duration of the task. In contrast, if they are encoding motor preparation or expectation, their firing rate should follow the hazard rate (increase around 0.5 s, decrease, and then increase again). This experiment has been performed while recording from ramping neurons in the parietal cortex, and the results show that these neurons encode the probability of the stimulus rather than absolute time (Janssen and Shadlen, 2005). It is not that timing signal need be monotonically changing but rather that the ramping often interpreted as timing signals may instead reflect functions such as action preparation that are driven by upstream timing signals.

Thus, while there is abundant experimental evidence that many neurons exhibit ramping firing rates during timing tasks, many issues remain to be addressed. In addition to whether ramping encodes time or motor preparation/expectation, it is not clear whether ramping reflects the timer per se or is produced by appropriately tuning the weights of upstream neurons that encode time through changing patterns of neural activity (Buonomano and Laje, 2010). Indeed, recent experimental evidence in CA1 place cells suggest that linear ramping of membrane voltage over 1–2 s is produced by sequentially active CA3 neurons with progressively stronger synaptic weights (Bittner et al., 2017).

Population Clocks. The term population clock refers to models in which time is encoded in the changing population of neural activity (Buonomano and Karmarkar, 2002). Thus, population clocks rely on a general property of neural circuits: their internal neural dynamics. We can think of a population clock as a neural trajectory in N-dimensional space, where N is the number of neurons participating in the population clock and each point on the trajectory codes for a moment in time (Figure 4). If these patterns are reproducible and unique at each moment in time, it is possible for downstream neurons to readout elapsed time.

Critical to the notion of population clocks is that the trajectories emerge from dynamics of the neural circuits; that is, the patterns occurring early in the trajectory are causally responsible for the later patterns. Thus, a simple array of non-interconnected neurons, each firing at different latencies (e.g., a labeled line model), would not constitute a population clock because the activity of the neurons firing later are independent of the activity of the neurons firing earlier. Population-clock models propose that a given neural trajectory encodes time from the onset of a given stimulus, or relative time depending on the context (e.g., producing the same motor pattern slowly or quickly may rely on very similar neural trajectories evolving at a fast or slow speed, respectively). In other words, one stimulus might elicit neural trajectory T_1 and another stimulus a distinct trajectory T_2—thus, the same population of neurons encode time from the onset of each stimulus. The advantage of these stimulus-specific "clocks" is that the population encodes not only time but the stimulus—in other words, temporal and spatial processing are intertwined. Computationally, this offers many advantages. For example, the first population-clock models were proposed in the context of the cerebellum in which the changing population of granule cells encode time since stimulus onset (Buonomano and Mauk, 1994; Mauk and Donegan, 1997) in order to account for the timing of conditioned responses. Since population clocks are inherently capable of encoding both the stimulus and elapsed time, it is relatively easy to account for the ability of distinct stimuli to elicit differentially timed response.

Population clocks can potentially take various forms, from sparse chain-like sequences of neural activation, to complex trajectories in which neurons can exhibit mononotonic and nonmononontonic temporal activity profiles. Evidence for both sparse (Figures 4C and 4D) and complex (Figures 4E and 4F) population clocks have been observed throughout the brain, including parietal cortex (Stokes et al., 2013; Crowe et al., 2014), premotor and motor cortex (Carnevale et al., 2015), frontal cortex (Wang et al., 2018), prefrontal cortex (Bakhurin et al., 2017), BG (Jin et al., 2009; Gouvêa et al., 2015; Mello et al., 2015; Bakhurin et al., 2017), hippocampus (Pastalkova et al., 2008; MacDonald et al., 2011), and in song birds (Hahnloser et al., 2002; Lynch et al., 2016)—although in most of these cases, it is not known whether the dynamics is generated within the circuit being recorded or rather driven by upstream circuits. But in many of these experiments, as mentioned above, it has been demonstrated that the speed of the population clock co-varies with behavior—i.e., when the population clock runs early in relation to the mean, so does the timed behavior (Crowe et al., 2014; Gouvêa et al., 2015; Bakhurin et al., 2017). Furthermore, some studies suggest that the individual neurons that compromise a population clock may reflect Weber's law; e.g., the half-width of the peak response can increase with the time of this peak (Mello et al., 2015; Tiganj et al., 2017).

Computational models have proposed that sparse population clocks (in which each neuron is active only once during a trajectory) are produced by synfire chains or functionally feedforward patterns of activity (Goldman, 2009; Liu and Buonomano, 2009). In these sequential trajectories, readout is very straightforward, as each neuron represents a given amount of elapsed time (or a "time field"). A number of models have proposed how sparse population clocks can emerge in a self-organizing manner (Buonomano, 2005; Liu and Buonomano, 2009; Fiete et al., 2010; Miller and Jin, 2013). The general idea is that homeostatic and/or associative forms of plasticity lead to the emergence of recurrent neural networks with an embedded feedforward architecture. More complex population clocks can take the form of patterns in which the temporal profiles of neurons is distinct and a given neuron might be active multiple times during trajectory—thus resulting population histograms that do not result in a simple diagonal line of latency-sorted neurons. Models of complex population clocks rely on relatively strong feedback inherent to recurrent neural networks. Specifically, networks with strong recurrent connections are capable of generating continuously changing patterns of self-perpetuating activity, and when the recurrent weights are appropriately tune the resulting neural trajectories can robustly encode time (Laje and Buonomano, 2013).

In contrast to ramping models, population clocks lack an intrinsic metric of time. For example, in a linearly increasing ramping model, if a cell fired at 5 Hz at the end of one interval and at 10 Hz at the end of another, we can infer that more time elapsed during the second interval. In contrast, in a population-clock model, if cell X was firing at the end of one interval and cell Y at the end of another, there is no inherent metric that allows one to infer *a priori* which interval was longer. Unless, of course, the code has been previously learned. This can be achieved, for example, by having a population clock drive the ramping of a readout neuron (Buonomano and Laje, 2010). While the encoding of some sensory features do have intrinsic metrics (e.g., firing rate is often monotonically related to stimulus intensity), many other features, including spatial localization and the orientation of lines, also don't have an intrinsic metric and thus require establishing a mapping between neurons and the relevant stimulus dimension to make quantitative judgments about left/right or clockwise/counterclockwise.

Both ramping and population-clock models have been shown to be able to account for an important feature motor timing: temporal scaling. Specifically, motor behaviors such as playing a musical instrument can be executed at different speeds. In the case of ramping models, the slope of the firing rate can be altered by changing the magnitude of the tonic input that is being integrated—thus increasing or decreasing the amount of time the integrator takes to reach some threshold (Simen et al., 2011; Murakami et al., 2014). In the case of population clocks, it has been shown that the trajectories produced by firing-rate based recurrent neural networks (RNNs) can be traversed at different speeds. Again, changing the magnitude of a tonic input to appropriately trained RNNs can produce very similar neural trajectories that are traversed more quickly or slowly (Hardy et al., 2017; Wang et al., 2018)—these "parallel trajectories" lie along a manifold in phase space. As mentioned above, temporal scaling of a sparse population clocks has also been implemented in a striatal model (Murray and Escola, 2017). This model relies on the fact that high-firing rates can accelerate short-term depression of inhibitory synapses, again accelerating the trajectory. While both ramping and population clocks can account for temporal scaling, a strength of population-clock models is that they are better suited to account for pattern timing—that is, generate complex spatiotemporal patterns, such as those that underlie speech or Morse code (Hardy and Buonomano, 2016).

Conclusions

It is increasingly well accepted that the ability to tell time, to predict when events will happen, and to process and represent temporal patterns are among the brain's most important and basic functions (Meck and Ivry, 2016; Buzsáki and Llinás, 2017). Thus, understanding the neural basis of timing and temporal processing will be a critical step toward generating general theories of sensorimotor processing, learning, and cognition. Here, we emphasize that precisely because of the importance of time to so many distinct aspects of brain function there is not a specific mechanism or area underlying timing, any more than there is a single area responsible for processing and representing information about space. Depending on the timescale of interest and the computational requirements of the task, the brain engages a diversity of mechanisms and areas to tell time, and to processes temporal patterns.

We argue that one of the most general mechanisms contributing to timing across many different areas and tasks is the inherent cellular and network dynamics of neural circuits. Neurons and neural circuits are richly dynamical systems, and this dynamics likely evolved in part to allow the brain to capture time and process temporal information. Conversely, the brain's natural dynamics was likely coopted to solve many types of temporal problems. This is not to say that there are not some specialized or centralized areas underlying some forms of timing in the millisecond to seconds range but rather that questions about the neural basis of timing must be placed in the context of the task at hand and the computational requirements of the task.

Future advances in the timing field will rely in part on an improved taxonomy of time. That is, a better understanding of which types of tasks and problems use shared mechanisms and circuits. Additionally, one of the most pressing problems in the timing field is the need to establish a causal relationship between the neural patterns of activity that seem to underlie many forms of timing and behavior. Given the evidence that timing is intrinsic to many neural circuits—and that even within the same task different areas may contribute to timing—such experiments are likely to be even more challenging than in other fields of systems neuroscience. Nevertheless, optogenetic and temperature manipulations that specifically slow or accelerate neural trajectories underlying population clocks offer promising approaches.

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