Introduction to the Neurobiology of Interval Timing

Hugo Merchant and Victor de Lafuente

Abstract

Time is a fundamental variable that organisms must quantify in order to survive. In humans, for example, the gradual development of the sense of duration and rhythm is an essential skill in many facets of social behavior such as speaking, dancing to-, listening to- or playing music, performing a wide variety of sports, and driving a car (Merchant H, Harrington DL, Meck WH. Annu Rev Neurosci. 36:313–36, 2013). During the last 10 years there has been a rapid growth of research on the neural underpinnings of timing in the subsecond and suprasecond scales, using a variety of methodological approaches in the human being, as well as in varied animal and theoretical models. In this introductory chapter we attempt to give a conceptual framework that defines time processing as a family of different phenomena. The brain circuits and neural underpinnings of temporal quantification seem to largely depend on its time scale and the sensorimotor nature of specific behaviors. Therefore, we describe the main time scales and their associated behaviors and show how the perception and execution of timing events in the subsecond and second scales may depend on similar or different neural mechanisms.

Keywords

Time perception • Sensory timing • Motor timing • Timing models

Time Scales and Their Neural Substrates

From microseconds to circadian rhythms, temporal information is used to guide behavior. Specific brain mechanisms have been suggested for the temporal processing of different time scales covering 12 orders of magnitude [1] (Fig. 1).

H. Merchant (✉) • V. de Lafuente (✉)
Instituto de Neurobiología, UNAM,
Campus Juriquilla, Boulevard Juriquilla No. 3001,
Querétaro 76230, Mexico
e-mail: hugomerchant@unam.mx; lafuente@unam.mx

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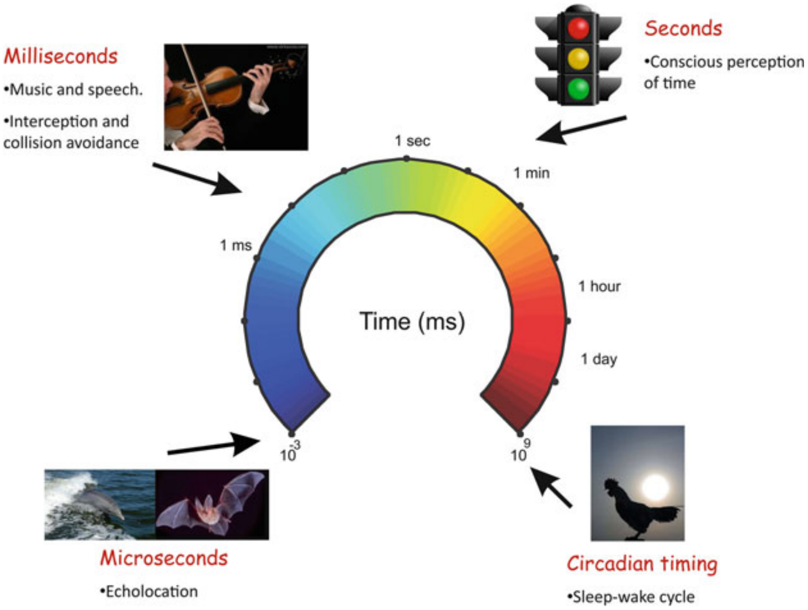

Fig. 1 Time across four different timescales. Different behaviors and brain mechanisms are engaged in the microseconds, hundreds of milliseconds, seconds to minutes, and circadian scales

Microsecond Scale

Information processing in the microseconds has been studied in binaural hearing and echolocation. In the case of binaural hearing the microseconds scale is used by the auditory system to determine the time differences in the action potentials coming for the two ears, called interaural delays, to determine the spatial origin of a sound. The sound will arrive slightly earlier in the near ear, usually in the order of 600–700 μs as natural interaural time differences (ITDs). To process these minimal binaural cues, birds and mammals have developed sensitive tympanic ears and highly specialized auditory brainstem circuits [2]. The neural processing stages that compare inputs from the left and right ears arise early, immediately after the first synaptic relay in the cochlear nucleus. Most neurons that are sensitive to ITDs are excited by inputs from the cochlear nuclei of both ears and are called EE (excitatory-excitatory) neurons. The EE neurons are in the mammalian medial superior olive (MSO) and are classically thought to be organized in a ‘delay line and coincidence detector’ arrangement. An influential model [3] suggests that individual neurons fire in response to precisely synchronized excitation from both ears, and systematically varied axonal conduction delays along the length of the MSO nucleus serves to offset ITDs, so that each neuron is ‘tuned’ to a best ITD value that cancels the signal delays from the left and right ear (However, see [2] for an alternative and more complex mechanism). Hence, neurons tuned to different ITDs are critical to encode small time changes in the binaural input in order to detect the spatial source of a sound.

On the other hand, echolocation (biosonar) is an active auditory process in which an animal emits a sound and then listens to the reflections of that sound (echo) to create neural images of its nearby environment. For example, bats and dolphins use the time interval between an outgoing sound pulse and its returning echo for the detection, identification, and localization of airborne and underwater targets, respectively [4]. A single echolocation call (a call being a single continuous trace on a sound spectrogram) can last between 200 μs and 100 ms, depending on the stage of prey-catching behavior that the bat is engaged in. Downward frequency modulated (FM) sweeps, used in most bat echolocation signals, provide for very good estimates of pulse–echo delays [5]. These time delays, ranging around 600–12,000 μs, are encoded within the inferior colliculus in the central auditory system of echolocating bats by specialized neurons that respond only to a limited range of pulse–echo delays [6]. These so-called delay-tuned neurons are sensitive to delays between the FM elements in the emitted pulse and in the returning echo. Thus, populations of delay-tuned neurons contribute to the analysis of the distance between the objects and the bat [7].

Milliseconds Range

Interval timing in the hundreds of milliseconds (200–1,000 ms) is involved in a broad spectrum of activities, ranging from object interception and collision avoidance to complex behaviors such as speech perception and articulation, and the execution and appreciation of music and dance. In addition, motion processing in the visual and tactile modalities, as well as the coordination of fine movements occurs in this time range [1]. The ability to quantify time in this scale is very flexible and organisms have great control of the onset and offset of time estimation depending on the contingencies of the environment. Therefore, temporal processing in the hundreds of milliseconds is quite sophisticated; yet, its neural underpinnings are largely unknown.

Seconds to Minutes Scale

The quantification of intervals in the seconds to minutes range is referred by many authors as interval timing and depends on conscious and cognitive control. Temporal processing in this range is involved in foraging [8], decision making [9], sequential motor performance [10], as well as multiple-step arithmetic [11], and associative conditioning [12]. Thus, timing in this scale serves as the contextual framework through which behavior is mapped onto the external world. Furthermore, timing in the seconds to minutes scale is highly influenced by other processes, such as attention and memory, which interact with the mechanism of a presumed internal clock. The cognitive nature of time quantification in this scale has made difficult the functional dissociation between the neural circuits involved in interval timing from those associated with attentional processes, working memory and the intention to execute a movement, between others.

Circadian Rhythms

The biological timing system that organizes the diurnal environmental oscillations every 24 h is known as the circadian clock. The two major functions of the circadian clock are: (1) to optimize the temporal manifestations of different biological activities during the day by the anticipation of recurring fluctuations in the environment, and (2) to separate incompatible biological processes such as feeding and sleeping. The circadian rhythms in mammals are governed by a complex network of cellular-molecular oscillators distributed throughout the brain and peripheral tissues [13]. The master clock is in the hypothalamic suprachiasmatic nuclei (SCN) that synchronizes the internal time with the external light–dark cycle, entraining the overall rhythmicity of a wide variety of peripheral clocks in the organism. The endogenous circadian clock in mammals possesses a rhythm with an approximate 24-h free-running period, and the major external synchronizing external signal is light. Therefore, SCN acts as a relay between the external light–dark cycle and the endogenous timing system [14]. The SCN innervates numerous brain nuclei in order to transmit circadian time information to other CNS clocks. On the other hand, the majority of the cells in the body contain a cell-autonomous circadian clock that is strongly linked to the metabolic pathways. An emerging view for the adaptive significance of circadian clocks is their fundamental role in orchestrating metabolism [15]. Thus, all these peripheral clocks are governed directly or indirectly by the SCN that controls the rhythms of activity and rest, feeding, body temperature, and hormone release.

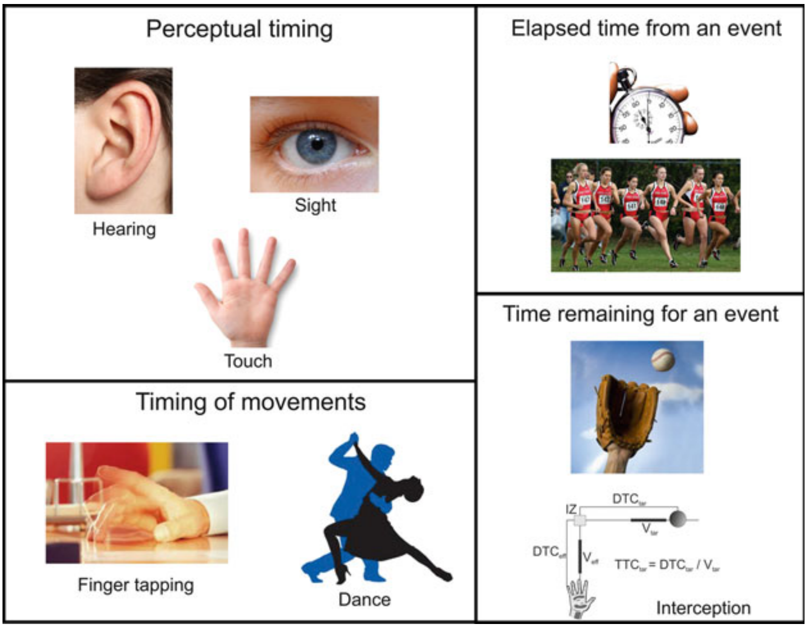

Fig. 2 Time can be computed using different sensory modalities, during the execution of rhythms and dance, and can be computed as elapsed time from an event or as the time remaining for an action, such as an interception of a moving target

Different Timing Behaviors Equal Different Timing Mechanisms?

The present book focuses mainly on the neural basis of temporal processing in the hundreds of milliseconds range, although some of the chapters also deal with the underpinnings of timing behaviors in the seconds to minutes scale. Many authors defend the notion of different brain mechanisms for the two time ranges, and there is still some debate on which is the threshold time where the clock for the hundreds of milliseconds scale is replaced by the time keeping mechanism for the seconds to minutes range. This time threshold seems to be in the order of 1,300–2,000 ms for perceptual and motor timing tasks that involve one interval or a set of isochronous intervals [see the chapter "About the (Non)Scalar Property for Time Perception" by Simon Grondin and chapter "Elucidating the Internal Structure of Psychophysical Timing Performance in the Sub-second and Second Range by Utilizing Confirmatory Factor Analysis" by Thomas H. Rammsayer and Stefan J. Troche]. However, some researchers sustain that these two time scales are governed by the same neural clock during complex behaviors, such as the perception and execution of music with a complex hierarchical structure of tempi (see chapter of Jessica Graham).

The word "timing" can have the connotation of either *how long* an event lasts or *when* an event occurs. This implies that the neural clock or clocks should have the ability to encode the elapsed time from a stimulus, an act, or process, such as the time between two notes in a song; along with the capacity to measure the time remaining for an action, where the system should select the precise moment for doing something for an accurate result, like when a tennis player hits a ball (Fig. 2; [16, 17]). In addition, the perception and production of time in the hundreds of milliseconds is deeply involved in a large repertoire of behaviors, not only using different sensory modalities but also a variety of effector systems [18]. Furthermore, in some behaviors an explicit representation of the interval to be timed is used as in tapping with a rhythm, while in others time processing is covertly present or implicit as during continuous drawing, where timing is an emergent property of the trajectory produced [18, 19]. Also, time intervals can be produced or estimated just once or as many times as needed [20, 21]. Finally, temporal processing can be associated to time synchronization to external events, as in the case of music played by groups of musicians, or can be internally timed like in the case of a soloist [22]. Therefore, some of the key elements of temporal processing include the time scale being quantified, the modality of the stimulus that guide timing, whether time is being measured for a movement or for a perceptual decision, whether the task involves single or multiple intervals, whether timing is externally or internally generated, and the implicit or explicit nature of timing (Fig. 2; [23]).

Researchers have generated two opposite views regarding the neural underpinning of temporal processing [24, 25]. On one side there is the hypothesis of a common mechanism that processes temporal information across many behavioral contexts and in a multimodal fashion; on the other, there is the notion of a totally ubiquitous mechanism that is context dependent and that has the dynamic properties of cortical networks as its underpinnings. The former has been supported by classical psychophysical observations [20, 26, 27] using a black box approach, and by lesion [28] and functional imaging studies [29]; whereas the latter has been suggested by modeling [30, 31], brain slice recordings [32], and new psychophysical approaches [32, 33]. A third possibility suggests the existence of a partially distributed timing mechanism, integrated by main core interconnected structures such as the cortico-thalamic-basal ganglia circuit (CTBGc), and areas that are selectively engaged depending on the specific behavioral requirement of a task [34, 35]. These task-dependent areas may interact with the core timing system to produce the characteristic temporal output profile in a specific task [36]. This intermediate idea is based on recent psychophysical studies [37, 38] and functional imaging meta-analysis [39] that do not support the existence of neither a common timing mechanism that functions equally every time a subject quantifies time, nor a set of timing mechanisms that are specific for each task context.

An Initial Taxonomy of Timing

The psychophysics of temporal quantification started as early as the late nineteenth century [40], and many timing tasks and species have been used to test the existence of one or multiple neural clocks. In contrast, the study of the neural basis of timing is quite recent (started in the 1980s), and there is still not enough evidence to accept or refute any of the hypotheses delineated in the previous section. Nevertheless, our current knowledge about the functional and anatomical organization of the brain gives us important hints about what are the possible rules governing temporal processing across different behavioral contexts. Importantly, we have thought that the field is in need of a classification scheme of temporal behaviors according to their sensorimotor nature. Thus, in the following text we attempt to provide a preliminary taxonomy of timing.

Sensory Timing

Organisms are able to extract temporal information from stimuli of all sensory modalities, even if there is no time sensory organ (Fig. 2). We still do not know how time is computed from the activation of different sensory systems nor where in the sensory hierarchy is the temporal information computed for perceptual or motor purposes. In order to answer these fundamental questions it is important to understand the general anatomofunctional arrangement of the auditory, visual and somatosensory systems that correspond to the most important modalities for temporal information processing, particularly in the hundreds of milliseconds range. These sensory systems include the following commonalities: the sensory transduction of physical information into action potentials in the sensory receptors; the projection of this information (through thalamic nuclei) to the primary sensory areas of the cerebral cortex; the processing of the different aspects of the stimuli in the cortical- and subcortical circuits engaged by the sensory input; and finally, the use of high order sensory processing for perception, learning and memory,

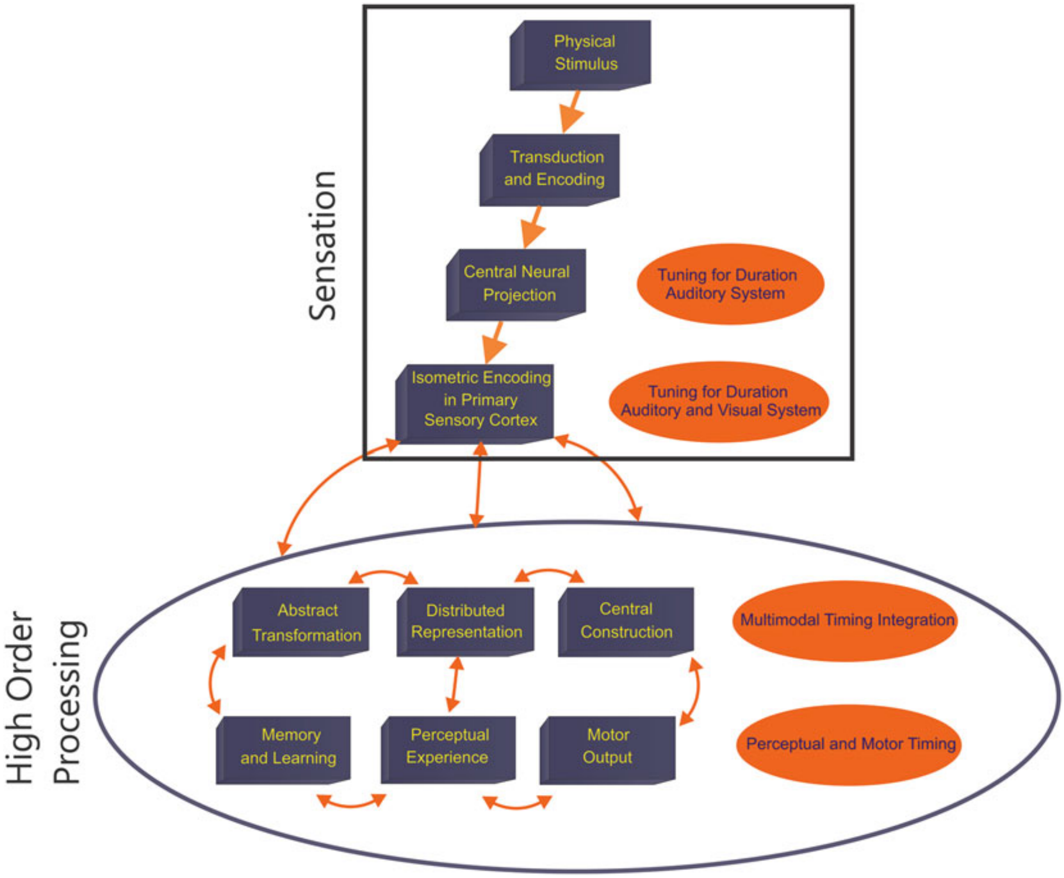

Fig. 3 A flux diagram for stimulus processing in the auditory, visual and somatosensory modalities, ranging from sensation (square) to high order processing (ellipse). The orange ellipses highlight the levels of processing where different aspects of time quantification may occur

and voluntary motor action (Fig. 3). Thus, initially, time information could be extracted from the transduction of the stimulus and the encoding of its physical properties in the first relays of the sensory systems. Few studies have focused on temporal processing during the transduction and projection phases of sensation. In this regard, the auditory midbrain of many vertebrates shows cells that are tuned to the duration of stimuli in the range of tens of milliseconds (10–100 ms). Studies across vertebrates have identified cells with preferred durations and temporal response bandwidths that mirror the range of species-specific vocalizations (see [41] for a review). Therefore, the auditory system has the ability to efficiently extract temporal information early in the chain of processing. In addition, the primary auditory cortex of the cat also shows cells that are tuned to the duration of auditory stimuli [42]. The duration tuning in this area is much broader, and the best duration was distributed over a wider range of durations (10–500 ms) than in the bat's inferior colliculus [42]. Hence, it has been suggested that duration selectivity in A1 results from integration along the time domain across the auditory ascending pathway. Overall, these studies suggest that the auditory modality has the strong ability to extract temporal information in the range of tens of milliseconds across the first relays of sensory processing, which indicates that time is a fundamental behavioral parameter for audition.

For vision, the first node in the visual pathway that shows duration tuned cells is the primary visual cortex or V1 (Fig. 3). These cells show an orderly change in response magnitude after a visual stimulus of a particular duration is presented in their receptive field [43]. The range of durations represented in V1 goes from 50 to 400 ms. Interestingly, no such tuned cells were found in the lateral geniculate nucleus of the thalamus [43], suggesting that time selectivity is a property arising from local processing in V1 Recent psychophysical studies have investigated the sensory adaptation for the temporal properties of stimuli, an effect that probably depends on the primary sensory cortical areas. For instance, the apparent duration of a visual stimulus can be modified in a local region of the visual field by adaptation to oscillatory motion or flicker, suggesting that there is a spatially localized temporal mechanism for the sensation of time of visual events in the first nodes of the cortical hierarchy of visual processing [32, 33].

The neurophysiological studies of time processing suggest that the auditory modality has a privileged capability for time quantification. Indeed, temporal processing measured in psychophysical tasks on humans is more accurate and precise when the intervals are defined by auditory than visual or tactile stimuli, and this occurs during both perceptual and production timing tasks. Furthermore, the time intervals marked by auditory signals are judged to be longer than those defined by visual stimuli [22, 44, 45].

Another property of the sensory input that affect the timing performance is whether the intervals are filled or empty. In sound cued empty intervals, for example, only the onset and the offset of the interval are marked by clicks, whereas in filled intervals, a tone or noise burst is presented continuously throughout the interval. Thus, it has been shown that filled intervals are perceived as being longer than empty durations of the same length, and that the discrimination threshold is smaller for empty than for filled intervals [46]. New experiments are needed to determine whether the effect of filled or empty intervals depends on the encoding of duration by tuned cells in the early stages of sensory processing.

At this point is important to make the distinction between a temporal code that is an extra channel for encoding information in the brain and that depends on the precise temporal structure of spike trains, and interval timing or temporal processing where the brain represents time itself as a variable, solving sensorimotor problems such as interval duration [47].

The time sensation, hence, seems to depend on specialized groups of cells in early nodes of the sensory processing that are tuned to the duration of auditory and visual stimuli (Fig. 3). Consequently, the sensation of the passage of time in the tens to hundreds of milliseconds is modality specific and depends on the anatomofunctional properties of each sensory system, where hearing has a clear advantage in timing.

Perception of Time

The integration of duration information across the senses appears to depend on extrastriate regions such as the posterior parietal cortex [48], the superior temporal sulcus [49], and dorsal medial superior temporal area [50]. The multimodal integration of time is then an intermediate step for time perception. Next, the recognition and interpretation of the sensation of the passage of time across senses can be used for the perception of time during discrimination or categorization tasks, or for the execution of voluntary movements with a strict temporal control (Fig. 3). Needless to say that the high order processing of time information for perception, learning and memory, and voluntary motor action depends of complex networks of cortical areas in the parietal, temporal and frontal lobes, as well as the basal ganglia and the cerebellum (Fig. 3). It is in these distributed networks where the core timing mechanism may lay.

The study of perceptual interval learning and the generalization properties of such learning have provided important insights into the neural underpinnings of multimodal temporal information processing. For example, using interval discrimination it has been shown that intensive learning can generalize across untrained auditory frequencies [51, 52], sensory modalities [53, 54], stimulus locations [53], and even from sensory to motor-timing tasks [55]. However, all these studies found no generalization toward untrained interval durations. In addition, it has been suggested that the learning transfer depends on the improvement of temporal processing and not on more efficient memory or decision processes, at least for auditory interval discrimination [52]. Therefore, these findings not only support the notion of a centralized or a partially overlapping distributed timing mechanism, but they also introduce the concept of duration-specific circuits. Regarding the first point we can speculate that the timing signals sent from the primary sensory cortical areas to the large and distributed core timing network during the learning period may increase the global efficiency of the temporal information processing. Thus, an efficient core timing network will transfer its improved timing abilities across senses during perceptual and motor contexts. Favoring this notion are fMRI studies that have reported that early and late visual or auditory areas are activated during production and perception tasks of intervals using visual or auditory markers, respectively [56–58]. In addition, these studies have found that a larger set of areas was activated in both sensory conditions, including SMA, dorsal premotor cortex, posterior parietal cortex, putamen, and the cerebellum [39, 57].

Overall, these findings support the idea that perception of time is a complex phenomenon that probably depends on the interaction of many cortical and subcortical structures conforming a dynamic network that can associate the incoming temporal sensory information with the time memory traces in order to generate perceptual decisions about the magnitude of time in a particular behavior (Fig. 3), such as the discrimination of two durations.

Motor Timing

As we mentioned before, interval timing in the milliseconds is a prerequisite for many complex behaviors such as the perception and production of speech [59], the execution and appreciation of music and dance [60], and the performance of sports [16]. Time in music comes in a variety of patterns which include isochronous sequences where temporal intervals are of a single constant duration or, more commonly; sequences containing intervals of many durations forming a meter (see the chapter "Perceiving Temporal Regularity in Music: The Role of Auditory Event-Related potentials (ERPs) in Probing Beat Perception" by Henkjan Honing et al. and the chapter "Neural Underpinnings of Music: The Polyrhythmic Brain" by Peter Vuust et al.). In addition, the ability to capture and interpret the beats in a rhythmic pattern allows people to entrain their behavior and dance in time to music [61]. Music and dance, then, are behaviors that depend on intricate loops of perception and action, where temporal processing can be involved during the synchronization of movements with sensory information or during the internal generation of movement sequences [60]. Many functional imaging studies have demonstrated that the circuits engaged in the perception of time are the same that are activated during motor timing [35, 39, 57]. The cortico-basal ganglia-thalamo-cortical circuit (CBGT), that includes the medial premotor areas [Supplementary (SMA) and Presupplementary motor areas (preSMA)], as well as the neostriatum, the globus pallidus and the motor thalamus, is a network that is engaged every time that an interval is perceived or a temporalized movement is executed. Hence, these studies support the notion that the CBGT circuit is a key element of the core timing network, and that it is activated during the categorization or discrimination of time intervals as well as during the perception and production of rhythms (Fig. 3). These imaging studies, however, do not have the temporal resolution to reveal the neural dynamics inside the CBGT circuit during temporal processing.

Recent neurophysiological experiments have revealed duration tuning in the medial premotor areas and the neostriatum of monkeys performing a set of tapping tasks [1, 36, 62]. Thus, these studies confirm the existence of interval tuning in the core timing network, which was inferred from learning and generalization studies of time intervals [53, 55, 63] and suggested in conceptual papers [64]. Importantly, it was found that a large population of tuned cells in the medial premotor areas and the neostriatum showed similar preferred intervals across tapping behaviors that varied in the number of produced intervals and the modality used to drive temporal processing [36]. Hence, interval-tuning invariance across the different tasks suggests that these two areas of the CBGT circuit can tag the timed durations as a context-independent neural signal. In contrast, the cells that are duration tuned in lower levels of sensory processing are modality specific.

A robust finding in experimental psychology is that temporal processing is improved when there are repeated presentations of the standard interval [65, 66]. Multiple-interval advantages have been reported for both auditory and visual sequences for tasks involving time-interval perception as well as temporalized tapping [21, 66, 67]. For example, in a time discrimination task, increasing the number of repetitions of the first interval reduces the duration-discrimination thresholds [68]. Similarly, the temporal variability is smaller during multiple rather that single interval production task, where subjects tap on a push-button [37]. The recording of cells in the medial premotor areas of monkeys producing one or six intervals in a sequence revealed a possible mechanism for the temporal improvement due to an increase in the number of executed or perceived intervals. The interval tuned cells in this area showed a multiplicative response scaling for more produced intervals with the corresponding increase in discharge rate in their preferred interval for six instead of one produced intervals [36]. Hence, the observed decrease in temporal variability with the number of timed intervals could be the result of the increase in discharge rate in the preferred interval of duration tuned cells in the core timing network.

A set of functional imaging studies have revealed the neural and functional overlap between perceptual and motor timing, and the conclusion is that the motor network of the CBGT is activated across a wide range of timing contexts. A critical question, then, is what is the meaning of this anatomofunctional overlap? One possibility is that the increase in the BOLD signal in the motor areas across timing tasks reflects the presence of confounding cognitive processes, such as effector selection and motor preparation, or working memory, and decision processes. This is unlikely however, since SMA, the CBGT circuit, and the prefrontal cortex are selectively activated even when duration estimates are registered with a perceptual discrimination [39], or after motor preparation and/or execution processes have been rigorously controlled for [35, 69] (see chapter “Getting the Timing Right: Experimental Protocols for Investigating Time with Functional Neuroimaging and Psychopharmacology” by Jennifer T. Coull). Another possibility is that timing shares the neural circuitry with motor function because our general sense of time has been developed through action since childhood [70, 71]. This proposal is similar in principle to other embodied theories of time perception [72]. Developmental studies have demonstrated that young children appear to represent time in motor terms [73]. Their duration estimates are more accurate when the duration is filled with an action than when it is empty [70] and they find it difficult to dissociate an estimate of duration from the motor act itself (see chapter “Getting the Timing Right: Experimental Protocols for Investigating Time with Functional Neuroimaging and Psychopharmacology” by Coull). Hence, it is possible that the motor circuits are engaged early in development to build up and acquire representations of time, forming a core timing network inside the motor system. This is not a new idea, the current knowledge of the relation between perception and voluntary acts, have sustained new hypotheses where different cognitive functions may share the same neural representations and circuits for action and perception [74, 75]. In the case of temporal processing, it is possible that the learned associations between particular actions and their durations have been engrained in the dynamics of the cortical and subcortical motor networks [31]. Thus, the dynamic representation of time in the activity of cell populations could become a generalized temporal representation, which is independent of the motor output, and can be used for motor and perceptual acts that require a strict temporal control (Fig. 3).

Book Overview

Successful behavior depends on the ability to execute motor actions within tightly constrained temporal intervals. An otherwise correct action is useless if triggered before or after a critical time period. Timing is thus deeply embedded in nervous system function and it is as critical for motor plans as it is for the analysis of sensory information. In this book, leading neuroscientists summarize and discuss the advances in their quest to understand the mechanisms of time perception and the ability to generate timely actions. The systematic study of time perception has a rich history, dating back to the work of Mach, Czermak and Helmholtz in the mid 1800s. As will be evident on the first part of the book, dealing with the psychophysics of time estimation, a basic question that researchers have repeatedly addressed is how good we are at telling time. Psychophysics researchers have found that when subjects are asked to indicate the end of a time interval, by pressing a push button for example, they sometimes fall short and sometimes overshoot the desired time interval. How the variability of these errors increase as a function of the magnitude of the time interval is sill a matter of debate. Linear increases in the standard deviation of errors as a function of interval length (Weber's law) have been observed within certain range of temporal intervals but it is often observed that different experimental settings can result in contradictory results. Whether Weber's law holds for time perception, and within which range it does, is an important question that could reveal separate timing mechanisms for different time scales.

The psychophysical study of time has uncovered a number of interesting phenomena. It has been observed, for example, that counting or performing a motor action at regular intervals near 0.6 s significantly increases the ability to time long intervals spanning several seconds. This preferred interval might be related to the time scale at which humans pace music, speech, and motor actions such as walking. As will be evident throughout the book, psychophysics is the source of the quantitative phenomena feeding our models and physiological investigations.

As in many fields of neuroscience, modeling has played an important role in timing research. Models allow exploring how well specific neuronal circuits or architectures can reproduce the diverse phenomena observed in interval timing. The book's second part deals with models of timing and the quest to describe the essential mechanisms of timing, of which, Weber's law (or scalar property as is often named), is of most importance.

An early influential model proposed that timing could be achieved with a pacemaker, an accumulator, and a memory/decision process to compare the measured interval. This model has been developed over the years and a modern proposal suggests that this mechanism could be implemented by cortico-striatal interactions in which cortical neurons act as oscillators and medium spiny neurons in the striatum as integrators and coincidence detectors.

Instead of a dedicated timing circuit, an important result from modeling efforts has shown that timing can be carried by linear decoders trained to recognize particular states of a neural network. If the activation states of a given network follow reproducible trajectories across time and space, then the output neurons could be used to mark time intervals and initiate timely motor actions. It has been shown that simulated neural networks can display activity dynamics that are familiar to physiologists, such as ramps and transient onsets, but importantly, modeling demonstrated that any network dynamic, represented by the trajectory of the network state across time, can be used to measure time. Timing, then, might not need dedicated neuronal elements but could be incorporated as an intrinsic property of every neuronal circuit.

Modeling efforts have also demonstrated that potential timing mechanisms exist at all levels of complexity in the nervous system, from calcium buffers within single neurons, to networks of cortical and subcortical areas. This is an important result. Rather than constraining the possible mechanism and neuronal substrates underlying timing, models have shown that timing can be carried at the level of single neurons with ramping activity, at the level of neuronal populations in which activity cascades spatially and temporally across ensembles of neurons, and at the level networks spanning cortical and subcortical structures such as the proposed coincide detectors of spiny neurons receiving periodic activity from the cortex.

A problem often encountered by theoretical scientists is that more than one model can reproduce any given phenomenon. Thus, it is important for theorists to constantly check their models against experimental results. Experimentalists have used a variety of techniques to probe the brain in the quest to understand the physiological basis of timing. Among these, fMRI, single neuron recordings and EEG have yielded important results. The fourth part of the book deals with the physiological processes that underlie the brain's ability to estimate time.

Single neuron recordings in the primate brain revealed increases in activity of primary motor neurons that start in anticipation not only to imminent movements, but also in anticipation of predictable sensory cues. Thus, the ability to anticipate changes in the environment that occur at predictable times is evident in the same circuits that initiate motor actions. Neurons in the medial premotor cortex, an area often called the supplementary motor cortex, also display time dependent activity that indicate remaining and elapsed time in relation to the initiation of periodic motor commands. However, instead of general purpose timing circuits, the activity of motor, premotor and striatal neurons are strongly dependent on the particular motor plan that the animals intend to generate. Until now, physiological investigations have failed to uncover a general purpose timing mechanism, and it is increasingly clear that the there is no timing area or general clock that the brain uses to tell time. This view is compatible with the findings of fMRI studies carried in humans performing timing tasks. Such findings, presented in the fourth chapter of the book, show that a large network of areas, comprising the SMA, frontal and parietal cortices as well as the basal ganglia, are recruited to perform tasks requiring the estimation of elapsed and remaining time. The suggestion that timing might be carried by motor circuits is further supported by evidence that patients with Parkinson's disease show motor as well as perceptual timing deficits.

The human ability to perceive and generate precisely timed intervals is most evident in musical performance and music appreciation. The final part of the book deals with the neuronal signals that correlate with our ability to perceive rhythm. Recording of brain potentials have shown that the human brain has an innate ability to predict rhythmic sensory events, and that error signals emerge when the music fails to meet metric expectations. While the belt and parabelt regions of the auditory cortex are fundamental to appreciate music structure, there is evidence that the premotor cortices are also engaged in following rhythmic patterns of sensory information. It is proposed that the joy of music comes from the ability to predict such rhythmic patterns.

As it will be evident throughout the book, the ability to predict sensory events and generate precisely timed actions seems not to depend on a localized general-purpose timing circuit. Rather, every neuronal network, from those involved in sensory perception to those executing motor commands, including those underlying our awareness of time, incorporates timing as an essential feature of the information it processes.

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