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Hugo Merchant
Victor de Lafuente *Editors*

Neurobiology of Interval Timing

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To our kids:
Carla, Matías, and Nina.
Mateo and Emilia.

Foreword

How the brain processes temporal information is a fundamental question relevant to systems, cellular, computational, and cognitive neuroscience, as well as to the psychophysics of music and language. During the last and present decades, interval timing has been intensively studied in humans and animals with a variety of methodological approaches. The present book brings together the latest information gathered from this exciting area of research, putting special emphasis on the neural underpinnings of time processing in behaving human and non-human primates. Thus, *Neurobiology of Interval Timing* integrates for the first time the current knowledge of animal behavior and human cognition related to the passage of time across different behavioral contexts, including perception and production of time intervals, as well as rhythmic activities, using different experimental and theoretical frameworks.

The book is composed of chapters written by leading experts in the fields of psychophysics, computational neuroscience, functional imaging, system neurophysiology, and musicology. This cutting-edge scientific work integrates the current knowledge of the neurobiology of timing behavior, putting in perspective the current hypothesis of how the brain quantifies the passage of time across a wide variety of critical behaviors.

With *Neurobiology of Interval Timing* neuroscientists, experimental psychologists, and ethologists will gain the necessary background to understand the psychophysics and neurophysiology of time, in perceptual and motor activities that involve rhythms or single intervals. This is a perfect textbook for graduate students in the field of neurobiology of timing.

Querétaro, Mexico — Hugo Merchant

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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).

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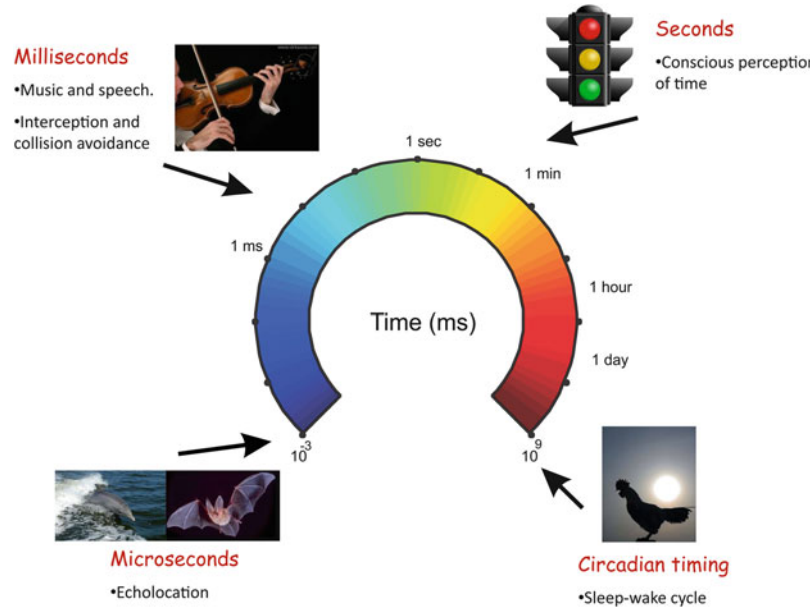

Fig. 1 Time across four different timescales. Different behaviors and brain mechanisms are engaged in the microseconds, hundreds of milliseconds, seconds to minutes, and circadian scales

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.

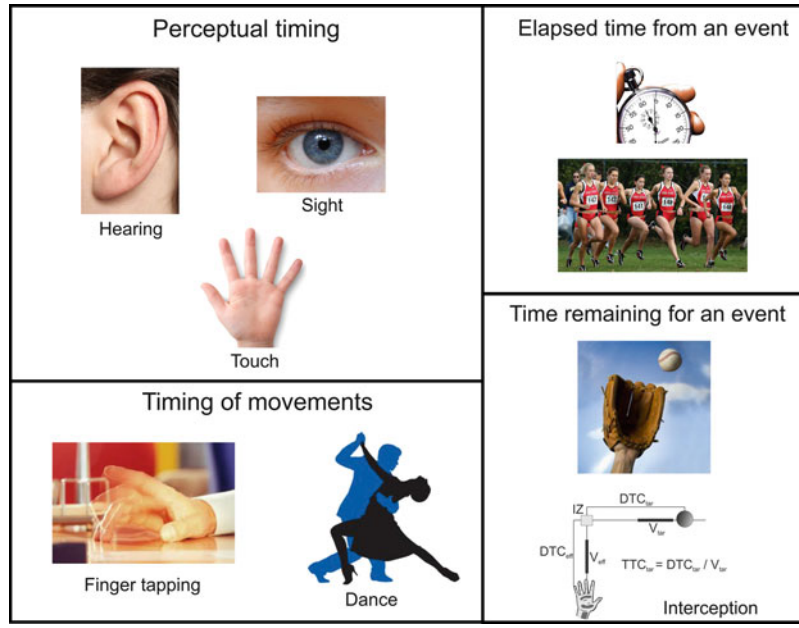

Fig. 2 Time can be computed using different sensory modalities, during the execution of rhythms and dance, and can be computed as elapsed time from an event or as the time remaining for an action, such as an interception of a moving target

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,

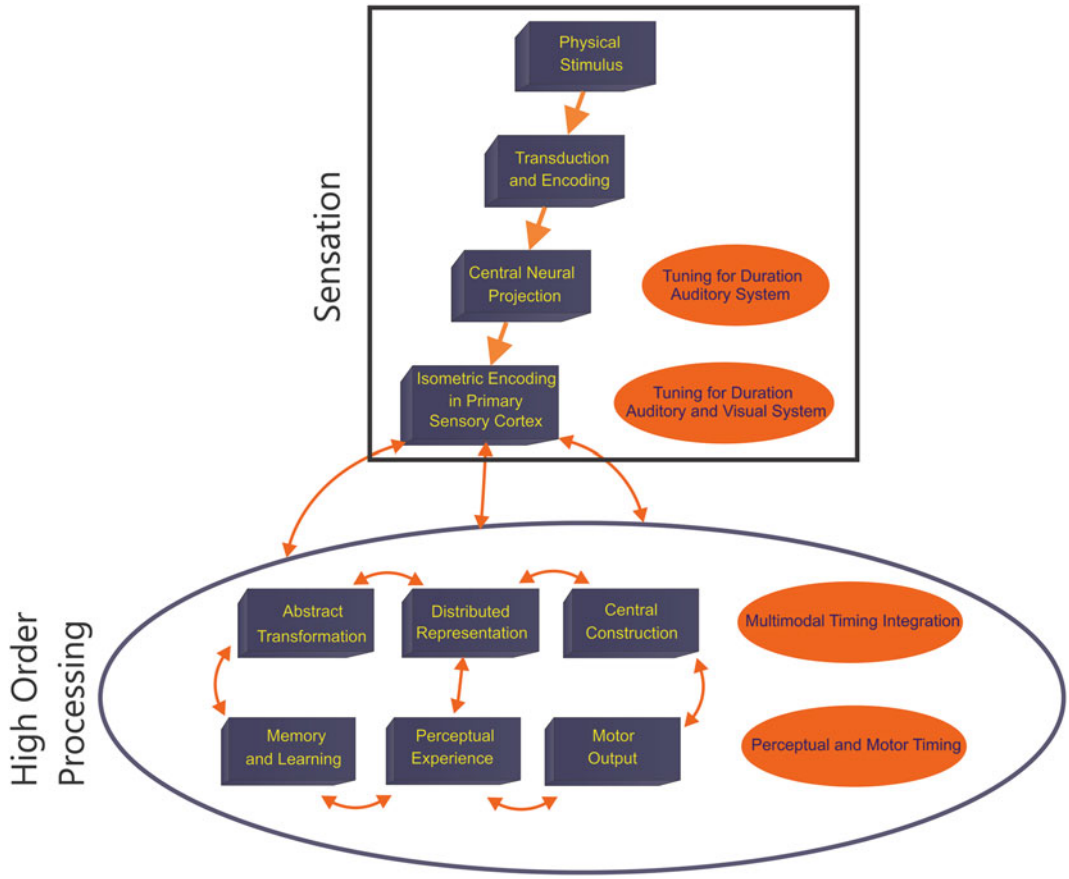

Fig. 3 A flux diagram for stimulus processing in the auditory, visual and somatosensory modalities, ranging from sensation (square) to high order processing (ellipse). The orange ellipses highlight the levels of processing where different aspects of time quantification may occur

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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Part I

Psychophysics of Interval Timing

About the (Non)scalar Property for Time Perception

Simon Grondin

Abstract

Approaching sensation scientifically is relatively straightforward. There are physical attributes for stimulating the central nervous system, and there are specific receptors for each sense for translating the physical signals into codes that brain will recognize. When studying time though, it is far from obvious that there are any specific receptors or specific stimuli. Consequently, it becomes important to determine whether internal time obeys some laws or principles usually reported when other senses are studied. In addition to reviewing some classical methods for studying time perception, the present chapter focusses on one of these laws, Weber law, also referred to as the scalar property in the field of time perception. Therefore, the question addressed here is the following: does variability increase linearly as a function of the magnitude of the duration under investigation? The main empirical facts relative to this question are reviewed, along with a report of the theoretical impact of these facts on the hypotheses about the nature of the internal mechanisms responsible for estimating time.

Keywords

Temporal processing • Scalar timing • Weber law • Internal clock

Experimental psychology is rich of a very long research tradition in the field of sensation and perception, and in the field of animal behaviour. The study of time perception has been part of this tradition. The reader can find in the literature old reports of fine investigations related somehow to psychological time. Amongst others, experimental psychology already offered, towards the end of the nineteenth century, a few systematic investigations by Vierordt [1] and Bolton [2] on rhythm. As well, in his classical book, *The Principles of Psychology*, James [3] already established several distinctions about the experiences of time, including the idea of a "specious" present (a unified moment, distinct from past or future), the transition from simultaneity to successiveness, and the difference between time

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in retrospect and experiencing the passage of time (referred to as retrospective and prospective timing in the next paragraph). Amongst the classical publications of the twentieth century, the books by Fraisse [4, 5] on rhythm and on psychological time were certainly, at the moment of their publication, significant syntheses of the main pieces of information in the field. Moreover, a meeting on timing and time perception, held in New York in 1983 and leading to the proceedings edited by Gibbon and Allan [6] proved to be a critical event as people from different perspectives on time perception were grouped together. Until then, time perception researchers studying humans and those studying nonhuman animals worked on similar topics, but quite independently. Both posited the use of an internal clock (the pacemaker-counter device described later in this chapter), and emphasized a fundamental characteristic of the clock. For researchers with a background in human psychophysics (usually interested in sensation and perception), the Weber law was a central concern; as well, researchers on animal timing paid special attention on a feature that is essentially equivalent, the so-called scalar property (described below). Since that meeting, many methods used for studying animal timing were used also for studying human time perception, which allowed for additional testing of the scalar property. Because a theory based on this internal clock perspective, and emphasizing this scalar property has been dominating the field of timing and time perception in the last decades, assessing the validity of this scalar property is a fundamental issue, an issue that is at the heart of this chapter.

Experimental and Analytic Tools for Studying Time Perception

Methods

The timing and time perception literature offers a myriad of methods for investigating the nature of psychological time, its functioning and properties [7]. Of critical importance when approaching the time perception literature is to distinguish retrospective and prospective timing (see Fig. 1). In the former case, participants in an experiment have to complete a task or an activity and they receive no prior warning that they will have to estimate the duration of this task or activity subsequently. With retrospective timing, which is associated with memory processes [8, 9], participants will either make a verbal estimate (with chronometric units) of the duration or reproduce the duration. The choice of activity is of course partly linked to the duration of the task, temporal reproduction being difficult to apply when an activity lasts many minutes for instance. The structure of events is critical for remembering duration retrospectively [10]. Note that recent investigations with retrospective judgments cover intervals lasting a few minutes up to almost an hour [11–15]. Finally, retrospective judgments about time could also cover the remembering of the duration of public events [16, 17] or autobiographical events [18, 19] lasting days or months and occurring years ago.

The investigations involving prospective timing, i.e., in conditions where participants are informed before they begin a task or an activity that timing will be required, are much more numerous in the timing literature, involve a large variety of methods (tasks or procedures), and are the focus of the present chapter. In addition to the methods described earlier—verbal estimates and interval reproduction—that can also be used for prospective timing, this paradigm includes the use of interval production where a participant produces an interval, with finger taps for instance, matching the interval reported in temporal units by an experimenter.

A fourth method used in a prospective timing condition could be referred to as interval comparison. There are various ways of comparing the relative durations of several intervals. On the one hand, it is possible to present two successive intervals and to ask whether the second one is shorter or longer than the first one (a forced-choice procedure); and it is also possible to make multiple repetitions of the first and of the second intervals (sequences of empty intervals marked by brief sensory signals) as is the case in experiments where rhythm is under investigation. This is a typical discrimination procedure in psychophysics. On the other hand, a participant

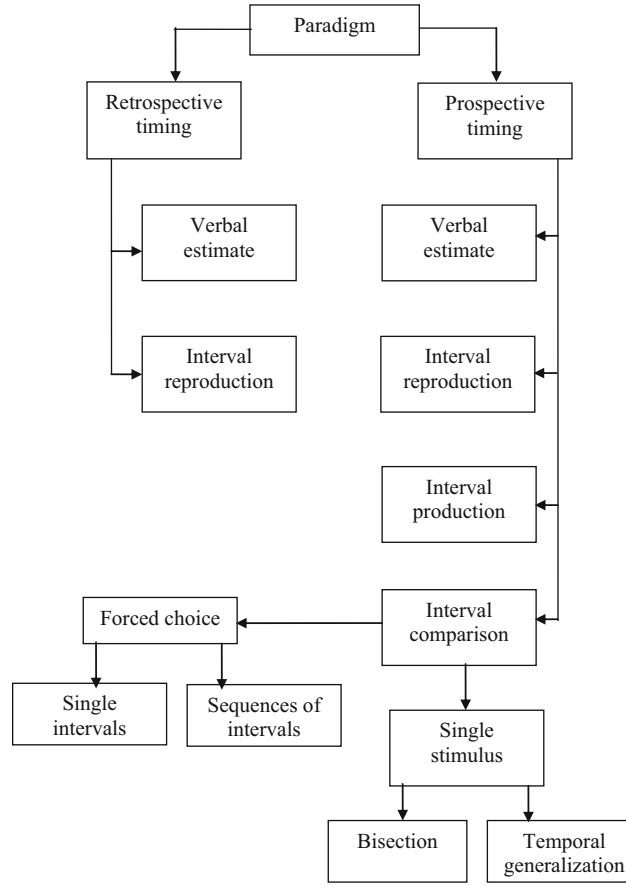

Fig. 1 Schematic view of the main experimental methods for studying time perception (from Grondin [24])

might be asked to judge one of two, or of many intervals, after each presentation of one interval. This general feature was referred to by Allan [20] as the single-stimulus method of presentation, and could also be viewed as a kind of categorization task. There are two classical cases of single-stimulus method in the animal, and now human, timing literature. One is the temporal bisection task where the shortest and the longest of a series of intervals are presented several times at the beginning of the experiment. After these presentations, a participant has to determine, on each trial, if the interval presented is closer to the short or to the long interval previously presented. With a temporal generalization task, the standard interval (at midpoint of a series of intervals) is first presented several times, and then, after each presentation of an interval, a participant should indicate whether the presented interval is similar or not to the standard. Note finally that there are many other methods used in prospective timing (for instance, the peak procedure developed in animal timing, and different adaptive procedures, developed in psychophysics, where the relative length of intervals to be discriminated are adapted from trial to trial).

In the case of the bisection method for instance, a psychometric function could be drawn by plotting the probability of responding "long" on the *y* axis as a function of the series of intervals (from the shortest to the longest) on the *x* axis. An index of performance (for instance one standard deviation on the curve[1]) can be

[1] Traditionally in psychophysics, when a psychometric function is used, the distance on the *x* axis corresponding to 75 and 25 % of "long" responses, divided by 2, is the discrimination threshold.

extracted from the function. This index, divided by the mid-point between the shortest and longest intervals provides an estimate of the Weber fraction for a given experimental condition. In the case where psychometric functions are based on a forced-choice procedure, i.e. when both standard and comparison intervals are presented on each trial the Weber fraction is obtained by dividing the discrimination threshold by the value of the standard interval.

Two Laws and One Theoretical Position

One should expect two fundamental qualities from a timekeeping device. This timing system must be able to remain close to the target duration to be timed, i.e., over a series of trials, the mean estimated intervals (central tendency) must be close to real duration. The deviation from the target duration is called the constant error. As well, the variability (dispersion) of this series of trials must be kept as low as possible by the device [21]. As we will see below, this temporal variability is quite important because it is a critical feature of the most cited model in the field of timing and time perception, the Scalar Expectancy Theory [SET—22, 23]. This variability is often described in terms of Weber fraction, described below.

Laws

Remaining close to real duration could be reformulated in term of the psychophysical law. If remaining close to real duration for one given interval is a critical issue, having a system for which the feature applies over a large range of duration is also critical. In psychophysics, one fundamental issue is the relationship, for a given sensory continuum, between the psychological magnitude and the physical value. For instance, does the psychological magnitude increase exponentially, linearly or logarithmically as with the increase of the physical magnitude? In general, for the different sensory continua, the relationships can take several forms that can be summarized within the so-called power law [25]. Applied to time, the law could be reported as follows:

$$E_T = kT^N \quad (1)$$

where E_T is the estimated time, T the physical time, k a constant related to the intercept. The exponent N, which is generally considered the signature of the sensory continuum under investigation, is close to 1 for time. Indeed, defenders of SET usually report that the exponent value is one [20]. However, there are reasons to believe that the exponent value is often closer to 0.9 (see the extensive review by Eisler [26]).

The psychophysical law is one of two major issues in psychophysics, the other one being related to the variability of the sensory experience: Does variability increase linearly as a function of the magnitude of physical stimuli? According to what is referred to in psychophysics as Weber's law, it does [27].

In its strict form, and in the context of timing, the variability (σ) of time estimates increases linearly with the duration of the interval to be timed (t):

$$\sigma = kt \quad (2)$$

where k is the Weber fraction ($k = \sigma/t$). In other words, the variability to time ratio, sometimes known as the coefficient of variation in the timing literature, should be constant. This relation (Eq. 2) is referred to as Weber's law. There are other forms of Weber's law (for instance, $\sigma^2 = k^2t^2$, Getty [28]; see Killeen and Weiss [29] for a general model of Weber's law for time). The next sections are dedicated to empirical reports where the validity of Weber's law for time is tested, and it is indeed the main focus of the present chapter.

Theory

Over the past 50 years, the field of time perception has been guided by one very important theoretical proposal: There is an internal, single, central clock, and this clock is a pacemaker-counter device [30, 31]. This view can be summarized as follows. The pacemaker emits pulses that are accumulated in a counter, and the number of pulses counted determines the

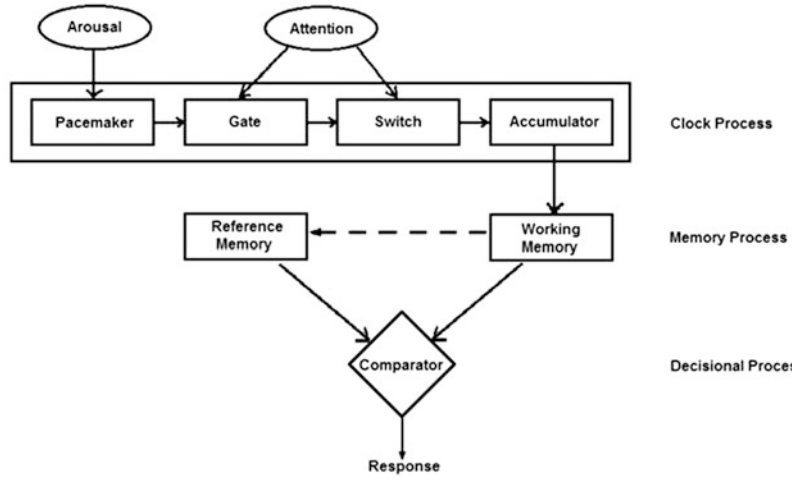

Fig. 2 An illustration of the three levels of processing in a timing task where errors could occur. Note that at the clock level, errors may also depend on arousal, which is influencing the pacemaker's rate, and on attention, which is acting on the amount of pulses passing (gate), and on the moments where the timekeeping activity starts and stops (switch) (adapted from Zakay and Block [8])

perceived length of an interval (the experienced duration). Why would someone make errors in judging time depends on several factors. While older studies have focussed primarily on the properties of the pacemaker [32], there are other sources of variance. Indeed, Allan and Kristofferson [33] pointed out that "...the input process is thought as one which takes a measure of the temporal extent of a stimulus pattern, compares the measure either to an internal standard or to the memory of a measure of a standard stimulus, and triggers a response, which may or may not be biased, depending on the outcome of the comparison process" [33, p. 26]. The reader probably recognizes the three levels of processing—the clock (the input process), memory and decision-making—which have been emphasized since in the information processing version of SET [34]. In other words, nearly 40 years ago, these authors noted how critical these three processing levels are for accounting for timing and time perception (Fig. 2).

SET, which has been a very popular theory of timing over the past 30 years, as noted earlier, is characterized by two basic features [35–37]. First, in terms of the psychophysical law, the relation is supposed to be linear and the exponent equal to 1, a feature that is disputable, as noted earlier. The second feature stipulates that the proportion between variability and mean is *scalar*, i.e., is supposed to be constant; in other words, Weber's fraction, k, is constant. When the psychometric functions obtained with different target durations are plotted on a relative time scale, they should superimpose. In brief, with SET, a time-scale invariance principle should apply. The reader will find in this book many chapters describing timing models where the scalar property is not that central (see also review articles: [24, 38, 39]).

Empirical Facts

This portion of the chapter is dedicated to a brief review of some experiments where the Weber's law for time was tested. When approaching the validity of this law for time, there are at least two key issues that might be considered: what range of durations are we dealing with and does the same conclusion hold when different methods are used for estimating the variability as a function of base duration. In the case of the first question, it would obviously not be reasonable to search for a mechanism that would account for the processing of microseconds or of few milliseconds (as is necessary in echolocation or sound localization) and for hours (like circadian rhythms: see [40–43]). The interest of experimental psychologists for Weber's law for time, or the scalar property of timing, usually covers a few hundreds of milliseconds up to a few

seconds, which corresponds to the range within which the processing of speech, motion coordination and the conscious estimation of time occur.

Recent Data: Restricted Range

In a recent article, Merchant et al. [44] completed a systematic investigation of Weber's law for time. What is interesting in this paper is the fact that not only perception and production methods were used, but the modality for marking intervals was manipulated (auditory vs. visual stimuli), as well as the number of intervals presented (single vs. multiple). With the tasks involving only perceptual processes (discrimination), it is known that changing the number of intervals presented for judging time influences the performance levels. Would the Weber fraction remain constant, for any temporal task, for specific conditions where different performance levels are expected?

Although there were quite a bit of differences among the experimental conditions, the results of Merchant et al. [44] showed a strict compliance to the scalar property: the variability increased linearly as a function of interval duration, and this observation applied in all tasks. Although the demonstration was convincing, there is one fundamental piece of information that should be reported here about this study: the standard intervals used in this study varied from 350 to 1,000 ms. Indeed, all intervals presented to the 13 participants of this study were briefer than 1,300 ms. As we will see in the next paragraphs, restricting the investigation to this duration range makes a huge difference when comes the moment to decide whether or not the scalar property holds for time perception.

That said not all reports with intervals briefer than 1 s revealed that the Weber fraction is constant. For instance, in a series of experiments where the single-stimulus (categorization) method was used, this fraction was higher at 1 than at 0.2 s, and this effect was neither due to the number of intervals used to determine threshold, nor to the range of intervals to be compared [45].

In one recent series of experiments designed specifically to test Weber's Law, the question was addressed this way. Let's have a restricted range of durations, between 1 and 2 s, and see if the Weber fraction is constant and if it is constant whatever the method used to determine the performance levels [46]. This could be seen as a kind of extension of the Merchant et al.'s study [44], but involving a new range of durations. Once again, the series of tests involves perception and production tasks, but also single and multiple interval presentations. Once again, even if the estimated variability was expected to differ across methods, the Weber fraction should remain constant. Would this also be true once again for another, admittedly restricted, range of durations, i.e. between 1 and 1.9 s?

In the first experiment of the series reported in Grondin [46], participants were presented with a standard interval 1, 3 or 5 times with a series of 2, 4, or 6 brief auditory signals. After 2,166 ms, a comparison interval was presented 1, 3 or 5 times with a series of 2, 4, or 6 brief auditory signals. The task of the participant was to report whether the second interval(s) was(were) shorter or longer than the first(s) (duration discrimination). There were 4 standard-interval conditions: 1, 1.3, 1.6, and 1.9 s. In the 1-s standard condition, the comparison intervals lasted 860, 900, 940, 980, 1,020, 1,060, 1,100, and 1,140 ms and in the other standard conditions, the comparison intervals were multiplied by 1.3, 1.6 and 1.9. In other words, the comparison intervals ranged, for instance, from 1,634 to 2,166 ms in the 1.9-s standard condition.

Individual psychometric functions were drawn in each experimental condition and a Weber fraction was calculated for each condition. As illustrated in the upper panel of Fig. 3, the Weber fraction is higher in the 1-interval condition than in the two other conditions. This is not surprising given that it is known that performance is better when multiple instead of single intervals are presented (see for instance

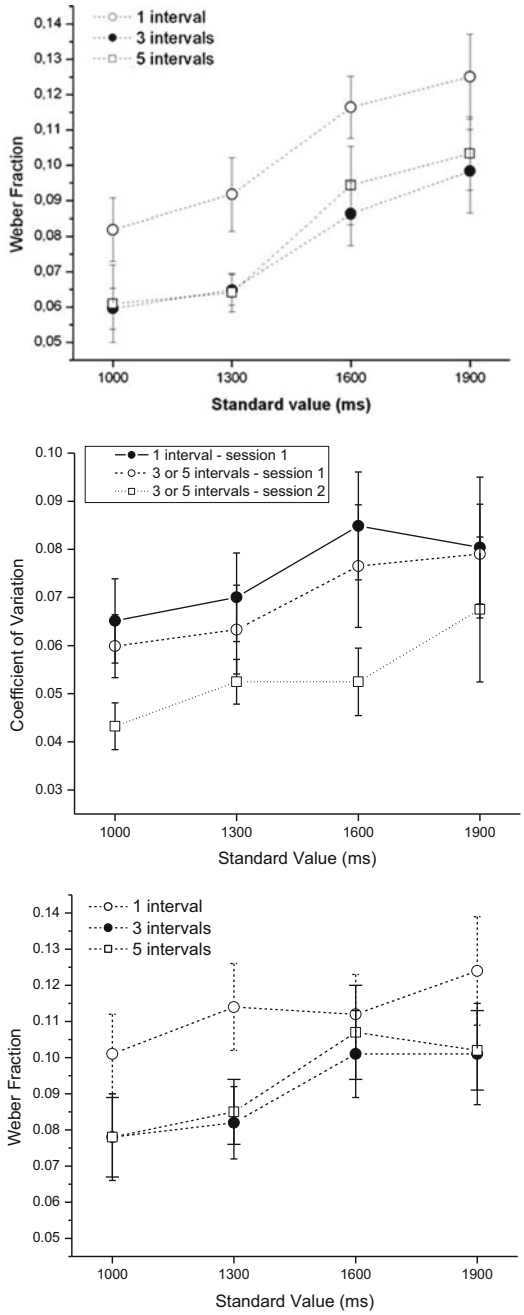

Fig. 3 Weber fractions as a function of time. *Upper panel*: discrimination (Experiment 1); *Middle panel*: reproduction (Experiment 2); *Lower panel*: categorization (Experiment 3) (in Grondin [46])

[47–49]). However, the results also revealed that in the three conditions under investigation, the Weber fraction is not constant. More specifically, the Weber fraction gets higher as the standard interval gets higher. The key finding here is the fact that essentially the same pattern of results was obtained, whatever the level of performance.

The same type of results was reported in Grondin [46] in two other experiments.

In one experiment, participants were presented 1, 3, or 5 intervals marked by 2, 4, or 6 brief sounds. The intervals lasted 1–1.9 s. Participants were asked to reproduce the interval(s) with two brief taps on the keyboard (in Session 2, restricted to the 3- and 5-interval conditions, they also synchronized their taps with sounds). The middle panel of Fig. 3 shows once again that the Weber fraction, which is indeed a coefficient of variation in this experiment (the inter-tap variability divided by the mean reproduction), is not constant. For instance, this coefficient is significantly higher in the 1.9- than in 1.0-s condition.

In the third experiment of this series, the conditions were exactly as in the first experiment. However, instead of presenting a standard and a comparison interval on each trial, the standard was present a few times at the beginning of a block; also, after each presentation of one of the comparison intervals, participants had to categorize the presented interval as shorter, or longer, than the standard. In addition to replicating that performance is improved when more than one interval is presented, the experiment once again showed (see lower panel of Fig. 3) that the Weber fraction gets higher as the standard gets higher.

In brief, whatever the method (discrimination, reproduction or categorization) used in Grondin [46], and whether single or multiple (rhythm) intervals are presented, a violation of Weber's law was observed. The fact that the same principle applies with single and multiple intervals is quite interesting. There are reasons to believe that the functional arrangement of neural systems responsible for timing differs according to whether single or multiple intervals are presented during a timing task [50]. In their attempt to categorize several timing tasks on the basis of the degree of relationships, Merchant and collaborators conducted hierarchical clustering and multidimensional scaling analyses that

revealed that single interval mechanisms probably engage neural substrates that are different from the one used when multiple intervals are involved in a timing task. Indeed, there are recent neuroscientific evidences showing that the role of the cerebellum, at least for the processing of subsecond intervals, differs according to the type of temporal processing required, duration-based (single interval presentation) vs. beat-based (multiple interval presentations) processing [51]. These evidences were obtained on the basis of both neurostimulation [52] and functional magnetic resonance imaging [53, 54] investigations.

Bangert et al. [55] also reported recent data suggesting that there is a violation of Weber's law for time. Indeed, they reported that the coefficient of variation is higher at 1,700 ms than at 1,350 ms, where the coefficient is already higher than at 1,175 or 1,000 ms. For brief intervals (270–1,175 ms), there was no such violation of the Weber's law but beyond that point, the Weber fraction increased. In their Experiment 3, which involved intervals ranging from 270 to 1,870 ms, the authors replicated previous findings obtained with a reproduction task, but contrary to what was reported in Grondin [46], there was no violation of the Weber's law for a duration discrimination task. Note however that their Weber fraction was higher (but not significantly different) at 1,700 or 1,870 ms than at 1,350 ms.

Recent Data: Extended Range

When extended to a much larger range of durations, the question of using explicit counting (or some segmentation strategy) or not becomes very critical. Explicit count of numbers reduces very much the Weber fraction from 1 to 2 s, but this fraction remains stable from 2 to 4 s ([56], Experiment 2). Some human data show that the Weber fraction remains constant, even without counting, for intervals up to 24 s for an interval reproduction task [57, 58], and that this fraction is even reduced with longer intervals when explicit counting is adopted [58]. The reduction of the Weber fraction with longer intervals was observed in Grondin and Killeen [57] only with musicians, not with non-musicians, and this observation applies with both the use of explicit counting and singing for segmenting time. Note finally that, when a series of intervals is produced sequentially, the Weber fraction increases with longer intervals (up to 24 s—non-musician participants) in spite of the use of explicit counting [59].

Some other recent data, issued from the animal timing literature, also exhibit a clear violation of the Weber's law when a large range of durations is under investigation [60]. This demonstration was conducted with pigeons with both a categorization and a production method (see Fig. 4).

Revisiting Older Data

The older literature is filled with demonstrations supporting some form of Weber's law, which might be a reason why SET remained so popular over the years. However, a closer look at some portions of what is available in the literature reveals some important signs of the non constancy of Weber's law at some point between 1 and 2 s.

Take for instance the study by Halpern and Darwin [61] on rhythm discrimination. They used a series of clicks marking intervals and reported a linear relationship between the threshold value (one standard deviation on the *y* axis of the left panel of Fig. 5) and the value of the inter-click intervals (ICI) on the *x* axis. A close look at the figure indicates that the two data points on the left (lower ICI values) are above the function, which is consistent with the generalized form of Weber's law where it is reported that the Weber fraction tends to get higher with very weak magnitudes of a sensory scale, including time [62]. This could be explained by the part of nontemporal variance in the process (represented

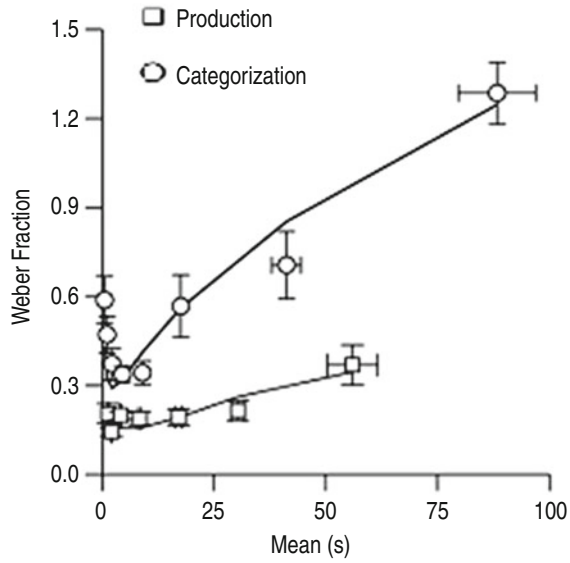

Fig. 4 Weber fraction as a function of the mean in two different temporal tasks, categorization and production, performed by pigeons (in Bizo et al. [60])

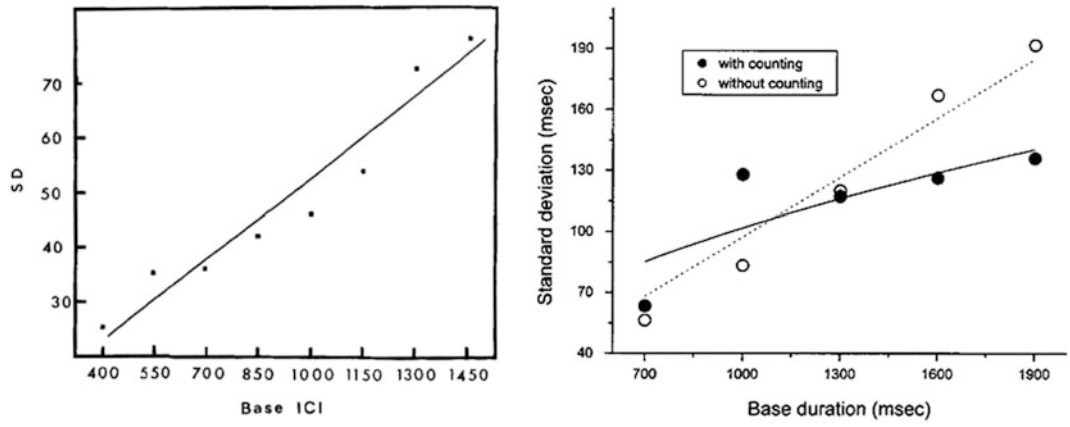

Fig. 5 Growth of the threshold value (one standard deviation on the y axis) as a function of inter-click intervals (in ms) in Halpern and Darwin ([61]—*left panel*) or base duration (standard) in Grondin et al. ([64]—*right panel*) (for specific explanations, see the text)

by a in the following description based on Eq. 2: $\sigma = kt + a$). The interesting point here is related to the two points on the right of the function. They are both above the fitted function. Indeed, there is a huge step in the standard deviation value when the base ICI increases from 1,150 to 1,300 ms. What could be argued here as demonstration of the robustness of Weber's law for rhythm discrimination rather contains a tangible sign that there is an important change somewhere around 1.3 s, a sign that there is a deviation from strict proportionality.[2]

[2] The reader will also find a Weber fraction increase for tempo discrimination, from 1 to 1.4 s, in Ehrlé and Samson [63, Table 5].

As well, the results on the right panel of Fig. 5 illustrate a similar phenomenon. In these data reported by Grondin et al. [64] on the duration discrimination of single intervals marked by brief sounds, the threshold value (one standard deviation) increases as a function of time. In this study, it is argued that function is fundamentally changed according to whether a participant is allowed (filled points) or not (empty points) to count explicitly during the task. The function in the no-counting condition (dotted line) accounts reasonably well for the data from 0.7–1.9 s. However, the first three points (lower value on *x*) are below the function and the other two points are above. There is a kind of step between 1.3 and 1.6 s that is negligible in the context of a comparison with a counting condition.

In addition to these two specific cases, the reader may also find several other examples of the violation of Weber's law in the older timing literature. In his review of a few reports on the relationship between the Weber fraction and time, Fraisse [65] reported three clear cases where the Weber fraction is not constant, that of Woodrow [66], Stott [67], and Getty [28]. While the fraction gets higher when the base duration is about 2 s in Stott, it increases after 1.5 s in Woodrow. The data from Getty [28] were collected on two participants, including the author. Their threshold was estimated for the discrimination of single auditory intervals for 15 base durations from 50 to 3,200 ms. The Weber fraction was quite constant from 200 to 2,000 ms, but clearly higher at 2,800 and 3,200 ms.

The reader may also find a composite figure in Grondin [68] where different reports also suggest that, with different methods, there is an increase in the Weber fraction for longer intervals. The data on auditory tempo discrimination from Drake and Botte [47] show a higher Weber fraction with 1.5-s than with 1-s standards. As well, the Weber fraction is higher at 1.2 than at 0.9 s for the discrimination of time intervals presented in sequences marked by visual signals [69]. Moreover, with a task involving the production of a continuous sequence of intervals, Madison [70] showed that the coefficient of variation gets higher when intervals are longer than 1.2 s.

Another composite figure, where the coefficient of variation as a function of time is reported, is proposed in the review paper of Gibbon et al. [71]. In this figure, the results from 28 human and 15 animal studies are reported. The mean features extracted from the general picture by the authors are the following. For very brief intervals (<100 ms), the coefficient of variation is higher as base durations get briefer (which is consistent with a generalized form of Weber's law). Then, from 0.1 to 1.5 s, the coefficient remains constant, and increases again over 1.5 s. Some signs of a new noticeable increase are observable at 500 s.

In brief, there were multiple indications in the old timing literature revealing that the Weber fraction is not constant. Nevertheless, in spite of these indications, many authors assumed that the scalar property holds for time.

Other Challenges: Outstanding Issues

Two main issues could be extracted from this review. First, there is a violation of the scalar property for time perception, and there are multiple reasons to believe that this non constancy of the Weber fraction occurs at some point between 1 and 1.9 s. Secondly, this non constancy is not due to some specific methodological features since the demonstrations were completed with different methods (production vs. perception), in conditions where time intervals are marked with sounds or flashes, and in conditions where either presentations of single or multiple intervals are used. Therefore, the violation of the scalar property seems to be quite a robust phenomenon.

The scalar expectancy theory, described earlier, has been one of the most, if not the most, useful theory of time perception in the past 30 years. One central feature of this theory has actually been its scalar property: the variability to time ratio, or Weber fraction, should be constant over a wide range of durations. Considering the series of evidences provided in the present review, this feature does not hold. Does that mean that SET is obsolete? Probably not, given its power to account for multiple data, either in the human and

animal timing literature [72]; however, it is necessary to try to understand the source and meaning of this non-constant Weber fraction.

One or Multiple Timing Devices

A fundamental question that should be asked is whether or not the same timing system is responsible for accounting for temporal judgments whatever the method of investigation employed and whatever the range of durations. If the timing system is a pacemaker-counter embedded within a framework that includes memory and decisional processes, and the predicted output of this entire mechanism is a scalar property, then the "same" (unique, central) perspective is a position difficult to defend. This however does not exclude the possibility that there is a central timing device, as long as the scalar property is not a pre-requisite of the model.

If the question of the central timekeeping device is restricted to a narrower range of durations such as the one used for obtaining the data reported in Fig. 3 (1–1.9 s), and the scalar property is expected from this device, the response is tricky. On the one hand, the Weber fraction is clearly not constant, which should lead to a rejection of the central/unique-device hypothesis. On the other hand, whatever the condition (perception vs. production; single- vs. multiple-interval presentations), the same phenomenon occurs: an increase of the fraction that mostly occurs between 1.3 and 1.6 s. With such a common feature, it remains reasonable to keep believing that the same system is used.

Maybe there is no need to consider if the scalar property holds when time comes to assess whether or not there is a central timekeeping device. And maybe there is no need for positing that there is a central timing device. If there is no unique timekeeping device, we may posit the hypothesis that there is a multiplicity of timekeeping mechanisms, actually because a complete adaptation to real life situations requires a multiplicity of temporal adjustments. Such an avenue though is a difficult one in science. We may also try to remain reasonable and propose the existence of two distinct timekeeping mechanisms, at least, for durations ranging from 100 ms up to a few seconds, i.e. for a range that would cover the processing of speech or motion coordination, as noted earlier.

Two Timekeeping Systems?

Let's return to the right panel of Fig. 5. This figure is essentially saying that there is a point, circa 1.2 or 1.3 s, beyond which there are benefits to be expected from the adoption of a different way of approaching a timing task [56, 58, 64, 73]. Beyond this point, the constancy of the Weber fraction is on shaky ground; but there is actually an option, at least for human observers. It is possible to count explicitly. One can choose to count numbers explicitly, and count rapidly or slowly, depending on the intervals to deal with. If not numbers, one may adopt other strategies including foot tapping like a drummer, imagining the hand of a clock for counting seconds, or even simply singing [57, 59].

Counting explicitly and not counting could be viewed like two different timekeeping systems. However, counting is nothing more than segmenting a long interval into a series of subintervals [29, 74]. The estimation of the duration of each subinterval may require the contribution of the same timekeeping system as the one used for the entire long interval. The idea is to minimize variance. If the summation of the variance of each subinterval, plus the variance associated with the count of the number of subintervals is lower than the variance associated with the timekeeping of the entire interval, then it is advantageous to count.

That said, having two different functions in Fig. 5 (right panel) could be interpreted as the presence of two mechanisms. Tentatively, the crossing point could be viewed like a critical phase change, i.e., a point where the system is transported in a new state or at least, where it is advantageous to adopt a new state. As noted above, this point occurs circa 1.2 or 1.3 s, and 1.3 s is actually a critical duration where the non-constancy becomes noticeable in numerous

timing tasks (Fig. 3). Interestingly, animal timing data also show that intervals in that duration range are critical. In their review of animal and human timing literatures, Gibbon et al. [71] pointed toward a 1.5-s critical value. Even more intriguing is the fact that, in the animal timing literature, 1.2 s is sometimes identified as one of the local maxima, on the time continuum, for sensitivity to time [75, 76]; beyond this value, there is a loss of sensitivity. Therefore, the increased Weber fraction between 1 and 2 s very likely reflects a fundamental limitation for processing temporal information.

The idea of chunking pieces of information for increasing the capability of the information processing system is not new [77, 78]. It is indeed one of the most important features of the human processing system. The same principle is applied here for increasing the efficiency to process temporal information. When intervals reach a point where the processing system begins to be less efficient, the other mechanism—call it chunking/segmenting/counting—is available for dealing more efficiently with the task. If one wants to venture an interpretation in terms of traditional information processing wording, it looks as if the space occupied by long intervals exceeds the temporal capacity of working memory [79–81].

As noted by Grondin [46], the concept of a limited temporal span may remind of the idea that was referred to by Michon [82] as *psychological present* (or *specious* present [3]; or *subjective* present [83]). This concept indeed describes a time window within which it is possible to form a coherent package of information. The point where the Weber fraction increase occurs, somewhere between 1 and 1.9 s, could be interpreted as a way for quantifying the temporal span of this window.

Resolving problems with a two-way approach is far from original in psychology. For instance, in the auditory system, there are two theories—temporal coding vs. place coding—to account for the capability to distinguish sound frequencies. And instead of rejecting one theory or another, it was proved convenient to associate the temporal coding avenue (and volley principle) with the processing of low-frequency components, and the place coding interpretation (including von Bekesy's classical traveling wave theory) with the high-frequency components of sounds. Along that line, there could be an interpretation of temporal information processing in terms of brief vs. long intervals, say, below or beyond 1.3 s, with both systems being always available but the level of sensitivity/efficiency being optimal only for a given duration range.

The reader will find traces of a dual-system approach in the timing literature. For instance, Grondin and Rousseau [84] adopted such an approach for explaining why brief empty time intervals marked by two signals delivered from the same modality are much easier to discriminate than intervals marked by intermodal signals (specific vs. aspecific processors). In their *dynamic attending* theory of time perception, Jones and Boltz [85] distinguished two modes for processing temporal information, a *future-oriented* mode, based on the regularities of events occurring in the environment, and an *analytic-oriented* mode.

Indeed, it would be difficult to specify the exact nature of the mechanism dedicated to the processing of brief intervals. It could be a mechanism dependent on the nature of the signals available in the environment or marking intervals, as noted in the past paragraph, or it could be a *state-dependent network*. According to Buonomano [40, 86] timing does not depend on a clock, but on time-dependent changes in the state of neural networks. In this model, being able to judge duration means to recognize spatial patterns of activity.

Note that other dichotomies are proposed in the time perception literature. As for the duration range, there are indications of sensory-based processing, by opposition to cognitively-based processing, when the discriminations of intervals around 50 ms vs. 1 s are compared [87, 88]. Other authors proposed to distinguish explicit timing, as in repetitive tapping like the one used in consecutive interval productions, and implicit timing like the one used in drawing movements [89, 90].

Conclusion

This review of the literature on the scalar property for timing and time perception reveals that there is actually no such scalar property. The literature is filled with demonstrations that Weber's law does not hold or at least, when it holds, it is for a much restricted range of durations, as in Merchant et al. [44], or when a general picture is taken and explicit counting not forbidden, as in Grondin [62] for instance. The violation of the scalar property for time calls for a re-examination of models, such as SET, based on a clock-counter device. The literature offers multiple alternatives, including the possibility to have multiple timers, to process temporal information on the basis of a frontal-striatal circuitry ([91]; see the chapter by Meck and co-workers in this volume) or, as noted earlier, to read time on the basis of the output of a state-dependent network (see the chapter by Buonomano in this volume).

On the other hand, there is a convergence of findings showing that sensitivity to time is significantly lost when intervals become too long (say > 1.3 s); moreover, we know that humans actually have a trick, explicit counting, for compensating this loss. This may indicate the presence of two fundamental ways of processing temporal information. Cognitive psychology is actually filled with numerous dual-process interpretations [92]. These interpretations, or theories, take several forms like a dichotomy between heuristic/holistic and systematic/analytic systems, associative vs. rule-based systems, or implicit vs. explicit systems, to name only a few. And on some occasions, these distinctions are associated with some specific way with which each cerebral hemisphere processes information. Apparently, it could be proved useful to undertake the neurophysiological study of temporal processing with such a dual-process approach in mind, a dual-process that is provoked by the fact that we have to deal with different duration ranges. Indeed, as stated by Rammsayer and Troche (this volume), one avenue is to posit that there are two functionally related timing mechanisms underlying interval timing. According to these authors, these mechanisms are associated either with the processing of sub-second intervals or with the processing of supra-second intervals.

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Elucidating the Internal Structure of Psychophysical Timing Performance in the Sub-second and Second Range by Utilizing Confirmatory Factor Analysis

Thomas H. Rammsayer and Stefan J. Troche

Abstract

The most influential theoretical account in time psychophysics assumes the existence of a unitary internal clock based on neural counting. The distinct timing hypothesis, on the other hand, suggests an automatic timing mechanism for processing of durations in the sub-second range and a cognitively controlled timing mechanism for processing of durations in the range of seconds. Although several psychophysical approaches can be applied for identifying the internal structure of interval timing in the second and sub-second range, the existing data provide a puzzling picture of rather inconsistent results. In the present chapter, we introduce confirmatory factor analysis (CFA) to further elucidate the internal structure of interval timing performance in the sub-second and second range. More specifically, we investigated whether CFA would rather support the notion of a unitary timing mechanism or of distinct timing mechanisms underlying interval timing in the sub-second and second range, respectively. The assumption of two distinct timing mechanisms which are completely independent of each other was not supported by our data. The model assuming a unitary timing mechanism underlying interval timing in both the sub-second and second range fitted the empirical data much better. Eventually, we also tested a third model assuming two distinct, but functionally related mechanisms. The correlation between the two latent variables representing the hypothesized timing mechanisms was rather high and comparison of fit indices indicated that the assumption of two associated timing mechanisms described the observed data better than only one latent variable. Models are discussed in the light of the existing psychophysical and neurophysiological data.

Keywords

Interval timing • Distinct timing hypothesis • Timing mechanisms • Confirmatory factor analysis • Sub-second range • Second range

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Introduction

Within the field of psychophysical research on timing and time perception, there are two competing major theoretical accounts on the mechanisms underlying the temporal processing of intervals in the range of seconds and milliseconds referred to as the *distinct timing hypothesis* and the *common timing hypothesis*. The distinct timing hypothesis acts on the assumption that processing of temporal information in the sub-second range depends upon a qualitatively different mechanism than processing of temporal information in the second range. The common timing hypothesis, on the other hand, acts on the assumption of a single, central timing mechanism. As depicted in the first chapter, over the past 50 years psychophysical research on time perception has been guided by the notion of a common timing mechanism underlying temporal processing of intervals irrespective of interval duration (cf. [1, 2]). Although such internal clock models based on neural counting provide a useful heuristic for explaining human and animal performance on timing of brief intervals, there is increasing empirical evidence challenging the assumption of a common, unitary timing mechanism (for a review see: first chapter of this volume; [2–4]). Over the past two decades, psychophysical research on interval timing has been in the search of a definite answer on whether a common timing mechanism or two distinct timing mechanisms account for the timing of intervals in the second and sub-second range.

In the present chapter, we will acquaint the reader with the basic assumptions of both the common and distinct timing hypotheses. Furthermore, we will provide a concise overview of the basic findings of psychophysical studies designed to experimentally dissociate the two timing mechanisms implied by the distinct timing hypothesis. As we will see, the available psychophysical studies, so far, failed to provide unambiguous experimental evidence against or in favour of either of the two competing hypotheses. Therefore, we will introduce a novel methodological approach, based on confirmatory factor analysis, for investigating the internal structure of psychophysical timing performance in the sub-second and second range.

The Common Timing Hypothesis: A Unitary Timing Mechanism Based on Neural Counting

To date, the most popular conception in time psychophysics represents the notion of a common timing mechanism underlying temporal processing of intervals in the sub-second and second range. This highly influential theoretical account of human and animal timing and time perception assumes the existence of a single internal clock based on neural counting (e.g., [2, 5–11]). The main features of such an internal-clock mechanism are a pacemaker and an accumulator. The neural pacemaker generates pulses, and the number of pulses relating to a physical time interval is recorded by the accumulator. Thus, the number of pulses counted during a given time interval indexes the perceived duration of this interval. Hence, the higher the clock rate of the neural pacemaker the finer the temporal resolution of the internal clock will be, which is equivalent to more accuracy and better performance on timing tasks.

The assumption of a unitary internal-clock mechanisms based on neural counting also represents the established explanation for the Scalar Expectancy Theory (SET) introduced by Gibbon [7, 12]. SET is one of the currently most prominent theoretical accounts of human and animal timing. According to SET, when estimating the duration of a given standard interval, a participant's responses follow a normal distribution around the interval duration. The width of this response distribution is predicted to be proportional to the standard duration. This linear covariation of the mean and the standard deviation of the response distribution across different standard durations, referred to as the scalar property of interval timing, is also asserted by Weber's law [9, 13].

Although direct experimental evidence for the notion of a single, common timing mechanism underlying temporal processing in the sub-second and second range is hard to obtain, some indirect psychophysical evidence can be derived from the failure to detect so-called 'break points' in the precision of interval timing across interval durations ranging from 68 ms to 16.7 min [14]. Such break points would be the expected outcome if different timing mechanisms, with different levels of absolute precision of timing, were used for measuring intervals of different durations [15, 16]. At the same time, however, the scalar property of interval timing for brief durations is seriously questioned by psychophysical research in humans (see Chapter 1; [8, 17]) and animals (e.g., [18]).

The Distinct Timing Hypothesis: Interval Timing in the Second and Sub-second Range Is Based on Two Distinct Timing Mechanisms

As early as 1889, Münsterberg [19] put forward the idea of two distinct timing mechanisms underlying temporal information processing. He assumed that durations less than one third of a second can be directly perceived whereas longer durations need to be (re-)constructed by higher mental processes. More recently, Michon [20] argued that temporal processing of intervals longer than approximately 500 ms is cognitively mediated while temporal processing of shorter intervals is supposedly "of a highly perceptual nature, fast, parallel and not accessible to cognitive control" [20, p. 40]. More recent studies, pursuing Michon's [20] conception, provided converging evidence that the transition from sensory/automatic to cognitively mediated timing might lie closer to 250 ms than to 500 ms [21, 22].

In a first attempt to provide direct experimental evidence for the validity of the distinct timing hypothesis, Rammsayer and Lima [23] applied a dual-task paradigm guided by the following considerations: If, as suggested by Michon [20], temporal discrimination of intervals longer than approximately 500 ms is cognitively mediated, one would expect that temporal discrimination under relatively high cognitive load would be more difficult than temporal discrimination under lower cognitive load. On the other hand, if discrimination of extremely brief intervals is based upon an automatic, sensory mechanism, performing a concurrent nontemporal cognitive task should produce no deleterious effect on temporal discrimination of intervals in the range of milliseconds. To test these predictions, a dual-task procedure was used with duration discrimination as the primary task and word learning as a secondary nontemporal cognitive task. Results from the dual-task conditions were compared with results from single-task conditions. If two tasks compete for the same pool of cognitive resources then simultaneous performance on both tasks should be impaired compared to performance on one task alone. With this approach, Rammsayer and Lima [23] found that temporal discrimination of intervals ranging from 50 to 100 ms is unaffected by a secondary cognitive task whereas duration discrimination of intervals in the range of seconds is markedly impaired by the same secondary task. The likely conclusion was that timing of intervals in the sub-second range is based on an automatic, sensory mechanism while timing of intervals in the second range is cognitively mediated.

To further test the distinct timing hypothesis, Rammsayer and Ulrich [4] investigated the effects of maintenance and elaborative rehearsal as a secondary task on temporal discrimination of intervals in the sub-second and second range. Unlike mere maintenance rehearsal, elaborative rehearsal as a secondary task involved transfer of information from working memory to long-term memory and elaboration of information to enhance storage in long-term memory. Temporal discrimination of brief intervals was not affected by a secondary cognitive task that required either maintenance or elaborative rehearsal. Concurrent elaborative rehearsal, however, reliably impaired temporal discrimination of intervals in the second range as compared to maintenance rehearsal and a control condition with no secondary task.

These findings support the notion of two distinct timing mechanisms involved in temporal processing of intervals in the sub-second and second range. While temporal processing of intervals in the second range demands cognitive resources, temporal processing of intervals in the sub-second range appears to be highly sensory in nature and beyond cognitive control.

The distinct timing hypothesis is also supported by neuropharmacological and neuroimaging studies on temporal information processing. Findings from neuroimaging studies are consistent with the notion of an automatic timing system for measuring brief intervals in the sub-second range and a cognitively controlled system, depending on the right dorsolateral prefrontal cortex, for temporal processing of intervals in the suprasecond range (for reviews see [24–26]). Similarly, neuropharmacological timing studies also suggest the existence of a prefrontal cognitive system for the processing of temporal information in the second range and a subcortical automatic system controlled by mesostriatal dopaminergic activity for temporal processing in the range of milliseconds (for reviews see [27–29]).

Statistical Approaches for Identifying the Internal Structure of Psychophysical Timing Performance

In the face of the rather ambiguous experimental findings with regard to the common timing and distinct timing hypotheses, additional statistical approaches became increasingly important. There are at least two basic statistical approaches to investigating whether tasks that require fine temporal resolution and precise timing depend upon a unitary timing mechanism. The *method of slope analysis* is derived from Getty's [30] generalization of Weber's law. With this approach, changes in timing variability as a function of timescale (e.g., sub-second vs. second range) can be compared across tasks. If the slope of the variability functions of two tasks is equivalent, a common timing mechanism underlying both tasks is inferred (for more information see [31]).

The *correlational approach* is based on the general assumption that if the same timing mechanism is involved in two tasks, the performance or timing variability of the two tasks should be highly correlated. Common forms of the correlational approach to the identification of the internal structure of psychophysical timing performance represent correlational analyses (e.g., [32]), exploratory factor analysis (e.g., [33]), and multiple linear regression [34].

In an attempt to apply the correlational approach to elucidate the dimensional properties of temporal information processing in the sub-second and second range, Rammsayer and Brandler [33] used exploratory factor analysis to analyse eight psychophysical temporal tasks in the sub-second (temporal-order judgment, and rhythm perception) and second range (temporal discrimination and generalization of filled intervals). Their main finding was that the first principle factor accounted for 31.5 % of the total variance of the eight different temporal tasks. More specifically, all the various temporal tasks, except rhythm perception and auditory fusion, showed substantial loadings on this factor. Rammsayer and Brandler [33] interpreted this outcome as evidence for a common, unitary timing mechanism involved in the timing of intervals in the sub-second and second range.

Confirmatory Factor Analysis: An Alternative, Theory-Driven Methodological Approach for Identifying the Internal Structure of Psychophysical Timing Performance

Confirmatory factor analysis (CFA) represents a methodological approach more sensitive to theoretical assumptions and given hypotheses than the exploratory factor analysis applied by Rammsayer and Brandler [33]. Similar to the exploratory factor analysis, CFA is based on the correlations (or actually unstandardized correlations, i.e. covariances) of a set of measurements. While exploratory factor analysis makes a proposal for the number of latent variables underlying a given covariance matrix without any theoretical assumptions, CFA probes whether theoretically

predefined latent variables can be derived from the pattern of correlations.

Assume, for example, that 100 participants performed on three timing tasks in the second range and three other timing tasks in the sub-second range. You compute the correlations among the six tasks and, hence, you produce an empirical correlation matrix. As a supporter of the distinct timing hypothesis, you expect statistically significant correlations between the three timing tasks in the second range. Because you assume that a specific timing mechanism for intervals in the second range accounts for these significant correlations, you derive a factor (i.e., a latent variable) from the three timing tasks in the second range which represents the timing mechanism for the second range. You also expect significant correlations between the three timing tasks in the sub-second range. As for the second range, these significant correlations suggest a timing mechanism specific to processing of temporal information in the sub-second range which is, consequently, represented by a factor (latent variable) derived from these sub-second timing tasks. In addition, you expect the pair-wise correlations between a given timing tasks in the second range, on the one hand, and a given timing tasks in the sub-second range, on the other hand, to be statistically non-significant. This is because the distinct timing hypothesis assumes different distinct mechanisms to underlie timing in the second and in the sub-second range, respectively. If the correlations between timing tasks in the second and the sub-second range are non-significant, also the correlation between the latent variables representing the timing mechanism in the second and sub-second range, respectively, should be low. Thus, a latent variable model derived from the basic assumption of the distinct timing hypothesis should contain a latent variable for timing in the second range and another latent variable for timing in the sub-second range with a non-significant correlation between these two latent variables.

In case, however, that you are a follower of the common timing hypothesis, you would expect that individual differences in one timing task go with individual differences in any other timing task—regardless of whether these tasks use stimulus durations in the second or sub-second range. As a consequence, there should be significant correlations among performances of all tasks (irrespective of the stimulus duration) suggesting a common latent variable which accounts for these relationships.

Thus, the two alternative timing hypotheses result in different predictions of how a correlation matrix of tasks in the second and in the sub-second range should look like. CFA compares the respective predicted correlation matrix with the empirically observed correlation matrix and, thus, provides indices of how accurately the expected matrix fits the observed matrix. These indices are, therefore, called fit indices and will be described in more detail below. On the basis of these model fit indices, it can then be decided which of the two models describes the observed data better and should be preferred. It should be noted, however, that CFA does actually not analyze the correlations but the covariances, i.e., the unstandardized correlations. Therefore, we will refer to "covariance" and "covariance matrix" in the following paragraphs.

Applying Confirmatory Factor Analysis for Identifying the Internal Structure of Psychophysical Timing Performance: An Example of Use

We will demonstrate the application of CFA by means of a study that was designed to probe whether covariances of interval timing tasks in the second and sub-second range can be described by the assumption of either one or two latent variables supporting the common or distinct timing hypothesis, respectively. In order to obtain a sufficient number of behavioral data for the CFA approach, a rather large sample of 130 participants (69 males and 61 females ranging in age from 18 to 33 years) had been tested.

Psychophysical Assessment of Interval Timing Performance

For psychophysical assessment of performance on interval timing, three temporal discrimination

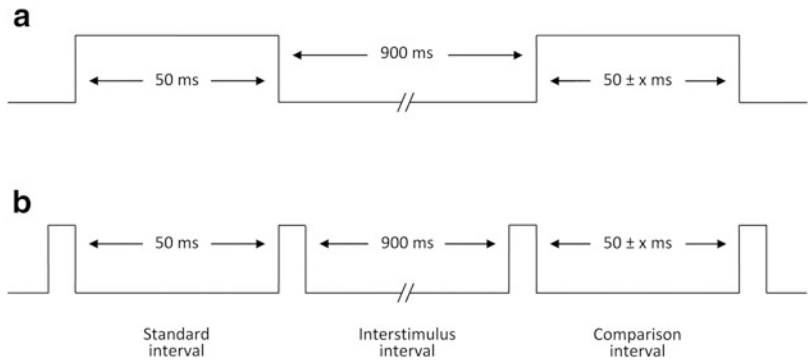

Fig. 1 Schematic diagram of the time course of an experimental trial of the temporal discrimination task with filled (Panel A) and empty (Panel B) intervals in the sub-second range. In filled intervals, a white-noise burst is presented continuously throughout the interval, whereas in empty intervals only the onset and the offset are marked by brief 3-ms white-noise burst. Thus, in empty intervals, there is no stimulus present during the interval itself. On each trial, the participant is presented with two intervals a constant 50-ms standard interval and a variable comparison interval (50 ± x ms). The participant's task is to decide which of the two intervals was longer. The duration of the comparison interval varied from trial to trial depending on the participant's previous response. Correct responding resulted in a smaller duration difference between the standard and the comparison interval, whereas incorrect responses made the task easier by increasing the difference in duration between the standard and the comparison interval

tasks and two temporal generalization tasks were used. Because the auditory system has the finest temporal resolution of all senses (for reviews see [35, 36]), auditory intervals were presented in all tasks.

On each trial of a typical *temporal discrimination task*, the participant is presented with two intervals and his/her task is to decide which of the two intervals was longer. There are two types of intervals commonly employed in temporal discrimination tasks. One type is the *filled* interval and the other type is the *empty* (silent) interval. In filled auditory intervals, a tone or noise burst is presented continuously throughout the interval, whereas in auditorily marked empty intervals only the onset and the offset are marked by clicks (see Fig. 1). Thus, in empty intervals, there is no auditory stimulus present during the interval itself. Most importantly, type of interval appears to affect temporal discrimination of auditory intervals in the range of tens of milliseconds. For such extremely brief intervals, performance on temporal discrimination was found to be reliably better with filled than with empty intervals. This effect seems to be limited to intervals shorter than approximately 100 ms and is no longer detectable for longer intervals [37].

Based on these considerations, our participants performed one block of filled and one block of empty intervals with a standard duration of 50 ms each, as well as one block of filled intervals with a standard duration of 1,000 ms. Order of blocks was counterbalanced across participants. Each block consisted of 64 trials, and each trial consisted of one standard interval and one comparison interval. The duration of the comparison interval varied according to an adaptive rule [38] to estimate *x.25* and *x.75* of the individual psychometric function, that is, the two comparison intervals at which the response "longer" was given with a probability of 0.25 and 0.75, respectively. Generally speaking 'adaptive' means that stimulus presentation on any given trial is determined by the preceding set of stimuli and responses. Therefore, the comparison interval is varied in duration from trial to trial depending on the participant's previous response. Correct responding resulted in a smaller duration difference between the constant standard and the variable comparison interval, whereas incorrect responses made the task easier by increasing the difference in duration between the standard and the comparison interval (for more details see [39]). As an indicator of

discrimination performance, the difference limen, *DL* [40], was determined for each temporal discrimination task.

In addition to the temporal discrimination tasks, two *temporal generalization tasks* (see first chapter) were employed with standard durations of 75 and 1,000 ms for the sub-second and second range, respectively. Like temporal discrimination, temporal generalization relies on timing processes but additionally on a reference memory of sorts [41, 42]. This is because in the first part of this task, participants are instructed to memorize the standard stimulus duration. For this purpose, the standard interval was presented five times accompanied by the display "This is the standard duration". Then the test phase began. On each trial of the test phase, one duration stimulus was presented. Participants had to decide whether or not the presented stimulus was of the same duration as the standard stimulus stored in memory. The test phase consisted of eight blocks. Within each block, the standard duration was presented twice, while each of the six nonstandard intervals was presented once. In the range of seconds, the standard stimulus duration was 1,000 ms and the nonstandard durations were 700, 800, 900, 1,100, 1,200, and 1,300 ms. In the range of milliseconds, the nonstandard stimulus durations were 42, 53, 64, 86, 97, and 108 ms and the standard duration was 75 ms. All duration stimuli were presented in randomized order. As a quantitative measure of performance on temporal generalization an individual index of response dispersion [43] was determined. For this purpose, the proportion of total "yes"-responses to the standard duration and the two nonstandard durations immediately adjacent (e.g., 900, 1,000, and 1,100 ms in the case of temporal generalization in the second range) was determined. This measure would approach 1.0 if all "yes"-responses were clustered closely around the standard duration.

The standard durations of the interval timing tasks for the sub-second and second range were selected because the hypothetical shift from one timing mechanism to the other may be found at an interval duration somewhere between 100 and 500 ms [20–22, 44, 45]. Furthermore, when participants are asked to compare time intervals, many of them adopt a counting strategy. Since explicit counting becomes a useful timing strategy for intervals longer than approximately 1,200 ms [46, 47], the long standard duration was chosen not to exceed this critical value.

Statistical Analyses Based on Confirmatory Factor Analysis: Different Indices for Evaluation of Model Fit

The two models investigated by means of CFA are schematically presented in Fig. 2. Proceeding from the common timing hypothesis, Model 1 assumes that one common latent variable underlies performance on all five interval timing tasks (see Fig. 2, model on the left). Model 2 refers to the distinct timing hypothesis assuming two distinct latent variables. One latent variable underlies performance on the timing tasks in the sub-second range, i.e., the temporal generalization and the two duration discrimination tasks with stimuli in the sub-second range. A second latent variable underlies performance on the temporal generalization and the duration discrimination tasks with stimuli in the second range. According to the distinct timing hypothesis, these two latent variables are not correlated with each other (see Fig. 2, model on the right). Since CFA provides an evaluation of how well a theoretical model describes the observed data, the comparison of so-called *model fit indices* helps to decide whether the unitary or the distinct timing hypothesis better predicts the empirical data.

In order to test whether the empirical data are well described by given theoretical assumptions, the observed covariance matrix is compared with the theoretically implied matrix. The dissimilarity can be tested for significance by the χ^2 *test* [48]. A significant χ^2 value requires rejecting the null hypothesis which says that the observed and implied covariance matrices are identical and differences are just due to sampling error. A non-significant χ^2 value, on the contrary, indicates that the theoretical model is not proven to be incorrect and that the empirical data fit the

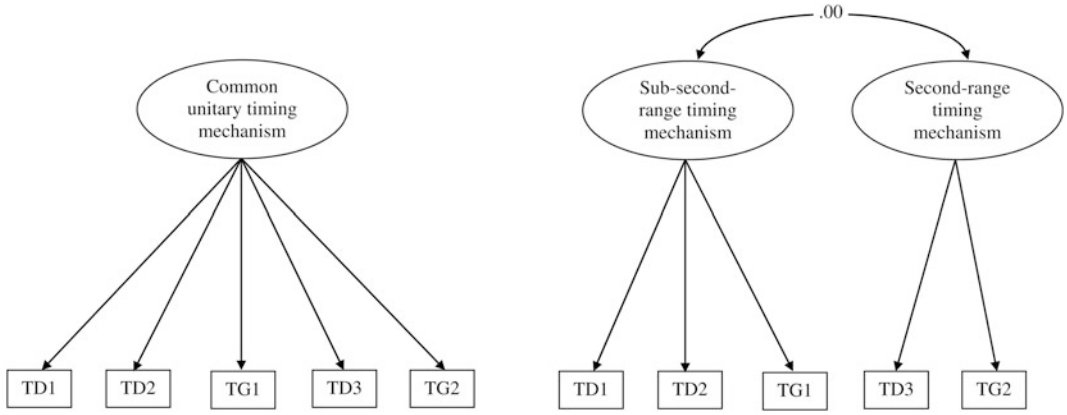

Fig. 2 Two models reflecting the common timing hypothesis (model on the *left*) and the distinct timing hypothesis (model on the *right*), respectively. The common timing hypothesis assumes correlational relationships among the five interval timing tasks, irrespective of interval duration, which can be explained by a common latent variable. The distinct timing hypothesis suggests that performances on the three interval timing tasks in sub-second range are highly correlated with each other and that these correlations are due to a specific mechanism for the timing of intervals in the sub-second range. Similarly, also performances on the two interval timing tasks for the second range are expected to correlate with each other due to a specific mechanism underlying the timing of intervals in the second range. Both these mechanisms, however, are conceptualized to be completely independent from each other as indicated by the correlation coefficient of $r = 0.00$. Note. TD1: temporal discrimination of filled intervals in the sub-second range; TD2: temporal discrimination of empty intervals in the sub-second range; TD3: temporal discrimination of filled intervals in the second range; TG1: temporal generalization of filled intervals in the sub-second range; TG2: temporal generalization of filled intervals in the second range

theoretical expectations. The χ^2 value, however, depends on the sample size and easily yields significance with large sample sizes which are required for the computation of CFA. Therefore, to avoid that models are rejected just because of too large sample sizes, further model fit indices are usually computed [49]. In the following, the most common and widely-used additional fit indices will be briefly introduced.

The *Comparative Fit Index* (CFI) estimates how much better a given model describes the empirical data compared to a null model with all variables assumed to be uncorrelated. The CFI varies between 0 and 1 and a value of more than 0.95 is acceptable [50].

The *Akaike Information Criterion* (AIC) is an explicit index of the parsimony of a model. This is important as it is required that models should be as parsimonious (i.e., as less complex) as possible. The AIC charges the χ^2 value against model complexity in terms of degrees of freedom. The lower the AIC, the more parsimonious is the model.

The *Root Mean Square Error of Approximation* (RMSEA) is relatively independent of sample size and tests the discrepancy between observed and implied covariance matrices. Furthermore, the RMSEA considers the complexity of a model so that higher parsimony is reinforced by this fit index. To indicate a good model, the RMSEA should be smaller than 0.05 but also values between 0.05 and 0.08 are considered acceptable [51]. Another advantage of the RMSEA is that a confidence interval can be computed which should include 0 to approximate a perfect model fit.

Eventually, the *Standardized Root Mean Square Residual* (SRMR) represents an index of the covariance residuals as the difference between empirical and implied covariances which should be smaller than 0.10 [52].

Model Evaluation by Means of Confirmatory Factor Analysis: Preliminary Considerations

The two models, depicted in Fig. 2, were evaluated based on the previously described model fit indices. Model 1 constitutes the common timing hypothesis, while Model 2 illustrates a schematic representation of the distinct timing hypothesis

suggesting two distinct timing mechanisms for processing of temporal information in the sub-second and second range, respectively. In this context, it is important to note that the finding of a non-significant χ^2 value for one model and a significant χ^2 value for the other model does not necessarily mean that the first model describes the data *significantly* better than the second model. Therefore, the general rule for comparing different theoretical models is to test whether differences of the model fits are substantial. In the case that two models are in a hierarchical (or nested) relationship, the difference between their χ^2 values and their degrees of freedom can be calculated and this difference value can be tested for statistical significance.

This, however, is only possible when the two models to be compared are in a nested relationship. A nested relationship means that one or more *paths* are freely estimated in one model, but fixed in the other one. In the present study, an example for a *path* refers to the correlation between the two latent variables in Model 2. In this case, the correlation between the two latent variables is fixed to zero because the distinct timing hypothesis predicts two independent mechanisms for interval timing in the second and in the sub-second range. In Model 1, the same correlation can be seen as being fixed to 1 indicating that the two latent variables in Model 2 are virtually identical or represent one and the same latent variable, i.e. one common timing mechanism irrespective of interval duration. Therefore, Model 1 and Model 2 are not nested models because they have the same number of degrees of freedom.

If, however, an alternative third model would imply a freely estimated correlation between the two latent variables of Model 2 (i.e., the assumed correlation coefficient is not theoretically fixed to a certain value of 1 [as in Model 1], or 0 [as in Model 2]), this alternative Model 3 can be considered a nested model compared to Model 1 and Model 2. This is because fixing this correlation in Model 3 to 1 would result in Model 1 and fixing the correlation in Model 3 to 0 would result in Model 2. Thus, the hypothesized Models 1 and 2 can be directly compared to Model 3 by means of a χ^2 difference test.

Our Models 1 and 2, as already pointed out, are not nested. Because non-nested models cannot be compared by χ^2 differences, this type of model has to be compared by their parsimony in terms of the AIC value (see above). As already explicated above, a difference in the AIC values indicates that the model with the lower AIC describes the data more parsimoniously and, therefore, better than the model with the higher AIC. Thus, it is the AIC which has to be used to directly compare Model 1 and Model 2 in the present study.

Model Evaluation by Means of Confirmatory Factor Analysis: Results of the Present Study

Descriptive statistics and intercorrelations of the five interval timing tasks are given in Table 1. In order to contrast the common with the distinct timing hypothesis, we computed CFAs on the two models presented in Fig. 2. Model 1 proceeded from the assumption of a common, unitary timing mechanism so that covariances among performance on all five psychophysical timing tasks were explained by one latent variable. This model, depicted in Fig. 3, explained the data well as can be seen from a non-significant χ^2 test [$\chi^2(5) = 6.27$; $p = 0.28$] as well as from CFI (0.99) which exceeded the requested limit of 0.95. Also the RMSEA was smaller than 0.08 (RMSEA = 0.04) and the 90 % confidence interval included zero (ranging from 0.00 to 0.14). The AIC was 2,396.0 and the SRMR = 0.03. Thus, the assumption of a common unitary timing mechanism is supported by our finding that the empirical data were well described by the theoretical assumption of a single latent variable underlying performance on interval timing tasks in both the sub-second and the second range.

Nevertheless, the finding of a model, that describes the empirical data quite well, does not necessarily mean that there are no other models which describe the empirical data even better. Therefore, we tested the distinct timing hypothesis by deriving a first latent variable from the

Table 1 Mean performance scores (M) and standard deviations (SD) as well as intercorrelations for the five interval timing tasks

		M	SD	Sub-second range		Second range	
	Indicator of performance			TD2	TG1	TD3	TG2
Sub-second range							
TD1	DL (ms)	7.7	2.7	0.43 ***	0.38 ***	0.20 *	0.36 ***
TD2	DL (ms)	16.0	6.7		0.44 ***	0.36 ***	0.41 ***
TG1	Response dispersion	0.38	0.12			0.19 *	0.37 ***
Second range							
TD3	DL (ms)	118.9	42.0				0.37 ***
TG2	Response dispersion	0.37	0.13				

Note: *TD1* temporal discrimination of filled intervals in the sub-second range, *TD2* temporal discrimination of empty intervals in the sub-second range, *TD3* temporal discrimination of filled intervals in the second range, *TG1* temporal generalization of filled intervals in the sub-second range, *TG2* temporal generalization of filled intervals in the second range

*$p < 0.05$ (two-tailed); ***$p < 0.001$ (two-tailed)

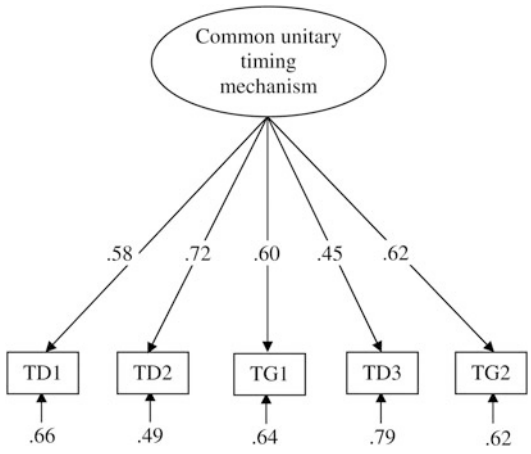

Fig. 3 Results of the common timing model (Model 1) with the assumption of one common latent variable underlying individual differences in all five interval timing tasks irrespective of interval duration. The model fit indices suggest a good model fit [$\chi^2(5) = 6.27$; $p = 0.28$; CFI = 0.99; RMSEA = 0.04; AIC = 2,396.0; SRMR = 0.03]. Presented are completely standardized factor loadings as well as residual variances of the five interval timing tasks. For abbreviations see Table 1

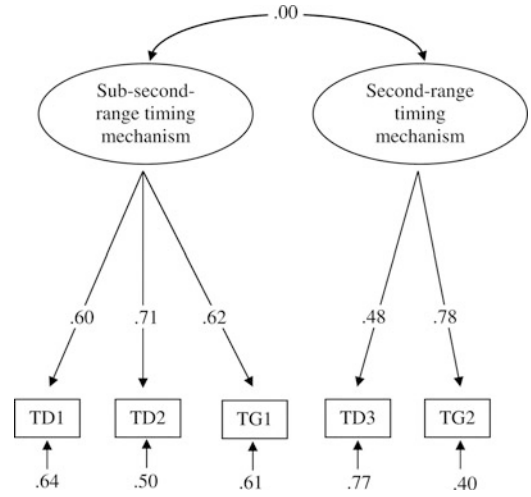

Fig. 4 Results of the distinct timing model (Model 2) with the assumption of two completely independent latent variables underlying temporal processing of intervals in the sub-second and second range, respectively. The model fit indices suggest a poor model fit [$\chi^2(6) = 42.88$; $p < 0.001$; CFI = 0.67; RMSEA = 0.22; AIC = 2,430.63; SRMR = 0.18]. Presented are completely standardized factor loadings as well as residual variances of the five interval timing tasks. For abbreviations see Table 1

three temporal tasks with stimuli in the sub-second range and a second latent variable from the two timing tasks with stimuli in the second range. Furthermore, in order to represent two *independent* mechanisms, the correlation between the two latent variables was fixed to zero (see Fig. 4). As indicated by all model fit indices, this model did not yield a sufficient fit to the data [$\chi^2(6) = 42.88$; $p < 0.001$; CFI = 0.67; RMSEA = 0.22; 90 %-confidence interval ranging from 0.16 to 0.28; AIC = 2,430.63; SRMR = 0.18]. Thus, the assumption of two distinct mechanisms underlying the processing of time intervals in the sub-second and second range

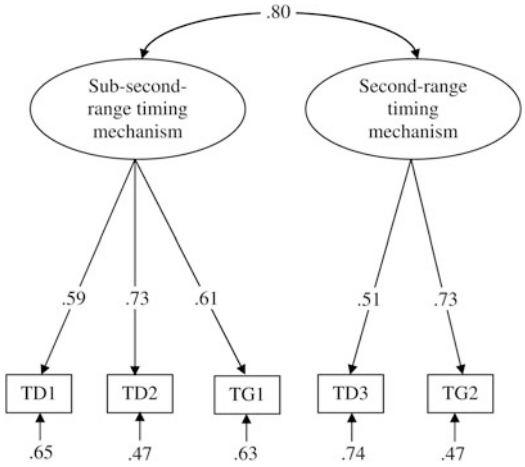

Fig. 5 Results of the third, rather exploratory, timing model (Model 3) assuming two dissociable but associated latent variables underlying the timing of intervals in the sub-second and second range, respectively. The model fit indices suggest a good model fit [$\chi^2(4) = 3.16$; $p = 0.53$; CFI = 1.00; RMSEA = 0.00; AIC = 2,394.9; SRMR = 0.02]. Presented are completely standardized factor loadings as well as residual variances of the five interval timing tasks. The correlation of $r = 0.80$ between the two latent variables is highly significant ($p < 0.001$). For abbreviations see Table 1

did not conform to the empirical data. Moreover, the AIC indicates that Model 1 is more parsimonious than Model 2 (despite more degrees of freedom in Model 2) suggesting that Model 1 describes the data better than Model 2.

It should be noted that Model 2 could only be computed when the factor loadings of the interval timing tasks in the second range were fixed. If not, the model parameters could not be estimated. This is sometimes the case if a latent variable is derived from only two manifest variables. The fact that we fixed this factor loading was the reason why the degrees of freedom of Model 2 do not equal the degrees of freedom of Model 1.

In a final step, we investigated whether temporal processing of intervals in the range of milliseconds may be dissociable from temporal processing of intervals in the second range even if the underlying processes are associated with each other. Therefore, in a third model, the correlation between the two latent variables of the distinct timing model was not fixed to zero but freely estimated. Without fixing this correlation, Model 2 turned into Model 3 which fit the data well [$\chi^2(4) = 3.16$; $p = 0.53$; CFI = 1.00; RMSEA = 0.00; 90 %-confidence interval ranging from 0.00 to 0.12; AIC = 2,394.9; SRMR = 0.02]. As can be seen from Fig. 5, this model revealed a correlation of $r = 0.80$ ($p < 0.001$) between the two latent variables. As described above, Model 3 and Model 1 are in a hierarchical relationship so that their model fits can directly be compared by means of a χ^2-difference test. This test revealed that the model fits of Model 1 and Model 3 did not differ significantly from each other [$\Delta\chi^2(1) = 3.11$; $p = 0.08$]. The AIC value of Model 1, however, was larger than the AIC value of Model 3. Hence, Model 3, assuming two dissociable timing mechanisms which are highly related to each other, describes the data comparably well as Model 1 but more parsimoniously relative to the model fit and, thus, should be preferred over Model 1.

A Common Timing Mechanism or Two Functionally Related Timing Mechanisms?

In order to elucidate the internal structure of psychophysical timing performance in the sub-second and second range, we employed a CFA approach. More specifically, we investigated whether CFA would rather support the notion of a common unitary timing mechanism or of two distinct timing mechanisms underlying timing performance in the sub-second and second range, respectively. The assumption of two distinct timing mechanisms which are completely independent of each other, as represented by Model 2, was not supported by the present data. All fit indices indicated a poor model fit. On the other hand, Model 1 assuming a single common timing mechanism underlying timing performance in both the sub-second and second range did not only describe the data quite well but also better than Model 2. At this stage of our analysis, however, it would be premature to conclude that a unitary timing mechanism is the best explanation of our data. As an alternative model, we therefore introduced and examined Model 3. This model

assumes two distinct, but functionally related, mechanisms underlying timing performance in the sub-second and second range, respectively. As a matter of fact, Model 3 described the data also very well and even somewhat better than Model 1. Thus, although the correlation between the two latent variables was quite high, the comparison of fit indices indicated that the assumption of two closely associated latent variables described the observed data better than the assumption of only one latent variable.

The large portion of shared variance of approximately 64 % between the two latent variables in Model 3 can be interpreted in terms of a 'simple' functional relationship between the two timing mechanisms involved in the temporal processing of extremely brief intervals in the range of milliseconds and longer intervals in the range of seconds, respectively. Such an association may be due to some operations common to both timing mechanisms or due to 'external' factors, such as specific task demands or task characteristics (cf. [4]) that exert an effective influence on both timing mechanisms. An alternative interpretation of Model 3, however, points to a hierarchical structure for the processing of temporal information in the sub-second and second range. According to this latter account, at a first level, temporal information is processed by two distinct timing mechanisms as a function of interval duration; one mechanism for temporal processing of information in the range of milliseconds and the other one for processing of temporal information in the range of seconds. This initial stage of duration-specific temporal processing is controlled by a superordinate, duration-independent processing system at a higher level.

Empirical Findings Are Required to Validate the Findings Based on the Confirmatory Factor Analysis Approach

It is important to note that we cannot decide statistically on these two alternative interpretations of Model 3. For this reason, we will provide some empirical findings in the following that support the general validity of Model 3 and also address the two tentative interpretations derived from this model.

With the timing tasks applied in the present study, participants had to attend to the intervals to be judged, maintain the temporal information, categorize it, make a decision, and, eventually, perform a response. Although not directly involved in the genuine timing process per se, these mainly cognitive processes are essential for succeeding in interval timing independent of the range of interval duration. Therefore, it seems mandatory to take into account the involvement of cognitive processes irrespective of the interval duration to be timed. This view is consistent with the idea expressed by Model 3 that the timing mechanisms underlying temporal processing of intervals in the range of milliseconds and seconds are not completely independent of each other but may share some common processes [24, 53, 54]. The involvement of various non-temporal processes, and especially the failure to control for it across different studies, may also account for the inconsistent results obtained from the few studies applying a dual-task approach for testing the distinct timing hypothesis (cf. [4, 55]).

In a recent imaging study by Gooch et al. [56], voxel-based lesion-symptom mapping analysis revealed that the right pre-central gyrus as well as the right middle and inferior frontal gyri are involved in the timing of intervals in both the sub-second and second range. These findings are complemented by neuroimaging data from Lewis and Miall [57] showing consistent activity in the right hemispheric dorsolateral and ventrolateral prefrontal cortices and the anterior insula during the timing of both sub- and supra-second intervals. All these reports are consistent with several previous imaging (for a review see [58]) and clinical (e.g., [59, 60]) studies demonstrating that specific regions of the right frontal lobe play a crucial role in interval timing in the sub-second and second range. As these regions were activated regardless of the interval duration to be timed, these brain structures may be part of a core neural network mediating temporal information processing.

In the light of these findings, the two tentative interpretations of Model 3, outlined above, can be substantiated as follows. According to our first interpretation of Model 3, temporal information in the sub-second and second range is processed by two functionally related timing mechanisms. Both these timing mechanisms may operate largely independent of each other but draw upon some working memory processes required to successfully perform any given interval timing task irrespective of interval duration. Thus, the observed correlation between the two latent variables in Model 3 may originate from working memory functions shared by the two mechanisms underlying temporal processing in the sub-second and second range, respectively. It remains unclear, however, whether these shared memory functions can account as a single contributing factor for the strong functional relationship between the two latent variables.

Also compatible with Model 3 is the notion of a hierarchical structure of the timing mechanism. According to this account, temporal information is processed in a duration-specific way at an initial stage that is controlled by a common superordinate duration-independent component. This superordinate component can be tentatively interpreted as an overarching neural network for the processing of temporal information (cf. [61]). Most interestingly, in their most recent review on the neural basis of the perception and estimation of time, Merchant et al. [31] also put forward the idea of a partly distributed timing mechanism with a core timing system based on a cortico-thalamic-basal ganglia circuit.

At first sight, our CFA analyses clearly argued against the distinct timing hypothesis. From this perspective, a clear-cut distinction between sensory/automatic and cognitively mediated temporal processing appears to be too strict. Nevertheless, Model 3 does not inevitably rule out the existence of distinct mechanisms for the timing of intervals in the sub-second and second range, respectively. Apparently, a 'hard' boundary between a sensory/automatic and a cognitive mechanism for millisecond and second timing is unlikely to exist. Nevertheless, the assumption of a transition zone from one timing mechanism to the other with a significant degree of processing overlap [21, 53] would also be consistent with our Model 3. Within this transition zone, both mechanisms may operate simultaneously and their respective contributions to the outcome of the timing process would depend on the specific nature and duration range of a given temporal task [21, 53, 62]. If this is true, one would expect a decreasing correlational relationship between both latent variables in Model 3 when the difference is increased between the base durations of the interval timing tasks in the sub-second and second range. This is because the processing overlap should vanish with increasing dissimilarity between the base durations. To our knowledge, however, the transition zone hypothesis has not been empirically tested yet.

Conclusions

Taken together, application of a CFA approach for investigating the internal structure of interval timing performance in the sub-second and second range clearly argues against the validity of the distinct timing hypothesis that assumes two timing mechanisms completely independent of each other. Although the model of a common unitary timing mechanism fitted the empirical data much better than the model based on the distinct timing hypothesis, the outcome of our CFA analyses supported the basic idea of two *functionally related* timing mechanisms underlying interval timing in the sub-second and second range, respectively. Future research is required to identify the major constituents of both these mechanisms and to further elucidate their functional interaction.

Although CFA cannot always warrant clear-cut solutions, an extension of the traditional psychophysical methodology by incorporating a theory-driven statistical approach, such as CFA, proved to be a useful and highly feasible procedure. Let us consider Grondin's review of the literature (see first chapter) which revealed that there is actually no scalar property for timing and time perception. This finding calls for a re-examination of existing and highly popular models, such as

pacemaker-counter models or SET. In that case, statistical approaches, such as CFA, provide a promising tool for developing, testing, and validating new models even on the basis of psychophysical data already at hand.

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Neurocomputational Models of Time Perception

Joachim Hass and Daniel Durstewitz

Abstract

Mathematical modeling is a useful tool for understanding the neurodynamical and computational mechanisms of cognitive abilities like time perception, and for linking neurophysiology to psychology. In this chapter, we discuss several biophysical models of time perception and how they can be tested against experimental evidence. After a brief overview on the history of computational timing models, we list a number of central psychological and physiological findings that such a model should be able to account for, with a focus on the scaling of the variability of duration estimates with the length of the interval that needs to be estimated. The functional form of this scaling turns out to be predictive of the underlying computational mechanism for time perception. We then present four basic classes of timing models (ramping activity, sequential activation of neuron populations, state space trajectories and neural oscillators) and discuss two specific examples in more detail. Finally, we review to what extent existing theories of time perception adhere to the experimental constraints.

Keywords

Computational modeling • Weber's law • Ramping activity • Synfire chains

Introduction

Time perception is crucial to survival in many species. Environmental resources, social interactions, escape from predators, availability of prey, or simply environmental responses triggered by one's own actions, may all depend on the right timing. Predictions of events ahead often may only be useful if the relative timing of the event can be predicted as well. Despite the wealth of studies on almost all aspects of time perception, its neurobiological basis is still elusive in many regards. For instance, there seems to be no anatomically or physiologically unique and

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well-defined basis for the perception and processing of temporal information. Human imaging studies so far do not provide a very coherent picture about the brain regions involved [1], although some networks start to emerge (see fourth chapter in this book). Also, lesion and patient studies so far were unable to identify any particular "timing area" in the brain. Likewise, there is no consensus on which of the several proposed neuronal mechanisms actually underlies the perception of time.

Time perception also shows a number of features which are not easily explained from the neurobiological point of view. Among those are the well known linear relations between objective time and subjective time on the one hand (the linear psychophysical law) [2–4], and the one between objective time and the variability or error of a time estimate on the other hand (the scalar property) [2, 3, 5–7]. These relations have been established in psychophysical experiments and are reminiscent of similar relations in other modalities, such as Weber's law. However, network mechanisms in the brain are usually highly non-linear, so that it is not immediately clear how linear relationships could be implemented (the problem of the neural integrator, e.g. Seung et al. [8]). The scalar property is even more puzzling: If temporal intervals were represented by some kind of counting or integration process, as often proposed [5, 7, 9–11], noise in each of the counted elements would lead to a linear increase of the variance of the total count, and thus the time estimate. However, the scalar property requires the *standard deviation*, the square-root of the variance, to increase linearly in time. This means that the scaling of actual timing errors with interval length is much worse than would be expected from a counting or integration process. As one would assume that evolution strives for optimality in information processing, this needs to be explained. Finally, subjective estimates of duration are prone to distortion by a number of non-temporal factors [5, 12], such as attention, stimulus intensity, and various neuromodulatory systems such as dopamine [13]. The neural mechanisms of these distortions and their potential biological function are not well understood.

Mathematical modeling of neural systems is a useful tool to gain insight into potentially underlying mechanisms and their psychological implications and neurodynamical properties. Such models could provide a kind of proof of the biological feasibility of a proposed mechanism. Furthermore, they can help to achieve a deeper understanding of the neural mechanics at work by providing complete control over all systems parameters, and reveal the exact statistical properties of the mechanism. For time perception, a large number of modeling studies exist and suggest a wide variety of potential neuronal mechanisms. In fact, almost any process in the brain that unfolds in time could be a potential candidate for encoding interval durations, as reflected in this plethora of proposed mechanisms, which makes the hunt for the actually biologically employed mechanisms even more difficult.

In the following, we first provide a brief overview over the history of computational timing models and define a number of constraints both from psychological and physiological experiments which can be used to assess the validity of a given timing model. One of the most often used criteria is the dependence of the magnitude of timing errors on the length of the estimated interval, which is often found to scale linearly with time (Weber's law). In the fourth section, we summarize results which may allow to assess whether a given timing model may be able to reproduce this scalar property or another form of error scaling, even without performing the corresponding simulations or knowing all the details of its implementation. The fifth section will then deal with various neurocomputational models of time perception, focusing on our own work [14, 15], and finally, we discuss how these are consistent with the constraints named above and current neurobiological knowledge.

A Brief History of Computational Models of Time Perception

The first mathematical models of time perception appeared in psychology as an attempt to explain the results of psychophysical experiments. These

information-processing models are meant as a mathematical description of the data and do not necessarily have any direct connection to neuronal processes. Among the first formalized ideas where the so-called "pacemaker-accumulator" models, introduced in the early 1960s by Creelman [11] and Treisman [16]. Creelman reproduced the limited performance in discriminating two intervals of slightly different duration by assuming a series of random pulses with a fixed frequency (the pacemaker), which are counted (accumulated) to form an estimate of time. Treisman used the same basic mechanism, but assumed an oscillator as pacemaker and offered a more complete model structure including processing stages for storing and comparing the intervals. Elements from both models were repeated, mixed and refined in a large number of subsequent pacemaker-accumulator models (see e.g. Grondin [5] for a review). By far the most popular variant is the "scalar expectancy theory" (SET) by Gibbon [7]. He formalized each processing stage according to its possible source of variance and introduced a scalar component that lead to timing errors that increase linearly with time (Weber's law, or the "scalar property"). SET quickly became the standard model in the animal timing literature [2], and later also for human time perception [2, 10]. Fifteen years after introduction of the pacemaker-accumulator models, Jones [17] proposed a fundamentally different information-processing model of time perception, which was more focused on the interaction of the sense of time with the external world and other sensory modalities. This model also constantly developed and is now known under the name of "dynamic attending theory" (DAT) [18]. It assumes a set of oscillators with frequencies that can be adapted to rhythms or other temporal cues in the external world. Rather than counting the revolution of these oscillators, the adapted frequency of the oscillator itself is used to encode the temporal information. Dynamic attending theory is still popular for the analysis of human responses to sequences and rhythms [19].

Along different lines, a number of theoretical advances [20] led to a renaissance of the field of *artificial ("connectionist-type") neural networks* during the 1980s. These models consist of a set of simple processing elements which are connected through synapse-like edges with variable weights. Although the equations describing these systems are fairly simple, they can emulate universal Turing machines with the corresponding computational power, given certain structural assumptions like recurrent links, and nonlinear input/output functions. In the context of temporal processing, connectionist networks have first been used to model the circuits in the cerebellum and the hippocampus underlying conditioned responses [21–23]: In a conditioning experiment, the interval between the conditioned and the unconditioned stimulus must be bridged in order to elicit the conditioned response at the correct time. Thus, these models can also be viewed at as implicit models of time perception. In this context, a guiding hypothesis was that time perception is realized by so-called delay lines, i.e. a neural signal traveling along a series of synaptic links, each of which induces a delay, such that the time elapsed can be encoded as the spatial position of the signal. This basic principle seems to hold, for instance, in the auditory system of barn owls, which use the submillisecond delay between signals from both ears to localize the spatial source of a sound [24]. In addition to connectionist-style models of conditioning, there were also more explicit attempts to translate existing information-processing models of time perception into a neural network formalism [25], as well as completely new ideas based on the unique properties of neural networks, such as the beat frequency model by Miall [26] (see section "Time Perception from Oscillators" below and Chapter 2.2 for more information).

In the 1990s, driven by accelerating advance in both neurobiology and computer power, it became possible to simulate *biophysical models* which had a structure similar to that of artificial neural networks, but were directly based on physical equations for describing voltage and current dynamics in neurons and synapses. Buonomano et al. pioneered detailed, biophysics-based simulations of the cerebellum (including conditioning experiments with time delays of several hundred ms [27]) and cortical

network models including synaptic short-term plasticity which enabled interval discrimination in an emergent and natural fashion (i.e. without much parameter tuning) [28, 29]. During the following years, a large number of neural timing models—both of the biophysical and connectionist type—were advanced, exploring a wide range of potential biological mechanisms, which range from properties of single neurons [30], neural oscillators read out by coincidence detectors [31] to reverberating loops within the cerebellum [32, 33], slowly climbing activity in neocortical neurons [14, 34], synfire chains [15, 35] and stochastic decay of memory traces [35].[1]

In parallel to the advances in neurocomputational modeling, psychological theories of timing also flourished. The scalar expectancy theory was on peak of its popularity, "probably the most widely cited model of time perception during the 1990s" [5], and still other information-processing models were proposed to challenge SET's success, such as the behavioral theory of timing [38] or pacemaker-free approaches [39]. In the 2000s, the number of models and experimental findings grew further, and the different fields and modeling approaches of time perception in psychology and in neuroscience slowly began to converge. To name but a few examples: The connectionist model by Miall [26] was embedded in a neuroanatomal architecture of striato-cortical circuits proposed by Matell and Meck [31], and implemented sources of variability as in SET. The concept of the delay line was implemented in spiking neuronal networks called synfire chains [15, 35] and analyzed in terms of timing errors. And the biophysical state-dependent network by Buonomano [29] was tested in a series of psychophysical experiments [40]. This trend of merging the different fields still continues to date, up to a point where models can be directly tested by experimental findings from both fields.

Experimental Constraints on Time Perception Models

Experimental work has unraveled a couple of psychological and biological constraints candidate mechanisms of time perception should obey to. On the biological side, besides the general requirement that the mechanism should be biophysically feasible and physiologically reasonable, it should account for the pharmacological modulation of time perception. Temporal processing can be strongly altered by drugs, such as agonists and antagonists of dopamine and acetylcholine receptors [13]. For instance, animal and human studies have shown that the duration of a temporal interval is perceived as longer under the influence of D2 receptor antagonists, implying a slow-down of the internal clock [41, 42], while intervals are perceived as shorter under D2 agonists, as if the clock would speed up. Such drug effects may be explained by neurocomputational models constructed with sufficient biological detail.

On the psychological side, the following three constraints are to be named:

1. **Linear psychophysical law:** Psychophysical laws describe how the subjective magnitude of a stimulus feature changes as a function of the physical magnitude of that feature. In time perception, it relates subjective time to physical or objective time. A large number of experiments have shown that this relation is best described by a linear function [2–4].
2. **Scalar property of timing errors:** Similar to the psychophysical law, one can also relate the standard deviation of a duration estimate (measured either directly by the variability of response times, or e.g. by the just noticeable difference between two similar intervals) to the real duration. Most often, this relation has been found to be linear, refereed to as Weber's law of time perception or the scalar property [2, 3, 5–7].[2] However, deviations

[1] All these models deal with the perception of single temporal intervals in the subsecond to minutes range. See [29, 36] for extensions to sequences of intervals, and [37] for longer and shorter durations.

[2] More precisely, the scalar property requires that the entire distribution of a time estimate scales with the physical duration, i.e. it also includes the linear psychophysical law.

from linearity have also been reported [2, 3, 5, 43]. In particular, the increase of the timing errors with duration is supra-linear (e.g. with the square or cube of time) for longer intervals [44–46] and sub-linear for shorter ones (e.g. with the square-root of time) [46].

3. **Modulation by non-temporal factors:** The subjective duration of an interval can be influenced by a number of stimulus features unrelated to interval duration itself, and by the current state of the brain [5, 12, 47]. For instance, intervals are overestimated if they are signaled by stimuli that are large, intense, or moving. Other factors that modulate subjective duration are attention, arousal or the position of a stimulus within a sequence.

Ideally, a neurocomputational model of time perception should not only be consistent with these constraints, but should actually be able to explain how they evolve from the underlying biophysics or network mechanisms. As the scalar property has often been highlighted as the most fundamental of these psychophysical constraints, we will start below with some theoretical, statistical considerations on it.

The Scalar Property and Its Relation to Basic Mechanisms of Time Perception

The scalar property is a recurring result in experiments on time perception and, as noted above, is not trivial to explain in neuronal terms. Many models of time perception have attempted to reproduce it. While some models just explicitly incorporated a source of scalar variance, thus not really explaining its origin, others directly aimed to provide a mechanistic explanation. Often, these mechanisms are only revealed by a thorough understanding of the underlying mathematics. The fact that there are some models that are intrinsically able to reproduce the scalar property and others which do not, raises the question of whether this former class of models has some common features that separates it from the latter. Moreover, empirically, the scalar property has been reported to hold not universally, but both error scalings that are supra-linear or sub-linear have been reported as well. Supra-linear increases predominantly occur at longer time scales, while sub-linear scaling is most often seen at shorter times. Almost no model of time perception is able to reproduce both of these deviations (but see [15, 39]), but for our understanding of the underlying biophysical and physiological mechanisms, the existence of different error scalings may be highly important and revealing.

The problem of explaining the scaling of timing errors is an intrinsically stochastic one, so it seems appropriate to interpret the mechanism underlying time perception as a stochastic process. A stochastic process can be loosely defined as a random variable (e.g. a neuron's firing rate) that evolves in time according to some rule that may be given purely in probabilistic terms (as, e.g., in a Markov chain) or may be formulated as a recursive or a differential equation that includes a probabilistic (noise) component. Hence, successive values will be defined by some (conditional) probability distribution rather than being determined strictly deterministically. In the brain there are many sources of intrinsic noise (such as thermal fluctuations, ion channel noise, or stochastic synaptic release) as well as noise introduced by the unpredictable nature by which environmental inputs may impinge on us. Thus, quite naturally, various noise sources could affect the neuronal processes of interval time estimation. In many models, noise is a pure nuisance qua definition, a factor that limits precise and accurate information processing. However, it has also been proposed that noise may play a potentially beneficial role [48], e.g. in the detection of weak stimuli (termed stochastic resonance) [48–50] or decision making [51]. In time perception, noise itself may also be an actual source of temporal information. As an example, consider the task of estimating time from the motion of all ink particles in a drop of ink. One way to do this would be to let the drop run down a sloped surface. On average, all ink particles move in the same direction in this case, so a good estimate of time could be derived from the mean distance the whole drop has passed, given knowledge of how fast it moves. Of course, not

all of the particles will move at the same speed, and because of this variability, there will also be a certain variability in the estimate of time. A fundamentally different way to measure time using the ink is to put the drop into a large pot of water and to observe the diffusion of the ink particles. Over time, the radius of the inky spot will increase, while the concentration of ink at the center of the spot decreases, so both of these quantities could be used to estimate the passage of time. In this case, however, on average the particles do no move at all, as on average the center of the spot will stay where the ink was injected. Rather, it is the variance that increases over time and which carries the temporal information.

In a similar manner, noise and variability naturally occurring in neuronal systems may be exploited to decode the duration of an interval. This raises the question of how the quality of this encoding can be quantified, and compared with the alternative encoding of time in the systematic changes of the mean. One way to measure this is the Fisher information, which quantifies how much information the system contains regarding one of the parameters p of the probability distribution $P(x, p)$ that underlies the stochastic process, such as the time.

Importantly, this information measure can be directly related to the variability of an estimator of interval time, which can be any quantity derived from the stochastic process (such as diameter of the ink spot in the example above) from which the time estimate can be directly read off. A mathematical theorem states that the variance $Var\left(\hat{t}\right)$ of such an estimator $\hat{t}$ can never fall below a lower bound

$$Var\left(\hat{t}\right) \geq \frac{1}{I_F(t)},$$

where $I_F(t)$ is the Fisher information of the time t. This so-called Cramer-Rao bound restricts the precision of any estimator of time, no matter which exact mechanism it relies on or which process it was derived from. Now, as the brain is a system under constant evolutionary pressure, one would expect that it is geared towards extracting as much information about the external world as possible, and to optimize information transfer [52, 53]. If this is true for time perception as well, then the above theory says that the optimal (lowest variability) estimate of interval time is given by the Cramer-Rao bound. Thus, timing errors observed in psychophysical experiments should follow the same functional form as computed by the Cramer-Rao bound.

In Hass and Herrmann [54], we computed the Cramer-Rao bound for an important class of processes, namely those with a Gaussian probability distribution, and compared the results to those from experiments and neurocomputational models. We assumed that the variance of these processes increases linearly in time. The assumption of this particular form of variance increase over time is justified whenever the timing process relies on some kind of counting or integration (see above).[3] Three different principle ways of time estimation were considered: First, temporal estimates can be based on the mean (systematic) changes in a process, like gradually rising activity. This is by far the most commonly suggested approach in both psychological and neurocomputational models of time perception. Under the assumption that the mean of the process increases linearly with time, as it is implied by the linear psychophysical law, we found that the timing errors (standard deviation of the estimate) increase like the square root of time. Such a scaling was also generally observed in the corresponding neurocomputational models, unless specific assumptions were deliberately put in to change the scaling. Second, we considered estimates based on linearly increasing variance of the process. Such an estimate can be easily obtained by dividing the observed variance at a given time by the variance observed at the start of the interval. For such an estimator, we found the scalar property to hold exactly, with a slope that does not depend on the parameters of the model. It is important to note that this does not trivially follow from the linearity of the

[3] Furthermore, it is required that the temporal correlations of the process decay to zero for sufficiently long times.

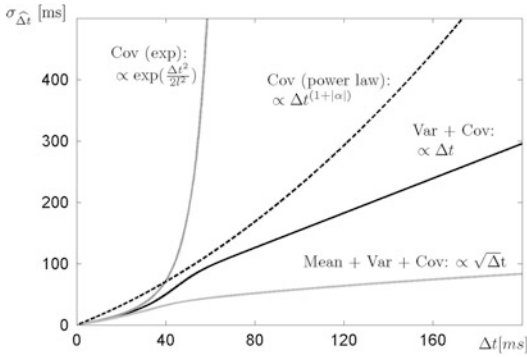

Fig. 1 Comparison of the minimal standard deviations of estimators of interval duration based on different sources of temporal information. All *solid lines* show processes with exponentially decaying correlation. *Dotted line*: Power-law correlation information only. *Solid gray line*: Exponential correlation information only. *Upper solid black line*: Correlation and variance information combined. *Lower solid gray line*: Correlation, variance and mean information combined. For long enough intervals, the error function is well approximated by the respective functional expressions. Reprinted with permission from Hass and Herrmann [54]. Copyright 2012 by the Massachusetts Institute of Technology

increase in variance, as we consider the *standard deviation* (square root of variance) of the estimate. For a mean-based estimator, the very same variance increase leads to a sub-linear scaling of timing errors. Finally, the third option considered was to estimate time from decaying correlations. Just as the variance in a noisy system increases over time, the correlation (e.g. among two spike patterns) will decay over time, unless specific mechanisms are in place to counteract this tendency. Thus, the amount of correlation present at a given time can also be used to estimate the passage of time [55]. We found that irrespective of the exact form of the correlation function, the increase in timing errors is steeper than linear (rather than linear, as claimed in Ahrens and Sahani [55]). Figure 1 shows two examples with an exponential and a power-law decay in correlations, both resulting in the same error scaling, and for comparison also the scaling for the mean- and variance-based estimators. When there are different sources of temporal information in a single process, combining them (e.g. in a maximum-likelihood estimator) may increase the precision of the estimate, but there is a hierarchy of temporal information conveyed by the process in the sense that mean-based estimators always dominate over variance-based ones, and variance-based estimators dominate over those relying on decaying covariances. These results still hold when several different processes are combined to generate a joint estimate of time, as it is likely the case in the brain.

This analysis has at least two interesting implications. First, using a time estimate that relies on the intrinsically stochastic features of a process, namely the variance increasing over time, is the only way for the scalar property to hold exactly (given the assumptions made). Although this was not explicitly stated in all of the neurocomputational studies in which the scalar property holds [34, 35, 56–59], a closer look at the proposed mechanisms indeed strongly suggests variance-based estimates [54]. Second, both supra-linear and sub-linear scaling of timing errors can result from fundamentally different types of estimators, based on correlations or on means, respectively. Potentially, the experimentally observed transitions among different scaling regimes (see above) are due to changes in the type of estimator used by the nervous system.

Neurocomputational Models of Time Perception

As mentioned above, there is a large number of modeling studies on time perception exploiting a vast variety of neuronal mechanisms. Here, we focus on those four currently most frequently discussed (Fig. 2), and review two of them in more detail (ramping activity and synfire chains), while for the other two (oscillator models and state space trajectories), we will just briefly discuss the experimental evidence in terms of the constraints introduced above.

Time Perception from Slowly Ramping Firing Rates

One class of models assumes that interval time estimates are derived from neural firing rates slowly ramping up or down during the interval to be encoded, and reaching peak activity when

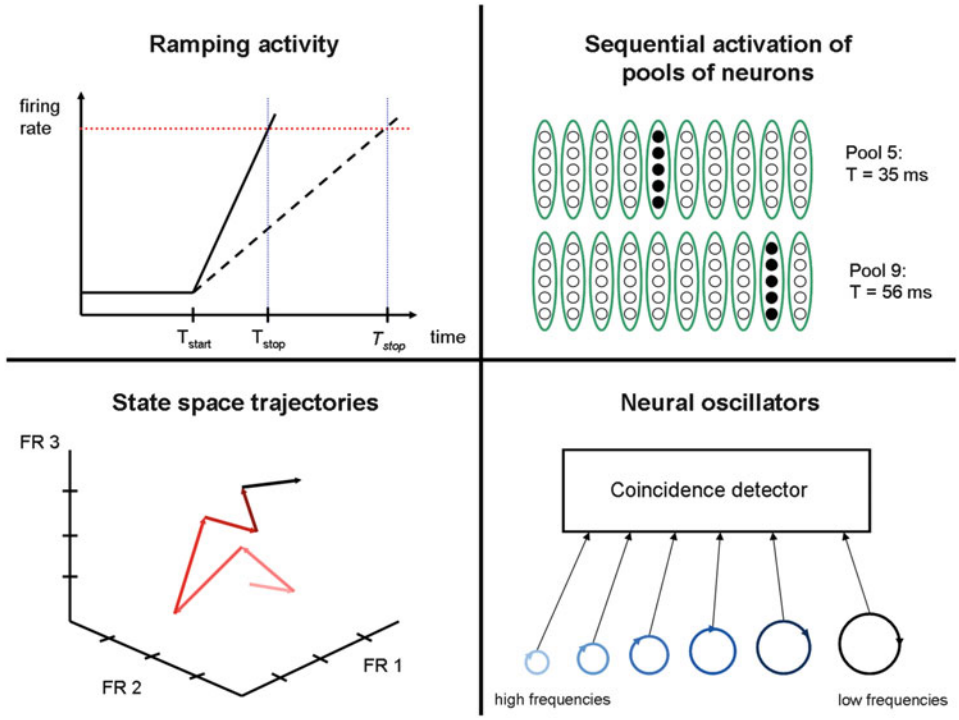

Fig. 2 Overview over four principle mechanisms of time perception that are currently supported by experimental evidence. See text for details

the to be estimated interval is about over [14, 60]. This kind of ramping or climbing activity has frequently been observed in in-vivo electrophysiological recordings from various cortical areas [61] such as the motor and premotor cortex [62, 63], lateral interpariatal cortex [64], SMA and preSMA [65] and PFC [66–69] (for more details, see section "Experimental Evidence for the Ramping Activity Model" below). To represent and read out different interval times, one may either adjust the slope of ramping activity to the interval to be estimated, such that after that time always a fixed threshold activity is reached which triggers a response in postsynaptic neurons, or downstream neurons or networks may be tuned to specific firing rates of the ramping neuron population. Both mechanisms may be combined of course. Adjusting the slope of climbing activity may be necessary in any case, however, since the range of firing rates of cortical neurons as well as the sensitivity to firing rate changes are limited, so that it would be advantageous to adapt the rate range dynamically to the set of interval times to be represented (as supported by experimental data, see below). Downstream neurons may also reset activity in the ramping neurons once the threshold (and thus the temporal interval) has been passed [14]. Ramping activity as observed experimentally has several properties that are not trivial to explain. Foremost, ramping activity can stretch over tens of seconds, which seems incompatible with many of the much faster biophysical time constants which govern electrical activity in recurrent cortical networks. Furthermore, ramping often is surprisingly linear [62, 65, 69, 70], and, as already noted, its slope seems to adjust to observed temporal intervals [60, 67, 69, 70].

One model that implements interval timing through adjustable ramping activity rests on a single cell positive feedback loop between spiking activity, spike-triggered Ca^{2+} influx, and Ca^{2+}-activated depolarizing (inward) currents [14], that slowly drives the cell from a low towards a high steady firing rate.

The mathematical model [14] contains only those biophysical ingredients essential for explaining the phenomenon at the spiking level.

It consists of a so-called leaky integrate and fire (LIF) unit where changes in membrane potential V are governed by a single differential equation

$$C\frac{dV}{dt} = g_L(V - E_L) + I_{\mathrm{AHP}} + I_{\mathrm{ADP}} + I_{\mathrm{ext}}. \quad (1)$$

This equation reflects a passive membrane circuit, with a membrane capacitance C in parallel to a leakage conductance g_L (representing always open ion channels) and a battery E_L (representing the passive resting potential to which the cell would relax in the absence of any other currents), to which three active current sources were added. These are I_{ext} which describes an external input to the neuron, mediated either by synapses or direct current injection through an electrode, an after-hyperpolarizing (AHP) current which ensures a realistic refractory period after a spike was triggered, and a calcium-dependent after-depolarizing (ADP) current as it has been described in pyramidal neurons [71, 72]. This simple neuron model does not contain voltage-dependent sodium and potassium channels which are usually responsible for the generation of action potentials in real neurons. Instead, a fixed threshold potential V_{th} is defined, and whenever the voltage crosses this threshold from below, a spike is recorded and the voltage is set to a reset value V_{r}. In agreement with empirical observations [73], each spike triggers a fixed amount of Ca^{2+} influx which then exponentially decays in time. Calcium influx in turn activates the ADP current

$$I_{\mathrm{ADP}} = g_{\mathrm{ADP}} m (V - E_{\mathrm{ADP}}) \quad (2)$$

which depends on a Ca^{2+}-dependent gating variable m which gives the proportion of open channels (or the opening probability) between zero and one. The Ca^{2+}-dependent gate m is governed by another differential equation

$$\tau_{\mathrm{ADP}}\frac{dm}{dt} = m_{\mathrm{inf}}\left(\mathrm{Ca}^{2+}\left(t - t_{\mathrm{sp}}\right)\right) - m. \quad (3)$$

m relaxes to a steady-state value m_{inf}, which depends on the cellular calcium concentration. As the reversal potential E_{ADP} of this current is far above spiking threshold (+35 mV [72]), opening this channel causes a depolarization of the cell, leading to further spiking activity, which in turn leads to further Ca^{2+} influx, and so on. Hence, once activated, this positive feedback loop will drive the cell towards higher and higher firing rates, up to a point where it is exactly counter-balanced through negative feedback loops given by the hyperpolarizing currents I_{leak} and I_{ADP} as well as inhibitory synaptic feedback (not further discussed here). This point at which the different positive and negative feedback loops and thus current sources are exactly in balance, is called a stable fixed point of the system, and corresponds to steady self-maintained spiking activity with a rate that depends on the different cellular parameters. Thus, once the cell is activated beyond a threshold that gets this positive feedback loop between spike-triggered Ca^{2+} influx, Ca^{2+}-activated ADP currents, and ADP-driven spiking, started, it will usually quickly approach this stable fixed point corresponding to persistent spiking activity. This transition is usually quite fast, on the order of the time constants of the cell membrane and the conductances of the involved ion channels, hence leading to a quick ramping-up of activity.

To examine the dynamics of the transition to the stable firing state in more detail, it is instructive to plot the instantaneous firing rate f (i.e. the inverse of the interval between two spikes) against the ADP current <ADP> averaged over this interval. In this so-called phase plane, the steady state is a point given by a pair of values (f_0, $<\mathrm{ADP}>_0$) which will remain constant once this state has been reached. This point is also defined by the intersection of two curves in this plane, the so-called nullclines (Fig. 3). The f nullcline is the set of all points at which the net change in firing rate becomes exactly zero, while the <ADP> nullcline is the set of all points at which there is no change in average ADP current anymore (consequently, the fixed or steady state point is exactly the point where both these quantities do not change anymore, as given by their intersection). Another way to put this is to note that the f nullcline gives the average amount of ADP current for each level of firing rate f needed to maintain exactly that particular rate,

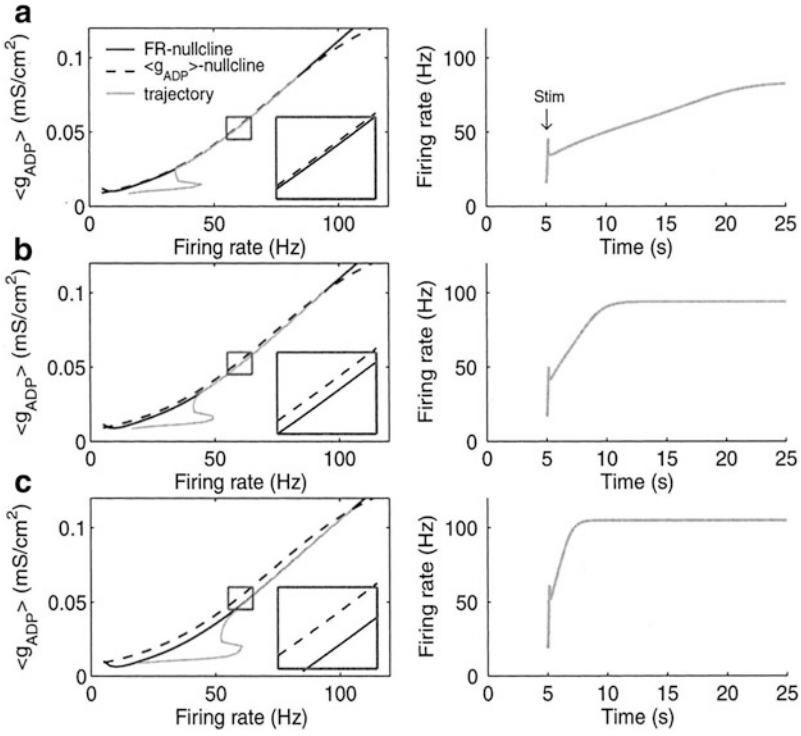

Fig. 3 Ramping activity in a single cell model based on a positive feedback loop [14] for three different configurations of the nullclines. *Left*: State space spanned by the instantaneous firing rates (FR) and the g_{ADP} conductance averaged over one inter-spike interval, including the FR nullcline (*dashed*), the <ADP> nullcline (*solid black*) and the trajectory that the system takes through the FR/<ADP> space when briefly excited by external inputs. *Right*: Time course of the firing rate for each configuration. The small bump at the beginning results from the brief initial stimulation. Modified from Durstewitz [14] with permission (Copyright 2003 by the Society for Neuroscience)

while, vice versa, the <ADP> nullcline represents the amount of average ADP current that is produced at a given firing rate *f*. Thus, wherever these two curves meet, demand and supply of ADP current are in perfect balance, and the system remains at that state if unperturbed.

A special situation arises when the parameters of the model are configured such that the two nullclines lie on top of each other for a larger range of firing rates. In this case, rate-driven ADP activation and ADP-driven spiking activity are in balance over a whole range of rates, resulting in a continuum of fixed points which is called a line attractor [8, 74, 75]. Thus, the system is able to maintain a range of steady firing rates and, in the absence of further perturbations, will remain at the rate at which it has been put by some input. However, if the overlap between the nullclines and thus the balance between ADP current supply and demand is slightly disturbed, the continuum of fixed points breaks down leaving a narrow corridor between two flanking fixed points through which activity can rise again, i.e. this cellular system, once pushed beyond some threshold, will move again towards the upper fixed point (Fig. 3, left panels). The essential feature of this system now is that the speed of ramping activity, i.e. the rate of change in firing rate, is determined by the distance between the two nullclines: As the system is still very close to the completely balanced line attractor configuration, at each firing rate the ADP input will only be a tiny little more than what would be needed to maintain this rate, so firing rate will increase

only slowly. In other words, the width of the corridor in Fig. 3 (left panels) defines an effective time constant, given through the system's dynamic, which can be many orders of magnitude longer than any of the system's biophysical time constants, and which will vary as the distance between nullclines is varied. Thus, the result is a slow ramping of firing rates as seen in the electrophysiological experiments (Fig. 3, right panels).

It is important to emphasize that the speed of the transition, i.e. the slope of ramping activity, and thus the length of the intervals that can be encoded depends directly on the amount of imbalance between ADP demand and supply, or in other words, the mismatch between the two nullclines: The smaller the imbalance, the slower the transition. In this manner, at least in principle, arbitrarily slow ramping could be achieved if the difference between the two nullclines becomes arbitrarily small over a large range of firing rates. On the other hand, if the nullclines are very far apart (Fig. 3, lower left panel), the transition is as fast as the internal time constants of the neuron would permit (Fig. 3, lower right panel).

One way to systematically manipulate this mismatch between f and <ADP> nullclines, thus regulating the slope of ramping activity, is to change the amount of input into the neuron: The higher this input, the lower the ADP input needed to maintain a given rate. This could be achieved either through changing synaptic input from another group of neurons which thus regulates the slope of ramping activity, or through synaptic plasticity within the circuit of the ramping neuron itself (which could be driven by a temporal difference error signal for instance, see [14] for details).

The question remains how the parameters of a real neuron could be adjusted such that the two nullclines are almost in parallel over a wide range of firing rates, which is a prerequisite for ramping activity. One possible way to achieve this is by means of a self-organization process that monitors long-term fluctuations of the calcium concentration: In a line-attractor configuration, noise-induced fluctuations tend to be large as along the line there is no force opposing fluctuations (i.e., movement along the direction of the line attractor can be conceived as "friction-free"). Hence, the system could potentially drive itself into a line attractor configuration by adjusting its parameters (here, the steepness of the <ADP> nullcline) such that the variance in calcium concentration is maximized.

Finally, another issue concerns how the slope of the timer could be adjusted to observed intervals. Figure 4 outlines a potential self-organizing mechanism based on an underlying network oscillation and spike-timing dependent synaptic plasticity (STDP). STDP is an experimental phenomenon where the direction and magnitude of synaptic long-term changes depend on the precise timing of the pre- and postsynaptic action potentials (first described by Markram et al. [76], reviewed e.g. in Bi and Poo [77]): A presynaptic spike preceding postsynaptic spiking will lead to long-term potentiation (LTP), i.e. an increase in synaptic plasticity with a magnitude depending on the precise temporal differences between the spikes as illustrated in Fig. 4a, while if, vice versa, the presynaptic spike follows the postsynaptic spike in time, long-term depression (LTD) will result. Hence, STDP formally obeys the ideas of Hebb [78] that neurons which contribute to the spiking of other neurons should increase their synaptic weights to those neurons, while if this "causal order" is reversed, the weight should be diminished. Now the key idea of Fig. 4 is that an underlying network oscillation translates the firing rates of a ramping neuron, encoding estimated time, and an "indicator neuron", encoding the actual occurrence of an event, into a spike time (phase) difference. Neurons firing at higher rates will spike earlier during each cycle of the network oscillation (an idea also common to hippocampal place coding by phase, e.g. Buzsáki and Draguhn [79]). Hence, if timer activity ramps up too slowly compared to the actual event time, the activity of the event indicator neurons will be higher than those of the timer neurons. Consequently, the indicator neurons will lead the timer neurons in phase during each oscillation cycle, and thus, synaptic

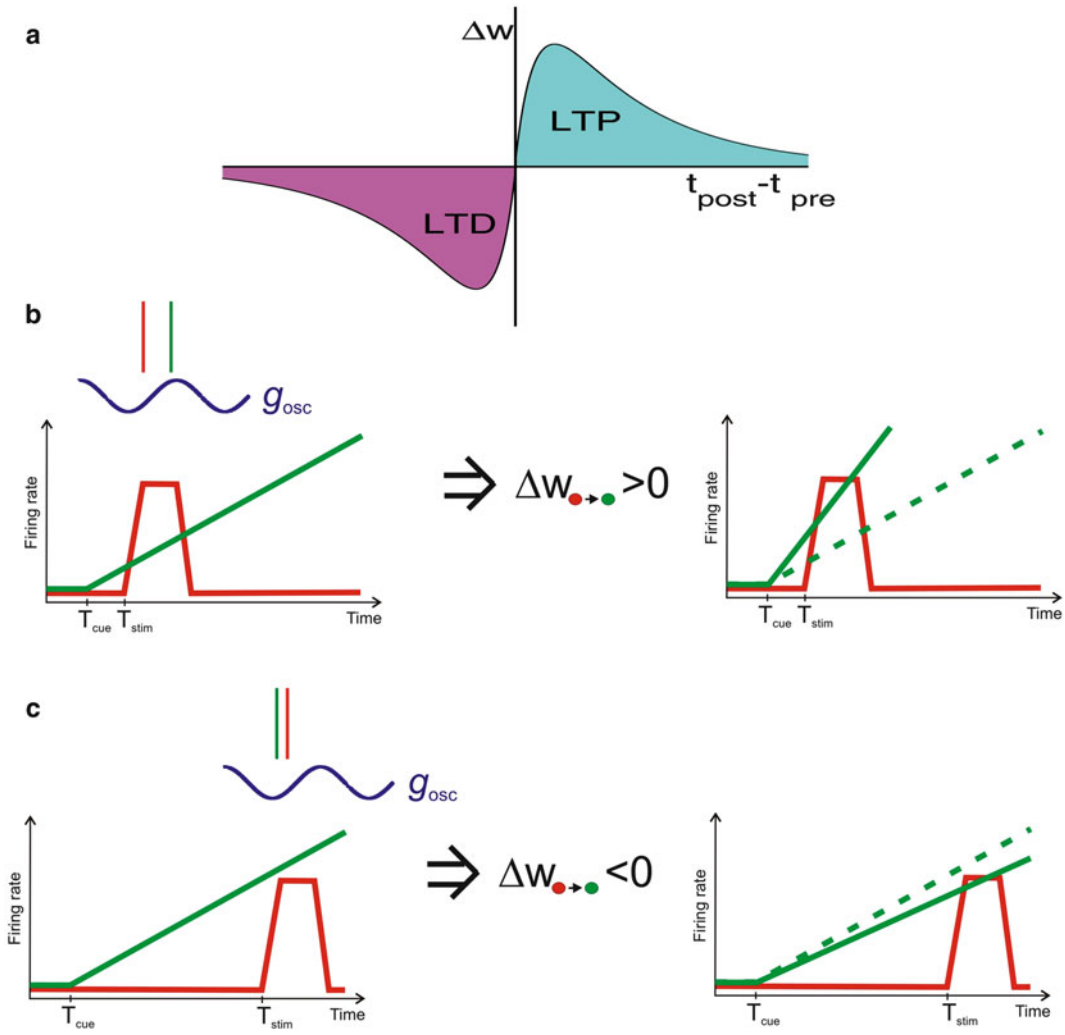

Fig. 4 Putative biophysical mechanism for adjusting the slope of ramping activity to observed intervals. (**a**) Spike-timing dependent synaptic plasticity (STDP) as observed in slice recordings: Direction and magnitude of the synaptic change depend on the precise time difference between the presynaptic (t_{pre}) and postsynaptic (t_{post}) action potential. (**b**) *Left*: An underlying network oscillation translates the differences in firing rates between a ramping (timer) neuron (started at T_{cue} by a cue) and an event-indicator neuron (firing at T_{stim} upon presentation of a stimulus) into a phase (spike time) difference within each oscillation cycle, as indicated in the inset. *Right*: This in turn will be converted by STDP into a proper synaptic efficiency change. (**c**) Same as **b** for a situation where ramping activity peaks too late compared to the actual event time

weights from the indicator to the timer neuron will increase due to the STDP rule, providing more synaptic drive and leading to a speed-up of ramping activity (Fig. 4b). Conversely, if timer activity ramps up too quickly and hence the timer neuron fires more than the event indicator neurons at the time of occurrence, the spike order between the two will be reversed during each oscillation cycle, and consequently STDP will translate this into depression of the respective synaptic weight to the timer neurons, slowing them down again. Only if the slope of ramping activity is properly adjusted, firing rates of timer and event-indicator neurons will be similar, and synaptic changes will be balanced.

Experimental Evidence for the Ramping Activity Model

As already noted, ramping activity is common in many cortical and sub-cortical structures, in fact providing the initial motivation for the above model. In addition, in some studies this kind of slowly ramping activity has indeed been observed to adjust to the temporal interval between a predicting cue and a sequent reward [60, 67, 69, 70]. EEG studies have revealed a similar phenomenon, the so-called Contingent Negative Variation (CNV). This component also ramps up during time perception tasks, and the slope of the increase is correlated with behavioral performance [80, 81]. The CNV originates from the median fronto-central region (FCz), most likely from the SMA, consistent with results from fMRI studies [81, 82]. Furthermore, the single neuron model was based on biophysical ingredients known to be present in many cortical pyramidal cells. In particular, the ADP current (also termed I_{CAN} [83]) which is central to the model has been demonstrated to be involved not only in single cell persistent activity [71], but in fact could establish a whole range of stable firing rates in single neurons [84] as predicted by a line attractor configuration (although other dynamical mechanisms for this phenomenon have been proposed as well, see Fransén et al. [85]). Furthermore, we recently re-analyzed the model with regards to dopaminergic modulation. According the current electrophysiological literature, the activation of D2 receptors caused a decrease of both inhibitory and excitatory conductances, but the decrease is much stronger in the GABAergic, inhibitory ones. The result is a net increase of the synaptic input to the model neuron, which shifted the firing rate nullcline downwards [86]. As a result, the gap to the ADP nullcline increases, and the high-rate fixed point is reached faster, consistent with the experimentally suggested speed-up of the internal clock [13, 41, 42]. Vice versa, inactivating the D2 receptors has the opposite effect. Of course, this finding strongly relies on the relative magnitude of the attenuation of excitatory vs. inhibitory conductances, and it should be pointed out that the literature on this is still quite scarce.

In summary, the model is quite well supported regarding its neurobiological substrate. With regards to the psychophysical support for the model, Fig. 3 shows that the firing rates increase roughly linearly with time, at least far away from the fixed point. Thus, assuming that temporal intervals are encoded by firing rates reasonably below the fixed point, a linear psychophysical law is approximately reproduced. The scaling of timing errors was not analyzed for this model so far, but from the information-theoretical analysis in fourth section one may infer that it should be a square-root function in time, as the interval estimation is clearly based on the deterministic (mean-based) ramping of the firing rates. Thus, the scalar property would not hold for this model without additional assumptions. However, it is conceivable that for very small differences between the nullclines (yielding longer transition times), the drift towards the upper fixed point is more and more dominated by noise in the system rather than by the systematic driving force. In this case, the estimator could effectively become variance-based and thus reproduce the scalar property. Another possibility is that it is not so much the current value of ramping activity that transports the interval estimate, but the adjustable slope and ultimately the read-out by postsynaptic neurons once a fixed threshold is reached (see above). In this case, shorter intervals would be estimated by timer neurons with a wider gap between their g_{ADP} and firing rate nullclines, reducing noise-induced variation as the flow towards the fixed point is stronger. Conversely, longer intervals would be estimated by timer neurons with a small gap between nullclines, leading to larger noise-induced variation. These additional mechanisms may change the usual square-root scaling for mean-based timers.

Time Perception from Synfire Chains

Another principal mechanism for time perception is the traveling of neuronal activity along a chain of neural groups, each of which

representing a specific temporal interval such that traveling time directly translates into an interval time estimate (Fig. 5, right panel) [15, 35, 87]. Hence, in the simplest scenario, pools of neurons would be chained through feedforward synaptic connections, so that each pool in the set would activate its successor pool. There is, however, an important problem with such a straightforward solution: For such a chain of neuronal pools to work as a reliable timer, on the one hand it must be ensured that each pool provides sufficient synaptic activation to make neurons in the next pool fire. If this fails only for a single pool, the chain is broken and time estimation would break down. Importantly, in this case, as the length of interval time increases, a complete failure in the ability to estimate that interval would increase in likelihood as the number of pools through which activity has to pass successfully (i.e., the chain length) increases with time. However, this is not observed experimentally and also contradicts our everyday experience.[4] One the other hand, synaptic connections among pools should not be too strong either, such that runaway excitation throughout the network is prevented. It turns out that for a specific chain-like network architecture, called a synfire chain (Fig. 5, left panel) [89], there exists a stable state that is characterized by the stable propagation of synchronous activity packages. Synchronous spiking is assumed to be particularly efficient in driving postsynaptic neurons as coincident input from many synapses tend to elicit a much larger excitatory postsynaptic potential than if these inputs were smeared out in time. A key feature of the synfire chain is a strongly converging and diverging connectivity, i.e. each neuron in one pool projects onto many other neurons in the subsequent pool (divergence) and also receives connections from many neurons in the preceding pool (convergence), such that small deviations in spike times tend to be averaged out by the multiple synapses. It can be shown that for this type of architecture a stable solution (fixed point) exists in a state space spanned by the fraction of activated neurons in a pool on the one hand side, and the jitter of spike times within a pool on the other. Hence, under certain conditions, too large jitter in spiking times (which would cause non-coincident and thus weaker overall postsynaptic input) would automatically shrink down again under the system dynamics. Likewise, the fraction of activated neurons in a pool also tends towards a stable number, i.e. if either too many or too few neurons were active in the preceding pool, the number of active neurons in the next pool would automatically return to the fixed point value. Thus, stable propagation of synchronous spiking activity throughout the chain is ensured, and both the dying out or runaway of activity is prevented, even in the presence of realistic synaptic background noise [90, 91]. The spiking jitter at the fixed point has been shown to be below one millisecond, thus the synfire chain was proposed as a possible candidate for precise spike time patterns that have been observed experimentally (e.g. Riehle et al. [92]).

The high precision in spike times also makes the synfire chain a promising candidate for a neural substrate for time perception. If the first pool of the chain is activated at the onset of an interval to be timed, temporal information will be translated into a spatial code as activity spreads through the chain in a wave-like manner, such that the time elapsed since initiation of the chain is represented by the spatial location of the pool that is currently most active [15] (Fig. 5). For this mechanism, one can also compute the full statistics of the time estimate from the temporal properties of the individual pools: On average, it takes a time Δt in the range of milliseconds for the activity to be transmitted from one pool to the next. The individual spike times jitter around this mean which can be well approximated by a Gaussian distribution with a standard deviation of $\sigma_{\Delta t}$ well below one millisecond (Fig. 5). Thus, the interval time T is estimated from the pool number i that is active at that time by the estimator $\widehat{T} = \sum_{l=1}^{i} \Delta t(l)$. As the mean of Δt is independent of the pool number, the average of this estimator is simply $\Delta t \cdot i$ and its standard

[4] It should be noted, however, that there is a computational study which considered such failures as a possible basis for the scalar property [88].

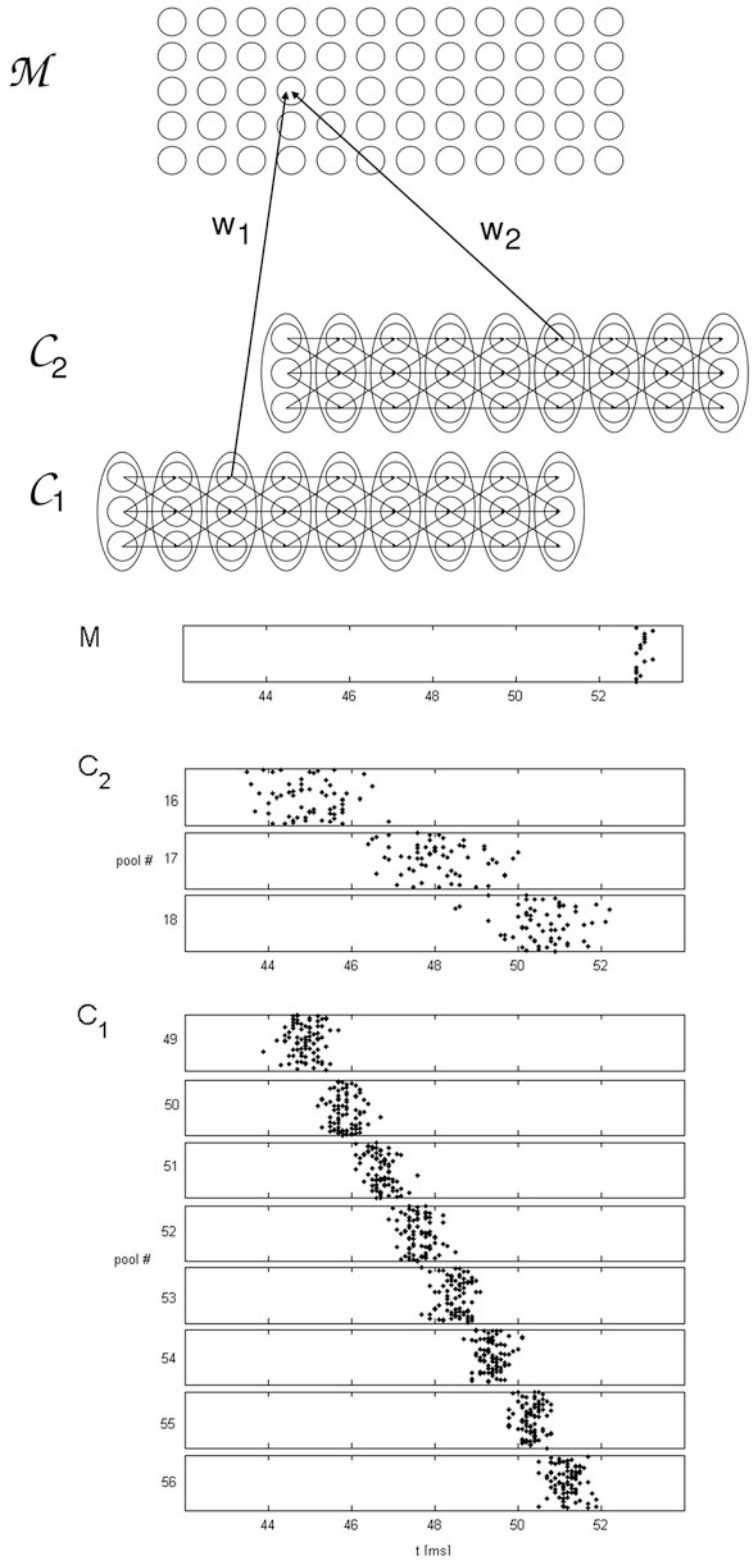

Fig. 5 (*Left*) Illustration of the synfire chain model structure. A readout network $\mathcal{M}$ receives convergent connections to from different synfire chains such as $\mathcal{C}_1$ and $\mathcal{C}_2$. By the competition between the respective weights, w_1 and w_2, the network determines which chain optimally responds at a time interval represented by the output unit in $\mathcal{M}$. (*Right*) Raster plot showing the spikes in the readout network $\mathcal{M}$ and selected pools from the chains $\mathcal{C}_1$ and $\mathcal{C}_2$. Each dot corresponds to a spike. In $\mathcal{C}_1$, activity propagates faster and with smaller jitter σ_P compared to $\mathcal{C}_3$. Reprinted from Hass et al. [15] with permission (Copyright 2008 by the authors)

deviation is $\sigma_{\Delta t}\sqrt{\widehat{T}}$, as the variance of the sum of weakly correlated Gaussian random variables approximately adds up as well. This scaling of the standard deviation is in line with the prediction of the information-theoretical framework (see "The Scalar Property and Its Relation to Basic Mechanisms of Time Perception" above), as this model clearly uses a mean-based estimator for time perception. Thus, as it stands, the scalar property would not be reproduced by this model.

However, physiological constraints may introduce additional sources of variability and potentially change the scaling of timing errors. In a synfire chain, one apparent constraint is the length of the chain. The synfire chain has been proposed as a model of the cortical column [93] which comprises ~10,000 neurons. Furthermore, based on the theoretical framework laid out above each pool would need a minimum of about 100 neurons to ensure stable transmission. Given a mean transmission time of about 1 ms, it follows that each chain could only encode intervals of up to 100 ms. If the chain length is anatomically fixed, the only way to encode longer intervals is to transmit the activity more slowly, i.e. to increase the transmission time Δt. To investigate how this could be implemented, a chain was modeled using integrate-and-fire neurons (see section "Time Perception from Slowly Ramping Firing Rates" above) connected by synapses with a physiologically realistic time course of postsynaptic potentials determined by a so-called alpha function with a single time constant α:

$$\mathrm{PSP}(t) = \frac{t}{\alpha}\exp\left(-\frac{t}{\alpha}\right). \tag{4}$$

In addition to the feedforward connections along the chain, each neuron received stochastic excitatory and inhibitory input to mimic synaptic bombardment originating from other neurons and areas outside the circuit. This input was adjusted to exhibit high variability as typical for real cortical networks. This random input is the basis for the temporal jitter in the spike times that result in timing errors.

To change the velocity of neural transmission along the chain, each of the parameters of the model was manipulated individually, with changes in the synaptic time constant α being the most effective means for changing the speed of propagation. It turned out that each of the parameter manipulations that increases Δt also increases the timing error $\sigma_{\Delta t}$. This result is illustrated in Fig. 6: Each curve shows the timing error as a function of the duration of the interval with a different Δt. While this error still follows a square-root function for each individual chain, increasing Δt leads to longer encoded intervals but also to a larger multiplicative factor in the square-root scaling function.

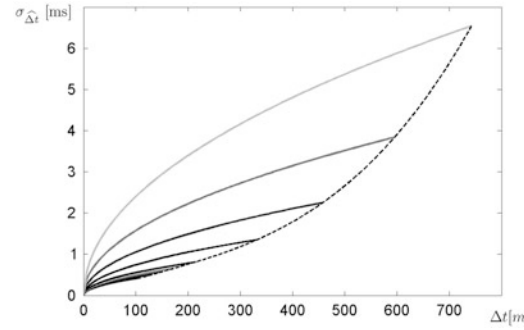

Fig. 6 Timing error, e.g. standard deviation of the duration estimate, as a function of the interval duration for various speeds of propagation. The *solid curves* depict simulation data and the *dotted line* represents the optimal timing error $\sigma_T^*(T)$ from Eq. (5). It is close to the lower envelope of the simulation data. Reprinted from Hass et al. [15] with permission (Copyright 2008 by the authors)

From Fig. 6, it is also apparent that there is an optimal chain for each temporal interval to be encoded, where by optimality we mean that the timing error is minimal. As the increase of this error with Δt is much larger (order 3) than the increase along the layers (order 1/2), it is always optimal to use the entire length of the chain with the lowest Δt that is able to encode the current interval. The form of the optimal timing error is [15]

$$\sigma_T^*(T) = \begin{cases} \sigma_{\min(\Delta t)} \cdot \sqrt{T} + D & \text{for } T \le \min(\Delta t) \cdot L \\ AT^3 + BT^2 + CT + D & \text{otherwise,} \end{cases} \tag{5}$$

where $\sigma^2_{\min(\Delta t)}$ is the variance of the minimal transmission delay Δt. The dotted line in Fig. 6 shows a fit of the simulated data to Eq. (5), which

is close to the lower envelope of all chains. For intervals below 100 ms, this line coincides with the square-root error function of the fastest chain. For intervals considerably above 100 ms, the scaling of the error becomes supra-linear, but one can also find an intermediate regime (~100–400 ms) where the scaling is approximately linear. Thus, if one assumes that there is a mechanism for selecting the optimal chain for each temporal interval, the anatomical constraint of a maximum chain length will produce all three regimes of error scaling that have been observed experimentally: Sub-linear scaling at short interval durations, supra-linear scaling at long durations, and (approximately) linear scaling for intermediate intervals. Also, the model explains why it is actually necessary to switch to a more unfavorable error scaling at longer times. Furthermore, as apparent from Fig. 6, only intervals of up to ~700 ms can be encoded by this mechanism. For much longer values of Δt, the spike time jitter becomes so high that a reliable transmission is no longer guaranteed. This value is close to the interval length that has been proposed as a transition point between different kinds of neural mechanisms for temporal encoding.

Experimental Evidence for the Synfire Chain Model

In general, the existence of synfire chains in cortical networks is supported by the observation of precise spatio-temporal spiking patterns which may be less well explained by other physiological or anatomical concepts [89, 92, 94–97] (but see Izhikevich [98] for an alternative concept). However, the results from these experiments are discussed controversially (see Abeles [94] and Grün [96] for current arguments), and direct evidence for synfire chains may be hard to obtain if the neural pools forming a chain are not spatially organized, as in that case even with current multiple unit recording techniques only a few neurons may be captured from each chain. It has also been argued that the statistical tests for detecting spatio-temporal spike time patterns may rest on incorrect or insufficient null hypotheses and are thus flawed (McLelland and Paulsen [99], see also Grün [96]), and that the occurrence of precise spatio-temporal patterns could therefore be explained by chance.

With regards to the evidence for synfire chains as a timing mechanism, this model provides a possible explanation for the temporal tuning curves of neurons in various neocortical areas [100–104]: When averaged across trials, neurons in a given pool representing a specific temporal interval will fire most often at the time that is given by the accumulated mean transmission time for that pool, but due to noise and spike time jitter in the chain, they will also tend to fire for longer and shorter intervals with a likelihood smoothly decaying with distance from the mean time. While modulation of interval timing by non-temporal factors or pharmacological conditions was not specifically addressed in this model, the fact that almost any change of a model parameter would change the transmission time highlights that subjective duration is easily susceptible to other factors in this framework. In particular, as discussed above (section "Time Perception from Slowly Ramping Firing Rates"), activation of D2 receptors may lead to an increase in net synaptic current [86], and if this holds in this model as well, the average membrane potential is shifted closer to the firing threshold under D2 activation, which also lead to a faster transmission and thus an increased speed of the internal clock, as observed experimentally.

Regarding psychological evidence, the model can obviously reproduce the linear psychophysical law as long as the average transmission time among neural pools is constant in time, which is fulfilled in a stable synfire configuration. Furthermore, while it was not possible to reproduce scalar timing with the basic one-chain model, a collection of multiple chains adapted to represent different interval times in an optimal manner could potentially explain the experimentally observed changes of scaling behavior for different interval durations. Finally, non-temporal factors such as attention or stimulus intensity are also likely to modify the net input currents and thus, the average distance from firing threshold, in a similar manner as D2 receptor activation does. Thus, one may naturally expect these factors to distort timing within this model framework.

Time Perception from State Space Trajectories

An intriguing and elegant possibility for representing time suggested by Buonomano [29] (see also Chapter 2.3 in this book) is that a neural system may just exploit the naturally occurring variation in neural and synaptic properties and the temporal evolution of neural states, without the need of explicitly and specifically tuned mechanisms (an idea related to the computational concept of a "liquid state machine" introduced by Maass et al. [105]). A neural system, once activated, would follow a unique trajectory through its state space (Fig. 2) [40, 51], e.g. the space spanned by the membrane potentials or the firing activities of all the neurons in a local network. In other words, at each point in time, due to the multiple feedback loops and effective time constants in a highly diverse neural network, the state of population activity will be different and unique. Thus, by adapting downstream networks to read out specific population states they could be tuned towards specific temporal intervals, alleviating the need for specific anatomical architectures or physiological mechanisms. Karmarkar and Buonomano [40] found the predictions of this kind of model to be consistent with human psychophysical experiments, at least within the range of up to hundreds of milliseconds. These experiments were explicitly tailored to probe the state-dependent nature of temporal representations by presenting context intervals before the actual test intervals. The authors also tested for timing errors, and found that the scalar property does not hold. Rather, the errors increased sub-linearly in time [40], as expected from a mean-based model. Unfortunately, the nature of the psychophysical law was not tested, and neither the effect of non-temporal factors nor of pharmacological manipulations.

In terms of the underlying neurobiology, the idea of using state space trajectories for time perception is supported by recent in vivo electrophysiological evidence from the rodent prefrontal cortex using multiple single-unit recordings [106]: While the activities of individual neurons may strongly vary over time, the "spatial" distance of neural population states in the neural state space (also termed the multiple single-unit activity [MSUA] space in this context), seemed to almost linearly increase with the passage of time across a wide range (Fig. 3 from Hyman et al. [106]). That is, temporal intervals were implicitly encoded in an approximately linear fashion, at least across some range, by the dissimilarity of neural population patterns (as measured by their distance in state space).

Time Perception from Oscillators

The final class of mechanisms for time perception to be discussed here is also one of the first proposed: Exploitation of the temporal properties of neuronal oscillators, which are ubiquitous in the brain at various frequency bands [79, 107–109]. An oscillator can be a single neuron or a set of neurons which fire at similar frequencies due to synaptic interactions (leading to mutual forcing and thus, frequency locking) or due to similar cellular properties. Timing models based on oscillations fall into three subcategories: In the simplest case, the interval that needs to be encoded is equal to the period of the oscillator, i.e. the time it needs for one full revolution. To be able to encode a range of intervals, either a bank of oscillators with different frequencies is assumed [25] or a single oscillator with variable frequencies that are entrained to external stimuli [19, 110, 111]. In the second class of models, the period of an oscillator is typically much smaller than the interval to be timed, and the estimate is formed by counting the number of revolutions the oscillator has made. These so-called pacemaker-accumulator models have been extremely influential in the psychological timing literature [5, 110]. However, they do not crucially rely on the regular oscillatory nature of the pacemakers. In fact, they are more commonly equipped with a Poisson pacemaker at a fixed rate, which also includes an element of variability. In a third class of models, the periods are also much smaller than the intervals in question, but they are not encoded by counting revolutions, but by

coincidence detection from a bank of oscillators with slightly different frequencies: Consider two oscillators with different frequencies which are initialized at the same time. Due to the different frequencies, their states evolve at different speeds, and it is only after several revolutions of both oscillators that they will meet again at the same phase (this is called a "beat"). If a set of downstream neurons detects these moments of coincidence, it will be able to encode intervals that are much longer than the intrinsic periods of the oscillators. This idea was originally proposed by Miall [26] and later embedded into a detailed framework of cortico-striatal structures by Matell and Meck [13, 31, 82]. This so-called "striatal beat model" (see Chapter 2.1 in this book) is currently the best supported of the oscillator models, although the exact nature of the oscillators is not discussed. Furthermore, it reproduces the scalar property and the linear psychophysical law. However, this is a not a generic property of the model. The authors assumed that the synaptic weights between the oscillators and the coincidence detector show a variability that reflects the distribution of the durations. This distribution was chosen Gaussian with a standard deviation of 10 % of the interval duration. Clearly, this assumed distribution perfectly follows the scalar property, and thus, the estimated durations also do. In a similar way, a later variant of this model [112] explains the modulatory effect of dopamine by assuming that dopaminergic drugs directly influence the firing rates of the oscillators. No mechanistic (biophysical) account of the scalar property or the distorting effects of dopamine or non-temporal factors was provided so far (but see Hass et al. [86] for preliminary results). Nevertheless, the more recent model [112] does include a more realistic neuron model and learning of new intervals by means of synaptic plasticity. Also, it seems to be the first to account for the effects of cholinergic drugs on temporal memory patterns.

Time Perception from Other Mechanisms

While we can not provide a comprehensive review over all existing timing models, it is worth mentioning two further classes of models with interesting properties. The first is the influential "spectral timing" theory with has been introduced by Grossberg and colleagues [23, 113] in the context of machine learning and later in a different form by Staddon and Higa [39]. In this model class, there is a range (a "spectrum") of elements with different time constants. The activity of each of these elements peaks at a certain interval duration, and the temporal information of all elements is combined into a single output signal by means of learning. In this sense, spectral timing bears similarities with the multiple synfire chain model discussed in section "Time Perception from Synfire Chains". Under certain assumptions, these models reproduce the scalar property of timing errors, but as for the oscillator models, this follows directly from specific assumptions.

The second class of models is based on the stochastic switching of bistable neuronal units. This switching happens at random times, and can be either from active to inactive [56, 58] or vice versa [59]. Depending on the direction of switching, this leads either to ramping up or ramping down of activity, similar as in the model in section "Time Perception from Slowly Ramping Firing Rates" [14]. Interestingly, these models reproduce the scalar property without further assumptions, and could also be classified as variance-based processes, in agreement with our analysis [54].

Conclusion

In this chapter we reviewed several candidate neurocomputational mechanisms of interval timing, as well as some of the experimental evidence for or against them. While a large variety of computational mechanisms has been proposed so far, we put the focus on those which we felt are particularly rooted in neurophysiological evidence. Table 1 gives an overview of how well each of the presented model classes are supported by the criteria we defined. From this comparison, it is obvious that none of the mechanisms we discussed in detail is able to reproduce the scalar property exactly without making additional assumptions. As discussed in fourth section, this is consistent with the fact that most of the

Table 1 Comparison of model classes according to the experimental criteria

Model class	Biological plausibility	Dopaminergic modulation	Linear timing	Scalar property	Non-temporal factors
Ramping activity	Yes	Yes	(Yes)[a]	No	Yes
Synfire chains	?	Yes	Yes	(No)[b]	Yes
State space trajectories	Yes	?	?	No	?
Oscillators	Yes	(No)[c]	?	(No)[c]	?
Spectral timing	No	?	?	(No)[c]	?
Stochastic decay of memory traces	?	Yes	No	Yes	?

Annotations: [a]For intervals represented by rates well below the threshold. [b]Approximates the scalar property in a limited region of intervals. [c]Involves specific assumptions that explicitly generate this behavior without giving a mechanistic explanation

mechanisms and models suggested up to date rely on mean-based estimators, which seems to be the most straightforward way to implement linear subjective interval timing in the nervous system, and which also agrees with neurophysiological observations like ramping activity. The only exception is the class of stochastic switching. However, the neural basis of these models and their relation to the remaining constraints is less clearly defined compared to the aforementioned classes of mechanisms, so this is a puzzle that still remains to be resolved. On the other hand, sub- and supra-linear errors in interval time estimation have been observed as well for some temporal range, and not all experimental data sets clearly and unambiguously support the existence of a scalar regime [43]. As outlined above, these regimes of different error scaling are likely based on fundamentally different underlying neuronal mechanisms, so it seems worthwhile to investigate the temporal constraints of different timing models, and thus the reasons to switch mechanisms at certain durations.

As a final remark, we would like to emphasize that there is very likely more than just one mechanism of time perception operating in the brain, as also suggested by the different scaling regimes and multitude of different areas preferentially involved in time perception in one or the other range. Timing is fundamental to almost any sensory and motor process, with different time frames relevant at different levels of the hierarchy (e.g., millisecond range for specific sequences of motor commands up to seconds, minutes or hours at the scale of behavioral organization). All brain areas harbor a rich repertoire of biophysical and network mechanisms that may be exploited for timing, and hence a variety of timing mechanisms tailored to specific computational needs may have evolved in different brain areas. This in turn brings up the question of how the estimates from many different individual timing processes are combined to form a coherent representation of time. Recent experiments [114–117] suggest that the temporal information from different sources is weighted in a statistical optimal (Bayesian) way. Understanding this integration may turn out as important as the clarification of the individual mechanisms of time perception themselves.

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Part II

Timing Models

Dedicated Clock/Timing-Circuit Theories of Time Perception and Timed Performance

Hedderik van Rijn, Bon-Mi Gu, and Warren H. Meck

Abstract

Scalar Timing Theory (an information-processing version of Scalar Expectancy Theory) and its evolution into the neurobiologically plausible Striatal Beat-Frequency (SBF) theory of interval timing are reviewed. These pacemaker/accumulator or oscillation/coincidence detection models are then integrated with the Adaptive Control of Thought-Rational (ACT-R) cognitive architecture as dedicated timing modules that are able to make use of the memory and decision-making mechanisms contained in ACT-R. The different predictions made by the incorporation of these timing modules into ACT-R are discussed as well as the potential limitations. Novel implementations of the original SBF model that allow it to be incorporated into ACT-R in a more fundamental fashion than the earlier simulations of Scalar Timing Theory are also considered in conjunction with the proposed properties and neural correlates of the "internal clock".

Keywords

Interval timing • Scalar timing theory • Striatal beat-frequency theory • Adaptive control of thought-rational cognitive architecture

Introduction

There are abundant examples of behavioral processes engaged in by humans and other animals in which short-timescale temporal information plays an critical role, ranging from estimation of how long one can safely look away from the highway during driving [1], to the subtle role that pauses in a speech signal play in language-based communication [2], to the trap-line foraging of bumblebees and hummingbirds that is partly guided by their knowledge of how long it takes a flower to replenish its nectar after a previous visit [3–5]. In all these examples, interval timing enables the organism to improve its prediction about the onsets and offsets of impending

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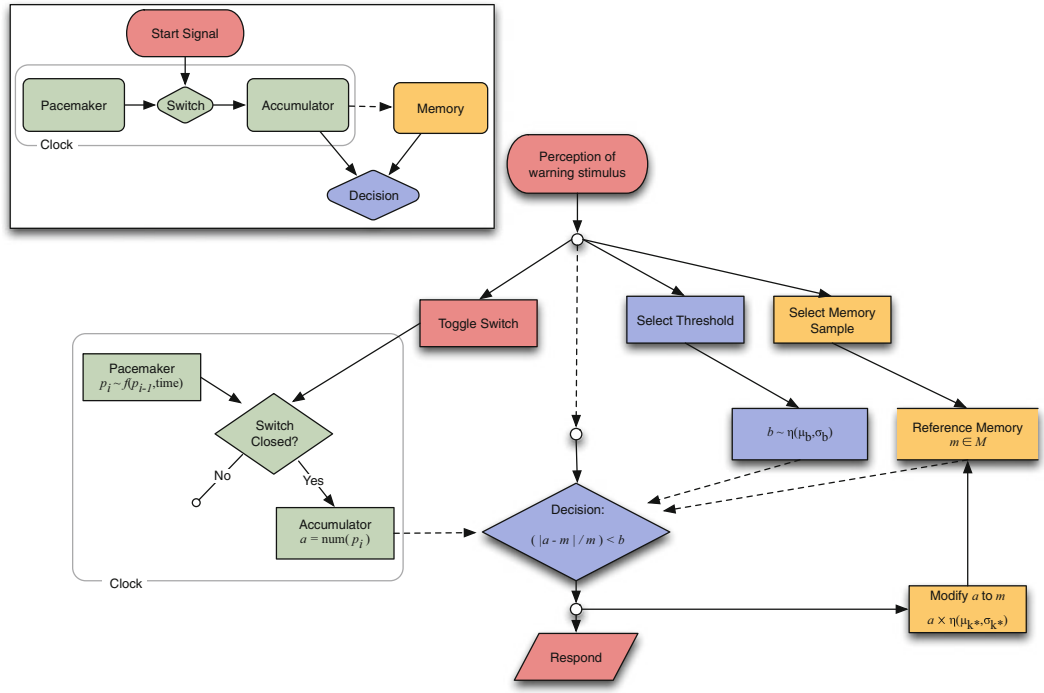

Fig. 1 *Top-left box* shows the outline of most information-processing models of interval timing based on a triad of clock, memory and decision stages [6, 17, 20, 64]. The main picture depicts one instance of these models; the Scalar Timing Theory as described in Church [24]. The main clock components are shown in *green*, the boxes processing input and output in *red*, the memory components in *yellow*, and the decision components in *blue*

environmental events. To allow for these predictions, an internal signal has to exist that provides the organism with a sense of time in order to anticipate these events. In the case of state-dependent models, categorically defined internal states are associated with specific behavioral actions attributed to each of the states [6]. By the pacing of transitions from one state to the other, behavior emerges that is attuned to the temporal regularities of the environment without the need of a dedicated clock or timing circuit (e.g., the behavioral theory of timing [7, 8]). In other state-dependent models, timing is an intrinsic property of the neural dynamics that elapse over the course of tens of milliseconds to a few seconds following the onset of a timed event (Buonomano, this volume; [9]).

However, the majority of dedicated models of time perception (for comparisons between dedicated vs. intrinsic models [6, 10–12]) assume that interval timing can best be described by a triad of clock, memory, and decision stages as depicted in the top-left box of Fig. 1. Most of the work that adheres to this triad can be traced back to the pioneering work of Creelman [13] and Treisman [14] who proposed the first information-processing (IP) models of interval timing. In these models, a dedicated clock stage provides a continuous or an interval-scale index of the passing of time since the onset of a temporally relevant event. Whenever the offset of the to-be-timed interval is observed, the clock reading is taken and stored in memory. After sufficient experience, the onset of upcoming stimuli can be predicted by comparing the current clock reading to the previously stored memory values. Although in the early work on interval timing most studies focused on the role of the pacemaker/accumulator, it was soon acknowledged that all stages of information processing (e.g., clock, memory, and decision) could contribute to the behavioral profiles observed in the

temporal control of behavior [15]. One of the best developed theories that fits this general description and specifies how the different IP components contribute to observed behavior is Scalar Timing Theory [16, 17]—sometimes referred to as Scalar Expectancy Theory as originally developed by Gibbon [18, 19]. The general properties of these interval-timing systems have been described by Church [20] and more recently by Allman et al. [21].

Scalar Timing Theory

Description of the General Outline

A detailed version of Scalar Timing Theory is shown in Fig. 1 in order to provide an appreciation of the model's various levels of complexity [16, 22, 23]. This outline and the following description are based on the computational implementation of Scalar Timing Theory described by Church [24], although slightly modified versions have been described elsewhere [25]. According to Scalar Timing Theory, the "internal clock" of an organism that is engaged in the measurement of the physical duration of an external event (T) is comprised of a pacemaker that emits pulses at a regular rate. Whenever a temporally salient event is observed, a start signal is sent that closes a switch (or gate) between the pacemaker and an accumulator, allowing for pulses to reach the accumulator where they are integrated as a function of time. As the switch has to be closed in order for an event to be encoded, a process that is assumed to take some time, the model accounts for variation in the duration between the physical onset of the event and the first pulse passing the switch. This duration is assumed to be normally distributed: $t_1 = \eta(\mu_{t1}, \sigma_{t1})$—see papers by Meck and colleagues [26, 27]. Any pulse that passes the switch is thought to increase the value of the accumulator by one. By means of this coupled pacemaker/accumulator process, a measure of subjective duration (D) is available to the organism. When the imperative stimulus is observed, the organism can read out the accumulator, noticing that the time between the warning and imperative stimulus took, for example, 32 pulses. Of course, perceiving the imperative stimulus might also have taken time, reflected in switch opening latency: $t_2 = \eta(\mu_{t2}, \sigma_{t2})$, so that the subjective duration is assumed to be $D = T - T_0$ [27], with T_0 representing $t_1 - t_2$.

As most psychophysical phenomena, interval timing adheres to Weber's law, with shorter durations being estimated with less variability than longer durations. As this is typically demonstrated by observing identical response distributions after a scale transform (e.g., divide all distributions by the mean of the distribution), such superimposition of timing functions is referred to as the scalar property of interval timing [17, 28–30]. In contrast to many other psychophysical theories that assume that the subjective percept is non-linearly related to the objective input [31, 32], Scalar Timing Theory puts forward that the clock stage provides a veridical mapping of objective, external time to subjective, internal time [18]. Although it is sometimes claimed that the veridical time assumption is supported by experiments in which subjects have to compare the amount of time that is still left during the perception of a previously learned interval with another previously learned interval—the Time-Left experiments by Gibbon and Church [33]; see also Wearden's study [34]. It has been argued that the behavior observed in these procedures might also stem from strategies that do not tap directly into the underlying time scales [35–38]. A stronger case for the support of a linear encoding can be found in studies in which empirical response distributions were observed that are similar to the theoretical distributions associated with the linear encoding of time [39, 40].

Because all of these accounts assume veridical timing, the clock stage typically isn't used to account for the scalar property. Instead, Scalar Timing Theory assumes that the memory stage is the source of the scalar property—see papers by Gibbon and Church [16, 22, 33] for general details, or more specifically, that the scalar property is induced by the process that copies values from the accumulator to the memory store. When the offset of a temporal interval is observed, the

current value of the accumulator, a, is multiplied by a memory translation constant k*—drawn from a normal distribution $\eta(\mu_{k*}, \sigma_{k*})$ [26, 41–43] before the value is copied to reference memory. This multiplication results in wider memory distributions for longer durations than for shorter durations, providing the basis for the adherence to the scalar property of interval timing. In the default version of Scalar Timing Theory, the memory store is considered to "consist of a large number of unorganized samples" [24, p. 9] although the samples must of course be associated with the environmental events that they encode for.

Whenever the organism wants to respond simultaneously with the onset of an upcoming event, it retrieves a random sample from memory that is associated with previous experiences with that event, and starts the accumulation process as soon as the warning signal is observed. However, since m, the sample from memory has been multiplied by the k* memory translation constant, a direct comparison between a, the value in the accumulator and m is not informative. Instead, Scalar Timing Theory assumes that a ratio comparison is made between m and a that is subsequently compared to a threshold parameter b to decide whether or not a response has to be made (i.e., if $(la - ml/m) < b$, then make a response). Like the other parameters, the threshold is assumed to be sampled from a random distribution: $b = \eta(\mu_b,\sigma_b)$.

Although Scalar Timing Theory was originally developed within the context of animal learning and conditioning procedures, it has been successfully applied to temporal processing in humans, in both healthy and clinical populations [44–46] and has aided in the interpretation of the changes in interval timing capacities over lifespan development, including age-related declines [47–49]. In these settings, Scalar Timing Theory has accounted for many different phenomena associated with interval timing, such as the effects of different experimental contexts and procedures [50, 51], of pharmacological manipulations [52–56] and of emotional [52–58] and attentional [59–62] influences.

Challenges for the Information-Processing Models of Interval Timing

In any task related to interval timing, all (or most) of the processes and stages mentioned above play a role. As these different processes and stages interact, it is sometimes not straightforward or even possible to attribute a particular empirical observation to a particular aspect of an IP model of interval timing because any change in a particular procedure can be mimicked by a change in another aspect of the model. Nevertheless, it is important to critically evaluate any model or theory, and especially assess the validity of those components that are central to the phenomena covered. Like in other complex domains, the approach has been to isolate particular components and to specifically manipulate the experimental setup so that conclusions can be drawn relating to that component. This approach has obviously been an important line of research in the field of interval timing, with for example studies (see also [63]) showing that the scalar property should be captured in the memory components instead of in the accumulation process associated with Scalar Timing Theory [33], that a single sample is selected from reference memory on each trial instead of multiple [64], and that memory samples stored in reference memory affect other memory samples [65].

Stable Representation and Modularity

Scalar Timing Theory could be seen as a self-contained module that provides temporal information to a cognitive system or architecture that performs a more general task which relies on temporal information. Although one could, of course, still study the components of this black box, this approach would allow for using the output of Scalar Timing Theory without worrying about which internal processes have given rise to that particular output. However, this does require that irrespective of the task that is modeled using Scalar Timing Theory, the components should always function in the same way, cf., Figure 3.2-1.2 in [24].

Although rarely explicitly acknowledged, but see [63], the inclusion of a more cognitive decision component makes it difficult to adhere to this strong claim. Let's take, for example, human performance in a duration bisection task [66]. In a bisection experiment, participants are presented durations that they have to classify as either more similar to a previously learned "short" duration or as more similar to a previously learned "long" duration. When the proportion of "more similar to long" responses is plotted as a function of the length of the physical duration, a smooth sigmoid psychometric curve is typically observed, but see [67] with almost none of the shortest durations being classified as "long" (and vice versa for the longest duration), and with the bisection point (i.e., the point at which both answer options are equally often chosen) typically at the geometric mean of both standards [30, 66]. At first sight, it might seem that Scalar Timing Theory can quite straightforwardly account for the performance observed in bisection tasks: at the onset of the to-be-judged duration, the switch is closed and pulses will be accumulated. However, on the basis of what information will Scalar Timing Theory make a decision? Since this is a judgment task (and not a reproduction task), one might assume that the participant just waits for the offset of the presented duration, and then decides "short" if the observed a is closer to a memory sample associated with the short standard than to one associated with the long standard. That is, if $(|a - m_{short}|/m_{short}) < (|a - m_{long}|/m_{long})$ then choose "short", otherwise choose "long". Although at cursory inspection it might seem that this process fits nicely with the outline presented in Fig. 1, it requires that the decision process compares a to both m_{short} and m_{long}, requiring two retrievals from memory and a more complex comparison than the typically assumed simple comparison to a preset threshold. One could, of course, assume that this comparison isn't made within Scalar Timing Theory, but that the output of the clock is transferred to later stages. However, this would then assume that "non-timing" processes have access to the memory stage that is embedded in the timing module, violating basic assumptions of modularity. A third alternative hypothesis entails the creation of a bisection criterion [68], which could act as an internal, subjective representation of the point of subjective equality. According to this view, participants could internally commit to a "long" response as soon as this bisection criterion has passed. This criterion could be based on the geometric mean of the samples representing the short and long standards—i.e., $sqrt(m_{short} \times m_{long})$. To allow for scalar variance, this point of subjective equality would have to be recalculated for each trial from two sampled values. Thus, to allow for this interpretation of the duration bisection task, the timing model outlined in Fig. 1 would have to be extended to represent a process that would result in a subjective bisection criterion that could take the place of m, but that is based on two retrievals from reference memory.

Although all three of these accounts would require modifications to the basic outline of Scalar Timing Theory illustrated in Fig. 1, recent electrophysiological data indicate that additional changes to the model might be necessary. Ng et al. [69] recorded EEG during a duration bisection task. From earlier work, it is known that during timing tasks a slow brain potential wave of negative polarity develops, referred to as the contingent negative variation (CNV), which resolves after a temporal decision has been made [70, 71]. If a bisection criterion is used by participants, one would expect the CNV to resolve at or around the point of subjective equality (e.g., geometric mean of the short and long standards). This pattern was indeed observed by Ng et al. [69], supporting the hypothesis that a comparison to the bisection criterion drives performance. However, the results also indicated that participants temporally prepared for the possible offset of the short tones, because the CNV increased starting at the onset of the comparison duration and reached its maximum amplitude around the time when the offset of the shortest duration would be presented. These results suggest that on the one hand a comparison is made based on a $m_{criterion}$ based on m_{short} and m_{long}, but on the other hand also indicate that a sample representing m_{short} is still available to the decision-making system given that value seems to be used to prepare for the upcoming stimuli.

Obviously, one could modify Scalar Timing Theory to account for these changes, and, as argued by Wearden [63], the basic properties of the timing system would still be the same. However, if one allows arbitrarily complex modifications to the original system (such as including a sequential timing process that first retrieves and estimates m_{short} and then retrieves m_{long} and estimates the average of m_{short} and m_{long}), a model consistent with Scalar Timing Theory can be constructed to fit almost any data set [63]. Moreover, because this more complex model provides considerable flexibility in decision processes, temporal arithmetic and, for example, the number and type of retrievals from reference memory, new parameters will need to be introduced that account for the latencies associated with these new processes. The inclusion of these parameters would make it difficult to constrain the model on the basis of empirical data from timing studies.

Degrees of Freedom Problem in Models of Interval Timing

The issues outlined above can be reduced to a straightforward "degrees of freedom" problem: although timing studies provide a wealth of data that can constrain theories of interval timing, the number of degrees of freedom enables Scalar Timing Theory to easily cover most or all possible outcomes of these studies, cf., non-constraining models in [72]. Two approaches can be taken to solve this problem that both focus on reducing the degrees of freedom. First, by introducing new behavioral measures that the theory should be able to account for, one can decrease the overall degrees of freedom. For example, if a particular model has 6 degrees of freedom, a new behavioral measure might require a certain parameter of that model to be set to a particular value to allow for a good fit, thus reducing the number of degrees of freedom to 5 for all other behavioral measures because that value has become fixed. This strategy can be seen as constraining the number of degrees of freedom by bringing in additional, potentially external constraints. Second, any process assumed by Scalar Timing Theory should eventually be identifiable in the neurobiology of the organism that demonstrates the capacity to time durations in the hundreds of milliseconds-to-minutes range. For example, if no brain area can be identified that corresponds to the accumulator as proposed by Scalar Timing Theory, one might need to reconsider the existence of an accumulator [73, 74] or if some proposals for the working of the memory stage are implausible from a neurobiological perspective, these alternatives might be rejected and thus constrain the theory. These constraints are derived from a reevaluation of the components already present in a theory, and could therefore be described as additional internal constraints.

In the remainder of this chapter, we will focus on four recent developments that focus on providing additional constraints on theories of interval timing by either incorporating additional external or internal constraints, or by providing cross-validation. First, we will discuss an integrated model of interval timing that embeds a dedicated clock structure consistent with Scalar Timing Theory in a more general cognitive architecture that provides externally validated constraints on the memory and decision stages [75]. Although this model could be seen as more complex than Scalar Timing Theory, this integrated model allows for modeling the interactions between non-temporal and temporal aspects of cognition. By incorporating the constraints that have been identified by fitting the cognitive architecture to other domains and tasks, models of interval timing become more constrained. Second, we will discuss how a model based on cortico-striatal interactions can replace Scalar Timing Theory's traditional clock and memory stages [44, 54, 76], removing a number of degrees of freedom from the original model because the basic properties of this clock have been directly derived from neurobiological observations. Third, we will discuss how this cortico-striatal model can be integrated into the architecture-based model and how a number of elementary neurobiological constraints bring about the scalar property in interval timing.

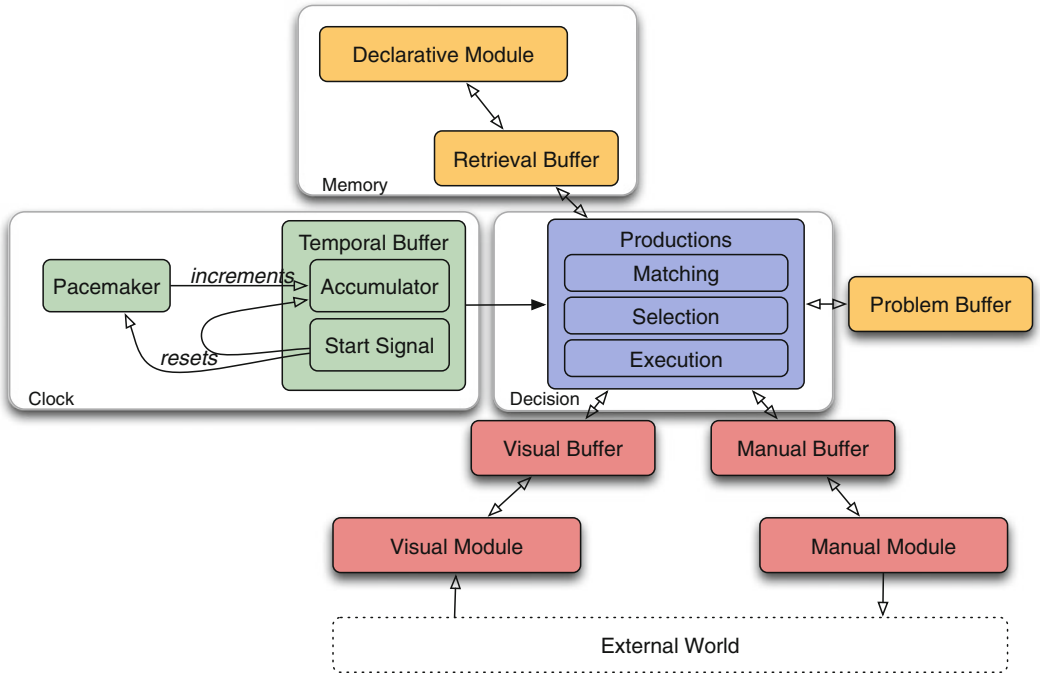

Fig. 2 An outline of the integrated-architecture timing model. The Clock component is similar to the clock stage found in Scalar Timing Theory [17], but with inter-pulse intervals approximating a geometric sequence. The Decision and Memory components are implemented by the decision rules and declarative memory system of ACT-R, the architecture that also provides the other components [75]. The color of the components matches the colors used in Fig. 1

Fourth, and finally, we will present the outline of a model that integrates interval timing in a more general framework of oscillation-driven cognitive behavior.

Integration of Cognitive Architectures

While working on computational models of behavioral tasks that were at first sight not obviously time dependent, Taatgen et al. realized that a number of phenomena they encountered were partly driven by their participants' sense of time. For example, Van Rijn and Anderson [77] had human participants perform a lexical-decision task at either normal speed or under speed stress and found evidence that the likelihood of guessing could be described as a function of the temporal distance to the response deadline. Given that Adaptive Character of Thought-Rational (ACT-R) [78, 79], the cognitive architecture frequently used for modeling these tasks, didn't provide any straightforward way to account for the passage of time, Taatgen et al. [75] extended ACT-R with a clock module based on the dedicated clock stage found in Scalar Timing Theory. Although Scalar Timing Theory also includes a memory stage, and several memory models have been proposed [80, 81], no model of temporal memory has been proposed that captures the more general features of memory systems utilized in human cognition. In contrast, the ACT-R theory provides an advanced and more constrained framework for modeling both memory and decision-making processes. Consequently, these default ACT-R components were used instead of incorporating the memory and decision stages from Scalar Timing Theory. The combination of both "internal clock" and ACT-R frameworks thus provides a best-of-both-worlds approach to modeling interval timing-based behavior. An outline of this integrated-architecture model of interval timing is illustrated in Fig. 2.

Although we discuss the three most important components of the integrated-architecture model of interval timing below, it should be noted that this architecture also provides for components that are involved with observing and acting on the environment. As a result of these additional components, models developed using this integrated-architecture can provide principled predictions about t_1 and t_2 which reflect the time that it takes to perceive and act on the onset and offset of a temporally salient event. That is, any visual event in the "External World" has to be observed via the "Visual Module", before decision rules in the Decision component can relay the start signal to the Clock component (see Fig. 2). As each component is based on formal theoretical work in the respective fields, the amount of time associated with t_1 (and t_2) can be predicted based on previous work instead of having it sampled from a normal distribution. Similarly, the incorporation of motor components (e.g., the "Manual Module") allows for estimating the delays associated with the actual response, an aspect of behavior not typically included in Scalar Timing Theory or similar models.

One of the challenges faced when integrating different theoretical approaches or frameworks is that certain assumptions that are necessary in the one framework, are difficult to account for in the other framework. For example, Scalar Timing Theory assumes that the accumulator value is multiplied by a before it's being copied to reference memory. In contrast, the ACT-R theory states that output from any module is automatically copied to memory, potentially subjected to some additive noise. However, the memory translation constant k* has a multiplicative effect [i.e., $a \times \eta(\mu_{k*}, \sigma_{k*})$, instead of $\eta(0, \sigma_a)$], and thus is not in line with the constraints of the architecture. Although one could, in principle, add explicit strategies that implement this multiplicative strategy, this process would be rather cumbersome, and add significant processing time. In addition to this, using the memory translation constant would imply the use of ratio rules for comparisons, a process that is also not easily accounted for (see also [82], which argued that ratio-rules are difficult to account for in neurobiological models). That is, a ratio-rule requires that whenever the system checks whether a particular duration has passed, (1) the current value from the accumulator has to be retrieved, (2) the reference value has to be retrieved from memory and (3) subsequently subtracted from the accumulator value, (4) divide the outcome of the subtraction by the reference value, to finally (5) compare the division to a threshold. Apart from requiring considerable processing and working memory resources, this suggests that timing an interval is a highly obtrusive process that would severely affect other cognitive tasks executed in parallel. This caveats could be perceived as a negative point for the integrated-architecture model, but it is also indicative of the consequences of adding external constraints to a theory: sometimes additional constraints require a change of thought.

In the sections below, we will discuss the three major components of the integrated-architecture model of interval timing, but we refer the interested reader to Taatgen et al. [75] and Van Rijn and Taatgen [83] for additional background.

Clock Stage

As the memory system in the integrated-architecture model cannot easily account for the scalar property of interval timing, the main source of scalar variance has to be found in the clock module. Therefore, a pragmatic approach was taken in which a pacemaker produces pulses with a gradually decreasing rate according to the following formula: $p_n = p_{n-1} \times a + \eta(0, p_{n-1} \times b)$ where p_n indicates the time between pulse n and $n - 1$ (and p_0 represents the initial value), a represents the pulse multiplier (the common ratio), and b the parameter determining the width of the noise distribution. It is important to note that although this function does provide a non-linear mapping, the non-linearity of this mapping is much dampened in comparison to the non-linearity suggested by logarithmic mappings of objective to subjective time. In fact, apart from the noise component, the subjective experience of time follows a geometric series, as a particular

pulse count n in the accumulator will be observed at time $\Sigma_{x \times \{1..n\}} (p_x \times a^x)$. By fitting this model to empirical data [83], the p_0 was determined to be 100 ms, a was set at 1.02, and b at 0.015. Interestingly, this set of parameters indicates that the average inter-pulse time for short event durations (i.e., around 1 s) is shorter (~120 ms) than has been suggested in the literature [27] but at longer durations (i.e., around 5 s), the average inter-pulse duration is about 200 ms indicating that the assumed pulse length for typical interval timing durations is comparable to previously identified values. Regardless of the precise values, this non-linear mapping of objective to subjective time results in a higher temporal resolution immediately after the onset of an event than at later phases. This non-linearity gives rise to scalar effects on subjective duration, since an interval of about 5 s can only be estimated with a precision of 200 ms, whereas an interval with a duration of about 1 s can be estimated with a precision of 120 ms. Together with the inherent noise in the system, which also scales up with event duration and has a multiplicative effect in the geometric sequence, the scalar property of interval timing emerges [84–86].

Memory Stage

As mentioned above, the integrated-architecture model incorporates the ACT-R memory mechanism. Although a full discussion of this mechanism is beyond the scope of this chapter (see [87] for an introduction, and [88] for more recent discussion of the functioning of declarative memory), the main aspects of the declarative memory system from the perspective of interval timing are that all facts stored in the system as memory traces are subject to decay, and that various forms of memory mixing (i.e., the blending of different facts) are accounted for [89]. The psychological processes underlying this memory system have been extensively tested, both at the level of aggregate behavior and at the level of between-trial effects [90]. It should be noted however, that a separate working memory—as proposed in Scalar Timing Theory [43, 91–93]—is difficult to align with ACT-R, because the most similar component or "problem state" [94, 95] plays a different functional role.

The "memory mixing" mechanism takes an average of several memory traces, weighted by the activity of each trace and how well they match the current experimental context. As the traces contain pulse counts copied from the clock system, this blending process will adjust the count associated with a particular interval downwards if that interval is presented in the context of "shorter" alternatives, but upwards if "longer" alternatives are present. This way, the memory system, developed outside of the context of interval timing, naturally accounts for Vierordt's law [96–98]. Moreover, the memory system also naturally predicts trial-by-trial effects, with estimates of more recent trials having a stronger effect than older trials that have been subjected to decay for a longer period of time [98, 99]. By means of statistical modeling, Taatgen and Van Rijn [100] showed that the impact of older trials quickly wanes, as the influence of two trials ago is about half the size as the influence of the previous trial. To summarize, by incorporating an existing memory system into the integrated-architecture model of interval timing, both existing (e.g., memory mixing [50, 65, 98]) and new (e.g., feedback-based contamination of reference memory [100]; see [99] for other phenomena associated with feedback processing) timing phenomena can be quantitatively explained without having to introduce additional cognitive processes or model parameters.

Decision Stage

Although ratio-rules are favored [67] in Scalar Timing Theory, the variable m to which the value of accumulator is compared (i.e., $|a - m|/m$) is not strictly defined, and can range from a simple count retrieved from memory (e.g., m_i) to the earlier discussed point-of-subjective-equality (e.g., $\text{sqrt}(m_{short} \times m_{long})$ in duration bisection studies. Although these choices imply different processes and will most likely be associated with different latencies, the choice of m is not separately

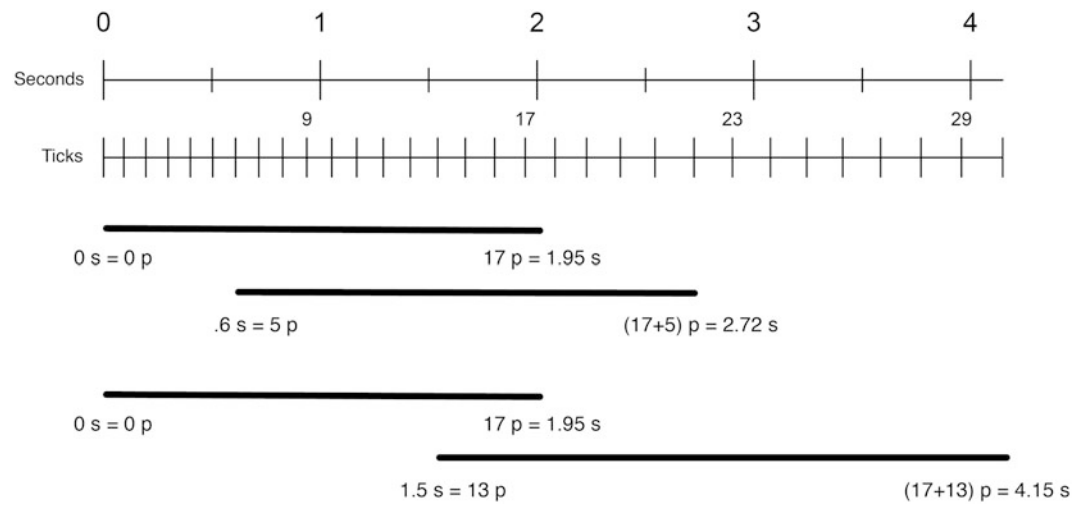

Fig. 3 Outline of the experimental procedures used to investigate the timing of multiple overlapping event durations [83]. In this example, the standard duration of 2 s is estimated to be 17 pulses. In the example shown at the *top*, the second duration starts 600 ms or 5 pulses after the first duration has started. The model thus estimates the end of the second event at 5 + 17 pulses, resulting in a duration estimate of 2.72 − 600 = 2.12 s. In the *bottom* example, the second event only starts at 1.5 s (13 pulses), so the response that signals the perceived offset of the second event duration is given at 13 + 17 pulses, resulting in an estimate of 4.15 − 1.5 = 2.65 s. This subjective lengthening result was attributed to a non-linear representation of time

modeled. In contrast, ACT-R's decision rules cannot perform complicated processes in a single step. For example, it is straightforward to test whether the current value in the accumulator is similar to a value retrieved from the memory store. However, multiple decision rules are needed to test whether the value of the accumulator is similar to the mean of two samples (e.g., separate steps for retrieving the samples, calculating the mean, etc.). Because this process is likely to take a reasonable amount of time (depending on the level of expertise, but probably more than 500 ms), ACT-R provides testable predictions regarding the nature of *m* and many other parameters.

Putting Everything Together

By integrating Scalar Timing Theory's clock stage into the ACT-R architecture, one can create models of tasks (e.g., peak-interval and other temporal generalization procedures) that have been typically analyzed using Scalar Timing Theory [75]. More interesting, the additional "non-clock" components also allow for creating models of more complicated behavior. For example, participants in a study reported in Van Rijn and Taatgen [83] had to reproduce durations with the start of the duration cued by the appearance of a stimulus on either the left or right side of a fixation point. On most trials, the next cue was presented before the duration associated with the previous cue had passed, resulting in partially overlapping intervals as shown in Fig. 3. This diagram also illustrates one of the main results from this study, which is that the later the secondary event started, the longer its estimated duration.

Obviously, there are many potential sources of variance in this model, ranging from how the onsets of the two events are perceived, to the time it would cost to retrieve memory traces or to calculate intermediate values, to the noise associated with motor responses. However, earlier work with the ACT-R architecture has provided us with reliable default parameters for all these components, so the integrated-architecture model can focus on explaining those aspects of the task that are most closely related to interval timing. In this particular task, the main question is, of course, how participants

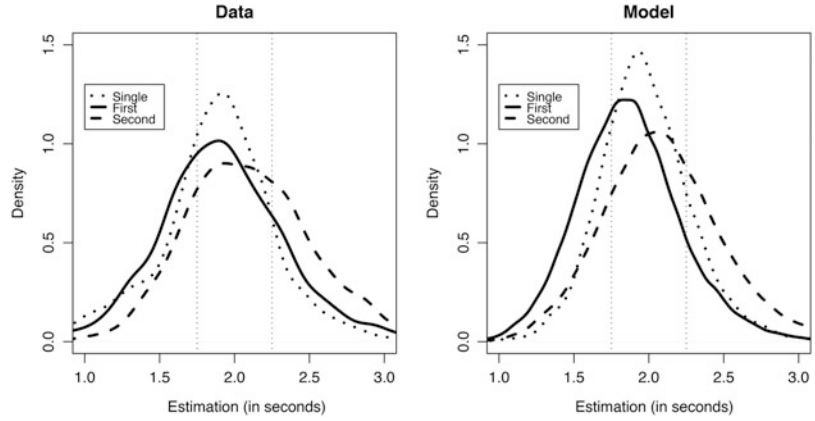

Fig. 4 Main results of the Van Rijn and Taatgen study [83]. The *left panel* shows the distributions for the empirical data, the *right panel* for the model fits. The *dotted line* shows the distribution during the last blocks of the training session, the *solid line* shows the distribution for the event duration that ended first, and the *dashed line* for the event duration that ended last. The model's explanation for the leftward shift of the *solid line* is based on the updating of the standard due to feedback, the rightward shift of the *dashed line* is due to the proposed non-linear representation of time. Adapted from Figure 4 in Van Rijn and Taatgen [83]

manage to estimate two (or more) event durations in parallel. A theoretical possibility, although not directly supported by either the integrated-architecture model nor by Scalar Timing Theory, is that the two durations would be estimated independently, as if a secondary clock-system was spawned [92, 101, 102].

Although recent findings from rats have provided strong evidence for simultaneous temporal processing, i.e., the use of multiple clocks that can be run, paused, and reset independently [101, 102], findings from human participants have tended to support sequential processing [83]. In this case it appears that when participants time overlapping event durations, the value of the accumulator is read out at the onset of the secondary duration, and that after finishing the first duration wait for the same number of pulses previously stored to determine their response. Because of the geometric series-based subjective time, the duration of the pulses added at the end will be longer than the duration of the same number of pulses integrated at the beginning of the interval, thus explaining the effect demonstrated in Fig. 3. Obviously, the later the onset of the second event, the more pulses have to be added at the end of the distribution, and thus the larger the overshoot of the estimation. At the same time, as participants were provided feedback based on their performance, it is to be expected that they would try to optimize their timing behavior, thus shortening their internal representations of the standard durations. Figure 4 shows the main results of the experiment and the model fit. The narrow distribution of the dotted line in the left panel indicates that participants had mastered reproducing the 2-s-interval during training. During the experimental phase of the experiment, the response distributions for the first and second event durations differ. The response distribution for the first event duration is shifted slightly forwards, whereas the response distribution of the second event duration is shifted backwards. As can be seen in the right panel, these patterns are well-described by the model. In the model, the forward shift is caused by the incorporation of the feedback. Each time an event duration is over- or underestimated, participants received feedback (either "too long" or "too short"). As on many trials the second duration was overestimated, participants often received "too long" as feedback, and as a result updated their memory representation of the standard event duration. The backward shift shown by the dotted line can be explained by inferring a non-linear

timescale, as discussed earlier. Although individual parameters could have been adjusted to improve the fit to this specific dataset even further, the parameters were chosen to provide the best fit to a series of experiments. Most importantly however, the best fit was obtained with a parameter larger than 1.0, reflecting a non-linear subjective time scale. Since this experiment, we have considered this estimate as fixed and have used the same parameters in all subsequent models [100], as have other researchers [103].

To summarize, using the integrated-architecture model of interval timing makes it possible to create models that provide quantitative estimates of behavior that allow for a much more thorough testing of alternatives than would be possible if one is limited to qualitative predictions. Nevertheless, even when computational models are constructed that provide a reasonable fit the empirical data, the underlying mechanisms should always be scrutinized to make sure that they still align to the latest insights in neuroscience (see Hass and Durstewitz, this volume).

Neural Mechanisms of Interval Timing

The central tenet of both Scalar Timing Theory and the integrated-architecture model of interval timing is that a dedicated clock or timing circuit provides access to an index of subjective time, but neither theory has made any specific claims on the neural instantiation of this timekeeper. Interestingly, the neuroscience literature has suggested that the (pre-) supplementary motor area (SMA) might be part of the neural instantiation of the clock as it has been suggested to act as the accumulator [54]. The main observation supporting this notion was that the amplitude of a slow electrophysiological wave (the contingent negative variation, CNV) that is supposed to originate from the (pre-) SMA appears to covary as a function of the event duration that was estimated, e.g., CNV magnitude effect [104–106]. However, more recent work questions this interpretation because the CNV magnitude effect has proven difficult to replicate [73] and more recent electrophysiological data fails to align with the assumption that the CNV represents the accumulation process proposed by Scalar Timing Theory [69], but see also [107]. As a consequence, the interpretation of the original CNV results and its specificity of this slow wave potential to interval timing remains uncertain [74, 108]. It is clear from the empirical data that this slow wave develops over time and that it quickly resolves after a criterion duration has passed. However, this assumption could also be explained by assuming that the buildup observed in the SMA is driven by another source and only serves as an indirect measure of time. This explanation aligns nicely with the original notion that the buildup of the CNV reflects expectancy [109, 110]; and see for more recent reviews [111, 112], something that requires a sense of time, but is not necessarily time itself. This explanation is also supported by fMRI-EEG co-recordings on the basis of which it has been suggested that thalamo-cortical interactions regulate CNV amplitude ([113], see also the next section). Obviously, this line of argument can be followed for any accumulation or ramping patterns observed in neural substrates: the accumulation could be the source of time as hypothesized in the Scalar Timing Theory or the integrated-architecture theory discussed above, or it could be a derivative of time—Hass and Durstewitz, this volume; [74].

Although the instantiation of the clock stage is the most critical, several other difficulties remain when attempting to integrate the IP models discussed above with neurobiological mechanisms. For example, no neurobiological mechanism has been identified that can perform the ratio comparisons as hypothesized by the Scalar Timing Theory [76, 82]. Although the possibility remains that the required neural mechanisms may be identified in the coming years, another view that has emerged assumes that interval timing is based on the coincidence detection of patterns of oscillating neurons in cortico-thalamic-basal ganglia circuits [12, 44, 54, 71, 114–116].

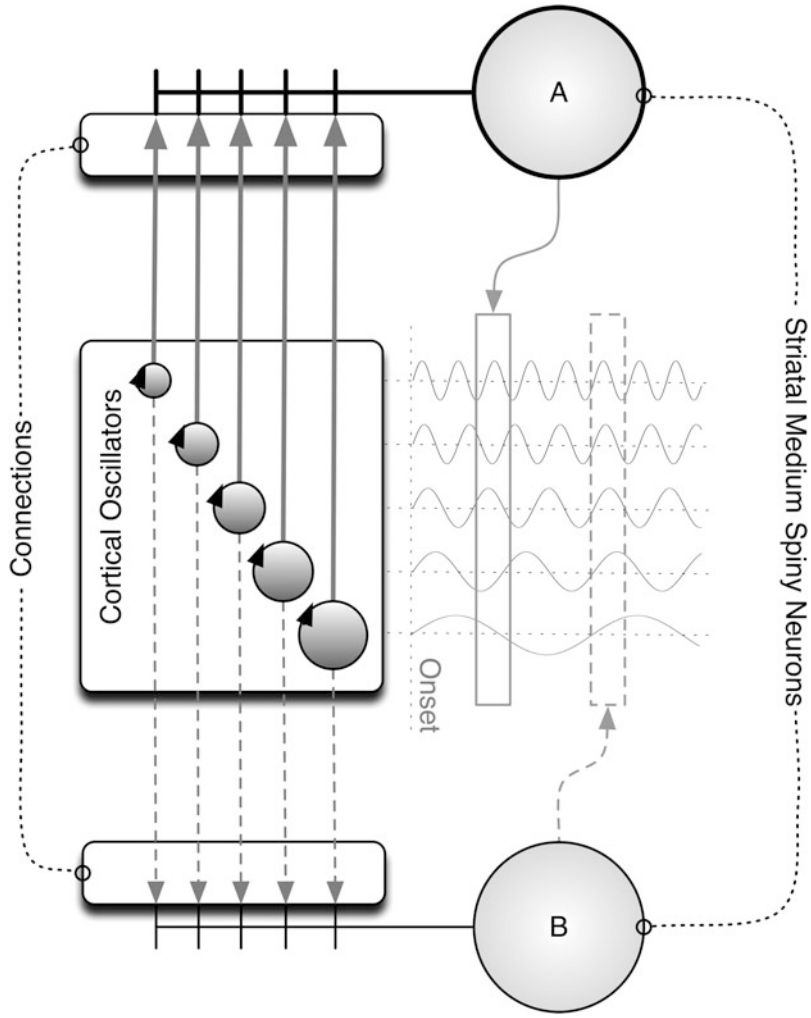

Fig. 5 Schematic depiction of the oscillatory-based timing circuit of the Striatal Beat-Frequency model [6, 76, 117]. At the start of an event, the phase of the Cortical Oscillators is reset after which the oscillations recommence. The different frequencies of the oscillators give rise to different activity patterns over time, depicted to the right of the Cortical Oscillators. Striatal medium spiny neurons (*A* and *B*) receive input from the oscillators via glutamatergic Connections. By dopaminergic input to the striatal neurons (not shown) after temporally salient events, the striatal neurons become sensitive to specific patterns in the oscillators (illustrated with *boxes* outlining activity patterns). In this illustration, striatal medium spiny neuron *A* has been reinforced to detect a coincidence pattern that occurs just after the onset of the event, and neuron *B* is sensitive to a pattern associated with a slightly longer event duration

Striatal Beat-Frequency Model

Based on the work of Miall [117], Matell and Meck [76] have proposed an alternative neural instantiation of the clock stage that assumes a cortico-striatal network as the primary source of temporal information. Although the full model is more detailed, especially with respect to the role of certain nuclei of the basal ganglia and the thalamus, the main outline is shown in Fig. 5. This SBF model is built around the notion that cortical neurons or neuron ensembles (the "Cortical Oscillators" in Fig. 5) oscillate at relative stable (over time) but different (over oscillators) frequencies, and that medium spiny neurons (MSNs –labeled A and B) act as detectors that

become active if a certain pattern is observed (via "Connections") among the oscillators. Because the oscillators have different frequencies, different points in time after resetting the phases of the oscillators will be associated with different patterns, thus allowing for the association between a certain coincidence pattern among the oscillators and a temporally salient event.

In the following sections, we will discuss the neurobiology and the functional properties of these different components of the SBF model.

The Oscillators

When discussing the role of oscillators in keeping track of time, the first concept that might come to mind is the suprachiasmatic nucleus (SCN), a tiny region in the anterior part of the hypothalamus. The SCN has an approximate period of 24 h and acts as the central timekeeper for circadian mediated behavior and body functions [118, 119]. In contrast to the SCN, which provides a single oscillating 24-period output signal, the oscillators in SBF models are assumed to play a more indirect role in the tracking of time from milliseconds to hours [120].

In the beat-frequency model proposed by Miall [117], populations of high-frequency (~10 Hz) oscillators are assumed to underlie the perception of event durations in the range of milliseconds to tens of seconds or minutes (i.e., durations $>$ 0.1 Hz). Each oscillator is assumed to have its own frequency, to become active when its activation has reached a certain threshold value, and will stay active until its activation drops below the threshold (this typically results in each oscillator being active for about 1–2 % of each cycle). In this basic beat-frequency model, all oscillators are connected to a single output unit or integrator. At the start of a to-be-timed event, the phase of all oscillators is reset after which the oscillations recommence. At the end of the event, Hebbian-type learning adjusts the connections between active oscillators and the output unit towards 1, and the other oscillators towards 0. After sufficient training, this model can reproduce the perceived duration of the event by resetting the phases of the oscillators at the start of the reproduction and responding when the integrator receives sufficient input from the oscillators. The simulations presented by Miall [117] elegantly demonstrate that populations of high-frequency oscillators with between-oscillator variation in period can act as a "clock" for interval timing as the system can accurately represent durations in the range of milliseconds to hours [12].

Using this basic beat-frequency model as a foundation, Matell and Meck [6, 76] have proposed the Striatal Beat-Frequency (SBF) model. Although the main extension is the augmented output unit (see the section "Striatal Medium Spiny Neurons"), these authors also refined what information is provided by the oscillators to later portions of the clock stage. Instead of assuming a binary output function per oscillator, with a single active period for a small proportion of every cycle and no activity during the remaining part of the cycle, the SBF model assumes a sinusoidal output pattern. This assumption is based on the idea that instead of a single neuron acting as an oscillator, each oscillator could be considered as an ensemble of neurons with a similar frequency (similar to the volley principle in auditory perception). Because neurons are known to fire probabilistically, with a firing rate that is a function of the phase [121], the output of each ensemble-based oscillator will follow a sinusoidal pattern [76, 122–124]. This idea has been further tested by Oprisan and Buhusi [85, 86], who have implemented this process using biophysically realistic Morris-Lecar (ML) cortical neurons [125, 126].

Assuming a similar Hebbian-type process for learning the connections between the output of the ensemble-oscillators and the output unit, Matell and Meck [6, 76] demonstrated that this extension was sufficient to elicit a more Gaussian-shaped pattern of activity in the output unit that is similar to what was observed in single cell recordings in the dorsal striatum. Moreover, by adding some global variability in the dopaminergic control of clock speed

[127–130]—resulting in all oscillators running either slightly faster or slower on each trial—longer durations are represented by a wider shaped distribution in the output unit, reflecting the scalar property even at the single-cell level [131]. Matell and Meck [76] have analytically shown how the scalar property can emerge from the SBF model of interval timing. In their implementation of the SBF model, they assume that virtually all of the cortical neurons that project onto MSNs fire regularly at frequencies in the 8–12 Hz band. Moreover, the output of each of these cortical neurons is modeled by a continuous sine curve oscillation. In contrast, the output of real neurons occurs as spikes, which are usually described by a point process. Although the sine wave description is used for its mathematical simplicity, each beat has a temporal width (e.g., ~50 ms broadening for a 10 Hz oscillation), which will likely have a significant influence on the timing variance. More recently, Buhusi and Oprisan [84] have examined the Morris-Lecar (ML) model for neuron firing, which generates non-linear, action potential-like beat oscillations. The "beats" produced with this ML model should also exhibit temporally broadening and hence affect timing variance in a manner currently unaccounted for. As a consequence, a more biologically realistic way to implement the SBF model would be to describe the output of cortical neurons by regular spikes (with a small jitter); each spike transmitted to the MSN evokes a postsynaptic excitatory current (EPSC); coincident spikes produce superimposed EPSCs that lead to spike discharge of the MSN, by which target durations are discriminated using the coincidence-detection mechanism described within the original SBF model [76].

Striatal Medium Spiny Neurons

Although the changes in the functioning of the oscillators are probably equally important in the development from the basic beat-frequency model to the SBF model, the Striatal Beat-Frequency model is named after the more precise neurobiological grounding of the output unit. According to the SBF model, striatal MSNs are the neurobiological implementation of the output unit of the basic beat-frequency model. This link is well supported by neurobiological evidence [54, 71, 132]. For example, the striatum is considered to be the main input system for the basal ganglia, with each striatal MSN receiving input from up to thirty thousand different cortical and thalamic units. The large number of connections aligns well with the assumption that the output unit is connected to a large number of oscillators. Second, the basal ganglia—and more specifically the dorsal striatum—are often considered to be a perceptual filtering system, with clear evidence that the striatal MSNs need a large number of coherent input signals before they fire. This, of course, is required to prevent the MSNs from firing as a result of limited oscillator input. Most importantly, Matell et al. [131] have shown that about 20 % of the measured dorsal striatal cell ensembles showed a temporally specific modulation in firing rate, with particular ensembles becoming active around 10 s after a signal, and other ensembles after around 40 s. This indicates that there are neurons in cortico-striatal circuits that are tuned to specific event durations [132, 133].

In the basic beat-frequency model, the output unit only fired when a specific number of output units were active at the same point in time. Using striatal MSNs as the output unit, Matell and Meck [6, 76] updated the temporal integration and detection process. Based on earlier work, the integration window for coincidence detection was set to 25 ms, reflecting the observation that multiple input signals need not arrive at exactly the same point in time to still be processed as if a coherent input pattern was observed. Moreover, based on the observation that less input is required to keep a MSN active once it has become active, an asymmetric threshold was implemented which results in a slight right skew in the output unit firing distributions. Such coincidence-detection processes and oscillatory processes are ubiquitous in the brain and are a major advantage for the SBF model [9, 44, 76, 134–136].

Connections

In both the original SBF model [6, 76] and in the SBF-ML model [84–86], the input to the striatal MSNs is mediated by the synaptic strength of the connections between oscillators and MSNs. In the SBF model, the synaptic strength is determined by averaging the state of the oscillators at previous times of reinforcement. This learning is driven by long-term potentiation modulated by the dopamine that is released upon the registration of a temporally salient event. The synaptic strengths will represent a distribution of oscillatory states, as global noise in the frequencies of oscillators will result in slightly different oscillatory states on different trials. As a result, the detection of longer event durations will more heavily rely on oscillators with lower frequencies. Because slower oscillators will have a longer period of higher activity, the MSNs encoding a long event duration will receive input for a longer period of time and thus stay active longer, giving an additional source of scalar variance.

Given that these simulations involve all striatal MSNs having identical properties (such as the way incoming information is integrated and similar firing thresholds), and each MSN could be connected to any oscillator, each MSN could, in principle, represent any event duration unless they are chronotopically organized [132]. Therefore, the ability to represent a particular event duration depends on the learned synaptic strengths. In both SBF and SBF-ML, the synaptic strengths of a particular MSN are based on a memory representation of all previous experiences with the event duration that that particular MSN encodes for. As such, these cortico-striatal synaptic strengths have the same functional role as the pulse counts stored in reference memory in Scalar Timing Theory [17] and in the integrated-architecture account of timing [100]: i.e., the synaptic strengths serve as a filtering mechanism that constrains the firing of a MSN to times associated with a particular event duration, in the same way as the pulse counts constrain a response to a particular accumulator value or clock reading stored in memory.

Interval Timing within the Striatal Beat-Frequency Model

In IP theories of interval timing, the memory stage links the clock—implemented as a combination of a pacemaker and accumulator—to the processes that should perform a certain action at a particular point in time: only when the value stored in the accumulator is equal to or similar enough to the value retrieved from memory will the decision rule be applied. The three main components of the SBF model can be straightforwardly mapped onto this description [44, 54, 76]. First, the oscillators provide the same type of information as the combined pacemaker-accumulator in the IP models—a unique pattern of activation versus a unique integer count for different event durations. Second, as mentioned above, the cortico-striatal connections serve a similar role as the memory traces in the IP models, with synaptic strengths acting as a filtering mechanism that constrains the firing of a MSN to times associated with a particular event duration, in the same way as the pulse counts constrain a response to a particular accumulator value. And third, the firing of a MSN is synonymous with the decision stage in the IP models. In Scalar Timing Theory, the firing of a decision rule indicates that later, unspecified processes can perform the action that was associated with the reproduced duration (i.e., start pressing a lever to receive the food reward), whereas in the integrated-architecture account, observing that the values in the accumulator and the retrieved memory trace are identical will cause a decision rule to be applied that sets in action the execution of the temporally constrained action.

The main difference between the SBF model and pacemaker-accumulator models is that pacemaker-accumulator models implicitly assume that there is one decision rule which could, in principle, be used for estimating different event durations. That is, the same ratio rule in Scalar Timing Theory or the same decision rule in the integrative-architecture theory could be used to estimate different event durations as

long as these durations can be uniquely encoded in and retrieved from memory. In the SBF model, the synaptic strengths are unique to each individual receiving MSN, which means that each subjectively unique event duration has to be encoded by a unique MSN. One could therefore say that after experiencing a particular duration *D* a number of times, which will have resulted in well-learned synaptic strengths, the associated MSN has become a temporal "feature detector" that will always fire after *D* time has passed. If, at a later point in time, another event has the same temporal structure, this particular MSN could be linked to that event as well, suggesting that striatal MSNs act in a very similar manner as feature detectors or perceptrons for other types of sensory input [137, 138].

Integration of Striatal Beat-Frequency and Models of Complex Interval Timing

Although the SBF and SBF-ML simulations focus on learning and reproducing a single duration, any timing system should be able to distinguish between or estimate multiple intervals. As acknowledged by Matell and Meck [76] and Oprisan and Buhusi [85, 86], and shown in Fig. 5, multiple striatal MSNs could be connected to the same set of oscillators. By means of different reinforcement patterns, each MSN would have different synaptic strengths and thus be attuned to different event durations. This raises the question as to whether each event will be associated to its own MSN, or whether different events that share a relatively similar temporal pattern will be encoded using the same MSN. It might be clear that it is theoretically impossible to have a separate MSN for each possible event duration this would require an infinite number of MSNs. At the same time, objective event durations that are sufficiently different should also be perceived as being different. The minimal objective duration that reliably results in subjective differences is called the just-noticeable-difference (JND) and, as described by Weber's law, is proportional to the length of the two to-be-distinguished durations. This would suggest that temporal precision is higher for shorter durations than for longer durations. That is, the distance between the event duration to which a MSN is most sensitive and the event duration of its direct neighbor should increase with the length of those durations.

This theoretical rationale for a nonlinear distribution of the MSNs is supported by computer simulations. Based on assumptions derived from the SBF model, we have constructed a novel variant of the SBF model (SBF*n*) that can learn to encode multiple ("*n*") distinct event durations. The initial state of this SBF*n* model is depicted in the left panel of Fig. 6. Each smaller distribution reflects the receptive field of a single detector that is modeled after the MSNs in the SBF model. Based on the simulations presented by Matell and Meck [76]—see for example their Figure 3.2-12, we expressed each neuron's sensitivity for a particular event duration as a skewed-normal distribution with a mean equal to the encoded duration, a standard deviation that is scalar in the mean, and a slight skew of 2. The left panel of Fig. 6 also shows the initial a-theoretic linear distribution of the detectors over the range of event durations for which they are sensitive. After creating this initial distribution, the SBF*n* model is presented with randomly drawn event durations, uniformly sampled from the entire range. For each sampled event duration, the MSN with the most active receptive field is selected, simulating that this particular objective duration is perceived as the subjective duration represented by that detector. In line with the idea that the synaptic strengths will be updated each time an event duration is encountered that results in the firing of a MSN, the mean of the distribution is updated following a simple reinforcement learning algorithm. The distributions shown in the right panel of Fig. 6 represent the detectors of SBF*n* after sufficient training has been provided and a relatively stable pattern has emerged. Clearly, a nonlinear pattern is exhibited, starting with high temporal resolution at shorter durations with a negatively accelerating decrement in temporal resolution for longer durations. The dotted line shown in the right panel of Fig. 6 is a best fit

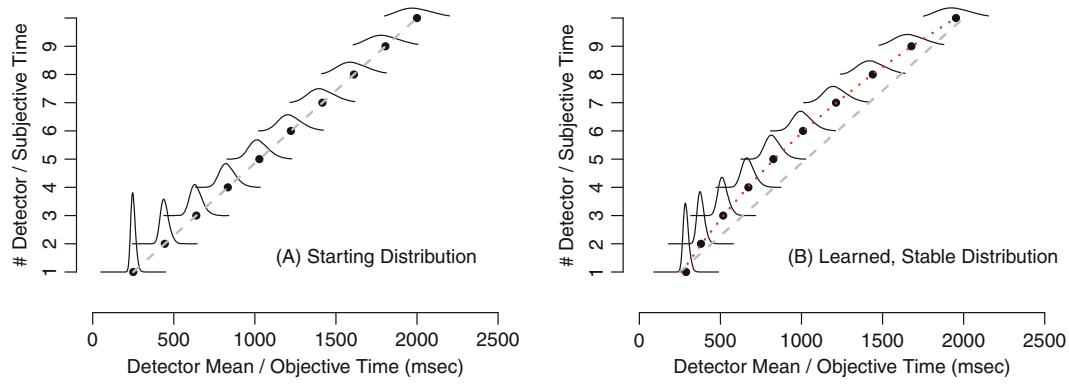

Fig. 6 Starting distribution (*left panel*) and learned, stable distribution (*right panel*) of an extended Striatal Beat-Frequency model that can represent multiple durations (SBF*n*). The x-axis depicts the objective time to which each of the ten simulated detectors modeled after striatal medium spiny neurons is sensitive. Each of the detectors has a skewed-normal receptive field that scales with the represented event duration. The initial state of the SBF*n* model, depicted in the *left panel* reflects linear temporal precision. The stable distribution of detectors, shown in the *right panel*, emerges after training. This distribution follows a geometric series as can be seen by the *dotted line* that follows the function $\sum(110 \times 1.1^{n}) + 150$

geometric series, indicating that the temporal resolution closely resembles Fechner's observation that the subjective experience increases arithmetically for geometrically increasing physical stimuli. Interestingly, many of the basic assumptions of these different SBF models could also be applied to the IP models of interval timing. For example, the assumption of global variability in the frequencies of the oscillators could be translated to variability in clock speed between trials in Scalar Timing Theory as was proposed by Matell and Meck [76]. This would remove the need for the memory translation based on k^*. However, to account for other effects associated with the scalar property, such as the JND effect, a ratio-rule would still be required.

As the distribution of simulated detectors in the SBF*n* model follows the same pattern of nonlinearity as was used in the integrated-architecture model of interval timing, it is straightforward to update this model to match the properties of the neurobiologically constrained SBF*n* model. That is, where the original integrated-architecture model assumed that the clock module provides a readout on an interval scale that represents the current time, an updated version could simply be provided with an indication of which MSN fired most recently. Because these feature detectors will always fire in sequence, the model will be able to predict which detector will fire next, thus providing an index of the passage of time even before the target detector has fired (concept of "shorter" than) as well as after it has fired (concept of "longer" than). This information could drive expectancy-based processes as it might provide the thalamocortical-based input to decision processes that regulate the CNV amplitude as hypothesized by Nagai et al. [113]. Although a complete SBF model as implemented by Matell and Meck [76] and Oprisan and Buhusi [85, 86] could be included in the integrated-architecture model, a more pragmatic approach would be to update the parameters of the geometric series in the model so that the mapping of objective to subjective time follows the distributions of the MSNs of the SBF*n* model.

Integration of Interval Timing and Models of Working Memory

One of the remaining questions is related to the source of the oscillations that provide the input to the MSNs as neither the SBF nor SBF*n* model

identifies the exact source. Interestingly, both theoretical and empirical work suggests that working memory and interval timing rely not only on the same anatomical structures, but also on the same neural representation of a specific stimulus [139, 140]. Specifically, cortical neurons may fire in an oscillatory fashion to form representations of stimuli, and the MSNs may detect those patterns of cortical firing that occur co-incident to important events. Information about stimulus identity can be extracted from which cortical neurons are involved in the representation, and information about duration can be extracted from their relative phase. Based on this link between working memory and interval timing [140], the SBF and SBF*n* models of interval timing can be extended to an oscillatory model of interval timing and working memory (SBF*m*). The principles derived from these biologically based models also fit well with a family of models that emphasize the importance of time in many working-memory phenomena [141–143].

Neural oscillation is an important feature in both interval timing and working memory. In particular, the activation of working memory is associated with increased gamma oscillations (e.g., 25–100 Hz) in the frontal cortex that are entrained to the hippocampal theta-frequency range (e.g., 5–12 Hz) in multiple brain areas including the cortex, striatum, and hippocampus—all relevant to interval timing [139, 144]. Recent evidence suggests that phase-amplitude coupling (PAC) of theta and gamma occurs during working memory maintenance [145–147]—where PAC refers to the phenomenon of coupling between the amplitude of a faster oscillation and the phase of a slower oscillation. Such a relation between different frequency ranges has been shown to be a prevailing feature of neural activity associated with cognitive function. Penttonen and Buzsaki [148], for example, showed a natural logarithmic relationship in the periods of delta, theta, gamma, and ultra-fast oscillations, while Lakatos et al. [149] have shown hierarchical relations in delta, theta, and gamma bands of activity. In this regard, the relations among these different frequency categories are thought to be important in controlling patterns of neural activation.

Computer simulations suggest that multiple oscillators with different frequencies produce these logarithmic and hierarchical relationships. Moreover, the simulated relation between different frequency ranges appears to be fractal, i.e., gamma oscillations are entrained within theta, which is, in turn, entrained within delta oscillations [139]. Consequently, it has been hypothesized that interval timing and working memory are decoded from different ranges of these oscillatory periods. More specifically, MSNs in the striatum could detect cortical target representations from the spatio-temporal patterns of gamma spikes entrained with theta (for stimulus attributes in working memory) or from synchronous patterns of theta oscillations entrained in slow oscillations (for event durations in interval timing). In this manner, the same patterns of oscillation in cortical networks can represent stimulus attributes and event durations simultaneously. Moreover, an optimal strategy for detection can distinguish between interval timing and working memory, i.e., a diverse range of delta–theta frequencies is favorable for encoding event duration, whereas synchronous theta oscillations are better for maintaining one or more items in working memory because this effectively increases the size of neuronal network. Therefore, the observed interference between interval timing and working memory [150–154] can be explained in terms of how the range of theta-oscillation frequencies is set (e.g., multiple theta frequencies or a single theta frequency synchronized with cortical oscillations). We suggest that network synchrony analyses, as described by Burke et al. [155] and Gu et al. [139], are able to distinguish between two types of spectral modulations: (1) those that reflect synchronous engagement of MSNs in the striatum with cortical or hippocampal neurons and (2) those that reflect either asynchronous modulations of neural activity or local synchrony accompanied by disengagement from other brain structures. The basic idea is that these different spectral modulations within cortico-thalamic-basal ganglia circuits have distinct

spatiotemporal profiles during the timing of event durations and the encoding of specific stimulus attributes in working memory [99, 132, 140], thus providing an integrative format for the representation of time and other types of episodic information.

Summary and Conclusions

In this chapter we have shown how over the years the original IP model of interval timing has been extended. At the basis of this work lies the original theory proposed by Treisman [14] which specified, in verbal terms, how the combination of clock, memory and decision stages could give rise to temporal behavior. Gibbon et al. [17] further developed this model in a series of papers that refined the original theory by providing specific and quantitative implementations of the different IP stages. A large proportion of the current work in the field of interval timing is still based on the ideas put forward in the context of this Scalar Timing Theory. Two lines of work can be identified that branched off from this original model. Work in one branch focused on improving the neurobiological foundations of Scalar Timing Theory. The main example of this work is the Striatal Beat-Frequency model [6, 76] which demonstrates that a cortico-thalamic-basal ganglia network can implement the clock stage as proposed in Scalar Timing Theory. The other branch has focused on complementing the IP-models of interval timing with an integrated cognitive architecture [75, 83]. On the one hand, this integrated-architecture allows researchers to create models of more complex tasks in which interval timing plays a crucial role, whereas on the other hand this integration provides further constraints on interval-timing theories as the putative processes need to be filled in with greater detail. This requirement can also result in new explanations for existing phenomena. For example, the processes underlying the long-term declarative memory system of the integrative- architecture model allow for the precise modeling of the memory effects [100] observed in interval timing (i.e., the "memory mixing" effect—[50, 65, 98]).

Current work in this field is focused on reuniting these two branches. In the SBF*n* model, the SBF and integrated-architecture model of interval timing are combined, providing a neurobiology-based model that can be used to model complex time-based tasks. Although extending the integrative-architecture model to include a SBF-based clock stage does not change its functional properties, the neurobiological basis of the SBF model provides further constraints for this architecture-based model. Another approach to unification is the proposed SBF*m* model. The idea for this model is based on extensive work that links working memory to oscillations in the same cortico-striatal network that serves as the basis of the SBF model. The SBF*m* model links working memory processes and interval timing by assuming that the firing patterns of the oscillating neurons could encode for content in the working memory system, whereas the phase of these oscillations could encode for temporal properties [139, 140]. Future work will focus on the implementation of this SBF*m* model, and at the same time testing the predictions of this model using, for example, network synchrony analyses [139, 155] and model-based fMRI analyses [156–158] in an attempt to unify prospective and retrospective time estimation [159–163].

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Neural Dynamics Based Timing in the Subsecond to Seconds Range

Dean V. Buonomano

Abstract

The brain must solve a wide range of different temporal problems, each of which can be defined by a relevant time scale and specific functional requirements. Experimental and theoretical studies suggest that some forms of timing reflect general and inherent properties of local neural networks. Like the ripples on a pond, neural networks represent rich dynamical systems that can produce time-varying patterns of activity in response to a stimulus. State-dependent network models propose that sensory timing arises from the interaction between incoming stimuli and the internal dynamics of recurrent neural circuits. A wide-variety of time-dependent neural properties, such as short-term synaptic plasticity, are important contributors to the internal dynamics of neural circuits. In contrast to sensory timing, motor timing requires that network actively generate appropriately timed spikes even in the absence of sensory stimuli. Population clock models propose that motor timing arises from internal dynamics of recurrent network capable of self-perpetuating activity.

Keywords

Millisecond timing • Neural dynamics • Short-term synaptic plasticity • Temporal processing • Motor timing

Introduction

The nervous system evolved to allow animals to adapt to and anticipate events in a dynamic world. Thus the need to tell time was among the earliest forces shaping the evolution of the nervous system. But telling time is not a singular biological problem: estimating the speed of moving objects, determining the interval between syllables, or anticipating when the sun will rise, are all temporal problems with distinct computational requirements. Because of the inherent complexity, diversity, and importance of time to animal evolution, biology has out of necessity devised numerous solutions to the problem of time.

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Humans and other animals time events across a wide range of temporal scales, ranging from microsecond differences in the time it takes sound to arrive in the right and left ear, to our daily sleep-wake cycles, and beyond if we consider the timing of infradian rhythms such as menstrual cycles. At a societal and technological level humans also keep track of time over many orders of magnitude, from the nanosecond accuracy of the atomic clocks used for global-positioning systems to the clocking of our yearly trip around the sun. It is noteworthy that in the technological realm we can use the same devices to tell the time across the full spectrum of time scales: for example, atomic clocks are used to time nanosecond delays in the arrival of signals from different satellites, as well as to make adjustments to the calendar year. Virtually all modern man-made clocks—from an atomic clock to a grandfather clock—rely on the same simple principle: an oscillator that generates events at some fixed interval and a counter that integrates events ("tics") to provide an estimate of time with a resolution equal to the period of the oscillator. In stark contrast, evolution has devised fundamentally different mechanisms for timing across different time scales, and even multiple mechanisms to solve temporal problems within the same time scale. The fact that there are numerous biological solutions to the problem of telling time likely reflects a number of factors. First, the biological building blocks of the brain lack the speed, accuracy, and counting precision of the electronic components that underlie modern man-made clocks. Second, the features required of a biological timer vary depending on whether its function is to process speech, or to control the circadian fluctuations of sleep-wake cycles. Third, different temporal problems, such as sound localization, capturing the temporal structure of animal vocalizations, or estimating when the sun will rise emerged hundreds of millions of years apart during evolution; and were thus subject to entirely different evolutionary pressures and potential solutions. The result is that while animals need to discriminate microsecond differences between the arrival of sounds to each ear *and* the hours that govern their sleep-wake cycles, the timing mechanisms responsible for both these tasks have nothing in common. In other words, the "clock" responsible for the millisecond timing does not have an hour hand, and our circadian clock does not have a second hand.

For the above reasons, any discussion of timing should be constrained to specific scales and tasks. This chapter will focus on the scale of tens of milliseconds to a few seconds. It is within this range in which the most sophisticated forms of timing lie. Computationally speaking, timing on shortest and longest scales is mostly limited to detection of isolated intervals and durations. But within the scale of tens of milliseconds to seconds, the brain must process and generate complex temporal patterns. It is within this range in which most animals generate and decode the complex temporal structure of auditory signals used for communication. For example, in human language, the duration and intervals between different speech segments is critical on many different levels, from the timing of the interval between syllables and words [1–4] to the overall prosody in which the rhythm and speed of speech influence our interpretation of affect speech recognition and for the determination of prosody [5]. For example, the pauses between words contribute to the interpretation of ambiguous sentences such as "Kate or Pat and Tony will come to the party" (i.e., will Kate or Pat as well as Tony come, versus, will Kate or, Pat and Tony, come) [2]. Additionally, on the motor side the complex motor patterns necessary for speech production, playing the piano, or performing highly coordinated motor patterns animals must perform to hunt are heavily dependent on the brain's ability to produce timed motor outputs [6]. Perhaps the easiest way to express the unique sophistication of temporal processing on the scale of tens of milliseconds to seconds is by pointing out that human language can be effectively reduced to a purely temporal code. In Morse code there is a single communication channel and all information is transmitted in the order, interval, duration, and pattern of events. It is a testament to the brain's ability to process temporal information that humans can learn to communicate with

Morse code, but this ability is constrained to a specific time scale, the brain simply does not have the hardware to understand Morse code with 'dot' and 'dash' durations of a few millisecond or of many seconds: the ability to process complex patterns is lost at both very fast and very slow speeds!

In this chapter we will focus on a class of models mentioned in fourth chapter (Hass and Durstewitz, this volume) termed state-dependent networks, that offers a general framework of the mechanisms underlying timing on the scale of tens of milliseconds to a few seconds. This class of models is unique in that it provides a framework to process both simple forms of interval and duration discrimination, as well as the ability to process complex spatiotemporal patterns characteristic of speech or Morse code. A key principle in this framework is that precisely because timing is such an important computational problem it is proposed that neurons and neural circuits evolved precisely to solve temporal problems, and thus that timing on the scale of tens of milliseconds to a few seconds should be seen as an intrinsic, as opposed to a dedicated (fifth chapter), computation. Thus under this framework timing is simply one of the main computational tasks neural networks were "designed" to perform.

Timing with Neural Dynamics

The principle underling most man-made clocks is that by counting the cycles of an oscillator that tics at a fixed frequency it is possible to keep track of time. It is important to note, however, that there are ways to tell time that do not rely on oscillators. In principle, any dynamic system, regardless of whether it exhibits periodicity or not, can potentially be used to tell time—indeed this statement is a truism since *dynamics* refers to systems that change over time. Consider a child sliding down a water slide, if she goes down from the same initial position every time, she will take approximately the same amount of time to reach the bottom every time. We could mark the slide to represent 1 s intervals, which would have smaller spacing at the top and larger spacings at the bottom where the velocity is higher. Thus as the child crosses the different lines we could tell if she started approximately 1, 2, 3, or 4 s ago. The point is, is that any dynamical system that can be follow the same trajectory again and again has information about time. Indeed, in his famous experiments on motion Galileo applied this same concept when analyzing the speed a ball roles down an inclined plane.

A slightly more appropriate analogy to prepare us for how neural dynamics can be used to tell time is a liquid. A pebble thrown into a pond will create a spatiotemporal pattern of ripples: the concentric waves that travel outwards from the point of entry. If you were shown two pictures of these ripples you could easily tell which picture was taken first based on the diameter of ripple pattern, and importantly with some knowledge of the system and a bit of math, you could estimate how long after the pebble was thrown in were both pictures taken. Now let's consider what happens when we throw in second pebble: the pattern produced by a second pebble will be a complex interaction between the internal state of the liquid (the current pattern of ripples). In other words the ripple pattern produced by the second pebble will be a function of the inter-pebble interval, because the interaction between the internal state of the system and subsequent "inputs". As we will see below this notion of an evolving internal state and the interaction between that internal state and new inputs is key to state-dependent network models—particularly in the context of sensory timing.

Networks of neurons are a complex dynamic system—not just any dynamic system, but arguably one of the most complex dynamic systems known. Defining the internal state of neural network, however, is not as straightforward as it might seem, so it will be useful to distinguish between two components that characterize the state of neural networks: the *active* and *hidden* state.

Active States

Traditionally, the state of a neural network is defined by which neurons are firing at a given

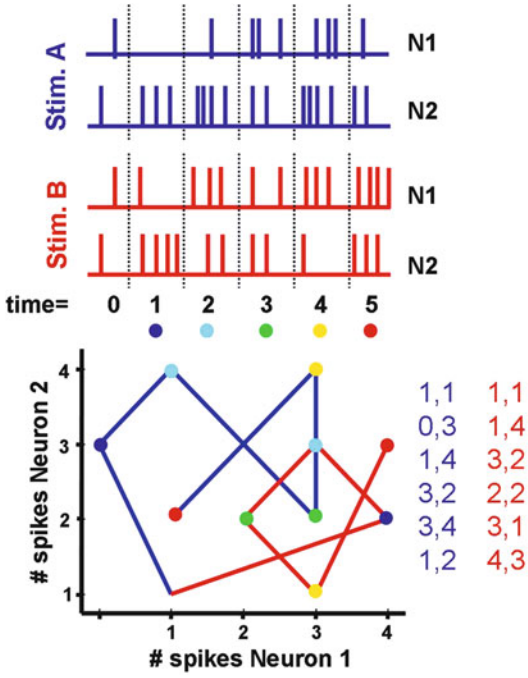

Fig. 1 Neural trajectories. A) The changing patterns of activity of a neural network can be represented as neural trajectories. Any pattern of activity can be represented in a space where the number of dimensions correspond to the number of units. In the simple case of two neurons trajectories can be plotted in 2 dimensional space where each point corresponds to the number of spikes within a chosen time window. In this schematic two different trajectories (*blue* and *red*) are elicited by two different stimuli, and because the trajectories evolve in time, the location of the each point in space codes for the amount of time that has elapsed since the onset of either stimulus (from Buonomano and Maass [73])

point in time–I will refer to this as the *active state*. We can formally define the active state of a network composed of N neurons as an N-dimensional vector that is composed of zeros and ones—where a zero signifies that a neuron is not firing and a one means that it is (depending on the size of the time bin we can also represent each value as a real number representing the firing rate). Such a vector forms a point in N-dimensional space, and defines which neurons are active at a time point *t*. Over the course of multiple time bins these points form a path (a neural trajectory) through state space (Fig. 1A). Because the trajectory plays out in time each point can potentially be used to tell time. One of the first models to suggest that the changing population of active neurons can be used to encode time was but forth by Michael Mauk in the context of the cerebellum [7–9]. The cerebellum has a class of neurons termed granule cells, and these are the most common type of neuron in your brain—more than half the neurons in the brain are granule neurons [10]. Mauk proposed that one reason there are so many granule cells is because they do not only code for a particular stimulus or body position but the amount of time that has elapsed since any given stimulus was presented. The model assumes that a stimulus will trigger a certain population of active granules cells, and that at each time point $t + 1$ this neuronal population will change, effectively creating a neural trajectory that plays out in time. Why would the population of granule cells change in time in the presence of a constant (non-time varying) stimulus? The answer lies in the recurrency, or feedback, that is characteristic of many of the brain's circuits. As we will see below the recurrency can ensure that which neurons are active at time *t* is not only dependent on the synapses that are directly activated by the input, but also depends on the ongoing activity within the network; thus the neurons active at $t + 1$ is a function of both the input and which neurons were active at *t*. Under the appropriate conditions feedback mechanisms can create continuously changing patterns of activity (neural trajectories) that encode time.

Numerous *in vivo* electrophysiology studies have recorded reproducible neural trajectories within neural circuits. These neural trajectories have been observed in response to either a brief stimulus or prolonged time-varying stimuli [11–14]. Other studies have demonstrated that these trajectories contain temporal information [15–20]. While these results support the notion that time can be encoded in the active state of networks of neurons, it has not yet been clearly demonstrated that the brain is actually using these neural trajectories to tell time.

Hidden States

Defining the state of a neural network is more complicated then simply focusing on the active

state. Even a perfectly silent network can respond to the same input in different manners depending on its recent history of activity. Put another way, even a silent network can contain a memory of what happened in the recent past. This is because neurons and synapses have a rich repertoire of time-dependent properties that influence the behavior of neurons and thus of networks. On the time scale of tens of milliseconds to a few seconds, time-dependent neural properties include short-term synaptic plasticity [21, 22] slow inhibitory postsynaptic potentials [23, 24], metabotropic glutamate currents [25], ion channel kinetics [26, 27], and Ca^{2+} dynamics in synaptic and cellular compartments [28, 29], and NMDA channel kinetics [30]. I refer to these neuronal and synaptic properties as the *hidden* network state, because they are not accessible to the downstream neurons (or to the neuroscientist performing extracellular recordings) but will nevertheless strongly influence the response of neurons to internally or externally generated inputs.

Much of the work on the hidden-states of neural networks has focused on short-term synaptic plasticity, which refers to the fact that the strength of a synapse is not a constant but varies in time in a use-dependent fashion. For example, if after a long silent period (many seconds) an action potential is triggered in a cortical pyramidal neuron might produce a postsynaptic potential (PSP) of 1 mV in a postsynaptic neuron. Now if a second spike is triggered 100 ms after the first spike the PSP could be 1.5 mV. Thus the same synapse can have multiple different strengths depending on its recent activity. This short-term plasticity can take the form of either depression or facilitation, depending on whether the second PSP is smaller or larger then the 'baseline' PSP, respectively. An example of short-term facilitation between cortical pyramidal neurons is shown in Fig. 2. Most of the brain's synapses undergo depression or facilitation for the duration of a time scale of hundreds of milliseconds [21, 31–33], but some forms short-term synaptic plasticity can last for seconds [21, 34, 35].

It is important to note that short-term synaptic plasticity is a type of a very short-lasting memory. The change in synaptic strength is in effect a memory that a given synapse was recently used. Furthermore, the memory is time-dependent: the change in synaptic strength changes smoothly in time. For example in the case of short-term facilitation of EPSPs between cortical pyramidal neurons the amplitude of the second of a pair of EPSPs generally increases a few tens of milliseconds after the first EPSP and then decays over the next few hundred milliseconds. Because of this temporal signature the STP plasticity provides a potential 'clock'—in the sense that it contains information about the passage of time. But as we will see it is unlikely that individual synapses are literally telling time, rather theoretical and experimental evidence suggests that short-term synaptic plasticity contributes to time-dependent changes in the active states of neural networks, which do code for time.

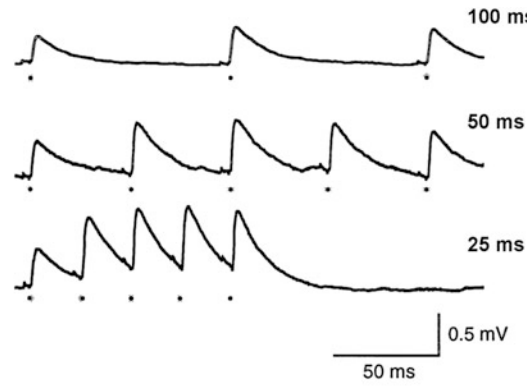

Fig. 2 Short-term synaptic plasticity. Each trace represent the voltage of a postsynaptic neuron during the paired recording of two connected layer 5 pyramidal neurons from the auditory cortex of a rat. The amplitude of the EPSP (that is, the synaptic strength) changes as a function of use. In this case facilitation is observed. The strength of the second EPSP is larger than the first, and the degree of facilitation is dependent on the interval, the largest degree of facilitation is observed at 25 ms (from Reyes and Sakmann [31])

Hidden and Active States, and Sensory and Motor Timing

Consider a highly sophisticated temporal task of communicating using Morse code. As mentioned above, Morse code is a temporal code, in the

sense that there is only a single spatial channel: all information is conveyed in the interval, order, and number of the "dots" (short elements) and "dashes" (long elements). Understanding Morse code requires that our auditory system parse the intervals and duration of the signals, but generating Morse code, requires that the motor system produce essentially these same durations and intervals. Does the brain use the same timing circuits for both the sensory and motor modalities? This important question, relates to one discussed throughout this book. Are the mechanisms underlying timing best described as *dedicated*—i.e., there is a specialized and centralized mechanism responsible for timing across multiple time scales and processing modalities. Or, conversely is timing *intrinsic*—i.e., is timing a general property of neural circuits and processed in a modality specific fashion [36]. State-dependent network models are examples of intrinsic models of timing, and argue that because virtually all neural circuits exhibit active and hidden states that most neural circuits can potentially tell time. But different circuits are likely to be more or less specialized to tell time. Additionally, different circuits likely rely on the active or hidden states to different degrees to tell time. This point is particularly important when considering the difference between sensory and motor timing. In a sensory task, such as interval discrimination, you might be asked to judge if two tones were separated by 400 ms or not; in a motor production task you might be asked to press a button twice with an interval as close to 400 ms as possible. Note that in the sensory task the critical event is the arrival of the second externally generated tone. Your brain must somehow record the time of this external event and determine whether it occurred 400 ms after the first. But in the motor task your brain must actively generate an internal event at 400 ms. This difference is potentially very important because sensory timing can be achieved 'passively': time is only readout when the network is probed by an external stimulus. But because the network could be silent during the inter-tone interval it is entirely possible that the time is 'kept' entirely by the hidden state (until the arrival of the second tone, when the hidden state is translated into an active state). In contrast, motor timing cannot rely exclusively on the hidden state: in order to generate a timed response there should be a continuously evolving pattern of activity (although there are some exceptions to this statement). Thus, although sensory and motor timing may in some cases rely on the same mechanisms and circuits, it is useful to consider them separately because of the potential differences between the contributions of hidden and active states to sensory and motor timing.

Sensory Timing

The central tenet of state-dependent network models of sensory timing is that most neural circuits can tell time as a result of the interaction between the internal state networks and incoming sensory information. Computer simulations have demonstrated how both the hidden and active states of neural networks can underlie the discrimination of simple temporal intervals and durations, as well as of complex spatiotemporal patterns such as speech [37–43]. These models have been based on spiking models of cortical networks that incorporate hidden states, generally short-term synaptic plasticity. The networks are typically recurrent in nature, that is, the excitatory units synapse back on to themselves. Critically, however, in these models the recurrent connections are generally relatively weak, meaning that the positive feedback is not strong enough to generate self-perpetuating activity. In other words in the absence of input these networks will return to a silent (or baseline spontaneous activity) active state.

To understand the contributions of the hidden and active states it is useful to consider the discrimination of intervals versus durations or complex time-varying stimuli. Interval discrimination must rely primarily on the hidden state. For example, consider the discrimination of two very brief auditory tones presented 400 ms apart. After the presentation of the first tone the network rapidly returns to a silent state—thus the active state cannot "carry" the timing signal—

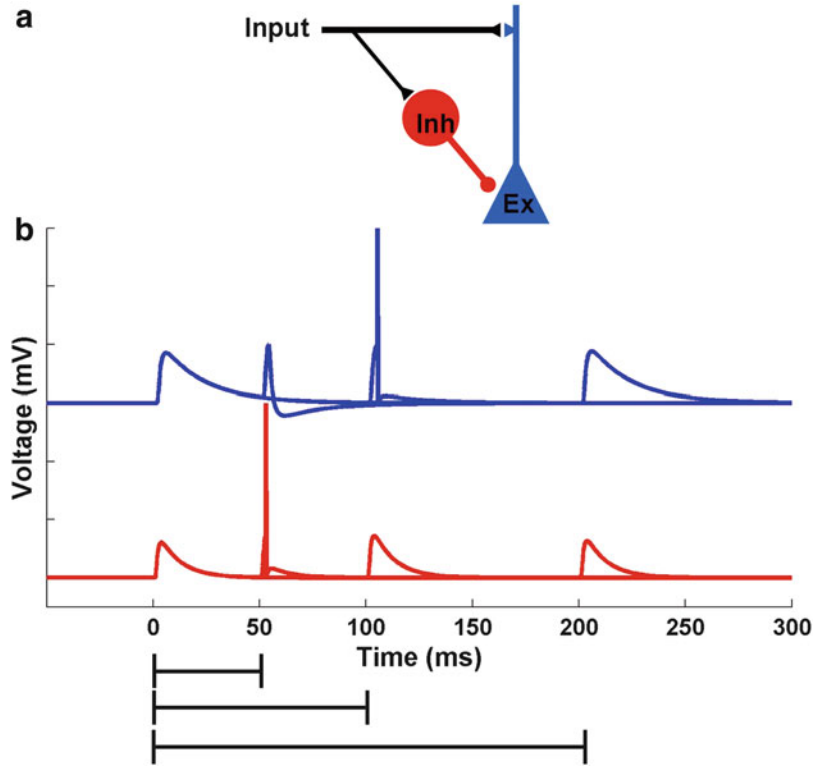

Fig. 3 Simulation of interval selectivity based on short-term plasticity. (**a**) Schematic of a feedfoward disynaptic circuit. Such circuits are almost universally observed throughout the brain. They are characterized by an input that excites both an inhibitory and excitatory neuron (for example, thalamocortical axons synapse on both excitatory and inhibitory neurons), and feedfoward inhibition (the excitatory units receives inhibition from the inhibitory neuron). Each of the three synapses exhibit short-term synaptic plasticity. (**b**) Short-term synaptic plasticity (the hidden state) can potentially be used to generate interval selective neurons. Perhaps the simplest scenario is one in which both the excitatory and inhibitory neurons receive inputs that exhibit paired-pulse facilitation. In this example, a the Ex units spikes is selective to the 100 ms interval because at 50 ms it is inhibited by the spike in the inhibitory neurons, and at the 200 ms interval short-term facilitation is no longer strong enough to drive it to threshold

but the hidden state can "remember" the occurrence of the first tone (provided the second tone is presented within in the time frame of the time constants of short-term synaptic plasticity). But for a continuous stimulus, such as duration discrimination, or the discrimination of words spoken forwards or backwards, the temporal information can be encoded in both the hidden and active state because the stimulus itself is continuously driving network activity.

To understand the contribution of hidden states alone to temporal processing we will first consider very simple feedforward networks (that is, there are no excitatory recurrent connections capable of driving activity in the absence of input). These simple circuits rely primarily on short-term synaptic plasticity to tell time, and while they cannot account for the processing of complex temporal patterns, experimental data suggest they contribute to interval selectivity in frogs, crickets, and electric fish [44–48].

Sensory Timing in a Simple Circuit

Figure 3 provides an example of a very simple feedforward circuit that can discriminate a 100 ms interval from 50 and 200 ms intervals. The circuit reflects a virtually universal architecture in neural circuits: feedforward excitation

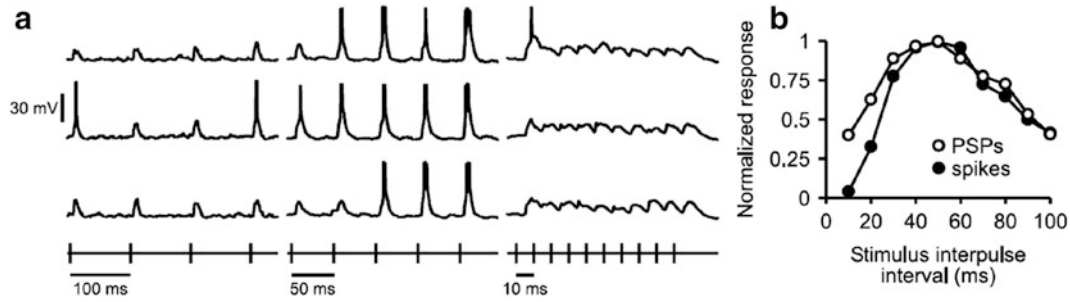

Fig. 4 Temporal selectivity in midbrain neurons. (**a**) Voltage traces from a neuron in the midbrain of an electric fish. Each trace represents the delivery of trains of electrical pulses presented at intervals of 100 (*left*), 50 (*middle*), and 10 (*right*) ms. The *rows* represent three separate repetition of the trains. The electrical pulses were delivered in the chamber, picked up by the fish's electroreceptors and indirectly transmitted to the neuron in the exterolateral nucleus. This neuron was fairly selective to pulses delivered at intervals of 50 ms. (**b**) The temporal tuning can be represented by plotting the mean number of spikes (normalized) per electrical pulse or the normalized mean PSP amplitude over a range of different intervals (10–100 ms). From Carlson [47]

and disynaptic inhibition [49, 50]. The prototypical disynaptic circuits is composed of a single Input, an excitatory (Ex) and inhibitory (Inh) neuron, where both neurons receive excitatory synapses from Input, and the excitatory neuron also receives inhibition from the inhibitory neuron for a total of three synapses: Input → Ex, Input → Inh, and Inh → Ex. There are many ways short-term synaptic plasticity can generate interval selectivity. In this example the excitatory synapses onto the excitatory and inhibitory neuron exhibit paired-pulse facilitation (the second EPSP will be stronger then the first). Selectivity arises from dynamics changes in the balance of excitation impose by short-term synaptic plasticity. In this example the short-term facilitation onto the Inh neuron is sufficient to make it fire to the second pulse at 50 ms but not during the 100 or 200 ms intervals. The short-term facilitation onto the Ex neurons is strong enough to make it fire to the 50 and 100 ms intervals, but it does not fire to the 50 ms interval because the spike in the Inh neuron prevents the spike in the Ex neuron. Note that this assumes the inhibition is fast enough to prevent the spike in the Ex neuron even though it must travel through an additional neuron. Experimental evidence clearly demonstrates this is the case [50, 51]: inhibitory neurons have faster time constants and synapse on the cell soma of pyramidal neurons (thus avoiding the dendritic conduction delay). Simply changing the synaptic strength of the Input → Ex and Input → Inh synapses can cause the Ex unit to fire selectively to the 50 or 200 ms interval.

This simple model provides an example of how dynamic changes in the balance of excitation and inhibition produced by short-term synaptic plasticity could potentially underlie the discrimination of intervals in simple feedforward circuits. Importantly, there is experimental evidence that suggest that this is precisely the mechanism underlying interval selectivity in some cases. Some species of frogs communicate though a series of "pulses" and the rate and the number of pulses provides species-specific signals. The neuroscientist Gary Rose and his colleagues have identified neurons in the midbrain of these species that respond with some degree of selectivity to the interval between the pulses [44, 46, 52, 53]. Similarly, the interval between brief auditory or bioelectrical pulses in crickets and electric fish, respectively, are important for communication [47, 48]. In these animals frequency and interval selective neurons have also been identified. Figure 4 shows an example of a fish midbrain neuron that does generally not spike to sequences of electrical discharges presented at intervals of 10 or 100 ms, but responds robustly to intervals of 50 ms. Analysis of the mechanisms underlying these example of temporal selectivity indicate that it arises from

dynamic changes in the balance of excitation and inhibition produced by short-term synaptic plasticity [44, 46–48]. In other words in these simple feedforward networks the hidden state of the networks (in the form of short-term synaptic plasticity) seems to account for the experimentally observed temporal selectivity.

Sensory Timing in Recurrent Circuits

While theoretical and experimental studies suggest that simple feedforward circuits can perform simple types of temporal discrimination, it is unlikely that such circuits can account for the flexibility, diversity, and complexity characteristic of discrimination of complex time-varying patterns typical of speech, music, or Morse code. For complex temporal and spatiotemporal forms processing, complex recurrent networks that contain a rich repertoire of connectivity patterns and hidden states are likely necessary.

Let's consider what might happen in the auditory cortex or an early auditory sensory area during a simple interval discrimination task, and the role of the active and hidden states. The main input layer of the sensory cortex is Layer IV, but neurons in all layers can be activated by the tone, and there is a high degree of both feedforward and recurrent connectivity within any given cortical circuit. Thus in response to a brief tone some complex pattern of active neurons will be elicited, and this pattern will comprise the active state. Generally speaking, within tens of milliseconds after the end of the tone neurons in the auditory cortex will return to their baseline levels of activity—suggesting that the active state does not encode the presentation of the tone after it is over. Now during an interval discrimination task a second tone of the same frequency will be presented at a specific interval after the onset of the first, let's assume the intertone interval was 100 ms. If there was no 'memory' of the first tone the second one should activate the same population of neurons. However, because of short-term synaptic plasticity (the hidden state) the strength of many of the synapses may be different at the arrival of the first and second tone resulting in the activation of distinct subsets of neurons. This is illustrated in Fig. 5a, which illustrates of a computer simulation of a network composed of 400 excitatory and 100 inhibitory neurons. Even when same exact input pattern is presented to $t = 0$ and $t = 100$ ms, many neurons respond differentially to the first and second tone because of the state-dependency of the network (in this case as a result of the hidden state). As show in the lower panels the change in the network state (defined by both the active and hidden states) can be represented in 3D space to allow for the visualization of the time-dependent changes in network state. The difference in these populations can be used to code for the interval between the tones [37, 39]. State-dependent network models predict that as information flows through different cortical areas, the encoding of temporal and spatiotemporal information may increase, but could begin at early sensory areas such as the primary auditory cortex. Indeed, a number of studies have reported that a small percentage of primary auditory cortex neurons are sensitive to the interval between pairs of tone of the same or different frequencies [54–56], however there is as yet no general agreement as to the mechanisms underlying this form of temporal sensitivity.

An elegant aspect of the state-dependent network models is that it provides a general framework for temporal and spatiotemporal processing, it does not simply address the mechanisms of interval selectivity, but the processing of complex temporal patterns and speech [37, 38, 40, 42]. This robustness arises from the fact that any stimulus will be naturally and automatically encoded in the context of the sensory events that preceded it. But this robustness is both a potential computational advantage and disadvantage. An advantage because it provides a robust mechanism for the encoding of temporal and spatiotemporal information—for example, in speech the meaning of the syllable *tool* is entirely different if it is preceded by an *s* (*stool*). But the strength of this framework is also its potential downside, that is, sometimes it is necessary to encode identify sensory events independently of their context—for example if

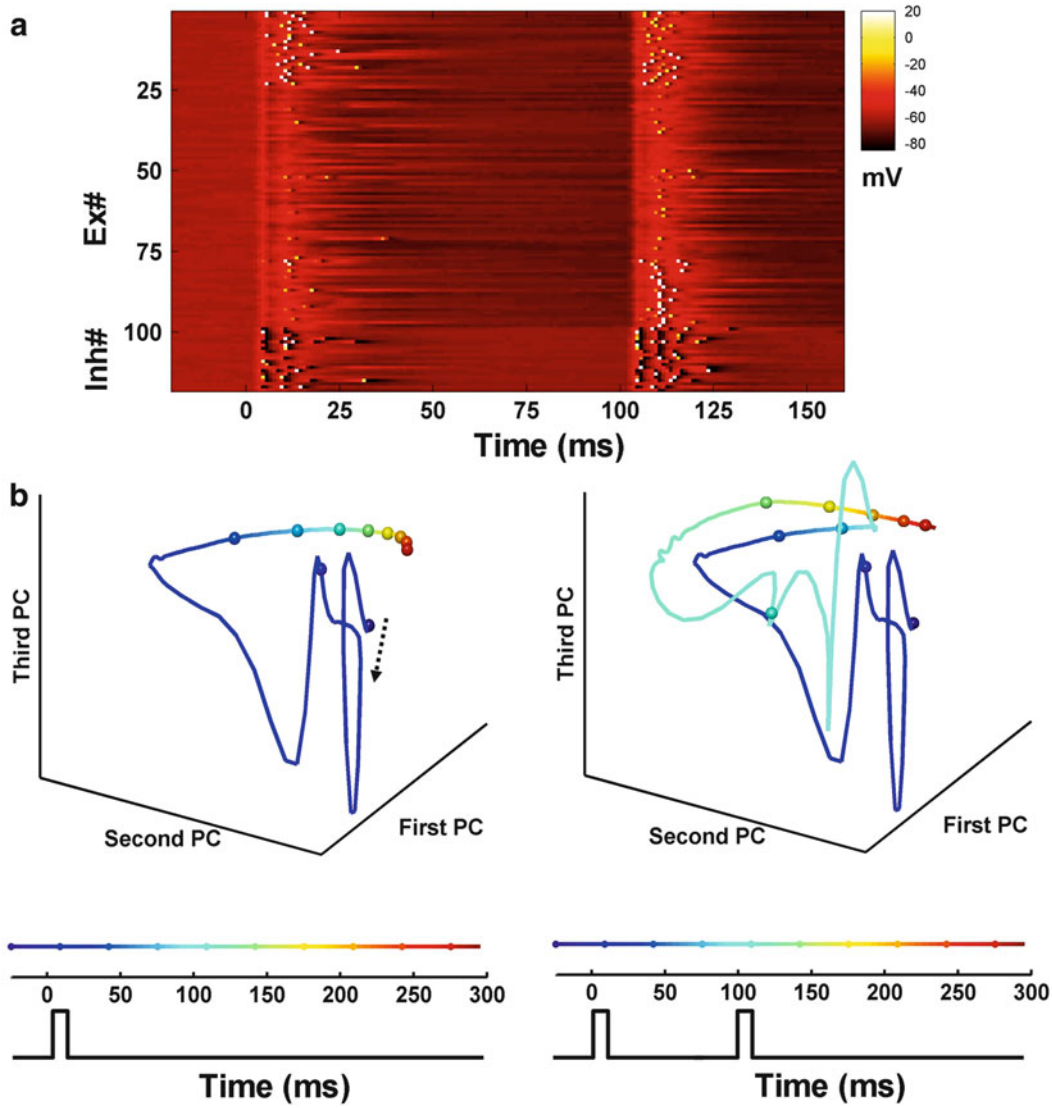

Fig. 5 Simulation of a state-dependent network. (**a**) Each line represents the voltage of a single neuron in response to two identical events separated by 100 ms. The first 100 lines represent 100 excitatory units (out of 400), and the remaining lines represent 25 inhibitory units (out of 100). Each input produces a depolarization across all neurons in the network, followed by inhibition. While most units exhibit subthreshold activity, some spike (*white pixels*) to both inputs, or selectively to the 100 ms interval. The Ex units are sorted according to their probability of firing to the first (*top*) or second (*bottom*) pulse. This selectivity to the first or second event arises because of the difference in network state at t = 0 and t = 100 ms. (**b**) Trajectory of the network in response to a single pulse (*left panel*). The trajectory incorporates both the active and hidden states of the network. Principal component (PC) analysis is used to visualize the state of the network in 3D space. There is an abrupt and rapidly evolving response beginning at t = 0, followed by a slower trajectory. The fast response is due to the depolarization of a large number of units (changes in the active state), while the slower change reflects the short-term synaptic dynamics (the hidden state). The speed of the trajectory in state-space can be visualized by the rate of change of the color code and by the distance between the 25 ms marker spheres. Because synaptic properties cannot be rapidly "reset," the network cannot return to its initial state (*arrow*) before the arrival of a second event. The *right panel* shows the trajectory in response to a 100 ms interval. Note that the same stimulus produces a different fast response to the second event, in other words the same input produced different responses depending on the state of the network at the arrival of the input (modified from Karmarkar and Buonomano [43])

you hear *one-two-three* or *three-two-one* the *two* in middle still has the same value independently of whether it was preceded by *one* or *three*.

The state-dependent nature of these networks has led to a number of experimental predictions. One such prediction is that in an interval discrimination task timing should be impaired if interval between two intervals being compares is itself short. One can think of this as being a result of the network not having sufficient time to 'reset' in between stimuli. This prediction has been experimentally tested. When the two intervals being judged (100 ms standard) were presented 250 ms apart, the ability to determine which was longer was significantly impaired compared to when they were presented 750 ms apart [43]. Importantly, if the two intervals are presented at 250 ms apart, but the first and second tones were presented at different frequencies (e.g., 1 and 4 kHz), interval discrimination was not impaired. The interpretation is that the preceding stimuli can 'interfere' with the encoding of subsequent stimuli when all the tones are of the same frequency because, all tones activate the same local neural network (as a result of the tonotopic organization of the auditory system); but if the first interval is presented at a different frequency there is less 'interference' because the low frequency tones to not strongly change the state of the local high frequency network. These results provide strong support for the hypothesis that timing is locally encoded in neural networks and that it relies on the interaction between incoming stimuli on the internal state of local cortical networks.

These results are not inconsistent with the notion that we can learn to process intervals, speech, or Morse code patterns independent of the preceding events. But they do suggest that the computational architecture of the brain might be to naturally encode the spatiotemporal structure of sensory events occurring together on the time scale of a few hundred milliseconds, and that learning might be necessary in order to disentangle events or "temporal objects" that are temporally proximal. Indeed, this view is consistent with the observation that during the early stages of learning a language words are easier to understand if they are presented a slow rate, and if the words are presented at a fast rate we lost the ability to parse speech and grasp the independent meaning of each one.

Motor Timing

If you are asked to press a button 1 s after the onset of a tone, there must be an active internal 'memory' that leads to the generation of a movement after the appropriate delay. In contrast to sensory timing, where an external event can be used to probe the state of a network, motor timing seems to require an active ongoing internal signal. Thus, motor timing cannot be accomplished exclusively through the hidden state of a network. Rather, motor timing is best viewed as being generated by ongoing changes in the active state of a neural networks.

Motor timing on the scale of hundreds of milliseconds to a few seconds encompasses a wide range of phenomenon studied with a number of different tasks including. (1) *Tapping*, where subjects are asked to tap a finger with a fixed period [57, 58]. (2) *Eyeblink conditioning*, many animals including mice, rabbits, and humans can be conditioned to blink at a certain interval (generally less than 1 s) after the onset of a conditioned stimulus such as a tone, by pairing the tone with the present of an aversive stimulus [59, 60]. (3) *Spatiotemporal reproduction*, motor timing has also been studied using a slightly more complex task in which humans are asked to reproduce a spatiotemporal pattern using their fingers—much like one would while playing the piano [61]. An example of such a task is shown in Fig. 6a. This task is of interest because it requires that multiple intervals be produced in succession, i.e., the end of one interval is the beginning of the next. The fact that this task is easily performed constrains the mechanisms underlying timing, for example it makes it unlikely that motor timing relies on a single timer that requires a significant amount of time to be reset. Indeed, analysis of this task has been used to argue that motor timing relies on a timer that times continuous from the first element ($t = 0$) through out

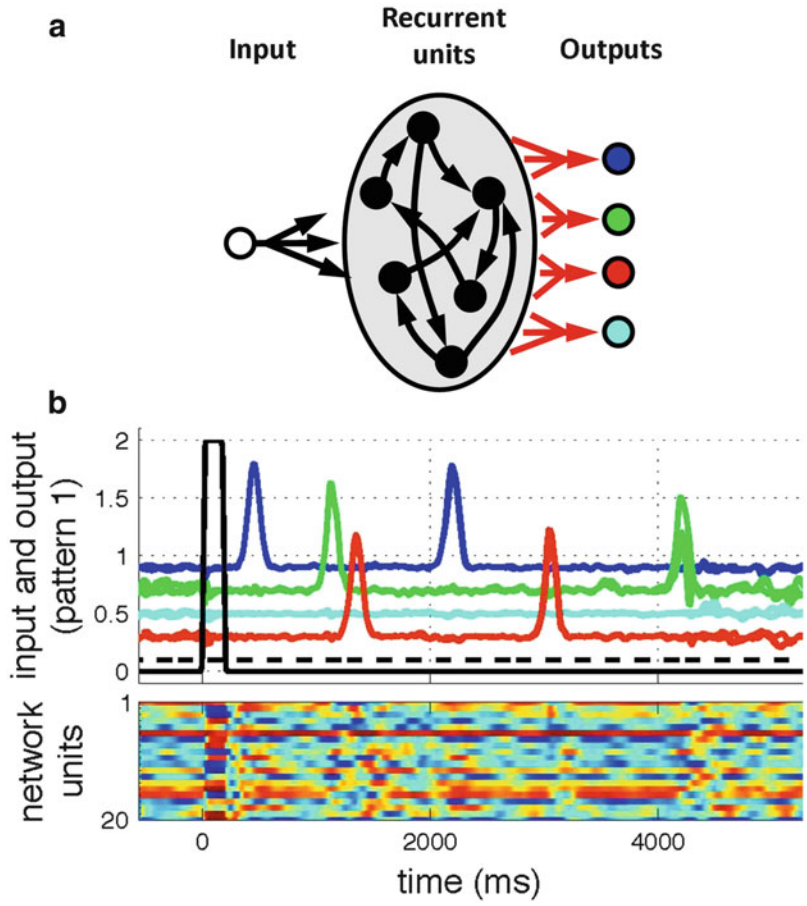

Fig. 6 Simulation of a population clock in a recurrent neural network. (**a**) Network architecture. A randomly connected network composed of 1,800 randomly connected firing rate units. This recurrent network receives a single input. The four outputs are used to generate a spatial temporal pattern, and can be interpreted as four finger that much press the keys of a piano in a specific spatiotemporal pattern. (**b**) The output units were trained to produce the pattern shown (three different runs overlaid) in response to a brief input (*black line*). Training consist of adjusting the weights of the recurrent units onto the readout units (*red lines* in panel **a**). Output traces are shifted vertically for visual clarity. The *dashed black trace* represents a constant input tonic input to the recurrent network. *Colored rasters* represent a subset (20) of the recurrent units. In these units activity ranges from −1 (*blue*) to 1 (*red*) (modified from Laje et al. [61]).

the entire pattern, as opposed to being reset at each interval [61].

It seems likely that there are multiple neural mechanisms contributing to different types of motor timing, of particularly importance may be the distinction between motor timing tasks that require the generation of simple intervals, or periodic or aperiodic patterns. But models based on dynamics changes in the population of active neurons can potentially account for not only a wide range of motor timing tasks, but for the generation of complex spatiotemporal motor patterns. Such models, have been referred to as a population clock [62, 63]. Specifically, in these models timing emerges from the internal dynamics of recurrently connected neural networks, and time is inherently encoded in the evolving activity pattern of the network—a population clock [6, 62].

As mentioned above, one of the first examples of such a population clock was proposed in the context of timing in the cerebellum [7, 8].

Specifically, that in response to a continuous tonic input a continuously varying population of granule cells will be active as a result of the a negative feed back loop where granule cells excite Golgi neurons, which in turn inhibit the granule cells. In response to a constant stimulus, conveyed via the mossy fibers, the Gr cell population response is not only a function of the current stimulus, but is also dependent on the current state of the Gr-Go network. As a result of the feed-back loop, simulations reveal that a dynamically changing trajectory of active Gr cells is created in response to a stimulus [7, 64, 65]. This pattern will trace a complex trajectory in neuron space, and since each point of the trajectory corresponds to a specific population vector of active Gr cells, the network inherently encodes time. Time can then be read-out by the Purkinje cells (the 'readout' neurons), which sample the activity from a large population of Gr cells. Importantly, the Purkinje cells can learn to generate timed motor responses through conventional associative synaptic plasticity coupled to the reinforcement signal from the inferior olive [60]. In this framework, the pattern of Gr cell activity would be expected not only to encode all potentially relevant stimuli, but also to be capable of generating a specific time-stamp of the time that has elapsed since the onset of each potential stimulus. This scheme clearly requires a very high number of distinct Gr cell patterns. Indeed, the fact that there are over 5×10^{10} Gr cells in the human cerebellum [49] suggests that they are uniquely well-suited and indeed designed to encode the large number of representations that would arise from having to encode the time from onset for each potential stimulus.

There is strong experimental evidence that the cerebellum is involved in motor timing [59, 64, 66]. But it is also clear that other areas of the brain are also capable of motor timing—indeed even in the presence of large cerebellar lesions timing is often only mildly impaired, not abolished. Additionally, because the cerebellum lacks any recurrent excitation it is not capable of generating self-perpetuating activity or time response in the absence of a continuous input. Cortical circuits, however, have abundant excitatory recurrent connections, and are able to operate in a truly self-perpetuating regime.

To understand how a network can generate self-perpetuating activity which can be used for timing it is useful to consider simpler and less biologically realistic models. An example of such a model is shown in Fig. 6. The units of the network do not spike but can vary their "activity" levels according to an analog input–output function. These "firing rate" units are typically represented by a sigmoid, and the output can take on any value between −1 and 1 [62, 67]. The network is composed of 1,800 sparsely connected units, each with a time constant of 10 ms (the time constant of the units is important because if the longest hardwired temporal property in the network is 10 ms, yet the network is capable of timing many second it means that timing arises as an emergent property of the network). As shown in Fig. 6, a brief input can trigger a complex spatiotemporal pattern of activity within the recurrent network; and this pattern can be used to generate multiple, complex spatiotemporal output patterns several seconds in duration. Different output patterns can be triggered by different brief input stimuli. The results shown are from a network with four outputs (each representing a finger). The network is trained to reproduce the desired target pattern every time the corresponding "go" signal is activated. In this scenario learning takes place by adjusting the weights on to the readout units.

A potential problem with this class of models, that will not be addressed in detail here, is that they tend to exhibit chaotic behavior—that is, they are very sensitive to noise. However, a number of studies have begun to address this limitation through feedback and training the weights of the recurrent networks [68, 69].

Note that the population clock framework shown in Fig. 6 does not simply encode time, but accounts for both the spatial and temporal aspects of complex spatiotemporal patterns. That

is, the spatial pattern, the timing, and the order of the fingers are all encoded in a multiplexed fashion in the recurrent network plus the readout.

Conclusion

Humans time events on scales that span microseconds to days and beyond. And in contrast to the clocks in our pockets and our wrists, which tell time across scales from milliseconds to years, biology has devised fundamentally different mechanisms for timing across scales. The framework proposed in this chapter proposed that, within the range of tens of hundreds of millisecond to a few seconds, timing is fundamentally unlike man made clocks that rely on oscillators and counters. Rather, theoretical and experimental studies suggest that timing on this scale is fundamentally related to dynamics: the changing states and patterns of activity that networks inevitably undergo as a consequence of the physical properties of neurons and circuits.

An important concept within this framework is that timing can be a local and inherent computation performed by neural networks. Yet these networks can operate in different modes or regimes, relying more on hidden states in the case of sensory timing, and more on active states in motor timing. A powerful feature of the state-dependent network framework is its generality, it is not limited to simple intervals or duration but equally well suited for complex sensory and motor patterns.

While there is not yet any concrete experimental data regarding the mechanisms underlying any form of timing there is mounting experimental evidence supporting the notion of state-dependent mechanisms and that timing relies on neural dynamics. For example in the sensory domain there are numerous examples of interval and frequency selectivity that seem to clearly rely on the hidden state, particularly short-term synaptic plasticity [44–48]. Similarly, *in vivo* studies in birds, rats, and monkeys have demonstrated that there is a population code for time. That is, in relation to an onset event it is possible to use the population activity of neurons to determine how much time has elapsed [15–17, 19, 20, 70], however it remains to be proven that this information is causally being used by the brain to tell time. Furthermore, *in vitro* data suggests that timed responses can also be observed in isolated cortical networks *in vitro* [71, 72].

Although the notion that timing is not the product of a central clock may run counter to our intuitions about the passage of time, it is entirely consistent with the fact that in most cases time is not an independent dimension of sensory stimuli, but rather spatially and temporal processing are often intimately entwined components of sensory and motor processing. Given the biological importance of time it seems suitable that timing on the scale of hundreds of milliseconds in particular would rely on local and general properties of the brain's hardware, rather than on a dedicated architecture that would require communication between a central clock and the diverse sensory and motor circuits that require timing.

Section Summary

These last three chapters on models or timing do not provide a comprehensive picture of all theoretical and computational work on the neural mechanisms of timing, but nevertheless, they highlight the diversity and complexity of the potential mechanisms of timing. A common theme in all three chapters is the issue of whether timing should be viewed as relying on dedicated or intrinsic neural processes. Fourth chapter (Hass and Durstewitz, this volume) provided a sample of different models including both dedicated and intrinsic models, while the last two chapters contrasted the prototypical examples of dedicated and intrinsic models. Fifth chapter (Meck and co-workers) reviewed the main instantiation of a dedicated model—one based on pacemaker-accumulator mechanisms—and subsequent extensions of this approach including the Striatal Beat-Frequency model. This chapter described an example of an intrinsic model in which most neural circuits could perform some

temporal computations as an inherent consequence of neural dynamics and time-dependent neural properties.

As highlighted in fourth chapter the models discussed above are in no way mutually exclusive. Timing encompasses are large range of different computations which likely rely on a collection of different mechanisms. Of particular relevance in the issue of time-scale, and it is possible that dedicated mechanisms contribute to timing on the scale of many seconds, while intrinsic mechanisms underlie timing on the subsecond scale. Indeed such a dichotomy resonates with the notion that timing on the longer engages subjective and cognitive mechanisms, while those on shorter scale are unconscious and perceptual in nature.

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Part III

Neural Correlates of Interval Timing

Signs of Timing in Motor Cortex During Movement Preparation and Cue Anticipation

Bjørg Elisabeth Kilavik, Joachim Confais, and Alexa Riehle

Abstract

The capacity to accurately anticipate the timing of predictable events is essential for sensorimotor behavior. Motor cortex holds an established role in movement preparation and execution. In this chapter we review the different ways in which motor cortical activity is modulated by event timing in sensorimotor delay tasks. During movement preparation, both single neuron and population responses reflect the temporal constraints of the task. Anticipatory modulations prior to sensory cues are also observed in motor cortex when the cue timing is predictable. We propose that the motor cortical activity during cue anticipation and movement preparation is embedded in a timing network that facilitates sensorimotor processing. In this context, the pre-cue and post-cue activity may reflect a presetting mechanism, complementing processing during movement execution, while prohibiting premature responses in situations requiring delayed motor output.

Keywords

Motor cortex • Timing • Delay tasks • Movement preparation • Cue anticipation

Introduction: Sensorimotor Delay Tasks

When a tennis player tracks a ball in motion during a match, he precisely times when his hand should swing the racket to intercept the ball. Similarly, when a driver anticipates the traffic light turning green, he/she uses an internal representation of elapsed (or remaining) time before stepping on the gas pedal. These examples illustrate that past experience and environmental clues are used to accurately anticipate the timing of predictable events, thereby improving sensorimotor behavior. In the laboratory, pre-cued motor tasks (Fig. 1) are often used to study movement preparation processes. In such tasks, movements are initiated faster when the GO signal timing is known in advance ([1–4], see reviews in [5, 6]).

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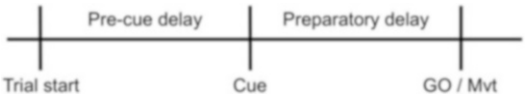

Fig. 1 A generic sensorimotor delay task. Instructed delay tasks typically use a (warning) cue followed after a delay by an imperative GO signal. The cue might provide full, partial or no information about the movement to be executed after GO. During the preparatory delay between the cue and GO, the movement can be prepared using the available information. Note that in some cases, there is not explicit GO signal, and movement onset (Mvt) should be timed by the subject (self-paced). Furthermore, there is often a pre-cue delay of predictable duration, whenever there is an initial external signal or self-generated movement (trial start) preceding the cue that provides temporal information. During the pre-cue delay, the subject can anticipate the moment of cue occurrence (temporal orienting) in order to optimize cue detection

More generally, when temporal uncertainty about the GO signal occurrence decreases, the behavioral reaction time (RT) also decreases. By introducing multiple delay durations presented at random from trial to trial, RT will significantly increase on average, as the notion of a predictable event is confounded. However, because in this case the conditional probability of receiving a GO signal increases with time, RT will decrease for increasing delay durations [1]. Furthermore, even when the delay duration is constant RTs vary from trial to trial, suggesting a variable representation of subjective delay duration across trials [6, 7].

The strong dependency of sensorimotor behavior on time estimation processes has motivated a growing interest to uncover their neural correlates. Niki and Watanabe [8] were the first to connect anticipatory single neuron delay activity to implicit time estimation. Since then, several studies interpreted neuronal discharge during delays as being related to timing processes, both in sensory and motor areas [3, 4, 7, 9–26]. These studies used tasks in which an informative cue is followed by a delay prior to an imperative GO signal or a self-timed movement initiation (Fig. 1), implying either *implicit* or *explicit* timing processes, respectively [27]. In an instructed delay task the subject must process the cue during the preparatory delay and prepare the movement, whilst simultaneously avoiding premature movement release. The preparatory delay between the cue and the GO signal either has a fixed duration or varies from trial to trial between a minimal and maximal duration. The presence of a GO signal obviates the need to estimate delay duration explicitly in order to perform the task correctly. However, the fact that RTs are faster when the timing of GO is more predictable confirms that this timing information is implicitly exploited in order to optimize performance (e.g., receiving the reward sooner in the case of animal subjects). A different approach is needed to study explicit timing. Here the subject is asked to provide an estimate of the delay duration, either by self-timing a movement initiation (no final GO signal provided; e.g., [3, 21, 22, 25, 28–30]), tapping rhythmically (e.g., [31–33]; reviewed in the following chapter in this volume), intercepting a moving target (see review in [34]), associating a particular motor response with a particular delay duration [3], or comparing two delay durations (e.g., [13, 35, 36]).

Importantly, most sensorimotor delay tasks also contain a well-defined pre-cue epoch, with either a fixed or a variable (but predictable) duration (Fig. 1). The event that marks the start of this pre-cue delay can either be self-generated by the subject, such as pressing a start-button or ending the movement in the preceding trial, or it can be an external signal presented to the subject. In sensory cortex, it was shown that the pre-cue anticipatory activity in visual area V4 was modulated by the hazard rate of the visual cue [12]. Furthermore, anticipatory activity preceding somatosensory stimulation has been shown in somatosensory cortex [37, 38], and in auditory cortex preceding auditory stimuli [39]. However, such cue anticipatory neuronal activity is not restricted to sensory areas, as it can also be found in motor cortex [9, 10, 40, 41].

In this chapter we will examine the different ways in which timing affects neuronal activity in motor cortex. We will first show that task timing organizes motor cortical activity during movement preparation, observable in both the spiking activity of single neurons and in different neuronal population measures. Sensorimotor behavior

is a distributed process, most likely with several areas working in parallel during different task epochs. In line with this idea, we will show that motor cortical activity is already modulated *before* movement preparation, e.g., during the anticipation of sensory cues.

We propose that the motor cortical activity during cue anticipation and movement preparation is embedded in a timing network that facilitates sensorimotor processing. In particular, activity prior to and following the sensory cue may reflect presetting mechanisms that complement the subsequent processing during movement execution, whilst prohibiting a premature response in situations requiring a delayed motor output.

Part 1: Timing During Movement Preparation

Spiking Activity During Movement Preparation

Neurons in many cortical and sub-cortical areas change their firing rate progressively during the preparatory delay [3, 4, 8, 9, 13, 16, 24, 25, 35, 42–46]. Such climbing activity can be observed in both self-paced, explicit timing tasks (see example in [47]) and implicit timing tasks using a GO signal (Fig. 2a, b). These neuronal activity patterns have been successfully used in single trials to decode the elapsed time of an event/movement and the onset time of subsequent events/movements [13, 25, 26]. Climbing activity has also been tested as a timing mechanism in modeling approaches [48–50]. One approach proposed that task timing modulates the slope, but not the final peak of activity. Thus, a threshold mechanism could read-out the end of a timed interval [50].

Okamoto et al. [51] suggested that climbing activity observable in across-trial averages might instead be a result of variable transition times of bimodal activity. They described single neuron activity from anterior cingulate cortex with bimodal firing rate distributions and a large across-trial variability, matching well their proposed model. The generality of this proposition still remains to be explored in other brain areas where climbing activity was reported. In data recorded from primary motor cortex (M1) and dorsal premotor cortex (PMd) previously presented in Confais et al. [41], we calculated spike count distributions of neurons with climbing activity. None of the 58 selected neurons with climbing activity had bimodal spike count distributions during the preparatory delay (all selected neurons had a minimal firing rate of 10 spikes/s at GO, spike counts measured in 200 ms sliding windows with 100 ms overlap). This preliminary result suggests that bimodal activity patterns do not account for the climbing activity observed in trial averages during movement preparation in motor cortical areas.

However, if climbing activity reflects a timing mechanism, the slope of the firing rate should be modulated with delay duration, the slope being steeper in short than in long delays. Furthermore, the onset of the climbing activity should start at the beginning of the delay, possibly preceded by an initial phasic response to the cue. Thus, the time of onset should be independent of the duration. When exploring this in the aforementioned dataset of 58 neurons, we found that only three neurons had similar onset latencies, but different slopes in short and long delays. Several neurons displayed a change in slope combined with a change in onset latency (13/58; see example neuron in Fig. 2a), and the majority kept the slope constant with a pure shift in onset latency (41/58). This suggests that motor cortical climbing activity clearly reflects task timing, and can even be used to decode time ([25]; note that neurons with an onset difference will also be informative for delay duration), but does not seem to be a self-sufficient mechanism responsible for tracking time. Rather, this activity might be embedded in a context-dependent timing network.

As time estimation is at the core of anticipatory behavior it is reasonable to ask if neuronal delay activity correlates with the subjective estimate of time. As a consequence of the scalar property of time estimation processes [52], the variability in time estimation increases continuously as time passes during the delay. This scalar

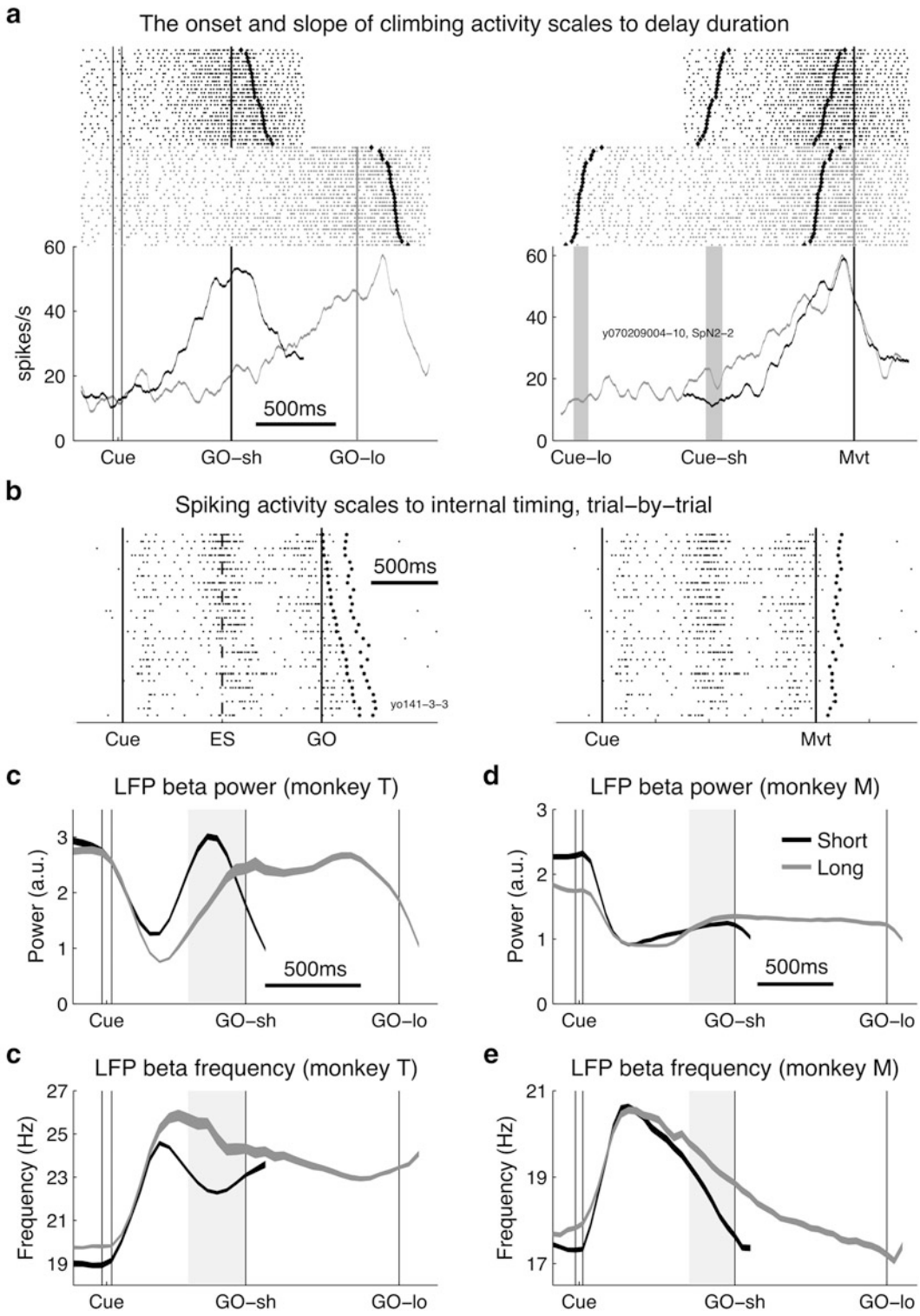

Fig. 2 Scaling of motor cortical activity during movement preparation. (**a**) Example of a neuron that adjusts (scales) both the onset and the slope of climbing activity during movement preparation to the delay duration between the cue and GO. On *top*, the trial-by-trial activity is shown for short and long delay trials as raster plots,

property may then be reflected in the increasing variability of neuronal delay activity. Renoult et al. [7] studied the influence of temporal prior information on neuronal delay activity in monkey motor cortex during a task in which two equally probable delay durations were randomly presented.

The neuron presented in Fig. 2b (left panel) showed three distinct epochs of increased activity during long delay trials: the first after presentation of the cue, the second around the expected GO signal (ES) at the end of the short delay (50 % probability), and the third towards the actual occurrence of the GO signal at the end of the long delay. The increased activity during the second and third epochs appeared without the presentation of any external signal, indicating a fairly accurate estimate of the delay durations. Whereas the activity increase following the cue was clearly time-locked to the stimulus, the activity during the third epoch was clearly aligned to movement onset, trial-by-trial. The activity during the second epoch around ES had an intermediate alignment. Thus, neuronal activity went from being aligned to the occurrence of an external signal (cue) to being aligned to movement onset via some intermediate alignment to an internal signal (ES), and across-trial variability in the temporal profile of neuronal discharge increased throughout the delay. Renoult et al. [7] hypothesized that if one considers the animal's subjective timing of the delay as the elapsed time between the cue and movement onset, then suppressing the temporal variability in RT should decrease the across-trial variability in neuronal discharge. Here the cue is considered as being t0, where time is reset in each trial. The time between the cue (t0) and movement onset was kept identical across trials by first defining a new time scale per trial and then rescaling it across trials. Each spike was then displaced in time accordingly (i.e., the farther a spike from t0 the larger its displacement). As expected, the variability in the timing of neuronal peak discharges no longer increased during the trial (Fig. 2b right panel). This suggests a

Fig. 2 (Continued) with individual lines for each behavioral trial and each dot representing an action potential. The peri-event time histograms (PETHs) are shown in the *bottom panels*. To the *left*, the data of short and long delay trials is aligned to cue onset. Clearly the onset of the increase in activity after the cue occurs later in long delay trials. To the *right*, the data is aligned to movement onset. Whereas the peak in activity shortly preceding movement onset is the same for short and long delay trials, the slope of the increase in activity is steeper for short delay trials. The *gray rectangles* represent the average (±std) time of cue onset in long and short delay trials. The *larger black dots* in the raster plots represent movement onset (*left plots*) or cue onset (*right plots*). Trials are aligned offline according to increasing RT. The duration of the cue was 55 ms, the short delay 700 ms and the long delay 1,500 ms. For more details on the task, see Confais et al. [41] (unpublished data from J Confais, BE Kilavik, A Ponce-Alvarez and A. Riehle). (**b**) Raster plots of an example neuron recorded during a task in which the GO signal could be presented either after a short or long delay duration. Here only long delay trials are shown, and ES (expected signal, *left plot*) represents the moment in which the animal expected the GO signal with 50 % probability. To the *left*, trials are aligned to external signals. To the *right*, trials are re-scaled according to the duration between the cue and movement onset (Mvt). See the text and Renoult et al. [7] for more details on the task and analysis (unpublished data from: A. Riehle, L. Renoult and S. Roux). (**c**, **d**) Averaged normalized beta peak power between cue and GO (±sem) across 191 LFPs for monkey T and 631 for monkey M, recorded in the same task as the example neurons shown in **a**. Monkey T (**c**) had a systematic difference between short and long delay trials, with a majority of LFPs having higher power in the end of short trials than in the middle of long trials (*light gray window*; same moment in time after the cue; 72 % of LFPs with significantly higher power in short than in long trials, compared to only 10 % with an opposite effect; 2-way ANOVA, movement direction and delay duration as factors). In monkey M (**d**), there was no systematic power difference between short and long trials across LFPs, but overall power changed only little during the preparatory delay. (**e**, **f**) Averaged beta peak frequency between cue and GO (±sem) for the same LFPs as shown in **c**, **d**. Many LFPs had significantly different beta peak frequency comparing the end of short trials with the middle of long trials (*gray window*). A majority had lower frequency in short trials (70 and 26 % of LFPs in monkey T and M, respectively; only 3 % had an opposite effect). For both monkeys, cue duration was 55 ms. For monkey T, the short and long delays were 700 and 1,500 ms, while they were 1,000 and 2,000 ms for monkey M. For more details of task and data analysis, please see Kilavik et al. [93] (**c**–**f**: unpublished data from Kilavik and Riehle; preliminary results presented in [47])

direct link between the temporal profile of spiking activity and time estimation. The timing of motor cortical activity reflects the *elasticity* ("rubberband") of the animal's subjective time.

Finally, Roesch and Olson [19] found that many of the neurons in frontal areas (including premotor cortex close to the arcuate sulcus) that were sensitive to delay duration, were also sensitive to reward magnitude in a saccade task. These neurons typically exhibited higher firing rate shortly after the presentation of a cue indicating a short delay or a large forthcoming reward. This result might, at least in part, be explained by the notion that waiting for a long delay before receiving a reward decreases the subjective value of the reward (time discounting; [53]), suggesting that reward and delay duration might both act on general motivation. Indeed, in monkey studies, effects related to reward and GO signal expectancy cannot be clearly dissociated from the effects related to timing in many cases (but see [26, 54]). However, climbing activity also occurs in the absence of immediate reward, reflected in population activity measures in human participants described below.

Population Activity During Movement Preparation

The extracellular local field potential (LFP) may be recorded from the same electrode as spikes, by low-pass filtering of the raw signal (e.g., below 250 Hz), and is modulated in parallel to single neuron discharge. It is considered to mainly reflect the (sub-threshold) synaptic activity in a large population of neurons, with additional contributions from spike-after potentials or intrinsic trans-membrane current changes [55–57]. Since the LFP sums activity around the electrode, modulations observable in the LFP must reflect more or less synchronous activity in a sufficiently large population of neurons, possibly indicating a degree of coherent network activity [58, 59]. Currently there is a great interest in understanding the relationship between the spiking activity of single neurons and the slower fluctuations of the LFP (e.g., [60, 61]). The intracerebral LFP is related to the externally recorded electro- and magneto-encephalographic (EEG/MEG) signal, usually recorded in human participants. EEG and MEG signals are less spatially specific than the LFP, but one might consider these external signals to represent some sort of spatial summation of many (local) LFPs.

Sensorimotor-related activity that scales to delay duration can also be observed in population measures such as the LFP, EEG and MEG. One example is the fronto-central contingent negative variation (CNV). The CNV is a slow negative wave that develops between the cue and GO, mainly studied in the human EEG/MEG. Originally, Walter et al. [62] proposed that this event-related potential might reflect time estimation. Indeed, the CNV is sensitive to the duration of a delay or a stimulus presentation [63–66], and while the slope is steeper for shorter durations, the peak at the end of the duration remains unchanged in size during both explicit and implicit timing tasks, suggesting duration independence [67, 68]. Overall, the timing-related dynamics of the CNV resembles the build-up spiking activity of single neurons described above. It was therefore proposed that both types of signals reflect the encoding of the timing of an upcoming event [67].

Oscillations are frequently observed in LFP, EEG and MEG signals. Power modulations in brain oscillations may be related to the degree of (rhythmic) spike synchronization [58] and/or the overall level of activity in neuronal populations [69]. Furthermore, the oscillation frequency may be related to the extent of neuronal networks [70–72] or the underlying excitation-inhibition balance [73–77]. Oscillations at different frequencies may therefore reflect different neuronal populations and/or network states. The typical oscillation frequency in motor cortex is within the so-called beta range (~13–30 Hz; [78, 79]). Beta oscillations can synchronize over large networks, spanning multiple cortical [80–83] and sub-cortical areas [84, 85]. These oscillations are not strictly time-locked to signals or movements, as is the case for event-related potentials such as the CNV described above. However, beta oscillations are clearly

modulated during sensorimotor behavior, being most prominent in epochs without overt movements (e.g., during delays) and during stable postures, and being minimal in power during movements as well as transiently following the presentation of sensory cues (see review in [86]). Motor cortical beta oscillations might reflect sensorimotor updating and planning processes [80, 81, 83, 86–89], and a handful of observations in monkeys and humans suggest that they are also sensitive to timing processes [39, 47, 90]. In a recent study using rhythmic streams of auditory stimuli, Fujioka et al. [39] recorded MEG in human participants and found beta power to peak just before each sound event in several areas, including motor cortex, even though participants were only required to passively listen to the rhythmic streams. The authors suggested that this distributed pre-cue increase in beta power provides a mechanism for maintaining predictive timing. Arnal [91] proposed that this motor cortical sensory prediction might rely on the simulation of movements via an internal model, allowing the prediction of stimulus timing and its sensory consequences. However, it is also possible that this activity is a reflection of an automatic, covert movement preparation entrained by rhythmic stimuli. Such an automatic facilitation of gait by rhythmic stimuli has already been shown in Parkinsonian patients [92].

We observed similar effects in the motor cortical LFP of monkeys performing a visuomotor task with two possible delay durations ([47], see also [93]). Figure 2d–g show the modulations in beta peak power and frequency between the cue and the GO signal, comparing short and long delay trials. In monkey T (Fig. 2d) the beta power increased substantially towards the GO signal, with a steeper increase in short than in long delay trials, following a post-cue transient power decrease. In this study [93] we demonstrated for the first time that not only peak power is task-modulated, but also the peak frequency of beta oscillations. Interestingly, even if beta power differed between short and long delay trials in only one of the two monkeys included in this study, beta frequency differed systematically between short and long delay trials for both monkeys (Fig. 2f, g). Following the cue, there was a transient increase in beta frequency, which was similar in onset and slope for short and long delay trials. Subsequent to this increase, the beta frequency slowly decreased towards the GO signal, with a steeper slope in short than long delay trials. Saleh et al. [90] recorded LFPs in primary motor cortex of a human patient who had to point to a spatial target with his chin. Five spatial cues were displayed successively, and he had to select either the second or the fourth cue in different trials. The power of beta oscillations peaked transiently before each spatial cue, with the highest pre-cue power for the correct cue. Furthermore, the beta power was phase-locked to slower delta oscillations (0.5–1.5 Hz) that matched the duration of the inter-cue intervals. In a similar way, Roux et al. [94] showed that the across-trial averaged LFPs systematically modulated as a slow wave during the delay period in relation to the temporal scheme of the task. This slow wave modulation also varied as a function of reaction time. In other words, the wave modulation varies in relation to the internal timing of delay duration of the animal from trial to trial; a similar effect was found for spiking activity of single neurons ([7]; see above).

Interestingly, modulations of duration-selective beta oscillations appear to be similar to the CNV and the neuronal spiking activity. This suggests that many different types of gradual changes in motor cortical activity are duration-sensitive, with faster modulations for shorter durations, and a tendency to reach the same level of activation at the expected end of the estimated duration (e.g., the GO signal). Importantly, the scaling of activity modulations to duration was also found in human participants that were not receiving immediate reward on a single-trial basis. Thus, even though certain populations of neurons in motor areas are sensitive to reward magnitude and delay duration [19], there are also clear signs of similar timing sensitivity in these areas in the absence of an immediate reward.

To conclude, motor cortical activity during movement preparation scales to delay duration and internal time estimation. This observation might reflect well-timed movement preparation, rather than an invariant timing mechanism. An alternative interpretation would be that motor cortex is part of a larger network coding time in a context-dependent manner.

Precise Spike Synchrony and GO Signal Anticipation

It is commonly accepted that sensorimotor functions are reflected in changes in firing rate in widely distributed populations of neurons [6]. However, the temporal coding hypothesis suggests that not only changes in firing rate but also precise spike timing constitute an important part of the representational substrate for perception and action. Precise spike timing here refers to spike synchronization or other precise spatio-temporal patterns of spike occurrences among neurons organized in functional groups, commonly called cell assemblies [95–98]. The concept of cell assemblies uses synchrony as an additional dimension to firing rate, as a candidate for information processing. The observation of precise spike synchrony between pairs of neurons [1] might be interpreted as activation of a functional cell assembly [99]. Motor cortical neurons synchronize their activity significantly at the moment of signal expectancy, indicating the end of an estimated delay duration, often without any corresponding firing rate modulation [1, 2, 100]. Thus, behavioral timing modulates both spike synchrony and firing rate independently. Both experimental and theoretical studies point to the importance of synchronous spiking activity, particularly in a low firing-rate regime (e.g., [101]). Indeed, synchrony and firing rate might be complementary coding strategies, allowing for efficient computation with less activity through increased synchrony.

Assuming such a complementarity, the question arises whether improving the behavioral performance in a timing paradigm can alter the interplay between synchrony and firing rate. To study this, we quantified the strength of synchrony across pairs of neurons recorded in three monkeys performing a choice RT task, and compared it to the mean firing rate in the same neurons. In this task, the monkeys were asked to select the correct movement direction based on the delay duration between a cue and the GO signal, thus requiring correct estimation of elapsed time (see [3, 100]). Two targets of different colors were presented at the start of each trial (cue). A non-directional GO signal (auditory) was presented after a short or a long delay, randomly and with equal probability. The monkey learned to associate target color with delay duration.

We developed a method that provides the strength of synchronous spiking activity of an entire population of neuron pairs (see [100]) for the population quantification, for the statistics see the review by [102]. This method is based on the comparison between the numbers of empirical coincident spikes in pairs of neurons and the numbers of predicted coincident spikes, taking into account the instantaneous trial-by-trial firing rates of the neurons [102]. The difference between the number of observed versus predicted coincident spikes yields an analytical measure for each time-point and indicates the statistical significance of having more (or less) synchrony than expected by chance. This analysis can be done across all trials for all pairs of neurons, giving a time-resolved measure of population synchrony ([100]; see Fig. 3a).

In this study, the monkeys progressively improved their performance during the months of recording, significantly shortening RTs and/or reducing RT variability, suggesting an improved estimation of the delay durations [100]. We therefore split the population of recorded neurons into the first and last part of the recording period. Due to the task structure, the monkey expected (with 50 % probability) a GO signal at the end of the short delay (ES; Fig. 3). In long delay trials, the synchrony strength of neuron-pairs recorded during the late sessions (black line) transiently increased after the expected GO signal (ES), exceeding the significance level of $p = 0.01$ by far (dashed horizontal line). This brief increase

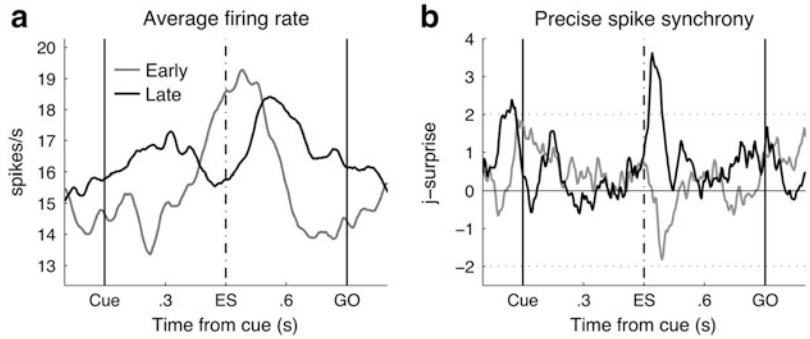

Fig. 3 Precise spike synchrony and GO signal expectancy. (**a**) Average firing rates (PETHs) of neurons recorded in one monkey during performance of a choice RT task, comparing early vs. late recording sessions (spanning several months). In this task, the monkey had to select the correct movement direction by estimating the delay duration between the cue and the GO signal (see main text). The GO signal could be presented either after a short or after a long delay duration. Here only long delay trials are shown, and ES (expected signal) represents the moment in which the animal expected the GO signal with 50 % probability. (**b**) The data was analyzed with the "Unitary Event" technique [102, 149]. We developed a measure that provides the strength of synchronous spiking activity of an entire population of neuron pairs [100]. We used a sliding window of 100 ms duration (shifts of 5 ms) moving through the entire length of the trial. We counted the number of empirical coincidences and calculated the number of coincidences that we would expect by chance by taking into account the instantaneous firing rate of the two neurons, for a temporal precision of up to 3 ms. We then summed the result over all trials and pairs of neurons and calculated the statistical significance (joint-surprise) of the difference between empirical and predicted coincidences. Whenever the significance value exceeded the threshold (*dashed line*, $p = 0.01$), this defined an epoch in which significantly more coincidences occurred than would be expected by chance. Coincidences within such an epoch are called "unitary events" [149]. Values around zero indicate that there are as many synchronous spikes as expected by chance, positive (negative) values indicate more (less) coincidences. The data is shown for 42 vs. 45 neuron pairs, in early vs. late sessions, respectively (figure reproduced from [100])

of precise synchrony might provide an internal switch signal, triggered by correct time estimation, allowing a change in movement preparation (movement time and/or movement direction). In the same trial epoch, the mean population firing rate decreased in late compared to early sessions (Fig. 3b). We concluded that performance optimization in timing tasks might be achieved by increasing precise spike synchrony in relation to temporal expectancy, thereby boosting network efficiency. This may be accompanied by fewer spikes overall [100].

Phasic Responses to the Cue

We have so far considered motor cortical activity during the preparatory delay up to movement execution. However, motor cortex also exhibits short-latency signal-related phasic responses (<200 ms) to informative sensory cues ([103, 104]; examples in Fig. 4a, b). Pure execution-related activity modulation patterns are more often observed in the central sulcus of M1, whereas delay- and signal-related activities are more common in PMd, the convexity of M1 being intermediate with respect to activity patterns [45, 103–108]. Auditory and visual cues are similarly efficient in eliciting signal-related directional responses [109]. Roux et al. [3] showed that even the absence of an expected GO signal (i.e., an internal event) was followed by a phasic response in neurons that otherwise responded to cues. The cue does not need to be spatial in nature; a central symbolic cue also elicits a phasic response [110–114], though with a longer latency than for a simple peripheral cue [107, 113]. However, a directionally non-informative cue does not elicit any phasic response in the motor cortex (e.g., [40, 103]).

Several lines of evidence suggest that the occurrence of a phasic response to a cue is related to movement preparation, rather than to a more general shift in spatial attention. First, neurons

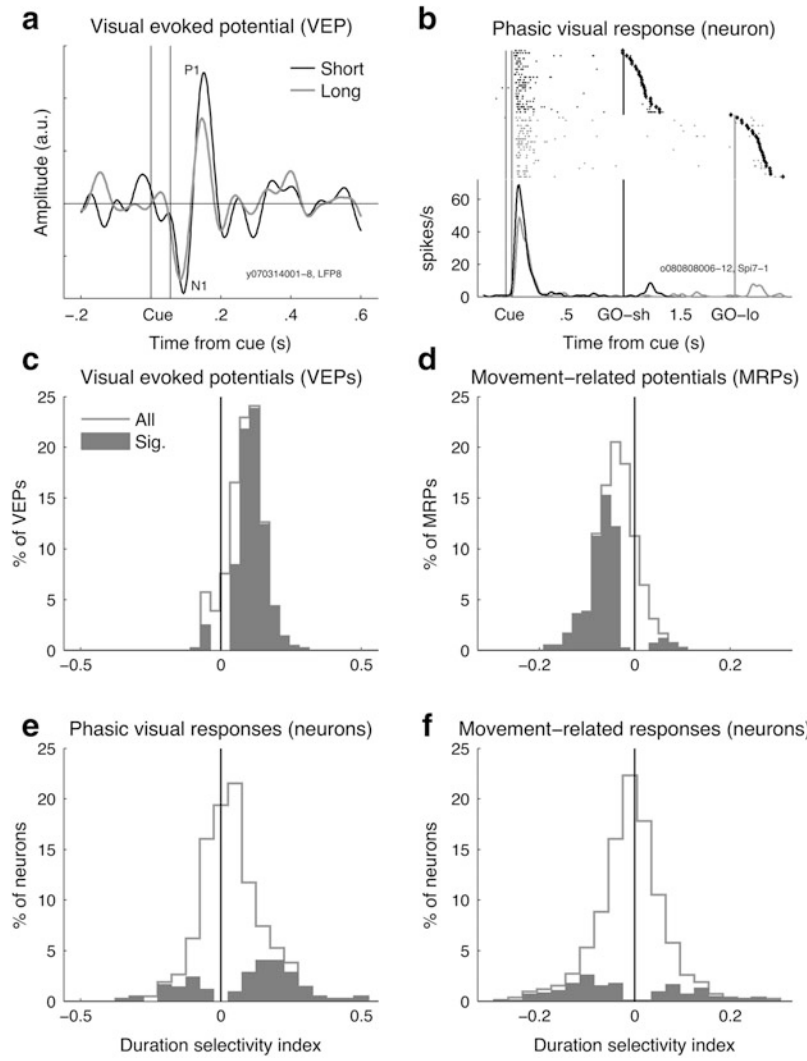

Fig. 4 Phasic responses to cues in motor cortex. (**a**) An example of a trial-averaged visual evoked potential (VEP) to the cue in one motor cortical LFP, comparing short and long delay trials. The labels N1 and P1 denote the two first typical components of the motor cortical VEP. (**b**) An example of a motor cortical neuron responding phasically to the cue, comparing short and long delay trials. The rasters are shown in the *upper plot* and the PETHs in the *lower plot*. The *larger black dots* to the right in the raster plot represent movement onset. (**c**, **d**) Distributions of duration selectivity indexes for all VEPs (n = 436) and movement-related potentials (MRPs; n = 419), around movement onset, of two monkeys. The VEP and MRP sizes were calculated using the root-mean-square in single trial, including the N1 and P1 components of the VEP and the three most prominent components of the MRP. The duration selectivity index was defined as a contrast comparing average sizes in short and long delay trials [(short − long)/(short + long)]. Positive values thus define short delay duration preference. As a reference value, an index of +0.33 would mean that the LFP amplitude is twice as big in short than in long trials. The outlines include all VEPs and MRPs and the filled bars only the VEPs and MRPs with a significant difference in size between short and long delay trials (n = 330 and 217 for VEPs and MRPs, respectively). Significance in individual VEPs and MRPs was tested with a two-way ANOVA (delay duration and movement direction as factors, $p < 0.05$). The medians of the distributions of significant VEPs and MRPs are +0.11 and −0.06, respectively, significantly shifted away from zero (Wilcoxon signed rank test; $p < <0.001$ for VEPs and MRPs). See Kilavik et al. [108] for more details on recording and analysis techniques (data from [108]). (**e**, **f**) Distributions of duration selectivity indexes for all neurons in two monkeys with a phasic response to the cue (n = 418) and for all

with a phasic response to the GO signal may show as well a phasic response to the cue [106]. Second, this phasic response to the GO signal may decrease strongly or even disappear if the preceding cue provided already spatial information ("pre-processing neuron" of 6, 45, 115). Third, neurons in PMd are much more responsive (and selective) to cues indicating the target of a movement than to cues indicating the target of a shift in attentional focus [40, 116–119]. Last, the signal-related activity in PMd reflects the planned action rather than the characteristics of the cue itself (shape, color, location) [111, 114, 120].

The earliest modulations in motor cortical activity start around 50–60 ms after cue onset [103, 104, 108] and are generally less spatially selective than the later ones [104]. Signal-related activity with slightly shorter latencies might reflect a first wave of information concerning targets of potential movements. This preliminary information becomes more refined as more complex processing of the cue continues to unfold. For instance, in both M1 and PMd the vast majority of initial phasic responses are selective to the direction of the target and not to the direction of the movement [12, 121, 122]. Even partial information about movement direction elicits a phasic response, though with a smaller amplitude than after complete directional information [107, 123]. Finally, the very early signal-related activity is relatively unaffected by the condition of a GO-NOGO task, unlike the subsequent delay-activity [124–126].

The signal-related phasic response is as sensitive to delay duration as the subsequent delay activity during movement preparation [3, 108]. Figure 4a, b show examples of a LFP visual evoked potential (VEP) (A) and a neuron with a phasic change in activity (B), both recorded in motor cortex as a response to the cue [41, 108]. In both cases, the amplitudes of the phasic response were larger in short delay trials than in long delay trials. This was true for a majority of motor cortical LFP VEPs (77 %, see Fig. 4c; [108]). Interestingly, this result is complementary to the fact that movement-related potentials (MRPs) observed during movement execution are larger in long delay than in short delay trials (significant in 52 %; Fig. 4d; [108]). We found that the phasic cue response in 25 % of these neurons was selective to delay duration (Fig. 4e; [41]), preferring, as in VEPs, mainly short delay trials. The influence of delay duration on the spiking activity during movement execution was less clear (17 % significant; Fig. 4f), even though a majority had higher firing rates in long delay trials, similarly to MRPs.

If the early phasic activity after the cue in motor cortex reflects a pre-processing mechanism, we can conclude that pre-processing is more prominent in short delay trials, observable in overall higher firing rates and larger VEPs. This is complementary to a lower activity in short delay trials during movement execution, particularly noticeable in the MRPs. Beyond this, we can currently only speculate on why there is such a large quantitative difference between the spiking activities and MRPs around movement onset. It is important to note that the LFP not only reflects sub-threshold synaptic activity, but also population activity. This means that a weak, but consistent, effect of delay duration in a sufficiently large population of neurons may be observed more clearly in the LFP. Importantly, the modulation of evoked LFP responses by delay duration suggests that there is a high degree of flexibility in the movement preparation process, which is significantly

Fig. 4 (Continued) neurons, independently of their activity pattern around movement onset (n = 847). The duration selectivity index was calculated as described above, using mean spike counts in 200 ms large windows, after cue onset and around movement onset. Significance was tested with a two-way ANOVA (delay duration and movement direction as factors; $p < 0.05$). Medians for the sub-sets of significant neurons (*filled gray bars*) are +0.14 for the phasic visual responses (n = 105) and −0.06 for the movement-related responses (n = 143), in both cases significantly shifted away from zero (Wilcoxon signed rank test; $p < <0.001$ and $p = 0.017$, respectively) (unpublished data from J Confais, BE Kilavik, A Ponce-Alvarez and A. Riehle)

influenced by the knowledge of the available time prior to movement execution [108].

Earlier we described how neuronal activity during movement preparation is scaled to delay duration and internal time estimation. Here we show that this scaling can also be extended to signal processing and movement execution epochs. One appealing interpretation is that for shorter delays it might be optimal to complete movement preparation early directly after cue presentation, whereas for longer delays it may become more 'economic' to encode only general aspects of the movement early in the delay (e.g., movement direction or goal) and to finalize more detailed aspects of the movement prior to and during its execution.

Part 2: Timing During Cue Anticipation

In the first part of this chapter, we described how the timing of a motor task profoundly shapes the activity of motor cortex during movement preparation. In this part, we will see how available information about time is also used to predict the timing of an upcoming cue, which carries relevant information for movement preparation. In this context, an anticipatory pattern of activity preceding the cue onset can be observed in motor cortical areas, even in absence of motor preparation.

In the movement preparation paradigm (see Fig. 1) a delay is used to temporally separate the moment when the subject is provided with information about the desired action (for example, a spatial cue indicating the position that should be pointed towards) and the moment when this action has to be performed (GO signal). However, in most experimental protocols, the subject can also estimate the duration preceding the informative cue. The timing of the cue can be predicted by keeping the preceding delay fixed in all trials (e.g., [9]) or by adding a "pre-cue" to indicate the length of the upcoming delay in each trial (e.g., [41]). Since the movement preparation paradigm was first implemented, it was regularly reported that a fraction of motor cortical neurons modulate their firing rate well before the presentation of the cue. However, this was only described as a side note [40, 106, 107, 109, 111, 122, 127] or examples of neurons with such an activity were shown [3, 103], but only a few studies examined this type of anticipatory activity directly [9, 10, 41]. Interestingly, this type of activity has been described in a wide range of brain structures, such as the caudate nucleus [128–130], the prefrontal cortex [8, 131], and the somatosensory cortex [37]. In this part we will review the main characteristics of this "cue-anticipatory activity" by focusing on motor preparation in motor cortical areas, and will suggest a possible functional significance. For convenience purposes, we refer to the neurons showing this type of activity as "cue-anticipatory neurons" in this chapter.

Prevalence of Cue-Anticipatory Activity in Frontal Areas

All works describing an anticipatory activity used a fixed or highly predictable pre-cue delay. Vaadia et al. [10] trained monkeys extensively in a task that included a fixed 3 s delay preceding the cue, whereas in our task the pre-cue delay duration was indicated in advance to the animal by an auditory signal [41]. We observed different patterns of motor cortical spiking activity during this delay: some neurons increase their activity preceding the cue (see Fig. 5b), others decrease it (Fig. 5a), and the remaining neurons do not modulate. Even if the ratios vary from study to study, most studies report more neurons with increasing than decreasing firing rates [10, 41, 106]. However, the ratio of neurons with anticipatory activity seems to depend on the cortical location. Most studies in frontal areas showed the strongest representation of anticipatory activity in PMd. Crammond and Kalaska [106] showed a higher percentage of anticipatory neurons in PMd than in M1. Additionally, they demonstrated that the ratio of anticipatory neurons with increasing versus decreasing activity changed with the distance to the central sulcus. The majority of anticipatory neurons increased their activity in PMd and in

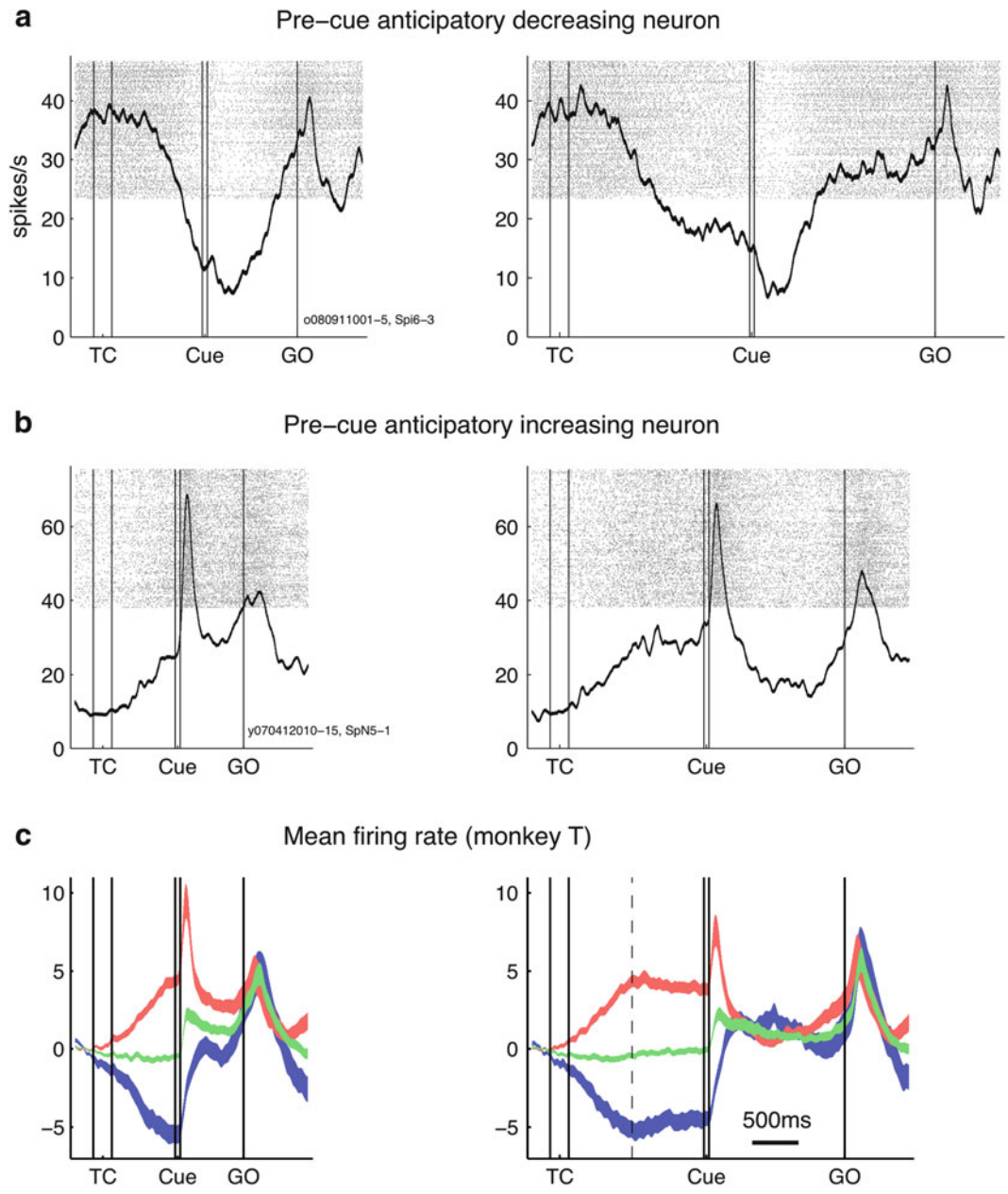

Fig. 5 Pre-cue anticipatory activity in motor cortex. (**a**, **b**) Raster plots and PETHs of two example neurons with pre-cue anticipatory activity (short delay trials on the *left*, long delay trials on the *right*). The trials are arranged chronologically. In **a**, please note the suppression of activity following the cue for this neuron with pre-cue decreasing activity. In **b**, note the phasic response to cue in this neuron with pre-cue increasing activity. (**c**) Averaged activity of all neurons in one monkey (±sem), classified according to pattern of pre-cue anticipatory activity. The baseline activity (final 200 ms before TC) of each neuron is subtracted prior to averaging. Pre-cue increasing neurons in *red* (n = 129), pre-cue decreasing in *blue* (n = 95), and non-anticipatory neurons in *green* (n = 228). TC: time cue presented for 200 ms, indicating delay durations, Cue: spatial cue presented for 55 ms, indicating target location, GO: directionally non-informative GO signal (data from [41])

the rostral part of M1, whereas all anticipatory neurons recorded in the caudal (sulcal) part of M1 decreased their activity. Interestingly, this caudal zone of M1 has the highest density of direct cortico-motoneuronal projections [132]. Hoshi and Tanji [111] showed more anticipatory neurons in PMd than in the ventral part of the premotor cortex (PMv). They also showed that anticipatory neurons in PMd were more sensitive to the expected information contained in the cue than those in PMv. Di Pellegrino et al. [40] and Vaadia et al. [10] showed similar differences between PMd and prefrontal cortex (PF), whereby anticipatory activity was observed more often in PMd than in PF neurons, accompanied by an increased sensitivity to the expected cue information in PMd neurons. In contrast, we did not find any difference in the proportions of anticipatory neurons between PMd and M1, but this may be due to the fact that our recording chamber only captured the rostral part of M1 [41].

Influence of Expected Cue Information

As mentioned above, some studies found an effect of different cue aspects on the anticipatory activity. In particular, three studies showed an influence of the expected information carried by the cue, albeit to a different extent. Vaadia et al. [10] used a block-wise presented task in which the cue in one block either indicated the target of the movement or was non-informative. They showed that a small fraction of the neurons changed selectively their activity preceding the cue, depending on the block. Similarly, in Di Pellegrino and Wise [40], the cue indicated either the movement target or a shift in attentional focus, irrespective of the movement target. Two-thirds of the anticipatory neurons modulated their firing rate depending on the information carried by the cue, with generally more activity in the "movement target" blocks than in the "attention only" blocks. Finally, Hoshi and Tanji [111] showed that the activity of more than 10 % of the anticipatory PMd neurons significantly changed their activity depending on whether the cue was expected to contain movement target information or to contain information about which arm to use. Interestingly, the expected reward can also modulate the cue anticipatory activity. Vaadia et al. [10] added a condition in which the trials were rewarded at random and showed that a subsample of anticipatory neurons stopped responding after several unrewarded trials in a row.

Although most of the anticipatory neurons in these studies show an increasing activity, some display a decreasing pattern. We will now describe how these patterns of anticipatory activity are predictive for the firing rate modulations during movement preparation [9, 41].

Relationship Between Cue Anticipation and Movement Preparation Activity

We recorded motor cortical single neuron activity in a delayed center-out reaching task [41]. Each trial contained two successive delays of equal duration, indicated at the beginning of each trial by an auditory cue. At the end of the first delay, a spatial cue indicating the direction of the upcoming movement was briefly flashed. At the end of the second delay, the (non-informative) GO signal requested to reach to the cued target. This task was conceptually different during the two delays: during the first delay, the monkeys used the temporal information provided by the temporal cue to accomplish at a given time a visual detection task, whereas they had to time and prepare the upcoming movement during the second delay. In about 40 % of the neurons the activity was modulated during the first delay and these neurons were therefore classified as anticipatory. From this group, 60 % increased and 40 % decreased their activity (examples in Fig. 5). When comparing the averaged activity of these different neuronal populations, a striking difference could be seen during the second delay (Fig. 5c). Following the spatial cue, the pre-cue anticipatory neurons with increasing activity showed an early phasic response, whereas the neurons with decreasing activity were largely suppressed during the same epoch. This confirms the finding by Mauritz and

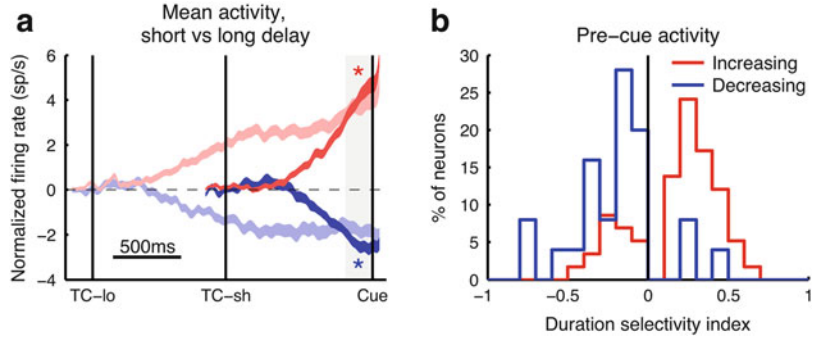

Fig. 6 Influence of delay duration on pre-cue anticipatory activity. (**a**) Mean activity (±sem) of the cue-anticipatory increasing (*red*, n = 170) and decreasing neurons (*blue*, n = 113) recorded in one monkey (monkey M). The activity in short and long delay trials are in *dark* and *light colors*, respectively. TC-lo and TC-sh is the onset of the time cue (200 ms duration) in long and short delay trials, informing about the delay duration. The data is aligned to Cue onset. The baseline activity has been subtracted. The *light gray rectangle* indicates the epoch used to compute the significance of the difference between short- and long-delay trials. (**b**) Distributions of the indexes of duration selectivity comparing short and long delay trials, using the pre-cue epoch marked in **a**. The index is defined as [(short − long)/(short + long)]. *Positive values* indicate a higher activity in short delay trials. Only the neurons with a significant difference (Mann–Whitney U test, $p < 0.05$) are shown (n = 58 and 25 for increasing and decreasing neurons, in *red* and *blue* respectively). The medians of both distributions are significantly shifted away from 0 (Wilcoxon signed rank test, $p < 0.05$) (unpublished data from J Confais, BE Kilavik, A Ponce-Alvarez and A. Riehle)

Wise [9] that almost all anticipatory neurons with an increasing activity show a phasic, short-latency response to the spatial cue. In addition, we show that the activity of the decreasing anticipatory neurons is suppressed after the cue. Simply put, the pre-cue increasing neurons are more active during the post-cue cue epoch than during the movement, whereas the pre-cue decreasing neurons are more active during movement execution [41].

Delay Duration Effects During Cue Anticipation

If the cue occurs probabilistically at one out of several, discrete points in time, the subject might expect a cue after shorter durations, even when the cue does not appear. This expectation has been shown in neurons that increase their activity until the time of the expected cue and then suddenly decrease their activity when the cue does not occur [3, 7, 9, 133]. In other words, if a neuron is classified as "increasing" during a short delay, it may change its pattern during a long delay [10].

Alternatively, the duration of the delay may be known with certainty, as in the study of Confais et al. [41]. Here, it becomes evident that the modulation depth in both increasing and decreasing anticipatory neurons is larger in short than in long delay trials (Fig. 6a). In the first part of this chapter, we described how the neuronal response to the spatial cue depended on delay duration, with both the phasic spiking activity and the VEP of the LFPs being larger in short than in long delay trials (Fig. 4). Most anticipatory neurons with an increasing pre-cue activity also show a phasic response to the cue. Therefore, the larger modulation of pre-cue firing rate observed in these neurons in short delay trials might mediate the subsequent larger responses to the cue. Furthermore, the differences in firing rate in short and long delay trials are clearly opposite for the increasing and decreasing sub-populations (Fig. 6b). This "mirrored" modulation of the pre-cue firing rate suggests that the two sub-populations of neurons have complementary roles.

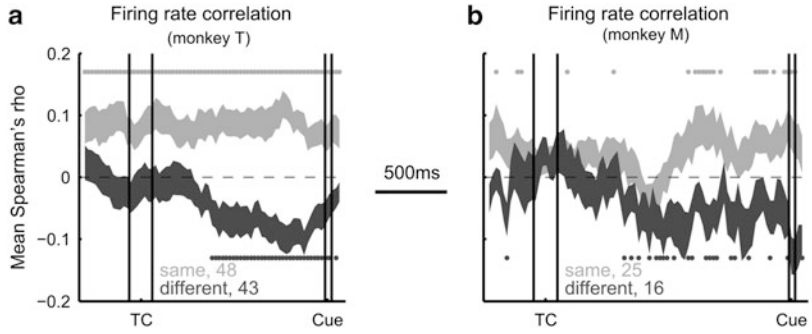

Fig. 7 Trial-by-trial correlations between cue-anticipatory neurons. The *curves* represent the mean coefficient of correlation (±sem), for pairs of cue-anticipatory neurons with the same activity pattern (both increasing or decreasing, in *light grey*) and with opposite activity patterns (one increasing and one decreasing, in *dark grey*). We used a sliding window of 250 ms to guarantee a sufficient amount of spikes, and selected only neurons recorded on different electrodes. In each window, we performed a Spearman rank correlation between the spike counts across trials of each neuron pair. The correlation coefficients were transformed in Fisher z before averaging across pairs, and then transformed back. We only analyzed the pre-cue delay in long delay trials. The *diamonds* at the *top* and *bottom* of the plots indicate time bins in which the mean coefficient of correlation is significantly different from 0 (Wilcoxon signed-rand test, $p < 0.05$). Only long-delay trials are shown. (**a**) Monkey T, $n = 48$ and 43 pairs of neurons of the same and different category, respectively. (**b**) Monkey M, $n = 25$ and 16 pairs of neurons of the same and different category, respectively (unpublished data from J Confais, BE Kilavik, A Ponce-Alvarez and A Riehle)

Possible Functional Role(s) of Pre-cue Anticipatory Activity

The anticipatory activity could be the reflection of attentional processes, as already shown in PMd [134, 135]. However, we did not find any difference in the pre-cue activity between correct and error trials, i.e., selecting the wrong cue, presumably because of attentional fluctuations [41]. Alternatively, it could reflect a general timing process. Durstewitz [49] proposes that climbing activity, like the one observed before the spatial cue, could be a possible substrate of time estimation. Furthermore, several fMRI studies show activation of the premotor cortex during tasks involving time estimation [136, 137]. However, as we discussed in Part 1, a timing mechanism based on climbing activity would need a fixed onset and a slope that differs according to delay duration. Yet, Fig. 5c (right panel) shows that the activity during the second part of the first delay in long trials is flat until the cue appears. This suggests that even if such an activity depends on the ability of the animal to estimate the delay duration, it is unlikely that it reflects timing *per se*. Another hypothesis would be that the anticipatory activity uncovers two parallel processes complementary to each other. One would facilitate the response to the spatial cue through an additive gain (as it is the case in the caudate nucleus, e.g., [129]), whereas the other would suppress a premature motor response, since the movement execution has to be withheld until the GO signal appears ("proactive volitional inhibition", e.g., [138], "impulse control", e.g. [139], "proactive control", see [140] for a review). Such an interpretation is supported by a modeling study of Moody and Wise [141] showing that an anticipatory activity emerges in some neurons before the cue during a match-to-sample task, but only if the cue timing is predictable. Removing these neurons either leads to false negative or false positive responses. The authors interpret this result as evidence for two parallel processes before cue occurrence, while preventing a premature response.

One prediction can be drawn from the idea that two sub-populations compensate each other's activity. The neuronal activities within a sub-population (e.g., neurons increasing their activity) would tend to positively co-vary trial-by-trial, whereas the neuronal activities of the

two different subpopulations would negatively co-vary. To test this hypothesis, we computed the mean trial-by-trial correlation ("noise correlation", see [142]) between spiking activities of pairs of neurons with the same anticipatory activity pattern and with opposite anticipatory activity, recorded simultaneously (Fig. 7). The mean trial-by-trial correlation of firing rates is dramatically different for pairs within the same category than for pairs from different categories. Neurons with the same pattern of pre-cue anticipatory activity are mainly positively correlated. Neurons with different patterns are not correlated initially, but become increasingly negatively correlated during the pre-cue delay. This again supports the idea that the two sub-populations play complementary roles in order to facilitate cue detection, while preventing premature motor output. These two sub-populations do not only negatively co-vary in relation to the pre-cue delay duration in their averaged activity (Fig. 6), but are also dynamically co-adjusted on a trial-by-trial basis (Fig. 7).

To conclude, the cue-anticipatory activity may reflect prospective facilitation of cue processing concurrent with proactive movement inhibition. As mentioned initially, cue-anticipatory activity is more prevalent in PMd than in other frontal areas. This idea is supported by studies linking PMd to the processing of spatial cues (e.g., [118]) and movement inhibition [143–145]. With this in mind, our results could therefore be interpreted as PMd playing a key role in the pre-setting of these processes.

Summary and Conclusion

The accurate estimation of time intervals is an essential aspect of motor performance; it is at the core of any anticipatory behavior. We have shown that timing processes are indeed represented in motor cortical single neuron and population activity, in a manner that is strongly dependent on context. It is tempting to speculate that the increase of firing rate and spike synchrony at specific task moments reflect a cognitive state; an internal representation of the precise timing of an expected event. This could favor the idea that timing, to some extent, is a constituent of currently active networks, and is therefore a distributed brain process. However, it is not clear if time itself is represented in the brain as an invariant process, separable from other processes, such as cue anticipation or movement preparation. The characteristics of the single neuron climbing activity observed during movement preparation in motor cortical areas suggest its origin upstream from the recorded neuron. Additionally, the effects of implicit and explicit timing in the activity of single neurons in motor cortex are very similar. It is difficult to discern in motor cortical activity whether different mechanisms are involved when timing is only implicitly used to improve performance or when timing is a crucial component of the task.

To conclude, if time estimation is a process independent of contextual features such as probability or movement preparation, then the signatures of time that we have described here are more likely the *result* of time estimation and not the time estimation process itself (see also the discussion in [3]). The question still remains open whether a general, context-independent neuronal correlate of time estimation exists (e.g., [146–148]).

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Neurophysiology of Timing in the Hundreds of Milliseconds: Multiple Layers of Neuronal Clocks in the Medial Premotor Areas

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Abstract

The precise quantification of time in the subsecond scale is critical for many complex behaviors including music and dance appreciation/execution, speech comprehension/articulation, and the performance of many sports. Nevertheless, its neural underpinnings are largely unknown. Recent neurophysiological experiments from our laboratory have shown that the cell activity in the medial premotor areas (MPC) of macaques can represent different aspects of temporal processing during a synchronization-continuation tapping task (SCT). In this task the rhythmic behavior of monkeys was synchronized to a metronome of isochronous stimuli in the hundreds of milliseconds range (synchronization phase), followed by a period where animals internally temporalized their movements (continuation phase). Overall, we found that the time-keeping mechanism in MPC is governed by different layers of neural clocks. Close to the temporal control of movements are two separate populations of ramping cells that code for elapsed or remaining time for a tapping movement during the SCT. Thus, the sensorimotor loops engaged during the task may depend on the cyclic interplay between two neuronal chronometers that quantify in their instantaneous discharge rate the time passed and the remaining time for an action. In addition, we found MPC neurons that are tuned to the duration of produced intervals during the rhythmic task, showing an orderly variation in the average discharge rate as a function of duration. All the tested durations in the subsecond scale were represented in the preferred intervals of the cell population. Most of the interval-tuned cells were also tuned to the ordinal structure of the six intervals produced sequentially in the SCT. Hence, this next level of temporal processing may work as the notes of a musical score, providing information to the timing network about what duration and ordinal

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element of the sequence are being executed. Finally, we describe how the timing circuit can use a dynamic neural representation of the passage of time and the context in which the intervals are executed by integrating the time-varying activity of populations of cells. These neural population clocks can be defined as distinct trajectories in the multidimensional cell response-space. We provide a hypothesis of how these different levels of neural clocks can interact to constitute a coherent timing machine that controls the rhythmic behavior during the SCT.

Keywords
Interval timing • Medial premotor areas • Interval tuning • Ramping activity • Network dynamics

Introduction

Time is a crucial variable in life and organisms have developed different mechanisms to quantify the passage of time along a wide range of durations. From microseconds to circadian rhythms, temporal information is used to organize behavior and specific brain mechanisms have been suggested for the measurement of different time scales. Indeed, the central nervous system does not have a time sensory organ; however, organisms are able to extract temporal information from stimuli of all sensory modalities and use it to generate timed behaviors. This chapter focuses on the neural underpinnings of interval timing in the hundreds of milliseconds, since it is a time scale involved in many complex behaviors such as the perception and production of speech [1, 2], the execution and appreciation of music and dance [3, 4], and the performance of a large variety of sports [5–7]. In music, for example, time comes in a variety of patterns which include isochronous sequences where temporal intervals are of a single constant duration or, more commonly, polyrhythmic sequences containing intervals of many durations. In addition, the ability to capture and interpret the beats in a rhythmic pattern allows people to move and dance in time to music [3]. Music and dance, then, are behaviors that depend on intricate loops of perception and action, where temporal processing can be engaged during the synchronization of movements with sensory information or during the internal generation of movement sequences [4]. In a simplified version of these activities, numerous studies have examined how subjects synchronize taps with rhythmic isochronous auditory stimuli and then continue tapping at the instructed rate without the advantage of the sensory metronome [8, 9]. Thus, the synchronization-continuation tapping task (SCT) has at least four main components, namely, a sensorimotor process during synchronization, an internal timing component during both synchronization and continuation, a cyclic element for repetitive interval production, and a working-memory component used during the continuation. The cyclic nature of this task implies that subjects must keep track of the time elapsed since the previous sensory and motor events as well as the time remaining until the next events [10].

The present manuscript describes the functional properties of neurons in the primate medial premotor cortex (MPC, i.e. supplementary motor area [SMA] and pre-supplementary motor area [preSMA]) during the execution of the SCT. We show how the single cell and population activity of this cortical area represents different aspects of the temporal processing involved in the execution of a rhythmic task that has been a backbone in the timing literature.

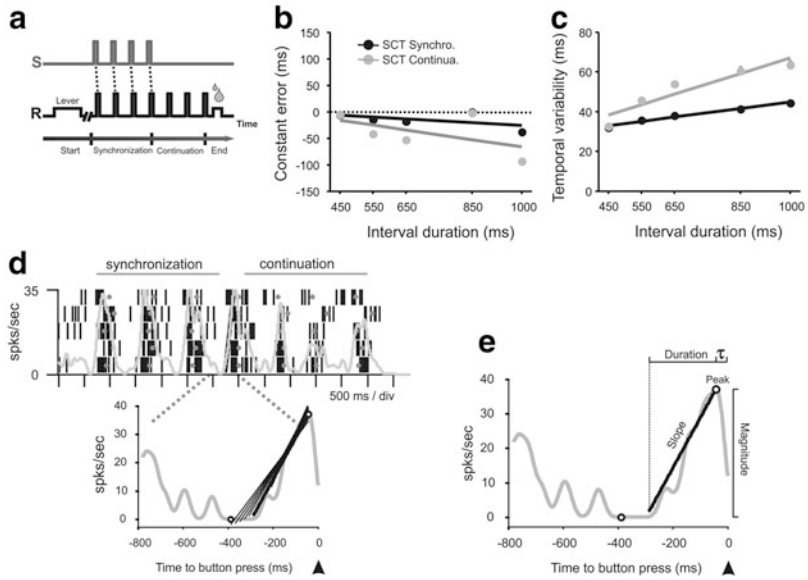

Fig. 1 (**a**) Sincronization-Continuation Task (SCT). Monkeys were required to push a button (R, *black line*) each time stimuli with a constant interstimulus interval (S, *gray line*) were presented, which resulted in a stimulus-movement cycle. After four consecutive synchronized movements, the stimuli stopped, and the monkeys continued tapping with a similar pacing for three additional intervals. The target intervals, defined by brief auditory or visual stimuli, were 450, 550, 650, 850, and 1,000 ms, and were chosen pseudo-randomly within a repetition. (**b**) Constant error (produced-target interval) during the performance of the SCT in the auditory interval marker condition. Monkeys slightly underestimated the interval durations during the synchronization (*black*) and continuation (*gray*) phases of SCT. The SEM is smaller than the dot diameter. (**c**) Temporal variability (i.e. the intertap SD) increased as a function of target interval during both phases of SCT. (**d**) Iterative algorithm used to find the best regression model to explain the increase or decrease of instantaneous activity over time with respect to a sensory or motor event. Top, raster plot and mean SDF (*gray function*) of a ramping cell aligned to the first tap of the continuation phase. The region indicated by the *dotted rectangle* is expanded below, where a series of linear regression functions are displayed, including the best model identified by the algorithm shown as the *thicker line*. (**e**) Parameters that were extracted from the linear regression model for the motor and relative-timing ramps. Modified from [10, 36]

Ramping Activity as an Instantaneous Timing Signal for Temporal Execution

We recorded the activity of MPC cells during a version of the SCT where monkeys were required to push a button each time stimuli with a constant interstimulus interval were presented, which resulted in a stimulus-movement cycle (Fig. 1a). After four consecutive synchronized movements, the stimuli stopped, and the monkeys continued tapping with the same interval for three additional intervals. Brief auditory or visual interval markers were used during the synchronization phase and the range of target intervals was from 450 to 1,000 ms [10, 11]. The monkeys were able to accurately produce the target intervals, showing an average underestimation of ~50 ms across interval durations during the synchronization and continuation phases of the SCT (Fig. 1b). In addition, we analyzed the temporal variability of the monkeys' tapping performance, which was defined as the SD of the individual inter-response intervals [12, 13]. Temporal variability increased linearly as a function of interval duration in both phases of SCT (Fig. 1c). These findings show that the monkeys had a remarkably accurate timing performance in this complex temporal tapping task. Furthermore, the data show a temporal variability that followed the scalar property of interval timing, a property that has been documented in many species and temporal tasks [14]. In a recent study, where the speed profile of

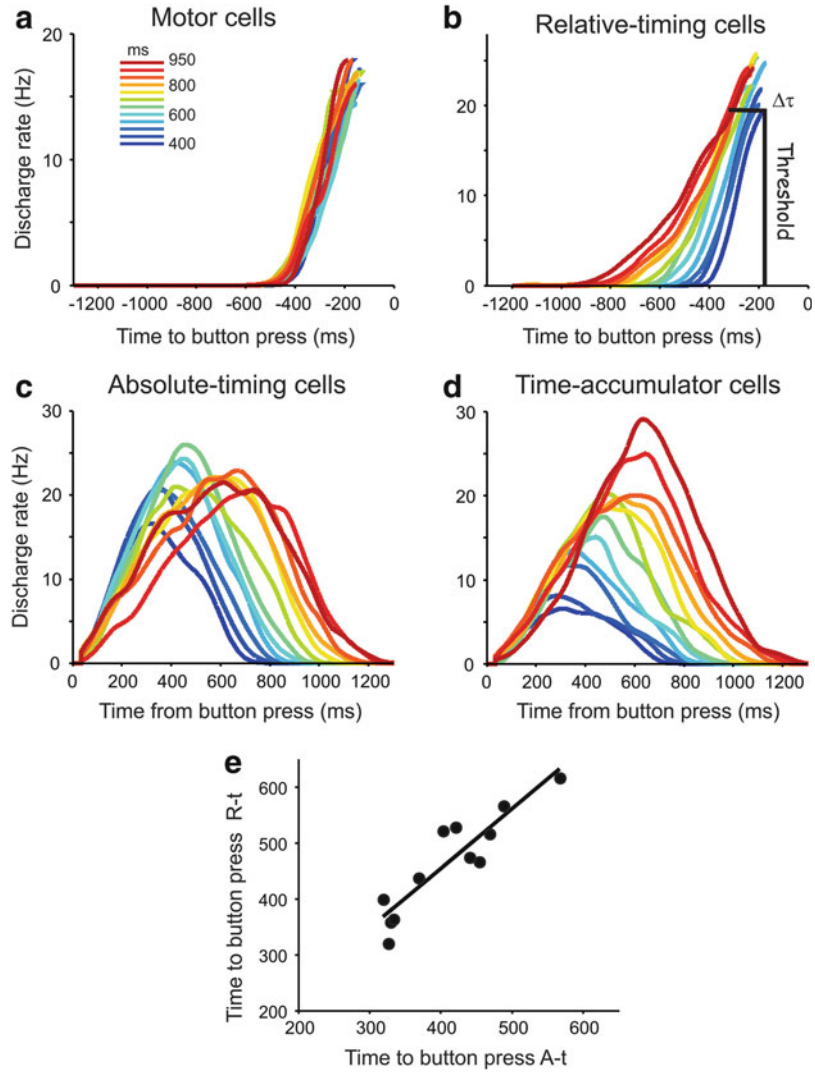

Fig. 2 Ramp population functions for motor (**a**), relative-timing (**b**), absolute-timing (**c**) and time-accumulator (**d**) cells. **a** and **b** are aligned to the next button press while **c** and **d** are aligned to the previous button press. The color code in the inset of A corresponds to the duration of the produced intervals during the SCT. (**e**) Time to button press of the ramp population functions at 14 Hz for absolute-timing (A-t) cells plotted against the time to button press associated with the ramp population functions at 7 Hz for relative-timing (R-t) cells. The ramp population functions are equal to the addition of the magnitudes of individual ramps over time. Modified from [10]

the tapping movements was computed using semiautomatic video tracking algorithms, we demonstrated that monkeys temporalize their movement-pauses and not their tapping movements during the SCT [15–17]. Macaques showed a strong ability to temporalize their movement-pauses for a wide range of intervals (450–1,000 ms), while their movements were similar across the duration of produced intervals, the sequential structure of the SCT, or the modality of the interval marker. These findings suggest that monkeys use an explicit timing strategy to perform the SCT, where the timing mechanism controlled the duration of the movement-pauses, while also triggered the execution of stereotyped pushing movements across each produced interval in the rhythmic sequence [15].

The extracellular activity of single neurons in the medial premotor areas was recorded during task performance using a system with seven independently movable microelectrodes (1–3 MΩ, Uwe Thomas Recording, Germany [10]). A large population of neurons showed ramping activity before or after the button press in the SCT (703 out of 1,083 recorded cells) [18]. Indeed, we developed a warping algorithm to determine whether the cells responses were aligned to the sensory or motor aspects of the

SCT, and we found that most MPC cells were aligned to the tapping movements instead of the stimuli used to drive the temporal behavior [18].

Next, an iterative algorithm was used to find the best regression model to explain the increase or decrease of instantaneous activity over time with respect to a sensory or motor event using the spike density function (SDF; Fig. 1d). With this method we defined for each ramp the following parameters: duration, slope, peak magnitude, and the time τ from the peak to the stimulus presentation or button press (Fig. 1e). Using this information, we classified different cell populations with ramping activity in four groups: motor, relative-timing, absolute-timing and time-accumulator [10]. For example, a large group of cells (n = 236) show ramps before the movement onset that are similar across produced durations and the sequential structure of the task, and therefore, are considered motor ramps (Fig. 2a). The inherent noise present in single temporal ramps, however, implies that the downstream reading neural node cannot rely on single cells to quantify the passage of time or produce accurately timed movements. Therefore, we propose a population code for encoding time during SCT, where the reading network adds the magnitudes of a population of individual ramps over time, resulting in a ramp population function [$R(t,I) = \frac{\sum_{n=1}^{N} r(t,I)}{N}$, where $r(t, I)$ corresponds to each individual ramp over time (t), from 1 to N total number of ramps of a cell type, and for a particular produced interval (I)]. Figure 2a shows the ramp population functions for the motor cells, where it is evident that the motor ramps are similar across the intervals produced by the monkeys during the SCT performance [10].

Interestingly, another cell population showed an increase in ramp duration but a decrease in slope as a function of the animals' produced duration, reaching a similar discharge magnitude at a specific time before the button press. These cells are called relative-timing cells, since their ramping profile could signal how much time is left for triggering the button press in the task sequence (n = 163 cells; Fig. 2b). Therefore, there is a population of MPC neurons that has the response properties to encode the time remaining for a motor event, and once the population reaches a firing magnitude threshold it could trigger the button press movements [10].

On the other hand, other groups of cells show a consistent increase followed by a decrease in their instantaneous discharge rate when their activity was aligned to the previous button press rather than to the next one (n = 304 neurons). In these absolute-timing cells the duration of the up-down profile of activation increases as a function of the produced interval (Fig. 2c), whereas in the time-accumulator cells there is an additional increase in the magnitude of the ramps' peak (Fig. 2d). Therefore, these cells could be representing the passage of time since the previous movement, using two different encoding strategies: one functioning as an accumulator of elapsed time where the peak magnitude and the duration of the activation period is directly associated with the time passed, and another where only the duration of the activation period is encoding the length of the time passed since the previous movement [10].

The rhythmic structure of the SCT may impose the need not only for the prediction of when to trigger the next tap to generate an interval, but also for the quantification of the time passed from the previous movement, in order to have cohesive timing mechanism to produce a repetitive tapping behavior. Indeed, the cells encoding elapsed (absolute-timing) and remaining time (relative-timing) showed some level of interaction during each cycle of time production in the SCT, supporting this notion [10] (Fig. 2e).

Cell activity changes associated with temporal information processing in behaving monkeys have been reported in the cerebellum [19], the basal ganglia [20], the thalamus [21], the posterior parietal cortex [22, 23], and the prefrontal cortex [24–27], as well as in the dorsal premotor cortex [28], motor cortex [29, 30], and the medial premotor areas MPC [10, 31]. These areas form different circuits that are linked to sensorimotor processing using the skeletomotor or oculomotor effector systems. Most of these studies have described climbing activity during different

timing contexts, which include discrimination of time, time estimation, single interval reproduction, and delay-related responses. Therefore, the increase or decrease in instantaneous activity as a function of the passage of time is a property present in many cortical and subcortical areas of the cortico-thalamic-basal ganglia circuit (CTBGc) that may be involved in different aspects of temporal processing in the hundreds of milliseconds scale. Indeed, recent studies have suggested the existence of a partially distributed timing mechanism, integrated by main core interconnected structures such as the CTBGc, and areas that are selectively engaged depending on the specific behavioral requirement of a task [12, 32, 33]. These task-dependent areas may interact with the core timing system to produce the characteristic pattern of performance variability in a paradigm and the set of intertask correlations described previously in psychophysical experiments [12].

The ubiquitous presence of cells' increments or decrements in discharge rate as a function of time across different timing tasks and areas of a potential core timing circuit suggests that ramping activity is a fundamental element of the timing mechanism. A key characteristic of ramping activity is their instantaneous nature and the fact that they normally peak at the time of an anticipated motor response. In the case of the SCT, the multiple neural chronometers must interact at some point in their ramping activity in order to define the rhythmic structure of the task. Thus, the tight interaction between the cells computing the elapsed time since the previous tap with the cells encoding the time remaining to the next tap generates a coordinated cycle of activation that ends with the triggering of a motor command, and the activation of motor cells involved in the execution of the tapping movement. Therefore, although the reported absolute-timing and the time-accumulator cells (Fig. 2c, d) are encoding the elapsed time since the previous motor event, it is evident that ramping cells are engrained in the temporal construction of motor intentions and actions [23, 34, 35]. This is a crucial point, since every timing task requires a movement, whether to express the perceptual decision in categorization or discrimination tasks or to produce accurately timed movements in tasks like SCT. Therefore, ramping activity may be part of the temporal apparatus that gates the motor responses to express a perceptual decision or produce a timed movement in a variety of behavioral contexts. An alternative possibility is that ramping activity reflects the accumulation of temporal information as described in the posterior parietal cortex [36, 37]. On the other hand, more abstract timing signals such as interval tuning, which are described below, can represent more cognitive elements of temporal processing.

Interval Tuning: An Abstract Signal of Temporal Cognition

Psychophysical studies on learning and generalization of time intervals give support to the notion that neurons in the timing circuit are tuned to specific interval durations, but can be activated in a modality- and context-independent fashion [38–40]. In addition, interval tuning has been suggested in conceptual papers [41]. In a recent paper, we described a graded modulation in the discharge rate of cells as a function of interval duration during the SCT in cells of MPC [42]. Figure 3a, b shows the profile of activation of a cell in the preSMA of a monkey performing this task. The neuron shows larger activity for the longest durations, with a preferred interval around 900 ms (Fig. 3c). In fact, a large population of MPC cells is tuned to different interval durations during the SCT, with a distribution of preferred intervals that covers all durations in the hundreds of milliseconds, although there was a bias towards long preferred intervals ($n = 487$ neurons; Fig. 3d). These observations suggest that the MPC contains a representation of interval duration, where different populations of interval-tuned cells are activated depending on the duration of the produced interval [42]. In addition, most of these cells also showed selectivity to the sequential organization of the task, a property that has been described in sequential motor tasks in MPC [43]. The cell in Fig. 3a, b

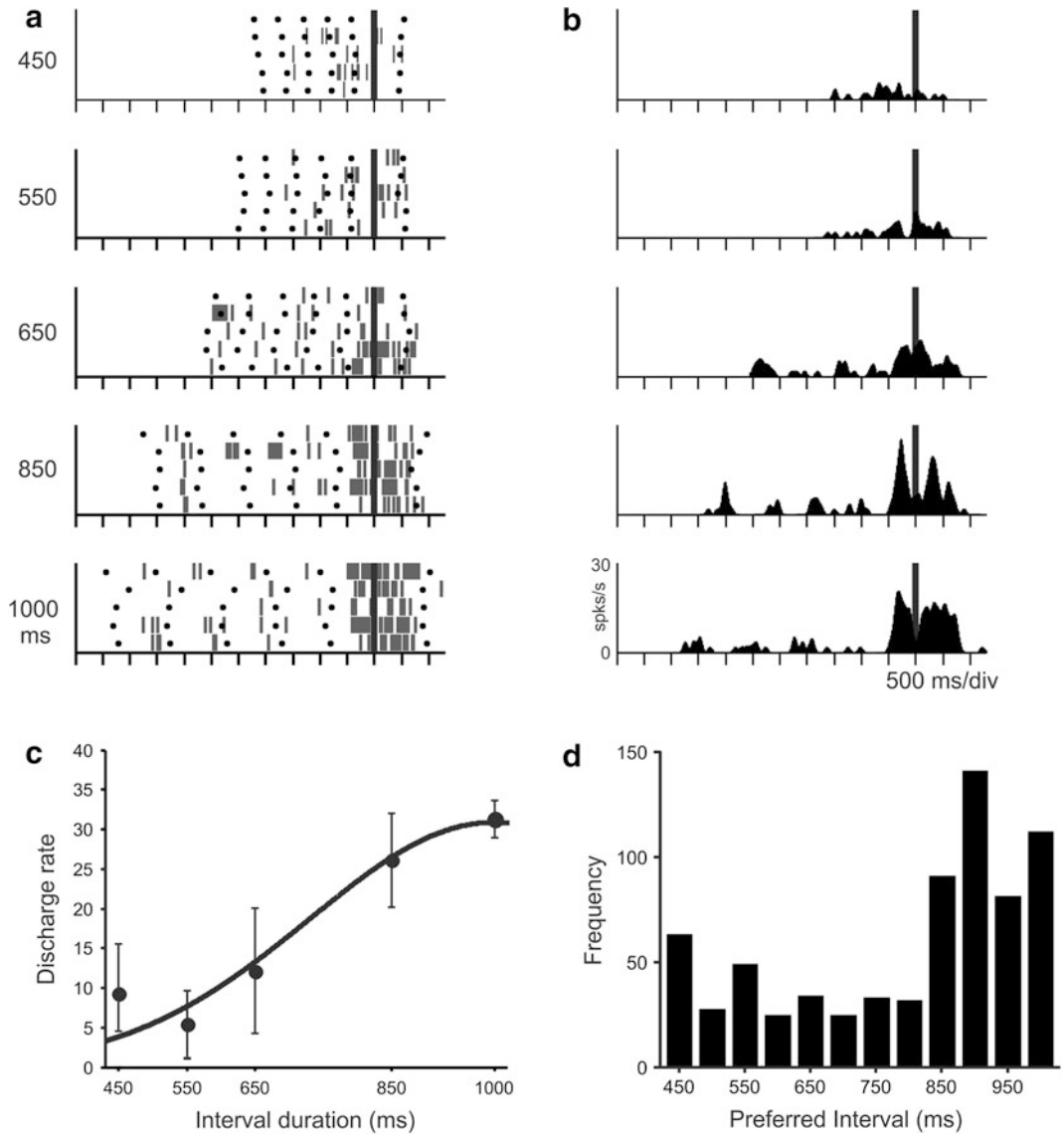

Fig. 3 Interval and ordinal-sequence tuning. (**a**) Responses of an interval-tuned cell with a long preferred interval and a sequential response to the last interval of the continuation phase during the SCT. Raster histogram aligned (*black line*) to the third tap of the continuation in the visual condition. (**b**) Average spike-density functions of the responses shown in **a**. (**c**) Tuning function for the same cell, where the mean (±SEM) of the discharge rate is plotted as a function of the target interval duration. The *continuous line* corresponds to the Gaussian fitting of the data. (**d**) Histograms of the preferred intervals in the visual marker condition for cells with significant interval tuning during the SCT. Modified from [36]

also shows an increase in activity during the last produced interval of the continuation phase of the task. Again, at the cell population level, all the possible preferred ordinal-sequences were covered (n = 426 neurons) [42]. These findings support the notion that MPC can multiplex interval duration with the number of elements in a sequence during the rhythmic tapping [42].

Cell tuning is an encoding mechanism used by the cerebral cortex to represent different sensory, motor, and cognitive features [44], which include the duration of the intervals, as reported here.

This signal must be integrated as a population code, where the cells can vote in favor of their preferred interval to generate a neural "tag" of the interval that is being executed during rhythmic tapping tasks. Interestingly, the cell tuning for duration is commonly accompanied by tuning to the ordinal structure of the SCT. Hence, the temporal and sequential information is multiplexed in a cell population signal that works as the notes of a musical score in order to define the duration of the produced interval and its position in the learned SCT sequence [10, 45].

As described above the elapsed or remaining time for a temporalized movement during the SCT is encoded in the ramping activity of MPC cells [10]. Relevant to the interval tuning phenomenon is the fact that one type of ramping cell shows a linear increase in its instantaneous discharge rate as a function of the elapsed time since a motor event, working as a time "accumulator". Here, we found that most of these time-accumulator cells were also significantly tuned to an interval, showing preferred intervals only for long durations. Therefore, a crucial question is what is the difference in functional impact between pure time-accumulator and pure interval-selective cells during the SCT? To try to answer this question we computed the Mutual Information (MI) between the spike density functions of the time-accumulator or the non-ramping interval-tuned cells and the target intervals using a sliding window for the auditory marker condition. The MI is a measure of the statistical dependency between the behavioral variable, in this case the target interval, and the neural activity. The MI of time-accumulator cells showed an up-down profile of activation with a MI maximum around the ramps' peak (Fig. 4a). In contrast, for interval-tuned cells that did not show a ramping profile in their instantaneous discharge rate, the MI was smaller but similar throughout the produced intervals (Fig. 4b). These findings support the notion that ramping cells are engrained in the dynamic construction of motor intentions and actions [10, 34, 46, 47]. On the other hand, interval tuning on the overall discharge rate may represent more cognitive aspects of temporal processing that are disengaged from the motor tapping output.

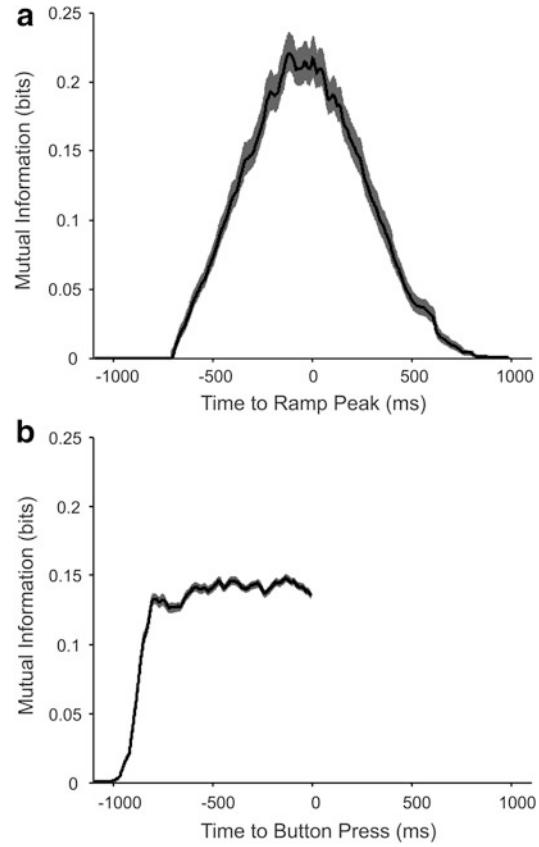

Fig. 4 Mutual Information for cells tuned to interval during the SCT. (**a**) Mean (*black*) and SEM (*gray*) of the mutual information as a function of time to ramp peak for the population of time-accumulator (n = 100) cells. (**b**) Mean (*black*) and SEM (*gray*) of the mutual information as a function of time to button press for the non-ramping duration-tuned (n = 304) cells

Neural Population Clocks in Behaving Primates: Temporal Processing in the Neural Dynamics

Time can be encoded in the unique temporal patterns of the integrated activity of groups of cells [47]. These cell populations should show time varying activity that is related to temporal processing. Different population clocks have been reported. For example, using a model of the activity of granule cells in the cerebellum, a

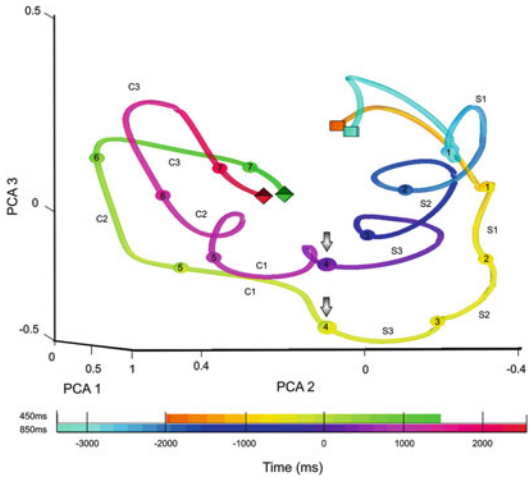

Fig. 5 Plot of the population dynamics of 549 cells during the SCT using the first three components of a Principal Component analysis on the time varying activity of the cells. The color code is associated to the passage of time for two network trajectories corresponding to 450 and 850 ms interval durations (see color codes at the *bottom*). The *cubes* correspond to the beginning of the trial, the *ellipses* to the median of the tapping movements (the tap ordinal number is inside), and the *diamonds* to the end of the trial. The trials are aligned to the fourth tapping movement as indicated by the *gray arrows*. S1–S3 correspond to the three synchronization intervals and C1–C3 to the three continuation intervals. Note the large difference in the network trajectories between interval durations and task phases. Unpublished observations

continuously changing population pattern can be read by Purkinje cells to tell time [48]. In addition, cell response simulations of recurrent cortical networks have been used to build population clocks that encode time in the context of temporal production [47] or perception [49]. In these models, time is implicitly encoded in the time-varying but repetitive state of the simulated networks.

Using the same logic, a clock population model was constructed using the task related activity of populations of MPC cells during the SCT. The history of the state of population responses can be depicted as an evolving trajectory in principal component space. Principal component analysis (PCA) is an analytical tool used to determine the most meaningful dimensions of a multidimensional dataset. Thus, Fig. 5 shows a 3D plot, using the first three PCAs, of the millisecond by millisecond change in the network state depicted here as a trajectory of the neural population during the six produced intervals of the SCT for a particular interval duration. Once the animal starts the tapping sequence in the task, the evolving trajectory of the population moves in a specific fashion to generate spirals for each of the produced intervals in the synchronization and continuation phases of the SCT (labeled as S1–S3 and C1–C3, respectively). Once the trial is finished (diamonds) the population returns to a state similar to the beginning (cubes) of the SCT. These trajectories of the recorded population are similar on different trials using the same interval, suggesting that the population clock reliably represents the passage of time. Indeed, there is a large difference in the population clock trajectories between interval durations (450 and 850 ms) and task phases. Hence, when reading the activity of task related cells, the next node of the core timing circuit can have access to information about the interval that is being produced and whether the subject is handling time in a sensory guided or an internally driven context.

Multiple Layers of Neuronal Clocks in the Medial Premotor Cortex

Our neurophysiological recordings in behaving animals indicate that MPC, an area of the core timing mechanism [32], uses multiple encoding strategies to represent different aspects of the temporal structure of the SCT. Ramping activity, the most reported timing signal in the literature, is close to the motor output and is used to trigger the multiple movements of the task sequence. Thus, the tight interaction between the cells computing the elapsed time since the previous tap with the cells encoding the time remaining to the next tap generates a coordinated cycle of activation that defines the rhythmic structure of the SCT. Figure 6 shows the ramping activity at the bottom of the encoding hierarchy of time during the SCT. We suggest that the ramps probably define the duration of each element of the rhythmic sequence, triggering the tapping

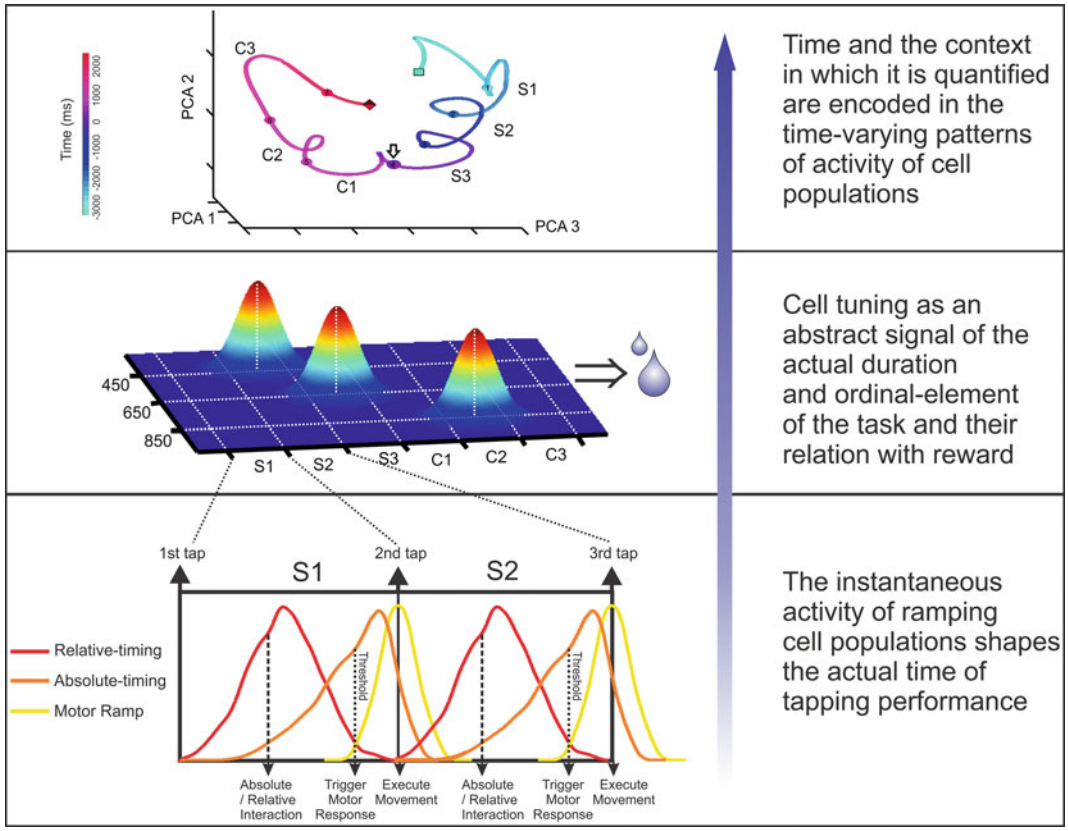

Fig. 6 A model of the interaction between the multiple layers of neuronal clocks in the medial premotor cortex. *Bottom*. Ramping activity defines the movement to movement temporal behavior of the animals during the SCT. *Middle*. Neuronal tuning to both duration and sequential order during the SCT as an abstract signal of what is the identity of the actually executed interval in an overlearned rhythmic task and its relation with the reward contingencies. *Top*. A population clock arises from the time-varying activity of a population of neurons dynamically interacting inside the MPC and across the core timing network

command that is probably generated in premotor areas and the primary motor cortex [34, 35]. Consequently, it is possible that the timing mechanism uses a temporal code in the form of ramp to encode timing actions [50, 51].

On top of these instantaneous signals we have neural tuning, which encodes the duration and the ordinal element of the six intervals produced sequentially during the SCT, as depicted in Fig. 6. This next level of temporal processing may work as the notes of a musical score, providing information to the timing network about what duration and ordinal element of the sequence is being executed. This information can be used to coordinate the networks that have been shaped by training to associate the temporal and ordinal structure of the SCT with the reward contingencies of our experiments [51].

Finally, the CNS uses dynamic neural representations of the passage of time and the context in which the intervals are executed by integrating the time-varying activity of populations of cells. Thus, the dynamics of the local cell ensemble and the overall flux of information in the core timing network can define the properties of the population clock observed in the MPC during the execution of the SCT. This integrated population signal is at the top of the hierarchy, since different nodes of the core timing network can: (1) read, (2) process, and (3) transmit the locally transformed population signal in a dynamic and reverberant fashion. This dynamic

and complex signal can encode the passage of time together with: (1) the history of the encoded interval in a rhythmic sequence, and (2) the context in which the intervals are produced, namely, using sensory cues or internal commands.

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The Olivo-Cerebellar System as a Neural Clock

James Ashe and Khalaf Bushara

Abstract

The cerebellum, and the olivo-cerebellar system in particular, may be the central mechanism of a neural clock that provides a rhythmic neural signal used to time motor and cognitive processes. Several independent lines of evidence support this hypothesis. First, the resting membrane potential of neurons in the inferior olive oscillates at ~10 Hz and the neural input from the olive leads to rhythmic complex spikes in cerebellum Purkinje cells. Second, the repeating modular microstructure of the cerebellum is ideally suited for performing computations underlying a basic neural process such as timing. Third, damage to the cerebellum leads to deficits in the perception of time and in the production of timed movements. Fourth, functional imaging studies in human subjects have shown activation of the inferior olive specifically during time perception. However, additional data on the exact role of rhythmic cerebellar activity during basis motor and sensory processing will be necessary before the hypothesis that the cerebellum is a neural clock is more widely accepted.

Keywords

Cerebellum • Inferior olive • Time • Perception • Motor control

Many of the chapters on the neural control of interval timing in this volume focus on the role of the cerebral cortex. As a counterbalance, here we provide an overview of the role of the cerebellum in the control of timing including data from a series of experiments we have done to elucidate that the issue. The putative role of the cerebellum in timing behaviors is intimately connected with the importance of the structure in the control of movement. Flourens [2] was the first to suggest that the cerebellum was responsible for the coordination of movement and since then an extensive literature has shown that damage to the cerebellum leads to tremor, unsteadiness of gait and poorly coordinated movements [3]. However, the

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clear association between the cerebellum and motor control has also presented something of a puzzle. The cerebellum does not appear to be responsible for the generation of movement *per se*. Neural recordings from Purkinje cells, which receive the principal inputs to the cerebellum, and from neurons in the deep nuclei, which constitute the only output, have shown only a modest relation to movement or movement parameters; detailed sensorimotor maps show that large areas of the cerebellum, particularly in the lateral hemispheres, are 'silent' [4, 5] in that they have no apparent relation to motor function. One potential solution to the discrepancy between the importance of the cerebellum in motor control and the lack of a strong relation to motor parameters, which also takes account of its homogenous and repetitive microstructure, is that the structure does not control individual movements but executes a basic neural process that is essential for normal movement and perhaps other brain functions (this is an elaboration of the 'functional equivalence' of different parts of the cerebellum first proposed by Flourens). A major hypothesis about this 'basic process' is that the cerebellum functions as a biological clock in the millisecond range [6, 7] with the beat of the clock provided by spontaneous rhythmic activity in the inferior olive [8–10]. In this scenario, the beat from the olive is transmitted via the climbing fibers to Purkinje cells (PCs) in which it is manifested by a complex spike. It has been suggested that the role of a biological clock in the cerebellum is not confined to the regulation of motor and sensory processes but might also track the temporal progression of cognitive processes [11–13].

The Olivo-Cerebellum Has Clock-Like Properties

The principal support for this hypothesis rests on several key findings: (1) the inherent rhythmic pacemaker activity of inferior olive (IO) neurons [14, 15] that elicit synchronous rhythmic activity in target Purkinje-cell neurons, (2) the oscillating resting membrane potential of IO neurons, (3) the effects of lesions on time perception and motor performance, and (4) functional imaging studies of the inferior olive during time during explicit and implicit timing behaviors.

Rhythmic Pacemaker Activity of Inferior Olive

The inferior olive located in the medulla projects to the contralateral cerebellar cortex through the climbing fibers whose synapse to the Purkinje cell (PC) is the most robust in the nervous system [16]. An action potential in a climbing fiber leads with high probability to a complex spike (multiphasic potential of high amplitude) in the PC to which it projects [17]. The property of rhythmicity in the timing of occurrence of complex spikes was first conclusively demonstrated by Bell and Kawasaki [15] using extracellular recordings in the guinea pig though and was also documented about the same time in the frog [18]; neurons in the IO also produce spontaneous action potentials in the 1–10 Hz range [14, 19].

Rhythmic activity in these structures might not be of any great import in itself and would not necessarily provide the ingredients from which to build a practical neural clock were it not for the additional property of synchronicity that is also evident in olivary neurons and their target Purkinje cells [20]. The gap junctions between adjacent IO neurons [21, 22] enable electrotonic coupling which is thought to be the physiological basis of the synchronous oscillations produced by the IO [20, 23] that are reflected at the level of the PCs in the cerebellum by synchronous complex spikes in PCs [22, 24]. Furthermore, we now know that synchronous PC activity leads to time-locked activation of cells in the target deep nuclei [25] providing a mechanism for the propagation of temporal information from the inferior olive to the principal output structure of the cerebellum (Fig. 1).

Oscillating Membrane Potential of IO Neurons

The resting membrane potential of IO neurons oscillates at a frequency close to 10 Hz [14, 26, 27] and this property is likely fundamental to the

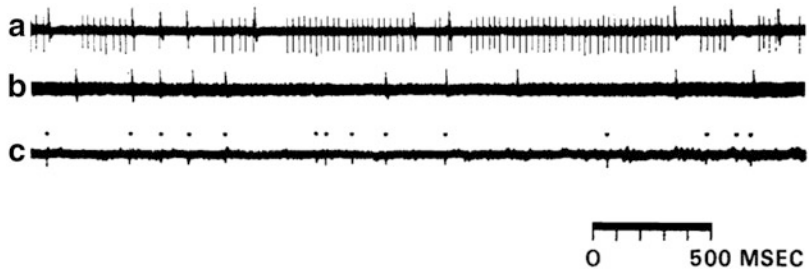

Fig. 1 Rhythmic simple and complex spikes in three different Purkinje cells. **a**: simple spikes (short duration biphasic complexes) and less frequent complex spikes (CS); **b**: CS only, and **c**: small primarily negative CS also indicated by *dots*. There is clear though not consistent rhythmic CS activity at a rate of 8–10 Hz. Modified from Bell and Kawasaki [15]

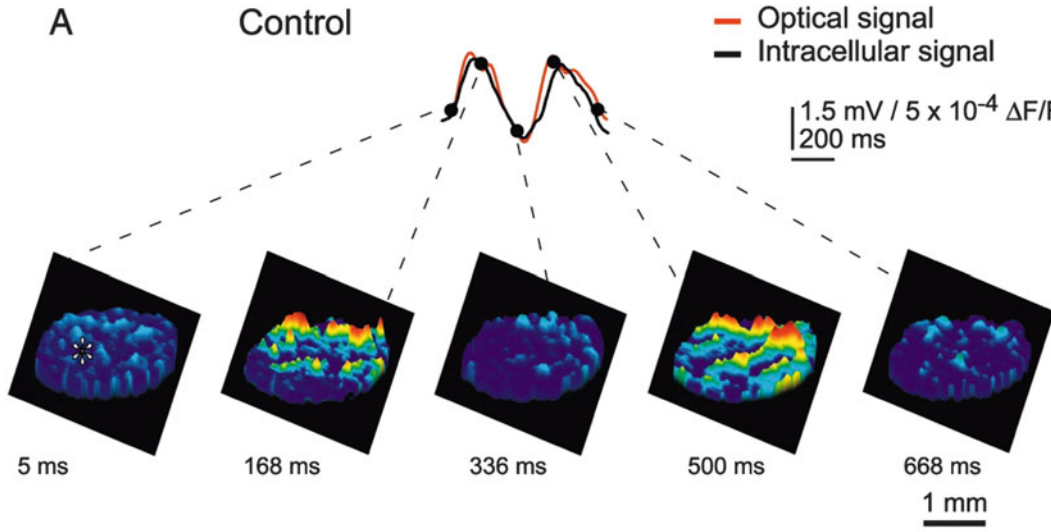

Fig. 2 Spontaneous oscillatory electrical activity in inferior olive neurons using simultaneous optical imaging and intracellular recording *upper panel*; superimposition of the optical signal (*red*) and intracellular voltage recording (*black*) shows the coherence of the temporal waveform. *Lower panels*; spatial distribution of voltage imaging at five different time points (*dots* in the *upper panel*). *Asterisk* indication the spatial location of intracellular recording (modified from [1])

rhythmic action potentials they generate [20, 28]. The peaks in the rhythmic oscillation are associated with an increased probability of action potential generation therefore this phenomenon would bias the IO neurons to spike rhythmically. The oscillations also influence the effect of IO output on its Purkinje cell targets in a less obvious way. It has recently been shown that a single somatic action potential in an olivary neuron results in bursts of multiple of axonal spikes and that the number of axonal bursts is positively correlated with the phase of the oscillations at which the action potential occurred [29]. In turn, the number of axonal bursts modulate the pattern of the complex spikes produced in the PCs providing yet another mechanism through the time dependent output of the inferior olive can be propagated through the cerebellum and beyond (Fig. 2).

Effects of Lesions in Humans and in Experimental Animals

Inferior Olive

One of the most distinctive neurological syndromes in humans, oculo-palatal myoclonus [30, 31], is defined by rhythmic involuntary movements of the eyes and soft palate that oscillate at 1–3 Hz and is caused by a lesion interrupting the projection from the deep cerebellar nuclei to the inferior [32]. The mechanism of the tremor in this condition is thought to be the removal of inhibitory projections to the electronic gap junctions in the olive thereby leading to hyperactivity and hypertrophy of the olivary neurons [33]. The association between hyperactivity in the olive and rhythmic oscillations is also supported by experiments involving the administration of harmaline to experimental animals. Harmaline is a psychoactive alkaloid obtained from the plant *Paganum harmala* that causes a rhythmic tremor ~8–10 Hz when administered in sufficient concentration to the cat and non-human primate [34, 35]. Neural recordings from the inferior olive during harmaline-induced tremor show rhythmic synchronous discharges at the same frequency as the tremor [9] and this is reflected in the cerebellum by a similar pattern of complex spike discharge in PCs. The tremor is not affected either by decerebration or by lesions of the Purkinje cell layer of the cerebellum. However, the tremor is abolished entirely following lesions of the inferior olive. Therefore, there is incontrovertible evidence that the inferior olive is capable of generating a rhythmic discharge resulting in tremor that is independent of input from, or modulation by, other brain structures. These findings may also be relevant to the pathogenesis of essential tremor one of the most common neurological disorders for which the cause and the pathophysiology are unknown. Essential tremor, which is often familial, is a progressive neurodegenerative disease that leads to bilateral hand tremor (6–8 Hz) which is often embarrassing and inconvenient and may become disabling. In patients with this condition, the most consistent abnormalities in brain imaging and in brain histology are found in the inferior olive and in the cerebellum. Postmortem examination of subjects with essential tremor showed 25 % fewer Purkinje cells on average and a sevenfold increase in degenerative changes in the intact PCs compared to normal controls [36]. Although neural recordings in the olivo-cerebellar structures have not been done in human subjects, one would predict that both the olive and the PCs would show rhythmic discharges in the 6–8 Hz range.

Cerebellum

Behavioral studies in human subjects with lesions of the cerebellar cortex due to disease or injury show a constellation of abnormalities for which disruption of the temporal organization of behavior may be the primary underlying cause. In these subjects, voluntary movements of the limbs are disrupted by tremor and errors in amplitude, and there is an inability to perform rhythmic movements at a specific rate [3]. Studies on the perception of time and the production of timed movements have shown that both are impaired in subjects with damage to the cerebellum leading to the hypothesis [12] that the cerebellum provides a basic timing mechanism common to motor, perceptual and even cognitive neural processes [11].

Imaging Studies in Human Subjects

Only recently has it become possible to perform functional imaging studies in human subjects with sufficient resolution to reliably image the inferior olive. These data have become all the more important because of the continuing controversy (see below) regarding the presence of

rhythmic IO activity in intact behaving animals and by extension its relevance to cerebellar function and to motor, sensory, and cognitive processes.

Olive Activation in Time Perception

As a prelude to a more comprehensive examination of the role of the olivo-cerebellar system in time processing, we performed a series of studies focused on the properties of this system in humans using functional MRI. The first question we addressed was whether these structures were activated during time perception when the perception was dissociated from any motor output; this starting-point was chosen because of doubts that the cerebellum had any role in time perception [37]. In the first study [38], we used three different visually-instructed behavioral tasks that involved the perception and motor performance of complex temporal sequences (rhythms) in the hundreds-of-milliseconds range, which, through the use of conjunction analysis [39] enabled us to dissociate brain activation related to temporal perception and performance. In the SYNCHRONIZE task subjects synchronized the movement of the right index finger with a rhythmic visual stimulus; in the REPRODUCE task, subjects observed a rhythmic visual stimulus (*observation*) and after a variable reproduced the rhythm from memory using the index finger (*performance*); in the MATCH task, subjects observed two visually instructed rhythms and were asked to indicate whether the rhythms were the same or different. We found that multiple areas within the cerebellar cortex were activated during temporal perception and performance (Fig. 3a, b); this result is consistent with the hypothesis that timing is a basic function of the cerebellum and establishes that neither motor performance nor motor preparation is a prerequisite for its activation during timing tasks. An important finding in the study was that the inferior olive was engaged exclusively during the perception of rhythmic visual stimuli; in Fig. 3c, we can see that the BOLD signal in the inferior olive increased during perception in two of the behavioral tasks (MATCH and REPRODUCE) but showed no change when temporal rhythms were tapped from memory (performance component in REPRODUCE) or when subjects tapped in synchrony with a rhythmic visual stimulus (SYNCHRONIZE). The activation of the olive during time perception alone demonstrated its specificity for timing processes independently of visual or somatosensory stimulation, which had previously been associated with olive activation in non-human primates [40, 41]. The failure to detect increased activation of the olive during the performance of rhythmic movements may be because of the suppressed 'responsiveness' of the olive in the context of upcoming voluntary movements [42–44] or, alternatively, it may be because timed motor performance is mediated by the much smaller dorsal and medial accessory olivary nuclei (DAO and MAO) and therefore unlikely to be detected using conventional fMRI methods.

Activation in Inferior Olive Specific for Stimulus Timing

Although the previously discussed experiment [38] provided evidence supporting a role for the inferior olive in time perception, an alternative interpretation of the results is that the olive is sensitive to unexpected sensory stimuli independent of modality and not necessarily specific for timing *per se*. Therefore, we performed an additional experiment in which we dissociated the temporal and non-temporal characteristics of different sensory stimuli [45]. Subjects were asked to focus on specific characteristics (orientation, color, or timing) of a visually displayed stimulus and indicate when it changed during individual trials. Attending to and perceiving the temporal and non-temporal properties of the stimuli led to increased activation in the

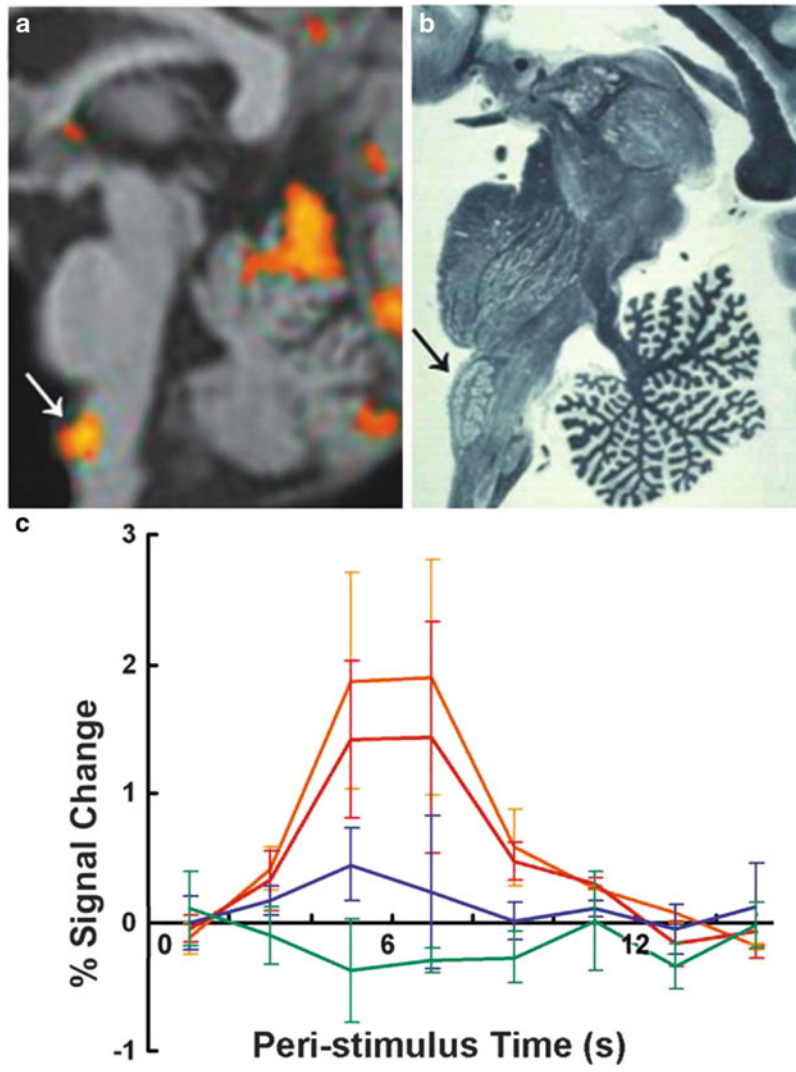

Fig. 3 (**a**) Event-related activation of the inferior olive (*white arrow*) time locked to the perception of rhythmic sequences of visual stimuli. (**b**) Corresponding sagittal anatomical section showing the inferior olive (*black arrow*). (**c**) Time course of the average hemodynamic response at inferior olive peak activation (−2, −32, −54) time locked to perception in REPRODUCE trials (*red*), perception in MATCH trials (*orange*), motor reproduction from memory (*green*), and stimulus-guided motor response synchronized to the temporal sequence (*blue*). *Error bars* indicate SD. Peri-stimulus time is in seconds

cerebellar hemispheres that was common to all three stimulus characteristics. The activation of the inferior olive, however, was specific for changes in the timing of the visual stimulus suggesting that attention to sensory stimuli alone was not sufficient to activate the olive (Fig. 4).

Activation of Inferior Olive During Implicit Timing

Much of our time-related behaviors are implicit and occur below the level of awareness. We can successfully intercept a moving target without explicit temporal computations, and learning

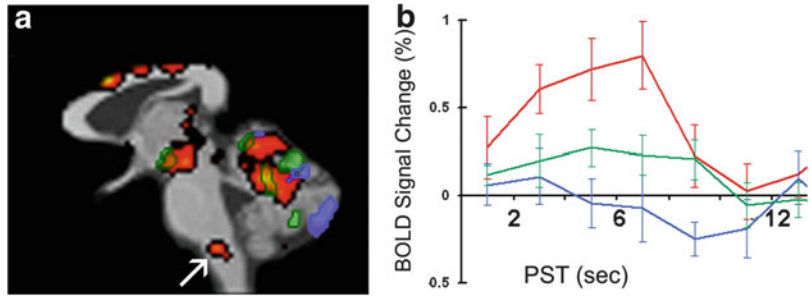

Fig. 4 Inferior olive response to stimulus timing change. (**a**) Event-related activation of the inferior olive (*arrow*) and cerebellum time-locked to the onset of stimuli. (**b**) Fitted hemodynamic response curves of inferior olive peak activation (2, −36, −52) time-locked to changes in timing (*red*), spatial orientation (*blue*), and color (*green*) of the visual stimuli. *PST*, post-stimulus time in seconds. *Error bars* indicate SE

temporal regularities is the basis of many of our skilled behaviors. In addition, implicit timing is a critical component of classical conditioning and other associative behaviors. It had long been assumed, using indirect evidence from classical conditioning and neural recording studies [46–49] that the olivo-cerebellar system mediated implicit timing. To directly test this hypothesis in human subjects, we used a temporal 'odd-ball' paradigm during event-related functional imaging [50]. We first measured the ability of each subject to detect an asynchronous stimulus with ~50 % probability (temporal detection threshold) within a series of otherwise synchronous visual stimuli (Fig. 5a); the mean detection threshold for the whole group was approximately 200 ms. During functional imaging, the subjects were asked to decide whether a series of visual stimuli was synchronous or asynchronous (containing one deviant stimulus at each subject's detection threshold) The experimental design enabled us to compare brain activation during detected and undetected deviant stimuli. Multiple areas within the olivary-cerebellar system showed equal activation during the detected and undetected deviant visual stimuli (Fig. 5b): bilaterally in the inferior olives land in lobule VIIIa of the cerebellum; right Crus I and left Crus II of the cerebellum.

These data show that changes in the timing of visual stimuli activate the inferior olives and areas within the cerebellar cortex independently of awareness and are consistent with the impairments in classical and trace eye-blink conditioning found in human subjects with cerebellar damage [51, 52]. The capacity of the inferior olive to encode temporal information is supported by physiological studies showing that stimulus timing is encoded relative to the phase of sub-threshold current oscillations [10, 29] and that external stimuli "reset" the olivary oscillations resulting in synchronized firing of a large population of neurons in phase with the external stimulus [53, 54]. Therefore it would appear that the low level information-processing of temporal information in the inferior olive is independent of attention and cognitive control mechanisms; the elaboration of this temporal signal in the cerebellum may indeed be the basic process for which the architecture of the cerebellum is ideally suited.

Dissenting Voices

The timing hypothesis of olivo-cerebellar function, however, is quite controversial [55] and is far from being generally accepted. Its validity has been challenged on the grounds that much of the supporting data has come from restricted experimental preparations, anesthetized animals, and from tissue-slice studies *in vitro,* The experimental finding that perhaps presents the greatest challenge to the timing hypothesis is the failure to find rhythmic neural activity in either Purkinje cells or in deep cerebellar nuclei in a crucial

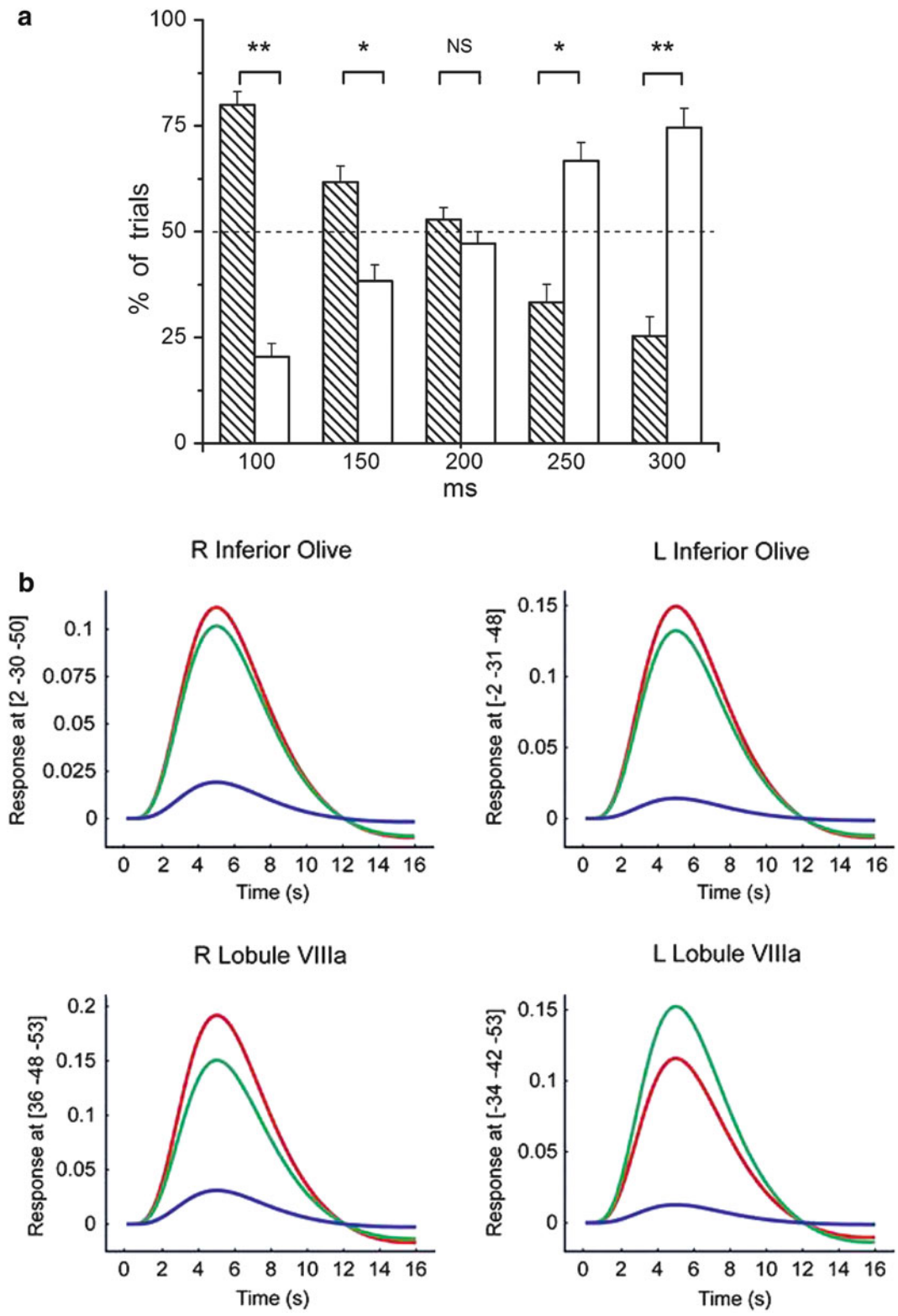

Fig. 5 (**a**) Percentage of trials in which subjects were aware (*blank columns*) or unaware (*hatched columns*) of the change in stimulus timing. In each trial, subjects observed a sequence of visual stimuli occurring at 1 Hz except for one deviant stimulus that occurred sooner than expected by 100, 150, 200, 250, or 300 ms. A deviation of 200 ms in stimulus

series of experiments in non-human primates [56, 57]. Although the inability of Thach and colleagues to detect rhythmic activity in these structures may be related both to the low sensitivity of single-channel extracellular recording for uncovering a process that is reflected at the level of the neural population [58, 59] and to the use of a behavioral paradigm not closely related to time perception or production, nevertheless, the controversy is unlikely to be resolved until rhythmic complex spiking activity or its functional equivalent* is documented in neural recordings from Purkinje cells in awake behaving non-human primates [60].

*It is possible that low frequency, apparently random, complex spikes in Purkinje cells have an underlying chaotic dynamic structure that can mimic rhythmicity within a certain time window [61]. The finding of such chaotic dynamics in the output of the inferior olive in awake behaving non-human primates would be one way in which the continuing controversy about whether the inferior olive behaves as a neural clock might be resolved. Therefore, examining time series of neural data, either the direct output of the inferior olivary neurons or complex spikes in cerebellar Purkinje cells, using sophisticated methodology is essential if we are to know the truth about the role of the inferior olive in neural timing behavior [60].

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Fig. 5 (Continued) timing corresponded to an approximate 50 % detection rate for the whole group (N = 17). *Error bars* indicate SEM (**$p \leq 0.0001$ and *$p \leq 0.001$; *NS* not significant). (**b**) Event-related BOLD response time-locked to detected deviant stimuli (*red*), undetected deviant stimuli (*green*), and stimuli with regular timing (*blue*) at peak voxels of areas activated in common between aware and unaware conditions

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From Duration and Distance Comparisons to Goal Encoding in Prefrontal Cortex

A. Genovesio and S. Tsujimoto

Abstract

Timing is a very abstract representation that shares with other magnitudes, such as numerosity, the peculiarity of being independent from any particular sensory modality. Not only we can time stimuli in different modalities but we can also compare the durations of different visual, auditory and somatosensory stimuli. Furthermore, even though time is not directly associated with space, and we are inclined to consider space and time as two different perceptual dimensions of our existence, an increasing number of studies challenge this idea by showing that timing and spatial processing have some relationship that involves sharing computation resources and that time may have a spatial representation. A more general theory, called theory of magnitude (ATOM), considers both timing and spatial computations, together with other magnitudes, as originating from a general magnitude system [Walsh VA, Trends Cogn Sci 7(11):483–8, 2003]. The neural underpinnings of time and its relationship to the processing of spatial information have started to be investigated only recently, but the field is rapidly growing. It is addressing the representation of time in several cortical and subcortical brain areas. Information processing of time and space are not strictly specialized in neural and cognitive mechanisms and we believe that studying them only separately may restrict our understanding of these processes. In this chapter, we will firstly introduce the role of the prefrontal cortex (PF) in coding relative durations. We will point out that the comparison of durations makes use of intermediate computations based on the order of the events. Secondly, we will describe the comparison mechanisms that are implemented by PF to make perceptual decisions about durations in relation to those involved in making decisions about spatial locations and distances. We will distinguish the decision processes

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from the goal choices, and we will examine which computational resources are shared between different magnitudes and which are domain-specific. We will summarize our results within the context of a more general PF function in promoting the generation of goals from the current context, consisting of domain- and modality-specific coding of stimuli of different modalities or magnitudes.

Keywords
Prefrontal cortex • Time • Distance • Magnitudes

Timing Function in PF

Timing functions have been associated with many brain regions, including the cerebellum, basal ganglia, and posterior parietal cortex [1–5], as well as PF. Among such areas, the role of PF in temporal perception has been shown by several neuropsychological [6, 7] and neuroimaging [8, 9] studies. For example, patients with right PF lesions show deficits in timing tasks [6, 10–12]. Likewise, transcranial magnetic stimulation (TMS) to the right PF cortex has been shown to impair explicit timing tasks in the suprasecond range of durations [13, 14]. In monkeys, inactivation of the dorsolateral prefrontal cortex (PFdl) through injections of bicuculline, a $GABA_A$ antagonist, produces deficits in the duration discrimination task, and the same task activates the PFdl in the context of a parietal-frontal network, in a positron emission tomography study, with covariation of activations between parietal and PF areas [8].

PF involvement in explicit timing has been also shown by adopting the variable foreperiod paradigm in which a target is presented after a foreperiod of different duration. In this paradigm, a progressive increase of the likelihood that a target will appear with the passage of time is associated with a reduction of the reaction time of the response to the target appearance. The reaction time advantage for longer foreperiods has been found to be compromised in patients with right PF damage [15–17]. Similar conclusions come from a TMS study of the right PF cortex [18].

In addition to neuropsychological and neuroimaging studies, an increasing number of studies have focused on the single cell level in primates. Since the early work of Niki and Watanabe [19] that proposed a role of cortical neurons in encoding durations, neurophysiological experiments in primates have investigated temporal processing in parietal cortex [20–23], PF cortex [24–31], motor and premotor cortex [4, 26, 32, 33, 35–38], and basal ganglia neurons both in monkeys [39] and in rats [40, 41]. Some of these neurophysiological experiments, including ours [42, 43], have investigated perceptual timing using paradigms that required subjects to compare the durations of two stimuli, whereas others have focused on the motor aspects of timing. Another approach to the study of time is to consider a particular type of temporal expectation: the time to reward. Several neurophysiological studies have shown that PF activity is modulated by the time until reward [30, 44]. Notwithstanding the importance of these studies, the interpretation of their results is challenged by the correlation, intrinsic to these paradigms, between value and time, because an earlier expected reward brings in itself also a greater value to the animal.

We started our investigation of the role of PF on timing encoding several years ago [24] by studying implicit timing in PFdl and PF area 9, by using a saccade strategy task with three different durations (1, 1.5, or 2 s) of stimulus presentation. Although originally designed for studying the neural correlate of learning strategies, variable durations of the stimulus presentations allowed us to investigate the representation of the elapsed time as well. We showed that the activity of ~9 % of the neurons was

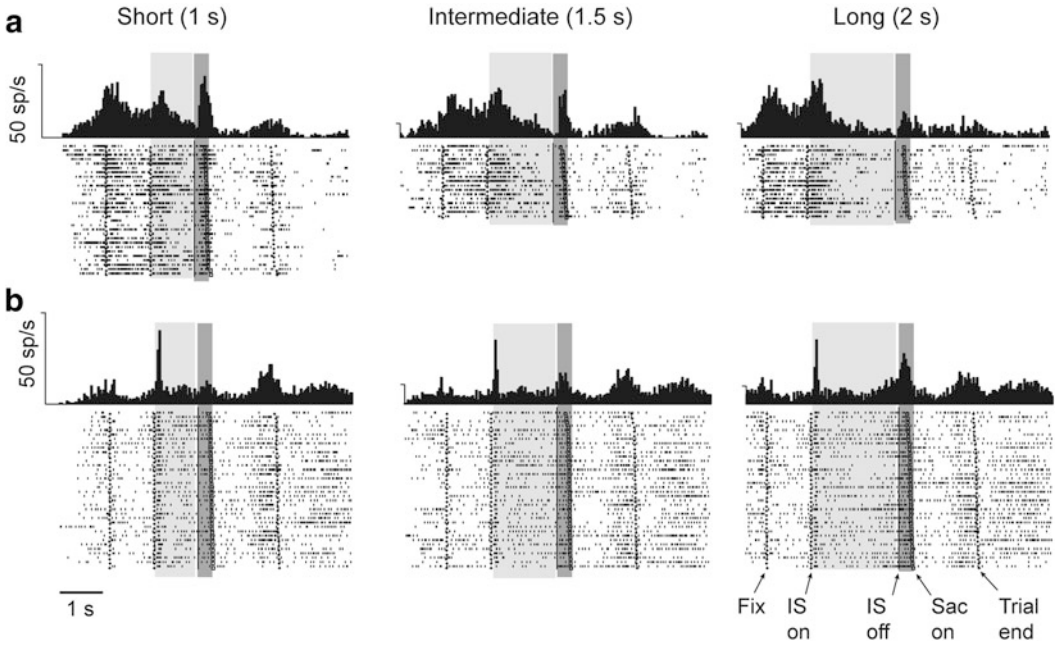

Fig. 1 Two examples of PF neurons encoding the duration of the previous stimulus. (**a**) Neuron with a preference for the shorter duration of the previous stimulus presentation. (**b**) Neuron with a preference for the longer durations. Activity (*raster dots*) is aligned on the end of the delay period (*vertical lines*), sorted by time to saccade onset (*square marks*). *Light gray background* shading indicates the delay period and the *dark gray background* shading indicates the post-delay period used for the analysis. Fix, onset of fixation; IS on, onset of IS; IS off, offset of IS; Sac on, onset of saccade. From Genovesio A., Tsujimoto S. Wise S.P J. Neurophysiol. 95, 3281-3285, 2006, with permission

modulated after the stimulus offset by the duration of the preceding stimulus presentation. This "elapsed time" modulation could not be explained by differences in saccadic reaction times. Most neurons showed a greater activity for either short (Fig. 1a) or long delays (Fig. 1b). A much smaller proportion of neurons (25 %) preferred intermediate delays. The modulation of the activity by stimulus duration was often preceded by a ramping up of the activity in the neurons with a long duration preference (Fig. 1b). It is worth noting that the elapsed-time effect on the neural activity emerged even though there was no requirement for the monkeys to time the stimulus duration.

Duration Task

Figure 2a illustrates the duration discrimination task adopted to study PF in two macaques. In this task, the monkey viewed two stimuli, a red square or a blue circle, of different durations presented sequentially. The monkey's task was to choose which of them lasted longer by touching a switch below it. The task was designed such that the monkey could not plan its motor response before the "go" signal (i.e., the targets appearance), because each choice stimulus could appear with the same probability on each side of the screen's center.

The duration of the two stimuli was defined according to one of two duration sets termed "V" and "square" distributions (Fig. 2d). We adopted these two sets of stimulus durations for different purposes. The 'V' distribution prevented the subject from predicting the second stimulus duration based on the duration of the first stimulus, but it did not allow us to distinguish absolute from relative duration coding. The 'square' set had the advantage of varying systematically the duration differences.

Figure 2e shows the location of the recorded neurons. The recordings were made in two cortical areas: rostral to the arcuate sulcus in the caudal PF cortex (area 8) and in both banks of the principal sulcus and the adjacent convexity cortex in the PFdl (area 46). Because we did not find any dramatic differences between the two areas, we pooled together the results from the two areas in this chapter.

The duration task required the monkey to perform several computations on the duration information. The monkeys should (1) encode the S1 duration, (2) maintain that duration in memory in the D1 period until S2 occurred, and (3) compare their durations. In this chapter we will focus only on the comparison process, first in the delay period and then in the decision period.

Encoding of Relative Duration in the Delay Period

We examined the representation of relative duration in the second delay of the duration task that starts after the first stimulus is turned off, in terms of the order of presentation of the two sequentially presented stimuli and in terms of their features (blue or red). Using a two-way ANOVA, we found that the activity of ~30 % of the neurons depended on whether either S1 or S2 lasted longer. Moreover, approximately 25 % of neurons showed a second type of representation that depended on whether the blue or the red stimulus lasted longer. We will take up both types later in the chapter, when we will focus our attention on the decision period.

By using ANOVA, alone, we could not asses whether these two classes of neurons were encoding categorically which stimulus lasted longer or how much the stimuli differed in duration parametrically. Furthermore, we could not disentangle the encoding of absolute and relative duration coding. That could be addressed by a stepwise regression analysis. We applied this analysis only to the data collected with the "square" distribution, which varied the duration difference between stimuli in a highly graded manner. With a first analysis, we assessed the role of four factors related to the order of presentation: the absolute stimulus duration of both S1 and S2, which stimulus lasted categorically longer (S1 or S2), and their difference in duration. In a second analysis, we assessed the role of other four factors associated to the stimulus features: the absolute duration of both the red and the blue stimuli, which of them lasted longer (blue or red) and their difference in duration.

We found that the strongest signals were represented by the categorical representation of the relative duration based on the order of presentation of the two stimuli (12–19 %) and based on their stimulus features (12–19 %), in addition to the absolute duration of the second stimulus (13–16 %). The representation of the parametric difference between S1 and S2 durations reached ~10 %. In contrast, we found a very small proportion of neurons that encoded the difference between the blue and the red stimuli durations parametrically (5–7 %), which was very close to chance levels. Based on these results, we can propose two ways in which duration information could be compared by neurons in PF. For example, consider a trial in which the first stimulus is blue, the second is red, and the red stimulus is longer than the blue one. One way to determine that the blue stimulus is longer than the red stimulus would be by integrating two pieces of information: (1) the second stimulus lasted longer than the first stimulus, and (2) the second stimulus was red. Neurons showing an interactive effect by the two-way ANOVA for the relative duration based on the order of presentation and on the stimulus features reflected this computation [42]. Alternatively, the representation of blue-stimulus duration could be compared directly with a representation of the red-stimulus duration. We also found neurons showing a duration-color conjunction encoding, such as a preference for a long stimulus but only when it was blue. Such neurons that could represent the information required for this second type of computation. Both integrative processes are likely to coexist and they should not be considered as mutually exclusive.

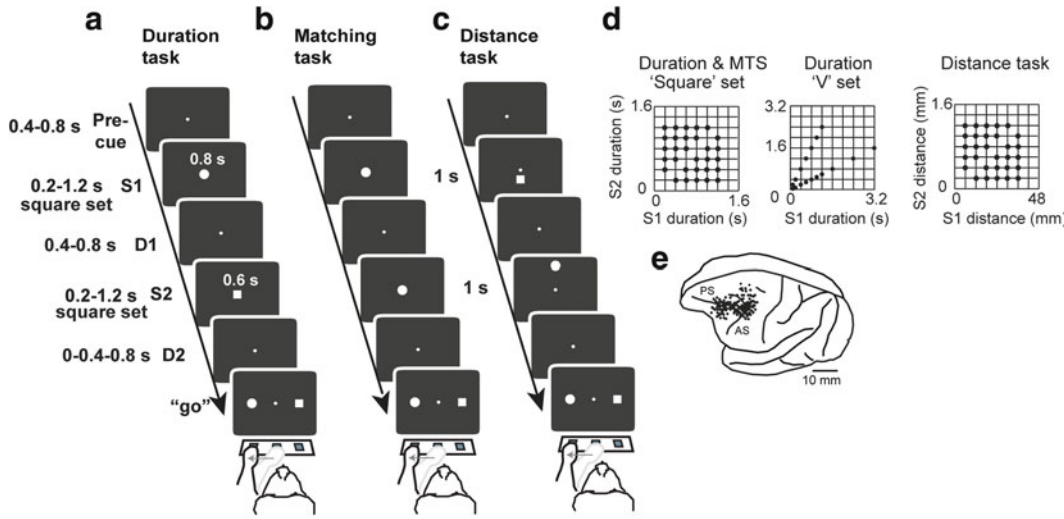

Fig. 2 (**a**) Duration discrimination task. When the monkey touched a central switch a *white circle* (pre-cue) appeared and the monkey was required to start fixation until a later "go" signal. After the pre-cue period, the monkey viewed the first stimulus (S1) followed by a first delay period (D1). After, the second stimulus appeared followed by a subsequent delay period (D2) of variable duration. After this second delay both stimuli reappeared, one to the left and the other to the right serving as a "go" signal and the monkey was required to choose the stimulus that lasted longer, indicating his decision by touching the switch below that stimulus. (**b**) MTS task. In this task the monkey viewed sequentially two identical stimuli called samples, either two *red squares* or two *blue circles* of different durations as those used in the "square set" of the duration task. The monkey's task was to choose the target that had appeared twice. (**c**) Distance task. In this task one stimulus appeared above and the other below the reference point in an order determined randomly. After the appearance of the two targets the monkey was required to choose the farthest stimulus from the reference point. (**d**) Distributions of durations. The distribution of duration could belong to one of two sets either the 'V' or the "square" set. The distance task had a square distribution identical to the duration task only with distances instead of durations. (**e**) Penetration sites. Composite of the two monkeys. Abbreviation: *AS* arcuate sulcus, *PS* principal sulcus

General Considerations on the Representation of Time in PF

So far, we have described neurons that encoded relative durations. We found that the encoding of relative duration was represented in two "formats", one associated to the order and the other to the stimulus features. The first can be thought as a conjunction of relative duration and order while the second as the conjunction of duration and stimulus color. The encoding of conjunctions of features represents a key difference with the parietal cortex. Such a role of PF in duration comparison agrees with an imaging study by Rao et al. [9] that associated PF activity to the later stage of the task corresponding to the duration comparison.

This result adds duration to the list of examples of conjunctive encoding identified by past studies using a variety of paradigms in PFdl [45–49]. For example, Tsujimoto and Sawaguchi [45] and Tsujimoto et al. [46, 50] have found neurons encoding conjunctions of goals and outcomes. In a cued strategy task Tsujimoto et al. [46] found neurons encoding the conjunction of stay and shift strategies with goals in PFdl, similar to the signal found by Genovesio et al. [47]. Another example can be found in a study by Hoshi and Tanji [49]. They have reported that PF neurons encoded the combination of arm (left/right) and spatial goal in a task in which two sequentially presented cues instructed which arm to use and the goal location.

We found that a substantial population of neurons encoded whether the red or the blue

stimulus had lasted longer during the delay. Later in this chapter, by comparing the information derived from other tasks, we will be able to separate the decision process from the goal representation functions performed by different subpopulations of the neurons that encoded which stimulus blue or red lasted longer. Notwithstanding the fact that our experiment did not impose any requirement to the monkeys to report whether the first stimulus had lasted longer or shorter, we found neurons performing this intermediate computation. This result underlines the importance of ordering temporally the contents of our experience, such as the stimuli to compare in our task.

Furthermore, we found neurons that encoded higher order conjunctions, combining the information on which stimulus was the first based on the order of presentation with the information on which stimulus was the longest, blue or the red. Such a hypothetical neuron would show a specific preference: for example, for the red stimulus being both the first of the sequence and the longest stimulus. Neither a longer red second stimulus nor a blue first longer stimulus would activate such a neuron.

To date, only a few neurophysiological studies have investigated PF's role in timing encoding [26–28, 38, 51, 52]. Three studies adopted a task similar to ours in PF [27, 28, 38] and we will compare their results to ours.

Oshio et al. [27] have described neurons encoding which stimulus had lasted longer but not neurons encoding duration differences and a relative duration encoding based on the order of stimulus presentation. We obtained different results, which are probably explained by some task differences. They used durations of the first stimulus that allowed the subject to predict the duration of the second upcoming stimulus, therefore no other duration comparison was necessarily required after the presentation of the first stimulus. Interestingly, when the second stimulus duration could not be predicted on the basis of the first stimulus duration, in a separate study on the basal ganglia, Chiba et al. [39] identified neurons with proprieties similar to those described in our study, such as the coding of the duration of the first stimulus presentation in the following delay period and the coding of whether the first or the second stimulus had lasted longer. It is likely that the differences between their PF and basal ganglia data depend on task differences, associated to the predictability of the duration of the comparison stimulus, rather than on different roles played by these two areas. In a more recent study, using the same task, Oshio et al. [28] recorded from PF using short and long stimuli that overlapped more than in their previous study [27], reducing the issue of predictability of the second stimulus duration. In this study the authors focused the analysis on the first stimulus period identifying neurons with both buildup and sustained activity in addition to others with phasic activities with unimodal peak times of response around 0.8 s. This duration corresponded roughly to the middle duration of the averages of the long and short stimuli. That suggests that the monkeys could have compared the duration of the first stimulus with this single *filtering duration* to separate durations into long and short categories.

Another neurophysiological study on timing used a matching-to-sample paradigm to examine duration coding in PFdl [29]. In contrast to our study, Sakurai et al. [29] did not report relative duration neurons. They identified only a small proportion of neurons designed as "comparison neurons" that might contribute to comparing the duration of the two stimuli. However, these neurons were defined only for having a phasic activity specifically associated with the presentation of the comparison stimulus and not with the sample presentation. As we have described before, contrary to their results, many neurons in our experiment encoded the relative duration. This discrepancy probably also results from task differences. As in the work by Oshio et al. [27], the monkeys studied by Sakurai et al. [29] could simply categorize stimuli as either short or long, rather than encoding the sample duration, and the use of only two durations (0.5 and 2.0 s) was the reason for this interpretational problem. Therefore, these "comparison neurons" might have represented a rank-order signal like the neuron in Fig. 3b, indicating that the stimulus presented

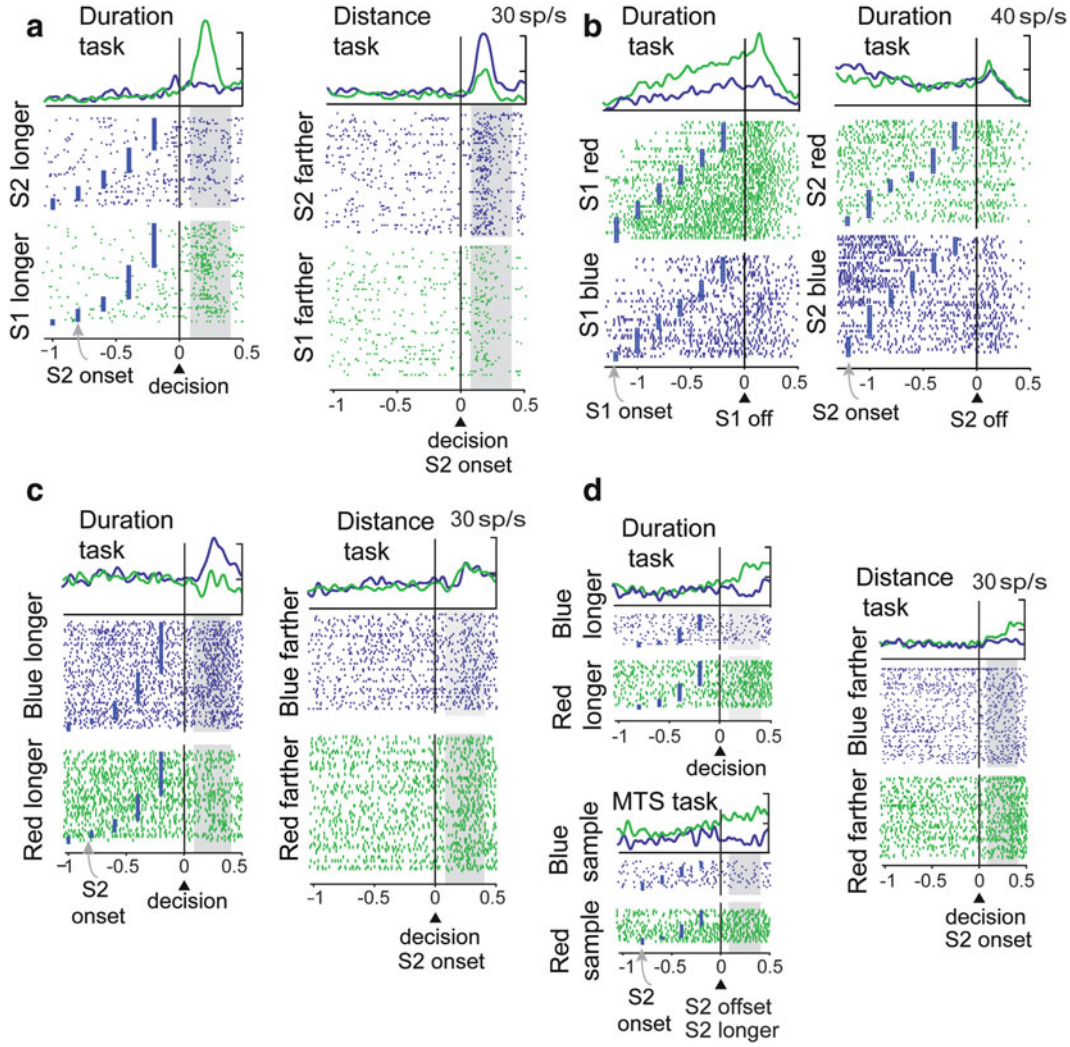

Fig. 3 (**a**) Neuron encoding which stimulus was farther and longer based on the stimulus order. *Background shading* indicates the decision period (80–400 ms after the ideal decision point). This neuron showed an higher activity when the first stimulus was longer (S1 of greater magnitude) in the duration task. The same neuron showed an opposite preference for the second stimulus farther (S2 of greater magnitude) in the distance task. (**b**) Rank-order and color selective neuron in the duration task. This neuron showed a preference for the first red stimulus. (**c**) Neuron encoding the relative magnitude based on the stimulus features in the duration task but not in the distance task with a preference for longer blue stimuli in the duration task. (**d**) Neuron encoding the same goal in all three tasks. This neuron showed the same preference for the red goal in all three tasks. Modified from Genovesio, A., Tsujimoto, S., Wise, S.P. Neuron 74, 656-662, 2012, with permission

was the second of the sequence, irrespective of any duration comparisons.

Order-encoding properties have been described previously by several studies for both colored patterns [53] and for spatial stimuli [54]. For example, in the experiment of Funahashi et al. [54] the monkeys performed a delayed sequential reaching task, in which they were required to remember the position of two of three cues and their temporal order of presentation. They found a consistent population of neurons that showed a rank-order activity either in combination with the cue position or irrespectively.

Sakurai et al. [29] also found neurons representing which stimulus was either short or long. Some neurons showed a phasic discharge when the stimulus could be categorized as either short or long. However, the experimental design could not rule out the possibility that these categories of neurons represented an abstract category instead than specific durations.

Other studies have focused on time reproduction [33, 51]. Yumoto et al. [51] have recorded from PF area 9 using a time reproduction task in which monkeys were trained to estimate and reproduce the duration of a visual stimulus with a button press. They found a first population of neurons which were modulated by the previous stimulus duration, similar to what we have previously described [24, 42]. They indentified also a second population of neurons modulated by the duration that the subjects needed to reproduce. Interestingly, only a minority of neurons belonged to both categories, pointing to a separation of functions between duration decoding and temporal organization of movement execution. Furthermore, inactivating the same area through injection of muscimol affected the reproduction of the duration interval. Specifically, this kind of temporary inactivation shortened the duration that the monkeys produced.

Another study [52] has examined the role of both PF and the caudate nucleus in a visuomotor task that required the monkeys to make sequential saccades to visual targets after short fixed intervals. This study did not impose any explicit training regarding the timing of the events. The authors identified a subpopulation of neurons with peaks of activity distributed in relationship to several task events that may represent time-stamps of different durations, as part of what the authors call the "infrastructure of neural representation of events and actions". They found very similar phasic discharges in both areas that are known to be connected through cortico-basal ganglia loops, supporting their combined role in timing [55].

We found stronger effects in periarcuate cortex compared to PFdl. Although most of the periarcuate cortex recordings were located in the cortex rostral to the arcuate sulcus we have included in the analysis a small number of neurons within the dorsal premotor cortex (PMd). PMd neurons are known to be involved in other non-motor [56] and attentional function [57], and their role in timing is compatible with their other functions. Lebedev et al. [25] have shown that from the ensemble of neurons recorded in PMd neurons it could be decoded both the elapsed time information from the previous hand movement and the time until the onset of the next movement in a task in which the monkeys released a key after a temporal interval. Similarly Lucchetti and Bon [34] have shown a buildup activity for predictable delays before movements in PMd.

Interaction Between Duration and Other Magnitudes

Temporal and spatial perceptions can interfere with each other and produce misperceptions in both humans [58–60] and monkeys [61]. However, most of the studies initially have focused on the interaction between space and number rather than between space and time. Therefore, we describe first briefly a variety of interactions between numbers and other magnitudes. It has been shown that numbers can have a spatial representation organized along a "mental number line" [62, 63] and that numerical processing can interact with saccade performance, shifting of spatial attention, pointing and grasping movements, and line bisection tasks [64, 65]. On the other hand, numerical processing can be influenced by visuospatial variables. For example, spatial cueing and visual hemifield presentations can produce an influence on numerical comparisons [66, 67]. Interestingly, even eye position can influence both the representation of numbers [68] and the representation of high-level cognitive processes such as non-propositional reasoning [69]. Moreover, physical space perception and the mental number line can be affected similarly in patients with hemineglect [70, 71].

To explain the influence of different magnitudes on each other, a domain-general system has been proposed that would encode abstractly a greater or lesser quantity, independent

of the specific metric such as duration, distance, or numerosity [1, 72]. Although several psychophysical effects support the ATOM theory, fewer studies have focused specifically on the interaction between space and time. In one of these, Srinivasan and Carey [73] showed that binding visible lines with tone duration appeared to be easier when their durations were relationally equivalent both in adults and infants.

Even saccadic eye movements can influence and compress magnitude judgments of both space and time [74, 75]. Two bars flashed one hundred ms apart around the time of the saccade are perceived compressed in time (closer in time) much like the spatial compression of a bar flashed around the time of the saccade towards the location of the saccade target [74].

In monkeys, Merritt et al. [61] found symmetrical interactions between temporal and spatial judgments. Other experiments, however, have shown asymmetries in the interference effects, suggesting a less complete overlap between representations of magnitudes. As an example of asymmetry, it has been shown that the duration of a visual stimulus could affect the perception of its length but not the reverse, and that this phenomenon occurs in both adults [58] and children [76]. The same asymmetry has been reported with language. Interestingly in metaphorical language, there are more words describing time in terms of space than describing space in terms of time. In contrast to the results of Merritt et al. [61], asymmetries between space and time have been found by Mendez et al. [77]. They have shown that a previous experience in categorizing distances could affect duration categorization but not the reverse. It is possible that findings about asymmetries may reflect differences in task difficulty for different kinds of magnitudes. Along this line, a recent study by Javadi and Aichelburg [78] has shown that a failure in finding a reciprocal interference between magnitudes may depend on selecting the appropriate range of magnitudes to enable the detection of interfering effects. By using high numerosities and short durations, they found an effect of temporal magnitudes on numerosities, in addition to the opposite direction of interference, which had been previously reported.

Even if the presence of some asymmetries might contradict a strong version of the theory of common magnitude, the interaction between space and time indicates that there is at least a partial overlap between space and time coding, which can affect perceptual decisions.

Further support for a common magnitude system comes also from the results of Stroop-like paradigms, such as the one adopted by Xuan et al. [79]. They have shown that stimuli of four different nontemporal magnitudes such as the number of dots, the numeric value of digits and the luminance and size of squares could affect a duration judgment: stimuli of greater magnitude were judged to last longer. Another study supporting the theory is an old pharmacological study by Meck and Church [80].

Using a psychophysical choice procedure, Meck and Church [80] have shown that methamphetamine shifted the psychophysical functions leftward for both number and duration comparisons in an experiment that used a psychophysical choice procedure.

Other studies goes beyond the ATOM proposal emphasizing that time, like numerosity [62, 63], is represented on a mental time line oriented along a left-to-right dimension that can be accessed through spatial attention mechanisms. The mental time line (MTL) proposal can be considered a more specific hypothesis than ATOM, emphasizing the organization of different magnitudes in a spatial layout. Attention would then operate on the spatial representation of the different magnitudes, probably by using the same parietal areas involved in visuospatial attention. Several studies have tested the MTL hypothesis using similar paradigms to those used for studying numerosity and we will refer here to just a few. In support of the MTL hypothesis it has been found that the presentation of lateralized irrelevant visual distracters can influence temporal perceptions producing underestimation for cues to the left and overestimation for cues to the right [81], the same way as it has been shown for numerical magnitudes. Right hemisphere parietal patients with left neglect show a rightward bias in duration bisection task requiring setting the midpoint of a time

interval [82], similarly to what emerged from past studies adopting line bisection tasks. Noteworthy, the same rightward bias has been produced by a TMS over the right parietal cortex [82]. The perception of stimuli duration can be also affected by their location, producing either an underestimation or an overestimation of the duration when presented in the left and in the right hemispaces, respectively [83]. Manipulation of spatial attention by optokinetic stimulation toward the right and left fields produced the same duration distortions [84]. In summary, a variety of psychophysical studies have shown that duration perception can be stretched by other magnitudes, at least to a certain degree. Notwithstanding all this evidence in support of an overlapping between magnitudes, other evidence suggests that the overlapping is only partial. For example, at least for the number and duration domains, it is possible to have dissociations between numerosity and duration functions following different parietal lesions [85], and temporal perception is not affected in adults with developmental dyscalculia [86].

At the single cell level, PF neurons encode space, time and number [24, 87–89], and several theories of the PF cortex have emphasized the domain generality processing of PF [90–92]. These considerations led us to investigate timing and spatial representations at the single cell level in PF recording the same neurons in the duration and in the distance discrimination tasks. An additional matching-to-sample (MTS) task served as a control for goal representations. We need to point out that our experiment [43], that we will describe later in this chapter, was not designed to distinguish between the ATOM and the MTL proposals. Its main objective was to investigate the role of PF in decision making within different magnitudes, studied in separate tasks and in absence of any interference between magnitudes.

Common Goal but Separate Decision Signals for Duration and Distance

Figure 2b, c illustrate the MTS and the distance tasks used in addition to the duration task.

We adopted as a control task a particular type of MTS task in which the presentation of the "sample" stimulus was repeated twice (Fig. 2b). In this task, the monkeys were required to choose the same stimulus presented as the sample on that trial (Fig. 2b). We introduced this control task to identify potential neurons sharing a common goal representation. Its main feature was that the goal choice did not depend on any magnitude comparison process. The first and second sample durations were the same as in the duration task but their duration difference was irrelevant to the task. The task was designed to preserve the same task events that characterized the duration task, such as each epoch's duration and the fixation requirement.

In the distance task on each trial, the monkey viewed two visual stimuli, presented sequentially, on a video screen at different distances from a reference point at screen center. In this task the two stimuli differed in relation to their distance from the reference point and not in their duration. The monkey's task was to choose the stimulus farther from the central reference point.

We recorded data from 1,209 neurons in the duration discrimination and from 1,671 neurons in the distance discrimination task (Fig. 2c). We recorded 621 neurons from both tasks and 261 neurons from all three tasks, and these subpopulations will be used in the comparison among tasks.

In this part of the chapter, we focus our task comparisons on a decision period immediately after the *decision point*. The decision point is defined as the moment in time in which the information available would suffice for an ideal observer to reach a decision. The decision point in the distance discrimination task corresponded to the presentation of S2. In the duration discrimination task, to define the decision point we need to distinguish two categories of trials based on which stimulus, either the first or the second, lasted longer. When S2 was shorter than S1, the decision on which stimulus had lasted longer could be made at S2 offset, and this was defined as the decision point for these trials. When S2 lasted longer, the *decision point* was not "marked" by the S2 offset, but corresponded

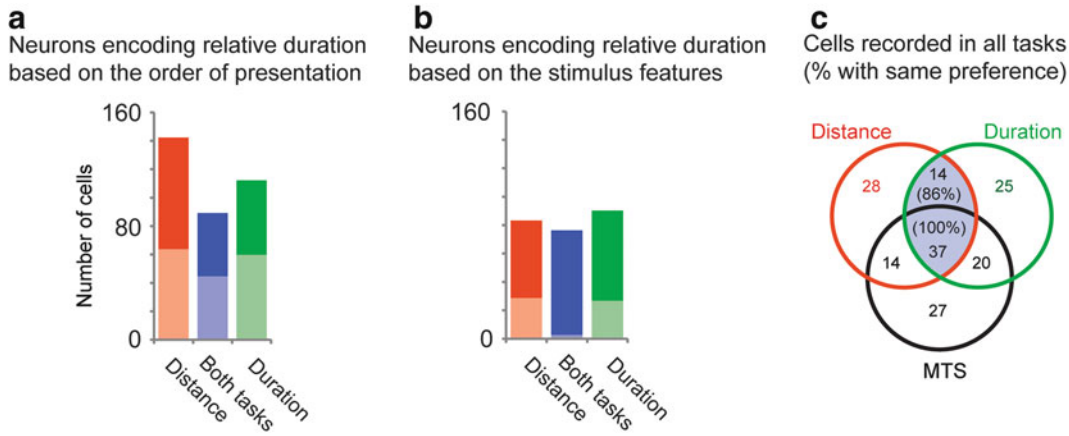

Fig. 4 Bar plot counting the neurons specific to one (*red* or *green*) or to both tasks (*blue*), with neurons having the same preference summed in the *dark-colored bar* and neurons with different preferences summed in the *light-colored bar*. (**a**) Neurons encoding relative information based on order. (**b**) Neurons encoding relative information based on the stimulus features in the format of **a**. (**c**) Subpopulation of cells in (**b**) recorded in all three tasks. The *Venn diagram* shows the number of cells with significant effects in all the various combinations of the tasks. Percentages refer to the cells showing the same preference (*red* or *blue*) in either two or three overlapping tasks

instead to the moment at which the S2 duration surpassed that of the S1.

As we have already described earlier in this chapter, which focused on the second delay period, for the decision period we classified (two-way ANOVA) the relative duration and the relative distance neurons in two classes, one encoding the relative duration or distance based on the order of the two stimuli and the other based on their features. In the MTS task, for the same task period as in the duration task, we identified goal-selective neurons modulated by the stimulus features (blue and red) of the two samples (one-way ANOVA).

Figure 3a shows an example of a neuron encoding relative duration and relative distance information based on the order of presentation of the two stimuli. This neuron shows a phasic increase of activity in the decision period when the first stimulus was the longest (S1 of greater magnitude) in the duration task and the closest (S2 of greater magnitude) in the distance task, therefore this neuron represents an example of a neuron contributing to different cognitive domains. However, looking at this neuron's activity, it is apparent that it did not reflect any abstract concept of magnitude. This is because the preference for which stimulus was the longest (higher magnitude) reversed to the smaller magnitude (closer) in the spatial domain. Neurons with a relative duration or distance encoding based on the stimulus order should not be confused with rank-order neurons. Rank-order neurons, in fact, are characterized by differences in activity between the first and the second stimulus. It is likely that the relative encoding signal shown in Fig. 3a might arise from the combination of duration and rank-order information. Figure 3b shows a rank-order neuron with greater activity elicitated by the presentation of S1 compared to that elicitated by the presentation of S2. The rank-order signal was maintained in the first delay, and it is possible that such neurons activated by the S1 presentation could lead later to the activation of other rank-order neurons with a preference for the second stimulus when the second stimulus is turned on. Without this information might not be possible to determine when the duration of the stimulus presented should be compared with the duration of the previous one. Notice that the neuron in Fig. 3b shows a further level of integration that goes beyond a "pure" rank-order signal, consisting of an additional modulation by the color of first stimulus, which

was absent during the presentation of the second stimulus. In other words, this cell was specifically tuned to the presentation of a first red stimulus.

To asses at the population level whether the type of encoding based on the stimulus order shown by the neuron in Fig. 3a represented a domain-general signal common to duration and distance computations, we compared the neural selectivity of the same neurons in different tasks.

Figure 4a shows a bar plot for neurons with significant encoding in the duration task only, the distance task only, or in both tasks, based on order of presentation of the two stimuli. We found that the majority of the neurons encoded the decision in each domain independently (two-way ANOVA), as indicated in Fig. 4a by the red and green bars, respectively in the distance and the duration tasks. Only a relatively small percentage of neurons (26 %) indicated by the blue bar participated to the decision process in both domains. We asked whether this last group of neurons could represent abstractly the relative magnitudes in a domain-general way. We found neurons sharing the same preference (dark blue bar), as predicted for neurons representing magnitude in the abstract, but we found them in roughly the same proportion as the neurons with opposite preferences (light blue bar). Therefore, the cell preference in one task appeared independent of that in the other. Although there was no complete dissociation of functions between neurons for distance and duration comparisons and the same neuron could participate to both computations, there was no tendency to share a common preferred magnitude.

In addition to the relative duration and distance encoding signals based on the order of presentation of the two stimuli, we also compared the relative encoding based on the stimulus features between tasks. We will examine now the proprieties of the neurons encoding which stimulus had the greatest magnitude in the duration and distance tasks based on the stimuli features, but first we start by examining the different type of neurons that could be expected.

Figure 5 shows the activity of four ideal neurons characterized by different proprieties. In this Fig. 5, all the four ideal neurons are chosen for having the greatest activity for the red longer stimuli. Examining the activity of the neuron of Fig. 5a in the distance task it appears that it shows an opposite preference in the two tasks and for this reason it could not represent any common magnitude. The neuron of Fig. 5b is not involved in distance comparisons because is a pure duration neuron. The neurons of Fig. 5c, d show the same preference for red stimuli of greater magnitude, making them potential candidates for representing a domain-general signal. However, after examining the activity of these neurons in the MTS task, it is apparent that only the neuron of Fig. 5c shows a true domain-general signal, while the neuron of Fig. 5c represents the red goal. In fact, only for the neuron of Fig. 5c the preference for red longer and farther stimuli cannot not be accounted in terms of red goal encoding. Now we will examine two example PF neurons in relationship to the categories defined for the ideal neurons. Figure 3c shows a neuron that encoded the relative duration based on the stimulus features during the decision period of the duration task. The neuron preferred the longest blue stimulus, but did not show any selectivity for which stimulus was the farthest in the distance task, resembling the ideal neuron shown in Fig. 5b.

Figure 3d shows a different type of neuron with a preference for red longer trials. The same neuron, when tested in the distance discrimination task, showed a similar relative distance encoding, with a preference for red farther stimuli. Therefore, not only was this neuron part of the comparison of both magnitudes, but it also shared the same preference. That is, it seemed to encode for "red-greater" in both tasks. To distinguish between the two possibilities exemplified by the neurons of Fig. 5c, d, we need to examine the activity in the MTS task. Was the neuron of Fig. 3d encoding "red greater" as a domain-general abstract signal, independent of goal encoding, or was it just encoding the red goal? Examining the activity of this neuron in the MTS task helps answering this question. Figure 3d (bottom) in fact shows that the same neuron maintained its preference in the MTS task. That is, it encoded the red goal, a finding that supports the second interpretation: this cell

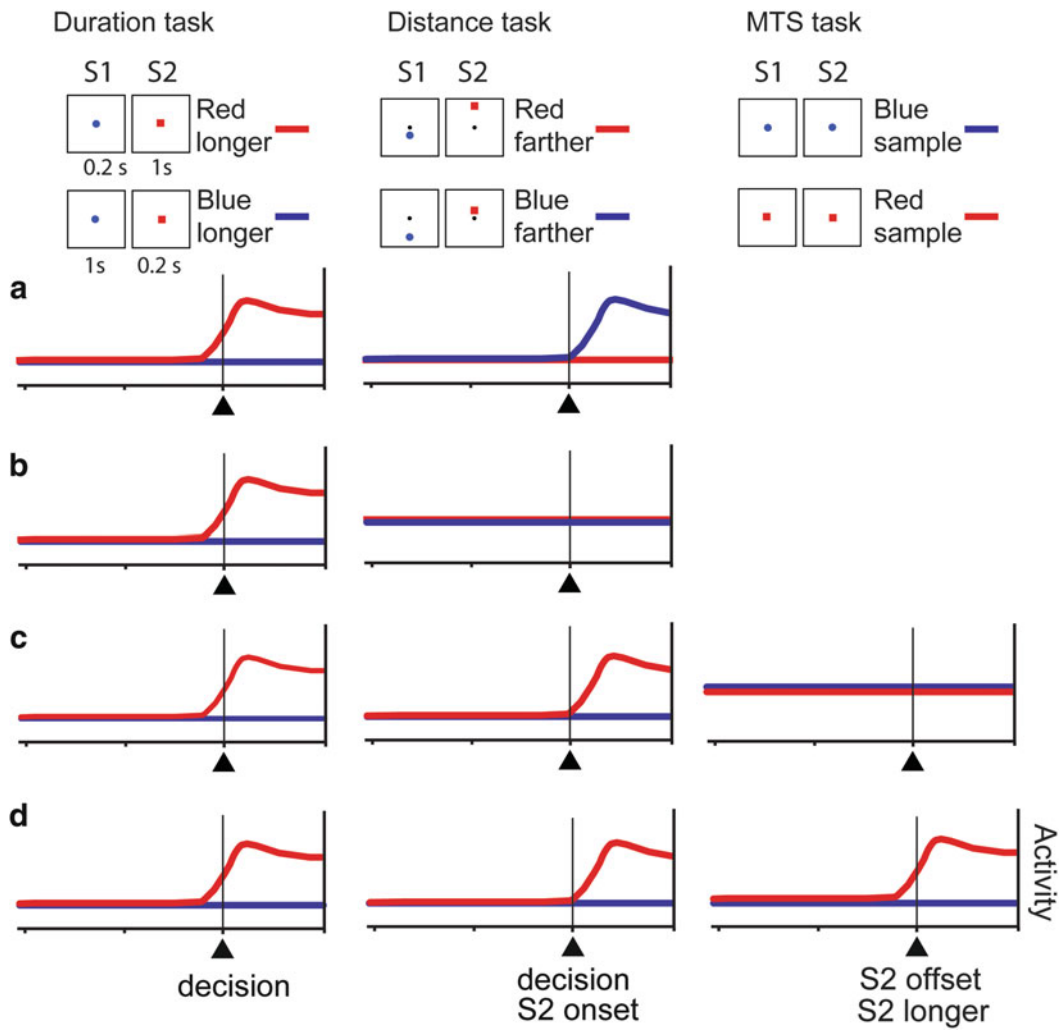

Fig. 5 Four ideal neurons modulated by the relative duration based on the stimulus features in the duration task. All the four ideal neurons show the highest activity for the red longer stimulus (**a**). This neuron shows an opposite preference in the distance discrimination task, with higher activity for the blue farthest stimulus, therefore, this neuron could not encode which stimulus had greater magnitude in a domain-general way. (**b**) Similarly to the neuron in (**a**), this ideal neuron cannot not encode domain-general information, but in this case it is because it is not modulated in the distance discrimination task. (**c**) Neuron showing a domain-general coding of relative magnitude. For this neuron the preference for the red stimulus of greater magnitude in both tasks could not be accounted in terms of goal encoding, because this neuron does not show higher activity for the red goal in the MTS task. (**d**) Neuron encoding the red goal. For this neuron, the red goal encoding in the MTS sample task can account for the preference for red longer and farther stimuli in the duration and distance tasks. On the top an example trial for each task, *blue lines* indicate trials with blue longer stimuli, blue farther stimuli, and blue samples, respectively in the duration, distance, and MTS tasks

encoded a goal signal as exemplified by the ideal neuron in Fig. 5d.

Then we asked what proportion of neurons encoded goals, similarly to the ideal neuron represented in Fig. 5d and to the neuron of Fig. 3d, rather than abstract magnitude as for the ideal neuron of Fig. 5c. Figure 4b shows the relative encoding in the duration and distance tasks based on the stimulus features. As with the duration encoding based on the order of presentation, the majority of neurons encoded relative magnitude in one domain only, either for

space (red bar) or for time (green bar), with only a third of neurons (blue bar) encoding it in both tasks (Fig. 4b). However, in contrast to the neurons of Fig. 4a, all of the neurons modulated in both tasks (blue bar in Fig. 4b), with rare exceptions, shared the preference for the same stimulus as the stimulus of greater magnitude (dark blue bar). We then tested the subpopulation of these neurons studied also in the MTS task for goal effects. We found that all these neurons, with rare exceptions, when studied in the MTS task, shared the same preference as in the duration task (see Fig. 4c) supporting the idea that neurons encoding which stimulus was farther and longer based on the stimulus features in both tasks encoded the goal chosen by the monkey. Note that without the MTS control task, we might have interpreted the activity of these neurons as an example of common magnitude encoding.

Examining the time course of the population activity averages of the three classes of neurons, it appeared that both the population of neurons encoding the perceptual decision on the relative magnitude only in one task based on either the order of presentation or their stimulus features showed a signal that dissipated earlier than the goal encoding neurons (see Fig. 3 in Genovesio et al. [43]) supporting a role in the initial decision process that lead to the goal selection.

Modality-Specific and Modality-Generality in a Strategy Task

The difference between the domain-specific activities and the domain-general goal neural activities and their time course, with the first leading to the second in the PF cortex, in some respects can be considered analogous to the difference between modality-specific and modality-general activities described in a previous study in monkeys [93], which used a strategy task to study PFdl, the orbitofrontal cortex, and the frontal pole cortex. In that task, a cue instructed one of two strategies: stay with the previous response or shift to the alternative. The cue could be either one visual stimulus or a specific reward amount. We compared the activity in two version of the task using different reward amounts and different visual stimuli as strategy cues.

We found that the spatial goal coding during the period of the strategy cue presentation was modality-specific, with the spatial goal preference (right or left) independent of the cue modality. Later in the delay period, the neurons transitioned from a modality-specific response to a modality-general response, one sharing the preference for the same position.

In contrast to the goal encoding, we did not find any correlation between the preferred strategies in the two tasks with different cue modalities. Therefore, strategy encoding appeared modality-specific in PFdl (and also in orbitofrontal cortex), in contrast to the modality-general goal encoding found after an initial modality-specific encoding.

The role of the PFdl in the generation of goals has been emphasized by several neurophysiological studies in monkeys [88, 94–96] as mentioned earlier. Furthermore, several brain-imaging studies in humans have confirmed goal encoding in PFdl. For example, Rowe et al. [97] have shown that self generated finger movements as opposed to externally dictated movements activated PFdl, and Jahanshahi et al. [98] have shown that the generation of more random numbers produced more activation in PFdl.

Conclusions

Several brain-imaging studies have implicated a parietal-frontal network in a domain-general representation of magnitudes [1, 8, 9, 62, 99, 100], and, as we have already discussed, cross-modal interference has been shown between several domains, such as spatial and temporal [1, 58, 61, 72, 74, 79, 84, 101].

Notwithstanding these studies, our findings suggest that considering the representation and the comparison of magnitudes as a unitary process can be an oversimplification. In our experiment, we have focused on the relative encoding of magnitudes such as “greater than” and “less than” rather than on the absolute magnitude codes, such as “large” and “small”. We asked whether a neuron that encoded “greater than” in the duration task

also encoded "farther than" in the distance task. We have not yet examined whether a neuron that encodes a "long" duration encodes also a "far" stimulus. To our knowledge, no other neurophysiological study has addressed the study of common magnitude in terms of relative coding. Tudusciuc and Nieder [102] have addressed the coding of absolute magnitude in monkeys in the context of numerosity and spatial length. Adopting a delayed matching-to-sample task design, they have described neurons that encoded absolute magnitudes either in only one domain or in both domains in both PF and in the ventral intraparietal area (VIP). However, it is not clear whether the neurons encoding both magnitudes shared the same preference for numerosity and line length. Moreover, their task did not require relative magnitude comparisons, such as "greater than" and "less than". Being domain-specific instead of domain-general, however, does not contradict with the role of PF in generating other, more abstract representations within each magnitude. For example, we have described for the same experiment a highly abstract coding of the relative distance [103], which was independent of the location of the two stimuli presented (above or below the reference point). In our experiment, we have identified domain-specific perceptual processing at the single-cell level. These neurons were located in the same PF location with no clear separation [43]. Therefore, it is not surprising that brain-imaging studies would detect common activations for different magnitudes because the activity of different classes of neurons overlaps within the same voxels. The differences between imaging data and ours might also be reconciled by assuming that the neurons encoding goals were shared by the duration and the distance domains. The presence of a goal representation was not surprising in view of the many previous studies that have reported such representations in PF [88, 94, 95, 104] and it is possible that the psychophysical interaction across cognitive domains occurs at the level of goal choices, rather than at the level of perceptual decisions.

Moreover, we have shown that spatial and temporal computations tended to share also a common representation in terms of left/right goal [43] or response and the level of action can represent another source of interactions among magnitudes. Our results are in line with the original idea of the ATOM proposal that suggests that the development of magnitude processing originates from the interaction with the external world through action to which it is strictly associated [1]. Several past studies have supported this proposal [105, 106]. In accordance with this idea, it has been shown that semantic information labelled on target objects such as "LARGE" and "SMALL" can affect the grip opening [105]. The grip aperture was larger when the objects were labelled with "LARGE" than when they were labelled with "SMALL". Numbers can similarly affect action: large numbers speed up the grip opening and small numbers speed up the grip closing [106]. To summarize, the neuronal population that encodes spatial goals and responses identified in PF might generate interference between different magnitudes and actions by serving as a shared resource for choosing among different options.

We cannot rule out the possibility that there is a domain-general representation in other parts of the brain, and the parietal cortex might be a candidate [1] and it has been shown [107] that some parietal cortex neurons represent the same rule in both spatial and numerical domains. Parietal cortex has also been proposed as an important node of a timing network [20, 52, 108, 109]. In support of a parietal representation of magnitudes, the parietal cortex has been found to be activated in brain-imaging studies by tasks that require orienting attention to spatial locations and time intervals [110] and by collision tasks that required the integration of spatial and temporal information to predict the collision [111]. However, as we have shown in PF, these brain-imaging studies in parietal cortex also cannot determine whether or not different networks of neurons participate in coding different magnitudes.

To better understand what is shared among magnitude representations, we should consider the distributed representation of time, where different computations can share resources with other magnitudes with different degree of overlapping. Following this idea, it is useful to identify the different stages in the processing of magnitude information. First, there could be a partial overlap of computational resources for different magnitudes in the parietal cortex, in which different magnitudes have been hypothesized to share a common representational format along a common mental, spatially organized line. Second, based on our results, we can assume that there is an additional level of resource sharing for goal and response representations in PF. In between the two stages, we have identified a dissociation of functions between neurons comparing magnitudes based on the order and on the features of stimuli for distances and durations.

Our results suggest that future experiments should address the study of magnitudes and their interplay by fractioning magnitude comparison in different computational steps, as we have started to do with our study. Considering a common magnitude representation as a unique system, although distributed through several brain areas, is apparently an oversimplification.

At the same time, we cannot rule out the possibility that domain-general representations in the comparison process might vary flexibly, based on whatever task demands happen to prevail at any given time, and especially when subjects are required to formulate cross-domain judgments.

In summary, in the context of the scalar timing theory [112], which postulates a model with different clock, memory and comparison modules, we have shown that the "comparison timing module" hypothesized by the model appears to be specific to durations.

In a comprehensive theory of the PF cortex, it has been proposed by Wise and Passingham [113] that the main role of PF is generating goals or sequence of goals based on the current context and the current needs. The current context can include information relative to different magnitudes, such as duration, distance, number and the order of the events. In a recent extension of the theory that includes the posterior parietal cortex, Genovesio et al. [114] have proposed that new prefrontal- posterior parietal cortex networks evolved in anthropoids as a specialization for rapid learning of what foraging goals to choose based on relative metrics, with the information about the relative metric provided by the parietal cortex. According to this view, this network that evolved in anthropoid primates to improve foraging choices served as a pre-adaptation for the development of human reasoning and intelligence.

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Probing Interval Timing with Scalp-Recorded Electroencephalography (EEG)

Kwun Kei Ng and Trevor B. Penney

Abstract

Humans, and other animals, are able to easily learn the durations of events and the temporal relationships among them in spite of the absence of a dedicated sensory organ for time. This chapter summarizes the investigation of timing and time perception using scalp-recorded electroencephalography (EEG), a non-invasive technique that measures brain electrical potentials on a millisecond time scale. Over the past several decades, much has been learned about interval timing through the examination of the characteristic features of averaged EEG signals (i.e., event-related potentials, ERPs) elicited in timing paradigms. For example, the mismatch negativity (MMN) and omission potential (OP) have been used to study implicit and explicit timing, respectively, the P300 has been used to investigate temporal memory updating, and the contingent negative variation (CNV) has been used as an index of temporal decision making. In sum, EEG measures provide biomarkers of temporal processing that allow researchers to probe the cognitive and neural substrates underlying time perception.

Keywords

Time perception • Interval timing • Implicit timing • Explicit timing • EEG • ERP • Mismatch negativity (MMN) • Omission potential (OP) • P300 • Contingent negative variation (CNV)

The ability to detect, remember, and use the temporal relations among stimuli is critical for anticipating their future occurrence [1–3]. Accurate anticipation facilitates stimulus processing and is reflected in improved perception, response times, and decision quality [4–8]. This chapter provides an introduction to the use of scalp-recorded electroencephalography (EEG) and event-related potentials (ERPs) as tools for investigating the cognitive and neural basis of timing and time perception. To this end, we first provide a brief description of the EEG technique and then review a broad selection of the EEG literature that addresses questions related to interval timing.

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Electroencephalography (EEG) & Event Related Potentials (ERPs)

Modern EEG amplifiers have made it relatively straightforward to non-invasively record brain electrical potentials in humans with electrodes placed on the scalp (Fig. 1). These scalp-recorded potentials reflect an instantaneous summation of excitatory and inhibitory post-synaptic potentials (EPSPs, IPSPs) from tens of thousands of neurons, primarily cortical pyramidal cells, spread over several cm^2 of brain surface [9].

Although EEG has excellent temporal resolution, it has relatively poor spatial resolution because the detectability of a brain potential at a particular scalp electrode is determined by the orientation of the neurons with respect to the scalp surface, the organization of simultaneously active neurons with respect to each other (i.e., open versus closed-field arrangement), and the number of simultaneously active neurons (see Fig. 2). Equally important, the signal originating from one neural source can be detected at multiple scalp locations due to volume conduction of the electrical potential. Consequently, the electrical potential recorded at a specific scalp location may be the summation of signals from multiple neural generators spread over a wide region of brain at a substantial distance from the electrode site [9, 10]. There are many EEG source localization techniques, but discussion of the strengths and weaknesses of these localization methods is beyond the scope of the present chapter (for discussion see [11]).

The ongoing EEG contains voltage fluctuations that are related to the perceptual or cognitive process of interest (i.e., the signal), but it also contains voltage fluctuations (i.e., so-called noise) that are due to task irrelevant perceptual and cognitive processes (e.g., the participant thinking about lunch) and/or physiological artifacts such as heart rate, whole body movements, or eyeblinks. A typical human EEG experiment includes a relatively large number of trials in each of the experimental conditions because averaging the EEG signal across many trials from the same condition amplifies EEG features that are time- and phase-locked to the events of interest while suppressing random noise [12, 13]. The output of this averaging procedure is referred to as an ERP, the components of which can be consistently identified by polarity, latency, and scalp topography. As illustrated in Fig. 3, ERP components are either transient, meaning they span a narrow time window and are evoked by rapid changes such as a stimulus onset, or sustained, meaning they span several hundred milliseconds or more and are evoked by both rapid and gradual changes [14]. It is worth emphasizing that a component does not necessarily reflect a single perceptual or cognitive process. Finally, although ERP analysis is the conventional approach to analyzing averaged EEG signals, it can be complemented by single-trial methods that examine the variability of the EEG signal across trials [15, 16].

Detailed introductory guides to using EEG/ERPs to address fundamental questions about perception and cognition are provided in a number of excellent texts [10, 17]. More advanced topics, including source localization, are covered

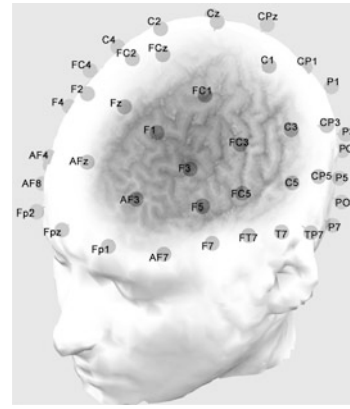

Fig. 1 Illustration of EEG electrode placement on a 3D head model. Electrodes are typically positioned based on percentage distances from various skull landmarks so that they can be placed consistently across participants, at least with respect to those landmarks. Across participants there is significant variation in the brain tissue that lies immediately below a particular electrode site. Moreover, because of volume conduction and summation of electrical potentials the source of the electrical signal at an electrode is not necessarily the tissue immediately beneath it (see text)

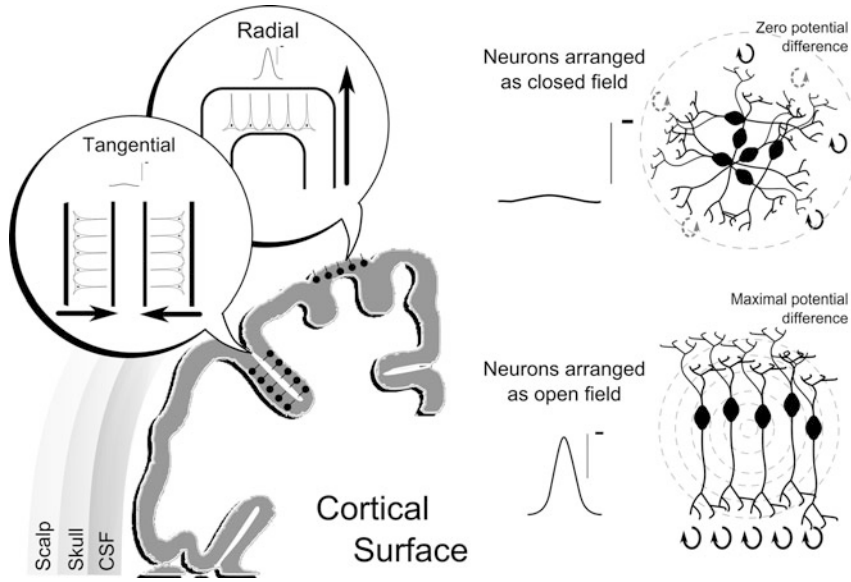

Fig. 2 Neuron orientation determines whether an electrical potential can be detected at the scalp. First, neurons must be aligned with respect to each other (open field arrangement; *lower right panel*), rather than positioned randomly (closed field arrangement; *upper right panel*), in order for simultaneous changes in membrane potential to be detectable by a scalp electrode. In other words, the dipoles formed by the individual neurons must sum, rather than cancel. Second, membrane potential changes from large groups of neurons, represented here as dipoles (*left panel*), are detectable at a scalp surface electrode when a group of neurons forming an open field is oriented perpendicularly with respect to that electrode, i.e., it comprises radial, rather than tangential, dipoles

in detail by Nunez and Srinivasan [9] and in edited volumes by Handy [17, 18] as well as Ullsperger and Debener [19].

To summarize, scalp-recorded EEG is a non-invasive recording of the neuroelectric signals generated by the brain. It primarily comprises the summation of post-synaptic potentials of cortical pyramidal neurons that are simultaneously active, in open-field configuration, and positioned radially with respect to the recording site. EEG possesses very good temporal specificity, but relatively poor spatial specificity. EEG measured during a cognitive task includes neuroelectric changes that are relevant and irrelevant to the task. The ERP is a time-locked and phase-locked brain response to the event of interest.

Implicit and Explicit Timing

Perhaps the most common lab-based approach to the study of interval timing in humans is to instruct participants to attend to the durations of stimuli and then make an explicit response based on a judgment about those durations (i.e., explicit timing). For example, the judgment could be a comparison of a standard and a probe duration, a decision about whether a target interval has elapsed, or a verbal estimate of a stimulus duration.

However, there are also situations in which actions or brain responses are clearly time based or time sensitive, but the stimulus duration is judged implicitly or pre-attentively. For example, if a 10 ms tone pip is presented once every 200 ms 20 times in a row, but on the 21st presentation the tone pip is delayed by 100 ms, the brain will respond to the change even if the participant has been instructed to ignore the tone stream [20]. This ERP component, known as the Mismatch Negativity (MMN), is a sensitive marker of pre-attentive stimulus processing (e.g., [21]) and, as described below, has been used to investigate pre-attentive or implicit timing.

The distinction between explicit and implicit timing tasks is important because the different objectives and procedures in these tasks can lead

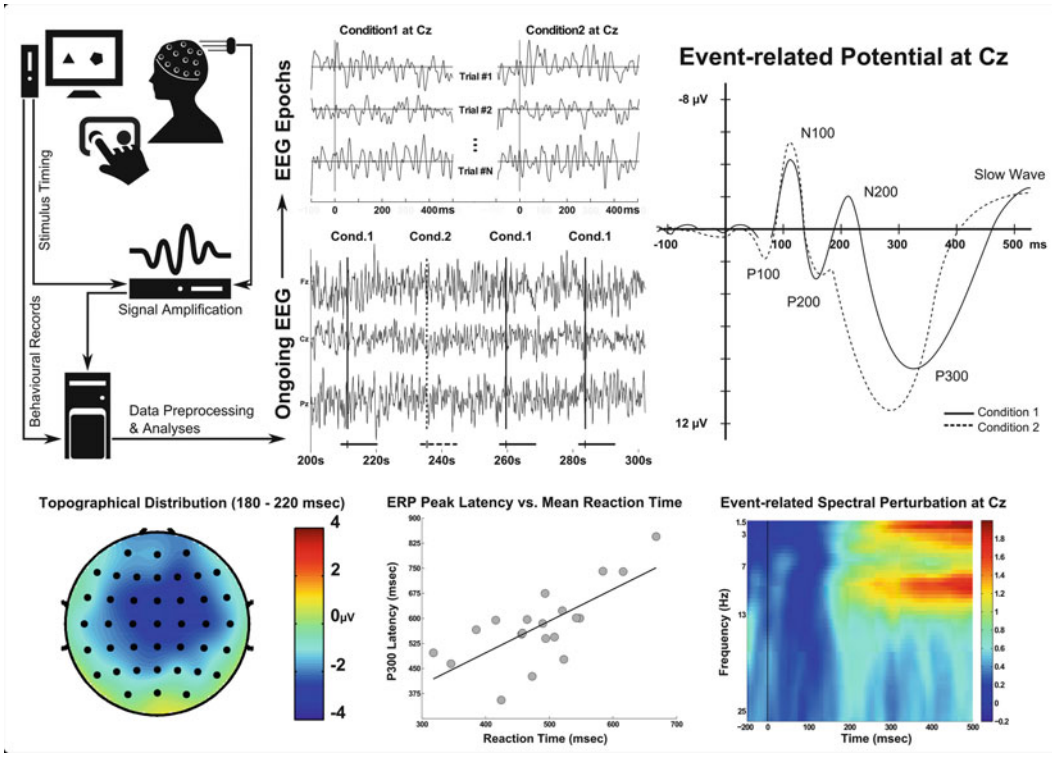

Fig. 3 Summary of the main steps involved in EEG data collection and analysis. *Top Left*: Electrodes are attached to the surface of a participant's scalp before she performs the experiment. The EEG amplifier receives neuroelectrical signals and stimulus timing information (i.e., triggers) so that the onset time of events of interest can be assigned to the correct time point in the EEG recording. Amplified and digitized EEG signals are then stored and ready for preprocessing and analysis. Behavioral data are often collected so that brain-behavior associations can be studied. *Top Center*: During preprocessing, multi-channel (electrode) ongoing EEG data of the whole experimental session are checked for contamination by noise and irrelevant signals are minimized. The processed EEG data are then epoched, so that only segments of EEG signals closely related to the events of interest are retained. Epochs are grouped according to experimental condition, and averaging is performed across epochs of the same condition. *Top Right*: Averaging reveals a waveform containing signals that are time- and phase-locked to the onset of the event of interest. Peaks and troughs of this Event Related Potential (ERP) that have functional implications are called components, and are assigned labels according to their polarity and peak latency, e.g., the positive peak at 100 ms that is sensitive to the perceptual features of the event is labeled the P1 or P100. *Bottom*: ERP parameters that may be sensitive to the experimental manipulations include component amplitude, latency, and distribution across the scalp, and their relationship with behavior or other physiological signals

to different behavioral and neural manifestations [5, 22] and this has direct consequences for the interpretation of neuroelectric signals.

Mismatch Negativity (MMN)

The auditory MMN is elicited when a stimulus violates a pattern or rule established by previously presented stimuli [21]. The rule may be defined by physical stimulus characteristics such as pitch, intensity, or duration such that an infrequent 900 Hz tone presented in a sequence of frequent 1,000 Hz tones will elicit a MMN, but also can be defined by the relationship between stimuli rather than physical characteristics [23]. For example, if participants hear a sequence of sounds in which each sound is higher in pitch than the previous one, then a lower pitch sound will elicit a MMN. The MMN component is obtained by subtracting the ERP response elicited by the more frequent (standard) stimuli from the ERP response elicited

by the rare (deviant) stimuli. It is easiest to distinguish when participants are not actively attending to the auditory stimulus stream because otherwise it can be concealed due to the partially overlapping and much larger P300 response [21].

Researchers have used duration changes in the context of mismatch negativity experiments to address questions about the auditory change detection system itself, as well as questions about the cognitive and neural substrates of interval timing. Several early studies suggested that the MMN could be elicited only when the standard stimuli were at most a few hundred milliseconds long [24, 25]. However, Näätänen et al. [26] reported a MMN for stimuli of several seconds, which indicates that under at least some circumstances the pre-attentive timing process is not limited to a brief temporal window of integration.

Of greater relevance here is use of the MMN response as a tool to investigate the perceptual and cognitive processes underlying interval timing [20, 27–29]. The pre-attentive nature of the MMN response lends itself to interval timing investigations that would otherwise be difficult to achieve. This includes examining sensitivity to time in the absence of attention allocation to the timing task and in the absence of explicit task instructions. Hence, the MMN allows the timing abilities of preverbal children to be tested and the functions of the adult timing system to be measured in a way that is unbiased by the instructions provided to participants.

Brannon et al. [27] used an auditory oddball task to investigate the interval timing abilities of 10-month old human infants and adults (Fig. 4). The standard intervals were defined by 50 ms tone pips separated by an inter-stimulus-interval (ISI) of 1,500 ms, whereas the rare deviant intervals had an ISI of 500 ms. The infants and adults showed comparable MMN responses to the deviant stimuli, which suggests that infants have at least some of the basic mechanisms underlying time perception. Subsequent work from the same group [28] demonstrated that although larger standard and deviant ISI ratios (1:4; 1:3; 1:2; 2:3) elicited larger MMN amplitudes, changing the duration values while keeping the standard to deviant ratio constant did not affect the MMN amplitude. Consequently, the data were interpreted as indicating that Weber's law for time holds in infants, as well as adults. These results are important because they reveal similarities in pre-attentive interval timing between infants and adults that would otherwise be impossible to demonstrate using behavioral measures that rely on explicit instructions.

Tse and Penney [20] used the MMN to investigate how people time empty intervals (i.e., intervals demarcated by two short stimuli, one at the beginning of the interval and one at the end). Whether such intervals are timed with respect to the onsets or offsets of the demarcating stimuli has been the subject of dispute in the timing literature. However, the rule used could easily be influenced by the task instructions provided to the participant, so Tse and Penney [20] used the instruction-free MMN paradigm. Specifically, they adjusted the durations of the markers so that the pattern of MMN amplitudes elicited across the five deviant conditions would indicate the rule being applied. For example, in one condition the standard duration would be experienced as 130 ms if the participant timed the stimuli from marker onset-to-onset whereas it would be experienced as 110 ms if the participant timed it from marker offset-to-onset. The deviant stimulus in this condition was selected so that the marker onset-to-onset rule would result in a 40 ms duration, whereas the marker offset-to-onset rule would result in a 20 ms duration. Hence, the magnitude of change was 69 % under the onset-to-onset rule, but 81 % under the offset-to-onset rule. Across five deviant conditions, the onset-to-onset rule resulted in a larger deviant change than the offset-to-onset rule in some conditions, but a smaller deviant change in the other conditions. Hence, the pattern of MMN amplitude effects across the conditions would provide support for one rule or the other. The data pattern revealed that pre-attentive timing is from stimulus offset to stimulus onset in the case of empty interval timing. This experiment demonstrates that it is possible to use ERP components to discriminate between competing models of timing behavior without biasing the participant by providing instructions.

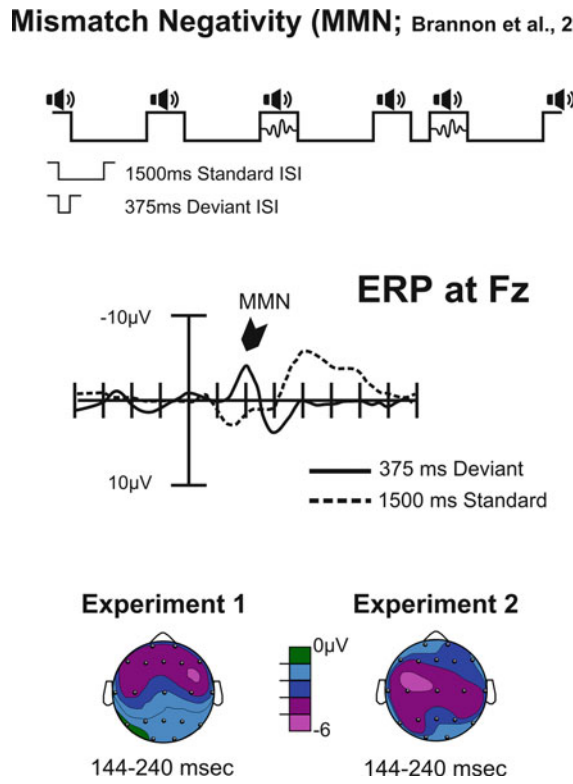

Fig. 4 Mismatch Negativity (MMN) in infants. *Top*: A MMN was elicited when infants heard a stream of predominately isochronous auditory tones (1,500 ms ISI) with rare shortened ISIs (375 ms). *Middle*: ERPs elicited by the two ISI types revealed a strong negative response when the ISI was a deviant. The MMN is typically shown as the difference wave between the ERP of the Standard interval and that of the Deviant interval. *Bottom*: Topographical distributions of the infant MMN. Although not illustrated in the figure, the MMN showed systematic changes in amplitude as a function of the ratio between standard and deviant (Experiment 1), but not as a function of stimulus duration when the standard to deviant ratio was held constant (Experiment 2). Redrawn from Brannon et al. [28]

In summary, the pre-attentive change detection system in the human brain is sensitive to duration changes on the order of tens of milliseconds to several seconds. In laboratory settings, the MMN is elicited when the regularity established by the presentation of the standard stimuli is violated by rare deviant stimuli. With appropriate experimental design, MMN paradigms allow researchers to study timing in the absence of instructional bias [20] across a wide range of participant populations [27].

Omission Potentials

When participants pay attention to a stimulus train comprising regularly occurring events (i.e., a constant ISI) the omission of a stimulus from the sequence elicits an ERP component referred to as an omission potential [30–37].

OPs are strongly sensitive to the temporal structure of the stimulus sequence, which suggests that they reflect neural processes related to interval timing, short term memory for time, and/or temporal expectations [32, 38]. For instance, jittering the stimulus sequence abolishes the OP for both visual and auditory stimuli [32, 39], whereas removing the task relevance of the omitted stimulus or the allocation of attention to it reduces OP amplitude, increases its latency, and latency variability [40]. Furthermore, OPs are not correlated with motor RT and are elicited even when a motor response is not required [41].

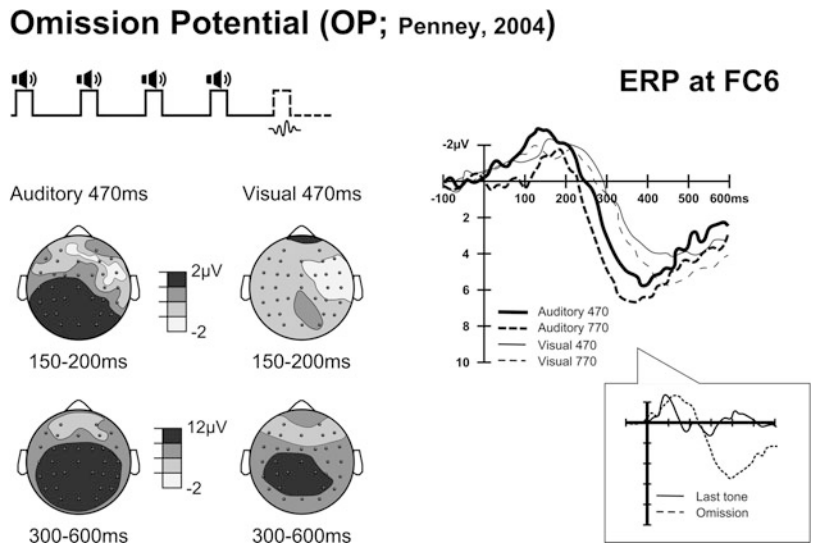

Fig. 5 Omission Potential (OP). *Top Left*: An Omission Potential can be elicited in a stop reaction time task, in which participants respond to the unpredictable termination of a stream of isochronous stimuli. The OP is measured from the time-point when the omitted stimulus would have occurred. *Bottom Left*: Illustration of the topographical distribution of the biphasic (negative-positive) OP reported in Penney [37] using either auditory or visual stimulus trains in the stop RT task. The early negative phase had a right frontal focus, while the late positive component had a strong parietal distribution. *Right*: The ERPs of the OP were comparable regardless of modality and ISI, suggesting amodal processes during implicit time estimation. The *inset* shows that a biphasic OP was not elicited when isochronous tones were presented, implying a relation of the OP to the violation of temporal regularity. Redrawn from Penney [37]

Bullock et al. [32] examined the effect of omission placement (end of the stimulus train vs. middle of a continuous train) and stimulus presentation frequency (from 0.3–40 Hz) on the visual OP. In the low presentation frequency range (0.3–2 Hz), sequences as short as two stimuli per trial across repeated trials gave rise to a stable positive OP. Jittering the ISI (e.g., regular ISI of 2 s vs. jittered ISI with mean of 2 s) or reducing attention to the stimulus train (e.g., participants were not required to count omissions) reduced the OP amplitude, demonstrating the importance of temporal regularity and attention for OP generation. Interestingly, changing the modality of the final stimulus before stimulus omission did not eliminate the OP. However, the authors did not examine whether the OP latency varied due to the modality change. In a subsequent study using auditory stimuli, Karamürsel and Bullock [39] observed a change in the OP latency. Systematic examination of OP differences across modalities is of interest because stimulus modality influences interval timing in some circumstances (see [42] for review). In this regard, the OP may serve as a useful tool for probing the origin of these differences and help reveal whether representation/processing of time is modality specific or amodal.

To this end, Penney [37] recorded participant's EEG while they performed a stop reaction time task [43]. This task requires participants to respond when they believe a sequence of stimuli has ended. Although no explicit instructions to time the stimuli are given, participants must be sensitive to the SOA between successive stimuli because this allows them to recognize that the delay since the last stimulus occurred is long enough to indicate that the sequence is over. Penney [37] presented visual and auditory sequences in two separate blocks. Within each block, the stimulus onset asynchrony (SOA) of a sequence was either 470 or 770 ms. Biphasic omission potentials were elicited in all conditions (Fig. 5), suggesting at least a partially shared timing process across

modalities. Specifically, a negative OP elicited between 150 and 200 ms after the scheduled onset of the omitted stimulus was comparable between modalities and was not related to the RT difference observed in the behavioral data. This result is consistent with an amodal regularity detection/decision mechanism.

In a single modality experiment, Busse and Woldorff [40] asked participants to perform an auditory oddball (pitch change) detection task in which the SOA between successive tones was either 1 or 2 s and which included task irrelevant tone omissions 11, 22, or 33 % of the time. They observed a biphasic OP in all conditions regardless of SOA and percentage of tone omissions, but the OP was smaller when the SOA was 2 s as compared to 1 s and smaller when tone omissions were most frequent (i.e., 33 %). In contrast to Penney [37], they observed that the OP in the long SOA condition had a broader latency than the short SOA condition, which they attributed to increased variability in the OP as SOA increased. However, they did not determine whether the variability increase was scalar [44].

Recently, Motz et al. [36] used the auditory OP to study how humans process violations in metrical patterns. In all blocks, the main beat was produced by periodic (SOA = 1,000 ms), pink-noise bursts. A weaker beat produced by periodic, but less frequent, white noise bursts was embedded in the main beat, generating a polyrhythm either at a simple integer ratio (1/3) or a non-metrical ratio of the pink-noise beat (metrical: 33 % of the between beat distance vs. non-metrical: 43 and 53 % of the between beat distance). Omission occurred at the last expected beat of the white noise bursts. The latency of the positive component of the biphasic OP recorded at the CPz electrode corresponding to omission at 33, 43, and 53 % of the between beat distance indicated a cognitive bias that regularized perception of non-metrical beats to the nearest simple integer ratio (50 %). While the OP latency at 43 % was later than that at 33 %, the OP latency at 53 % was earlier than that at 33 %, showing up-regulation (bias towards later) and down-regulation (bias towards earlier), respectively. However, the regularization was not complete, as shown by smaller than expected changes in the OP latencies, suggesting flexibility in metric perception. In a related vein, Jongsma et al. [45] compared the OP elicited in musically trained (average of 15.6 years) and untrained individuals when they listened to rhythmic percussion sounds (ISI = 800 ms) with an unpredictable omission after three to seven beats. The amplitudes and latencies of single-trial positive OPs at the Pz electrode were identified using wavelet de-noising [46]. OP latency variability was smaller in the group of musically trained participants, suggesting better ability of implicit timing (e.g., beat perception) and/or temporal deviant detection with musical training.

To summarize, similar to the MMN, the OP reflects detection of a violation of the temporal regularity of a stimulus stream. However, unlike the MMN, elicitation of the OP appears to require that the omitted stimulus be task relevant and attended, suggesting a different underlying mechanism. The morphology of the OP also appears to change according to the temporal variability inherent in the preceding stimuli [40]. Recent timing studies using the OP suggest that certain timing processes are amodal [37] and that the brain imposes regularity in environments of high temporal predictability [36]. Finally, as with the MMN [47], the timing system contributing to the OP is susceptible to effects of training, especially for auditory stimuli [34, 45]. As demonstrated by Busse and Woldorff [40], omission of a stimulus is likely perceived as a change in stimulus probability or stimulus expectancy, thus the OP is often considered a close relative of another prominent late positive component—the P300 [38, 48–50].

P300

The P300 has long been associated with decision-making [51] and is usually triggered after stimulus evaluation, but before response selection and motor execution (see [52] for review). It reflects memory and/or expectancy match [53, 54] or evaluation of the conditional

probability of the occurrence of a rare target [55]. There are two types of P300: the novelty-related, frontally distributed P3a that is associated with stimulus-driven attention processes in the frontal cortical regions, and the memory-based, parietally distributed P3b that is associated with attention and memory processes in the temporal and parietal cortices [52, 56].

Posterior positive slow waves (PSW) such as the P300 and anterior negative slow waves (NSW) such as the contingent negative variation (CNV; discussed below) can co-occur in anticipatory and timing paradigms (e.g., [57, 58]), with the NSWs likely providing the context for the functions reflected by the PSWs [48, 59]. Larger NSW-PSW for interval timing tasks relative to non-timing tasks is claimed to reflect a stronger and wider activation of neural populations that is not due to difficulty differences between the two task types. For example, Gibbons et al. [60] asked participants to perform temporal generalization and pitch discrimination tasks on identical auditory stimuli. The participants were less accurate in the pitch task, but the NSW-PSW amplitudes were larger in the temporal generalization task. Moreover, this pattern remained when participants were sorted into better-timing/worse-pitch-discrimination and better-pitch-discrimination/worse-timing groups. The authors interpreted this result as indicating a stronger involvement of working memory in the timing task than in the non-timing task. A similar interaction between the CNV and P300 specific to timing tasks was also reported by Gontier et al. [61] in a contrast of duration and size discrimination.

Miniussi et al. [62] asked participants to perform a simple reaction time task in which a visual cue predicted the cue-target interval (SOA) correctly 80 % of the time (600 or 1,400 ms). The P300 elicited by the valid visual target had a shorter peak latency and was more positive for the 600 ms SOA. The authors suggested that the provision of temporal information 'synchronizes or prepares motor processes, or sharpens decision processes' [62, p. 1516]. The P300 in this study had a parietal distribution, resembling the P3b. Synchronization of behavior, cognitive processes, and/or neural activity is the thesis of the Dynamic Attending Theory (DAT) (see [63] for a review). DAT states that different oscillators, whether in the brain or the environment interact with one another and may result in entrainment (synchronization). Attention to stimuli is maximal at the moments of maximal entrainment, leading to more effective stimulus processing [64].

Schmidt-Kassow et al. [65] recently tested this idea by comparing the P3b amplitude and latency elicited by oddball tones when participants listened to tone sequences with varying degrees of temporal predictability. The P3b amplitude was largest and the latency shortest when tones were isochronous. The authors attributed the stronger and faster response to deviants to an entrainment effect on attention brought about by the regular temporal structure of the task.

However, effective use of the P300 to investigate interval timing requires careful consideration of exogenous factors [49]. Specifically, although a P300 amplitude difference may be observed by comparing durations that are longer and shorter than the target duration, the effect may not reflect timing-specific processes. Instead, it simply may be due to overlap from exogenous, negative ERP components when the durations are long, leading to the commonly reported effect that the P300 elicited by the offset of durations longer than the target is less positive than that elicited by durations shorter than the target (e.g., [60, 66]). Gibbons and Rammsayer [66] specifically controlled for this possibility by including a condition in which participants passively listened to the same stimuli that were used in the temporal generalization condition (ranging from 125 to 275 ms). Two late positive potentials, a parietal P300 and a frontal P500, were elicited only when duration estimation was required. The P300 decreased in amplitude as duration increased, whereas the P500 was larger when the durations were non-targets. Furthermore, these components were not modulated by variation in tone pitch. The authors proposed a two-stage model for processing brief durations. The duration-modulated, parietal P300 was

interpreted as a memory-based P3b time-locked to stimulus onset, which indicates an immediate temporal processing of the stimulus that can only be completed when the stimulus is shorter than the target. The duration-insensitive, fronto-central P500 component was interpreted as a novelty P3a timelocked to the expected duration offset at the target duration (200 ms) that indicates a violation of expectation.

The P300 also has been related to performance in temporal tasks. Gibbons and Stahl [67] asked participants to reproduce a 2-s empty auditory target duration as accurately as possible. Timing performance was evaluated by median split of the sample based on either mean reproduction accuracy (absolute error) or variation of reproduction (coefficient of variation, CV). The amplitude of the marker offset P300 at Cz was more positive in the group with less variable reproductions (smaller CV). There was also a negative correlation between the offset P300 amplitude and the CV. A similar, but weaker, relationship obtained between the marker onset P300 and the CV. Consistent with their two-stage model of temporal generalization (cf. [66]), the authors proposed that the offset P300 during the target presentation indicated a comparison between the presented target and the internal representation of the target. Thus, participants did not passively attend to the presented target, but actively revised their internal representation when necessary. Better performers engaged in these processes more efficiently, forming more accurate expectations about the time of offset of the target duration, which resulted in larger offset P300 amplitudes.

Using temporal discrimination with a delayed response (1 s after the offset of the probe duration), Rebaï and colleagues [61, 68–71] observed a prefrontal P300-like component after the offset of the probe duration, which they termed a late positive component of timing (LPCt). Paul et al. [70] asked participants to discriminate the visual durations in one of the three possible pairs (100/200 ms, 300/600 ms, and 1,000/2,000 ms), presented either in the order short-long or long-short. For short-long trials, an increased positive amplitude LPCt coincided with increased S2 duration, higher discrimination accuracy, and shorter RTs. In a subsequent study, Paul et al. [71] manipulated the difficulty of a visual temporal generalization task (600 ms standard) by adjusting the linear spacing between probe durations (difficult: 75 ms; easy: 150 ms). Task difficulty is believed to modulate decision thresholds in temporal generalization [72] and here the difficult version yielded fewer "same duration" responses than the easy version. The LPCt amplitude was significantly more positive for the Difficult condition than the Easy condition. The authors posited that the LPCt reflects temporal decision-making processes. Moreover, they also noted the importance of investigating both negative and positive ERP components together in order to fully reveal the temporal network [48, 59]. For example, the decision threshold and/or response uncertainty, as reflected by P300 and LPCt, may be a function of the efficiency of attentional 'mobilization' during the monitoring of the to-be-timed interval, as reflected by the CNV.

To summarize, the P300 has been associated with attention, memory, and the evaluation of stimulus probability and expectancy of occurrence [52, 55]; processes that have direct impact on decision making [51, 59, 70]. Changes in amplitude and latency have allowed researchers to infer the brain's sensitivity to temporal regularity among stimuli [65] and how temporal information is tracked and updated when the time judgment has to be made in a discrete fashion [66]. The latter is consistent with the increased emphasis on the influence of contextual temporal information on temporal judgments through Bayesian principles [73–75].

Contingent Negative Variation (CNV)

Walter et al. [76] first identified the CNV as an electrophysiological marker of expectancy. In this classic study, an initial stimulus (S1) served as a cue for presentation of a second stimulus (S2) that appeared 1 s later. In some conditions the S2 served as an imperative stimulus indicating a response requirement (i.e., a button

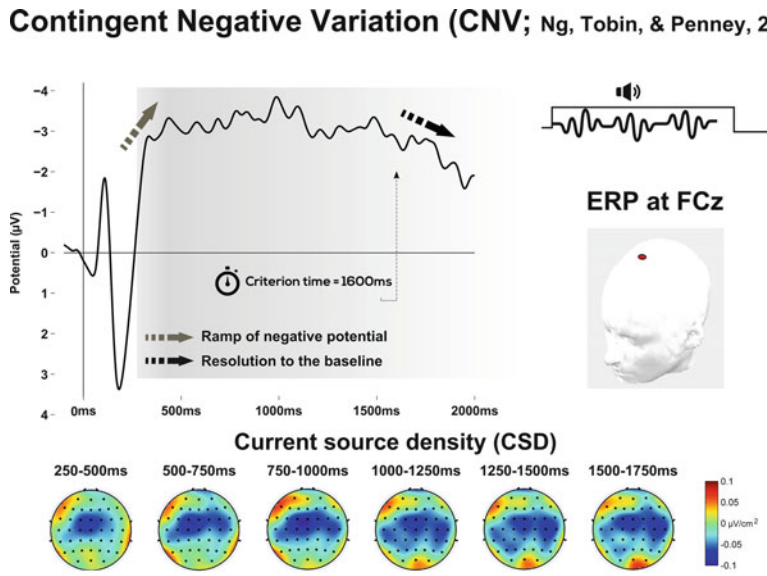

Fig. 6 *Top Right*: The CNV is reliably evoked in S1–S2 paradigms. S1 and S2 can be individual stimuli or the onset and offset of a continuous tone (i.e., a filled interval). The ERP is usually time-locked to the onset of S1. *Left*: The CNV recorded at the FCz electrode when participants completed an auditory duration bisection task in which they had to judge whether the probe duration was more similar to the short (800 ms) or long (3,200 ms) anchor duration. The results imply that participants treated the geometric mean (1,600 ms) as the criterion duration (see text). The CNV amplitude often ramps steadily after the early perceptual ERP components such as N100 and P200. Depending on task details, the CNV may reach maximal negativity and remain sustained at that voltage value for several hundred milliseconds. *Bottom*: Current source density (CSD) of the CNV shows that the CNV is a long-lasting negativity over fronto-central electrode sites. CSD reduces volume-conducted signals and is thus more sensitive to superficial neural sources in the proximity of the electrode. Consequently, the topographical distribution suggests the medial frontal cortices as potential contributors to the CNV. Redrawn from Ng et al. [77]

press) and in others it did not. A slow negative potential with a fronto-central topographical distribution (i.e., the CNV) appeared during the S1–S2 period, but only when the S2 served as an imperative stimulus or participants were asked to estimate a 2 s duration before the button press. Typically, the CNV displays a gradual increase or ramp in negativity until it reaches a plateau and then resolves back to baseline or a positive potential value, as illustrated in Fig. 6. In some cases, the plateau is sustained for several hundred milliseconds (e.g., [77, 78]). Over the years, the CNV has been associated with a variety of physiological and cognitive functions such as arousal, motivation, attention, and anticipatory preparation [78–83].

The stimuli used to elicit a CNV may consist of a cue and an imperative stimulus [4, 62, 76], onset-offset of a continuous signal [77, 84, 85], onset-offset markers that demarcate an 'empty' duration [86], coincidental timing from stimulus onset to time to contact [87], a delay period between an imperative stimulus and performance feedback [88, 89], or an oddball design in which one duration is designated as the standard and one or more other durations as the deviants [90]. The CNV can also be seen in paradigms that employ isochronous stimulus sequences. For instance, Pfeuty et al. [91] analyzed the CNV elicited when participants had to discriminate two auditory sequences of three to six tones based on tempo. Praamstra et al. [92] studied the sensorimotor CNV with an implicit timing task in which participants had to make manual responses to isochronous visual cues.

The CNV has at least two subcomponents. The initial CNV (iCNV) is elicited within about 1 s of S1 onset and sometimes peaks within 1 s. It is modulated by the perceptual properties of the S1 stimulus [57, 85, 93–95], S1–S2 duration

probability [96–98], and task-specific anticipation [79, 99]. It may reflect the orientation to S1, which prepares the participant for subsequent reaction (the 'O' wave; e.g., [100, 101]). The second subcomponent, the termination CNV (tCNV), overlaps with the iCNV when the S1–S2 interval is short, usually appears 1 or 2 s before S2, and increases in negativity as the S2 onset approaches. It is modulated by stimulus anticipation [102, 103], task load [79], and motor preparation [104–106], but is distinct from the readiness potential (the 'E' wave; e.g.,) [102, 107, 108]. If the S1–S2 duration is long enough (>4 s), the two subcomponents appear as a bimodal, long-lasting CNV [109, 110]. Finally, based on a comparison of the CNVs generated in a simple reaction time task, a 4-s foreperiod task, a 4-s temporal production task, and the encoding phase of a 4-s temporal reproduction task Macar and colleagues [35, 111] argued for the existence of a third CNV component that reflects the temporal and probabilistic linkage between S1 and S2.

In general, a CNV is consistently observed only when the participant pays attention to a stimulus and/or the stimulus is task-relevant. For example, Campbell et al. [84] asked participants to respond to a 20 ms gap that appeared early (300 ms) or late (1,300 ms) in an otherwise continuous 1,400 ms tone when the tone frequency was 500 Hz, but not when it was 1,500 Hz. A sustained slow negative wave (SNW) related to the auditory stimulation was present in all conditions regardless of response requirements, but the CNV was present and superimposed on the SNW only when a response was required. The relationship of the CNV to anticipation and time perception is bolstered by findings showing a CNV for duration comparisons of auditory stimuli, but not pitch or intensity comparisons [112, 113], and in a temporal discrimination task, but not in a size discrimination task in the same test session [61].

Numerous studies have revealed an association between the CNV and time perception performance (e.g., [114, 115]). For example, Ladanyi and Dubrovsky [116] compared performance and CNVs of participants making verbal estimates of 10 or 20 s. Compared to less accurate estimators, the more accurate estimators showed smaller amplitude CNVs that resolved faster and had a slower ramping to the maximum negativity. More recently, Pfeuty et al. [85] tested temporal discrimination for filled tones and empty intervals demarcated by two brief tones. They found that the CNV amplitude was significantly larger (see also [117]) and performance (accuracy) significantly worse when the intervals were filled (69 % correct) as compared to empty (77 % correct). A recent experiment by Wiener et al. [118] demonstrated a relationship between the processes contributing to the CNV amplitude and time perception using repetitive transcranial magnetic stimulation (rTMS), which perturbs neural activity by non-invasive application of strong external magnetic fields. Participants performed temporal discrimination with and without rTMS applied to the right superior marginal gyrus (SMG). The difference in the mean CNV amplitude (270–470 ms) between rTMS and non-rTMS trials and the difference in an index derived from the proportion of 'longer than standard' responses in rTMS and non-rTMS trials were computed and a positive correlation was found between the two measures.

Furthermore, the putative neural sources of the CNV are implicated in interval timing, as shown by the agreement between electrophysiological source localization and functional neuroimaging data. Surface Laplacian [119, 120] EEG/MEG (a magnetic counterpart of EEG) source localizations [121–123], and intracranial EEG recordings (e.g., [124, 125]) show that the supplementary motor area (SMA) and the pre-SMA, together with the right dorsal lateral prefrontal cortex (DLPFC) and posterior cortices, are among the major neural generators of the sensorimotor CNV. fMRI analyses also consistently identify the involvement of the SMA in sub- and supra-second timing (see [5, 126–131] for reviews).

The CNV frequently has been interpreted within the framework of the pacemaker-accumulator model of Scalar Timing Theory (STT; [44]). According to this model, the number of pulses stored in an accumulator represents the

duration of the event of interest. Comparison of this pulse count with representations of relevant durations held in long-term memory forms the basis of the decision process [72]. Although the debate about the existence and putative neural mechanisms of the 'internal clock' is ongoing [132–135], the idea that neurons or groups of neurons acting as signal accumulators give rise to cognition is common. For example, it has been used to explain and predict performance in perceptual decision-making (e.g., [136, 137]), response competition and inhibition (e.g., [138]), as well as numerical cognition (e.g., [139–141]).

Assuming there is a linear relationship between real time and perceived time [142, 143], the STT pacemaker-accumulator model asserts that neural activation increases over time, longer intervals are represented by more total clock pulses, and thus higher final neural activation. In line with this rationale, early investigations of the neural mechanisms underlying the CNV suggested that it resulted from the summation of excitatory post-synaptic potentials (EPSP) at the apical dendrites in deeper cortical layers, an indication of cortical excitability [79, 144]. Furthermore, the ramping negative potential of the CNV resembles an accumulation process resulting from spreading activation or signal integration of neurons in medial frontal brain areas [35, 120, 135, 145–150].

CNV Amplitude

The hypothesis that the CNV amplitude reflects neural accumulator function during duration estimation has received some empirical support. Macar et al. [120] showed a relationship between the CNV amplitude, as determined from a surface Laplacian computation, and the subjective/perceived duration of a 2,500 ms target interval in a temporal reproduction task. The authors assigned the reproduction trials to one of three categories based on accuracy (2,600–2,800 ms; 2,400–2,600 ms; 2,200–2,400 ms) and then generated response locked CNVs for each category by participant. Comparison of the grand average waveforms of the three groups of trials indicated that the CNV amplitude decreased (i.e., became less negative) as the produced intervals decreased, even though the participants were attempting to reproduce the same 2,500 ms target duration in all cases. In a subsequent experiment, Macar and Vidal [119] further showed that the amplitude of the surface Laplacian CNV reflected a consolidated representation of the memory (Experiment 2) rather than learning or updating of the temporal memory of the target duration (Experiment 1). The importance of memory consolidation in determining the CNV was also suggested by Mochizuki et al. [151], who varied the retention period (3,000 or 9,000 ms) between encoding of a 2,700 or 3,000 ms stimulus and its reproduction. The CNV during the reproduction phase was larger for the 9,000 ms retention interval, which the authors attributed to the stronger need to reactivate the decayed memory of the target duration when the retention interval was 9,000 ms. Bendixen et al. [152] replicated and extended the amplitude effect of Macar et al. [120] using a temporal discrimination task with much shorter intervals (500 ms on average). Comparing the grand averaged onset-locked CNV from trials that received a 'short' response to the CNV from those classified as 'long', they found that N100 and CNV amplitudes were more negative when the response was 'long', in line with the pacemaker-accumulator hypothesis.

However, Macar and Vidal [153] failed to replicate the association between CNV amplitude and perceived duration/temporal performance when untrained participants were tested on a temporal discrimination task using intervals of about 2 s. More recently, Kononowicz and van Rijn [81] also failed to find the association in a replication of the paradigm used by Macar et al. [120]. Instead, these authors found evidence for a habituation effect on the CNV amplitude across the experimental session. Ng et al. [77] also failed to find evidence relating CNV amplitude to perceived duration in a duration bisection task with anchor durations of 800 and 3,200 ms. Intermediate probe duration trials were sorted into those that received a 'short' response and those

that received a 'long' response and onset-locked CNVs were determined. There was limited support for a difference in CNV amplitude based on duration classification and when there was a difference, it tended to be opposite to the predicted direction (i.e., larger CNVs for shorter perceived durations).

Several experiments using temporal discrimination, or implicit timing tasks with sub- and supra-second durations with untrained participants also failed to find a difference in the CNV amplitude as a function of the interval duration [92, 109, 148, 154]. To summarize, although some studies demonstrated a consistent relationship between CNV amplitude and performance in a variety of timing tasks, interpreting these results as evidence for the pacemaker-accumulator model of time perception appears unwarranted given the sum total of available evidence [82, 155].

CNV Peak Latency and Slope

The initial ramping and subsequent resolution of the CNV (i.e., return to baseline from the peak negative potential) has also been claimed to reflect the memory representation of the target duration. For the initial ramp, researchers [149, 150, 156, 157] have drawn attention to the resemblance between the CNV's gradual increase in negativity and the gradual change in the firing rate of single cells in response to different cue-target contingencies [158]. This climbing neural activity hypothesis has been used to account for the CNV elicited in timing tasks (see [159], seventh chapter of this book, for a discussion of this hypothesis in motor preparation and cued anticipation). Pfeuty et al. [157] proposed that whereas the unchanging CNV amplitude in some studies may reflect a fixed criterion of the accumulator to trigger a decision, duration encoding and differentiation is achieved by adjusting how rapidly this criterion is reached. Moreover, once the criterion is reached, a decision can be made (e.g., 'longer than the target') without further accumulation of temporal information, which means the CNV may resolve before stimulus offset. In fact, several authors [86, 160] noted that a critical difference between the CNV evoked by perceptual or motor preparatory experiments and the CNV evoked by time perception experiments is the early resolution of the CNV in the latter case. For example, using relatively long durations (e.g., >5 s) in a temporal discrimination task, Macar and Vitton [86] observed that the CNVs corresponding to the standard and target durations resolved before stimulus offset, while the standard—target delay (3 s) and the delay between target termination and response (3 s) elicited typical expectancy CNVs that did not resolve until the end of the specific interval. Many researchers claim that the CNV resolution marks the moment of decision-making in interval timing [77, 153, 157, 161]. It is purported that a positive decision-making or motor programming component may be superimposed on the CNV [160], consistent with the often cited co-occurrence of the CNV and late positive components such as the P300 and Late Positive Component of time [57, 70, 71, 161, 162].

Quantification of the ramping and resolution of the CNV is also done by calculating the slope of the CNV [77, 92, 161, 163, 164]. Macar and Vidal [153] used both visual and tactile temporal generalization tasks to show that the CNV peaked at the memorized target duration (2,000 ms) rather than at the end of the probe duration (2,500 or 3,100 ms). Pfeuty et al. [164] obtained similar results with a S1–S2 duration comparison task. During S2, the CNV reached its negative peak at the S1 target duration (700 ms) at left hemisphere and medial frontal electrode locations, while at right hemisphere frontal electrode sites the CNV peaked at the end of S2. The authors suggested that the distinct CNV profiles at the right and left hemisphere electrodes reflected distinct memory representations for the S1 target duration and the elapsing S2 duration. Furthermore, there was a correlation between CNV peak latency and the subjective standard derived from the generalization gradient. In a subsequent S1–S2 experiment [157], the authors showed that given the same S2 probe duration (794 ms), the peak latency of the CNV corresponded to the S1 target duration (600 vs.

794 ms), although they failed to obtain an effect of target duration on CNV amplitude. Finally, in a bisection task Ng et al. [77] found that the CNV did not ramp to its maximum at the assumed criterion, which was the geometric mean of the short and long anchor durations (1,600 ms), but did so closer to the duration of the short anchor (800 ms). The negativity remained at the same level until the geometric mean and then resolved, hinting that more temporal information is available to the participants in the bisection task than in an S1–S2 temporal task. Similar to the results of Pfeuty et al. [164], they also found that the slope of the iCNV was positively correlated with the participant's bisection point, which is in line with an 'accumulator-with-fixed-criterion' hypothesis. Using a temporal discrimination task with durations of 800, 1,000, and 1,200 ms, Tarantino et al. [161] also reported an early resolution of the CNV close to the target interval.

Praamstra et al. [92] replicated the peak latency and slope effects [153, 157] in an implicit motor timing task. In this task, participants pressed one of two keys depending on whether an arrow pointed to the left or the right. Each trial comprised a short sequence of cues, each presented isochronously (2,000 ms) with the exception of the final cue. A CNV occurred between successive cues, but when the final cue was presented late (2,500 ms), the CNV peaked at the expected inter-stimulus interval (2,000 ms) and then began to resolve. Mento et al. [90] obtained similar results using an oddball task with empty visual durations. Participants were instructed to attend to the stimuli, which lasted 1,500 (70 % of the trials; standard), 2,500, or 3,000 ms (15 % each; deviants), but there was no response requirement. ERPs elicited by the two deviants showed an orderly decrease in the CNV amplitude (i.e., peak) at about the standard interval of 1,500 ms, suggesting that participants established a representation of the temporal structure of the task [165].

In contrast to the CNV amplitude results, those for the CNV peak latency and slope appear to be reasonably consistent. Indeed, studies that failed to show a relationship had a focus or experimental design that did not allow the authors to do similar analyses (e.g., [117]), or the design of the experiment did not allow participants to consolidate a temporal criterion [29, 61, 69]. The latter possibility emphasizes the importance of careful consideration of task requirements when interpreting the data [166–168]. In sum, the available evidence suggests a relatively robust relationship between interval timing and CNV peak latency and slope [90], while the relationship between CNV amplitude and timing stimulus duration is equivocal at best [81, 155].

In summary, the CNV is elicited consistently in timing tasks with intervals spanning hundreds of milliseconds to several seconds. Its putative neural generators are active in both 'automatic' and 'cognitively mediated' time perception [127]. Similar to the OP, attention to the to-be-timed stimulus is required for the timing-related CNV to occur [84] and like the MMN and OP, the CNV can be elicited in paradigms without explicit timing instructions [90, 92], and like the P300, the CNV can be elicited during the timing of discrete events [91, 164]. The CNV amplitude and peak latency are influenced by the temporal information in the task [77, 120]. It is possible that the CNV reflects a temporal representation based on neural ramping and integration (pulse accumulation). This would be consistent with the pacemaker-accumulator model of STT and the climbing activity model [35, 149]. The accumulation stops and the CNV resolves when a temporal decision can be made [153, 157]. However, recent investigations of ERP components that follow the CNV resolution, such as the potentials elicited by the offset marker of an empty interval [155] and the error-related negativity (ERN; [74]), suggest that these components change depending on the magnitude of difference between the target interval and the test interval. This implies that at least some timing processes continue after the CNV has resolved. Hence, the specific relationship between the CNV and timing processes remains to be determined.

Conclusion

In this chapter, we have provided a brief overview of the range of timing and time perception questions to which scalp-recorded EEG

methods have been applied. We have seen EEG/ERP measures used as a proxy for behavioral measures in situations where a task requiring behavioral response was not possible (e.g., MMN in infants) or instructions about how to complete a timing task could strongly bias the results obtained (MMN, OPs). We have also seen from the CNV literature the critical importance of seeking corroborating evidence from multiple paradigms and methods when interpreting EEG/ERP features as biomarkers of the specific cognitive processes posited by timing models. In sum, scalp-recorded EEG/ERP has great potential as an investigative tool for the study of interval timing, but much remains to be discovered.

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Searching for the Holy Grail: Temporally Informative Firing Patterns in the Rat

Matthew S. Matell

Abstract

This chapter reviews our work from the past decade investigating cortical and striatal firing patterns in rats while they time intervals in the multi-seconds range. We have found that both cortical and striatal firing rates contain information that the rat can use to identify how much time has elapsed both from trial onset and from the onset of an active response state. I describe findings showing that the striatal neurons that are modulated by time are also modulated by overt behaviors, suggesting that time modulates the strength of motor coding in the striatum, rather than being represented as an abstract quantity in isolation. I also describe work showing that there are a variety of temporally informative activity patterns in pre-motor cortex, and argue that the heterogeneity of these patterns can enhance an organism's temporal estimate. Finally, I describe recent behavioral work from my lab in which the simultaneous cueing of multiple durations leads to a scalar temporal expectation at an intermediate time, providing strong support for a monotonic representation of time.

Keywords

Premotor cortex • Cingulate cortex • Striatum • Interval timing • Rat • Behavior • Electrophysiology

Introduction

Timing and time perception in the seconds to minutes range, interval timing, is of fundamental importance for survival, being implicated as a necessary process for foraging [1, 2] and associative conditioning [3, 4], and it serves as the contextual framework through which behavior can efficiently map onto the external world. Despite the importance of this capacity, our understanding of the neural mechanisms through which temporal perception and control are achieved remains minimal. As such, the "Holy Grail" of the field is to identify the neural structures, activity patterns, and computational processes that serve as the "internal clock". While this task will necessarily be achieved by

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triangulating across a range of methodologies, such as pharmacological manipulations [5–7], anatomic lesion studies [8–11], functional brain imaging [12–15], and genetic analyses [16, 17], electrophysiological recordings in behaving animals are likely to be of foremost importance due to their capacity to provide exquisite temporal and spatial resolution of neural activity.

Recording single neuron activity in behaving non-human primates and relating this activity to cognitive processes has been occurring for nearly half a century [18, 19]. In the vast majority of work carried out since then, the subjects are trained over the course of several months to remain motionless during a behavioral task in which a specific cognitive operation is being investigated. This approach developed due to concerns that overt behavioral changes could be used as a mediating "placeholder" for the cognitive operation under investigation. For example, in the frequently used delayed matching to sample task, a subject is briefly presented with a stimulus (e.g., a red cue light) and then after a short stimulus-free delay is asked to choose the corresponding stimulus when presented along with an alternative (i.e., choose the red, rather than green, cue light). As the delay lengthens, the task requires working memory (as opposed to iconic memory), and alternate strategies might be utilized by the subject to improve performance. One such strategy would be a differential behavioral response in which the subject engages in a specific behavior during the delay (e.g., squeezing its hand following a red cue light), and then evaluates its behavioral state, rather than its working memory store, at test. Since such a strategy eliminates the working memory demands, thereby preventing the study from achieving its goals, these overt behaviors are eliminated during training by having the subject remain motionless, and requiring the subject to specify its decision with a highly stereotyped behavioral response (e.g., looking left or right) that can be recorded using electromyography (EMG) or electrooculography (EOG), to verify that the behavior is not being covertly executed. While it is important to keep in mind that other covert behaviors that are not being recorded could potentially be functioning in a similar vein, in general, these techniques have provided considerable evidence about the neural mechanisms underlying a number of cognitive processes (e.g., that neurons in prefrontal cortex are activated in a stimulus-specific manner during the delay, thereby suggesting an important role in working memory [20–22]).

Not surprisingly, this restricted behavior strategy has also been extensively used in the non-human primate studies investigating the electrophysiological activity patterns underlying interval timing [23–31]. While these studies have revealed a number of important findings, ethical and monetary considerations somewhat prohibit us from carrying out other important studies on non-human primates. For example, although showing that a certain neural structure has firing patterns that are consistent with it serving as an internal clock process is important, removing the structure to assess its necessity in timing is a critical next step. Furthermore, it would be quite useful to be able to evaluate how these neural firing patterns, and the corresponding temporal control of behavior, change in response to lesions of the region's input structures. Such studies can be more feasibly done in rodents. In addition, the vast majority of studies on interval timing behavior conducted over the last three decades have been done in rats and pigeons, and identifying the neural underpinnings of timing behavior in these species provides a necessary direct link to such work.

Neurophysiology of Timing in the Rat

For these reasons, a number of years ago, we began conducting ensemble electrophysiological studies on rats trained to respond in a temporally controlled manner for food reinforcement. In the spirit of this book serving as an educational resource, I will briefly reflect on my observations and thoughts from my initial forays into the electrophysiology of time in rats. While it may go without saying, the most important element in task design is to consider appropriate experimental control. Simply recording neural activity

while a rat engages in a temporal production task (e.g., the peak-interval procedure—[32]), does not provide sufficient leverage for identifying the mechanisms contributing to temporal perception. Obtaining peak-shaped neural activity may be evidence of an internal temporal representation that functions in a non-linear manner, computing similarity to previously reinforced neural "clock" states, or it may be that one is recording from an effector process, such as that used for generating the motor output to make the behavioral responses. As described above, the necessary approach is to shape the subject's behavior so that it differs from the obtained neural activity pattern. In this way, the neural pattern can potentially be interpreted as reflecting a central, cognitive operation, rather than the reflection of an input or output signal. In the non-human primate studies described above, by keeping the subject motionless, the dynamic evolution of neural activity cannot be directly related to behavior, which is essentially stationary.

Following a similar strategy, we initially thought that a temporal perception task, such as the duration discrimination task [33], would serve this function. In a duration discrimination task, the subject is exposed to a stimulus (e.g., a tone) for one of two different durations, after which it classifies the length of the duration by making a choice response. In contrast to a temporal production task in which the animal responds at times when it anticipates that food reinforcement is available, there is no need to respond during the to-be-timed interval. Instead, it can conserve energy by simply perceiving the duration of the stimulus, and then making a decision regarding stimulus length once the stimulus has terminated. However, a paper was published at roughly the time at which we were considering experimental designs that demonstrated that rats would utilize a behavioral strategy to facilitate their temporal decisions, such that they would position themselves in front of the "short" response lever early in the trial, and then switch to being in front of the "long" response lever in a probabilistic manner as a function of elapsed time [34]. This behavioral sequencing strategy is in some ways similar to humans counting seconds to enhance their temporal precision [35, 36], in that the rats are using a mediating spatial sequencing strategy. We decided to make it more difficult for the rats to utilize this strategy by requiring them to hold down a central lever during the to-be-perceived interval, thereby preventing this sequential behavior approach. Remarkably, the rats simply suppressed their locomotor behavior without eliminating it completely. Specifically, they held down the central lever with their forelimbs, while probabilistically directing their rump toward the appropriate lever as a function of time. While we considered incorporating further behavioral restrictions to prevent such behavior, I began to believe that we ran a strong risk of simply blinding ourselves to the rat's behavioral strategies, rather than eliminating them. Indeed, a topic of discussion in the lab at this time was whether all electrophysiological studies suffer from the so-called "sphincter problem" (i.e., whether an internal behavior exists that co-varies with the cognitive event being studied and is the source of the neural activity, but as we are unable to see this internal behavior, we conclude that it doesn't exist).

As a result, I decided it would be more profitable to allow our subjects to engage in whatever behaviors they wished to mediate time, and to record these freely emitted behaviors as they emerged in time. In this way, we would be able to identify periods of time in which the subject's behavior was stationary (e.g., a continuous bout of operant responding), thereby allowing us to examine the dynamics of neural activity that occurred during these behavioral states. These neural dynamics could then be interpreted in the same way that one would interpret neural activity obtained while the subject was in a motionless state. Moreover, this approach has several advantages in comparison to a motionless recording strategy. First, it dramatically minimizes the problem of covert behaviors contributing to the neural activity profiles because we are not training our subjects to suppress overt behaviors, thereby potentially facilitating the adoption of covert behavioral strategies. Second, the training time required to teach subjects to remain

motionless is eliminated. Third and most importantly, we are allowing the subjects to generate temporally controlled behavior in an unconstrained manner, which provides the best approximation to the cognitive and behavioral strategies used in the real world.

Specifically, we adopted a matched behavior strategy [37] in which the same overt motor behaviors are elicited under different cognitive or motivational states, here different temporal expectations. In this manner, the neural activity associated with the operant behaviors can be "subtracted out", and firing rate differences can be associated with the different temporal expectations. Specifically, we utilized a multiple duration peak-interval procedure. A peak-interval procedure is a variant of a discrete trials, fixed-interval schedule in which a to-be-timed stimulus commences and the first operant response (e.g., a lever press) after the criterion duration has elapsed (e.g., 10 s) provides reinforcement and terminates the signal. Responses made prior to the criterion duration have no programmed consequence. In the peak procedure, a proportion of trials are non-reinforced probe trials in which the signal stays on for three to four times the criterion duration, before it terminates in a response-independent manner. The average response rate as a function of signal duration on these probe trials (the peak response function) rises gradually from a low operant rate at trial onset to a peak around the criterion time, and then returns in a nearly symmetrical manner to the baseline rate following the criterion duration. The time of maximal responding, the peak time, is used as a measure of the subject's temporal expectation of reinforcement, and the spread of responding is used as a measure of the subject's temporal precision. The response rate at the peak time, the peak rate, is used as a measure of motivation. When tested with multiple durations with equal payoff likelihoods, it is commonly found that the peak rate for a short duration (e.g., 10 s) is greater than the peak rate for a longer duration (e.g., 40 s), potentially reflecting a greater value of obtaining reward with a shorter delay [38]. A hallmark of interval timing behavior is that it obeys the scalar property, or Weber's Law applied to temporal control [39–41]. It is seen behaviorally in that the breadth of the peak function is proportional to the peak time. In other words, the peak spread when timing 10 s is four times smaller than the peak spread when timing 40 s. The scalar property is often graphically depicted by normalizing the peak functions as a function of peak rate and peak time, so that the resulting functions are plotted as a proportion of maximal rate on the ordinate, and a proportion of peak time on the abscissa. When this is done, the peak functions for different durations overlap, or superimpose, suggesting that the subject's decision to respond is based on a proportional similarity to the criterion duration, and is simply scaled for different durations.

At first glance, the differences in peak spread and peak rate for different durations appear to hinder the use of a matched behavior strategy, as the behavior is not identical across the different durations. However, these differences in behavior are an artifact of averaging across multiple trials, and this concern is mitigated when the subject's behavior is examined on the level of individual trials. Specifically, the behavior on single trials is well characterized by a sequence of three response rate states, a low-rate state in which the subject is not actively engaged in operant responding, a high-rate state in which the subject responds repeatedly on the operant manipulandum at a high rate, and then another low-rate state. While the low-rate states may be composed of a variety of behaviors (e.g., sitting quietly, grooming, general locomotor activity, checking the food magazine, occasional operant behavior, etc.), the high-rate state is composed of continuous operant behavior, emitted at a near constant rate. Importantly, the rate of responding during this high rate state does not tend to differ across durations. Rather, the differences in peak rate and peak spread seen in the mean functions are a result of increased variability in the start and stop times associated with the high rate state. I should note here that the claim that the high rate state is identical across all durations needs to be examined more closely in the future, perhaps utilizing the change point detection algorithm

recently developed by Gallistel and colleagues [42, 43], as we have seen that the high rate state for long durations is sometimes composed of periods of high rate responding interspersed with brief visits to the food magazine, whereas these excursions are less common when responding for short durations (see also [44]). At any event, by selecting periods of time in which the operant behavior is emitted at equivalent high rates, the neural activity during these periods can be directly compared, and differences in neural activity can be ascribed to differences related to temporal expectancy or directly related variables such as value.

Over the past decade we have published several papers using this approach, and I will review our findings in this chapter. Matell et al. [45] trained rats on a two-duration fixed-interval procedure to lever press for possible food reinforcement at 10 s and 40 s from signal onset (see Fig. 1, Panel A). Briefly, onset of a tone signaled that the trial had begun. On some trials, the first response after 10 s was reinforced and the trial was terminated. On other trials, the first response after 40 s was reinforced, and the trial terminated. Subjects did not know which duration would pay off on each trial, and therefore began responding around 10 s, and if this didn't pay off, they paused responding, and then initiated responding again around 40 s. Because of the probabilistic nature of reinforcement for the 10 s duration (25 %), but 100 % reinforcement at 40 s (if the trial wasn't reinforced and terminated at 10 s), response rates peaked at similar levels at 10 s and 40 s. A hallway and barrier were constructed around the response lever, so that the rats could only respond using their right forepaw, with their body directed away from the front wall, to more adequately match the behavioral state across durations. Single unit firing rates were recorded from the anterior dorsal striatum and the anterior cingulate cortex while the rats engaged in this task. The majority of the neurons in both areas showed firing rate fluctuations that peaked (or dipped) at the times of lever pressing activity, suggesting either a direct relationship with the motor activity of lever pressing which peaked at the criterion times, or with the associated expectation of reinforcement that motivated the lever pressing. More importantly, a modest proportion (~25 %) of these neurons had different firing rates during a response window just prior to the 10 s criterion compared to an equally wide response window just prior to the 40 s criterion (see Fig. 2). Close investigation of these response windows revealed that they were composed of a mix of behaviors, including lever pressing, food cup checking, and moving between these locations. As such, we restricted our analysis to the periods of time within these windows during which the rats were actively poking (i.e., a high response rate state), and we used the lever press topography (e.g., the press duration) as a covariate in our analysis. This analysis revealed that 22 % of the striatal neurons and 15 % of the anterior cingulate neurons had different firing rates during equivalent behavioral segments that occurred at different times. We interpreted these differential rates at the two intervals as indicating that these cells are sensitive to elapsed time.

These results are consistent with the postulates of the Striatal Beat Frequency Model [46, 47] that striatal neurons are integrating time-varying cortical activity patterns to generate a temporal expectation. Specifically, the Striatal Beat Frequency model proposed that a broad array of cortical neurons have sub-threshold oscillations in their membrane potentials, with different neurons having different underlying periodicities. These sub-threshold oscillations would result in a pattern of spiking that carries this oscillatory signature (i.e., a Fourier analysis would reveal maximal power at the neuron's oscillation frequency). The model proposes that the onset of a biologically relevant signal would synchronize the oscillatory phase of these neurons, but because of their different intrinsic periodicities, their firing should rapidly desynchronize. As a result, the dynamic pattern of activity across the cortex will evolve and could represent the amount of time elapsed from the synchronizing event. As individual striatal neurons receive input from 10,000 to 30,000 different cortical neurons [48], they are in a unique position to detect a specific

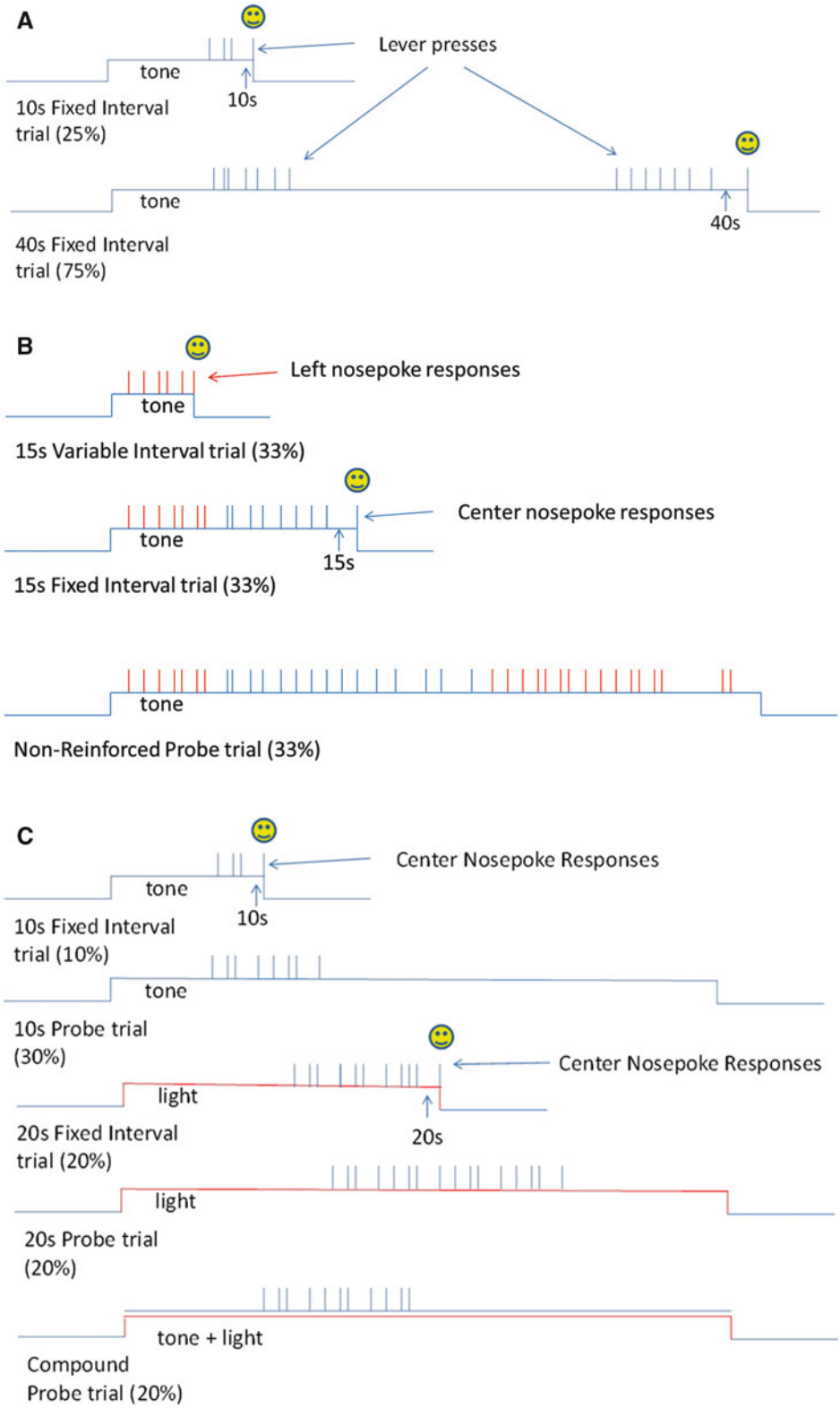

Fig. 1 Graphical representation of the timing tasks discussed in this chapter, as well as the typical single trial behavioral pattern. Panel **A**. In this two duration fixed-interval procedure, a tone commences signaling the start of a trial. On "short" trials (*top*), the first lever press after 10 s earns reinforcement and terminates the

constellation of cortical activity [49]. We proposed that dopamine-mediated long-term potentiation would strengthen the synaptic weights of those neurons that were firing around the time of reinforcement, whereas long-term depression would dampen synaptic inputs that were uncorrelated with reward. As such, individual striatal neurons would be stimulated in proportion to the degree to which the current cortical activity pattern matched the pattern associated with previous reinforcement. When the amount of stimulation surpassed a threshold, the striatal neuron would fire, indicating that "time is up". In this way, the dynamic evolution of cortical activity reflects the clock stage of an information processing account of timing, the cortico-striatal synaptic weights reflect the memory stage, and striatal activity reflects the decision stage. Intriguingly, the difference in firing rate across the two trained durations was consistently larger in the striatal neurons than the cortical neurons. This finding is consistent with the fact that striatal output through the basal ganglia feeds back to the cortex and merges with on-going cortical activity, which should cause the firing pattern of the cortical neurons to reflect a dampened version of the striatal decision stage output. On the other hand, we did not see any oscillatory activity in the cortical activity, which is inconsistent with the proposed clock process of the striatal beat frequency model. Furthermore, the model did not simulate the effects of feedback, so it remains unclear whether the model's ability to generate temporal expectancy would be helped or hindered by such striatal-thalamo-cortical feedback. Nevertheless, while the first issue is a bit of a thorn in the side of the model, the basic tenets of dynamic cortical activity being filtered by a synaptically based memory and read out by striatal neurons remain consistent with the data.

Motor Timing or Abstract Timing?

While the results of the study described above provided clear information that elapsed time modulates striatal activity, the results were ambiguous in regards to what aspect of temporal information was being represented. Take for example the neuron depicted in Fig. 2, which was representative of the majority of temporally informative firing patterns. There is a prominent peak at 10 s, and a secondary, smaller, rise to 40 s. One possible coding scheme that is consistent with this pattern is what we can call "abstract temporal coding". In this scheme, times of high spike activity correspond to times at which the rat expects food to be available, irrespective of the motor actions concurrently emitted by the rat. The difference in maximal firing rate at the two

Fig. 1 (continued) signal. On "long" trials (*bottom*), the first lever press after 40 s earns reinforcement and terminates the signal. There is no programmed consequence of responding prior to the criterion duration, and no signal is provided regarding which duration will be reinforced. As a result, the rats tend to respond around 10 s, and if no reinforcement is received, pause for some time and then respond again around 40 s. Panel **B**. In this concurrent variable-interval/fixed-interval procedure, a tone commences signaling the start of the trial. On variable-interval trials (*top*), reinforcement is delivered with a low probability (e.g., 1 %) for each moment that the rat's snout is in the left nosepoke. On fixed-interval trials (*middle*), reinforcement is delivered for the first response on the center nosepoke after 15 s have elapsed since trial onset. On probe trials (*bottom*), no reinforcement is provided and the signal stays on for at least 40 s. As no signal is provided to indicate trial type, the rat begins responding on the left, variable-interval, nosepoke, switches to responding on the center, fixed-interval, nosepoke as time approaches 15 s, and then switches back to responding on the left nosepoke after 15 s has passed. Panel **C**. In this two-modality, two-duration peak-interval procedure, a signal commences signaling trial onset. On 10 s fixed-interval trials, a tone commences, and the first center nosepoke response after 10 s is reinforced and the signal is terminated. On 20 s fixed-interval trials, a light commences, and the first center nosepoke response after 20 s is reinforced and the signal is terminated. A proportion of trials are probe trials in which either the tone or light commences and stays on for three to four times the associated fixed-interval duration, but no reinforcement is delivered and the stimulus terminates in a response-independent manner. Rats respond on these trials around the time that reinforcement is normally delivered. In addition, compound probe trials were presented in which the tone and light were simultaneously presented. On these trials, rats responded maximally at a time in-between the two fixed-interval durations

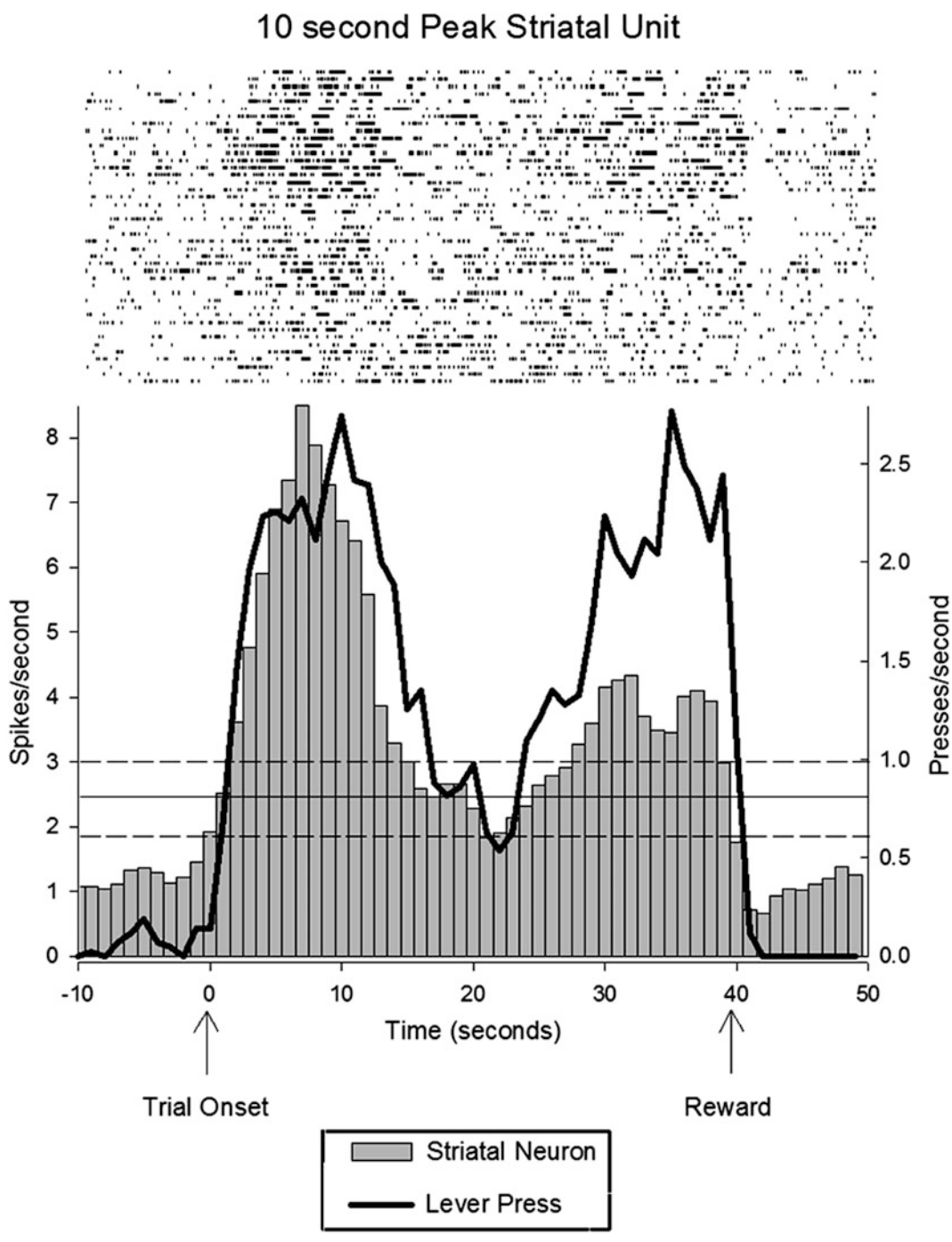

Fig. 2 Peristimulus time raster and histogram displaying the activity pattern of a representative striatal neuron showing differential activity at two times associated with possible reinforcement (10 s and 40 s), thereby indicating the striatum's sensitivity to a specific temporal interval. The average firing rate of a striatal neuron is shown as a *grey histogram*, while the subject's lever pressing is shown as a *black line*. Importantly, the lever pressing rate was equivalent at these two times of reward, thereby ruling out a simple motor coding role of the firing rate differences in the striatal neuron. This figure from Matell, M.S. Meck, W.H., & Nicolelis, M.A., Interval timing and the encoding of signal duration by ensembles of cortical and striatal neurons. Behavioral Neuroscience, 117(4), 760-773, 2003, APA, adapted with permission

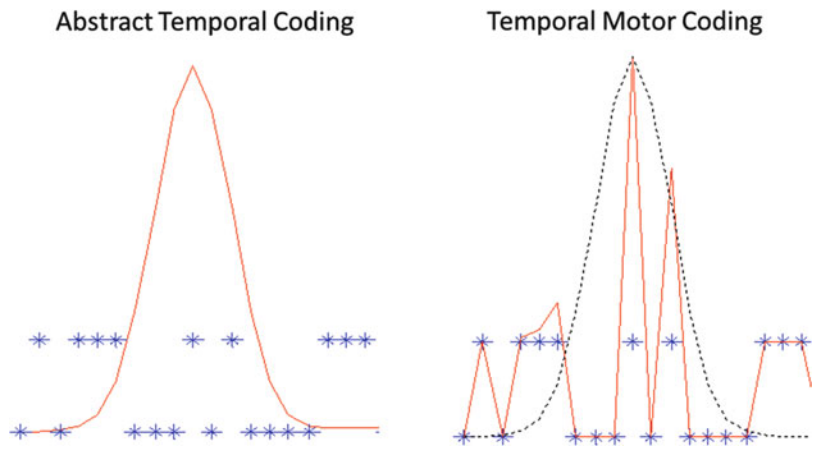

Fig. 3 Graphical representation of two different mechanisms for temporal coding. The *red lines* in the figures show the firing pattern of a temporally sensitive striatal neuron, while the *blue crosses* indicate the concurrent behavior. In contrast to Fig. 2, in which the behavior showed temporal control, thereby preventing a dissociation between motor and abstract timing, we have intentionally disrupted the behavior in this example so that it does not show temporal control. An "abstract temporal code" is shown in which the neuron's firing rate peaks around the expected time of reinforcement. The behavior in this coding scheme is generated downstream from the striatum, such that although there is temporally informative activity in the striatal neuron, the behavior does not necessarily reflect this activity. (*right*) In contrast, the firing pattern displayed on the *top right* represents temporal motor coding. In this case, the neuron's activity is driven by the behavior, but temporal information (represented here as the *black dotted line*) modulates the firing rate. Thus in this scheme, the behavior and time are represented in an integrated manner within the striatal neuron

criterion times might reflect that the neuron is specifically tuned to the 10 s duration, or it could reflect the increased precision of representing 10 s compared to 40 s (i.e., scalar timing), with both times being fully represented by the neuron. In this coding scheme, the temporal information contained in striatal firing rates would be passed to downstream structures that control motor behavior, thereby allowing temporally appropriate responding. This coding scheme can be contrasted with "temporal motor coding" in which the firing rate of the neuron partially reflects the motor behaviors being emitted. In this case, the firing fluctuations are a result of behavioral fluctuations (rather than the cause), and the neuron firing more at 10 s than 40 s would be due to a temporally informative signal generated either intrinsically or extrinsically (i.e., from another brain structure) and enhancing or diminishing the strength of the motor-related firing. To make this distinction clear, imagine that we were able to disrupt the rat's motor behavior, such that responding was occurring in a random manner across time, as shown in a graphical manner in Fig. 3. In the "abstract temporal coding" scheme, the striatal neuron's firing rate would nevertheless continue to peak at the criterion time. In contrast, in the "temporal motor coding" scheme, the firing rate co-varies directly with the response pattern, while a temporally-specific signal (shown in black) modulates the strength of the response-related activity.

To investigate this issue, we wanted to conduct another experiment in which the rats would respond without a corresponding temporal expectation (e.g., comparing responding on a fixed-interval schedule with responding under a fixed-ratio schedule). However, this brings up a point of possible contention, namely whether a behavior can be executed without a corresponding temporal expectation. In other words, it seems possible that an organism might always know something about the average time until reward, even if elapsed time is not the contingent factor, as in a fixed-ratio schedule. If this is the case, then comparing across so-called timing versus non-timing conditions would be meaningless, as there are no non-timing

conditions. Indeed, a recent theory of learning by Gallistel and Gibbon [3] proposed that all associative learning is based upon establishing the temporal relationships between events. Therefore, we opted to compare responding for a temporally predictable reward to responding for a temporally unpredictable (or at least much less predictable) reward. Specifically, we trained and tested rats on a discrete trials, probabilistic, concurrent variable-interval, fixed-interval reinforcement schedule (see Fig. 1, Panel B). In this procedure, all trials began with the onset of a tone. On some proportion of the trials (33 %), responding at one nosepoke aperture (e.g., one on the left) would be reinforced on a 15 s variable-interval schedule, meaning that reinforcement was "primed" at a constant low probability at each moment the rat had its snout in the nosepoke aperture. The probability was set so that a rat who simply held its nose in the left aperture would earn reinforcement *on average* after 15 s, but the precise time at which reinforcement was delivered varied randomly across trials. Upon reinforcement, the trial ended. On other trials (33 %), responding on the center nosepoke was reinforced on a 15 s fixed-interval schedule, such that the first center response at or after 15 s would be reinforced, and the trial would terminate. Additionally, in order to facilitate stable responding, if the rat was holding its snout in the center nosepoke aperture at the moment 15 s elapsed, reinforcement was delivered (see [50]). Finally, 33 % of the trials were non-reinforced probe trials which lasted at least 40 s and terminated independently of responding [51]. No signal was provided to the rat to indicate what type of trial was in effect. Finally, aluminum hallways were constructed around the nosepoke apertures to prevent rapid switching between nosepokes and to minimize any postural differences across nosepokes or elapsed time.

Our goal here was to have the rats responding on the fixed-interval nosepoke around 15 s, but responding at the temporally unpredictable variable-interval nosepoke at all other times. In this manner, motor behavior (i.e., nosepoking) would be emitted at a relatively constant rate across the entire trial, except for the times at which the rat switched from one nosepoke to the other. Figure 4 (top) shows the rat's likelihood of occupying the nosepoke, and the pattern of behavior on a representative single trial (Fig. 4, bottom). As can be seen, the rat was either responding on the VI or FI nosepoke, or switching between the nosepokes. As such, we could compare the firing rates across time, as well as across different levels of temporal predictability of reward, while the nosepoking behavior was roughly constant. Further, because overt motor behaviors were most prominent during the transition periods when the rat switched nosepokes, we could address the temporal modulation versus abstract timing question described above. Specifically, if striatal activity represents time in an "abstract" manner, divorced from any motor behaviors required for reinforcement, then average firing rates should be characterized by ramp shaped or peak-shaped activity profiles over the entire trial, without abrupt changes in firing at the transition periods in which a broad array of motor behaviors are emitted [52]. In contrast, if the striatal activity is dependent on motor activity, there should be abrupt changes in firing rates during the transition periods, above and beyond any modulation related to elapsed time.

Our recordings demonstrated that 82 % of the cells had different firing rates when comparing the same behavior (e.g., nosepoke holding) across different response phases (e.g., variable-interval responding compared to fixed-interval responding), thereby supporting the notion that striatal neurons are a major contributor to interval timing behavior as suggested by our [45], and others [8, 29, 53, 54] findings, as well as the Striatal Beat Frequency model [46]. Intriguingly, some neurons had clear peak or ramp shaped activity profiles across the trial or within select phases of the trial (Fig. 5) when we restricted the analysis to the periods of time in which the rat's snout was held within one or both nosepoke apertures (i.e., when it's behavior was controlled for). However, when we examined firing rates across the entire trial (i.e., including the transition periods—the periods of time in which the rat was moving between the fixed-interval and

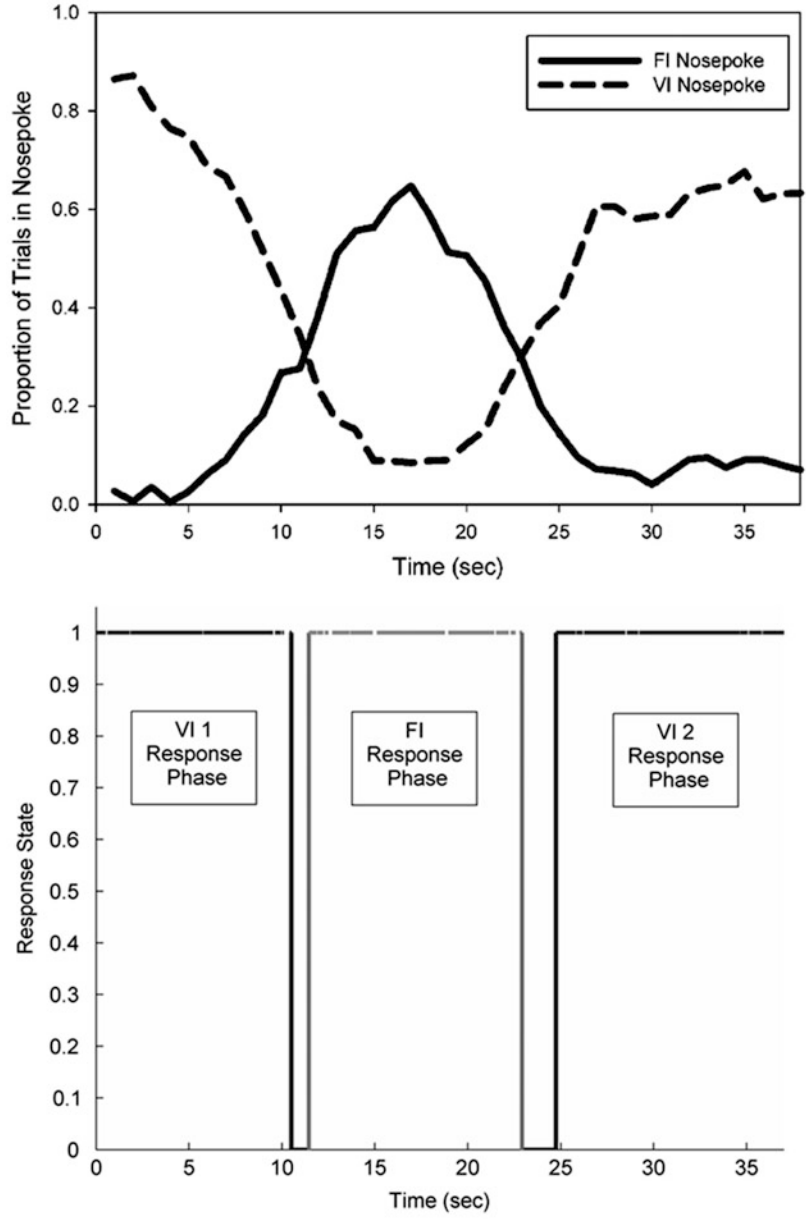

Fig. 4 Session average and single trial behavior during a concurrent 15 s variable-interval/fixed-intervaI procedure (see Fig. 1B). The *top panel* shows the average proportion of time in which a representative rat had its snout within either the VI or FI nosepoke. As can be seen, FI responses peaked in a symmetrical manner around the criterion time of 15 s, with VI responding occurring with high likelihood during all other times. The *bottom panel* shows VI (*black lines*) and FI (*grey lines*) nosepoke occupancy on an individual probe trial. As can be seen, the rat initially occupied the VI nosepoke, before switching to the FI nosepoke around the criterion FI time. After the FI duration had elapsed, the rat switched back to occupying the VI nosepoke. Note the short (~1–2 s) periods of transition, during which the rat backed away from the nosepoke it was occupying, and approached the nosepoke it was about to occupy. This figure was originally published in Portugal, G. S., Wilson, A. G., & Matell, M. S. (2011). Behavioral sensitivity of temporally modulated striatal neurons. *Front Integr Neurosci, 5*, 30. doi: 10.3389/fnint.2011.00030

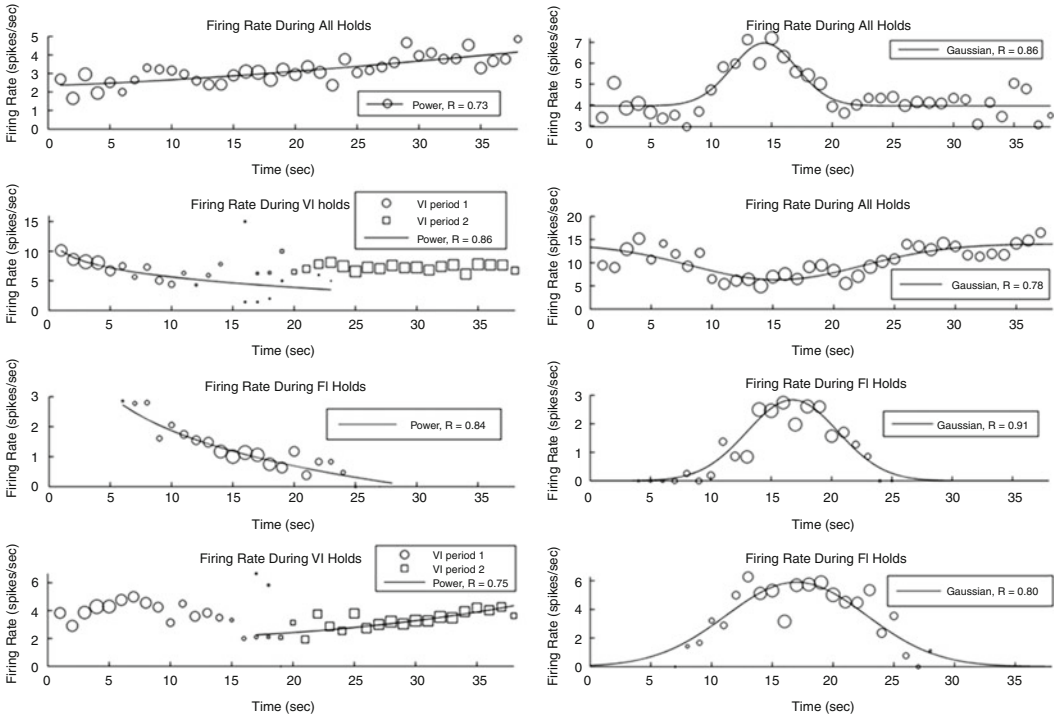

Fig. 5 Examples of striatal neurons that exhibited monotonic ramp (*left*) or peak-shaped (*right*) changes in spike rate when in the process of holding their snout in the nosepoke (defined as continuous occupancy in the nosepoke aperture for at least 500 ms) as a function of elapsed time in the trial. Because nosepoke occupancy occurred at different times on different nosepokes across trials, the size of the data points reflect the number of trials contributing to each data point. Some neurons had firing rates that fluctuated in a systematic manner irrespective of the nosepoke aperture on which they were responding, whereas others showed these patterns only within certain phases (either on the FI nosepoke or one/both of the VI nosepokes). The degree (fit) to which a power function (indicative of a ramp) or Gaussian function characterized the data is provided in each plot's legend

variable interval nosepokes), we almost always saw dramatic modulation of firing rates during these transition periods. Indeed, of those cells showing a difference in firing rate across the hold periods (55 % of all cells), 91 % of them showed significant modulation of firing rates during one or more of the transition periods as compared to both of the surrounding hold periods. For example, Fig. 6 shows the average firing rates from several representative neurons during the nose-poking periods and during the transition periods. The nose-poking periods that were analyzed were restricted to the periods of time in which the rat was holding its snout within one of the nosepoke apertures. The transition periods are composed of two sub-periods: the first 200 ms after the rat left the nosepoke aperture at which it had been responding (e.g., the variable-interval nosepoke), and the last 200 ms before the rat entered the nosepoke aperture in which it would subsequently be responding (e.g., the fixed-interval nosepoke). Based on visual inspection of the rats' behavior, these transition sub-periods were composed of either backing away from the nosepoke (the first sub-period), or locomoting toward the nosepoke (the second sub-period). As can be seen, the firing rates during one or more of the transition behaviors are dramatically different than that found for the surrounding hold periods. Indeed, in most of the cases, the firing rates during the transition behaviors moved in the opposite direction from what would be expected from a neuron whose firing rates showed ramp or peak patterns. For example, in Fig. 6a, the neuron showed a peak-like structure, firing on average at 4.8 spikes/s

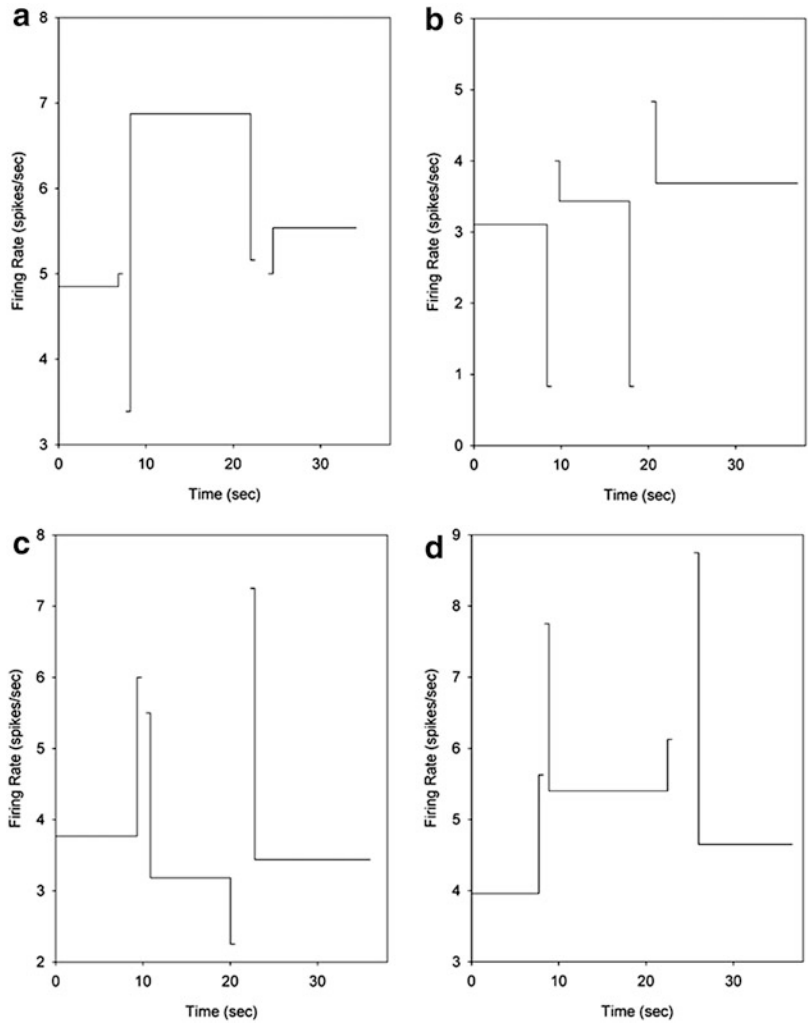

Fig. 6 Mean firing rates during the phases of nosepoke occupancy and during the first 200 and last 200 ms of the transition period illustrated in Fig. 4. The firing rate of each phase is plotted at the mean time at which these phases began and ended, but was computed with respect to each trial's actual transition times. Although the firing rates were not constant throughout the nosepoking phases (see Fig. 5), the pattern of activity across the trial are inconsistent with a monotonic or peak-shaped firing pattern that develops irrespective of the co-occurring motor behaviors, thereby suggesting that the striatum is encoding both the time at which overt behaviors are executed, and the expected reward time or elapsed trial time (i.e., temporal motor coding). The four panels display four representative neurons, but 100 % of task-modulated neurons had qualitatively similar patterns. To facilitate display, the duration of the transition segments is shown over 500 ms, rather than the 200 ms used for analysis. This figure was originally published in Portugal, G. S., Wilson, A. G., & Matell, M. S. (2011). Behavioral sensitivity of temporally modulated striatal neurons. *Front Integr Neurosci, 5*, 30. doi: 10.3389/fnint.2011.00030

while initially holding its snout in the variable-interval nosepoke, rising to 6.8 spikes/s during the period of time in which it was holding its snout in the fixed-interval nosepoke, and dropping to 5.5 spikes/s upon returning to the variable-interval nosepoke. However, when the rat was approaching the fixed-interval nosepoke, its firing rate was significantly below the firing rates of all of these hold-periods, which is incompatible with a peak shaped activity profile that is un-perturbed by motor activity. A similar situation is seen in Fig. 6b, in which the firing rates

during the hold periods grow in a monotonic manner across the three hold phases. If this neuron were solely coding time, irrespective of motor activity, one would expect the firing rates during the transition periods to be in-between the firing rates of the surrounding hold periods. In contrast, the firing rates during the transitions were both below (while the rat was backing away from the nosepokes) and above (while the rat was approaching the nosepokes), the surrounding hold period rates. As such, these data are clear in demonstrating that striatal neurons are not solely encoding time as an abstract entity. Instead, the passage of time appears to interact with their behaviorally-linked activity, thereby supporting the idea that the striatum represents time through temporally-modulated motor coding.

A Variety of Temporally Informative Patterns

Given the lack of an abstract representation of time in the striatum, we therefore turned to the inputs of the striatum to attempt to locate the structure(s) that might represent the passage of time in a monotonic or unimodal manner, without the influence of co-occurring behaviors, as predicted by many psychological models. The majority of excitatory striatal inputs come from the cortex, with some additional inputs arising from the thalamus, as well as modulatory dopaminergic inputs from the substantia nigra pars compacta [55]. Given work showing that the firing patterns of substantia nigra neurons relate to signal onset as well as trial outcomes [56–58], rather than showing across trial patterns of activity associated with elapsed time (although see [59]), we felt that the search for a representation of elapsed time should be focused on the cortex. Of course, the cortex is a broad area, and despite the general topographic organization of cortico-striatal inputs, with motor cortical areas projecting to motor striatal areas, etc. [60], there is sufficient overlap in projections to keep the search open across all cortical areas. Related to this issue is the current question in the field regarding whether the timing system is centralized (and amodal) or localized to specific sensory systems [61–63]. To the extent that the striatum is critically involved in timing, one might surmise that both situations may be simultaneously instantiated, as the majority of cortico-striatal inputs would remain largely segregated to specific sensory, motor, or association cortical channels (thus being sensory-specific), whereas the sparser overlap in projections could allow a limited degree of cross-modal interaction (thus being amodal).

In our initial work described above [45], we recorded from the anterior cingulate cortex, which makes up a substantial portion of the inputs to the dorsal lateral striatum that was recorded in the above studies. However, we found scant evidence of monotonic or peak-shaped (uni-modal) activity patterns. Based on evidence from other electrophysiological, functional imaging, and ERP studies [24, 28, 64–69], the premotor and supplementary motor cortices appeared as likely areas to provide a temporal signal. As such, in collaboration with Shea-Brown and others [70], we decided to record from the medial agranular cortex, which has been suggested to be the rodent homologue of premotor cortex [71, 72]. In this study, we continued to use a matched behavior design, a two-modality, two-duration peak procedure, such that the same response nosepoke and nosepoke requirements were used to earn reward for two different durations (i.e., 10 s and 20 s), with two different discriminative stimuli (i.e., tone and light) signaling which duration to time (see Fig. 1, Panel C). To equate response strength across the two durations, the 10 s cue was reinforced on 25 % of trials in which it occurred, with the other 75 % of its trials being non-reinforced probe trials lasting three to four times the criterion duration, whereas the 20 s cue was reinforced on 50 % of the trials on which is occurred, and the other 50 % of its trials being non-reinforced probes. In addition, non-reinforced stimulus compound trials were presented in which both the 10 s and 20 s cues were presented simultaneously.

As shown in Fig. 7, peristimulus time histograms showed a range of patterns across

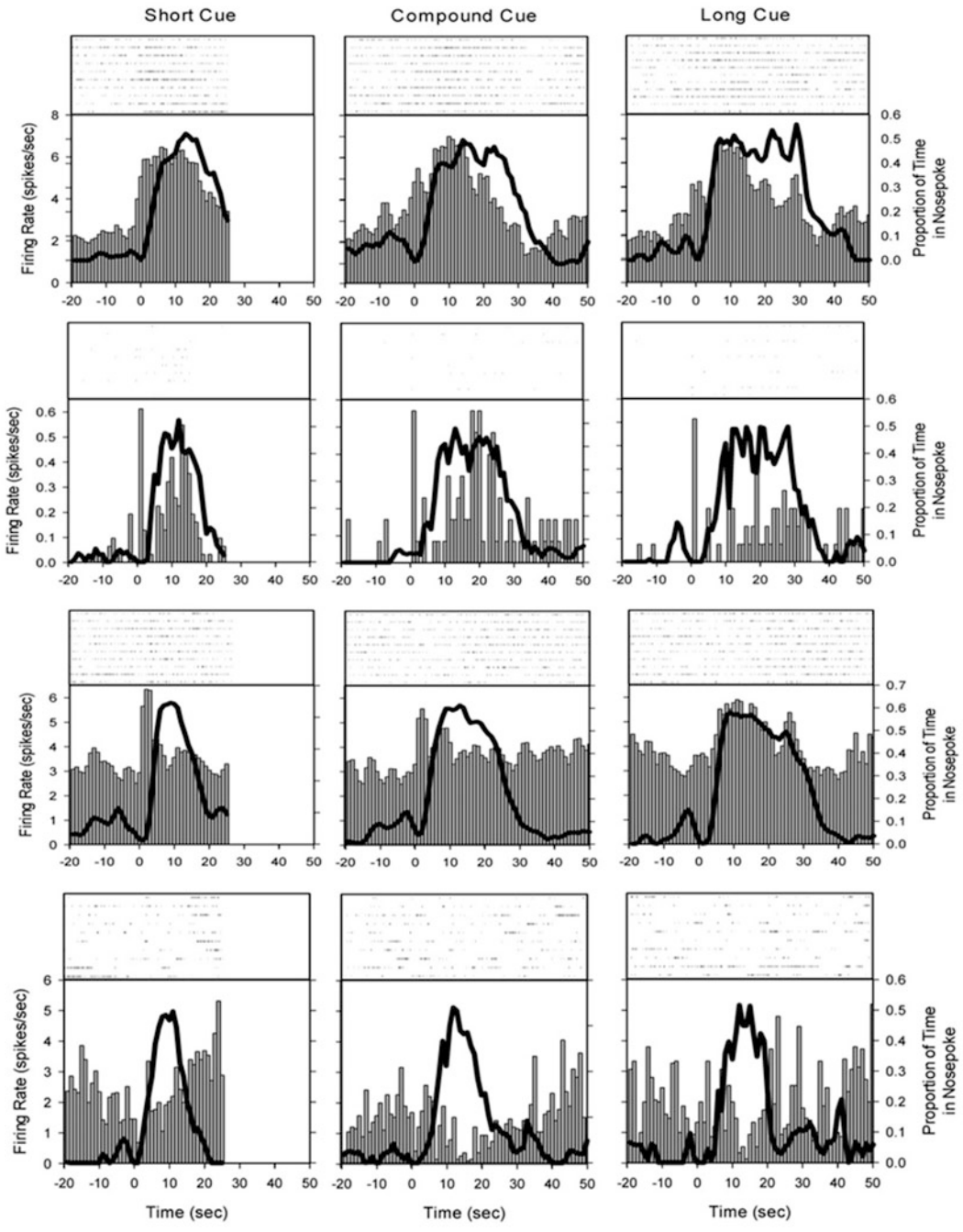

Fig. 7 Perievent rasters and histograms from representative neurons on a two-modality, two-duration peak procedure (see Fig. 1C). Each row displays a different neuron, and each column corresponds to the short (10 s) cue (*left*), the simultaneous compound cue (*middle*), and the long (20 s) cue (*right*). The *thick black line* shows the relative occupancy of the rat's snout in the nosepoke. Notice the dynamics of firing rates across neurons, time within a trial type, and across trial types. This figure from Matell, M.S. Shea-Brown, E., Gooch, C., Wilson, A.G., & Rinzel, J., A heterogeneous population code for elapsed time in rat medial agranular cortex. Behavioral Neuroscience. *125* (1), 54-73, APA, with permission

time and trial type, with roughly half of the neurons (46 %) having significant fluctuations in rate as a function of time in the trial. Of these task sensitive neurons, 59 % had peak shaped activations, whereas 21 % were ramp-like on at least one of the trial types. Intriguingly, only 4 cells out of the 155 recorded (e.g., Fig. 7, top) showed the same pattern of activation across all trials types. Thus, it appears unlikely that neurons representing a purely abstract temporal signal that operates across modalities and behavioral domains are contained within this structure. However, as there is no reason to require the same neurons to provide a temporal signal for all scenarios, and as a substantial proportion of neurons showed patterns of activity across the trial that could provide an effective clock signal that maps onto time, we felt these data deserved further examination. As with the studies above, because these subjects were freely behaving, the possibility remained that the activity patterns shown in Fig. 7 might be related to overt motor activity and not directly associated with the passage of time.

Indeed, the behavior of the rats in this procedure was similar to what is seen in a single duration peak-interval procedure, where the rate of operant responding is very low at the beginning of the trial, abruptly switches to a high rate sometime before the criterion duration has elapsed, and then abruptly returns to a low rate sometime after the criterion duration has passed [73]. In the current experiment, we captured this state of temporally controlled, goal-directed, responding by plotting the occupancy (i.e., in or out) of the rat's snout in the nosepoke as a function of time in the trial, and then exhaustively fitting all possible "out-in-out" step functions until the deviation between the data and the step function was minimized. We saw that the rat's snout occupied the nosepoke less than 10 % of the time during the obtained "Out" states, whereas it was within the nosepoke more than 60 % of the time during the obtained "In" state. We then restricted our analysis of the firing patterns to those periods of time in which the rats were in the "In" state, so that the temporal evolution of overt motor behaviors across the trial could not account for the fluctuations in firing rate. Figure 8 shows the firing rates of a representative sample of neurons as a function of time during this "In" state, as well as the rat's occupancy of the nosepoke. Because the length of the "In" state varied across both trials and trial types, we plotted these PSTHs using a relative measure of time, the proportion of the "In" state period. As can be seen, nosepoke occupancy during the "In" state was not constant, but fluctuated to some degree as a function of time. Therefore, to further account for this non-stationarity of the rat's behavior, we used the nosepoke occupancy as a covariate when analyzing the firing rate fluctuations across time. In this way, fluctuations in firing rate that are related to fluctuations in occupancy can be "subtracted out".

Our primary goal here was to ascertain the shape of the firing (i.e., whether it was peak or ramp shaped), as well to assess whether the firing rate on an individual trial was reliable enough for an ideal observer to discriminate elapsed time. To do this, we utilized linear discriminant analysis (LDA), which allows one to ask whether a dataset, when split into two (or more) categories, has sufficient separation in its measured statistics, here spike rates, to be reliably segregated [74]. Given the limited number of trials available before the subjects became satiated, we asked the simplest question possible: whether the pattern of firing provided sufficient information to predict whether the rat was in the first or second half of the "In" state. The assumption here is that the rat begins responding some time before it expects to get food, but doesn't stop responding until it is sure that food is not available (e.g., onset of "In" state at 7 s, expectation of food at 10 s, end of "In" state at 13 s). We are then asking whether the pattern of activity from 7 s to 10 s (i.e., early half of the "In" state) is different from the pattern of activity from 10 s to 13 s (i.e., late half of the "In" state). A graphical example of the approach is shown in Fig. 9, and described here. To assess whether either the rate of firing, and/or pattern of firing, of a hypothetical neuron is different between the early and late halves of the "in state", we split each half period into two bins

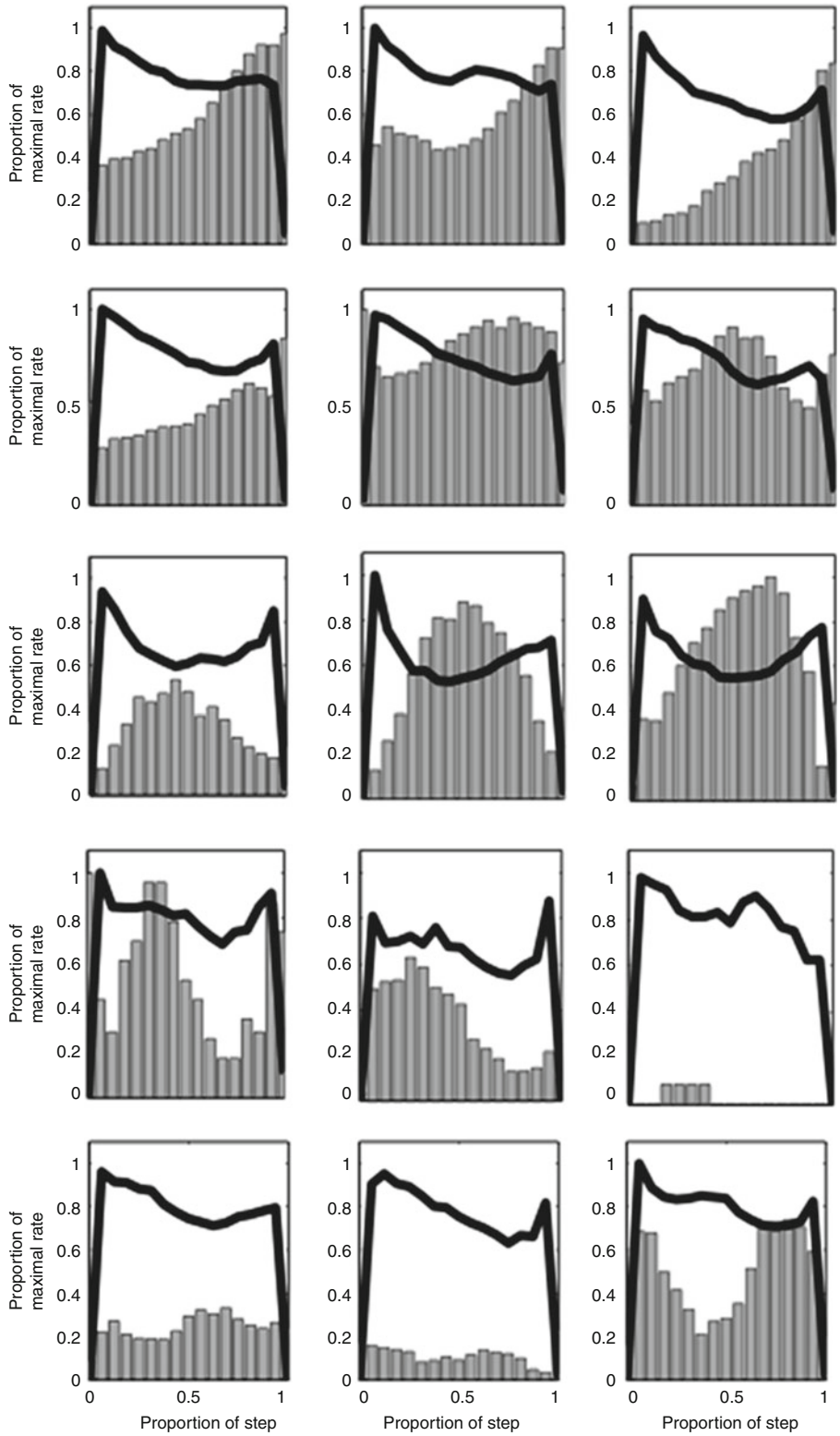

Fig. 8 Heterogeneous patterns of firing rate changes in medial agranular cortex neurons during the high nosepoke occupancy "In" state, on probe trials in the mixed 10 s/20 s peak procedure. Different neurons are shown on different rows, and different trial types are shown in different columns, as in Fig. 7. To account for trial by trial

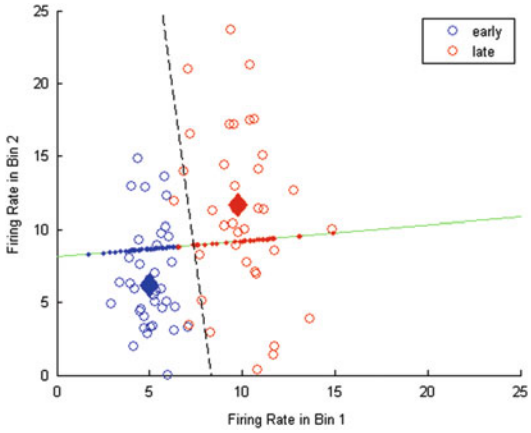

Fig. 9 A graphical example showing the optimal feature and boundary line separating the firing rates of a hypothetical neuron that increases in rate the across the "In" state. The "In" state is split into two halves (early versus late), and each half is split again (Bin 1 and Bin 2). The firing rate during these bins is plotted as a point in 2-d space. These points are plotted for each trial, and in separate colors for the early and late halves of the "In" state. The means of these points are plotted as *filled diamonds*. The feature direction that optimally separates these clusters of points is plotted in *green* (as identified by linear discriminant analysis). The data points are "projected" in an orthogonal direction onto the feature line, and the boundary by which the two clusters of points are maximally separated is plotted as a *dashed line*. Notice that due to greater variability during Bin 2 in both the early and late halves of the "In" state, the best discriminability is not along the dimension that goes through the cluster means, but that the optimal feature is one that utilizes the Bin 1 rates more heavily than the Bin 2 rates

(i.e., early bin 1, early bin 2, late bin 1, and late bin 2). We then plot a point (here in blue) specifying the firing rate during the first half of the "In" state from a single trial on a Cartesian plane, with the firing rate in early bin 1 specifying distance along the X-axis, and the firing rate in early bin 2 specifying distance along the Y-axis. The firing rate of this hypothetical neuron during the second half of the trial is plotted in a similar manner, but with a different symbol (here in red). For example, imagine on trial 1, the firing rate during the "In" state progresses as follows [spike rate = 3, 5, 8, 12 spikes/s for early bin 1, early bin 2, late bin 1, late bin 2, respectively]. The point in blue at [3, 5] and the point in red at [8, 12] represent this trial. From these two points, one can see that the neuron monotonically increased its firing rate from the first to the fourth bin (i.e., ramped). In comparison, if the two points on a single trial were at [5, 10] and [9, 6], the firing rates would be construed as peaking. A line that connects these dots specifies what is referred to as the feature dimension in which the difference between categories (early versus late) is maximal. By crossing this feature line with a perpendicular "boundary" line at the midpoint, one could then evaluate in a subsequent trial, whether the current firing rate is more similar to the early half or the late half of the first trial, simply by asking which side of the line it falls on. For example, if you observed that the spike rate was 4 spikes/s in the first bin of time you watched the neuron and six in the second bin of time, you should predict that you are in the early half of the "In" state. Instead of doing this for one trial, LDA allows one to do this for all of the trials, such that the feature line identifies the dimension over which the clusters of blue and red are maximally separated based on their means as well as their variances. Finally, because we were interested in evaluating how reliable single neuron firing was at providing this information, we utilized the standard approach of leave-one-out

Fig. 8 (continued) variability in the length of the "In" state, the figures are binned using varying bin widths, that are 1/15 the width of the "In" state on each trial. Firing rates are shown as *vertical bars*, and occupancy in the nosepoke aperture is plotted as a *thick black line*. Firing rates and nosepoke occupancy within the "In" state have been smoothed with a 5 s running mean for presentation and were normalized by the maximum rate across trial types. The lack of stationarity in nose-poke occupancy was accounted for by using the time-varying occupancy as a covariate in the quantitative analysis. This figure from Matell, M.S. Shea-Brown, E., Gooch, C., Wilson, A.G., & Rinzel, J., A heterogeneous population code for elapsed time in rat medial agranular cortex. Behavioral Neuroscience. *125*(1), 54-73, APA, with permission

cross validation, which computes the feature and boundary line based upon all trials but one, and then asks whether the remaining data point is classified correctly. This process is reiterated, such that every trial is assessed using the features and boundaries from all other trials, and the overall percent correct is compared to chance (using a standard binomial test with n trials).

This analysis revealed that 55 % of the recorded neurons provided information that could be used by an ideal observer to reliably discriminate whether the rat was in the early or late half of the "In" state. The trial types on which a particular neuron provided information differed, with 34 % of the neurons providing information on short trials, 25 % on long trials, and 39 % on compound trials. Only 10 % of neurons could reliably discriminate time on all three trial types when each trial type was examined individually. On the other hand, when the same analysis was performed after pooling across trials, thereby increasing power, but also requiring the neural activity pattern to transcend trial type specific activity, we found that 43 % of the neurons provided reliable information regarding relative time in the "In" state. Intriguingly, when we examined the firing patterns that provided this information, we found a roughly equal distribution of all possible patterns that could be described by four bins (i.e., positive and negative ramp patterns as well as positive and negative peak patterns). Similar variation of patterns was seen for all trial types. To more thoroughly explore this variability in firing patterns, we simplified our description of the pattern by re-binning the data into three bins, rather than four, such that a monotonic increase or decrease represented a ramp pattern, while a non-monotonic pattern of activity across the three bins represented a peak or dip. We then graphically characterized the shape of firing as a vector in Cartesian space, by plotting the relative change in rate from bin 1 to bin 2 on the abscissa and the relative change in rate from bin 2 to bin 3 on the ordinate. In such a plot, lines falling in quadrants 1 and 3 indicate positive and negative ramping, respectively, with the slopes indicating the degree and direction of non-linearity. Similarly, lines falling in quadrants 2 and 4 indicate peak or valley shaped firing, respectively, with the slopes indicating the degree and direction of skew. As shown in Fig. 10, there were not only a variety of firing patterns in terms of ramps versus peaks, but also in terms of the non-linearities and asymmetries.

Surprised by this variety of temporally informative firing patterns, we asked whether such a scenario provided some benefit to the organism. Specifically, we compared the errors in temporal estimation produced by a model that relates spike counts to elapsed time. We first considered a hypothetical population of ramping cells with Poisson noise, and found that the estimation error was minimized when the rate of ramping was maximally steep (under constraints of maximal firing rates of 40 Hz). This outcome results from the fact that the steeper the slope, the larger the change in spike counts per unit of time, thereby providing maximal discriminability across time. Additionally, the relative rate change is maximal at low firing rates, so sensitivity is greatest at the beginning of the trial for a positively ramping cell, and the end of a trial for a negatively ramping cell. The next model we considered was composed of neurons which peaked or dipped rather than ramped. This model provided a 27 % improvement over the ramping models, due to the maximal firing rate changes occurring over a smaller window of time (i.e., the slope of the ramp is steeper as the change in rate occurs from trial start to the peak time, rather than to trial end), and essentially equivalent performance for peaks and dips. Finally, we considered a model in which the population was constructed of a mixture of peaks, dips, and ramps, and in which the peaks/dips could be maximal/minimal at different times across neurons. This heterogeneous model improved the estimation error of the homogeneous peak/dip case by an additional 13 %. The basis for this further improvement resulted from the minimal firing rates occurring at different times (i.e., the dips hit 0 spikes/s at different times for different neurons). As stated above,

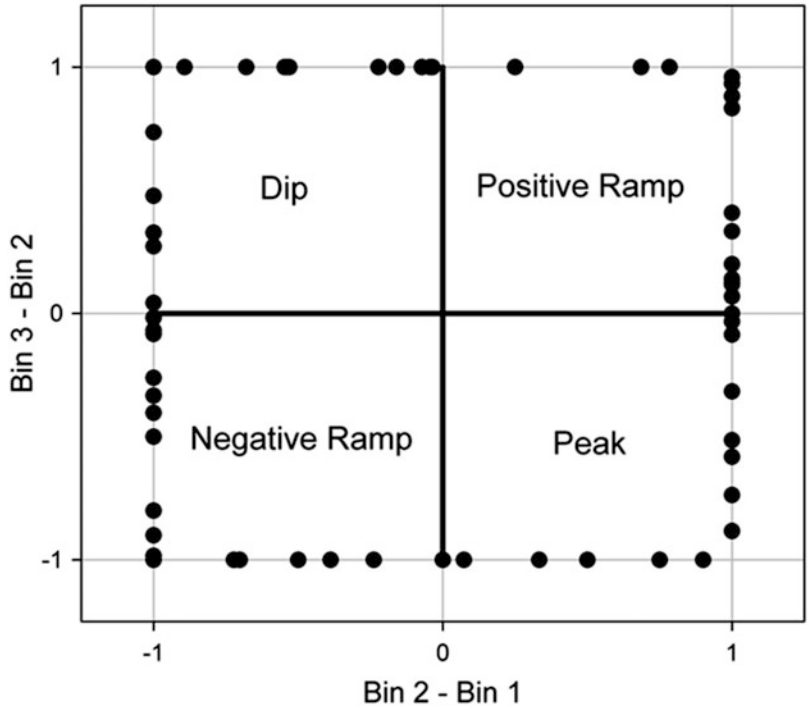

Fig. 10 Shapes of the firing rate patterns in neurons whose rates differed across the "In" state defined by three relative duration bins, irrespective of trial type. The abscissa provides the change in rate from Bin 1 to Bin 2, while the ordinate provides the change in rate from Bin 2 to Bin 3. The rate changes were normalized by the maximum change, such that all points fall along the unit square. Points in quadrants 1–4 correspond to a positive ramp, a dip, a negative ramp and a peak, respectively. This figure from Matell, M.S. Shea-Brown, E., Gooch, C., Wilson, A.G., & Rinzel, J., A heterogeneous population code for elapsed time in rat medial agranular cortex. Behavioral Neuroscience. *125*(1), 54-73, APA, with permission

the relative change in firing rate for a given slope is maximal when the firing rate is minimal, so by having the maximum relative change at a variety of temporal locations, timing is maximally precise at each point in time.

These findings suggest that animals have access to neurons with a variety of different firing patterns which could be used to estimate elapsed time, and if accessed as an ensemble, could enhance perceptual sensitivity. It should, of course, be noted that the availability of these patterns in no way implies that these patterns or neurons are actually used by the animal to control behavior in time. Such limits for interpretation are true for every recording experiment, as they are simply correlational. Nevertheless, the fact that we found that so many different patterns co-vary in a reliable manner as a function of time serves as a bit of a cautionary note for further study. Indeed, due to the relatively small number of trials, and to prevent overfitting in the LDA, we used the smallest number of bins (i.e., 4) that could provide a time-varying pattern of activity, which in turn means we had the lowest resolution for identifying temporal dynamics. Thus, the neural firing patterns that are actually available to the animal could be considerably more complicated than this, and our theories may not be sufficiently advanced to provide incentive to look for such patterns. Indeed, while a number of studies have found or suggested ramp-like activity during timed or delay intervals [22, 25–27, 69, 75–77], one must be prudent in identifying the degree to which other patterns may have been present but unreported and unexplored due to biases resulting from the analytic technique used.

Temporal Memory Averaging

In the above experiment, we occasionally presented the rat with compound probe trials in which both the "short" cue that signaled reinforcement might be available after 10 s and the "long" cue that signaled that reinforcement might be available after 20 s were presented simultaneously, and no reinforcement was provided. We added these compound probe trials in order to verify that the differential firing patterns seen across trials were not simply the result of different sensory stimuli being concurrently present. Indeed, we found that approximately half the neurons (35/75) that fired with a different pattern during the "In" state on short versus long trials, also had reliably different patterns on the compound trials as compared to both of the component, single cue, trials. In other words, similar to the differences in firing seen across time within a trial, these neurons had reliably different patterns across trial types that were not related to the presence or absence of a sensory stimulus. As such, these data further support the notion that premotor neurons are sensitive to the amount of time that has elapsed in the trial.

When we designed this task, we anticipated that the rats would adopt a "cover the bases" response strategy on these compound trials, initiating responding as though reinforcement might be earned after the short duration elapsed, and continuing to respond until the long duration elapsed. Unexpectedly, we found that the rats' behavior on these compound trials peaked at a time in between the peak times of the component trials, and furthermore, that the peak function was scalar. Given the remarkable nature of this finding, and out of concern that the electrode implant surgery or recording cables might have somehow contributed to the effect, we reran the experiment in naïve rats that were not implanted with electrodes [78]. As shown in Fig. 11, we again found scalar responding at a time (16 s) in between the component peak times of 10 s and 20 s. Importantly, the fact that responding was scalar is not consistent with a scenario in which the rats respond to both of the cues in an independent manner. Rather, we interpreted these data as indicating that the presentation of each component cue led to the retrieval of the appropriate temporal memory, and due to the presumed discrepancy in when reward is judged to be available, the subjects averaged or integrated these temporal memories and timed this average expectation in an otherwise normal manner.

Subsequent studies [79, 80] have demonstrated that this temporal memory averaging occurs across a range of component durations and duration ratios, indicating that this is not a one-shot phenomenon related to a specific set of durations. Intriguingly, this scalar averaging is only seen when the reinforcement densities of the component cues are approximately equal (i.e., when an increased probability of reinforcement for the long duration offsets the diminished subjective value associated with the longer delay [81]). Furthermore, across five different studies, the time of peak responding on compound trials could be accurately predicted by an average of the component peak times, but only when each time was weighted by its relative probability of reinforcement. Together, these data suggest a tight link between value and time, and suggest that future recording studies will profit from examining these factors simultaneously (see [44]).

While my lab is actively investigating the boundary conditions and moderating factors associated with temporal memory averaging, the phenomenon itself provides important constraints on the possible mechanisms underlying interval timing. Specifically, it is very difficult to explain temporal memory averaging in the context of a network-state based timing model, such as the instantiation of SBF described above [46]. This difficulty results from the fact that different times in these models are associated with different states of the network (i.e., patterns of neural activity), but these states do not evolve in a monotonic manner as a function of time (i.e., there is nothing "bigger" about a complex ensemble firing pattern associated with 20 s as compared to 10 s). As such, the network states that correspond to times in between the component durations are not in any obvious manner "in

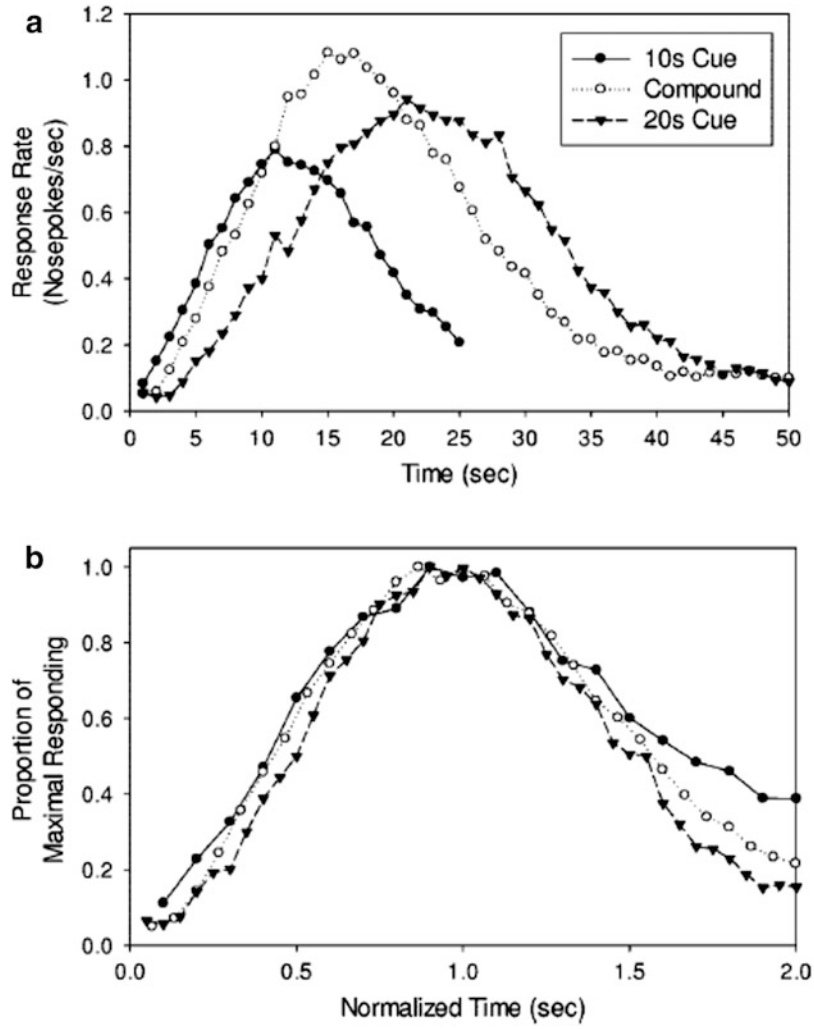

Fig. 11 Normal, peak-shaped, scalar responding at a time in between the trained criterion times when tested with the stimulus compound. Rats were trained that one modal stimulus (e.g., a tone) predicted probabilistic food availability (25 % of tone trials) at 10 s, whereas a different modal stimulus (e.g., a light) predicted probabilistic food availability (50 % of light trials) at 20 s. The different probabilities of reinforcement led to equivalent peak rates on the component stimuli probe trials as shown (*top*). Presentation of the stimulus compound (tone + light) led to responding that peaked in between the criterion times. These compound trials were never reinforced. The *bottom panel* shows the superimposition of component and compound responding after normalizing the response functions by the obtained peak times, thereby indicating that the compound response was scalar. Such a result strongly suggests normal timing processes operating on an average temporal expectation. This figure from Swanton, D.N., Gooch, C.M, & Matell, M.S. Averaging of temporal memories by rats. Journal of Experimental Psychology: Animal Behavior Processes, 35(3), 434-439, 2009, APA, with permission

between" the network states associated with the component durations themselves. In contrast, monotonic clock models, such as Scalar Expectancy Theory [39], the Multiple Timescales model [82], or the Drift-Diffusion timing model [75], have neural activity patterns that grow or decay in a monotonic manner, and an average of component memories, whether they are instantiated as thresholds or clock speeds, would result in maximal responding at a time that falls in between the component peak times. Of course, the ability of these monotonic models

to deal with the finer complexities of this phenomenon, such as the weighted averaging and modality-associated asymmetries remains to be seen. Dealing with such issues may require refinement of these models.

The phenomenon of temporal memory averaging may also be helpful in clarifying the functions of neurons that are found to co-vary with time in electrophysiological recording studies. Presumably, the first explanation considered by neuroscientists finding neurons with temporally-informative activity patterns, is that these neurons are used as the basis for temporal perception. However, during a perusal of the numerous posters reporting on electrophysiological investigations on interval timing at the 2012 Society for Neuroscience Annual Meeting, a colleague remarked to me that he wondered whether there were any areas that didn't show co-variation of neural activity with time. While some of us believe that "Timing is everything," it is somewhat hard to imagine that every area of the brain is contributing in a direct manner to the temporal control of behavior. Instead, these neurons are likely involved in other facets of behavior, but are nevertheless influenced by temporal factors, perhaps via a temporally informative input signal. For example, as described earlier, we showed that neurons in the anterior cingulate cortex had firing rates that co-varied with time [45]. However, current theories of this brain area ascribe its function to one of error detection [83]. Such error related processing might be expected to co-vary in intensity as a function of time between expected and obtained outcomes similar to that seen in the activity of dopamine neurons [57], but such temporally varying error signals need not be the source of the subject's temporal perception. Similarly, Shuler and Bear [84] have demonstrated that primary visual cortex neurons have firing rates that peak at the time that reinforcement is typically provided, thereby providing a temporally informative signal. While this is a fascinating finding given the "low-level" sensory functionality classically ascribed to this cortical area, it remains to be seen whether such activity is generated within this structure, or whether it is provided by another area. Similarly, it remains to be seen whether this activity is responsible for the temporally specific overt behaviors produced by the subject (i.e., licking at the spout at the right time), or whether it instead functions to temporally moderate processing of visual inputs. As such, examining the activity of temporally varying neurons in novel and/or conflicting situations, such as that produced by a stimulus compound, may help us to identify how and where different components of the system (clock, memory, decision, output) are integrated. For example, if one recorded from visual, auditory and motor areas in rats while presenting them with stimulus compounds, one might see activity in sensory-specific areas that represent the component expectations, but activity in motor areas that represent the integrated expectations.

Summary

The work presented here supports the idea that cortical and striatal neurons are modulated by the temporal relationships between external events and may temporally modulate the animal's behavior to deal with these contingencies. The involvement of an array of cortical and sub-cortical areas in timing and time perception has also been demonstrated recently by other investigators using electrophysiological techniques in behaving animals (see the preceding chapters, as well as [24, 28–30, 85–87]). While this body of work shows that a number of structures have firing patterns that provide an index of elapsed time, whether a "pure" temporal signals exist anywhere in the brain remains to be seen, and will require the adoption of experimental designs that go beyond simply searching for neurons that co-vary with time in stationary subjects. We have also shown that a variety of temporally informative firing patterns are simultaneously present, and that this variation in patterns may facilitate temporal expectations. As such, I believe that we need to be open to the possibility that complex neural activity patterns may contribute to temporal expectations. Indeed, recent work has demonstrated temporal

information encoded in complex network states [88, 89], as well in the temporally specific activity of tuned "time cells" in the hippocampus [90] and premotor cortex [91]. Nevertheless, as we have found that the cued retrieval of multiple discrepant temporal memories can lead to temporal memory integration, monotonic coding of time such as that obtained with ramp and decay patterns, seems likely to be a critical component [22, 75]. With all of these outstanding questions, I think it is clear that this is an exciting time to be studying timing.

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Part IV

Functional Imaging and Interval Timing

Getting the Timing Right: Experimental Protocols for Investigating Time with Functional Neuroimaging and Psychopharmacology

Jennifer T. Coull

Abstract

Functional Magnetic Resonance Imaging (fMRI) is an effective tool for identifying brain areas and networks implicated in human timing. But fMRI is not just a phrenological tool: by careful design, fMRI can be used to disentangle discrete components of a timing task and control for the underlying cognitive processes (e.g. sustained attention and WM updating) that are critical for estimating stimulus duration in the range of hundreds of milliseconds to seconds. Moreover, the use of parametric designs and correlational analyses allows us to better understand not just where, but also how, the brain processes temporal information. In addition, by combining fMRI with psychopharmacological manipulation, we can begin to uncover the complex relationship between cognition, neurochemistry and anatomy in the healthy human brain. This chapter provides an overview of some of the key findings in the functional imaging literature of both duration estimation and temporal prediction, and outlines techniques that can be used to allow timing-related activations to be interpreted more unambiguously. In our own studies, we have found that estimating event duration, whether that estimate is provided by a motor response or a perceptual discrimination, typically recruits basal ganglia, SMA and right inferior frontal cortex, and can be modulated by dopaminergic activity in these areas. By contrast, orienting attention to predictable moments in time in order to optimize behaviour, whether that is to speed motor responding or improve perceptual accuracy, recruits left inferior parietal cortex.

Keywords

fMRI • Functional neuroimaging • Motor timing • Perceptual timing • Temporal prediction • Temporal orienting • Temporal preparation • Temporal expectation • Dopamine

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Timing is integral to a great number of cognitive processes, such as language, sensorimotor control or decision-making. Closing one's fingers at just the right moment to catch a ball, for

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example, requires an exquisite sense of time in the range of tens of milliseconds. Deciding whether or not you have time to race safely through the amber traffic light before it turns red requires a sense of time in the range of hundreds of milliseconds to seconds. In these examples timing is automatic and covert. Yet we can also access a more conscious or overt representation of time. For instance, you could probably give a fair estimate of how long it has taken to read the first few sentences of this chapter; and whether this duration is shorter or longer than the time it would take for an amber traffic light to turn red. But despite this 'sense' of time, there is no dedicated neural machinery for perceiving the *duration* of a stimulus in the way that there are dedicated areas of the brain for perceiving other features of a stimulus, such as colour, form, or motion.

This lack of functional localization may be due, in part, to the complexity of estimating duration, which depends upon a number of accessory cognitive processes, such as sustained attention and working memory, in addition to the timing process itself [1–5]. To perceive a stimulus feature like colour or spatial location, external sensory input simply needs be high enough to pass the threshold for conscious perception. To perceive stimulus duration, on the other hand, we not only need external sensory input (to mark the beginning and end of the duration to be timed) but also an *internal*, memorized representation of elapsed time. These phenomenological differences were eloquently articulated more than a hundred years ago by James [6]: "*To 'realize' a quarter of a mile we need only look out of the window and feel its length by an act which… seems immediately performed. To realize an hour, we must count 'now! – now! – now! – now!' – indefinitely…and the exact sum of the bits never makes a very clear impression on our mind*." In a monograph by the French philosopher Guyau [7], published post-humously in the same year, he stated that *"time can only be perceived … as representations rather than immediate sensations*" [8].

Today, these philosophical observations can be investigated in the laboratory. Imagine a coloured circle presented in the centre of a computer screen for 2 s. An estimation of its colour or spatial location can be accomplished within the first couple of hundred milliseconds making the remainder of its presentation time redundant. On the other hand, an estimation of its duration can be accomplished only once the entire two second presentation time has elapsed. Moreover, in contrast to colour or spatial processing, duration estimation requires that the initial moment of stimulus onset be held in working memory (WM), for attention to then be maintained on the stimulus throughout its entire presentation, and for the contents of WM to be continually updated as a function of elapsing time. The difference between the 200 ms or so required to perceive colour or location and the 2,000 ms necessarily required to perceive duration explains each process' differential reliance on sustained attention and WM. That timing (at least in the range of hundreds of milliseconds and beyond) requires attention to be sustained and WM to be updated very likely contributes to the extensive network of regions typically observed in neuroimaging studies of duration estimation (e.g. [9–11]). A crucial challenge for experimental investigations of timing is how to disentangle the attentional and mnemonic processes required for estimating duration from the temporal ones. For timing of stimuli in the hundreds of milliseconds to seconds range, the need to sustain attention and to update WM cannot be eliminated. They can, however, be controlled for.

Controlling Time: Minimizing Sensorimotor and Cognitive Confounds

A well-designed fMRI study in any cognitive domain should control for basic sensorimotor processes of non-interest. Imagine a perceptual timing task in which the duration of two consecutively presented visual stimuli are compared, with a same/different response being registered with a choice button-press. That this task will activate visual cortex (due to the sensory

stimulation) and motor cortex (due to the button-press) is obvious and trivial. Ideally, we would like to remove these activations of non-interest from our map of timing-related brain areas to clarify interpretation. To do so, we need simply include a control task that presents two consecutive stimuli, of the same form, shape and location as those used in the timing task, and which requires the same button-press response. Subtracting the control task activation map from that of the timing task should remove any activity related to low-level visual and motor processing. Ideally, if the study is event-related, the contribution of motor execution processes can be further minimised by incorporating a variable temporal jitter between the stimulus to be estimated and the moment of the motor response, and then synchronising the event-related haemodynamic fMRI response to the moment of stimulus presentation. By temporally dissociating the stimulus and response stages of the task in this manner, activations induced by the later motor response can be distinguished from the stimulus-evoked signal.

However, while these procedures may control for basic sensorimotor aspects of the timing task, they do not address its higher *cognitive* demand. The perceptual timing task described above requires the first stimulus to be held in WM, compared on-line to the second stimulus, and for a decision to be made and translated into a motor response. So we need to complexity our control task to match the cognitive demands of this temporal discrimination task. For instance, we may ask participants to compare some other feature of the two stimuli, making a same/different decision on this feature (e.g. colour discrimination) rather than its temporal features. In this way, we can minimize activations induced by general higher-level cognitive processes, such as WM maintenance, on-line comparison and decision-making, as well as the low-level sensorimotor aspects of the task.

Some of the early neuroimaging studies of timing failed to control for accessory cognitive processes, comparing timing tasks to basic sensory stimulation [12], simple button-pressing [13] or rest [14]. Generally, these studies identified an extremely widespread timing-related network of activation, which, given the low-level nature of the control task to which the timing task was compared, it was impossible to unambiguously attribute to temporal processing: instead activations may have reflected the attentional, mnemonic or decisional processes necessary that were for the timing task, but not the control. Fortunately, most investigators have now adopted a more rigorous approach. For example, perceptual timing tasks are routinely compared to cognitively challenging control tasks, such as pitch discrimination in the auditory domain (e.g. [15–18]), or to colour (e.g. [15, 19–23]), intensity [24] or length [25] discrimination in the visual domain.

Many of the earliest neuroimaging studies of timing investigated motor, rather than perceptual, timing (e.g. [14, 26, 27]). Typically, these studies employed finger tapping tasks, in which participants first tapped along to a sensory pacing rhythm (synchronisation phase) then continued to tap at the same rate once the pacing rhythm had been removed (continuation phase). To isolate activity related to internally generated timing whilst controlling for accessory cognitive processes, brain activity recorded during the synchronization phase can be subtracted from that recorded during the continuation phase (e.g. [28, 29]) or to activity induced by syncopated, rather than synchronized, tapping [30–32]. More recent motor timing studies have often used temporal reproduction tasks in which participants produce a single, discrete motor response after a timed interval, and compare timing-related brain activity to that induced by control reaction–time tasks [33–35], force reproduction tasks [36, 37] or self-paced, randomly timed button presses [38]. A recent meta-analysis by Wiener et al. [11] has shown that the areas most consistently activated by motor timing (both synchronisation and reproduction paradigms) are bilateral SMA, bilateral prefrontal cortices, left insula and right inferior parietal cortex whereas perceptual timing (mostly temporal discrimination paradigms) consistently activates bilateral SMA, right prefrontal cortex and insula, and left putamen, This meta-analysis further pinpointed SMA and right

inferior frontal cortex as being the only two regions common to both perceptual and motor timing, as well as to timing in both the subsecond and suprasecond range.

Motor Preparation

Although these studies highlight a key role for SMA in timing processes, SMA has more traditionally been implicated in motor preparation (e.g. [39, 40]). Yet motor preparation itself includes temporal, as well as motor, components: when preparing a motor response, the specific motor effector with which the response will be given is selected (motor component), then prepared in advance and maintained (temporal component) until response execution. Unfortunately, the temporal component of motor preparation has sometimes been inadvertently confounded with duration estimation in neuroimaging studies of timing. For example, if reproduction of long intervals are compared directly to that of short intervals (e.g. [27, 33, 41]) the longer intervals not only make greater demands on timing but also afford greater opportunity for motor preparation: the longer the participant waits to make their response the longer they have to prepare it. Indeed, behavioural data showing faster [41] and more accurate [33] responses for long, versus short, intervals confirmed the greater degree of motor preparation in long intervals trials. Activation of SMA in these studies may have therefore reflected increased motor preparation, rather than (or as well as) increased temporal processing.

One straightforward way of minimising motor preparation confounds is to use a non-timing control task that is matched not only for the motor effector with which the response will be given (motor component of motor preparation) but also for the length of the preparatory interval (temporal component of motor preparation). In addition, it is generally easier to control for motor preparation in perceptual timing tasks than motor ones, although motor preparation confounds may still intervene. Consider again the temporal discrimination task in which the duration of a stimulus must be judged as being the same or different to that of a previous stimulus, with the decision being registered with an index or middle finger button-press. As soon as the temporal decision has been made (e.g. different), the appropriate motor response (e.g. middle finger) can be prepared. If the decision can be made before the stimulus presentation time has completely elapsed, then activity recorded during this period will confound motor preparation processes with timing ones. To avoid this, Coull et al. [20] varied the motor effector (index/middle/ring finger) associated with a particular temporal decision (shorter/equal/longer) on a trial-by-trial basis (Fig. 1a). The stimulus–response contingencies were not known until the response screen was presented at the end of each trial. In this way, even though participants could make their decision on a *temporal* level (e.g. shorter) during presentation of the stimulus, they could not begin to prepare the appropriate response effector at the *motor* level (e.g. index finger) until the response screen appeared. Processes of timing and motor preparation were thereby unconfounded.

Sustained Attention and WM Updating

These measures help control for the sensorimotor and cognitive demands of the timing *task*, whether it's motor temporal reproduction or perceptual temporal discrimination. However, these measures are not sufficient for controlling for the cognitive demands of the stimulus itself. As outlined earlier, estimating the duration of a stimulus depends upon processes of sustained attention and WM updating, processes that are not required when estimating, for example, its colour or location. Sustained attention and WM updating are dynamic, constantly evolving cognitive processes. One solution to the problem therefore is for the control task to make similarly dynamic demands. Lewis and Miall [25] pioneered just such an approach, developing a stimulus whose length fluctuated constantly throughout stimulus presentation. Their timing task required participants to estimate the duration for which this stimulus was presented, whereas

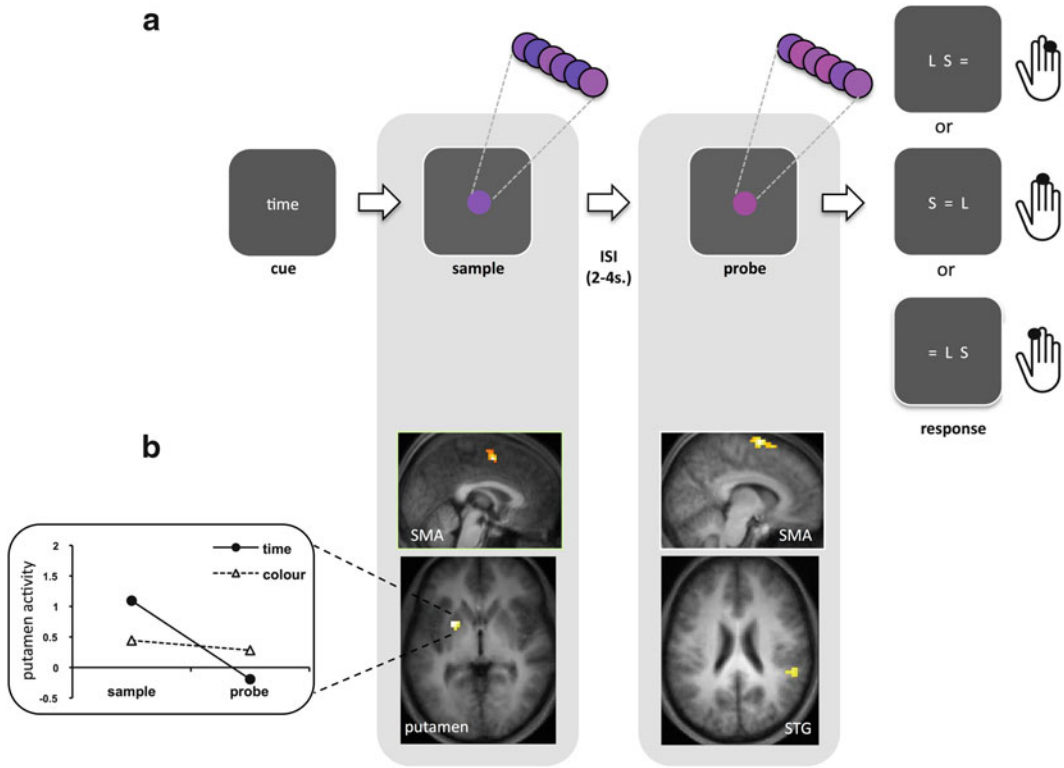

Fig. 1 (**a**) A cue (the word "time" or "colour") instructed participants to estimate either the duration or colour of two forthcoming consecutive stimuli. The first (sample) and second (probe) stimuli were presented for one of three durations (540, 1,080, 1,620 ms) and had an overall percept of one of three shades of purple (maroon, violet, or indigo). According to the cue instruction, participants estimated whether the probe was shorter (S), longer (L), or the same (=) duration as the sample (time condition) or redder (R), bluer (B), or the same (=) shade of purple as the sample (colour condition). The stimuli to be estimated were not a uniform color. Instead, five different shades of purple were presented rapidly (90 ms) and in pseudo-random order to give an overall percept of either maroon, purple, or indigo (see *insets* at top of figure). In the colour task, the subject estimated the average shade of purple by amalgamating all shades presented during the flickering percept. At the onset of the response signal, participants indicated their duration or color estimate with a three-choice button press. To minimize the possibility for motor preparation, stimulus–response contingencies varied on a trial-by-trial basis. One of three possible response screens (see right-hand side of figure) could be presented on any given trial. The left, middle, and right-sided spatial locations of the response choices (S/=/L for the time task; R/=/B for the colour task) on the computer screen mapped respectively onto a button located under the index, middle, or ring finger of the right hand. If the character corresponding to the subject's estimate appeared in e.g. the leftmost position on the screen the subject pressed on the leftmost button (i.e. with the index finger). By way of illustration, the black circles on each of the hand symbols indicate which button would have to be pressed for each of the response screens if the subject's estimate were "equal to" (represented by the symbol "="). This figure shows a trial from the time condition. The colour condition was identical apart from the substitution of the word "colour" at the cue stage, and the characters R/=/B at the response stage. (**b**) In comparison to the colour control condition, the time condition activated Supplementary Motor Area (SMA) at both sample and probe stages of the task. By contrast, the time condition activated putamen selectively at the sample stage but not at the probe, whereas right superior temporal gyrus (STG) was activated by the time condition selectively at the probe stage, not at the sample. The accompanying plot shows the mean level of putamen activity during the time and colour conditions, separately for the sample and probe stages of the task

the control task required participants to estimate its average length. In both conditions therefore, participants had to maintain attention throughout stimulus presentation and constantly update their representation of stimulus duration or length, in order to accurately perform either the timing or control tasks. Unfortunately, despite Lewis and Miall's clever use of dynamic stimuli, the timing

task was significantly more difficult than the control task, compromising clear interpretation of their results. Inspired by their ingenious solution to the problem of sustained attention and WM updating, we devised our own control stimuli, though we chose to manipulate stimulus colour, rather than length, in order to avoid illusions of movement that may have inadvertently provided temporal cues [19, 20].

We developed temporal and colour discrimination tasks, in which participants saw two consecutively presented stimuli and had to compare either their duration (timing task) or colour (control task). However, the stimuli were not of a uniform colour but instead changed shade rapidly (every 90 ms) and constantly throughout stimulus presentation (coloured insets Fig. 1a). Participants estimated the *average* colour of the stimulus by amalgamating all shades presented during the flickering percept. Therefore, for colour, as well as timing, tasks, participants had to maintain attention for the entire stimulus presentation time, integrating in WM information presented throughout this period. Importantly, there were no significant differences in accuracy of temporal and colour discrimination, suggesting these tasks were well-matched for difficulty [19, 20]. Areas activated by the timing task were compared to those activated by the colour task, revealing timing-specific activations in SMA, right prefrontal and temporal cortices, and basal ganglia [19, 20]. Given the deliberate matching of sustained attention, WM updating and task difficulty across tasks, these activations were unlikely to reflect differential recruitment of attentional or mnemonic processes, allowing us to conclude more confidently that they reflected more temporal components of stimulus processing. Investigators from several different research groups have since adopted similarly dynamic colour control stimuli [21–23].

Task Difficulty

As mentioned briefly above, an important parameter to be controlled for in any well-designed fMRI study of timing (indeed, in fMRI studies of almost any sort of cognitive processing) is task difficulty. If the timing task is more difficult than the control task it will place greater demands on attentional or effortful processing, which could contribute to timing-related activations in attention-related areas such as parietal and frontal cortices. To minimize this potential confound, it is crucial to demonstrate that the levels of performance of timing and control tasks are matched (e.g. [16–18]). Using a control task that necessitates similar levels of sustained attention and WM updating as the timing task is one way of matching difficulty across tasks [19, 20, 22]. Unfortunately, this approach is not always successful: despite Lewis and Miall's [25] pioneering use of dynamic stimuli, coupled with a sophisticated psychometric staircase procedure designed to maintain task difficulty at constant levels for both timing and control tasks, performance in their timing task was significantly worse than that for their control task. An alternative experimental approach is to deliberately manipulate task difficulty, rather than trying to match it. Tregallas et al. [42] compared easy and difficult versions of an auditory timing task, while Livesey et al. [21] took this a step further, by comparing patterns of timing-induced activity when the control task was either easier or more difficult than the timing task. They reasoned that areas differentially activated by whichever task was more difficult, whether that was the timing or the control task, were not specifically concerned with timing, whereas areas activated by the timing task, whether it was relatively easier or more difficult, reflected true timing-induced activations. Interestingly, although these two groups adopted similar approaches, the results of the two studies were quite different. Using visual stimuli in the range of 1,000–1,500 ms (similar to the dynamic colour stimuli used by ourselves), Livesey et al. [21] observed timing-selective activation of putamen, inferior frontal gyrus and a small region of left inferior parietal cortex. Conversely, Tregallas et al. [42] observed timing-selective activation of cerebellum and superior temporal gyrus with their auditory stimuli in the range of 200 ms. The anatomical differences between these two studies

most likely reflect differential activation of a stimulus-specific "automatic" timing system [9] by the brief 200 ms stimuli in the Tregallas et al. [42] study, and of a "cognitive" timing system by the seconds-range stimuli used in the Livesey et al. [21] study. The brief auditory stimuli in the Tregallas et al. study [42] were most likely processed by modality-specific systems in temporal cortex, as well as cerebellum, which has previously been associated with timing of short millisecond, rather than longer seconds-range, stimulus durations [43].

Parametric Experimental Designs

It should, by now, be clear that many parameters must be controlled for when investigating timing with fMRI. Most obviously, these include basic components of task performance, such as sensorimotor processing, selective attention, maintenance in long-term or working memory, decision-making and task difficulty. However, processes related to the dynamic nature of time itself must also be considered: motor preparation, sustained attention and WM updating. The choice of an appropriate control task is therefore critical for the success of the timing experiment. One way of circumventing the search for the perfect control task however, is instead to parametrically vary a specifically temporal component of the task. For example, by identifying areas of the brain whose activity increases as a function of increasing stimulus duration (e.g. [44]). Parametric designs are particularly powerful in isolating cognitive processes of interest as they test for systematic relationships between cognitive and neural activity: incremental changes in the cognitive process of interest (e.g. stimulus duration) are associated with corresponding changes in brain areas responsible for implementing that cognitive change. However, as mentioned earlier, long stimulus durations are confounded with high levels of motor preparation, as well as greater sustained attention and WM demands. Therefore, to minimize the influence of these dynamic cognitive confounds, the experimental paradigm should incorporate a control task whose stimuli are processed for the same parametrically varying lengths of time (e.g. [22, 23]).

We sidestepped this potential problem in one of our own experiments by parametrically modulating the amount of attention paid to stimulus duration, rather than the length of the duration itself [19]. This approach was inspired by one of the earliest, and most robust, findings in the functional neuroimaging literature: attending to a perceptual stimulus feature, such as shape, colour, speed [45] or spatial location [46], increases neural activity in sensory brain regions specialised for processing that feature, even though the comparison stimuli are perceptually identical. By analogy, we hypothesised that attending to stimulus duration would increase neural activity in brain regions specialized for processing time. We manipulated attention to duration by parametrically varying the degree of attentional selectivity to temporal or colour stimulus features (Fig. 2a). Attention-sharing instructions indicated how attention should be allocated within a particular trial: selectively to stimulus duration, more to duration than colour, to duration and colour equally, to colour more than duration, or selectively to colour. Appropriate attentional allocation was encouraged by varying the relative likelihood that the trial would require a temporal or colour discrimination (Fig. 2a). For example, half of the "attend duration and colour equally" trials required a temporal discrimination and the other half required a colour discrimination, but the participant didn't know until the trial-end which would be required, meaning both parameters had to be attended equally. By contrast, every single one of the "attend duration only" trials required a temporal discrimination, meaning the participant could ignore colour and focus exclusively on duration. In "attend duration more than colour", most of the trials required a temporal discrimination with only a few requiring a colour discrimination, meaning that participants should pay attention mostly to duration but should "keep an eye" on colour.

Behavioural and neural data confirmed that attention was allocated appropriately across the

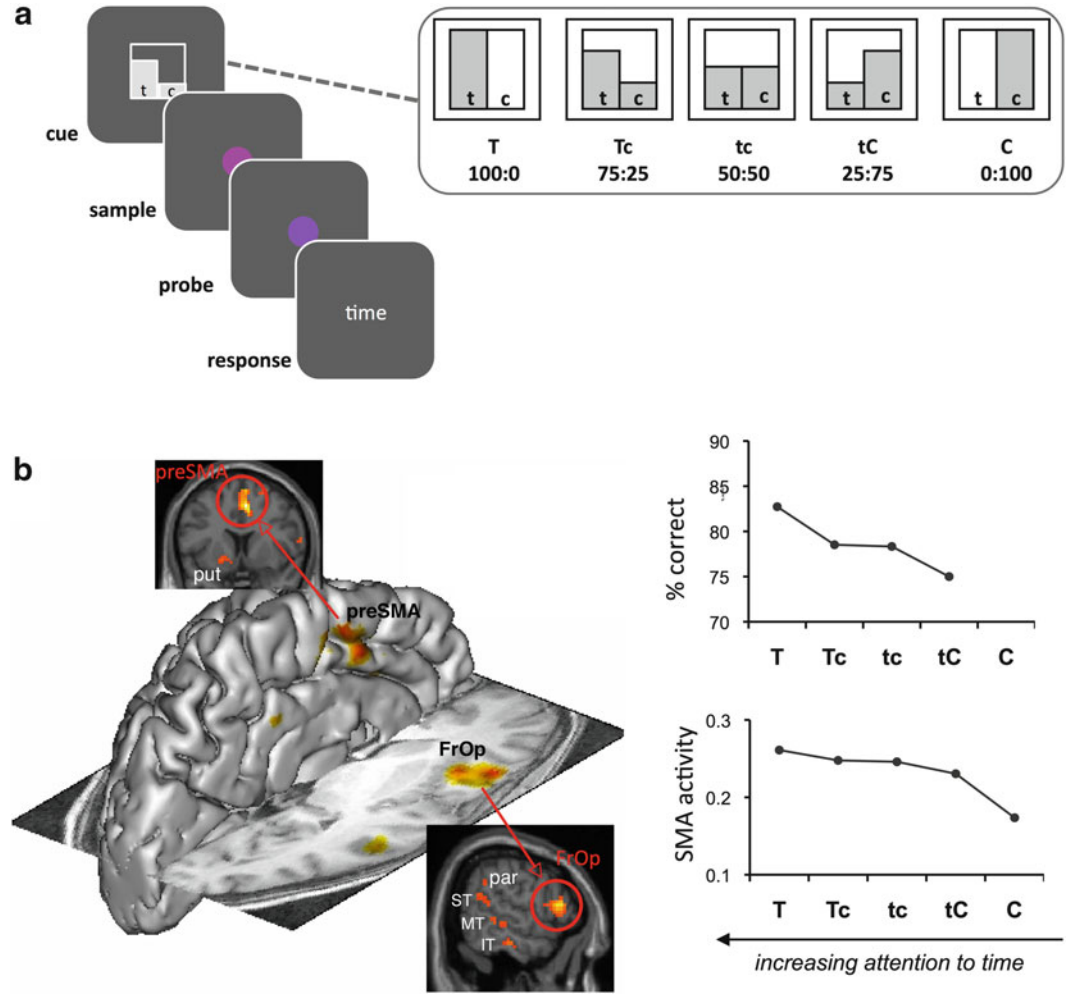

Fig. 2 (**a**) One of five attentional cues (see *inset* on the right) instructed participants to attend either selectively to stimulus time (T), to time more than color (Tc), to both parameters equally (tc), to color more than time (tC), or selectively to color (C). As a function of the cue, participants then estimated whether the duration of the probe was shorter, equal to, or longer than the sample (time condition) *and/or* whether the probe was redder, equal to, or bluer than the sample (colour condition). So, for instance, if the trial began with the 'T' cue participants had to estimate duration only, whereas if it began with the 'tc' cue they had to estimate duration and colour equally. Participants then gave a discriminatory response according to the instruction presented on the response screen, either "time" or "colour", giving a single estimate of duration *or* of colour even though they may have been instructed to estimate both. Each attentional cue condition comprised a specific ratio of temporal:colour discrimination trials (see *inset*). All trials in the T condition required a temporal discrimination (a ratio of 100:0 temporal:colour discrimination trials) whereas all trials in the C condition required a colour discrimination (a ratio of 0:100); half of the trials in the tc condition required a temporal discrimination while the other half required a colour discrimination (50:50); most (75 %) of the trials in the Tc condition required a temporal discrimination but only a few (25 %) required a colour discrimination (75:25); and most of the trials in the tC condition required a colour discrimination with only a few requiring a temporal discrimination (25:75). In this way, knowing that a temporal discrimination would be required on every single T trial should encourage participants to focus on duration and ignore colour. On the other hand, knowing there was 50:50 chance that the response required in tc trials would be either a temporal or a colour discrimination should encourage participants to divide attention equally between duration and colour characteristics. Varying the response ratios in this way encouraged attention to be allocated parametrically to either duration and/or colour across the five cue conditions. (**b**) As participants paid progressively more attention to stimulus duration across the five cue conditions, brain activity increased most notably in preSMA and right inferior frontal cortex, around the frontal operculum (FrOp). The *upper plot*

five attentional conditions: the more participants were instructed to attend to colour, the more colour discrimination gradually improved and the more activity in visual area V4, the colour processing area of occipital cortex, monotonically increased [19]. We reasoned that if parametric modulation of attention to colour modulated activity in the brain area fundamental for colour perception, then parametric modulation of attention to duration should modulate activity in brain areas fundamental for time perception. We found that the more participants were instructed to attend to duration, the more temporal discrimination gradually improved and the more activity increased primarily in preSMA and right inferior frontal cortex (Fig. 2b). Interestingly, these were precisely the two regions later identified by Wiener et al.'s [11] meta-analysis as being critical for timing.

Deconstructing Time: Distinguishing Temporal Task Components

In a version of the temporal discrimination task commonly used in fMRI studies of timing, the participant times the duration of a first (standard or sample) stimulus, storing it in memory for later retrieval. They then time the duration of a second (comparison or probe) stimulus, comparing it in WM to that of the first. With careful use of event timing and randomization, the temporal resolution of event-related fMRI allows activity associated with these two discrete stimuli to be dissociated. This, in turn, allows identification of brain areas that respond more to initial storage of temporal information (sample) than its subsequent retrieval and comparison (probe). Rao et al. [16] were the first to dissociate the initial storage component of temporal discrimination from the later comparison stage using event-related fMRI. As compared to a performance-matched cognitive control task, early timing processes were linked to activation of the basal ganglia (right caudate and putamen), whereas later processes recruited right prefrontal cortex (PFC). However, the designation of "early" and "late" processing stages lacked temporal precision, making it difficult to conclude whether brain activations represented stimulus-evoked activity related to the presentation of the first (encoding and storage) or second (retrieval and comparison) stimulus, or some mixture of the two.

We circumvented these problems by precisely time-locking the fMRI signal to presentation of the sample and probe stimuli independently [20], to achieve a more direct measure of brain activity at each stage of the task. We used the same coloured stimulus pairs as described previously, except that the sample and probe stimuli were now separated by a longer and variable inter-stimulus interval (Fig. 1a), allowing their stimulus-evoked activity to be distinguished. As before, we compared activations evoked by the timing task to those evoked by the colour task, but this was conducted separately at the sample and probe stages of the task. Notably, Harrington et al. [18] and Wencil et al. [44] later used the same approach (time-locking the fMRI signal to events separated by a variable jitter) to dissociate events in perceptual timing paradigms (auditory or visual temporal discrimination respectively), as did Wittman et al. [35] and Bueti and Macaluso [23] for motor timing (temporal reproduction). We hypothesised that timing of stimulus duration is necessary for both sample and probe stimuli, that the encoding and storage of stimulus duration into WM would occur during presentation of the sample stimulus only, whereas retrieval and comparison of stimulus duration would occur during presentation of the probe only. Whole-brain analyses revealed that putamen was selectively activated by the sample, but not probe, stimulus while right superior temporal gyrus was activated by the probe, but not

Fig. 2 (continued) demonstrates that participants were allocating attention as required: as they paid more attention to stimulus duration, their temporal discriminations were increasingly accurate. The *lower plot* shows how activity in the SMA cluster increases progressively as a function of increasing attention to duration

sample, stimulus (Fig. 1b). SMA was the only region to be equally engaged by temporal processing of *both* sample and probe (Fig. 1b). Since the only process common to these two stimuli is the timing of elapsing duration, we suggested SMA plays a fundamental role in the perceptual timing of a duration that is currently unfolding in time [20]. Collectively, these results indicated a role for SMA in timing stimulus duration, for putamen in storing duration for later recollection, and for superior temporal gyrus in retrieving and comparing stored representations of duration.

Notably, the finding that timing-induced basal ganglia activity was restricted to the initial encoding and storage of stimulus duration confirms the earlier results of Rao et al. [16], who compared temporal to pitch discrimination of auditory intervals. It was also, in turn, confirmed by a later study from the same group using the same auditory task [18] and also by Wencil et al. [44] using temporal discrimination of visual durations. Similarly, Bueti and Macaluso [23] found basal ganglia activity during the encoding, but not reproduction, phase of a motor timing task, as did Wittmann et al. [35], although this was true only for the shortest (3 s) durations, not the longer (9 and 18 s) ones. Although timing-specific putamen activation during both initial storage *and* later comparison stages of the task has been reported [16, 18], this was observed only when the temporal discrimination task was compared to a low-level sensorimotor control task that did not control for the attentional, mnemonic and executive processes necessary for stimulus comparison and decision-making. In conclusion, whether the stimuli whose duration to be estimated are auditory empty intervals [16, 18, 35] or visual filled durations [20, 23, 44], or whether the temporal decision is measured with a perceptual discrimination [16, 18, 20, 44] or a timed motor response [23, 35], the fMRI results are broadly consistent, demonstrating that timing-related basal ganglia activation is restricted to the initial encoding and storage phase of the task. Collectively, these data cast doubt on Matell and Meck's [47, 48] model of interval timing, in which basal ganglia are proposed to perform the comparison function ("coincidence detection") that would, presumably, be taking place at the probe stage of the task.

Differential activation of putamen during storage versus comparison phases of the timing task may also go some way to explaining the inconsistent nature of timing-induced basal ganglia activation reported in the fMRI literature. Figure 1b illustrates the pattern of activity in putamen during our temporal and colour discrimination tasks [20]. It shows that the putamen was preferentially activated by the timing versus colour task during presentation of the initial sample, but was *less* activated by the timing than the colour task during presentation of the subsequent probe. When data were averaged across both stages of the task, timing-specific putamen activity was effectively cancelled out. If we had not utilized the temporal resolution of event-related fMRI to separate out the individual trial components, we would have deduced that basal ganglia were not involved in the timing task.

The functional selectivity of the putamen for storing stimulus duration into WM was further corroborated by correlational analyses showing significant links between brain activity and behaviour. Specifically, the more putamen was activated by the initial sample stimulus of the timing task, the more accurately participants eventually performed the task [20]. Conversely, there was no significant correlation between timing performance and the putamen activity recorded during the subsequent probe. Nor was there any correlation between activity in the putamen and performance on the colour discrimination task, further demonstrating the temporal selectivity of the putamen activation. The link between increased timing performance and neural activity at the storage phase of the task may reflect enhanced encoding of the sample stimulus into WM (mediated by the putamen), which results in a more accurate representation of stimulus duration. Our results confirmed those of Harrington et al. [49], who had already reported a significant correlation between a performance measure of temporal sensitivity in auditory

perceptual timing, the co-efficient of variation, with activity in basal ganglia (caudate) during initial encoding of stimulus duration. More recently, Bueti and Macaluso [23] found that performance measures of the subjective perception of time (degree of overestimation) correlated significantly with putamen activity during the encoding phase of their motor timing task.

Generally, these results illustrate the utility of correlational analyses in interpreting fMRI data. First, this approach helps tease apart which aspects of performance (e.g. accuracy, variability, clock-speed) correlate with activity in which brain regions and during which phase of the task (e.g. storage/retrieval). Second, showing that activation of a particular area varies as a function of performance provides a more convincing demonstration that the activation observed is truly reflective of the cognitive process of interest, rather than an incidental, co-occurring process that has not been adequately controlled for. The cognitive selectivity of the effect can be further confirmed if it is shown that no such correlation exists between activity in the region of interest and performance on a suitable *control* task.

Altering Time: Neurochemically Modulating the Perception of Time

I hope to have highlighted the importance of controlling for incidental cognitive processes, such as sustained attention or WM, when investigating the neuroanatomical substrates of timing with fMRI. This is also good practice when investigating the neuro*chemical* substrates of timing. Ideally, psychopharmacological experiments should aim to demonstrate both psychological and pharmacological specificity of the drug effect. Pharmacological specificity can be achieved by showing that a particular drug affects performance on a task, but that a different drug (or at least a placebo) does not. Psychological specificity can be achieved by showing that a drug affects performance on one kind of task or process, but not on a different kind. A lack of pharmacological or psychological specificity would suggest that observed drug effects derive from more general consequences of drug administration, such as the anxiogenic nature of the experimental protocol or the generally sedative/excitatory properties of the drug. Therefore, to be able to confidently interpret the deleterious effects of a drug on a timing task as a truly temporal effect, it must be demonstrated that the effect is (a) significantly different from the effects of a placebo or comparison drug and (b) independent from any collateral effects of the drug on attentional and mnemonic processes.

Warren Meck and colleagues have contributed enormously to our understanding of the neurochemical bases of timing, consistently showing in rats that dopaminergic (DA) agonists and antagonists have complementary effects on timing: agonists speed up the internal clock while antagonists slow it down (e.g. [50–55]). Similarly, Thomas Rammsayer has conducted a large number of psychopharmacological timing studies in healthy volunteers, demonstrating that while DA drugs impair timing in both the tens of milliseconds and seconds time-range, drugs acting on other neurotransmitter systems have either no effect or impair only seconds-range timing. For example, the D2 receptor antagonist haloperidol impairs accuracy of perceptual timing for durations in either the tens of milliseconds range (50 ms) or the seconds (1,000 ms) range [56–60]. By contrast, the benzodiazepine midazolam [60, 61], the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine [62], or the selective noradrenaline reuptake inhibitor, reboxitine [63] significantly affect timing in the seconds range but have no effect on timing in the tens of milliseconds range. Since timing in the seconds-range requires support from accessory processes, such as WM or sustained attention, processes known to be affected by benzodiazepines [64], noradrenergic drugs [65, 66] and NMDA antagonists [67], Rammsayer [60, 63] concluded that drug effects on seconds-range timing were secondary to their effects on attention and WM. Wittmann et al. [68] drew similar conclusions after observing deleterious effects of the 5-HT2A agonist psilocybin on motor timing of long (4–5 s) but not

short (~2 s) durations. Rammsayer [60, 63] further argued that the fact that haloperidol was the only drug tested to impair timing of in the tens of milliseconds range, which does not depend upon additional processes of sustained attention or WM, suggests a more selective effect on timing *per se*.

Rammsayer's studies tackled the potentially confounding effects of drugs on attentional and mnemonic processes by comparing effects on timing in the seconds versus tens of milliseconds range, which differentially engage sustained attention and WM. However, just because a drug affects timing in the seconds, but not tens of milliseconds, range does not necessarily mean that its effects reflect modulation only of WM or attentional processes. Timing of longer, seconds-range durations depends not only upon sustained attention and WM but also, of course, upon an index of elapsed time itself, for example accumulation of temporal pulses [69, 70] or temporal integration of steadily climbing neuronal activity [71]. Therefore, it's possible that drug-effects in this time-range could reflect impairment of a specifically seconds-range timing mechanism (e.g. accumulation), which is distinct from that used to time durations in the tens of milliseconds range. Mounting evidence suggests that timing in these two different duration ranges are underpinned by distinct mechanisms [9, 72–74]. Thus it is possible that a drug-induced deficit in the seconds but not tens of milliseconds, range could reflect a specifically temporal, rather than just WM or attentional, deficit.

Controlling for Cognitive Confounds

By asking participants to time durations only tens of milliseconds long, Rammsayer was able to discount the attentional and WM contributions to drug-induced timing effects. However, for timing in the longer hundreds of milliseconds to seconds range sustained attention and WM are fundamentally necessary and cannot be disentangled from the process of timing. We therefore approached this problem from a different angle. Since it's impossible to time longer durations without sustained attention and WM, we decided instead to control for them. Specifically, we sought to dissociate drug effects on seconds-range timing from their collateral effects on attentional and/or mnemonic processes by directly comparing effects on performance of timing and control tasks that were matched for attentional and WM demand. Specifically, we used the temporal and colour discrimination tasks [19, 20], described earlier (Fig. 1a). Drug-induced impairment of the timing, but not colour, task would provide evidence for neurochemical modulation of seconds-range timing independent from any mnemonic or attentional effects.

We first examined the effects of the NMDA receptor antagonist ketamine on timing [75]. Ketamine induces perceptual and cognitive changes similar to those found during prodromal stages of schizophrenia [76–78], thus providing a useful pharmacological model of the illness [79]. Numerous studies have shown that patients with schizophrenia have difficulties in timing durations in the hundreds of milliseconds to seconds range [80–85]. Since schizophrenia is often accompanied by WM deficits, and WM is critical for timing, some of these studies controlled for possible effects of the illness on WM by examining performance on digit span, a task that requires patients to repeat a list of numbers forwards and backwards. Digit span was either uncorrelated with timing performance [82, 84] or was correlated only with clock-speed, not temporal sensitivity [86], leading authors to conclude that patients' timing impairments could not be entirely explained by WM deficits. However, the kind of verbal WM required to maintain a list of numbers in WM is quite distinct from the kind of WM required to continually update information as a function of elapsing time. We therefore controlled for WM by using the colour discrimination task described earlier (Fig. 1) that employed exactly the same stimuli as the timing task, the only difference between tasks being whether participants had to attend to the stimulus' temporal or colour characteristics.

As compared to placebo, administration of an acute dose of ketamine to healthy volunteers selectively impaired temporal, but not colour,

discrimination of visual stimuli in the hundreds of milliseconds to seconds time-range [75]. Since both temporal and colour tasks placed similar demands on sustained attention and WM updating, the lack of effect of ketamine on colour discrimination suggests ketamine-induced impairments of timing of seconds-range durations did not simply reflect a side-effect of the drug on attention and WM. Rammsayer et al. [62] had concluded that the deleterious effects of the NMDA receptor antagonist memantine in the seconds duration-range were secondary to its mnemonic effects, yet the results of our ketamine study suggest that they could in fact have reflected effects on a distinct, seconds-range, timing mechanism independent from any incidental effects on sustained attention and WM updating. However, one difference in the WM requirements of the timing and colour tasks was the way in which information was manipulated in WM. For the timing task, information was incrementally accumulated, whereas for the colour task it was averaged. Accumulation implies a unidirectionality, a fundamental feature of the flow of time itself ("time's arrow" [87]). Averaging does not imply this unidirectionality. It is possible therefore, that ketamine influenced timing behaviour more specifically by selectively impairing the ability to increment information in WM in a particular direction or order.

Identifying Anatomical Substrates of Neurochemical Modulation

The patients included in investigations of timing in schizophrenia are generally medicated with neuroleptics. This could seriously confound the timing effects observed. In one study, for example, timing deficits were found in medicated patients whereas non-medicated patients were no different to healthy controls [88]. This suggests that the timing deficits typically observed in schizophrenic patients could, in fact, be a side-effect of their neuroleptic medication. This hypothesis is strengthened by consistent demonstrations of the deleterious effects of neuroleptics on timing in rats [51, 53, 54, 89] and healthy human volunteers [56–60]. We therefore decided to investigate the effects of a DA manipulation on seconds-range timing, using our temporal and colour discrimination paradigm to carefully control for potential effects on attentional and mnemonic processes. Moreover, we conducted the study with fMRI in order to identify the regions of the timing network that were modulated by DA [90].

Functional neuroimaging adds a useful third dimension to psychopharmacology research, allowing the complex relationship between cognition, neurochemistry and anatomy to be explored in the healthy human brain [91]. In particular, it allows the anatomical bases for neurochemical modulation of human cognition to be localised. Ideally, a psychopharmacological fMRI study should control for psychological, as well as pharmacological, mechanisms by including both a control cognitive task and a placebo treatment condition within a factorial design that comprises task (timing vs. control) and treatment (drug vs. placebo) as the factors of interest. By examining differential effects of the drug on the timing task compared to the control, any effects on non-timing factors (e.g. inhibitory effects on the vasculature) are subtracted out since these would be equally present during both the timing and control tasks. The factorial design therefore provides an index of the modulatory effects of drugs on timing-related networks, not their ability to directly excite or inhibit neural tissue. Or, in other words, the drug effect manifests itself as an attenuation or enhancement of activity in brain areas that are preferentially activated by the timing task. By contrast, simply comparing the effects of drug versus placebo on the pattern of activity induced by a timing task, *without* including a control task, would confound physiological effects of non-interest with neuromodulatory effects on timing-related areas.

In our study, we manipulated DA non-pharmaceutically, using Acute Phenylalanine/Tyrosine Depletion (APTD). This is an amino acid drink deficient in the DA precursors phenylalanine and tyrosine and has been shown to reduce striatal DA release [92, 93]. Behaviourally, as compared to a balanced amino-acid drink, APTD

selectively impaired performance of the temporal, but not the colour, discrimination task. APTD effects on timing were therefore unlikely to simply reflect DA modulation of sustained attention and WM processes. Neurally, in order to identify which regions of the timing network were modulated by APTD, we directly compared time-specific activations maps (i.e. areas activated more by temporal than colour discrimination) across the APTD and balanced drink sessions. APTD affected just two of the regions of the time-specific network, attenuating activity in the left putamen of the basal ganglia and SMA [90]. These results demonstrate the anatomical, as well as cognitive, specificity of the APTD effect.

These anatomical data also allowed us to dissect the cognitive effects of APTD even more finely by examining the effects of APTD on neural activity separately at the sample and probe stages of the task (see also Fig. 1). The APTD effects on activity in putamen and SMA occurred selectively at the initial sample stage of the timing task [90]. By contrast, there were no effects of APTD on activity in *any* of the regions associated with the probe stage of the timing task (a distributed network comprising prefrontal and temporal cortices, caudate and cerebellum). Furthermore, the APTD-induced neural changes at the sample stage correlated significantly with its behavioural changes: the more APTD attenuated activity in putamen or SMA, the more it impaired accuracy of temporal discrimination. In other words, APTD's effects on activity at the initial sample stage of the task predicted participant's subsequent timing performance. This suggests that the mechanism by which APTD impairs timing is to reduce activity in those areas of the brain responsible for the initial storage of temporal information into WM. Since putamen and SMA are functionally [94] and anatomically [95] connected components of the nigrostriatal "motor" pathway [96], our fMRI approach provided direct confirmation of Rammsayer's [59] speculation that DA modulates timing via the nigrostriatal, rather than mesocortical, pathway. Moreover, the spatial and temporal resolution of event-related fMRI allowed us to pinpoint not only the neuroanatomical (putamen and SMA) substrates of the APTD modulation of timing, but also its functional ones (initial storage into WM). In addition, the matched control task allowed us to exclude the possibility that results merely reflected modulation of confounding cognitive processes, such as WM or sustained attention.

Yet our results are at odds with prior fMRI studies reporting a predominantly frontal, rather than striatal, pattern of DA modulation during timing [97, 98]. This discrepancy could be explained, however, by the fact that participants in these previous studies were patients with Parkinson's Disease, whose underlying basal ganglia dysfunction may have influenced the pattern of effect. Alternatively (though not mutually exclusively), the discrepancy might be due to the fact that APTD preferentially targets striatal, rather than frontal, activity [99]. Future studies in healthy volunteers using DA agents that preferentially modulate mesocortical, rather than nigrostriatal, pathways may yet reveal modulation of timing-induced activity in prefrontal cortex.

Choosing the Right Time: Temporal Orienting of Attention

In the laboratory, as in the real-world, the term "timing" can be used to refer either to *how long* an event lasts or *when* an event occurs. The online Merriam-Webster English dictionary (www.merriam-webster.com/dictionary/timing) gives two distinct definitions for the word "timing". One is the "observation and recording of the elapsed time of an act, action or process". Here, the critical parameter is *how long* an event lasts. Estimating the duration of an event is the form of timing that has been discussed so far in this chapter. The other definition is "the ability to select the precise moment for doing something for optimum effect (e.g. a boxer with impeccable timing)". Here, the critical parameter is *when* best to act. Selecting a moment in time in order to optimise behaviour is the focus of the final section of this chapter.

The semantic distinction between these two definitions of timing is reminiscent of the distinction between explicit and implicit timing that can be found in the scientific literature [10, 100–104]. Explicit timing tasks have a temporal task goal, which is usually to measure and register the duration of a motor act or sensory stimulus [74, 105]. In other words, an overt estimation of stimulus duration is required. Conversely, implicit timing tasks have a non-temporal, often sensorimotor task goal, that nevertheless makes use of inherent temporal regularities in either movement dynamics [101, 102] or sensory stimuli (e.g. [10, 106, 107]). Temporal regularities may simply emerge as an intrinsic property of ongoing behaviour, e.g. tapping one's foot while waiting. Alternatively, temporal regularities in the environment may be used to enhance information processing for events occurring at predictable moments in time e.g. accelerating away more quickly after a 3-2-1 countdown. Of course, elapsed time must be tracked covertly to enable timely responding, but this temporal percept is never registered in explicitly temporal terms as, for example, a verbal estimate ("2 seconds") or a perceptual discrimination (shorter/longer than a memorised standard). Rather, it is indexed implicitly by the relatively improved speed (or accuracy) of stimulus processing.

The use of the phrase "select the precise moment" in the second of the two dictionary definitions of timing illustrates the attentional nature of this process: "select" implies that only certain aspects of the environment will be attended to and processed. The phrase "doing something for optimum effect" highlights the purpose of selective attention generally, which is to process certain elements of the environment whilst ignoring others so as to optimise behaviour. In this case, attention operates to select precise moments in time but, equally, it may also select particular locations in space or specific features of objects. Yet while the cognitive neuroscience of feature or spatial attention is a vast and well-established field, the cognitive neuroscience of temporal attention is in its infancy. This is despite the fact that the behavioural benefits of temporal preparation have now been known for almost a century [108].

Temporal Orienting of Attention

The neuroscientific investigation of spatial attention is frequently conducted with variants of the spatial orienting of attention task, first devised by Posner et al. [109]. In the classic version of this task, pre-cues provide information regarding the likely location of an upcoming target. Attentional resources can then be directed ("oriented") to that location, enabling faster detection of targets appearing there. Valid cues accurately predict where the target will appear, whereas invalid cues incorrectly predict the target's location. Neutral cues provide no spatially predictive information. Typically, RTs are faster for targets appearing in validly cued, rather than invalidly or neutrally cued, locations due to a process of spatial attentional orienting. My colleague Kia Nobre and I hypothesised that target detection would also be faster for stimuli appearing at validly cued temporal intervals, due to a putative process of temporal attentional orienting [110]. We therefore devised a temporal analogue of the Posner task, in which visual cues provided valid, invalid or neutral information concerning the likely interval before an imminent target was presented. Speed of target detection was measured in a paradigm in which pre-cues provided either spatial or temporal information independently, both spatial and temporal information together, or neither spatial nor temporal information (Fig. 3a). Sensorimotor demands were matched across conditions, with the only difference being whether attention was oriented within the spatial and/or temporal domain.

As predicted, target detection was faster following valid, rather than neutral or invalid, cues in the temporal, as well as the spatial, domain [10]. This result demonstrates that it is behaviourally advantageous not only to know where a target is likely to appear but also *when* it is likely to appear. The benefits of spatial attentional orienting had already been well documented, but this was the first time such

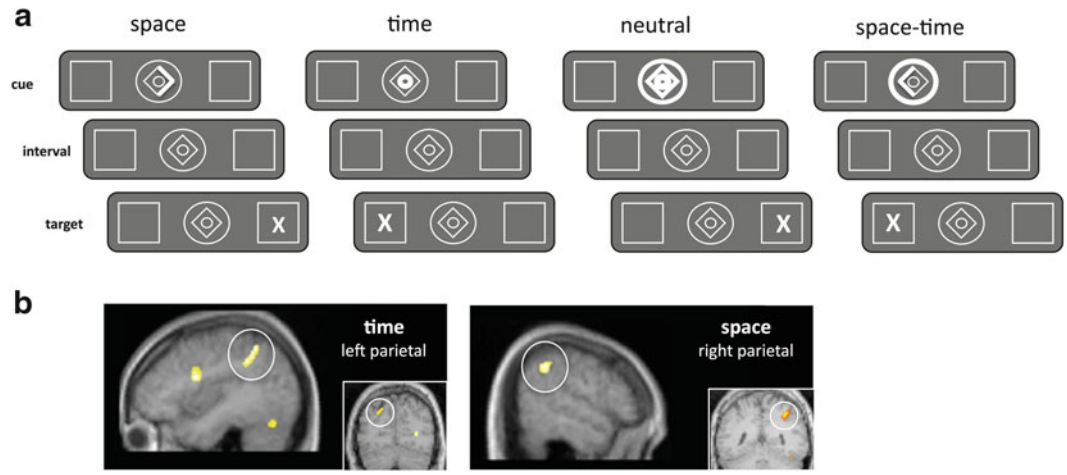

Fig. 3 (**a**) A central endogenous cue predicted the likely location (left/right box) and/or onset-time (short/long interval) of a forthcoming target (X). Cues directed attention either to the left or right location ("space"), to a short (300 ms) or long (1,500 ms) onset-time ("time"), to both location and onset-time ("space–time") or to neither location nor onset-time ("neutral"). Brightening of the left or right side of the diamond within the central cue predicted that the target would appear in the left or right peripheral box respectively. Brightening of the *inner* or *outer circle* predicted that the target would appear after a short or long interval respectively. Brightening of the entire cue in the neutral condition effectively provided no spatially or temporally predictive information. In the time condition illustrated here, the cue predicts that the target will appear after a short interval (*bright inner circle*) but provides no information concerning its location. (**b**) Spatial (versus temporal) cueing preferentially activated right-lateralised inferior parietal cortex, confirming previous reports. By contrast, temporal (versus spatial) cueing preferentially activated left-lateralised inferior parietal cortex

benefits had been shown to manifest themselves in the temporal domain. We speculated that similar attentional mechanisms operated in both spatial and temporal domains, with resources being directed in an anticipatory way to the location in space or the moment in time at which the event was predicted to happen, thus enhancing selectivity of processing at that point. Yet although spatial and temporal orienting appeared functionally similar, the brain regions underpinning these attentional processes were anatomically distinct. We directly compared the pattern of brain activity induced by spatially valid trials to that induced by temporally valid trials, which cancelled out any activations common to both tasks (e.g. those linked to processes of attentional orienting generally), leaving only areas that were differentially activated by orienting within the spatial versus temporal domain. Notably, we found hemispheric lateralization in parietal cortex for spatial versus temporal orienting of attention [110]. Spatial orienting activated right inferior parietal cortex, confirming numerous previous studies [46, 111, 112], whereas temporal orienting preferentially activated left inferior parietal cortex, specifically around the intraparietal sulcus (Fig. 3b). This result was replicated in two different groups of participants, first using PET then fMRI technologies [110], underlining the robustness of the result.

Optimising Behaviour or Estimating Duration?

At this point, it is crucial to remember that what these neuroimaging data primarily reflect are *attentional* processes: resources being oriented towards a particular moment in space or time in order to optimize behaviour. In the temporal orienting task, even though the participant has to accurately estimate duration in order to respond at the right moment, they were not required to provide an overt estimate of that duration. Their primary goal was a motor one: to respond to the target as quickly as possible.

Activation of left inferior parietal cortex by temporal orienting is therefore not incompatible with activation of SMA and right inferior frontal cortex by duration estimation (as described in preceding sections). These distinct anatomical substrates merely reflect the distinct functional characteristics of these two forms of timing: estimating duration so that attentional resources can be oriented towards the measured time in order to optimise behaviour (left inferior parietal) as opposed to estimating duration in order to register a temporal measure of elapsed time (SMA and right inferior frontal). In agreement with this, SMA and right-sided frontoparietal cortices were found to be activated in a temporal orienting task [113] when the participant was required to convert the predicted time of target appearance into an explicit judgement ("did the target appear earlier or later than expected?") rather than using the predicted time of its appearance to enhance stimulus processing.

In a recent fMRI study, we directly compared the neural substrates of these two forms of timing within the same experimental paradigm [38]. Timing was measured either explicitly, by a timed motor response (temporal reproduction task), or implicitly, by speeded detection of a temporally predictable target (temporal orienting task). In both tasks, a previously learnt visual cue preceded the interval to-be-timed, and either indicated (temporal cues) or not (neutral cues) the duration of the ensuing interval (Fig. 4a). These four conditions constituted a 2×2 factorial design, with task (reproduction/orienting) and cue (temporal/neutral) as the experimental factors. In the reproduction task, participants internally generated the cued interval, making a brief response when they estimated it had elapsed. In the orienting task, participants responded as quickly as possible to the appearance of an externally specified event that appeared at the cued interval. Neutral cue conditions, in which participants either generated a random interval (reproduction task) or detected a target appearing after a random interval (orienting task), controlled for the contribution of internally versus externally guided movement generally.

Behavioural data confirmed that participants acquired accurate representations of the cued durations in both tasks [38]. In the temporal reproduction task, duration estimates were very close to cued intervals, with variability being greater for long intervals than for short ones (i.e. timing behaviour was scalar). In the temporal orienting task, responses were faster for temporally valid targets than for neutrally cued ones. Yet although participants were using the same temporal representation in both reproduction and orienting tasks, distinct patterns of neural activity were evoked as a function of the way in which this temporal representation was used. When the temporal cue was translated into an overt estimate of elapsing time in the temporal reproduction task, SMA, basal ganglia and right-lateralised frontal and parietal cortices were preferentially recruited. Conversely, when the temporal cue was used to optimise sensorimotor processing at precise moments in time in the temporal orienting task, left inferior parietal cortex, left premotor cortex and cerebellum were preferentially engaged (Fig. 4b). By matching sensorimotor requirements across tasks, we were able to directly compare the temporal reproduction to temporal orienting tasks, confirming the fundamental role of SMA and right inferior frontal cortex in explicit duration estimation, and of left inferior parietal cortex in temporal orienting [38].

Independence from Motor Responding

Two further fMRI studies were designed to confirm the ubiquity of left inferior parietal cortex in temporal orienting. First, we aimed to show that activation of this area was independent of the type of motor response (left/right; manual/ocular) used to register stimulus detection. Second, we hoped to show that its activation was not only independent of the *type* of motor response but was, in fact, independent of the need to make a motor response of any kind. Specifically, we aimed to show that it was independent of the type of stimulus processing (motor/sensory) being optimised.

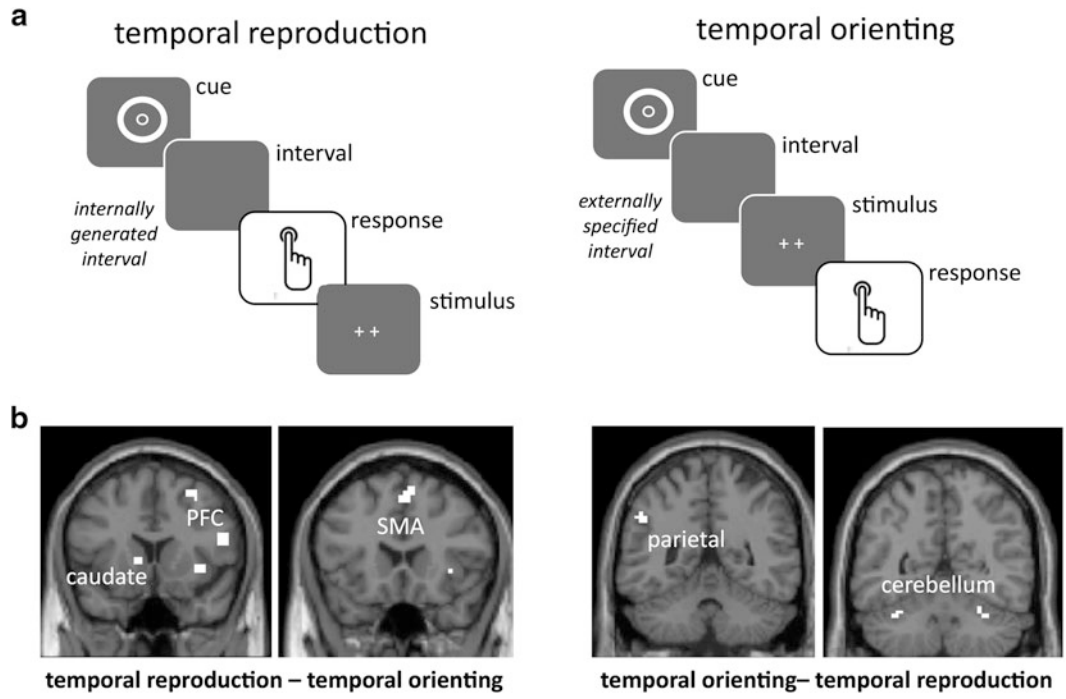

Fig. 4 (**a**) All cues comprised two concentric circles. For temporal cues, the *inner* or *outer circle* was brightened, indicating a short (600 ms) or long (1,400 ms) cue-stimulus interval respectively. For neutral cues, both *inner* and *outer circles* were brightened, indicating a random cue-stimulus interval. In the examples illustrated here, both tasks begin with a long temporal cue. In the temporal reproduction task, participants internally generated the duration indicated by the cue (short or long) then pressed a button when they estimated that that duration had elapsed. Pressing the button immediately elicited presentation of the visual response stimulus (++). In the temporal orienting task, the duration of the cue-stimulus interval was externally specified and determined by the onset-time of the response stimulus. Participants pressed a button as soon as the response stimulus was presented. The neutral cue version of each task had the same task structure except that the trial began with a neutral cue rather than a temporal one. The neutral cue version of the temporal reproduction task was a self-paced movement task in which participants pressed a button after a random interval of their choosing, thereby eliciting presentation of the response stimulus. The neutral cue version of the temporal orienting task was a simple reaction-time task in which participants pressed a button in response to a response stimulus that was presented after a random interval. (**b**) Direct comparison of the temporal reproduction and temporal orienting tasks revealed preferential activation of right prefrontal cortex, preSMA, right inferior parietal cortex and left caudate by the temporal reproduction task, but of left inferior parietal cortex and cerebellum by the temporal orienting task. Importantly, these activations do not simply reflect the neural substrates of internally versus externally guided movement. The activation maps illustrated here were first masked by the comparison of each task to its respective neutral cue condition. For example, the temporal reproduction minus temporal orienting comparison was masked by the temporal reproduction minus self-paced movement comparison. Since the neutral cue conditions engaged internally or externally guided movement to the same degree as the relevant temporal condition, but for random, rather than precisely timed, intervals, any activations related to internally or externally guided movements would be subtracted out

The impetus for these studies was the observation that a very similar area of left inferior parietal cortex had been implicated in another variant of the Posner paradigm, in which cues predicted the motor effector (e.g. index/middle finger) with which the speeded response should be made [114, 115]. It was therefore possible that activation of left inferior parietal cortex by temporal orienting may have simply reflected selective motor preparation of a speeded response. This is unlikely since motor preparation requirements were always matched across temporal orienting and comparison tasks. However, to explore this possibility more thoroughly, we

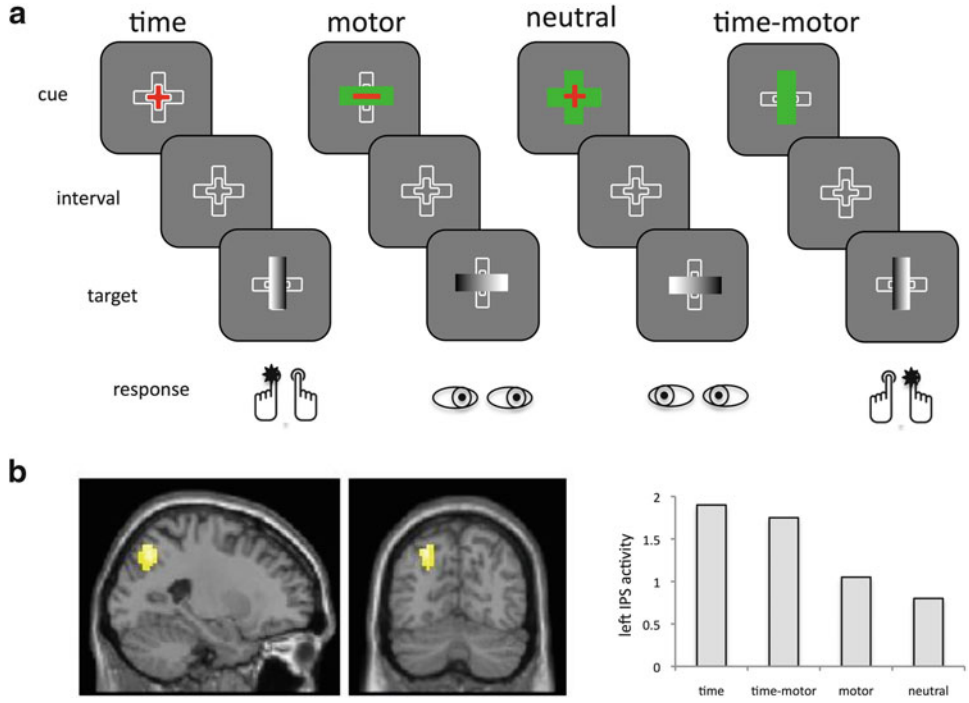

Fig. 5 (**a**) A crosshair cue predicted the onset-time (short/long interval) and/or the motor effector (manual button-press/ocular saccade) with which a response to a forthcoming target would be made. Cues directed attention either to onset-time ("time"), to motor effector ("motor"), to neither onset-time nor motor effector ("neutral"), or to both onset-time and motor effector ("time-motor"). Colouring of the inner or outer components of the crosshair cue indicated that the target would appear after a short (750 ms) or long (1,500 ms) interval respectively. Colouring of the horizontal or vertical components of the crosshair cue indicated that the target would call for an ocular saccade or a manual button-press respectively. Correspondingly, the orientation of the *target* specified the motor effector with which the motor response should be made, with vertical targets specifying manual button-presses and horizontal targets specifying saccades. The shading of the target specified the laterality of the response, with left/right responses being made towards the lighter side of the target. In the time-motor condition illustrated here, the cue predicts that the target will appear after a long interval (outer component) and will call for a manual button-press response (vertical component). When the target appears, it specifies a button-press response (vertical target) to be made with the right hand (lighter shading to the right of the target). (**b**) Temporal (versus neutral) cueing activated left intraparietal sulcus whether participants responded with manual button-presses or ocular saccades, either to the left or to the right. The accompanying plot shows that left intraparietal sulcus was activated more whenever temporal information was available, whether the effector used to register the response could also be prepared in advance (the time-motor condition) or not (the time condition)

designed a variation of the Posner task in which motor and temporal components of response preparation were independently cued within the same experimental paradigm [116]. Specifically, temporal or motor pre-cues informed participants as to when (short/long interval), and/or with which motor effector (oculomotor saccade/index finger button-press), a speeded response to an upcoming target should be made (Fig. 5a). By comparison, neutral cues provided neither temporal nor motor information. Behaviourally, temporal cues speeded responding as compared to neutral cues. This was true even when the motor effector used to register the response could not be prepared in advance, confirming that temporal preparation could benefit performance independently from motor preparation [116]. Similarly, temporal orienting activated left inferior parietal cortex, specifically within the intraparietal sulcus, whether the motor effector used to respond to the target could be prepared in advance or not (Fig. 5b). The robustness of this activation was further demonstrated by the fact that temporal orienting activated left

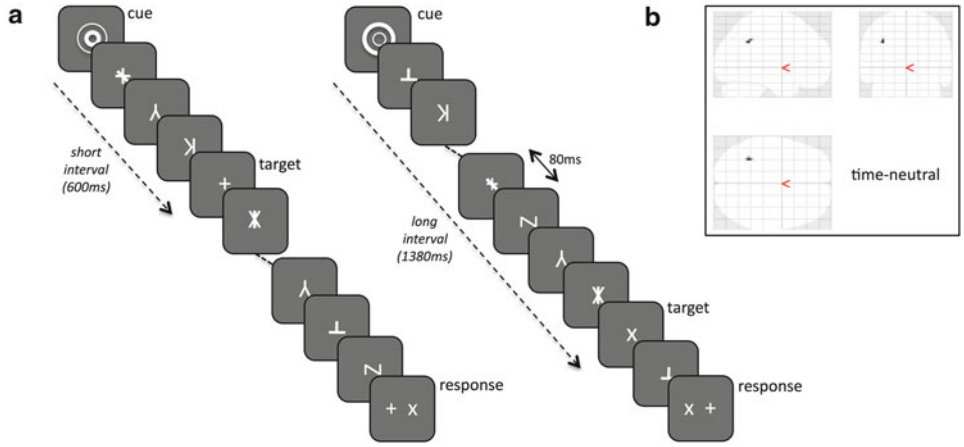

Fig. 6 (**a**) A temporal cue predicted the onset-time (short/long) of a target (either + or ×) that was embedded within a rapid serial visual presentation stream of visually similar distractors. The trial on the left shows a short temporal cue (*brightened inner circle*) and the trial on the right a long temporal cue (*brightened outer circle*), with targets appearing after a short (600 ms) or a long (1,380 ms) interval respectively. For the neutral cue (not illustrated here), both *inner* and *outer circles* were brightened, providing no temporal information. Participants indicated whether they had seen a + or x target by providing a delayed discriminatory response at trial end. To minimize the possibility for motor preparation, stimulus–response contingencies varied on a trial-by-trial basis. There were two possible response screens, and the relative positions (*left*/*right*) of the + and × symbols on the screen specified either a left or right button press, located under the index and middle fingers of the right hand. In the examples given here, the correct response would be a left button press in each case. (**b**) The only area preferentially activated by temporal versus neutral cueing in this perceptual version of the temporal orienting task was left intraparietal sulcus

intraparietal sulcus whether the laterality of the movement was left or right-sided, and whether the response was registered with a manual button-press or an oculomotor saccade [116]. We therefore concluded that left intraparietal sulcus represented an effector-independent substrate for temporal orienting and did not simply represent a motor preparation confound during the temporal orienting task. We further proposed that temporal orienting is an attentional mechanism that operates with similar principles on either the manual or ocular motor systems, in a manner analogous to that already proposed for spatial orienting [117, 118].

In a follow-up experiment, we aimed to show that temporal orienting would activate left inferior parietal cortex even when a speeded motor response was not required. Prior behavioral studies had demonstrated that temporal orienting not only confers faster motor response times [110, 119] but also enables faster and more accurate stimulus perception [120–122]. If left inferior parietal cortex is a core substrate for temporal orienting, it should also be activated when the task requires a perceptual discrimination, rather than a motor response. We therefore designed a perceptual version of the temporal orienting task [123], based on the paradigm used previously by Correa et al. [121], and compared its neural correlates directly to those of the motor version described previously. In the perceptual discrimination version of the task, participants were asked to discriminate which of two targets had been presented within a rapid serial presentation of visually similar distractors (Fig. 6a). In the motor detection version of the task, no visual distractors were presented and the participant had simply to detect the presence of the target as soon as possible after its appearance. In order to minimise the motor component of the perceptual version as much as possible, participants did not respond as soon as they had seen the target, but instead had to wait until the offset of the visual stream, at which point a choice response screen was displayed. To

minimise motor processing further still, and similar to the manipulation described earlier in the *Controlling Time* section, the stimulus–response mapping changed from trial to trial so that participants could not begin to prepare a motor response as soon as the target had been detected.

Analysis of behavioural data confirmed that temporal cues significantly enhanced both speed of motor detection and accuracy of perceptual discrimination. Crucially, fMRI results revealed that, as compared to neutral-cue control conditions, temporal orienting activated left inferior parietal cortex, deep in the intraparietal sulcus, whether temporally informative cues were used to react more quickly or, critically, to enhance perceptual sensitivity (Fig. 6b), thereby identifying this region as a core neural substrate for temporal orienting (see also [124]). Intriguingly, the level of activity in this region co-varied differentially with sensory or motor brain regions as a function of the task being performed: its activity correlated with activity in bilateral premotor/motor cortex during the motor detection task, but with activity in bilateral visual cortex during the (visual) perceptual discrimination task [123]. We suggested that, analogous to the biased competition model of spatial attention [125, 126], left intraparietal sulcus may generate a top-down biasing signal for activity in task-specific sensorimotor areas (i.e. areas recruited for processing of specific stimulus features or motor task goals) so as to bias information processing for stimuli appearing at the cued time.

Endogenous and Exogenous Temporal Cues

In the temporal orienting studies discussed so far, timing was measured implicitly by speed of motor responding or accuracy of perceptual discriminations. The way in which attention was oriented to discrete moments in time by the temporal cues, however, was explicit and voluntary. In a very recent study [127], it was not only the way in which timing was measured that was implicit but also the way in which attention was oriented in time. Specifically, we used metrically structured isochronous rhythms to manipulate temporal orienting implicitly. By analogy with the spatial attention literature, isochronous rhythms direct attention in an automatic, stimulus-driven "exogenous" manner whereas symbolic temporal cues direct attention in a more voluntary, goal-directed "endogenous" way [128]. We examined whether the temporal predictability of metrically structured rhythms would share functional and neural properties with that of symbolic temporal cues.

Prior fMRI studies of rhythm have compared temporally regular (isochronous or beat-based) to temporally irregular sequences, finding SMA and basal ganglia to be preferentially activated by temporal regularity (e.g. [15, 129–132]). Very recently, Marchant and Driver [133] found that targets were better detected when presented amidst temporally regular, rather than irregular, visual stimulus streams, and was accompanied by activity in bilateral PFC, insula, basal ganglia and, notably, inferior parietal cortex lateralized to the left hemisphere. They concluded the left parietal activation was most likely due to the temporally predictable nature of the isochronous sequence, which helped optimize target detection. In our experiment, we also examined brain activity associated with rhythmically induced improvements in target detection, but instead of comparing rhythmic to non-rhythmic sequences, we compared activity induced by strong versus weak beats of a metrically structured rhythm. Critically, all experimental conditions were equally rhythmic, in order to equate (or cancel out) processes related to rhythm perception *per se*. Behavioural responses were faster for targets presented on strong, rather than weak, beats, indicating increased allocation of attention to strong beats (see also [106, 107]). This behavioural benefit was accompanied by selective activation of left inferior parietal cortex [127]. Therefore, although basal ganglia and SMA may be activated by the perception of rhythm in the first place (e.g. [131]), left inferior parietal cortex is activated whenever temporally salient elements of that rhythm capture attention, thereby optimising processing of stimuli occurring at that time. This neuroanatomical distinction once again

reflects the functional difference between timing in order to estimate duration (perceiving rhythmicity or not) and timing in order to optimize sensorimotor processing (using rhythmicity to improve target detection).

Using Action Circuits for Time

To summarise, estimating event duration, whether the estimate is provided with a motor response or a perceptual discrimination, typically recruits basal ganglia, SMA and right inferior frontal cortex, and can be modulated by dopaminergic activity in these areas. By contrast, orienting attention to predictable moments in time in order to optimize behaviour, whether that is to speed motor responding or improve perceptual accuracy, recruits left inferior parietal cortex. Strikingly, these are areas that have all previously been implicated in motor preparation, with Goldberg [134] proposing that distinct motor areas would be recruited depending on whether the movement being prepared was internally or externally guided. Indeed, numerous neuroimaging studies of motor preparation have shown that SMA and prefrontal cortex are activated particularly by preparation of internally generated (i.e. self-willed) movements [39, 40, 135–139] and the voluntary intention to act [140], whereas left parietal and premotor cortices are activated by preparation of externally cued movements [141, 142]. This neuroanatomical distinction between internally and externally guided movement neatly parallels that between duration estimation and temporal orienting respectively, perhaps reflecting a corresponding functional parallel: responses in a temporal reproduction task are guided by internal estimates of elapsed duration whereas responses in a temporal orienting task are triggered by the onset of externally timed imperative sensory stimuli.

Highlighting the neural and functional overlap between timing and motor control is one thing. A more intriguing question is to ask what this overlap might signify? One possibility, taking us right back to the beginning of this chapter, is that this overlap simply reflects the presence of confounding cognitive processes. For example, in studies of internally generated motor preparation (e.g. [135, 138]), activation of SMA and prefrontal cortex may actually represent the timing of the intended response rather than selection of a particular motor effector: indeed, Wencke et al. [143] have noted that such studies typically examine the voluntary intention of *when* to move, not *which* motor effector to move (see also 144). Conversely, in studies of duration estimation, activation of SMA and prefrontal cortex may simply reflect confounding processes of motor preparation. This is unlikely however, since SMA and prefrontal cortex are selectively activated even when duration estimates are registered with a perceptual discrimination [11], or after motor preparation and/or execution processes have been rigorously controlled for (e.g. [20]).

A more appealing possibility is that timing shares neural circuitry with motor function because our sense of time is acquired early in development through action ([145, 146]; see also [147]). This proposal is similar in principle to other embodied theories of time perception although, given the neuroanatomical overlap between timing and motor areas, I suggest time is grounded more fundamentally in action, rather than interoception (e.g. [148, 149]) or motion perception [150, 151]. These propositions are not incompatible, of course, since action implies both motion and interoception. To begin on a personal note, I noticed that when my children were younger I often gave them motor reference frames when they asked how long a particular period of time was: for example, 15 min was the time it took to walk to school, or an hour was the time their judo/ballet class lasted. This anecdotal account is supported empirically by the results of developmental studies demonstrating that young children appear to represent time in motor terms. Their duration estimates are more accurate when the duration is filled with an action than when it is empty [152] and they find it difficult to dissociate an estimate of duration from the motor act itself. For example, 3 year-olds' could not reproduce the duration of one action with a different

action (e.g. "press the button. . .now, squeeze the bulb for the same amount of time"), although by the age of 5 such temporal transfer was possible [153]. Moreover, Droit-Volet [154] found that when 3 year-olds' were asked to press a button "longer than before" the duration of their responses did not differ, but when asked to press "harder than before" their responses lengthened. In these young children, duration actually appears to have been coded as a force parameter rather than a temporal one. A tantalizing possibility therefore is that action circuits are engaged early in development to build up and acquire representations of time, resulting in shared neural representations for action and the perception of time. Even in adults, there is evidence that when motor skills are learned incidentally temporal information is bound to the specific action in which it was learnt rather than being represented at an effector-independent level [113]. Many neuroscientific theories of different aspects of cognitive function propose shared neural representations for action and perception (e.g. [155–158]). Applied to the temporal domain, learned associations between particular actions and their durations might ultimately lead to shared neural representations for motor acts and their perceptual (i.e. temporal) correlates.

The association between action and perception is bidirectional: an internally generated action may become associated with its perceptual consequences (action-effect pairing) and an external stimulus may become associated with the motor response it evokes (stimulus–response pairing). It is tempting to consider that this functional distinction maps onto the neuroanatomical dissociation between duration estimation (basal ganglia, SMA, prefrontal cortex) and temporal orienting (left inferior parietal cortex). Therefore, for action-effect pairings, when an internally generated action results in a particular temporal percept (e.g. the child who learns that the amount of time it takes to walk to school represents a duration of 10 min), the representation for time perception is instantiated within the fronto-striatal motor circuits underlying voluntary action. By contrast, for stimulus–response pairings, when the timing of a sensory stimulus evokes a particular motor response (e.g. learning to clap in time to the music), the representation for timing may instead become instantiated in the parietal circuits necessary for sensorimotor learning. Data derived from modern neuroimaging techniques are beginning to converge with developmental evidence in children to suggest that the ontogenetic roots of our notion of time might be embedded within action circuits, an idea that was first advanced by Guyau [7, 8] over a hundred years ago.

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Motor and Perceptual Timing in Parkinson's Disease

Catherine R.G. Jones and Marjan Jahanshahi

Abstract

Neuroimaging has been a powerful tool for understanding the neural architecture of interval timing. However, identifying the critical brain regions engaged in timing was initially driven by investigation of human patients and animals. This chapter draws on the important contribution that the study of patients with Parkinson's disease (PD) has made in identifying the basal ganglia as a key component of motor and perceptual timing. The chapter initially describes the experimental tasks that have been critical in PD (and non-PD) timing research before systematically discussing the results from behavioural studies. This is followed by a critique of neuroimaging studies that have given insight into the pattern of neural activity during motor and perceptual timing in PD. Finally, discussion of the effects of medical and surgical treatment on timing in PD enables further evaluation of the role of dopamine in interval timing.

Keywords

Parkinson's disease • Basal ganglia • Dopamine • Motor timing • Perceptual timing • Temporal processing • Internal clock

Introduction

Psychological research has a long history of being informed by clinical populations. Atypical performance in a patient group open a window for understanding the neural mechanisms of a given psychological process. This has been particularly true of Parkinson's disease (PD) and research into interval timing, with a focus on both motor and perceptual timing in the milliseconds and seconds range. The following chapter summarizes the contribution that research on PD has made to the field of interval timing. Starting with descriptions of the key timing tasks used, the chapter then goes on to review evidence from behavioural studies of motor and perceptual timing in PD. This is then supplemented by a summary of neuroimaging

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studies of timing in PD, as well as investigation of studies that have analyzed treatment effects. To enable conclusions to be drawn we will present the percentage of studies showing evidence of impairment in PD across a range of different task factors. We have a relatively small pool of studies, which differ in terms of methodology and experimental rigor, which means that the calculation of percentages has limitations. However, whilst recognizing this caveat, it also proves a valuable approach for identifying patterns in the results across tasks.

Parkinson's Disease as a Model of Basal Ganglia Mediated Dysfunction in Temporal Processing

Parkinson's disease (PD) is neurodegenerative movement disorder associated with the loss of dopamine producing neurons in the substantia nigra pars compacta, a midbrain structure. This pathological process has implications for the efficacy of the nigrostriatal dopaminergic pathway that transmits dopamine from the substantia nigra to the striatum, the input area of the basal ganglia. Thus, PD is a disorder of dopamine deficiency within the basal ganglia, a group of closely connected nuclei that play an important role in the control of movement, cognition and motivation. The cardinal symptoms of PD include akinesia, bradykinesia, rigidity and tremor. Akinesia translates as 'lack of movement' and manifests as symptoms including difficulty initiating movement, and reduced frequency and amplitude of spontaneous movements. Affected movements include blinking, facial expression and gesticulation during speech. Akinesia also leads to the characteristic shuffling and short stepping during walking, alongside reduced arm swinging. Bradykinesia refers to the slowness in executing movements, whereas rigidity is due to increased muscle tone. These features are seen alongside a characteristic 4–6 Hz tremor present at rest. Other clinical symptoms can include pain, sleep disturbance, psychiatric disturbance including depression, apathy and anxiety, cognitive impairment, and dementia in the later stages (see [1] for a review). The most common treatment for PD is dopaminergic medication to increase the amount of dopamine in the brain and redress the neurochemical imbalance in the basal ganglia. A more invasive surgical treatment option is to directly stimulate key targets in the basal ganglia using chronically implanted electrodes, a technique called deep brain stimulation (DBS).

The slowness of movement in PD has led to interest in characterizing the temporal processing profile of patients with this disorder. From an initial case study exploring motor timing in PD [2], the field has expanded to encompass a range of motor and perceptual timing tasks. Testing patients both 'on' and 'off' medication or DBS has also enabled researchers to directly evaluate the impact of the efficacy of dopaminergic neurotransmission and the manipulation of striatofrontal connectivity on timing performance. This research has dovetailed with the quest to characterize the neural substrates of an 'internal clock' that meters time (e.g. [3]). Thus, investigation of temporal processing in PD has been instrumental in the argument that the basal ganglia are a critical component of the internal clock. This argument has been bolstered by more recent neuroimaging research that has found evidence of basal ganglia activation during a range of tasks involving temporal processing (see [4] for a review).

Tasks Commonly Used to Study Perceptual and Motor Timing

Motor timing can be considered as any temporal process where the temporal decision is intrinsically tied with movement. For example, the split second adjustments required to catch a ball or the ability to clap in rhythm with others. In contrast, perceptual timing is a subjective judgment of perceived time and is not defined by movement. For example, perceptual timing processes enable a person to judge that their kettle has boiled or to estimate that a friend travelling a familiar route will have returned home. Perceptual timing sometimes includes a motor element and there is some grey area in these distinctions. However,

commonly motor timing is a description reserved for repetitive and continuous movements (e.g. clapping in time with music), as opposed to a discrete movement that may be employed to indicate a temporal decision but can be separated from the perceptual decision (e.g. returning to the kitchen because the kettle is judged to have boiled). Studies have shown a significant correlation between performance on motor and perceptual timing tasks (e.g. [5, 6]), leading many to assume a common neural substrate.

Classic motor and perceptual timing tasks are summarized in Table 1 and the most frequently used with PD patients are described in more detail below. Figure 1 illustrates the duration discrimination, time estimation, time production and time reproduction tasks. Tasks commonly use a computerized presentation of simple auditory (e.g. pure tone) or visual (e.g. small square) stimuli to denote the intervals being timed. The duration being estimated can either be 'filled' e.g. a stimulus such as an auditory tone is present for the duration of the interval, or 'unfilled' e.g. the onset and offset is bounded by two short auditory tones but the actual interval is empty (e.g. [25]). For certain tasks, sometimes the interval is filled with counting or reading aloud random numbers (e.g. [30]), which will be discussed in more detail below. The **duration discrimination** task is the most popular 'pure' method of measuring perceptual timing. The task is considered pure as movement is not tied to the temporal decision. In this task, two durations are presented, typically sequentially (although see [24] for an alternative approach), and the participant has to make a discrimination based on their durations. This might be to judge which interval is longer (e.g. [20]), or to decide whether the second interval is longer or shorter than the first (e.g. [11]). Either a set number of trials and duration differences are presented [24] or, more commonly, an adaptive staircase is presented to calculate the threshold at which (for example) 75 % of discriminations are correct (e.g. [20]). It is important in studies with a patient population that group differences can be designated as specific to the process of interest and not to the general perceptual and cognitive demands (e.g. stimulus detection, attention, memory, decision making). This issue is particularly pertinent when investigating a clinical group such as PD, where cognitive deficits are well documented (e.g. [38]). Unfortunately, most timing tasks cannot be matched with an adequate control task and researchers rely on carefully matched groups (age, IQ, education), as well as screening for cognitive impairment and psychiatric problems (depression, apathy and anxiety) that may additionally impact on timing performance. An advantage of the duration discrimination task is that control tasks can be used. Most studies of PD have used an auditory version of the duration discrimination task and a sound intensity or frequency discrimination control task (e.g. [11, 12, 25]). Line length or colour discrimination are common options when a visually presented duration discrimination task is used, although not all studies include such a control task (e.g. [22, 24]). Typically, control discrimination tasks are performed with proficiency by PD patients (e.g. [11, 25]), which adds weight to the argument for a specific timing deficit. However, a major caveat is that all of these control tasks can be solved in the first few hundred milliseconds; for example, it is not necessary to attend to the stimulus for its entire duration to decide its frequency. This is in contrast to the duration discrimination task, which makes it intrinsically more cognitively demanding. The neuroimaging field has led the way in designing inventive control tasks that match well for additional demands, including attention, working memory and motor preparation. These are covered comprehensively in seventh chapter of this book.

Time estimation assesses how well a participant can apply temporal labels to intervals of time. For example, the participant is presented with an interval and asked to estimate its length to the nearest second (e.g. [29]). Rather than relying on direct comparative judgments, this task assesses the ability to map understanding of the common units of time to an internal sense of time passing. A very similar task, which also relies on the participant's ability to label units of time, is the **time production** task. Here, the participant is asked to indicate when

Table 1 Summary of motor and perceptual temporal processing tasks, the key processes measured, and studies that have used the tasks in Parkinson's disease

Task	Description	What is measured	Studies using task
Motor timing			
Synchronization-Continuation task/ repetitive tapping task	Tap in time with a regularly paced stimulus (synchronization phase) and then maintain the rhythm (continuation phase) in the stimulus's absence	Paced and unpaced motor timing	Cerasa et al. [7]; Claassen et al. [8]; Duchek et al. [9]; Elsinger et al. [10]; Harrington et al. [11]; Ivry and Keele [12]; Jahanshahi et al. [13]; Jones et al. [14]; Joundi et al. [15]; Merchant et al. [6]; O'Boyle et al. [16]; Pastor et al. [17]; Spencer and Ivry [18]; Wojtecki et al. [19]
Perceptual timing			
Duration discrimination	Pairs of intervals are presented. Participants indicate which is longer/ shorter	Detection of a temporal difference between two durations	Guehl et al. [20]; Harrington et al. [11]; Harrington et al. [21]; Hellström et al. [22]; Ivry and Keele [12]; Rammsayer and Classen [23]; Riesen and Schnider [24]; Wearden et al. [25]; Wojtecki et al. [19]
Peak-interval procedure	Participants reproduce a learnt interval by pressing a response button repeatedly within the boundaries of its judged offset	Reproduction of a learnt interval	Malapani et al. [26]; Malapani et al. [27]
Temporal bisection	Participants learn short and long standard intervals. They then classify subsequent intervals as more similar to the short or long standards	Classifying stimuli based on duration	Merchant et al. [6]; Smith et al. [28]; Wearden et al. [25]
Temporal generalization	Participants learn a standard interval. They then judge if subsequent intervals are the same length as the standard	Judge if stimuli is same or different to a standard	Wearden et al. [25]
Time estimation	A temporal interval is presented. Participants are asked to estimate the duration, using seconds and minutes	Assigning a temporal label to a duration	Lange et al. [29]; Pastor et al. [30]; Riesen and Schnider [24]; Wearden et al. [25]
Time production	Participants press a button when a defined interval of time (e.g. 60 s) has elapsed	Subjective time sense for a given unit of time	Jones et al. [31]; Lange et al. [29]; Perbal et al. [32]; Wild-Wall et al. [33]; Wojtecki et al. [19]
Time reproduction	A temporal interval is presented. Participants press a button to indicate when an identical interval has elapsed	Reproduction of a presented interval	Jones et al. [31]; Koch et al. [34]; Koch et al. [35]; Koch et al. [36]; Merchant et al. [6]; Pastor et al. [30]; Perbal et al. [32]; Torta et al. [37]; Wojtecki et al. [19]

Stimuli are typically simple pure tones or simple visual displays (e.g. a square on a computer screen)

they think a pre-specified period of time has elapsed, for example, to press a button when they think 60 s has passed (e.g. [31]). The **time reproduction** task requires the participant to attend to an interval and then reproduce the duration by pressing a response button when they think an identical period of time has elapsed (e.g. [31]). The latter three tasks can vary in their design, but one crucial feature is whether participants are instructed to count. Counting out the intervals, at a self-paced and self-preferred [32], self-paced but specified (e.g. 1 s) (e.g. [29, 30]), or externally paced [30] rate, introduces a timed motor element that can confound interpretation. It becomes unclear whether the task is measuring perception of a discrete interval or the ability to time a short continuous sequence that is intrinsically tied to motor production. Thus, many purported perceptual timing tasks have an implicit motor timing element. As an

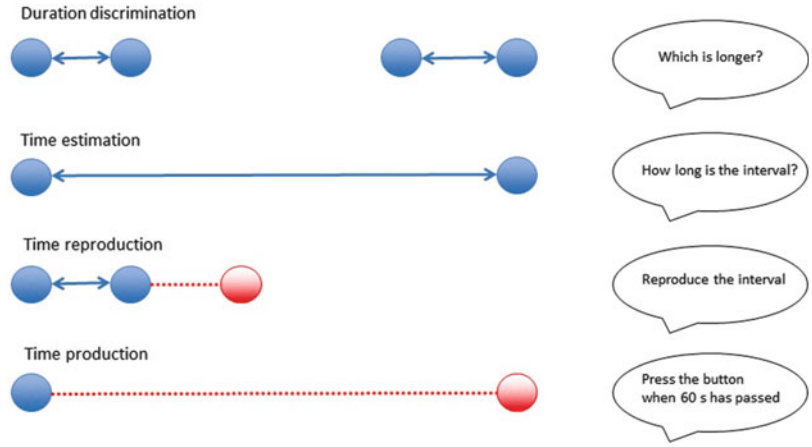

Fig. 1 Illustration of the four most popular perceptual timing tasks. *Blue circles* indicate stimulus presentation (auditory or visual) and *red circles* indicate the participant's response

additional confound, the psychophysical properties of chronometric counting and interval timing are different, with only the variance in interval timing conforming to the scalar property [39]. Arguably, chronometric counting may still activate the internal clock (e.g. to generate individual counts), but it is a less pure measure of internal timing processes and results in more precise estimations [40]. Cognizant of these issues, some studies take the opposite approach and require that random numbers are read aloud to inhibit counting (e.g. [24, 26, 35]). However, managing the competing demands of two separate tasks is differentially more demanding for PD patients than healthy controls (e.g. [32, 41]) and the confounding motor element is still present. Some researchers have asked participants not to count (e.g. [31]). The downside of this is that the data become more noisy as it is difficult to control what strategies participants employ when timing intervals.

Three classic tasks from the animal timing literature, the **peak interval procedure**, the **temporal generalization** task and the **temporal bisection** task, have been used to good effect when investigating perceptual timing in PD. All three tasks plot a response curve and schematic examples of these curves, along with interpretation of results can be seen in Fig. 2. Malapani and colleagues have used an adaptation of the peak interval procedure in humans [26, 27]. The task can be thought of as a time reproduction task in which many intervals are reproduced and then plotted to produce a frequency distribution. The participants are first trained in the target duration by monitoring the length of time a rectangle is displayed on a computer screen. In the testing phase, the rectangle appears but remains on the screen for a longer period. Participants have to press a button when they think the target duration has elapsed. Unlike a classic time reproduction task the participants are told to make multiple guesses on each trial, pressing the button before the estimated duration has elapsed and continuing until they judge it has passed. Feedback regarding accuracy is provided. This procedure enables responses to be plotted, showing a peak at the time where responses are most frequent. With time plotted on the x axis, a curve with a peak shifted to the right would imply relative overestimation, whereas a peak shifted to the left would imply underestimation. The human version of the temporal bisection task (e.g. [25]) has participants learn two standard durations, one 'short' and one 'long'. Once learnt, the participant is presented with a range of intermediate durations, spaced at equal intervals, as well as the standard durations. They have to classify each duration as more similar to the 'short' or 'long' standards that they learnt. The data produces a sigmoid curve, plotting the probability of making a 'long' response as a function of stimulus duration. With durations plotted on the x axis, a leftward

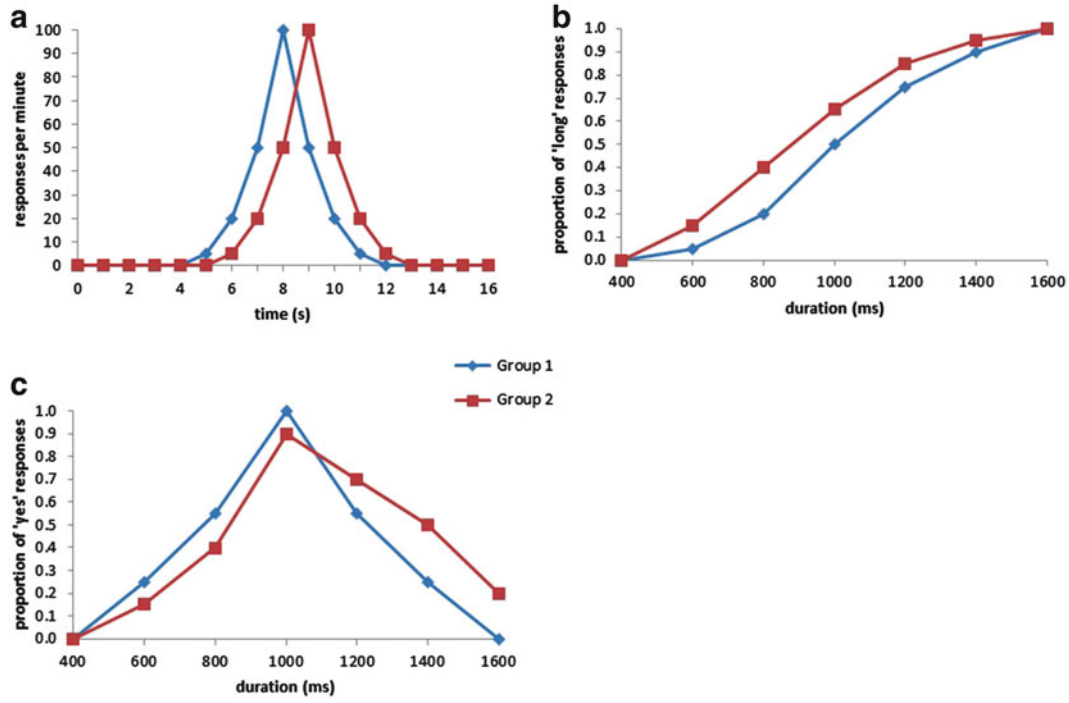

Fig. 2 Schematic illustration of the (**a**) peak interval procedure, (**b**) temporal bisection task and (**c**) temporal generalization task. For each illustration, Group 1 illustrates typical performance, while Group 2 illustrates relative overestimation compared to Group 1. For (**a**) the duration being reproduced is 8 s, for (**b**) the standard durations are 400 and 1,600 ms, and for (**c**) the standard duration is 1,000 ms

shift in the curve reflects a relative overestimation of time. The bisection point (or point of subjective equality) is the duration at which long and short responses occur with equal probability. In the human version of the temporal generalization task (e.g. [25]), participants are initially presented with examples of a standard duration that becomes learnt. During the testing phase, a range of different durations are presented including the standard duration. After each interval presentation the participant responds 'yes' if they judge that the interval is the standard duration and 'no' if they think otherwise, with feedback given. The proportion of 'yes' responses for each duration are plotted to create a temporal generalization gradient, which illustrates the probability of a response as a function of signal duration. With duration plotted on the x axis, a rightward skew of the generalization function would indicate overestimation of the standard duration, whereas a leftward skew would suggest underestimation.

Motor timing is almost exclusively measured using the **synchronization-continuation task**, also known as the repetitive tapping task. The task assesses the ability to entrain a motor response to a regularly paced cue and then to maintain the learnt rhythm without the pacing cue (all studies discussed in this chapter use an auditory cue). Thus, there are two phases to the task, which are analyzed separately. In the synchronization phase the participant is required to tap in time to regularly paced stimuli, typically a pure tone. Tapping usually uses the index finger of the dominant had and the inter tone interval of the pacing tone is generally within the range of a couple of seconds, most commonly around 500 ms. After a certain number of taps the tone ceases and the participant has to maintain the entrained rhythm as accurately as possible. This

is the continuation phase. The accuracy of the tapping rate, usually measured by the mean inter-response interval, is important in determining whether tapping is unusually slow or fast. For measuring the variability of responses, Wing and Kristofferson [42, 43] proposed a model that decomposed tapping variability into 'clock' and 'motor' components. The model assumes that a centralized internal clock that meters time can be dissociated from a motor implementation process, which is triggered by the clock. Although highly influential, the model has certain caveats. First, it assumes that the clock and motor processes are independent and second it does not allow for drift in the length of the participant's taps, despite this being a common phenomenon (e.g. [44, 45]). The Wing and Kristofferson [42, 43] model was designed to delineate the variability of unpaced tapping, which has meant that very few studies report performance on the synchronization section of the task. However, the synchronization phase provides important information about motor timing performance, particularly as a comparison with the continuation phase. For example, performance on the continuation phase would be interpreted differently if the ability to keep pace with the tone in the synchronization phase was poor, compared to if it was good.

It is important to note that varying durations have been used in behavioural timing studies. Perceptual timing tasks range between 50 ms and 120 s, which is in contrast to a far narrower span of between 250 and 2,000 ms for motor timing (see Tables 2 and 3). For perceptual timing tasks, time estimation and time production tasks tend to use longer intervals than the duration discrimination and time reproduction measures. As duration discrimination and time reproduction tasks involve remembering an interval within a trial, the durations are kept short to reduce interference from cognitive demands. A complete understanding of motor and perceptual timing in PD requires direct comparison of task performance using the same durations. Particularly as different time ranges (e.g. millisecond vs. seconds-range) are thought to recruit different neural regions (e.g. [3, 46]) and patients with PD can show differential performance across different time ranges (e.g. [14]).

Behavioural Studies of Temporal Processing in Parkinson's Disease

Perceptual Timing in Parkinson's Disease

A summary of the results from four of the most popular perceptual timing tasks can be seen in Table 2. When investigating perceptual timing in a group with a movement disorder the most effective tasks, and certainly the most easily interpretable, dissociate movement from the temporal decision. The duration discrimination task fits this criterion and performance of patients with PD is compromised in six of ten tasks (60 %) across nine published studies (see Table 2). Using a slightly different paradigm, where a ball moved across a computer screen, individuals with PD showed difficulty at distinguishing velocities as low or high speed [47]. However, the same individuals were successfully able to predict the time at which the moving ball would reach the bottom edge of the screen. This indicates intact temporal prediction in PD, which has also been reported elsewhere [48].

Other perceptual measures that are dissociated from motor performance are the temporal bisection and temporal generalization tasks. Using temporal bisection, Merchant et al. [6] found evidence of increased variability when patients were tested 'off' medication, while Smith et al. [28] found impairment in PD patients tested 'on' medication in both the visual and auditory modality for durations of 1–5 s, although not for a shorter range of 100–500 ms. However, Wearden et al. [25] draw attention to a probable miscalculation of the key timing variables in Smith et al. [28]. In contrast, Wearden et al. [25] found no evidence of impairment in either the temporal bisection or temporal generalization task within the milliseconds range (100–800 ms), and no effect of dopaminergic medication on

Table 2 Summary of findings from studies of perceptual timing in patients with Parkinson's disease when compared to healthy controls

Study	Medication state	Modality	Counting	Type of interval	Standard duration	Results
Duration discrimination						
Guehl et al. [20][a]	Off	Auditory	No	Unfilled	50 ms	Impaired
Harrington et al. [11]	On	Auditory	No	Unfilled	300 and 600 ms	Impaired
Harrington et al. [21][c]	Off	Auditory	No	Unfilled	300 and 600 ms	Impaired
Hellström et al. [22]	On	Auditory	No	Filled	400, 800, 1,200, 1,600 ms	No impairment at group level, although gender differences reported
Ivry and Keele [12]	On	Auditory	No	Unfilled	400 ms	No impairment
Rammsayer and Classen [23]	On	Auditory	No	Unfilled	50 ms	Impaired
Riesen and Schnider [24]	On	Visual	No	Filled	200 ms and 1 s	Impaired
Wearden et al. [25]	On & Off	Auditory	No	Short delay condition: both; long delay condition: filled	400 ms with short delay between the two tones (1,100 ms); 350–650 ms with long delay (2, 4, 8 s)	Short delay: No impairment Long delay: Impairment
Wojtecki et al. [19][a]	Off	Auditory	No	Unfilled	1,200 ms	No impairment
Peak-interval procedure						
Malapani et al. [26]	On & Off	Visual	Random number	Filled	8, 21 s	Impaired accuracy for 21 s. Greater variability for 8 s (Off only)
Temporal bisection						
Merchant et al. [6]	On & Off	Auditory	No	Filled	350, 1,000 ms	Greater variability (Off only)
Smith et al. [28]	On	Both separate	No	Unfilled	100, 500 ms and 1,000, 5,000 ms	Impaired for long (1,000, 5,000 ms) intervals
Wearden et al. [25]	On & Off	Auditory	No	Filled	200, 800 ms	No impairment
Temporal generalization						
Wearden et al. [25]	On & Off	Auditory	No	Filled	400 ms	No impairment
Time estimation						
Lange et al. [29]	On & Off	–	Yes	Filled	10, 30, 60 s	Underestimation (Off only)
Pastor et al. [30]	Off	Visual	Yes	Filled	3, 9, 27 s	Underestimation
Riesen and Schnider [24]	On	Visual	Random number	Filled	12, 24, 48 s	No impairment
Wearden et al. [25]	On & Off	Auditory	No	Filled	10 durations between 77 and 1,183 ms	No impairment
Time production						
Jones et al. [31]	On	Auditory	No	Unfilled	30, 60, 120 s	Overestimation
Lange et al. [29]	On & Off	–	Yes	Filled	10, 30, 60 s	Overestimation (Off only)

(*continued*)

Table 2 (continued)

Study	Medication state	Modality	Counting	Type of interval	Standard duration	Results
Perbal et al. [32]	On	Visual	Yes, and a random number condition	Filled	5, 14, 38 s	Counting condition: No impairment Random number condition: underestimation
Wild-Wall et al. [33]	On	Visual	No	Filled	1,200 ms	No impairment
Wojtecki et al. [19][a]	Off	Visual	No	Unfilled	5, 15 s	Underestimation at 15 s
Time reproduction						
Jones et al. [31]	On	Auditory	No	Unfilled	250, 500, 1,000, 2,000 ms	Reduced variability. Violation of Scalar property
Koch et al. [34][a]	Off	Visual	Random number	Filled	5, 15 s	Overestimate 5 s, Underestimate 15 s
Koch et al. [35]	Off	Visual	Random number	Filled	5, 15 s	Left-hemi PD: Overestimate 5 s, underestimate 15 s Right-hemi PD: Overestimate 5 s
Koch et al. [36]	On & Off	Visual	No	Filled	Short: 400, 450, 500, 550, 600. Long: 1,600, 1,800, 2,000, 2,200, 2,400 ms	Standard condition: Underestimation of long intervals. 1 h delay between short and long trials: No impairment
Merchant et al. [6]	On & Off	Auditory	No	Unfilled	350, 450, 550, 650, 850, 1,000 ms	Increased variability
Pastor et al. [30][b]	Off	Visual	Yes	Both	2, 3, 4.5, 6, 9 s	Overestimation
Perbal et al. [32]	On	Visual	Yes, and a random number condition (during encoding only)	Filled	5, 14, 38 s	Counting condition: No impairment Random number condition: increased variability
Torta et al. [37][a]	On & Off	Both	No	Both	Seconds-range, varied for each participant	Unfilled: No impairment Filled (simple motor task during encoding phase): Underestimation (off only)
Wojtecki et al. [19][a]	Off	Auditory	No	Unfilled	5, 15 s	No impairment

[a]Patients had undergone STN DBS, data in the table are reported when stimulation was turned off
[b]Pastor et al. [30] tested five variations of the time reproduction task. As all tasks produced the same result we present the data as one result in the table, with reference to the different manipulations discussed in the chapter
[c]Data collected during a neuroimaging (fMRI) experiment

Table 3 Summary of findings from studies of the synchronization-continuation task in Parkinson's disease when compared to healthy controls

Study	Medication	Duration (ms)	Synchronization: variability	Synchronization: accuracy	Continuation: variability	Continuation: accuracy
Cerasa et al. [7][a]	Off	750	Increased	PD = Controls	PD = Control	PD = Control
Duchek et al. [9]	On	550	–	–	Decreased (MV) PD = Control (SD)	PD = Control
Elsinger et al. [10][a]	On & Off	600	Increased	PD = Control	Increased	Faster
Harrington et al. [11]	On	300, 600	–	–	Increased (CV, TV)	PD faster
Ivry and Keele [12]	On	550	–	–	PD = Control	PD faster
Jahanshahi et al. [13][a]	On & Off	1,000	PD = Control	PD = Control	PD = Control	PD = Control
Jones et al. [14]	On & Off; De novo	250, 500, 1,000, 2,000	No consistent pattern across durations	Faster at 250 ms	No consistent pattern across durations	Faster at 250 ms
Joundi et al. [15][b]	On	500, 2,000	Increased (CoV)	PD = Control	Increased (CoV, CV, MV)	PD = Control
Merchant et al. [6]	On & Off	350, 450, 550, 650, 850, 1,000	–	–	Increased (SD)	Not reported
O'Boyle et al. [16]	On & Off	550	–	–	Increased (CV, MV, TV) (only CV sig. when On)	PD faster (only sig. when On)
Pastor et al. [17]	On & Off	400, 500, 667, 1,000, 2,000	–	PD slower at 400 and 500 ms	Increased (CV, MV, TV)	PD slower at 400 and 500 ms
Spencer and Ivry [18]	On & Off	550	–	–	PD = Control	PD = Control
Wojtecki et al. [19][b]	Off	800	PD = Control	PD = Control	PD = Control	PD = Control

CoV coefficient of variation, *SD* standard deviation; using the Wing and Kristofferson [42, 43] model: *CV* clock variance, *MV* motor variance, *TV* total variance. The Wing and Kristofferson model is only applied in the continuation phase

[a]Data collected during a neuroimaging (PET or fMRI) experiment

[b]Patients had undergone STN DBS, data reported in the Table are when stimulation was turned off

performance. Of the studies that have reported on the time estimation and time production tasks, both of which require application of a temporal label to intervals, 50 % (2 of 4) of time estimation tasks and 67 % of time production tasks (4 of 6) record impairment in PD (see Table 2). The time reproduction task is a significant source of difficulty in PD on 67 % (8 of 12) occasions. However, the pattern of findings is inconsistent, with reports of both increased and reduced variability and of over and underestimation. Notably, the time reproduction task has the greatest motor demand of all perceptual tasks, with a short temporal decision (commonly < 5 s) having to be made precisely through a motor response. However, studies that have required two different intervals to be reproduced in the same session have found that the longer interval is underestimated, while the shorter interval is overestimated (see below for a full description of this 'migration' effect) (e.g. [34–36]). This effect is not compatible with a simple motor explanation (e.g. slowed motor execution).

The pattern of findings for different tasks can prove illuminating. Lange et al. [29] and Pastor et al. [30] report a compelling finding of underestimation in patients with PD when deciding the length of a temporal interval (time estimation) and overestimation when producing a temporal interval (time production). This pattern is consistent with an internal clock that runs at a slowed rate. However, in both studies the participants were trained to count aloud at a rate of 1 digit per second, which does not give a true estimate of perceptual deficits (see above). However, Jones et al. [31] found similar evidence of overestimation in time production in PD but this time in a condition where participants were explicitly told not to count (although see [19] for a different pattern of results).

Perceptual timing research in PD has uncovered another important phenomenon, the 'migration' effect. When presented in consecutive blocks, it has been noted that shorter intervals ($<$10 s) are overestimated while longer intervals ($\geq$15 s) are underestimated, causing an apparent 'migration' [26, 27]. Using the peak interval procedure in a series of experiments that manipulated task factors including medication state, Malapani and colleagues concluded that two types of dysfunction were evident in PD [27]. First, when individuals with PD learn an interval 'off' medication they subsequently overestimate the interval when medicated; this indicates a storage dysfunction. Second, when individuals with PD reproduce the intervals when 'off' medication (regardless of their medication state when learning) they produce the migration effect; this indicates a retrieval dysfunction. Importantly, the data indicate that the memory for the learnt durations is the source of the temporal deficit, rather than the 'clock' process itself. Using the time reproduction task, a similar migration effect was reported for intervals of 5 and 15 s [34, 35]. In a study using shorter intervals (500 and 2,000 ms), Koch et al. [36] found significant underestimation of the 2,000 ms in PD group. However, when the short and long intervals were separated by a delay of an hour, the migration effect disappeared. Thus, Koch et al. [36] suggest the phenomenon has a general cognitive explanation, such as set-shifting. In a novel re-working of the time reproduction task, Torta et al. [37] required the time taken for the participant to perform an activity (unscrewing a bolt from a nut) to be reproduced, without replication of the activity (participants had to tap a desk to mark the onset and offset of the interval). This meant that a filled interval was learnt in the context of a dual task and reproduced in an unfilled context. Whereas performance was unimpaired in a standard version of the time reproduction task, the group with PD significantly underestimated on the motor version. The authors interpret the data in terms of attentional allocation (e.g. [49]), arguing that the motor task is demanding for the patients and therefore routes attention away from the secondary task of time perception. The relative lack of attention given to temporal processing leads to underestimation.

The Importance of Cognitive Factors

These findings lead to an important area of debate, does the temporal deficit in PD reflect the dysfunction of critical timing regions or is impairment of global cognitive processes (e.g. attention, memory, executive skills) the root cause? One way of testing the specificity of the temporal deficit is to use carefully selected control tasks. Studies have commonly found a deficit on the duration discrimination task in PD, while performance on other types of discrimination task (e.g. frequency) remains unaffected (e.g. [11]). However, as discussed above, whether these control tasks are sufficiently cognitively demanding is questionable. Using a rhythm discrimination task, Grahn and Brett [50] showed that participants with PD were as proficient as controls when the rhythm did not contain a beat but showed poorer performance when a beat was present. This study is particularly notable as rhythms with a beat structure are easier to discriminate than non-beat rhythms. A specific deficit in the easier beat condition suggests that global and non-specific cognitive or perceptual difficulties are not the explanation.

Another way for testing the independence of the temporal deficit is to measure the extent to

which cognitive impairment is correlated with timing task performance. Using exploratory factor analysis, Jones et al. [31] found that the time production of seconds range intervals (30–120 s) and a measure of attention (Paced Auditory Serial Addition Test) formed a common factor, distinct from time reproduction (250–2,000 ms) and a warned and unwarned reaction time task. This supports the hypothesis that cognitive mechanisms relate to the production of time intervals in the seconds-to-minutes range, a cognitive load that is not common to all timing tasks. In a rigorous study testing participants with PD on five different perceptual timing tasks, Wearden et al. [25] found that the only task that significantly discriminated the group with PD from the control group was a duration discrimination task that required the standard interval to be held in memory for 2–8 s. Wearden et al. [25] comment that studies that find temporal processing differences in PD tend to use tasks where two stimuli have to be processed. They therefore suggest a cognitive explanation for the difficulties, for example, impaired sequential processing or attention-switching. This interpretation aligns with Riesen and Schnider [24] who found impairment on a duration discrimination task using an unusual protocol where the two intervals were presented simultaneously but with different onsets and offsets. They suggest their results may be best explained by a failure of divided attention or working memory, although further research using additional manipulations (e.g. a comparison with sequential durations) would be needed to more fully support this interpretation. Guehl et al. [20] reported that participants with PD were impaired on a duration discrimination task with a standard interval of 50 ms (defined by two clicks) and a comparison interval that was longer to varying degrees. However, they were unimpaired on a very similar duration discrimination task where trains of clicks paced at 50 ms intervals were used. Participants had to determine which of the two trains of isochronous clicks had one long interval ($>$50 ms) in the middle. Thus, although the durations were identical the context they were embedded in was different. One interpretation suggested by the authors was that the first task requires a greater allocation of attentional resources, as the onset of the stimuli cannot be predicted as easily. However, Merchant et al. [6] found that performance on a range of cognitive tasks (working memory, go/no-go reaction time and verbal learning) did not discriminate those with PD who did well or poorly on a range of motor and perceptual timing tasks with intervals $\leq$1 s. This suggests that impaired memory and attention were not driving timing difficulties in their sample. However, surveying across all of the studies, there seems to be evidence that cognitive factors can influence performance on perceptual timing tasks in PD, which aligns with the documented cognitive deficits of this group. Of course, this does not preclude that genuine clock dysfunction is also present. Certainly, data such as those presented by Grahn and Brett [50] are compelling. Also, the finding of duration discrimination deficits using very short intervals (50 ms) (e.g. [20, 23]) compared to preserved performance using equivalent tasks with much longer durations (e.g. [19, 22]), albeit in different samples, would not be predicted by a purely cognitive explanation.

The Importance of Task Factors

Across the range of most common perceptual timing tasks (Table 2), 23 of 37 tasks (62 %) demonstrate a different pattern of performance in PD. This is perhaps low given the publication bias for positive findings. However, both the heterogeneity of PD and the effects of aging on temporal processing (see [33]), which means a well-matched control group is critical, may in part explain the mixed findings. Another reason for the variation in the results is task differences. When looking at relevant tasks (peak-interval procedure, time estimation, time production, and time reproduction) that included a timed motor element, 4 of 6 (67 %) of the tasks that using counting reported between-group differences, whereas 5 of the 6 (83 %) that used random numbers reported differences. For both, this is higher than for tasks where no counting was included (6 of 11, 55 %). Therefore, the presence of a paced element, which may change

the nature of the temporal and cognitive processes being utilized, is more likely to produce impairment. Another important distinction is the length of the intervals being used. Previous research has suggested that the time range may affect the type of timing and the pattern of neural activation (e.g. [46]). A particular emphasis has been placed on millisecond vs. seconds-range timing (e.g. [3]). If millisecond-range timing is defined (arbitrarily) as between 1 and 1,000 ms and seconds-range timing as intervals >1,000 ms, 6 of 15 (40 %) millisecond-range tasks find evidence of impairment compared to 16 of 26 (62 %) seconds-range tasks. If the cutoff is increased to 5 s and above then the proportion of longer interval tasks that the PD group perform poorly on increases to 71 % (12 of 17). This suggests that temporal processing in the seconds-range is more challenging, which may relate to the additional cognitive demands (e.g. [31]). It is worth commenting that this is collapsing across all studies and the pattern is more nuanced if a task breakdown is used. For example, for the duration discrimination task, both studies that used very short millisecond standard intervals of 50 ms reported impairment [20, 23], whereas the studies with durations from 200 to 1,600 ms presented with more mixed results. Importantly, although it has previously been suggested that the basal ganglia are only implicated in seconds-range timing [3], this does not seem to be the case when reviewing the studies. These data complement neuroimaging work that has found the basal ganglia are active in both millisecond and seconds-range temporal processing [46].

Focusing on the five types of task that present a stimulus to be timed (time reproduction, duration discrimination, temporal bisection, temporal generalization, and peak-interval procedure), there are group differences for 9 of the 16 (56 %) tasks using the auditory modality but for 9 of the 11 (82 %) tasks that use the visual modality. Modality of presentation is known to have an effect on temporal processing, with auditory stimuli judged as longer than equivalent visual stimuli [51]. Further, temporal sensitivity is poorer in the visual modality in healthy adults and children [52]. Zélanti and Droit-Volet [52] also found that temporal performance in the visual modality was significantly associated with visual selective attention, but that there was no equivalent association in the auditory modality. It was concluded that temporal processing in the visual domain is more cognitively demanding. This task-related difference may therefore indicate the influence of general cognitive factors on performance on these tasks for individuals with PD. An alternative interpretation is that there are separable modality-specific neural clocks and that the visual clock is more compromised. However, recent research reports that auditory judgments are influenced by the presentation of visual durations, and vice versa, which suggests that visual and auditory durations are timed by a 'common code' and not by modality-specific processors [53]. As the tasks using visual cues were more likely to be seconds-range than the auditory tasks, further studies are needed to corroborate the interpretation that the auditory domain is differentially more demanding in PD.

Looking across all the tasks in Table 2, of the 14 using unfilled intervals, 9 showed differences between groups (64 %), which contrasts with 15 of the 25 tasks using filled intervals (60 %). However, if the 13 tasks that used counting, random numbers or motor activity are removed and the focus is just on tasks that used simple visual stimuli or pure tones to fill the interval, then just 5 of the 12 (42 %) studies with filled interval tasks reported a deficit in PD. Filled intervals are routinely judged as longer than unfilled intervals (e.g. [54]), with animal research suggesting that filled intervals are also timed with more precision [55]. Therefore, when comparing across studies it appears that tasks that are unfilled (compared to filled) and visual (compared to auditory) are more demanding for individuals with PD. Wearden et al. [25] required participants to complete both unfilled and filled versions of the duration discrimination task. Supporting the pattern across studies, the difference between the PD and control groups appeared more marked in the unfilled condition, although a direct comparison across stimulus

type was not reported. On the other hand, Pastor et al. [30] found no difference in the time reproduction of filled and unfilled intervals in PD, although participants were given no specific instructions in the unfilled condition so may have used the counting that they were trained to apply in the filled condition. It has been suggested that the internal clock ticks at a slower speed for unfilled and visual intervals (i.e. producing less clock ticks per unit of time) compared to their filled and auditory equivalents, and that this explains the relative overestimation in the filled and auditory versions in healthy populations (e.g. [51, 54]). Why auditory and filled durations produce a faster clock is not clear, although it may relate to differences in arousal. Further, it remains to be established why stimuli that induce a slower clock pace are more problematic in PD and whether this relates directly to their hypothesised slowed clock (e.g. [30]) or to generic cognitive demands. Future research would benefit from exploring this finding.

In summary, individuals with PD often perform poorly on measures of perceptual timing, implicating the basal ganglia in interval timing. These results have been interpreted in terms of a slowed internal clock, but it is likely that compromised cognitive functioning also influences performance. The data suggest both millisecond and seconds-range perceptual timing are impaired in PD, and cognitive factors may be more important for longer durations. Finally, stimuli that are unfilled and presented in the visual modality are the most challenging in PD. Greater consideration needs to be given to the extent to which these stimulus properties influence temporal processing in PD and what they can tell us about the role of the basal ganglia in timing. Finally, greater consideration of the interaction between time-dependent computations and supportive cognitive processes is required.

Motor Timing in Parkinson's Disease

As mentioned previously, investigation of motor timing has focused on the synchronization-continuation task, with the majority of studies only investigating continuation performance. However, although both healthy participants and those with PD perform better at synchronization than continuation tapping (e.g. [14]) there is no convincing evidence that the pattern of impairment in PD differs significantly between the two phases (e.g. [14, 15, 17, 19], although see [10]). A summary of the studies into motor timing in PD can be found in Table 3.

There have been varied results for accuracy on the synchronization-continuation task. Tapping rate in PD has been shown to be faster [10–12, 14, 16], slower [17], and unimpaired [7, 9, 13, 15, 18, 19]. To help make sense of these inconsistencies it is important to focus on the differences between the tasks used. Notably, there is a cluster of studies compatible with the hypothesis that accuracy of repetitive finger movement is only impaired at rates faster than 500 ms, at slower rates patients with PD are able to demonstrate preserved performance (e.g. [7, 9, 13–15, 18, 19]). This pattern is also observed in tasks that have just measured synchronized tapping [56–58]. In contrast, many studies report that individuals with PD tap significantly faster than a control group at intervals of 300–600 ms [10–12, 16]. One interpretation of these findings is that individuals with PD are demonstrating festination at these shorter intervals. Festination is a clinical phenomenon often observed in PD and is the tendency to speed up when performing a repetitive movement. Experimentally it is identified when movement speed exceeds that in a control group by a specified margin (e.g. 2 standard deviations) and has been recorded for a variety of movement types, including oral, finger and wrist (e.g. [56, 59–61]). Reflecting these findings, other studies demonstrating the phenomenon of festination report it in movement rates of 500 ms and faster [56, 59–61]. In contrast, two studies [17, 59] found evidence of slowed tapping at short intervals (200–500 ms), but they used repetitive wrist movements, making a comparison with the traditional synchronization-continuation tasks difficult.

It appears that the interval range of 400–600 ms is of critical importance in PD, as

this is the threshold at which performance switches from impaired to unimpaired. It has been suggested that movement rates of around 500 ms (i.e. movement frequencies of 2 Hz) are associated with a transition in control strategy. At this faster rate, the timing of continuous movements to a cue shifts from a synchronization strategy (i.e. individually controlled movements), to a syncopated strategy (i.e. control over the rhythm of movements rather than each individual movement, as indicted by a lag in producing the movement) [62]. While slower movements can be executed in a closed-loop fashion, where motor commands are continuously compared to afferent information, the execution of faster movements depends on a motor program being generated before movement onset and controlling performance in the absence of feedback (e.g. [63]). This dissociation is supported by neuroimaging (positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)) evidence that the pattern of sensorimotor activation during repetitive index finger tapping is different for slower (0.25–0.5 and 0.5–1 Hz) compared to faster (1–4 and 1.5–5 Hz) rates of movement [64, 65]. Thus, in PD the difference in motor control strategy may make timing faster movements differentially more demanding. Using an electroencephalogram (EEG) to measure β band oscillations, Toma et al. [62] found that timing a repetitive thumb movement with a slow pacing signal (below 2 Hz) activated motor cortical areas (i.e. event-related desynchronization of neuronal populations) and was followed immediately by deactivation (i.e. event-related synchronization). In contrast, for faster movements (above 2 Hz) the motor cortical areas were continuously activated without any synchronization. It has been suggested that the impairment of faster repetitive movements in PD may relate to a difficulty in the desynchronization of elevated β band oscillations [57]. Logigian et al. [56] argue that there is 'attraction' of repetitive voluntary movements to the strong neural synchronization that drives pathological tremor in PD. As such, the movements become 'entrained' to the tremor rate.

Reviewing the findings for variability, a majority of studies reported elevated levels of variability on the synchronization-continuation task in PD (e.g. [6, 7, 10, 11, 15–17]) but other studies found no impairment [12, 13, 18, 19] or decreased variability [9]. There is no consistent pattern that relates timing variability to interval length, although Jones et al. [14] observed that variability for both patients with PD and healthy controls was lowest at 500 ms. Five hundred milliseconds is close to the natural tapping rhythm (i.e. when tapping at their most comfortable pace) of individuals with and without PD [58]. Combined with the pattern of findings from the accuracy of synchronization-continuation performance, the variability results again suggest the importance of evaluating the shorter interval ranges when investigating motor timing performance in PD.

In summary, ten (77 %) of the thirteen studies report group differences in the variability and/or accuracy of motor timing, making motor timing more discriminating than perceptual timing. However, close analysis of the pattern of findings suggests that focus should be given to intervals under 600 ms, with particular emphasis on identifying the shift from impaired to unimpaired accuracy at around 400–600 ms. This may reflect the conceptual and neural shift in the way that the shorter intervals are timed, with the timing and production of shorter intervals being more demanding in PD.

Neuroimaging Studies of Temporal Processing in Parkinson's Disease

Although highly informative, behavioural studies only provide a limited window on the role of the basal ganglia in temporal processing. The basal ganglia are a highly connected set of structures and the pathology in also PD influences the functioning of these other regions. PD is associated with excessive inhibitory outflow from the basal ganglia, which means that cortical sites are not adequately activated. The frontostriatal motor loop is particularly affected, which implicates the supplementary motor area (SMA) and pre-SMA [66]. As the disease

progresses more widespread areas of the frontal cortex are implicated. As such, it is feasible that cortical, as well as subcortical, dysfunction is driving the temporal deficits observed in PD. One obvious way to test this hypothesis is to use neuroimaging techniques to reveal the extent of cortical and subcortical patterns of neural activation during a timing task. A handful of studies have used imaging to examine the neural substrates of perceptual and motor timing in PD. The results of these studies are summarized in Table 4.

To date, only two studies have investigated the neural correlates of perceptual timing in PD. In the first study, Harrington et al. [21] scanned 21 patients with PD both 'on' and 'off' dopaminergic medication and 19 healthy controls during a duration discrimination task. Standard durations of 1,200 or 1,800 ms were presented followed by a comparison duration and participants had to decide if the comparison was longer or shorter than the standard. Data were obtained during both the encoding and decision phases of the task. Striatal dysfunction was found in both phases, highlighting its key role in timing. However, activation in distributed areas of the cortex were also recorded. During the encoding phase, activation interpreted as part of a working memory network (middle frontal-inferior parietal regions, supplementary motor area (SMA), and lateral cerebellum) was dysfunctional, whereas during the decision making phase activation in regions relevant to executive processes and memory retrieval were atypical (posterior-cingulate, parahippocampus). Dopamine medication did not alleviate the timing deficits on the task in the patients, and effective connectivity between the striatum and cortex was modulated by dopamine medication in the decision phase. Specifically, there was greater connectivity between the striatum and medial frontal gyrus, SMA, pre- and postcentral cortex, insula and parietal cortex 'off' compared to 'on' medication. This authors interpreted this as reflecting excessive synchronicity in corticostriatal circuits. In contrast, the connections between the striatum and left superior frontal gyrus were greater 'on' than 'off' medication.

In another fMRI study, Dušek et al. [67] scanned 12 PD patients 'on' and 'off' medication in the encoding and reproduction phases of a time reproduction task with short and long intervals (range 5 to 16.82 s). Medication had no effect on performance of the task. However, in the reproduction phase, significantly greater activation in the precuneus was found 'on' than 'off' medication, which was not present during a control random button pressing task. It was concluded that differences in activation of the precuneus during retrieval of an encoded duration may underlie the time perception deficits in PD (as documented in the 'migration effect' for example), which is partly alleviated by dopaminergic medication.

As shown in Table 4, the neural correlates of motor timing in PD has been investigated in four studies, three of which employed the synchronization-continuation task [7, 10, 13], whilst Yu et al. [80] just used the synchronization phase. Elsinger et al. [10] and Jahanshahi et al. [13] assessed patients both 'on' and 'off' medication, whereas Cerasa et al. [7] and Yu et al. [80] only scanned patients in the 'off' state after overnight withdrawal of dopaminergic medication. The study of Jahanshahi et al. [13] was the only one with an additional reaction time task to control for the non-temporal aspects of the synchronization-continuation paradigm, such as anticipation of the tone, motor preparation, and execution of a motor response. For the controls, relative to the control task, motor timing in the synchronization and continuation phases was associated with increased activation in the right middle frontal gyrus (BA 8) and the left caudate compared to the PD patients. In contrast, compared to the controls, PD patients showed greater activation of the midbrain/substantia nigra, vermis and the cerebellar lobule V during motor timing relative to the control task. Thus, while the controls were recruiting fronto-striatal areas more than PD, the patients were relying on the vermis and cerebellum for motor timing. For both groups, the internally controlled timing in the continuation phase was associated with significantly greater activation of the DLPFC compared to the externally paced

Table 4 Summary of imaging studies of perceptual or motor timing in Parkinson's disease

Study	Imaging technique	Sample	Medication state	Task	Duration	Main findings
Cerasa et al. [7]	fMRI	10 PD 11 HC	Off	S-C finger tapping	750 ms	See Table 3 for behavioral results. No differences between S and C phases for either PD or HCs except in visually related areas. During S phase, relative to HCs, PD showed increased activation in cerebellum, putamen, SMA and thalamus, inferior frontal gyrus, frontal operculum, lingual gyrus and insula. In the C phases, relative to HCs, PD showed greater cerebello-thalamic activation
Dušek et al. [67]	fMRI	12 PD	On & off	Time Reproduction & Control random button pressing	5, 5.95, 7.07, 8.41, 10, 11.89, 14.4, 16.82 s	A 'migration effect' was observed, with intervals $\leq$ 11.9 s overestimated and intervals $\geq$ 14.1 s underestimated in the 'off' compared to the 'on' medication state. Significantly greater activation in the precuneus 'on' than 'off' medication during the reproduction but not encoding phase
Elsinger et al. [10]	fMRI	10 PD 13 HC	On & off	S-C finger tapping	600 ms	See Table 3 for behavioral results. PD less activation in SMC, cerebellum and SMA than HCs. SMA, thalamus and putamen active in PD during the C phase when on but not off medication. NB. Direct statistical comparison of the conditions not reported.
Harrington et al. [21]	fMRI	22 PD 10 HC	On & off	Duration discrimination	1,200, 1,800 ms	See Table 2 for behavioral results. Striatal dysfunction evident in both the encoding and decision phases when PD were compared 'off' to HCs. During encoding, PD also showed underactivation of a working memory network (middle frontal-inferior parietal, SMA, lateral cerebellum). During the decision making phase there was abnormal activation of regions involved in executive processes and memory (posterior-cingulate, parahippocampus). Connectivity between the striatum and areas of frontal and parietal cortex was greater 'off' than 'on', and the putamen showed greater connectivity with the left superior frontal gyrus 'on' compared to 'off'

(*continued*)

Table 4 (continued)

Study	Imaging technique	Sample	Medication state	Task	Duration	Main findings
Husárová et al. [68]	fMRI	20 PD 21 HC	Off	Target interception task	Not applicable	Similar hit ratios in the two groups, but the groups differed in the distribution of early errors relative to hits and in trial by trial adjustments of performance. During successful trials, more activation in the right cerebellar lobule VI in HC than in PD. In HCs compared to PD, successful trial by trials adjustments were associated with higher activity in the right putamen and cerebellar lobule VI
Jahanshahi et al. [13]	PET	8 PD 8 HC	On & off	S-C finger tapping & Control RT task	1,000 ms	See Table 3 for behavioral results. Relative to control task, motor timing (S + C) associated with greater fronto-striatal activation for HCs, but greater activation of the cerebellum, vermis, midbrain/ substantia nigra for PD. Relative to S, C associated with greater activation of DLPFC for both HC and PD. Cortical activation more predominant 'on' medication, whereas pallidal and cerebellar activation more evident 'off' medication. Greater caudate-frontal connectivity 'on' medication and greater striatal-cerebellar connectivity 'off' medication
Yu et al. [80]	fMRI	8 PD 8 HC	Off	Synchronization thumb tapping	900, 2,400 ms	No difference in behavioral performance for PD and HC. Underactivation in PD of the SMA, pre-SMA, DLPFC, caudate and putamen. Overactivation in PD of the cerebellum and primary motor cortex. This pattern was observed for both durations. Negative correlation between putamen and cerebellum in PD

PD Parkinson's disease, *HC* healthy control, *PET* Poistron emission tomography, *fMRI* functional magnetic resonance imaging, *S-C* synchronization-continuation, *SMC* sensorimotor cortex, *SMA* supplementary motor area

synchronization phase. Overactivation of the cerebellum in PD during motor timing has also been reported in Cerasa et al. [7] and Yu et al. [80]. Yu et al. [80] additionally reported underactivation of the striatum when 'off' medication, although Cerasa et al. [7] found overactivity in frontostriatal regions during the synchronization phase in patients tested 'off' medication. When looking at medication effects, Jahanshahi et al. [13] reported that cortical activation was significantly more predominant 'on' medication, whereas pallidal and cerebellar activation was greater 'off' medication. Two distinct patterns of effective connectivity were found 'on' and 'off' dopaminergic medication. While there was greater task-related connectivity between the caudate and the left DLPFC and the right middle prefrontal cortex (BA 10/32) 'on' than 'off' medication, striatal-cerebellar connectivity was greater 'off' than 'on' medication.

These findings align with Yu et al. [80], who reported a negative correlation between activation of the ipsilateral cerebellum and contralateral putamen during synchronized tapping in patients with PD. Further, Elsinger et al. [10] found activation of the motor frontostriatal loop in patients with PD during the continuation phase when they were 'on' medication but not when they were 'off'.

In contrast, Husárová et al. [68] used a computerized target interception task, which requires implicit processing of time rather than the explicit engagement demanded by classic motor and perceptual tasks. A target moved at three different angles and speeds across the screen and the participants had to press a button to fire a cannonball that would intercept the moving target. The study used fMRI with 20 early stage (mean duration of illness of 2.5 years, including 8 de novo cases) patients with PD tested 'off' medication and 21 controls. Similar hit ratios were observed in the two groups, but the groups differed in the distribution of early errors relative to hits and in their trial by trial adjustment of performance. During successful trials, there was more activation in the right cerebellar lobule VI in the controls than in PD. For the controls, but not the PD patients, successful trial by trials adjustments were associated with higher activity in the right putamen and cerebellar lobule VI. Indeed, PD was characterized by hypoactivation of the striatum and cerebellum relative to the healthy controls. This study therefore implicates both the basal ganglia and the cerebellum in the adaption of motor actions to achieve optimal temporal performance. However, as a note of caution, none of the patients in this study had started levodopa medication. As levodopa responsiveness is a key criterion for distinguishing idiopathic PD from other Parkinsonian syndromes such as progressive supranuclear palsy or multiple systems atrophy, it is possible that not all participants in the patient group had idiopathic PD.

In summary, the results of these imaging studies indicate that, relative to healthy controls, perceptual and motor timing deficits in PD are associated with underactivation of a range of frontal, temporal and parietal cortical areas as well as the striatum. Medication does not fully normalize these dysfunctional patterns of brain activation. In addition, the findings of some (e.g. [13]), but not all (e.g. [21]), studies suggest that patients with PD rely on the cerebellum for temporal processing, particularly in the 'off' medication state when task-related striatal-cerebellar connectivity is increased.

Effects of Medical Treatments on Temporal Processing in Parkinson's Disease

Pharmacological treatment and DBS are the two common medical treatment options in PD. The primary pharmacological treatment is a precursor to dopamine, levodopa. Levodopa is converted to dopamine in the central nervous system by the enzyme DOPA decarboxylase, which brings therapeutic benefit in PD. More recently, direct acting dopamine agonists have come into use. DBS involves implanting electrodes in key target areas, most commonly the sub-thalamic nucleus (STN). These electrodes are then connected to an implanted device in the chest cavity, generating electrical impulses to stimulate the STN. A recent study has shown that both STN DBS and a dopamine agonist (apomorphine) deactivate regional cerebral blood flow (rCBF) in the supplementary motor area, precentral gyrus, postcentral gyrus, putamen and cerebellum, and increase rCBF in the substantia nigra/sub-thalamic nucleus and superior parietal lobule [69]. However, the treatments also had distinct effects. Notably, STN DBS affected wider areas of the SMA, precentral gyrus and postcentral gyrus as well as uniquely affecting the globus pallidus, whilst apomorphine affected wider areas of the putamen and cerebellum and uniquely activated the superior temporal gyrus. Further, the direction of the effects on particular regions was often different between treatments. Certain areas (e.g. posterolateral cerebellum, ventrolateral thalamus) had their rCBF increased by STN DBS but decreased by apomorphine.

Thus, although both treatments have proven efficacy in ameliorating the cardinal symptoms of PD, they will not necessarily have identical effects on temporal processing. Further, it is important to recognize that both treatments do not just produce isolated effects on the basal ganglia, but rather both treatments induce changes in activation in the cortex [69]. Related to this, in addition to the targeted motor benefit, both medical treatments affect cognition, both positively and negatively, (e.g. [70, 71]).

The Effects of Dopaminergic Medication

Close to half the studies reviewed in this chapter compared performance both 'on' and 'off' medication (see Table 5). For studies of motor timing, one study found that levodopa improved accuracy for short intervals [17] and one found an ameliorating effect on variability [16]. However, two studies found that medication did not improve motor timing [12, 14]; with a further two studies not reporting a direct comparison [6, 10]. A final two studies [13, 18] found no evidence that medication improved performance but interpretation is difficult as performance was also unimpaired 'off' medication. Overall, for the studies reporting a direct comparison in the context of impairment in the 'off' medication state, 3 of the 5 (60 %) reported a beneficial effect of dopamine replacement therapy. For the perceptual tasks, 6 of 12 tasks reporting a direct comparison found that medication benefits perceptual timing (50 %), while 4 (33 %) found no difference. Two studies (17 %) found better performance 'on' medication than 'off' [31, 36], which may reflect the negative effect dopamine can have on relatively preserved basal ganglia circuits, known as the 'dopamine overdose' effect. Therefore, although dopaminergic medication clearly can have a positive effect, there are many instances where it is not sufficient to impact upon performance. This may reflect a range of factors, including the different types of dopaminergic medication that patients take, as well as their effectiveness on the individual. Further, there are likely to be lingering effects of medication in patients tested 'off' medication, which would diminish the extent of the performance difference observed 'on' vs. 'off'. Patients can also vary in their disease severity and duration of illness, which are factors that can also influence the impact of medication. Merchant et al. [6] tested the effect of dopaminergic medication across a range of perceptual and motor timing tasks. They found that while variability on their three timing tasks correlated in the 'on' medication state, the effect was not apparent when 'off' medication. They argued that the dopamine depleted state causes a major disruption to a common timing mechanism, located in the basal ganglia-thalamocortical pathway, that underpins motor and perceptual timing. It is also important to consider the wide-reaching effects that medication have on cortical structures. Thus, improvements following medication may reflect better cognitive control during the task. For example, Koch et al. [36] found that patients with PD showed greater underestimation on a time reproduction task when 'off' medication compared to 'on'. They suggested that this could reflect impulsivity or delay aversion when in the unmedicated state.

The Effects of Deep Brain Stimulation of the Subthalamic Nucleus

Testing patients with STN DBS, Koch et al. [34] found that when 'off' DBS and 'off' medication the patients showed overestimation of 5 s and underestimation of 15 s intervals (i.e. the migration effect) compared to a control group. Performance was improved when the patients were either 'on' DBS (whilst 'off' medication) or 'on' medication (whilst 'off' DBS). The data are presented as evidence of the importance of thalamo-cortical projections to the prefrontal cortex in temporal processing. Similarly, Wojtecki et al. [19] found that there was improvement in time production of 15 s intervals for 130 Hz STN DBS compared to being in an untreated state. However, when they used a much lower 10 Hz DBS, time reproduction and production of 5 and 15 s intervals worsened. They

Table 5 Effect of dopaminergic medication on motor and perceptual timing tasks

Study	Effect of dopaminergic medication
Synchronization-continuation	
Elsinger et al. [10][a]	Off less accurate (Cont only) and more variable than Control On less accurate (Cont only) and more variable than Control
Ivry and Keele [12]	Off = On
Jahanshahi et al. [13][a]	Off = On
Jones et al. [14]	Off = On
Merchant et al. [6]	Off more variability than Control On more variability than Control
O'Boyle et al.[16])	Off more variability than On
Pastor et al. [17]	Off less accurate and more variable than On for 500 and 667 ms (no statistical test)
Spencer and Ivry [18]	Off = On
Duration discrimination	
Guehl et al. [20]	Off = On
Harrington et al. [21][a]	Off = On
Wearden et al. [25]	Short delay: Off = On Long delay: Off = On
Peak interval procedure	
Malapani et al. [26]	Off more error than On
Temporal bisection	
Merchant et al. [6]	Off more variability than Control On = Control
Wearden et al. [25]	Off = On
Temporal generalization	
Wearden et al. [25]	Off = On
Time estimation	
Lange et al. [29]	Off underestimate compared to Control On = Control
Pastor et al. [30]	Off more error than On
Wearden et al. [25]	Off = On
Time production	
Jones et al. [31]	On more error than Off
Lange et al. [29]	Off overestimate compared to Control On = Control
Time reproduction	
Jones et al. [31]	Off = On
Koch et al. [34]	Off less accurate than On
Koch et al. [35]	L hemi PD: Off less accurate than On for 15 s interval R hemi PD: Off less accurate than On for 5 s interval
Koch et al. [36]	On less accurate than Off Off = On when 1 h delay between short and long trials
Merchant et al. [6]	Off more variability than Control On more variability than Control
Torta et al. [37][b]	Unfilled: Off = On Filled: Off underestimate compared to On
Pastor et al. [30]	Mixed results [Off generally worse than On for shorter intervals, and Off = On for most longer interval conditions (6 and 9 s)]

Direct comparison of 'off' vs 'on' reported where relevant. Two comparisons with Control groups reported in absence of direct comparison. *Cont* continuation phase

[a]Data collected during a neuroimaging (PET or fMRI) experiment

[b]Patients had undergone STN DBS, data reported in the table are when stimulation was turned off

interpret this as STN DBS having a frequency-dependent modulatory impact on memory representations of time, with a frequency of 10 Hz causing further disruption to an impaired temporal processing system, in contrast to the beneficial effects of 130 Hz. A further study found no effect of STN DBS on time reproduction of a seconds-range interval, albeit where performance was unimpaired without treatment, although STN DBS and medication both improved performance when the learnt interval was filled with performance of a motor task [37]. Wojtecki et al. [19] found no effect of STN DBS on millisecond-range repetitive tapping or duration discrimination, although again in patients who showed no difference from controls under any treatment state. However, a more recent study found that patients with PD who were 'on' medication had elevated variability on the synchronization-continuation task and this was improved when STN DBS was turned 'on' [15].

In summary, both medication and DBS can produce beneficial effects on temporal processing in PD. This is further evidence that the efficacy of the dopamine-rich basal ganglia is necessary for interval timing. From studies that investigated medication effects, medication is more beneficial in motor than perceptual timing, which may relate to the dominant motor demands of the former task.

Conclusions and Future Directions

The phenotype of PD is broad, encompassing a range of motor, autonomic and cognitive symptoms (e.g. [72]). To better understand the mixed nature of some of the results reviewed above, an obvious point of exploration is to investigate heterogeneity of PD. The commonly identified clinical subtypes include those with predominantly akineto-rigid symptoms versus patients with tremor predominant symptoms [73]. Subgroups of patients can also be distinguished by age of onset, progression rate, and affected motor and non-motor domains (e.g. [74, 75]). The mixed results for motor and perceptual timing deficits in PD may be clarified through greater attention to clinically or experimentally defined subtypes. Using an experimental approach, Merchant et al. [6] have sought to examine heterogeneity in timing in PD. They were able to divide their nineteen patients into those with 'high' variability on three diverse perceptual and motor timing tasks, and those with 'low' variability. Those with low variability did not differ in performance from a control group, which was in contrast to the group with high variability. Within the high variability group they found a further subdivision of just three individuals who did not show the scalar property, a hallmark of temporal processing. The two groups did not differ in a clinical evaluation of motor dysfunction or an experimental assessment of tapping speed, suggesting a specific difference in timing proficiency rather than a general difference in disease progression. More studies are needed that consider the effect of heterogeneity in PD. Heterogeneity may be the key to better understanding the specific clinical and biological markers of disordered motor and perceptual timing in PD.

Although the evidence on motor and perceptual timing deficits in PD is mixed, some clear conclusions can be drawn. First, there is evidence of both motor and perceptual timing dysfunction in PD. This suggests the importance of the basal ganglia in both types of timing and is compatible with the role of these subcortical nuclei as a neural clock that meters timing processes. However, this is still very much an area for debate. Although the basal ganglia may play a clock-type role in both types of timing tasks, the specific nature of this role may differ. Alternatively, they may play a timing-related role in limited types of timing task, with other findings being largely driven by cognitive or motor factors. While perceptual timing is compromised in both the milliseconds and seconds-range in PD, the deficits are confined to short (commonly 500 ms or below) intervals in motor timing. The very nature of motor timing does not lend itself to very long intervals. Long seconds-range motor timing would lose the continuous quality and become

a serious of remembered, discrete intervals, much like a time reproduction task. However, studies suggest motor timing performance is preserved even at 1,000 and 2,000 ms intervals (e.g. [14]). Consistent with a critical role for the basal ganglia in temporal processing, medical treatment of PD with dopaminergic medication and STN DBS often has a positive effect on task performance. Better understanding of why some studies do not report evidence of a temporal deficit in PD, which may relate to task factors, cognitive factors or patient heterogeneity, is likely to be critical in furthering characterizing the role of the basal ganglia in interval timing.

Many researchers have considered a cognitive explanation for some of the timing deficits in PD, particularly on the perceptual timing tasks, and this alternative explanation needs to be empirically investigated in future studies. Understanding issues such as whether it is meaningful to separate memory for a timed interval from a 'clock' process would further interpretation of the data. Theoretical work on temporal processing has been limited, and has been dominated by the very influential scalar expectancy theory [76, 77]. More recently, the striatal beat frequency [78, 79] has aimed to provide a biologically plausible model of temporal processing. The field could benefit from further testable models of timing behaviour that could guide empirical investigation. This is clearly an important avenue for future progress in timing research.

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Part V

Neural Underpinnings of Rhythm and Music

Music Perception: Information Flow Within the Human Auditory Cortices

Arafat Angulo-Perkins and Luis Concha

Abstract

Information processing of all acoustic stimuli involves temporal lobe regions referred to as auditory cortices, which receive direct afferents from the auditory thalamus. However, the perception of music (as well as speech or spoken language) is a complex process that also involves secondary and association cortices that conform a large functional network. Using different analytical techniques and stimulation paradigms, several studies have shown that certain areas are particularly sensitive to specific acoustic characteristics inherent to music (e.g., rhythm). This chapter reviews the functional anatomy of the auditory cortices, and highlights specific experiments that suggest the existence of distinct cortical networks for the perception of music and speech.

Keywords

Auditory cortex • fMRI • Spectro-temporal • Music • Speech

Introduction

Music is defined as a set of sounds with specific attributes (such as frequency and timbre) that are presented temporally as patterns, following rules that can be adjusted to create different sensations based on cultural and stylistic categories. Time is evident in music at different scales, with the smallest oscillations in frequencies being the backbone of timbre, periods producing rhythms, and contours supporting melodies. Temporal features are, therefore, of particular interest in the analysis of auditory stimuli, particularly music.

Music perception is based on the detection and analysis of acoustic events, including their duration and position along time. The particular organization of time intervals between one sound and another creates the perception of a rhythm or pattern; therefore, rhythm is the perceived musical structure, and its perception depends on *a priori* existence of an internal time frame (i.e., metric). By contrast, beat perception seems to be a basic and innate phenomenon that does not depend on prior learning of metric structures, but rather on the salience and regularity of the pulse inherent to the acoustic signal. However, the perception of an underlying beat can be

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modulated by the stimulus itself, namely the temporal structure of acoustic events and their accents, but also by the listener, such as his or her preferred tempo rage or fluctuations in attention.

In this chapter we review the literature regarding music perception. First, a brief review of the flow of information within the auditory cortex is presented. Next, we compare the perception of music to that of speech, as these two acoustic categories share important traits in terms of their communicative functions, evolution and temporal and spectral characteristics, highlighting their differences in terms of temporality and acoustic patterns. Particular aspects of music parameters are addressed elsewhere in this book (see, for example, previous chapter on beat induction).

The Auditory Cortices

The characterization of the auditory cortices has been studied from different perspectives, all of which reveal a detailed subdivision that can be seen in the cat, ferret, macaque, the chimpanzee and in man, with more than ten areas identified [1, 2]; each of these areas have different functional, cytological and neurochemical features [2–4], and their afferents come from different thalamic nuclei (e.g., dorsal, ventral and medial portions of the medial geniculate complex, pulvinar and posterior nuclei). All these aspects, besides their different neurochemical gradients/neurochemical profile provide distinctive features in auditory processing, so we will make some brief remarks on their anatomical and functional organization.

Anatomical Organization of the Auditory Cortices

The primary auditory cortex, or *core* region [Brodmann's Area (BA), 41], is located on the dorsal surface of the superior temporal gyrus (STG), covered by the frontoparietal operculum. The core is surrounded postero-laterally by the *belt* (BA 42 and possibly BA 52), and antero-laterally by the *parabelt* region (corresponding to BA 22), the latter two regions being considered secondary and tertiary auditory cortices, respectively (Fig. 1).

In turn, these three regions have been subdivided into around 12 regions, using functional and anatomical criteria that have been obtained mainly from non-human primates [1, 7, 8], but also by *post mortem* studies in humans, which have allowed a precise cytological characterization of three sub-areas of the primary auditory cortex (T1.0, T1.1 and T1.2, according to Morosan et al. [3]) within Heschl's gyrus [4, 9].

The core, belt and parabelt form, strictly, the auditory cortex, because they are direct targets of the acoustic radiation, which emerges from the medial geniculate complex (MGC), although each region has a specific pattern of thalamic afferents: the projections from the ventral portion of the MGC (MGv) are mainly distributed in BA 41 or core, while the belt and parabelt regions are mainly contacted by the dorsal portion (MGd), and finally all the regions are reached by fibers emerging from the medial subdivision (MGm). Thus, each cortical region receives a unique blend of fibers from several thalamic nuclei, and therefore each thalamic nucleus provides a distinct variety of information to its cortical targets [6, 10, 11]. The anatomical distribution of these three regions is not only based on their thalamic afferents but also in the cytoarchitecture of each region which presents a precise pattern of cellular distribution (e.g., dense concentration of small granular cells in layer II and IV in the core compared with the less granular appearance, larger pyramidal cells in layer IIIc and smaller width of layer IV in the parabelt) [3, 4]. Furthermore, it should be mentioned that the intrinsic connectivity (i.e., the local circuits of each cortical region), provides pathways for communication among neurons within or between the cell columns that constitute functional units [12, 13].

Seldon [14] described the cytoarchitecture and the axonal and dendritic distributions in the human auditory cortex in an attempt to establish the morphological correlates of speech perception, making a distinction in different patterns of columnar organization between primary and secondary regions. In addition, clear inter-

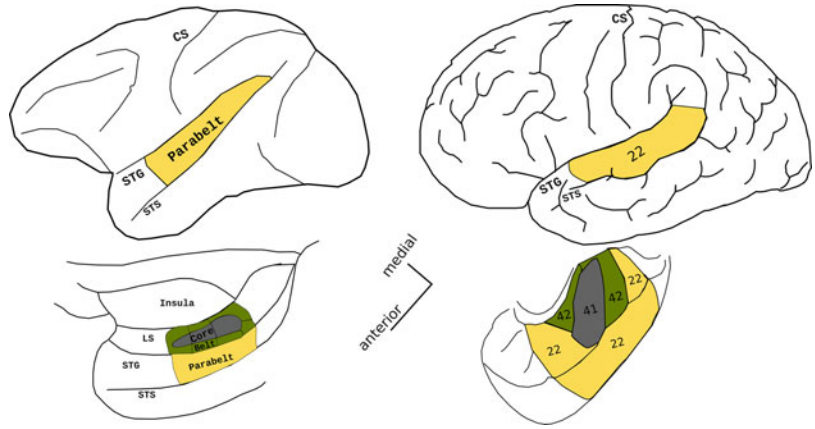

Fig. 1 Schematic representing the distribution of the auditory cortex in human and macaque monkey. *Upper panel*: lateral views of the macaque monkey (*left*) and human (*right*) brains; *lower panel*: dorsolateral view showing the location of auditory cortex on the lower bank of the lateral sulcus. Primary auditory areas (core) are shown in *dark gray*, belt (*yellow*) and parabelt areas (*green*) are colored. *Left*: macaque monkey map by Hackett et al. [5]; *right*: human distribution by Brodmann [6]. Schematics are not to scale. *STG* superior temporal gyrus, *STS* superior temporal sulcus, *LS* lateral sulcus, *CS* central sulcus. Modified from Hackett [6]

hemispheric differences were noted, such as the enlargement of the left *planum temporale* (Wernicke's area), different sizes of neuronal columns and intervals between them and, different values of fractional volume of neuropil. Thus, anatomical features are important factors to consider when making functional inferences from a particular region, since neither the intrinsic connectivity, thalamic afferents or cytoarchitectural organization are identical in each region [13–15].

Functional Distribution of the Auditory Cortex

Tonotopy (i.e., the spatial arrangement of structures devoted to particular acoustic frequencies) is the functional characteristic more commonly used to classify the primary auditory cortex (A1) or core. The ordered arrangement of the frequency distribution from the cochlea to A1 allows the identification of tonotopic cortical maps. In non-human primates these maps are extended to the belt (albeit in a less precise pattern) [8, 16]. In humans, tonotopic maps have a frequency distribution in a gradient of high to low (posterior-anterior), repeated in a mirror array, and are located along Heschl's gyrus (even if the gyrus is bifurcated) [16]. The role of the auditory cortex is not limited to decomposition of frequencies of a complex acoustical stimulus, but is also sensitive to its spectral profile, as suggested by the increased activation of A1 during stimulation with harmonic tones in comparison with pure tones [17].

Functional assessment of the surrounding auditory cortices (belt and parabelt) is more difficult because it breaks the linearity in the representation of the stimulus evident in A1. Besides, the total area of the human belt and parabelt extends approximately 9.6 times more than their equivalents in the macaque brain (in contrast to the core region which covers a greater cortical surface in the macaque). These inter-species differences have been proposed as the cornerstones of language development in humans [8] and highlight the poor suitability of animal models for the study of inherently human traits, such as music and speech. However, different studies have reported that regions adjacent to the core and belt share tonotopic gradients. Woods et al. [8] evaluated functional magnetic resonance imaging (fMRI) activations on the cortical surface of the STG in response to

attended and non-attended tones of different frequency, location, and intensity, in humans. They reported that the core regions presented mirror-symmetric tonotopic organization and showed greater sensitivity to sound properties than belt fields, which showed greater modulation for processes driven by attention. These data show that the belt region is probably involved in analyses prone to modulation by other factors, such as attentional resources, as evidenced by its greater activation during tasks requiring auditory recognition [8], or during stimulation with more behaviorally relevant sounds [18].

Manipulation of acoustic characteristics such as amplitude or frequency generate little or no modulation of activity of BA 22 or parabelt (divided into rostral and caudal parabelt; RP or CP, respectively), suggesting that its topographic organization is not related to the physical properties of stimulus (as in the core or some portions of the belt) [19, 20]. Activation of the parabelt has been associated with verbal processing, semantic integration, formation of "auditory faces", among others [21]. The parabelt also shows a positive correlation between activation levels and the level of spectral and temporal complexity of the stimuli, showing differences between the right and left hemispheres. Temporal modulations, for example, produce increased activation of the parabelt in the left hemisphere, while spectral modulations do so in the right hemisphere [22]. All these data suggest that higher level auditory areas combine information obtained previously (e.g., temporal and spectral), to form a unified representation of what is being heard [23].

Information Flow Within the Auditory Cortex

Kaas and Hackett [7] reported a hierarchical organization in the primate auditory cortex by using invasive electrophysiological methods, but an analogous hierarchical organization can be inferred from anatomical and functional data obtained from fMRI in humans [8, 20, 24]. Most studies attempting to assess complex aspects of auditory processing have focused on speech and language due to their relevance to humans. Okada et al. [25], evaluated the sensitivity to acoustic variation within intelligible *versus* unintelligible speech, and they found that core regions exhibited higher levels of sensitivity to acoustic features, whereas downstream auditory regions, in both anterior superior temporal sulcus (aSTS) and posterior superior temporal sulcus (pSTS), showed greater sensitivity to speech regardless of its intelligibility, and less sensitivity to acoustic variation.

There are other auditory-like areas involved in higher order processing, receiving sensory information from other systems besides the strictly auditory regions (e.g., STS also receives visual and somatosensory input). For example, speech processing and voice selective areas have been demonstrated in the upper bank of the STS [26–28].

Zatorre and Schönwiesner [29], while studying the involuntary capture of auditory attention, observed temporal and spatial flow of information that depended on the characteristics of acoustic stimuli. They showed that primary and secondary cortices respond to acoustic temporal manipulations in different ways: primary areas were involved in the detection of acoustic changes, whereas secondary areas extract the details of such acoustic change; a subsequent activation (with lag of ~50 ms) in the mid-ventrolateral prefrontal cortex was associated to memory-based decisions and to the novelty value of the acoustic change (regardless of the magnitude of this change) [30]. A similar result was reported by Patterson et al. [31], from an fMRI experiment that involved spectrally matched sounds that produced no pitch, fixed pitch or a melody, in order to identify the main stages of whole melody processing in the auditory pathway. Based on their results, they suggested the following information flow during melody processing: (1) extraction of time-interval information (neural firing pattern in the auditory nerve) and construction of time-interval histograms (likely within the brain stem and thalamus); (2) determination of the pitch value

and its salience from the interval histograms (probably occurring in lateral Heschl's gyrus); and (3) identification of pitch changes in discrete steps and tracking of changes in a melody (regions beyond auditory cortex in the superior temporal gyrus (STG) and/or lateral *planum polare* (PP).

Popescu et al. [32], also studied the information flow, but from the standpoint of rhythm, and they found widely distributed neural networks during music perception (by changing the rhythmical features of a musical motif). They reported activations, soon after the onset of the stimulus, within and around the primary and secondary auditory cortices, but also in SM1 (primary somatomotor area), the supplementary motor area (SMA) and premotor area (PMA). These data suggest an important role for the motor cortex in music perception and more precisely in the perception of the temporal patterns embodied in the musical rhythm, proposing the existence of two interrelated subsystems that mediate the auditory input and an internal rhythm generator subsystem (see Chapter 5.2 and 5.3).

The above-mentioned studies show that the perception of sound stimuli is a distributed process that follows a hierarchical order, which in the case of complex sounds, such a music or speech, includes regions within and beyond the auditory cortices (e.g., premotor, supplementary motor areas, frontal regions). We must consider, however, that complex sounds are formed of simple elements (intensity, frequency, onset) that form patterns as a function of time. The location and intensity of cortical activations derived from complex acoustical stimuli are extremely dependent on the time scale of the stimulus itself, which can range from only a few ms to the entire contour of a melody [32, 33]. Some of these data are supported by lesion and psychophysical studies of higher-order temporal processing (analysis of sound sequences such as patterns of segmented sounds or music), suggesting that these deficits are produced by temporal lobe lesions that involve superior temporal lobe areas beyond the primary auditory cortex [34, 35].

Music and speech are two examples of complex acoustical stimuli with great relevance to our species, given their role as information carriers. While the neural mechanisms required for their perceptions may be shared to a great extent [36], certain pathologies that affect one, domain, but not the other, suggest a certain degree of independence [37, 38]. In this final section we will mention several studies that suggest that the selectivity for musical sounds exists, showing evidence of cortical regions sensitive to music stimuli over other types of complex sounds.

The Musical Auditory Cortex

In brain-music research, one of the most studied topics is pitch perception, and it has been reported that lesions encroaching into the right Heschl's gyrus result in deficits in the perception of pitch of spectrally complex stimuli with no energy at the fundamental [39]. This was demonstrated in an experiment by Zatorre and Belin [40], where they found distinct areas of the auditory cortex, in each hemisphere, that respond to distinct acoustic parameters: the anterior auditory region on the right hemisphere showed a greater response to spectral than temporal variation; a symmetrical area on the left hemisphere showed the reverse pattern; finally, a region within the right superior temporal sulcus also showed a significant response to spectral modulations, but showed no change to the temporal changes. In brief, cortical activity of specific areas within the left hemisphere was modulated by temporal manipulations, while spectral variations modulated the activity of right-hemispheric cortical structures (Fig. 2). With these data the authors support the hypothesis of right hemisphere dominance for music perception, specially in pitch processing, in comparison with the putative role of the left hemisphere in temporal processing.

With this evidence as context, the following question is: How is spectral information processed when it also contains linguistic information, as is the case in tonal languages? Current

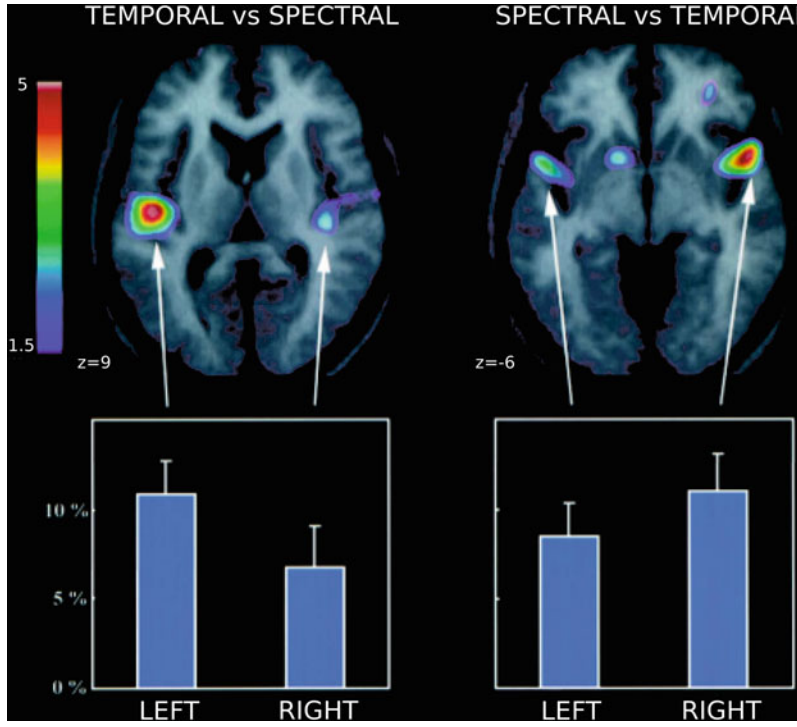

Fig. 2 *Top panel*: MRI images superimposed with the functional activation assessed through positron-emission tomography. The *left superior* image shows a horizontal view trough Heschl's gyrus (z = 9 mm in MNI standard space). This region shows more activation in the temporal modulation conditions in comparison with the spectral conditions. The *right superior* image corresponds to a horizontal view locating the anterior superior temporal region (z = −6 mm), which shows more activation in response to spectral manipulations *versus* temporal conditions. *Bottom panel*: *Error bars* showing percentage of cerebral blood-flow difference in temporal and spectral conditions. In this figure, the right hemisphere is presented in the right side of the image. Modified from Zatorre and Belin [40]

theories answer this question in two ways: (a) based on the cue-specific hypothesis (which determines that interhemispheric asymmetry is based on low-level acoustical features of the stimulus), linguistically relevant pitch patterns would depend on processing carried out in right-hemisphere networks; and (b) based on the domain-specific model (which states that low-level acoustical features are not relevant for predicting hemispheric lateralization), analysis of speech is processed in an exclusive system engaging higher-order abstract processing mechanisms, primarily in the left hemisphere. Both proposals show that there is a hemispheric specialization to specific basic aspects of sound: the right hemisphere is more sensitive to slow temporal acoustic patterns (contour), while the left hemisphere has a higher spectral and temporal resolution (phonemes). Hemispheric specialization is also evident in higher-order analyses, as evidenced by the left hemisphere dominance for speech perception. Using variations in pitch to create differences in word meaning in tonal language speakers, it has been demonstrated that tonal perception is lateralized to the left hemisphere. In experiments where Mandarin speakers were asked to discriminate Mandarin tones and low-pass filtered homologous pitch patterns, there was increased activity of the left inferior frontal regions, in both speech and non-speech stimuli, in comparison to English-speaking listeners who exhibited activation in homologous areas of the right hemisphere [41, 42]. The conclusion proposed was that pitch processing can be lateralized to the left hemisphere only when the pitch patterns are

phonologically significant to the listener; otherwise, the right hemisphere emerges as dominant and is involved in the extraction of the long-term variations of the stimulus.

Gandour et al. [43], also demonstrated that the left hemisphere appears to be dominant in processing contrastive phonetic features in the listener's native language, showing fronto-parietal activation patterns for spectral and temporal cues, even during the non-speech conditions. However, when acoustic stimuli are no longer perceived as speech, the language-specific effects disappear, regardless of the neural mechanisms underlying lower-level processing of spectral and temporal cues, showing that hemispheric specialization is sensitive to higher-order information about the linguistic status of the auditory signal.

Following this line of thought, Rogalsky et al. [44] explored the relation between music and language processing in the brain, using a paradigm of stimulation with linguistic and melodic stimuli that were modified at different rates (i.e., 30 % faster or slower that their normal rate). This experiment evaluated if the temporal envelope of a stimulus feature (that according to several studies plays a major role in speech perception), can elicit domain-specific activity that highlight the regions that were modulated by periodicity manipulations. They found some overlap in the activation patterns for speech and music restricted to early stages of processing, but not in higher-order regions (e.g., anterior temporal cortex or Broca's area); perhaps the most important result was that there was no overlap between regions that showed a correlation between their activity and the modulation rate of sentences (i.e., anterior and middle portions of the superior temporal lobes, bilaterally), and those that showed correlation with the modulation rate of melodies (dorsomedial regions of the anterior temporal lobe, primarily in the right hemisphere). This experiment attempted to isolate regions sensitive to rate modulation correlations (higher-order aspects of processing), finding that music and speech are processed largely within distinct cortical networks. As the authors acknowledged, it is important not to conclude from the apparently lateralized pattern for music processing, that the right hemisphere preferentially processes music stimuli (as is often assumed), because the lateralization effect described was due to the comparison of the activation patterns to music *versus* speech.

Selectivity for Music and Musicianship

Our group conducted an experiment to evaluate music perception, with the main objective of evaluating whether there are specific temporal regions that preferentially respond to musical stimuli (using novel melodies with different timbres and emotional charge), as compared to other complex acoustic stimuli including speech and non-linguistic human vocalizations, monkey vocalizations and environmental sounds. With this paradigm, we tried to evaluate the cortical responses associated to music perception but within an ecological context, using complex sounds without any kind of experimental manipulation (i.e., as we normally hear them in our everyday life). Our intention was to elicit the activation of cortical regions involved in the perception of music without disturbing any of its parameters, and then compare with the activity elicited by other types of complex stimuli, particularly speech. Finally, we wanted to assess whether these hypothesized music-selective regions are modulated by prior musical training, considering that previous studies have revealed that specific musical abilities can modify the distribution of the functional networks but also the neuroanatomical characteristics associated to their processing [45–47]. To achieve our goals, we included individuals with and without formal musical training (groups did not differ in terms of age or gender). This group comparison allowed us to look for differences in music processing based on the individual history of interactions (ontogeny) and to explore how experience can modify the overall processing of auditory stimuli. We used a paradigm of acoustic stimulation in an fMRI experiment, which included two main categories: (a) Human vocal sounds such as non-linguistic vocalizations sounds

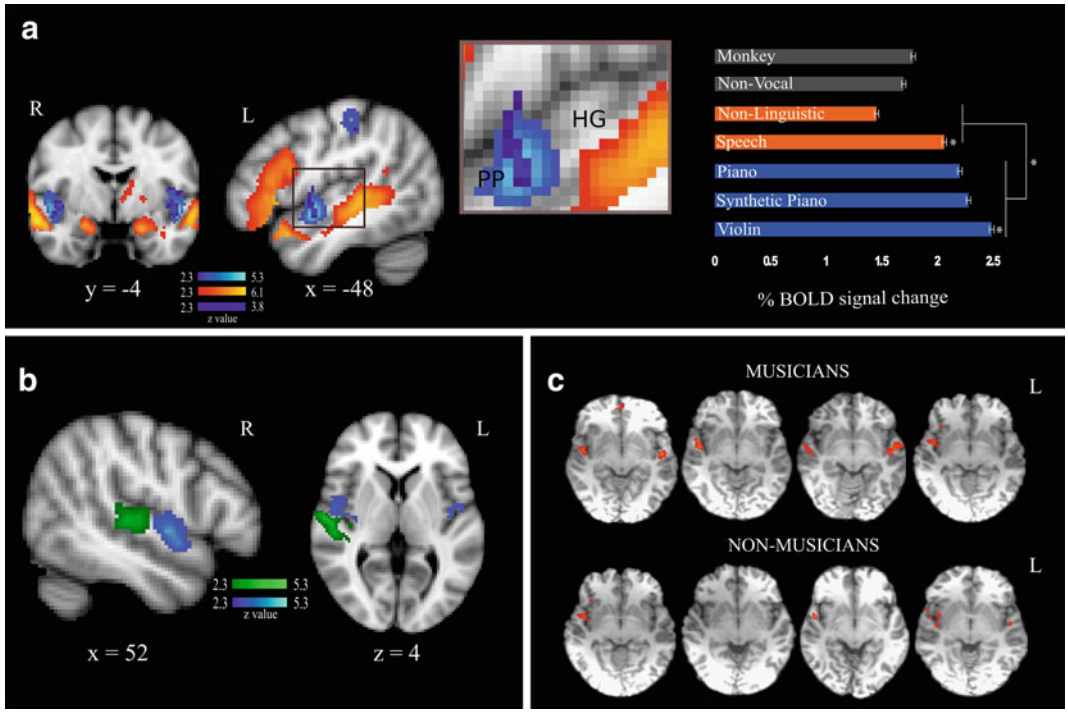

Fig. 3 Music-selective cortical regions. Voxels with significant activation (corrected cluster $p < 0.05$) are overlaid on the MNI-152 atlas, in radiological convention. (**a**) Music sensitive regions (*blue colors*). Coronal and sagittal views (left and right, respectively), the clusters in light blue (music > human vocalizations [speech + non-linguistic vocalizations]) and *dark blue* (music > speech) show no overlap with the cluster in orange (human vocalizations > music); amplification of the sagittal view showing part of Heschl's gyrus (**HG**) and the *planum polare* (**PP**). Bar plot showing BOLD signal change for each of the stimuli, obtained from the peak of maximal activation of the contrast testing for music > human vocalizations (speech and non-linguistic vocalizations). *Error bars* show the standard error. (**b**) Sagittal and axial views (left and right, respectively), showing the results from contrasts testing music > human vocalizations in musicians > non-musicians. Differential BOLD activity of the right *planum temporale* (*green color*), elicited by music or human vocalizations, was present only in musicians, the blue cluster (PP) is shown for reference. (**c**) Individual statistical maps from the analyses for music > human vocalizations (*red color*; $p < 0.01$ uncorrected), overlaid in T1-weighted images of 4 representative musicians (*upper panel*) and 4 representative non-musicians. *R* right, *L* left

(e.g., yawning, laughs and screams); and speech (sentences in several languages); and (b) musical stimuli, excerpts of novel musical passages played on piano and violin. We found a functional segregation when we compared the cortical activity associated with the processing of any type of human vocalization *versus* the activity generated by musical sounds. The comparison among music *versus* human vocalizations revealed a discrete bilateral area located in the anterior portion of the STG (Fig. 3a; light and dark blue colors) which responded significantly more to music than to human voices; this region was located within Brodmann's area 22, but extending to a more rostral portion named *planum polare*. Notably, these differences remain significant even when comparing only violin *versus* speech, two stimuli with very similar spectro-temporal acoustic characteristics (Fig. 3a, bar graph). The regions activated during the perception of speech or nonverbal vocalizations (i.e., the opposite contrast) coincide with those reported in the literature: bilateral activation of the lateral STG, medial temporal gyrus (MTG), predominantly in the left hemisphere where the cluster extended to the edge of

the STG and STS; and other regions such as the hippocampus, the amygdala, and the inferior frontal gyrus (Fig. 3a, warm colors).

One way to interpret these results is to consider the *planum polare* as a relay in the stream of musical stimuli (and perhaps other complex acoustically rich sounds), that receives information from the core and belt regions (among other association areas), and integrates complex acoustic attributes, serving as an integrator required for the analysis of diverse features of the stimulus. Indeed, previous results demonstrate that this region co-participates with frontal regions in tasks involving pitch and melodic discrimination [48–50].

One of the strongest arguments for questioning the selectivity observed in the *planum polare*, is to attribute the differences observed in the patterns of activity of each sound (e.g., speech or music), to differences in the spectro-temporal properties of each acoustic stimuli. However, Schönwiesner and colleagues [22, 51, 52], have shown that manipulations of spectro-temporal patterns along the time dimension are not sufficient to explain the activation of tertiary or high-order cortices. Using complex broadband stimuli with a drifting sinusoidal spectral envelope (dynamic ripples), they measured spectro-temporal modulation transfer functions (MTFs) in the auditory cortex, finding that dynamic ripples elicited strong responses from primary to secondary cortices (on and around Heschl's gyrus), but not in higher-order auditory cortices (e.g., posterior superior temporal gyrus and PT or STS). They argued that the lack of activity in higher areas may be due to two important characteristics of dynamic ripples (1) their low acoustical complexity, i.e., higher-order areas might integrate information across the spectrum modulation (units with simple summing responses MTFs); and (2) their lack of behavioral significance, arguing that higher auditory areas do not faithfully represent the physical properties of sounds but rather the relation between a sound and its behavioral implications [52]. Another fact that supports selectivity for music was observed in musicians, since only their group showed modulation of the *planum temporale*, whereas musicians presented similar activation for music and human vocalizations, non-musicians showed higher activity in response to human vocalizations (ascompared to music).

Subject-level analyses of our fMRI data revealed that bilateral activation of the *planum polare* was more prevalent in the group of musicians (27/28) compared to non-musicians (13/25) (Fig. 3c) during music listening. Previously we discussed that the functional asymmetry in musical processing postulates the right hemisphere as dominant, but in this experiment we found that this functional asymmetry was modified in musicians, which showed no differences in BOLD signal modulation between the left an the right *planum polare* during music perception. Even though musicians and non-musicians likely have the same neural substrates for musical processing (both perceive and distinguish what is and what is not music), musicians may demand similar resources in both hemispheres, while non-musicians do so in an asymmetric fashion, suggesting a functional specialization relative to musicianship.

Conclusions

The evidence presented in this chapter indicates that cortical responses to music are distributed and sophisticated; each area in the auditory cortex reveals its specialization according to its stage of processing in the flow of information. Several studies provide data regarding a musical processing network that differs from the network associated with speech perception [44, 50, 53], this means that the particular attributes of these two complex stimuli are processed by specialized networks, which are sensitive to spectral and temporal patterns that distinguish each sound category. As a summary of the information flow, we can say that the right primary auditory cortex is more sensitive to the changes in frequency and timing that characterize music; that belt regions (besides presenting extensions of the tonotopic maps) start to exhibit singularities, such as increased activation during directed attention to sounds, harmonic tones preference, among others; and that the parabelt region is involved in more complex processes,

exhibiting preference or selectivity for acoustic elements inherent in music, or showing activation with frontal regions during tasks involving discrimination of tones and tunes [48, 54, 55]. Furthermore, it can be concluded that the networks involved in the perception of music show some specificity, which may be evident in plasticity processes such as training (i.e., by the history of the interaction between the listener and the stimulus) ([44, 55–57]). These concepts will serve to develop more advanced and integrative models for the comprehension of music and speech processing.

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Perceiving Temporal Regularity in Music: The Role of Auditory Event-Related Potentials (ERPs) in Probing Beat Perception

Henkjan Honing, Fleur L. Bouwer, and Gábor P. Háden

Abstract

The aim of this chapter is to give an overview of how the perception of a regular beat in music can be studied in humans adults, human newborns, and nonhuman primates using event-related brain potentials (ERPs). Next to a review of the recent literature on the perception of temporal regularity in music, we will discuss in how far ERPs, and especially the component called mismatch negativity (MMN), can be instrumental in probing beat perception. We conclude with a discussion on the pitfalls and prospects of using ERPs to probe the perception of a regular beat, in which we present possible constraints on stimulus design and discuss future perspectives.

Keywords

Auditory perception • Music cognition • Rhythm • Beat induction • Event-related potentials (ERP) • Mismatch-negativity (MMN) • Temporal expectation • Music

Introduction

In music, as in several other domains, events occur over time. The way events are ordered in time is commonly referred to as *rhythm*. In musical rhythm, unlike in other domains, we often perceive an underlying regularity in time, which is known as the pulse or the *beat*. The beat is a regularly recurring salient moment in time [1]. The beat often coincides with an event, but a beat can also coincide with plain silence ([2]; see Fig. 1). At a higher level, we can hear regularity in the form of regular stronger and weaker beats and at a lower level, we can perceive regular subdivisions of the beat. We thus can perceive multiple levels of regularity in a musical rhythm, which together create a hierarchical pattern of saliency known as *metrical structure* or simply, *meter*. In this chapter, we will mainly focus on the processes underlying the perception of the most salient level of regularity in this perceived metrical structure: the beat.

The sensory and cognitive mechanisms of beat perception have quite a history as a research topic [3–8]. These mechanisms have been examined in

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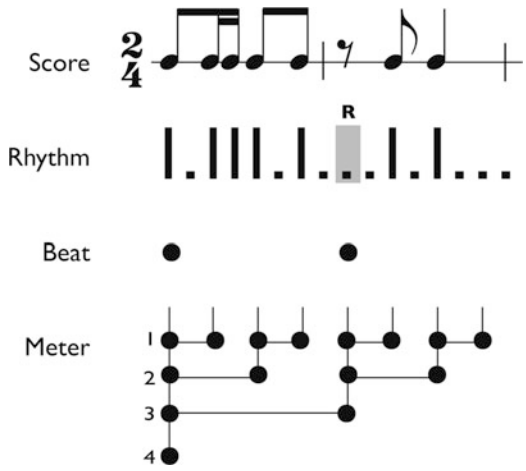

Fig. 1 A rhythm notated in common music notation (labeled Score) and as *dashes* (sound) and *dots* (silence) on a *grid* (labeled Rhythm). The perceived beat is marked with *bullets*; one possible metrical interpretation is marked with a metrical tree, with the length of the branches representing the theoretical metric salience and bullets marking the regularities at each metrical level. The rest (labeled R) marks a 'loud rest' or *syncopation*: a missing event on an induced beat

many music perception studies, mostly from a theoretical and psychological point of view [4, 6, 9, 10]. More recently, beat perception has attracted the interest of developmental psychologists [11], cognitive biologists [12], evolutionary psychologists [13], and neuroscientists [14, 15]. In addition, in the last decades a change can be observed from studying beat perception from a psychophysical perspective (studying the relation between stimulus and sensation) using relatively simple stimulus materials [16], to studying beat perception with more ecologically valid materials that take the task and the effect of musical context into account [8, 17]. In its entirety this has resulted in a substantial body of work using a variety of methods. In this chapter we will focus on studying the perception of the beat using electrophysiological methods.

Beat Perception as a Fundamental Cognitive Mechanism

It seems a trivial skill: children that clap along with a song, musicians that tap their foot to the music, or a stage full of line dancers that dance in synchrony. And in a way it is indeed trivial. Most people can easily pick up a regular pulse from the music or can judge whether the music speeds up or slows down. However, the realization that perceiving this regularity in music allows us to dance and make music together makes it a less trivial phenomenon. Beat perception might well be conditional to music [18], and as such it can be considered a fundamental human trait that, arguably, has played a decisive role in the origins of music [13]. Three properties of the ability to perceive a beat can be looked at when considering its role in the origins of music: whether it is an innate (or spontaneously developing) ability, whether it is specific to the domain of music and whether it is a species-specific ability.

Innateness, Domain- and Species-Specificity

Scientists are still divided whether beat perception develops spontaneously (emphasizing a biological basis) or whether it is learned (emphasizing a cultural basis). Some authors consider a sensitivity to the beat to be acquired during the first years of life, suggesting that the ways in which babies are rocked and bounced in time to music by their parents is the most important factor in developing a sense for metrical structure [19]. By contrast, more recent studies emphasize a biological basis, suggesting that beat perception is already functional in young infants [20] and possibly even in 2–3 day old newborns [21]. These recent empirical findings can be taken as support for a genetic predisposition for beat perception, rather than it primarily being a result of learning.

Furthermore, developmental studies suggest that infants are not only sensitive to a regular pulse, but also to regularity at a higher level (two or more levels of pulse; [22]). Thus it is possible that humans possess some processing predisposition to extract hierarchically structured regularities from music [23, 24]. To understand more about these capacities to hear regularity in music and to examine whether they are indeed

(partly) innate, research with newborns provides a suitable context [18, 21].

With regard to the domain-specificity of beat perception convincing evidence is still lacking, although it was recently argued that beat induction does not play a role (or is even avoided) in spoken language [25]. Furthermore, the perception of a beat occurs more easily with auditory than visual temporal stimuli [26], with audition priming vision [27], but not vice versa [28].

With regard to the species specificity of beat perception, it is still unclear which species have this ability. It was recently shown that rhythmic entrainment, long considered a human-specific mechanism, can be demonstrated in a select group of bird species [29–31], and not in more closely related species such as nonhuman primates [32, 33]. This is surprising when one assumes a close mapping between a genetic predisposition (specific genotypes) and specific cognitive traits. However, more and more studies show that genetically distantly related species can show similar cognitive skills; skills that more genetically closely related species fail to show [34]. The observations regarding beat perception in animals support the *vocal learning hypothesis* [35] that suggests that rhythmic entrainment is a by-product of the vocal learning mechanisms that are shared by several bird and mammal species, including humans, but that are only weakly developed, or missing entirely, in nonhuman primates [36]. Nevertheless it has to be noted that, since no evidence of rhythmic entrainment was found in many vocal learners (including dolphins and songbirds; [30]), vocal learning may be necessary, but clearly is not sufficient for beat perception and rhythmic entrainment. Furthermore, vocal learning itself may lie over a continuum rather than being a discrete ability, as for example sea lions (*Zalophus californianus*) seem capable of rhythmic entrainment [37] while there is little or no evidence of vocal learning [38]. Whereas research in human newborns can answer questions about the innateness of beat perception, research in various animals can answer questions about the species-specificity of beat perception.

Beat Induction

We use the term *beat induction* for the cognitive mechanism that supports the detection of a regular pulse from the varying surface structure of musical sound. This term stresses that the perception of a beat is not a passive process but an active one in which a listener induces a particular regular pattern from a rhythm. It emphasizes that a beat does not always need to be physically present in order to be perceived. This is, for example, the case when we hear a *syncopation* (or 'loud rest'; see Fig. 1), in which the beat does not coincide with an event in the musical surface, but with a silence [18].

As we have seen, beat perception and beat induction can be considered fundamental to music perception and production. Questions of innateness, domain-specificity and species-specificity need to be addressed to further reveal the relationship between beat perception and the origins of music. Before we turn to a possible method to answer these questions, first, the possible mechanisms that constitute beat perception and beat induction will be discussed.

Possible Mechanisms of Beat Induction

The Perception of a Beat

The perception of a beat is a bi-directional process: not only can a varying musical rhythm induce a regular beat, a regular beat can also influence the perception of the very same rhythm that induces it. Hence beat perception can be seen as an interaction between bottom-up and top down sensory and cognitive processes [10]. Initially, we induce a beat from various cues in the music. Once a context of regularity is established, we use the inferred beat to interpret the music within this context and to predict future events [7]. A perceived pulse is stable and resistant to change [39]. However, if the sensory input provides clear evidence for a different metrical structure, our perception of the

beat can change. The relation between the events in the music and the perceived temporal regularity thus is a flexible one, in which the perceived metrical structure is both inferred from the music and has an influence on how we perceive the music [40, 41].

Boundaries on Beat Perception

We can perceive regularity in music at different metrical levels and thus at different timescales. It should be noted that the perception of temporal regularity is restricted by several perceptual boundaries. We can perceive temporal regularity with a period roughly in the timescale of 200–2,000 ms [42]. Within this range, we have a clear preference for beats with a period around 600 ms or 100 beats/min. This rate is referred to as *preferred tempo* [3]. A beat at this tempo is usually very salient. Most empirical studies looking at beat perception use a rate of stimulus presentation that makes it possible to hear a beat at preferred tempo level.

Beat Induction Through Accent Structure

To infer a metrical structure from music we make use of accents. In a sequence of events, an accent is a more salient event because it differs from other, non-accented events along some auditory dimension [43]. When accents exhibit regularity in time, we can induce a regular beat from them. Accented tones are then usually perceived as on the beat or, on a higher level, as coinciding with a strong rather than a weak beat [44].

A sequence of events in time, such as a musical rhythm, also contains purely *temporal accents* that arise from the structure of event onsets rather than from acoustic changes in the sound. Events are perceived as more or less salient depending on their length and position in a rhythm. Povel and Essens [4] describe three ways in which a temporal accent can occur. First, when an onset is isolated relative to other onsets, it sounds like an accent. Second, when two onsets are grouped together, the second onset sounds accented. Finally, for groups of three or more onsets, the first and/or last tone of the group will be perceived as an accent.

While it has been suggested that beat induction is mainly guided by these temporal accents [45], recently it has been shown that pitch accents also play a role in perceiving the beat [43, 46]. It is very likely that in natural music, many features of tones can contribute to an accent structure and our perception of the beat, including not only pitch, but also timbre and intensity. In line with this, Bolger et al. [27] and Tierney and Kraus [47] showed that the use of ecologically valid stimuli can actually enhance the perception of a beat. However, to date, melodic, timbre and intensity accents have been largely ignored in many studies examining beat perception.

Beyond Accents

While accents explain a large part of how we infer a beat and metrical structure from music, several other processes must be taken into account. First, it must be noted that we sometimes perceive temporal structure without any accents present. Rather, we actually imagine accents where they are not psychically present. This phenomenon has been termed *subjective rhythmization* and is very apparent when listening to a clock. Whereas every tick of a clock is equal, we often hear every other tick as an accent (e.g., 'tick-tock' instead of 'tick-tick'). Direct evidence for the presence of subjective rhythmization in isochronous sequences comes from studies comparing the brain response to tones in odd positions (which are subjectively accented) with the response to tones in even positions (which are not subjectively accented). It was found that slightly softer tones were perceived as more salient in odd than in even positions [48]. While this shows the presence of the effect, the mechanism underlying subjective rhythmization is still unclear [49].

A second influence on beat induction is our previous experience. Hannon and Trehub [50]

showed how cultural background and exposure to music can affect how well we can discern a metrical structure. In their study, participants listened to folk melodies with either a simple or a complex metrical structure. They were subsequently presented with two alterations of the melody, one in which the metrical structure was preserved, and one in which the metrical structure was violated. Participants then rated the similarity of the altered melodies to the original melody. Adults of Bulgarian and Macedonian origin, who are accustomed to complex metrical structures (i.e., compound meters like 5/8 or 7/8), differentiated between structure-preserving and structure-violating alterations in both complex and simple metrical structures. However, participants with a Western background did so only in the melodies with a simple meter. This was most likely due to the fact that Western listeners are not familiar with complex meters. Interestingly, 6 month-old infants responded differentially to structure-preserving and structure-violating alterations regardless of whether they occurred in a simple or complex metrical structure. This implies that the difference between the adults from Western and Balkan cultures is due to enculturation, which takes place sometime after the age of 6 months. It shows that the culture with which we are familiar influences how we perceive the metrical structure (for more evidence regarding the effect of culture on beat and meter perception, see [51]). In addition to the familiarity of different metrical structures, our culture can also provide us with template of certain patterns that specify a certain metrical structure. For example, snare drum accents in rock music often indicate the *offbeat* rather than the beat [7].

Finally, in addition to the influence of an accent structure, subjective rhythmization and our previous experience, the perception of a beat can also be guided by conscious effort. By consciously adjusting the phase or period of the regularity we perceive, we can influence which tones we hear on the beat. For example, when we listen to an isochronous series of tones, without any instruction, we will hear every other tone as accented [49]. However, by conscious effort, we can project a beat on every third tone, thus adjusting the period of the beat to our will. This ability has been very useful in examining beat and meter perception, because it can allow us to hear a physically identical stimulus as on the beat or not, depending on the (instructions for examples, see [52, 53]). Any change in neural activity found can then reliably be attributed to beat perception, without having to control for physical differences between tones that are on or off the beat.

To summarize, beat induction is guided by the temporal and acoustic structure of events. It is constrained by our perceptual system and can be influenced by our earlier exposure to music, subjective rhythmization and conscious effort. When we listen to music, we induce a beat from the sensory input and then use that information to predict future events within a metrical framework. One way of understanding the mechanisms of beat perception is in the framework of the *predictive coding theory* (see Vuust et al., last chapter of this volume). Another prominent theory explaining the interaction between the varying sensory input and beat perception is the Dynamic Attending Theory [54].

Dynamic Attending Theory

Dynamic Attending Theory (DAT) explains the perception of metrical structure as regular fluctuations in attention. It proposes that internal fluctuations in attentional energy, termed *attending rhythms*, generate expectancies about when future events occur. When attentional energy is heightened an event is expected. Such a peak in attentional energy is perceived as a metrically strong position, i.e., on the beat. The internal fluctuations in attentional energy can entrain to the rhythm of external events, by adapting their phase and period, which corresponds to how we infer a metrical structure from events in the music. The attending rhythms are self-sustaining and can occur at multiple levels, tracking events with different periods simultaneously [6, 55]. These features correspond respectively to the stability of our metrical percept and the

perception of multiple hierarchical levels of regularity [39]. As such, DAT can explain many aspects of beat and meter perception. Behavioral support for DAT comes from studies showing a processing advantage in metrically strong positions for temporal intervals [6], pitch [56] and phonemes [57]. This is thought to be the result of the peaks in attentional energy associated with metrically salient positions.

At a neural level, beat and meter perception have been hypothesized to originate from neural oscillations that resonate to external events (*neural resonance*, see [39]). This view on the perception of metrical structure can be seen as an extension of DAT and makes largely the same predictions. Like the attending rhythms in DAT, neural oscillations are suggested to be self-sustaining and are suggested to adapt their phase and period to an external rhythm. In addition to these features, neural oscillations may arise at frequencies that are not in the stimulus, which may be an explanation for the phenomenon of subjective rhythmization [39].

Snyder and Large [58] provided some empirical evidence for the neural resonance theory, by showing that high frequency neural oscillations reflect rhythmic expectancy. They presented participants with a rhythm consisting of alternating loud and soft tones, while measuring their brain activity using electroencephalography (EEG). With this method it is possible to measure the electric activity of the brain with high temporal precision and thus, it is possible to show high frequency neuronal oscillations. The results showed that a peak in induced gamma oscillations (20–80 Hz) coincided with the sounds. When a loud sound was omitted, this peak was still present, which was interpreted as evidence that the induced activity represented the regular underlying beat, which continued even without physical input. Additional evidence in this line was provided by Zanto et al. [59], Iversen et al. [52] and Fujioka et al. [60]. In each of these studies, induced oscillatory activity was shown to relate to metrical expectations. The question remains, however, whether neural resonance is actively influencing rhythm perception or whether it is an emergent attribute of the EEG response induced by the rhythmic structure of the stimulus itself [61]. Also, to date, support for neural resonance as an explanation for beat perception only comes from studies using isochronous stimuli. Whether neural resonance also explains phenomena such as subjective rhythmization and beat perception with more complex stimuli remains to be tested.

Metrical Structure Is Perceived in Motor Areas of the Brain

EEG provides excellent temporal resolution. However, to localize the networks involved in beat perception, the superior spatial resolution of functional magnetic resonance imaging (fMRI) is needed. The overall picture emerging from fMRI studies looking at beat perception is that of large involvement of the motor areas in the brain. Grahn and Brett [14] examined beat perception using different rhythmic sequences, containing temporal accents (i.e. accents that arise from the structure of event onsets; cf. [4]). In some rhythms these accents were spaced evenly, while in other rhythms they were irregular. Rhythms with regular accents were considered to be metrical rhythms and rhythms with irregular accents non-metrical. Only metrical rhythms induced a beat, as was confirmed by a behavioral test. Using fMRI it could be shown that during listening to metrical rhythms the basal ganglia and the supplementary motor area (SMA) were more active than during listening to non-metrical rhythms, implicating these areas in beat perception. The findings of Grahn and Brett [14] were confirmed by several subsequent studies showing activations not only in the basal ganglia and SMA, but also in the cerebellum and pre-motor areas [62–64]. Importantly, activity in a network of motor areas was consistently observed, even when participants were asked not to make overt movements. This shows that these areas are involved when people just listen to a metrical rhythm (for a review on the neural correlates of beat and meter perception, see [65, 66]).

Motor areas have been implicated in time perception in general. However, recently it was

shown that specific networks are dedicated to perceiving absolute and relative durations respectively. While a network comprising the cerebellum and the inferior olive is involved in absolute *duration-based* timing, a different network, including the basal ganglia and the SMA, is active for relative or *beat-based* timing [67]. The perception of a beat, which requires the perception of temporal regularity, thus appears to be a distinct process from the general perception of temporal intervals. We will refer to this as the auditory timing *dissociation hypothesis* (see also [68, 69]).

To summarize, regular fluctuations in attentional energy and neural resonance have been suggested to explain the perception of metrical structure. Also, a role for a network of motor areas in the brain, including the basal ganglia and the SMA, has been implicated. Finally, a dissociation between rhythm perception and beat perception has been suggested.

Beat Perception in Human Adults, Human Newborns, and Nonhuman Primates

As discussed in the Introduction, some of the main questions regarding beat perception are concerned with whether beat perception is innate (or spontaneously developing) and/or species-specific. These questions about beat perception can potentially be answered by testing human newborns and nonhuman animals. These questions ask for a method that is non-invasive and does not require an overt response from the participant. EEG is well suited for this task and has the temporal resolution to track the perception of a beat over time. One way of looking at beat perception with EEG is by measuring neural oscillations. While this provides a promising way of examining beat perception, this line of research is very recent and has mostly been tested in adult participants under attended conditions. It is not yet clear whether beat perception can be measured through neural resonance in special groups of participants, like children, newborns or animals, and in conditions in which participants do not attend to the rhythm. Questions regarding the innateness and species-specificity of beat perception have been addressed using EEG with the more traditional and well-studied approach of looking at *event-related potentials* (ERPs). In the remainder of this chapter we will therefore focus on using auditory ERPs in probing beat perception.

Measuring Beat Induction with Event-Related Potentials (ERPs)

Using ERPs to Probe Beat Perception

ERPs are hypothesized to reflect the sensory and cognitive processing in the central nervous system associated with particular (auditory) events [70]. ERPs are isolated from the EEG signal by averaging the signal in response to many trials containing the event of interest. Through this averaging procedure, any activity that is not time-locked to the event is averaged out, leaving the response specific to the event of interest: the ERP. While ERPs do not provide a direct functional association with the underlying neural processes, there are several advantages to the technique, such as the ability to record temporally fine-grained and covert responses not observable in behavior. Also, several ERP components have been well studied and documented, not only in human adults, but also in newborns and animals. Some of these components, used in testing beat perception, are elicited with an *oddball paradigm*.

An auditory oddball paradigm consists of a regular sequence of stimuli (standards), in which infrequently a stimulus is changed (deviant) in some feature (e.g., pitch, intensity, etc.). The deviant stimulus thus violates a regularity that is established by the standard stimuli. Depending on the task of the subject a deviant stimulus elicits a series of ERP components reflecting different stages and mechanisms of processing. The *mismatch negativity* (MMN), which is a negative ERP component elicited between 100 and 200 ms after the deviant stimulus, reflects automatic deviance detection

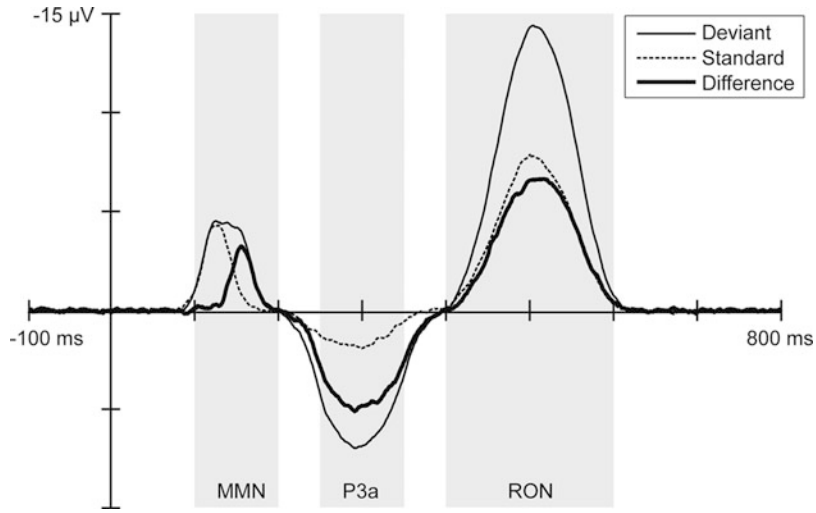

Fig. 2 Idealized event-related potential (ERP) responses to unattended stimuli in an oddball paradigm, showing the standard (*dotted line*), deviant (*solid line*) and deviant minus standard difference waveform (*bold line*). The mismatch negativity (MMN), P3a and reorientation negativity (RON) components are highlighted with *grey shading* indicating standard latency windows

through a memory-template matching process (see Fig. 2). The N2b is a component similar to the MMN in latency, polarity and function, but it is only elicited when the deviant is attended and relevant to the task. At around 300 ms after the deviant stimulus, a positive component can occur, known as the P3a, which reflects attention switching and orientation towards the deviant stimulus. For task relevant deviants, this component can overlap with the slightly later P3b, reflecting match/mismatch with a working memory representation [71, 72]. Finally, the reorientation negativity (RON; 400–600 ms) reflects switching back attention to the original task [73]. Several of these ERP components are known to index the magnitude of a regularity violation. A larger deviation from regularity yields a MMN, N2b, P3a and P3b with earlier latency and larger amplitude [74–77]. This property is exploited when probing beat perception with ERPs.

The general idea of using ERPs to probe beat perception is that an event on the beat is perceived differently from an event occurring not on the beat and thus that two physically identical events in different metrical positions should yield different brain responses. Moreover, because we perceive events on the beat as different from events not on the beat, we also perceive deviants on the beat as different from deviants not on the beat. An effect of metrical position on the ERP response to a deviant event is therefore interpreted as evidence for the presence of beat perception. In general, it is thought that deviant events on the beat are detected better than deviant events not on the beat and thus that the former elicit earlier and larger amplitude ERP responses than the latter [78].

An example of how deviant detection can show the presence of beat perception comes from studies examining subjective rhythmization [48, 49]. In these studies, participants were presented with an isochronous series of tones. They were hypothesized to perceive the tones in odd positions as stronger than tones in even positions. Infrequently, a softer tone was introduced, either in odd or in even positions. These deviants elicited an N2b and a P3b. The P3b to deviants in odd positions had a larger amplitude than the P3b to deviants in even positions, showing that the deviants were indeed detected better—or perceived as more violating—on the beat. Other studies have shown that the P3b component to deviants is

larger when the deviants occur in a regular sequence than when they occur in a sequence with random inter-onset intervals [78, 79].

While the elicitation of an N2b and a P3b requires attention and a conscious effort towards detecting deviant stimuli, the MMN is automatic and mostly independent of attention. As such, it has been possible to show MMN-like responses in newborn infants as well as in nonhuman species. This makes the MMN an ideal ERP component for interspecies comparisons and for testing the innateness of beat perception, provided that the MMN response is indeed sensitive to metrical structure and that beat perception can be shown to be *pre-attentive* in human adults. In the following sections, the MMN component and its relation to beat perception is discussed.

The Mismatch Negativity (MMN)

In general, the MMN is elicited when incoming sounds mismatch the neural representations of regularities extracted from the acoustic environment. Violations of the regularity in sound features such as pitch, duration or timbre can elicit an MMN [80, 81]. Also violations of abstract rules (i.e. one auditory feature predicting another; [82]) or stimulus omissions [83] can cause an MMN. The MMN is regarded as a predictive process [84] reflecting the detection of regularity-violations (for reviews see [85, 86]).

The processes underlying the MMN are thought to be automatic, however, the MMN can be modulated by attention [87] and even be completely eliminated when deviations in attended and unattended auditory streams vie for feature specific processing resources [88]. The fact that MMN can be elicited even in comatose patients [85], sleeping newborns [89] and anesthetized animals [90] illustrates the relative independence from attention. The latency and amplitude of the MMN are sensitive to the relative magnitude of the regularity violation [74, 76] and correspond to discrimination performance in behavioral tasks [91]. These properties can be exploited when, for example, beats on metrically strong and weak positions are compared or the relation between attention and beat perception is tested.

Using MMN to Probe Beat Perception in Human Adults

To date there has been only a handful of studies that used MMN to study beat perception. The different methods in these studies have two common design goals: First, all studies present subjects with stimuli that induce a metrical structure and the responses to regularity violations occurring on different metrical positions (e.g. on the beat and not on the beat) are compared. Second, all studies try to control attention to test whether the processes involved in differentiating between different metrical positions are automatic or dependent on attention, i.e. to study whether beat perception is pre-attentive [92]. The existing literature, however, contains inconsistent results (for a related review, see [65]).

Geiser et al. [93] presented subjects with rhythmic patterns containing temporal accents consistent with a regular 3/4 bar (e.g. the metrical structure of a waltz). In these metrically regular sequences infrequently a pitch deviant, a violation of the metrical structure or a violation of the temporal surface structure of the rhythm was introduced. The meter violations consisted of the addition or removal of an eight note to the regular 3/4 bar. To create the rhythm violations, one or two eight notes were substituted by two or four sixteenth notes, leaving the metrical structure intact. Subjects had to either ignore the changes in the temporal domain and detect the pitch changes (unattended condition) or ignore the pitch changes and detect the temporal changes (attended condition). Regardless of subjects' musical training, rhythm violations elicited an MMN-like component in both attended and unattended conditions. Meter violations however only elicited an MMN-like component in the attended condition, implying that attention is required to induce a beat. In an experiment with similar attentional control, Vuust et al. [94, 95] did find MMN responses to large temporal violations of the metrical

structure regardless of musical training and attention. Unfortunately the large changes violated not only the meter but also other parameters, like the underlying temporal grid. As this in itself would lead to a MMN response, it is not clear from these results whether the MMN system is indeed sensitive to metrical structure.

A converse result comes from the experiment of Geiser et al. [96] who used identical regular 3/4 bar sequences as in their earlier study [93]. However, in this study deviants in the form of intensity accents were introduced at meter-congruous and meter-incongruous positions. The attention control was achieved in this experiment by asking subjects to attend to a silenced movie, a common procedure in many MMN experiments [86]. Geiser et al. [96] found an enhanced MMN to accents in meter-incongruous positions for musicians and, to a lesser extent, for non-musicians, providing evidence in support of beat perception being pre-attentive. The conclusions drawn by this and the previous [93] study are radically different, while identical beat inducing stimuli were used. As such, these studies very clearly show how large the influence of different attentional controls and experimental design on the results can be.

Ladinig et al. [23, 24] took a somewhat different approach to meter perception in a study where they compared the responses of musically untrained subjects to omissions of tones with two different levels of metrical salience in a rock drum pattern (see Fig. 3). Two different levels of attention control were employed. In the *passive* condition subjects were attending to a silent movie, as in Geiser et al. [96]. In the *unattended* condition subjects were attending to intensity changes in a continuous stream of white noise. The latter condition was designed to be a strict control for attention as it required attention in the same modality, but for a different auditory stream. Results showed that the MMN responses elicited by infrequent omissions on the first beat (deviant D1; large violation of the metrical structure) and the second beat (deviant D2; smaller violation of the metrical structure) differed in latency but not in amplitude. The latency difference indicates faster processing for the larger metric violation, suggesting that the metrical structure was picked up without attention.

Studying pre-attentive beat perception using the MMN is not as straightforward as one might like. Most notably, the use of acoustically rich stimuli (with potential differences between sounds in different metrical positions) may interfere in unforeseen ways with the ERP results (cf. [92]). One possible future direction is to strive for even more minimalistic paradigms and to test whether the auditory system automatically imposes structure to incoming unattended stimuli that have no apparent structure (e.g., isochronous sequences of the same sounds; subjective rhythmization). Alternatively, priming paradigms could be used that test how long externally imposed structure persists when the input is no longer structured. As the MMN responds not only to temporal but also to pitch and timbre deviants, it does allow studying more complex accent structures, a topic mostly ignored so far.

In summary, while the automatic nature of beat perception is not yet fully understood, MMN seems to be a promising candidate for measuring beat perception. In the next sections, we will discuss how ERPs in general and the MMN in particular can be used to examine beat perception in human newborns and nonhuman primates and other animals.

Measuring ERPs in Human Newborns

MMN-like ERP responses in newborns were first measured by Alho et al. [89]. Since then several studies tried to identify the correlates of developing and adult-like auditory processing. Recordings from newborns are inherently noisier than recordings from adults therefore MMN-like responses in newborns are not very robust. On the one hand the brain is in extremely rapid development during the first years of life. On the other hand the length of experiments are necessarily short and do not allow for complex experimental designs or extensive data collection to improve signal to noise ratio. ERPs both negative and positive in polarity and within a wide variety of latency ranges from about 80 ms up to

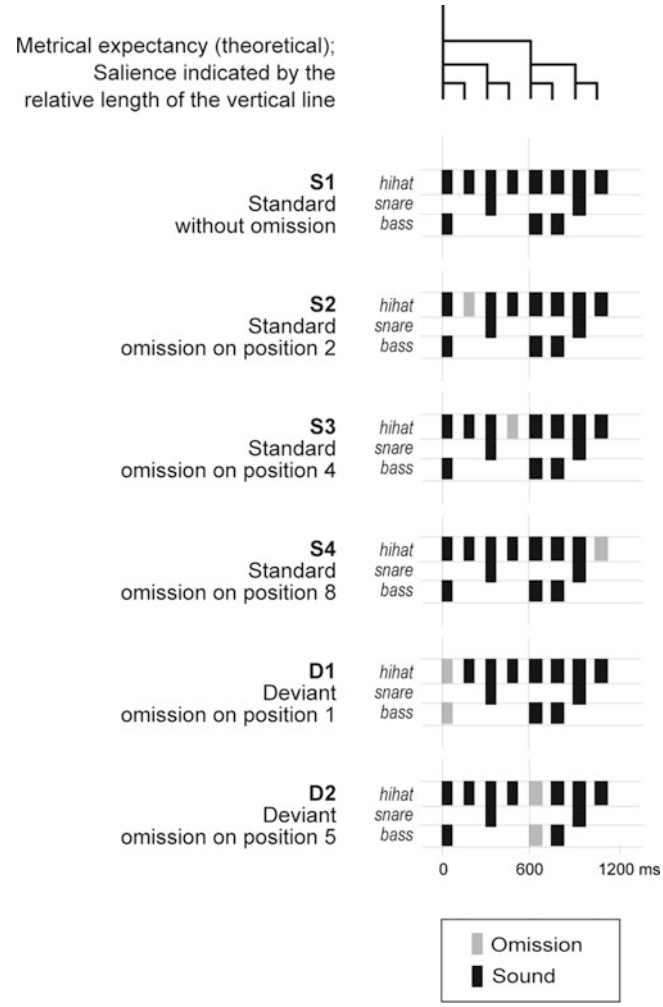

Fig. 3 Stimuli as used in several studies on beat and meter perception e.g., [21, 23, 33]. S1–S4 are the standards and D1 and D2 the deviants used in an oddball paradigm. The different percussion sounds are marked as hi-hat, snare and bass (see for more information www.mcg.uva.nl/newborns/ and www.mcg.uva.nl/monkeys/)

500 ms were found in response to oddball designs, also in absence of attention (the EEG recording in newborns is made during sleep). It is not yet clear whether the infants' responses are identical or only analogous to the adult MMN responses, but based on the different ERP responses to deviant and standard tones we can assume that the information on which the deviant-standard discrimination is based is available to the infant's brain. However, further processing steps are unclear. With these caveats in mind in the discussion below we will refer to these ERP responses found in newborns and young infants as MMN.

Several abilities that underlie music perception seem to be functioning already at birth. Newborns are able to separate two sound streams based on sound frequency [97] and detect pattern repetitions which they incorporate into their model of the auditory scene [98]. Most important to beat perception is the ability to process temporal relations. Presenting a stimulus earlier or later than expected in an isochronous sequence elicits an MMN in 10-month old infants (Brannon et al. 2004), at least for large time intervals (500–1,500 ms). Newborns are also sensitive to shorter changes (60–100 ms) in stimulus length [99, 100] and 6-month old infants detect even shorter gaps (4–16 ms) inserted in tones [101, 102] showing the remarkable temporal resolution of the auditory system. Furthermore, Háden et al. [103] showed that newborns are sensitive to

changes in the presentation rate of the stimulation, can detect the beginning of sound trains, and react to the omission of expected stimuli. These results indicate that investigating phenomena reliant on temporal processing (e.g., beat perception) is viable.

Using MMN to Probe Beat Perception in Human Newborns

In the only experiment to date on beat perception in newborns Winkler et al. [21] used a variant of the paradigm used in Ladinig et al. ([23], see Fig. 3) to test whether newborns are able to extract a regular beat from a varying rhythmic stimulus. Sounds at the position of the strongest beat (the 'downbeat') in a 4/4 rock drum pattern were occasionally omitted (D1 in Fig. 3). The response to these omissions was compared to the response to omissions on weak metrical positions (e.g. not on the beat, S2–S4 in Fig. 3) and the response to omissions in a control sequence consisting of patterns in which the downbeat was always omitted. The ERP responses to the omissions on the downbeat differed significantly from responses to patterns without omission, omissions on weak positions and also omissions in the control sequence. The results were interpreted as proof to newborns ability to detect a beat.

Some reservations remain however. In the experimental design used there is no guarantee that the perceived phase of the control sequence was the same as the perceived phase of the other sequences (see also [23]). This is important because a different interpretation of the control sequence would mean that the position of the beat in the sequence might also be different. Another possible problem is that the acoustic context of weak and strong metrical positions is not identical. Finally, the omitted sounds on weak and strong positions are not physically identical. Therefore comparing them might be problematic (see also Discussion section).

The available evidence points to beat perception as an innate ability that is shaped by learning later on [11]. However, there is still some confirmation needed for newborn beat perception. New experiments should take into account the weaknesses of the Winkler et al. [21] design. In doing so, it would be beneficial to examine responses to temporal or spectral violations of regularity instead of omissions, as this would produce clearer electrical signals. In addition, this would allow for varying the tempo of the stimuli and loosen the constraint for relatively fast tempi (i.e., 150 inter-stimulus interval or shorter) that is needed for omission studies [83].

Measuring ERPs in Nonhuman Animals

There is quite some discussion on whether beat perception is species-specific [36]. The evidence that is in support of beat perception in certain species comes from experiments that test entrainment to a beat through overt behavior (e.g., [29]). However, if the production of synchronized movement to sound or music is not observed in certain species, this is no evidence for the absence of beat perception. It could well be that certain animals are simply not able to synchronize their movements to a varying rhythm, while they can perceive a beat. With behavioral methods that rely on overt motoric responses it is difficult to separate between the contribution of perception and action. Electrophysiological measures, such as ERP, that do not require an overt response, provide an attractive alternative to probe beat perception in animals.

Since the discovery of the MMN component researchers have tried to find analogous processes in animal models [104] and to integrate deviance detection and predictive processing into a general framework of auditory perception [105]. A wide range of electrophysiological methods from scalp electrodes to single-cell recordings have been used on animal models. These methods highlight different phenomena of varying spatial and temporal resolution. The most vital difference is that scalp and epidural recordings may yield components similar to the human MMN (i.e. electric responses generated by large brain areas), whereas local field potential, multiunit activity and single-cell recordings

work on a lower spatial scale and reflect *stimulus specific adaptation* (SSA; [106]). SSA has many common properties with MMN; both can be observed in similar paradigms and it is still debated whether SSA reflects the cellular level activity underlying MMN. However, this does not concern the main aim of this chapter and will not be discussed further (see Chap. 9 for more information on this topic).

Using epidural recording, MMN-like responses have been shown in different species including rats (for a review see [107]), cats [90, 108, 109] and macaque monkeys [110, 111]. In most of these studies, frequency and amplitude violations were used. In rats, deviance detection was shown for both a temporal feature, sound duration [107], as well as to an abstract feature, namely melodic contour [112]. Recordings from scalp electrodes showed MMN responses in mice [113] and in a single chimpanzee [114]. While not all attempts at recording MMN-like responses from animals were successful, it seems that MMN can be reliably elicited in animal models and thus can be used to study auditory processing in nonhuman animals.

Using MMN to Probe Beat Perception in Nonhuman Primates

Honing et al. [33] recorded ERPs from the scalp of macaque monkeys. This study demonstrates that an MMN-like ERP component can be measured in rhesus monkeys *(Macaca mulatta)*, both for pitch deviants and unexpected omissions. Together these results provide support for the idea that the MMN can be used as an index of the detection of regularity-violations in an auditory signal in monkeys.

In addition, the study showed that rhesus monkeys, using stimuli and an experimental paradigm identical to Winkler et al. [21], are not able to detect the regularity—the beat—induced by a varying rhythm, while being sensitive to the rhythmic grouping structure. These findings are in support of the hypothesis that beat perception is species-specific, and it is likely restricted to vocal learners such as a selected group of bird species, while absent in nonhuman primates such as rhesus monkeys.

The result is also in support of the dissociation hypothesis that posits different neural networks being active for interval-based and beat-based timing, of which only the former is shared between non-vocal learning species [33, 69].

Testing beat perception in animals has only started recently and there is still much work to be done [36]. The MMN component seems like a good index of beat perception as it can be elicited in several different species. Unfortunately most of the vocal learning species, such as cetaceans and pinnipeds, are not typical targets for ERP studies. Interestingly, a recent study suggests at least some level of vocal learning in mice [115]. This might prove to be an alternative starting point for testing beat perception in nonhuman animals.

Discussion and Conclusion

In this chapter we have seen that the perception of metrical structure seems specific to the domain of music and is shared with only a limited number of non-human animals. Nonetheless, this ability seems very basic to humans. People readily synchronize to a beat in a wide variety of settings, like concerts, demonstrations, when marching and when singing a song together. This apparent contradiction between the ease with which we are capable of hearing a beat and the uniqueness of this skill raises several questions about how fundamental the perception of metrical structure really is.

We have shown how ERPs can be used to answer fundamental questions about beat perception. Measuring ERPs is relatively straightforward, it can be realized in populations that are difficult to study behaviorally (like infants and monkeys), and it is a well-researched method. However, several issues remain.

One of the challenges in examining beat perception is to balance the need for highly controlled stimuli with the aim to use stimuli that are ecologically valid. On the one hand, future research must address the role of

different acoustic features in beat perception. Most research in this area has focused on temporal accents and has used either very simple or even isochronous sequences. While this is useful in controlling acoustic factors, it is not a very natural way of testing beat induction. In natural music, different types of accents often work together in shaping our metrical expectancies. The role of intensity accents, melodic accents and our previous experience has only been looked at very sparsely. However, using more natural stimuli can create problems in interpreting the results.

In natural music, a beat is induced by creating accents on the beat. Because accented sounds by definition need to stand out from non-accented sounds, this often means that tones on the beat have a different sound than tones that are not on the beat. When comparing the response to events on the beat and events that are not on the beat, these sound differences need to be taken into account. An example of this problem can be found in the work of Winkler et al. [21], who showed that newborn infants respond to the omission of a beat, but not to the omission of a sound that was not on the beat. While these results showed that the newborns differentiated between sounds in different metrical positions, it cannot be completely ruled out that they did so on the basis of differences in sound rather than position. The sounds that were on the beat were composed of a bass drum and a hi-hat sound, while the sounds that were not on the beat were composed of a single hi-hat sound. This means it is possible that the newborns responded differently to the omission of different sounds. To exclude alternative explanations like these, stimuli must be designed in which physical differences between the sounds in different metrical positions cannot influence the results [92]. Thus, balancing the design of ecologically valid stimuli with the experimental control needed to draw firm conclusions continues to be a challenge.

Another issue to be addressed in future research is the apparent gap between the sometimes contradicting, results obtained with the different methods used in probing beat perception. Some consensus is emerging on which brain networks are involved in the perception of beat and meter and how brain dynamics might be accountable for our metrical expectations. However, the connection between these findings remains unclear. Also, studies to date have all used slightly different stimuli and tasks, which in some cases results in radically different or even contradicting conclusions [23, 66, 93]. Once the different methods are used with similar paradigms, tasks and stimuli, it will be possible to directly compare the results and this will hopefully allow us to get a more coherent picture of the perception of beat and meter, and address its apparent innateness, domain- and species-specificity. All in all, this research will contribute to a better understanding of the fundamental role that beat and meter perception play in music.

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Neural Mechanisms of Rhythm Perception: Present Findings and Future Directions

Li-Ann Leow and Jessica A. Grahn

Abstract

The capacity to synchronize movements to the beat in music is a complex, and apparently uniquely human characteristic. Synchronizing movements to the beat requires beat perception, which entails prediction of future beats in rhythmic sequences of temporal intervals. *Absolute timing mechanisms*, where patterns of temporal intervals are encoded as a series of absolute durations, cannot fully explain beat perception. Beat perception seems better accounted for by *relative timing mechanisms*, where temporal intervals of a pattern are coded relative to a periodic beat interval. Evidence from behavioral, neuroimaging, brain stimulation and neuronal cell recording studies suggests a functional dissociation between the neural substrates of absolute and relative timing. This chapter reviews current findings on relative timing in the context of rhythm and beat perception.

Keywords

Rhythm • fMRI • Music • Timing • Neuroscience

Of many uniquely human behaviours, the capacity to move to the beat in music is one of the most fascinating. To synchronize movements to the beat, we must rapidly predict the timing of future beats in rhythmic sequences of temporal intervals. Despite its complexity, this ability appears spontaneously in humans, without training. Sensitivity to the beat in temporal sequences cannot be easily accounted for by most theories of timing, as they generally focus on 'absolute' timing (also termed duration-based timing), in which patterns of temporal intervals must be encoded as a series of absolute durations. Instead, some human predictive timing behaviors, such as beat perception, seem better accounted for by relative timing mechanisms, in which the temporal intervals of a pattern are coded relative to each other. This relative timing is sometimes called 'beat-based' timing, because the intervals can be encoded relative to a regular, periodic beat interval. Converging evidence from behavioral, neuroimaging, brain stimulation and neuronal cell recording studies suggests

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a functional dissociation between the neural substrates of absolute and relative timing. Absolute timing research has been described in depth elsewhere [1, 2], and will only be briefly reviewed here. Relative timing, particularly in the context of rhythm, will be the focus of this chapter. To orient the reader, we will first provide some definitions of key terms.

Rhythm is defined as the pattern of time intervals demarcating a sequence of stimulus events. In rhythms, the onsets of stimulus events (such as tones or light flashes) tend to be the most important markers of the intervals in a rhythm, and the time between onsets (inter-onset-intervals) generally defines the lengths of the temporal intervals in the rhythmic sequence. This reliance on onsets, not offsets, to indicate intervals in a rhythm is the reason that we can recognize a rhythm whether it is played with long, connected notes (as bowed on a violin) or with short, disconnected notes (as plucked on a guitar). Listening to a musical rhythm gives rise to a sense of *pulse*, sometimes termed the *beat*. The pulse or beat is a series of regularly recurring psychological events that arise in response to a musical rhythm [3, 4]. The time interval between beats is called the *beat period* or *beat interval*, and relates to *tempo,* the rate of the beat: a shorter beat period leads to a faster tempo. Although a sense of beat arises in response to a rhythmic stimulus, it is not purely a stimulus property: beat perception is a psychological response to rhythm [5–8]. For example, beats do not always have to coincide with stimulus onsets (as evidenced by our ability to mentally continue the beat through gaps or breaks in music). Although perception of the beat can be enhanced by volume or timbral accents, such perceptual accents are not necessary for beat perception, suggesting that beat perception can arise purely from particular temporal characteristics of a rhythm. The specific temporal characteristics that induce beat perception, and thus trigger beat-based timing mechanisms, are not entirely clear, but some common heuristics have been used.

Beat-inducing rhythms (sometimes termed *metric simple* rhythms) can be formed by creating rhythmic sequences from intervals whose lengths are related by integer ratios (e.g., 1:2:4), particularly if the interval onsets systematically occur at rates known to be salient for human beat perception (440–1,080 ms) [9, 10]. The opposite of beat-inducing or metric simple rhythms are *nonmetric rhythms*, which have no beat. These can be formed by creating sequences from intervals whose lengths are related by complex or noninteger ratios (e.g., 1:2.3:3.7), or even intervals of randomly selected lengths. In these rhythms, no beat can be felt, because no regularity of onsets is present. Between metric simple and nonmetric rhythms are rhythms that are less likely to induce a sense of beat, but in which it would be possible to sense a beat (i.e., the structure is not so irregular as to preclude a beat 'fitting' to the rhythm). These are often termed metric complex rhythms. Metric complex rhythms are generally closely matched to metric simple rhythms in terms of sequence length, number of intervals in a sequence, and the lengths of individual intervals that comprise the sequence. Unlike metric simple rhythms, the intervals are arranged in such a way that a beat is not readily perceived, generally by not having onsets consistently occur at rates salient for beat perception. Different researchers use somewhat different heuristics for determining the 'complexity' of a metric rhythm, but the underlying idea is similar: simple rhythms induce clear beat perception, complex rhythms less so, and nonmetric rhythms not at all.

Behavioral Evidence of Beat-Based Timing Mechanisms

Without beat perception, the durations of each interval in the rhythm must be measured and stored in memory separately as they occur, and our capacity to remember a series of separate, unrelated time intervals is limited. Perception of the beat enables temporal intervals to be encoded as multiples or subdivisions of the beat, rather than as a series of individual and unrelated intervals. Therefore, the percept of a beat has repeatedly been shown to improve performance

on temporal processing tasks (e.g., [9, 11–13]). In general, behavioural temporal processing tasks can be categorized as either belonging to the perceptual paradigm, or the production paradigm. *Perceptual paradigms* require subjects to make perceptual judgments about sets of temporal stimuli. One commonly used perceptual task is the rhythmic discrimination task, which requires subjects to listen to a "standard" temporal sequence of rhythmic stimuli, followed by a second "test" sequence. Subjects are then asked to compare the standard and the test sequences and make judgments about the sequences (e.g., are the rhythms same or different?) When asked to discriminate if rhythms are same or different, subjects are typically better at discrimination of metric simple rhythms than with metric complex rhythms [14]. Furthermore, beat-inducing rhythms elicit better performance even when the task is not temporal: discrimination of intensity differences is better with beat rhythms than non-beat rhythms [15]. *Production paradigms* require subjects to produce a specified temporal pattern. For example, in rhythm reproduction tasks, subjects listen to rhythms and then reproduce them from memory [9]. Another commonly used production task is the synchronization-continuation task. In the synchronization phase, subjects synchronize movements (typically finger taps) to the onset of each tone of a rhythm, or to each beat in the rhythm. In the continuation phase, the sound is removed, and subjects continue to reproduce the rhythm, or only the beat, from memory. As with perceptual paradigms, performance in production paradigms is more accurate and precise with beat-inducing rhythms than with non-beat rhythms [9, 12, 13, 16, 17]. The individual intervals in beat and non-beat rhythms are the same (only the interval order differs), and the rhythms are equal in all other temporal processing requirements (such as length and number of intervals), therefore the performance advantage for beat-inducing rhythms does not result from any differences in timing of individual intervals. Instead, in beat rhythms, temporal processing performance is improved by the use of relative timing mechanisms: the intervals are perceived and organized relative to the beat interval [1]. Even though the use of relative timing can lead to better performance, its use is limited: only sequences that are structured relative to a beat can be timed this way, so absolute timing mechanisms are still required for timing of non-beat sequences.

Functional Neuroimaging Evidence

Non-invasive neuroimaging methods have contributed to our understanding of how timing and rhythm are processed in the human brain. Unlike in other areas of timing research, non-human primates do not appear to spontaneously perceive and respond to the beat. Thus, we cannot fully extrapolate mechanisms derived from invasive neural recordings in non-human primates to humans, as non-human primates may not have the same relative timing mechanisms as humans. For example, primates do not appear to match tapping movements to metronome tones in the same way as humans. Unlike humans, whose finger taps anticipate tone onset by ~50 ms, primate finger taps lag behind by approximately 250 ms [18] (for a review, see [19]). Non-invasive neuroimaging techniques can therefore provide a much needed bridge between data acquired between human and non-human primates, such that neural bases for behavioral differences between these groups can be determined. Currently, some techniques used in non-human primates, such as intracranial recordings, are too invasive for human use, making cross-species comparisons difficult. By using non-invasive methods, researchers can collect the same type of data, using the same paradigms, across species, enabling them to see which differences are the result of genuine processing differences, and which differences were simply the result of trying to compare across different methodologies.

Broadly, non-invasive neuroimaging techniques fall into two categories. The first category measures the electrical potentials or concomitant magnetic fields generated by neuronal activity using electroencephalography (EEG) or

magnetoencephalography (MEG) respectively. The second category measures the metabolic or hemodynamic consequences of neuronal activity using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI). These two categories of techniques are complementary: EEG and MEG have high temporal resolution, which shows the time-course of neural activity, whereas fMRI and PET have high spatial resolution, which shows the spatial location of activity in the brain. Here, we focus on findings obtained with fMRI techniques, as EEG and MEG findings have been reviewed elsewhere (Vuust et al., final chapter of this book).

Absolute Timing

Absolute timing mechanisms are necessary for the encoding of non-beat rhythms, as the intervals have no relationship to each other. This differs from beat rhythms, in which all intervals can be encoded relative to the beat interval. Converging evidence shows that the **cerebellum** plays a key role in absolute timing. Several studies have shown that such rhythms activate cerebellar structures [17, 20–22]. For example, memorizing non-beat rhythms evokes greater cerebellar activity than memorizing beat rhythms [23]. Greater cerebellar activity is also evident for non-beat rhythms compared to beat rhythms when subjects are reproducing them [9], or make perceptual judgments about them [20, 22], or synchronize finger taps to them [17]. The ability to encode single durations is impaired when cerebellar function is disrupted through disease [24] or through transcranial magnetic brain stimulation [25]. Importantly, the deficits in encoding single durations that occur with cerebellar disruption are not accompanied by deficits in encoding beat sequences [24, 25], supporting the idea that the cerebellum is involved in absolute but not relative timing mechanisms.

Relative Timing

Beat perception necessarily requires relative timing, as all intervals are encoded relative to the beat interval. Relative encoding confers flexibility in the representation of a sequence. One can recognize the iconic 'William Tell' rhythm whether it is played very quickly or very slowly: the rhythm can be accurately rescaled. Absolute representations are not as flexible, and even trained musicians cannot rescale them [26]. This behavioral dissociation between absolute and relative representations is supported by neuroimaging work. There is reasonable consensus that the cerebellum is involved in absolute timing mechanisms (as mentioned above), and basal **ganglia-thalamo-cortical circuits** are involved in relative timing mechanisms [1]. This view arises from mounting evidence showing activation of the basal ganglia, supplementary motor area, and premotor cortex in beat perception tasks that engage relative timing mechanisms [9, 16, 20, 27–30]. In particular, perceiving a beat appears to selectively activate the basal ganglia and SMA, as beat rhythms consistently elicit greater basal ganglia and SMA activity across studies employing different perception and production paradigms [9, 15, 20–22]. Importantly, increases in basal ganglia and SMA activity during beat-inducing rhythms compared to non-beat rhythms do not arise from greater difficulty performing tasks with non-beat rhythms: even when the task difficulty is systematically manipulated to equate performance for beat and non-beat rhythms, greater basal ganglia and SMA activity is still evident for beat rhythms [9]. Furthermore, beat-inducing rhythms evoke greater activity of the basal ganglia than non-beat rhythms even when subjects are not specifically instructed to attend to any part of the rhythms [29], or when subjects attend to non-rhythmic aspects of the stimuli such as loudness [15] and pitch [21]. This suggests that greater basal ganglia activity does not arise from beat rhythms engaging more attention to temporal aspects of the rhythms than non-beat rhythms.

One question that arises is whether the neural substrates that are attributed to beat perception are specific to the auditory modality. Although beat perception certainly seems to occur more readily with auditory stimuli, it appears that the role of the basal ganglia networks in beat

perception might not be specific to the auditory modality. Visual rhythms do not usually evoke a sense of the beat the way auditory rhythms do, however, a sense of beat *can* be induced for a visual rhythm if it is preceded by an auditory version. When visual rhythms are perceived after auditory counterparts, the basal ganglia response increases during the visual rhythm presentation, and the amount of that increase predicts whether a beat is perceived in that visual rhythm [31]. This suggests that an internal representation of the beat formed during an auditory presentation may influence beat perception in subsequently presented visual rhythms, and that the basal ganglia mediate beat perception that occurs this way.

In addition to neuroimaging findings, basal ganglia involvement in beat perception is also evident from neuropsychological work showing that impaired basal ganglia function leads to worse performance on tasks assessing beat perception [14]. For example, patients with Parkinson's disease are worse than controls at discriminating changes in beat rhythms, but are similar to controls at discriminating changes in non-beat rhythms [14]. Unlike rhythm reproduction or beat synchronization tasks, discrimination tasks do not require any motor responding and therefore the results are unlikely to be explained by a motor deficit. More importantly, the patients are impaired only in the condition that is generally found by subjects to be easier. This rules out the possibility that nonspecific impairments, such as greater fatigue or poorer working memory function, caused the deficit. Any nonspecific impairment would be expected to be present across all conditions, and if anything, to a greater extent in the non-beat condition, as it is usually more difficult for healthy subjects. The selective deficit in beat rhythms and not non-beat rhythms supports the proposal that the basal ganglia are primarily involved in relative timing mechanisms. There is also preliminary evidence suggesting that Parkinson's disease patients have difficulty perceiving and synchronizing movements to the beat in music [32]. Other forms of basal ganglia dysfunction, such as in Huntington's disease patients, also show deficits in tasks assessing relative timing [33]. However, unlike the Parkinson's disease patients in the previous study [14], the Huntington's disease patients also showed deficits in tasks assessing absolute timing mechanisms. This apparent discrepancy in results might be because the pattern of basal ganglia degeneration differs substantially between Parkinson's disease and Huntington's disease: degeneration in Huntington's disease starts in the caudate nucleus, whereas degeneration in Parkinson's disease starts in the putamen [34]. Future studies comparing the same temporal processing tasks in both patient groups can help determine if striatal networks impaired in Huntington's disease but spared in Parkinson's disease are important to absolute timing mechanisms.

Basal ganglia deficits appear to selectively affect temporal processing performance around a rate that humans find ideal for beat-perception (500–700 ms). For example, patients with focal basal ganglia lesions are less able to detect tempo changes or adjust finger taps to rate changes at rates close to the ideal beat rate [35]. Parkinson's disease patients also show selective deficits in tapping at the ideal beat rate of 500 ms, but not at 1,000 or 1,500 ms [36]. This appears consistent with neuroimaging findings which show basal ganglia activity does not correlate with the speed of the beat, but shows maximal activity around the ideal beat rate and then decreases as rates are too slow (McAuley et al. 2012) or too fast for a beat to be felt [37]. Therefore, the basal ganglia are not simply responding to perceived temporal regularity at any rate in auditory stimuli, but are most sensitive to regularity at the rate that best induces a sense of beat.

Although poor beat perception has been observed in patients with impaired basal ganglia function, it is not limited to neurological patients. Healthy individuals have been diagnosed as "beat-deaf". These individuals have no other form of musical impairment, yet beat perception deficits are evident across a number of behavioral paradigms: perceiving the beat, synchronizing movements to the beat, detecting when metronome cues are off the beat in music, and detecting when a dancer's movements are off

the beat [38]. Even apart from the most severe beat impairments, there is a wide range of ability to perceive the beat in healthy individuals [39–41]. Several studies have recently attempted to examine the neural correlates of individual differences in beat perception. One study showed that good beat-perceivers more readily engage supplementary and premotor areas when making temporal judgments than poor beat-perceivers [39]. Another study found that better beat perception was positively correlated with activation of the supplementary motor area and premotor cortex during a rhythm discrimination task [41]. Better synchronization performance to rhythms has also been associated with larger ventral premotor cortices [42]. Overall, the fMRI evidence points to a key role for motor areas, rather than auditory areas, in beat perception ability. Why do healthy, neurologically intact individuals show poor beat perception? One possible explanation is that such individuals possess dopamine genetic polymorphisms which selectively impair temporal perception at intervals that are most salient for beat perception (500–700 ms). For example, individuals with the DRD2/ANKK1-Taq1a genetic polymorphism have a reduced density of D2 receptors in the basal ganglia. These individuals also show significantly greater variability in temporal discrimination of single intervals of 500 ms (at the ideal beat rate) but not 2,000 ms [43]. These commonly found genetic polymorphisms appear likely to influence individual differences in ability to perceive the beat, although this possibility has yet to be systematically examined.

Coupling Between the Auditory and Motor Areas in Beat Perception

Although many studies have shown involvement of several motor regions in rhythm processing, it is still unclear *how* these motor regions interact with each other, as well as with auditory regions, to give rise to a beat percept. The analyses that characterize the communication and interactions between brain areas are called functional connectivity analyses. Greater functional connectivity between two or more areas is thought to denote greater communication between those areas. Recent studies exploring the communication between motor areas in beat perception showed that during beat perception, greater connectivity was observed between the putamen and the supplementary motor area, as well as between the putamen and the premotor cortex (see Fig. 1) [21]. The increases in connectivity were evident regardless of whether the beat was induced by the temporal pattern of interval durations in the rhythm, or by regularly occurring volume accents (see Fig. 1) [21]. Another study showed greater connectivity between the putamen and the ventrolateral prefrontal cortex (VLPFC) when synchronizing finger taps to the beat of non-beat rhythms than to beat rhythms [17]. The VLPFC is thought to be involved in monitoring performance by comparing internal and external sensory representations [44]. Synchronization requires subjects to continuously monitor performance by comparing the output of their motor responses with internal representations of the beat intervals. Synchronizing to non-beat rhythms has more performance monitoring demands than synchronizing to beat rhythms, because unlike beat rhythms, non-beat rhythms cannot be encoded automatically through relative timing mechanisms. The VLPFC is therefore thought to interact with the basal ganglia so that beat intervals could be compared, selected and maintained for production during synchronization [17].

Individual differences in connectivity between cortical motor and auditory areas might be a useful marker of rhythmic ability. In musicians, superior performance on a synchronization task was associated with greater connectivity between the auditory and premotor cortex [12]. Furthermore, a different study found greater connectivity between the premotor and auditory cortex in musicians, even when activity of these areas was similar (see Fig. 1) [21]. That is, increased connectivity between two regions can exist in the absence of increased activity in either region. Exactly how coupling between the auditory areas and the premotor cortex improves rhythmic performance remains unclear, although it has been suggested that increased functional

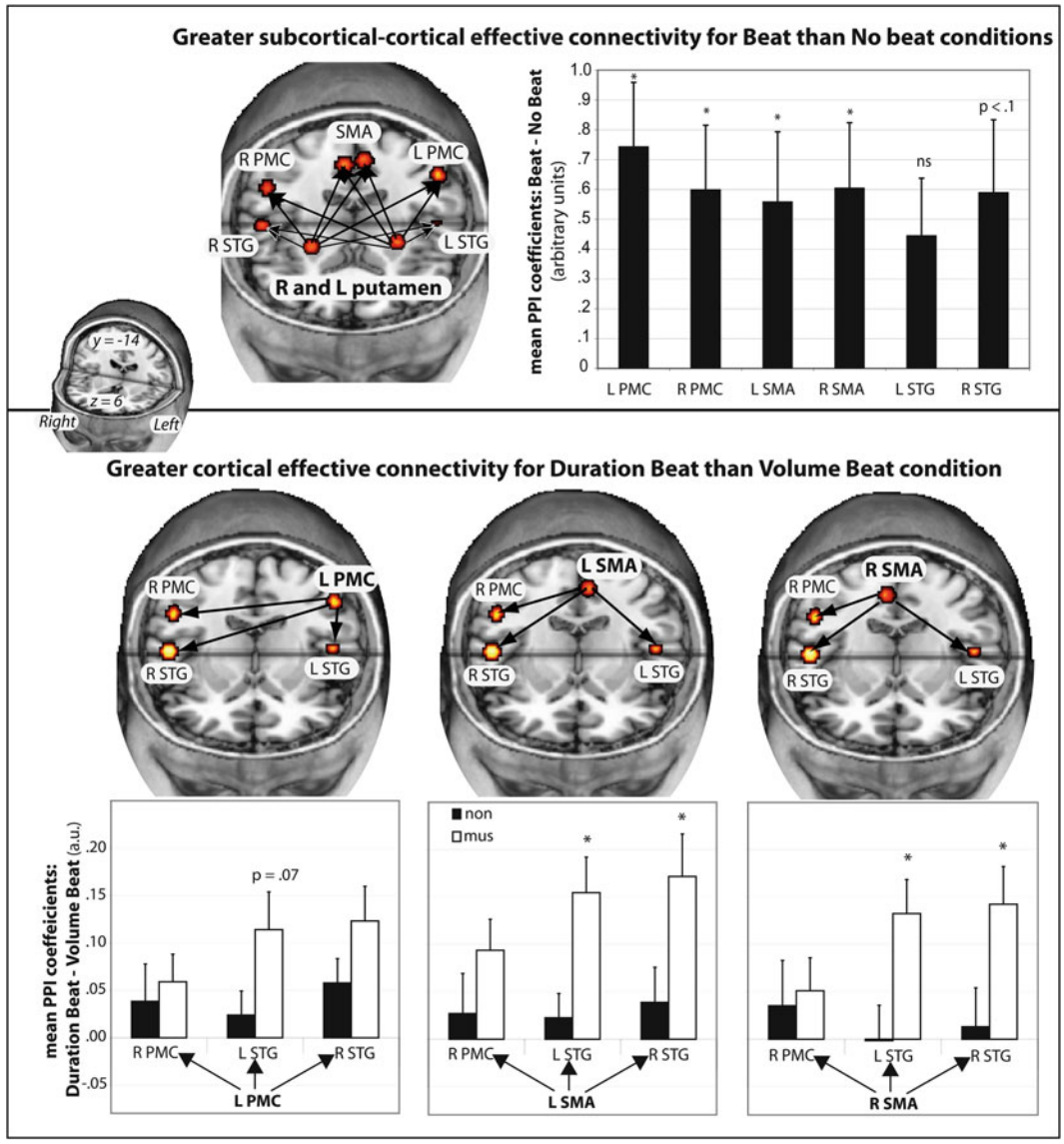

Fig. 1 *Top panel* shows functional connectivity between the putamen and the SMA and premotor cortices in Grahn and Rowe [21]. Greater subcortical-cortical connectivity was evident with beat rhythms than with non-beat rhythms. Mean PPI coefficients (arbitrary units) from the target regions for each of the significant source to target pairs are shown in the *top right* graph ($p < 0.05$; small volume corrected). *Middle panel* shows regions with increased coupling in condition where the beat was indicated by relative interval durations (duration beat condition) compared to conditions where the beat was indicated by strong external volume accents (volume beat condition). *Bottom panel* shows coefficients for musicians and nonmusicians: *$p < 0.05$, significant difference between groups (independent samples t test). *R* right, *L* left, *mus* musician, *non* nonmusician

connectivity between the premotor cortex and superior temporal gyrus might be important for integrating auditory perception with a motor response [12]. Kung et al. [17] also showed that beat perception and synchronization performance was correlated with activity in STG and VLPFC; they suggest that the connectivity between the STG and VLPFC could be important for retrieving, selecting, and maintaining the musical beat.

The Role of the Basal Ganglia in Beat Perception

Although many studies demonstrate the involvement of the basal ganglia in beat perception, its specific role in beat perception remains unclear. Recent studies have started to address this question by examining the basal ganglia's role in the component processes of beat perception. Beat perception has been proposed to require at least three processes: *beat finding*, during which the regular beat interval is detected, *beat continuation*, during which predictions of beat intervals are created and maintained, and *beat adjustment*, during which predictions of future beat intervals are updated based on accumulating evidence resulting from sensory feedback [22]. In a recent study, these processes were distinguished by having participants listen to sequentially presented beat and non-beat rhythmic sequences. For each sequence, the preceding sequence provided a temporal beat context for the following sequence. Beat sequences preceded by non-beat sequences were proposed to elicit *beat finding,* as subjects must detect the beat in the beat sequence without any previous beat information. Beat sequences preceded by beat sequences at the same beat rate elicited *beat continuation* as subjects would ostensibly maintain their internal representation of the beat intervals from the preceding sequence, and simply continue them on to the subsequent sequence. However, if the beat rate changed from one beat sequence to the subsequent beat sequence, then the internal representation of the beat would require adjustment. FMRI was used to measure brain activation during each process. Putamen activation was greatest when listening to rhythms at the same beat rate (beat continuation), was lower when the rhythms changed rated (beat adjustment), and was lowest when rhythms were preceded by non-beat rhythms (beat finding) (see Fig. 2). The finding of highest putamen activation during beat continuation suggested a role for the putamen in maintaining the internal representation of the beat interval. The suggestion that basal ganglia and SMA are involved in maintaining an internal representation of beat intervals is supported by findings of greater basal ganglia and SMA activation during the continuation phase, and not the synchronization phase, during the synchronization-continuation task [30, 45]. Similarly, patients with SMA lesions also show a selective deficit in the continuation phase but not the synchronization phase of the synchronization-continuation task [46]. Taken together, these findings strongly implicate a role of the basal ganglia and SMA networks in maintaining forward predictions of the beat. That is, when a detectable beat is present in a rhythm, human spontaneously generate predictions about the timing of future beats in the pattern. Successful predictions enhance the speed of perceptual organization of the sequence, reduce working memory load, and thus improve temporal processing performance. Accurate prediction improves performance in many domains, and beat perception may simply be one example of how humans' exploit regular structure to reduce processing load.

Recent cell recording findings in macaque monkeys have also furthered our understanding of the SMA-BG networks' role in beat perception and in rhythmic timing behavior. A first study indicated that distinct SMA cells encoded either the time left for movement (i.e., "relative timing cells"); or the time elapsed after movement (i.e., "absolute timing cells") in a synchronization-continuation task, as evidenced by distinct patterns of ramping behavior pre and post-movement [47]. Crucially, these absolute and relative timing cells interacted during selective phases of the synchronization-continuation task, revealing that rhythmic timing behavior requires the interaction of both absolute and relative timing mechanisms [47]. A subsequent study showed that many SMA cells were selectively tuned to different intervals ranging from 450 to 1,000 ms, and these cells showed the same preferred intervals across different behavioral paradigms (the synchronization-continuation task and a single interval reproduction task) [48]. These SMA cells also showed selectivity for the different task phases during the synchronization-continuation task: some cells

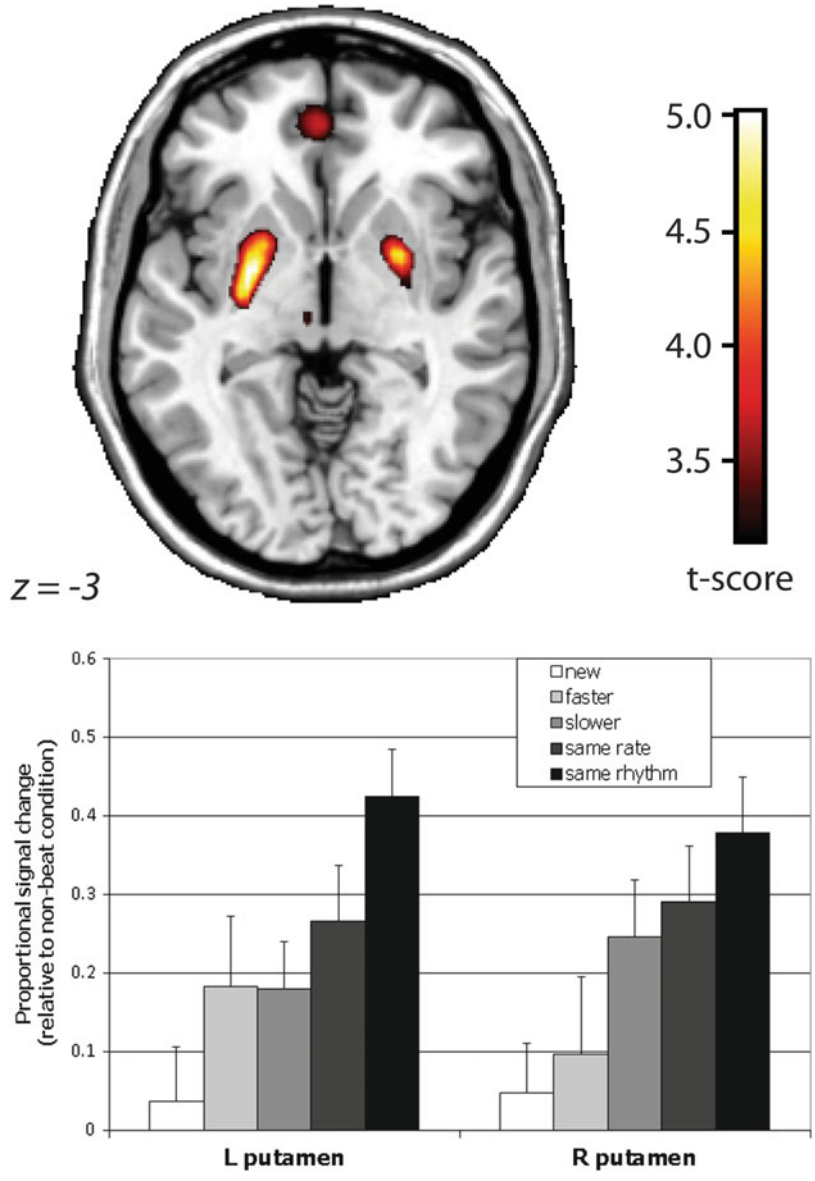

Fig. 2 *Top panel* shows the activation contrast for beat versus non-beat rhythms in Grahn and Rowe [22]. Contrasts were overlaid on a template brain, thresholded at $PFDR < 0.05$. Z refers to the level of the axial slice shown in stereotaxic Montreal Neurological Institute space. *Bottom panel* shows mean activation graphs from left and right putamen regions of interest for each beat condition relative to the nonbeat control condition. A positive value means greater activity for that particular beat condition compared with the nonbeat condition. Putamen activation was greater in conditions where the rhythms increased in similarity: greatest putamen activation was evident in beat continuation (same rhythm)

were biased to respond during synchronization phase, whereas other cells were biased to respond during the continuation phase. These findings are consistent with subsequent work showing differential beta and gamma activity in local field potentials recorded from the putamen: greater beta band activity was evident in the continuation phase, whereas greater gamma band activity was evident in the synchronization phase, in certain local field potentials [49]. Together, these findings support the proposal of distinct processes in rhythmic timing behavior: a process that underlies synchronization of rhythmic behavior, and another process that underlies continuation of rhythmic behavior. The existence of cells in both SMA and basal ganglia which are

preferentially activated by the continuation of rhythmic behavior suggests that SMA and basal ganglia networks maintain forward temporal predictions [22].

Challenges in the Study of Rhythm Processing

Localizing the neural substrates of rhythm has proven challenging, partly because rhythm is supported by processes common to temporal processing, and temporal processing unavoidably engages many distributed brain areas. One view proposes that sub and supra-second timing engage partially distinct neural mechanisms [50, 51]. Sub-second timing appears to preferentially engage the cerebellum, while supra-second timing tasks appear to preferentially engage the supplementary motor area and prefrontal cortex (for a review, see [52]). The basal ganglia is thought to be engaged by both sub and supra-second timing [50]. How this dissociation affects our current understanding of beat perception is unclear. Beat perception requires both sub-second and supra-second timing, as individual sub-second beat intervals must first be perceived, and then an internal representation of these intervals must be maintained across supra-second timescales. The component processes in beat perception (such as beat finding, beat continuation, beat adjustment) might differentially rely on sub and supra-second timing mechanisms, and this remains to be systematically examined.

An additional challenge to the study of rhythm processing is the fact that even the simplest rhythm processing task might have multiple cognitive and motor demands. Patterns of neural activation that are attributed to experimental manipulations in rhythm processing tasks can sometimes result from task demands. For example, working memory is required to compare standard rhythms with test rhythms, as subjects must remember the standard rhythm to compare with the test rhythm. It is unclear whether the memory benefits resulting from beat perception underpin the performance advantages for beat-inducing rhythms. The synchronization-continuation paradigm also relies on several cognitive and motor processes beyond just timing. During synchronization, subjects must encode and maintain the beat interval, produce a synchronized motor response, evaluate the accuracy of that response after each tap, and correct the timing of the next tap, if necessary. Better synchronization to beat rhythms might result from better encoding and maintenance of the beat interval, or from better evaluation and error correction. Hence, although temporal performance is thought to be improved by using relative timing, exactly how this mechanism improves specific aspects of performance is unclear.

Another challenge is that while many studies employ rhythms that are manipulated in terms of perceived beat strength, it remains unclear *what* factors lead to a beat percept. It has been proposed that integer-ratio relationships between intervals in a sequence induce beat perception, whereas noninteger-ratios do not [30, 53]. However, to the best of our knowledge, no studies have shown statistically reliable differences in brain activation between integer ratio and noninteger ratio rhythms. A previous study by Sakai et al. [53] did not directly compare brain activation between integer-ratio and noninteger-ratio rhythms [53]. Another study showed that integer-ratio and noninteger-ratio rhythms could result in statistically indistinguishable brain activation [9]. The integer/noninteger-ratio distinction therefore appears insufficient to fully account for what features induce beat perception, especially in rhythms composed of more than only one or two interval lengths.

Beat perception in musical rhythms typically occurs in an ongoing fashion: we spend only a very small portion of time perceiving the beginning of a rhythmic sequence. Knowledge acquired from prior context is therefore likely to drive internal predictions about the beat, optimizing estimations of beat intervals and beat onsets. Some studies have examined the role of context in the perception of individual intervals (e.g., [54]), but debate remains on its role [55]. One view suggests that time perception occurs through

interactions of a core timing network with cortical areas that are activated in a context-dependent fashion [2]. Computational studies suggest that prior contextual knowledge about temporal uncertainty is used to optimally adapt internal interval timing mechanisms to the temporal statistics of the environment [56, 57] (for a review, see [58]). Although context appears intuitively important to beat perception, little is known about how to integrate contextual information into mechanistic accounts of relative timing.

Finally, beat perception is also affected by other aspects of musical structure, such as melody, harmony, and timbre. The influence of musical structure on beat perception have been examined [59–67], but these findings have yet to be integrated into a single unifying model. Additional basic research that tests the influences of these non-temporal musical factors on beat perception will need to be done to extrapolate modes of beat perception to apply in real music, rather than monotone rhythmic sequences.

Future Directions

As we move towards more complete understanding of the neural mechanisms underlying relative timing and rhythm processing, converging evidence from complementary techniques becomes increasingly important in overcoming the limitations of individual techniques. For example, the use of Parkinson's disease patients as models of impaired basal ganglia function is limited by the fact that areas connected to the basal ganglia are also affected in Parkinson's disease. Furthermore, neurodegenerative diseases like Parkinson's disease result in heterogenous degeneration of striatal pathways, and the different patterns of degeneration are associated with different behavioral impairments on timing tasks [36, 68]. An exciting new complementary approach involves testing individuals with particular genetic variants that alter function of the basal ganglia. For example, one could examine how beat perception is affected by selective reductions in dopamine receptor function in healthy adults, such as carriers of specific genetic polymorphisms which reduce dopamine neurotransmission within the basal ganglia, but do not affect dopamine neurotransmission outside the basal ganglia. Studies that combine neuroimaging and genetic approaches have already shown promising results. For example, individuals with genetic polymorphisms that reduce striatal dopamine receptor function showed worse performance on a temporal discrimination task [69]. Interestingly, in these individuals, better temporal discrimination performance was associated with greater activation in the basal ganglia and right dorsolateral prefrontal cortex, as well as greater cerebellar volume [69]. One possible interpretation is that these findings indicate functional and structural compensatory mechanisms for poor temporal discrimination.

There is also increasing interest in why non-human primates differ from humans in rhythmic timing behavior. It has recently been proposed that non-human primates lack connectivity between the auditory and motor regions which enable rhythmic timing behavior in humans [19]. Comparative studies using non-invasive neuroimaging techniques may help bridge the gap in understanding the inter-species differences in rhythmic timing behavior (e.g., [70]). FMRI and EEG studies can be conducted with both humans and macaques, often with identical equipment and using identical paradigms. In addition, the increasing availability of intracranial recordings in patients may make it possible to make compare invasive neural recordings in humans and in primates [18, 19].

Overall, advances in analysis methods for existing techniques, adaptation of these techniques to different species, and adoption of new techniques are leading to better understanding of the characteristics of human rhythm processing. In coming years, greater integration of data acquired across different methodologies will be important to progress our understanding of how the complexities of rhythmic behaviour arise.

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Neural Underpinnings of Music: The Polyrhythmic Brain

Peter Vuust, Line K. Gebauer, and Maria A.G. Witek

Abstract

Musical rhythm, consisting of apparently abstract intervals of accented temporal events, has the remarkable ability to move our minds and bodies. Why do certain rhythms make us want to tap our feet, bop our heads or even get up and dance? And how does the brain process rhythmically complex rhythms during our experiences of music? In this chapter, we describe some common forms of rhythmic complexity in music and propose that the theory of predictive coding can explain how rhythm and rhythmic complexity are processed in the brain. We also consider how this theory may reveal why we feel so compelled by rhythmic tension in music. First, musical-theoretical and neuroscientific frameworks of rhythm are presented, in which rhythm perception is conceptualized as an interaction between what is heard ('rhythm') and the brain's anticipatory structuring of music ('the meter'). Second, three different examples of tension between rhythm and meter in music are described: syncopation, polyrhythm and groove. Third, we present the theory of predictive coding of music, which posits a hierarchical organization of brain responses reflecting fundamental, survival-related mechanisms associated with predicting future events. According to this theory, perception and learning is manifested through the brain's Bayesian minimization of the error between the input to the brain and the brain's prior expectations. Fourth, empirical studies of neural and behavioral effects of syncopation, polyrhythm and groove will be reported, and we propose how

The supplementary audio material can be downloaded from http://extras.springer.com

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these studies can be seen as special cases of the predictive coding theory. Finally, we argue that musical rhythm exploits the brain's general principles of anticipation and propose that pleasure from musical rhythm may be a result of such anticipatory mechanisms.

Keywords
Music • Rhythmic complexity • Prediction • Pleasure

Introduction

Music has a remarkable ability to move our bodies and brains. The ways in which apparently abstract rhythmic intervals of accented temporal events relate to each other can make us want to tap our feet, bop our heads and get up and dance. With the advent of musical styles of the twentieth century, developed in the aftermath of the meeting between music brought to America from Africa and Western music, rhythm has become an increasingly important aspect of the listening experience. Why is rhythm so compelling, and how does the brain facilitate the rich and complex experiences we have with rhythm in music? In this chapter, we describe some of the most common forms of rhythmic complexity in music, review some theories of how rhythm and rhythmic complexity is processed in the brain, with particular focus on the theory of predictive coding, and propose why we may be attracted to rhythmic tension in music. First, we will present the music-theoretical and neuroscientific framework for understanding rhythm perception as an interaction between what is heard ('rhythm') and the brain's anticipatory structuring of music ('the meter'). Accordingly, the rhythmic experience is seen as the result of tension or discrepancy between rhythm and meter. Second, we will discuss the experience of three different musical examples of tension between rhythm and meter: syncopation, polyrhythm and groove. Third, we will present the theory of predictive coding of music, which posits a hierarchical organization of brain responses, reflecting fundamental, survival-related mechanisms associated with predicting future events. It argues that perception and learning occurs in a recursive Bayesian process by which the brain tries to minimize the error between the input and the brain's expectation. Fourth, we describe a number of empirical studies in which the neural and behavioral effects of syncopation, polyrhythm and groove were investigated, and propose how these studies can be seen as special cases of the predictive coding theory. Here, we will touch upon the effect of individual background in rhythm processing, as exemplified by differences between groups of individuals with varying musical competence. Finally, we shall propose that neural processing of rhythm may be music's way of exploiting general principles of anticipatory brain processing and that our extraordinary capacity for anticipating the future may be one of the reasons why we find so much pleasure in music.

Rhythm and Meter

Most theories of rhythm perception involve the notion of meter. *Rhythm,* broadly, is a pattern of discrete durations, and is largely thought to depend on the underlying perceptual mechanism of grouping [1, 2]. *Meter*, again broadly, is the temporal framework according to which rhythm is perceived. When we listen to a certain piece of music, we often automatically start tapping our feet in relation to the rhythm with isochronously spaced beats (a process also known as beat perception, or -production), and we may even accentuate some beats more than others. This process of differentially accentuating isochronously spaced beats is an expression of meter. Meter is often described as the temporal framework of

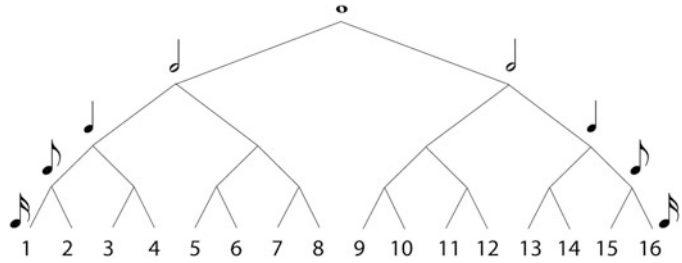

Fig. 1 Metric tree-model. Each metric level (or value) is recursively subdivided into equally spaced parts (or values) at the level below, determining the metric salience of positions within the metric framework. The higher the value in the hierarchy, the more salient the position in the meter. Numbers designate serial positions within the meter, at 16th note resolution

rhythmic expectations [3]. In other words, the meter provides the listener with a hierarchical expectancy structure underlying the perception of music, according to which each musical time-point encompasses a conjoint prediction of timing and salience [4].

Despite growing interest in music research for the cognitive underpinnings of music perception, the definitions of meter, and particularly its relationship with rhythm is still under significant debate. This is despite music psychology researchers having attempted to define meter since the 1970s, using a number of different theoretical and empirical approaches (e.g., [5–10]).

In formal terms, meter generally refers to the alternation of strong and weak temporal accents, which provide a metric framework for a rhythmic pattern. According to music theory, this is expressed in the time signature of a given piece of music, such as 4/4, 3/4 or 6/8. This formal expression of meter, however, can be quite different from how the meter is actually perceived or how it is expressed in sensorimotor synchronization, such as foot-tapping, since it is possible, in principle, to notate any given piece of music in more than one time signature. Furthermore, while the formal definition is relatively easy to handle, there is more disagreement about the perceptual definition of meter. At the most basic level, meter perception is understood as a subjective sense of pulse. Listeners often recognize the main pulse in rhythm, which is the pattern of isochronously spaced beats that commonly elicits spontaneous foot-tapping or synchronized body-movement [11]. However, the hierarchical differentiation of pulse sequences beyond the main pulse (i.e. faster or slower pulses), the exact structure of this hierarchy and whether they determine the differences in metric salience of pulse events within a sequence, still remain unclear. An example of a highly hierarchical view of meter is proposed in Lerdahl and Jackendoff's Generative Theory of Tonal Music [6]. They claim that rhythm perception is underpinned by a framework of meter organized in a tree-like structure (Fig. 1), implemented on the basis of a set of cognitive rules. Within this tree-structure, every node on a given hierarchical level is recursively subdivided into equally spaced nodes at the level below. The level of a given node, as well as the number of connections to other nodes at lower levels, determines the metric salience of notes occurring at that position in the framework. The higher up in the hierarchy, and the more connections, the stronger the metric accent. Although their emphasis on cognitive rules is often criticized for giving too much attention to top-down processes of music cognition and not enough focus on the role of the body, many researchers have since also adopted metric tree models in studying rhythm and meter [12–16].

Other models, in particular the dynamic attending theory (DAT), direct considerably more attention to the body. DAT was originally proposed by Jones and colleagues [10, 17–19] in order to conceptualize the cognitive mechanisms for time perception more broadly, but has since

been widely appropriated to music, specifically [20–24]. Here, the claim is that rhythm induces metric frameworks by way of entrainment: the listeners' attention is captured and driven by the periodicities (or oscillations) in the rhythmic pattern, and the experience of metric salience corresponds to the relative strength of attention directed towards each rhythmic event. The hierarchical nature of meter in DAT is considerably more flexible and adaptive compared to Lerdahl and Jackendoff's model [6]. It was originally proposed as a *conceptual* model, using oscillation and resonance as metaphors for the functions of rhythm and meter in music. However, recent evidence suggests that the electrophysiological firing patterns of neurons in the brain are characterized by entrainment, and models of neural resonance are believed by some to explain rhythm and meter perception directly [9, 25].

Another relatively new way of modelling rhythm and meter perception is by way of computational models [26–30]. One particularly influential theory is proposed by Temperley [13–15], who argues that probabilistic models of rhythm are the most appropriate ways of capturing the generative principles behind compositional processes. In one of his studies [15], he tests the performance of six probabilistic models based on the *Bayesian rule of probability* on two corpuses of music, the Essens Folk Song Collection [7] and a collection of string quartets by Haydn and Mozart. The Bayesian model is one that allows the drawing of conclusions about how well an expression of data (e.g. a rhythmic pattern) fits with other expressions of the same type of data more generally (a model of rhythm, or meter). As will be discussed below, this type of model comparison, relying on Bayesian inference, is also integrative to the predictive coding theory.

When Metric Expectancy Is Broken

Syncopation

A key factor in our experience of rhythm is the extent to which a rhythmic pattern challenges our perception of meter. The most common example of such tension between rhythm and meter is *syncopation*. Most researchers and theorists generally define syncopation as an instance of rhythm that violates listeners' metric expectations. Generally, it is assumed that listeners expect the majority of onsets in a rhythm to occur at metrically salient positions in a metric framework, while rests are expected to occur at metrically less salient positions (Fig. 2a, Audio Example 6.4- 1). A syncopation occurs when these expectations are violated (Fig. 2b, Audio Example 6.4- 2) and the rhythmic event coincides with the metrically less salient position, while the rest coincides with the metrically salient position. Building on the assumption of a hierarchical model of meter, Longuet-Higgins and Lee [12] proposed a particularly influential theory of syncopation, formalizing an index of syncopation that can be used to calculate the perceptual effect of syncopation based on its contextualization within a model of metric salience.

Since it was proposed, a number of researchers have tried to test Longuet-Higgins and Lee's index [12]. Ladinig, Honing and colleagues have primarily been interested in determining how the model reflects the actual perceptual properties of rhythm and meter, using syncopation as a tool [31–33]. Ladinig et al. [32] tested the perceptual effects of syncopations on listeners' metric expectations and found that the degree of unexpectedness or perceived stability depended on the metric location at which the syncopation occurred. Their findings broadly support the idea that syncopation relies on the differentiation of metric salience in rhythm. Furthermore, their participants were all non-musicians, suggesting that not only listeners with extensive musical training exhibit hierarchical processing of meter and rhythm, as has previously been suggested [34]. However, the metric frameworks indicated by these studies were not found to be as strictly hierarchical as the tree-model suggests. Generally, it seems we can be relatively confident that the downbeat has the strongest accent, but beyond that, the model remains unclear.

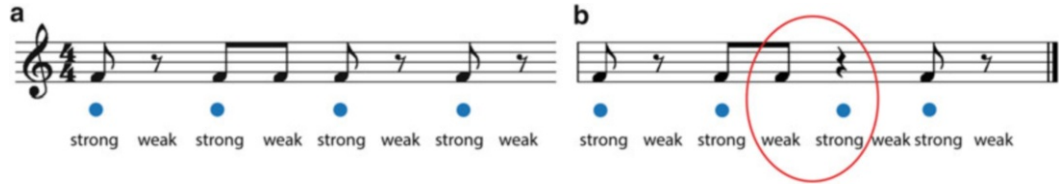

Fig. 2 (**a**) Pattern with no syncopation (Audio Example 6.4- 1). (**b**) Pattern with syncopation, in *red circle* (Audio Example 6.4- 2). *Blue dots* designate the main pulse (the background click in Audio Examples 6.4-s 1 and 2), and metric salience indicated above (strong and weak)

Other researchers have been more concerned with how syncopation affects sensorimotor synchronization: using syncopations as a way of increasing complexity in rhythmic patterns, they have investigated the extent to which such complexity affects the experience of a stable meter and the ability to synchronize body movements [16, 35–37]. Fitch and Rosenfeld [16] adopted Longuet-Higgins and Lee's index [12] and showed that participants' number and magnitude of tapping errors correlated linearly with the degree of syncopation. Furthermore, as the degree of syncopation increased, participants were more likely to "reinterpret" the rhythmic patterns as unsyncopated by resetting the phase of the perceived main pulse. In other words, the more syncopated a rhythmic pattern, the less likely listeners are to accurately perceive the meter and successfully synchronize body movements to it.

Importantly, syncopation is a way to musically conceptualize rhythmic complexity since it challenges the presumed perceptual model of the meter. In fact, in a correlational comparison of different measures of rhythmic complexity in music, Thul and Toussaint [38] found that measures of syncopation outperformed other measures of rhythmic complexity, such as entropy, in explaining the behavioral data from four separate studies.

Polyrhythm

In some styles of music, the meter may at times be only weakly (or not at all) acoustically actualized in the music itself, creating extreme instances of perceptual rhythmic complexity. An example is Cuban Son Montuno (e.g. Guillermo Portabales "Mi son Cubano" 1976). In this musical style, it is common for the bass to continuously avoid playing on the downbeat, i.e. the most salient position in the metric framework. As a listener unfamiliar with Cuban music, it is likely that the meter is 'misinterpreted' and the phase of the downbeat is shifted to comply with less complexly manifested rhythmic-metric relationships. An even more radically complex rhythmic practice is the pervasive use of polyrhythm, or even polymeter,[1] throughout musical compositions, especially in (but not restricted to) jazz music [39]. During polyrhythms, the formal meter may be completely absent in the actual acoustic signal and musicians rely on listeners' ability to predict the formal metric framework. One example of polyrhythm is 'cross-rhythm', in which different overlaid rhythmic patterns can be perceived as suggesting different meters. A typical example is the so-called 3-against-4 pattern, which may be experienced by playing, for example on the drums, at the same time three equally spaced beats in one hand and four equally spaced beats in the other hand, so that the periods of both patterns add up at the end. In this case, it is possible to perceive the meter as a triple waltz meter (formal meter 3/4) and the four-beat pattern as a counter-metric pattern (Fig. 3a, Audio Example 6.4- 3) or as a duple meter (formal

[1] Although often used interchangeably, the difference between polyrhythm and polymeter is important to maintain. In the former, more than one rhythmic pattern is played simultaneously, underpinned by the same meter, while in the latter, more than one rhythm based on different meters is played simultaneously.

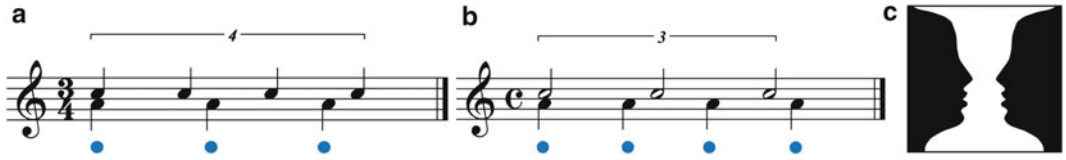

Fig. 3 (**a**) Three-beat triple meter with four-beat pattern as counter-rhythm (Audio Example 6.4- 3). (**b**) Four-beat duple meter with three-beat counter-rhythm (Audio Example 6.4- 4). *Blue dots* designate the main pulse. (**c**) The bistable percept of Rubin's vase

meter 4/4) with the three-beat pattern as the counter-metric pattern (Fig. 3b, Audio Example 6.4- 4). The rhythmic organization of these two patterns is exactly the same, that is, the cross-rhythmic relationships between the two streams within each pattern are identical. The lower pitch expresses the meter and the higher pitch the counter-rhythm in both patterns, but in the first pattern, the meter is triple, while in the second pattern, the meter is duple. These two experiences of the same polyrhythm (albeit with inverted instrumentation, i.e. whether the four- or three-beat pattern has the lower pitch) are phenomenologically different, and is thus analogous to ambiguous images such as the Rubin's vase, which can be seen either as a vase on black background or faces on white background (Fig. 3c). In the case of the cross-rhythms, the meter is the background and the counter-metric rhythm is the foreground. Experiencing cross-rhythm in music can sometimes force the inexperienced listener to either shift the meter to comply with the counter-meter or to reinforce the sense of the original meter, for example through sensorimotor synchronization, such as foot-tapping. Polyrhythms thus provide the listener with a bistable percept [40] that affords rhythmic tension and embodied engagement in music.

Another example of polyrhythm is metric displacement, a structural strategy in which a rhythmic motif is first presented in relation to a specific metric framework (Fig. 4a, Audio Example 6.4- 1), and later shifted to start at a new metrical location, causing different layers to interlock in novel ways and form new rhythmically complex relationships (Fig. 4b, Audio Example 6.4- 5). The beginning of a metric displacement will therefore always be heard as metric incongruity and the tension caused by the displacement is prolonged, compared to other more momentary instances of rhythmic tension (e.g. syncopation).

In some jazz music, such as the music of the Miles Davis Quintet, polyrhythmic structures were used extensively during improvisation as an important means of communication [41]. In fact, when applying established linguistic communicational models, such as Roman Jacobson's model [42], the interactive exchange of polyrhythms in music displays functions comparable to the functions of spoken language. In jazz, the metric displacements and the accompanying rhythmic incongruities are often used for attracting attention and establishing communicational paths between musicians, whereas cross-rhythms are more typically used for building and playing with tension once a connection between musicians is established. In both cases, the effect of the polyrhythm relies on the listeners' or musicians' ability to predict the original meter.

Albeit rarely, polyrhythms have been used in empirical investigations of rhythm and meter perception [34, 43–49]. The idea is that the ways in which complex rhythmic structures are processed can reveal the mechanisms underpinning rhythm and meter perception more generally. As will be described below, polyrhythms also provide unique insights into the ways in which the brain processes temporally incongruous information.

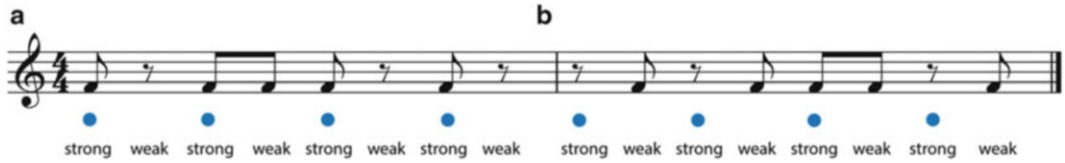

Fig. 4 (**a**) Metrically congruous pattern (Audio Example 6.4- 1). (**b**) Pattern metrically displaced by one eight-note, resulting in a metrically incongruous pattern (Audio Example 6.4- 5). *Blue dots* designate the main pulse (the background click in Audio Example 6.4-s 1 and 5) and metric salience indicated above (strong and weak)

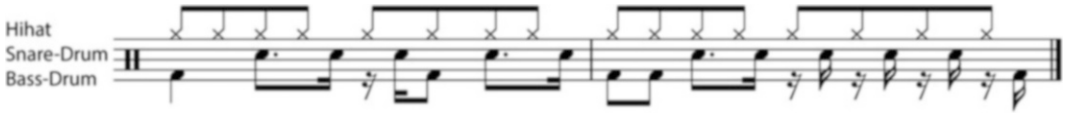

Fig. 5 Drum-break of "Ode to Billy Joe" by Lou Donaldson (1976)

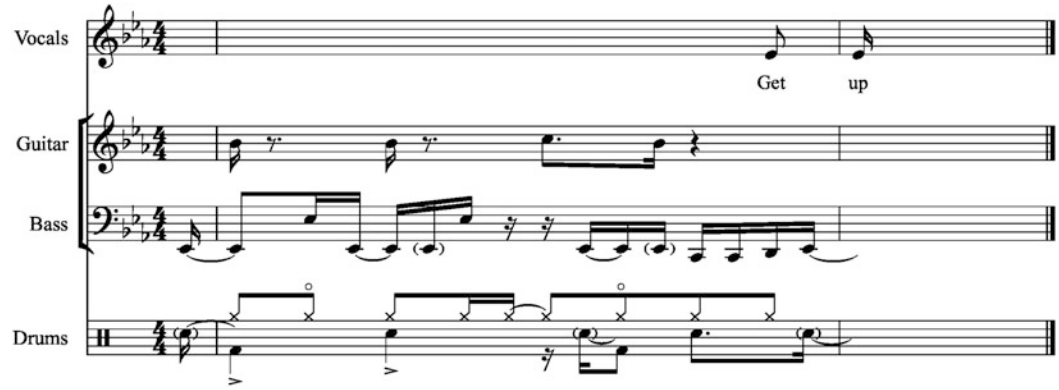

Fig. 6 Groove of "Sex Machine" by James Brown (1970)

Groove

Within musicology research, groove usually refers to music that is characterized by some degree of rhythmic complexity and expectancy violation, such as syncopation, metric displacement, cross-rhythms or microtiming.[2] A groove can be just a drum-kit playing and repeating a two-bar pattern (Fig. 5) or it may be the sonic interplay of a whole rhythm section of a band (e. g. drums, guitar, bass and vocals, Fig. 6) Examples of groove-based genres are funk, soul, hip-hop, jazz and electronic dance music. In the context of groove, the rhythmically complex musical-structural strategies engender a somewhat different behavioral effect than when they are experienced in isolation. Importantly, in groove, the rhythmic complexity is continuously repeated, and the experiential result is a desire to move the body in synchrony with the meter [53–56]. Witek [57, p. 4] provides the following definition of groove: Grooves are continuous multi-layered patterns of repeating units, commonly 2–4 bars in length, with varying degrees and expressions of rhythmic complexity, associated with a pleasurable desire to move.

Groove has until recently mainly been addressed theoretically, particularly in the context of embodied cognition [50, 58] and prediction

[2] Microtiming, otherwise known as expressive timing or 'swing', refers to patterns of rhythmic events that do not occur exactly 'on' the pulse, but slightly 'late' or 'early' in relation to it [50–52].

[39]. Furthermore, the first empirical studies on the subject have tended to focus on the behavioral effects exclusively, and only broadly drawn parallels between the musical structure and the psychological effects. In these studies, the positive drive towards body-movement has been the main focus [53–55]. For example, Madison et al. [55] found that the salience of the beat (i.e. the main pulse) and event density (i.e. sub-beat variability) correlated positively with ratings of groove (i.e. wanting to move). Janata et al. [53] showed that groove was consistently defined by listeners in terms of movement-inducing properties, but also positive affective feelings. Through phenomenological considerations, behavioral investigations and computational correlations, their research demonstrated that the 'quality' of groove experience depends on the degree of sensorimotor synchronization coupling in ways that interacted with positive affect. Thus, it seems that in the context of continuous repetition, rhythmic structures that violate expectations, such as syncopation, metric displacement, cross-rhythm and microtiming, acquire subjectively manifested pleasurable effects.

Music Anticipation and Predictive Coding

The idea that our experience of rhythm is dependent on the mental anticipatory framework of meter and that this can be modeled as a Bayesian process [13–15, 59] resonates well with a novel theory about fundamental brain function, namely the *predictive coding theory* proposed by Karl Friston. As a general theory of brain function, it explains how brain areas exchange information [60]. It was first applied to sensory perception, describing how the brain determines the sources of sensory input based on Bayesian inference. According to this argument, the brain predicts the causes of sensations based on the actual sensory input as compared with previous 'knowledge' [60, 61]. This comparison is essential to the system, since a variety of environmental causes can result in similar sensory input. The predictive coding theory overcomes this perceptual challenge by using internal generative predictive models, which have been formed based on previous experience. These models continuously predict the causal relationship between sensory input and environmental events. In changing environments, the models are gradually updated to maximize the correspondence between the sensory input and the predictions and minimize prediction errors. In this way, the causes of our sensory input are not solely backtracked from the sensory input, but also inferred and anticipated based on contextual cues and previous sensory inputs. Thus, perception is a process that is mutually manifested between the perceiver and the environment.

Hence, the predictive coding theory offers a novel perspective on how specialized brain networks can identify and categorize causes of its sensory inputs, integrate information with other networks, and adapt to new stimuli by learning predictive patterns. It posits that perception and learning occurs in a recursive Bayesian process by which the brain tries to minimize the error between the input and the brain's expectation (Fig. 7). In other words, predictive coding is the mechanism by which the brain extracts the salient parts of the incoming signals and avoids processing redundant information [62].

Perception and Learning According to the Predictive Coding Theory

In addition to the idea of minimizing prediction error, predictive coding theory is characterized by the hierarchical organization of neural networks in the brain. Each hierarchical level in the recursive process provides a predictive model (or models, since competing models at the same hierarchical level are present as soon as the situation becomes ambiguous or uncertain) of what the input to the specific level is expected to be. The hierarchical levels 'communicate' through forward and backward connections [60, 63]. The internal predictive models are communicated from high-level structures to specialized low-level structures through backward connections. These backwards connections have a strong modulatory effect on the

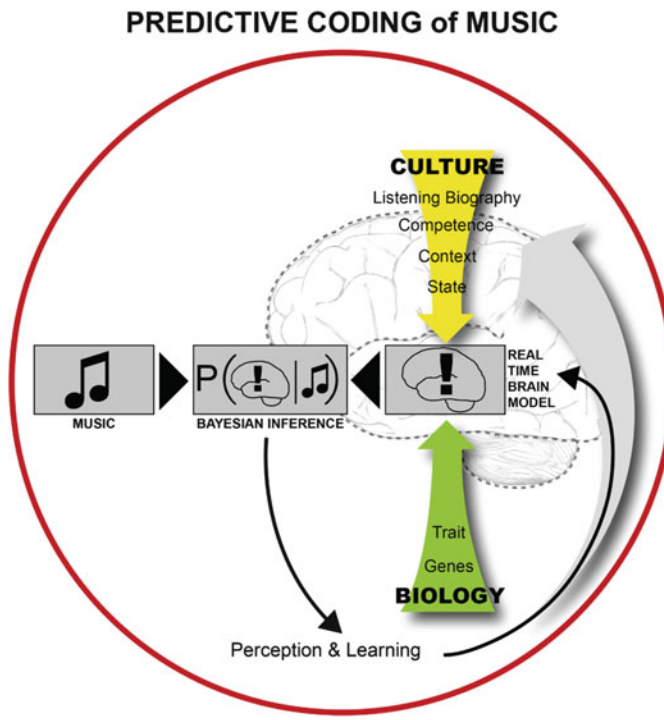

Fig. 7 The experience and learning of music takes place in a dynamic interplay between anticipatory structures in music, such as the build-up and relief of tension in rhythm, melody, harmony, form and other intra-musical features on one side, and the predictive brain on the other. The real time brain model is dependent on cultural background, personal listening history, musical competence, context (e.g. social environment), brain state (including attentional state and mood), and innate biological factors. The brain is constantly trying to minimize the discrepancy between its interpretation model and the musical input by iteratively updating the real time brain model (or prior) by weighting this model with the likelihood (musical input) through Bayes' theorem. This leads to a constantly changing musical experience and long-term learning

functionally specialized brain areas, and can thus exert contextual constraints on the models of lower levels. Sensory information is processed through forward connections from lower to higher cortical levels, and works as driving signals. At each level, the sensory information is matched to the internal predictive model. If there is a mismatch between the model and the sensory input at any level of the hierarchy, a prediction error occurs and a neuronal error-message is fed forward to higher, more integrative levels. Here the prediction error is evaluated and depending on the degree to which it violates the internal prediction, the brain can either change its internal model or it can change the way it samples information from the environment. Consequently, prediction errors are fundamental for adaptive learning. When predictions change, the connectivity between neurons is believed to change accordingly. In this way, neuron A predicts neuron B's response to a stimuli in a given context [60, 63]. The brain is constantly trying to optimize its internal model to correspond to the world, and thereby minimize prediction errors [63–65]. Thus, the minimization of prediction errors is imperative for brain function, because neuronal prediction error signals are fundamental to learning and improvement of the internal model.

Importantly, the predictive coding theory states that the brain relies on prior experience to model expectations for the future. This prior experience gives a prior probability, describing the degree of probability of the internal hypothesis (or model). Prior probabilities are context-sensitive and hierarchical, hence we have a

range of possibilities available to us, some more likely to be correct than others, and they change according to context. Thus, the hypotheses generated by the brain in a specific situation are constrained by hypotheses at the same or higher levels and guide the processing at lower levels [63, 66]. Therefore, when we have access to accurate information about the context, more specific hypotheses will be generated, due to the many contextual constraints, and hence the predictions of the sensory input will improve. Consequently, these predictions are a product of the interplay between the subject's prior experience and the available sensory information, which forms the internal hypothesis. In this way, our predictions are built on prior experience and learning, but are still dynamic and context-sensitive.

Predictive Coding in Music

The principles of predictive coding align very closely with the statistical learning approach proposed by Pearce and Wiggins, accounting for melodic perception in music [67, 68]; the theory's notion of initial neuronal error message followed by synchronized activity in various brain areas in response to low-probability sequences corresponds to a local prediction error at a low hierarchical level in predictive coding, while the following synchronization across various brain areas is analogous to the integration of new information into the models at higher hierarchical layers.

Recently, Vuust and colleagues [47, 69, 70] have suggested that the predictive coding theory can provide a useful framework for understanding music perception in general and rhythm perception in particular. If meter is seen as the mental model and rhythm is the input, the relationship between the two complies with the predictive coding framework in a number of ways:

Influences on meter perception: First, the model can describe how the brain infers a hierarchical prediction model (the meter) from a given piece. Brochard et al. [71], as mentioned elsewhere in this book (fourteenth chapter of this book), provided strong evidence for the automaticity of this process in the simplest possible experimental setting. Specifically, they showed that listening to an undifferentiated metronome pattern causes the brain to register some beats as automatically more salient than others, in a duple meter. In predictive coding terms, the brain is interpreting the input, in this case metronomic beats, according to its own anticipatory framework. These anticipatory brain mechanisms are dependent on long-term learning, familiarity with a particular piece of music, deliberate listening strategies and short-term memory for the immediate musical past during listening [72]. Brain structures underlying musical expectation are thus shaped by culture, personal listening history, musical training and biology (Fig. 7).

Brain processing of syncopation: Second, rhythmic violations of the brain's metrical model, such as syncopations or metric displacement, should give rise to prediction error. Since the meter may be supported by the actual musical sounds to a varying extent, different expressions of syncopation and different types of rhythmic patterns could hence give rise to smaller or greater prediction error. These would first occur at certain lower level brain areas, which would subsequently be evaluated in a larger network including brain areas at higher hierarchical levels, leading to subjective evaluation and learning. This is an automatic process, and the size of the prediction error is affected by cultural and biological factors. In particular, the size of the error term is influenced by rhythmic or musical expertise. Expertise in predictive coding terms means that the metrical model is strengthened. Hence, musicians should show stronger brain signatures of prediction error than non-musicians, according to the predictive coding theory.

Brain processing of polyrhythm: Third, extreme instances of prediction error, such as in the case of continuous tension caused by polyrhythms suggesting counter-meter, should either cause the model to break down or lead to a continuous effort to sustain the main metrical model. Compared to instances of model shift and prediction error, the continuous effort in turn

leads to sustained activity in the relevant brain areas and networks, including areas at a higher level than those primarily generating the prediction error. In contrast to the prediction error at the lower level, this brain activity at higher levels should reflect an inverse relationship between expertise and brain activity, since experts need less effort in order to maintain the main meter.

Brain processing of groove: Fourth, when the rhythmic violations are continuously repeated, such as in the context of groove, the string of hierarchically related prediction errors at different parts of the neural network should facilitate the characteristic experiential effect of groove, namely the positive drive towards body-movement. Because the tension between rhythm and meter repeats throughout the groove, the prediction errors at the lower levels of the coding hierarchy, caused by for example syncopation, metric displacement or instances of cross-rhythm, become predicted at the higher levels.[3] Thus, the original metric model is maintained, while the metrically deviating rhythmic structures facilitate embodied and affective responses.

Predictive Coding Error Messages Indexed by the MMN

As mentioned, the predictive coding mechanism can account for the extracting of the salient parts of an incoming signal and the avoidance of processing redundant information. Accordingly, neuronal networks extract the statistical regularities in the incoming stimulus and reduce redundancy by removing the predictable components, leaving only what is not predictable (the residual errors in prediction). This mechanism has received significant attention from researchers interested in visual perception, as it is consistent with both the spatial and temporal receptive fields found in the retina [62].

The predictive coding theory provides an equally feasible explanation for pre-attentive auditory prediction and this has been studied extensively through the 'mismatch negativity' (MMN) paradigm. The MMN is a component of the auditory event-related potential (ERP) in the brain that can be recorded using electroencephalography (EEG) and relates to change in different sound features, such as pitch, timbre, location of sound source, intensity, rhythm or other more abstract auditory changes, such as streams of ascending intervals [74, 75]. The trajectory of the response peaks around 100–200 ms after deviation onset and the amplitude and latency of the MMN depends on deviation magnitude and related perceptual discriminability, such that larger deviations yield larger and faster MMNs [76]. The MMN, primarily originating in the auditory cortices bilaterally, is often accompanied by a later component, the P3a, also in the auditory cortices, which is usually associated with the evaluation of the salient change for subsequent behavioral action. It is believed to indicate activity in a network which contains frontal, temporal and parietal sources [77].

The MMN signal appears to have properties analogous to the error signal in a predictive coding framework. It is dependent on the establishment of a pattern or model and responds only when the predictive pattern is broken. MMNs have been found in response to pattern deviations determined by physical parameters, such as frequency [78], intensity [76], spatial localization [79], and duration [79], but also to patterns with more abstract properties [80, 81]. Importantly the size of the mismatch negativity adjusts as the pattern adapts [82], hence the size of the error message is dependent on the brain's model of the incoming input as well as on the input itself.

The MMN is also strongly dependent on the expertise of the participants. Musicians who adjust the tuning of their instrument during performance, such as violinists, display a greater sensitivity to small differences in pitch compared to non-musicians and other musicians playing

[3] According to this understanding, the meter can be seen as conveying what has elsewhere been termed schematic expectations, whereas the perceptually syncopated rhythmic patterns are perceived according to veridical expectations [73].

other instruments [83]; singers respond with a stronger MMN than instrumentalists to small pitch changes [84]; and conductors process spatial sound information more accurately than professional pianists and non-musicians [85]. Recently, it was shown that the characteristics of the style/genre of music played by musicians influence their perceptual skills and the brain processing of sound features embedded in a musical context as indexed by larger MMN [86, 87].

The Influences of Musical Expertise on Brain Processing of Syncopation

Vuust and colleagues investigated whether differential violations of the hierarchical prediction model provided by musical meter would produce error messages indexed by the MMN and whether musical expertise influenced the ERPs [47]. They compared rhythmically unskilled non-musicians with expert jazz musicians on two different types of metric violations: syncopations in the bass drum of a drum kit pattern (a musically common violation), and a more drastic disruption of the meter (a musically less common violation). Jazz musicians perform highly complex rhythmic music and are therefore ideal candidates for identifying putative competence-dependent differences in the processing of metric violations. The researchers found event-related responses to strong rhythmic incongruence (metric disruption) in all subjects, the magnetic equivalence of the MMN (MMNm) peaking at 110–130 ms and the P3am around 80 ms after the MMNm in expert jazz musicians. Some of the rhythmically unskilled subjects also exhibited the P3am. Furthermore, responses to more subtle rhythmic incongruence (syncopation) were found in most of the expert musicians. The MMNms were localized to the auditory cortices, whereas the P3am showed greater variance in localization between individual subjects. MMNms of expert musicians were stronger in the left hemisphere than in the right hemisphere in contrast to P3ams showing a slight non-significant right-lateralization.

The MMNm and P3am were interpreted as reflecting an error term generated in the auditory cortex and its subsequent evaluation in a broader network including generators in the auditory cortex as well as higher level neuronal sources. The researchers also found evidence of model adjustment in two of the jazz musicians. These findings are thus in keeping with expectations based on the predictive coding theory and suggests that there is a congruous relationship between perceptual experience of rhythmic incongruities and the way that these are processed by the brain. However, it should be noted that other researchers have suggested that the predictive coding processes possibly underlying the MMN generation could in principle happen within the different layers of the auditory cortex [88]. More research is needed to determine the localization of the computational networks supporting the predictive models leading to the MMN.

The study by Vuust et al. [47] described above, showed quantitative and qualitative differences in brain processing between the participant groups indicating that the prediction error generated by meter violation correlates positively with musical competence, A predictive coding interpretation of this would posit that the metrical model of musicians is stronger than that of non-musicians, leading to greater prediction error. However, greater competence does not necessarily lead to more efficient brain processing in a linear fashion. “More” is not necessarily “more”.

Predictive Coding of Polyrhythmic Music

As described above, polyrhythm is an extreme example of how rhythmic complexity is established as interplay between the brain’s anticipatory framework and the incoming stimulus during music listening and performance. For example, when listening to the soprano sax solo on Sting’s “The Lazarus Heart”, the rhythm suddenly changes to a different meter for the duration of six bars, with no trace of the original meter in the actual sound. It is still possible to

keep the original meter overall, since the subdivisions and metric frameworks of the two different meters eventually coincide after the six bars. However, what makes it almost impossible for a listener to avoid adjusting to the new beat during the six bars, for example by shifting the phase of foot-tapping or head-nodding, is that the saxophone's melodic solo completely switches to the new meter by emphasizing its complete hierarchical structure of subdivisions. For a listener with jazz music training, it would be imperative to try to keep the original meter, primarily since the rhythmic tension between the old and new meter is important to the experience of this piece, but also because it is necessary for all musicians to mentally maintain the original metric framework in order for collective improvisation to work. Hence, there is a big difference in experienced complexity between an expert listener who stays in the original meter, and the inexperienced listener who switches back and forth between the two meters, avoiding much of the tension.

In two studies of polyrhythm, Vuust and colleagues used this Sting example to investigate neural correlates of polyrhythmic tension by way of functional Magnetic Resonance Imaging (fMRI) [46, 49]. fMRI is a brain scanning technique which enables the measurement of the blood oxygenated level dependent (BOLD) signal in the brain, by contrasting this signal during different perceptual or task-related epochs. As the source of the signal can be localized with great spatial resolution in the brain, this technique provides, indirectly, indications of the activity in areas of the brain that are associated with different tasks. The extent of the spatial resolution is greater in fMRI than in MEG/EEG, but when studying auditory stimuli such as music, there are important drawbacks of using fMRI. Importantly, the temporal resolution of this technique is of the order of seconds or more and can thus not capture sub-second musical temporal events, such as microtiming.

However, since the experience of polyrhythm typically evolves over seconds, fMRI was found suitable for a study in which the neural correlates of epochs of polyrhythm (counter-meter and main meter) were contrasted with epochs containing only the main meter [46]. Seventeen subjects, all 'rhythm-section' players, specifically drummers, bassists, pianists and guitarists, were recruited for the study. During the first experiment, they were required to tap along to the main meter while being asked to focus first on the main meter, and second on a strong counter-meter. In the second experiment, the participants listened to the main meter throughout the study but were asked to tap the main meter followed by the counter-meter. In both experiments, the BOLD analyses showed activity in a part of the inferior frontal gyrus, specifically Brodman's area 47 (BA 47), most strongly in its right-hemispheric homologue (Fig. 8). This area is typically associated with language, in particular semantic processing (for reviews, see [89, 90]). Hence, this area may serve more general purposes, such as sequencing or hierarchical ordering of perceptual information than formerly believed. Interestingly, BA 47 was active both in relation to the experience of polyrhythmic tension (experiment 1, in which the motor task was identical throughout) and the production of polyrhythmic tension (experiment 2, in which the auditory input was constant). It thus seems that this area, bilaterally, reflects processing of the

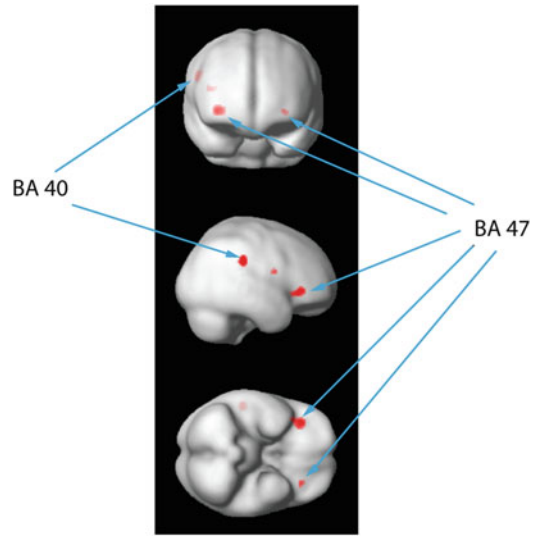

Fig. 8 Areas of activity in the brain during tapping to polyrhythms. Modified from Vuust et al. [46]

prediction error in the polyrhythm per se. Importantly, the activity in BA 47 was inversely related to the rhythmic expertise of the subjects as measured by the standard deviation of tapping accuracy. Hence the effort to maintain the metrical model shows a negative correlation between expertise and brain activity, presumably since experts need less effort to maintain the main meter. It was also found that BA 40, an area previously related to language prosody and bistable percepts (e.g. Rubin's vase, Fig. 3c), was active during tapping to polyrhythms (Fig. 8). Thus, the results showed that this area might be involved in the encoding of stimuli that allow for more than one interpretation, across as language, vision and audition. However, the fMRI data does not allow us to conclude whether the activity in the inferior frontal lobe could be preceded by a prediction error at a lower hierarchical level in the brain directly related to the polyrhythms, since the temporal resolution of fMRI is limited. Broca's area has recently also been suggested to have a more general role related to hierarchical organization of information [91].

Predictive Coding in Groove

In recent experiments, Witek and colleagues [92] investigated the relationship between syncopation in groove and the desire to move and feelings of pleasure. Their stimuli consisted of 50 groove-based (funk) drum-breaks, in which 2-bar rhythmic phrases were repeated 4 times, with varying degrees of syncopation. Using a web-based survey, participants were asked to listen to the drum-breaks and rate to what extent the rhythms made them want to move and how much pleasure they experienced with the rhythms. The results showed an inverted U-shaped relationship between degree of syncopation and ratings, indicating that a positive increase in syncopation in groove increases embodied and affective responses, until an optimal point, after which a continued increase in syncopation causes the desire to move and pleasure to decrease. The inverted U is a familiar shape in aesthetics psychology, and has been found in the relationship between a number of forms of perceptual complexity in art and arousal (e.g. physical, physiological and evaluative). Berlyne [93] famously proposed that appreciators of art prefer medium degrees of perceptual complexity, and this has been supported in a number of studies involving music [61, 94, 95]. Accordingly, Witek et al.'s study showed that systematic increase in a form of rhythmic complexity, namely syncopation, increased the positive drive towards body-movement, but that beyond medium degrees of rhythmic complexity in groove, embodied and affective engagements with the music was prevented. Interestingly, rather than being affected by the participants' formal musical training, it was found that those who enjoyed dancing and often danced to music rated the drum-breaks as eliciting more desire to move and more pleasure, overall. Thus, it seems that more broadly embodied previous engagements with music may affect the subjective experience of rhythmically complex music, such as groove, rather than institutionalized formal training, such as the ability to play an instrument.

The inverted U-shape found between degree of syncopation in groove and wanting to move and feelings of pleasure can again be seen as complying with the predictive coding theory. At low degrees of syncopation, there is little incongruence between the rhythm of the groove (the input to the model) and the meter (the predicted model), and thus the experiential effect, facilitated most explicitly at the higher levels of the hierarchical neural network, is weak. At high levels of syncopation, the degree of complexity is so high and the rhythm deviates too much from the metric framework causing the model to break down, and preventing pleasure and desire for movement. However, at intermediate degrees of syncopation in groove, the balance between the rhythm and the meter is such that the tension is sufficient to elicit positive affective and embodied responses, yet not so complex as to cause the meter to break down. In terms of predictive coding, the input and the model are incongruent, but not incompatible, and the prediction error affords the string of hierarchical encoding and

evaluation from lower to higher levels in the brain. It is important to remember that the effect of syncopation in groove relies on the repetition of the syncopated patterns, and that it is the continuous effect of the tension caused by the relationship between rhythm (input) and meter (model) that causes the subjectively experienced tendencies towards body-movement and pleasure. In this way, the experience of groove is different from the experience of polyrhythm, as it is used in e.g. jazz, since polyrhythmic epochs usually have a relatively short duration and thus constitutes a momentary shift between weak and strong rhythmic tension.

Perspectives

In this chapter, we have considered interval timing in music as integrated in a general view of brain processing, characterized by a dynamic interplay between an internal model, represented by the meter, and the incoming input, provided by rhythms in music. We have shown how such an understanding of the relationship between rhythm and meter supports theories of predictive coding mechanisms by which the brain tries to minimize the error between the rhythm and the meter. This mechanism can be exemplified by processing of different forms of rhythmic complexity in music, such as syncopation, polyrhythms and groove, and can also account for the experience of these phenomena as well as interpersonal differences in preference and competence. Importantly, the pleasure that many people experience with rhythms that do not conform entirely to the prescribed meter may be part of a predictive coding balance between meter and rhythm. Such notions fit nicely with theories of reward processing taking place during pleasure cycles mediated by the brain's constant search for a balance of dopamine levels [96, 97]. However, a discussion of such links between prediction in music and reward are beyond the scope of the present chapter (cf. [69]). As an important footnote, it should be mentioned that dopamine mediates both pleasure and motor processing in the brain [98], which points to a possible link between predictive coding theories and embodied approached to music cognition [99]. While predictive coding is still a novel theory, which needs to be further empirically investigated in order to be more confidently applied as a general theory of brain function, the examples shown in the present chapter demonstrate how it has the potential to encompass different aspects of musical experience, particularly with regard to rhythm and meter. On the one hand, brain science thus offers a window into the underlying mechanisms of people's rich and complex, affective and embodied engagements with music. On the other hand, the study of musical rhythm may provide us with novel insights into the predictive brain.

Current State of the Field

As the three chapters of this part have demonstrated, the study of the neurobiology of music and rhythm offers greater understanding of not just how we perceive music, but how the brain operates more generally. Thirteenth chapter (this book) has described how the functions associated with music are distributed in the brain, in ways that both overlap and are dissociable from language and speech processing. Using state-of-the-art neuroimaging techniques, as reported in fourteenth chapter of this book, there is now increasing evidence that beat perception is both a fundamental and innate cognitive mechanism, the functions of which go beyond purely musical listening. And in the present chapter, we show how complex musical rhythms, such as syncopation, polyrhythm and groove, are processed, allowing us to make inferences about the role of temporal prediction as a fundamental organizing principle of the brain. However, a number of crucial aspects of the neurobiology of rhythm remain to be determined. The study of non-human animal perception of rhythm is still in its infancy, and a continued interest in such issues has great prospects for revealing the biological origin of music. Questions regarding the exact nature of metric hierarchies are still unanswered, and developing computational

models that offer empirical tools for applying the hierarchical model of predictive coding might prove fruitful in answering such questions. Finally, although great progress has been made in the acknowledgement of action and body-movement in rhythm perception, more can be done to integrate such embodied theories of rhythm with affective models. With new neuroscientific tools developing rapidly, we might soon be able to tell you more about why abstract patterns of interval timing, such as rhythm, give us so much pleasure.

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