
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, poly-rhythmic 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.

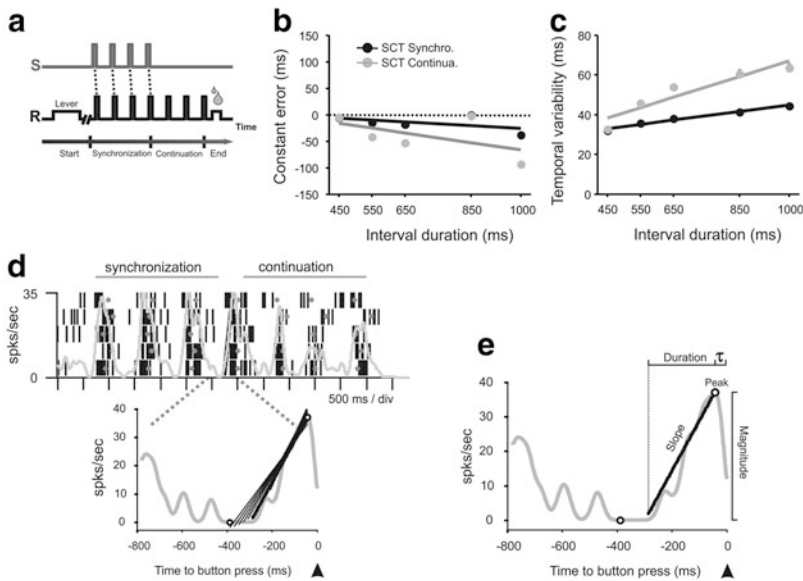


Fig. 1 (a) Synchronization-Continuation Task (SCT). Monkeys were required to push a button (R, *black line*) each time stimuli with a constant interstimulus interval (S, *gray line*) were presented, which resulted in a stimulus-movement cycle. After four consecutive synchronized movements, the stimuli 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

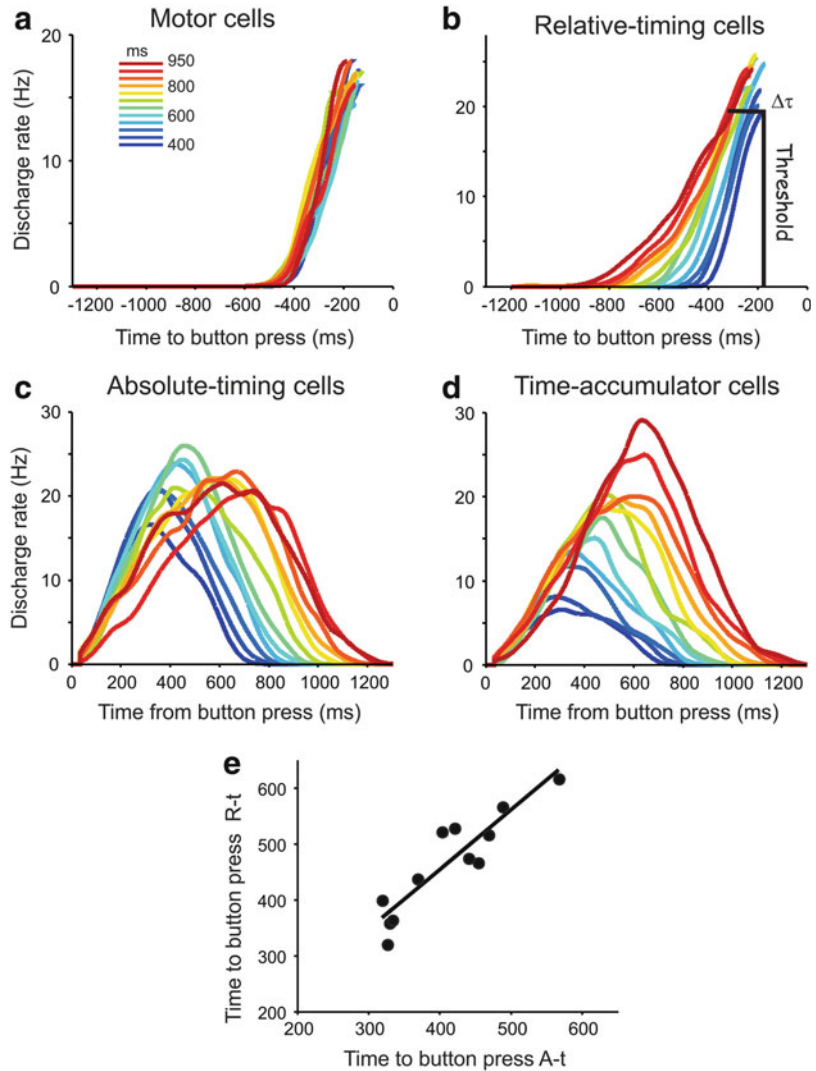
diameter. (c) Temporal variability (i.e. the intertap SD) increased as a function of target interval during both phases of SCT. (d) Iterative algorithm used to find the best regression model to explain the increase or decrease of instantaneous activity over time with respect to a sensory or motor event. 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 M Ω , 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

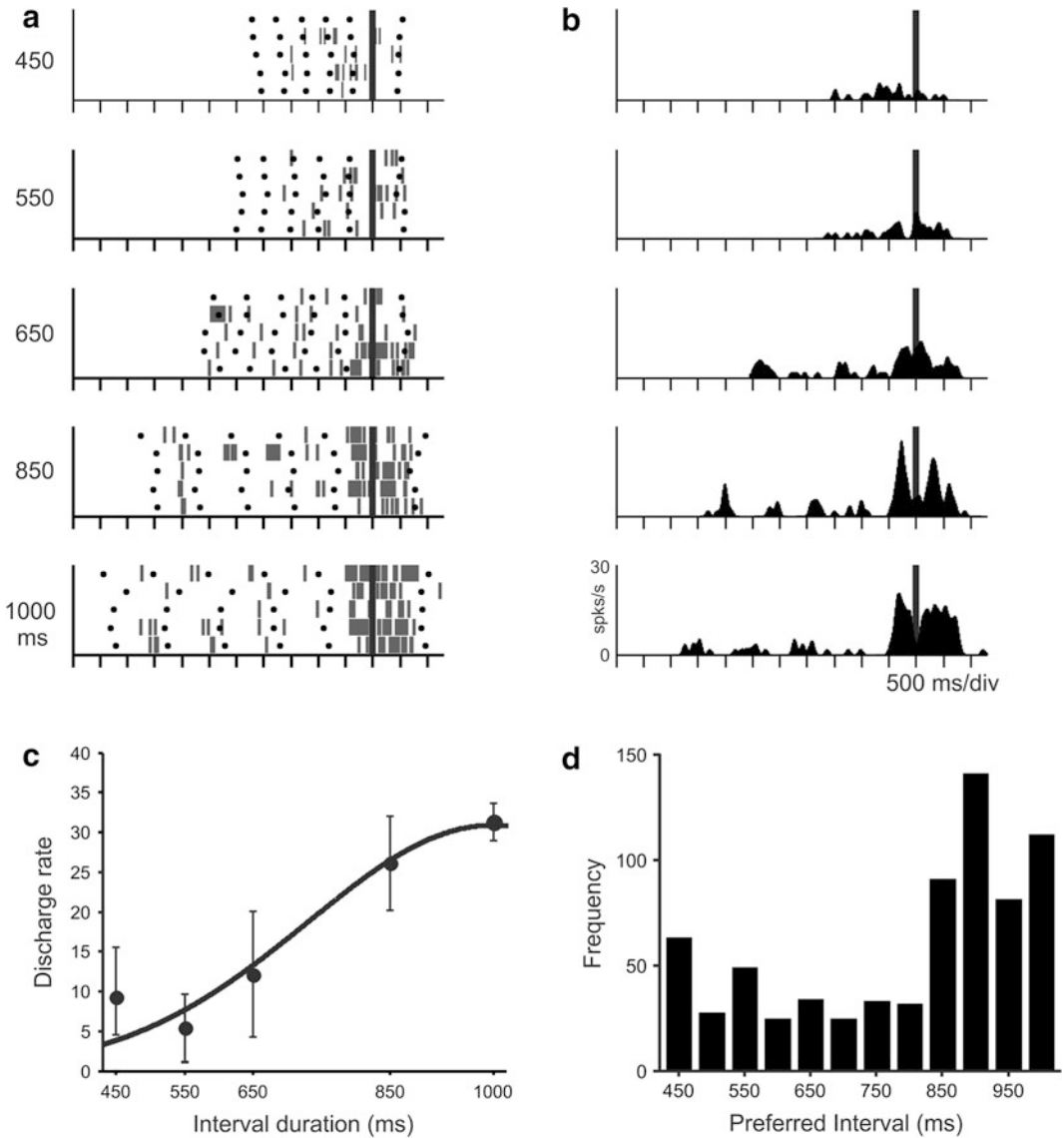


Fig. 3 Interval and ordinal-sequence tuning. **(a)** Responses of an interval-tuned cell with a long preferred interval and a sequential response to the last interval of the continuation phase during the SCT. Raster histogram aligned (*black line*) to the third tap of the continuation in the visual condition. **(b)** Average spike-density functions of the responses shown in **a**. **(c)** Tuning function for the

same cell, where the mean (\pm 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

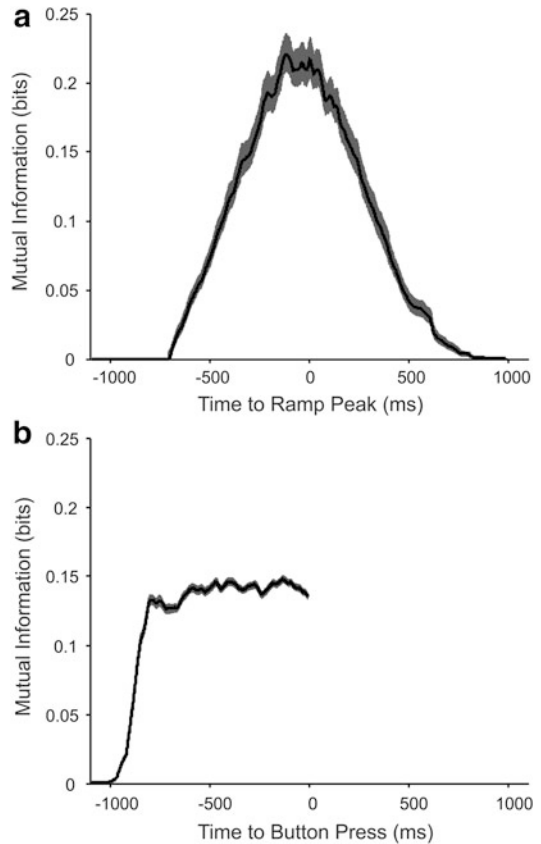


Fig. 4 Mutual Information for cells tuned to interval during the SCT. (a) Mean (black) and SEM (gray) of the mutual information as a function of time to ramp peak for the population of time-accumulator ($n = 100$) cells. (b) Mean (black) and SEM (gray) of the mutual information as a function of time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

aspects of temporal processing that are disengaged from the motor tapping output.

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

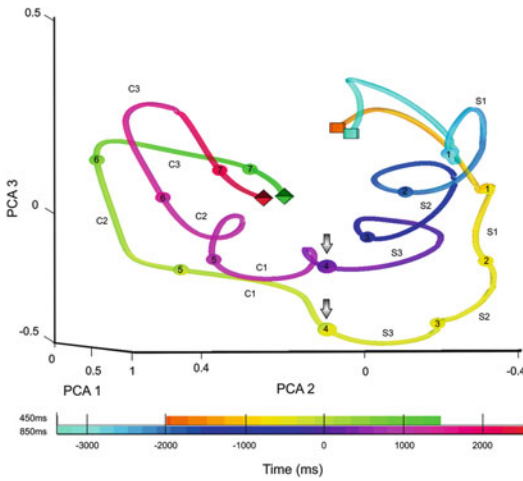


Fig. 5 Plot of the population dynamics of 549 cells during the SCT using the first three components of a Principal Component analysis on the time varying activity of the cells. The color code is associated to the passage of time for two network trajectories corresponding to 450 and 850 ms interval durations (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

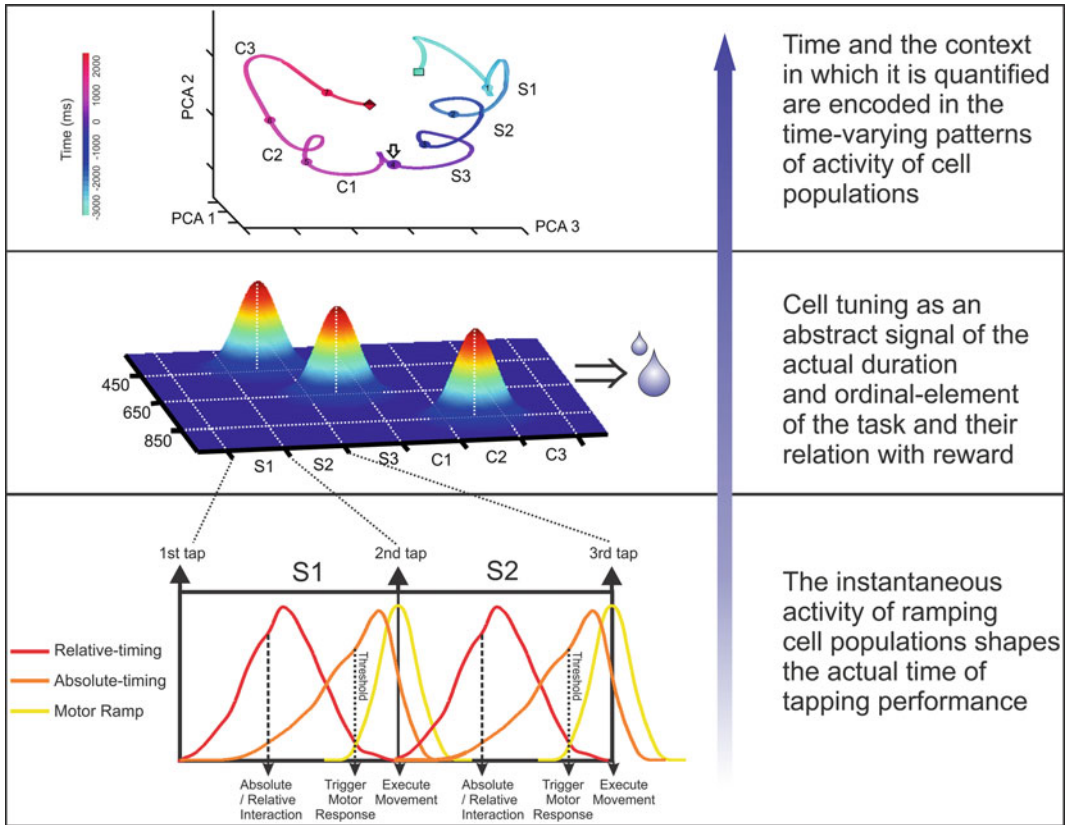


Fig. 6 A model of the interaction between the multiple layers of neuronal clocks in the medial premotor cortex. *Bottom.* Ramping activity defines the movement temporal behavior of the animals during the SCT. *Middle.* Neuronal tuning to both duration and sequential order during the SCT as an abstract 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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