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The Time-Budget Perspective of the Role of Time Dimension in Modular Network Dynamics during Functions of the Brain

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Additional information is available at the end of the chapter

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Abstract

Information processing plays a key role in the daily activities of human and nonhuman primates. Information processing in the brain, underlying behavior, is constrained by the four-dimensional nature of external physical surroundings. In contrast to three geometric dimensions, there are no known peripheral sensory organs for the perception of time dimension. However, the representation of time dimension in modular neural networks is critical for the brain functions that require interval timing or the temporal coupling of action with perception. Recent experimental and theoretical studies are shedding light on how the representation of time dimension in neural circuits plays a key role in the diverse functions of the brain, which also includes motor interactions with environment as well as social interactions, such as verbal and nonverbal communication. Although different lines of evidence strongly suggest that rhythmic neural activities represent time dimension in the brain, how the information represented by rhythmic activities is processed to time behavioral responses by the brain remains unclear. Theoretical considerations suggest that the rhythmic activities represent a physical aspect of the time dimension rather than the source of simple additive temporal units for coding time intervals in neural circuits.

Keywords: time dimension in the brain, mirror neuron, modular network in the brain, visuomotor synchronization, muscle synergy, interval timing, movement timing

1. Introduction

The manner in which a primate allocates its waking hours to various activities is considered to represent an important aspect of its ecologic adaptation [1]. Surveys and analyses of time budget have been applied successfully to many diverse fields, which include mass media contact, service

sector, urban planning, consumer behavior, the sexual division of labor, the informal economy and household economics, social accounting, social indicators, quality of life, way of life, social structure, etc. [2]. In this chapter, we will apply the time-budget analyses to various brain functions at subsecond to seconds range to understand the behavior of human and nonhuman primates during an interaction with their external surrounding.

Emerging data suggest that online behavior—the active response to changing demands in a current task—can be understood in terms of the allocation of various networks to distinct phases of a working memory function of the brain. Arguably, the human behavior must conform to the constraints of space-time fabric of surroundings, which makes cognitive time management an essential human function. Moreover, the importance of time budget is underscored by a recent meta-analysis, which concludes that common networks support modulation of efforts during nontemporal cognitive and timing tasks [3]. Defects of allocation of networks during online behavior may contribute to the development of psychiatric illnesses, such as schizophrenia, which characteristically exhibits a pattern of disconnectivity of timing circuits [4].

Time budgeting, the time allocation of various computing resources, available from distributed circuits in the brain to dynamic networks underlying brain functions, plays an important role in the online behavior of primates at the level of both individuals and groups. We will argue how the allocation of the brain's limited computing resources plays a crucial role in achieving optimal interaction of brain circuits at the level of both individuals and groups.

2. Dynamic interaction of primates with external space-time fabric directs the resource allocation to brain networks

Interval timing functions of the brain have played a key role in the survival of the human species during most of their existence as humans have been sustained by hunting and foraging [5]. Various activities, essential for the survival of humans, required interaction with external physical surrounding, with a spectrum of space-time fabric, which include stationary bodies of water to cascading streams, plains to mountains, diverse to simple to complex fauna and flora, presenting complex challenges for the human brain. Meeting diversely complex challenges requires the temporal coupling of various functions of the brain as well as processing time intervals on scales that may vary from subsecond range to several seconds.

Physical surroundings with which primate brain interacts is four-dimensional, three-geometric dimensions and the time dimension. Psychologic time has been a subject of intellectual curiosity for most of the known history, but the time dimension was studied as the fourth physical dimension only recently [6, 7]. Time dimension, unlike other physical qualities, is never perceived as a novelty, but only reported as the flow of time [8], and therefore, it is not easy to study by observation alone.

During interactions with external surroundings, dynamic networks are formed by synchronizing the activities of neurons, which results in the temporal coupling of information by distributed local circuits in the network [9]. Local circuits in networks generate patterns of neuronal activities in multidimensional domains, which represent information encoding motor response,

sensory perception, as well as timing the behavior. For example, when someone catches a ball in flight or a fruit falling from a tree, brain networks produce information encoding the following: a series of muscle activation patterns called muscle synchrony [10, 11], resulting in the catch, timing muscle contractions and the time estimation of the arrival of the object at a suitable height. Activities of neurons, forming networks, produce synchronous neuronal activity patterns that represent information, which is processed during a successful interaction of the organism with its environment.

As suggested by the above examples, a successful interaction of the primate brain with four-dimensional space-time fabric of the external physical world requires interval timing functions at various time scales. A distributed modular neural clock mechanism is proposed by Gupta [12] to explain timing functions of the brain during online behavior.

2.1. Modular connections between small cortical information-processing areas establish dynamic networks that form the basis of timing the behavior

The modular nature of connections of local circuits forming dynamic networks in the cortex can be understood based on cytoarchitectural and electrophysiologic data. The cortical surface is divided into tiny computational units of millimeter range size, called the canonical microcircuits [13]. The neurons forming the canonical microcircuits have limited but conserved patterns of inputs and outputs [14]. Although the neurons within a canonical microcircuit are interconnected in a specific manner, the connectivity rates between most neuron pairs in the cortex are very low, rising only to 10–20% in specific cases when they are co-tuned to the same stimulus [14]. Since there is a low level of connectivity among neurons, it gives the canonical microcircuits the flexibility to form multiple configurations of neuronal circuits, and therefore, the ability to perform a wide variety of computations. This feature is useful for the role of small areas of the cortex to serve as relatively independent modules in neural networks.

Moreover, when inputs going to the cortex, primarily from the thalamus, are relayed in a topographically specific manner, there is a very little overlap between the inputs received by canonical circuits due to the low level of connectivity in the horizontal direction. Thus, this results in sparsely interconnected small divisions of the cortex, which act as independent circuits or modules that can be connected by synchronization. Synchronization of local circuits is due to the oscillating states of excitability and inhibition, which allows neurons to fire during a specific phase of a long-range oscillation when neurons are excitable: coupling the modules of a neural network. Periodic excitability of neurons during synchronization, due to the pacing by inhibitory neurons, produces oscillating extracellular currents that are recorded as neural oscillations [15].

2.2. Distributed modular neural clock mechanisms are responsible for timing behavior in primates

Modular model of distributed neural clocks is proposed by Gupta [12] for interval timing functions of the brain, such as timed-motor movements, time reproduction and time estimation. As depicted in the schematic in **Figure 1**, the proposed neural clock mechanism has three main modular components [12]: (a) calibration module, which are sensory and motor circuits of the brain that are involved in feedback interaction with the external four-dimensional surrounding,

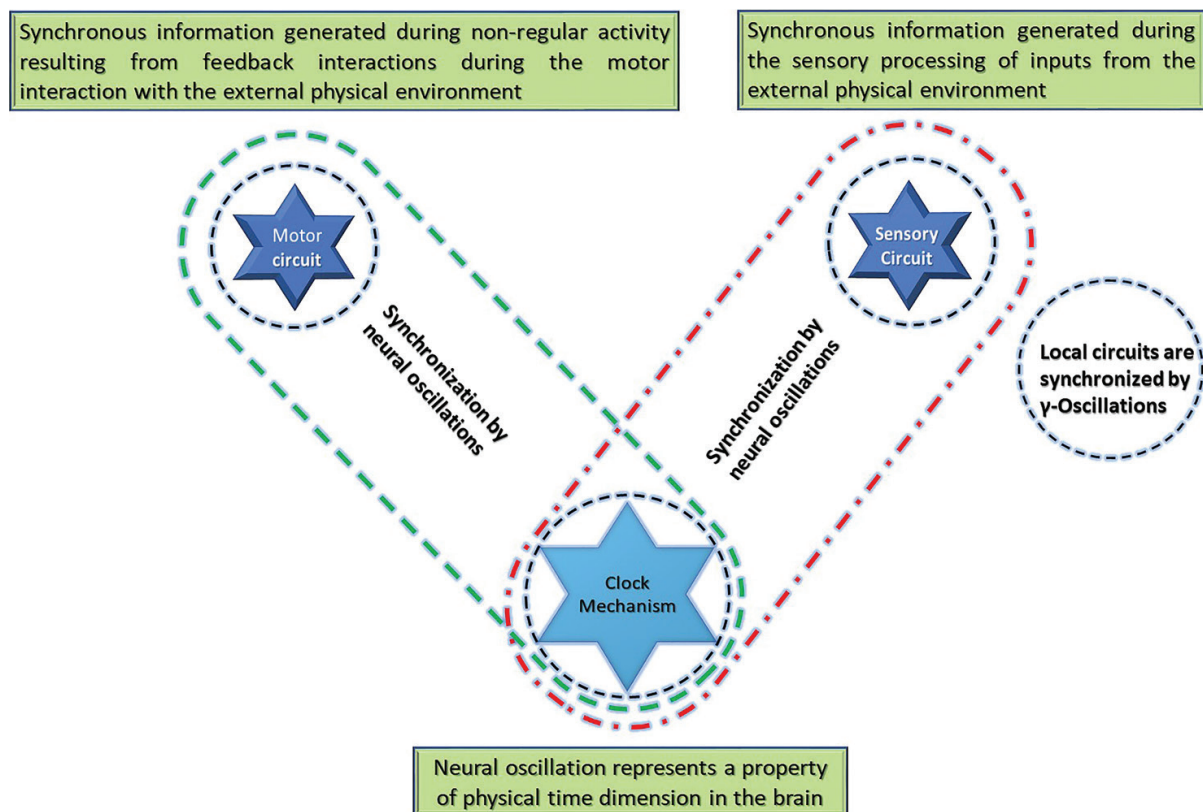


Figure 1. Schematic diagram depicts the modular clock model [12]:

- Synchronization (shown by dotted line of ovals) of neural clock mechanism with calibration modules: motor and sensory circuits, processing motor and sensory information during the interaction with space-time fabric of the external environment.
- Information is coded by the patterns of neural activities, which include spikes, spike bursts, logic states of circuits and slopes of ramping activity neurons.
- Synchronization is due to coherent, but oscillatory increase in the excitability of neurons in the network during specific phase of neural oscillations.
- Synchronization is responsible for the temporally coupling of information, produced by different neural activities, which encodes timed behavior.

(b) endogenous neural oscillator to represent physical time in neural circuits and (c) a clock mechanism for timing a behavioral response.

The functional role of the calibration module in the neural clock mechanism is to transfer information about physical time into neural circuits. Physical time information is transferred into neural circuits when motor and sensory information is processed by feedback mechanisms during an interaction of the brain with the external surroundings. During the feedback interaction, circuits associated with the motor and sensory functions produce neuronal activities that parallel the interactions between effector organs, muscles, sensory organs and the external space-time fabric. Moreover, the comparison of the intervals between changes outside the body and the intervals between corresponding feedback changes in neuronal activities in the brain would serve as a basis for the calibration of neural clocks.

An alternate mechanism for the calibration module is the cortico-basal ganglia-thalamocortical circuit, which, due to reciprocal connections and the consequent feedback process, could globally calibrate the neural circuits of the brain for the optimized interaction with external physical surroundings. This calibration mechanism predicts the presence of cortical neurons that are strongly coupled to population activity, but invariant to the stimulus conditions, which have been detected in monkey and mouse visual cortex [16].

Endogenous neural oscillator is the second component of the proposed modular neural clock mechanism. Neural oscillators are the rhythmic neural activities within the brain, such as neural oscillations, periodic bursts or rhythmic circuits. The idea of neural oscillator to represent time dimension is very old which is based on the intuitive role of the pendulum in mechanical clocks. Treisman [17] had originally proposed pacemaker-accumulator model. According to this model, a neural oscillator generates pulses, which are accumulated by a counter to encode time intervals in neural circuits.

Instead of serving as the source for temporal units for pulse accumulation, as in the Treisman model, the neural oscillation in the modular clock mechanism represents only a property of physical time. Thus, note that the periodicity of the endogenous oscillator does not simply represent a number that is added numerically to process time intervals for neural or psychologic processes. However, as mentioned later, the numerical quantification of time intervals in neural processes is likely encoded by spike patterns and their temporal relationship. Neural oscillators, representing physical time, along with calibration module and various task-specific circuits, synchronously generate information in networks, forming modular clock mechanism (**Figure 1**) to encode timed behavior by the brain.

Task-relevant neural clock is the third module, which is present in various parts of the brain, depending on the nature of the task. For example, the neural timers for visual time reproduction tasks in seconds range are present in the right dorsolateral prefrontal cortex [18–20].

At present, it is not clear how neural patterns, representing information, are coded and decoded to represent behavior, such as timing movements or time estimation. It is likely that a combination of different patterns such as spike patterns, logic states of circuits and ramping activity of neurons play various roles in coding and decoding information, leading to timed-behavioral responses [12].

Quantitative measurements, such as time intervals, are likely represented in neural circuits in numerical representations [21], such as spike patterns, which can be read as the binary numbers [8, 9]. Variable rather than fixed size of the time-bin that contain spikes or spike bursts in a neuronal activity will play a role in the representation of spike patterns as Shannon information [8]. Gallistel [21] has noted that studies suggest that the information about behaviorally relevant quantities such as timing behavior is not represented by the rates of spikes but rather by the intervals between their arrivals at synapses. Although the neurobiological basis of information processing, underlying the timing of behavior, remains far from clear [21], some consensus is present, such as neurons encode sensory information using a small number of active neurons at a particular time point [22]. This view is consistent with the cytoarchitectonic data that show a low level of connectivity among the neurons of the cortex.

2.3. Stochastic processes underlie the synchronization of circuits during motor movements

Motor movements play a key role in the interaction of primates with external physical world. But how the synchronization of different circuits leads to meaningful motor interactions with physical environment is not well understood. In a study of spatial visuomotor error during a speeded reaching movement, it was found that while subjects' objective distributions, task-related representation of external surroundings, are unimodal, their internal representations of the external task are typically mixtures of a small number of distributions [23]. This suggests that the central nervous system uses many possible neural circuits initially and synchronizes them in a limited number of combinations, which is the result of the constraints imposed by the external physical conditions. This is also consistent with the influential uncontrolled manifold theory, which postulates that control of limb movements gives priority to spatial shape of the movement over the trajectories of the individual joints [24, 25]. Current consensus favors that the movement planning by the human brain is best characterized in external, task-relevant coordinates—external surroundings—such as the direction of movement of the hand in reaching a target in external space [25].

Studies in primates have shown that the central nervous system uses flexible combinations of a limited number of muscle synergies—defined as a relative level of muscle contraction—to produce a variety of motor behaviors [10, 11]. Since muscle synergies may vary between individuals [10], it suggests the basis of the individual differences in the cytoarchitecture of the cortex that accompany possible differences in circuits underlying activation patterns. Muscle synergies likely result from the synchronization of a limited combination of circuits, reflecting a limited number of limb movements, conforming to the spatial coordinates of the target.

In a study of reaching movement task, joint angle variability peaked mid-way during the task [26]. Another study showed that reaching movements are characterized by high accuracy of end results [27], which indicates that the least variability is present after effector—the hand—reaches the target. Together, these observations suggest that individual circuits are synchronized more tightly at the end of reaching task when the hand reaches the target. Tighter synchronization of a given number of circuits will reduce the variability during the time-series activation of muscle synergies in the execution of motor tasks.

The mechanistic explanation, wherein a stochastic selection process chooses from an initially larger number of processing circuits to fine-tune final movements to reach a stationary external target, can be extended to the movements for catching moving objects. In case of moving targets, an accurate four-dimensional internal representation will be required for a successful task. This will require that the activity of multiple circuits, during various stages of movements, must be optimized to produce an efficient temporal coupling at the endpoint of reaching movements. This optimization process will also require time budgeting via synchronization to allocate different computing resources of the brain.

2.4. Brain networks undergo dynamic changes in connections during working memory function

Since working memory function of the brain is the ability to maintain and manipulate information over periods of seconds [28], it plays a key role during the online interaction with the

space-time fabric of external surroundings. The ability to maintain and manipulate information in a working memory task is correlated with those patterns of neuronal activities that persist in the prefrontal cortex after the stimuli that elicited them no longer exist [28–30]. The limited amount of information, available for the manipulation by working memory [31, 32], suggests that there can be only a limited number of active networks present at a given time during a phase of working memory function. Thus, the limited number of connections of active networks must dynamically change during a working memory task to update the information processing to meet new demands.

Studies have shown that the prefrontal cortex and parietal cortex are the important regions for working memory functions [33, 34]. Furthermore, consistent with the dynamic changes in the networks for working memory function, reflecting the brain's interaction with four-dimensional surroundings, a past study reported that the functional connectivity patterns of frontoparietal region, across various task states, shifted more than other networks in the brain [35]. Another study demonstrated that the functional connectivity of the frontoparietal networks is greater in tasks demanding greater cognitive control in normal and schizophrenic groups but showed an overall deficit in schizophrenia [36]. Given that the parietal cortical areas are the sites for processing of sensory information, such as visual, spatial and multisensory [37–39], the above study underscores the importance of the role of working memory networks in the cognitive control of the interaction with external surroundings.

2.5. Role of the thalamus in regulating the network connections in the brain during various arousal states

The thalamus plays a key role in regulating the brain oscillations that characterize various arousal states (**Figure 2**). A great variety of wave frequencies and patterns is controlled by the thalamus, which is attributed to the electrophysiologic properties and connectivity patterns of the cortical, thalamic reticular (RE), corticothalamic neurons (CT) and thalamocortical (TC) neurons [40]. The RE nucleus is a neuronal sheet made of GABAergic cells that envelops most of the surface of the thalamus [41, 42]. Unlike specific relay nuclei, neurons of the RE nucleus do not project directly to the cortex, but they receive collaterals from TC and CT neurons [42]. RE neurons provide both feedforward and feedback inhibition to excitatory TC relay neurons [41, 43] (**Figure 2**).

Multiple TC cells provide excitatory projections to each RE cells, and in turn, multiple RE cells contact each TC cell [43]. The sleep spindles result from strong reciprocal connections between excitatory TC neurons and inhibitory RE neurons [43]. When RE neuronal terminals become active, they inhibit TC neurons. The TC neurons exhibit a postinhibition burst of 7–15 Hz frequency called sleep spindles. This postinhibition burst of activity in TC neurons excites the inhibitory RE neurons, which consequently inhibits TC neurons via reciprocal connections. The inhibition of TC neurons, relaying sensory signals, prevents the cortex from receiving sensory information during sleep [44].

The slow wave (0.5–1 Hz), which is characteristic of NREM sleep, originates in the frontal regions and propagates in the anterior to posterior direction with a rapid speed of 1.2–7 m/s. Since the slow wave synchronizes the entire brain from the thalamus to the cortex, it prevents independent synchronization of smaller areas of the brain, which as a result interferes with the ability of the brain to form networks, necessary for the interaction with external environment.

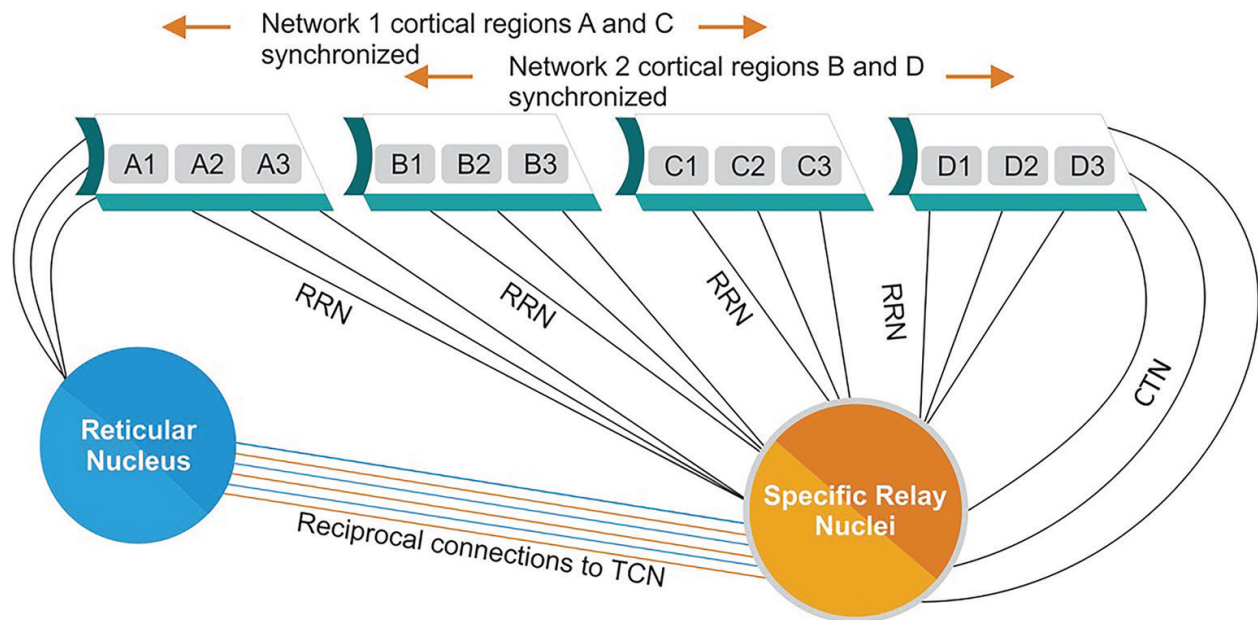


Figure 2. A schematic of connections between the cortex and thalamic reticular nucleus and specific thalamic nuclei:

- Cortical neurons in canonical microcircuits (shown as lettered gray rectangles, letters specify modules and numbers indicate component microcircuits in a module).
- Canonical microcircuits receive inputs from rapid relay thalamocortical neurons (RRN).
- Very scant horizontal connections are present between individual canonical microcircuits.
- There are rich divergent, convergent connections between the neurons of the reticular nucleus and thalamocortical neurons (TCN).
- There are heavy reciprocal and nonreciprocal projections from corticothalamic neurons (CTN) in layer 6 of the cortex.
- Hypothetical networks 1 and 2 result from the synchronization of different cortical areas representing modules.

However, the desynchronization of the slow wave paves the way for independent synchronization of smaller networks by neural oscillations during awoken state, covering distinct regions of the brain, making possible the online interaction with the environment. During an alert state, the slow wave oscillation is replaced with faster and short range and synchronized oscillations in the beta (15–30 Hz) and gamma (30–80 Hz) ranges [40, 45].

Note that the function of the thalamus is more than a passive relay center for sensory stimuli or the regulation of arousal states of the brain. Recent evidence indicates that the thalamus regulates functional connectivity between cortical microcircuits, which determines how cognitive processes are implemented [46]. TC neurons carry rapid sensory and motor relay information from specific thalamic nuclei project in a topographic fashion to sparsely interconnected microcircuits at the level of layer 4 of the cortex [14]. This enables the processing of relayed sensory information that occurs in modular neural circuits, comprising canonical microcircuit units.

Evidence suggests that the RE nucleus is an important hub in the communication between the thalamus and the cortex, which plays a key role in the cognitive processes that are affected in schizophrenia [47]. The RE nucleus covers the thalamus like an egg shell, and therefore, all fibers connecting the thalamus and the cortex must pass via the RE nucleus. Moreover,

the anatomical data [48] argue against a global control of thalamocortical functions by the RE nucleus. Studies show that the RE nucleus can be subdivided into multiple sectors, each of which connects with a particular group of thalamic relay nuclei and cortical areas [48] and also due to a limited divergence from the thalamus to the cortex, the direct global control of cortical functions by the thalamus is highly improbable. Instead of global control, synchronization of small cortical areas can occur due to their direct specific connectivity to sectors in the RE nucleus. Moreover, it is plausible that the control of the function at the level of individual sectors of the RE nucleus can synchronize relatively distant areas to form dynamic networks in the cortex.

CT axons, exiting layer 6 [49], are more numerous than TC neurons synapsing in layer 4 [50]. CT axons provide massive inputs to the thalamus that are both reciprocal and nonreciprocal [50], and therefore can dynamically influence the excitability and sensory throughput of the thalamus [49]. Thus, the thalamus can help in the selection as well as the maintenance of dynamic networks during various task states of the brain. Moreover, the oscillations synchronizing network, due to the nonreciprocal connections of CT axons, can dynamically influence the periodicity of other oscillations, affecting timing functions by other circuits.

3. Timing circuits and neural networks during social interactions

3.1. Mirror neurons in sign language and vocalization: communication in humans and nonhuman primates

The ability to communicate, among individuals who are active in groups, has played a key role in the evolution of primitive human societies. Speech developed as a method of communication about 10 millennia ago when creatures with large cranial capacity first appeared [5]. It is now believed that manual gestures are directly linked and have preceded the development of language in the humans as a method of communication [51]. Influential mirror system hypothesis posits that what counts for speaker (signer) must count approximately the same for hearer (observer) [52]. This parity rule underlies the basis of the development of communication in the nonhuman and human primates [51].

In an area of the macaque's ventral premotor cortex, area F5, which is homologous to the human Broca's area, the speech area, a new class of neurons called the mirror neurons, was discovered by Rizzolatti and his colleagues (**Figure 3**) [51, 53, 54]. The mirror neurons fire when monkeys perform a specific motor act or when they observe another primate, human or non-human, perform the same act [51, 53, 54]. More recently, Keysers, et al. [55] described a distinct population of neurons in the ventral premotor cortex of the monkey that discharges when the animal performs a specific action and it hears or sees the same action performed by another individual. In contrast to the mirror neurons, these neurons, called audiovisual neurons, also fire when monkeys hear specific sounds related to an action. Studies of both classes of neurons have added considerably to our understanding of how primates read others' intention and produce context-related responses [56]. Series of studies of mirror neurons in F5 and the intraparietal sulcus, summarized in a review by Rozzi and Coude [56], have shown that depending

upon the intention of motor act, for example grasping to eat or grasping to put into a container, the activities of neurons differed. Thus, the mirror neurons provide a mechanism to read motor intentions of other primates [56]. Imaging studies done in human subjects showed that the posterior parietal areas and premotor areas become active during action-observation and imitation [57, 58]. Rich reciprocal connections are present between different areas of the posterior parietal cortex and premotor cortex in monkeys, which serve as the anatomical basis of the mirror neuron mechanism (**Figure 3**) [56, 59]. The ability to read others' intentions would have played a key role during the human evolution due to the critical importance of this capability against the savage attacks by rival clans or species.

We note that the mirror and audiovisual neurons have an ability to synchronize parietal frontal circuits for the mirror system between two individuals. When two individuals are communicating by hand gestures or hear sounds representing the same action, then, the same neurons would fire in both the individuals: synchronizing the same set of circuits. This could be a basis of the development of communications among primates as the same sound or gesture may

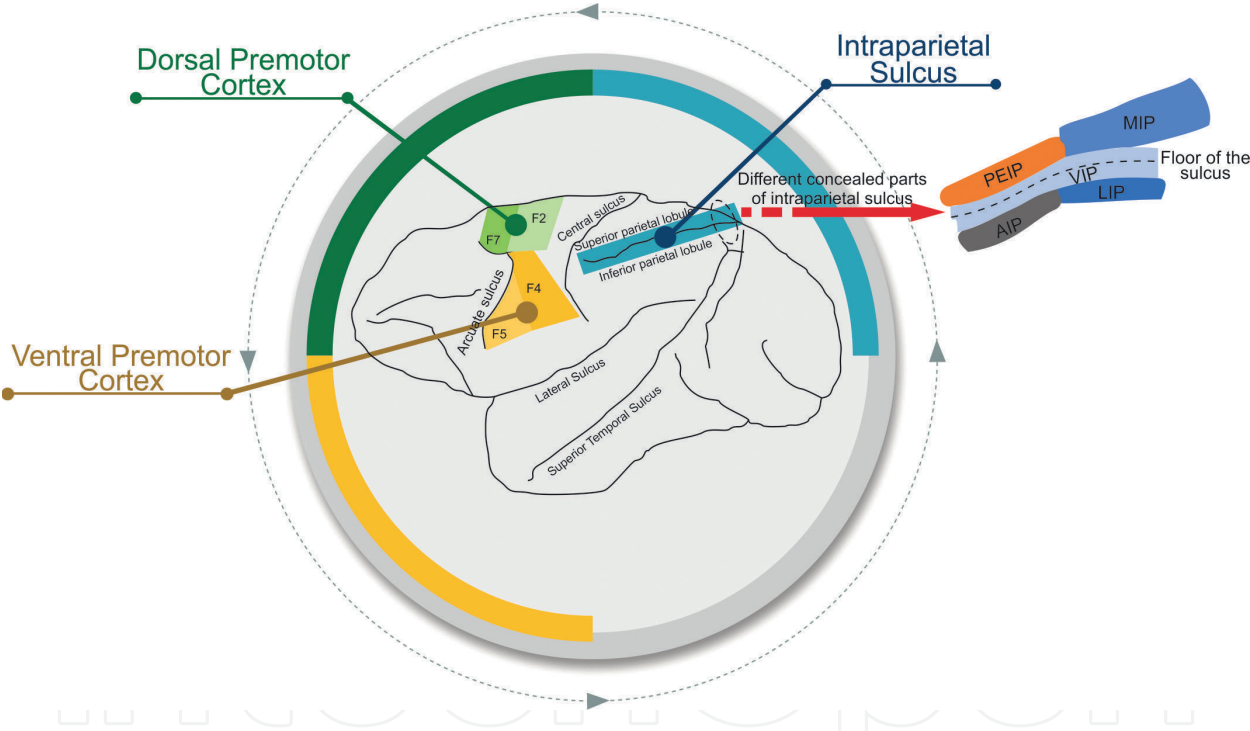


Figure 3. Anatomical basis of mirror neuron system in macaque brain:

- Ventral premotor cortex (areas represented by shades of yellow) contains frontal areas F5 and F4.
- Dorsal premotor cortex (areas represented by shades of green) contains frontal areas F7 and F2.
- Following parts of the intraparietal sulcus (blue) are depicted:
 - Anterior intraparietal area (AIP)
 - Medial intraparietal area (MIP)
 - Lateral intraparietal area (LIP)
 - Ventral intraparietal area (VIP).

lead to similar perception due to the activation of the same networks by common stimuli. The synchronization of common circuits by mirror neuron system would serve as a mechanism for same perception or meaning of a sound or gesture. It is believed that the Broca's area, the speech center of the human brain, was developed from the mirror neuron system in monkeys [51]. Moreover, F5 in the macaque brain, which contains mirror neurons and has a rich reciprocal connections with the posterior parietal cortex, is found to be homologous to the Broca's area based on the cytoarchitectonic and imaging data [60].

A recent study provides the evidence that the mirror neuron mechanism synchronizes networks spanning the ventral premotor cortex and posterior parietal cortex in the monkey brain (Figure 3) [61]. This study, which measured spiking activity, during a delayed grasping task by macaque monkeys, from the anterior intraparietal area (AIP) and ventral premotor area (Figure 3), both of which show strong connectivity [59], found that 18% of variability in reaction time was accounted by the ventral premotor area F5 but only 6% by the AIP. These observations suggest that there is a tighter coupling of mirror neurons in area F5 to physical time dimension, which is related to the greater contribution of the activity in F5 motor to the variability in reaction time. This study shows the presence of functional connectivity between the ventral motor area, F5, and the posterior parietal area, AIP, during the motor interaction with the external physical environment via delayed grasping task. This study is also consistent with the ability of mirror neuron system in F5 to synchronize the activity of the AIP in the posterior parietal cortex during a motor task.

When same mirror neurons in the brain of different individuals are stimulated by a common stimulus, then, the activity of those neurons will be locked to the same time point by the stimulus. This may serve as an important mechanism for the synchronization of perception of the shared space-time fabric of the surroundings among the individuals in a group. Without a mechanism to synchronize the perception by two individuals, who are communicating, a situation may develop analogous to two persons, who are watching the same action movie in two separate rooms, but the frames of movies being screened are fractions of a second apart. When they meet in a third room to discuss the last scene they had just watched, they will differ in their exact last version.

4. Representation of time dimension in the brain

4.1. Accurate representation of external physical time in the neural circuits is crucial for primate's interaction with the space-time fabric of external surroundings

Representation of time dimension in the brain is important for human and nonhuman primate's ability to survive. As we argued before, the representation of time dimension in neural circuits plays a key role in information processing underlying complex cognitive functions of the primate brain. Survival in many circumstances depends on the temporal coupling of actions with the perception of external environment.

Depending upon the demands of a task, the degree of coupling between action and perception may vary. For example, to dodge a falling rock requires a tighter temporal coupling

between action and perception in comparison with the tasks to reach for a cup of water. To temporally couple actions with sensory inputs, an accurate representation of time information in neural circuits is required. Without an accurate representation of time dimension in neural circuits, the ability of the brain to successfully couple actions—motor movements dodging a falling rock—with the perception of falling rock would not be possible due to a mismatch with the external physical time scale. Tasks requiring a tighter coupling between action and perception, such as the ability to dodge a falling rock and to kill animals with projectiles, are likely to have played a significant role in the survival of humans and would have significantly guided the evolution of the human brain. Thus, it is interesting to note that the cerebellum evolved relatively more rapidly than the other parts of the human brain, including the neocortex [62].

4.2. Neural temporal unit as a measurement unit of time axis in the neural circuits

Representation of time units by regular events is inherent in the definition of regular events, which repeats itself after the same interval every time. Time units, such as seconds, measured by swings of pendulum in a mechanical clock, can help in measuring duration by counting the number of seconds or swings of a pendulum. Using this analogy, a neural temporal unit is defined as the interval between two adjacent regular spikes, spike bursts and is proposed to represent time units in neural circuits [12].

According to the pacemaker-accumulator model, when neural temporal units are added by the accumulator, it processes neural time intervals in a subjective or motor task. According to this model, if the neural temporal units represented by neural oscillators in the brain's timing circuits are smaller on physical-time scale, then subjective time reported in a task will be greater than the elapsed physical time. This will be the result of greater number of neural temporal units present within a given external time duration. As predicted by the pacemaker-accumulator model greater number of neural temporal units within a timed interval will lead to subjective over-estimation of intervals. This is supported by a study in which entrainment using visual flickers with faster frequency increased time measurement in a time-reproduction task [63]. Entrainment by faster flickers increases the frequency of neural oscillators in the brain, which leads to smaller temporal unit. Another study used auditory click trains to increase the speed of neural clocks, and studied its effects on pairwise duration comparison and verbal time estimation task, and had arrived at similar conclusions [64]. However, not all entrainment studies agree with these conclusions [65]. Thus, a different role of neural oscillator is suggested within the modular clock model [12]. According to this formulation, the role of rhythmic activity is only to represent a physical property of the time dimension in neural clock mechanisms. Rhythmic activities are shown to be important for cognitive functions and various forms of behavior as reviewed by Herbst and Landau [66], but its precise role is yet to be understood.

4.3. Role of beta oscillations in the representation of time dimension

Accumulating body of evidence suggests that the beta-range neural oscillations represent physical time information in the brain (**Figure 1**) [65, 67–71]. A recent study has concluded

that beta oscillations play an important role in the retention and manipulation of time information held in working memory [68]. In another study, where monkeys performed a synchronization-continuation task, after an initial increase in the beta power of local field potential recording in the striatum, there was a decrease in the beta power during the synchronization phase, which was followed by a rebound during the continuation phase [71]. The synchronization of the neural activity of the striatum by increase in beta oscillations in this study agrees with the networking of the components of cortico-basal ganglia-cortico-thalamic circuit in the neural clock mechanism during the continuation phase. Moreover, the causal relationship, between beta oscillations and the control of movements [72], also suggests that beta oscillations are responsible for coupling the neural-timer mechanism with the motor circuits for the control of movements.

4.4. Representation of time dimension in lower motor circuits

Central pattern generators (CPG) are networks of interneurons in the spinal cord forming a part of the hierarchical control by the central nervous system that plays a role in generating rhythmic motor activities in animals, such as walking and chewing [73]. The rhythmic activity of CPG networks, according to the formulations of distributed modular clock mechanism, represents the time dimension in spinal cord motor circuits that help maintain the temporal characteristics of locomotion. Although, CPG activity is observed after deafferentation or spinal cord injury, but sensory inputs, especially proprioceptive signals, are crucial for its role in locomotion [74]. The function of proprioceptive signals is chiefly the calibration of time dimension represented in rhythmic activity of the CPG during locomotion.

The evidence for the direct role of spinal cord CPG networks in human locomotion is scant and is mostly indirect [75, 76]. Some beneficial effects are seen in spinal cord injury patients following locomotor training [77], which can be explained by “learning by spinal cord CPG networks” about optimal incorporation of physical time-dimension information from sensory, especially proprioceptive inputs in lower motor circuits, processing movements after spinal cord injury.

5. Conclusion

There are many challenges that remain in trying to understand how the time dimension is incorporated in information processing that underlie the timing of behavior in primates. At present, we do not understand how time dimension represents information within the patterns of spikes or spike bursts. A key challenge is to understand how synchronous neural activity patterns in distinct local circuits in brain networks represent timed behavior during interaction with external world.

A better understanding of the answers to above questions will help us improve the management of a wide ranging group of illnesses, such as schizophrenia, Parkinson’s disease and spinal cord injury among others.

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