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Symposium

Time in Cortical Circuits

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Time is central to cognition. However, the neural basis for time-dependent cognition remains poorly understood. We explore how the temporal features of neural activity in cortical circuits and their capacity for plasticity can contribute to time-dependent cognition over short time scales. This neural activity is linked to cognition that operates in the present or anticipates events or stimuli in the near future. We focus on deliberation and planning in the context of decision making as a cognitive process that integrates information across time. We progress to consider how temporal expectations of the future modulate perception. We propose that understanding the neural basis for how the brain tells time and operates in time will be necessary to develop general models of cognition.

Significance Statement

Time is central to cognition. However, the neural basis for time-dependent cognition remains poorly understood. We explore how the temporal features of neural activity in cortical circuits and their capacity for plasticity can contribute to time-dependent cognition over short time scales. We propose that understanding the neural basis for how the brain tells time and operates in time will be necessary to develop general models of cognition.

Introduction

Time plays a key role in cognition. Our experiences and thoughts occur in the present and are stored as the past. We combine the present and the past to anticipate events, direct attention, make decisions, and formulate plans for the future. In the remote past, our capacity to predict and anticipate the actions of predators, prey, and environmental events enhanced our ability to survive and to reproduce. In the modern world, the value of time to human cognition is immediately visible in the clinical setting. When patients become disorientated in time, their cognitive capacities degrade and their ability to function independently declines. Although time is vital for normal cognition, our understanding of the neural basis for time-dependent cognition remains rudimentary.

Psychophysical experiments have explored the relationship between time and cognition (Fraisse, 1964, 1984). However, there remains a large explanatory gap between psychological studies of time and our knowledge of the neural circuits that generate our perception of time. In this review, we aim to bridge that gap by building from both the bottom up and from the top down. We start with bottom-up approaches that explore how neural circuits use time. Here, time refers to “physical time,” that is, time measured with chronometers. The questions focus on the temporal properties of signaling between cortical neurons, how that signaling can be modified, and what the signaling may contribute to time-dependent cognition. Building from the top down, we consider cognitive processes that involve time as we perceive it (Fraisse, 1964, 1984; Allman et al., 2014). We focus on cognitive processes that operate in the present or anticipate events or stimuli in the near future. The scientific questions focus on the activity of single neurons or populations of neurons in behaving subjects. Finally, we seek to combine advances from the reductionist and the intact-subject approaches to explore how recent work is laying the foundations for a deeper understanding of the neural basis for time-dependent cognition.

Inevitably, we have had to be highly selective. There are excellent reviews on the role of internal clocks in time perception (Allman et al., 2014). Similarly, numerous insightful reviews discuss the past and memory (Martin et al., 2000; Frankland and

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Bontempi, 2005; Silva et al., 2009). Several brain regions have been implicated in time-dependent cognition. We focus on cortical circuits. Comprehensive reviews consider the contribution to time-dependent cognition of extracortical brain regions, such as the basal ganglia and cerebellum (Ivry, 1996; Merchant et al., 2013).

Time, timing, and plasticity of cortical microcircuits

Signaling between two neurons has temporal properties that could be used as building blocks for time-dependent cognition. Most obviously, communication between two neurons takes time. An action potential has to propagate down an axon and invade the axon's presynaptic terminals to elicit release of neurotransmitter. The neurotransmitter then diffuses across the synaptic cleft and evokes a postsynaptic response (Katz and Miledi, 1965; Sabatini and Regehr, 1996). The time taken for the entire series of events is referred to as the synaptic latency. Despite the multiplicity of processes, the synaptic latency usually remains relatively constant for any given connection in mature cortex, even when the connection is activated repeatedly (<40 Hz) (Barnes et al., 2015). The time course of the excitatory postsynaptic response is modified by factors intrinsic to the postsynaptic neuron (e.g., passive membrane properties, ion channel distribution) and by inhibition. Therefore, the time window over which an excitatory input contributes to firing of the postsynaptic neuron can be narrowed or widened by adjusting the temporal profile of the postsynaptic response that the excitatory input evokes (Pouille and Scanziani, 2001).

Temporal information is not just encoded in the temporal characteristics of neural activity. The frequency of activation of a neuron-to-neuron connection affects the amplitude of the postsynaptic response (Zucker and Regehr, 2002). This variation is referred to as either the short-term synaptic dynamics or short-term synaptic plasticity. The consequence of synaptic dynamics is that each synaptic response carries information about the recent history of activity at that synapse.

In neuronal networks, the temporal properties of neural activity may be characterized by measuring the time difference between neurophysiological events such as action potential firing or postsynaptic responses. This raises an important point when discussing the role of time and temporal processing in brain function. A crucial distinction should be made between the timing of neurophysiological events and the ability to tell time. Inevitably, the timing of neurophysiological processes and the ability to tell time intersect because the only way to tell time is to use mechanisms that play out or change in time in some reproducible fashion.

The timing of neural activity has been implicated in long-term plasticity processes that enable mature networks to learn temporal processing (Feldman, 2012). Probably the best known example of this is spike-timing-dependent plasticity. Here, the timing of action potential firing in a presynaptic neuron and in a postsynaptic neuron determines whether synapses strengthen or weaken and by how much (Debanne et al., 1994; Markram et al., 1997; Bi and Poo, 1998). Computational studies indicate that spike-timing-dependent plasticity can support learning of temporal sequences, temporal difference learning, and the ability to predict future events from past stimuli (Feldman, 2012). In principle, therefore, cortical circuits could be trained to contribute to time-dependent cognition.

Synaptic plasticity alters the strength of existing synapses, but does it also change the timing of synaptic responses? We noted above that the synaptic latency changes little during short-term

synaptic plasticity (Barnes et al., 2015). Furthermore, synaptic latency is preserved during experience-dependent plasticity, when changes in synaptic strength are accompanied by structural changes at synapses (Cheetham et al., 2008; Cheetham et al., 2014; Barnes et al., 2015). However, an exception to this general rule has been identified in cortex that is undergoing extensive, experience-dependent connection loss: synaptic latency is not maintained at recurrent excitatory connections that have been weakened (Barnes et al., 2015).

Reconfiguration of the architecture of cortical circuits, either by forming new connections to recruit neurons into a network or by losing connections to expel neurons from the network, is a form of rewiring (Barnes and Finnerty, 2010). During experience-dependent plasticity, new connections between pyramidal neurons (Pyr→Pyr) can be formed within a few days. These Pyr→Pyr connections typically comprise multiple synapses. Despite the relatively rapid formation of new Pyr→Pyr connections, their synaptic latency and short-term synaptic dynamics are normal (Albieri et al., 2015). In contrast, Pyr→Pyr connections that are weakened and are in danger of being lost exhibit prolonged synaptic latency and diminished temporal precision of neurotransmission (Barnes et al., 2015).

The ability to vary the latency and precision of neurotransmission has consequences for firing of action potentials in recurrent excitatory networks. In the neocortex, recurrent excitatory connections are weak (Bruno and Sakmann, 2006; Cheetham et al., 2007), which means that multiple presynaptic neurons must fire synchronously to drive the membrane potential of the postsynaptic neuron to the firing threshold (Crochet et al., 2011). Delaying the synaptic response of a subset of the presynaptic neurons can alter the number and timing of spikes fired by the postsynaptic neuron (Barnes et al., 2015). Delaying the postsynaptic response offers a mechanism to remove a neuron functionally from a network. It has been proposed that this enables the effects of losing an established connection to be tested without physical destruction of the connection. This would allow the process of connection loss to be reversed if spiking output is adversely affected (Barnes et al., 2015).

There has been a drive to characterize the architecture of the neural circuits in the brain termed the connectome. However, it is not clear that knowing the brain's wiring diagram in isolation will enable predictions about neural activity in real time. The configuration of excitatory and inhibitory connections within the circuit will affect the time taken for activity to propagate through that circuit (Siegel et al., 2015). If we are to understand time-dependent cognition, then we need to integrate the timing of neural activity into the connectome. This combination will provide a stronger basis for understanding cognition in behaving subjects.

Mechanisms of temporal processing on the millisecond to second scale

The mechanisms that allow the brain to tell time in the range of milliseconds and seconds remain, for the most part, a mystery (Mauk and Buonomano, 2004; Ivry and Schlerf, 2008; Merchant et al., 2013). For example, it is not clear how cortical circuits discriminate or reproduce specific durations (Jazayeri and Shadlen, 2010; Laje et al., 2011; Merchant et al., 2013) or anticipate the emergence of a stimulus that generally follows a cue by a fixed interval (Nobre et al., 2007; Cravo et al., 2013). In addressing these issues, it is first necessary to acknowledge that the brains of animals tell time across scales spanning >12 orders of magnitude, from detecting microsecond differences in interaural delays

to tracking the 24 h cycle of the rotation of the Earth. It is clear that, across these time scales, the brain uses fundamentally different mechanisms and areas to tell time. For example, in the extremes, one can see that the microsecond timing necessary for sound localization is independent of the molecular clocks that track the 24 h cycles that govern our circadian rhythms (Buonomano, 2007).

Within the range of milliseconds to seconds, however, a long-standing debate has focused on the degree to which different temporal ranges and tasks may or may not rely on shared mechanisms. Models of the passage of time have been divided into two classes (Ivry and Schlerf, 2008; Muller and Nobre, 2014). One class comprises dedicated models that propose the presence of a centralized timer. The timer relies on specialized timing mechanisms that enable the timer to function as a master clock across a wide range of tasks. In contrast, the second class of models, termed intrinsic models, propose that most neural circuits are inherently capable of telling time and that temporal processing can be performed in many different brain areas on an as-needed basis.

A strong test of the intrinsic model would be to determine if cortical slices *in vitro* could, in effect, learn to tell time. This approach was taken by A. Goel and D. V. Buonomano (unpublished results) using optogenetic stimulation. Specifically, organotypic slices were trained by pairing electrical activity and light at intervals of 100, 250, or 500 ms. In such slices, electrical stimulation can evoke polysynaptic activity; that is, a pattern of network activity produced by the internal dynamics of the network. Analysis of the temporal structure of the network activity evoked by the trained and untrained pathway was significantly different and the pattern evoked by the trained pathway reflected the trained interval; that is, there was an increased likelihood of observing events around the time of the expected interval. Mechanistic analyses suggested that the interval learning relied in part on time-varying changes in the balance of excitation and inhibition.

These results are consistent with the notion that, because timing is such an important computation, it is also one that cortical circuits are intrinsically capable of learning. The observed timing appears to rely on the neural dynamics generated by the recurrent circuitry. Understanding such dynamics, however, has proven to be a long-standing challenge at the computational level in part because the dynamic regimes generated by recurrent neural networks capable of supporting self-perpetuating activity tend to be chaotic—that is, highly sensitive to noise and thus not reproducible (Sompolinsky et al., 1988). The chaos problem has recently been addressed using computational models based on firing rate units (Laje and Buonomano, 2013). Moreover, it has been shown that it is possible to tune the weights of recurrent networks in a manner that the network will generate complex but stable neural trajectories. These trajectories effectively implement a “dynamic attractor.” Specifically, rather than the dynamics of an attractor converging to a standard fixed point that represents a memory, the memory is a spatiotemporal “object” represented in the evolving neural trajectory. Although it is not known how such pattern could emerge in spiking networks in an unsupervised fashion (Liu and Buonomano, 2009; Litwin-Kumar and Doiron, 2012), these results establish that recurrent networks can generate computationally powerful regimes with long memories and provide a robust and flexible manner to encode time. Importantly a strength of these models is that they do not only encode simple temporal intervals or durations, but rather complex temporal patterns such as those necessary for speech recognition or

production (Buonomano and Maass, 2009; Buonomano and Laje, 2010).

Planning, decision making, and the encoding of time

A hallmark of cognitive functions such as planning, anticipating, and deciding is the ability to process information over an extended time frame. For example, to hit a flying tennis ball, the brain must integrate sensory and motor information over hundreds of milliseconds. Similarly, to make a decision under uncertainty, the brain must assess the quality of information accrued over time.

Recent physiological recordings in animal models of higher brain function indicate that neurons involved in deliberation and planning are themselves time keepers (Brody et al., 2003; Janssen and Shadlen, 2005; Maimon and Assad, 2006; Hanks et al., 2011). A key feature of these neurons is their ability to maintain high discharge rates, persistent activity, in the absence of any direct sensory input and motor output. Although the synaptic and biophysical underpinnings of persistent activity are not known, it is thought that the modulations of this persistent activity, which we refer to as firing-rate dynamics, allow these neurons to track time.

Prior studies have examined how firing rate dynamics in different sensorimotor brain regions might represent time in behavioral tasks. For example, the firing rate of many neurons in the lateral intraparietal cortex either increases or decreases with elapsed time when monkeys categorize an interval as shorter or longer than a standard interval (Leon and Shadlen, 2003). This is a type of sensory timing. Conversely, when a sensory cue is used as a “go” signal, the firing rate of neurons associated with the motor response represent a hazard function of the expected cue (Janssen and Shadlen, 2005). Finally, when animals are asked to produce a time interval proactively (i.e., motor timing), neurons could exhibit complex patterns of firing rate dynamics at both the level of single neurons and across the population (Merchant et al., 2011; Schneider and Ghose, 2012; Crowe et al., 2014). In many brain areas, a primary component of the dynamics is a linear increase in firing rates (Maimon and Assad, 2006; Mita et al., 2009), which we refer to as ramping activity. These findings underline the importance of the firing-rate dynamics of sensorimotor neurons in timing. However, the computational principles that coordinate sensory and motor timing remain elusive.

A hint of the underlying mechanism comes from a recent study in which monkeys were trained to measure a sample time interval and then reproduce that interval as accurately as possible (Jazayeri and Shadlen, 2015). Analysis of the animals’ behavior indicated that they learned to reproduce the time interval accurately using a Bayesian strategy, as shown previously in humans (Jazayeri and Shadlen, 2010). Extracellular recording from neurons in the lateral intraparietal area revealed distinct firing rate dynamics during the measurement and production phases of the task. Neural responses in the measurement phase had a nonlinear profile that increased monotonically with the duration of the sample interval. In contrast, firing rates in the production phase increased linearly and the slope of this ramping activity encoded the production interval on a trial-by-trial basis. Importantly, the firing rates in the measurement and production were linked. Specifically, the nonlinear firing rate dynamics in the measurement phase predicted the slope of ramp in the production phase. Therefore, in the measurement phase, the firing rate dynamics anticipated the slope of the ramping activity in the production phase, whereas, during the production phase, the firing rate dynamics anticipated the time of the upcoming motor response. These findings raise an intriguing idea. Just as knowledge (gnosis)

of space appears to correlate with persistent activity associated with intention to look toward, reach for, or grasp (Merleau-Ponty, 1962; Shadlen et al., 2008), so might our sense of time correlate with dynamical activity associated with intention to reproduce, tap, or stomp.

Temporal attention: using temporal regularities to anticipate sensory events

Timing is a major determinant of the environment that we experience. Although our introspection suggests that we apprehend the entirety of our surroundings, many decades of empirical research teach us instead that our perception is highly limited. At most, a handful of items occupy our mind and guide our actions at any given moment (Helmholtz, 1867; James, 1890; Simons and Levin, 1997; Mack and Rock, 1998). When all works well, our perception is proactively and selectively focused on currently relevant events to guide adaptive behavior. These privileged percepts, extracted from countless other possibilities, provide the footing for our thoughts, decisions, and memories.

The functions responsible for goal-based prioritization of information processing are typically investigated under the domain of “attention.” According to prevailing models of attention, representations related to current task goals modulate (“bias”) neuronal excitability throughout sensory cortices to facilitate processing of relevant stimuli and suppress distraction from competing, irrelevant stimuli (Nobre and Kastner, 2014). Until recently, most efforts have gone into understanding top-down modulation of neuronal activity. This work has revealed mechanisms for spatial and feature-based attention. It is only recently, however, that researchers have recognized the essential role of temporal attention.

There are multiple sources of temporal regularities in the environment. The brain is able to make use of these to optimize the selection of the relevant items and events occurring at the right moments. Therefore, top-down biases not only carry information about receptive field properties, but also harbor information about how those receptive field properties are likely to unfold in time (Nobre et al., 2007; Nobre et al., 2012; Nobre and Rohenkohl, 2014).

Temporal expectations can be based on a variety of factors, including the natural rhythm of events, their consistent evolving temporal conditional probability for occurring within a given context (hazard rates), or their fixed temporal associations to other events (cues). Behavioral studies in human observers show that temporal expectation can improve perceptual sensitivity and response times when detecting or discriminating task-relevant stimuli (Jones, 1976; Coull and Nobre, 1998; Rohenkohl et al., 2012; Vangkilde et al., 2012). However, it is not clear how cortical circuits anticipate the emergence of a stimulus after the predicted time interval.

Brain imaging studies relying on hemodynamic measures have implicated a cortical network of parietal and inferior frontal areas in temporal orienting of attention (Coull and Nobre, 1998; Coull and Nobre, 2008). Noninvasive recording studies with high temporal resolution have been aimed at revealing modulatory mechanisms. Different sources of temporal expectations—rhythms, hazards, and cues—may use at least partially dissociable mechanisms. In all cases, however, changes in the timing or power of ongoing low-frequency oscillations have been observed (Cravo et al., 2011, 2013). These findings place critical constraints on models of how neural oscillations contribute to the prioritization, coordination, and routing of neural information to select and integrate features of relevant events. Interestingly, recording

studies have also revealed that temporal expectations combine synergistically with expectations about stimulus location to enhance early perceptual analysis of incoming stimuli (Doherty et al., 2005; Rohenkohl et al., 2014). One possibility is that the top-down modulation of perceptual processing attributable to temporal expectations may rely heavily on foreknowledge of other stimulus attributes coded in receptive-field properties. Such a scheme might suggest that timing becomes an intrinsic part of anticipatory circuits as a consequence of rhythmic or learned relations among events.

Conclusion

The nature of time has been debated extensively. What has emerged is that our perception of time does not accurately reflect an objective reality external to ourselves (Kant, 1781; James, 1890; McTaggart, 1908). Furthermore, time-dependent cognition is fundamentally different from other sensory domains in that there is no sensory organ for time. Instead, our perception of time is generated internally within our brains. Our capacity for time-dependent cognition enables us to focus our attention and interact in real time with a rapidly changing environment. The temporal features of neural activity in cortical circuits and their capacity for plasticity suggest that cortical circuits can play a central role in many forms of time-dependent cognition. The cellular and network mechanisms that we review here are general properties of neural circuits. Therefore, they are not limited to the cortex and apply equally well to more distributed neural circuits that have been hypothesized to contribute to timing and temporal processing. Finally, we propose that an understanding of how the brain tells time and operates in time will be necessary to develop general models of brain function.

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