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Ramping activity is a cortical mechanism of temporal control of action

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A fundamental feature of the mammalian cortex is to guide movements in time. One common pattern of neural activity observed across cortical regions during temporal control of action is ramping activity. Ramping activity can be defined as consistent increases or decreases in neuronal firing rate across behaviorally relevant epochs of time. Prefrontal brain regions, including medial frontal and lateral prefrontal cortex, are critical for temporal control of action. Ramping is among the most common pattern of neural activity in these prefrontal areas during behavioral tasks. Finally, stimulating prefrontal neurons in medial frontal cortex can influence the timing of movement. These data can be helpful in approaching human diseases with impaired temporal of action, such as Parkinson's disease and schizophrenia. Cortical ramping activity might contribute to new diagnostic and therapeutic strategies for these and other debilitating human diseases.

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Introduction

Finding food and evading threats is critical for mammalian behavior and requires the ability to guide movements in time. For humans, the temporal control of action is central to complex activities such as cooking and driving. In this review, I argue that ramping activity in the prefrontal cortex critically regulates how movements are guided in time to achieve behavioral goals. I focus on epochs of several seconds, as temporal processing at shorter or longer scales can involve distinct neural systems [1,2].

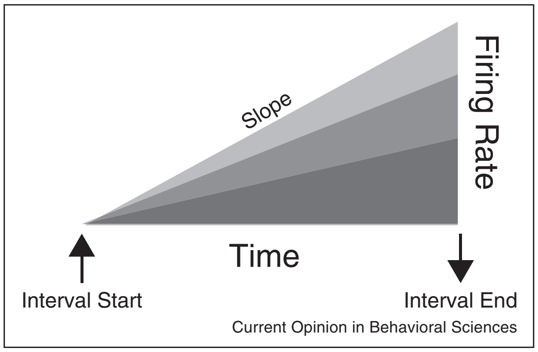
Timing has been extensively addressed by theoreticians for decades [3]. Much of this work concerns the perception of time by the brain. Perceptual timing consistently recruits subcortical networks in the cerebellum, striatum, and brainstem [4]. In the last decade, evidence has accumulated that frontal and visual cortical areas are also required for temporal control of action. Posterior cortical areas are discussed in a companion review by Shuler *et al.*, in this issue. Here, I focus on the frontal cortex, which is chiefly concerned with motor control.

Neurophysiology facilitates investigation into how neural networks instantiate timing processes that allow movements to be coordinated in time. Most neurophysiological tasks involve some amount of temporal expectation, or the anticipation of when events or movements will occur in time. Temporal expectation can be captured mathematically via a 'hazard' function [5]. For instance, when an event is likely to occur within a given amount of time, if the event fails to occur at time x, then the probability that it will occur at time $x + 1$ will increase. Organisms capitalize upon temporal information when preparing movements, as certainty regarding when events will occur will progressively increase as time unfolds. For instance, sprinters might respond to the starting gun fastest after waiting a long time, because after a long delay they are fully prepared to respond [6]. Temporal preparation can be 'embodied' in movements [7]. In this sense, temporal control of action is a subset of motor control. Furthermore, temporal control demands executive resources such as working memory and attention [8,9] albeit at an elementary level [10,11]. That is, loading executive functions such as working memory or attention can interfere with guiding movements in time [8]. These data indicate that timing shares resources with classical executive processes such as working memory, attention, and reasoning [8,10].

Ramping activity

One pattern of cortical neuronal activity that robustly encodes temporal information is *ramping*, which can be defined as consistent increases or decreases in firing rate over time (Figure 1). Ramping is the most common pattern of activity in frontal cortex during timing tasks [12,13•,14•], and typically starts at the beginning of the interval and consistently changes until the end of the interval. This pattern of activity could readily encode the accumulation of temporal evidence; i.e., as time passes, temporal expectation increases and neural activity increases or decreases. In this sense, ramping reflects temporal integration as has been suggested by detailed modeling of timed behavior using drift-diffusion or integrative models [15,16•]. Precise temporal information can

Figure 1



Ramping activity. Neural activity increases after the start of a temporal interval, as indicated by a predictive stimulus or preparatory movement. Temporal expectation anticipating movement and/or reward grows over time and neural ramps accordingly. The slope of the ramp can also encode interval duration. Ramping activity can also decrease which would be the inverse of the pattern represented here, and can also have logarithmic features.

be encoded in the slope and maximum activity of the ramp (Figure 1), as was first shown in recordings from inferotemporal cortex [17]. Increasing variance at longer temporal intervals might be a correlate of the scalar property of timing [3,18]. The pattern of ramping neurons need not be linear; indeed, if cortical neurons encode hazard functions they would be expected to have exponential features [16•,19•]. Ramping might also occur across a population of neurons via recurrent network interactions [20]. Other patterns such as persistent activity are also commonly observed that explicitly encode mnemonic information. Many cells with persistent activity can have ramping features [21]. Moreover, ramping is the integral or cumulative sum of persistent activity, indicating that ramping could encode cognitive variables in addition to timing, such as error signals or working memory [13•].

One correlate of population-level ramping might be the *Bereitschaftspotential*, or 'readiness potential' [22]. This potential is a several microvolt-range deflection in EEG prior to voluntary movement which can begin seconds prior to movement initiation, as measured by EMG. While these potentials are largest over somatotopic motor cortex, early components of *Bereitschaftspotential* are distributed across frontal cortex and occur earliest over medial regions of frontal cortex [23,24]. Late components of readiness potentials also ramp, but it is as-of yet unclear how neural activity is transformed into readiness potentials.

Because of the distributed nature of temporal processing [25], it is critical to establish how cortical signals contribute to behavior. One set of criteria are that neuronal signals must be (a) *necessary* — disruption of the signal decreases temporal control of action, (b) *correlated* — the signal is correlated with temporal control on single trials, and (c) *sufficient* — introducing or enhancing the temporal signal must improve how movements are guided in time. While many neuronal signals meet at least one these criteria, even signals that appear to correlate strongly with temporally-controlled behavior can fail this test. For instance, motor cortical neurons are strongly correlated with when animals move. However, disrupting these neurons degrades specific movements but not the timing of movement initiation [26]. Similarly, ramping neurons in parietal and temporal cortex can encode highly specific aspects of temporal processing [17,18,27]; to our knowledge there is no evidence that disruption or stimulation of these areas influences timing [28]. This set of criteria can be vulnerable to conceptual flaws as the massive redundancy of neural systems makes them resistant to disruption, makes behavioral correlations omnipresent, and can make stimulation experiments difficult to interpret [29].

Prefrontal cortex ramps while animals wait to respond

Prefrontal regions include medial frontal cortex (MFC; cingulate/prelimbic cortex, BA 24/32; lead Cz from EEG) and lateral prefrontal areas in the middle frontal gyrus (BA 9/46) [30]. Several studies have shown that these areas are required for temporal processing. For example, humans with lesions of superior medial or right lateral frontal cortex have increased variability in tasks requiring temporal control [31,32]. Reversible lesions with rTMS of human right lateral frontal cortex shortened the duration that subjects pressed a spacebar when reproducing either 5 or 15 s durations [33]. Rodents lack lateral frontal regions, but rodent MFC encompasses anterior cingulate and supplementary motor areas have homologies with structures in primates [30]. Disrupting rodent MFC increases temporal errors during a time-estimation task [34]. Lesions or reversible disruptions of MFC also impair rodents' ability to move at the right time by increasing the variability of responses during interval-timing tasks, in which subjects must estimate an interval of several seconds as instructed by a stimulus [35,36,37•]. Furthermore, inactivating MFC impairs neuronal activity related to inhibiting temporally inappropriate responses in motor cortex [38].

Temporal control in MFC depends requires dopaminergic signaling via D1 dopamine receptors (D1DR). Disrupting dopamine in mesocortical pathways impairs interval timing [14•,36,39•]. Focal dopamine receptor blockade in MFC implicates D1 but not D2 receptors in temporal processing [36,40]. MFC D1DR agonists or antagonists attenuates MFC ramping activity [14•,41], consistent with the role of prefrontal D1DRs in cognition [42]. Optogenetic inhibition of medial frontal neurons expressing D1DRs impairs temporal control of action on single trials [36]. These data provide convergent evidence that MFC D1DRs are necessary for temporal control of action.