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Medial prefrontal cortex and the temporal control of action

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Abstract

Across species, the medial prefrontal cortex guides actions in time. This process can be studied using behavioral paradigms such as simple reaction-time and interval-timing tasks. Temporal control of action can be influenced by prefrontal neurotransmitters such as dopamine and acetylcholine and is highly relevant to human diseases such as Parkinson's disease, schizophrenia, and attention-deficit hyperactivity disorder (ADHD). We review evidence that across species, medial prefrontal lesions impair the temporal control of action. We then consider neurophysiological correlates in humans, primates, and rodents that might encode temporal processing and relate to cognitive-control mechanisms. These data have informed brain-stimulation studies in rodents and humans that can compensate for timing deficits. This line of work illuminates basic mechanisms of temporal control of action in the medial prefrontal cortex, which underlies a range of high-level cognitive processing and could contribute to new biomarkers and therapies for human brain diseases.

Deciding *When* to Act

Animal behavior – or the complex symphony of coordinated action in the world – is precisely sequenced in time (Finnerty et al., 2015). Although perceptual events can indicate potential rewards or threats, temporal control of actions over several seconds is required to maximize positive and minimize negative outcomes (Tallot and Doyère, 2020). For mammals, this is critical to foraging and successfully avoiding predators (Bateson, 2003). For humans, temporal control of action is critical for routine activities such as cooking, driving, and crossing the street, and complex activities such as math, language, poetry, and art. Perceptual decision making has been the focus of many neuroscientific studies (Gold and Shadlen, 2007). However, deciding *when* to act is as important as selecting appropriate actions; indeed, the right action at the wrong time can lead to disastrous consequences. Thus, understanding the underlying neural circuitry involved in temporal control of action has far-reaching importance (Fuster, 2001).

The timing of movements is critical to higher-level cognition. Indeed, temporal control of action underlies many higher-level executive functions such as attention, flexible behavior, reasoning, and working memory. Dual-task studies in which participants perform executive functions concurrently with timing operations reveal marked bidirectional interference; i.e., performing a time production and randomization task concurrently degrades performance

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of either task (Brown, 2006). Estimating a temporal interval can impair concurrent working-memory performance (Bi et al., 2013). These data imply that temporal control of action and executive functions recruit shared cognitive resources and neural circuits (Parker et al., 2013b).

We argue that the medial prefrontal cortex critically controls movements in time. We focus on medial regions of prefrontal cortex that are conserved across mammalian species. Medial prefrontal regions of frontal cortex have been defined by projections from thalamic nuclei and a lack of a prominent cortical layer IV (i.e., 'agranular'; Rose and Woolsey, 1949; Akert, 1964). Lateral prefrontal human specializations in dorsal and inferior frontal regions have been implicated in specialized functions such as working-memory and language (Fuster, 2008). While these lateral regions have unclear mammalian homologies in rodents, primate medial prefrontal regions can have anatomical and functional homologies with rodents (Preuss, 1995; Uylings et al., 2003; Laubach et al., 2018). Although there are differences between primate and rodent nomenclature because the granular lateral prefrontal cortex does not exist in rodents, the human/primate agranular anterior cingulate cortex covering Brodmann areas 24 and 32 has anatomical homologies to rodent medial prefrontal regions including the anterior cingulate cortex and the prelimbic cortex (Fig 1) (Laubach et al., 2018). For instance, both the human and rodent medial prefrontal cortex have a similar laminar architecture, receive similar neurotransmitter input, and have highly conserved connectivity with thalamic, striatal, hypothalamic and brainstem nuclei (Gabbott et al., 2003, 2005). Although medial prefrontal regions are vastly expanded in primates and humans, there are important differences between cingulate, prelimbic, and supplementary motor regions (Amiez and Procyk, 2019), in this chapter, we argue that across species, medial prefrontal regions have a significant functional homology: the temporal control of action. We start by discussing paradigms to study temporal control of action and then discuss medial prefrontal neurotransmitter systems involved in temporal control of action. We then review diseases with impairments in temporal control of action and lesion studies that disrupt the medial prefrontal cortex and impair timing of movements. Finally, we discuss both neuronal and local field potential correlates of how movements are controlled in time and then relate these signals to protocols that deliver brain stimulation that improves temporal control of action.

Paradigms for studying the temporal control of action

Time suffuses all paradigms and tasks in behavioral neuroscience, which generally require a specific action in a narrow temporal window. In human studies, the timing of movement is critical to inferences about cognitive processing. For instance, reaction-time linearly increases with the number of working-memory items (Sternberg, 1969; Narayanan et al., 2005) and can be harnessed in perceptual decision-making to capture trade-offs between speed and accuracy (Herz et al., 2017) or countermanding (Verbruggen et al., 2019).

However, the most elementary response in simple-reaction time tasks can be profoundly affected by temporal processing. To 'control' for time in responding to a stimulus, many reaction-time tasks included a variable delay or 'foreperiod' between a warning cue and the imperative stimulus (Luce, 1991). Studies with the variable delay revealed that human –and

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non-human participants –were more prepared to respond the longer they waited, leading to delay-dependent speeding (or 'foreperiod-effect'; Fig 2A) (Naatanen, 1971, 1972; Naatanen et al., 1974; Narayanan et al., 2006). Furthermore, response distributions could be influenced by the temporal probabilities of the task; that is, if a short delay was more likely, response times would decrease (Naatanen et al., 1974). These data suggest that actions are profoundly influenced by the temporal probabilities as specified by the hazard function (Luce, 1991).

Another paradigm to explicitly study temporal control of action is interval timing (Fig 2B) (Merchant and de Lafuente, 2014). This family of tasks requires participants to estimate an interval of several seconds with a motor response. Although interval timing was designed to capture how time is 'perceived', these tasks require a motor report of temporal estimates and thus are inherently tied to action (outside of bisection tasks (Stubbs, 1976)). A beautiful aspect of these tasks is that they are conserved across many species, including mammals and birds (Buhusi and Meck, 2005) and can be performed in a broad range of conditions, from rodent operant behavior to human patients with severe brain diseases or with interoperative human neurophysiology (Carroll et al., 2009; Craig et al., 2014; Kelley et al., 2018). Temporal control of action may influence more complex motor sequences or language (Averbeck et al., 2006; Long et al., 2016); however, we will focus on reaction-time and interval-timing tasks as they are 1) well-suited to isolate temporal control of action from other processes, 2) they are simple enough to study in rodents and humans with cognitive impairments, and 3) complementary evidence across species facilitates convergent inferences on medial prefrontal function.

Neurotransmitter Systems

Human and rodent prefrontal regions receive dense innervation from ascending neurotransmitter systems such as dopamine, acetylcholine, norepinephrine, and serotonin (Narayanan et al., 2013b). Human brain diseases and their treatments involve perturbations of these neurotransmitter systems (Arnsten et al., 2012). Prefrontal norepinephrine and serotonin can have specific effects on goal-directed behaviors, but specific evidence for their role in temporal control of action is lacking. Conversely, dopamine and acetylcholine reliably regulate the timing of movements.

Primate prefrontal dopamine-depletion impairs behaviors across a delay (Brozoski et al., 1979; Goldman-Rakic, 1998). Our group has found specific effects during timing tasks. During simple reaction-time tasks, we found that rodent prefrontal dopamine-depletion and focal infusions of drugs blocking the D1-type dopamine receptors (D1DRs) blunted delay-dependent speeding with faster responses at short intervals. However, we did not observe increased premature responding (Parker et al., 2013a). During interval-timing tasks, we found that disrupting prefrontal dopamine by specific RNAi against tyrosine hydroxylase or dopamine depletion flattened time-response histograms (Narayanan et al., 2012; Parker et al., 2015a; Kim et al., 2017). Focal pharmacology has implicated prefrontal D1DRs but not D2DRs in temporal control of action (Narayanan et al., 2012; Parker et al., 2014, 2015a). Critically, transgenic mouse lines facilitate cell-type-specific experiments, and we have shown that optogenetic inactivation of prefrontal D1DR+ neurons in the mouse medial prefrontal cortex decreased responding at the end of a fixed-interval (Narayanan et al.,

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2012). These data provide convergent and consistent evidence that prefrontal D1DRs are required for the temporal control of action.

Cholinergic systems also play a clear role in timing tasks. For instance, systemic disruptions of acetylcholine with scopolamine (a muscarinic antagonist) or mecamylamine (a nicotinic antagonist) reliably impair reaction-time tasks (Jones and Higgins, 1995). Cholinergic signaling can affect prefrontal firing (Gill et al., 2000; Parikh and Sarter, 2008). These agents also impair interval timing; however, we found that scopolamine impairs stimulus-processing but not temporal processing by prefrontal neurons (Zhang et al., 2019). These data may be consistent with a view that cholinergic systems are important for attention rather than the temporal control of action (Sarter and Bruno, 1997; Klinkenberg and Blokland, 2010). Indeed, all timing tasks require attention to the passage of time as well as imperative cues. Future work with specific manipulations of cholinergic circuits and localized manipulations in the prefrontal cortex might clarify how acetylcholine modulates prefrontal circuits.

Significance for human disease

The timing of movement provides a unique window into human brain diseases that affect the prefrontal cortex. Because it can be rapidly and objectively assessed, assays built on studying the timing of movement have the potential to contribute to novel biomarkers, diagnostics tools, and intraoperative assays.

Patients with Parkinson’s disease have slow movements. This ‘bradykinesia’ slows all reaction times (Evarts et al., 1981); nonetheless, Parkinson’s disease patients have intact delay-dependent speeding (Jurkowski et al., 2005; Wearden et al., 2008). By contrast, Parkinson’s disease patients have impaired interval timing as a function of levodopa (Malapani et al., 1998, 2002; Jones and Jahanshahi, 2014). When multiple intervals are presented, patients with Parkinson’s disease are not simply slow; rather, they have increased variability by overestimating short intervals and underestimating long intervals. These deficits may reflect, in part, deficits in executive functions in Parkinson’s disease patients (Narayanan et al., 2013b; Parker et al., 2013b p.201).

Another disease with profound prefrontal abnormalities is schizophrenia (Andreasen et al., 1997; Okubo et al., 1997; Abi-Dargham et al., 2002). Like Parkinson’s disease, schizophrenia does not consistently involve delay-dependent speeding but does involve interval-timing impairments (Ward et al., 2011). Indeed, patients with schizophrenia are more variable and less efficient in their temporal estimates but do not reliably under- or overestimate an interval compared to healthy controls (Carroll et al., 2009, 2009; Parker et al., 2017; Thoenes and Oberfeld, 2017). Interestingly, this deficit extends to first-degree relatives (Penney et al., 2005). To date, most studies include patients undergoing therapeutic interventions and little work has been done to explore the role of specific medications in patients, meaning that these interval timing deficits may be more significant than reported. This is particularly important as first-line interventions are thought to target the medial prefrontal dopamine system. While there are inconsistencies in the literature and medication

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status may play a role; taken together, these data suggest that medial prefrontal dysfunction drives timing deficits in schizophrenia.

By contrast, attention-deficit hyperactivity disorder (ADHD) patients have uniform deficits in timing (Barkley et al., 1997). For instance, patients with ADHD have delay-dependent deficits during reaction-time tasks (Leth-Steensen et al., 2000) as well interval timing deficits (Smith et al., 2002). This interval timing deficit includes both consistent increases in timing variability and the overestimation of perceived time (Rommelse et al., 2008; Hove et al., 2017). Unlike schizophrenia-related timing deficits, several studies have examined the impact of first-line interventions for ADHD. For example, medications that primarily act on the medial prefrontal dopamine system, such as methylphenidate, have been shown to normalize both timing behavior and prefrontal function in ADHD (Hart et al., 2012; Luman et al., 2015). Furthermore, the medial as well as lateral prefrontal regions are dysfunctional in ADHD (Bush, 2011). These data suggest that timing dysfunction may be linked to medial prefrontal dysfunction (Valera et al., 2010; Hart et al., 2012; Noreika et al., 2013; Bluschke et al., 2018).

A broad range of other neurological and psychiatric illness can degrade prefrontal circuits, including Alzheimer's disease and Huntington's disease (Hinton et al., 2007; Caselli et al., 2009). More work needs to be done to clarify the role of medial prefrontal networks in these diseases. Nonetheless, this line of work in Parkinson's disease, schizophrenia and ADHD firmly establishes the clinical relevance of understanding how medial prefrontal regions guide actions in time. Thus, a detailed understanding of these circuits will not only have far-reaching basic-science significance but could lead to new biomarkers, diagnostic tools and neuromodulation therapies for human brain diseases.

Lesion studies

The critical nature of the prefrontal cortex in acting over a delay was identified by Carlyle Jacobsen, who trained macaque monkeys on delayed response and delayed-alternation tasks (Jacobsen, 1935; Jacobsen and Nissen, 1937). Animals with extensive bilateral prefrontal lesions had permanent deficits at a variety of delays, but animals with unilateral lesions or with lesions of premotor or frontal motor areas had no deficits. Although not formally measured, Jacobsen insightfully concluded that frontal lesions in humans and primates affected the "temporal patterning of movement". This finding was replicated by subsequent primate lesion studies that mapped lesions to lateral and medial regions of the baboon prefrontal cortex (Pribram, 1950; Pribram et al., 1952) and then extended to working memory (Mishkin and Pribram, 1955; Pribram and Mishkin, 1956). Although we are unaware of medial frontal inactivation or lesions during reaction-time tasks, primate medial frontal inactivation increases timing variability during a time-production task (Wang et al., 2018).

Human lesion studies from the laboratory of Donald Stuss definitively implicate human medial prefrontal regions in the temporal control of action. These authors found that superior medial prefrontal lesions spanning Brodmann Areas 24 and 32 slowed reaction-times. By contrast, other prefrontal regions did not produce consistent effects on overall reaction-

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time, but right lateral prefrontal lesions blunted delay-dependent speeding and prevented speeding of responses at longer intervals (Stuss et al., 2005). Subsequent studies revealed that human prefrontal lesions consistently increased the variability of responses during time-reproduction (Picton et al., 2006a, 2006b). Taken together, these unique human data connect human medial prefrontal areas to the temporal control of action.

In rodents, medial prefrontal regions are reliably involved in guiding movements in time. Excitotoxic prelimbic/infralimbic lesions that spared cingulate regions increased premature responding during simple-reaction time performance in rats; fascinatingly, this premature responding recovered in several days (Risterucci et al., 2003). Work by Narayanan and Laubach that reversibly inactivated dorsal prelimbic / ventral anterior cingulate regions replicated the increased premature responding and decreased delay-dependent speeding and found that animals had faster responses at short intervals (Narayanan and Laubach, 2006; Narayanan et al., 2006). Strikingly, prefrontal inactivation also impaired the ability to optimize responses after errors and improve performance (Narayanan and Laubach, 2008).

During interval-timing, rodent medial prefrontal disruptions impaired selection of a long temporal interval during a maze-running temporal bisection task (Kim et al., 2009). Prefrontal cooling of superficial areas slowed temporal estimates in a time-reproduction task (Namboodiri and Hussain Shuler, 2014; Xu et al., 2014). Our group has reliably shown that reversible prefrontal inactivation impairs fixed-interval timing by ‘flattening’ peaks of time-response histograms, resulting in responses that are more random in time (Narayanan et al., 2012; Parker et al., 2014; Emmons et al., 2017). During peak-interval timing, which allows estimates of both the start and the stop of temporal estimates, medial prefrontal inactivation increased the variability in a dose-dependent fashion (Buhusi et al., 2018). These data provide support for the idea that medial prefrontal lesions reliably increase the variability of how movements are controlled in time. In reaction-time tasks where response distributions are highly skewed, one form of this increased variability might include increased premature or slow responses.

Neuronal Correlates

Recording from single neurons and networks can provide insights into how movements are guided in time (Paton and Buonomano, 2018). Although these patterns can be diverse, and representation of impending movements can be ubiquitous in frontal cortex, recordings from our group and others have identified a common theme in temporal control of action.

This pattern is characterized by ‘ramping’ – or monotonic changes in firing rate over a temporal interval - and is a key form of temporal processing (Narayanan, 2016). In seminal recording studies by Niki and Watanabe, anticipatory patterns of neuronal activity (i.e. ramping activity) were the most common pattern (~25%) during timing and delayed-response tasks (Niki and Watanabe, 1976,1979). These neurons were observed in the cingulate cortex and more common than sustained activity (~20%). While sustained activity may be related to working-memory (Niki and Watanabe, 1976; Goldman-Rakic, 1996), this pattern of activity may also represent ‘time estimation’.

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We have found that during timing tasks, ramping activity is the most common pattern of activity in the medial prefrontal cortex (Fig 3A–B) (Narayanan, 2016). This can be quantified by data-driven methods such as principal component analysis or by linear regression (Narayanan and Laubach, 2006, 2009). Linear patterns are a major player in higher-order representation such as neuronal manifolds (Wang et al., 2018). During interval-timing tasks, this pattern is also commonly observed (Matell et al., 2003; Xu et al., 2014), and our work has found that neurons anticipating the interval end are the most common pattern of activity in mice and rats, explaining ~30% of prefrontal variance (range-15–51%) (Narayanan and Laubach, 2009; Parker et al., 2014, 2015c; Emmons et al., 2017; Kim et al., 2017; Emmons et al., 2019). In humans, scalp electrical potentials can steadily depolarize until a voluntary action and represent temporal signals (Shibasaki and Hallett, 2006; Kononowicz and van Rijn, 2014). Notably, human single-unit recordings also reveal ramping patterns of activity (Sheth et al., 2012; Kamiński et al., 2017; Fu et al., 2019).

Ramping activity is notable for several reasons. First, the temporal code is readily evident in that the firing at any given moment represents elapsed time and lends itself to quantitative models based on drift-diffusion dynamics (Simen et al., 2011; Luzardo et al., 2013). These models predict that ramping activity ‘scales’ among prefrontal ensembles to encode short or long intervals and correlates with responses without predicting specific movements (Emmons et al., 2017; Wang et al., 2018). Second, linear models can explain high amounts of variance in ramping activity, although one study reported a logarithmic component to ramping activity during a maze-running task (Kim et al., 2013). While higher order manifolds or multivariate methods may capture additional population encoding (Paton and Buonomano, 2018; Remington et al., 2018; Wang et al., 2018), linear features of ramping activity are important because they are predicted by cellular and behavioral models (Durstewitz, 2003; Simen et al., 2011) and might readily be represented by downstream brain areas. In addition, the degree to which the system is linear might facilitate powerful mathematical tools to understand complex neuronal dynamics. Third, pharmacological manipulations such as dopamine-depletion and D1DR-receptor manipulations that impair temporal control of action also impair ramping patterns of activity without affecting other prefrontal patterns of activity (Parker et al., 2014, 2015b, 2015c). Furthermore, inactivating medial prefrontal cortex disrupts ramping activity in other areas, such as the dorsomedial striatum (Emmons et al., 2017). Fourth, time can be robustly decoded from ramping signals, although non-ramping signals can also contribute (Emmons et al., 2017). Taken together, these data make the compelling case that ramping activity is closely linked to the temporal control of action. Notably, other patterns of neuronal activity can encode temporal features (Matell and Meck, 2004; Karmarkar and Buonomano, 2007; Laje and Buonomano, 2013), but in our hands, ramping activity explains the majority of variance and correlates with behavioral manipulations.

In our work, we argue that medial prefrontal ramping activity is related to guiding upcoming movements in time rather than controlling specific movements. Our premise is supported by three lines of evidence: 1) ramping is observed when animals are holding a lever above a force threshold and not moving (Narayanan and Laubach, 2006, 2009), 2) ramping patterns of neuronal activity are prominent prior to the initial response during interval timing tasks (Emmons et al., 2017), 3) ramping activity persists even when movement-related activity is

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explicitly accounted for in regression models (Emmons et al., 2017, 2019). Combined with microstimulation studies showing that medial prefrontal stimulation does not reliably evoke movements, and anatomical studies suggesting that medial prefrontal cortex does not have strong links to cortical or subcortical motor nuclei (Neafsey et al., 1986; Gabbott et al., 2005), together these data suggest that medial prefrontal cortex plays a key role in planning movements in time.

At the macro-level, we have consistently observed bursts of midfrontal 4 Hz activity in ‘delta’ or ‘theta’ bands during timing tasks (Narayanan et al., 2013a; Parker et al., 2014, 2015b; Kim et al., 2017). These bursts originate from the human medial prefrontal cortex (Kelley et al., 2018) and are remarkable because they are highly conserved in humans and rodents and depend on dopamine in both species (Narayanan et al., 2013a; Parker et al., 2015b; Kim et al., 2017). Midfrontal 4 Hz activity is a mechanism of cognitive control and is phase-locked to salient events such as novelty, errors, feedback, and to imperative stimuli during timing tasks (Cavanagh and Frank, 2014). Timing-related midfrontal 4 Hz oscillations can be dysfunctional in diseases with impaired temporal control of action such as Parkinson’s disease and schizophrenia (Parker et al., 2015b, 2017; Kim et al., 2017). Because these oscillations can be specifically coherent with distant brain areas and with prefrontal neurons involved in temporal and error-related processing (Narayanan et al., 2013a; Parker et al., 2014, 2015b; Kim and Narayanan, 2018), our working model is that these oscillations engage prefrontal ramping neurons instantiating temporal control of action. Accordingly, midfrontal 4 Hz power is a cognitive control signal that represents the ‘starting gun’ that initiates temporal processing in timing models (Church, 2003).

Stimulation

Preceding lines of evidence from lesion, pharmacology and neurophysiology suggest that there might be opportunities to modulate the temporal control of action, particularly when it is dysfunctional. In addition to the basic-science significance of this manipulation, brain stimulation has the possibility to deliver therapies for human brain diseases (Kim et al., 2015; Zhang et al., 2019). Indeed, for motor symptoms of Parkinson’s disease, detailed circuit mapping and neurophysiology led to breakthroughs for clinical deep-brain stimulation, which vastly improve motor symptoms of Parkinson’s disease (Limousin et al., 1998; Deuschl et al., 2006). Because temporal control of action is intimately linked to a range of cognitive functions in diseases such as Parkinson’s disease, ADHD and schizophrenia, improving temporal control of action may have real-world benefits.

We found that low-frequency brain stimulation at 2 Hz — in the range of midfrontal cognitive control signals — improved interval timing in dopamine-depleted animals (Kim et al., 2017). This intervention was highly specific, targeting prefrontal D1DR+ neurons in the medial prefrontal cortex of mice. Amazingly, 2 Hz brain stimulation also boosted medial prefrontal ramping activity and temporal decoding. Subsequent work from our group found that D1DR+ neurons had specific coherence with ramping neurons and that stimulation early in the interval was sufficient to improve interval timing. Non-specific stimulation of all prefrontal neurons or stimulation in non-dopamine-depleted animals had no reliable effect (Kim and Narayanan, 2018). Similarly, we found that stimulation of cerebellothalamic

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afferents at 2 Hz could compensate for timing deficits caused by disrupting medial prefrontal D1DRs (Parker et al., 2017). Finally, we found that stimulating corticostriatal projections at 20 Hz could compensate for medial prefrontal inactivation during interval timing (Emmons et al., 2019). These data suggest that specific prefrontal stimulation has the potential to compensate for dysfunctional prefrontal circuits.

These studies also raise the possibility that brain stimulation can improve temporal control of action in human diseases. Fortuitously, clinical deep-brain stimulation targeting the subthalamic nucleus can modulate medial prefrontal networks, possibly via backfiring monosynaptic 'hyperdirect' projections (Chen et al., 2020; Narayanan et al., 2020). Subthalamic and prefrontal neurons can have coherence at 4 Hz (Herz et al., 2016; Zavala et al., 2016). Low-frequency clinical deep-brain stimulation of the subthalamic nucleus is able to modulate interval-timing (Wojtecki et al., 2011). We found – to our surprise – that 4 Hz subthalamic brain stimulation increased midfrontal cognitive control signals and improved temporal control of action in Parkinson's disease patients (Kelley et al., 2018). This finding was supported by data showing that 5 Hz subthalamic nucleus stimulation could also improve conflict tasks (Scangos et al., 2018). This line of work is exciting because it suggests that targeted prefrontal brain stimulation has the potential to improve temporal control of action in human brain diseases, which may point the way for future neuromodulation strategies targeted at cognition.

Conclusion

In summary, we have reviewed the medial prefrontal neurophysiology in the temporal control of action. Much of this data comes from two paradigms: simple-reaction time tasks and interval timing, which can be markedly abnormal in human diseases such as Parkinson's disease, schizophrenia, and ADHD. Lesion evidence in humans and rodents implicates medial prefrontal regions as well as dopaminergic and cholinergic neurotransmission in temporal control of action. Medial prefrontal recordings consistently report 'ramping' patterns of activity in anticipation of temporally controlled movements and ~4 Hz activity in response to imperative stimuli. Low-frequency stimulation can improve temporal control in rodent models of human disease as well as in Parkinson's disease patients. Together, these studies illuminate how medial prefrontal regions orchestrate behavior in time, which could inspire novel neuromodulation therapies for human diseases.

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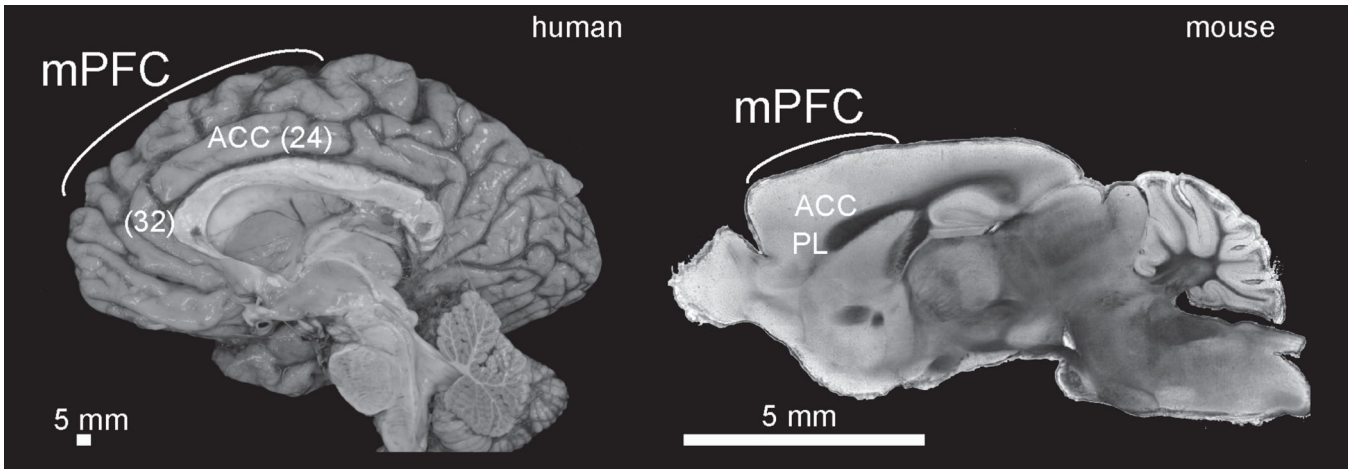

Figure 1: Medial prefrontal cortex in humans and rodents:
Sagittal brain section of the medial prefrontal cortex from humans and brightfield microscopy from the mouse. mPFC –medial prefrontal cortex; ACC –anterior cingulate; PL –prelimbic. Brodmann areas in parentheses. Human gross anatomy courtesy of Marco Hefti and the Iowa Brain Bank.

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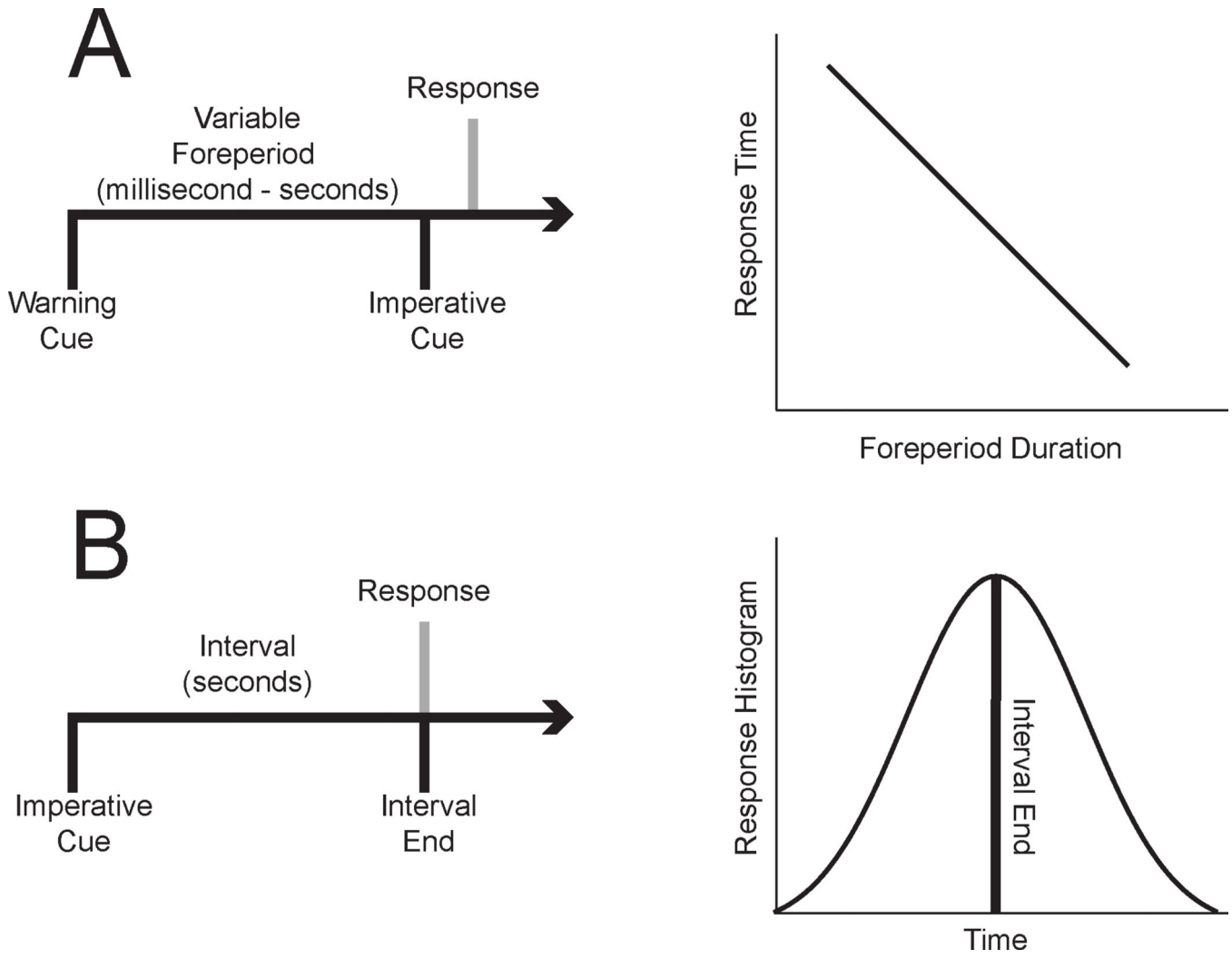

Figure 2: Paradigms to study temporal control of action:

Temporal control of action can be studied using two paradigms. A) The simple reaction-time task requires participants to respond as fast as possible to an imperative cue. A warning cue is typically delivered at a variable interval prior to the imperative cue; the time between the warning and imperative cue is called ‘foreperiod’ or ‘delay’. Participants’ reaction-times are higher for short foreperiods compared to long foreperiods, when they are fully prepared to respond. This phenomenon is called the ‘foreperiod-effect’ or ‘delay-dependent speeding’. Another paradigm is B) interval-timing, which requires participants to estimate an interval of several seconds by making a motor response. In this task, the imperative cue indicates the start of the interval. The timing of responses is typically distributed around the end of the interval.

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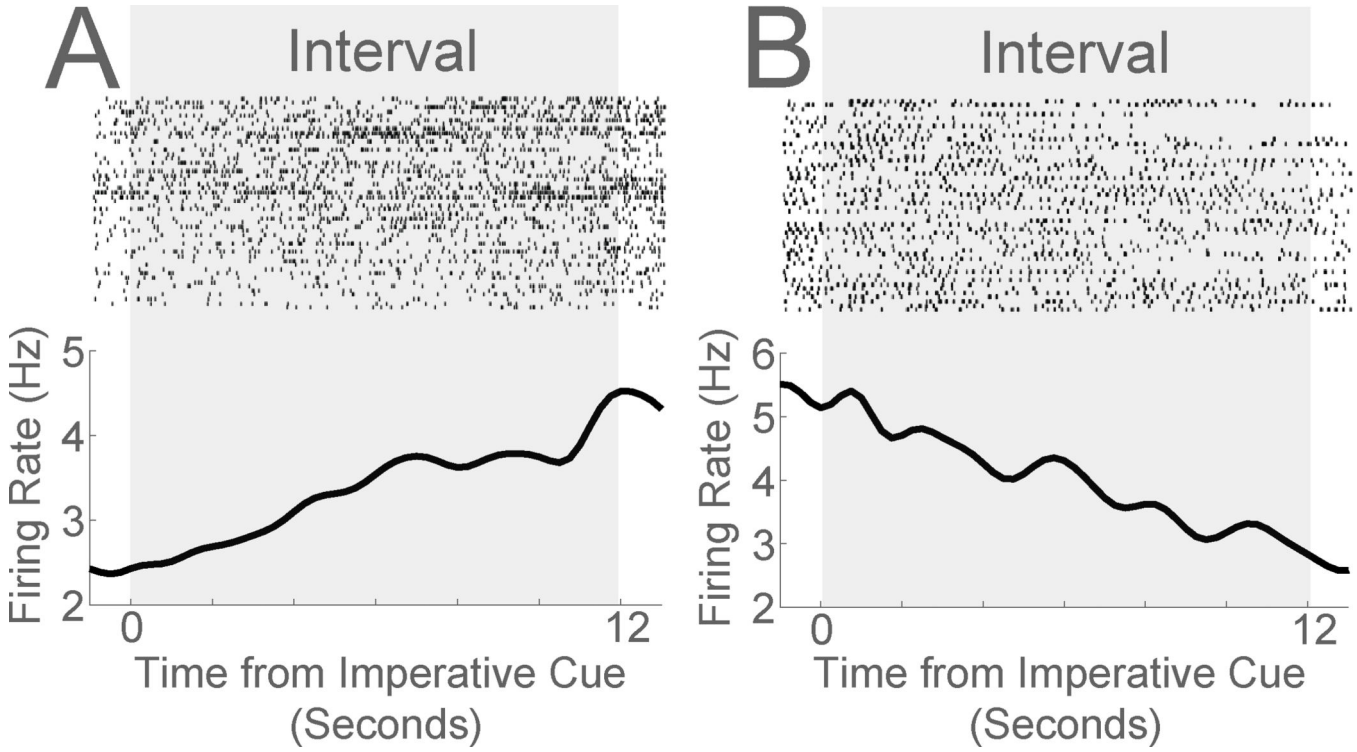

Figure 3: Ramping neurons in medial prefrontal cortex during a 12-second fixed-interval timing task.

Peri-event rasters of mouse medial prefrontal single neurons during a 12-second fixed-interval timing task. Ramping neurons can exhibit A) monotonic increases or B) monotonic decreases in firing over the fixed interval. Data from recordings described in Zhang et al., 2019.