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The Medial Premotor Cortex as a Bridge from Internal Timekeeping to Action

Robert W. Nickl

Department of Biomedical Engineering, Johns Hopkins University, Baltimore, Maryland 21218
Review of Merchant and Averbeck

Animals have a remarkable ability to keep time both with and without cues, as humans know from experience. Whether for dancing, making music in a group, playing sports, or speaking with another, we often seamlessly detect environmental cues, cognitively analyze them, and coordinate our behavior to their temporal structure. Absent external cues, we can still perform these activities with high enough timing accuracy to be useful for skill development.

A classic paradigm for studying timekeeping in motor control is the sensorimotor synchronization task, where the objective is to perform some action (such as tapping a surface) in time with an external signal (typically light or sound) (Repp, 2005). A synchronization-continuation task (SCT) (Wing, 2002; Merchant et al., 2011) requires one to pace actions initially to a constant metronome (synchronization phase), and then maintain this pacing after the cue is extinguished (continuation phase). In the language of control theory, the SCT tests one's ability to reach a temporal operating point under feedback, and to maintain stability in open loop. Useful models of mental timekeeping must account not only for the

ability of humans and other animals to synchronize their actions to various rhythms, but also for the scalar property: a tendency, widely observed across the animal kingdom, for response time variability to increase with interstimulus duration (Gibbon, 1977).

Computationally, mental timekeeping may be analogous to running a stopwatch. It likely involves enumerating events (such as neural spikes) in a manner that can be started, stopped, or reset with respect to a criterion or reference stored in memory (Gibbon et al., 1984; Schöner, 2002). The neural basis has been difficult to pinpoint, however, partly because timekeeping in the brain is diverse and widespread. Previous fMRI studies show that sensory and motor cortices are constantly engaged in both synchronization and continuation phases of the SCT, with additional recruitment of the supplementary motor area (SMA), cerebellum, and midbrain during continuation (Rao et al., 1997). The SMA may indeed be a key nexus between motor planning and execution stages (Wing, 2002).

The medial premotor cortex (MPC), encompassing the SMA and pre-SMA (Merchant et al., 2013), is the focus of a recent study of neural time coding and its behavioral correlates (Merchant and Averbeck, 2017). During experiments, macaques ($n = 2$) performed an SCT, which required pressing a button 4 times in synchrony with an audio or visual cue,

followed by 3 times in open loop. Within a given trial, cue intervals were uniformly 450, 550, 650, 850, or 1000 ms. During each interval condition, MPC multiunit activity was recorded.

Merchant and Averbeck (2017) hypothesized that MPC contains a timing mechanism comprising excitatory and inhibitory neuron pools that compete as an opponent Poisson process (Simen et al., 2011). If excitatory neurons preponderate, the population dynamics would result in a net firing rate that increases over time and can be modeled as a drift-diffusion process. Firing rate variance would increase linearly over time, obeying the scalar property. The existence of MPC neurons satisfying these properties would provide evidence both for SMA and pre-SMA as sites of a behavioral clock, and for a particular mental timekeeping mechanism based on recurrent networks. Behaviorally, tap times coincided with a drift-diffusion model reproducing the scalar property (Merchant and Averbeck, 2017, their Fig. 1). Response times for each interval condition were qualitatively inverse-Gaussian distributed (Merchant and Averbeck, 2017, their Fig. 4A), also as expected from a drift-diffusion model.

MPC multiunit activity was analyzed by calculating neuronal firing rates relative to tap onsets. For each trial, the authors first subdivided intervals between taps into 50 ms bins, and then averaged firing rates in each bin. This resulted in

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Correspondence should be addressed to Robert W. Nickl, Johns Hopkins University, 137 Hackerman Hall, 3400 N. Charles Street, Baltimore, MD 21218. E-mail: rnickl@jhu.edu.

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estimates of firing rate trajectories between consecutive taps. For each condition, a mapping between firing rates and internal time representation was inferred by comparing firing rates in each trial to the average firing rate trajectory across the remaining trials (Merchant and Averbeck, 2017, their Fig. 3).

Merchant and Averbeck (2017) uncovered a subpopulation of neurons that fired at rates that were linearly mapped to the time elapsed since a tapping cue. Linear coding was observed across multiple sessions and over all intervals in a trial, although it tended to be slightly less commonly found during the continuation phase, when explicit cues were absent (Merchant and Averbeck, 2017, their Fig. 6A). That this linear coding was prominent, even after explicit timing cues were switched off, raises the interesting possibility that MPC rate coding may track elapsed time relative to a working memory representation of a metronome. Distributions of decoded times tended to center around actual elapsed times relative to cues (Merchant and Averbeck, 2017, their Fig. 7B,C) and were approximately Gaussian near interval midpoints.

Interestingly, in bins just after an interval began, a group of neurons was observed to code for the total interval duration (Merchant and Averbeck, 2017, their 7B,D–H). The authors hypothesized that, if the linearly coding neurons represented an internal “clock,” this later secondary mode indicated a lingering time accumulation that could result in sluggish resetting of the clock. Accordingly, they demonstrated that, when this later mode manifested, the monkeys tended to tap later than if no secondary modes existed (Merchant and Averbeck, 2017, their Fig. 7J). Similarly, at the end of 1000 ms intervals, a group of neurons coding for short intervals emerged, presumably indicating early reset of the internal clock. In these trials, taps were generally premature. This phenomenon might explain a tendency for the monkeys’ continuation phase tapping to be slightly anticipative on average (Merchant and Averbeck, 2017, their Fig. 1B). A general linear trend was found between decoded and behavioral time for both synchronization (Merchant and Averbeck, 2017, their Fig. 8A) and continuation phases (Merchant and Averbeck, 2017, their Fig. 8B), and was a robust finding across conditions (Merchant and Averbeck, 2017, their Fig. 8C–F).

Collectively, the above evidence suggests that rate-coding neurons in MPC are linked to internal representation of predictable

motor timings. As a control to assess their role amid unpredictable events, the monkeys performed a paced tapping task where cued intervals were random. In this case, when it is more advantageous to tap in closed loop instead of internalizing a rhythm, MPC neurons were relatively insensitive to elapsed time (Merchant and Averbeck, 2017, their Fig. 10A).

Merchant and Averbeck (2017) provide evidence that SMA and pre-SMA may be sites of neural accumulator circuitry, which stores an internal representation of event timing that strongly correlates with behavioral timing. Accumulators, prevalent in the decision-making literature (see e.g., Hanes and Schall, 1996), are intuitively appealing, as they allow us to interpret action initiation as a decision process predicated on the passage of time relative to an event. Remarkably, the rate-coding cells reported in Merchant and Averbeck (2017) not only track the progression of real-world time but also provide a physiological explanation for accurate and misjudged action timing.

Decision-making models beg the question of how the brain implements accumulator thresholds. One possibility is that they are implemented within MPC. Notably, Mita et al. (2009) observed in a go/no-go task that a family of neurons coding for stimulus duration (superficially similar to absolute timing cells in Merchant et al., 2011) was active until button release, suggesting a possible action inhibition mechanism. Another possibility is that thresholds are the product of interactions between the SMA, the basal ganglia, and the prefrontal cortex (Durstewitz and Seamans, 2002). The striatum in particular is associated with action selection and may communicate dopaminergically with the prefrontal cortex to implement a relevant timing threshold in working memory (see, e.g., Striatal Beat Frequency model in Meck et al., 2008).

Another open question is how MPC timing is transmitted to other areas of the brain to generate action. The cerebellum and basal ganglia are critical to proper action timing, as supported by evidence of timing impairments in both patients and healthy participants of virtual lesion studies (O’Boyle et al., 1996; Del Olmo et al., 2007). Merchant and Averbeck (2017) add to an emerging body of knowledge about timekeeping at a cellular level. The existence of duration-tuned neurons in parietal cortex (Leon and Shadlen, 2003), midbrain (Aubie et al., 2014), basal ganglia, and the frontal lobe (Bakhurin et al., 2017) indicates that these regions may be

involved in the translation of timing features to a decision threshold. Recent discoveries of ramping neurons in SMA (Merchant and Averbeck, 2017) and the cerebellum (Ashmore and Sommer, 2013) that explicitly code for elapsed time suggest that MPC may be a station where temporal stimulus features are first translated into a rate code used more directly in motor execution.

The findings of Merchant and Averbeck (2017) show a compelling convergence between motor timing and physiological evidence predicted by a theoretical model (Simen et al., 2011). The involvement of the premotor cortex in other continuous rhythmic behaviors (Schaal et al., 2004) suggests that this timing mechanism may not be restricted to repetitive tapping, and its generalizability to additional behaviors and timescales remains an open but intriguing question.

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