Journal Club

Onset Matters: How Collicular Activity Relates to Saccade Initiation during Cortical Cooling

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Review of Peel et al.

We interact with the world through actions. Initiating these actions at the correct moment is crucial for survival. Imagine a cheetah hunting a gazelle. Although cheetahs are the fastest sprinters, they can be outrun by gazelles over longer distances. Therefore, initiating the chase at the appropriate moment is paramount in this life-or-death struggle. As in this example, deciding when to act is a critical part of adaptive behaviors, linking decision commitment with subsequent reward or punishment.

How the brain integrates external stimuli and internal states to commit to an action is a fundamental question in neuroscience. It has been extensively investigated in the primate oculomotor system, especially in the context of ballistic eye movements (saccades). Neural activity involved in saccade initiation has been identified in two interconnected brain areas: the frontal eye fields (FEFs) and the midbrain

superior colliculus (SC; Gandhi and Katnani, 2011). According to stochastic accumulator models, when subjects are preparing for a saccade, neural spiking in these areas ramps up from baseline to a certain threshold, at which point the saccade is triggered (Hanes and Schall, 1996).

Based on traditional stochastic accumulator models, saccade reaction time is determined by the following three parameters: baseline activity, ramp rate, and a fixed threshold (Fig. 1A). However, these model parameters failed to explain reaction time in several recent studies. For example, recordings in SC and FEFs showed evidence of a variable threshold (Jantz et al., 2013) and argued against a simple relationship between threshold and reaction time, as predicted by the model (Heitz and Schall, 2012). Instead, other parameters, such as the onset time of ramping activity, were suggested to be important factors for saccade initiation (Pouget et al., 2011).

Although simply recording from neurons while an animal performs saccades provides critical constraints for mechanistic models, it is hard to resolve the discrepancies between classic studies and recent evidence using only correlative observations. To directly probe the biological plausibility of saccade initiation models, perturbation of the underlying circuit is required. In a recent article

in *The Journal of Neuroscience*, Peel et al. (2017) set out to investigate which parameters of SC activity could account for behavioral changes during FEF inactivation.

The authors trained monkeys to perform visually and memory-guided saccade tasks and recorded SC activity before, during, and after cryogenic cooling of unilateral FEF neurons. They found that FEF inactivation significantly increased the reaction time of monkeys (Peel et al., 2017, their Fig. 1), and decreased visual, delay, and saccade-related activity in the ipsilesional SC (Peel et al., 2017, their Fig. 5). This general reduction of SC activity during FEF cooling confirmed that FEF provides an excitatory drive to SC, as described by previous physiological recordings with antidromic stimulation (Sommer and Wurtz, 2000).

Concomitant changes in SC activity and the behavior of animals during FEF cooling provided an opportunity to directly probe neural mechanisms of saccade initiation. However, these analyses require careful controls for motor confounds. For example, because motor-related activities in the SC are tightly linked with saccade metrics and kinematics, changes in saccade-related activity may simply reflect altered saccade vector or peak velocity during cooling. To control for this, the authors focused their analyses only on pairs
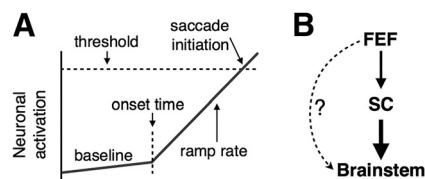
Figure 1. Saccade initiation model and circuitry. **A**, Schematic of a stochastic accumulator model of saccade initiation and model parameters. **B**, Hypothesized FEF–SC circuit diagram during saccade generation.

of saccades (one from FEF cool condition and one from FEF warm condition) with similar metrics and kinematics for each SC neuron (Peel et al., 2017, their Figs. 1 E and F). These strict saccade-matching criteria provide a critical foundation for subsequent analyses that investigated which aspects of SC activity change accounted for the reaction time changes beyond motor confounds.

Parameters such as baseline activity, ramp onset time, ramp rate, and threshold activity were extracted from SC dynamics to associate with saccade reaction time within the framework of stochastic accumulator models. Although all parameters were altered during FEF cooling, only the delay in onset of ramping activity was significantly correlated with increased reaction times (Peel et al., 2017, their Figs. 6, 7). Even combining baseline, ramp rate, and threshold into a "time-to-threshold" term, without incorporating the onset parameter, yielded a poor prediction of reaction time (Peel et al., 2017, their Fig. 8 B). Conversely, the importance of ramp onset time remained after subtracting the effects of all other parameters (Peel et al., 2017, their Fig. 8 C). These results went beyond previous correlative observations that relate onset time to saccade initiation (Woodman et al., 2008; Pouget et al., 2011), and demonstrated that manipulation of ramp onset time was indeed accompanied by corresponding changes in reaction time.

After establishing the role of SC ramp onset in saccade initiation during FEF cooling, Peel et al. (2017) tested whether this was a general principle that extended to the FEF intact condition. They found that the strong correlation between SC ramp onset and reaction time persisted regardless of FEF functioning (Peel et al., 2017, their Fig. 8). These data provide important insights regarding the neural circuitry of saccade initiation. Because FEF projects to the brainstem saccade burst generator both directly and indirectly through the SC (Huerta et al., 1986), either or both pathways might participate

in determining reaction time (Fig. 1B). However, their findings suggest that reaction time is ultimately governed by the SC–brainstem pathway, consistent with previous accounts suggesting that the FEF–brainstem pathway that bypasses the SC plays only a limited role in saccade generation (Hanes and Wurtz, 2001). It should be noted, however, that cortical inputs still make significant contributions by modulating SC activity, hence influencing when the onset of ramping activity ultimately occurs.

Combining challenging perturbation methods with model-based examination of neural activity, Peel et al. (2017) argued against traditional stochastic accumulator models in which increased reaction time results solely from decreased ramp rate or increased threshold level. Instead, the authors revealed the pivotal role of the onset time of saccade-related activity in the SC for determining reaction time. These results demand an expanded model of saccade initiation in which activity onset is incorporated as an important parameter.

Why is the onset time of saccade-related activity essential for predicting reaction time? It is possible that there is a fixed, programmed delay between the onset of ramping activity and saccade commitment. If this were the case, the strong correlation between ramp onset and reaction time would simply be an epiphenomenon due to the unstoppable nature of motor bursts once they start. However, physiological recordings in the SC during the countermanding task argued against this interpretation (Paré and Hanes, 2003). In this behavior, animals were trained to either saccade toward a visual target or cancel the planned movement if a stop signal appeared. Responses of SC neurons in these aborted trials also showed the initial rise of saccade-related activity. Yet, this initial rise did not automatically trigger a saccade and could be suppressed later on to withhold an unwanted action. Therefore, the activity rise onset is not an obligatory representation of saccade commitment, but maintains an independent role in governing reaction time.

Despite the significance of the study by Peel et al. (2017), readers should avoid overgeneralizing the onset of ramping activity as the main determinant for reaction time under all situations. Different behavioral contexts, brain areas, and motor effectors could involve distinct mechanisms of action initiation. For example, in a perceptual decision-making task where decision formation and motor preparation

may occur simultaneously, other parameters such as the rate of accumulation in parietal cortex (Roitman and Shadlen, 2002) or baseline activity in the striatum (Ding and Gold, 2012) likely play a major role in governing reaction time.

It is also worth noting that saccades are ballistic relative to other motor systems, such as orienting or reaching, whose control can be adjusted on the fly. In the monkey hand reach paradigm, movement commitment has been shown to rely on the population readout in motor cortex rather than on the heterogeneous responses of single neurons (Kaufman et al., 2014). Whether the collicular mechanisms of saccade generation provide a general framework for understanding action initiation across different motor effectors remains to be tested.

Finally, FEFs and SC are densely interconnected with other cortical regions, multiple thalamic nuclei, and the basal ganglia. Therefore, similar work that characterizes the contributions of these circuit components and their interaction with the SC during pathway-specific cortical perturbation will be required to fully understand the effect of FEF inactivation on SC activity and its relationship with saccade initiation. Nevertheless, the endeavor undertaken by Peel et al. (2017) emphasizes the importance of testing commonly accepted models against biological data. Such detailed investigations of neural circuit mechanisms help to constrain theoretical intuitions and inspire more biologically plausible models.

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