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COMMENTARY
Cerebellar output encodes a corrective saccadic command (Commentary on Sun *et al.*)

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The integrity of the cerebellum is critical for accurate eye movements. Disruption of neurons in either the cerebellar oculomotor vermis or its projections to the most medial output nucleus of the cerebellum, the caudal fastigial nucleus (cFN), results in significant saccadic dysmetria (Ritchie, 1976; Ohtsuka *et al.*, 1994; Goffart *et al.*, 2004; Buzunov *et al.*, 2013). The relationship between cFN neuron firing rates and saccade kinematic parameters is quite variable across neurons (Hepp *et al.*, 1982; Fuchs *et al.*, 1993), suggesting that a direct encoding of saccade parameters may not occur in the responses of individual neurons of cFN. However, previous studies have generally agreed that saccade-related cFN neurons tend to fire earlier for horizontal saccades made in the contraversive vs. ipsiversive directions (Ohtsuka & Noda, 1991; Fuchs *et al.*, 1993; Helmchen & Büttner, 1995; Kleine *et al.*, 2003).

Taken together, these results have led to the hypothesis that saccade properties are related to the timing of responses in cFN rather than response magnitude. Under this hypothesis, neurons should fire early for contraversive saccades, helping to accelerate the eye, whereas the delayed firing of ipsiversive neurons serves to decelerate and stop the eye at saccade termination. However, new data reported by Sun *et al.* (2016) call this view into question.

Sun and colleagues recorded single-unit cFN neuron activity while primates made saccades of various magnitudes. These saccades included very small saccades, made during periods of fixation (microsaccades), as well as larger magnitude goal-directed saccades to peripheral targets. Their results suggest that cFN neuron responses exist on a continuum between these two types of saccades. That is, micro- and macro-saccades likely share common neural mechanisms of generation. Therefore, the responses of cFN neurons can be interpreted similarly across a large range of saccadic amplitudes (e.g. 0.5–15°).

The duration of a typical saccade is on the order of 60 ms. Taking advantage of the temporally short nature of saccades, Sun *et al.* combined the responses of individual cFN neurons recorded across different sessions to yield an estimate of the firing of a population of simultaneously recorded neurons. This population response represents an estimate of the combined response of all saccade-related cFN neurons during a saccade. Strikingly, the timing of the population response did not occur earlier for contraversive compared to ipsiversive saccades, as would be anticipated by previous single-unit studies. Rather, both directions of saccades resulted in a population response that preceded the start of the saccade, and began at approximately the same time. How can these two deep nuclei be involved in saccade acceleration and deceleration when the timing of the responses to contraversive and ipsiversive saccades are not different?

We recently suggested that populations of Purkinje cells (P-cells) in the oculomotor vermis (OMV) of the cerebellum encode the velocity and direction of an impending eye movement as a gain-field (Herzfeld *et al.*, 2015). In this encoding, the population response of P-cells in OMV increases linearly with increasing eye velocity, whereas the direction is encoded as a cosine in which the population response is smallest for the direction of error that produces the highest probability of complex spikes (called CS-on), and highest for the direction of error that produces the lowest probability of complex spikes (CS-off). Given that inferior olive neurons project to the contralateral P-cells, P-cell simple spike encoding has the highest gain for contraversive saccades, and lowest gain for ipsiversive saccades. These P-cells inhibit neurons in cFN. Data from Sun et al. are consistent with this P-cell encoding, demonstrating that the cFN population response is larger for ipsiversive saccades than contraversive, a property which is not reliably found in the responses of individual cells. Combining this new experimental evidence with previous studies, it seems likely that the encoding of saccade kinematic parameters in cFN is not temporal in nature but rather results from differences in the magnitude of the overall cFN response.

How can we interpret the results of previous studies in this framework? Goffart *et al.* (2004) have previously suggested that cFN inactivation and lesion studies could be understood by interpreting experimental results in the context of the bilaterality of cFN. Under this encoding scheme, cFN activity does not strictly encode acceleration and deceleration, but rather the two nuclei act as antagonists, in which one cFN can be thought of as 'pushing' the eye while the other cFN 'pulls.' In this framework, equal activity in the two nuclei does not result in horizontal movement of the eye – cerebellar-dependent movement results only when the magnitude of the responses in the two nuclei are different. In this way, the output of the cerebellum is defined by the difference in the activities of the two cFNs, providing a 'correction' on top of the current movement (Fuchs *et al.*, 1993).

The population-level analysis presented by Sun *et al.* further clarifies this hypothesis. During a saccade, both sides of OMV are simultaneously active with a higher gain on the contralateral side (Herzfeld *et al.*, 2015). This, in turn, results in the opposite scenario for the fastigial nuclei: higher firing rates for the ipsilateral vs. contralateral sides, without any differences in the timing of the response. Projections from cFN synapse throughout the brainstem saccadic circuitry, particularly on inhibitory and excitatory burst neurons, eventually acting on the motor

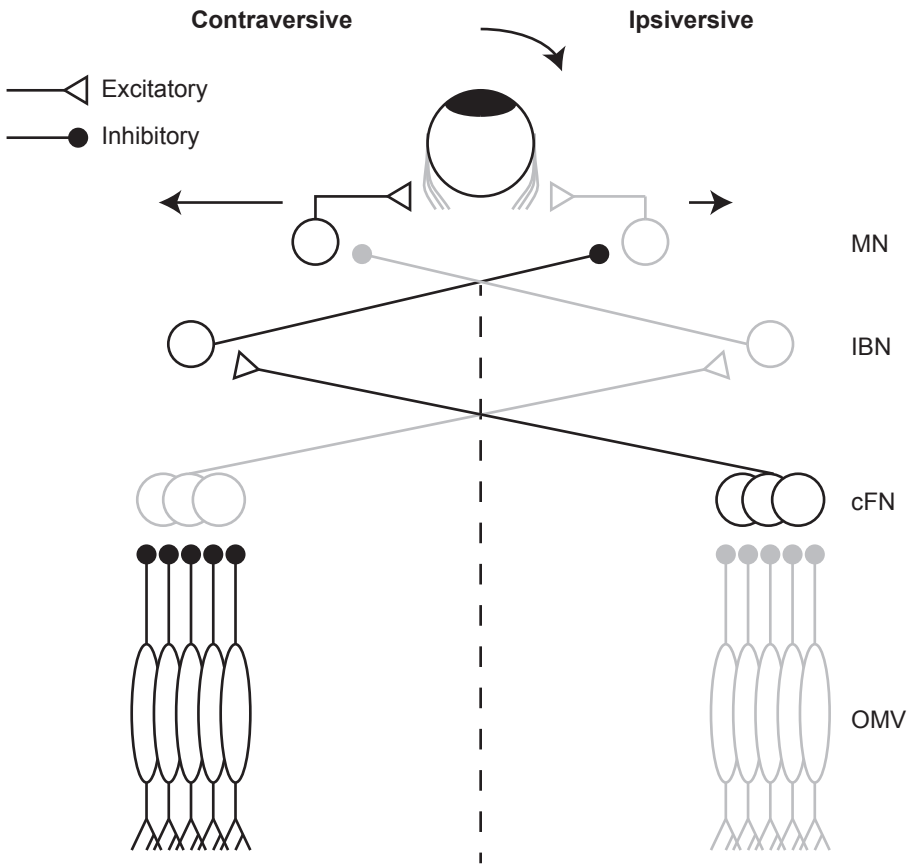

FIG. 1. Simplified schematic of the cerebellar oculomotor circuitry. A rightwards saccade results in simultaneous activity in both sides of the oculomotor vermis (OMV). However, population activity on the contralateral side (left) is larger (black) than on the ipsilateral side (gray) (Herzfeld *et al.*, 2015). Purkinje cells in OMV send inhibitory projections to the caudal fastigial nucleus (cFN), where the population response characteristics are opposite those of OMV: the response on the ipsilateral side is larger than the contralateral response (Sun *et al.*, 2016). These neurons project to brainstem neurons, especially inhibitory burst neurons (IBNs), which, in turn, synapse on motor neurons (MNs). Under this hypothesized activation scheme, the net cerebellar contribution to a rightwards saccade is a slight pull to the left, essential providing 'braking' of the saccade.

neurons that drive movement of the eye (simplified schematic in Fig. 1). During an ipsiversive saccade, the net cerebellar contribution to the motor neurons is a 'pull' toward the contraversive side, essentially applying a brake to the motion of the eyes. Unilateral lesion experiments can be understood as simply changing the balance of cerebellar pushing and pulling on the eye.

While the timing hypothesis is attractive due to its inherent simplicity, it is particularly difficult to understand how the inputs to cFN neurons result in the differences in timing of saccadic bursts since Purkinje cell projections to cFN do not appear to have differently timed responses as a function of direction (Herzfeld *et al.*, 2015). While some studies have invoked hyperpolarizing rebound to explain potential differences in the timing of responses in cFN (Gad & Anastasio, 2010) the data of Sun and colleagues provide a more parsimonious explanation: individual neurons may show a difference in the timing of their responses, but across a large population of neurons these timing results disappear. Rather, it is the magnitude of the population response that differs across directions.

Timing differences in the peak of the discharge in cFN have been most clearly observed in large magnitude or long duration eye movements (such as those in head-free saccades) (Fuchs *et al.*, 2010). Therefore, an important caveat is that the current study's results provide a compelling view of a specific class of movements: small- and medium-sized saccades.

There are several lessons which we can glean from recent cerebellar studies of saccades. First, the results highlight the benefits of performing population-based analyses, either via simultaneous recordings or by leveraging the short temporal duration of movements such as saccades. Second, at least part of the output of the cerebellum represents a motor correction which is added to the ongoing motor commands. This correction is likely sculpted through error-based learning in the internal machinery of the cerebellum.

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