**The neural coding of action in the Purkinje cells of the cerebellum**

David J. Herzfeld[1], Yoshiko Kojima[2], Robijanto Soetedjo[2], and Reza Shadmehr[1]
[1]Dept of Biomedical Eng., Johns Hopkins Univ., [2]Wash. Natl. Primate Center, Dept. of Physiology and Biophysics, Univ. of Washington

Execution of accurate eye movements depends critically on the cerebellum, as evidenced by the deficits observed in lesion studies[1]. These observations have suggested that Purkinje cell (P-cell) discharge should predict the state of the eye (e.g., velocity or direction) during a saccade. Yet, this encoding has remained a long-standing puzzle: although inactivation of the oculomotor vermis (OMV) affects saccade execution[2,3], P-cell firing shows no obvious modulation with respect to saccade velocity[4] or direction[5]. How can the P-cells be involved in predicting or controlling the eye if their discharge is poorly correlated with changes in this state?

We analyzed simple spike activity of 72 OMV P-cells from 5 monkeys during saccadic eye movements. This population included neurons that increased activity during the saccade (bursting), as well as cells that decreased their activity (pausing). Mean firing rates of the neurons during the saccade period showed little or no modulation with saccade amplitude (Fig. 1a). This lack of modulation was in sharp contrast to the fact that changes in saccade amplitude coincided with changes in the state of the eye (e.g., velocity, Fig. 1b). In addition, the durations of activity in both neural populations were significantly longer than the saccade (Fig. 1c). Therefore, neither the mean firing rates of P-cells, nor their time course, appeared to encode state of the eye.

P-cells in OMV project to the caudal fastigial nucleus (cFN), where about 50 P-cells converge onto a single cFN cell. We computed what a typical cFN cell would receive from OMV by randomly selecting 50 P-cells, regardless of laterality, and then estimating the resulting inhibitory post-synaptic current (IPSC) at cFN. The result unmasked a remarkable feature: the time course of the post-synaptic current precisely predicted the time course of the saccade (Fig. 2). Therefore, whereas mean P-cell discharge was not modulated by state of the eye, the population induced inhibition at the cFN seemed to predict this state.

The state of the eye includes both speed and direction. How are these variables encoded in the activity of P-cells? A typical approach is to examine the saccade direction for a cell which shows the largest mean discharge. However, saccade direction is a poor modulator of P-cell activity[6]. Therefore, we took a different approach: we systematically induced post-saccadic error by displacing the target during the saccade, and then measured the probability of complex spikes (CS) as a function of direction of this error. For each P-cell the direction of error that produced that largest probability of CS in the post-saccade period was labeled as CS-on, and CS-on+180° was labeled as CS-off. Application of this coordinate system to each P-cell unmasked a critical new feature of the resulting IPSC. Fig. 3 shows the IPSC induced when a saccade is made in the CS-off direction, as a function of saccade peak velocity. Peak IPSC and velocity are correlated with $R^2 = 0.95$, demonstrating that the variability in the peak IPSC almost entirely predicted the variability in peak eye velocity.

How is direction of the saccade encoded? We found that the peak current was greater if the saccade was in the CS-off direction as compared to the CS-on direction (Fig. 4a). Indeed, the peak current rose linearly as a function of peak velocity in both directions, but with a larger gain for the CS-off direction (Fig. 4b). Therefore, the peak IPSC induced at cFN, but not the individual P-cell activity, exhibited gain-field encoding.

Our model predicts that the encoding of saccade kinematics occurs only if there is a specific organization in the cerebellum: a typical cFN neuron cannot receive random projections from P-cells, but rather inputs from an approximately equal number of pause and burst P-cells, all with the critical feature of similar CS-off directions. We tested our model by examining the effects of lesion. We created populations of P-cells with CS-off directions placed uniformly throughout the direction space, and connected cells with similar CS-off to single cFN neurons, and then applied a virtual lesion to cFN. The results (Fig. 5) correctly predicted that unilateral lesion would produce ipsilateral hypermetria and contralateral hypometria.

In summary, our results suggest two new principles of cerebellar function: 1) transformation of efference copy into a prediction of kinematic state does not occur in mean P-cells activity, but via combined activity onto the nucleus, producing an inhibition that precisely predicts state of the eye as a gain field combination of direction and speed. 2) The anatomical projections from P-cells to cFN neurons are not random, but are likely organized by CS properties of the P-cells: a cFN neuron receives input from only those P-cells that have similar CS fields. This second principle predicts that the specific P-cells that project to a cFN neuron are largely selected due to the influence of the inferior olive.

1 Leigh, R. J. & Zee, D. S. *The neurology of eye movements*, (2006).
2 Kojima, Y., Soetedjo, R. & Fuchs, A. F. *Brain Res* **1366**, 93-100 (2010).
3 Kojima, Y., Soetedjo, R. & Fuchs, A. F. *Brain Res* **1401**, 30-39 (2011).
4 Helmchen, C. & Buttner, U. *Exp Brain Res* **103**, 198-208 (1995).
5 Thier, P., Dicke, P. W., Haas, R. & Barash, S. *Nature* **405**, 72-76 (2000).
6 Soetedjo, R. & Fuchs, A. F. *J Neurosci* **26**, 7741-7755 (2006).

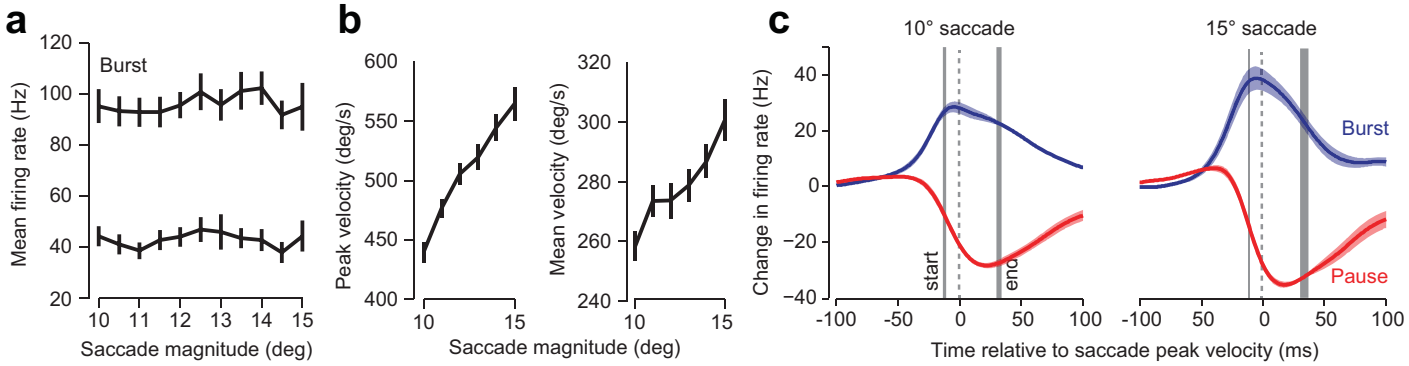


**Fig. 1. Neuron firing rates are unrelated to saccade kinematics.** We record from n=72 cells in OMV. **a.** Mean firing rate, computed over the duration of the saccade, for the bursting and pausing populations in the direction of maximal firing. **b.** While the mean neural activity did not change, there was a large increase in the eye peak and mean velocities for the same saccade magnitudes. **c.** Bursting and pausing neuron firing rates for 10° and 15° saccades. Activity of the two populations significantly exceeded the duration of the saccade (vertical grey bars). Error bars denote mean±SEM across neural recordings.

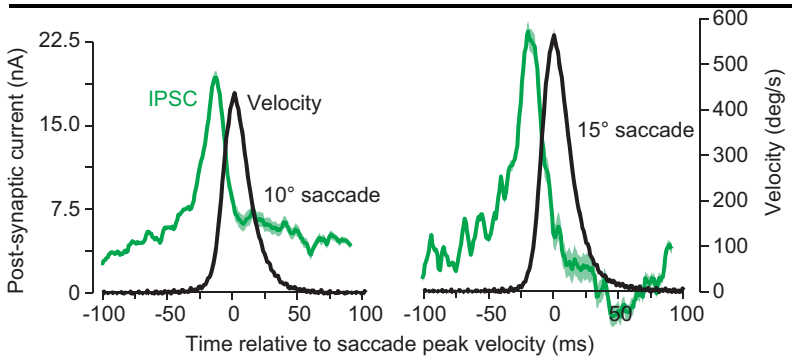


**Fig. 2. IPSCs encode saccade kinematics.** Saccade velocity (black) and IPSCs (green) for 10° and 15° saccades. IPSC time course matches the velocity timeseries characteristics. However, the IPSC is shifted forward in time by 9.1±1.3ms relative to saccade peak velocity, suggesting that the IPSC predicts state of the eye. The IPSC increased in magnitude when peak velocity increased and critically, the current returned to baseline before saccade termination. Error bars denote mean±SEM across 50 bootstrapped cFN neurons.

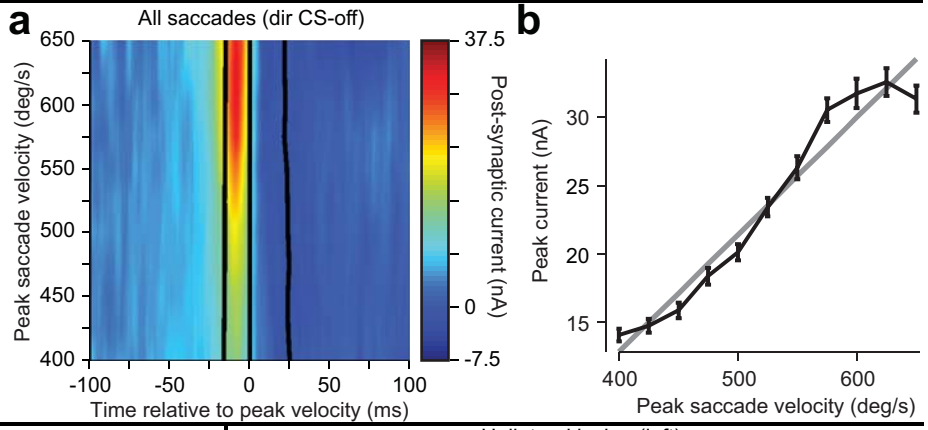


**Fig. 3. IPSCs encode saccade velocity.** IPSC as a function of saccade peak-velocity in 25°/s bins. **a.** Data was aligned to saccade peak velocity. Vertical black bars represent saccade onset, peak velocity, and saccade offset, respectively. The IPSC begins at saccade onset, peaks prior to saccade peak velocity, and then returns to baseline activity. **b.** The peak current of the IPSC increases with increasing peak saccade velocity ($R^2$ = 0.95; $p < 10^{-6}$).

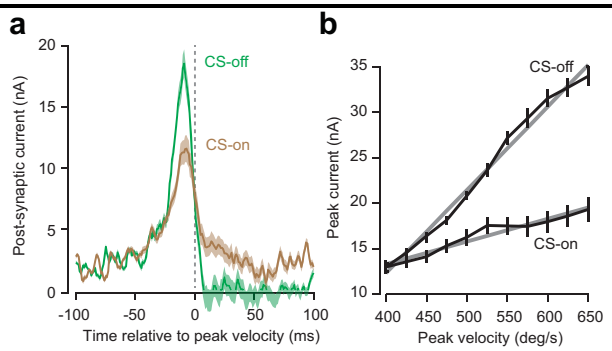


**Fig. 4. IPSCs encode saccade magnitude and direction as a gain-field. a**. IPSCs for 650°/s saccade in CS-off (green) and CS-on (brown), aligned to peak velocity. **b.** Peak current as a function of peak saccade velocity. Current induced at cFN for saccades in the CS-on direction increases with a smaller slope, suggesting a gain-field.

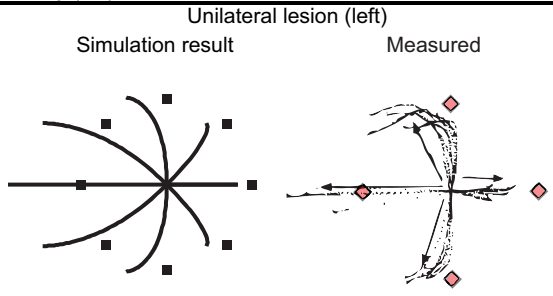


**Fig. 5. IPSCs predict effect of cerebellar lesions.** Predicted motor behavior for 10° saccades following unilateral (left-side) inactivation. Measured data (right) is modified from Robinson, et al. Role of the caudal fastigial nucleus in saccade generation. II. Effects of muscimol inactivation. J Neurophysiol (1993).