Error-dependent changes in cerebellar Purkinje cells during saccade adaptation

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When simple spikes of Purkinje cells (P-cells) are organized based on their complex-spike tuning, the resulting population response of simple spikes encodes motion of the eye during a saccade as a gain-field. This raises the possibility that the fundamental computational unit in the cerebellum is not a single P-cell, but a micro-cluster of P-cells that all share the same preference for error. Here we used this hypothesis to analyze P-cell activity during saccade adaptation. For each P-cell we quantified its preference for error by measuring tuning of complex spikes (CS) with respect to error. We then induced errors during saccades and recorded changes in discharge of the P-cells. We found that when a movement produced an error, two events took place simultaneously: for the micro-cluster that preferred that error, there was a reduction in the gain of the gain-field, but for the micro-cluster that had a low preference for that error, the gain of the gain-field increased.

We analyzed the spiking activity of 67 P-cells from the oculomotor vermis (OMV) during saccade adaptation[4,5]. Consistent with previous observations[3], simple spike rates of individual P-cells were poorly correlated with saccade kinematics, showing little or no modulation with saccade amplitude (Fig. 1a). In addition, the duration of individual neuron responses greatly exceeded the duration of the saccade[6] (Fig. 1b). 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 hypothesized that the micro-cluster of P-cells that project to an individual cFN neuron are not selected randomly, but rather share a common climbing fiber input, functionally expressed via CSs (Fig. 2).

The theory of cerebellar learning suggests that CSs signal errors. To test this hypothesis, we systematically induced post-saccadic error by displacing the target during the saccade, and then measured the probability of CSs as a function of error direction. All P-cells showed a robust encoding of the error direction following the saccade (Fig. 3a). For each P-cell the direction of error that produced the largest probability of CS in the post-saccadic period was labeled as 'CS-on', and CS-on+180° was labeled 'CS-off.' We found that the probability of CSs during the post-saccadic period was unrelated to direction of the preceding saccade, only to the direction of the error (Fig 3b). We also analyzed the probability of CSs following initial presentation of the target, before a saccade is made. During this period, the monkey experiences a foveal error from the current fixation location to the target, but no movement has been made. We found that P-cells encode foveal error during this pre-saccadic period with the same tuning properties as the post-saccadic error (Fig. 3c). That is, P-cell complex spikes consistently encode foveal error.

Using our hypothesized anatomy (Fig. 2), we organized our P-cells into micro-clusters wherein P-cells shared a common preference for error. We found that the combined SS activity of P-cells in this micro-cluster encoded saccade speed and direction as a gain-field[7] (Fig. 4a,b). Using this encoding of saccade kinematics, we can begin to address the question of adaptation.

Previous studies had reported that P-cell changes during saccade adaptation are heterogeneous, not revealing consistent changes with adaptation[8]. We took a different approach: we analyzed the micro-cluster activity over the course of gain-down adaptation rather than individual cells. We found a robust decrease in SS micro-cluster activity with decreasing saccadic gain (Fig 5a, R^2=0.83). Does this reduction in SS activity reflect adaptive changes in the cerebellum or alternatively correspond to the reduced eye velocity associated with gain-down adaptation (Fig. 5b, R^2=0.93)?

To address this question, we first asked whether the presence of an individual CS in the post-saccadic period affected behavior. Indeed, we found that whereas the absence of a CS on trial *n* resulted in a slight increase in saccade speed on the next trial, the presence of a CS in trial *n* resulted in a decrease in velocity on trial *n+1*, suggesting cerebellar CSs are directly responsible for adaptation (Fig. 6). Additionally, we analyzed the micro-cluster encoding of saccade speed at the beginning and end of adaptation. We found that when errors were in the CS-on direction, the encoding of saccade speed decreased over the adaptation period. However, when errors were in the CS-off direction, the population encoding of saccade speed increased, suggesting that the gain-field encoding of saccade kinematics changed over the course of adaptation (Fig. 7).

In summary, while adaptive changes in the SS response of P-cells may appear heterogeneous, P-cell changes are remarkably consistent when organized via their preference for error. That is, the anatomical projections from P-cells to cFN neurons are not random, but likely organized by the CS properties of the P-cells. Errors, signaled by CSs, result in plasticity within this micro-cluster, changing the encoding of saccade kinematics, producing behavioral adaptation. Taken together, our results further support the role of the cerebellum as a forward model, crucial for adaptation. During saccade adaptation, the goal of the movement remains the same, but through plasticity the cerebellum modifies its predictions.

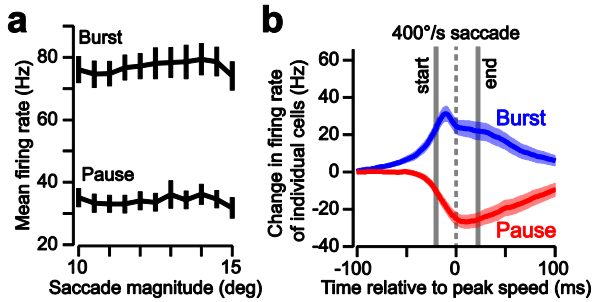

Fig. 1. Individual P-cell SS firing rates are unrelated to saccade kinematics. We recorded from n=67 P-cells in OMV. **(a)** P-cells displayed both bursting and pausing activity, yet the mean activity of neither of these cell types changed with saccade amplitude. **(b)** The time-course of P-cell activity greatly exceed the duration of the saccade (grey vertical lines). Error bars are ±SEM across neurons.

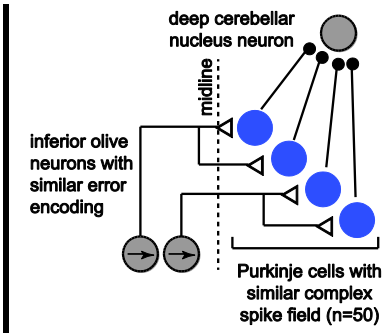

Fig. 2. Hypothesized anatomical organization of the cerebellum. A population of 50 P-cells project to a single neuron in the deep nucleus. In our hypothesis, these cells are not selected at random, but share a common preference for error via climbing fiber projections from the inferior olive. The projections are functionally expressed by the P-cell's complex spike properties.

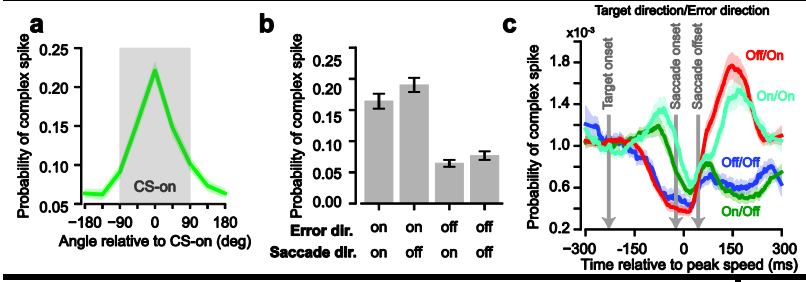

Fig. 3. Complex spikes encode foveal error. We systematically jumped the target during the saccade to elicit post-saccadic foveal error. **(a)** The probability of CS in the post-saccadic period encodes error direction across the population. **(b)** Post-saccadic complex spikes were not dependent on the direction of the preceding saccade. **(c)** Foveal errors are consistently encoded foveal error during two periods: (1) following target presentation and (2) following termination of the saccade. Labels refer to the direction of the target and the direction of the post-saccadic error. Errors bars are ±SEM.

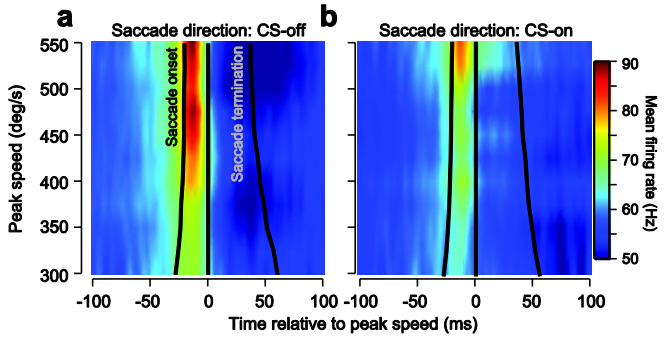

Fig. 4. Micro-cluster simple spikes encode saccade kinematics as a gain-field. We organized the P-cells into micro-clusters wherein each P-cell shared the same CS tuning properties (Fig. 2). The micro-cluster response encoded speed linearly in all directions, but was largest when the saccade was made in the CS-off direction **(a)** and smallest when the saccade was in CS-on **(b)**, suggesting a gain-field field encoding of state of the eye.

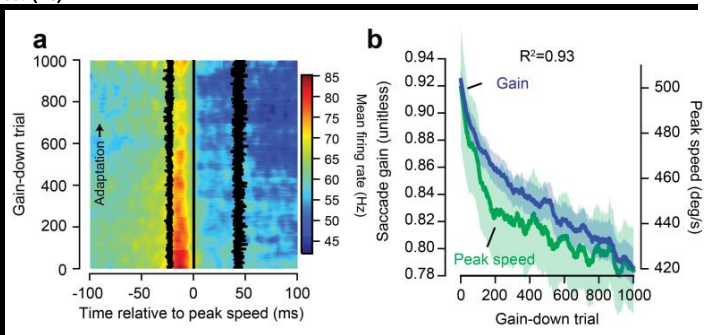

Fig. 5. Micro-cluster response decreases during gain-down adaptation. Changes in the responses of individual P-cells following saccade adaptation are heterogeneous. **(a)** Rather that focus on changes in individual cells, we organized P-cells into micro-clusters (Fig. 2). We saw a robust decrease in micro-cluster activity over the course of gain-down adaptation (R^2=0.83). **(b)** Gain-down adaptation resulted in reduced peak velocity (R^2=0.93)

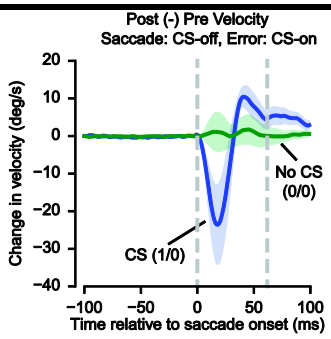

Fig. 6. Complex spikes result in behavioral changes on the next trial. We assessed whether the presence of a complex spike on trial *n* results in a velocity change in trial *n+1*. We found that lack of a complex spike in both trials (0/0) does not change the velocity of trial *n+1* whereas the presence of a complex spike in trial *n* (1/0) results in a significant decrease in peak velocity.

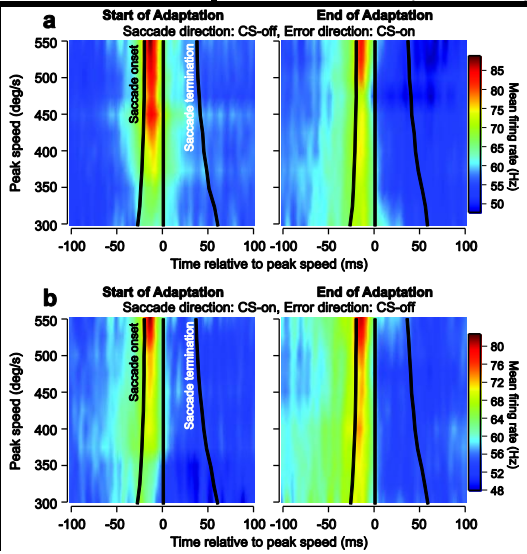

Fig. 7. Gain-field encoding of saccade kinematics is modified following gain-down adaptation. (a) When the post-saccadic error is in the CS-on direction (high probability of CSs), micro-cluster encoding of saccade speed decreases from the start (left) to the end of adaptation (right). **(b)** In contrast, when the error is in the CS-off direction, adaptation results in increases in the gain-field encoding of saccade speed. That is, the encoding of state of the eye is modified following adaptation. The direction of the activity change is dependent on the post-saccadic error.

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