A Pathway in Primate Brain for Internal Monitoring of Movements

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It is essential to keep track of the movements we make, and one way to do that is to monitor correlates, or corollary discharges, of neuronal movement commands. We hypothesized that a previously identified pathway from brainstem to frontal cortex might carry corollary discharge signals. We found that neuronal activity in this pathway encodes upcoming eye movements and that inactivating the pathway impairs sequential eye movements consistent with loss of corollary discharge without affecting single eye movements. These results identify a pathway in the brain of the primate *Macaca mulatta* that conveys corollary discharge signals.

When the brain initiates a movement, it also generates internal information that is used by sensory systems to adjust for resultant changes to peripheral receptors and by motor planning systems to prepare subsequent movements (*1*–*7*). Information about an impending movement arises as a correlate, or corollary discharge, of the neuronal movement command (*8*). The concept of corollary discharge has been invaluable for understanding disparate behaviors such as the circling of insects, fish, and amphibians after visual field inversion (*9*, *10*), electrolocation in fish (*4*), and song learning in birds (*11*). In humans, psychophysical studies have demonstrated that corollary discharge signals exist (*3*, *5*, *6*) and lesion studies have emphasized that the thalamus and cerebral cortex are crucial for using corollary discharge information (*2*, *12*–*14*). Some neurons in the cerebral cortex of nonhuman primates receive corollary discharge signals (*15*–*17*), but where these signals come from has remained unknown.

To identify neurons as conveying corollary discharge signals, one must show that they have movement-related activity and project upstream, away from motor neurons, instead of downstream, toward motor neurons. That is, their activity must transmit information about movement without causing movement. A promising system in which to look for such neurons is that for producing saccadic eye movements. An important node in this system is the superior colliculus—specifically its intermediate layer, which contains neurons that fire just before saccade generation (*18*). Some projections of the intermediate layer go downstream to saccade-generating circuits in the midbrain and pons (*19*), and some go upstream to mediodorsal thalamus (MD) relay neurons that project to a frontal lobe region known as the frontal eye field (*20*). Our hypothesis is that the ascending pathway carries corollary discharges of saccadic commands.

To test this hypothesis, first we recorded from 46 MD relay neurons in *Macaca mulatta* (*21*), all physiologically verified as receiving input from the superior colliculus and projecting to the frontal eye field (Fig. 1A). We studied their activity while monkeys made delayed saccades to visual targets (Fig. 1B), a procedure that facilitates determining whether the activity is related to vision or to movement (*21*). Most neurons (74%; 34/46) had increased activity just before saccades (Fig. 1B) that began on average 144 ms before saccade generation (SD, 106 ms; median, 101 ms; range, 23 to 392 ms). Because this activity began before movement, it could not have represented proprioception. Most of the saccade-related neurons (82%; 28/34) were spatially tuned, firing most strongly for saccades made within a restricted range of amplitudes and directions. For all tuned neurons, the best direction was contraversive.

Second, we reversibly inactivated MD by injecting muscimol unilaterally at the sites of previously recorded MD relay neurons (Fig. 2A) (*21*). Muscimol is a γ-aminobutyric acid type A ($GABA_A$) agonist and inhibits neuron cell bodies, not axons (*22*), so it should suppress MD relay neurons without affecting transthalamic fibers passing nearby. We tested monkeys on a double-step task, in which they had to make successive saccades to two flashed targets (Fig. 2B, top) (*21*, *23*, *24*). Correct execution of the second saccade requires knowledge about the first saccade's metrics. Visual feedback regarding performance is not available, because the saccades begin after the targets disappear, and proprioception is unlikely to contribute because it plays little if any role in the online control of saccades (*25*–*28*). The ability to make a correct second saccade, therefore, is thought to rely critically on corollary discharge information about the first saccade (*12*–*14*). If inactivation totally disrupts corollary discharge (Fig. 2B, bottom), a monkey will be able to make a first saccade correctly but will have no internal information that the saccade was made. If the monkey then tries to complete the trial by making a saccade to the second target location, the second saccade will travel as if starting from the fixation point. The observed effect will be a contraversive shift of the second saccade end points.

Results from an example injection are shown in Fig. 2C. Before inactivation, the monkey made saccadic sequences correctly. Because the saccades were made in total darkness, first saccades were shifted slightly upward (*29*). Second saccades went nearly straight up, which indicates that corollary discharge was intact. During inactivation, the second saccade end points shifted contraversively, which indicates that corollary discharge was impaired. Quantitatively (Fig. 2D) (*21*), the second saccade end points were indeed shifted horizontally [contraversive 2.5° shift; $P < 0.001$ (*21*)] but not vertically during the injection. Neither the initial fixation locations nor the first saccade end points were shifted significantly in either direction.

We performed a total of seven muscimol experiments in which there were a total of 22 cases of before versus during saccadic sequence pairs to analyze (*21*). In every case, the principle for identifying a corollary discharge deficit was the same as in Fig. 2. In 82% of the cases (18/22), there was a contraversive shift in second saccade end points (Fig. 3A), and the overall mean shift (1.12°) was significantly greater than zero. The contraversive shift in 11 of these cases was individually significant [and always reversible (*30*)]. First saccade end points did not exhibit a significant mean horizontal shift (Fig. 3B); neither did initial fixation locations (−0.09° shift; $P > 0.025$). In the vertical direction, there were no mean shifts in any of the data (*31*). For controls, we randomly interleaved trials in which targets appeared ipsilaterally. Identical target configurations were used but were flipped across the vertical meridian. In these trials, the first saccades were ipsiversive, a direction poorly represented by MD relay neurons. Accordingly, we found no corollary discharge deficits: the mean horizontal shift for second saccade end points was not significantly different from zero (−0.41°; $P > 0.025$).

We also considered whether inactivation might have degraded a monkey's ability to see the second target or to remember its location. If visual or memory deficits oc-

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curred, there should have been greater scatter of the second saccade end points during inactivation because of greater uncertainty about the second target location. This did not occur, however (Fig. 3C). If there were subtle visual or memory deficits, they did not appear to affect performance in our task.

Although we consistently observed effects indicative of impaired corollary discharge, we never found as large a shift in second saccade end points as expected from a total deficit. In Fig. 2D, for example, second saccade end points shifted 2.5° horizontally instead of the 10° expected (cf. Fig. 2B); hence, in this case there was a 25% deficit. On average, there was a 19% deficit (Fig. 3D). We see three possible reasons for the partial deficit. (i) Other pathways may also contribute to oculomotor corollary discharge (*20*). (ii) Our injec-

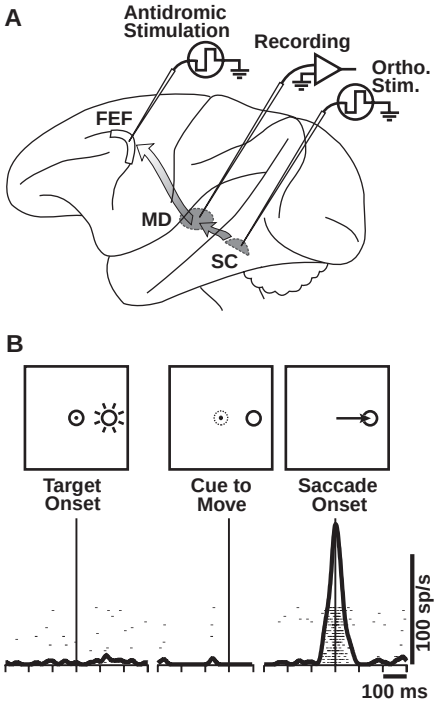

Fig. 1. Saccade-related activity in the ascending pathway from superior colliculus (SC) to frontal eye field (FEF) via MD. (**A**) We recorded from relay neurons in MD that were antidromically activated by electrical stimulation in FEF and orthodromically activated by stimulation in SC. (**B**) Activity of an MD relay neuron that exhibited a presaccadic burst. The task performed by the monkey is depicted above, and neuronal activity (rasters of individual action potentials and spike density curve of the averaged firing rate) is shown below, with scale at right (sp, spikes). (Left) After the monkey looked at a fixation spot (dot in circle), a target appeared in the periphery (right circle). (Middle) After a delay period of 500 to 1000 ms, the fixation spot disappeared (dotted circle), which was the cue to move. (Right) The monkey then made a saccade (arrow) to the target location.

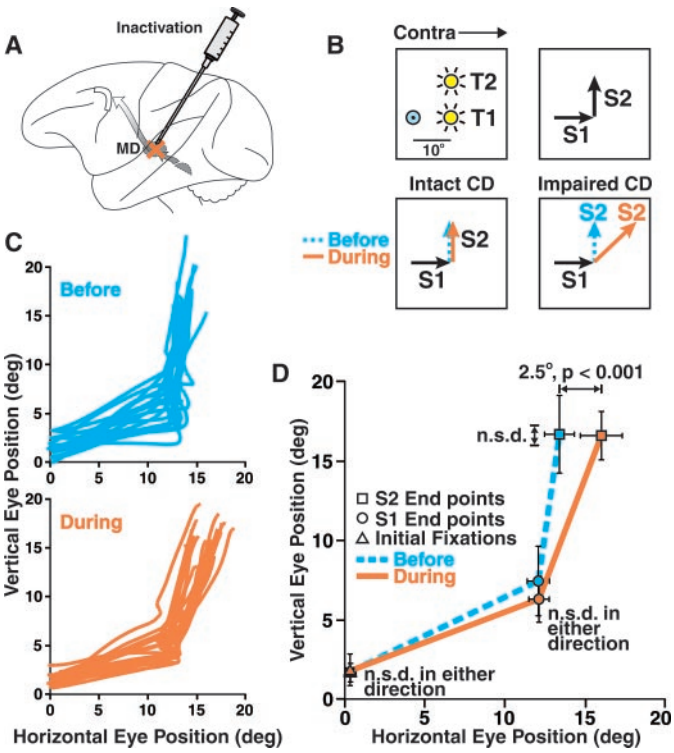

Fig. 2. Corollary discharge deficits during inactivation of the ascending pathway. (**A**) Muscimol was injected into MD to inactivate the relay neurons. (**B**) Monkeys performed a double-step task. (Top) After the monkey looked at a fixation spot (dot in blue circle), two targets were flashed sequentially (yellow circles, T1 and T2). The monkey then made sequential saccades (S1 and S2) to the target locations. Contra, contraversive direction. (Bottom) If corollary discharge (CD) remained intact (left), S1 would go rightward and S2 would go straight up before and during inactivation. If corollary discharge were completely impaired (right), S1 would go rightward and S2 would go upward before inactivation but would go at an angle during inactivation so that the S2 end points would shift contraversively. (**C**) Individual saccadic sequences from one experiment, before and during inactivation. (**D**) Means (and SDs) of initial fixation locations, first saccade end points, and second saccade end points for the same example. n.s.d., Not significantly different.

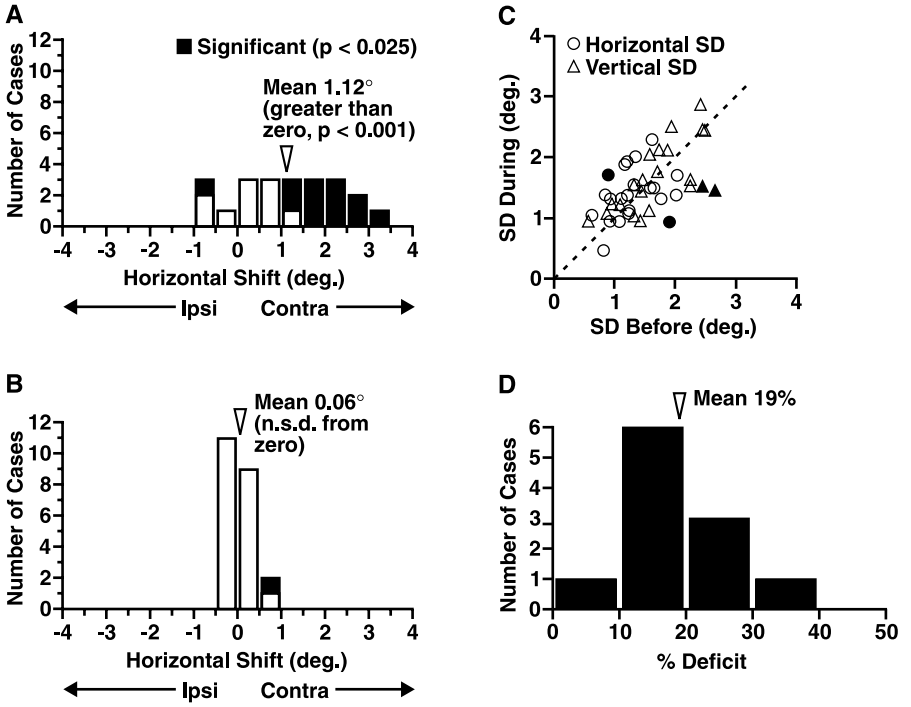

Fig. 3. Results from all the inactivations. (**A**) Histogram of the horizontal shift in second saccade end points for all cases ($n = 22$). Mean shift is indicated. Cases that were individually significant are shown in black. Ipsi, ipsiversive; Contra, contraversive. (**B**) Histogram of the horizontal shift in first saccade end points. (**C**) Scatter of second saccade end points. Standard deviations (SD) of end-point clusters are plotted during (ordinate) and before (abscissa) inactivation. Horizontal and vertical SDs are plotted separately. Filled symbols represent significant differences during inactivation (F test, $P < 0.025$ criterion). SD increased during inactivation in only one case (filled circle above dashed unity line). (**D**) Severity of deficits for the 11 individual cases in which there was a significant horizontal, contraversive shift in second saccade end points. See text for calculation of percent deficit.

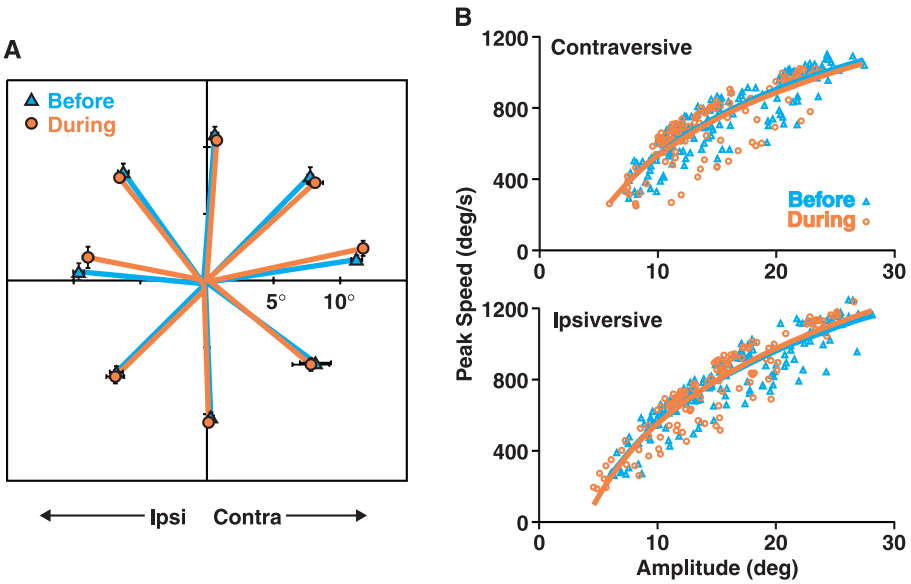

Fig. 4. Single saccade controls. (**A**) Vector diagram showing mean (and SD) of single saccade end points for one experiment. All saccades started at the center and were made to one of eight possible visual targets. (**B**) Graphs summarizing the dynamics of contraversive and ipsiversive saccades. Curves show logarithmic fits.

tions may have been too small, so that we failed to inactivate all the MD relay neurons. (iii) The monkeys may have been able to exploit proprioceptive input after losing corollary discharge signals during inactivation.

In principle, the monkeys could have made preplanned sequences of saccades (*32*). For example, the target flashes shown in Fig. 2B could have triggered a saccadic program to "look right then look up." With this strategy, corollary discharge signals could be ignored. We discouraged this by randomizing the target configurations across trials and modifying them between experiments (*21*). Inactivation never caused deficits consistent with disruption of preplanned sequences (such as generation of errant sequences or random scattering of first and second saccade end points).

Finally, we examined whether MD inactivation impaired the general ability to execute saccades. Notably, recall that inactivation did not impair first saccades in the double-step task (Fig. 3B). To test this in more detail, with four muscimol injections we also had monkeys make single saccades to visual or remembered targets at several eccentricities and directions (*21*). An example is shown in Fig. 4A; in this experiment, there were no significant changes in single saccade accuracy during inactivation, although there were significant deficits in the double-step task (similar to the deficits shown in Fig. 2). Overall, significant changes in the accuracy (and reaction time) of single saccades were infrequent, small, and dissimilar between experiments. To examine saccadic dynamics, we plotted peak speed versus amplitude (Fig. 4B) with data from two experiments in which we elicited a broad range of amplitudes of single-step saccades. There were no clear impairments during inactivation, and logarithmic fits did not change significantly. In sum, the inactivations negligibly affected single saccades.

These results support our hypothesis that the pathway from superior colliculus to frontal eye field via MD conveys corollary discharge information. Neurons in the pathway have activity appropriate for representing corollary discharge; interrupting this activity causes deficits consistent with loss of corollary discharge, even as the ability to make single saccades remains intact. Signals in this pathway carry information about movement but do not appear to be involved in generating movement, matching the definition of corollary discharge.

Corollary discharge signals are used not only for planning sequential movements but also for maintaining a stable visual percept despite the sudden retinal shifts caused by saccades (*1*, *5*, *6*). Additional work is needed to determine whether the corollary discharge signals described here are used for such a sensory function. In particular, it would be intriguing to test whether these signals cause the presaccadic shifts in visual receptive fields of cerebral cortical neurons that are thought to help stabilize perception across saccades (*15*, *16*, *33*).

References and Notes

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30. Of these 11 cases, 8 (73%) recovered by the following day, and the rest recovered by the next time the monkey was tested (1 to 3 weeks later).
31. Vertical mean shifts during inactivation were as follows (all $P > 0.025$): 0.08° and 0.03° for second and first saccade end points, respectively, and −0.03° for initial fixation locations.
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Supplementary Material

Materials and Methods

Recording procedures and anti- and orthodromic identification. In each of two monkeys (*Macaca mulatta*) a cylinder was implanted over MD (centered at A8, L3) and neurons were recorded extracellularly using single microelectrodes and standard amplification, spike discrimination, and computerized data collection procedures. For anti- and orthodromic stimulation, cylinders were implanted over the superior colliculus and frontal eye field and each region was identified and mapped physiologically. Arrays of two to four monopolar tungsten stimulating electrodes were implanted for ~2 to 6 weeks with their tips in the frontal eye field or the intermediate layer of the superior colliculus. The only MD neurons studied were those that could be both antidromically activated from frontal eye field and orthodromically activated from superior colliculus as determined using multiple techniques including the collision test (*S1*, *S2*). These neurons were presumed to be at the lateral edge of MD according to a previous anatomical study (*S3*), and this was confirmed histologically in one of the monkeys. Details of surgical and physiological procedures are described elsewhere (*S4*).

Analysis of neuronal activity related to saccades. During the recording experiments monkeys sat in a dimly lit room facing a tangent screen onto which visual stimuli were presented using a liquid crystal display (LCD) projector. Two versions of the delayed saccade task were randomly interleaved: a visual version, shown in Fig. 1B, and a memory version, in which the target appeared for only 100 ms such that the eventual saccade was made to a remembered target location (the two versions were used for characterization of tonic activity that might occur during the delay period, an issue not pertinent to the present report). Correct performance was rewarded with drops of water. A neuron had increased activity just before saccades if, in either the visual or memory version of the task, its average activity in the last 50 ms before saccade initiation exceeded both the average baseline activity (in the last 300 ms before target onset) and the average delay activity (in the last 300 ms before the cue to move), according to ANOVA ($P < 0.01$ criterion) and multiple comparison tests (Student-Newman-Keul's or Dunn's; $P < 0.05$ criteria).

The time course of the presaccadic activity was analyzed by creating, for each neuron's data during the visual version of the task, spike density functions showing the average firing rate (Gaussian width sigma = 4 ms) and then moving back in time from saccade initiation to find the first time at which the average firing rate dropped below a threshold set to the mean + 2SD of the prior delay period activity, after which it stayed below this threshold for another 100 ms. This crossing time was judged to be when the presaccadic activity began.

For mapping movement fields, during preliminary characterization of each neuron, we first found the part of the visual field where target presentation yielded the highest task-related activity. Then we quantitatively analyzed the extent of the movement field by

having monkeys make saccades to targets presented at a series of amplitudes (8 target locations from 2° to 60° amplitude) and directions (eight target locations every 45° in angle as shown in Fig. 4A). Movement field sizes were similar to those that have been described for frontal eye field (*S5*) and superior colliculus neurons (*S6*).

Reversible inactivations. Before every muscimol injection, we recorded at the targeted site to verify that neurons were active there and not damaged by prior experiments. During an injection, we inserted a 30 gauge needle connected to a 10 μl Hamilton syringe through a guide tube down to the site and injected 1.0-3.0 μL of muscimol (concentration 5 μg/ μl) in steps of 0.2 μl every 30 s. "Before" data were collected the day before injection and "during" data from ~10 min. after injection until the monkey quit performing tasks (usually 2 to 3 hours after injection). We note that $GABA_A$ receptors are found on neurons throughout MD (*S7*), and it is reasonable to assume this includes the neurons we studied. Because we targeted our injections directly at the sites of physiologically identified MD relay neurons, we are confident that the inactivations suppressed at least some of those neurons, but we cannot rule out the possibility that adjacent neurons, not part of the SC-MD-FEF ascending pathway, also were inactivated.

Double-step task. After the fixation spot disappeared, T1 immediately appeared for a typical duration of 150 ms and T2 then immediately appeared for a typical duration of 30 ms. The duration for each target was adjusted to yield optimal performance in each monkey. A variety of target configurations were used to make the task less predictable. All configurations were similar in requiring contraversive first saccades, but they differed depending on whether correct second saccades had to go upward, downward, or at an oblique, ipsiversive angle. In five experiments, two configurations were randomized by trial, and in two experiments, six configurations were randomized by trial, yielding the 22 total cases analyzed. Results were similar regardless of target configuration. We used 10° first saccades because this amplitude was well represented by the movement fields of MD relay neurons. Visual stimuli were provided either by lasers (four experiments) or by an LCD projector (three experiments); results were similar regardless of how the stimuli were produced.

When the double-step task results were analyzed, a shift was considered significant if the end points differed in their horizontal or vertical components according to Student's *t* test or the Mann-Whitney rank sum test, using the former if the data were normal (determined with the Kolmogorov-Smirnov test) and of equal variance (Levene Median test) and the latter otherwise. Because two comparisons were performed for every data set, i.e., in the horizontal and vertical directions, the standard criterion level of $P < 0.05$ was adjusted by Bonferroni correction to $P < 0.025$. We also analyzed the data using two other methods. First, we tested whether second saccade vectors rotated during inactivation using circular statistics techniques. Second, we used methods from discriminant analysis as described below (in the Single-Step Tasks section) to more precisely quantify the shifts in second saccade end points during inactivation. The method of analysis did not matter; all of these techniques yielded results similar to those described in the text and figures.

Single-step tasks. In all the single-saccade experiments, gap tasks (*S4*), in which targets appeared ~200 ms after fixation spot disappearance, were used, and in two of the experiments, delayed saccade tasks also were used (similar to the tasks described above in the Analysis of Neuronal Activity Related to Saccades section). In the gap tasks, a visual condition was created by having the target remain after its appearance until the end of the trial, and a memory condition was created by presenting the target very briefly (~30 ms duration), so that its location had to be remembered during the saccadic reaction time (this made the memory requirement similar to that in the double-step task). Amplitudes from 5° to 30° and a broad range of both contra- and ipsiversive directions were tested. In two of the experiments, we also specifically controlled for initial fixation location by having single saccades start from the same orbital position as the second saccades of the double-step task (nonetheless the single saccades remained unperturbed by inactivation). Results were identical using visual stimuli provided by lasers (two experiments) or by the LCD projector (two experiments).

Because there was no a priori hypothesis as to how inactivation might affect the accuracy of single saccades, we tested whether saccadic end points shifted in any direction before versus during inactivation. To do this we used a method from discriminant analysis that revealed the axis between "before" and "during" end-point clusters along which the clusters were maximally segregated. The segregation along this axis was tested for significance (criterion level $P < 0.05$). Details regarding this method can be found in many sources (*S8*, *S9*). When analyzing saccadic dynamics, to see whether the logarithmic fits differed before versus during inactivation we linearized the fits using a semilog graph and found that they were coincident (i.e., not significantly different in their slopes or their intercepts; $P > 0.05$).

Supporting References

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