



HAL
open science

**Review of "Neural encoding of instantaneous kinematics of eye-head gaze shifts in monkey superior Colliculus"
by Dr John van Opstal**

Laurent Goffart

► **To cite this version:**

Laurent Goffart. Review of "Neural encoding of instantaneous kinematics of eye-head gaze shifts in monkey superior Colliculus" by Dr John van Opstal. Neural Encoding of Instantaneous Kinematics of Eye-Head Gaze Shifts in Monkey Superior Colliculus, 2023, https://static-content.springer.com/esm/art%3A10.1038%2Fs42003-023-05305-z/MediaObjects/42003_2023_5305_MOESM1_ESM.pdf. hal-04282092

HAL Id: hal-04282092

<https://cnrs.hal.science/hal-04282092v1>

Submitted on 13 Nov 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Review of Dr **John van Opstal**'s article

“Neural encoding of instantaneous kinematics of eye-head gaze shifts in monkey superior Colliculus”

Laurent Goffart^{1,2}

Communications Biology 6: 927, 2023

<https://www.nature.com/articles/s42003-023-05305-z#peer-review>

¹ Aix Marseille Université, Centre National de la Recherche Scientifique, Institut de Neurosciences de la Timone, Marseille, France.

² Aix Marseille Université, Centre National de la Recherche Scientifique, Centre Gilles Gaston Granger, Aix-en-Provence, France.

THIRD ASSESSMENT REPORT:

Extending the conclusions of Smalianchuk et al. (2018) to gaze shifts made with the unrestrained head, the author concludes that the “SC population activity encodes the instantaneous kinematics of the desired gaze shift through its firing rates” based on a “tight correlation” between the velocity profile and the spike density profile of individual neurons (L728-729, L734, L746-748, L752). He contends that “the finding that single-trial and single-unit firing dynamics at a central neural stage correlate well with the instantaneous motor output of a highly complex and nonlinear synergistic system (comprising the multiple-degrees of freedom oculomotor, head-motor, and vestibular systems; see Fig. 1B) is quite remarkable” (L769-771).

In spite of careful readings of his manuscripts, this reviewer remains unconvinced. In each of her/his reviews, she/he exposed several concerns that prevented her/him from admitting the author's conclusion. The author and this reviewer agree on several points. However, regarding the correlation between the spike density and the saccade velocity, this reviewer suspects that it is actually an artefact for the following reasons.

1) From looking at the figures (Fig. 3C: activity of neuron Sa1007, Fig. 4B, Fig. 10B and Fig. S1: activity of neuron Sa3006, Fig. S15: activity of neuron Sa0107), the reader is led to the impression that all saccade-related neurons in the SC cease emitting action potentials shortly before the gaze shift ends. However, this inference may result from the author's choice of example neurons. Indeed, all saccade-related neurons in the SC do not exhibit an abrupt cessation of activity shortly before saccade end. In the head-unrestrained monkey, Choi and Guitton (2009) documented several neurons that continue to fire after the end of the gaze shift (see the middle row of their Figure 6C). In the head-restrained monkey, numerous studies documented neural discharges that persist after saccade end (Anderson et al. (1998);

Goossens and van Opstal (2000); Keller et al. (2000), Munoz and Wurtz (1995), Munoz et al. (1996); Rodgers et al. (2006); Sparks and Mays (1980); Waitzman et al. (1991)). The author did not document how many neurons exhibited this persistent activity after gaze saccade end. It is also unclear whether his analysis was only restricted to the so-called “clipped” saccade-related cells.

2) If the time course of the instantaneous spike density and the time course of “gaze-track” velocity look remarkably similar for the neuron (Sa0107) illustrated in Fig. 10 A-B, it is also because the spikes that preceded the saccade-related burst were removed. The graph at the bottom of Fig. 10A shows that twenty milliseconds before gaze onset, the firing rate rises from 0 to 200 spikes per second. However, examination of Fig. 4A (same neuron) reveals that such an enhancement (from zero to 200 spikes/s) is rare. It seems that the author removed the spikes that were emitted before the onset of an analysis interval (elapsed from 20 ms before gaze saccade onset to 20 ms before gaze saccade end). However, numerous studies (see references listed above) reported collicular saccade-related neurons that emit spikes sometimes within a long prelude before saccade onset.

Thus, by selecting only the spikes emitted from 20 ms before saccade onset to 20 ms before saccade end, the spike density exhibits a rising phase like the acceleration part of the velocity profile, and a decline like the deceleration part of the velocity profile. The correlation between the instantaneous firing rate and the gaze velocity may be the consequence of selecting a portion of the neuron’s activity.

The author may wish to explain to the readers that the premotor neurons are sensitive to the spikes that collicular neurons emit during a specific time interval, that this interval starts 20 ms before saccade onset and terminates 20 ms before saccade end. He may wish to add that the onset and the end of this interval is determined by the pause of firing from a specific group of inhibitory neurons located in the nucleus raphe interpositus: the so-called omnipause neurons. If so, then the author should warn the readers that this scenario remains controversial. Indeed, if this hypothesis were true, then experimentally increasing the pause duration should lead to hypermetric saccades. Empirical studies actually show the lesion of these neurons does not lead to dysmetric saccades (Kaneko 1996; Soetedjo et al. 2000). The author may also explain why these results are not convincing.

3) Moreover, plotting the number of trials (or responses) as a function of the correlation coefficient between spike density and gaze velocity (Fig. 10) does not teach us anything about the proportion of neurons that were concerned. Fig. 10C shows that for one neuron (Sa0107), the correlation coefficient ranged from 0.8 to 1.0 in approximately 330 trials out of a total number of 664 trials. Fig. 10D shows that for 20 best-recorded cells, the correlation coefficient ranged from 0.8 to 1.0 in approximately 1022 trials out of 3981 trials. Thus, 32% (330/1021) of the correlation coefficients that ranged from 0.8 to 1.0 are only due to neuron Sa0107. How many neurons account for the remaining 691 correlations? Three neurons like Sa0107 would be sufficient to account for the 1021 trials. In other words, the claim of a “tight correlation” between the velocity profile and the spike density profile of individual neurons” (L728-729, L734, L746-748, L752) is a hasty conclusion if it concerns a small

percentage of neurons. Three neurons out of 20 best recorded cells or three neurons out of 43 cells correspond to a small percentage of cells (15% and 7 %, respectively).

For these reasons and for other reasons exposed in her/his previous reviews (see also reservations expressed by Goffart et al. 2018 about the encoding of velocity by central neurons), this reviewer thinks that the author's conclusions are not yet sufficiently founded.

However, for the sake of pedagogy to the uninformed readers and for the sake also of reminding the tremendous knowledge acquired by previous neurophysiological studies in the awake and trained monkey, this reviewer supports the publication of the author's work as long as the readers are warned about its limitations and shortcomings.

Minor comments:

Abstract:

The last sentence sounds weird. The author may remove "we hypothesize that"

L5: perhaps "amplitude and direction" instead of "coordinates"?

Introduction:

L157: in Goffart et al. (2017), the saccades were not triggered during smooth pursuit tracking but from fixating a static target. The author could replace "occurring during smooth pursuit tracking" by "toward a moving target". Moreover, the word "always" could be inserted between "does not" and "incorporate" because the difference of firing rate between "centrifugal" and "centripetal" did not concern all cells.

L164: this reviewer suggests removing "FEF-mediated" because one cannot exclude the involvement of the cortico-ponto-cerebellar channels originating in the parietal eye fields.

L166: the author might add "in the SC" after "microlesions".

L173: perhaps "primary" instead of "central"?

L174: the author might add "other neural regions such as" between "taken over by" and "the FEF".

Results:

L272: the author might add "various" before "directions"

L418: For the readers who are not familiar with the notion of "multiplicative noise", it would be helpful to explain its meaning.

L486: "by fitting a linear regression line through the measured phase trajectory" instead of "by fitting linear regression lines through the measured phase trajectories"?

L496: "as a function of" instead of "as function of"

L501: what does "c.q." mean?

L506-508: the author forgot to remove his comment.

L610-611: “for the trial (#670) that yielded the largest number of spikes” instead of “for trial 670 that yielded the largest number of spikes”

Discussion:

L836: “Moschovakis” instead of “Moschiovakis”

References:

Page 28, second reference: “Moschovakis” instead of “Moschiovakis”

Page 29, 16th reference: “Sparks DL” instead of “Sparks DJ”

Methods:

L927: the minimum value of the range of successful trials is unclear: “1-0”

L950: “gaze” instead of “eye-“.

L1065: “a SC neuron” instead of “an SC neuron”

L1072: “velocity” instead of “vlocity”

L1137: “as a function of” instead of “as function of”

Figure 4A:

The dashed line that indicates the gaze onset does not look cyan but green.

Figure 10A:

It seems that the panel A does not show all action potentials that the cell (Sa0107) emitted but only those that were emitted during the interval elapsed from 20 ms before gaze shift onset to 20 ms before gaze shift end (small black lines). Figure 4A shows numerous examples in which the same cell exhibits a prelude activity. The author should warn the reader that the curve representing the purportedly “instantaneous” firing rate (black) at the bottom of Fig. 4A is rare, or that it is not the true instantaneous firing rate. This reviewer wonders whether it is a fictive instantaneous firing rate, merely created by selecting the spikes emitted during a time interval that the author chose to elapse from 20 ms before gaze shift onset to 20 ms before gaze shift end.

Table 1: the eye position sensitivity “EPSILON ZERO” should be replaced by “EPSILON” to be consistent with the definition in the methods (L1027) and the numerous instances elsewhere in the text (pages 11 and 14).

Based on the major comment, it would be useful to add information about the firing rates at two times: 20 ms before saccade onset and at saccade end.

Figure S10:

L1268-1269: there is no Fig. 6C

REFERENCES:

- Anderson, R. W., Keller, E. L., Gandhi, N. J., & Das, S. (1998). Two-dimensional saccade-related population activity in superior colliculus in monkey. *Journal of Neurophysiology*, 80(2), 798-817.
- Choi, W. Y., & Guitton, D. (2009). Firing patterns in superior colliculus of head-unrestrained monkey during normal and perturbed gaze saccades reveal short-latency feedback and a sluggish rostral shift in activity. *Journal of Neuroscience*, 29(22), 7166-7180.
- de Carrizosa, M. A. D. L., Morado-Díaz, C. J., Miller, J. M., de la Cruz, R. R., & Pastor, Á. M. (2011). Dual encoding of muscle tension and eye position by abducens motoneurons. *Journal of Neuroscience*, 31(6), 2271-2279.
- Goffart, L., Burreilly, C., & Quinton, J. C. (2018). Neurophysiology of visually guided eye movements: critical review and alternative viewpoint. *Journal of Neurophysiology*, 120(6), 3234-3245.
- Goossens, H. H. L. M., & Van Opstal, A. J. (2000). Blink-perturbed saccades in monkey. II. Superior colliculus activity. *Journal of neurophysiology*, 83(6), 3430-3452.
- Hu, X., Jiang, H., Gu, C., Li, C., & Sparks, D. L. (2007). Reliability of oculomotor command signals carried by individual neurons. *Proceedings of the National Academy of Sciences*, 104(19), 8137-8142.
- Kaneko, C. R. (1996). Effect of ibotenic acid lesions of the omnipause neurons on saccadic eye movements in rhesus macaques. *Journal of neurophysiology*, 75(6), 2229-2242.
- Keller, E. L., Gandhi, N. J., & Vijay Sekaran, S. (2000). Activity in deep intermediate layer collicular neurons during interrupted saccades. *Experimental brain research*, 130, 227-237.
- Munoz, D. P., & Wurtz, R. H. (1995). Saccade-related activity in monkey superior colliculus. I. Characteristics of burst and buildup cells. *Journal of neurophysiology*, 73(6), 2313-2333.
- Munoz, D. P., Waitzman, D. M., & Wurtz, R. H. (1996). Activity of neurons in monkey superior colliculus during interrupted saccades. *Journal of Neurophysiology*, 75(6), 2562-2580.
- Rodgers, C. K., Munoz, D. P., Scott, S. H., & Paré, M. (2006). Discharge properties of monkey tectoreticular neurons. *Journal of neurophysiology*, 95(6), 3502-3511.
- Soetedjo, R., Kaneko, C. R., & Fuchs, A. F. (2002). Evidence that the superior colliculus participates in the feedback control of saccadic eye movements. *Journal of neurophysiology*, 87(2), 679-695.
- Smalianchuk, I., Jagadisan, U. K., & Gandhi, N. J. (2018). Instantaneous midbrain control of saccade velocity. *Journal of Neuroscience*, 38(47), 10156-10167.
- Sparks, D. L., & Mays, L. E. (1980). Movement fields of saccade-related burst neurons in the monkey superior colliculus. *Brain research*, 190(1), 39-50.
- Waitzman, D. M., Ma, T. P., Optican, L. M., & Wurtz, R. H. (1991). Superior colliculus neurons mediate the dynamic characteristics of saccades. *Journal of Neurophysiology*, 66(5), 1716-1737.

SECOND ASSESSMENT REPORT:

The author made substantial changes in his article. His answers to the comments of this reviewer were more or less satisfactory. Part of this reviewer's dissatisfaction comes from answers that were either incomplete or irrelevant (off topic). However, this study remains very important for several reasons:

- its conclusion contradicts the synthesis that this reviewer reached,
- the experimental work (unit recording in the monkey tested with the head unrestrained) was a difficult challenge,
- the collected data are extremely precious and
- this work illustrates very well the extraordinary advancement of knowledge that the community of primate neurophysiologists have achieved in order to understand how the brain networks enable to orient the gaze and head toward a visual target.

That being said and considering the following facts, i.e.,

- 1) that a model factoring eye position, muscle tension and its first derivative accounts for the firing rate of motor neurons, better than a model factoring eye position and its first and second derivatives (velocity and acceleration) (Davis-Lopez de Carrizosa et al., 2011),
- 2) that the resemblance between the firing rate of premotor burst neurons and the instantaneous velocity of the saccade disappears when the spikes are not convolved with a Gaussian kernel (see Figs. 2 and 3 in Hu et al. (2007), Fig. 3C in Sparks & Hu (2006) and Fig. 4 in van Gisbergen et al. (1981)),
- 3) that the activity of premotor neurons is under the influence of neurons located in the left and right caudal fastigial nuclei (see Fig. 9 of Bourrelly et al. 2021),
- 4) that the the cFN is not part of the pathway that controls head movement (Fuchs et al. 2010; Quinet & Goffart 2017, 2009),
- 5) that the connection between the Superior Colliculus and the premotor burst neurons is not monosynaptic (Keller et al. 2000),
- 6) that the firing rate of dSC cells is not related to the velocity of saccades toward a moving visual target (see Fig. 11 in Goffart et al. 2017),
- 7) and that the correlation between the firing rate of single neurons and eye kinematics must be interpreted with the greatest caution, especially for those neurons located several synapses upstream from the motor neurons (Goffart et al. 2018),

it is hard not being skeptical after reading:

- a) that "single-trial and single-unit firing dynamics at a central neural stage correlate so well with the instantaneous motor output of a highly complex and nonlinear synergistic system (comprising the multiple-degrees of freedom oculomotor, head-motor, and vestibular systems ...)" (L536-539),

b) that “the population of recruited saccade-related burst neurons in the SC specifies the detailed kinematics (trajectories and velocity profiles) of saccadic eye-head gaze shifts (abstract L8-9) and

c) that “the same principles may apply to a wide range of saccadic eye-head gaze shifts with strongly varying kinematics” (abstract L10-11).

When the author declares having shown that the population of recruited saccade-related burst neurons in the SC “specifies the detailed kinematics (trajectories and velocity profiles)” of saccadic eye-head gaze shifts (abstract L8-9), the readers should be warned that:

I) this conclusion is based upon the analysis of the correlation between a particular analysis of neuronal activity and the instantaneous velocity of gaze shifts. The methods that he used for quantifying this activity are popular (many electrophysiologists used them). However not all neurophysiologists did. According to this reviewer, these methods create artefacts that are foreign to the physiological reality. Indeed, by convolving each action potential with a Gaussian, the author transforms the sequence of discrete events into a continuous function (the so-called spike density function), which permits to study its correlation with another continuous function like the velocity profile of gaze orienting movement. However, this method has several drawbacks about which the readers should be warned. Firstly, the transformation of the sequence of spikes into a continuous function feeds the illusion that a kinematic parameter is encoded by the activity of neurons and transmitted to post-synaptic neurons. In fact, the post-synaptic neurons integrate input from multiple neurons located in several regions. If the time course of SC activity looks like the velocity of eye (or gaze) saccade, how do we explain the fact that the firing rate of burst neurons does not (see their quasi-constant interspike intervals in Hu et al. 2007). Secondly, the cumulative Gaussian curves create an event (the peak firing rate) that may not have any physiological counterpart if its value and its timing differ from the actual shortest interspike interval and its timing. Secondly, the symmetry of the Gaussian curve creates a situation in which each convolved spike exerts an influence backward in time, shifting the putative peak firing rate toward the gaze saccade onset. As explained in the first review (sixth major concern and comments on the previous Fig. 9), if a causal relation exists between the firing rate of neurons and the gaze velocity profile, then spikes emitted AFTER the time of gaze peak velocity cannot influence the gaze peak velocity value. If they do, it is a mathematical artefact resulting from convolving each spike with a symmetric curve (Gaussian). Therefore, this reviewer invites the author to warn the readers about this concern and to document both the time of peak firing rate (estimated by the spike density function) and the time of shortest interspike interval (ordinate), both as a function of the time of peak gaze velocity (abscissa).

II) the conclusion that the population of recruited saccade-related burst neurons in the SC specifies the detailed kinematics of gaze shifts cannot be supported by the reported data insofar as the physical trajectory of gaze direction (as schematized in Fig. S3 by $G1(t)$ or $G2(t)$) is projected onto the imaginary line segment (DELTA_G) that connects the starting gaze position to the final gaze position. Because of this projection, it is not the detailed kinematics that is described. Let's consider the trajectory $G2(t)$ in Fig. S3, it is below the imaginary line segment DELTA_G. We can imagine its symmetrical image $G2SYM(t)$ with respect to the same

line segment DELTAG. The projection of $G2(t)$ onto DELTAG is identical to the projection of $G2SYM(t)$ in spite of different trajectories, in spite of different ratios between the horizontal and vertical velocities. Yet, the firing rate of SC neurons can still support these two different trajectories ($G2(t)$ and $G2SYM(t)$) if the detailed distribution of activity is different in the SC, skewed toward the medial border of the SC during $G2(t)$, skewed toward the lateral border of the SC during $G2(t)$. This a point that the author could have explained to the readers. However, the concern remains that IMAGINARY line segment ($DELTA_{g2}(t_0)$) is correlated with the ARTIFICIAL estimate of neurons' firing rate (density function). This reviewer does not want to prevent the author from analyzing his data the way he likes; she/he merely requests that the author warns the readers about its associated limitations and about the theoretical estimated and empirical data.

Despite these two major concerns, this reviewer is inclined to agree with the idea that the population of active neurons in SC steers gaze toward the target location and that the saccade curvature results from fluctuations in the firing rate of recruited neurons. However, as mentioned in her/his first review, the development of this idea largely benefited from electrical microstimulation studies in the head-restrained and head-unrestrained monkey (Stanford et al. 1996; Freedman et al. 1996). These studies showed that electrically-evoked gaze shifts stop as soon as the microstimulation stops and that a minimum number of electrical pulses is required to evoke the saccade vector (amplitude and direction) specific to each site of stimulation. They also showed that reducing the stimulation frequency (increasing the duration of the interval between two electrical pulses) evoked slower saccades, the amplitude of which was maintained if the stimulation was prolonged (see Figures 5, 8 and 12 of Stanford et al. 1996 and Figure 3 and 4 of Freedman et al. 1996). Although this reviewer appreciates very much the author's efforts to corroborate, with electrophysiological recordings in the head-unrestrained monkey, the hypothesis that Dr Sparks and his colleagues defended 27 years ago, she/he does not share the same surprise as the author wants to transmit to the readers (abstract L11). By neither reminding their results nor by explaining how his recording results are consistent with them, the author does not do a fair justice to the seminal studies of Dr Sparks' group. Likewise, it is also unclear why the author does not discuss his results with regard to the suggestion that the locus of activity in the Superior Colliculus would encode target eccentricity (relative to gaze direction) instead of gaze saccade amplitude (Bergeron et al. 2002; 2003). Finally, it is important reminding the readers that the firing rate of neurons also depends upon the animal's alertness and motivation, both of which do not vary from one trial to the next. This massive and sluggish influence likely explains the loss of trial-by-trial correlation between the firing rate and gaze velocity when the velocity profiles are shuffled (Fig. 10).

Still concerning the relation to previous studies, the report of the results obtained by Peel et al. (2021) is biased. During FEF inactivation, the number of action potentials emitted by SC neurons is neither increased, nor slight, nor restricted to memory-guided saccades (L141-143). Their figure 1b shows an impressive impairment of delayed-saccades: the total number of spikes during FEF cooling is reduced almost by half ($N=13$) in comparison to the number of spikes recorded during control saccades ($N=22$). The horizontal and vertical amplitudes of saccades were barely changed whereas their velocity was severely reduced. The longer

interspike intervals associated with the slowing of saccades is consistent with the influence of SC activity upon saccade velocity. Sparks, Lee & Rohrer (1990) reported a similar dramatic decline in velocity with no change in saccade direction and amplitude (see their Figure 3). Although Sparks and colleagues could not record the firing rate of neurons, the observations of Hanes et al. (2005) that the response fields of neurons adjacent to a small collicular lesion do not expand leads to infer that the lidocaine injection also reduced the number of active neurons. Thus, the suppression of neurons and the lower firing rate of peripheral neurons (peripheral with respect to the center of the normally active population of neurons) can account for the reduced velocity. It is also worth reminding that Soetedjo et al. (2002) showed that after muscimol injection in the pontine reticular formation, the number of spikes emitted by SC neurons remained the same despite prolonged saccade duration (as expected by the author). However, they provided a different explanation (feedback to the SC). Note that projections from the nucleus prepositus hypoglossi to the SC are consistent with such feedback. It is unclear why the author ignores this anatomical fact (Hartwich-Young et al. 1990). All these observations constitute precious empirical clues that are useful to identify the physiological parameters that can vary from one trial to the next, i.e., the duration of activity, the firing rate, the number of spikes and the number of active neurons.

From the viewpoint of this reviewer, these neurophysiological results obtained sometimes during tedious experiments in the awake and trained monkey do not deserve less emphasis than theoretical speculations such as “additive” (L354, 356) and “multiplicative” (L320, 347, 357) noises in the brain. The neurophysiological meaning of these notions is unclear and possibly misleading. Unit recordings show that the firing rate of any SC neuron is rarely the same from one trial to the next in spite of quasi-identical initial conditions. In his article, the author prefers reporting the mismatch between his equations and the real data rather than reporting the actual data. Neither the variability of interspike intervals (during the burst) nor the variability of cumulative spikes counts are documented. By not showing the staircase of segments composing the cumulative spike numbers, the author prevents the readers from realizing that the emission of action potentials by SC neurons is neither a periodic process nor a continuous one. Freedman and Sparks (1997) showed that the interspike intervals are neither constant nor reproducible from one trial to the next (see their Fig. 5). By barely reporting the measured data, he prevents the readers not only from understanding what is variable but also comparing them with observations reported by others, seeing consistency and discrepancies.

Still concerning the report of real data, this reviewer noticed that the values of gaze amplitude and direction in Table S1 do not match the values plotted in Fig. S2. For instance, according to Table S1, $R_0=98.2$ and $\text{THETA}_0=-68.9$ for the neuron Sa0907. This neuron is not visible in Fig. S2. Reciprocally, Fig. S2 shows two blue circles with R values larger than 80 whereas Table S1 reports only one R value larger than 80 ($R_0=94.6$, neuron Pc2406).

Likewise, contrary to the author’s claim, the data in Fig. 6A do not show “the variability of the burst-related spike count as [a] function of the expected total number of spikes in the burst”. In the legend of Fig. 6A, one reads “the error in the predicted number of spikes” (L938). If this definition is correct, then one is led to infer that the plotted error (ordinate

axis) corresponds to the difference between the number of spikes predicted by equation 9 and the number of spikes that were actually measured. In other words, it is an index of the goodness of the model (the equation) to capture the data (measured values). Consequently, plotting the difference between the prediction of a model and the data as a function of the predicted number of spikes does not describe a so-called “signal dependent noise” (L305) if by “signal dependent noise”, the author refers to something related to the firing rate of neurons. The difference between the number of spikes predicted by an equation and the number of spikes emitted by a biological neuron has no physiological meaning. Plotting this difference as a function of a predicted value is even more speculative. This other example illustrates the necessity to warn the readers about differences between empirical data and theoretical notions.

Regarding the increase of the standard deviation with the mean number of spikes (Fig. 6B), it would be useful to show this relation for the neuron sa0107 also (Fig. 5B). Indeed, we can estimate (although with some difficulty) the various amplitudes of gaze shifts that were recorded with this neuron (note that a plot or an inset showing the variability of amplitude and direction of gaze shifts would be helpful in Fig. 5). Note Fig. 5B shows a counter example to the increase of the standard deviation with the mean number of spikes. Considering a number of spikes close to the maximum ($N > 25$), the values of straight-line gaze displacement ranged from approximately 25 to 48 degrees. Curiously, considering a smaller number of spikes ($N = 14$), the values of straight-line gaze displacement ranged from approximately 15 to 66 degrees. In other words, the variability is not larger with more numerous spikes. The description of Fig. 5B should be improved because it contains a lot of information. On the one hand, we know that the measured number of spikes depends upon the location of the visual target with respect to the center of the response field (RF). It is larger when the visual stimulus falls in the center of the RF (leading to the maximum saccade-related burst) than when the visual stimulus falls closer to the boundary of the RF (leading to a less vigorous burst). On the other hand, we also know that the size of the RF increases with the target eccentricity, and thus with the location of collicular activity along the rostrocaudal axis (see Fig. 2 of Taouali et al. 2015 and Fig. 8 of Munoz & Wurtz 1995). Therefore, we wonder whether the relation between the mean measured number of spikes and the standard deviation of the measured number of spikes is not the consequence of presenting the target at various locations in the response field of neurons. Finally, it is worth reminding the readers that the firing rate also depends upon the alertness and the motivation of the animal. Keeping these physiological facts in mind, the readers can eventually understand, or not, the meaning of “multiplicative noise in the cell’s activity”.

The statement of “excellent agreement between data and model” (L366) illustrates the theoretical inclination of the author. Unfortunately, such a statement is qualitative and rushed. After drawing the $y=x$ line, one sees that the majority of data points are situated above the diagonal. In other words, the predicted slopes overestimate the measured slope. Table S1 tells us that for cell Sa0508, when the gaze amplitude is 11 deg, the predicted number of spikes is 23, making a ratio of 2.09 spikes per degree. The turquoise line in Fig. 8A shows that for a predicted slope of a slope of 2.09, the measured slope is 1.82 spikes per degree. In other words, for a gaze amplitude of 11 deg, the average measured number of

spikes was $11 \times 1.82 = 20$ spikes, i.e., 3 spikes less than the predicted number of spikes ($N_0=23$). Equation (9) overestimated the measured number of spikes by 15% for a gaze amplitude of 11 deg. Unfortunately, from looking at Fig. 8A, it is impossible to see neither the number of spikes measured during a gaze shift of 44 deg amplitude, nor the predicted number of spikes. Therefore, to facilitate the readers' understanding, before plotting the predicted number of spikes as a function of the measured number (as in Fig. 8A), the author should plot these two numbers (measured and predicted numbers of spikes) as a function of gaze amplitude for iso-directional gaze shifts ($\text{THETA} = \text{THETA}_0 \pm$ e.g. 5 deg or 10 deg). The plot in Fig. 8A could then be presented using open and filled symbols to distinguish iso-directional gaze shifts from others. Then, the slopes and y-intercepts of the relations between predicted and measured spikes could be documented for all cells so that the readers can see whether equation (9) systematically overestimated the measured number of spikes for each cells.

Below, the author will find more detailed comments on the figures and on the text. They are not exhaustive because reading this article was rather time-consuming and difficult for this reviewer.

COMMENTS ON THE OTHER FIGURES:

Figure 3:

panel A: Looking at the values for the head at gaze onset, this reviewer suspects that the title of the ordinate axis is G/H Displacement instead of G/H Position. It is also very rare that gaze direction is strictly equal to zero. The legend should be corrected accordingly (L900 and 901).

Panel B: one red curve (out of eight) is shifted toward negative values. It seems that the onset of the corresponding gaze shift was not properly detected (its velocity is larger than 250 deg/s at gaze onset). The author should check the impact of this mistake on the red curves illustrating the spike density function and the mean cumulative spike count.

Figure 4:

Panel C: The blue curves are barely visible. The author could use either a lighter blue (e.g., turquoise) or change the color of the background from black to grey. A scale for the color codes (number of spikes) would be welcome or an indication of the number of spikes corresponding to the thin white contour lines. What is Fopt? The same comments hold for Fig. S5.

Figure 5:

Legend:

L929: NSTMF instead of NMFST, in accordance with equation 9 (L771)

The author name this plot "Dynamic movement field" whereas the term "phase trajectory" is used in several place in the text (L289, L293, L364, L378, L523, L962). If the two

terminologies denote the same plot, the author should use only one to remove ambiguities. If they do not denote the same plot, then the author add an explanatory note.

Panel B: Ordinate axis: Which “Cumulative Spike Count” is plotted? The predicted spike count (as in panel C) or the measured spike count? It would be useful to make it clear in the figure.

Panel C: It may be preferable to plot the measured (ordinate) as a function of the predicted cumulative spike count (abscissa) as in Fig. 4C and Fig. S5. Maybe not.

Figure 6:

Title of y-axis: Model’s prediction error

Figure 8:

Panel A: The scales of x and y-axes do not facilitate the calculations that some readers would like to perform. A step of 0.5 is preferable to a step of 0.52. It is fine to use 3.0 as maximum values. Drawing the diagonal $y=x$ will enable the readers to see that the predicted slope overestimates the measured slope (majority of data points above the diagonal). The turquoise line likely illustrates the slope of the scatter. Unfortunately, it is not defined in the legend. Its slope, y-intercept and the number of datapoints should be documented in the legend.

Panels A and B: The cell identification number (Sa0508) should be inserted in order to facilitate the distinction between the plots corresponding to one cell and those corresponding to several cells.

Figure 9:

Panel A: As requested in the previous review, it is preferable, for conventional reasons, to use the word “amplitude” instead of “shift”.

Panel B: An inset should be added to show the delay between the time of peak firing rate and the time of peak gaze velocity. It is important for the readers to realize that in order to influence the peak velocity, the peak firing rate leads and not lags time to peak firing rate (see major comment).

Panel C: A graph plotting the time to peak gaze velocity as a function of time to peak firing rate should be added to assure that the peak firing rate led (and not lagged) time to peak firing rate (see major comment).

Table 1

The names of parameters do not match between table 1 and L778.

Legend, second line: FMFST=?

Fig. S5:

Legend: last sentence: “faster” instead of “fastest”?

MORE DETAILED COMMENTS:

L30-35: It would be useful to warn the readers that gaze shifts may also consist in multiple saccades (e.g., Bergeron & Guitton 2002; Anastasopoulos et al. 2015). The readers should also be warned that very large gaze shifts performed within a single step may result from experimental constraints (reinforcement learning) if the monkeys are required to perform their primary gaze saccades so that gaze lands within a (relatively) small window for obtaining a reward.

L 48-49: The references Quinet & Goffart (2007, 2009) are inappropriate to raise an objection against the author's statement. Indeed, the results of both studies may indicate that the activity of neurons in the caudal fastigial nuclei contributes to coupling the eye and head movements insofar as inactivating one side impairs the eye-head coupling. Together with other anatomical and electrophysiological data (see their discussion), they indicate that eye-head gaze shifts are under cerebellar control and that the fastigial exerts its influence primarily upon the oculomotor network. This reviewer invited the author to consider these works in order to warn the readers that the kinematics of eye and head movements is also influenced by the activity of neurons in the caudal fastigial nucleus and that a gaze feedback control is controversial.

L140: "Peel et al. (2021)" instead of "Peel et al. (2020)".

L143: "smaller" instead of "slightly higher".

L147: The word "however" should be removed because the following sentence ("the variability ... difficult to detect") is consistent with the previous sentence ("Further, Zhang et al. (2022) ... for all conditions"). Or the argument is not clear.

L153: This reviewer fears that the suggestion that "the SC has no central role in saccade control (Daye et al. 2014)" (L153) misleads the readers. She/invites the author to either remove it or insert "Moreover" before "immediate deficits in saccade metrics ..." (L156) and add "immediately" between "observed" and "after acute reversible microlesions" (L157).

L162-166: It would be useful to inform the young readers that this crucial role of both SC and FEF was suggested by the lesion study performed by Schiller, True & Conway (1980).

L196: It would be useful to add a reference showing that the rotation axes of the head do not intersect in a fixed point.

L216: "during experiment Sa1007" instead of "of experiment Sa1007"

L220: "when the eye looked ipsilateral to the target" is clumsy and potentially confusing because the target is being foveated. Does the author mean "when the eye was deviated toward the side ipsilateral to the direction of the imminent gaze shift"?

L223: "with ipsilateral eye deviations" instead of "with the eye ipsilateral"?

L224: It would be neat to document the percentages of prolongation (for the duration) and reduction (for the peak velocity).

L234: "Figure 3 shows a selection of gaze shifts recorded during this experiment and initiated from the three initial eye positions" instead of "Figure 3 shows a selection of gaze shifts from this experiment from the three initial eye positions"

L237-248: The author should check whether the statements about the peak firing rate and its timing remain true after modifying Fig. 3. L249: "ipsi-condition (blue)" instead of "contra-condition (blue)"

L244-253: The author should warn the reader that the interspike intervals vary considerably across the trials and that the mean cumulative spike counts masks the variable firing rate of SC neurons, which contrasts with the clock-like firing rate of premotor burst neurons (Hu et al. 2007).

L249: "the timing of its peak" instead of "its peak location"

L258: "all action potentials" instead of "all neural responses"

L264-265: Choi & Guitton (2009) showed that the population the burst does not always ends before gaze end (see middle row of Figure 6C). Therefore, this reviewer suggests replacing "as reported in earlier studies (Freedman & Sparks, 1997; Choi and Guitton, 2009)" by "as reported by Freedman & Sparks (1997), but not always (see e.g., Choi & Guitton 2009)".

L268: "toward the center of the movement field" instead of "into the center of the movement field".

L268: "as well as" instead of "as well."

L271: "cumulative spike count (CSC) instead of "CSC" because the abbreviation has not been previously defined.

L271-272: The author remarks that "the CSC trajectories nearly fully overlap along the $y=x$ diagonal, despite the considerable variation in gaze-shift kinematics". The overlap indicates a good match between the measured and the predicted cumulative spike counts". Note that the methods used to measure the number of spikes (Fig. 5) are not documented.

L275: "which is indeed seen in the CSC trajectories": an arrow would be useful to indicate at which location the reader must look to see.

L274: $N_{opt}=30$ whereas $F_{opt}=25$ in Fig. 4C. What is F_{opt} ? What is N_{opt} ?

L291: Fig. 5B shows that for a given value of measured total number of spikes (e.g., $N=16$), the straight-line gaze displacement amplitude can range from 19 deg to 62 deg? The author should explain why a large

L301: "predicted" instead of "expected"

L302: "ranged from 16 to 24 spikes" instead of "varied between 16 and 24 spikes"

L303: "the mismatch between the predicted and the measured number of spikes" instead of "this variability". By using the word "variability", the author makes a semantic drift which leads the readers to confound the variable firing rate of neurons visible across the trials (as

illustrated in Fig. 3 and Fig. 4) with the ability of an equation to fully account for the measured values.

L303: +/- 20% ? How was this calculated ? Is it the average value?

L307-312: This paragraph is unclear and should be rephrased.

L309-310: "a predicted number of spikes is calculated for all saccade vectors that lie ..." would be preferable instead of "a particular expected number of spikes is predicted for all saccade vectors that lie ..."?

L318: "predicted" instead of "expected"

L317-318: See major comment

L322: "slope=0.141" instead of "Cv=0.141"

L332: Suggested change: "invariant to changes in starting eye positions" instead of "invariant to changes in starting eye positions"

L344: For the sake of simplicity, the sentence "Figure 7C provides histograms for the coefficients of variation (slopes of the relationship), Fig. 7D shows the distribution of correlations" can be replaced by "Figure 7C provides histograms for the slopes of the relationship and Fig. 7D the distribution of correlation coefficients between the average number of spikes and standard deviation.

L346: The wording "the neuronal variability" is vague. The author meant "the variability in the number of spikes during the gaze movement related burst".

L347: The author should explain the physiological meaning of "multiplicative noise".

L349-351: For consistency, the sentence "The median value for the population, CV = 0.24, is comparable to the mean CV = 0.28 ± 0.16 reported by Goossens and Van Opstal (2012) for head-restrained eye saccades from >100 neurons across the SC motor map." Could be replaced by "The median slope value for the population (0.24) is comparable to the mean slope = 0.28 ± 0.16 reported by Goossens and Van Opstal (2012) for >100 neurons across the SC motor map during head-restrained eye saccades."

L351-352: The sentence "The low values of CV ($\ll 1.0$) 352 indicate that SC cells are typically characterized as being low variance" should be rephrased because it is unclear. It sounds like a tautological statement.

L358-359: The sentence "for a typical maximum of 25 spikes, the standard deviation is $0.24 \times 25 = \pm 6$ spikes (i.e., ranging from 19-31 spikes)" is unclear and seems to be wrong. The author estimates the minimum value to $25 - 6 = 19$ spikes and the maximum value to $25 + 6 = 31$ spikes, but the interval mean +/- one standard deviation does not contain 100 % but 68 % of values. In fact, 99 % of values are contained in the interval mean +/- 3 standard deviations.

L364: Could "(as in Fig. 5B)" be added after "phase trajectories"? If it cannot, then it is unclear what the measured slope is.

L368-379: This paragraph is unclear and should be rephrased. This reviewer understands that Fig. 8B plots the difference between measured cumulative number of spikes and the predicted cumulative number of spikes. Contrary to the predicted cumulative number of spikes, the measured cumulative number of spikes is NOT a line, i.e., a continuous function. The cumulative number of spikes is a step function (like a staircase) with irregular steps (see for instance Sparks 1976, 1978, Sparks & Porter 1983; Moschovakis et al. 1988; Freedman & Sparks 1997; Goffart et al. 2017). It is important to warn the young and unwary readers that the interspike interval is neither constant nor reproducible from one trial to the next. Therefore, this reviewer requests a figure that shows the difference between the predicted and the measured cumulative number of spikes by plotting 1) both of them as a function of time from saccade onset to gaze end and 2) the difference between the measured interspike intervals and the predicted interspike intervals. See also major comment.

L402-409: See major comment

L471: "Kolmogorov" instead of "Kolomogorov"

REFERENCES:

- Anastasopoulos, D., Naushahi, J., Sklavos, S., & Bronstein, A. M. (2015). Fast gaze reorientations by combined movements of the eye, head, trunk and lower extremities. *Experimental brain research*, 233, 1639-1650.
- Bergeron, A., & Guitton, D. (2002). In multiple-step gaze shifts: omnipause (OPNs) and collicular fixation neurons encode gaze position error; OPNs gate saccades. *Journal of neurophysiology*, 88(4), 1726-1742.
- Bergeron, A., Matsuo, S., & Guitton, D. (2003). Superior colliculus encodes distance to target, not saccade amplitude, in multi-step gaze shifts. *Nature neuroscience*, 6(4), 404-413.
- Bourrelly, C., Quinet, J., & Goffart, L. (2021). Bilateral control of interceptive saccades: evidence from the ipsipulsion of vertical saccades after caudal fastigial inactivation. *Journal of Neurophysiology*, 125(6), 2068-2083.
- de Carrizosa, M. A. D. L., Morado-Díaz, C. J., Miller, J. M., de la Cruz, R. R., & Pastor, Á. M. (2011). Dual encoding of muscle tension and eye position by abducens motoneurons. *Journal of Neuroscience*, 31(6), 2271-2279.
- Freedman, E. G., & Sparks, D. L. (1997). Eye-head coordination during head-unrestrained gaze shifts in rhesus monkeys. *Journal of neurophysiology*, 77(5), 2328-2348.
- Freedman, E. G., & Sparks, D. L. (1997). Activity of cells in the deeper layers of the superior colliculus of the rhesus monkey: evidence for a gaze displacement command. *Journal of neurophysiology*, 78(3), 1669-1690.
- Fuchs, A. F., Brettler, S., & Ling, L. (2010). Head-free gaze shifts provide further insights into the role of the medial cerebellum in the control of primate saccadic eye movements. *Journal of neurophysiology*, 103(4), 2158-2173.

- Goffart, L., Burrell, C., & Quinton, J. C. (2018). Neurophysiology of visually guided eye movements: critical review and alternative viewpoint. *Journal of Neurophysiology*, 120(6), 3234-3245.
- Goffart, L., Cecala, A. L., & Gandhi, N. J. (2017). The superior colliculus and the steering of saccades toward a moving visual target. *Journal of Neurophysiology*, 118(5), 2890-2901.
- Hanes, D. P., Smith, M. K., Optican, L. M., & Wurtz, R. H. (2005). Recovery of saccadic dysmetria following localized lesions in monkey superior colliculus. *Experimental Brain Research*, 160, 312-325.
- Hartwich-Young, R., Nelson, J. S., & Sparks, D. L. (1990). The perihypoglossal projection to the superior colliculus in the rhesus monkey. *Visual neuroscience*, 4(1), 29-42.
- Hu, X., Jiang, H., Gu, C., Li, C., & Sparks, D. L. (2007). Reliability of oculomotor command signals carried by individual neurons. *Proceedings of the National Academy of Sciences*, 104(19), 8137-8142.
- Keller, E. L., McPeck, R. M., & Salz, T. (2000). Evidence against direct connections to PPRF EBNs from SC in the monkey. *Journal of Neurophysiology*, 84(3), 1303-1313.
- Moschovakis, A. K., Karabelas, A. B., & Highstein, S. M. (1988). Structure-function relationships in the primate superior colliculus. II. Morphological identity of presaccadic neurons. *Journal of Neurophysiology*, 60(1), 263-302.
- Munoz, D. P., & Wurtz, R. H. (1995). Saccade-related activity in monkey superior colliculus. I. Characteristics of burst and buildup cells. *Journal of neurophysiology*, 73(6), 2313-2333.
- Quinet, J., & Goffart, L. (2007). Head-unrestrained gaze shifts after muscimol injection in the caudal fastigial nucleus of the monkey. *Journal of neurophysiology*, 98(6), 3269-3283.
- Quinet, J., & Goffart, L. (2009). Electrical microstimulation of the fastigial oculomotor region in the head-unrestrained monkey. *Journal of neurophysiology*, 102(1), 320-336.
- Schiller, P. H., True, S. D., & Conway, J. L. (1980). Deficits in eye movements following frontal eye-field and superior colliculus ablations. *Journal of neurophysiology*, 44(6), 1175-1189.
- Soetedjo, R., Kaneko, C. R., & Fuchs, A. F. (2002). Evidence that the superior colliculus participates in the feedback control of saccadic eye movements. *Journal of neurophysiology*, 87(2), 679-695.
- Sparks, D. L. (1978). Functional properties of neurons in the monkey superior colliculus: coupling of neuronal activity and saccade onset. *Brain research*, 156(1), 1-16.
- Sparks, D. L., Holland, R., & Guthrie, B. L. (1976). Size and distribution of movement fields in the monkey superior colliculus. *Brain research*, 113(1), 21-34.
- Sparks, D. L., & Hu, X. (2006, January). Saccade initiation and the reliability of motor signals involved in the generation of saccadic eye movements. In *Percept, Decision, Action: Bridging the Gaps: Novartis Foundation Symposium 270* (pp. 75-91). Chichester, UK: John Wiley & Sons, Ltd.

Sparks, D. L., Lee, C., & Rohrer, W. H. (1990). Population coding of the direction, amplitude, and velocity of saccadic eye movements by neurons in the superior colliculus. In Cold Spring Harbor symposia on quantitative biology (Vol. 55, pp. 805-811). Cold Spring Harbor Laboratory Press.

Taouali, W., Goffart, L., Alexandre, F., & Rougier, N. P. (2015). A parsimonious computational model of visual target position encoding in the superior colliculus. *Biological cybernetics*, 109, 549-559.

Van Gisbergen, J. A., Robinson, D. A., & Gielen, S. T. A. N. (1981). A quantitative analysis of generation of saccadic eye movements by burst neurons. *Journal of Neurophysiology*, 45(3), 417-442.

FIRST ASSESSMENT REPORT:

Neurophysiological works in the awake behaving monkey are not only a very tough job but also socially thankless. Yet they are crucial for identifying the biological substrates of neurological and psychiatric disorders and for understanding the physiological processes that constrain our interactions with the external environment. People who are courageous to do this kind of job have become very rare because of its multiple difficulties.

This reviewer makes this introduction in order to congratulate the author for the beautiful set of data that he managed to collect in two monkeys, which were tested with the head unrestrained. Recording the activity of neurons in the head unrestrained monkey is a very challenging task and the collected data are rare and precious.

It has long been known that the sustained activity of neurons in the deep superior colliculus (SC) is an important aspect of their involvement in orienting gaze. The maintenance of firing only concerns the activity generated during saccades and not the complete activity that elapses from the target onset until the saccade end. Using the microstimulation technique, Drs Stanford, Freedman and Sparks indeed showed that if the SC activity is not long enough, the electrically-evoked movement is truncated; the amplitude specified by the locus of activity in the SC cannot be fully accomplished (Freedman et al., 1996; Stanford et al., 1996). In this article, the author completes this seminal result by recording the firing rate of SC neurons and proposes that, in addition to feeding the premotor neurons with the drive required to change the orientation of the eyes and head, the SC neurons also determine the instantaneous velocity of gaze movements. This proposal is important and timely because this kinematic control has recently been questioned by Zhang et al. (2022) and by Goffart et al. (2018, 2019) based on empirical and logico-theoretical arguments, respectively.

This reviewer made an extensive work in order to 1) help the author to sharpen his arguments, 2) sustain the important value of the data that he collected in the head-unrestrained monkey and 3) reward him for his efforts to complete such a challenge. However, she/he encountered several concerns. The author should be able to correct them because they do not concern the data per se, but their theoretical context and interpretation.

I. The first concern is that the author wrote his article in the spirit of providing arguments that support his preferred hypothesis without considering observations that refuted it, or without explaining why his hypothesis remains valid despite them. More specifically, the author ignored the observations that Lee, Rohrer and Sparks (1988) made on the accuracy and velocity of saccades after injecting small quantities of lidocaine in the SC. He also ignored the observations that Peel et al. (2021) made in the saccade-related burst of SC neurons after cryogenic inactivation of the FEF. From the point of view of this reviewer, these two studies refute the author's hypothesis because they invalidate its predictions: if the cumulative number of spikes in the burst of SC neurons dictates the vectorial gaze movement amplitude, then reducing the number of active neurons in the SC or reducing their firing rate should render the saccades hypometric.

A) Yet, inactivation of the center of the population of active neurons does not lead to hypometric saccades. The figure 3 in Sparks, Lee & Rohrer (1990) and in Lee, Rohrer & Sparks (1988) show that despite a severe reduction in their velocity, the saccades are normometric (see also figure 12A in Goffart et al. 2012).

B) Moreover, by cooling the FEF and recording its consequences on the firing rate of saccade-related burst neurons in the SC, Peel and colleagues (2021) found that the total number of spikes emitted by SC neurons was decreased while the amplitude of saccades remained unchanged. The number of spikes was reduced both at the center and throughout the entire movement field.

Therefore, before extending to the control of combined eye and head movements a hypothesis that is potentially invalid, the author should explain in the introduction why the results of these other studies do not refute his dynamic ensemble-coding hypothesis.

II. The second major concern is the lack of consideration of results that relate to the firing rate of neurons targeted by the SC neurons, the premotor burst neurons constituting the so-called “brainstem burst generator”:

C) Hu et al. (2007) showed in the head-restrained monkey that the premotor burst neurons do not fire at a rate that mimics the eye velocity profile but at a relatively constant rate. They reported instantaneous firing rates that resemble the recordings of van Gisbergen et al. (1981).

D) Walton & Sparks (2011) showed in the head-unrestrained monkey that the peak and average firing rates of premotor burst neurons decrease as the duration of the movement increases and as gaze amplitude increases.

From the point of view of this reviewer, these results are not compatible with the author’s model, in which the instantaneous firing rate of neurons in the “brainstem burst generator” dictates the instantaneous eye velocity. Therefore, the author should explain in the introduction why these other empirical data do not invalidate his model. This concern leads to the next one.

III. The third concern is related to the interpretation of results. Studying the correlation between the firing rate of central neurons and the kinematics of gaze shifts should be made with caution. Several elements separate the spikes emitted by SC neurons and the contraction of extraocular muscle fibers. On the one hand, there are the post-synaptic neurons (premotor burst neurons) and their targets, the motor neurons. All these neurons do not passively transmit the collicular spikes to the extraocular muscles. On the other hand, the premotor burst neurons also receive crucial input from saccade-related neurons in the contralateral caudal fastigial nucleus whose activity influences the velocity and accuracy of saccades in the head restrained (Goffart et al. 2004) and the unrestrained monkey (Quinet & Goffart 2007). The fact that the author did not incorporate these findings in his model should not prevent him from warning the readers about the limitations of his hypothesis and about the blinkers of other theoreticians. By warning the readers, he offers to future readers

the opportunity either to think about these other results or to understand why they can be discarded.

IV. Still related to results from past studies, the fourth concern is the delay of 20 ms between the emission of action potentials in the SC and the change in eye orientation. Why did the author choose a value of 20 ms instead of 8 ms? Miyashita & Hikosaka (1996) explained that when an electrical microstimulation was applied to the SC during a saccade, a small, conjugate contraversive eye movement was evoked with latencies much shorter than when the stimulation was applied while the eye fixated or did not move. The mean latencies of the stimulus-evoked eye movements were 7.9 ms (ipsilateral eye) and 7.8 ms (contralateral eye) when the stimulation was intrasaccadic. The author should warn the readers and discuss the consequences that taking a delay twice longer have upon the conclusions.

V. The fifth concern is that the author interprets his results within a theoretical framework that seems to rest upon no physiological evidence. In the discussion, the reader is taught “a trade-off for the oculomotor system that deals with the detrimental effects of multiplicative noise in its neural control” (L555). He/she is also taught that “by reducing the powerful, but noisy, pulse from the brainstem saccadic burst generator on the eye plant for large saccades, the system would thus avoid the danger of saccadic overshoots” (L559). In the introduction, the author tells us that “the saccadic gaze shifts result from a control principle that optimizes some joint performance criterion by trading off speed, accuracy and control effort, to minimize the impact of internal noise and uncertainty in the system and the resulting variability in its output performance measures”. These speculations are based upon behavioral studies, which did not consider the reliable firing rate of burst neurons reported by Hu et al. (2007) in the pontine reticular formation. Therefore, the author should explain what he means with “internal noise”, “uncertainty in the system” and “powerful, but noisy, pulse from the brainstem saccadic burst generator”.

VI. Regarding the interpretation of Fig. 8B and Fig. 9B, it is not surprising that the correlation between the number of spikes and the peak gaze velocity is weak. Indeed, the peak velocity is a measurement made at a specific instant whereas the number of spikes is a measurement made over a longer time interval, the duration of the complete gaze shift. This reviewer does not understand how spikes emitted AFTER the peak velocity of gaze shifts can be related to it. If a causal relation exists between the firing rate of neurons and the gaze velocity profile, then spikes emitted after the peak velocity cannot influence it anymore. Would not it be preferable to plot the relation between the gaze peak velocity and the number of spikes that were emitted before its occurrence? Or more simply, the relation between the average firing rate and the average velocity of gaze shifts?

Besides these general comments, the author will find below several difficulties that the reviewer encountered while reading this manuscript.

INTRODUCTION

L29-31: “Programming a gaze shift is a redundant task, as it can be generated by infinitely many combinations of eye-and head contributions” is an odd statement. The author assumes the existence of a “smart” gaze-control system that selects “reproducible movement strategies”. This idea contrasts with the less anthropomorphic view according to which there is no selection. Given the orientation of the eyeballs in the orbits and the orientation of the head relative to the trunk, the combinations of the eye and head movements are not infinite but determined by neuro-muscular constraints.

L35: The meaning of the sentence “the saccadic gaze shifts result from a control principle that optimizes some joint performance criterion by trading off speed, accuracy and control effort” is unclear. Neurophysiologically speaking, what is a “control principle”? It is also unclear how a set of active neurons are informed about physical measurements, such as the amplitude of a movement, its duration and the amplitude/duration ratio? What does “control effort” mean?

L44: Bizzi et al. (1971) and Freedman & Sparks (2000) did not show that head movements depended on the initial-eye-in-head orientation.

L48-49: The idea that “the eye- and head movement interact within a common gaze-feedback loop” is refuted by several observations made in the caudal fastigial nucleus. This region contains a group of cells that project to the pontomedullary reticular formation (Noda et al. 1990) and that burst during saccades without modulating their firing during head movement (Fuchs et al. 2010). Their exclusive oculomotor function is confirmed by the absence of head movement when the caudal fastigial nucleus is electrically stimulated (Quinet & Goffart 2009) and also by the oculomotor deficits when muscimol is injected locally (Quinet & Goffart 2007). After muscimol injection, the amplitude and velocity of contralesional saccades are reduced and these reductions are not compensated, neither by an increase of saccade duration nor by an enhanced contribution of the head, refuting therefore the notion of a gaze feedback loop.

L57-58: The references Gandhi (2012) and Phillips et al. (1995) could be added because they also illustrate these relations in several monkeys.

L65: Scudder (1988) did not provide evidence for “a topographically organize motor map of saccadic eye movements” in the SC. Hafed & Chen (2016) did.

L66-68: The statement that “a large population of cells encodes amplitude and direction by the location of its center within the map” contained in the Superior Colliculus is an inaccurate statement. An injection of lidocaine in the peripheral part of the population of active neurons spares its center but renders saccades inaccurate (Lee et al. 1988; Sparks et al. 1990). Sparks and colleagues also showed that the saccades remain accurate when the center of the active population was inactivated (their velocity is reduced and their duration increased).

L68: The reference Anderson et al. (1998) could be added to support the recruitment of a large population of cells.

L73-74: Contrary to the author's claim, the results of Lee et al. (1988) do not lead to the conclusion that "higher mean firing rates lead to faster saccades than lower rates". By local injections of a small volume of lidocaine in the SC, they showed that the suppression of a subset of SC neurons leads to slower saccades.

L127-128: The references Pelisson et al. (1989), Guitton et al. (1990) are irrelevant to illustrate the point that the author wants to make. The reference Pare & Guitton (1994) is more appropriate. It would be preferable to replace the reference Munoz et al. (1991) by Munoz & Guitton (1991) in order to prevent the unwary readers from thinking that the activity spreads across the SC during gaze shifts (see Sparks (1992) and Moschovakis et al. (2001)).

L181: "the firing rate of SC neurons during eye-head gaze shifts" instead of "the encoding of eye-head gaze shifts by SC neurons"

RESULTS

L230: It seems that the author means "horizontal and vertical amplitudes" instead of "endpoint" (which refers to a position).

Figure 3: The yellow dashed line is barely visible. A different color (green ?) would make it more visible. The interpretation of the plot A is impossible because all the movements are mixed. This reviewer and the readers would prefer to see the spikes emitted when the monkey made gaze shifts of comparable horizontal and vertical amplitudes. Separating gaze shifts made from the eyes centered in the orbits from those launched from deviated eyes would also be more informative than the mixture shown in panel A. An additional plot showing the same rasters aligned on gaze shift end would show whether this neurons stopped firing before gaze shift end (as Freedman & Sparks (1997) reported) or after (Choi & Guitton (2009)).

L242-244: the text tells us that Figure 4A compares the predicted and the measured number of spikes but it does not tell us what lesson should be taken from this comparison. It would be useful to document this comparison for movements with matched amplitude and direction. The readers are unable to see whether the big mismatch between the predicted and measured number of spikes is due to variable (uncontrolled) gaze metrics. For example, when we consider the case of 20 measured spikes, we see that the number of spikes predicted by equation (7) ranges between 14 and 23. We are also unable to know whether this prediction is good or not if we are not told what movement is associated with 14 and 23 (measured) spikes. In other words, how well does the equation predict the gaze shift amplitude based on the recorded spikes? The plots in Figure 4 show that the red, blue and black dots overlap. Unfortunately, the author does not explain the meaning of the overlap. Likewise, he does not explain the meaning of the slope of the relation between the cumulative number of spikes and the gaze-target vector (so-called "straight-line gaze displacements). Adding a plot showing individual phase trajectories that correspond to the same gaze amplitude would help the readers to interpret them.

L244-246: the sentence “The cell had its center ... spikes/deg” should be moved in the previous section. It should also be rewritten because reading that “the cell had its center at (X,Y)=(36.0, 23.3), a peak of $N_o=25$ spikes, and an eye-position sensitivity of 0.003 spikes/deg” sounds like a jargon. The author likely meant “the movement field of that cell”.

L252-253: Is it not equation 9 that predict “cumulative spike counts”?

Figure 5: this reviewer would like to see the plots of cumulative spike count as a function of the gaze-target distance. They would provide support to the statement that “the phase trajectories were remarkably similar” (L270-271). In the legend, the word “velocity” should be inserted between “head-movement” and “profiles” (L276-277).

L268 and L270: “velocity” instead of “kinematics”

L296: “27 and 32 spikes” instead of “27.75 and 32.25 spikes”?

L303: “movement fields” instead of “gain fields”?

L315: Is N_c = measured number of cumulated spikes and N_c with circumflex accent = predicted number of cumulated spikes?

FIGURE 7B: title of y-axis: number of gaze shifts? “Number of Data Points” is unclear.

L331: “differences” instead of “deviations”

L333: “differences” instead of “errors”

L334: “difference” instead of “error”

FIGURE 8:

Different colors should be used to facilitate the distinction between the 7 clusters.

Plot A: titles of x- and y-axes: “Gaze-Amplitude” instead of “Gaze-shift”

Plot B:

Title of x-axis: what is Peak DESIRED Gaze Velocity? Is it not the MEASURED peak velocity of gaze shift that is plotted?

Title of y-axis: “spk/s” instead of “Hz”

L346-347: “gaze-shift velocity” instead of “gaze-shift kinematics”

L346: The claim that “peak firing rate strongly covaried with peak velocity” is not convincing. The author’s perception seems to be biased by the three largest values of peak gaze velocity. Did the author verify that these three gaze shifts were not recorded at the beginning of the recording session, i.e., when the monkey was the most motivated? Moreover, a careful look at the data points in Fig. 8B shows multiple examples where the peak firing rate does not change despite a doubling of peak velocity. The author should teach the readers how to read figures in order to prevent them from making premature conclusions.

L361: what is “gaze peak track-velocity”?

L364: what is the “velocity gain for the number of spikes”?

L369: the meaning of each variable should be specified.

L372: “a cell’s maximum firing rate” instead of “a cell’s firing rate”. The word “strong” should be removed unless the author provides a numerical value. Moreover and more crucially, for the peak firing rate to be a “predictor” for the peak gaze velocity, the time of peak firing rate must precede the time of peak velocity. The author did not document this crucial information.

FIGURE 9:

Why are some dots red colored? Do they correspond to the cell sa1007 (as suggested by L472)?

L386: Considering that collicular spikes precede and contribute to the contraction of extraocular muscles, it is confusing to read that it is the instantaneous firing rate that is delayed instead of the gaze velocity.

The middle panel is meaningless because the interval during which the number of spikes is equal to gaze shift duration. During this interval, both the gaze position and the cumulative spike number increase. It is impossible that the cumulative spike number decrease. Some positive correlation is expected. Moreover, the author distorted the cumulative number of spikes. It should not appear as a continuous ramp but as a kind of staircase. The author should warn the readers about these numerical manipulations.

The plot at the bottom of Fig. 10A does not show the instantaneous firing rate but the convolved firing rate. Each spike was convolved by a Gaussian curve. This transforms a sequence of discrete events (the action potentials) into a continuous curve and enables the author to test the correlation with velocity profile. The author declares this correlation “reasonable” (L390) while this reviewer remains cautious because there is a gap between a single sequence of action potentials and the combination of multiple post-synaptic and poly-synaptic sequences. Studying this kind of correlation prevents the readers from realizing that, between the recorded SC neuron and the contraction of extraocular muscle fibers, there are intermediate neurons, at last two sets of neurons, the premotor neurons and the motor neurons. The premotor neurons receive spikes also from other neurons, some of which are located in the caudal fastigial nucleus and play a major role in the generation of gaze shifts.

L390: what means “25 top-activity trials”?

L394-395: the author should document the delay between the peak of the convolved firing rate and the peak gaze velocity. The difference between the time of smallest interspike interval (highest firing rate) and the time of the peak of the convolved firing rate should also be documented in order to help the readers estimate the impact of convolving the spikes with Gaussian curves.

L417-418: Is the “straight-line gaze displacement” the vectorial gaze displacement amplitude?

L386: what is “gaze track-velocity”? Is it different from the vectorial gaze velocity? If not, then the “gaze track-velocity” should be replaced by “vectorial gaze velocity” throughout the manuscript.

L428 and L445: If “gaze-track velocity” is the same as vectorial gaze velocity, then use the latter wording?

L428: what means “best-recorded cells”?

L434: the author should define what $P(r)$, P_0 and r mean.

L444: the word “convolved” should be inserted between “instantaneous” and “firing rate”.

DISCUSSION:

L459: the small values of epsilon (eye position sensitivity factor) in Table S1 does not seem consistent with the statement that “eye position strongly influenced the SC firing-rate profiles in all neurons”. Indeed, all epsilon values are smaller than 0.02 spikes / degree, i.e., 1 spike / 50 degrees.

L463-465: This reviewer also thinks that the high firing rate of SC neurons increases the probability of observing synchronized action potentials within the population of bursting neurons. However, it is unclear why the correlation of the activity of single SC neurons with “the behavioral outcomes” leads the author to imagine “a tight synchronization of the activity patterns within the population”. The sentence should be rephrased.

L472: It is unclear why Fig. 9 is mentioned. Do the red data points correspond to the unit #sa1007 during which these movements were recorded?

L476: “unchanged” instead of “unaffected”?

L478: A correlation between the instantaneous firing rate and instantaneous gaze velocity does not imply a causal chain. The changes in firing rate must precede the change in eye velocity.

L543-544: Contrary to the author’s belief, Hepp et al. (1993) did not report that “large bilateral injections of muscimol in monkey demonstrated that the animal no longer generated any visual evoked saccades”. Nothing was demonstrated in fact. Hepp et al. (1993) merely reported a reduction in the frequency and velocity of spontaneous rapid eye movements made spontaneously in the light. The amounts of reduction were not documented.

L544-547: Likewise, neither Goossens and Van Opstal (2006) nor Peel et al. (2020) or Zhang et al. (2022) showed that small local reversible lesions led to “immediate and specific deficits in the metrics (endpoints away from the lesion) and kinematics (substantially slower, by more than 20%) of saccades”. These references should be removed. The study of Goffart, Hafed & Krauzlis (2012) could be added because it documented correlated changes in the latency and peak velocity of contralesional saccades after the local injection of a small amount of muscimol in the SC (their Fig. 12A).

FIGURE S3:

Is “track displacement” the same as vectorial displacement?

FIGURE S8:

The titles of y axes and the legend must be corrected. The plots A and C do not show gaze and head positions as a function of time but the amplitude of gaze and head displacements.

METHODS:

It is unclear whether the deviations of the head relative to body sagittal plane were only horizontal. Presumably, the values of horizontal and vertical orientation of the head were required to be within a range.

L703: the author should indicate how the accuracy of gaze shifts was controlled. Presumably, the gaze direction was required to land within a window relative to the target location. What was its radius?

Figure S1: scales for the gaze position and velocity should be added.

REFERENCES MENTIONED IN THE COMMENTS:

- Anderson, R. W., Keller, E. L., Gandhi, N. J., & Das, S. (1998). Two-dimensional saccade-related population activity in superior colliculus in monkey. *Journal of Neurophysiology*, 80(2), 798-817.
- Choi, W. Y., & Guitton, D. (2009). Firing patterns in superior colliculus of head-unrestrained monkey during normal and perturbed gaze saccades reveal short-latency feedback and a sluggish rostral shift in activity. *Journal of Neuroscience*, 29(22), 7166-7180.
- Fuchs, A. F., Brettler, S., & Ling, L. (2010). Head-free gaze shifts provide further insights into the role of the medial cerebellum in the control of primate saccadic eye movements. *Journal of neurophysiology*, 103(4), 2158-2173.
- Gandhi, N. J. (2012). Interactions between gaze-evoked blinks and gaze shifts in monkeys. *Experimental brain research*, 216, 321-339.
- Goffart, L. (2019). Kinematics and the neurophysiological study of visually-guided eye movements. *Progress in Brain Research*, 249, 375-384.
- Goffart, L., Burrelly, C., & Quinton, J. C. (2018). Neurophysiology of visually guided eye movements: critical review and alternative viewpoint. *Journal of Neurophysiology*, 120(6), 3234-3245.
- Goffart, L., Chen, L. L., & Sparks, D. L. (2004). Deficits in saccades and fixation during muscimol inactivation of the caudal fastigial nucleus in the rhesus monkey. *Journal of neurophysiology*, 92(6), 3351-3367.

- Goffart, L., Hafed, Z. M., & Krauzlis, R. J. (2012). Visual fixation as equilibrium: evidence from superior colliculus inactivation. *Journal of Neuroscience*, 32(31), 10627-10636.
- Hafed, Z. M., & Chen, C. Y. (2016). Sharper, stronger, faster upper visual field representation in primate superior colliculus. *Current Biology*, 26(13), 1647-1658.
- Lee, C., Rohrer, W. H., & Sparks, D. L. (1988). Population coding of saccadic eye movements by neurons in the superior colliculus. *Nature*, 332(6162), 357-360.
- Miyashita, N., & Hikosaka, O. (1996). Minimal synaptic delay in the saccadic output pathway of the superior colliculus studied in awake monkey. *Experimental brain research*, 112, 187-196.
- Moschovakis, A. K., Gregoriou, G. G., & Savaki, H. E. (2001). Functional imaging of the primate superior colliculus during saccades to visual targets. *Nature neuroscience*, 4(10), 1026-1031.
- Noda, H., Sugita, S., & Ikeda, Y. (1990). Afferent and efferent connections of the oculomotor region of the fastigial nucleus in the macaque monkey. *Journal of Comparative Neurology*, 302(2), 330-348.
- Peel, T. R., Dash, S., Lomber, S. G., & Corneil, B. D. (2021). Frontal eye field inactivation alters the readout of superior colliculus activity for saccade generation in a task-dependent manner. *Journal of Computational Neuroscience*, 49, 229-249.
- Phillips, J. O., Ling, L., Fuchs, A. F., Siebold, C., & Plorde, J. J. (1995). Rapid horizontal gaze movement in the monkey. *Journal of neurophysiology*, 73(4), 1632-1652.
- Quinet, J., & Goffart, L. (2007). Head-unrestrained gaze shifts after muscimol injection in the caudal fastigial nucleus of the monkey. *Journal of neurophysiology*, 98(6), 3269-3283.
- Quinet, J., & Goffart, L. (2009). Electrical microstimulation of the fastigial oculomotor region in the head-unrestrained monkey. *Journal of neurophysiology*, 102(1), 320-336.
- Sparks, D. L. (1993). Are gaze shifts controlled by a 'moving hill' of activity in the superior colliculus? *Trends in neurosciences*, 16(6), 214-218.
- Sparks, D. L., Lee, C., & Rohrer, W. H. (1990). Population coding of the direction, amplitude, and velocity of saccadic eye movements by neurons in the superior colliculus. In *Cold Spring Harbor symposia on quantitative biology* (Vol. 55, pp. 805-811). Cold Spring Harbor Laboratory Press.
- Sparks, D. L., Holland, R., & Guthrie, B. L. (1976). Size and distribution of movement fields in the monkey superior colliculus. *Brain research*, 113(1), 21-34.
- Van Gisbergen, J. A., Robinson, D. A., & Gielen, S. T. A. N. (1981). A quantitative analysis of generation of saccadic eye movements by burst neurons. *Journal of Neurophysiology*, 45(3), 417-442.
- Zhang, T., Malevich, T., Baumann, M. P., & Hafed, Z. M. (2022). Superior colliculus saccade motor bursts do not dictate movement kinematics. *Communications Biology*, 5(1), 1222.