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Triggering mechanisms in microsaccade and saccade generation: a novel proposal

Jorge Otero-Millan,[1,2] Stephen L. Macknik,[1] Alessandro Serra,[3,4] R. John Leigh,[3,4] and Susana Martinez-Conde[1]

[1]Barrow Neurological Institute, Phoenix, Arizona. [2]University of Vigo, Vigo, Spain. [3]Veterans Affairs Medical Center, Cleveland, Ohio. [4]Department of Neurology, Case Medical Center, Cleveland, Ohio

Address for correspondence: Susana Martinez-Conde, Ph.D., Director, Laboratory of Visual Neuroscience, Division of Neurobiology, Barrow Neurological Institute, 350 W. Thomas Road, Phoenix, AZ 85013. smart@neuralcorrelate.com

Saccades are rapid eye movements that change the line of sight between successive points of fixation. Even as we attempt to fixate our gaze precisely, small rapid eye movements called microsaccades interrupt fixation one or two times each second. Although the neural pathway controlling saccade generation is well understood, the specific mechanism for triggering microsaccades is unknown. Here, we review the evidence suggesting that microsaccades and saccades are generated by the same neural pathway. We also discuss current models of how the saccadic system produces microsaccades. Finally, we propose a new mechanism for triggering both microsaccades and saccades, based on a circuit formed by omnipause and long-lead burst neurons and driven by activity in the superior colliculus. Our model differs from previous proposals in that it does not require superior colliculus activity to surpass a particular threshold to trigger microsaccades and saccades. Rather, we propose that the reciprocal inhibition between omnipause and long-lead burst neurons gates each microsaccadic or saccadic event, triggering the eye movement whenever the activity in the long-lead burst neurons overcomes the inhibition from the omnipause neurons.

Keywords: eye movements; fixational eye movements; omnipause; superior colliculus; burst neurons; burst generator

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Introduction

Saccades are rapid eye movements that change the line of sight between successive points of fixation. They include a range of behaviors that encompasses both voluntary and involuntary shifts of fixation as well as the quick (i.e., saccadic) phases of vestibular and optokinetic nystagmus and the rapid eye movements that occur during REM sleep.[1]

Even as we attempt to aim our gaze precisely, small rapid eye movements called microsaccades interrupt fixation one or two times a second. Microsaccades have been linked to the restoration of faded visual images[2,3] and to fixation correction,[4,5] among other potential functions.[6] Mounting evidence suggests that microsaccades are generated by the same neural mechanisms that produce voluntary saccades,[5–10] but the precise circuit and mechanism that trigger microsaccades remain a mystery.

Here, we review previous studies of the neural mechanisms generating saccades and microsaccades. We also propose a novel neural circuit model to reconcile discrepancies in the literature and to explain how saccades and microsaccades are triggered in the oculomotor system.

Three possible signals could trigger microsaccades. First, a motor error signal could trigger microsaccades to foveate the target in response to a fixation error.[4] Second, spontaneous fluctuations of neural activity could trigger microsaccades at random times.[9] Third, insufficient image motion on the retina could trigger microsaccades to counteract visual adaptation and fading.[11]

These three possibilities—fixation error, neural noise, and insufficient retinal motion—may not be mutually exclusive. Indeed, the published evidence[4,5,12] supports a combined role of both fixation error and neural noise in triggering

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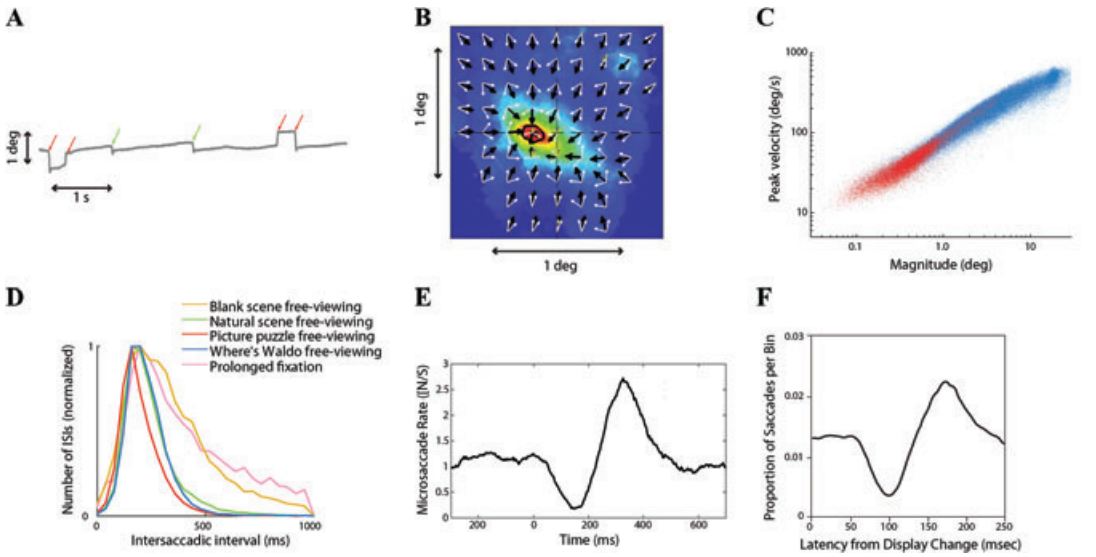

Figure 1. **Common properties of microsaccades and saccades. (A) Corrective (micro)saccades, also known as "square-wave coupling," occur for large but not small (micro)saccades. A 4 s horizontal eye position trace for one subject is illustrated. The red arrows indicate pairs of larger saccades forming square-wave jerks. The green arrows point to unpaired smaller saccades (from Ref. 5). (B) Microsaccades tend to correct large or moderate fixation errors (microsaccade directions after small errors are random). Black arrows represent the median direction of microsaccades starting from eye positions within a squared 0.25° area around the fixation spot. Pairs of white vectors enclose 68% of all microsaccade directions (from Ref. 12). (C) (Micro)saccades during fixation (red) and free-viewing (blue) share the same magnitude/peak velocity relationship (from Ref. 8). (D) The intersaccadic interval distributions for (micro)saccades during fixation (pink) are comparable to those in several free-viewing tasks (from Ref. 8). (E) Microsaccade inhibition after changes in peripheral stimuli (modified from Ref. 23). (F) Saccadic inhibition (modified from Ref. 22). The waveforms of microsaccade inhibition (E) and saccadic inhibition (F) are equivalent, although their timing differs.**

microsaccades, and further suggests that the contribution of each signal depends on the magnitude of the fixation error. For example, if a subject's gaze deviates from the visual target by a large error (i.e., about 0.5° or more, due to drift, microsaccades, or other eye movements), corrective microsaccades bring the fovea back to the target[4,5] (Fig. 1A). If the fixation error is small or insignificant, neural noise may instead trigger microsaccades, albeit with longer intersaccadic intervals and random directions and magnitudes[5] (Fig. 1A). If the amount of fixation error is intermediate, neural noise may add to it to trigger microsaccades that are corrective on average, though more variable in direction than with large fixation errors[12] (Fig. 1B).

Despite recent studies showing that microsaccades counteract visual fading and improve visibility during attempted fixation,[2,3,13] the data supporting the hypothesis that insufficient retinal motion and/or visual adaptation may trigger microsaccades are less conclusive.[7,11,14]

Many quantitative models simulate saccade generation.[15] Most of them require external (i.e., originating outside the modeled circuits) executive commands to change eye position and initiate the saccade. The effects of neural noise on such "command signals" for saccades have not been studied in detail, however (Table 1). Further, no quantitative model has addressed the generation of microsaccades during fixation. Two recent qualitative models of microsaccade generation assign a central role to neural fluctuations in the superior colliculus (SC).[9,10,16] Both models suggest that microsaccades are triggered when neural activity in the SC exceeds a hypothetical threshold (the nature of the threshold varies for each model), yet neither model proposes an explicit circuit for its implementation. Here, we present a specific neural circuit and mechanism that can trigger microsaccades and saccades without an external executive command or a thresholding mechanism.

Microsaccades and saccades

During ordinary visual search or exploration, large saccades shift our gaze to those visual features that capture our interest. During maintained fixation,

Table 1. Saccade generation models and their implementation of the trigger mechanism

Model	Areas modeled	Trigger signal
Trappenberg *et al.*[52]	SC	Internal trigger; activity in SC reaches a threshold at some location
Bozis & Moschovakis[53]	BG, SC	Internal trigger, driven by the SC motor error signal
Lefèvre, *et al.*[54]; Quaia, *et al.*[55]	CB, SC	Internal trigger, driven by the external motor error input and external fixation command
Gancarz & Grossberg[51]	BG	Internal trigger, driven by the external motor error input
Breznen & Gnadt[50]	BG	Internal trigger, driven by the external motor error input
Grossberg, *et al.*[56]	BG, SC	Internal trigger at the SC; eye movement initiates when the activity at the peak SC cell is greater than a threshold value
Arai, *et al.*[57,59]; Das *et al.*[58]	BG, SC	Internal trigger depending on the presence of fixation spot (global inhibition) and target location (motor error)
Optican[60]	SC	External trigger; cortical input to the fixation neurons that stops during saccades
Dominey & Arbib[61]	BG, basal ganglia, FEF, SC, parietal cortex	External "fovea ON" signal
Lefèvre & Galiana[62]	BG, SC	External trigger; threshold in motor error signal triggers the saccade
Scudder[49]	BG	Internal trigger, driven by the external motor error input
Grossberg & Kuperstein[48]	BG	Internal trigger, driven by the external motor error input
Jürgens *et al.*[47]	BG	External trigger input
Robinson[46]	BG	External trigger input

microsaccades may allow us to scan a small region near the fixation target. Thus, microsaccades during fixation may serve a function similar to large saccades during visual exploration.[7,8,10,17,18] Numerous research findings support the hypothesis of a common origin for microsaccades and saccades.[5,6,8–10]

First, microsaccades and saccades show common dynamic properties. Both are binocular and conjugate—that is, the two eyes move simultaneously in the same direction.[19] Both follow the same magnitude/peak velocity relationship[8,20] (Fig. 1C). The distributions of time intervals between saccades and microsaccades have comparable characteristics[8,21] (Fig. 1D).

Second, microsaccades and saccades are both affected by covert attention and distracters. Saccades are inhibited after visual stimuli changes during visual search, reading, and simpler tasks[22] (Fig. 1E). Microsaccades show the same type of transient inhibition during maintained fixation[9,23] (Fig. 1F). Furthermore, peripheral stimuli can bias the direction of both microsaccades and saccades.[23–25]

Third, volitional control may affect microsaccades and saccades in equivalent fashion. Even though microsaccades are usually considered involuntary, subjects can suppress them voluntarily for extended periods[17] and produce voluntary saccades of the size of microsaccades.[7]

Fourth, the properties of microsaccades produced during certain tasks resemble those of saccades made during equivalent tasks. For instance, subjects threading a virtual needle produced microsaccades that were directed to the target accurately, suggesting that microsaccades can scan small visual regions just as saccades do larger regions.[14] Microsaccades produced while a visual stimulus moved in a constant direction in the background resembled the quick (i.e., saccadic) phases of (micro) optokinetic nystagmus.[26]

Finally, microsaccades and saccades interact temporally with one another, suggesting a common triggering mechanism. Rolfs *et al.* reported that the latency of a saccade made to a target was longer if a microsaccade occurred up to 300 ms before the saccade.[27] Otero-Millan *et al.* found equivalent time intervals between microsaccades and saccades during visual exploration and search.[8]

The saccadic system

Many brain areas are involved in saccade generation.[28–30] We categorize them according to three functions: target selection, saccade execution, and saccade calibration. To select the target, the SC integrates multisensory inputs to produce voluntary or reflexive saccades directed to visual, auditory, somatosensory, or remembered targets. To execute the saccade, the burst generator (BG) in the brainstem receives a saccadic command from the SC and generates a motor signal to the eye muscles to move the eye to the appropriate target. To calibrate the saccade, the cerebellum provides a parallel feedforward pathway that ensures saccade accuracy by correcting for intertrial variability as well as long-term drifts or slow changes in gain, for example, due to fatigue.[31] To explain how the saccadic system triggers microsaccades, we will focus on the final common pathways for all saccades, the SC and the BG: activity in these circuits is correlated to microsaccade generation. We note that the cerebellum may play a role as well, given that saccadic intrusions disrupt fixation in cerebellar disorders.[32]

The SC receives excitatory inputs from the frontal eye fields (FEF), the parietal eye fields, and the supplementary eye fields, inhibitory inputs from the basal ganglia, and direct inputs from the visual and other sensory systems. All this information is combined into a two-dimensional retinotopic map that encodes the position of the desired target. Repeated microstimulation of the same location produces saccades of the same size and direction, according to a polar map.[33] The SC is divided traditionally into two areas, the rostral fixation zone, with neurons that are suppressed during saccades, and the caudal saccade zone, with neurons that activate during saccades. Recent studies have challenged this view, however, by modeling the SC as a continuous map of motor error,[16,34] in which the activity of neurons in the fixation zone represents small motor errors during fixation.

The BG neural network is responsible for transforming the spatially encoded saccadic command from the SC into a pulse-step, temporally encoded motor signal (Fig. 2) to contract or relax the eye muscles during a saccade, as follows. Burst neurons (BNs) in the reticular formation fire strongly during saccades, producing a pulse of innervation to contract (excitatory BNs) or relax (inhibitory BNs) the corresponding eye muscles. The neural integrator, a network distributed between the brainstem and cerebellum, integrates the pulse signal from the BNs; this integrated copy is referred to as the step of innervation. Motor neurons (MNs) combine the pulse of innervation and the step of innervation to generate the pulse-step signal. The pulse-step waveform insures high acceleration (pulse) to compensate for the viscous drag of the eye, and produces the necessary tension (step) to hold the eye at the new position once it reaches its target.

Omnipause neurons (OPNs), lying in the pontine raphe, fire at a fairly constant rate between saccades to inhibit the BNs; they cease their inhibitory discharge completely during saccades. The SC sends two complementary excitatory projections to OPNs and BNs. Rostral SC neurons send strong direct projections to OPNs [35] and seem to be important for maintaining fixation. Caudal SC neurons project indirectly to BNs via long-lead burst neurons (LLBNs), also in the reticular formation; this pathway seems important for saccade initiation.[36] During saccades, LLBNs inhibit OPNs through a hypothetical latch circuit.[37] At the end of saccades,

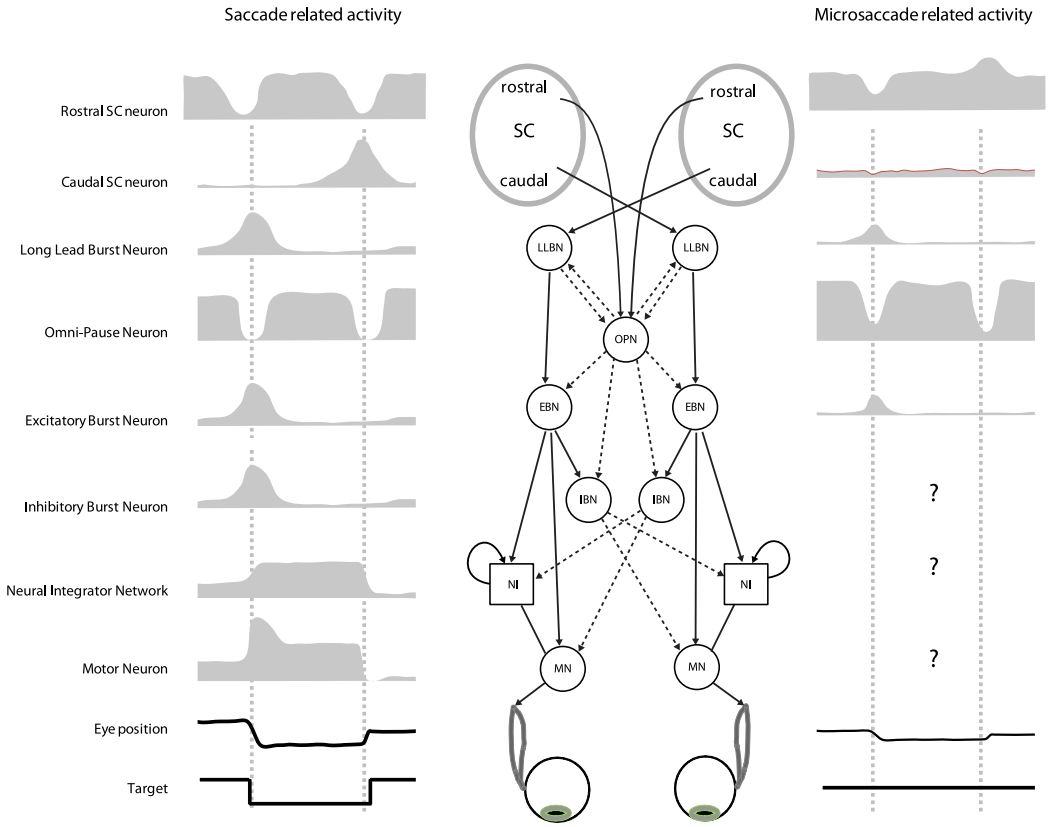

Figure 2. **The saccadic system. Comparison of neural activity during horizontal saccades (left) and microsaccades (right). Modified from Ref. 29.**

OPNs resume discharge. We propose that the mutually inhibitory circuit between OPNs and LLBNs, driven by the SC, is a likely candidate for the mechanism that normally triggers and suppresses saccades and microsaccades (Fig. 3C).

Activity of different brain areas during microsaccades

Recent research has provided a good picture of how the various subsystems that control saccades may also serve to generate microsaccades. In each brain area examined to date, neural activity around saccades has proven equivalent to that around microsaccades.[6,10] Van Gisbergen *et al.* found that BNs activate during saccades and microsaccades.[38,39] Brien *et al.* found that OPN activity modulates during microsaccades,[40] although whether it is completely suppressed, as during saccades, or merely reduced, remains unclear.[40,41] Munoz and Wurtz found some SC rostral neurons as active for small saccades as caudal neurons for large saccades.[42] Hafed *et al.* further showed that neurons in the rostral SC fire strongly before microsaccades of specific sizes and directions, just as SC caudal neurons do before saccades.[16] The fastigial oculomotor region in the cerebellum also shows equivalent activity for microsaccades and saccades.[12]

It remains an open question whether higher cortical areas may show equivalent neural activities for microsaccades and saccades. No study has yet investigated the activity of the "fixation" zones in the FEF or the basal ganglia during microsaccades. The large movement fields of neurons in these areas is a potential hurdle to overcome in carrying out such experiments.[43]

A new hypothesis for microsaccade triggering

Many quantitative models have simulated saccade production in the SC and BG (see Ref. 15 for a comprehensive review), but none have incorporated a specific mechanism to simulate microsaccades. Two

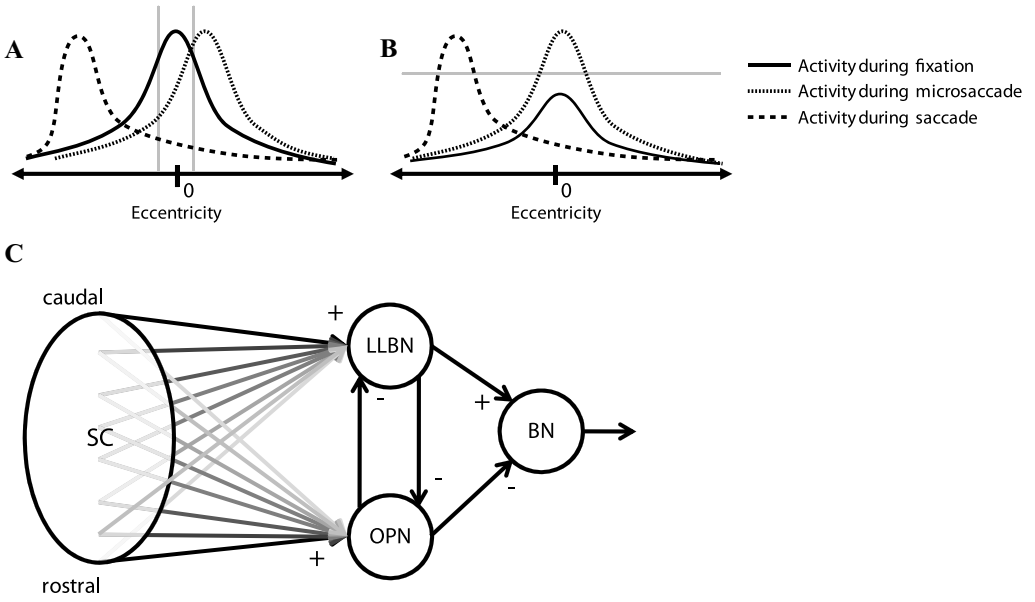

Figure 3. **Microsaccade triggering models. (A) Hafed *et al.*'s model: microsaccades are triggered when SC activity moves away from the center of mass beyond a threshold eccentricity (vertical gray lines); inspired by Ref. 16. (B) Rolfs *et al.*'s model: microsaccades are triggered when SC activity reaches a threshold firing rate (horizontal gray line); inspired by Ref. 9. (C) A novel model for microsaccade triggering based on the connectivity between the SC and the OPNs and LLBNs. Neurons in the SC present two gradients of connectivity, one that is strongest between rostral SC and OPNs, and one that is strongest between caudal SC and LLBNs (darker lines represent stronger connections). The mutually inhibited OPNs and LLBNs act as a trigger. During fixation, rostral activity drives the OPNs that inhibit the LLBNs. Directly preceding the launch of a (micro)saccade, rostral activity drops, and caudal activity begins to grow. At some point the balance of inhibition is broken, and the LLBNs inhibit the OPNs more than the OPNs inhibit the LLBNs. Then the LLBNs start to burst and drive the BNs.**

qualitative models for microsaccade generation have been proposed. Hafed *et al.*[10,16] based their model on physiological data, whereas Rolfs *et al.*[9] based theirs on psychophysical data. Both models are built on the idea that microsaccades and saccades arise from a common motor map in the SC. Buildup neurons in the rostral SC encode foveal goal locations (small motor errors)[34] in both models. During maintained fixation, the center of mass of this activity fluctuates around the neurons encoding the center of gaze (zero). These fluctuations trigger microsaccades.

Although the two models are similar, they differ in the precise physiological conditions that trigger microsaccades. Hafed *et al.*[10,16] propose an eccentricity threshold: a microsaccade is triggered when the location of the center of mass of activity in the SC map moves away from the center of gaze beyond a threshold distance. They hypothesize that this threshold is implemented by OPNs, but they do not offer a specific mechanism (Fig. 3A). Rolfs *et al.*[9] propose a firing rate threshold: a microsaccade is triggered when the firing rate at the center of mass of activity in the SC map exceeds a threshold amount. They also speculate that the activation of SC neurons encoding locations near the fovea is less likely to trigger a microsaccade than that of neurons encoding more peripheral locations, but they do not provide a mechanism (Fig. 3B).

Here, we propose a model of the connectivity between the SC and the BG to reconcile these apparent contradictions. A simple circuit, composed of OPNs and LLBNs, serves to trigger microsaccades without the need for a hypothetical threshold mechanism (Fig. 3C). The key to this proposal is the balance of reciprocal inhibition between OPNs and LLBNs, modulated by the projections they both receive from the SC.[44,45] The rostral SC drives OPNs more strongly than LLBNs, whereas the caudal SC drives LLBNs more than OPNs. During fixation, the activity of the SC map is centered in the rostral area that represents the center of gaze. Therefore, the OPNs are tonically active and keep the LLBNs

inhibited. Due to random activity (neural noise) and/or fixation error, the center of the activity of the SC map may fluctuate away from the location that represents the center of gaze. This fluctuation will decrease the input to the OPNs while increasing the input to the LLBNs. At some point, the input to the LLBNs will be high enough to overcome the decreased inhibition coming from the OPNs. This will result in a small burst of activity in the BNs, triggering a microsaccade. This same mechanism will trigger large saccades as well, though the burst of activity from BNs will be greater in magnitude and duration. Thus, our model does not rest on an unspecified threshold mechanism for triggering microsaccades, but explains microsaccade and saccade triggering through the simple balance of excitatory and inhibitory connections between the SC, the LLBNs, and the OPNs.

The proposed model accounts for the biases in microsaccade direction in the presence of peripheral distracters.[23,24] A peripheral distracter may not activate the SC in sufficient amount to trigger a saccade to the distracter's location, but it could bias the center of mass of activity and thus influence the direction of microsaccades (at those times that microsaccades are triggered through the mechanism above).[9,10,16]

Discussion

Implications for models of the saccadic system: the trigger

Since the creation of the first mathematical model of the saccadic system,[46] much of the research effort has been directed to explaining saccadic targeting and accuracy (i.e., the process by which the brain controls when the eye stops once it has reached its target).[28] The saccadic trigger mechanism has received far less attention[15] (Table 1).

The first BG models relied on dual inputs: a binary input that indicated whether to trigger a saccade or not at any given time and a nonbinary input that specified the saccade amplitude (i.e., the absolute desired eye position in some models[39] or the desired change in eye position in other models[47]). Current BG models generally use a single nonbinary input that indicates the desired change in eye position and triggers a saccade whenever its value exceeds zero.[48–51] Present BG models offer the possibility of adding noise to their nonbinary input to trigger microsaccades (unlike earlier BG models relying on binary inputs). This idea has not been tested yet.

Some SC models generate a specific trigger signal when the neural activity reaches a given threshold only at some caudal location in the map (i.e., representing peripheral eccentricities). Thus, they produce only relatively large saccades (i.e., $\sim 2^{\circ}$ or more)[52] and cannot account for microsaccadic triggering.

We propose that a general model of the saccadic system should generate saccades of all sizes and trigger microsaccades as a consequence of random fluctuations of neural activity. For any model to be correct, the saccade triggering circuit must be shared by all systems that are known to produce saccades (i.e., such as the vestibular system, which generates the quick phases of nystagmus). Thus, it stands to reason that the saccade triggering circuit should be located as far downstream as possible within the oculomotor system: the brainstem nuclei satisfy this requirement. Indeed, in our view, the saccadic system can be conceptualized as a chain of triggers. For example, the FEF produce saccades by triggering the SC, which in turn triggers the brainstem. Yet, the brainstem circuit formed by LLBNs and OPNs, being last in the chain, is the only trigger mechanism both necessary and sufficient to generate saccades.

Potential tests of a model for microsaccade generation

Saccade models are tested typically by simulating, for example, accurate saccades, interrupted saccades (OPN stimulation), staircase saccades (SC stimulation), double-step saccades, and gap task.[15] Models aimed to simulate microsaccades should meet the following requisites:

1. produce saccades as a consequence of neural noise;
2. replicate the behavioral intersaccadic interval distributions for microsaccades and saccades (Fig. 1D);[8]
3. produce microsaccades that are corrective on average (as in Guerrasio *et al*.'s analysis;[12] Fig. 1B) and lead to square-wave coupling[5] (Fig. 1A); and
4. replicate the timing and waveforms of microsaccadic and saccadic inhibition (Fig. 1E–F).[9,22]

A possible role of adaptation in microsaccade generation

We have proposed a microsaccade generation model that solely relies on input from random neural fluctuations and motor error correction signals. Adaptation could play an additional role in triggering microsaccades in this context.[11,16] Inputs to the rostral SC may weaken during fixation because of a decrease in visual input due to neural adaptation (i.e., visual fading). If so, the weakened rostral SC activity would lead to decreased activity in the OPNs and thus increased activity in the LLBNs, resulting in the triggering of a microsaccade.

Conclusions

Current evidence indicates that microsaccades are a type of saccade, that all saccades are generated by a common brain mechanism, and that random fluctuations of neural activity in the SC, as well as small fixation errors, may trigger microsaccades. We propose that the microsaccade (and saccade) triggering circuit is formed by OPNs and LLBNs, with each neuronal population driven mainly by the respective activity in the rostral and caudal SC. Unlike in previous proposals,[9,10,16] our model does not require a hypothetical thresholding mechanism to evaluate the SC activity and to trigger a microsaccade when that threshold is surpassed. Rather, it relies on the reciprocal inhibition between OPNs and LLBNs. Fluctuations in SC activity, due to noise and/or fixation error, increase excitation to the LLBNs and decrease inhibition from the OPNs, triggering a microsaccade whenever LLBN activity overcomes OPN inhibition.

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Conflicts of interest

The authors declare no conflicts of interest.

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