Journal of Computational Neuroscience
https://doi.org/10.1007/s10827-021-00784-7

ORIGINAL ARTICLE

The unknown but knowable relationship between Presaccadic Accumulation of activity and Saccade initiation

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Received: 3 April 2020 / Revised: 6 January 2021 / Accepted: 16 February 2021

Abstract
The goal of this short review is to call attention to a yawning gap of knowledge that separates two processes essential for saccade production. On the one hand, knowledge about the saccade generation circuitry within the brainstem is detailed and precise – push-pull interactions between gaze-shifting and gaze-holding processes control the time of saccade initiation, which begins when omnipause neurons are inhibited and brainstem burst neurons are excited. On the other hand, knowledge about the cortical and subcortical premotor circuitry accomplishing saccade initiation has crystalized around the concept of stochastic accumulation – the accumulating activity of saccade neurons reaching a fixed value triggers a saccade. Here is the gap: we do not know how the reaching of a threshold by premotor neurons causes the critical pause and burst of brainstem neurons that initiates saccades. Why this problem matters and how it can be addressed will be discussed. Closing the gap would unify two rich but curiously disconnected empirical and theoretical domains.

Keywords Brainstem saccade generator · Decision-making · Nucleus raphe interpositus · Omnipause neuron · Stochastic accumulator

1 Introduction

For some reason, Lance Optican attended only one Gordon Research Conference on Eye Movements. In 2017 he contributed to a session entitled, "Transition from Response Time to Saccade". The goal of that session was to bring together researchers working on the premotor circuit of saccade initiation – principally superior colliculus (SC) and frontal eye field (FEF) -- and researchers working on the brainstem circuit of saccade production. The hope was to frame and motivate research to bridge the gap between the activity of premotor saccade neurons reaching a threshold and omnipause neurons (OPN) being inhibited to initiate a saccade. What starts a saccade has received less attention, compared to the great deal of empirical and modeling research that has addressed the question "What stops a saccade?" (Optican & Pretegiani, 2017a). The purpose of this short review is to summarize the problem, explain why it is important, and suggest how it can be addressed.

2 The gap of knowledge

In one thread of scientific literature, evidence from neurophysiological, microstimulation, and inactivation studies demonstrate that saccades are initiated when the premotor balance tips from gaze holding to gaze shifting processes and omnipause neurons are inhibited. In another thread, evidence from neurophysiological measurements and computational models demonstrate that saccades are initiated when the discharge rates of particular neurons reach a critical threshold. Here we summarize the two threads before considering how they could be woven together.

Saccades are initiated when premotor saccade neuron activity reaches a threshold. The research supporting the claim that presaccadic circuits can be described as stochastic

Action Editor: Barry Richmond.

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Published online: 12 March 2021

accumulators has been reviewed extensively (e.g., Forstmann et al., 2016; O'Connell et al., 2018; Schall, 2019) (Fig. 1). Here we will just survey the central observations and key conclusions.

That saccades are initiated when the discharge rates of premotor saccade neurons reach a value that is effectively invariant with response time was evident in original investigations of SC (e.g., Sparks, 1978), confirmed systematically in FEF (Hanes & Schall, 1996), and has been observed in the central thalamus (Tanaka, 2007). Using testing conditions with visual discrimination tasks for which accumulator models have been formulated the description of a random accumulation to a fixed threshold

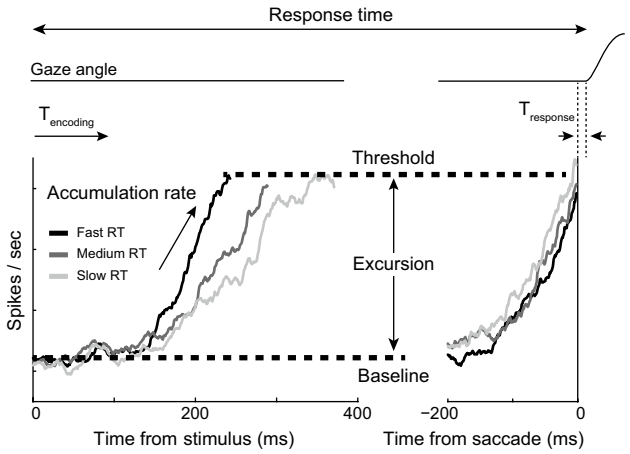


Fig. 1 Relationship between response time and premotor saccade neuron activity. Average discharge rate of premotor saccade neurons during experimental trials when saccades were produced with the fastest (black), intermediate (darker gray), or slowest (lightest gray) RT. The plots are shown aligned on time of stimulus presentation (left) and saccade initiation (right). Saccades were initiated when the discharge rate reached a particular level. The variation in saccade response time was accounted for by variation in the time taken for the discharge rate to reach that level. This relationship to response time resembles that of stochastic accumulator models of decision making. Accumulator models are characterized by particular parameters. Accumulation begins at a baseline level and terminates when the accumulated value reaches a specified threshold. Neural accumulation is judged to terminate when the overt response is produced. The difference between threshold and baseline is referred to as excursion. Larger excursion amounts in longer RT (for a given accumulation rate). Accumulation does not begin until some interval needed for encoding the stimuli elapses ($T_{encoding}$). In addition, some time elapses after the threshold is reached before the overt response is produced ($T_{response}$). For saccades $T_{response}$ is ~10 ms because this is the interval from inhibition of omnipause neurons until saccade initiation. The sum $T_{encoding} + T_{response}$ is referred to as the residual or non-decision time, because it is presumed not to contribute to much of the duration and any of the variation of RT. The accumulation rate parameter is supposed to be proportional to the quality or magnitude of evidence, which assumes random values across trials. The residual time is supposed to be invariant. The baseline and threshold (excursion) values are supposed to be under strategic control to enable speed-accuracy tradeoff

has been reported for the lateral intraparietal (LIP) area (e.g., Roitman & Shadlen, 2002), FEF (Ding & Gold, 2010), and the SC (Ratcliff et al., 2007). The stochastic accumulation of movement-related activity to a threshold has also been observed in visual search tasks (Woodman et al., 2008) and explained through a multi-alternative stochastic accumulator model (Purcell et al., 2010, 2012).

However, we must note that the critical threshold of discharge rate in FEF and SC can appear to vary when response times are manipulated by warning signals (Fecteau & Munoz, 2007), when response conflict must be overcome (Everling et al., 1999; Everling & Munoz, 2000; Jantz et al., 2013; Hauser et al., 2018) and when speed versus accuracy must be explicitly adjusted (Heitz & Schall, 2012; Reppert et al., 2018).

Saccades are initiated when gaze holding tips to gaze shifting. Saccade preparation, initiation, and generation are accomplished by a reasonably well-understood, distributed network stretching from the frontal lobe to the brainstem (Fig. 2). The accumulation of activity leading to gaze shifting is accompanied by reduction of activity supporting gaze holding. In addition to OPNs, neurons with fixation-related activity contributing to gaze holding have been described in the rostral SC (Munoz &,, Wurtz, 1993a), in FEF (Hanes et al., 1998; Izawa et al., 2009), in central thalamic nuclei (Schlag & Schlag-Ray, 1984), and in the substantia nigra pars reticulata (SNpr) (Hikosaka & Wurtz, 1985a). Saccades are initiated when inhibition from the SNpr (Hikosaka & Wurtz, 1985a,b) and from rostral SC fixation neurons is released on caudal SC saccade neurons (Munoz & Wurtz, 1993b).

Electrical stimulation of rostral SC inhibits saccade production (Munoz & Wurtz, 1993b). Across its motor map, the SC embodies mutual inhibition whereby preparation of one saccade inhibits preparation of other saccades so that just one movement would be produced at a time (Munoz & Istvan, 1998). The mutual inhibition is also present between the rostral gaze-holding and caudal gaze-shifting neurons of the SC. This interplay of gaze-holding and gaze-shifting is paralleled in FEF (e.g., Hanes et al., 1998; Izawa et al., 2005, 2009). Hence, during fixation, the rostral SC and associated fixation neurons in FEF, SNpr, and elsewhere are active, and the caudal SC and associated premotor neurons in FEF and elsewhere are silent. Preparation of a saccade occurs when the activity of premotor saccade neurons coding the metrics of the desired saccade accumulates. The accumulation of this gaze shifting activation is permitted by the release of inhibition by gaze holding neurons. When the accumulated activity reaches a particular level, the saccade is initiated.

Compelling evidence for how the dynamics of gaze holding and gaze shifting control saccade initiation has been provided by studies using saccade countermanding and related tasks. In the saccade countermanding task monkeys

are rewarded for shifting gaze to a visual target as quickly as they can. However, on a minority of trials this stimulus is followed by a second visual stimulus that means "stop", and monkeys are rewarded only if they do not initiate the saccade that they would have made. Performance in this task is explained as the outcome of a race between two stochastic processes, a GO process and a STOP process (Logan & Cowan, 1984). When the GO process finishes, a saccade is made. Presentation of the "stop" signal begins the STOP process. Only if the STOP process finishes before the GO process is movement planning canceled and the saccade not initiated. The mathematical formulation of this model applied to measures of performance affords measurement of the duration of the covert STOP process, a quantity known as *stop signal reaction time*. The same race model formulation applies to double-step versions of the task in which inhibition of one saccade is followed by production of a different saccade (Camalier et al., 2007; Ramakrishnan et al., 2012; see also Salinas & Stanford, 2018).

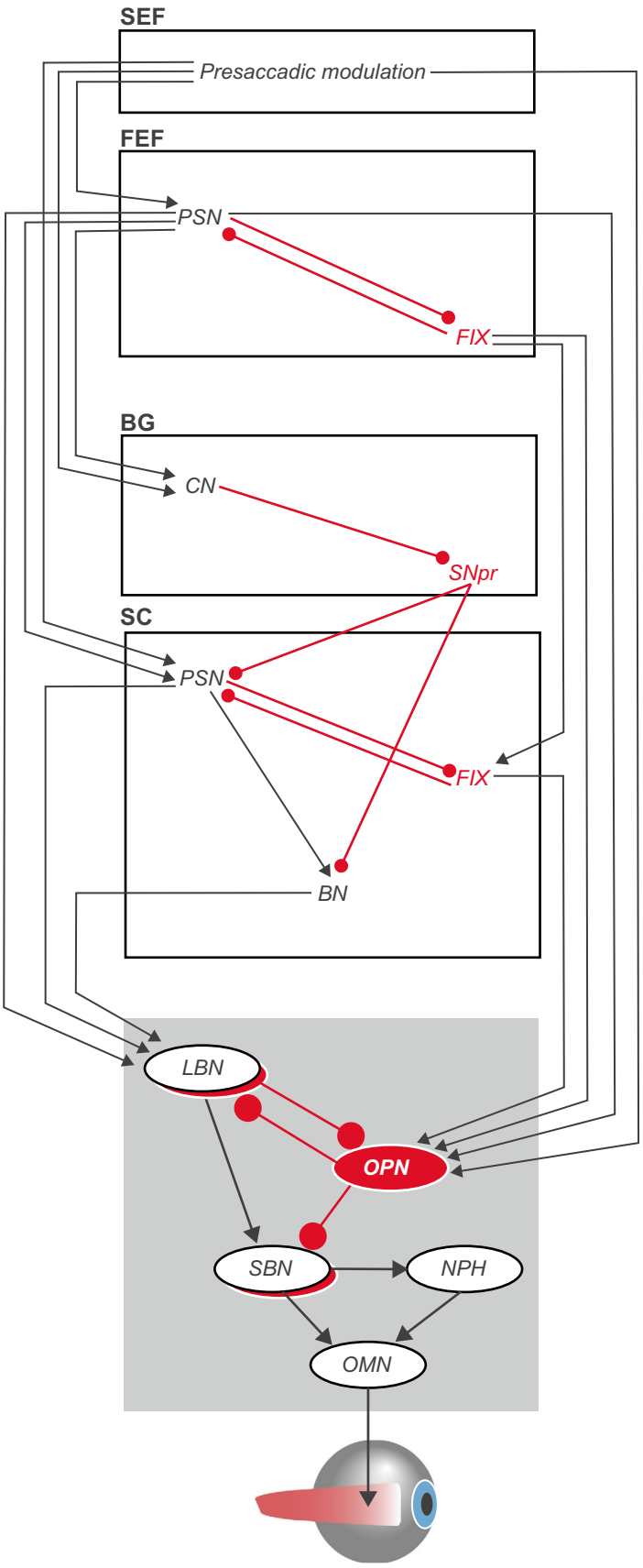
This task with its theoretical framework provides a powerful test of the contributions of neurons to saccade initiation. Simply, for a neuron to contribute to the process of saccade initiation, it must discharge differently when saccades are initiated as opposed to withheld, and this difference must arise before the stop signal reaction time has elapsed. In monkeys performing the saccade countermanding task, premotor saccade neurons in FEF and SC exhibit just this pattern of modulation (Hanes et al., 1998; Paré & Hanes, 2003; Middlebrooks et al., 2020) (Fig. 3). This observation has been replicated in double-step saccade tasks (Murthy et al., 2009; see also Costello et al., 2013). Simultaneously, a complementary pattern of activation was also found in FEF and SC fixation neurons (Hanes et al., 1998; Paré & Hanes, 2003). Among SC burst neurons, though, a recent inspection of the Paré and Hanes (2003) data reveals that among those neurons with distinct high-frequency saccade-related bursts only low-frequency discharges were observed when saccades were inhibited; in other words, SC burst neurons discharged vigorously if and only if saccades were initiated.

We do not know how SNpr neurons in primates respond during saccade countermanding. However, an investigation of rats using a stop signal task with head orienting movements reported that SNpr neurons modulate when the movements were canceled but not otherwise (Schmidt et al., 2013).

Not every neuron in the premotor circuit modulates before stop signal reaction time. The neurons in FEF with only visual responses do not modulate at all or only after saccades are canceled (Hanes et al., 1998). SC visual neurons modulate similarly (Paré & Hanes, unpublished observations). Likewise, in LIP no neuron has been found to modulate before stop signal reaction time (Paré & Dorris 2011). Similarly, during saccade countermanding neurons in the supplementary eye field modulate in many interesting ways (Stuphorn et al., 2000; Sajad et al., 2019) but do not contribute directly to the process of saccade initiation (Stuphorn et al., 2010). Neurons in the caudate nucleus of monkeys performing the saccade countermanding task exhibit both suppression and facilitation when saccades are canceled, but the modulation occurs largely after stop signal reaction time (Ogasawara et al., 2018). These results confirm the diagnostic utility of saccade countermanding for clarifying the contributions of neurons and circuits to saccade initiation.

A formal identification of gaze-shifting and gaze-holding neurons with stochastic accumulation was established through interactive race models of saccade countermanding (Boucher et al., 2007; Logan et al., 2015; see also Schall et al., 2017; Bompas et al., 2020). The STOP and GO processes were instantiated as stochastic accumulators with lateral or feedforward inhibition. The GO accumulator begins after a delay required to encode the target, accumulating activation until it reaches a threshold, whereupon a response occurs. The STOP accumulator begins after a delay required to encode the stop signal, whereupon it interrupts the GO accumulator. If the STOP accumulator becomes active soon enough, that is, if the latency of STOP accumulation plus the delay of the stop signal is less than the finish time of the GO accumulator, then it prevents the GO accumulator from reaching threshold and the response is inhibited. If the STOP process becomes active too late, then the GO accumulator reaches threshold and the response is initiated. This model was formulated first at the algorithmic level, but it has also been implemented in a network of biophysically plausible spiking excitatory and inhibitory units (Lo et al., 2009). Thus, the stop signal countermanding task and associated model framework provides a framework in which to articulate how the balance of gaze-holding and gaze-shifting dictates saccade initiation.

Now, before proceeding, we must acknowledge that the description of the function of the rostral SC that we offered above has been questioned by other investigators (Krauzlis et al., 1997; Goffart et al., 2012; Hafed et al., 2008, Hafed & Krauzlis 2012; Krauzlis et al., 2017). According to the alternative view, neurons in rostral SC actually contribute to saccades near the point of fixation, so that gaze-holding is accomplished just by maintaining an equilibrium of activation across the two SC saccade maps at the rostral poles. Gaze holding, then, is implemented as the OPNs detect deviations in the balance of activity across the two SCs, rather than just the level of rostral SC activation. When the distribution of SC activity becomes imbalanced toward a target location, then a gaze shift is initiated, which can be a microsaccade or a macrosaccade. Such imbalance is thought to occur during maintained fixation, with fluctuations of rostral SC activity triggering microsaccades (see Otero-Millan et al., 2011). This alternative hypothesis predicts that the rostral


SEF
Presaccadic modulation
FEF
PSN
FIX
BG
CN
SNpr
SC
PSN
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LBN
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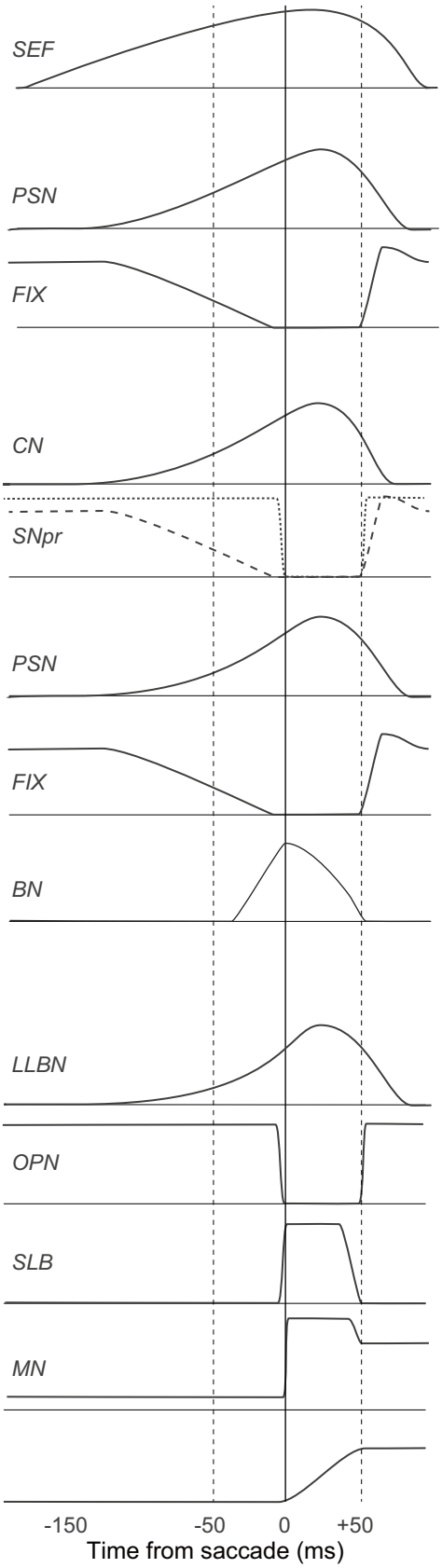
SEF
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-150
-50
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Time from saccade (ms)

◂**Fig. 2** Neural circuit balancing gaze-holding with gaze-shifting. Selected connectivity of key cell types (left) and associated patterns of discharge rates (right) highlight key functional relationships. Black connectors with arrow terminators illustrate excitatory pathways. Red connectors with circle terminators illustrate inhibitory pathways. Neural elements are included in the supplementary eye field (SEF), frontal eye field (FEF), basal ganglia (BG), superior colliculus (SC), and brainstem saccade generator (gray box). SEF includes neurons with presaccadic activity that is indirectly related to saccade production. FEF includes premotor saccade neurons (PSN) with activity accumulating to a threshold before saccades and fixation neurons (FIX) with activity decreasing before and during saccade generation. The mutual inhibition illustrated between these populations of neurons in FEF is hypothetical. BG includes neurons in the caudate nucleus (CN) with activity accumulating before saccades and neurons in the substantia nigra pars reticulata (SNpr) with activity decreasing before and during saccade generation. Whether the decrease before saccade generation is gradual (dashed) or more synchronized on saccade initiation (dotted) requires further investigation. —The excitatory inputs from SEF and FEF to CN and the inhibition from CN to SNpr are observed. The SC includes PSN, FIX, and burst neurons (BN). The excitatory inputs to SC from SEF, the excitatory inputs to PSN and FIX neurons from FEF, and the inhibitory inputs from SNpr to PSN and BN are observed. The brainstem saccade generator includes excitatory (white fill) and inhibitory (red fill) long-lead burst neurons (LBN) with activity accumulating before saccades, short lead burst neurons (SBN) that discharge strongly immediately before and during saccade generation, a neural integrator circuit in the *nucleus prepositus hypoglossi* (NPH) that maintains eye position, and oculomotor neurons (OMN) that produce the pulse and step of force necessary to generate saccades. The excitatory inputs to LLBN from SC and FEF are observed. The excitatory inputs from SC, FEF, and SEF to OPN are observed. The intrinsic circuitry within the brainstem is observed. When the balance of activation of the PSN and FIX neurons tips from gaze-holding to gaze-shifting, then SC BN turn on, and OPNs are turned off, releasing inhibition on SLB that activate the OMN that cause the extraocular muscles to contract rapidly to produce the saccade

SC activity is enhanced after the stop signal appears and throughout the stop signal reaction time to maintain fixation on the central spot and prevent a macrosaccade to the visual target. Given the noise inherent in neural processes, such sustained activity in the rostral SC would predict a higher likelihood of fluctuation and thus microsaccade production.

Still, gaze holding that prevents even microsaccades during fixation must have a neural substrate (e.g., Rucci and Poletti 2015). Measurements of microsaccade production during the saccade countermanding task contradict this prediction (Godlove & Schall, 2016). Instead, when monkeys withheld the macrosaccade to the target, microsaccade production was also strongly attenuated. Moreover, the number of microsaccades produced before the target appeared did not affect stop-signal reaction time or alter the probability of canceling saccades following stop signals. Additional evidence is provided by measurements of the oculomotor neuron electromyogram through cranial EEG (Godlove et al., 2011). Saccade production results in a spike potential in the EEG. If inhibition of a macrosaccade is accomplished by production of microsaccades (resulting from the elevated activity observed in rostral SC on canceled countermanding trials), then an EMG signature must be observed. In fact, the observations were opposite this prediction; when saccades are inhibited, the saccade-related EMG measurement is actually lower than the baseline value. Further evidence challenging the equilibrium hypothesis will be described in the next section. Therefore, we think that these results demonstrate that gaze-holding and gaze-shifting are dissociable processes mediated by distinct neuronal populations.

Saccades are initiated when OPNs are inhibited. The research supporting this claim has been reviewed many times (e.g., Scudder et al., 2002; Sparks, 2002; Shinoda et al., 2019). OPNs are located in the nucleus raphe interpositus (***RIP***) (Büttner-Ennever et al., 1988; Ohgaki et al., 1987) and exhibit high tonic firing rates during fixation and cease discharging just before and during saccades of any direction (Cohen & Henn,, 1972; Luschei & Fuchs, 1972; Keller, 1974; Evinger et al., 1982; Paré & Guitton, 1998; Everling et al., 1998; Schultz et al., 2010; Van Horn & Cullen, 2012) (Fig. 4).

In a sample of ~20 OPNs, the last spike occurred on average 10.1 (±0.9 standard error) ms before leftward and 11.7 (±0.9 standard error) ms before rightward saccades (Everling et al., 1998). In a sample of ~100 OPNs, the last spike occurred on average 14.5 (±3.9 standard deviation) ms before saccade initiation, and an estimate of the instant when the OPN were inhibited occurred on average 9.5 (±3.1 standard deviation) ms before saccade initiation (Schultz et al., 2010). Intracellular and local field potential recordings indicate that the amplitude, duration, and timing of OPN hyperpolarization correlates with saccade metrics (Yoshida et al., 1999; Van Horn et al., 2010).

OPN activity prevents saccades by tonically inhibiting both excitatory and inhibitory burst neurons (EBN and IBN) (Strassman et al., 1987). OPN exerts this inhibition using the neurotransmitter glycine, which appears to confer particular capacities, which will be discussed below (e.g., Optican, 2008). Electrical stimulation delivered in ***RIP*** prevents the occurrence of saccades in all directions (Keller, 1974; Keller & Edelman, 1994). However, experimental lesions of ***RIP*** only reduce saccade velocity; they do not impair fixation stability (Kaneko, 1996). The absence of irrepressible saccades after lesions of ***RIP*** is difficult to reconcile with the hypothesis that gaze-holding is accomplished only by OPN detecting the balance of activity across the SC map. The observation indicates that other gaze-holding neurons of the premotor circuit, perhaps in the SNpr or rostral SC, are essential for controlling the initiation of saccades. These gaze-holding neurons presumably exert such control by suppressing the activity of premotor SC neurons (Fig. 2).

How does presaccadic activity reaching a threshold cause inhibition of omnipause neurons? We wrote this review because we know of no clear or compelling answer to this

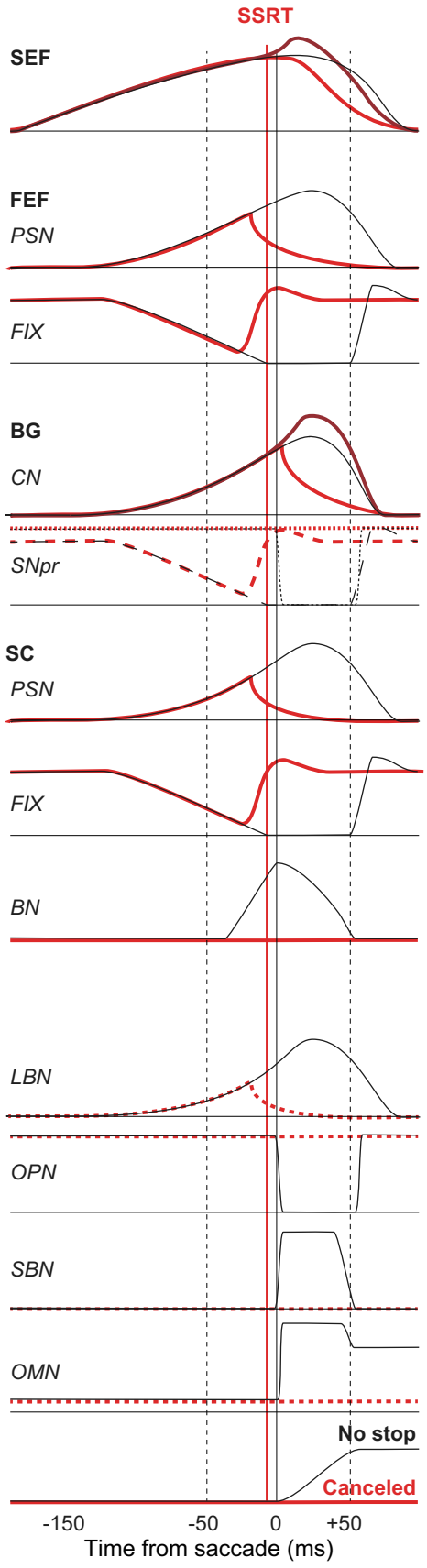

Fig. 3 Neural activity for saccade generation and cancellation. Profiles of neural activity observed (solid) or hypothesized (interrupted) when saccades are executed (black) or canceled (red) during a saccade countermanding task. To contribute to controlling saccade initiation, neural activity must differ before stop signal reaction time (SSRT). Neurons in SEF and CN exhibit facilitation or suppression when saccades are inhibited but only at or after SSRT. PSN and FIX neurons in FEF and SC modulate immediately before SSRT to cancel saccade initiation. Meanwhile, SC BN burst only if saccades are initiated. The nature of SNpr activity during saccade countermanding is uncertain. SNpr neurons may parallel the activity of FIX neurons with a gradual reduction interrupted by a rapid resumption of activity before SSRT (dashed). Alternatively, if they operate in parallel with OPN as a strong gate on saccade initiation, then little or no modulation would be observed (dotted). No data on the activity of the brainstem saccade circuit during saccade countermanding has been obtained, but the predictions are straightforward for OPN, SLB, and OMN. Whether LLBN resemble PSN in FEF and SC remains an interesting but unanswered question

question. However, detailed anatomical and physiological studies provide a framework in which to address it.

The ***RIP*** is innervated by multiple premotor structures known to contribute to saccade generation. Superior colliculus (SC) innervates OPNs directly (Buttner-Ennever et al., 1999) and indirectly via the central mesencephalic reticular formation (***cMRF***) (Wang et al., 2013). Long-lead burst neurons (LLBNs) in the midbrain and in the paramedian pontine reticular formation (***PPRF***) as well as EBNs and IBNs also innervate OPNs (Cromer & Waitzman 2006; Kaneko, 2006). The ***RIP*** is also innervated by FEF (Huerta et al., 1986; Stanton et al., 1988) and SEF (Huerta & Kaas, 1990; Shook et al., 1990). Another influence of the ***RIP*** is the fastigial nucleus (Noda et al., 1990). This convergence of influences from so many structures and types of neurons further highlights the challenge of understanding just how OPNs turn off and saccades begin.

SC stimulation orthodromically activate OPNs with monosynaptic latencies (Raybourn & Keller, 1977; Paré & Guitton 1994; Shinoda et al., 2011), and saccade and fixation neurons in the SC can be antidromically activated through ***RIP*** stimulation (Gandhi & Keller, 1997; Rodgers et al., 2006). The rostral SC appears to be preferentially connected with OPNs within ***RIP*** (Paré and Guitton 1994; Gandhi & Keller, 1997; Büttner-Ennever et al., 1999; Ohtsuka & Nagasaka, 1999). In contrast, caudal SC primarily innervates nuclei comprised of EBNs and IBNs (May, 2006).

Electrical stimulation delivered to the rostral SC most efficiently activates OPNs, compared to stimulation of caudal sites (Paré & Guitton, 1994). Rather than eliciting saccades, as from caudal sites, rostral SC stimulation prevent saccades or interrupt them in midflight (Munoz & Wurtz, 1993; Paré & Guitton, 1994). Thus, saccades can be initiated when a pause in activity from rostral SC disfacilitates OPNs. Consistent with this hypothesis, the activity of SC fixation neurons generally begins to

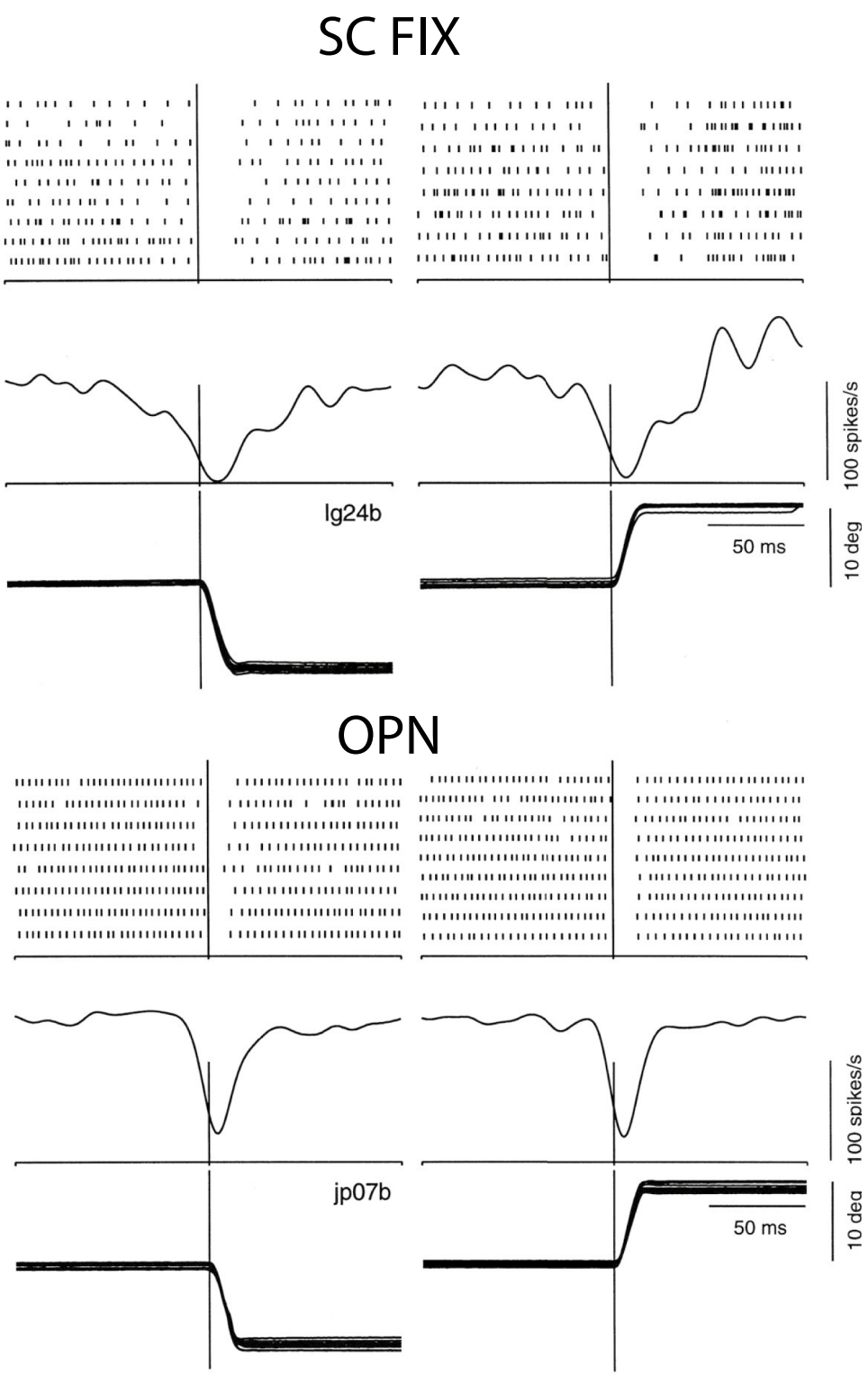

Fig. 4 Comparison of activity of SC FIX neuron and OPN. Activity of SC FIX (top) and OPN (bottom) exampless aligned on the initiation of leftward (left) and rightward (right) saccades. Activity is illustrated in rasters and average spike-density functions plotted above horizontal eye position traces with upward deflections for rightward and downward deflections for leftward saccades. Whereas the SC FIX neuron activity decreased gradually before the saccade, the OPN manifest an abrupt pause during the saccades

decline and cease in advance of the OPN pause (Everling et al., 1998; Bergeron & Guitton, 2002) (Fig. 4); unfortunately, we do not possess any information about the temporal profile of the neuronal subpopulations that are connected.

Whereas the direct SC projection onto OPN is excitatory, the indirect projection is inhibitory (Raybourn & Keller, 1977) and may instantiate the 'trigger' signal that turn off the OPNs. Inhibitory LLBNs found in the ***cMRF*** may well play that role, along with other LLBNs in the ***PPRF***

(Scudder et al., 1996; Kaneko, 2006). In cats, intracellular recordings offered evidence that brainstem IBNs are activated orthodromically and monosynaptically from the caudal SC and that their terminals contact OPNs (Shinoda et al., 2019). Some of these IBNs could participate in causing the OPNs pause, but most importantly, their burst can act as a latch to maintain the OPNs pause during the saccade. This last scenario is consistent with evidence suggesting that the pause in activity in OPNs is caused by glycinergic inputs (Kanda et al., 2007), which could originate from IBNs (Spencer et al., 1989). OPNs also use glycine as a transmitter to exert their inhibition and they are immunoreactive to parvalbumin, which is associated with highly active neurons (Horn et al., 1994). In rodents, parvalbumin-expressing neurons typically co-express the gap-junction-forming proteins connexin and/or pannexin (Condorelli et al., 2000; Barbe Monyer, 2006). It is therefore plausible that the rather homogenous OPNs act as a cell assembly through electrical synaptic transmission. The postulated reduction in excitation of OPNs from the pause in activity of rostral SC neurons could well be crucial to turn them off. Further investigation in the molecular signature of OPNs is needed.

In parallel, layer 5 pyramidal neurons in FEF also innervate OPNs. This has been observed anatomically (Huerta et al., 1986; Stanton et al., 1988), and physiologically (Segraves, 1992). The neurons in FEF projecting to OPNs are most commonly presaccadic and less commonly fixation neurons with visual responses to stimuli in the fovea. Electrical stimulation of FEF causes OPN to stop discharging within <5 ms. The duration of OPN inhibition varies proportionally with the intensity of stimulation. The same electrical stimulation causes brainstem burst neurons to begin discharging with 4–10 ms latencies consistent with a di-synaptic connection. Thus, both SC and FEF directly change OPN state to balance gaze-holding and gaze-shifting.

Based on the foregoing and other observations, sophisticated and reasonably complete models of saccade generation have been formulated (e.g., Robinson, 1975; Bozis & Moschovakis, 1998; Lefevre et al., 1998; Quaia et al., 1999; Optican & Quaia, 2002; Optican, 2008; Shaikh et al., 2011; Daye et al., 2013, 2014; Optican & Pretegiani, 2017b; Optican et al., 2019). The original models assumed two parallel command signals; one driving the burst neurons to produce the desired saccade vector, and the other initiating the saccade by inhibiting the OPNs. More recent evidence for a linkage between initiation and generation of saccades led to a model of the brainstem saccade generator that incorporate membrane biophysics including T-type Ca^{2+} channels (Miura & Optican, 2006). According to this framework, saccades are initiated when the neurons in rostral SC cease firing, thereby reducing excitation of OPNs. Simultaneously, the OPNs receive strong inhibition from selected IBNs, reducing their discharge rate to zero. The tonic inhibition of burst neurons by OPNs during fixation hyperpolarizes their membrane potentials and prevents inactivation of the T-type Ca^{2+} channel. At saccade onset, the rapid reduction of this tonic hyperpolarization caused by reduced OPN firing activates T-type Ca^{2+} currents, while rapid excitatory input from the caudal SC simultaneously depolarizes the membrane potentials to cause strong burst spike activity in burst neurons. In addition, glycine is a co-agonist of NMDA receptors, which are expressed at excitatory glutaminergic synapses of burst neurons. A lack of spillage from the terminals of glycinergic OPNs could thus weaken the excitation of burst neurons, and hence lower saccade velocity. Thus, the combination of biophysical membrane properties of burst neurons and the output of OPNs can determine the velocity of the saccade. This mechanism may provide an explanation for the observed variation in saccade velocity (also referred to as vigor) with task conditions (e.g., Manohar et al., 2015; Shadmehr et al., 2019).

To summarize, saccade initiation happens when premotor saccade neuron reaches some threshold which coincides with decisive changes of neural state in OPNs, IBNs, and EBNs. Yet, just how the former produces the latter remains unknown.

3 Why the gap matters

Every model framework has boundaries. Models of the brainstem saccade generator begin when the OPNs turn off and take for granted just how they are turned off. Models explaining the variation of saccade response time end when the saccade is initiated and take for granted just how the initiation is accomplished. How the reaching of a threshold causes the inhibition of OPNs is a yawning gap of knowledge. Science progresses by unifying empirical and theoretical domains. At the moment, the two domains of research on saccade production reviewed above are juxtaposed anatomically and temporally but not unified conceptually.

As noted above, a rich variety of models explain how stochastic accumulation of evidence accounts for response times in a variety of tasks and conditions (reviewed by Forstmann et al., 2016; O'Connell et al., 2018; Schall, 2019). Accumulator models are characterized by particular parameters. Accumulation begins at a baseline level and terminates when the accumulated value reaches a specified threshold. The difference between threshold and baseline is referred to as excursion. Larger excursion amounts in longer response time (for a given accumulation rate). Accumulation does not begin until some interval needed for decoding the stimuli elapses. In addition, some time elapses after the threshold is reached before the overt response is

produced. For saccades, this execution time is the interval from inhibition of OPNs until saccade initiation. The sum of these intervals is referred to as the residual or non-decision time. The interesting "decision" process begins when the evidence accumulates at a particular rate. This accumulation can begin from a baseline level that is above a zero level. For a given threshold and rate, a higher baseline will result in shorter response time because the accumulation requires less excursion. The rate parameter is supposed to be proportional to the quality or magnitude of evidence, which assumes random values across trials. The residual time is supposed to be invariant. The baseline and threshold (excursion) values are supposed to be under strategic control to enable speed-accuracy tradeoff.

Understanding how the reaching of a threshold by premotor saccade neurons causes the inhibition of OPNs would clarify mechanistically and theoretically what is meant by "threshold". As detailed elsewhere (Schall, 2019), the concept of threshold can be articulated both neurally in terms involving connections between FEF, SC, basal ganglia, and brainstem and computationally in terms of stopping rules for evidence accumulation processes. However, the relationship between those two kinds of answers is complex and not transparent. Knowing how OPNs are turned off by the activity of premotor saccade neurons reaching a threshold level could help constrain the range of plausible neuro-computational models and thus resolve model mimicry involving, for example, how urgency influences decision making and whether or not thresholds can collapse with time (e.g., Drugowitsch et al., 2012; Thura et al., 2012; Evans et al., 2017).

Whether the activation at response time of FEF and SC saccade neurons is actually invariant has been questioned, because it can vary across tasks and conditions. For example, the activation of FEF and SC neurons at saccade initiation is lower before anti- relative to pro-saccades (Everling et al., 1999; Everling & Munoz, 2000; Jantz et al., 2013).

The variation of premotor saccade neuron discharge rates when saccades are initiated has particular theoretical importance in experiments investigating the neural mechanisms of with speed-accuracy tradeoff (SAT). Haste makes waste is the principle investigated by instructing or cuing participants to respond sooner but less accurately or more accurately but later. Canonical stochastic accumulator models achieve SAT through a principled adjustment of the threshold for accumulation of evidence, making it higher for more accurate responding and allowing it lower for less accurate but more rapid responses (e.g., Bogacz et al., 2010). Many investigators have identified the activity of premotor saccade neurons with this evidence accumulation process (e.g., Ratcliff et al., 2007; Purcell et al., 2010, 2012). If this identification is correct, then when monkeys perform a task with SAT requirements, the discharge rate when saccades are initiated should be higher when accuracy is stressed and lower when speed is stressed. To test this conjecture, monkeys were trained to perform a visual search task with explicit SAT cues and premotor saccade neurons were recorded in FEF (Heitz & Schall, 2012) and in SC (Reppert et al., 2018). In neither structure did neurons conform to the predicted pattern. Instead, premotor saccade neurons in FEF exhibited lower discharge rates when accuracy was stressed and higher, when speed was stressed. Meanwhile, premotor saccade neurons in SC exhibited equivalent discharge rates across SAT conditions. Major elements of these results were found independently by two other laboratories in monkeys performing other choice tasks with different SAT manipulations with saccade responses (Hanks et al., 2014) and manual responses (Thura & Cisek, 2016).

Assuming that the trigger signal in the brainstem must be invariant in spite of pronounced variation of premotor saccade neuron activation levels, Heitz and Schall (2012) reasoned that the influence of FEF and SC on brainstem circuits could be approximated by subjecting the premotor neuron activity to leaky integration and found that this integrated value was invariant across SAT conditions and RT. Even if this conjecture is incorrect, the results from pro/anti-saccade tasks and tasks with SAT indicate that the trigger signal influencing OPNs is more complex than has been appreciated. For example, ***RIP*** is innervated by the supplementary eye field (SEF) (Huerta and Kaas 1990; Shook et al., 1990), which does not control directly saccade initiation (Stuphorn et al., 2010). Instead, broadly considered, SEF contributes to monitoring the performance of gaze shifting tasks (e.g., Sajad et al., 2019) and can exert executive control to slow or speed saccade initiation (Stuphorn & Schall, 2006). Thus, the direct influence of premotor saccade neurons in FEF and SC on OPNs seems to be combined with or modulated by the less persuasive but more judgmental influence of SEF.

The fact that inputs from many neurons from multiple areas converge on ***RIP*** raises another conundrum. How are the influences from multiple, redundant, idiosyncratic neurons synthesized? The term-of-art "integration" will not be used in reference to this process because it already has two specialized meanings, "integration of evidence" before the saccade and "integration of velocity" during the saccade. If saccades are initiated when the activity of neurons reaches a threshold, but the activity of neurons is variable such that neurons reach their respective threshold at different times, then when is the saccade produced? This question was investigated through simulations of multiple, redundant, idiosyncratic accumulators with different amounts of variability in growth rate and different stopping rules (Zandbelt et al., 2014). Distributions of ensemble RT did not vary with ensemble size if the accumulators share modestly correlated accumulation rates and RT is

not governed by the extremely fast or slow accumulators. Under these parameters the termination times of individual accumulators corresponded to the ensemble RT.

The foregoing examples chart the boundary of our knowledge about how ensembles of premotor saccade neurons contribute to initiating saccades. The theoretical framework in which these observations have been made and interpreted loses interest once the movement is initiated, so this has not been considered a problem. Meanwhile, models of saccade generation from Robinson (1973, 1975) forward tend to take for granted that the model process commences with inhibition of the OPNs. Indeed, careful examination of the earliest models of the brainstem saccade generator have a disembodied trigger input to the OPNs. Thus, for models of the premotor process the trigger after the threshold is *ad hoc*. And, for models of the motor process the threshold before the trigger is *ad hoc*.

4 How to address the gap

We conclude with a non-exhaustive list of empirical tests and model challenges that would elucidate the linkage between the threshold observed in gaze shifting premotor saccade neurons and the pause in OPN activity that specifies when brainstem burst neurons produce a saccade. The following empirical neurophysiological studies would address the gap.

First, how are OPNs and gaze-holding fixation neurons (SC, FEF, and SNpr) modulated in the testing conditions used to describe the rise-to-threshold pattern of activity and its variations? Do they exhibit any modulation during saccade countermanding before stop signal reaction time? Or are they the all-or-none switch at the point of no return? Unlike the premotor saccade neurons in FEF and SC that modulate across SAT conditions, OPNs should remain invariantly associated only with the saccades that are produced. Based on previous results (Everling et al., 1998), it is likely that during saccade countermanding the OPN should modulate not at all unless saccades are actually initiated. How do their states vary when the trigger threshold of gaze shifting premotor neurons appears to vary when stimulus-response mapping is complex, or speed-accuracy is stressed? An account for lower thresholds associated with longer reaction times might be a gradually increasing recruitment of SC and FEF premotor neurons, which would thus collectively exert a constant 'drive' despite collapsing thresholds. Alternatively, OPNs might reduce their discharge rate before saccades produced after very long response times.

Second, among pools of SC and FEF premotor saccade neurons recorded simultaneously, how much agreement or disagreement is observed in the timing of reaching the trigger threshold? Or, how often are saccades initiated before the discharge rate of a given neuron has reached its threshold? Of course, to answer these questions requires clearer specification of how the functionally meaningful threshold is measured. To date, it has been just the average discharge rate measured in the 10–20 ms before saccades are initiated. However, this would necessarily be an overestimate, because saccades were initiated on all of the trials when the discharge rate was less than the average.

Third, during simultaneous recordings of OPNs with either premotor gaze-holding or gaze-shifting neurons, how much agreement or disagreement is observed between the time when premotor saccade neurons reach the trigger threshold and the time when OPN activity pauses? Such measurements would provide more insight on how to measure premotor saccade neuron threshold.

Fourth, how do LLBNs neurons modulate in the testing conditions used to describe the rise-to-threshold pattern of activity and its variations? They are the most likely source of SC and FEF feed-forward inhibition onto OPNs, hypothesized to carry the trigger signal to initiate a saccade (Wang et al., 2013). LLBNs can be found in both the ***PPRF*** and the ***cMRF***. With the exception of Handel and Glimcher (1997), who reported preparatory activity as well as saccade-related discharges, no one has recorded from LLBNs in decision making tasks or during saccade countermanding. Will the stochastic accumulation pattern of premotor activity described in FEF and SC be paralleled by LLBNs? Will the systematic variation in pre-stimulus and pre-saccadic activity observed across SAT conditions be present in LLBN spiking? If so, the cognitive penetrability of the brainstem would be greater than expected, which would surprise the psychologists studying decision making. If not, then the nature of the synthesis of modulated descending influences would become a more vivid question.

Fifth, saccades are described as all-or-none, ballistic movements because the point of no return is so discrete. The accumulation to threshold of the activity of SC and FEF premotor saccade neurons is interrupted during successful saccade countermanding in a manner that accomplishes the discrete transition (reviewed by Schall et al., 2017). However, saccade dynamics can be more variable during decision-making tasks in which multiple saccade commands collide (e.g., Camalier et al., 2007; Keller et al., 2008). The typically all-or-none nature of saccades is supposed to arise from the gate-keeping role of the OPN. But, are OPN really as oblivious as the soldier in the foxhole to the orders and countermanding occurring at higher levels?

In addition, the gap can be narrowed through models. Formally linking models of stochastic accumulation of evidence with models of brainstem mechanisms of saccade production would expose many assumptions (Fig. 5). In fact, we anticipate that such combinations across modeling

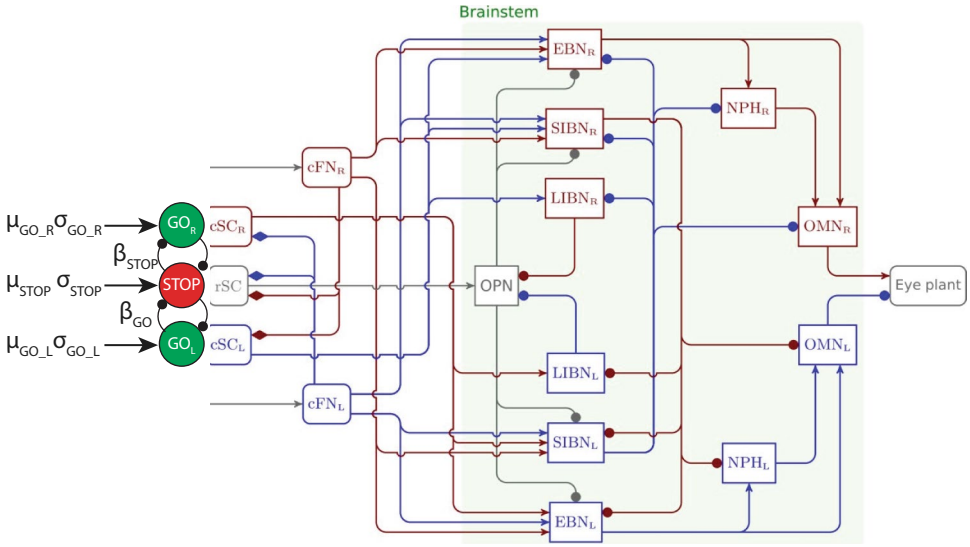

Fig. 5 Linking models of premotor stochastic accumulation with models of saccade production. The GO and STOP units of the interactive race model of saccade countermanding are proposed for the dynamics of the caudal (cSC) and rostral (rSC) elements of the Optican neuromimetic model of saccade generation. The activation of the GO and STOP units is excited by inputs with some mean (μ) value and associated standard deviation (σ) and inhibited by inputs from the other units with some strength (β). The neuromimetic model shows only feedforward connections between neurons that act bilaterally (gray) or for rightward (red) or leftward (blue) saccades. The light green region encloses brainstem neurons. The neuromimetic model consists of the caudal fastigial nucleus (cFN), OPNs, long-lead inhibitory burst neurons (LIBN), short-lead inhibitory burst neurons (SIBN), excitatory burst neurons (EBN), NPH, and OMN. Three kinds of connections are drawn: excitation (arrowhead), inhibition (filled circle), and facilitation (filled diamonds)

domains can offer converging constraints from the two perspectives that could resolve model mimicry within each perspective. For example, how might collapsing bounds be implemented neurally?

Models of this flavor have been developed. For example, Lo and Wang (2006) created a biophysically plausible network of spiking neurons with a cortical evidence accumulation module communicating with a SC module and an interposed basal ganglia module. The local dynamics within the SC yielded an all-or-none burst response that marks when upstream cortical premotor saccade neurons reach threshold. As informative as this is, we note two limitations of this particular model. First, it does not incorporate the brainstem circuitry. Second, it cannot really be tested by the quality of fitting performance data, unlike more abstract decision-making models. Nevertheless, such biophysically plausible models will certainly be necessary to fill the gap, because they can gracefully incorporate phenomena like countermanding of saccades (Lo et al., 2009) or speed-accuracy tradeoff (Lo et al., 2015; Standage et al., 2013, 2018).

More recent models have addressed the triggering problem more comprehensively. For example, Lance Optican and colleagues (Otero-Millan et al., 2018) developed a model of brainstem saccade circuitry with drives from the SC which is guided by a basic FEF and basal ganglia mechanisms. Computationally, the OPNs are necessary to ensure the all-or-none transition between gaze-holding and gaze-shifting. The SC is modeled with two types of neurons in a topographic arrangement. The first are the neurons we have been referring to as premotor saccade neurons, which instantiate the noisy, gradual accumulation of activation until the saccade is triggered. To prevent the noisy buildup activity from triggering a saccade prematurely, a pool of burst neurons was included. The simulated burst neurons were designed to become activate only when the premotor saccade neuron activation reaches a specified threshold. Hence, like Low and Wang (2006), this model takes as given that the SC bursting activity signals whether and when the threshold is crossed, and the point of no return reached. Like all useful models, the two just considered expose a particular assumption that can guide further empirical investigation.

Given the signaling advantages of bursts of action potentials (e.g., Lisman, 1997; Sherman. 2001), we hypothesize that the burst of SC premotor neurons corresponds to the point of no return for saccade initiation. A more detailed account of this event would yield a physiologically and functionally meaningful signature if not mechanism of the threshold. In previous research, Paré and Hanes (2003) showed that SC premotor saccade neurons can discharge up to about 100 sp/s without initiating a saccade during the saccade countermanding task, similar to previous observations (e.g., Sparks, 1978; Paré & Wurtz 2001; Paré & Munoz, 2001). The ramping activity of these neurons

in decision-making tasks certainly excludes any bursting activity (Ratcliff et al., 2007; Crapse et al., 2018). Some neurons seem to display only a burst of activity (Munoz & Wurtz, 1995). A closer, albeit qualitative examination of the countermanding data from Paré and Hanes (2003; e.g., see their Fig. 3) indicates that some single SC saccade neurons do occasionally emit a burst-like discharge in the absence of a saccade, but among neurons with the distinct high-frequency saccade-related burst only low-frequency discharges are observed when saccades are inhibited.

Now, the bursting activity of SC premotor saccade neurons often reaches frequencies of 1000 sp/s, significantly higher than what is observed in FEF neurons, which rarely exceeds 100 sp/s (e.g., Hanes and Schall 1996). How do SC neurons produce such high-frequency bursts? Burst firing in several neural systems depends on intrinsic cellular rather than distributed circuit mechanisms (see for review Krahe & Gabbiani, 2004). For example, bursting of the pyramidal cells within the hindbrain (lateral line lobe) of the gymnotiform weakly electric fish is known to rest on the activation of sodium channels and results from interactions between soma and proximal dendrites (Metzen et al., 2016). Such burst firing can, however, be regulated by feedback signals and by neuromodulators.

Are burst discharges also intrinsic to individual SC premotor saccade neurons? *In vitro* experiments in slices from rat SC suggest that this is not the case. They revealed instead that burst-like discharges observed in intermediate-layer neurons (including tecto-reticular neurons) are attributable to local circuitry and synaptic transmission mediated by NMDA receptors and calcium independent mechanisms (Saito & Isa, 2003; Sooksawate et al., 2005). These burst-like discharges are unmasked when the circuit is released from GABAergic inhibition, which endows SC neurons with a highly nonlinear input-output relationship. The bursting activity of SC neurons would therefore rely on inhibitory inputs from local interneurons and SNpr as well as lateral excitatory connections from recurrent collaterals (Moschovakis et al., 1988a,b). And, the influence of neuromodulators like acetylcholine cannot be overlooked (Kobayashi et al., 2001). We must note that much of the foregoing information was derived from *in vitro* experiments using slices from rat SC. We are not guaranteed that the results will generalize to primate species. Hence, we lack a sufficient mechanistic understanding of how the bursts of spiking preceding saccades are generated.

Another domain in which this question can be addressed is the clinic. Optican and colleagues have measured the gaze behavior of patients to test model plausibility, and the models have been tools with which to understand clinical manifestations and possibly to target therapies. For example, saccade oscillations (ocular flutter or opsoclonus) can be understood as arising from a specific ion channel dysfunction in the membrane of brainstem burst cells (Shaikh et al., 2008). Evidence for this was provided through a biologically realistic model of the brainstem saccade generator, in which the dynamics of reciprocal inhibition between premotor saccadic burst neurons result in inherent instabilities that produce saccade oscillations. This instability, which is arrested by external inhibition, is hypothesized to be mediated through two particular ion channels, the hyperpolarization-activated, inward-mixed, cation current and low threshold calcium currents. Reduction of the low-threshold calcium currents in the model decreased the amplitude but increased the frequency of the simulated oscillations. Combined reduction of the hyperpolarization-activated cation current with the low-threshold calcium currents abolished the simulated oscillations. The model was verified with a selective blocker of the of the hyperpolarization-activated cation current (ethosuximide) in healthy controls and with a nonselective blocker of both the hyperpolarization-activated cation current with the low-threshold calcium currents (proponolol) in a patient with saccadic oscillation (Shaikh et al., 2011).

This work demonstrates the possibility of treatments offered by mechanistic insights gained. We expect that further mechanistic insights into the control of the initiation of saccades will point toward possible treatments for disorders that involve impaired control of saccade initiation such as schizophrenia (e.g., Thakkar et al., 2011), Huntington's and Parkinson's disease (e.g., Antoniadis & Kennard, 2015; Pretegiani et al., 2017), and Alzheimer's disease (e.g., Peltsch et al., 2014).

5 Conclusions

A critical gap in our understanding of how saccades are initiated was exposed by our review of two threads in the rich literature about saccade production to which Lance Optican has contributed so powerfully. We cannot explain the mechanism(s) that link the instant when premotor saccade neurons reach a discharge rate threshold and the instant when OPNs pause activity and burst neurons create the pulse of force to rotate the eye. Understanding this relationship will refine and enrich both threads. We have proposed a number of particular research questions that we believe will close this gap. Investigation of these questions would require new focused effort, most productively by teams of collaborators with expertise in both threads of the literature. Hopefully, this review might inspire such a synthesis.

Acknowledgements We thank the many colleagues whose creative and insightful work was reviewed and apologize to those whose work was not highlighted enough or at all owing to limits of space or knowledge.

Authors' contributions The authors are solely responsible for the content of this mini-review.

Funding MP is supported by the Canadian Institutes of Health Research and the Natural Sciences and Engineering Research Council of Canada. JDS was supported by the National Institutes of Health and by Robin and Richard Patton through the E. Bronson Ingram Chair in Neuroscience.

Declarations

Ethical approval All experimental procedures performed in JDS laboratory are in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, the Society for Neuroscience Guidelines and Policies, and approved by the Vanderbilt University Institutional Animal Care and Use Committee. All experimental procedures performed in MP laboratory are in accordance with the Canadian Council on Animal Care in science and approved by Queen's University Animal Care Committee.

Conflict of Interest The authors declare no conflict of interest.

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