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Microsaccade production during saccade cancelation in a stop-signal task

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ABSTRACT

We obtained behavioral data to evaluate two alternative hypotheses about the neural mechanisms of gaze control. The "fixation" hypothesis states that neurons in rostral superior colliculus (SC) enforce fixation of gaze. The "microsaccade" hypothesis states that neurons in rostral SC encode microsaccades rather than fixation *per se*. Previously reported neuronal activity in monkey SC during the saccade stop-signal task leads to specific, dissociable behavioral predictions of these two hypotheses. When subjects are required to cancel partially-prepared saccades, imbalanced activity spreads across rostral and caudal SC with a reliable temporal profile. The microsaccade hypothesis predicts that this imbalance will lead to elevated microsaccade production biased toward the target location, while the fixation hypothesis predicts reduced microsaccade production. We tested these predictions by analyzing the microsaccades produced by 4 monkeys while they voluntarily canceled partially prepared eye movements in response to explicit stop signals. Consistent with the fixation hypothesis and contradicting the microsaccade hypothesis, we found that each subject produced significantly fewer microsaccades when normal saccades were successfully canceled. The few microsaccades escaping this inhibition tended to be directed toward the target location. We additionally investigated interactions between initiating microsaccades and inhibiting normal saccades. Reaction times were longer when microsaccades immediately preceded target presentation. However, pre-target microsaccade production did not affect stop-signal reaction time or alter the probability of canceling saccades following stop signals. These findings demonstrate that imbalanced activity within SC does not necessarily produce microsaccades and add to evidence that saccade preparation and cancelation are separate processes.

1. Introduction

The saccade stop-signal task has provided tremendous insight into the neurophysiological basis of eye movements (Asrress & Carpenter, 2001; Atsma et al., 2014; Bissett & Logan, 2013; Born, Mottet, & Kerzel, 2014; Boucher et al., 2007; Brown et al., 2008; Cabel et al., 2000; Camalier et al., 2007; Corneil & Elsley, 2005; Emeric et al., 2007; Goonetilleke, Wong, & Corneil, 2012; Gulberti, Arndt, & Colonius, 2014; Hanes & Carpenter, 1999; Hanes & Schall, 1995, 1996; Joiner, Lee, & Shelhamer, 2007; Kornylo et al., 2003; Lo et al., 2009; Logan & Irwin, 2000; Morein-Zamir & Kingstone, 2006; Pouget et al., 2011; Ray, Pouget, & Schall, 2009; Scangos & Stuphorn, 2010; Stevenson, Elsley, & Corneil, 2009; Stuphorn, Brown, & Schall, 2010; Walton & Gandhi, 2006; Wessel, Reynoso, & Aron, 2013; Wong-Lin et al., 2010). Participants are occasionally instructed to cancel saccades shortly after a cue to respond (Fig. 1). By analyzing subjects' accuracy and reaction times as the outcome of a race between go and stop processes, investigators can estimate the time required for subjects to inhibit actions (Logan, 1994; Logan & Cowan, 1984). This metric, referred to as stop-signal reaction time (SSRT), specifies the duration in which neurons participate in initiating or withholding motor responses. Investigators have reported detailed profiles of neural activity recorded from many ocular motor structures during the saccade stop-signal task (Hanes, Patterson, & Schall, 1998; Stuphorn, Brown, & Schall, 2010; see also Brunamonti, Thomas, & Paré, 2008; Mirabella, Pani, & Ferraina, 2011; Murthy, Ray, Shorter, Schall, & Thompson, 2009; reviewed by Schall & Godlove, 2012a), and these data can be used to generate novel predictions about oculomotor behavior. For instance, when monkeys inhibit eye movements during the stop-signal task, pools of neurons in caudal and rostral superior colliculus (SC) are

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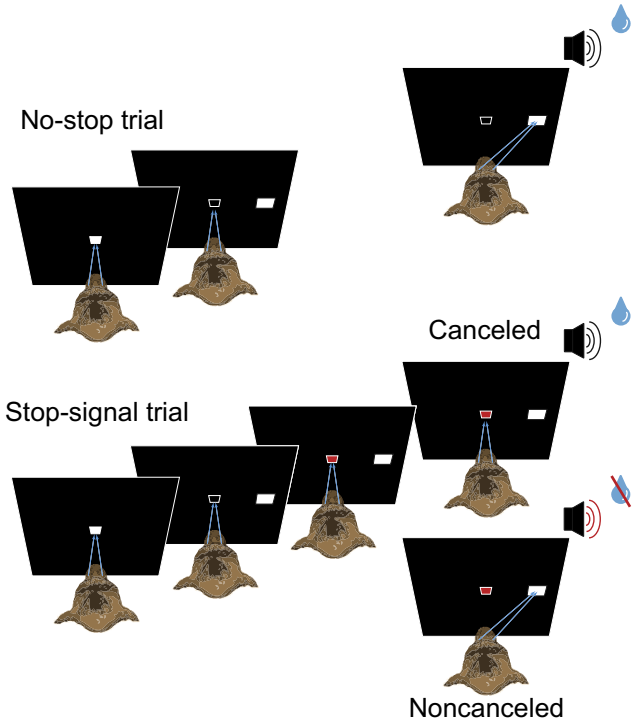

Fig. 1. The saccadic stop-signal (countermanding) task. Top: No-stop trials were initiated when monkeys fixated a central point. After a variable time, the center of the fixation point was extinguished leaving an outline. A peripheral target was presented simultaneously at one of two possible locations. Monkeys were required to fixate targets with quick saccades. On correct trials, a speaker sounded a tone indicating success and a juice reward was delivered. Bottom: Stop-signal trials were initiated in the same way. After a variable time (SSD), the center of the fixation point was reilluminated in a different color, instructing the monkeys to withhold movement. Successful inhibition of saccades resulted in rewarded Canceled trials, but errant saccades resulted in unrewarded Noncanceled trials accompanied by a different speaker tone.

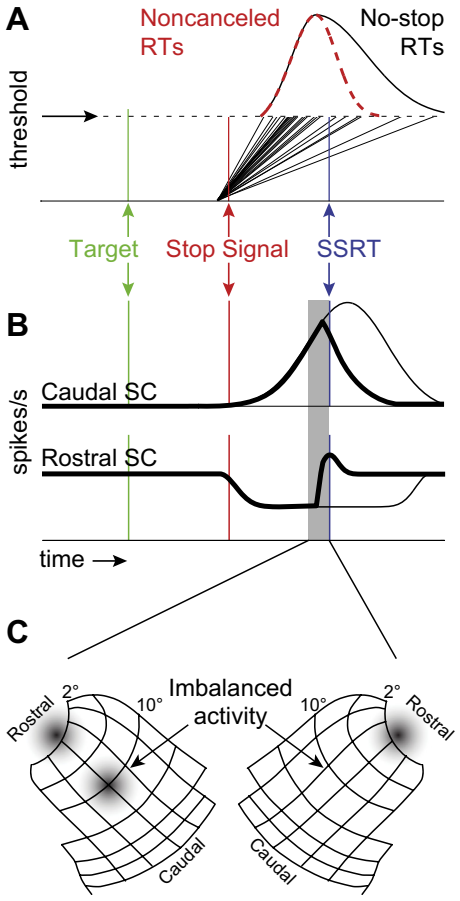

Fig. 2. Timing and spatial distribution of imbalanced activity in superior colliculus (SC) during the stop-signal task. (A) Application of Logan's race model to reaction time and accuracy data yields estimates of stop-signal reaction time (SSRT blue). This is the median time necessary for movements to be canceled. Given the presentation of a stop-signal on a particular trial, motor processes on trajectory to reach threshold after SSRT will not result in movement, effectively truncating the reaction time distribution. (B) Imbalanced activity in SC shows a predictable spatial and temporal evolution during the saccade stop-signal task. Thick traces represent activity on canceled trials. Thin traces depict activity on latency matched no-stop trials. Diagram is adapted from data presented by Paré and Hanes (see their Figs. 3 and 7). (C) Spatial activity in SC is stereotyped around SSRT. Putative neural activity is taken from gray window in (B). Rostral and caudal SC show coactivation just before and concomitant with SSRT on canceled trials.

simultaneously active before and during SSRT producing an imbalance across the saccade trajectory map in this area (Paré & Hanes, 2003; Fig. 2). As detailed below, these data lead to predictions about the patterns of microsaccades that should be elicited when monkeys cancel saccades during the stop-signal task.

It is well-accepted that neurons in the intermediate layers of SC encode target positions and are arranged in an orderly saccade polar coordinate map (Gandhi & Katnani, 2011; Krauzlis, 2008; Lee, Rohrer, & Sparks, 1988; Munoz & Schall, 2004; Munoz et al., 2000; Robinson, 1972). But disagreement persists about the function of neurons in rostral SC at the origin of this coordinate system. An early line of work indicated that neurons in rostral SC enforce fixation (Büttner-Ennever et al., 1999; Gandhi & Keller, 1997; Munoz, Waitzman, & Wurtz, 1996; Munoz & Wurtz, 1993a, 1993b; Paré & Guitton, 1994). According to this view, neurons in the rostral pole of SC inhibit saccades regardless of the activity level of neurons in caudal SC. This view assumes the existence of two different neuron types in SC, one responsible for gaze-shifting and another responsible for gaze-holding. To describe the function of the rostral SC, we will refer to this as the *fixation hypothesis*.

More recent work emphasizes the contribution of all neurons in the intermediate layers of SC to gaze-shifting (Goffart, Hafed, & Krauzlis, 2012; Hafed, Goffart, & Krauzlis, 2008; Hafed & Krauzlis, 2012; Krauzlis, Basso, & Wurtz, 1997). According to this view, neurons in rostral SC simply contribute to saccades near the point of fixation, and gaze-holding is accomplished by maintaining equilibrium across the saccade map. When the equilibrium of SC activity becomes imbalanced toward a target location (as illustrated in Fig. 2C) microsaccades or larger gaze shifts are initiated. To describe the function of the rostral SC, we will refer to this as the *microsaccade hypothesis*.

Given the pattern of activity that was previously reported in SC when monkeys canceled eye movements during the stop-signal task (Paré & Hanes, 2003; see also Hanes, Patterson, & Schall, 1998), the microsaccade hypothesis and fixation hypothesis make different predictions about the pattern of microsaccades that should be observed before and during SSRT. The microsaccade hypothesis predicts that imbalanced activity in SC during the interval that normal saccades are inhibited (i.e. SSRT) will lead to increased microsaccade production with most directed toward the target. The fixation hypothesis predicts that elevated activity of gaze-holding neurons in rostral SC will lead to decreased microsaccade production.

To test predictions of the microsaccade and fixation hypotheses explicitly, we used high-resolution eye tracking and analysis techniques to record micro- and normal saccades from four monkeys trained to perform the saccade stop-signal task. The use of monkeys instead of humans provides several advantages. They were highly trained and would readily complete thousands of trials

per experimental session. Neural activity has also been described in several monkey ocular motor structures including SC and FEF allowing us to test predictions of the microsaccade and fixation hypotheses in a reliable animal model. The results provide new evidence that saccade initiation and inhibition are distinct and dissociable processes and that fixation need not depend on equilibrium in SC as previously suggested (Goffart, Hafed, & Krauzlis, 2012). We discuss how these findings relate to general mechanisms of response inhibition and to recent anatomical studies, and we suggest that the fixation hypothesis bears reappraisal. Parts of this paper have been published previously in a conference abstract and a doctoral dissertation (Godlove, 2013; Schall & Godlove, 2012b).

2. Material and methods

2.1. Animal care

Data were collected from 3 male bonnet macaques (*Macaca radiata* 6.9–8.5 kg) and one female rhesus macaque (*Macaca mulatta* 6 kg). Animal care exceeded policies set forth by the USDA and Public Health Service Policy on Humane Care and Use of Laboratory Animals and all procedures were carried out with supervision and approval from the Vanderbilt Institutional Animal Care and Use Committee. Titanium headposts were surgically implanted to facilitate head restraint during eye tracking. Surgical methods have been described in detail (Godlove et al., 2011).

2.2. Stimuli and task

Monkeys were seated in enclosed primate chairs with heads restrained using surgically implanted head posts. Depending on primate chair and recording setup, monkeys sat 43–49.5 cm from a 70 Hz CRT monitor subtending 47.8–51.8° horizontal visual angle and 34.5–37.4° vertical visual angle. Stimulus presentation, task contingencies related to eye position, and delivery of liquid reinforcement were all under computer control in hard real time (TEMPO, Reflective Computing, Olympia, WA). Stimuli were presented using computer-controlled raster graphics (TEMPO Videosync 640×400 pixel resolution, Reflective Computing, Olympia, WA). Stimulus sizes and eccentricities were automatically adjusted by the computer program to account for subject viewing distance and had luminance values of 10 cd/m^2 on a 0.02 cd/m^2 background or 39 cd/m^2 on a 10 cd/m^2 background depending on which recording setup was used.

Details about the behavioral training regime and task have been described previously (Hanes, Patterson, & Schall, 1998; Hanes & Schall, 1995). Trials were initiated when monkeys fixated a centrally presented square which subtended 0.34° of visual angle. After a foreperiod ranging from 600 ms to 1100 ms, the center of the fixation point was extinguished, leaving an open square outlined 1 pixel thick, and a target subtending 3° of visual angle simultaneously appeared centered at 10° to the left or right of fixation. To minimize anticipation effects, the foreperiod was approximately non-aging being randomly sampled from a distribution described by the function:

$$p(t) = e^{-t/k}$$

where the probability of selecting a specific foreperiod $p(t)$ is an exponential function with time constant of k. We set k equal to 250 ms and shifted the distribution to fall between 600 and 1100 ms. On no-stop trials (Fig. 1, top), no further visual stimuli were presented. Monkeys were required to make a saccade to the target within 800 ms and hold fixation for 600 ms to obtain reward. Correct trials were rewarded with an audible tone followed 600 ms later by several drops of juice. On stop trials (Fig. 1, bottom), the center of the fixation point was re-illuminated either red or green (constant for each monkey) after a variable delay providing a stop-signal which instructed the monkeys to cancel their impending eye movements and maintain central fixation. In practice, two trial outcomes were then possible. If monkeys successfully withheld the eye movement and maintained fixation for a minimum of 1600 ms, they obtained tone and juice reward. These trials were designated as "canceled" (also known as "signal inhibit"). If monkeys were unable to inhibit the movement, an audible tone signaling timeout sounded and a variable timeout was added to the normal inter-trial interval. These trials were termed "noncanceled" (also known as "signal respond"). Except where noted, canceled trials provided the data for the current study. During some recording sessions with monkey X, a third trial type was introduced containing an irrelevant visual stimulus. These trials will be the subject of a future report, and their presence did not change behavior in the main task. An initial set of SSDs was selected for each recording session based on the animals' previous behavior. We then manipulated SSD using an adaptive staircase algorithm that adjusted stopping difficulty based on performance. When monkeys failed to inhibit responses, the SSD was decreased by a random step of 1, 2, or 3 increasing the likelihood of success on the next stop trial. Similarly, when monkeys successfully inhibited an eye movement, the next SSD was increased by a random step of 1, 2, or 3 decreasing the future probability of success. This procedure ensured that monkeys failed to inhibit saccades on ~50% of all stop trials but did not experience predictable changes of SSD. Stop trials comprised 30–50% of all trials in a given session with a typical session consisting of several thousand trials.

We adopted the procedures of Logan and Cowan (1984) implemented by Hanes, Patterson, and Schall (1998) to estimate SSRT. In brief, we estimated this value using one method that assumes that SSRT is a constant, and another method that assumes that SSRT is a random variable. Because there is no reason to assume an advantage of either of these methods, we averaged the two estimates together to obtain final SSRT measures (but see Verbruggen, Chambers, & Logan, 2013).

2.3. Data acquisition

All data were streamed to a single data acquisition system (Plexon, Dallas, TX). Time stamps of trial events were recorded at 500 Hz, while eye position was recorded at 1 kHz. Eye position data were acquired, calibrated, and streamed to the Plexon computer using the EyeLink 1000 infrared eye-tracking system (SR Research, Ontario, Canada). This system has an advertised resolution of 0.01°. Several recent reports (Kimmel, Mammo, & Newsome, 2012; Otero-Millan et al., 2011) have shown that, with appropriate positioning, illumination, and calibration, this system can be used to detect microsaccades with performance approaching that of the magnetic search coil technique (Robinson, 1963).

2.4. Saccade detection

All saccade analyses were performed in the MATLAB programming environment using custom written code. Eye channels were first convolved with a 12 ms Gaussian polynomial to remove small line voltage fluctuations. We used a modified version of the algorithm proposed by Engbert and Kliegl (2003) to detect microsaccades. In this method, instantaneous velocity measures are obtained by calculating the first derivative across a 20 ms window separately for horizontal and vertical eye positions. This procedure yields a representation of eye positions in 2 dimensional velocity space. Values tend to cluster around zero, and outliers signal eye movements. Trial by trial noise levels are calculated and used to

set detection thresholds. Since horizontal and vertical eye velocities are calculated separately, detection thresholds assume elliptical shapes in velocity space reflecting horizontal and vertical noise levels on each trial. Finally, monocular eye movement events are excluded since microsaccades are binocular. We modified this procedure in the following ways. Because our task included normal saccades, we focused on periods of fixational eye movements for threshold estimation by removing periods when radial eye velocity exceeded 30°/s. We were unable to judge binocularity with our monocular eye tracking recordings, so we excluded drift and false positives using several other common-sense criteria. First, we excluded post-saccadic drift and eye tracker ringing by removing eye movements that began less than 50 ms prior to the end of the preceding eye movement. Respecting the eye tracker limitations, we excluded eye movements with amplitude <0.01°, and eye movements that strayed outside of the calibrated field of the central 22° × 22°. (This could occur during an aborted trial or during the inter-trial interval; we detected all saccades that occurred from the beginning to the end of the recording session.) Finally we excluded saccades with excessively short or long durations. Inspection of color-coded main sequence plots showed that 10–65 ms provided a reasonable range for acceptable saccade durations. We defined microsaccades as those with amplitude ⩽1° (Martinez-Conde et al., 2009). We obtained qualitatively identical results when we repeated our analyses using the more conservative definition of amplitude ⩽15′ (Collewijn & Kowler, 2008). Under the assumption that the smallest microsaccades we detected were those most likely to be contaminated by artifacts, we also repeated our analyses using only saccades that were >20′ in amplitude. We obtained identical results using this subset of the data.

2.5. Saccade analysis

We analyzed (1) changes in microsaccade rate in relation to task events to evaluate predictions of the microsaccade and fixation hypotheses, (2) the direction of microsaccades relative to target position as a function of time to study the effects of putative imbalanced SC activity on microsaccade direction, and (3) the effect of microsaccades on subsequent saccade initiation and cancelation to study possible interactions between producing microsaccades and canceling normal saccades.

To visualize and analyze microsaccade rate in relation to task events, we constructed rasters and peri-event time histograms of microsaccade rate sorted by different trial intervals. We used standard methods identical to those employed to analyze the number of action potentials elicited by neurons (Lemon, 1984). To approximate continuous functions for visualization and analysis purposes, we convolved each peri-event time histogram with a Gaussian kernel (σ = 10 ms).

To judge the times at which microsaccade rate became significantly elevated or depressed relative to baseline levels, we used a running Wilcoxon rank-sum test. First, we constructed microsaccade density functions for each session as described above. To obtain a baseline rate, the average microsaccade rate was measured in the 50 ms interval before target presentation. The rate of microscaccade production was contrasted with this baseline in a 1 ms sliding window advanced in 1 ms increments. Each session contributed a single observation to each bin for these tests, and significance was assessed at the $p < 0.01$ level. The results were not different if 10 or 50 ms sliding windows were used. This approach was also used to test for differences between the number of microsaccades made toward or away from the peripheral target as a function of time.

To examine more closely the proportion of microsaccades made toward the target independent of microsaccade rate, we binned microsaccades made directly toward and opposite the target (±45°), constructed microsaccade density functions as described above, and represented them as proportions (Hafed & Ignashchenkova, 2013; Pastukhov et al., 2013). Because so few microsaccades were made during SSRT, we collapsed across subjects for this and the following analyses. To test whether microsaccades were biased toward or away from the target we determined the proportion of saccades made toward the target (±45°) in each session during a given window (±50 ms centered on SSRT or −100 to 0 ms before target onset). Each session contributed a single data point to these statistical tests.

To assess the effect of the presence or absence of a pre-target microsaccade on subsequent RT, we divided no-stop trials (Fig. 1) into two groups based on whether a microsaccade had been made during 500 ms preceding target onset. We performed statistical tests on session median RTs of trials grouped in this way. To assess the effect of the presence or absence of a pre-target microsaccade on subsequent SSRT, we similarly grouped all trial types according to the presence or absence of a pre-target microsaccade. For these analyses, we matched the number of trials in groups with and without microsaccades during the pre-target interval. This ensured that RT and SSRT variability were matched between trials that contained microsaccades in the pre-target interval and those that did not

3. Results

3.1. Behavior

To test the predictions of the fixation and microsaccade hypotheses, we recorded data from 4 monkeys while they performed the saccade stop-signal task (Fig. 1). Table 1 summarizes behavior of each monkey. RTs and the probability of committing errors show that monkeys were appropriately sensitive to the stop signal. Mean noncanceled saccade RTs were less than mean saccade RTs on trials with no stop signal. Fig. 3 shows normalized inhibition functions and Weibull distribution fits for each monkey collapsed across all sessions. *Z*-scoring inhibition functions normalizes them in time, allowing them to be compared across recording sessions regardless of incidental RT differences due to normal fluctuations in arousal and motivation. These inhibition functions increase monotonically with SSD; short SSDs yielded near 0% errors while long SSDs yielded near 100% errors. Error rates on stop signal trials were close to 50% for all monkeys demonstrating the success of the SSD tracking algorithm. Thus, the performance validates the SSRT estimates. SSRT values fell within the range of those reported previously for monkeys performing this task. These considerations validate the use of SSRT as an index of maximally imbalanced activation in SC based on previous work (Paré & Hanes, 2003).

3.2. Microsaccade dynamics

We used a modified version of Engbert and Kliegl's (2003) algorithm for saccade detection. The relationship between saccade velocity, duration, and amplitude, known as the "main sequence" (Bahill, Clark, & Stark, 1975; Zuber & Stark, 1965) is displayed for each monkey in Fig. 4. Our saccade detection method identified

Table 1
Summary statistics for stop-signal task performance. Values are means ± SD.

Monkey	No-stop RT (ms)	Noncanceled RT (ms)	p (Error|Stop trial)	SSRT (ms)
A	355 ± 44	321 ± 38	0.49 ± 0.02	93 ± 15
F	350 ± 34	315 ± 27	0.47 ± 0.02	120 ± 10
U	399 ± 80	368 ± 73	0.50 ± 0.02	102 ± 18
X	371 ± 43	353 ± 41	0.45 ± 0.03	130 ± 20

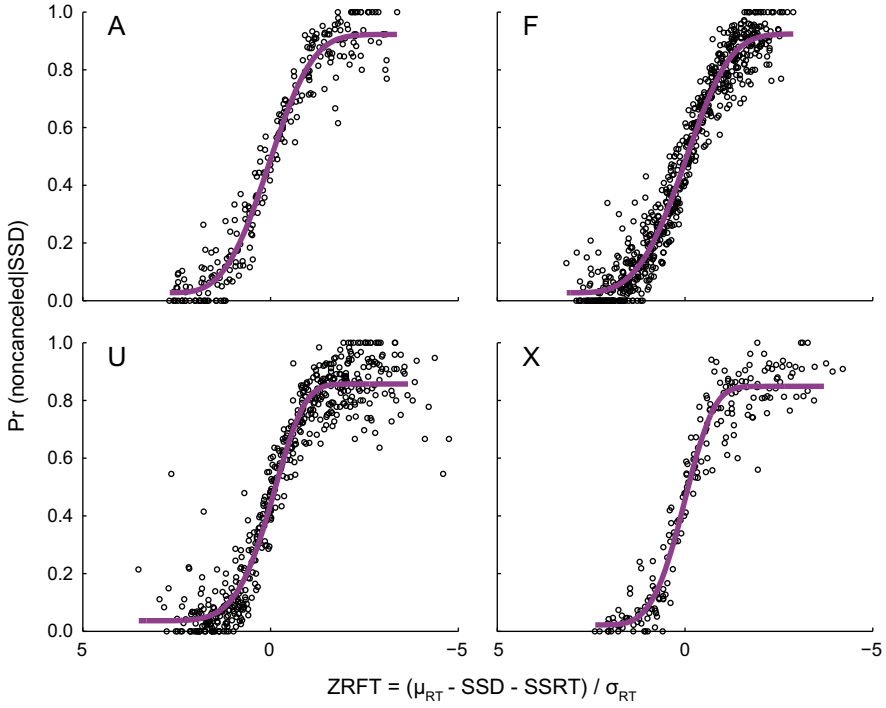

Fig. 3. ZRFT (*z*-scored inhibition) functions and Weibull distribution fits for each monkey. Letters in upper left denote the monkey. Inhibition functions plot the probability of committing a noncanceled error at each SSD.

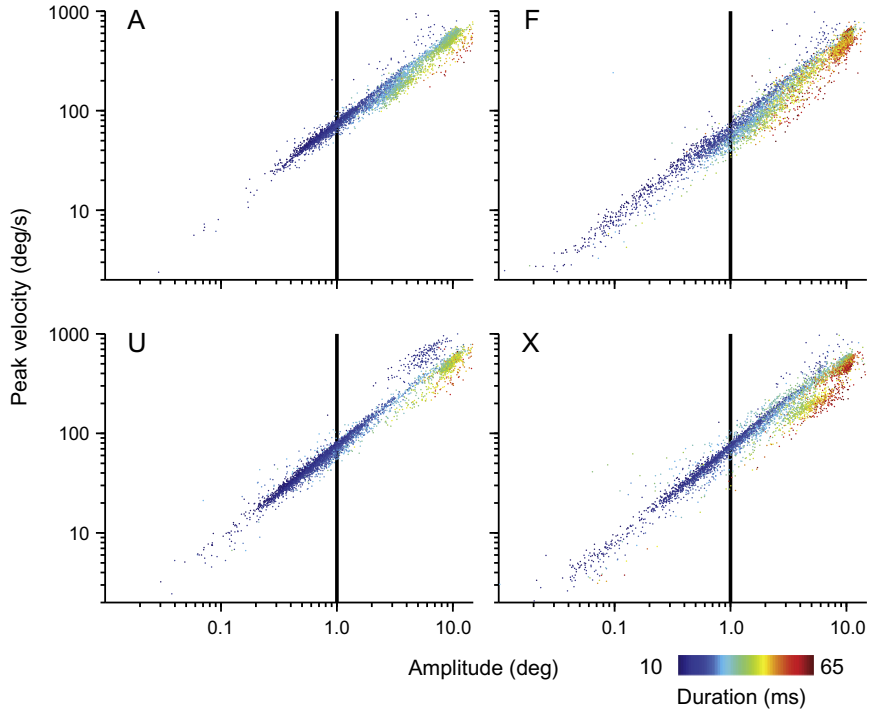

Fig. 4. Saccade velocity plotted against saccade amplitude with duration color-coded for each monkey. Microsaccades (defined as <1°, left of vertical black lines) are continuous with main sequence of normal saccades (right of vertical black lines). Letters in upper left denote the monkey. Each plot displays 5000 randomly sampled saccades made at any time during the recording session (including the inter-trial interval) drawn from complete data sets.

eye movements with very small amplitude having the same main sequence relationship as those with larger amplitude. This finding replicates well-known observations and demonstrates the robustness of our saccade detection approach.

3.3. Microsaccade rate

We studied microsaccade rate during canceled trials by constructing rasters marking the time of each microsaccade and

deriving density functions collapsed across sessions for each monkey (Fig. 5).[1] Data were aligned on target presentation, on stop-signal presentation and on average subject SSRT. The raster plots show the variability in microsaccade rate in relation to trial events, while the density functions show the trends in microsaccade rate relative to pre-target levels. We used a running Wilcoxon test to identify periods of elevated or reduced microsaccade rate relative to baseline (see Section 2.5). Gray bars beneath microsaccade density functions show periods of depressed microsaccade rate, while black bars show periods of elevated microsaccade rate ($p < 0.01$). Microsaccade rate was reduced before and during SSRT when SC activity is imbalanced across the saccade polar coordinate map.

Following changes in visual stimuli, we observed clear microsaccade inhibition. Each monkey made significantly fewer microsaccades after target presentation, beginning at very short latencies[2] (Fig. 5 left column gray bars after target onset; latencies relative to target Monkey A 40 ms, F 65 ms, U 36 ms, X 65 ms). The rasters of monkeys A and U show distinct microsaccade inhibition associated with both target and stop-signal presentation. At shorter SSDs, microsaccade inhibition associated with the target and the stop-signal overlap. It is less clear if the decrease associated with the stop-signal is absent for monkeys F and X, or if two periods of microsaccade inhibition have simply merged into one. Subsequent to this inhibition and following SSRT, all monkeys showed elevated microsaccade production beginning ~220 ms after the stop-signal and ~50–170 ms after SSRT (Fig. 5 right column black bars after stop signal and SSRT; latencies relative to stop signal Monkey A 178 ms, F 239 ms, U 276 ms, X 182 ms, latencies relative to SSRT Monkey A 85 ms, F 119 ms, U 174 ms, X 52 ms). The rasters show clearly that this elevation is synchronized on the stop-signal but occurs well after SSRT. This late peak in microsaccade production was followed by reduced microsaccade production throughout the 1600 ms period until reward delivery (data not shown).

3.4. Microsaccade direction

Based on the observed imbalanced neural activity across the collicular map during successfully canceled trials in the stop-signal task (Paré & Hanes, 2003, Fig. 2), we investigated whether greater incidence of microsaccades were directed toward the target location during SSRT (Hafed, Goffart, & Krauzlis, 2008, 2009). Fig. 6 plots the rate of microsaccades toward (cyan) and away (magenta) from the peripheral target (±45°) as a function of time. We used a running Wilcoxon approach to test for differences between the rate of saccades directed toward or away from the target within subjects (see Section 2.5). Black bars beneath microsaccade density functions illustrate periods of significant differences between microsaccade directions ($p < 0.01$). Around 200–300 ms after the target appeared, all monkeys except for U made significantly more microsaccades toward the target location (Fig. 6 left column black bars after target onset). In contrast, the microsaccades observed after SSRT (Fig. 6 right column black bars after stop signal and SSRT) were directed away from the target more often than expected by chance (A, F, U) or showed no significant directional bias (X). Although these microsaccades tended to move the eyes away from the target location, they did not cause the eyes to exit the invisible fixation window.

Because the direction of microsaccades made during SSRT was obscured by the overall paucity of microsaccades during this period, we pooled the data across monkeys and plotted the proportion of microsaccades made toward the target (±45°) vs. away from the target (±45°) (Hafed & Ignashchenkova, 2013; Pastukhov et al., 2013). Across monkeys, there is large variability in the proportion

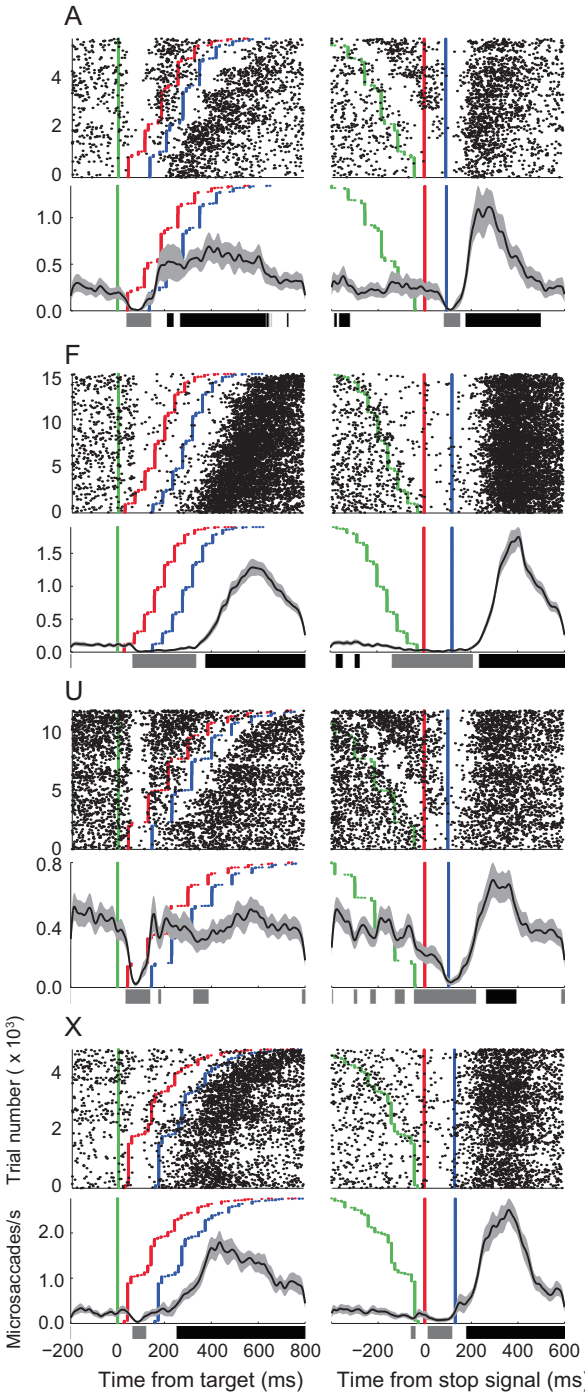

Fig. 5. Microsaccade production plotted for each monkey in rasters (top) and density functions (bottom) aligned to presentation of target (left) and stop-signal (right). Letters in upper left denote the monkey. Target presentation (green), stop-signal presentation (red), and average SSRT (blue) are indicated. Gray outlines on density functions indicate 95% confidence intervals across recording sessions. Gray bars beneath density functions denote periods when microsaccade rate is suppressed below baseline levels, while black bars denote periods when microsaccade rate exceeds baseline levels ($p < 0.01$). Axes are scaled to accommodate idiosyncratic differences in microsaccade rate. Each monkey exhibited a pronounced reduction of microsaccades after the stop signal followed by an equally clear elevation after SSRT.

[1] In these and following plots, please note differences in ordinate scale of microsaccade density functions. In particular, all monkeys showed similar baseline levels of microsaccade production. Monkey U showed the same patterns of microsaccade modulation as the other monkeys, but peak levels of microsaccade production were reduced for this monkey compared to the other monkeys. This is consistent with individual differences noted in humans (Collewijn & Kowler, 2008).

[2] Note that the 10 ms Gaussian (non-causal) convolution kernel will make onset times appear earlier.

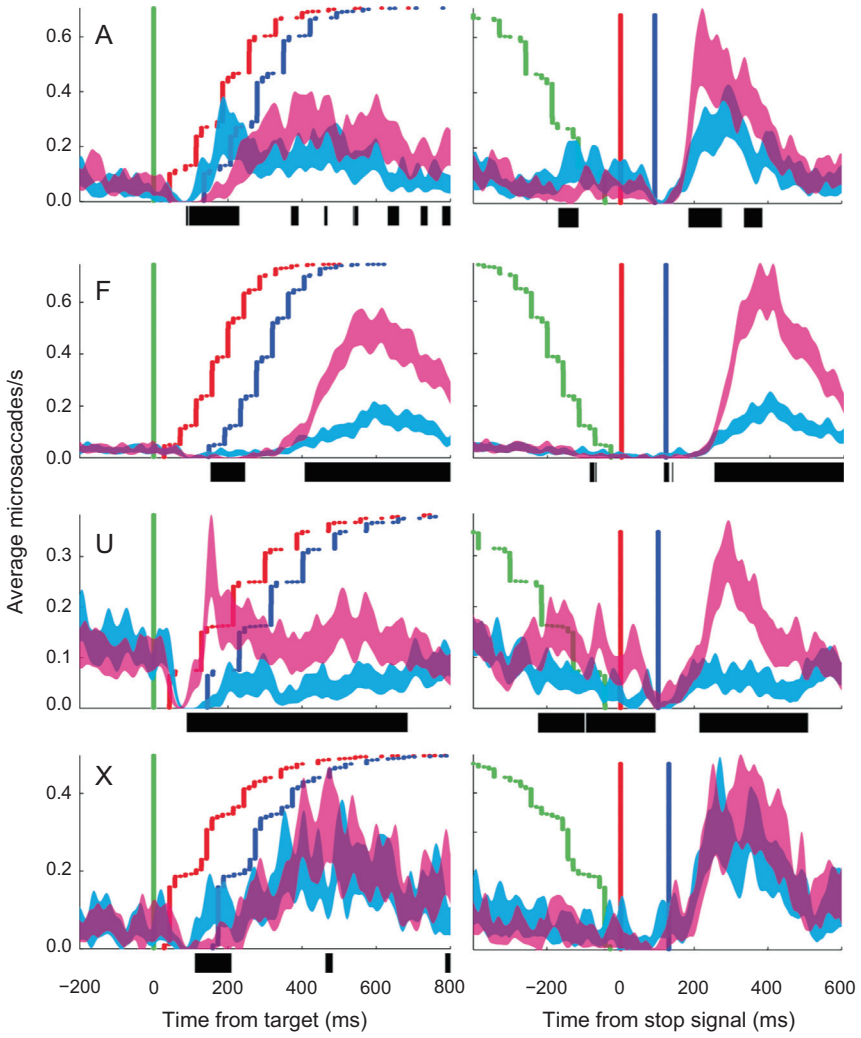

Fig. 6. Microsaccades produced toward (cyan) or opposite (magenta) the target (± 45°) aligned to target (left) and stop-signal (right) presentation. Black bars denote periods of significant differences between density functions. Conventions as in Fig. 5.

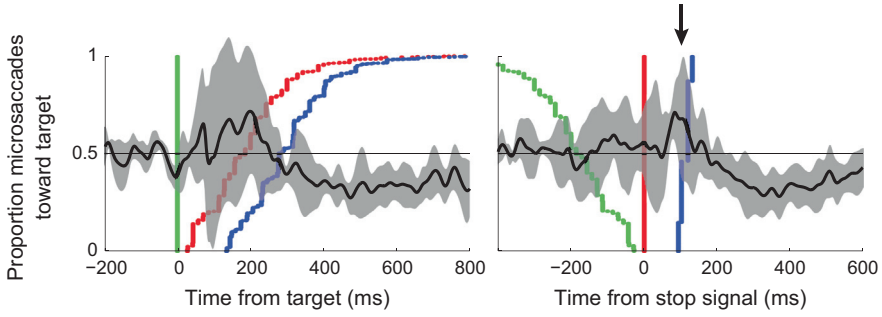

Fig. 7. Proportions of microsaccades made toward the target collapsed across sessions. Black arrow on right indicates period before and during SSRT when more microsaccades were made toward the target location. Conventions as in Fig. 5.

of microsaccades made toward the target location following target onset (Fig. 7, left). But during SSRT, the few microsaccades that escaped inhibition tended to be directed toward the target location reflecting the spatial readout of neural activity across the collicular map on canceled trials reported previously (Fig. 7, black arrow). During a 100 ms window centered on SSRT, the elevated proportion of microsaccades directed toward the target was marginally significant ($t_{(90)} = 1.98$, $p = 0.05$). For comparison, no bias of microsaccade direction was observed during a 100 ms window preceding target onset ($t_{(173)} = 0.22$, $p = 0.83$). Polar plots of microsaccade direction during these time intervals are displayed in Fig. 8.

3.5. RT and SSRT following microsaccades

Given the well-known postsaccadic refractory period (Carpenter, 1988), we wondered if microsaccades might influence the speed or accuracy with which task-related saccadic responses were

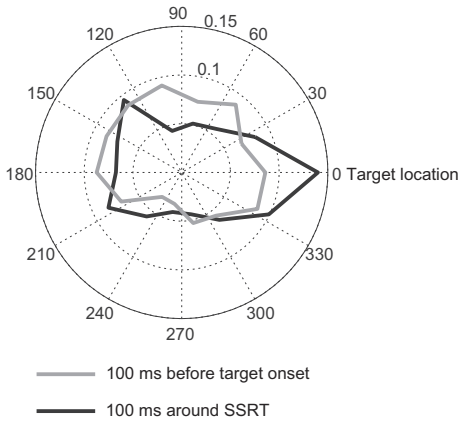

Fig. 8. Polar plots of microsaccade direction made during a 100 ms window preceding target onset (gray) and a 100 ms window centered on SSRT (black). Directions were reflected 180° on trials with leftward targets so that 0° always indicates target direction while up and down are preserved at 90° and 270° respectively.

executed or inhibited. We first investigated if the presence of microsaccades early in a trial influences the subsequent RT. To test this, we divided no stop trials into two groups, those in which microsaccades were and were not detected during the 500 ms preceding target onset. We found that median session RTs were 21 ms longer on average when microsaccades preceded target onset ($t_{(162)} = 11.82$, $p < 0.001$; Fig. 9A).

The stop-signal literature shows that responses with longer latencies are more likely to be inhibited when stop signals occur (Nelson et al., 2010), and a recent study of microsaccade inhibition suggests that consecutive saccade motor programs inhibit one another (Hafed & Ignashchenkova, 2013). Because we found that pre-target microsaccades lead to longer RTs and because microsaccades and later task-related saccades are produced by two motor programs that might inhibit one another, we predicted that the presence of microsaccades early in a trial will lead to more efficient saccade cancelation later in the same trial. To test this prediction, we first investigated whether SSRT is faster when microsaccades precede target presentation. SSRT did not differ across sessions based on the presence or absence of pre-target microsaccades ($t_{(162)} = 0.82$, $p = 0.41$; Fig. 9B). Thus, pre-target microsaccade production exhibits behaviorally dissociable effects on subsequent motor preparation and motor inhibition indexed by RT and SSRT respectively (Fig. 9C).

We also investigated this issue from the opposite direction by asking if the presence of a microsaccade early in a given trial is related to the later probability of successfully canceling normal saccades. Specifically, we tested if the probability of observing a microsaccade during the pre-target interval was increased on successfully canceled trials. Across sessions, microsaccades were present during the 500 ms pre-target interval on 16.8% of successfully canceled trials. Microsaccades were present on 16.2% of noncanceled trials during the same interval. These percentages did not differ significantly (Wilcoxon rank sum $W = 49{,}032$, $p = 0.36$). Thus, even though RTs were longer when they followed microsaccades, the presence of microsaccades was not directly related to the success with which saccades were canceled.

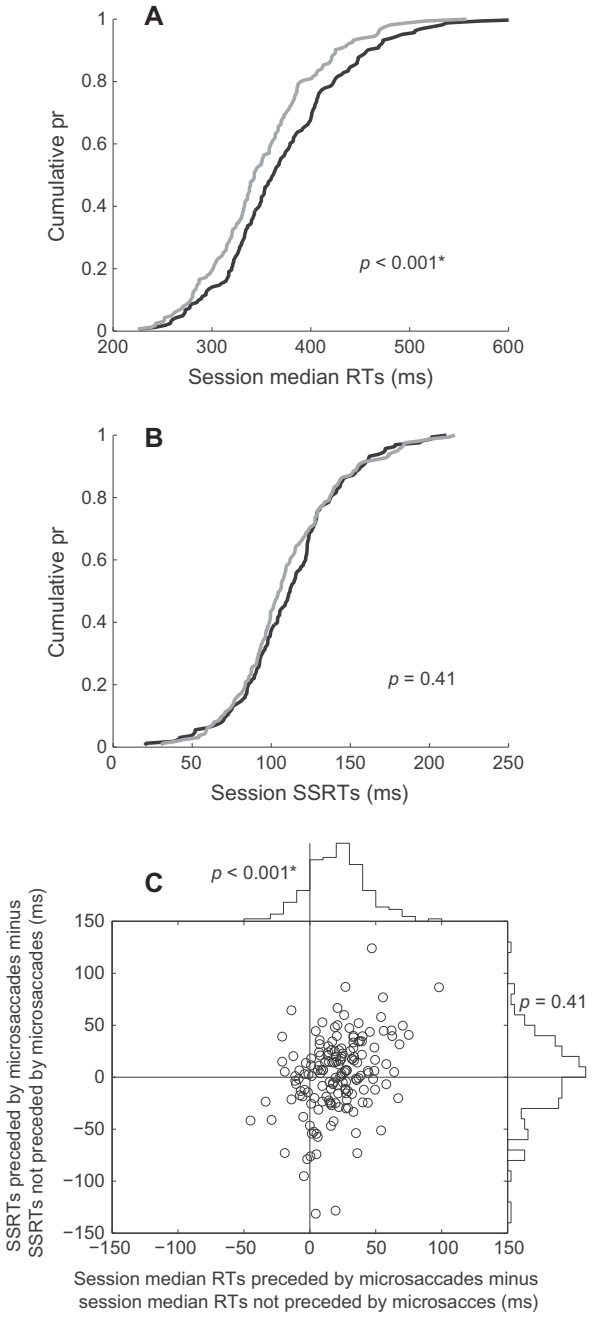

Fig. 9. RT and SSRT conditionalized on the presence of a microsaccade during the pre-target interval. (A) Cumulative probability distributions of median session RTs without microsaccades in the pre-target interval (gray) and with microsaccades in the pre-target interval (black). Median RTs were significantly longer across sessions when pre-target microsaccades were present. (B) Cumulative probability distributions of SSRTs calculated from each session without microsaccades in the pre-target interval (gray), and with microsaccades in the pre-target interval (black). This difference did not reach significance. (C) Summary plot of differences between median RTs of trials with and without microsaccades in pre-target interval (abscissa), and differences between SSRTs of trials with and without microsaccades in pre-target interval (ordinate).

4. Discussion

We evaluated predictions of two models of SC function by measuring the rate of microsaccades produced by monkeys as they voluntarily cancel eye movements in response to explicit stop signals. We observed fewer microsaccades (i.e. stable fixation) under conditions previously shown to have imbalanced activity across the saccade map in SC (Paré & Hanes, 2003; see also Hanes, Patterson, & Schall, 1998). This finding is consistent with our previous discovery of a small but reliable decrease of the extraocular electromyogram (EMG) before and during SSRT (Godlove et al., 2011). The few microsaccades that escaped inhibition tended to be directed toward the target location as expected based on this

imbalance. These findings are consistent with the fixation hypothesis but are inconsistent with the microsaccade hypothesis. Our results cannot determine whether population equilibrium in SC is sufficient to produce fixation, but they demonstrate clearly that such an equilibrium is not necessary for visual fixation. Therefore, another mechanism must be invoked to inhibit eye movements and maintain gaze while activity is not at equilibrium in SC.

We also observed longer task-related saccade RTs when microsaccades occurred during the pre-target interval. But the presence of microsaccades in the pre-target interval did not affect monkeys' ability to inhibit eye movements as measured by SSRT, and trials with successfully canceled saccades were no more likely to be preceded by microsaccades. This behavioral dissociation between RT and SSRT suggests that separate physiological mechanisms control saccade preparation and cancelation.

4.1. Microsaccade inhibition during saccade canceling

Anticipating microsaccade data collected during the stop-signal task, a recent study modeled microsaccade inhibition in terms of the saccade canceling framework (Hafed & Ignashchenkova, 2013). Microsaccade inhibition refers to the often-reported finding that an abrupt stimulus change leads to a transient decrease in microsaccades (Brien et al., 2009; Cui et al., 2009; Engbert & Kliegl, 2003; Hafed, Lovejoy, & Krauzlis, 2011; Laubrock, Engbert, & Kliegl, 2005; Valsecchi & Turatto, 2007; reviewed by Rolfs, Kliegl, & Engbert, 2008). Hafed and Ignashchenkova (2013) proposed that microsaccade inhibition occurs because all peripheral or central stimuli are treated as implicit stop signals by the oculomotor system. Stimuli that appear during the preparation of a saccade are thought to generate competing motor commands that cancel the ongoing plan. Overall, the pattern of microsaccades that we observed when monkeys explicitly and voluntarily canceled eye movements is very similar to that observed under the conditions that were hypothesized to result in microsaccade inhibition in the previous study lending credence to Hafed and Ignashchenkova's proposal. But the dissociable effects of microsaccades on response preparation and response inhibition do not support the conjecture that these motor programs compete against one another. In combination with other reports that have studied the same question (Bissett & Logan, 2013; Camalier et al., 2007; Ramakrishnan, Sureshbabu, & Murthy, 2012), we consider it unlikely that saccade cancelation in the stop-signal task results from a competition between ocular motor programs *per se* following the sudden onset of a stimulus.

In a related vein, one may hypothesize that microsaccade production interacts with saccade cancelation. The rationale for this conjecture may be understood by considering stop-signal experiments carried out in the skeletal motor system. Most stop-signal investigations involve responses like key presses or joystick deflections. These movements can be arrested in multiple ways ranging from preventing contraction of agonist muscles, contracting antagonist muscles, or co-contracting both. Contraction of antagonists, amounting to producing an antisaccade, does not normally occur in saccade countermanding in our experience. And co-contraction is not possible for eye movements (Hikosaka et al., 1978; Scudder, Kaneko, & Fuchs, 2002; Sparks, 2002). However, one way to prevent task-related saccades may be to produce more microsaccades. In fact, this could be viewed as the ocular motor equivalent of a co-contraction strategy. Our data do not, however, support this conjecture. Very few microsaccades were observed when subjects canceled normal saccades, and pre-target microsaccades were not associated with reduced SSRT or the probability of successfully canceling saccades during stop trials. Thus generating microsaccades and canceling normal saccades appear to be governed by independent and dissociable processes.

4.2. The case for gaze holding fixation neurons

If equilibrium across the SC map is not necessary for visual fixation, then what other sources of saccade inhibition are possible? Certainly, ominpause neurons (OPNs) in the nucleus raphe interpositus (nRIP) of the paramedian pontine reticular formation play a central role (Cullen & Van Horn, 2011; Hafed & Ignashchenkova, 2013). These neurons fire tonically during fixation and pause during eye movements (reviewed by Corneil & Munoz, 2014; Goldberg, Eggers, & Gouras, 1991; Krauzlis, 2008; Scudder, Kaneko, & Fuchs, 2002). Microstimulation of the nRIP prevents eye movements and can interrupt saccades in mid-flight. OPNs show a small transient increase in activity following visual stimulation (Dorris, Pare, & Munoz, 1997; Everling et al., 1998; Missal & Keller, 2002), so these neurons seem well positioned to play a role in microsaccade inhibition following sudden stimulus onset.

Cells that have historically been considered fixation neurons in FEF and rostral SC may issue the upstream commands that direct brainstem OPNs to inhibit eye movements. Fixation neurons demonstrate activity similar to that of brainstem OPNs (Gandhi & Keller, 1999; Paré & Guitton, 1994; but see Everling et al., 1998). As in the nRIP, microstimulation in rostral SC can interrupt saccades midflight (Munoz, Waitzman, & Wurtz, 1996; Munoz & Wurtz, 1993b; Paré & Guitton, 1994). The majority of projections from SC to nRIP arise from the rostral pole of SC, and these terminate in thick collateral axons suggestive of driving input, whereas projections to nRIP from more caudal regions terminate in thin branching axons (Büttner-Ennever et al., 1999; Huerta & Kaas, 1990; Stanton, Goldberg, & Bruce, 1988; Wang et al., 2013). Intracellular recordings confirm that rostral SC neurons form monosynaptic inputs on OPNs, contrasting with the disynaptic projections from caudal SC to OPNs through brainstem inhibitory burst neurons (Shinoda et al., 2011). Careful double-labeling and immunohistochemical experiments also show that some neurons in SC disynaptically inhibit OPNs through GABAergic projections originating in the central mesencephalic reticular formation (Wang et al., 2013). Thus, all of the elements of circuitry necessary for SC to exert direct control over both saccade execution and inhibition via the brainstem saccade generator have been confirmed.

Neurons that support visual fixation are a common motif repeated throughout the oculomotor system. Though monosynaptic connections from FEF to functionally defined OPNs have not yet been identified, fixation neurons in FEF and SC show similar physiological responses (Bizzi, 1968; Hanes, Patterson, & Schall, 1998; Izawa & Suzuki, 2014; Izawa, Suzuki, & Shinoda, 2009; Paré & Hanes, 2003). Both movement and fixation neurons in FEF and SC modulate firing rates on canceled trials in the stop-signal task with timing sufficient to play a direct role in initiating and canceling movements (Hanes, Patterson, & Schall, 1998; Paré & Hanes, 2003; Schall & Godlove, 2012a). Additionally, neurons in the substantia nigra pars reticulate have long been known to contribute to gaze holding through monosynaptic inhibitory projections to movement neurons in SC (reviewed by Hikosaka, Takikawa, & Kawagoe, 2000).

In sum, the bulk of the anatomical and physiological evidence of which we are aware supports the view that saccade cancelation is most likely instantiated by a direct gaze holding signal conveyed by a distributed network including contributions from fixation neurons in FEF and SC that project directly to the brainstem.

4.3. The case for microsaccade neurons

Other evidence challenges the historical view that individual neurons in the rostral SC enforce gaze holding *per se*. Although often overlooked, the original experiments that characterized some cells in the rostral SC as fixation neurons also showed that most of

the neurons interspersed throughout this area also contribute to saccade initiation (Munoz & Wurtz, 1993b). More recently, several studies have demonstrated that neurons in rostral SC extend the saccade polar coordinate map found in caudal SC by encoding the smallest detectable microsaccades, and that some neurons at the extreme rostral pole code for ipsilateral microsaccades. Thus, a complete and partially overlapping map of target position space is distributed between hemispheres (Hafed, Goffart, & Krauzlis, 2009; Hafed & Krauzlis, 2012). These findings have led to the proposal that gaze holding is achieved indirectly by an equilibrium of population activity balanced across both superior colliculi (Engbert, 2012; Goffart, Hafed, & Krauzlis, 2012; Hafed, Goffart, & Krauzlis, 2009). We have interpreted this view as predicting increased microsaccade rate on canceled trials during SSRT in the stop-signal task (Godlove, 2013; see also Rolfs, Kliegl, & Engbert, 2008). But recent work has sought to reconcile the microsaccade inhibition that occurs concomitant with imbalanced activity in rostral SC following stimulus onset by proposing a secondary saccade gating mechanism, possibly instantiated by brainstem OPNs (Hafed & Ignashchenkova, 2013). According to this view, SC activity must become imbalanced beyond a given threshold to produce a saccade, and this threshold may be set dynamically at the level of OPNs. Thus, it may seem that the distinction between fixation and movement neurons in SC is largely semantic; the activity of individual neurons can encode either fixation or movement depending on the population dynamics across the entire system.

4.4. Remaining questions

Based on the current findings and previous studies, we believe that it is premature to rule out the existence of neurons in rostral SC that enforce gaze holding directly and irrespective of the population activity within SC and the brainstem. In Munoz and Wurtz's (1993b) classic recordings in rostral SC, 35% of neurons failed to increase activity before eye movements in any direction suggesting that they were unrelated to movement initiation. In the subsequent experiments of Hafed, Goffart, and Krauzlis (2009), neurons were excluded from analysis if they failed to demonstrate build up activity in the interval before memory-guided saccades. This leaves open that possibility that fixation neurons may have been inadvertently excluded from analysis in the later report. The contrasting inactivation results from those studies also remain puzzling. In the former study (Munoz & Wurtz, 1993a) muscimol inactivation produced

> *"...difficulty maintaining visual fixation and suppressing unwanted saccades"*

while in the latter study (Hafed, Goffart, & Krauzlis, 2008) muscimol inactivation

> *"...reduces microsaccade rate without otherwise compromising fixation".*

4.5. Conclusions

Our results contribute to a better understanding of the neural mechanisms underlying saccade initiation and inhibition. They extend our finding that partial muscle contraction does not occur when saccades are successfully canceled (Godlove et al., 2011). Furthermore, they demonstrate that gaze holding does not require equilibrium activity across the SC map and that motor preparation and inhibition are dissociable processes. We conclude that saccade inhibition in a stop-signal task is accomplished by explicit motor inhibition enforcing gaze holding, and that this inhibition is likely carried out by a distributed network that includes brainstem OPNs and explicit fixation neurons in rostral SC and in FEF.

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