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RESEARCH ARTICLE | *Control of Movement*

Gaze direction as equilibrium: more evidence from spatial and temporal aspects of small-saccade triggering in the rhesus macaque monkey

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Hafed ZM, Goffart L. Gaze direction as equilibrium: more evidence from spatial and temporal aspects of small-saccade triggering in the rhesus macaque monkey. *J Neurophysiol* 123: 308–322, 2020. First published December 11, 2019; doi:10.1152/jn.00588.2019.— Rigorous behavioral studies made in human subjects have shown that small-eccentricity target displacements are associated with increased saccadic reaction times, but the reasons for this remain unclear. Before characterizing the neurophysiological foundations underlying this relationship between the spatial and temporal aspects of saccades, we tested the triggering of small saccades in the male rhesus macaque monkey. We also compared our results to those obtained in human subjects, both from the existing literature and through our own additional measurements. Using a variety of behavioral tasks exercising visual and nonvisual guidance of small saccades, we found that small saccades consistently require more time than larger saccades to be triggered in the nonhuman primate, even in the absence of any visual guidance and when valid advance information about the saccade landing position is available. We also found a strong asymmetry in the reaction times of small upper versus lower visual field visually guided saccades, a phenomenon that has not been described before for small saccades, even in humans. Following the suggestion that an eye movement is not initiated as long as the visuo-oculomotor system is within a state of balance, in which opposing commands counterbalance each other, we propose that the longer reaction times are a signature of enhanced times needed to create the symmetry-breaking condition that puts downstream premotor neurons into a push-pull regime necessary for rotating the eyeballs. Our results provide an important catalog of nonhuman primate oculomotor capabilities on the miniature scale, allowing concrete predictions on underlying neurophysiological mechanisms.

NEW & NOTEWORTHY Leveraging a multitude of neurophysiological investigations in the rhesus macaque monkey, we generated and tested hypotheses about small-saccade latencies in this animal model. We found that small saccades always take longer, on average, than larger saccades to trigger, regardless of visual and cognitive context. Moreover, small downward saccades have the longest latencies overall. Our results provide an important documentation of oculomotor capabilities of an indispensable animal model for neuroscientific research in vision, cognition, and action.

fastigial oculomotor region; fovea; microsaccades; saccadic latency; superior colliculus

INTRODUCTION

The sudden appearance of a visual target is often followed by a saccadic movement of the eyes. In nonpathological conditions, this movement brings the image of the target within the central visual field. During the subsequent fixation, small saccades can still be triggered, even though the target location in space has not changed. This suggests that gaze fixation is a highly active process requiring continuous regulation of the contraction of extraocular muscles and also constant coordination among them. This physiological fact can sometimes be overlooked, especially given that, in the majority of studies using monkeys as behavioral research subjects, so-called computer-controlled "fixation windows" are used to make sure that the animal effectively looks at the appropriate target, and not elsewhere, for a period of time. Although such windows can constrain the range of saccade sizes that the monkey is allowed to make during fixation, they do not completely eliminate them. Moreover, the generation of fixational saccades in the monkey is not a mere function of computer-controlled constraints on fixation accuracy. Their amplitude remains small even when large fixation windows are used (see, e.g., Guerrasio et al. 2010), and high-acuity visual tasks often require that small saccades are directed in highly precise manners. In addition, monkeys can make microsaccades that accurately and consistently orient a restricted zone of their retina toward the location of tiny visual spots (Tian et al. 2016, 2018). Another aspect that influences the generation of "fixational" saccades is the target size. Minuscule targets indeed elicit smaller saccades than larger targets (see Fig. 6 in Goffart et al. 2012).

Besides these spatial aspects, there are also temporal aspects, such as variabilities in the timing of saccade onset. From the excitation of ganglion cells in the retina to the recruitment of motor neurons and the contraction of extraocular muscles, action potentials are transmitted through several relays in the brain [thalamus, cerebral cortex, superior colliculus (SC), and reticular formation]. The latency of saccades reflects the time (duration) taken by the action potentials to recruit a sufficient number of neurons to ultimately contract the agonist muscles

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while relaxing the antagonist ones and rotate the eyeballs. Thus any lesion that compromises the visuomotor transmission leads to increasing the oculomotor reaction time. In humans, the visuomotor delay depends upon the eccentricity of the target in the visual field (Kalesnykas and Hallett 1994, 1996; Wyman and Steinman 1973) insofar as the latency of saccades toward foveal targets is much longer, on average, than other saccades. However, since these observations were made, it was not entirely clear whether the origin of these longer latencies was visual or motor. Later experiments testing saccades toward auditory targets (Zambarbieri et al. 1995) or gaze shifts that were rendered dysmetric by a cerebellar pharmacological perturbation (Goffart and Pélisson 1997) suggested that the dependence might be motor related: the smaller the saccade, the longer the time to initiate it. We hypothesize that this effect is related to a recent proposal that gaze direction is not a passive state but an active equilibrium and that an eye movement (saccadic or slow) is not initiated as long as the visuo-oculomotor system is within a mode where opposing commands (or movement tendencies) counterbalance each other (Goffart 2019; Goffart et al. 2018; Krauzlis et al. 2017).

Here we document the timing of saccade triggering in rhesus macaque monkeys in a variety of behavioral tasks. We particularly focus on very small saccades, as well as differences between saccade directions, in order to investigate hypotheses related to recent neurophysiological findings (Chen et al. 2019; Goffart et al. 2018; Guerrasio et al. 2010; Hafed and Chen 2016; Krauzlis et al. 2017) and also to motivate future ones. Our results are consistent with the model positing that saccade triggering, or lack thereof, depends on balance of different opposing oculomotor commands, with particular dependence on spatial visuomotor maps magnifying the representation of the central visual field.

METHODS

Ethics approvals. All monkey experiments were approved by ethics committees at the Regierungspräsidium Tübingen. The experiments were in line with European Union directives and the German laws governing animal research. Some monkey data were analyzed from Willeke et al. (2019) for the new purposes of this article. In these cases, the same committees had approved the experiments.

We also analyzed anew human data from the same study (Willeke et al. 2019) as well as collecting additional data from one author [Z. M. Hafed, *subject ZH*] and three naive subjects (2 men and 1 woman, aged 25–33 yr). These human experiments were approved by ethics committees at the Medical Faculty of Tübingen University, and the subjects provided written informed consent.

Laboratory setups. Monkey experiments were performed in the same laboratory environment as that described recently (Buonocore et al. 2019; Chen et al. 2018; Chen and Hafed 2018; Skinner et al. 2019; Willeke et al. 2019). Human experiments were done in the laboratory described in Grujic et al. (2018) and Hafed (2013).

Briefly, the monkeys viewed stimuli on a cathode-ray-tube (CRT) display running at 120 Hz refresh rate. The humans viewed stimuli on a CRT display running at 85 Hz refresh rate. In all cases, the display used was gamma-corrected (linearized), and the stimuli were grayscale. Background and stimulus luminance values are described below with the behavioral tasks. Stimulus control for both monkeys and humans was achieved with the Psychophysics Toolbox (Brainard 1997; Kleiner et al. 2007; Pelli 1997). In the monkey experiments, the toolbox acted as a slave device receiving display update commands from a master device and sending back confirmation of display updates. The master system consisted of a real-time computer from National Instruments controlling all aspects of data acquisition (including digitization of eye position signals) and reward of the animals (in addition to display control). The real-time computer communicated with the Psychophysics Toolbox with direct Ethernet connections and universal data packet (UDP) protocols (Chen and Hafed 2013). In the human experiments, the Psychophysics Toolbox was used as the primary controller, and it synchronized display updates with eye tracker data samples (Hafed 2013).

Monkey eye movements were recorded at 1 kHz with electromagnetic induction of electrical current in a scleral eye coil (Fuchs and Robinson 1966; Judge et al. 1980). As stated in Willeke et al. (2019), we used video-based eye tracking for the human subjects, again sampling at 1 kHz (EyeLink 1000; desktop mount). For best eye tracking performance, we fixed the heads of the monkeys and the humans during the sessions. For the former, this was achieved with surgically implanted head holders (Chen and Hafed 2013). For the latter, we used a custom-built chin and forehead rest with additional head position guides on the temples and behind the head (Hafed 2013).

Animal preparation. We collected behavioral data from two adult male rhesus macaques (*Macaca mulatta*). *Monkeys M* and *N* (aged 7 and 10 yr and weighing 8 and 11.5 kg, respectively) were implanted with a scleral coil in one eye to allow measurement of eye movements with the electromagnetic induction technique (Fuchs and Robinson 1966; Judge et al. 1980). The monkeys were also implanted with a head holder to stabilize their head during the experiments; details on all implant surgeries were provided previously (Chen and Hafed 2013; Skinner et al. 2019). They were part of a larger neurophysiology project beyond the scope of the present report.

Monkey behavioral tasks. The monkeys were trained to perform a visually guided saccade task. Each trial started with the presentation of a central white fixation spot (86 cd/m^2) over a uniform gray background (29.7 cd/m^2). The fixation spot was a square of 5.3 × 5.3-min arc dimensions. After 300–900 ms of fixation (i.e., maintaining eye position within a prescribed distance from the spot; see below), the fixation spot was jumped to a new location, instructing the monkeys to generate a visually guided saccade to follow the spot. The size of the jump was varied randomly across trials. Target locations were chosen from among 96 predefined possibilities as follows: the target could jump by a distance of 0.06°, 0.1°, 0.2°, 0.3°, 0.5°, 0.7°, 1°, 1.5°, 2°, 3°, 5°, or 10° in either the horizontal or vertical dimension, or it could jump obliquely along a diagonal (in which case we used the same sampling resolution of each of the horizontal and vertical dimensions of any given jump: 0.06°, 0.1°, 0.2°, 0.3°, 0.5°, 0.7°, 1°, 1.5°, 2°, 3°, 5°, or 10° of each of the horizontal and vertical components). Moreover, the jump could be to either side of display center (rightward or leftward in the horizontal dimension; upward or downward in the vertical dimension). Therefore, we sampled horizontal, vertical, and diagonal target locations of different eccentricities, with denser sampling of foveal and perifoveal locations. In all data analyses and graphs, we used the convention of positive target locations being to the right of or above display center (for either horizontal or vertical dimension, respectively) and negative target locations being to the left of or below display center. If the monkeys fixated the new spot location within 500 ms after it had jumped, and held their eye position there for another ~300 ms, they were rewarded with a liquid reward.

We controlled the monkeys' fluid reward system in real time by employing a virtual computer-controlled window around target location. If eye position entered the virtual window within the prescribed "grace" period, a reward was triggered. Otherwise, the trial was aborted, and a new trial was initiated. Our virtual "target windows" across trials had radii of 2–2.5°. Note that a radius of 2–2.5° was still employed even for foveal target locations of smaller eccentricities. This means that for such small target eccentricities we exploited the natural tendency of the monkeys to perform the task without any computer monitoring to ensure that they generated the required

saccades. This was not a problem at all, because after the monkeys were trained on the task with eccentricities of 5° and higher, they very naturally generalized their trained rule when tested on smaller target eccentricities. This was also the case in more complicated variants of the task (Willeke et al. 2019), and it was also consistent with human results (e.g., see Fig. 10). We felt that this approach of large virtual target windows was better than the alternative of enforcing tiny target windows, because, in the latter case, any potential increases in reaction times of saccades could have been interpreted as being the consequence of increased task difficulty or a potential speed-accuracy trade-off.

We analyzed a total of 928 trials from *monkey M* in this task and 1,246 trials from *monkey N*.

We also analyzed visually guided delayed saccades and memory-guided delayed saccades made by the same two monkeys. These data were collected during an earlier experiment, with detailed methods described elsewhere (Willeke et al. 2019). The purpose of the present reanalysis was to explore saccade latency as a function of target eccentricity and to examine how this relationship might be affected by task instruction. We also wanted to directly compare results from the same animals used in the (immediate) visually guided saccade experiments described above. Briefly, the delayed saccade task was similar to the (immediate) visually guided saccade task described above, except that there was a delay period of 500–1,000 ms during which the fixation spot remained visible when the saccade target was visible. The presence of the central spot instructed the monkeys to maintain fixation despite the presence of the peripheral target. When the fixation spot disappeared, the monkeys could make the saccade to the peripheral target. This task allowed us to investigate whether increased saccadic latencies for small target eccentricities (see RESULTS) were necessarily linked to sudden visual onsets in the (immediate) visually guided saccade task.

The memory-guided saccade task was similar to the delayed visually guided saccade task, except that the target duration was brief (duration: 58 ms). When the fixation spot disappeared, the monkeys generated an eye movement to the remembered location of the earlier target flash. This task was useful to dissociate increased reaction times for small target eccentricities from the presence of a visual target.

In all tasks, we started out with the monkeys already being experts in oculomotor tasks requiring fixation of a small target (similar to *subject ZH* in Fig. 10). The monkeys were used in earlier studies demonstrating their level of precision in eye movement control (e.g., Tian et al. 2016, 2018 for *monkey N* and Buonocore et al. 2019; Skinner et al. 2019 for *monkey M*). Therefore, even though we analyzed thousands of trials in the present study, we did not characterize learning processes. From personal observation, the naive monkeys naturally fixated similarly sized fixation spots to a precision significantly higher than that required by computer-controlled virtual windows. The quality of their fixation therefore started out being good and improved fairly quickly within a matter of a few trials within a single session.

Human behavioral tasks. For supporting comparisons of the results from our monkeys in the (immediate) visually guided saccade task to those reported in the literature on human subjects (e.g., Kalesnykas and Hallett 1994, 1996; Wyman and Steinman 1973), we ran one human expert (*subject ZH*) and three naive subjects on the same task as that performed by our two expert monkeys (see Figs. 10 and 11). We analyzed 1,966 trials from *subject ZH* and 783–974 trials from each of the naive subjects. In separate sessions, we also ran a variant of the same task, but the fixation spot now remained visible after target jump. The subjects' task was to maintain fixation and press a button (with the right thumb) as quickly as possible after target onset. The goal was to measure manual reaction times for perceptual detections not requiring an eye movement. This allowed us to compare and contrast manual reaction times to saccadic reaction times from the original variant of the task. We analyzed 1,924 from *subject ZH* in this task variant and 799–945 trials from each of the three naive subjects. In all experiments, the fixation spot and target were a small square of 4.4×4.4 min arc. Their luminance was 97.3 cd/m^2, and the background luminance was 20.5 cd/m^2. In addition, two of the subjects (*ZH* and *MB*) were instructed to perform the manual task first before the saccade task, and two other subjects (*FK* and *HB*) performed the saccade task first before the manual task. The results (see Figs. 10 and 11) did not depend on the order in which the two tasks were performed and therefore cannot be explained by learning or practice effects in one or the other task.

Because we were particularly interested in the monkey memory-guided saccade reaction time results as a function of target eccentricity (see RESULTS), we also decided to explore their generalizability to human memory-guided saccades, an aspect that was not well explored in the existing human saccade literature so far. Therefore, we reanalyzed human data that we had collected earlier (Willeke et al. 2019) with the same task. Briefly, the human subjects made the same memory-guided saccade task with target locations being chosen randomly across trials from among 480 possibilities, with heavy sampling of small eccentricities. Specifically, target eccentricities in this experiment ranged from 6 min arc to 12°, with 288 of the 480 target locations lying within the square of eccentricities within ±0.8 (horizontally) by ±0.8° (vertically).

Behavioral analyses. We detected saccades and microsaccades using established methods reported elsewhere (Bellet et al. 2019; Chen and Hafed 2013). Both methods rely on a mathematical differential (i.e., speed) or more (i.e., acceleration) of the digitized eye position signals acquired by our systems, with specific parameters for the classification of saccadic events depending on the specific signal noise levels in the digitized signals. We manually inspected each trial to correct for false alarms or misses by the automatic algorithms, which were rare. We also marked blinks or noise artifacts for later removal. In scleral eye coil data, blinks are easily discernible because of well-known blink-associated changes in eye position. In video-based eye tracking, blinks are equally easy to detect because they are associated with an absence of eye position data due to the closed eyelids.

In the (immediate) visually guided saccade task, we analyzed the first saccade that was triggered after the target jump. We excluded all trials in which there was a blink within ±100 ms from target jump, since this could impair visual detection of the jump. We also excluded all trials in which a microsaccade occurred within the period from −100 ms to 60 ms relative to target jump occurrence. Our reason was that microsaccades around stimulus onset reduce target visibility and increase reaction time (Beeler 1967; Bellet et al. 2017; Chen et al. 2015; Chen and Hafed 2017; Hafed and Krauzlis 2010; Tian et al. 2016; Zuber and Stark 1966). Similar exclusion criteria were also used in human analyses (e.g., Figs. 10 and 11). We defined as a successful reaction any eye movement made within 70–500 ms after target jump (throughout this article, we interchangeably refer to the time interval between target jump and saccade onset as the "saccadic latency" or "saccadic reaction time"). When plotting reaction time as a function of target eccentricity or direction or both, we binned nearby eccentricities, and we only showed summary measurements (e.g., mean and SE) if each bin contained at least five measurements. We also only included saccades if the measurements had movements with direction error relative to the target (defined as the difference in the angular direction of a saccade relative to the angular direction of the target displacement vector) of <45° (this was the great majority of data, e.g., Fig. 9).

For the reanalysis of the delayed visually guided and memory-guided saccade data of Willeke et al. (2019), we used procedures similar to those described above. Since the sampling of target locations in these tasks was slightly different from that performed in the present experiments (i.e., for the visually guided saccade task), we adjusted the binning windows accordingly, and we only included any measurement bins in which there were at least 7 saccades per bin. We also accepted as a minimum reaction time 100 ms instead of 70 ms,

since we observed that reaction times in these "delayed" types of saccade tasks were generally longer than in the immediate visually guided saccade task.

For the reanalysis of the human memory-guided saccade data of Willeke et al. (2019), we again used similar procedures. As in the monkey memory-guided saccade task, we considered a minimum reaction time of 100 ms. In reality, this was conservative, since the human reaction times were significantly longer, in general, than those of the monkeys in the same task (as described in RESULTS and also in Willeke et al. 2019).

We additionally binned trials in the delayed visually guided saccade task according to the length of the delay period used in the task. For analyzing trends of reaction time as a function of delay period duration, we used a running average spanning the total range of delay periods (500–1,000 ms). The running average started at a delay period of 600 ms, with time bin steps of 50 ms until 900 ms. At each of these time bin steps, we averaged trials with ±100-ms delay period duration from the current bin step. For example, the average in the first bin step of 600 ms had all trials with delay period durations of 500–700 ms, and the average of the next bin step had all trials with delay period durations of 550–750 ms, and so on.

Finally, for the visually guided saccade task, we plotted saccade amplitude and direction error as a function of target eccentricity, using binning procedures similar to those described above for reaction times.

In all analyses, we were interested in comparing saccades to upper and lower visual field target locations, since eye movement-related structures like the superior colliculus (SC) represent them differently (Hafed and Chen 2016). Specifically, SC visual responses to stimulus onsets (as well as neuronal contrast sensitivity) are both significantly stronger and earlier in SC neurons representing the upper visual field than in neurons representing the lower visual field (Hafed and Chen 2016), and there is a concomitant reflection of this difference in saccade reaction times; this corroborates a very strong correlation between SC visual response strength/latency and saccadic reaction times in general and under a variety of conditions (Chen et al. 2018; Chen and Hafed 2017). We therefore divided trials according to whether the target location was in the lower visual field (one group) or otherwise (that is, purely horizontal or in the upper visual field; the second group).

Statistical analyses. Our purpose was to document patterns of rhesus macaque reaction time values as a function of visual field location across a variety of well-established oculomotor tasks. We therefore largely present descriptive statistics in all figures, showing mean and SE measurements as well as numbers of observations. All trends that we focus on are immediately visible in the mean and SE plots that we present.

Data availability All data presented in this report are stored in institute computers and are available upon reasonable request.

RESULTS

Monkeys exhibit increased saccadic reaction times for foveal target eccentricities. Our goal was to document the saccadic reaction times of rhesus macaque monkeys when target displacements are small. We were motivated by the fact that in humans it is known that small-eccentricity target displacements are associated with increased saccadic reaction times (De Vries et al. 2016; Kalesnykas and Hallett 1994, 1996; Wyman and Steinman 1973). Figure 1 shows example eye position and velocity traces from one monkey (*monkey M*) when the target displacement was small (Fig. 1*A*) and when it was much larger (Fig. 1*B*). In both cases, the target displacement was to the right of central fixation, and we plotted horizontal eye position as well as radial eye velocity in the

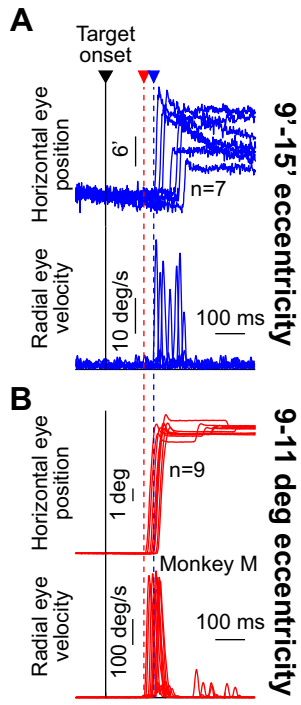

Fig. 1. Example horizontal visually guided saccades of different amplitudes in a rhesus macaque monkey. *A*: eye position (*top*) and velocity (*bottom*) measurements from 7 example trials in monkey *M* for rightward target onsets at eccentricities between 9 and 15 min arc. Upward deflections in each eye position trace (*top*) mean rightward eye position displacements, and the position scale bar denotes 6 min arc. The vertical dashed blue line indicates the reaction time of the fastest saccade to occur in the set shown, to facilitate comparison to the data in *B*. *B*: similar analyses for 9 example movements from the same monkey, but now for target eccentricities between 9° and 11°. The position scale bar (*top*) now indicates 1°. The vertical dashed red line indicates the reaction time of the fastest movement to occur in the set shown. Comparison of the blue and red traces reveals a clear increase in reaction times for the small saccades. Subsequent figures further characterize such an increase.

interval around target jump ("target onset" in Fig. 1). In both cases, a saccade was made to the target, which scaled appropriately in size with target eccentricity (also see Fig. 9). However, when the target eccentricity was small (Fig. 1*A*), the small saccades had significantly longer reaction times than the big saccades generated when the target eccentricity was large (Fig. 1*B*). This is illustrated in Fig. 1 with dashed vertical lines delineating the reaction times of the fastest small (Fig. 1*A*) and large (Fig. 1*B*) saccades in the two data sets shown. As can be seen, there was a clear difference between fastest reaction times as a function of target eccentricity. Moreover, the overall distribution for the small saccades was shifted toward longer and more variable reaction times compared with the bigger saccades. These examples demonstrate that rhesus macaque monkeys exhibit the same latency increase for small visually guided saccades as human subjects (De Vries et al. 2016; Kalesnykas and Hallett 1994, 1996; Wyman and Steinman 1973).

We summarized the above results across the entire set of measurements. In Fig. 2*A*, *left*, we plotted the mean (surrounded by SE boundaries) saccadic reaction time of *monkey M* as a function of target eccentricity. The smallest target eccentricities (<1°) were associated with long reaction times, reaching a mean of ~240 ms. Reaction time then dropped down to ~150 ms for eccentricities >1°. Larger eccentricities (ap-

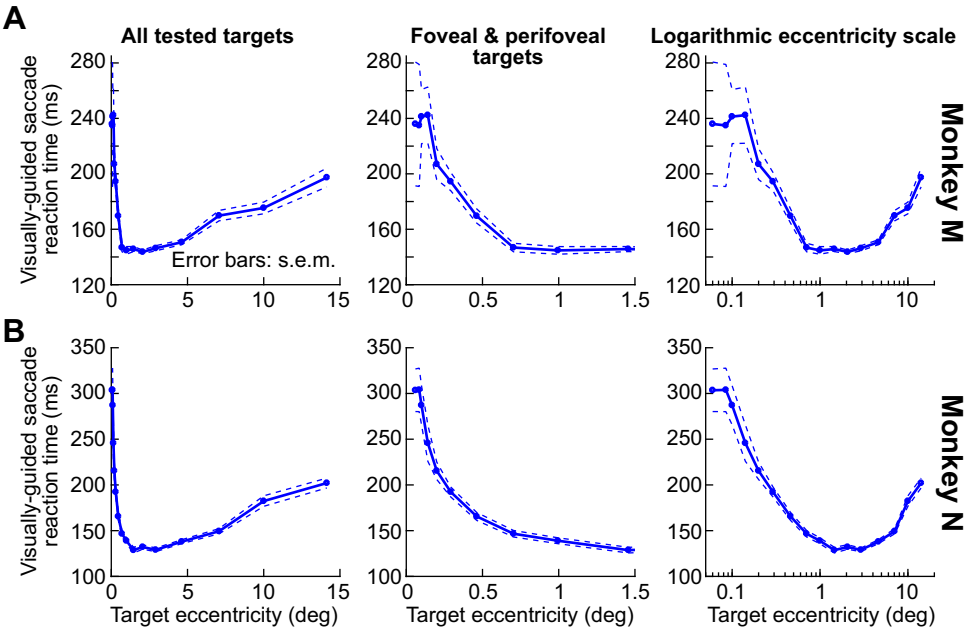

Fig. 2. Longer visually guided saccade reaction times for small target eccentricities in rhesus macaque monkeys. *A*: in *monkey M*, we plotted visually guided saccade reaction times as a function of target eccentricity (*left*). Reaction times for small-amplitude saccades were the longest. Zooming in to the central 1.5° (*center*) revealed a monotonic decrease in reaction time with increasing amplitude within foveal target eccentricities. The plot on *right* shows the same data as at *left* and *center* but using a logarithmic *x*-axis scale to clarify the strong increase in reaction time when small-amplitude saccades are triggered. Note that the reaction times also increased again for larger target eccentricities (e.g., > 5°). $n = 928$ trials; error bars in each panel denote SE. *B*: similar results from *monkey N*. There was an even stronger increase in reaction times for foveal target eccentricities. $n = 1{,}246$ trials.

proximately >5°) were associated with another increase in saccadic reaction times, albeit not as large as that for the foveal target eccentricities. This strong increase for the foveal targets is more vivid in Fig. 2*A*, *center*, zooming in on only the central 1.5° of target eccentricities. Similarly, Fig. 2*A*, *right* plots the same data as in Fig. 2*A*, *left*, but now on a logarithmic eccentricity scale, again demonstrating the longer saccadic reaction times associated with small target eccentricities. Similar results were obtained in *monkey N* (Fig. 2*B*), except that this monkey showed an even more dramatic increase in reaction times for foveal target eccentricities (from a minimum mean reaction time of <150 ms to a peak of ~300 ms). Therefore, across all target locations and eccentricities that we measured, there was a clear and consistent increase in saccadic reaction times of the two monkeys for foveal targets. There was another increase in reaction times, albeit weaker, for large target eccentricities, as also observed in human subjects (Kalesnykas and Hallett 1994, 1996).

To statistically confirm the above interpretations (Fig. 2), we binned target eccentricities into three groups: <1°, 2–5°, and >7°. Reaction times were significantly faster for the <1° group than for the 2–5° group (*monkey M*: $P = 1.6 \times 10^{-17}$, *monkey N*: $P = 1.6 \times 10^{-41}$; *t* test). Moreover, reaction times were significantly faster for the 2–5° group than for the >7° group (*monkey M*: $P = 1.3 \times 10^{-32}$, *monkey N*: $P = 6.2 \times 10^{-43}$; *t* test).

We also inspected overall reaction time distributions to confirm that our method for accepting successful trials during the experiments did not artificially penalize specific ranges of reaction times. Specifically, our monkeys were rewarded based on the use of virtual computer-controlled windows surrounding target location. If the eye position was not inside the virtual target window within 500 ms from target onset on a given trial (METHODS), then the trial was aborted and the monkey was not rewarded. It is therefore conceivable (although unlikely; METHODS) that we artificially truncated reaction time distributions at 500 ms, especially for target eccentricities showing increased reaction times (Fig. 2). However, this was not the case. For example, Fig. 3, *A* and *B*, *top*, show the reaction time distributions when foveal target eccentricities of 12–36 min arc were tested. The distributions were not truncated at 500 ms, suggesting that the monkeys were still able to generate visually guided saccades to these foveal targets within the prescribed grace period of 500 ms. Similarly, Fig. 3, *A* and *B*, *bottom*, demonstrate that for another range of target eccentricities in which reaction times increased (Fig. 2), the increase was again not affected by the truncation at 500 ms forced by our grace period.

Targets in the lower visual field are associated with increased reaction times also for foveal eccentricities. Because the SC exhibits a strong asymmetry between the representation of the upper and lower visual fields (Hafed and Chen 2016), with direct consequences for saccadic reaction times for large saccades, we next analyzed the reaction times of small visually guided saccades to foveal targets in the upper and lower visual fields. Specifically, it was not known so far whether differences in saccadic reaction times between upper and lower visual field target locations also occur for very small eye movements. For the same data as in Fig. 2, we divided trials according to whether the target was in the lower visual field or whether it was along the horizontal meridian or in the upper visual field (Fig. 4, *A* and *C*). Using the same formatting conventions as in Fig. 2, we found that there was, essentially, a global upward shift in the relationship between saccadic reaction time and target eccentricity for targets in the lower visual field. That is, the reaction time increase associated with lower visual field target locations also happened for tiny foveal eccentricities (Fig. 4, *A* and *C*, *center*). This was confirmed statistically when we tested reaction times across the two groupings of target locations in Fig. 4, *A* and *C* (*monkey M*: $P = 2 \times 10^{-8}$, *t* test comparing the 2 groups of data in Fig. 4*A*; *monkey N*: $P = 1.6 \times 10^{-28}$, *t* test comparing the 2 groups of data in Fig. 4*C*). Moreover, this effect was not restricted to cardinal target/saccade directions. For example, in Fig. 4, *B* and *D*, we plotted, for each monkey, the saccadic reaction time as a function of oblique target location. We plotted target location bins on

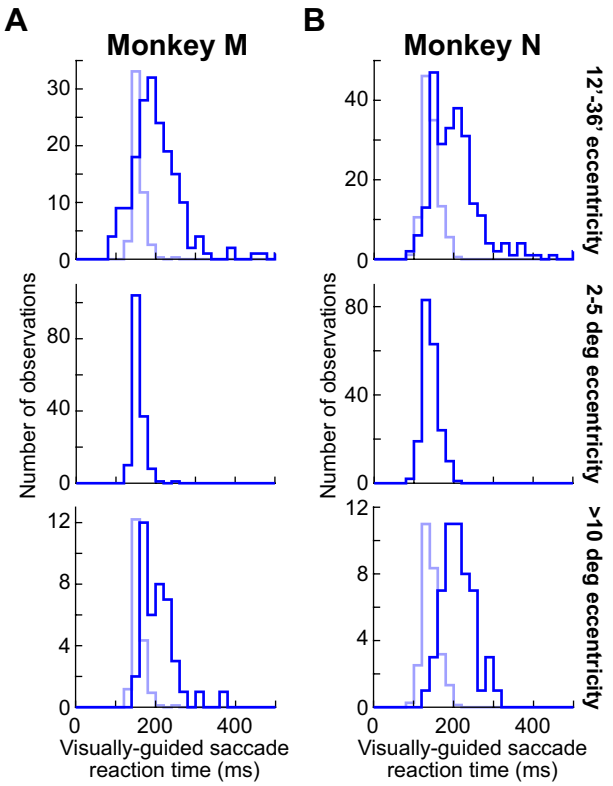

Fig. 3. Distributions of visually guided saccade reaction times for different representative target eccentricities. *A*: in *monkey M*, we plotted the distributions of saccade reaction times for 3 ranges of eccentricities chosen based on the results of Fig. 2. The faint-colored curves at *top* and *bottom* are copies (with arbitrary *y*-axes) of the curve at *middle*, to facilitate comparison of the distributions. Note how the distributions at *top* and *bottom* demonstrate that the increased reaction times observed in Fig. 2 at these eccentricities were not due to a potential artifact caused by a cut-off grace period of 500 ms for responding with an eye movement (METHODS). *B*: similar results from *monkey N*. In all panels, target directions (e.g., lower vs. upper visual field target locations) were equally distributed across all trials. Also note that numbers of observations are directly inferable from the histogram counts in each panel.

log-polar coordinates (Hafed and Krauzlis 2012) in order to cover the large span of eccentricities tested, and we color-coded each binned target location (*z*-axis) with the mean saccadic reaction time for that location. In both monkeys, the same general dependence of saccadic reaction time on target eccentricity (Fig. 2, Fig. 3, and Fig. 4, *A* and *C*) occurred for all target directions. That is, foveal locations had the longest reaction times; there was a minimum of reaction times at intermediate eccentricities; and there was then a more modest increase in reaction times once again for larger eccentricities. Moreover, lower visual field locations (including foveal ones) were associated with the longest reaction times (also see Figs. 10 and 11 for a human replication of all of these observations).

Delayed visually guided saccades show reaction time patterns largely similar to immediate visually guided saccades. To demonstrate that increased reaction times for small saccades are indeed related to motor programming (our equilibrium hypothesis) rather than only due to visual processing of foveal targets, we also ran our monkeys on a delayed saccade task. In this task, the target remained persistent for a certain delay period while the fixation spot was visible. Only when the fixation spot was removed were the monkeys allowed to make the saccade (METHODS).

We found an increase in reaction time in the delayed condition similar to that in the immediate visually guided saccade task for small target eccentricities. This happened even though the target was persistent and the instruction to trigger the saccade was the offset of a fixation spot instead of the onset of the target. The task also had temporal expectation inherently built into it (discussed further below), since the longer the delay period was, the more likely it was that the "go" signal for the saccade was to come; there was also sufficient time with short delay periods to plan a saccade. Figure 5 plots reaction time data from this task in a format identical to that in Fig. 4 for both monkeys. The same general pattern of results was observed. Namely, small, foveal target eccentricities were associated with the longest reaction times, and lower visual field locations were also associated with long reaction times compared with horizontal and upper visual field locations.

An interesting difference that emerged in this condition relative to the (immediate) visually guided saccade condition was the behavior of saccadic reaction times for large eccentricities (e.g., >10°). In this variant of the task, the increase in saccadic reaction times with increasing target eccentricities was less consistent than with the (immediate) visually guided saccade task (Figs. 2–4). Instead, lower visual field targets of intermediate eccentricities (e.g., between ~4° and 10°) exhibited a small increase in reaction time relative to larger target eccentricities (and upper visual field target locations). Thus, in the same two animals, changing the task seemingly modified the pattern of results for large eccentricities.

We also explicitly investigated the potential role of temporal expectations in this task. We divided our trials based on the length of the delay period. That is, we asked whether saccadic reaction times decreased when the delay period was long, since longer delay periods necessarily increase the likelihood of the instruction to generate the required saccade. For each monkey, we plotted in Fig. 6, *A* and *C*, reaction time as a function of target eccentricity (pooling upper and lower visual field locations together) after dividing the trials into different bins based on the duration of the delay period. There was indeed an effect of temporal expectations (faster reaction times for longer delay period durations), but this effect was absent for the most foveal target eccentricities. We confirmed this in Fig. 6, *B* and *D*, by plotting reaction time as a function of delay period duration for different target eccentricity bins. In both monkeys, targets within <1° of eccentricity did not show a dependence of reaction time on delay period duration. In *monkey N*, such a dependence emerged for more eccentric targets as close as 2°; in *monkey M*, this dependence emerged for more eccentric targets approximately >7° in eccentricity. These effects were the same whether targets were in the upper or lower visual fields (except for the globally elevated reaction times of lower visual field targets shown in Fig. 5).

Thus, even though knowledge of target location and expectation to generate a saccade altered the detailed patterns of saccadic reaction times for extrafoveal target locations (Figs. 5 and 6), the same increases in reaction times for foveal targets were evident in this task just as in the (immediate) visually guided saccade task.

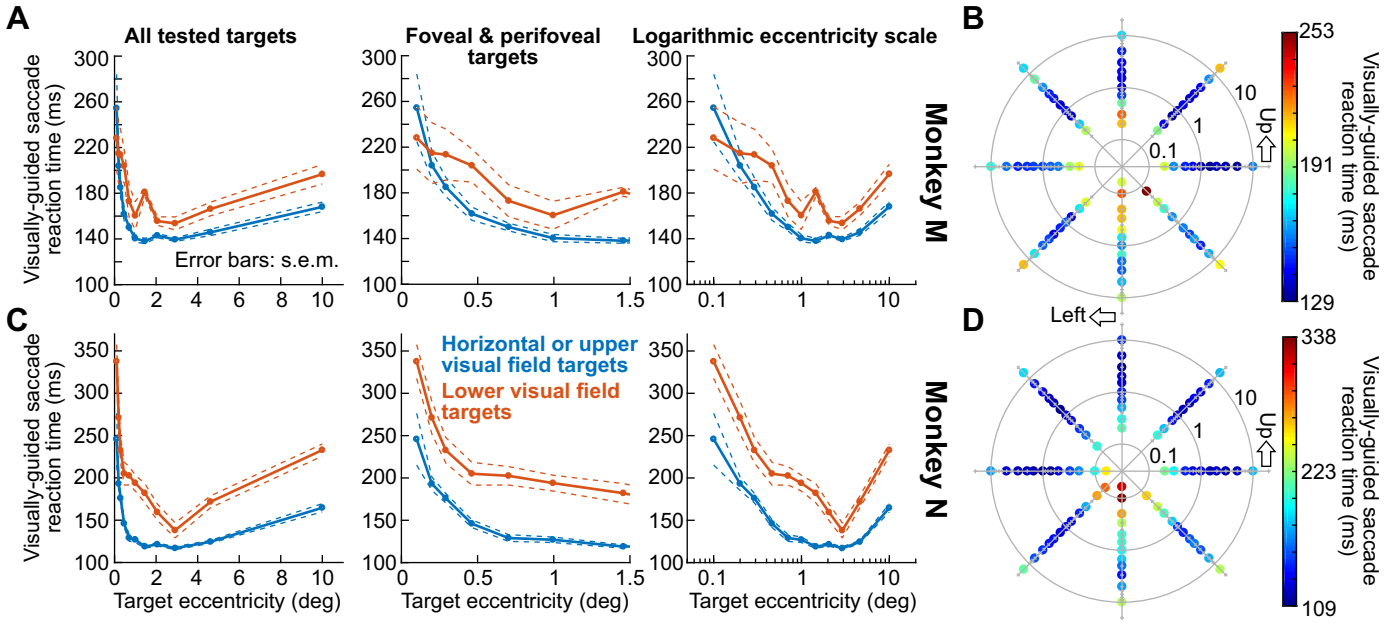

Fig. 4. Dependence of monkey visually guided saccade reaction times on upper vs. lower visual field target location. *A*: similar analyses as in Fig. 2*A* for *monkey M*. However, here, we separated targets as being located in the lower visual field relative to the line of sight (red) or otherwise (that is, located horizontally or in the upper visual field; blue). Reaction times were longer for lower visual field targets, consistent with Hafed and Chen (2016). This also happened for small target eccentricities (*center*). *B*: log-polar plot of the same data as in *A* demonstrating how intermediate eccentricities had the lowest reaction times in all directions and how lower visual field target locations were associated with longer reaction times than upper visual field target locations at all eccentricities tested. *C* and *D*: same as *A* and *B* but for *monkey N*. Error bars denote SE.

Small memory-guided saccades are also associated with increased reaction times, despite the absence of a visual target. To further demonstrate the independence of small saccade reaction times from foveal visual responses (whether in SC or elsewhere), we also trained our monkeys to generate small memory-guided saccades (Willeke et al. 2019). In this case, the instruction to generate a saccade was the offset of a fixation spot displayed on an otherwise blank screen. The saccade itself was not directed to a visual stimulus but instead to a remembered location (Willeke et al. 2019). We found similar in-

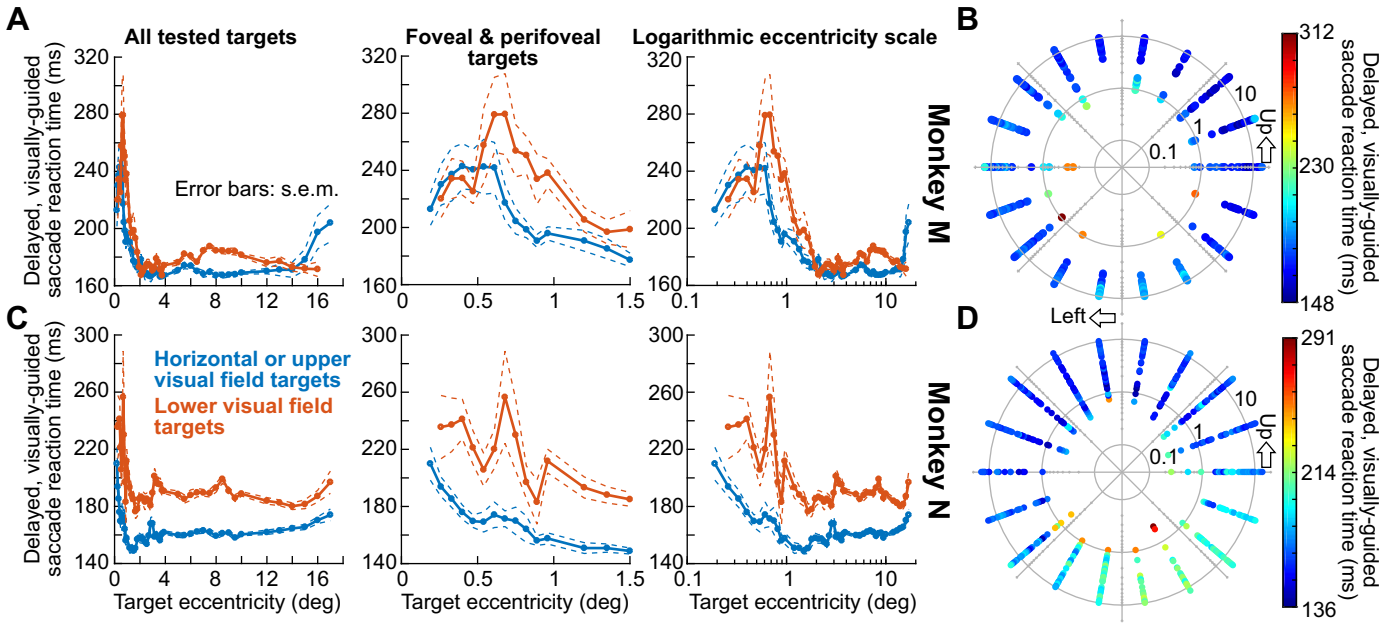

Fig. 5. Increased reaction times for small delayed visually guided saccades in the rhesus macaque monkey. *A*: analyses similar to those in Fig. 4*A* for *monkey M*, but now during the delayed visually guided saccade task. As in the (immediate) visually guided saccade task, small saccades had increased reaction times compared with larger saccades. Also as in the visually guided saccade task, upper visual field target locations were associated with faster reaction times than lower visual field target locations. However, an increase in reaction times for large target eccentricities was less clear here than in the (immediate) visually guided saccade task. Instead, lower visual field targets of intermediate eccentricities (e.g., 5–12°; red reaction time curves) were associated with increased reaction times relative to eccentricity-matched upper visual field targets. $n = 3{,}265$ trials; error bars denote SE. *B*: log-polar plot showing the underlying data of *A* across space. *C* and *D*: similar results were obtained with *monkey N*. $n = 4{,}277$ trials.

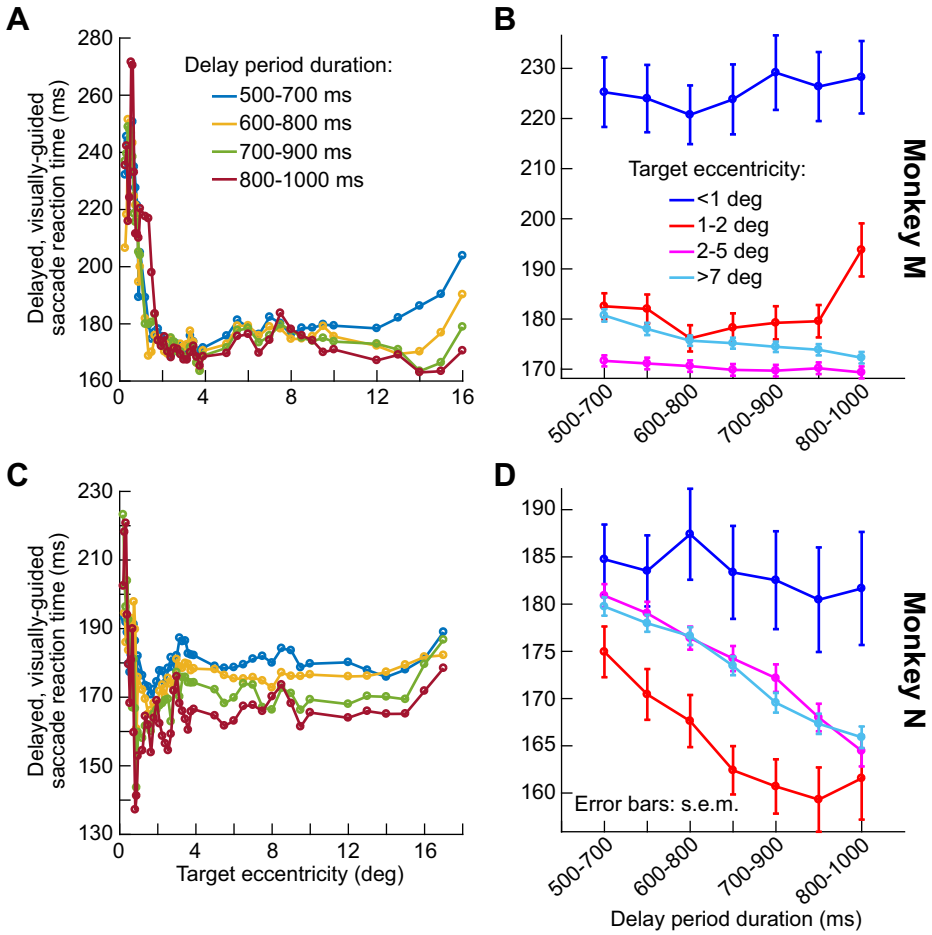

Fig. 6. Impacts of temporal expectations on small and large delayed visually guided saccades. *A*: for *monkey M*, we plotted the same data as Fig. 5*A* but after dividing trials based on delay period duration. For the smallest target eccentricities, the same reaction time increases seen in Fig. 5*A* were present, regardless of delay period duration. For large eccentricities, longer delay periods were clearly associated with shorter reaction times. *B*: we plotted the same data as a function of delay period duration. Each curve shows targets of a given eccentricity bin. Foveal targets (eccentricities <1°) did not show dependence of reaction time on delay period duration. More eccentric targets did (most prominently for targets >7°). *C* and *D*: same as *A* and *B* but for *monkey N*. In this monkey, the dependence of reaction time on delay period duration emerged for targets as close as 2° in eccentricity (*D*). As in *monkey M*, more foveal targets (<1°) still showed reaction times that were largely independent of delay period duration. Error bars denote SE.

creases in saccadic reaction times for foveal target eccentricities (Fig. 7; formatted identically to Figs. 4 and 5). Interestingly, for foveal target eccentricities (Fig. 7, *A* and *C*, *center*), there was no clear difference in reaction times between locations in the upper and lower visual fields, unlike when there was a visual stimulus as the target for the saccade (Figs. 4 and 5). Thus, even with memory-guided "microsaccades" (Willeke et al. 2019), there was an increase in saccadic reaction times, although the presence or absence of a visual target could alter the detailed properties of such an increase. It is also worth noting that the reaction time in this condition did not increase for larger eccentricities as in the (immediate) visually guided saccade task. Instead, and as in the delayed visually guided saccade task, it was specifically the lower visual field saccades for intermediate eccentricities that seemed to increase.

Small memory-guided saccades in humans show patterns similar to small memory-guided saccades in monkeys. Intrigued by the results in Fig. 7, we sought to test whether similar observations could also be made in human subjects. We had human subjects perform the same task as the monkeys (Willeke et al. 2019) and found very similar results (Fig. 8). Small memory-guided microsaccades (Willeke et al. 2019) were associated with the longest reaction times relative to all other eccentricities, just like in the monkeys. Therefore, in all tasks, small saccades were always associated with the longest average latencies, regardless of whether the saccades were reflexive (Figs. 1–4), delayed (Figs. 5 and 6), or memory guided (Figs. 7 and 8).

Small visually guided saccades show differences in spatial accuracy for upward and downward targets. Because of the global changes in reaction times in the (immediate) visually guided saccade task for different visual field locations (Fig. 4), we searched for other asymmetries in saccade parameters that also depended on foveal (or extrafoveal) target location. We found that saccade amplitude and direction differentially depended on visual field target location for foveal targets. Specifically, when we plotted saccade amplitude as a function of target eccentricity (Fig. 9, *A* and *C*), we found that amplitude scaled nicely with target eccentricity even for foveal target locations, but there was larger overshoot in saccade amplitude for foveal targets in the lower visual field than in the upper visual field or along the horizontal meridian. On the other hand, when we plotted saccade direction error relative to target direction (Fig. 9, *B* and *D*), we found that the overshooting lower visual field small saccades were more directionally accurate than the saccades to foveal targets in the upper visual field or along the horizontal meridian. Therefore, besides strong increases in reaction times for foveal target eccentricities (Figs. 1–4), small visually guided saccades showed differential effects of amplitude versus directional accuracy as a function of target visual field location. These effects (Fig. 9) were not so clearly visible in the other variants of the task, such as the delayed visually guided saccade task or the memory guided saccade task.

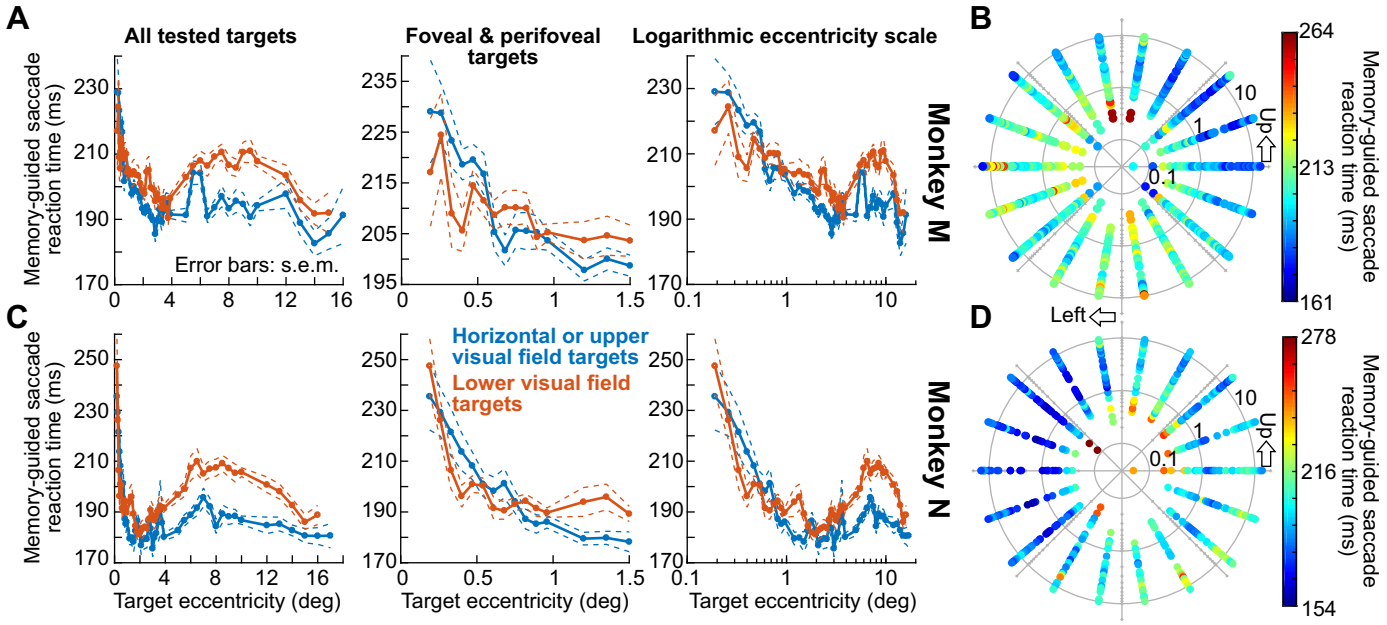

Fig. 7. Increased reaction times for small memory-guided saccades in the rhesus macaque monkey. *A* and *B*: analyses similar to Fig. 4, *A* and *B*, for *monkey M* but during the memory-guided saccade task. Small memory-guided saccades were associated with increased reaction times (compared with larger saccades) despite the absence of a visual target. Note that for memory-guided saccades the increase in reaction time for larger target eccentricities that was obvious for (immediate) visually guided saccades (e.g., Fig. 2) did not take place so clearly. Instead, lower visual field saccades of intermediate sizes (e.g., 5–12° amplitudes; red curves) showed elevated reaction times compared with upper visual field saccades. Also note that there was no strong difference in reaction time between upper and lower visual field targets for small amplitudes (*A*, *center*), unlike for visually guided saccades (Figs. 2–5). n = 6,346 trials; error bars denote SE. *C* and *D*: same results for *monkey N*. n = 4,245 trials.

Increased reaction times for small eccentricities are specific to eye movements and absent in manual reactions. Finally, we further investigated the absence of increased reaction times for large saccades made in the memory-guided task compared with the visually guided saccade task. We hypothesized that the increase in the latter task might critically depend on the perceptual detectability of the appearing target. Specifically, we used a small spot as the target in all of our experiments, even for eccentricities of 10° or 15°. This means that, at these eccentricities, the small spot would be harder to perceptually detect than in the foveal or parafoveal regions (because of limits of the contrast sensitivity function). Therefore, even

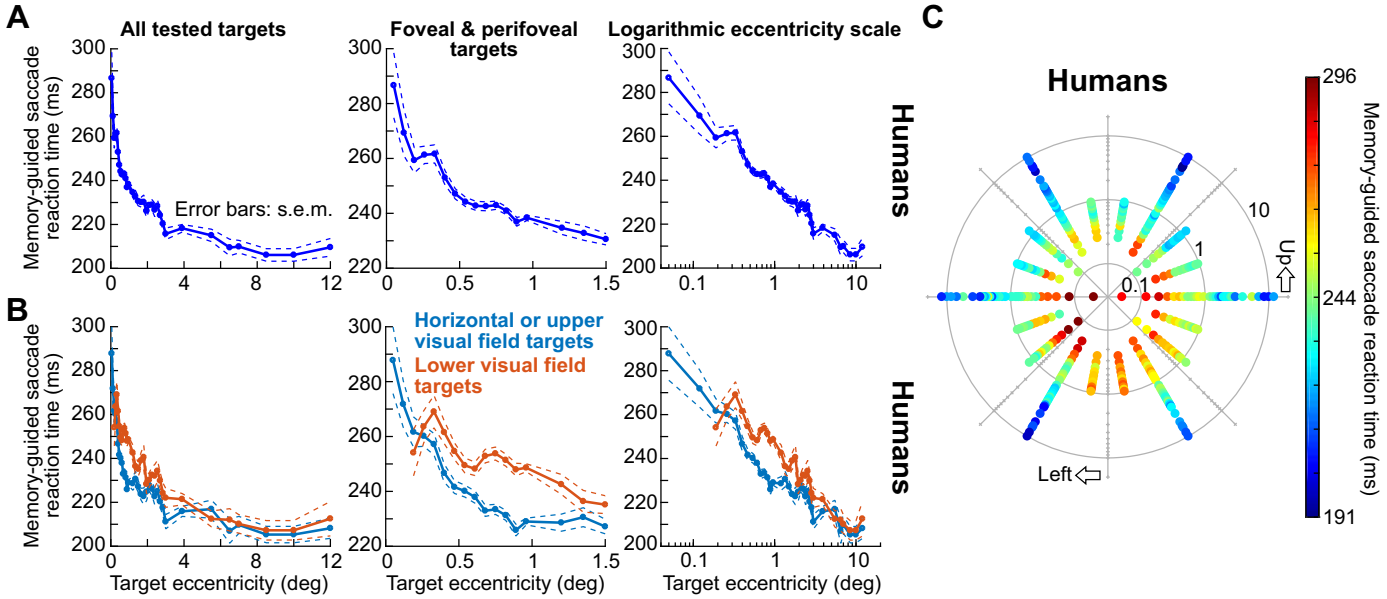

Fig. 8. Memory-guided saccades in humans showed the same eccentricity dependencies as monkey memory-guided saccades. *A*: analyses similar to Fig. 2 but for our human subjects' data combined. The smallest saccades were associated with the longest reaction times, as in the monkeys (Fig. 7). n = 13,531 trials; error bars denote SE. *B*: the same data but now with upper and lower visual field target locations separately, as in Fig. 7. Results similar to those in the monkeys were obtained. Note that for small amplitudes (*center*), there was a clearer difference between upper and lower visual field saccades than in the monkeys (Fig. 7). Thus the data appeared more similar to those in visually guided saccades (Fig. 4, *A* and *C*, *center*). *C*: the same data but in a format similar to that of Fig. 7, *B* and *D*, demonstrating that, in humans as well, small memory-guided "microsaccades" in all directions are associated with increased reaction times.

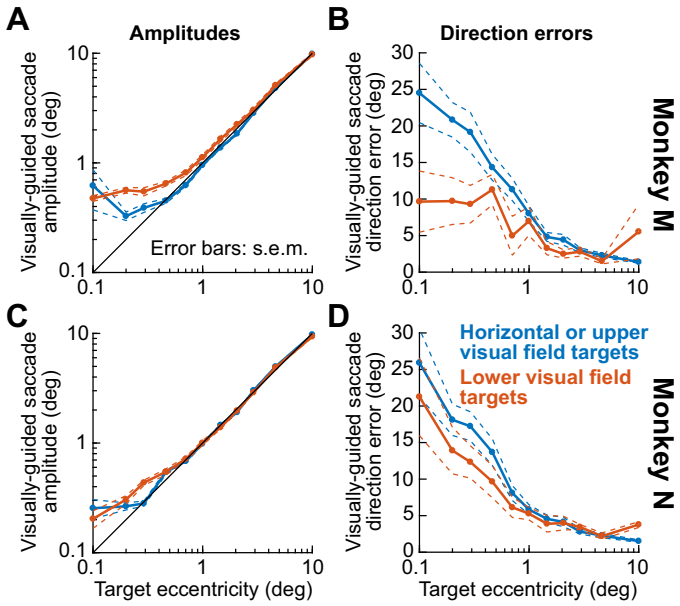

Fig. 9. Small visually guided saccades in the rhesus macaque monkey were more accurate in size for upper visual field targets but more accurate in direction for lower visual field targets. *A*: saccade amplitude as a function of target eccentricity in *monkey M*. We used logarithmic axes to display the data so that the effects with small eccentricities are more visible. Small saccades to lower visual field targets (red) overshot the target significantly more than small saccades to horizontal and upper visual field targets (blue). $n = 928$ trials. *B*: for the same data as in *A*, we plotted saccade direction error (relative to target direction) as a function of target eccentricity. Direction error was smaller for small saccades to lower visual field targets (red) than for small saccades to horizontal and upper visual field targets (blue). *C* and *D*: similar results for *monkey N*. $n = 1{,}246$ trials. In all panels, error bars denote SE.

without saccadic responses, decreased perceptual detectability at far eccentricities could delay reaction times.

We explicitly tested this hypothesis by performing additional experiments with one of us (*subject ZH*) being the experienced subject (similar to our 2 experienced monkey subjects). In Fig. 10*A*, we replicated the findings of human saccadic reaction times as a function of target eccentricity (Kalesnykas and Hallett 1994, 1996). Note how, in addition to the dramatic increase for small saccades, saccadic reaction times increased with increasing target eccentricity for extrafoveal targets (similar to our monkeys in Fig. 2). Critically, for Fig. 10*B*, we ran the same subject on a perceptual detection task, in which no saccade was required at all. Instead, the subject had to press a button as soon as the target appeared in the periphery (METHODS), and we confirmed that no microsaccades occurred between target onset and button press. Two notable observations are clear from the data. First, there was no strong increase in reaction times for foveal target eccentricities, suggesting that the increased reaction times of small saccades are specific to the fact that the motor behavior was to generate small saccades (see Fig. 4.14 in Kalesnykas 1994). Second, the same increase in reaction times for larger target eccentricities as in Fig. 10*A* was still evident.

This latter observation is much more obvious when the two curves are superimposed together in Fig. 10*C* using the same *y*-axis scaling (but with arbitrary *y*-axis positioning of the curves due to the different absolute values of saccadic and manual reaction times). Both tasks were associated with increased reaction times for peripheral targets, but only the saccadic task was associated with increased reaction times for foveal targets. Therefore, the increases in Fig. 2 and Fig. 10*A* for large eccentricities were not specific to saccade generation.

These same conclusions were reached when we repeated these same experiments on three additional naive subjects (Fig. 11*A*). Interestingly, all four subjects also showed the dependence of saccadic reaction times on upper versus lower visual field target locations (Fig. 10*D* and Fig. 11*B*) that we observed in our monkeys (Fig. 4), but this effect was again specific only to saccade generation (Fig. 10*E* and Fig. 11*C*).

DISCUSSION

We investigated spatial and temporal aspects of triggering small saccades in the rhesus macaque monkey and compared our results to those obtained in human subjects both from the existing literature and through our own additional measurements. We specifically found that, in the monkey, small saccades require more time than larger saccades to be triggered. This observation is true whether the small saccades are visually driven, delayed (but still visually driven), or memory guided. We also found a strong asymmetry in the reaction times of small visually guided saccades to upper and lower visual field locations, similar to larger saccade results (Hafed and Chen 2016; Schlykowa et al. 1996; Zhou and King 2002). For larger saccades, there was a gradual increase in reaction times with increasing target eccentricities but primarily in the immediate visually guided saccade task and not in the delayed visually guided saccade task or the memory-guided saccade task.

Our results are important to document in the oculomotor system literature because there has been no systematic attempt to investigate small-saccade triggering properties in the rhesus macaque monkey. In humans, it is well known that small-saccade reaction times are long (Kalesnykas and Hallett 1994, 1996; Wyman and Steinman 1973), although the mechanistic reasons for this phenomenon seem to be still not fully understood. In the monkey, there have basically been only casual inferences about small-saccade reaction times in macaques (Boch et al. 1984; Skinner et al. 2019; Willeke et al. 2019) but either with tasks that were not explicitly designed for such analyses or without sufficient sampling of small target eccentricities. Therefore, our results provide an important reference catalog of small-saccade triggering in macaque monkeys. This is especially important nowadays to guide investigations of neural mechanisms associated with foveal visual and motor processing (Chen et al. 2019; Guerrasio et al. 2010; Willeke et al. 2019).

One interesting aspect of our results is the observation that the reaction times of small saccades are shorter for upper visual field target locations than for lower visual field target locations (e.g., Fig. 4). This was in addition to the observation of increased reaction times in general for small saccades (Figs. 1–3). Therefore, not only are foveal targets associated with long saccadic reaction times (Figs. 1–3), but longer times are particularly prominent with foveal targets located in the lower visual field (Fig. 4). Interestingly, in one of their control conditions, Wyman and Steinman (1973) required a small downward saccade, which exhibited prolonged reaction times in humans as well, although this aspect of the data was not explicitly mentioned in that study. This is consistent with our human results of Figs. 10 and 11. It is also consistent with the

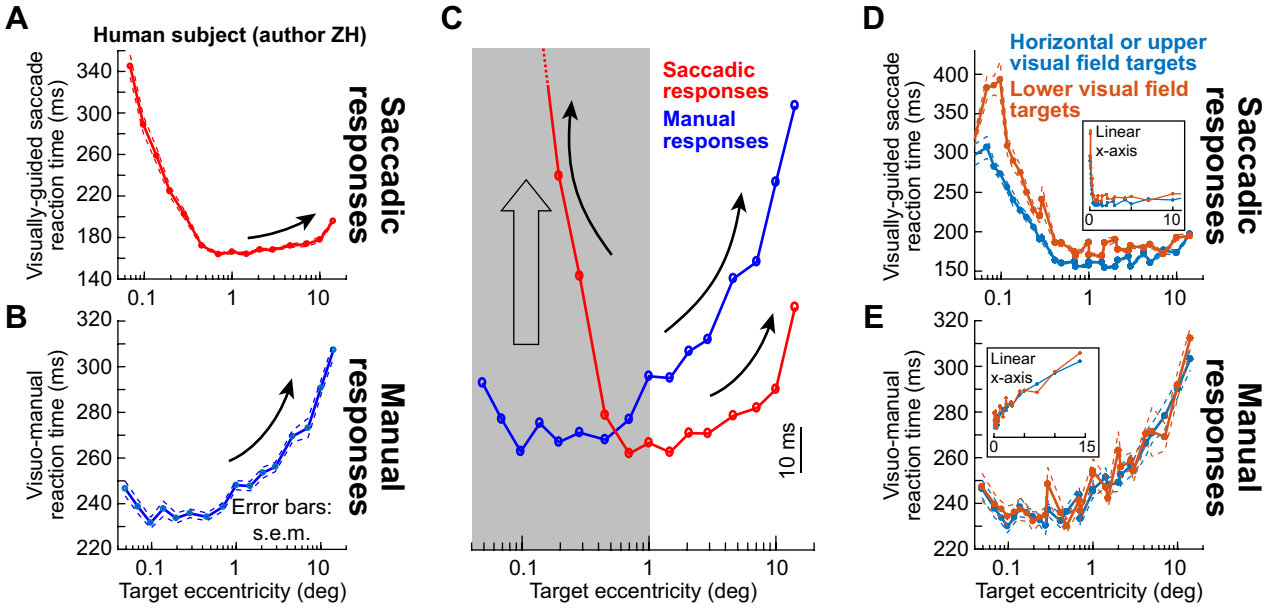

Fig. 10. Both saccadic and manual reaction times increased for large target eccentricities in a human subject; only saccadic, but not manual, reaction times increased for small saccades as well as for lower visual field target locations. *A*: Z. M. Hafed (*subject ZH*) performed the same task as in Fig. 2. Small saccades had very long reaction times. Large saccades also showed a modest reaction time increase (curved black arrow). *B*: results from the same subject in the manual version of the task (METHODS). *C*: same data as in *A* and *B* but now using the same *y*-axis scaling (see vertical scale bar) but arbitrary *y*-axis placement to visually align the curves. Both tasks showed increased reaction times for large target eccentricities (black curved arrows), but only saccadic responses had strong increases for small target eccentricities (gray rectangle). *D*: same data as in *A* but separating upper and lower visual field target locations as in Fig. 4. *E*: similar to *D* but for the manual task's data. Error bars denote SE. Fig. 11 shows similar results from 3 additional naive subjects.

asymmetric representations of upper and lower visual fields in the SC, in such a manner that can directly affect gaze direction, saccadic reaction times, and landing errors (Hafed and Chen 2016; Goffart et al. 2006). As we elaborate more below, these effects are also consistent with our theory of gaze direction as an equilibrium insofar as an eye movement is not initiated as long as the visuo-oculomotor system is within a state of balance among opposing commands (Goffart 2019; Goffart et al. 2012, 2018; Krauzlis et al. 2017).

We also noticed interesting contrasts between the reaction times of small and large saccades. For example, immediate visually guided saccades showed a marked increase in reaction times for large saccades (e.g., Fig. 2), but this effect was not as strong as that for small saccades. It has been reported in humans that large saccades also become associated with increased reaction times (Kalesnykas and Hallett 1994, 1996). However, are the causes similar to the causes of increased reaction times of small saccades? This issue remains unaddressed. On the basis of our data, we believe that the two increases are driven by quite different underlying causes. Specifically, in the delayed and memory-guided saccade tasks, the increase in reaction times for large saccades was much less obvious than in the immediate visually guided saccade task, even though small saccades showed strong increases in all three tasks. Therefore, increased reaction times for large saccades are likely to be driven by mechanisms different from those affecting small-saccade reaction times. Indeed, our experiments of Figs. 10 and 11 demonstrate that perceptual detectability of far peripheral targets might explain the increased reaction times associated with large eccentricities.

If perceptual detectability can affect reaction times of large target eccentricities (Figs. 10 and 11), we think that equilibrium states in the oculomotor system explain the long reaction times of small saccades. Specifically, evidence from pharmacological inactivation experiments in either the SC or the caudal fastigial nucleus suggests that gaze direction is an equilibrium and that an eye movement (saccadic or slow) is not initiated as long as the visuo-oculomotor system is within a state of balance where opposing commands counterbalance each other (Goffart 2019; Goffart et al. 2012, 2018; Krauzlis et al. 2017). Thus the longer reaction times of small saccades are the signature of enhanced times to create a symmetry-breaking condition, which puts the downstream premotor neurons into a push-pull regime that is responsible for the firing rates of motor neurons innervating the agonist and antagonist extraocular muscles (reciprocal innervation). Such enhanced times can occur for the following reason. Before bursting during both contralateral and ipsilateral saccades, saccade-related neurons in the rostral SC and caudal fastigial nucleus fire in a sustained manner during visual fixation (Hafed and Krauzlis 2012; Kleine et al. 2003). More importantly, they also increase firing before and during both contralateral and ipsilateral saccades. Such bilateral activity carries, at the level of saccade-related premotor neurons, commands that are antagonist to each other (see Fig. 10 in Goffart et al. 2004). Thus the longer reaction times of small saccades result from the fact that the bilateral and conflicting drives exerted by collicular and fastigial neurons become stronger as the activity becomes more rostral in the SC and/or as the ipsilateral and contralateral presaccadic spikes emitted by fastigial neurons are simultaneous. The longer lead times of firing activity (before saccade bursts) that some inhibitory premotor neurons emit before small saccades strikingly illustrate this concept (e.g., see Fig. 8 in Scudder et al. 1988).

A second mechanistic reason for enhanced times is related to spatial representation itself. Consistent with the large amount

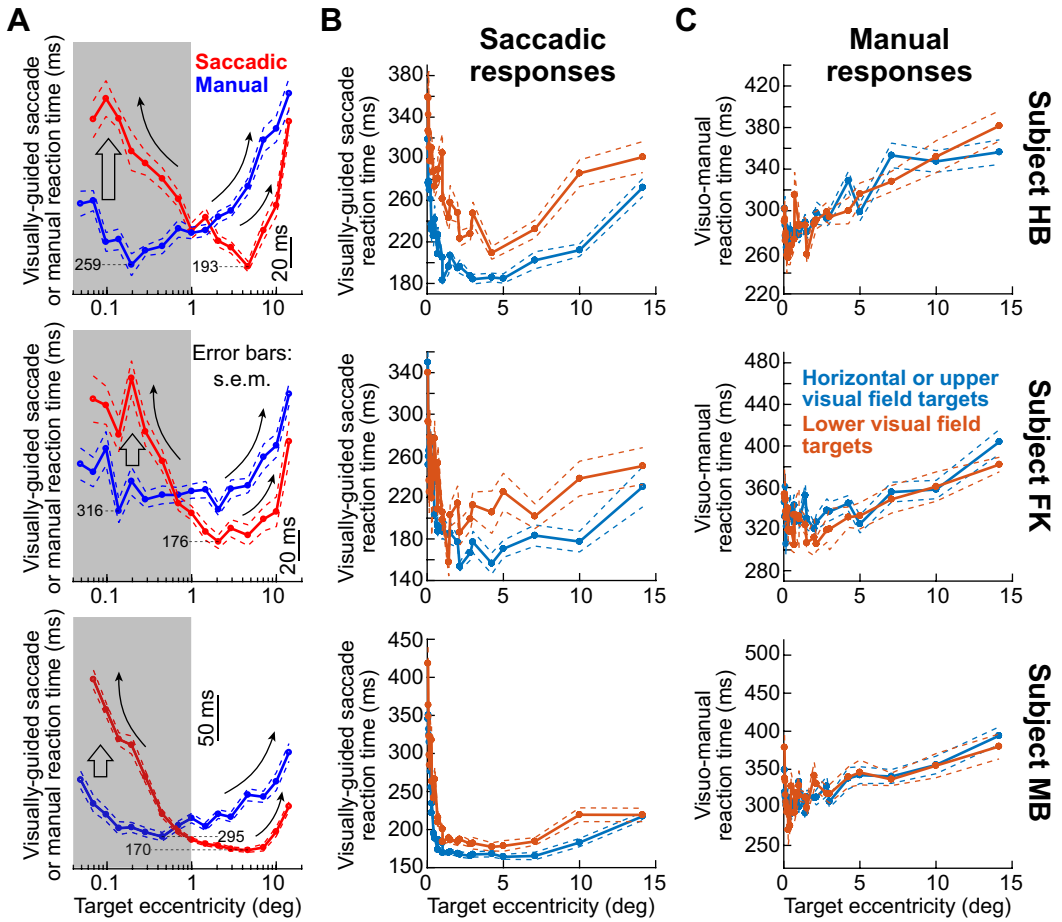

Fig. 11. Same observations as in Fig. 10, but with data from 3 additional naive subjects. Each row of plots represents data from a single subject. *A*: same as Fig. 10*C*, showing a comparison between manual and saccadic reaction times. The same *y*-axis scale bar applies to both tasks, but absolute values are not presented (for reference, absolute values are shown from 1 data point per curve). *B*: same data as in *A* from the saccade task but separating targets as being either in the upper or lower visual fields, as in Fig. 10*D*. *C*: same data as in *A* from the manual task but separating targets as being either in the upper or lower visual fields, as in Fig. 10*E*. For each subject, the same *y*-axis scaling was used in *B* and *C* to facilitate comparison of effect sizes between the 2 tasks. All other conventions are identical to those in Fig. 10.

of foveal magnification in the SC (Chen et al. 2019), the equilibrium idea is actually a natural extension of SC population coding of saccade metrics, but this time to aid in the specification of gaze direction during fixation. Specifically, Sparks and colleagues proposed that "precise saccadic movements are not produced by the discharge of a small population of finely tuned neurons but result from the weighted sum of the simultaneous movement tendencies produced by the activity of a large population of less finely tuned neurons" (Sparks et al. 1976). If the deep SC is a continuum representing different movement tendencies, then the absence of movement during fixation may be viewed as the simple result of simultaneous movement tendencies for small saccades counterbalancing each other. Indeed, rostral SC neurons active during fixation do individually represent small movement vectors (Hafed and Krauzlis 2012). Thus the foveal magnification in the SC contributes not only to ensure precise microsaccades (Chen et al. 2019; Guerrasio et al. 2010; Ko et al. 2010; Tian et al. 2018), but it does also imply that a sizable population of neurons is active at any one moment in time to represent the current fixated goal (Goffart et al. 2012; Hafed et al. 2008; Hafed and Krauzlis 2008). The implication of this is that a given displacement (in anatomical coordinates) of the center of mass of such an active population would correspond to only a tiny displacement of the represented "movement vector" in visual coordinates (the same displacement in the caudal SC would correspond to much larger changes in the represented movement vector). Thus achieving a shifted center of mass to create sufficient imbalance in the downstream readout of SC activity is harder because of the tiny visual field locations represented by the rostral SC. Movements effected by readout of the rostral SC would indeed be infinitesimally small for very small shifts of rostral SC populations.

If balance among multiple gaze commands is what maintains gaze stability and increases reaction times for small saccades, then one might wonder how an imbalance may be generated at all during fixation in the first place. In other words, why is reaction time not infinite once balance among competing gaze shift commands is achieved? One possible explanation is behavioral and invokes the slow fixational eye movements that often happen between saccades. These ocular drifts change the retinotopic location of the fixated object and thus create the imbalance needed to activate the colliculoreticular streams innervating the eye muscles. In fact, we recently found that the generation of tiny microsaccades during fixation is highly consistently associated with small, instantaneous retinotopic

gaze position errors, even in the presence of peripheral "attention-capturing" cues (Tian et al. 2016, 2018). Another explanation is physiological and lies in the fluctuations of the activity of neurons, which, from the foveal ganglion cells to the saccade-related premotor burst neurons, exhibit sustained firing rates whenever gaze is held stable. Among this immense number of neurons, we find not only long-lead burst neurons in the pontine reticular formation but also neurons in the caudal fastigial nucleus (Kleine et al. 2003; Sun et al. 2016). After unilateral inactivation of this nucleus, not only are fixational saccades dysmetric (Guerrasio et al. 2010) but the direction of gaze during fixation and pursuit is also always deviated toward the lesioned side (Bourrelly et al. 2018; Goffart et al. 2004; Guerrasio et al. 2010). The fact that the head can also be deviated after a unilateral SC or fastigial lesion indicates that the balancing of activity is a process that is not restricted to the determination of eye gaze direction (Goffart et al. 2018); head direction is also an equilibrium. Thus, gaze and head movements, instead of reducing putative signals encoding the angular distance between gaze (or head) and target locations in physical space, may be separate processes that consist of restoring symmetries (Goffart 2019; Goffart et al. 2018).

An interesting additional consequence of the oculomotor balance idea is that we can predict express, rather than slow, reaction times for small saccades under the right conditions related to instantaneous gaze position error. Indeed, so-called "express microsaccades" can happen when peripheral stimulus onsets momentarily bias a state equivalent to "unstable equilibrium" (Tian et al. 2018). Specifically, in that study it was found that a peripheral stimulus onset during fixation was sometimes associated with a distinct population of so-called express microsaccadic reactions, which were highly precise in their timing and direction relative to the appearing stimulus. These movements had latencies significantly <100 ms even though they were small eye movements (as in the present study), but it was found that they occurred under very specific conditions of lack of prior microsaccades for a prolonged period of time as well as eye position being in a state of almost "zero" position error relative to the fixated spot (Tian et al. 2018).

Of course, the oculomotor balance referred to in all of the above can be implemented in different forms in different oculomotor nuclei. For example, omnipause neurons (OPNs) in the nucleus raphe interpositus exhibit tonic activity in the absence of saccades, similar in principle to other neurons in other brain areas (e.g., rostral deep SC neurons or caudal fastigial nucleus neurons) (Krauzlis et al. 2017). Because these OPNs completely pause during saccades, they are believed to be an all-or-none mechanism for "fixing gaze." However, OPNs do show evidence of reflecting the state of balance among multiple movement tendencies, which is consistent with our equilibrium hypothesis. For example, OPNs clearly modulate their tonic rate with eye velocity in a continuous manner (Missal and Keller 2002). It is thus conceivable that even during so-called "gaze fixation," their tonic rate is systematically variable, reflecting fixational drift eye movements. In that case, even these neurons would show variability that is inconsistent with a theoretical "command to fix gaze." These neurons, like other brain stem premotor neurons, can be part of a network likely coordinating balance or imbalance from among multiple competing movement tendencies. However, there is no convincing evidence to date that inactivating OPNs results in impairments in gaze fixation or even saccade latency (Kaneko 1996; Soetedjo et al. 2002).

Naturally, the role of vision needs to be considered also when thinking about oculomotor behaviors, and that is why we performed our delayed and memory-guided saccade tasks. Previous experiments in humans have attempted to dissociate between visual and oculomotor (or other) sources of increased reaction times for small target eccentricities, and they attributed the increase to a difficulty in specifying the saccade metrics (Kalesnykas and Hallett 1996; Wyman and Steinman 1973). Similarly, in the rhesus macaque SC, although some visual bursts for foveal target onsets might show dependence on foveal eccentricity in their response latency (first-spike latency), this does not seem to be a general property of foveal SC neurons (Chen et al. 2019). Specifically, superficial SC neurons (which generally exhibit marginally shorter visual response latencies than deeper SC neurons) show decreases in first-spike latency of the visual response with increasing foveal eccentricity (consistent with our behavioral findings above); on the other hand, deeper SC neurons show no such dependence of visual burst latency on foveal target eccentricity (Chen et al. 2019). Since it is the deeper SC neurons that show higher correlations between visual burst latency and saccadic reaction times (Chen and Hafed 2017; Marino et al. 2012), this might suggest that increased reaction times for small target eccentricities may not be intrinsically visual in nature (i.e., caused purely by visual-only mechanisms). Consistent with this, other studies showed that the latencies of gaze shifts increase for the smallest gaze displacements, though not for the smallest target eccentricities (Goffart and Pélisson 1997; Zambarbieri et al. 1995), suggesting that saccade triggering can depend on premotor signals related to the impending movement in addition to incoming visual signals from the retina. Our results from the delayed and memory-guided saccade tasks (e.g., Fig. 5) further corroborate these ideas.

Finally, future experiments could investigate the neural mechanisms for learning to fixate visual objects under different visual and oculomotor conditions, and in which various amounts of asymmetry would be incorporated. For example, if target shape is changing, whether for the currently fixated position or for next target positions, what are the consequences for the oculomotor balance? How does this change alter SC and caudal fastigial nucleus population activity? It will also be important to characterize the neural mechanisms underlying the coordination between saccades and slow eye movements (including the ocular drifts), with or without a concurrent head movement.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Z.M.H. and L.G. conceived and designed research; Z.M.H. performed experiments; Z.M.H. and L.G. analyzed data; Z.M.H. and L.G. interpreted results of experiments; Z.M.H. prepared figures; Z.M.H. drafted manuscript; Z.M.H. and L.G. edited and revised manuscript; Z.M.H. and L.G. approved final version of manuscript.

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