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2 **Normal Correspondence of Tectal Maps for Saccadic Eye Movements**
3 **in Strabismus**
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ABSTRACT

The superior colliculus is a major brainstem structure for the production of saccadic eye movements. Electrical stimulation at any given point in the motor map generates saccades of defined amplitude and direction. It is unknown how this saccade map is affected by strabismus. Three macaques were raised with exotropia, an outwards ocular deviation, by detaching the medial rectus tendon in each eye at age one month. The animals were able to make saccades to targets with either eye and appeared to alternate fixation freely. To probe the organization of the superior colliculus, microstimulation was applied at multiple sites, with the animals either free-viewing or fixating a target. On average, microstimulation drove nearly conjugate saccades, similar in both amplitude and direction, but separated by the ocular deviation. Two monkeys showed a pattern deviation, characterized by a systematic change in the relative position of the two eyes with certain changes in gaze angle. These animals' saccades were slightly different for the right eye and left eye in their amplitude or direction. The differences were consistent with the animals' underlying pattern deviation, measured during static fixation and smooth pursuit. The tectal map for saccade generation appears to be normal in strabismus, but saccades may be affected by changes in the strabismic deviation that occur with different gaze angles.

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NEW AND NOTEWORTHY SECTION

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Electrical stimulation of the superior colliculus drives a rapid eye movement, or saccade,

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that is nearly identical in each eye. In strabismus, the eyes are offset, but microstimulation still

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generates similar saccades. Minor discrepancies in saccade amplitude and direction are

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sometimes present, which are likely due to altered downstream ocular motor pathways that also

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mediate smooth pursuit and steady fixation.

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INTRODUCTION

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81 Most patients with divergent strabismus (exotropia) have normal visual acuity in each
82 eye. They usually have a dominant eye, but can freely alternate fixation on visual targets.
83 Objects are localized with surprising precision, by either eye or hand, despite the fact that images
84 falling on each retina fail to land on locations that normally correspond (Agaoglu et al. 2014;
85 Bucci et al. 2009; Das 2009; Das et al. 2004; Griffiths et al. 2011; Niechwiej-Szwedo et al.
86 2014). Diplopia is prevented by suppression of the peripheral temporal retina in each eye
87 (Cooper and Record 1986; Economides et al. 2012; Herzau 1980; Joosse et al. 1997). Confusion
88 is avoided by shifting the perceived location of objects sensed via the deviating eye (Cooper and
89 Feldman 1979). Typically, the magnitude of the shift is equal to the ocular deviation, effectively
90 cancelling it (Economides et al. 2012). The fovea of the deviating eye, by becoming
91 perceptually realigned, acquires a common visual direction with a point in the temporal retina of
92 the fixating eye (Herzau 1996). Consequently, the center of gaze of the deviating eye in
93 retinotopic coordinates is mapped anomalously to a peripheral location in a body-centered frame
94 of reference. Where this transformation is represented in the brain is unknown.

95
96 In normal monkeys, the superior colliculus contains binocular cells organized in a
97 topographic map, with sensory cells in the superficial layers and sensory/motor cells in the
98 deeper layers (Schiller 1984; Wurtz and Albano 1980). The latter cells have receptive fields
99 activated by visual stimuli and movement fields encoding a saccade of corresponding size and
100 direction. Electrical activation of a locus in the tectal map generates conjugate saccades
101 (Robinson 1972). The superior colliculus plays a critical role in the guidance of eye-hand

102 movements, as well as in the selection of targets (Gandhi and Katnani 2011; Glimcher and
103 Sparks 1992; Horwitz and Newsome 1999; Schall 2001; Song and McPeck 2015).

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105 Few studies have been undertaken of the superior colliculus in strabismus, although it is a
106 logical place to begin the effort to understand how the brain achieves accurate spatial localization
107 despite ocular misalignment. In cats, after early transection of eye muscles, neurons in the
108 superior colliculus have been reported to remain binocularly driven (Gordon and Gummow
109 1975; Gordon and Presson 1977). This result is surprising because strabismus has the opposite
110 effect in striate cortex. Lack of concordant visual stimulation during early life leads to enhanced
111 segregation of geniculate inputs within ocular dominance columns and to a striking loss of
112 binocular neurons (Wiesel 1982). In the superior colliculus, eye input to the superficial layers is
113 organized into separate zones that are analogous to the ocular dominance columns in striate
114 cortex (Hubel et al. 1975). One would expect strabismus to increase the segregation of this
115 direct retinal input. The indirect visual input that comes from striate cortex should also show
116 reduced binocularity.

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118 If neurons in the superior colliculus remain binocular despite strabismus, then the visual
119 system faces a challenge when it comes to controlling which eye will acquire a visual target. For
120 example, a stimulus situated between the fixation points in an exotropic subject falls on the
121 temporal retina in the left eye and the nasal retina in the right eye (**Fig. 1**). The stimulus evokes
122 sensory responses at two different loci within the superior colliculi (**Fig. 1B**). Given that
123 neurons are binocular, the responses cannot be coded by eye, yet only one eye is destined to
124 acquire the target. Somehow, the ocular motor system must disregard or suppress sensory

125 responses at one locus, and allow neurons at the other locus to generate an appropriate saccade.
126 To explore this phenomenon, it would be interesting to compare neuronal activity at a given site
127 during trials when a target was presented, and then subsequently fixated by either the left eye or
128 the right eye.

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130 We have recorded from single units in the superior colliculus of three macaques raised
131 with alternating exotropia while they were engaged in alternating fixation onto targets. To
132 localize the superior colliculus for recordings, electrical microstimulation was applied. This
133 report describes the impact of strabismus on the eye movements obtained from electrical
134 stimulation. A subsequent report will describe single unit observations.

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METHODS

Animals

Three male macaques (*Macaca mulatta*) were reared with strabismus at the California National Primate Research Center, Davis, CA by performing a tenotomy of the medial rectus muscle in each eye at age 4 weeks. The muscle eventually re-attaches to the sclera, but fusion is disrupted during the critical period for binocular vision. This leads to an alternating exotropia without amblyopia, which shares many features of decompensated intermittent exotropia in humans (Economides et al. 2007). It differs, however, in some important respects. First, adduction remains reduced compared with normal animals, in part because the muscle insertion site may be abnormal. Second, the onset of exotropia is sudden and irrevocable, rather than occurring via a process of gradual decompensation. Other models of strabismus have been developed successfully, each with advantages and disadvantages (Crawford and von Noorden 1980; Das et al. 2005; Kiorpes 1992; Tychsen and Burkhalter 1997).

After the monkeys reached age 3 years, they were transferred to our laboratory at the University of California San Francisco. A titanium headpost and recording chamber were implanted, as described previously (Adams et al. 2007; Adams et al. 2011). The chamber was situated on the right side over medial parietal cortex, just anterior to the lunate sulcus, to avoid making penetrations through striate cortex. The right superior colliculus was stimulated in most experiments, but the left superior colliculus was stimulated in two monkeys by making penetrations near the medial edge of the chamber (**Fig. 1B**). All procedures were approved by

164 the Institutional Animal Care and Use Committee at UC Davis or UC San Francisco. Monkey 1
165 was referred to as “Monkey 2” in an earlier study (Economides et al. 2007); Monkey 2 and 3
166 have not been previously reported.

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170 **Video Eye Tracking and Target Presentation**

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172 Each monkey’s eye movements were recorded while head-restrained in a primate chair.
173 Computer-generated targets (Cambridge Research Systems, Rochester, England) were rear-
174 projected onto a tangent screen by a digital light projector (Hewlett Packard, Palo Alto,
175 California) with a 60 Hz refresh rate. The tangent screen, subtending $\pm 45^\circ$ horizontally and
176 vertically, was placed 57 cm in front of the monkey. Eye movements were monitored by two
177 independent eye trackers, operating at 60 Hz, each using an infrared video camera
178 (SensoMotoric Instruments, Teltow, Germany). The comparatively slow sampling rate limited
179 the precision of saccade measurements, but should not affect comparisons between the eyes. The
180 cameras were mounted overhead; a dielectric mirror that reflected infrared light was oriented
181 obliquely to obtain video images of the animal’s eyes. Each eye was illuminated by a separate
182 infrared light source, positioned laterally. This arrangement enabled us to track each eye over a
183 wide range, from 20° nasally to almost 80° temporally. This was an important advantage, given
184 the large exotropia present in the strabismic monkeys. The position of each eye and the location
185 of visual stimuli on the tangent screen were sampled at 120 Hz by a Power1401 data acquisition
186 and control system (Cambridge Electronics Design, Cambridge, England). To calibrate the eye

187 trackers the digital gain and offset were adjusted on-line to match eye and target locations while
188 the monkey tracked a spot oscillating sinusoidally in a horizontal, and then vertical direction.
189 Each eye was calibrated independently, with the other eye covered. The monkey was rewarded
190 with food puree for accurate fixation within an adjustable window.

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193 **Superior Colliculus Stimulation**

194

195 A plastic grid with holes 1 mm apart was placed inside the recording chamber. A 30-
196 gauge guide tube was lowered to approximately 10 mm above the superior colliculus.

197 Recordings were made with quartz-platinum/tungsten tetrodes (Thomas Recording, Giessen,

198 Germany), having an impedance of 0.5 – 1.0 M Ω . As the tetrode was advanced, electrical

199 stimulation was employed to locate the surface of the superior colliculus (MultiChannel Systems,

200 STG 1001, Reutlingen, Germany). Typically, trains of biphasic square wave pulses, 500 μ s at

201 500 Hz, 20 – 400 μ A, were applied for 500-1,000 ms to generate repetitive saccades (Katnani

202 and Gandhi 2012). After staircase saccades were observed, the tetrode was often advanced

203 another 500 – 1,500 μ m to reduce the current required to elicit eye movements (20 – 200 μ A).

204 Sites stimulated in each monkey are shown in **Fig. 1B**. The average number of stimulation trials

205 at each site was 30.

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207 For each monkey, saccade size and direction elicited by electrical stimulation were

208 compared for the right eye and the left eye. Each staircase eye movement was comprised of

209 saccades that were similar, but there was a tendency for successive saccades to diminish in

210 amplitude (Breznen et al. 1996; Stryker and Schiller 1975). Successive saccades also tended to
 211 be more variable than initial saccades. This was due to several factors, including intrusion of
 212 volitional saccades, limits in ocular excursion (a major issue in strabismic animals), and eye
 213 tracker inaccuracy at extreme gaze angles. For this reason, only the first saccade in each
 214 staircase was analyzed to compare right eye and left eye movements.

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216 To obtain eye velocities, horizontal and vertical position signals for each eye were
 217 differentiated using a 3-point central difference algorithm (Spike 2, Cambridge Electronics
 218 Design, Cambridge, England). After stimulus onset, each saccade duration was defined as the
 219 period when the absolute value of the mean of all 4 velocity signals exceeded the steady state
 220 fixation baseline by 3 standard deviations (usually, about 75°/sec). To determine saccade
 221 amplitude and direction, position was compared at the beginning and end of each eye movement.
 222 Saccades under 3° were excluded, because of the limited resolution of the video eye trackers.
 223 The amplitude of saccades made by each eye were compared as follows (Walton et al. 2014):

224

$$225 \quad \textit{Amplitude Ratio} = \textit{Saccade Amplitude}_{\textit{left eye}} / \textit{Saccade Amplitude}_{\textit{right eye}}$$

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227 When the left eye and right eye saccades are equal, the Amplitude Ratio = 1. Unequal
 228 saccades by the left eye and the right eye yield Amplitude Ratio values that are asymmetrical
 229 around 1. Therefore, Amplitude Ratios were normalized for statistical comparisons by using
 230 their common logarithm as the final measurement unit.

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232 The difference between the polar angle of each eye's saccade was calculated as follows:

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234 $Direction\ Difference = Polar\ Direction_{left\ eye} - Polar\ Direction_{right\ eye}$

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236 For any given tectal site, Amplitude Ratio, log Amplitude Ratio, and Direction

237 Difference were calculated for each stimulation trial and then averaged to derive mean values \pm

238 sd for each parameter. For the log Amplitude Ratio and Direction Difference, confidence

239 intervals were calculated based on the critical value of the t-distribution for each sample size,

240 with an $\alpha = 0.05$.

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RESULTS

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245 In all 3 exotropic monkeys, stimulation of the superior colliculus resulted in a series of
246 consecutive saccades (**Fig. 2**). The cardinal finding was that for any given stimulus site, the
247 saccades in each eye evoked by current application were approximately equal in size and
248 direction. In other words, tectal stimulation elicited saccades that were essentially conjugate.
249 The eyes moved in parallel, by the same amount, with their relative positions determined by the
250 animal's underlying strabismic deviation. In the 3 monkeys, 48 tectal sites were stimulated in
251 total. Stimulation of the right superior colliculus always produced leftwards movement of the
252 eyes, and vice versa. Ipsiversive saccades were never evoked.

253

254 In each animal, we stimulated repeatedly the same site in the superior colliculus. **Fig. 3**
255 shows data from Monkey 1, an animal with an alternating exotropia measuring 35-40°. His
256 ocular deviation remained relatively constant with changes in gaze angle. The relative positions
257 of Monkey 1's eyes over a 40° range of vertical and horizontal static fixations have been
258 reported previously (see Fig. 9, Economides et al (2007)). The animal was rewarded for fixation
259 with either eye on a target located at the center of the tangent screen (**Fig. 3A,B**). At this
260 location he preferred to use his right eye. After fixation was acquired, current was delivered to
261 drive a staircase of saccades. The Amplitude Ratio (saccade amplitude_{left eye} / saccade amplitude_{right eye})
262 was 1.00 ± 0.09 for trials initiated with the right eye ($n = 55$) and 0.90 ± 0.07 for trials
263 initiated with the left eye ($n = 28$). The Direction Difference (polar direction_{left eye} - polar
264 direction_{right eye}) was $2.2^\circ \pm 4.8^\circ$ for right eye trials and $2.1^\circ \pm 3.8^\circ$ for left eye trials. Regardless

265 of which eye fixated on the target at the origin, the saccades in each eye evoked by stimulation
266 drove movements of the eyes that differed little in amplitude or direction.

267

268 When the location of the initial fixation point was moved along the horizontal meridian,
269 the monkey's fixation behavior changed. He preferred to acquire targets on the left with the left
270 eye, and on the right with the right eye (**Fig. 3C**). Combining the data for all fixation starting
271 positions tested in **Fig. 3** ($n = 149$), the right eye saccades had a mean amplitude of $21.3^\circ \pm 3.9^\circ$
272 [95% CI, $20.7^\circ - 21.9^\circ$] and a mean polar angle of $124.7^\circ \pm 7.4^\circ$ [95% CI, $123.5^\circ - 125.9^\circ$]. The
273 left eye saccades had an amplitude of $20.4^\circ \pm 3.6^\circ$ [95% CI, $19.8^\circ - 21.0^\circ$] and a polar angle of
274 $127.9^\circ \pm 8.2^\circ$ [95% CI, $126.5^\circ - 129.2^\circ$]. The confidence intervals for saccade amplitude
275 overlapped, indicating that there was no significant difference in the magnitude of saccades
276 driven in each eye by electrical stimulation at this site in the superior colliculus. For saccade
277 direction, however, there was a small yet significant difference (**Fig. 3D**).

278

279 In Monkey 1, 5 sites were stimulated, all in the right superior colliculus (**Fig. 1B**). For
280 these sites, the mean Amplitude Ratio was 1.07 ± 0.16 . The mean log Amplitude Ratio was
281 0.017 ± 0.067 [95% CI, $-0.066 - 0.101$]. The 95% confidence interval included 0, indicating that
282 there was no significant difference in the size of saccades for the left eye and right eye. The
283 mean Direction Difference for saccades was $3.9^\circ \pm 7.7^\circ$ [95% CI, $-5.7 - 13.5$]. The Direction
284 Difference was also not significant.

285

286 In Monkey 1 the superior colliculus was stimulated while the animal was being rewarded
287 for fixating a target. In Monkey 2, we tested the effect of applying stimulation while free-

288 viewing either random dot noise patterns or natural scenes (**Fig. 4A**). The images were needed
289 to maintain alertness, because no reward was being provided. Given that tectal stimulation was
290 not linked to behavior, the eye of fixation was indeterminate and saccade starting points were
291 widely scattered. Nonetheless, the saccades made by each eye were similar, with an Amplitude
292 Ratio = 1.13 ± 0.13 and Direction Difference = $1.2^\circ \pm 9.2^\circ$ (**Fig. 4B**).

293

294 In Monkey 2 electrical stimulation was applied at 18 collicular sites, 16 on the right and
295 2 on the left (**Fig. 1B**), while either free-viewing or fixating a target. The mean Amplitude Ratio
296 was 1.14 ± 0.17 . The mean log Amplitude Ratio was 0.038 ± 0.066 [95% CI, 0.005 – 0.071],
297 indicating that saccades for the left eye were significantly larger than those for the right eye. The
298 mean Direction Difference was $-3.6^\circ \pm 8.2^\circ$ [95% CI, $-7.6^\circ - 0.49^\circ$]. This difference was not
299 significant.

300

301 The positions of the two eyes for Monkey 2 during static fixation by the left eye on a 9-
302 point grid is shown in **Fig. 5A**. In addition to an alternating exotropia of 40-45°, the visual axis
303 of the animal's left eye was nearly 20° above that of his right eye. This left hypertropia accounts
304 for the fact that left eye vectors were always higher than corresponding right eye vectors (**Fig.**
305 **4A**). This vertical offset had a negligible impact on the conjugacy of saccades. However, the
306 arrays of static fixations revealed another feature of this animal's strabismus that did affect the
307 conjugacy of saccades. The horizontal separation of left eye positions and corresponding right
308 eye positions increased with left gaze. For example, left eye positions on the vertical meridian
309 (0° horizontal) matched right eye positions at a mean of 40.5°, whereas left eye positions at -40°
310 matched right eye positions at a mean of 5.5°. Moving the left eye from primary gaze to -40°

311 increased the horizontal deviation of the eyes from 40.5° to 45.5° . This effect of gaze angle on
312 the horizontal separation between the eyes was also evident during smooth pursuit (**Fig. 5B**).
313 Tracking a target with the left eye that moved from the midline leftwards by 40° resulted in an
314 increase in the exotropia. To summarize: shifts in gaze angle by the monkey towards the left side
315 caused an increase in exotropia due to a 12% greater movement of the left eye compared with the
316 right eye.

317
318 Monkey 3 had the largest alternating exotropia, measuring 60 - 65° (**Fig. 6A**). He
319 preferred to fixate with the right eye. He had an unusual pattern deviation: his exotropia
320 decreased on upgaze. In addition, his left eye became hypertropic on left gaze, but hypotropic on
321 right gaze. As a result, a 9-point grid of targets fixated by the right eye corresponded to a
322 rotated grid of matching left eye positions (**Fig. 6A**). The left eye grid was rotated clockwise
323 about 17° compared with the right eye grid. Note that the plot does not show that the left globe
324 was cyclorotated, but rather, that the left eye array of static fixation positions was rotated.

325
326 When engaged in smooth pursuit (**Fig. 6B**) Monkey 3 usually employed his right eye, but
327 switched to the left eye when the target moved far enough to the left side (**Fig. 6C**). The angle
328 between the trajectory of right eye positions and left eye positions equaled about 16° during
329 smooth pursuit of a target moving back and forth along the horizontal meridian (**Fig. 6B**). This
330 rotation recapitulated the relative angle between right eye and left eye positions during static
331 fixation.

332

333 Stimulation was delivered to 17 sites in the right superior colliculus and 8 sites in the left
334 superior colliculus, while either free-viewing or fixating a target (**Fig. 1B**). For all 25 sites, the
335 mean Amplitude Ratio was 1.00 ± 0.20 . The mean log Amplitude Ratio was -0.015 ± 0.084
336 [95% CI, -0.050 – 0.020]; there was no significant difference in the magnitude of saccades by the
337 left eye and the right eye. The mean Direction Difference was $-15.0^\circ \pm 9.9^\circ$ [95% CI, -19.1° – -
338 10.9°]. The polar direction of saccades was significantly different, with left eye saccades rotated
339 clockwise relative to right eye saccades (**Fig. 7**). The mean Direction Difference was close to the
340 difference observed in the angular alignment of the static fixation grids (**Fig. 6A**) and in the
341 relative trajectory of eye movements during smooth pursuit (**Figs. 6B,C**).

342
343 The data for all stimulation sites in each monkey are shown in **Fig. 8**. As mentioned
344 previously, the recording chamber was mounted on the right side of the head in each animal,
345 causing us to stimulate the right superior colliculus more often than the left superior colliculus.
346 Consequently, the majority of saccades were elicited to the left. There was variability in the log
347 Amplitude Ratio from site to site in each animal, but only Monkey 2 showed a systematic bias
348 (**Fig 8A**). The saccades made by his left eye were greater in amplitude than those made by his
349 right eye, reflected by positive values for log Amplitude Ratio. For Direction Difference there
350 was also variability among stimulation sites (**Fig. 8B**). The mean Direction Difference was close
351 to 0, except in Monkey 3, the animal with a clockwise rotation of left eye saccades relative to
352 right eye saccades.

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355 **Conjugacy of Saccades in Normal Subjects**

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357 It is possible that the rather small disconjugacies observed in these strabismic monkeys
358 were due to measurement error by the eye trackers. It would be ideal to perform parallel
359 experiments in normal monkeys, but we had none available in our laboratory. As an alternative,
360 we tested 5 human subjects with normal visual function and orthotropic eye alignment, following
361 a protocol approved by the UCSF Committee on Human Research. The eye movement
362 recordings were made with the same apparatus used for the strabismic monkeys.

363

364 Subjects fixated a central target on a tangent screen at a distance of 57 cm. A peripheral
365 target appeared briefly at a given eccentricity and polar angle. The subjects made a saccade to
366 the peripheral target. Trials were repeated for a single peripheral target locus, before testing the
367 next target locus. A total of 30 trials were analyzed for each target locus. **Fig. 9** shows examples
368 of saccades to a target at 20° eccentricity made by two subjects. In the first subject, the
369 Amplitude Ratios ranged between 0.92 and 1.08; the Direction Differences ranged between -1.3°
370 and 5.4°. In the second subject, the Amplitude Ratios ranged between 0.93 and 1.11; the
371 Direction Differences ranged between -1.5° and 4.4°. Many of the mean saccade vectors for
372 each eye differed significantly in amplitude or direction.

373

374 One can assume the human subjects made saccades that were nearly perfectly conjugate
375 (the change in vergence angle required to maintain eye alignment on a flat screen induces only
376 minor disconjugacy). The discrepancy in the size and direction of saccades that was measured in
377 our subjects is due mostly to inaccuracy in eye position measurements generated by each eye
378 tracker. Although they are calibrated carefully, they are susceptible to errors from many sources,

379 such as fluctuations in eyelid height, pupil thresholding, pupil size, ocular surface reflectivity,
380 image quality, and subject position.

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DISCUSSION

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Our main finding was that in strabismus, although the eyes' fixation points are offset in position, they move nearly conjugately when the superior colliculus is stimulated electrically. Stimulation did not cause a major change in the magnitude of the strabismic deviation or any tendency for the eyes to converge on a location in visual space. It has been reported that disconjugate movements related to shifts in vergence angle can be evoked by stimulation at the rostral pole (Chaturvedi and Van Gisbergen 2000; Van Horn et al. 2013). We did not stimulate this region, and hence, only conjugate eye movements were observed in our experiments.

At individual stimulation sites, there were often minor differences in the amplitude or direction of saccades evoked in each eye (**Fig. 8**). Some differences attained statistical significance, but they were not significant in biological terms. For example, the stimulation site illustrated in **Fig. 3** yielded saccades with a 3.2° Direction Difference. However, this Direction Difference fell within the range of Direction Differences encountered in normal subjects engaged in conjugate eye movements. The trackers monitoring each eye, even when calibrated fastidiously, yield small errors in position signals that can make conjugate saccades appear slightly disconjugate (**Fig. 9**). The problem is compounded in strabismic monkeys because of their large ocular deviations. For example, with extreme globe rotations, the tracking of position can be degraded by movement of the illuminator light reflex from the cornea to the sclera.

404 The discrepancies we measured in saccade size or direction from one stimulation site to
405 another were usually small and variable in sign (**Fig. 8**). Most importantly, except as noted
406 below, there was no systematic trend or pattern to the saccade asymmetries. For this reason, it
407 seemed valid to average the data obtained from tectal stimulation sites in each animal.

408

409 In Monkey 2, the mean Amplitude Ratio compiled from all 18 stimulation sites was 1.14.
410 This was a significant deviation from an equal amplitude ratio, and well outside the range of
411 tracker error. Comparison of relative left eye and right eye positions during static fixation (**Fig.**
412 **5A**) and smooth pursuit (**Fig. 5B**) showed that with shifts in gaze angle to the left, the animal's
413 exotropia increased by 12%. The most likely explanation is that the surgery on the medial rectus
414 muscles performed during infancy resulted in asymmetrical weakness. If the right medial rectus
415 were weaker than the left medial rectus, then the animal's exotropia would increase on left gaze,
416 just as shown in **Fig. 5**. In this animal we happened to stimulate the right superior colliculus on
417 16/18 trials, driving the eyes to the left. Accordingly, tectal stimulation evoked 14% larger
418 saccades in the left eye compared to the right eye.

419

420 In strabismus, a shift in the relative positions of the two eyes that occurs with changes in
421 gaze angle is known as "incomitance". The increase in exotropia on left gaze in Monkey 2
422 represents a horizontal gaze incomitance. In Monkey 3 there was a different type of
423 incomitance. Left eye saccades showed a mean clockwise shift of 15° relative to right eye
424 saccades (**Fig. 8**). A clockwise shift was observed for saccades of all amplitudes, directions, and
425 starting points. The most likely cause was an unusual property that this animal displayed,
426 namely, a 16° – 17° rotation in the relative positions of the eyes' fixation points that occurred

427 with either vertical or horizontal changes in gaze angle (**Fig. 6A**). With upgaze, the animal's
428 exotropia was reduced – a form of incomitance known as an A-pattern. An A-pattern produces a
429 clockwise Direction Difference (i.e., left eye clockwise relative to right eye), but only for the
430 vertical component of saccades (**Fig. 6A**, left inset). Consequently, the Direction Difference is
431 maximal for pure vertical saccades and absent for pure horizontal saccades. In addition to an A-
432 pattern exotropia, Monkey 3 had a left hypertropia on left gaze and a left hypotropia on right
433 gaze. This change in relative vertical position of the eyes as a function of horizontal gaze
434 induces a clockwise Direction Difference, but only for the horizontal component of saccades
435 (**Fig. 6A**, right inset). The combination of a relative shift in the horizontal separation of the two
436 eyes with vertical gaze (A-pattern), and a relative shift in the vertical separation with horizontal
437 gaze, account for the 15° clockwise rotation of the left eye's saccades.

438
439 It is debated whether incomitant strabismus patterns are due to orbital mechanical forces,
440 such as oblique muscle dysfunction, altered rectus muscle action, or displaced pulleys (Ghasia
441 and Shaikh 2013; Ghasia et al. 2015; Hao et al. 2016; Kushner 2010; Narasimhan et al. 2007; Oh
442 et al. 2002). The surgery performed to induce strabismus in Monkeys 2 and 3 caused changes in
443 eye muscle mechanics that contributed to the incomitance of their ocular deviation. Monkey 3
444 also had a very large deviation, which would be likely to alter extraocular muscle action in
445 different gaze positions. However, such pattern deviations have been observed in monkeys with
446 a much smaller deviation, whose strabismus was induced without eye muscle surgery. For
447 example, Das and Mustari (see their Monkey S1 in Figure 1, 2007) reported a pattern deviation
448 in a monkey rendered strabismic by early bilateral visual deprivation that was nearly identical to
449 the pattern in Monkey 3. Incomitance – especially A- and V- pattern deviations – is also
450 encountered frequently in humans with strabismus who have not undergone eye muscle surgery

451 (Deng et al. 2013; Dickmann et al. 2012). This suggests that the incomitance in Monkeys 2 and
452 3 was not simply an odd feature of the surgical model of strabismus.

453

454 Recently, Fleuriet and colleagues (Fleuriet et al. 2016) have reported observations from
455 electrical stimulation of the superior colliculus in strabismic monkeys. They also recorded small
456 differences in the size and direction of saccades made by each eye. Our results are in close
457 agreement with their findings. They suggested that in strabismus, activation of a single location
458 in the superior colliculus is not interpreted by the saccade generator as the same desired
459 displacement for each eye. This notion implies two separate, shifted motor maps in the superior
460 colliculus, one for each eye. If offset monocular motor maps were present, it is interesting to
461 consider the outcome of microstimulation applied to a single site. The result can be predicted
462 from experiments stimulating at two different sites in the superior colliculus of normal animals.
463 The ensuing saccade resembles the vector sum of the saccades driven at either site alone
464 (Katnani et al. 2012; Noto and Gnadt 2009; Robinson 1972; Vokoun et al. 2014). The saccade is
465 conjugate, because tectal output is conveyed to a saccade generator that drives yoked eye
466 movements. For the same reason, one would expect microstimulation to drive conjugate
467 saccades in strabismus, even if there were monocular maps comprised of separate populations of
468 neurons encoding different vectors for each eye. It seems doubtful that the technique of
469 microstimulation could reveal separate monocular maps in strabismus, even if present. This
470 point holds true, regardless of which eye is engaged in fixation at the moment of
471 microstimulation.

472

473 Fleuriet and colleagues (2016) found that the eyes' peak saccadic velocities remain equal,
474 leading them to conclude that disconjugate saccades could not be fully explained by changes in
475 the oculomotor plant. We previously compared adducting and abducting saccades after
476 tenotomy of the medial rectus, and also found equal saccadic velocities (Economides et al.
477 2007). Saccadic velocity, however, is only one facet of muscle function. Other changes in
478 muscle action could contribute to saccadic disconjugacy.

479

480 In Monkeys 2 and 3, evoked saccades were disconjugate, but smooth pursuit and static
481 fixations also showed disconjugacy (**Fig. 5B, 6B,C**). This fact provides the strongest evidence
482 that disconjugate saccades did not arise from plasticity of the map in the superior colliculus, but
483 were a general property of all gaze angle shifts in these animals. Evidence has emerged that
484 pattern deviations are due to cross-axis eye movements generated by the firing behavior of ocular
485 motoneurons (Das 2011; Das and Mustari 2007; Walton et al. 2015; Walton et al. 2013). Even in
486 normal animals, saccade metrics can adapt without any change in the tectal saccade map (Quessy
487 et al. 2010). Incomitance in strabismus is likely due to perturbations downstream from the
488 colliculus, at sites that control yoking of eye position in different gaze angles for saccades,
489 smooth pursuit, and steady fixation.

490

491 In this context, Monkey XT1 in the report by Fleuriet and colleagues (2016) had a pattern
492 deviation that was extremely similar to that recorded in our exotropic Monkey 3 (compare **Fig.**
493 **6A** to Walton et al. 2014, **Fig. 1 C, D**). Their Monkey XT1 had a -20° Direction Difference for
494 saccades, similar to the value of -15° in Monkey 3. Reasons suggested for this Direction

495 Difference included: density of eye muscle innervation, site of medial rectus reattachment,
496 altered vergence tone, and abnormalities in the saccade generator (Walton et al. 2014).

497

498 When strabismic subjects plan a saccade to a target, they must decide which eye to use
499 and then calculate the appropriate saccade vector for that eye. Sometimes the target is detected
500 by the same eye that acquires it, but strabismic subjects are also capable of perceiving the
501 location of a target with one eye and then making a saccade to it with the other eye – a
502 phenomenon known as a “crossover” saccade (Economides et al. 2014). It remains unclear how
503 this process is controlled in the visual system. Any given visual target evokes a sensory
504 response at two different locations in the superior colliculus, but motor activity to drive a saccade
505 occurs at only one site. Single unit recordings, currently underway, should provide further
506 insight into how sensory responses are gated to yield subsequent motor activation at a single site
507 in the superior colliculus.

508

509

510

511

FIGURE LEGENDS

512

513

514 **Fig. 1)** Electrical stimulation of the superior colliculus of strabismic monkeys. **(A)** Diagram
515 showing right eye (RE) fixating at the origin and exotropic left eye (LE). A target (black circle)
516 presented between the eyes' fixation points could be acquired by the left eye with a 30° saccade
517 or by the right eye with a 20° saccade. **(B)** Schematic map of the superior colliculus (SC), dorsal
518 view, showing where sensory responses would be evoked by the target in **(A)** for the left eye
519 (blue circle) and the right eye (red circle). Sensory responses at only one site would be followed
520 by a motor discharge to bring an eye onto the target. Small circles denote sites where
521 microstimulation was delivered in each monkey.

522

523

524 **Fig. 2)** Saccades elicited by stimulation of the superior colliculus are essentially conjugate.
525 Representative eye position traces from three exotropic monkeys showing staircases of saccades
526 after current application in the right superior colliculus. The ocular deviation remains constant in
527 each animal as the eyes are driven to the left. Positive values = upgaze or rightgaze.

528

529 **Fig. 3)** Repeated stimulation at a single site in the superior colliculus yields saccades of similar
530 size and direction in each eye of Monkey 1. **(A)** Saccade vectors for the right eye (red arrows)
531 fixating at a target (green dot) at the screen center. Vectors were computed from initial saccades
532 of staircases driven by electrical stimulation **(B)** Saccade vectors for the left eye fixating at the

533 origin. **(C)** Saccade vectors for intermediate target positions along the horizontal meridian. **(D)**
534 Mean saccadic vectors (bold arrows) for all trials **(A-C)** are similar for the two eyes.

535
536 **Fig. 4)** Stimulation of the superior colliculus while free-viewing produces nearly conjugate
537 saccades in Monkey 2. **(A)** Saccadic vectors for the left eye (blue arrows) and the right eye (red
538 arrows), resulting from electrical stimulation applied every 5 sec while the animal looked at
539 patterns on a tangent screen. **(B)** The amplitudes and directions of saccades made by each eye
540 are similar, despite initiation from widely scattered positions in visual space.

541
542 **Fig. 5)** Horizontal incomitance in Monkey 2. **(A)** Eye positions during static fixations by
543 Monkey 2 with the left eye (blue points) on a grid of 9 targets spaced 20° horizontally and
544 vertically. The grid for the right eye (red points) is displaced downwards because the animal has
545 a left hypertropia. The clouds of points are also elongated, because he has a small vertical
546 pendular nystagmus. Note by comparing matching positions for the two eyes (brackets), that the
547 exotropia increases when the animal moves the left eye from the midline to the left. **(B)** Smooth
548 pursuit by the left eye shows an increase in the horizontal exotropia (black trace) from 40° to 45°
549 when the eye moves leftwards from primary gaze to -40° . Note low gain, saccadic smooth
550 pursuit, which is typical of strabismus.

551
552 **Fig. 6)** Pattern deviation in Monkey 3. **(A)** Static fixation by Monkey 3 with the right eye on a
553 grid of points separated horizontally and vertically by 20° . The corresponding positions for the
554 non-fixating left eye produce a grid rotated by $\sim 17^\circ$. The left inset depicts schematically an
555 incomitant deviation known as an A-pattern. It results in a clockwise Direction Difference for

556 the vertical component of gaze shifts (compare orientation of lines connecting central 3 grid
557 points). In addition to an A-pattern, the left eye of Monkey 3 moves down relative to the right
558 eye as the animal looks to the right (the right inset shows this effect schematically). **(B)** Smooth
559 pursuit by Monkey 3 of a target oscillating sinusoidally $\pm 30^\circ$ (green line). He tracks it with his
560 right eye (red), except beyond 20° to the left. Note the sloping trajectory (blue line) of the non-
561 fixating left eye positions, which forms a $\sim 16^\circ$ angle with the trajectory of the right eye's
562 positions. **(C)** Monkey 3 switches to fixate with the left eye when the target in **(B)** moves more
563 than 15° to the left of the midline. Note the corresponding rotation of the deviated right eye's
564 positions.

565

566 **Fig. 7)** Saccades generated by tectal stimulation differ in polar angle because of pattern
567 deviation. Families of saccades and their mean vectors obtained in Monkey 3 are shown for 4
568 representative stimulation sites. At all sites, left eye saccades were rotated clockwise in polar
569 angle with respect to right eye saccades, due to the animal's combination of pattern deviations
570 **(Fig. 6)**. Number in the polar plots represents scale for saccade amplitude.

571

572 **Fig. 8)** Data from tectal stimulation sites in 3 monkeys. **(A)** Log Amplitude Ratio plotted versus
573 polar angle; most points are on the left side because the right superior colliculus was stimulated
574 in 38/48 experiments. The points are scattered around 0 (dotted line), which equals an
575 Amplitude Ratio of 1. Only Monkey 2 had a mean log Amplitude Ratio that differed
576 significantly from 0. **(B)** Histograms of Direction Differences (10° bins) for stimulation sites in
577 each monkey; Monkey 3 had a mean Direction Difference of -15.0° .

578

579 **Fig. 9)** Noise in video eye tracker measurements of saccade conjugacy. Examples from two
580 normal human subjects making 30 consecutive saccades to targets at an eccentricity of 20°
581 (circle) spaced every 45° . Bold blue (left eye) and red (right eye) vectors represent mean
582 saccades. Both subjects show non-systematic discrepancies in saccade amplitude ($AR = \text{left eye}$
583 $\text{saccade}/\text{right eye saccade}$) and direction ($DD = \text{left eye polar angle} - \text{right eye polar angle}$).
584 Asterisk denotes significant difference at 95% confidence level.
585

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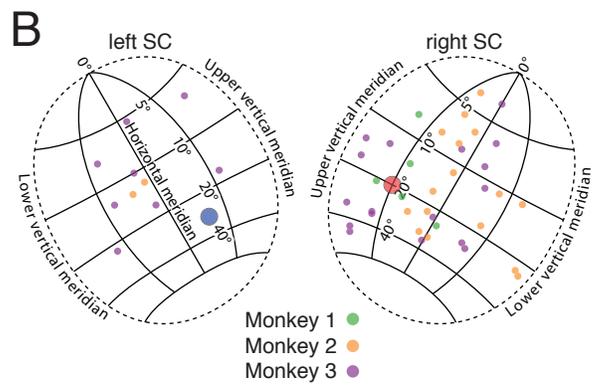
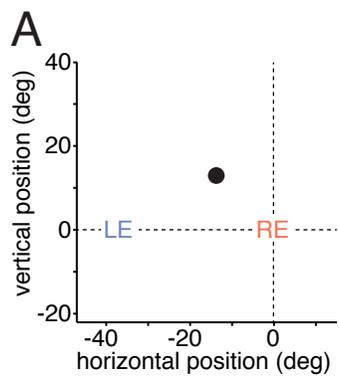
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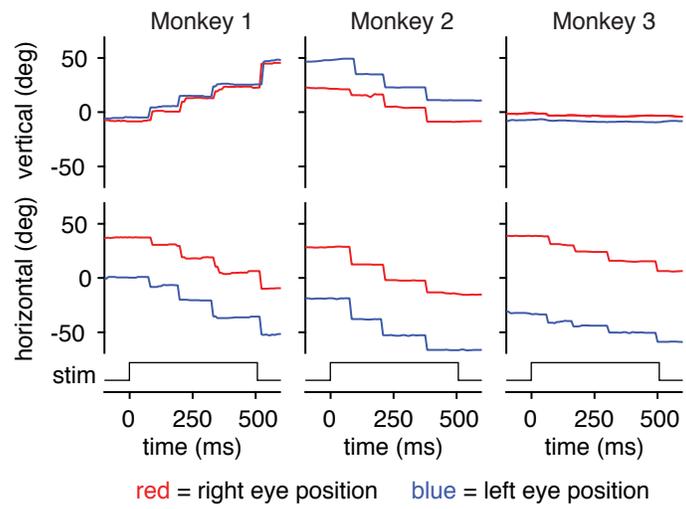
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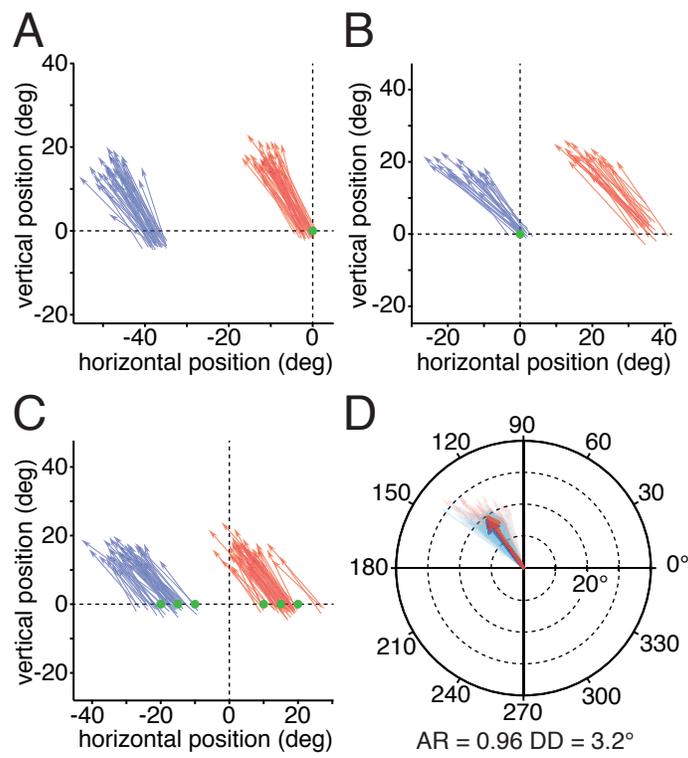
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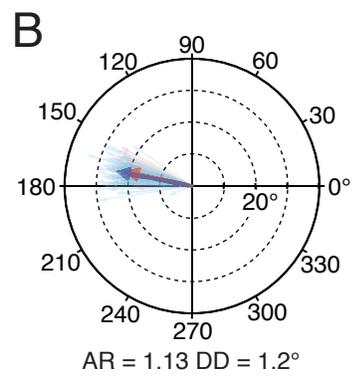
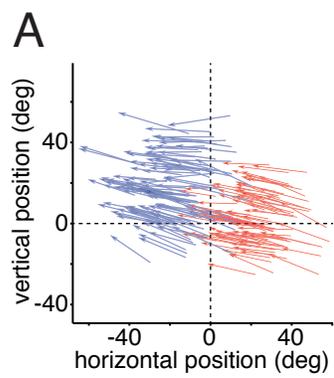
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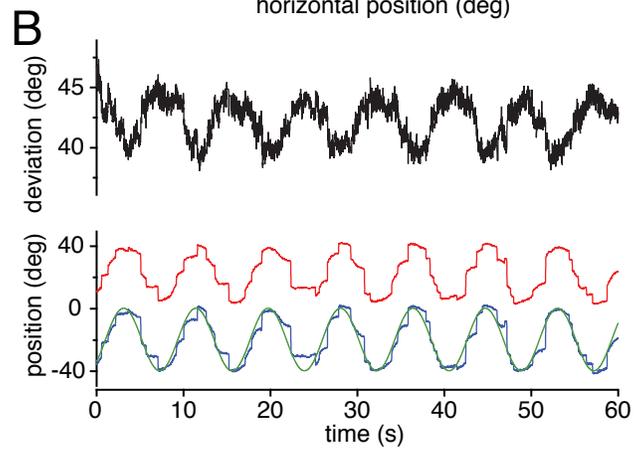
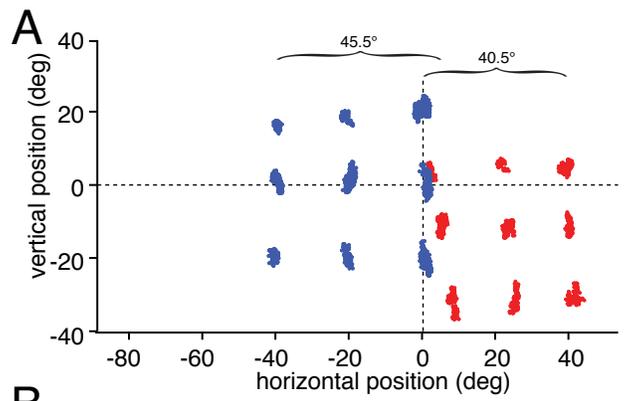
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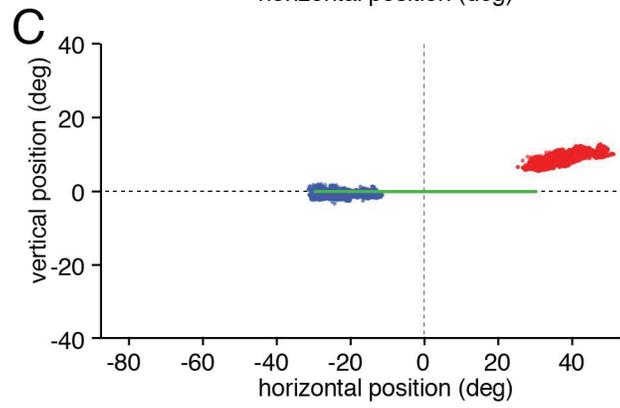
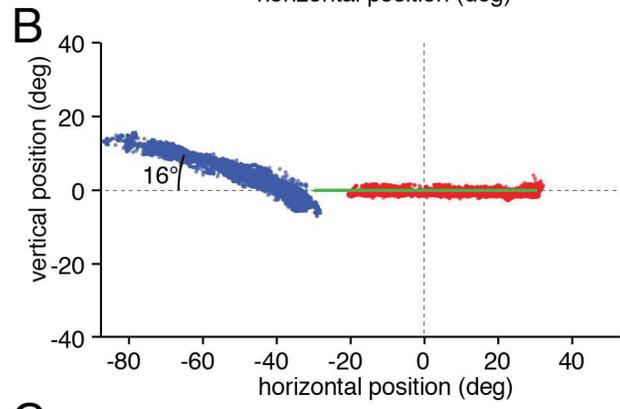
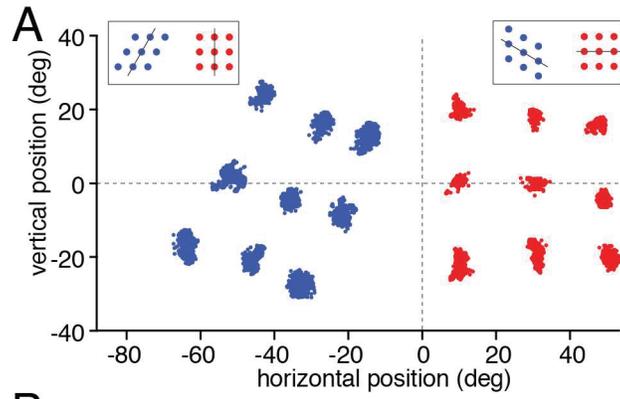


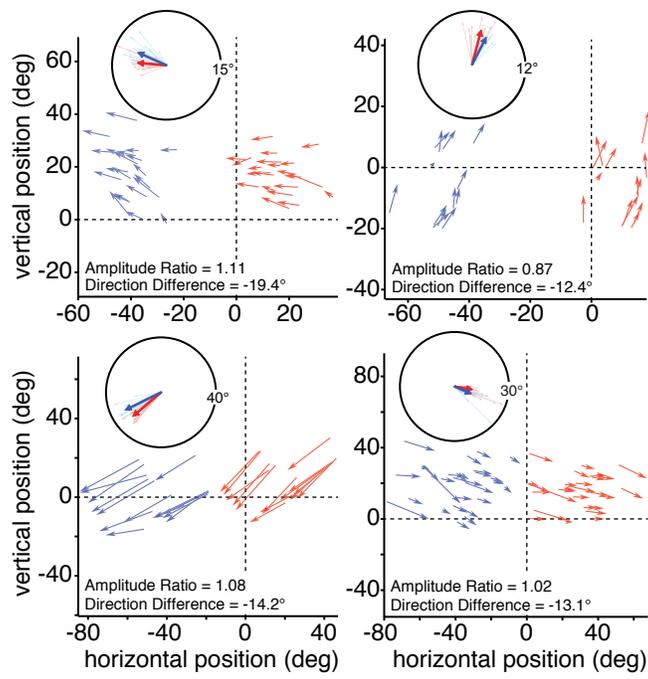


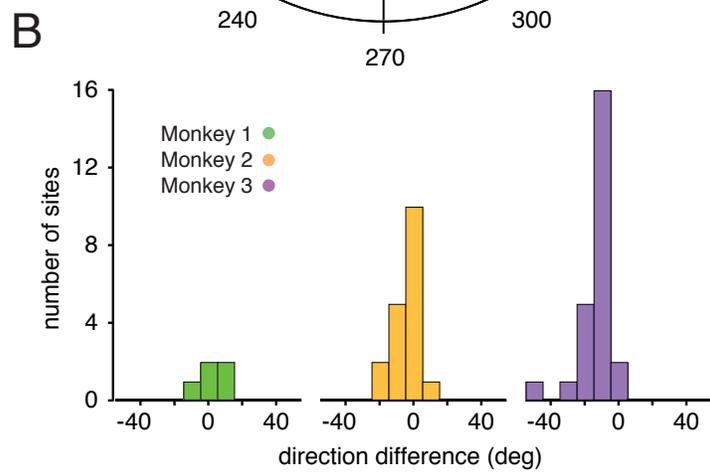
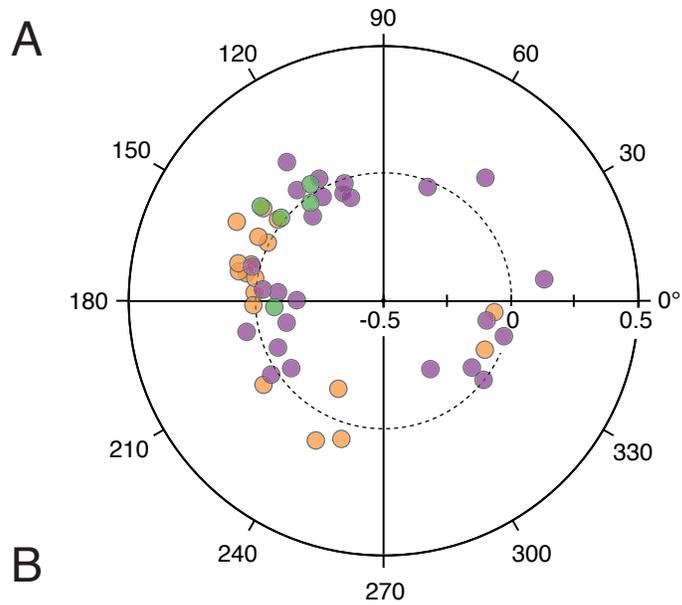




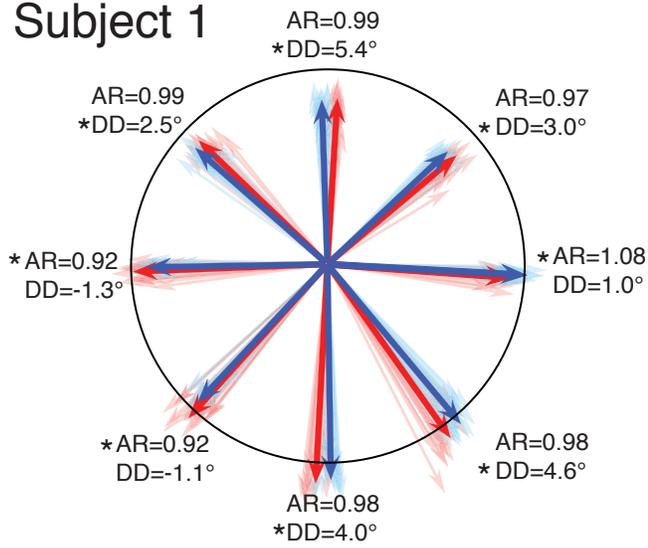








Subject 1



Subject 2

